SYNTHESIS OF CENTRO-SUBSTITUTED TRIQUINACENE DERIVATIVES

by

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Derivatives of tricyclo[5.2.1.0^4,10]deca-2,5,8-triene (triquinacene) bearing substituents at C-10 are compounds of long-standing synthetic and theoretical interest. The preparation of a series of these centro-substituted triquinacene derivatives would allow for a series of studies of the structure and reactivity of the non-planar, tris-homoallylic C-10-centred triquinacyl cation, anion and radical to be undertaken. Moreover, derivatives possessing centro-substituents capable of non-covalent bonding interactions could be employed in an approach to the elusive [6π+6π] photochemical dimerization reaction of triquinacene to prepare the cage hydrocarbon dodecahedrane.

Towards these ends, a series of novel synthetic routes to prepare centro-substituted triquinacene derivatives were developed. One approach, in which the centro substituent was installed regioselectively by means of a conjugate addition reaction of an organocuprate reagent to a protected bicyclic enone, furnished 10-phenyltriquinacene in twelve steps. An extension of this route to prepare other centro-substituted triquinacene derivatives, whereby the installation of the quaternary centro-substituent was achieved by the use of an appropriately substituted glyoxal in a Weiss-Cook condensation reaction, is also presented. This approach afforded both 10-(4'-bromophenyl)triquinacene and the corresponding 1-substituted regioisomer in thirteen steps. Efforts towards the
preparation of 1- and 10-(hydroxymethyl)triquinacene by this route are also described.

Two strategies based on the use of olefin metathesis chemistry to establish the triquinacene framework are also outlined. In the first of these routes, an attempted double ring-closing metathesis process resulted in the discovery of an unexpected and unprecedented cyclopropanation reaction. The second approach highlighted the synthetic challenge in installing quaternary centres in these highly condensed ring systems.

The final approach presented featured the attempted installation of the centro-substituent by means of a Stetter reaction and further elaboration by an aldol condensation cascade.

In the final chapter, the results of a series of \textit{ab initio} molecular modeling studies of the C-10-centred triquinacyl radical, cation and anion, as well as of the dimerization reaction of triquinacene to dodecahedrane, are presented.
For my wife, Kelly and my parents, Jacques and Roberta.
“First, then, let us consider this, that it is the nature of things to be destroyed by defect and excess, as we see in the case of strength and of health (for to gain light on things imperceptible we must use the evidence of sensible things); both excessive and defective exercise destroys the strength, and similarly drink or food which is above or below a certain amount destroys the health, while that which is proportionate both produces and increases and preserves it. So too is it, then, in the case of temperance and courage and the other virtues. For the man who flies from and fears everything and does not stand his ground against anything becomes a coward, and the man who fears nothing at all but goes to meet every danger becomes rash; and similarly the man who indulges in every pleasure and abstains from none becomes self-indulgent, while the man who shuns every pleasure, as boors do, becomes in a way insensible; temperance and courage, then, are destroyed by excess and defect, and preserved by the mean.”

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LIST OF ABBREVIATIONS

(+)- dextrorotatory
(-)- levorotatory
(±)- racemic
Ac acetyl
Ac₂O acetic anhydride
AcOH acetic acid
AIBN 2,2'-azobisisobutyronitrile
Anal. elemental microanalysis
aq. aqueous
atm atmospheres
Å Ångstrom (0.1 nm)
br broad (spectroscopy)
BRSM based on recovered starting material
Calcd. calculated (elemental analysis)
CAN ceric ammonium nitrate
cat. catalytic (amount)
Cl chemical ionization (mass spectroscopy)
cm⁻¹ wavenumbers (IR spectroscopy)
conc. concentrated
COSY ¹H-¹H correlation spectroscopy
δ chemical shift (NMR)
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<td>doublet of doublets of doublets (NMR spectroscopy)</td>
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<tr>
<td>DDQ</td>
<td>2,3-dichloro-5,6-dicyano-p-benzoquinone</td>
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<td>dq</td>
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<td>dt</td>
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</tr>
<tr>
<td>DCM</td>
<td>dichloromethane (methylene chloride)</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>diisobutylaluminum hydride</td>
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<td>DME</td>
<td>1,2-dimethoxyethane (glyme)</td>
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<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
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<td>Et₂O</td>
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<tr>
<td>EWG</td>
<td>electron-withdrawing group</td>
</tr>
<tr>
<td>GC</td>
<td>gas chromatography</td>
</tr>
<tr>
<td>GLC</td>
<td>gas-liquid chromatography</td>
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</table>
\( \Delta H_f \)  heat of formation
\( \Delta H_{\text{hyd}} \)  heat of hydrogenation
h  hour(s)
h\( \nu \)  irradiation (generally ultraviolet)
HMPA  hexamethylphosphoramide
HMQC  heteronuclear multiple quantum coherence spectroscopy
HPLC  high performance liquid chromatography
HRMS  high-resolution mass spectroscopy
Hz  Hertz (cycles per second)
i-Pr\(_2\)EtN  \( N,N,N \)-diisopropylethylamine (Hünig’s base)
i-PrOH  isopropanol (2-propanol)
IR  infrared (infrared spectroscopy)
J  coupling constant (NMR)
kcal  kilocalorie
LDA  lithium \( N,N \)-diisopropylamide
lit.  literature value for a physical or spectral property
m  multiplet (NMR spectroscopy)
M  molecular ion (mass spectroscopy)
\( M \)  molarity of a solution
\( m \text{CPBA} \)  \( m \)-chloroperoxybenzoic acid
Me  methyl
MeCN  acetonitrile (methyl cyanide)
Me\(_2\)CO  acetone
MeI  methyl iodide (iodomethane)
<table>
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<th>Abbreviation</th>
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<tr>
<td>MeOH</td>
<td>methanol (methyl alcohol)</td>
</tr>
<tr>
<td>Me2SO4</td>
<td>dimethyl sulfate</td>
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<tr>
<td>mg</td>
<td>milligram</td>
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<td>MHz</td>
<td>megahertz (NMR field strength)</td>
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<td>min</td>
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<td>µL</td>
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<tr>
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<tr>
<td>NMO</td>
<td>N-methylmorpholine-N-oxide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance spectroscopy</td>
</tr>
<tr>
<td>¹H NMR</td>
<td>proton nuclear magnetic resonance spectroscopy</td>
</tr>
<tr>
<td>¹³C NMR</td>
<td>carbon nuclear magnetic resonance spectroscopy</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>NOESY</td>
<td>nuclear Overhauser effect spectroscopy</td>
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<tr>
<td>t</td>
<td>triplet (NMR spectroscopy)</td>
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<tr>
<td>TBAF</td>
<td>tetra-n-butylammonium fluoride</td>
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</table>
$t$-BuLi $t$-butyllithium

$t$-BuOH $t$-butanol (2,2-dimethylethanol)

$t$-BuOK potassium $t$-butoxide

$td$ triplet of doublets (NMR spectroscopy)

TBS $t$-butyldimethylsilyl

TBSCI $t$-butyldimethylsilylchloride (chlorodimethyl-$t$-butylsilane)

TFA trifluoroacetic acid

THF tetrahydrofuran

TLC thin layer chromatography

TMS trimethylsilyl

TMSCI trimethylsilylchloride (chlorotrimethylsilane)

TsCl tosyl chloride ($p$-toluenesulfonyl chloride)

UV ultraviolet

UV/vis ultraviolet/visible spectroscopy

$v/v$ volume by volume

$w/v$ weight by volume

$w/w$ weight by weight
CHAPTER ONE: GENERAL INTRODUCTION TO THE CHEMISTRY OF TRIQUINACENE AND ITS DERIVATIVES

1.1 Thesis Introduction

This thesis concerns a series of novel syntheses of centro-substituted derivatives of tricyclo[5.2.1.0^4,10]deca-2,5,8-triene (triquinacene). These compounds are of long-standing theoretical interest, as their efficient preparation would permit a series of studies of the structure and reactivity of the triquinacene ring system to be performed. As well, these C-10-substituted triquinacene derivatives would be of use in a potential new approach to the triquinacene dimerization problem (the yet-unrealized photochemical [6π+6π] dimerization reaction of triquinacene to dodecahedrane). As the few existing syntheses of these derivatives were unsuitable in terms of their overall yield and potential for introducing a diverse set of centro-substituents, new approaches to this class of target molecule were developed and are described herein.

1.2 The Triquinacene Ring System

1.2.1 Introduction and physical properties of triquinacene

Tricyclo[5.2.1.0^4,10]deca-2,5,8-triene 1, which bears the trivial name "triquinacene", is a member of the polyquinane family of hydrocarbons (Figure 1).1
Triquinacene 1 has the molecular formula \( \text{C}_{10}\text{H}_{10} \) and consists of three cis-fused five-membered carbocyclic rings, each of which contains one double bond. The three bridgehead carbons, namely C-1, C-4 and C-7, are bis-allylic, whereas the C-10 carbon (the centro position) is common to all three five-membered rings and is tris-homoallylic. The three-dimensional molecular structure of triquinacene 1 resembles that of a bowl or a hemisphere, with H-10 protruding from the apex of the "hemisphere". The two faces of the ring system are designated \( \beta \) or exo (for the convex face) and \( \alpha \) or endo (for the concave face), with the latter possessing greater inherent steric hindrance. Triquinacene 1 is \( \text{C}_{3v} \)-symmetric, with the three-fold axis of rotation coincident with the C-10/H-10 bond and the three mirror planes \( (\sigma_v) \) each bisecting one of the carbon-carbon double bonds. Triquinacene has never been found in Nature and is considered a purely synthetic material.

Below its melting point of 18-19 °C, triquinacene 1 is a colourless crystalline solid. At atmospheric pressure, the boiling point of this hydrocarbon is 78-79 °C. In CDCl₃ solution, the \(^1\text{H}\) NMR spectrum of triquinacene shows two sharp bands, one at \( \delta = 3.71 \) ppm (H-1, H-4, H-7 and H-10) and another at \( \delta = 5.63 \) ppm (six olefinic protons). The \(^{13}\text{C}\) NMR spectrum contains peaks at \( \delta = 29.3 \) ppm (C-1, C-4 and C-7), \( \delta = 48.0 \) ppm (C-10) and \( \delta = 132.9 \) ppm (six
olefinic carbons). The electron-impact mass spectrum of triquinacene exhibits peaks at $m/z = 130$ (M), 129 (M - 1), 115 (M - 15), 78 (M - 52) and 77 (M - 53). The infrared spectrum of an evaporative film contains bands at 3040, 2460, 2380, 1605 and 1348 cm$^{-1}$. The ultraviolet spectrum of triquinacene 1 has an absorption maximum at 187 nm ($\varepsilon = 13000$) along with a shoulder at 205 nm ($\varepsilon = 5000$). The elemental constitution of triquinacene is 92.26% w/w carbon and 7.74% w/w hydrogen.

1.2.2 The X-ray crystal structure of triquinacene

In 1976, Paquette and co-workers obtained the X-ray structure of a crystal of triquinacene 1 at 90 K which had been grown by cooling a drop of the liquid sealed in a glass capillary with a stream of cold nitrogen gas. The crystal structure, with thermal ellipsoids drawn at 50% probability, is depicted below (Figure 2).

Triquinacene crystallized under these conditions into the R3 (bar) space group with a hexagonal unit cell containing six triquinacene molecules. The individual triquinacene units had nearly ideal $C_{3v}$ symmetry, although on account of intermolecular contacts between hydrogen atoms the unit cell was found to be only $C_{3}$-symmetric. In the crystal structure, the molecules were arranged in slightly offset alternating layers with the intermolecular contacts switching between “top-to-top” (i.e. close contact between the exo faces of two molecules) and “bottom-to-bottom” (endo faces in close contact) relative orientations. The overall geometry of triquinacene was described as “cup-shaped” with the olefin
\( \pi \) orbitals projected towards the centre of the endo (concave) face. The three five-membered rings were found to be slightly distorted from planarity.

**Figure 2.** The crystal structure of triquinacene at 90 K. The \( C_3v \) axis lies along the C-4 to H-4 bond. Atoms labeled with prime and double prime superscripts were obtained by 120° and 240° rotations, respectively, about the three-fold rotation axis. Reproduced in part with permission from *The Journal of Organic Chemistry*, volume 41, number 13, page 2268. Copyright 1976 The American Chemical Society.

### 1.2.3 Selected chemical properties of the triquinane ring system

**1.2.3.1 Catalytic hydrogenation**

Catalytic hydrogenation of the three double bonds of triquinacene 1 to afford perhydrotriquinacene 2 was readily accomplished under standard conditions (Scheme 1).\(^3\)
Scheme 1 - Catalytic hydrogenation of triquinacene (1)

\[
\begin{align*}
\text{1} & \overset{\text{(a)}}{\longrightarrow} \text{2} \\
\end{align*}
\]

Reagents and conditions: (a) \( \text{H}_2 \) (1 atm), Pd/C, EtOAc, 99%.

1.2.3.2 Epoxidation and tosylate solvolysis

Oxidation of triquinacene 1 with peracetic acid afforded the corresponding epoxide 3 with delivery of the oxygen atom occurring exclusively from the less-hindered exo (convex) face of the triquinacene ring system (Scheme 2).\(^4\) Lithium aluminum hydride reduction of the epoxide 3 furnished the exo-alcohol 4, which was then converted to the corresponding tosylate 8 under standard conditions. Oxidation of the exo-alcohol 4 afforded the ketone 5, which then underwent lithium aluminum hydride reduction with delivery of hydride from the exo face to furnish the endo-alcohol 6. This alcohol was then transformed into its corresponding tosylate 7.

Scheme 2 - Preparation of the tosylates (7) and (8)

\[
\begin{align*}
\text{1} & \overset{\text{(a)}}{\longrightarrow} \text{3} & \text{4} & \overset{\text{(c)}}{\longrightarrow} \text{8} \\
\text{7} & \overset{\text{(f)}}{\longrightarrow} \text{6} & \overset{\text{(e)}}{\longrightarrow} \text{5} \\
\end{align*}
\]

Reagents and conditions: (a) \( \text{CH}_3\text{CO}_3\text{H} \), 75%; (b) LiAlH\(_4\), THF; (c) TsCl, py, DCM; (d) CrO\(_3\), py, DCM; (e) LiAlH\(_4\), THF; (f) TsCl, py, DCM.
Acetolysis experiments carried out on the tosylates 7 and 8 showed that the rate of solvolysis was 4.4 times faster for the exo isomer 8 at 100 °C. In order to gauge the extent of homoallylic participation of the neighbouring double bond, the above experiment was repeated using the saturated analogues of these tosylates. In the absence of the double bonds, acetolysis of the exo isomer was 3.2 times faster than that of the endo tosylate. The small difference between the $k_{exo/endo}$ values for these two systems, in combination with the observation that the only isolated products were those of solvolysis without participation, led to the conclusion that the C-2-centred triquinacyle cation, unlike the norbornyl carbocation, does not undergo neighbouring group participation to an appreciable extent. This result was attributed to the $p\pi$ orbitals in the exo isomers, which point toward the centre of the endo (concave) face, having poor alignment for such participation.

In a 1998 study of the tris-epoxidation of triquinacene 1, de Meijere and co-workers found that these reactions generally took place with a high degree of exo selectivity (Scheme 3).

**Scheme 3 - Exhaustive epoxidation of triquinacene (1)**

![Scheme 3 - Exhaustive epoxidation of triquinacene (1)](image)

Reagents and conditions: (a) dimethyldioxirane, Me$_2$CO, 100%; (b) $m$-CPBA, NaHCO$_3$, DCM, 63%; (c) Oxone®, NaHCO$_3$, aq. Me$_2$CO, 58%.
In all three cases, only the all-exo tris-epoxide 9 and the exo,exo,endo-isomer 10 were obtained. The absence of the exo,endo,endo- or all-endo isomers was indicative of the high selectivity for oxygen delivery to the more accessible exo (convex) face of the triquinacene ring system. Epoxidation with dimethyldioxirane afforded the isomers 9 and 10 in a ratio of 1:1.5, whereas the ratio upon treatment with m-CPBA was 1:1.3. Epoxidation with Oxone® was more selective for the exo,exo,endo-isomer 10, affording these isomers in a ratio of 1:6.3. Furthermore, treatment of the all-exo isomer 9 with lithium aluminum hydride afforded the corresponding known regioisomeric all-exo 2,5,8- and 2,5,9-triols (1:2), confirming the previous result (c.f. Scheme 2) that exo-epoxide opening by hydride ion takes place exclusively from the endo face.

1.2.3.3 Inherent reactivities of the triquinane ring system positions

The relative reactivities towards free radicals of the different positions of the triquinacene ring system were probed using perhydrotriquinacene 2, which was prepared by the method of Jacobsen (c.f. Section 1.3.2). Treatment of perhydrotriquinacene 2 with a sub-stoichiometric amount of carbomethoxynitrene, generated by thermal decomposition of methyl azidoformate at 120 °C in a sealed ampoule, led to the formation of three regioisomeric methyl carbamates (Scheme 4).
Scheme 4 - Nitrene insertion into perhydrotriquinacene (2)

Reagents and conditions: (a) $\text{N}_3\text{CO}_2\text{Me}$ (0.11 equiv.), 120 °C, sealed tube, 3.5 h, 71%.

The three carbamates 11, 12 and 13 were obtained in a ratio of 1.0:2.9:3.1, respectively, which on a per-hydrogen basis corresponds to a relative reactivity ratio of 4.0:3.8:1.0 for the tertiary apical (C-10), tertiary nonapical and methylene protons, respectively. These values, which indicated a preference for reaction at tertiary centres, were consistent with the observation that tertiary centres more readily accommodate free-radical character (present in the transition states of these nitrene insertion reactions) than do secondary centres. Furthermore, the tertiary:secondary reactivity ratio generally decreases with increasing ring strain, since strained centres are forced away from the ideal tetrahedral geometry which efficiently stabilizes free-radical character. The value of this parameter for perhydrotriquinacene (~4:1) more closely resembled those of the unstrained adamantane (6:1) and 2-methylbutane (3.2:1) systems than it did that of the strained bicyclo[2.2.2]octane (1.8:1) system. From these data, one may conclude that the perhydrotriquinacene ring system is relatively free of ring strain.

Perhydrotriquinacene 2 has been oxidized with chromyl acetate and the ratio of the oxidation products 14, 15 and 16 was determined (Scheme 5).
Scheme 5 - Chromyl acetate oxidation of perhydrotriquinacene (2)

Reagents and conditions: (a) CrO\textsubscript{3} (2 equiv.), AcOH/Ac\textsubscript{2}O (1:1), 5 °C to rt, 30 h.

The ketone 14, the tertiary alcohol 15 and the tertiary acetate 16 were obtained in a ratio of 37:51:12. Of note, no products of oxidation at C-10 were detected. As these oxidation reactions are known to lead to significant carbonium ion character in their transition states, these reactions may serve as a probe for the ability of a given ring position to achieve sp\textsuperscript{2} hybridization.\textsuperscript{11} The absence of any C-10 oxidation products was attributed to the inability of the centro position, whose geometry is constrained by the ring system, to achieve planarity. This result was independently confirmed by Baum and Gutsche, who reported that the solvolysis of 10-tosylperhydrotriquinacene took place 10\textsuperscript{9} times slower than the rate predicted on the basis of semi-empirical calculations.\textsuperscript{12} The centro-position in this ring system achieves planarity with difficulty and is hence reluctant to accommodate a positive charge.

1.2.3.4 The rearrangement of perhydrotriquinacene (2) to adamantane (17)

Perhydrotriquinacene 2, having a molecular formula of C\textsubscript{10}H\textsubscript{16}, was isomerized on heating in the presence of Lewis acids to the thermodynamically more stable hydrocarbon adamantane 17 (Scheme 6).\textsuperscript{10}
Reagents and conditions: (a) AlCl₃ (excess), hexanes, reflux, 45 h, 91%; (b) FSO₃H, DCM, -78 °C, 30 min, then H₂O, -78 °C to rt, 16-32%.

The aluminum trichloride-promoted isomerization reaction of perhydrotriquinacene 2 to adamantane 17 was nearly complete after 45 h at reflux in hexanes. Moreover, treatment of the tertiary alcohol 15 or either diastereoisomer of the secondary alcohol 19 with fluorosulfonic acid led to 1-adamantol 18 upon quenching of the reaction with water. In light of the observation that the rates of these transformations were slower than those of twistane 20 but more rapid than those of tetrahydrodicyclopentadiene 21, a mechanistic rationale for the rearrangement reactions of perhydrotriquinacene 2 was proposed. As the rates of adamantization are retarded in cases where a bridgehead carbonium ion intermediate must be involved (as is the case with tetrahydrodicyclopentadiene 21), the proposed rearrangement pathway for perhydrotriquinacene 2 did not involve such intermediates. The greater rate of adamantization of twistane 20 versus that of perhydrotriquinacene 2 was due to the greater structural similarity of twistane and the final product, adamantane 17.
1.2.3.5 The debate over the neutral homoaromaticity of triquinacene

The concept of homoaromaticity was first proposed by Winstein in 1959, who defined homoaromatic compounds as those which "display aromaticity despite one or more saturated linkages interrupting the formal cyclic conjugation". By analogy with aromaticity, the usual measure of homoaromaticity is in terms of stabilization energy, i.e. an increased stability with respect to a suitable nonhomoaromatic reference molecule resulting from the delocalization of π electrons. This delocalization may be either through-bond or through-space in nature and results in either case in an equilibration of bond lengths to values different from both normal single or double bonds.

The phenomenon of homoaromaticity is well-documented for cations such as the homocyclopropenium cation 22 (an example of a 2-electron homoaromatic system) and the monohomotropylium cation 23 (a 6-electron system), where the delocalization of charge serves as an additional stabilizing factor (Figure 3). On the other hand, the existence of homoaromaticity in anionic systems such as the bicyclo[3.2.1]octadienyl anion 24 or in neutral species such as cycloheptatriene 25 remains highly controversial and is an area of active theoretical and experimental research.
In 1986, Liebman and co-workers reported evidence for neutral homoaromaticity in triquinacene 1. It was suggested that the positioning of the double bonds about the “bottom” or “base” of the triquinacene ring system was appropriate for homoaromatic interaction (Figure 4).

The heats of hydrogenation of triquinacene 1, dihydrotriquinacene 26 and tetrahydrotriquinacene 27 were determined by calorimetry. The results of these thermochemical experiments are presented below (Figure 5).

Based on the observation that the heat of hydrogenation of triquinacene 1 (possessing 3 double bonds) was less than three times that of
tetrahydrotriquinacene 27 (1 double bond) by \(~4.5\) kcal mol\(^{-1}\), the authors concluded that this difference was due to homoaromatic stabilization energy. As anticipated, the heat of hydrogenation of dihydrotriquinacene 26 (2 double bonds) was exactly twice that of tetrahydrotriquinacene 27, as only the \(6\pi\) triquinacene system 1 would be expected to exhibit homoaromaticity. The authors concluded that triquinacene 1 exhibited a small but nontrivial homoaromaticity.

This conclusion was not met with universal acceptance, especially in the absence of the observation of any ring current (by \(^1\)H NMR chemical shift analysis) in triquinacene 1 and in light of the X-ray crystal structure of triquinacene, which showed no evidence of interaction between the \(\pi\) electrons.\(^2\) A 1988 ab initio study at the MP2/6-31G* level of theory did not support the observed trend in the heats of hydrogenation.\(^20\)

Other theoretical studies have reproduced the experimental results but have invoked arguments other than homoaromaticity in order to rationalize the anomalous heat of hydrogenation of triquinacene 1. A MM2 molecular mechanics study published by Dewar and Holder in 1989 concluded that this discrepancy was the result of differences in the propensities of triquinacene 1, dihydrotriquinacene 26 and tetrahydrotriquinacene 27 to relieve strain by twisting.\(^21\) This was followed by a MM3 molecular mechanics study reported by Storer and Houk in 1992, which refuted the Dewar-Holder hypothesis, instead attributing the anomalous heat of hydrogenation of triquinacene 1 to the relief of nonbonded 1,4-interactions between the hydrogen atoms on the endo face upon
hydrogenation. Moreover, a 1993 analysis by Holder of the bonding pattern in triquinacene 1 using the computational AIM (atoms-in-molecules) approach failed to locate any significant interactions between the double bonds.

In 1998, a paper claiming definitive experimental and theoretical disproof of the neutral homoaromaticity of triquinacene 1 was published by de Meijere and Schleyer. The experimental component of this study consisted of the microcalorimetric evaluation of the heat of formation (obtained from the heat of combustion), rather than the heat of hydrogenation, of triquinacene 1. The more precise experimental value so obtained led to a revised value for the heat of formation of triquinacene which was higher than the previously determined value by about 4 kcal mol⁻¹. This revised value was in agreement with that obtained by the aforementioned theoretical studies. In combination with extensive ab initio computational work employing density functional theory at a high level (B3LYP/6-31+G**+ZPE), the authors concluded that homoaromaticity was completely absent in triquinacene 1 and that the thermochemical anomaly reported by Liebman was the result of experimental error.

While this study provided very strong evidence for the absence of neutral homoaromaticity in triquinacene 1, a further ab initio study published in 2000 by Rogers and McLafferty could not completely rule it out. This study consisted of the evaluation of the heats of formation of triquinacene 1, dihydrotriquinacene 26, tetrahydrotriquinacene 27 and perhydrotriquinacene 2. The authors cited the inherent difficulties in accurately determining a homoaromatic stabilization energy of ~4 kcal mol⁻¹, which is only 0.0016% of triquinacene's total energy, within
experimental error and argued that further thermochemical and computational experiments were required.

1.3 Syntheses of Triquinacene\textsuperscript{26}

1.3.1 Woodward (1964)

The first synthesis of tricyclo[5.2.1.0\textsuperscript{4,10}]deca-2,5,8-triene \textsuperscript{1} as well as the assignment of the trivial name “triquinacene” to this hydrocarbon were performed forty years ago by R.B. Woodward and co-workers (Scheme 7).\textsuperscript{27}

This eighteen-step linear synthesis began with isodrin \textsuperscript{28}, a polychlorinated twelve-carbon tetracyclic diene which was once readily available given its former widespread use as an insecticide.\textsuperscript{28} On modification of a procedure developed by Winstein, hydroboration/oxidation of the disubstituted olefin moiety of isodrin \textsuperscript{28} afforded the hexachloro alcohol \textsuperscript{29}.\textsuperscript{29}
**Scheme 7 - Woodward's synthesis of triquinacene (I) (Part I)**

![Scheme 7 - Woodward's synthesis of triquinacene (I) (Part I)](image)

Reagents and conditions: (a) B₂H₆, Et₂O, then H₂O₂, NaOH; (b) Li, t-BuOH, THF; (c) CrO₃, py, 74%; (d) 40% CH₃CO₃H-AcOH, NaOAc, DCM, 92%; (e) t-BuOK, THF/Et₂O, 90%; (f) H₂Cr₂O₇, Et₂O, 70%; (g) Pb(OAc)₄, PhH, reflux, 36%; (h) hot MeOH, 100%; (i) CH₂N₂, then NaOMe, MeOH; (j) NaOH, MeOH/H₂O, 67% over two steps; (k) SOCl₂, reflux; (l) NaN₃, PhMe.

This was followed by the complete dechlorination of the alcohol 29 under radical conditions, furnishing the alcohol 30. Oxidation of the secondary alcohol moiety to the corresponding ketone 31 was accomplished in good yield by treatment with chromic anhydride in pyridine. Epoxidation of the olefinic moiety of the ketone 31 with peracetic acid in the presence of acetic acid and sodium acetate in dichloromethane afforded the epoxy ketone 32 in excellent yield. In the only carbon-carbon bond-forming reaction in this synthesis, treatment of the epoxy ketone 32 with potassium t-butoxide effected a transannular cyclization
reaction through enolization of the ketone function followed by nucleophilic attack on the epoxide moiety, furnishing the hydroxy ketone 33 in excellent yield.

**Scheme 8 - Woodward's synthesis of triquinacene (1) (Part II)**

Reagents and conditions: (m) PhMe, reflux; (n) hot MeOH, 84% over four steps from the diacid 38; (o) LiAlH₄, THF, reflux, 84%; (p) 37% aq. CH₂O, HCO₂H, reflux, 94%; (q) 30% aq. H₂O₂, MeOH; (r) vacuum pyrolysis, 125-140 °C, 78% over two steps.

Subsequent oxidation of the hydroxy ketone 33 with aqueous chromic acid in ether afforded the unusual and stable diketone hydrate 34 in good yield. In the key step which established the triquinane framework, heating the diketone hydrate 34 at reflux in benzene in the presence of lead tetraacetate cleaved the cage-like structure of the diketone hydrate 34, furnishing the anhydride 35. Methanolysis of the anhydride 35 afforded the mono-ester 36 in quantitative yield as a mixture of *endo* and *exo* stereoisomers. Conversion of the mono-ester 36 to the diester 37 was accomplished by reaction with diazomethane. Treatment of the diester 37 with sodium methoxide in methanol furnished an equilibrium mixture containing 70% of the desired *exo,exo*-diester 37 along with 30% of the corresponding *endo,exo*-diastereomer. Saponification of this mixture afforded
the corresponding dicarboxylic acids; the desired exo,exo-diacid 38 was isolated in good overall yield from this mixture of isomers by fractional recrystallization from chloroform.

With the desired diacid 38 in hand, a Curtius degradation sequence was undertaken in order to complete the synthesis. The diacid 38 was converted into the corresponding diacyl halide 39 on treatment with thionyl chloride. This intermediate was transformed into the diazide 40 with sodium azide in toluene. Heating the diazide 40 in toluene effected a Curtius rearrangement, furnishing the bis-isocyanate 41. This isocyanate was heated in methanol to afford the bis-urethane 42 in 84% yield over four steps from the diacid 38. Lithium aluminum hydride reduction of the bis-urethane 42 afforded the bis-methylamino derivative 43, which was then converted to the corresponding bis-dimethylamino derivative 44 in excellent yield upon reductive amination with hot 37% aqueous formaldehyde and formic acid. Finally, formation of the corresponding bis-amine-N-oxide 45 by oxidation with 30% aqueous hydrogen peroxide in methanol and pyrolysis of this intermediate in vacuo (10-30 mmHg, 125-140 °C) afforded triquinacene 1 in good yield.

As Woodward did not report yields for the first two steps and considered the alcohol 30 to be the starting point for his synthesis, the overall yield can not be determined. However, the overall yield for the sixteen steps from the alcohol 30 was 5%.
1.3.2 Jacobson (1967)

The next synthesis of triquinacene 1 was reported by Jacobson (Scheme 9).31 This seven-step preparation started with 1,4-diaminobutane 46, which was transformed to the bis-urethane 47 on reaction with methyl chloroformate. The nitrosylation method of Samour and Mason was then employed to prepare the corresponding bis-nitrosourethane derivative 48, which was obtained in 74% yield over two steps.32

Scheme 9 - Jacobson's synthesis of triquinacene (1)

Reagents and conditions: (a) methyl chloroformate, K$_2$CO$_3$, rt; (b) NaNO$_2$, aq. H$_2$SO$_4$, 0-5 °C, 74% over two steps; (c) K$_2$CO$_3$, MeOH:THF (1:1), -10 to 10 °C, 37%; (d) p-tosylhydrazine, HCl, EtOH, reflux, 3 h, 86%; (e) Na, acetamide, 90-175 °C, 87%; (f) Cl$_2$, CCl$_4$, hv, rt, 30 h, 55% (53 + 54); (g) n-BuCl, i-BuOH, Li, THF, reflux, 3 h, 72%.
Generation of 1,4-bis(diazo)butane 49 from the bis-nitrosourethane 48 in the presence of cyclohexanone 50 then furnished the doubly ring-expanded ketone, 10-ketobicyclo[5.2.1]decane 51, in moderate yield. Treatment of this ketone with p-tosylhydrazine under acidic conditions afforded the corresponding p-tosylhydrazone 52.

Heating the p-tosylhydrazone 52 in molten acetamide in the presence of sodium metal afforded the corresponding p-tosylhydrazone sodium salt, which upon vigorous heating decomposed to furnish the corresponding carbene. In turn, this carbenoid intermediate underwent a transannular cyclization reaction, affording perhydrotriquinacene 2 as the major reaction product. Perhydrotriquinacene 2 was then converted to triquinacene 1 in a two-step procedure. Chlorination of perhydrotriquinacene 2 under forcing conditions afforded a mixture of highly chlorinated products, including perchlorotriquinacene 53 (37%) and the related 1,2,3,4,5,6,7,8,9-nonachlorotriquinacene 54, which lacked a chlorine substituent at the centro (C-10) position (18%). Radical dechlorination of the mixture of these two compounds with lithium metal and t-butyl alcohol in tetrahydrofuran then afforded triquinacene 1 in good yield. Of note, the use of n-butyl chloride as an additive was found to be essential in order to obtain more than trace amounts of triquinacene 1 in this reaction and the potential role of n-butyl chloride as a metal-halogen exchange catalyst was proposed by Jacobson.

The route devised by Jacobson furnished triquinacene 1 in 8% overall yield in seven steps from the simple starting materials 1,4-diaminobutane 46 and
cyclohexanone 50. In subsequent years, Jacobson reported a number of refinements to his initial synthesis. \(^{35,36,37}\) Of note, the mixture of perchlorotriquinacene 53 and the nonachloro derivative 54 obtained by the forcing photochemical chlorination reaction could be converted in high yield to pure perchlorotriquinacene 53 by heating the mixture with hexachloroethane and a catalytic amount of iodine in a sealed tube. Moreover, the reaction conditions for the chlorination/dechlorination process, which converted perhydrotriquinacene 2 to triquinacene 1, were optimized.

### 1.3.3 de Meijere (1971)

The third synthesis of triquinacene 1 was reported in 1971.\(^ {38}\) Irradiation of the known compound, snoutene 55,\(^ {39}\) with ultraviolet light for 48 h at -10 °C afforded the isomeric compound, diademane 56.* Heating diademane 56 then afforded triquinacene 1 through a symmetry-allowed \([\pi 2_s + \pi 2_s + \pi 2_s]\) cycloreversion process (presumably driven by relief of ring strain) which had a half-life of 1 h at 90 °C.

**Scheme 10 - de Meijere's synthesis of triquinacene (1)**

![Scheme 10](image)

Reagents and conditions: (a) hv, pentane, -10 °C, 48 h, 53%; (b) 90 °C, 3 h, 100%.

* The preparation of diademane 56 and derivatives thereof are discussed in Section 1.4.3.
1.3.4  Deslongchamps (1973)

An expedient preparation of triquinacene 1 was first reported in preliminary form by Deslongchamps and co-workers in 1973 (Scheme 11). The full paper on this work was published, along with several other related studies, in 1978. This six-step preparation began with the commercially-available twelve-carbon starting material Thiele’s acid 57, which can be obtained from cyclopentadiene.

\[ \text{Scheme 11 - Deslongchamps' synthesis of triquinacene (1)} \]

Reagents and conditions:  
(a) $\text{NaN}_3$, $\text{H}_2\text{SO}_4$ (conc.):TFA (5:3), 45-50 °C, 5 h, 35%;  
(b) $\text{hv}$, MeOH, 30 min;  
(c) 3 M aq. HCl:acetone (1:15), rt, 2 h, 75% over two steps;  
(d) LiAlH$_4$, THF, reflux, 5 h, 80%;  
(e) MsCl, py, DCM, -20 to 0 °C, 24 h, 92%;  
(f) activated neutral Al$_2$O$_3$, DCM, rt, 23 h, 42%.

Deslongchamps’ initial preparation of the dione 58 from Thiele’s acid 57 involved treatment of this starting material with oxalyl chloride in dichloromethane to obtain the corresponding diacid chloride, followed by treatment with sodium azide. Heating the resultant diazide in aqueous dimethoxyethane then afforded the desired dione 58. However, a direct conversion of Thiele’s acid 57 to the
dione 58 could be achieved in moderate yield, on a multi-gram scale, by heating a solution of Thiele’s acid 57 in a mixture of concentrated sulfuric acid and trifluoroacetic acid in the presence of sodium azide.

Photochemical degradation of the dione 58 was accomplished by irradiation with ultraviolet light of a methanolic solution of this dione using a mercury lamp in a quartz vessel under an atmosphere of nitrogen for 30 min. The resultant bicyclic aldehyde 59 was then, without purification, dissolved in a mixture of acetone and 3 M aqueous hydrochloric acid (1:15). After stirring for 2 h at room temperature, the tricyclic keto alcohol 60 was obtained in good yield via an aldol condensation reaction. The tricyclic keto alcohol 60, which has the desired triquinane framework, was obtained as a mixture of epimers (exo:endo = 5.3:1). Lithium aluminum hydride reduction of the tricyclic keto alcohols 60 furnished the diols 61 in good yield. Activation of both hydroxyl functions on reaction with methane sulfonyl chloride afforded the dimesylates 62 in excellent yield as a mixture of stereoisomers. Finally, stirring the dimesylates 62 with neutral, activated alumina (Brockman Grade I) as a slurry in dichloromethane furnished triquinacene 1 in 8% overall yield in six steps from Thiele’s acid 57.

1.3.5 Paquette (1974)

The shortest reported synthesis of triquinacene 1 is that of Paquette and co-workers (Scheme 12). This four-step preparation began with the generation of a solution of 9,10-dihydrofulvalene 64 in tetrahydrofuran by means of an oxidative coupling reaction of two equivalents of sodium cyclopentadienide 63 with molecular iodine. Treatment of this solution with diethyl azodicarboxylate
afforded the bis-carbamate 66 in a domino Diels-Alder process upon warming to room temperature. Hydrolysis of the two carbamate moieties of the intermediate 66 with potassium hydroxide in isopropanol, followed by oxidation with manganese dioxide furnished the azo compound 68, which upon irradiation with ultraviolet light afforded triquinacene 1 in 34% yield over four steps.

Scheme 12 - Paquette's synthesis of triquinacene (1)

Reagents and conditions: (a) I$_2$, THF, -78 °C, then diethyl azodicarboxylate 65, -78 °C to rt, 72%; (b) KOH, i-PrOH, reflux, 4 h; (c) MnO$_2$, 79% over two steps; (d) hv, pentane, rt, 60%.

1.3.6 Cook (1985)

The synthesis of triquinacene 1 by Cook and co-workers was reported in preliminary form in 1985$^{46}$ and a full paper was published in 1989 (Scheme 13).$^{47}$
Reagents and conditions: (a) NaOH, NaHCO₃, H₂O, rt, 3 days, 45%; (b) CH₂N₂, DCM, rt, 2 h; (c) KH (2.3 equiv.), DMF, -25 °C, 1 h, then allyl iodide (5 equiv.), -58 °C, 5 h; (d) AcOH, aq. HCl, reflux, 1.5 h, 90% over three steps; (e) NaIO₄, OsO₄ (cat.), dioxane:H₂O (65:35), 4 h, 91%; (f) THF:2 M HCl (100:7), rt, 7 days, 86%; (g) BH₃•THF, THF, 0 °C to rt, 16 h, 92%; (h) HMPA, reflux, 2 days, 80%.

The starting point for this eight-step preparation of triquinacene 1 was a Weiss-Cook condensation reaction (c.f. Section 1.7) between two equivalents of di-t-butyl-1,3-acetonedicarboxylate 70 and one equivalent of glyoxal 69. After stirring for 3 days under alkaline conditions, the tetraester 71 was isolated in 45% yield. In order to block two of the four possible sites of alkylation in the ensuing allylation reaction, both enol moieties present in the intermediate 71 were converted into their corresponding methyl enol ethers by treatment with
diazomethane. The dimethylated tetraester intermediate 72 was then treated with excess potassium hydride, followed by a large excess of allyl iodide. It was hoped that the aforementioned blocking strategy, in conjunction with the four bulky t-butyl substituents, would favour monoalkylation at the expense of dialkylation. Indeed, following saponification and decarboxylation with hot aqueous acid, an excellent yield of the monoallylated dione 74 was obtained.

The synthesis was completed by oxidative cleavage of the allyl moiety of the bicyclic dione 74 to furnish the diketo aldehyde 75, followed by an acid-catalyzed intramolecular aldol condensation to afford the tricyclic diketo alcohols 76. Attempted reduction of both carbonyl moieties present in the diketo alcohols 76 with sodium borohydride led to ring opening via a retro-aldol condensation process. However, Lewis acid-mediated reduction of the diketo alcohols 76 by borane-tetrahydrofuran complex in tetrahydrofuran afforded the corresponding triols 77 in high yield. Finally, elimination of three equivalents of water from the triols 77 was accomplished by heating a solution of this intermediate in neat hexamethylphosphoramide at reflux for 2 days, which furnished triquinacene 1 in good yield.

This route offered several practical improvements over its predecessors. Not only was the overall yield of this synthesis relatively high (23% over eight steps), but it was well-suited for the preparation of multi-gram quantities of triquinacene 1. The Weiss-Cook condensation reaction could be performed on scales above 200 g without complications, and every other step could be carried out on scales exceeding 50 g. Many of the steps had yields in excess of 90%.
Finally, many of the intermediates required little or no purification before proceeding to the next step.

1.4 Syntheses of centro-Substituted Triquinacene Derivatives

An exhaustive search of the Chemical Abstracts and Beilstein databases revealed that only five purely centro-substituted (i.e. bearing substituents solely at C-10) triquinacene derivatives have been reported. Their preparations are outlined below.

1.4.1 10-(Triquinacyl)triquinacene (80)

In a study which followed his preparation of the parent triquinacene 1,31 Jacobson reported in 1974 the synthesis of 10-(triquinacyl)triquinacene 80, i.e. a triquinacene dimer with the two triquinacene moieties joined by a single bond between their centro positions (Scheme 14).48,49

**Scheme 14 - Synthesis of triquinacyltriquinacene (80)**

![Scheme 14](image)

Reagents and conditions: (a) Zn, I2, THF:EtOH (8:3), reflux, 6 h, 60%; (b) 280-290 °C, sealed tube, 10 min, 57%; (c) Li, t-BuOH:THF (1:11), reflux, 3 h, 43%.
The starting point for this route was perchlorotriquinacene 53, an intermediate of Jacobson's synthesis of the parent triquinacene 1 (c.f. Scheme 9). Heating this starting material for 6 h at reflux in a mixture of tetrahydrofuran and ethanol in the presence of a large excess of zinc afforded the dimer 78, which underwent thermal rearrangement upon vigorous heating (280-290 °C) for 10 min in a sealed tube to furnish the thermodynamically more stable dimer 79. 10-(Triquinacetyl)triquinacene 80 was obtained upon radical dechlorination of the dimer 79 with lithium metal, a step which also cleaved the four-membered ring present in the precursor.

1.4.2 10-Phenyltriquinacene (84)

In 1996, de Meijere and co-workers reported the preparation of 10-phenyltriquinacene via an unexpected palladium-catalyzed substitution reaction of 2,3,5,6-tetrahydrotriquinacene-3,5-dione 82. In an attempt to carry out a Heck-type coupling reaction on the double bond of 2,3,5,6-tetrahydrotriquinacene-3,5-dione 82, which was expected to afford a domino coupled product bearing a fused 4'-phenyl-9,10-dihydrophenanthrene unit, a DMF solution of the dione 82 was treated with excess phenyl iodide in the presence of sodium bicarbonate and a catalytic amount of palladium (II) acetate (Scheme 15). However, none of the expected annulated product 81 was obtained; rather, the only isolated product (34% yield) was that of substitution at the centro position, 10-phenyl-2,3,5,6-tetrahydrotriquinacene-3,5-dione 83.
Scheme 15 - Synthesis of 10-phenyltriquinacene (84)

Reagents and conditions: (a) phenyl iodide (5 equiv.), Na₂CO₃ (3.2 equiv.), Pd(OAc)₂ (cat.), DMF, 80 °C, 24 h, 34%; (b) LiAlH₄, THF, reflux; (c) MsCl, NEt₃, DCM, 0 °C to rt; (d) activated neutral Al₂O₃, DCM, rt, 17% over three steps.

This unexpected product, the phenyl-substituted dione 83, was then converted to 10-phenyltriquinacene 84 in 17% yield over three steps by an adaptation of the method of Deslongchamps for the synthesis of the parent triquinacene 1.⁴¹

The formation of the phenyl dione 83 was rationalized by de Meijere (Scheme 16). Upon treatment with sodium carbonate, the β-diketone 82 was deprotonated and the resultant enolate carried out a nucleophilic attack on palladium (II) acetate, furnishing the intermediate 85. Reductive elimination of a palladium (0) species then afforded the enone 86. Oxidative addition of palladium (0) to the carbon-iodine bond of phenyl iodide afforded phenylpalladium iodide, which then underwent a cross-coupling reaction with the strained enone 86 to afford the 10-phenyl-substituted intermediate 87. Finally, the intermediate 87 reacted with further quantities of the starting material, dione 82, to afford the product dione 83 along with the intermediate 85, completing the catalytic cycle.
The scope of this Heck-type reaction was then examined. Substitution of a variety of aryl and vinyl iodides for phenyl iodide all furnished the corresponding 10-substituted products in low yield, and in no cases were the anticipated annulated products formed (Scheme 17).

**Scheme 17 - Scope of the Heck-type substitution reactions of dione (82)**

Reagents and conditions: (a) RI (5 equiv.), Na$_2$CO$_3$ (3.2 equiv.), Pd(OAc)$_2$ (cat.), DMF. See Table 1.

**Table 1 - Reaction conditions corresponding to Scheme 17.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>RI</th>
<th>Temperature / time</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C$_6$H$_5$I</td>
<td>80 °C / 24 h</td>
<td>34%</td>
</tr>
<tr>
<td>2</td>
<td>p-MeC$_6$H$_4$I</td>
<td>80 °C / 11 h</td>
<td>11%</td>
</tr>
</tbody>
</table>
The yields of the centro-substituted triquinanedione derivatives 88 did not change appreciably when electron-donating (Entry 3) or electron-withdrawing (Entry 4) substituents were introduced on the phenyl ring, nor when a vinyl iodide (Entry 5) was employed. Only the 10-phenyl-substituted dione 83 (Entry 1) was converted to its corresponding triquinacene derivative.

1.4.3 10-(Trimethylsilyl)triquinacene (98), 10-(acetoxyethyl)triquinacene (102) and 10-methyltriquinacene (106)

In 1986, Bengston and de Meijere succeeded in preparing three centro-substituted triquinacene derivatives by thermal rearrangement of the corresponding diademane derivatives (c.f. Section 1.3.3). This work formed part of a doctoral thesis; however, it was not reported in the primary chemical literature until 2003.

The starting materials for these preparations were the substituted cyclooctatetraene derivatives 89 (R = trimethylsilyl or acetoxyethyl). These derivatives, through their bicyclo[4.2.0]octatriene valence tautomers 90, underwent Diels-Alder reactions with maleic anhydride, affording the endo-anhydrides 91 (Scheme 18).
Scheme 18 - Synthesis of the substituted snoutenes (95)

Reagents and conditions: (a) maleic anhydride, 80 °C, PhH, 36-48 h, 75% (R = TMS) and 46% (R = CH2OAc); (b) hv, Me2CO, PhH, rt, 48 h, 75% (R = TMS) and 57% (R = CH2OAc); (c) NaHCO3, H2O, rt, then 12 M aq. HCl, 0 °C, 92% (R = TMS) and 85% (R = CH2OAc); (d) Pb(OAc)4, py, 55 °C, 3 h, 48% (R = TMS) and 50% (R = CH2OAc); (e) AgNO3, MeOH, 50 °C, 48 h, 85% (R = TMS) and 85% (R = CH2OAc).

Acetone-sensitized [2+2] photocyclization of the Diels-Alder adducts 91 then furnished the basketene derivatives 92 in moderate to good yield.56,57,58

Alkaline hydrolysis of the anhydride moieties of the basketane derivatives 92 afforded the corresponding diacids 93, which were decarboxylated with lead tetraacetate to furnish the substituted basketanes 94. Isomerization of these basketanes to the corresponding snoutenes 95 was accomplished with silver nitrate in anhydrous methanol at 50 °C.39,59 Thus, the snoutenes 95 were obtained in a 21% (for R = trimethylsilyl) and in a 9% (for R = acetoxyethyl) yield over five steps from the corresponding substituted cyclooctatetraenes 89.

In order to prepare 10-(trimethylsilyl)triquinacene 98, 4-(trimethylsilyl)snoutene (95, R = TMS) was photochemically isomerized to a regioisomeric mixture of 6-(trimethylsilyl)diademane 96 and 1-
(trimethylsilyl)diademane 97 in a manner analogous to that employed in de Meijere's preparation of the parent triquinacene 1 (Scheme 19).  

Scheme 19 - Synthesis of 10-(trimethylsilyl)triquinacene (98)

\[
\begin{align*}
95, R = \text{TMS} & \quad \rightarrow \quad 96 \quad \text{(a)} \quad + \quad 97 \quad \text{(b)} \\
 & \quad \text{TMS} \\
98 & \quad \text{TMS} \\
99 & \quad \text{TMS}
\end{align*}
\]

Reagents and conditions: (a) hv, pentane, -65 °C, 72 h, 23% (98) + 8% (99); (b) preparative gas chromatographic separation, 100%.

Irradiation of the snoutene (95, R = TMS) in pentane for 3 days at -65 °C afforded in a 3:1 ratio the 6- and 1-substituted diademanes 96 and 97 in low yield. Over the course of an unsuccessful preparative gas chromatographic separation of these two derivatives, complete thermal isomerization to a mixture of 10-(trimethylsilyl)triquinacene 98 and 1-(trimethylsilyl)triquinacene 99 took place. Hence, 10-(trimethylsilyl)triquinacene 98 was obtained in 4% yield over six steps.  

On the other hand, 4-(acetoxymethyl)snoutene (95, R = CH₂OAc) was poorly soluble in pentane, and the use of ether as a co-solvent for the photochemical rearrangement reaction was required (Scheme 20).
Scheme 20 - Synthesis of 10-(acetoxymethyl)triquinacene (102)

Reagents and conditions: (a) hv, pentane/Et₂O, -30 °C, 24 h; (b) preparative gas chromatographic purification.

Irradiation of this snoutene derivative afforded a complex mixture of products, including small amounts of the diademane derivatives 100 and 101. The loss of the acetoxy group under these photochemical conditions was extensive.⁵⁴ Attempted preparative gas chromatographic purification of this mixture again led to a mixture of products, including the products of thermal rearrangement, the 10- and 1-(acetoxymethyl)triquinacenes 102 and 103. These triquinacene derivatives could not be isolated; however, the ¹H NMR spectrum of this mixture of regioisomeric triquinacene derivatives was consistent with them being formed as a mixture (102:103 = 2.2:1).⁵³

Thirdly, in a related experiment, the known 4-methylsnoutene (95, R = CH₃)⁶⁰ was prepared by a method analogous to that employed for the preparation of 4-(trimethylsilyl)snoutene (95, R = TMS) and 4-(acetoxymethyl)snoutene (95, R = CH₂OAc). Following irradiation of 4-methylsnoutene (95, R = CH₃) in pentane solution, the regioisomeric diademane derivatives 104 and 105
were obtained in low yield along with a complex mixture of side-products (Scheme 21).

**Scheme 21 - Synthesis of 10-methyltriquinacene (106)**

\[
\begin{align*}
\text{95, } R = \text{CH}_3 & \quad \overset{(a)}{\rightarrow} \quad \text{104} + \text{105} \quad \overset{(b)}{\rightarrow} \quad \text{106} + \text{107} \\
\end{align*}
\]

Reagents and conditions: (a) hv, pentane, -65 °C, 72 h, 17% (104) + 2% (105); (b) preparative GC separation, 5.4% (106) + 0.6% (107).

In this case, the preparative gas chromatographic separation was successful. Under these conditions, thermal rearrangement of these regioisomers to the corresponding 10- and 1-methyltriquinacenes 106 and 107 took place, and these two products were isolated separately in very low yield.\(^{54}\)

1.4.4 **Discussion of the validity of known routes to prepare centro-substituted triquinacene derivatives**

The preparation of 10-(triquinacyl)triquinacene 80 employed methodology suitable only for the preparation of this dimer. It was unlikely that the approach of Jacobson could be modified to prepare other centro-substituted triquinacene derivatives suitable for furthering the long-term objectives of this research project (c.f. Section 1.6). Moreover, de Meijere's unanticipated installation of a centro-substituent by means of a Heck reaction took place in low yield in his preparation of 10-phenyltriquinacene 84. The potential for introducing a variety of centro-substituents by this method would be limited by the scope and efficiency of the Heck reaction. The preparation of triquinacene derivatives 98, 102 and 106 via
the thermal rearrangement of substituted diademanes took place in low overall yield and required difficult separations as well as specialized photochemical apparatus. In light of the above findings, it was clear that none of the existing syntheses could be adapted to provide a practical and general method for the preparation of centro-substituted triquinacene derivatives and that new approaches would have to be devised.

1.5 Syntheses of Related Triquinacene Derivatives

Over 100 derivatives of triquinacene have been reported, the vast majority of which are benzoannulated derivatives, such as 10-methyltribenzotriquinacene 174 (c.f. Section 1.5.9). The preparation of several derivatives of triquinacene of relevance to this research project are outlined below.

1.5.1 1,10-Cyclohexanotriquinacene (116)

While 1,10-cyclohexanotriquinacene 116 is a centro-substituted triquinacene derivative, it also bears a substituent at C-1 and therefore cannot be considered a purely centro-substituted derivative. This derivative, which contains the [4.3.3]propellane ring system, was prepared in 1988 by Cook and co-workers. The motivation behind the preparation of this derivative was to use the fourth ring as a "blocking group" for the exo (convex) face of the triquinacene ring system. It was hoped that this would force two triquinacene moieties into the required endo,endo orientation in order to achieve the dimerization of this triquinacene derivative to afford an analogue of dodecahedrane (c.f. Section 1.6). In a modification of their preparation of the parent triquinacene (c.f.
Scheme 13), 1,2-cyclohexanedione 108 was used in the Weiss-Cook condensation reaction with 1,3-di-t-butylacetone dicarboxylate 70 (Scheme 22). The tricyclic tetraester 109 was obtained in moderate yield; however, this reaction could easily be carried out on a 100 g scale. The seven remaining steps were virtually identical to those performed in the parent synthesis. After protection of both enol moieties with diazomethane, enolization with potassium hydride and trapping of the resultant enolate with allyl iodide, the allyl diketone 112 was obtained. Ozonolysis of the allyl moiety, followed by acid-catalyzed aldol condensation to establish the third five-membered ring, afforded the diketo alcohol 114. Finally, reduction of both carbonyl groups with borane-tetrahydrofuran complex and elimination by heating in hexamethylphosphoramide furnished the triquinacene derivative 116 in 18% yield over seven steps.
Scheme 22 - Synthesis of 1,10-cyclohexanotriquinacene (116)

Reagents and conditions: (a) K₂CO₃, NaHCO₃, MeOH:H₂O, rt, 48%; (b) CH₂N₂, Et₂O, 90%; (c) KH (2 equiv.), DMF, rt, then allyl iodide (5 equiv.), -35 °C to rt; (d) 1 M aq. HCl:AcOH (1:3), 90-100 °C, 86% over two steps; (e) O₃, EtOAc, -60 °C, then Me₂S, rt; (f) 2 M aq. HCl:THF (1:1), rt, 86% over two steps; (g) BH₃ • THF, THF, 0 °C, 95%; (h) 230 °C, HMPA, 60%.

1.5.2 1,10-Dimethyltriquinacene (119)

In their full paper describing their synthesis of the parent triquinacene 1, Cook and co-workers also reported the preparation of 1,10-dimethyltriquinacene 119. The approach chosen was virtually identical to that employed in their synthesis of 1,10-cyclohexanotriquinacene 116 (c.f. Scheme 22), with 2,3-butanedione 117 serving as the 1,2-dicarbonyl component in the Weiss-Cook condensation reaction (Scheme 23). The product of this reaction, the tetraester 118, was then converted to 1,10-dimethyltriquinacene 119 using the aforementioned six-step sequence.
1.5.3 **Azatriquinacene (128)**

In 1996, Mascal and co-workers reported the synthesis of azatriquinane 125 (Scheme 24).\(^{63}\) This methodology was extended four years later to the complete preparation of azatriquinacene 128.\(^{64}\) The starting point for this synthesis was the pyrrole 2,5-bis(propanoate) ester 120, which was obtained via the two-fold addition of pyrrole to methyl acrylate.\(^{65}\) Stereoselective catalytic hydrogenation using rhodium on alumina as a catalyst furnished the corresponding pyrrolidine derivative 121, which was then cyclized by heating at reflux in xylenes to afford the pyrrolizidinone 122. After saponification of the ester moiety with aqueous sodium hydroxide, distillation from sodalime (a mixture of sodium hydroxide along with calcium oxide and calcium hydroxide) afforded the tricyclic hemiaminal 124. Finally, azatriquinane 125 was obtained by treatment of this hemiaminal with lithium aluminum hydride under forcing conditions.
Azatriquinacene 128 was elaborated from azatriquinane 125 by means of a photochemical perchlorination-dehydrochlorination reaction which furnished perchoroazatriquinacene 126. Reduction of the three α-chlorine substituents was accomplished by treatment with tri-\textit{n}-butyl hydride to afford 2,3,5,6,8,9-hexachloroazatriquinacene 127, which in turn was reduced to azatriquinacene 128 with lithium metal. Overall, azatriquinacene 128 was obtained in 2% yield over eight steps from the pyrrole 2,5-\textit{bis}(propanoate) ester 120.
1.5.4  

*Isotriquinacene (129)*

Tricyclo[5.2.1.0^4,10]deca-1,5,8-triene (isotriquinacene) 129, which differs from triquinacene 1 by the location of one of the three double bonds, which is at a bridgehead position, was prepared in 1984 by Paquette and Kramer. This compound was prepared in one step from the dimesylate 62, which was an intermediate prepared by Deslongchamps and co-workers in their synthesis of triquinacene 1 (c.f. Scheme 11). Whereas in the latter report triquinacene 1 was obtained from the dimesylate 62 by stirring over highly activated neutral alumina, performing this elimination reaction under kinetic conditions (treatment with potassium t-butoxide in DMSO) afforded the thermodynamically less stable compound, isotriquinacene 129 (Scheme 25).

**Scheme 25 - Synthesis of isotriquinacene (129)**

![Scheme 25 - Synthesis of isotriquinacene (129)](image)

Reagents and conditions: (a) t-BuOK (3 equiv.), DMSO, rt, 24 h, 69%.

Interestingly, although theoretical calculations had predicted that isotriquinacene 129 would be thermodynamically less stable than triquinacene 1 by 4.1 kcal mol\(^{-1}\) on account of the bridgehead double bond, no double-bond isomerization was detected on stirring isotriquinacene 129 over activated alumina for 48 h. This result ruled out isotriquinacene 129 as an intermediate in Deslongchamps’ alumina-promoted elimination reaction of the dimesylate 62 to.
afford triquinacene 1 (c.f. Section 1.3.4). However, Cook and co-workers reported in 1989 that this isomerization reaction could be achieved in under 3 h by treating a solution of isotriquinacene 129 in a mixture of pentane and dichloromethane with a catalytic amount of p-toluenesulfonic acid at room temperature (Scheme 26).47

**Scheme 26 - Acid-catalyzed isomerization of isotriquinacene (129)**

Reagents and conditions: (a) p-TsOH (cat.), pentane:DCM (1:12), rt, 3 h, 98 % (GLC yield), 48% (isolated yield).

1.5.5 2,3-Dihydrotriquinacen-2-one (138)

Three syntheses of this derivative, which was pivotal in several approaches to the triquinacene dimerization problem (c.f. Section 1.6) have been reported.

1.5.5.1 Deslongchamps (1971)

In his 1978 full paper that described the synthesis of the parent triquinacene 1 (c.f. Scheme 11), Deslongchamps also reported the preparation of racemic 2,3-dihydrotriquinacen-2-one 138.41 The initial and unoptimized preparation of this derivative had been reported in preliminary form in 1971.68 Their approach started with the dione 58 (sometimes referred to as “Deslongchamps’ diketone” in the context of polyquinane chemistry), which was a key intermediate in their preparation of the parent triquinacene 1 (Scheme 27).
Protection of one of the two carbonyl moieties of the dione 58 as its corresponding acetal was achieved by a condensation reaction with neopentyl glycol. The desired monoketal 130 was separated from its regioisomer by fractional crystallization. Next, Baeyer-Villiger oxidation of the monoketal 130 was accomplished with m-chloroperoxybenzoic acid, affording the lactone 131 along with a regioisomeric lactone product which could be removed by selective hydrolysis with sodium hydroxide in aqueous dimethoxyethane. Reduction of the lactone 131 with diisobutylaluminum hydride then afforded the bicyclic keto aldehyde 132 as a single diastereoisomer in quantitative yield. This material was
then treated with aqueous acid in order to effect a deprotection/aldol condensation sequence, which afforded the cis tricyclic dihydroxyketone 133. As this diol proved difficult to isolate on account of it being obtained as an impure amorphous solid, this material was then epimerized to the corresponding trans dihydroxyketone 134 with sodium ethoxide. This highly crystalline compound was obtained in 63% yield over two steps from the aldehyde 132. Protection of the carbonyl group of the trans dihydroxyketone 134 was achieved under standard conditions by condensation with ethylene glycol and then both hydroxyl groups were activated by conversion to the dimesylate 136. The two double bonds present in the target molecule were installed by treating the dimesylate 136 with potassium t-butoxide in dimethylsulfoxide to furnish the ketal diene 137. Finally, deprotection of the carbonyl group with aqueous acid afforded racemic 2,3-dihydrotriquinacene-2-one 138 in 17% yield over nine steps from diketone 58.

1.5.5.2 Paquette (1975)

The synthesis of optically pure (+)-2,3-dihydrotriquinacene-2-one (+)-138 was reported by Paquette and co-workers in 1975 (Scheme 28).
This synthesis, which contained a number of remarkable transformations, began with the cycloaddition reaction of cyclooctatetraeneiron tricarbonyl 139 with tetracyanoethylene 140.\textsuperscript{71,72} Oxidative degradation of the resultant \( \sigma,\pi \)-Fe(CO)\(_3\) complex 141 with ceric ammonium nitrate in 95\% aqueous ethanol afforded, in excellent yield, the tricyclic tetranitrile 142. Treatment of the tetranitrile 142 with hot concentrated hydrochloric acid for 28 h furnished the
carboxylactone 143 (through hydrolysis of the four nitrile moieties, decarboxylation of two of the four carboxyl groups, hydration of one of the alkene functions and lactonization). Irradiation of a benzene/carbon tetrachloride solution of the carboxylactone 143 in the presence of lead tetraacetate and iodine effected a photochemical decarboxylation reaction and trapping of a radical intermediate by iodine, which furnished the iodolactone 144. Hydrolysis of the lactone with potassium carbonate in aqueous tetrahydrofuran proceeded with simultaneous dehydroiodination to afford the hydroxy ester 145. Elimination of the elements of water from the hydroxy ester 145 could be accomplished either with Deslongchamps’ method of mesylation and elimination on stirring with highly activated neutral alumina or directly, in moderate yield, by treatment with a tetrahydrofuran solution of ethyl(carboxysulfamoyl)triethylammonium hydroxide inner salt at room temperature. Saponification of methyl triquinacene-2-carboxylate 146 with potassium hydroxide in aqueous ethanol afforded racemic triquinacene-2-carboxylic acid 147 in quantitative yield.

The carboxylic acid derivative 147 was resolved by diastereomeric salt formation with (+)-α-phenethylamine followed by repeated fractional recrystallization from methanol until the optical rotation of the product remained constant. The free acid was then regenerated by treatment with dilute aqueous hydrochloric acid. The optically pure (-)-triquinacene-2-carboxylic acid (-)-147 was converted to (+)-2,3-dihydrotriquinacene-2-one (+)-138 through a modified Curtius rearrangement process. Treatment of the carboxylic acid (-)-147 with triethylamine and diphenylphosphonic azide in t-butanol afforded (via the
corresponding t-butyl urethane, which was easily hydrolyzed by mild acid) the optically pure ketone (+)-138 in 4% yield over nine steps.

1.5.5.3 **Serratosa (1984)**

In 1984, Serratosa and co-workers reported a third synthesis of 2,3-dihydrotriquinacene-2-one 138. Their method was loosely based on that of Deslongchamps (vide supra). Most notably, this approach featured a direct and far more practical approach to the key intermediate, Deslongchamps’ diketone 58, from endo-dicyclopentadiene 148 (Scheme 29).

**Scheme 29 - Serratosa’s synthesis of 2,3-dihydrotriquinacene-2-one (138)**

Reagents and conditions: (a) Hg(OAc)$_2$, sodium laureth sulfate, H$_2$O, 4 days, then NaBH$_4$, then PCC, DCM, 40%; (b) hv, MeOH; (c) 2 M aq. HCl; (d) MsCl, py, DCM; (e) PhSeLi, PhH, 77% over four steps; (f) 2,2,5,5-tetramethyldioxane, PhH, $p$-TsOH (cat.), reflux; (g) $m$-CPBA, DCM; (h) Me$_2$CO, $p$-TsOH (cat.), 38% over three steps.
Oxymercuration of *endo*-dicyclopentadiene 148 with mercuric acetate over 4 days in an aqueous solution of the detergent sodium laureth sulfate\(^7\) afforded after sodium borohydride reduction the corresponding diol, which then was converted to Deslongchamps' diketone 58 by oxidation with pyridinium chlorochromate. This direct preparation of the diketone 58 obviated the need to begin the synthesis with Thiele’s acid 57. The preparation of Thiele’s acid 57 as well as its subsequent conversion to Deslongchamps’ diketone 58 have been reported to be low-yielding and unamenable to scale-up.\(^{41,77}\) The photochemical rearrangement of the dione 58 to the keto aldehyde 59 employed in the subsequent step had previously been reported by Deslongchamps.\(^{41}\) Treatment of the resultant keto aldehyde 59 with aqueous acid then furnished the tricyclic keto alcohol 60, which was converted to the corresponding mesylate 149 under standard conditions. Nucleophilic displacement of the mesylate moiety with phenylselenyllithium\(^7\) furnished the selenide 150 with inversion of configuration. Protection of the ketone moiety of the selenide 150 by condensation with the neopentyl glycol surrogate, 2,2,5,5-tetramethyl-1,3-dioxane, was necessary to block Baeyer-Villiger oxidation in the subsequent step. Treatment of the acetal 151 with *m*-chloroperoxybenzoic acid led to the elimination of the selenoxide group, installing the second double bond of the target compound. Finally, acetal hydrolysis under standard conditions afforded racemic *endo*-dihydrotriquinacene-2-one 138 in 29% yield over eight steps from *endo*-dicyclopentadiene 148.
1.5.6 Triquinacene-2,5,8-trione (160)

In 1986, Serratosa and co-workers reported the preparation of triquinacene-2,5,8-trione 160 and proposed that this compound could be converted to a dodecahedrane-like structure (c.f. Section 1.6).80

The starting point for Serratosa's preparation of this triketone was the known lactol 153 (Scheme 30).81 Addition of ethynylmagnesium bromide to this lactol afforded the diol 154 in excellent yield. Both hydroxyl groups were then protected as their corresponding t-butyldimethylsilyl ethers by treatment with t-butyldimethylsilyl chloride in the presence of imidazole.82 Abstraction of the alkynyl proton with n-butyllithium followed by trapping of the resultant lithium acetylide with trimethylsilyl chloride afforded the alkyne 155. Treatment of this alkyne with dicobaltoctacarbonyl furnished the corresponding complex 156, which upon heating in a sealed tube for 3 days at 160 °C underwent a Pauson-Khand bis-annulation reaction83 which elaborated the two remaining five-membered rings of the triquinacene framework. The product of this reaction, silylenone 157, was reduced by catalytic hydrogenation to afford the tricyclic ketone 158. The two TBS moieties were deprotected with hydrofluoric acid84 and the resultant dihydroxyketone 159 was readily converted to triquinacene-2,5,8-trione 160 upon oxidation with pyridinium chlorochromate.
Reagents and conditions: (a) ethynylmagnesium bromide, THF, 0 °C, 5 h, 95%; (b) (i) TBSCI, imidazole, DMF, rt, 30 h; (ii) n-BuLi, THF, -30 °C, 30 min, then TMSCl, -30 °C to rt, 2 h, 88%; (c) Co₂(CO)₆, isooctane, rt, 16 h, 82%; (d) 160 °C, isooctane, CO atmosphere, sealed tube, 3 days, 76%; (e) H₂ (1 atm), 10% Pd/C, EtOH, 16 h; (f) 45% aq. HF, MeCN, rt, 16 h; (g) PCC, py, DCM, rt, 16 h, 85% over three steps.

Triquinacene-2,5,8-trione 160 was obtained from the lactol 153 in 44% yield over seven steps. While the proposed dimerization of this derivative to a substituted dodecahedrane was never reported, the preparation of triquinacene-2,5,8-trione 160 represented a novel means of accessing the triquinacene ring system through Pauson-Khand chemistry.
1.5.7 Benzotriquinacene (165)

In 1976, Paquette and co-workers reported a method for the benzoannulation of ketones bearing an adjacent α-methylene group. One of the examples chosen to illustrate the utility of this method was the conversion of 2,3-dihydrotriquinacene-2-one 138 to benzotriquinacene 165 (Scheme 31).

**Scheme 31 - Synthesis of benzotriquinacene (165)**

Reagents and conditions: (a) vinylmagnesium chloride, THF, reflux, 5 h, 93%; (b) I₂, THF, 95 °C, 3 h, 74%; (c) dimethyl acetylatedicarboxylate, 90 °C, 20 h, then DDQ, PhH, rt, 18 h, 66%; (d) NaOH, H₂O, 55 °C, 36 h, 60%; (e) Cu, quinoline, reflux, 10 h, 36%.

Treatment of 2,3-dihydrotriquinacene-2-one 138 with vinylmagnesium chloride in THF afforded the carbinol 161 in high yield. In turn, dehydration of the carbinol 161 was readily accomplished by treatment with molecular iodine, furnishing the diene 162. This diene then served as the 4π component in a Diels-Alder reaction with dimethyl acetylatedicarboxylate. DDQ oxidation of the resultant Diels-Alder adduct furnished the diester 163 in moderate yield. The synthesis of benzotriquinacene 165 was accomplished by saponification of the two ester moieties under standard conditions, which was followed by
decarboxylation of the resultant ortho-diacid 164 with powdered copper in quinoline. Benzotriquinacene 165 was elaborated from 2,3-dihydrotriquinacene-2-one 138 in 10% yield over five steps.

1.5.8 **Triquinacene-2-carboxylic acid (147)**

Triquinacene-2-carboxylic acid 147 was prepared and resolved by Paquette and co-workers in their synthesis of (+)-2,3-dihydrotriquinacene-2-one (+)-138 (c.f. Section 1.5.5.2). An alternative preparation was reported by Deslongchamps and Soucy in 1981. The starting point for this synthesis was the tricyclic keto alcohol 60, an intermediate prepared over the course of Deslongchamps’ original synthesis of the parent triquinacene 1 (c.f. Scheme 11).

Treatment of the keto alcohol 60 with acetic anhydride in pyridine afforded the ketone acetate 166 in high yield (Scheme 32). Addition of methylmagnesium bromide to the carbonyl group of the ketone acetate 166 afforded the diol 167. Treatment of this diol with excess methanesulfonyl chloride in the presence of triethylamine initially formed the corresponding bis-mesylate, which under the reaction conditions spontaneously underwent elimination of the tertiary mesylate function to afford the mesylate 168. During the purification of the mesylate 168 by column chromatography on alumina, the elimination of the second mesylate moiety took place, furnishing 2-methyltriquinacene 169. Allylic oxidation of the pendant methyl group with selenium dioxide yielded triquinacene-2-carboxaldehyde 170 in high yield.
Scheme 32 - Synthesis and resolution of triquinacene-2-carboxylic acid (147)

Reagents and conditions: (a) Ac₂O, py, rt, 97%; (b) MeMgI, Et₂O, reflux, 3 h, 67%; (c) MsCl, NEt₃, PhH, 0 °C, 24 h; (d) alumina chromatography, 65% over two steps; (e) SeO₂, p-dioxane:H₂O (1:50), reflux, 5 h, 93%; (f) MnO₂, NaCN, AcOH, MeOH, rt, 16.5 h, 81%; (g) KOH, H₂O:MeOH (1:1), rt, 2.5 h, 85%; (h) resolution by salt formation with (-)-quinine monohydrate and fractional recrystallization from benzene.

Oxidation of this aldehyde to methyl triquinacene-2-carboxylate 146 was performed by activated manganese dioxide in the presence of sodium cyanide and acetic acid in methanol. Saponification under standard conditions then furnished racemic triquinacene-2-carboxylic acid 147, which was then efficiently resolved by diastereomeric salt formation with (-)-quinine monohydrate. Multiple recrystallizations from benzene afforded (-)-triquinacene-2-carboxylic acid (-)-147. This chiral material was ultimately employed in an attempt to solve the triquinacene dimerization problem (c.f. Section 1.6.2.3).
1.5.9 Tribenzotriquinacene derivatives

The research group of Kuck, since 1979, has been actively investigating the synthesis of centropolyindanes, which include several centro-substituted tribenzotriquinacene derivatives. The typical methodology employed for their synthesis, as illustrated by the preparation of 10-methyltribenzotriquinacene 174, is depicted below (Scheme 33).

Scheme 33 - Representative preparation of tribenzotriquinacene derivatives

Reagents and conditions: (a) p-TsOH (cat.), Ph₂CHOH, PhH, reflux, 90%; (b) LiAlH₄, Et₂O, 92%; (c) H₃PO₄, xylenes, reflux, 33%.

The known compound, 2-methyl-1,3-indanedione 171, was condensed with benzhydrol under acid-catalyzed conditions to afford the corresponding 2-benzhydryl derivative 172 in high yield. Lithium aluminum hydride reduction furnished a mixture of the cis,trans-diol 173 along with the analogous all-cis isomer (3:1). This mixture of isomers was heated in the presence of phosphoric acid to afford the C₃ᵥ-symmetric benzoquinacene derivative 174 through a double cyclodehydration process. The corresponding 10-allyl, 10-ethyl, 10-benzyl and 10-diphenylmethyl derivatives have also been prepared by this method and were obtained in similar yield, as were a wide variety of products bearing substituents on the aromatic rings. The development of
centropolyindane chemistry continues to be an area of active research, especially in light of the interest in this ring system as a building block in supramolecular chemistry.\textsuperscript{91}

1.5.10 1,4,7-Trisubstituted triquinacene derivatives

Allylic halogenation of triquinacene 1 with either N-chlorosuccinimide or N-bromosuccinimide afforded the corresponding 1,4,7-trihalotriquinacenes 175 (Scheme 34).\textsuperscript{92,93}

\textit{Scheme 34 - Allylic bromination of triquinacene and subsequent reactions with secondary amines}

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {\includegraphics[width=0.5\textwidth]{Scheme_34}};
\end{tikzpicture}
\end{center}

Reagents and conditions: (a) NBS (X = Br) or NCS (X = Cl), CCl\textsubscript{4}, reflux; (b) R\textsubscript{2}NH, rt, 36-86\% over two steps.

In an attempt to prepare the theoretically interesting acepentalene 177,\textsuperscript{94} related to triquinacene 1 by a double dehydrogenation, Butenschön and de Meijere then treated the trihalides 175 with a variety of secondary amines (dimethylamine, diethylamine, piperidine, morpholine and 3,5-dimethylpiperidine).\textsuperscript{95} The formation of the dihydroacepentalene derivatives 176 was rationalized in terms of a twofold elimination/addition sequence followed by an elimination to install the fourth double bond. Further attempts to convert the
dihydroaceptalene derivatives to the corresponding substituted acepentalenes were unsuccessful.

1.6 The Triquinacene Dimerization Problem

1.6.1 Introduction

In his 1964 report of the first synthesis of the parent triquinacene 1, Woodward proposed that the \( \text{C}_{20}\text{H}_{20} \) hydrocarbon dodecahedrane 178 could be accessed by means of a photochemically-allowed \([6\pi+6\pi]\) dimerization reaction of triquinacene 1 (Scheme 35).\(^{27}\) This dimerization process, which involves the simultaneous breaking of six C-C \( \pi \) bonds along with the formation of six C-C \( \sigma \) bonds, would be expected to be exothermic by about 97 kcal/mol.\(^{96}\) However, despite numerous efforts over the past 40 years, the dimerization reaction has yet to be realized.

\textit{Scheme 35 - The triquinacene dimerization problem}

Despite the predicted strongly exothermic nature of the dimerization reaction, it suffers from statistical, entropic and steric disadvantages. In order for the dimerization reaction to take place, the rehybridization of no fewer than twelve sp\(^2\) centres to sp\(^3\) centres must take place simultaneously. Moreover, the formation of the six new \( \sigma \) bonds must occur on the far more hindered endo (concave) face of both triquinacene moieties. This is further aggravated by the
requirement that the triquinacene monomers must approach each other with a rotational offset of 60° (with respect to their $C_{3v}$ axes), a conformation which leads to six sets of sterically unfavourable interactions between the vinylic protons. Another complication is the photochemical nature of this process. As this 12 $\pi$ electrocyclic process is photochemically allowed by the Woodward-Hoffmann rules, the dimerization must proceed through an excited intermediate of unknown stability and lifetime.

Woodward and co-workers reported that triquinacene 1 had an absorption maximum at 187 nm ($\varepsilon = 13,000$). However, irradiation of solutions of triquinacene with light of similar wavelength failed to induce the dimerization reaction. A potential explanation for this result was that, in solution, given the relatively large number of degrees of freedom, the probability of two triquinacene moieties adopting the requisite sterically-unfavourable relative orientation for the dimerization reaction was extremely small. It then became apparent that some means of favouring the aforementioned conformation would be required.

Two independent syntheses of dodecahedrane 178 have been reported, neither of which employed the triquinacene dimerization strategy. The landmark twenty-three step synthesis by Paquette and co-workers, reported in preliminary form in 1982 and in a full paper the following year, was the culmination of two decades of active pursuit of this essentially spherical hydrocarbon. No less impressive was the preparation of pagodane by Prinzbach and co-workers in 1983 and the subsequent conversion of this undecacyclic hydrocarbon to dodecahedrane 178, which was reported in 1987. The pagodane approach to
dodecahedrane 178, along with many improvements to the original route, have been reviewed.\textsuperscript{103}

1.6.2 The covalent tether strategy

1.6.2.1 Bivalvane approach

The first reported attempt at using a covalent tether in order to investigate the potential utility of this approach for dimerization of triquinacenes to dodecahedranes was the preparation of bivalvane 182 by Paquette and co-workers in 1975.\textsuperscript{104}

**Scheme 36 - Synthesis of the bivalvane (182)**

\[
\text{Reagents and conditions:} \quad \text{(a) Mg/Hg amalgam, TMSCI, THF, rt, 24 h, then EtOH:H}_2\text{O (3:8), reflux, 45 min, 62%}; \quad \text{(b) KH, THF, rt, 2 h, then CS}_2, \text{THF, 70 °C, 15 min, then Mel, THF, 60 °C, 5 min, 67%}; \quad \text{(c) P(OEt)}_3, \text{reflux, 70 h, 81%}; \quad \text{(d) H}_2 (50 \text{ psi), 5% Rh/C, EtOAc, 8 days, 83%}. \]

Optically pure (+)-2,3-dihydrotriquinacene-2-one (+)-138, which had previously been prepared and resolved by the research group of Paquette (c.f. Section 1.5.5.2)\textsuperscript{70} served as the starting material for this synthesis (Scheme 36). A pinacol-type coupling of this compound with magnesium amalgam\textsuperscript{105} in the presence of trimethylsilyl chloride followed by silyl group cleavage under mild
conditions furnished the optically active diol 179 as the sole reaction product. The observation that this reaction proceeded with very high stereoselectivity for coupling on the exo (convex) face of the triquinacene ring system was illustrative of the steric hindrance inherent to the system's endo (concave) face. Moreover, in a parallel experiment with the racemic ketone (±)-138, only the two diastereomeric products of exo,exo-coupling were obtained, reinforcing the above observation.

Treatment of the diol 179 sequentially with potassium hydride, carbon disulfide and methyl iodide afforded the cyclic thionocarbonate 180, which upon heating at reflux in triethylphosphite furnished the alkene 181. Catalytic hydrogenation over a rhodium catalyst then afforded bivalvane 182 (again resulting from reduction from the convex face) in 28% yield over four steps.

The $^1$H and $^{13}$C NMR spectral data for bivalvane were consistent with a mixture of rotamers of bivalvane 182. Attempts at accomplishing a dehydrogenative dimerization reaction of this material to dodecahedrane were unsuccessful, potentially as a result of the cis rotamer of bivalvane 182 being disfavoured on the basis of steric.

1.6.2.2 Ester linkage approach

In 1976, Woodward and Repic succeeded in resolving the hydroxy acid 183 with quinine. This hydroxy acid was first treated with diazomethane to afford the hydroxy ester 184 (Scheme 37). In parallel, the hydroxy acid 183 was converted to the corresponding mesylate and treated with activated neutral
alumina to furnish the carboxylic acid 185, which was then converted to its corresponding acyl halide 186.

**Scheme 37 - Synthesis of the ester-linked dimer (188)**

Scheme text and diagram.

Reagents and conditions: (a) CH$_2$N$_2$, Et$_2$O; (b) MsCl, py, DCM, then Al$_2$O$_3$, DCM; (c) (COCl)$_2$; (d) lithium 2,2,6,6-tetramethylpiperidide; (e) hv, MeCN.

The coupling reaction of the hydroxy ester 184 and the acyl halide 186 was accomplished using lithium 2,2,6,6-tetramethylpiperidide, furnishing the diester 187. It was hoped that the use of two optically active components in the above coupling reaction, in combination with this ester linkage strategy, would impart some degree of stereochemical control to the intramolecular cyclization reactions of the diester 187. Indeed, sensitized irradiation of the diester 187 furnished the lactone 188, the product of an intramolecular [2+2] cycloaddition reaction from the *endo* (concave) faces of both triquinacene moieties. However, investigations on this system were halted when it became apparent that lactone moiety in this cycloadduct could not be opened, despite a number of attempts using hydroxide ion and other standard reagents.
1.6.2.3  *Imidate salt approach*

A third covalent tether approach to the triquinacene dimerization problem was reported by Deslongchamps and Soucy in 1981. The starting material for this preparation was (-)-triquinacene-2-carboxylic acid (-)-147 (c.f. Section 1.5.8). Conversion of this carboxylic acid to the corresponding acyl chloride 189 was accomplished under standard conditions with oxalyl chloride (Scheme 38). Treatment of this acyl halide with sodium azide furnished the acyl azide 190, which upon heating underwent a Curtius rearrangement reaction to afford the isocyanate 191. Reduction of this isocyanate with lithium borohydride then furnished (+)-2-formamidotriquinacene 192 in 49% yield over four steps. Treatment of the derivative 192 with a solution of the acyl chloride 189 afforded \(N\)-formyl-\(N\)-(2-triquinacenyl)triquinacene-2-carboxamide 193 in high yield. Deformylation with methanolic sodium carbonate then furnished the crystalline \(+\)-\(N\)-(2-triquinacenyl)triquinacene-2-carboxamide 194 in good yield. Installation of the covalent tether was achieved by \(N\)-alkylation of secondary amide 194 with 1-bromo-3-chloropropane under standard conditions, affording the \(N\)-alkylamide 195. Finally, treatment with silver tetrafluoroborate furnished the dextrorotatory oily cyclic imidate salt 196 (obtained in 23% yield over eight steps from optically active acid [(−)-147] which served as the starting material for a series of attempted dimerization reactions carried out in the hope of obtaining the dodecahedrane derivative 197.
Scheme 38 - Synthesis of the imidate salt (196)

(-)-147

191

Reagents and conditions: (a) (COCl)₂, PhH, 16 h, rt; (b) NaN₃, Me₂CO/DCM/H₂O, 0 °C, 30 min; (c) PhH, reflux, 2.5 h; (d) LiBH₄, THF, rt, 45 min, 49% over four steps; (e) NaH, THF, 0 °C, 10 min, then triquinacyle halide 189, THF, rt, 4 h, 80%; (f) Na₂CO₃, MeOH, rt, 30 min, 65%; (g) NaH, THF, rt, 5 min, then 1-bromo-3-chloropropane, THF, rt, 22 h, 94%; (h) AgBF₄, PhH:DCM (5:1), rt, 22 h, 98%.

However, all attempts at effecting the cyclization reaction of the cyclic imidate salt 196 to the dodecahedrane derivative 197 by photochemical, electrochemical or thermal methods were unsuccessful. This result could be attributed to the rotational degrees of freedom present in the imidate salt 196, which made the achievement of the correct relative orientation between the triquinacene moieties necessary for dimerization statistically improbable. In addition, the desired product 197 would be inherently strained.
1.6.2.4 Dithiatriquinaceneophane approach

In 1981, Roberts and Shoham also reported a related approach to the triquinacene dimerization problem whereby the installation of a double thioether covalent tether led to the “triquinaceneophane” derivatives 203 and 204. It was hoped that the conformational rigidity imparted by the use of two covalent tethers would increase the probability of achieving the correct relative orientation between the two triquinacene moieties such that the aforementioned dimerization reaction could take place.

The starting material for this dithiatriquinaceneophane synthesis was the tricyclic keto diol 61, an intermediate in Deslongchamps’ synthesis of the parent triquinacene 1. The carbonyl group and its adjacent methylene centre present in the diol 61 were converted to an olefin moiety by means of a modified Shapiro reaction (condensation of the carbonyl group with 2,4,6-triisopropylbenzenesulfonyl hydrazide followed by treatment of the resultant tosylhydrazone with excess methyllithium). Following oxidation of both hydroxyl groups of the resultant enediol 198 with pyridinium chlorochromate, the enedione 199 was obtained in 30% yield over two steps. Conversion of the enedione 199 to the dialdehyde 200 was accomplished in a three-step sequence whereby addition of methyllithium to both carbonyl groups furnished the corresponding bis-carbinol, which upon heating in the presence of acid underwent the elimination of two equivalents of water. Allylic oxidation of both methyl groups with selenium dioxide then furnished the dialdehyde 200 in moderate yield. The dibromide 201 was prepared from the dialdehyde 200 in two
steps by lithium aluminum hydride reduction of both aldehyde moieties to the corresponding primary alcohols, followed by conversion of the hydroxyl groups to bromides upon treatment with triphenylphosphine and carbon tetrabromide. Conversion of the dibromide 201 to the dithiol 202 was achieved by treatment with thiourea, followed by ethylenediamine, at reflux in aqueous isopropanol.

Scheme 39 - Synthesis of anti-dithia[3.3](2,6)triquinaceneophane (203)

Reagents and conditions: (a) 2,4,6-triisopropylbenzenesulfonyl hydrazide, MgSO₄, DCM, then MeLi (6 equiv.), THF/Et₂O; (b) PCC, DCM, 30% over two steps; (c) MeLi (excess), THF/Et₂O, then p-TsOH (cat.), PhH, reflux, then SeO₂, p-dioxane/H₂O, reflux, 50%; (d) LiAlH₄, THF, reflux, then PPh₃, CBr₄, MeCN, 97%; (e) H₂NCSNH₂, H₂NCH₂CH₂NH₂, i-PrOH/H₂O, reflux, 85%; (f) 201 (1 equiv.), KOH (2.5 equiv.), PhOH (4 equiv.), 95% aq. EtOH, 31%.
The formation of the triquinaceneophanes 203 and 204 from equimolar amounts of the dibromide 201 and the dithiol 202 was carried out by the slow addition of a benzene solution of these two derivatives to a solution of potassium hydroxide in 95% aqueous ethanol in the presence of a phenol buffer. This procedure afforded the desired anti-dithia[3.3](2,6)triquinaceneophane 203 isomer as the major reaction product (31%) along with a small amount (9%) of the syn isomer 204. These isomers could be separated either by preparative thin-layer chromatography or by careful recrystallization from chloroform. An X-ray crystal structure of the anti isomer 203 was obtained, and the authors commented that the relative orientation between the two triquinacene moieties in the solid state was close to that required for the dimerization reaction. On the other hand, the syn isomer 204 was expected to dimerize via three [2+2] cycloaddition reactions, affording a cage hydrocarbon containing 4- and 6-membered rings instead of dodecahedrane's fused pentagonal array. However, no dimerization studies on this interesting triquinaceneophane system have been reported.

1.6.3 Transition metal complexes

An alternative approach to the triquinacene dimerization problem was proposed by Sorensen and co-workers in 1982. It was suggested that two molecules of triquinacene could be held in proximity with the correct relative orientation for dimerization by the formation of the transition metal complexes 207 (Scheme 40). Here, the three \( \pi \) bonds of each triquinacene would serve as ligands for Group 6 metals (Cr, Mo and W).
Scheme 40 - Synthesis of tricarbonyl (triquinacene)-molybdenum and -tungsten

Reagents and conditions: (a) Mo(CO)$_6$, isoctane, 110-115 °C, 20 h, 11% or W(CO)$_6$, MeCN, reflux, 44 h, then triquinacene 1, hexanes, reflux, 16 h, 16%.

Treatment of hexacarbonylmolybdenum with excess triquinacene 1 for 20 h at reflux in isoctane afforded tricarbonyl (triquinacene)molybdenum (206, M = Mo) in low yield. This material was obtained as a relatively air-stable yellow crystalline solid and was recrystallized from a mixture of dichloromethane and cyclohexane. This complex was characterized by $^1$H and $^{13}$C NMR as well as by X-ray diffraction, which revealed that the only significant changes to the dimensions of triquinacene (c.f. Figure 2) upon complexation were a lengthening of the double bonds from 1.319 Å to 1.341 Å along with a reduction in the external angles of the allylic carbons from 113.8° to 107.6°. However, none of the desired bis(triquinacene)molybdenum complex (207, M = Mo) could be obtained by this method.

The attempted direct preparation of the analogous tungsten species (206, M = W) was not successful as hexacarbonyltungsten proved to be insufficiently reactive. Conversion of hexacarbonyltungsten to the more reactive corresponding tris(acetonitrile)tricarbonyl compound was accomplished by heating at reflux in acetonitrile. After removal of excess acetonitrile \textit{in vacuo}, a
solution of triquinacene I in hexanes was added, furnishing after 16 h at reflux the tricarbonyl (triquinacene)tungsten complex (206, M = W) in low yield. Unlike its molybdenum analogue, this yellow-green complex was not air-stable. Moreover, this method did not provide access to the desired bis(triquinacene)tungsten complex (207, M = W).

Finally, no complex could be isolated from the reactions of triquinacene with hexacarbonylchromium. However, the tricarbonyl (triquinacene)chromium complex (206, M = Cr) has been studied by computational methods. On a related note, a computational investigation of potential inclusion complexes of dodecahedrane 178 found that, given the relatively small size of the dodecahedrane cage, the only potential candidate for inclusion was the Be$^{2+}$ ion.

1.6.4 **Aldol condensation approach**

In their report of the preparation of triquinacene-2,5,8-trione 160 (c.f. Section 1.5.6), Serratosa and co-workers proposed that this compound could be dimerized via unspecified “aldol-type reactions” to a dodecahedrane derivative such as 208 (Scheme 41). However, no further reports on this approach have appeared since its initial suggestion in 1984.
1.7 The Weiss-Cook Condensation Reaction

The Weiss-Cook condensation reaction, which features prominently in several of the synthetic routes presented in this work, represents an expedient means to prepare cis-bicyclo[3.3.0]octan-3,7-dione derivatives 217. First reported in 1968 by Weiss and Edwards, this condensation process between two equivalents of a dialkyl ketoglutarate 209 and one equivalent of a 1,2-dicarbonyl compound 210 is generally performed in water at slightly alkaline pH. The proposed mechanism for the Weiss-Cook condensation reaction is illustrated below (Scheme 42).

The first step of this process is the rapid and reversible nucleophilic attack of one equivalent of dialkyl ketoglutarate 209 (which is readily enolized under the alkaline reaction conditions) to one of the carbonyl functionalities of the 1,2-dicarbonyl compound 210. A second, intramolecular, nucleophilic attack upon the second carbonyl group then affords the cyclopentanone derivative 212, which loses an equivalent of water to furnish the enone 213.
A second equivalent of the enolized dialkyl ketoglutarate 209 then undergoes Michael addition to the enone 213, leading to the intermediate 214, which again loses an equivalent of water to afford the enone 215. The bicyclic ring system is formed by an intramolecular Michael addition process which furnishes the bicyclic tetraester 216. This tetraester, which is generally highly enolized, may be isolated at this stage or can be carried through the following step of the sequence, which generally involves heating the tetraester intermediate 216 in aqueous acid. This process leads to the hydrolysis of the four ester moieties present in the intermediate 216, followed by the loss of four...
equivalents of carbon dioxide to afford the desired cis-bicyclo[3.3.0]octan-3,7-dione derivative 217.

This condensation reaction has been carried out with the parent glyoxal (210, R = R' = H), leading to cis-bicyclo[3.3.0]octan-3,7-dione.\(^{115}\) The use of substituted glyoxals (210, R = various, R' = H), which lead to 1-substituted-cis-bicyclo[3.3.0]octan-3,7-dione derivatives, has also been investigated.\(^{116,117,118}\) Furthermore, the analogous reaction with various 1,2-diketones (210, R = R' = various) has been exploited with success in the preparation of 1,5-disubstituted-cis-bicyclo[3.3.0]octan-3,7-diones.\(^{119,120,121,122}\)

The Weiss-Cook condensation reaction has been extensively employed in polyquinane chemistry as it leads to the formation of two functionalized cis-fused five-membered rings in one step from simple precursors. Moreover, several of these condensation reactions are amenable to scale-up, making possible the preparation of > 100 g batches of the corresponding cis-bicyclo[3.3.0]octan-3,7-dione derivatives.\(^{47}\)

1.8 Thesis Objectives and Overview

1.8.1 Thesis objectives

The objective of the work presented in this thesis is the development of novel and practical syntheses of a variety of centro-substituted triquinacene derivatives. Efficient preparations of these derivatives are required in order to further the long-term goals of our research group's interests in triquinacene chemistry which consist, inter alia, of both the study of the structure and reactivity
of the non-planar, tris-homoallylic C-10-centred triquinacyl cation, anion and radical as well as a novel approach to the triquinacene dimerization problem (c.f. Section 1.6). As none of the existing preparations of centro-substituted triquinacene derivatives outlined earlier was suitable for these purposes, a variety of alternative approaches were devised and investigated.

\[ \text{Br} \]

218 \rightarrow \text{AlBN} \rightarrow \text{radical trap}

\[ \text{219} \rightarrow \text{e.g.} \rightarrow \text{220} \]

\[ \text{Br} \]

218 \rightarrow \text{Li}^+ \rightarrow \text{electrophile}

\[ \text{221} \rightarrow \text{e.g.} \rightarrow \text{222} \]

\[ \text{O}_2\text{N} \]

223 \rightarrow \text{solvolysis} \rightarrow \text{nucleophile}

\[ \text{224} \rightarrow \text{e.g.} \rightarrow \text{225} \]

**Figure 6 - Proposed studies of the C-10-centred triquinacyl radical (219), anion (221) and cation (224)**

The preparation of 10-bromotriquinacene 218 would allow for the preparation of the C-10-centred triquinacyl radical 219 upon treatment with a suitable radical initiator such as AlBN (Figure 6). The reactivity of this radical could be probed by trapping with a radical trap such as allyltributyltin and examining the products and rates of radical substitution. For instance, the presence of products of substitution at positions other than C-10 could be
indicative of 1,2-shifts and/or double bond migration reactions of this reactive intermediate. Likewise, a similar analysis of the C-10-centred triquinacyl anion 221 could be carried out by metallation of 10-bromotriquinacene 218, followed by trapping with suitable electrophiles (e.g. aldehydes). The preparation of 10-hydroxytriquinacene followed by its conversion to an activated derivative such as the p-nitrophenyl ester 223 or the corresponding tosylate would allow the C-10-centred triquinacyl cation 224 to be generated by solvolysis. Nucleophilic trapping would then allow an analogous product analysis to be performed.

Our research group has proposed a novel approach to the triquinacene dimerization problem based upon molecular recognition using non-covalent bonding interactions to orient the two triquinacene moieties 226 (Figure 7).

"Host" structure, e.g. part of crystal lattice

\[ \text{[6+6] Photochemically allowed dimerization then decarboxylation} \]

2 x 226

Directional hydrogen bonding interaction

DODECAHEDRANE 178

\[ \text{Figure 7 - Proposed approach to the triquinacene dimerization problem} \]

For instance, centro-substituted triquinacene derivatives bearing carboxylic or p-benzoic acid substituents should prove particularly amenable to such studies in light of the directional hydrogen bonding properties of carboxylic acids and their propensity for forming intermolecular hydrogen-bonded dimers.\textsuperscript{123} Initially, attempts would be made to grow crystals of these derivatives which would then be subjected to X-ray crystallographic studies. If the triquinacene
moieties were appropriately oriented in the crystal, a solid-state photochemical study would be undertaken. Alternatively, in order to achieve the correct orientation, the carboxylic acids could be co-crystallized with various additives capable of non-covalent interactions with the substituents of the triquinacene derivatives. A key practical advantage of this approach is that the non-destructive nature of the co-crystallizations would allow for a large number of experiments to be performed with a relatively small amount of material.

As detailed in the following section, the development of novel syntheses of centro-substituted triquinacene derivatives, which constitutes the body of this thesis, was carried out with these long-term objectives in mind.

1.8.2 Thesis overview

In Chapter Two, a synthetic route to centro-substituted triquinacene derivatives in which the key step is the regioselective installation of the centro substituent by means of a conjugate addition reaction to a bicyclic enone is presented. The utility of this approach is exemplified by the preparation of 10-phenyltriquinacene. Several attempts to extend this methodology to other centro-substituents are also discussed.

In Chapter Three, a second synthetic strategy in which the centro substituent is installed early in the synthesis by the use of a substituted glyoxal (in this case, p-bromophenylglyoxal), rather than the parent glyoxal, in the Weiss-Cook condensation reaction, is outlined. The preparations of 10-(4'-bromophenyl)triquinacene as well as the regioisomeric 1-substituted analogue are presented.
In Chapter Four, a second application of the approach outlined in Chapter Three, with hydroxypyruvaldehyde serving as the 1,2-dicarbonyl component in the Weiss-Cook condensation reaction, is described. Efforts towards the preparation of 10-(hydroxymethyl)triquinacene and its corresponding 1-substituted congener are discussed.

In Chapter Five, an alternative approach, predicated on olefin metathesis chemistry, to centro-substituted triquinacene derivatives is detailed. The key step of this sequence, a double ring-closing metathesis reaction, afforded a novel and unexpected cyclopropane derivative in high yield. The results of studies directed towards determining the origin of this unusual reactivity are presented.

Chapter Six concerns a second olefin metathesis-based approach to centro-substituted triquinacene derivatives. The preparations of cis-bicyclo[3.3.0]octan-2,8-dione and several derivatives thereof, which could serve as precursors for the triquinacene ring system, are discussed. The synthetic challenges posed by steric hindrance in the triquinacene ring system are highlighted.

In Chapter Seven, a novel approach to the triquinacene ring system based on the Stetter synthesis of 1,4-dicarbonyl compounds and an aldol cyclization cascade is outlined.

In Chapter Eight, the results of a series of ab initio computational studies of the C-10-centred triquinacyle radical, cation and anion are presented. In addition, the energetics of the dimerization reaction of triquinacene to dodecahedrane in both the ground and excited states are discussed.
Chapter Nine contains the experimental protocols and data relating to Chapters 2-8 as well as a general experimental section. In general, all compounds which had been previously reported were characterized by their melting/boiling points (where applicable), $^1$H and $^{13}$C NMR, IR, and mass spectra. For new compounds, in addition to the above, 2-dimensional NMR (where needed) and elemental microanalysis data were also obtained.
CHAPTER TWO: RESULTS AND DISCUSSION - CONJUGATE ADDITION ROUTE

2.1 Overview and Retrosynthetic Analysis

This chapter details the synthesis of 10-phenyltriquinacene 84 using a twelve-step synthetic route in which the key step involved the installation of the quaternary, centro phenyl substituent by a trimethylsilyl chloride-promoted conjugate addition reaction of an organocuprate reagent derived from phenylmagnesium bromide to the known protected bicyclic enone 230. 10-Phenyltriquinacene 84 was chosen in order to demonstrate the proof of principle for this conjugate addition approach, as phenyl organocuprate reagents have been well-studied and are readily prepared.

A retrosynthetic analysis of 10-phenyltriquinacene 84 is presented in Scheme 43. The target compound 84 could be obtained from the diketo alcohol 227 via a series of functional group transformations. In turn, this intermediate can be obtained from the aldehyde 228 by means of an aldol condensation/deprotection sequence. The aldehyde 228 can be derived from the olefin 229 through oxidative cleavage. The olefin 229 could be obtained by conjugate addition of a phenyl moiety to the enone 230, followed by C-alkylation of the resultant enolate with allyl bromide. The key bicyclic enone intermediate 230 (the Michael acceptor) in turn could be obtained from cis-bicyclo[3.3.0]octan-

* Portions of this chapter have been reported. See: Cadieux, J.A.; Buller, D.B.; Wilson, P.D. Org. Lett. 2003, 5, 3983-3986.
3,7-dione 232, which is the product of a Weiss-Cook condensation reaction between commercially-available glyoxal 69 and 1,3-dimethylacetone dicarboxylate 233.

Scheme 43 - Retrosynthetic analysis of 10-phenyltriquinacene (84)

In the latter portions of this chapter, two attempts at extending this methodology to carry out similar conjugate addition reactions, with a view towards the installation of centro substituents capable of engaging in non-covalent bonding interactions, are presented. The inherent difficulties of forming quaternary centres in highly congested systems is also discussed.

2.2 Synthesis of the Monoacetal (231)

The starting point for this approach to centro-substituted triquinacene derivatives was the Weiss-Cook condensation reaction between one equivalent of glyoxal 69 and two equivalents of dimethyl 1,3-acetonedicarboxylate 233.
(Scheme 44). The procedure involved the modification of a literature preparation.124

**Scheme 44 - Synthesis of cis-bicyclo[3.3.0]octan-3,7-dione (232)**

Reagents and conditions: (a) NaOH, MeOH:H₂O, rt, 24 h; (b) aq. HCl, AcOH, reflux, 3 h, 59% over two steps.

The initial condensation reaction, carried out by treating a solution of the diester 233 with methanolic sodium hydroxide, followed by the dropwise addition of an aqueous solution of glyoxal 69, led to the formation of the disodium salt 234 which precipitated from the reaction mixture as a yellow crystalline solid. In the original literature preparation, this intermediate was isolated by filtration, acidified with dilute aqueous hydrochloric acid, extracted into chloroform and recrystallized. Instead, the impure disodium salt 234 so obtained was directly subjected to the ester hydrolysis/decarboxylation conditions. This practical modification had little effect on either the reaction’s yield or on the ease of product isolation. The crude material was readily purified by recrystallization from methanol. This reaction was amenable to scale-up, and batches in excess of 10 g of material were prepared in similar yields.
The next step involved the protection of one of the two ketone moieties in the dione 232 as its corresponding 2,2-dimethylpropylidene acetal. This transformation is in effect a desymmetrization and was required in order to obviate bis-oxidation in the following step (i.e. if left unprotected, formation of bicyclo[3.3.0]oct-1,5-dien-3,7-dione as a side product could occur). The difficulties associated with the symmetry breaking in these systems have been well-studied by Bertz. As the two carbonyl groups in the dione 232 are equivalent by symmetry, selective protection of one of the groups could only be achieved in this system by forming a mixture of the dione 232, the known, desired monoacetal 231 as well as the bis-acetal 235.

\[ \text{Scheme 45 - Synthesis of the monoacetal (231)} \]

\[
\begin{align*}
232 & \quad \xrightarrow{(a)} \quad \begin{array}{c}
\text{231 (52\%)} \\
\text{235 (21\%)}
\end{array} \\
& \quad \text{232 (22\%)}
\end{align*}
\]

Reagents and conditions: (a) neopentyl glycol (1 equiv.), p-TsOH (cat.), PhH, reflux, Dean-Stark apparatus, 4 h.

Reaction of the dione 232 with neopentyl glycol (1 equiv.) catalyzed by p-toluenesulfonic acid in benzene at reflux with azeotropic removal of water by means of a Dean-Stark apparatus (Scheme 45) afforded a mixture of the above three products. The mixture appeared to have reached equilibrium after 4 h at reflux. The three components were readily separable by flash chromatography.
The molar ratio of isolated products (dione 232 : monoacetal 231 : bis-acetal 235) of 22:52:21 was close to the expected statistical ratio of 25:50:25.

The neopentyl glycol-derived acetal moiety was selected for use as a protecting group on account of its greater stability with respect to other cyclic acetals. For instance, it has been reported that the analogous monoacetal 236, derived from ethylene glycol, cannot be stored on account of its tendency to disproportionate to the corresponding dione 232 and the bis-acetal 237. Furthermore, in a study by Lok and Coward, when a condensation reaction analogous to that depicted above (Scheme 45) was attempted using ethylene glycol, the isolated yields of all three components were lower than those obtained with neopentyl glycol. (Scheme 46)

**Scheme 46 - Analogous protection of the dione (232)**

![Chemical structure](image)

Reagents and conditions: (a) ethylene glycol (1 equiv.), p-TsOH (cat.), PhH, reflux, Dean-Stark apparatus, o/n.

The monoacetal 231 showed no evidence of disproportionation by TLC after three years of storage at -20 °C. Moreover, in the ensuing steps, the integrity of the protecting group was expected to be maintained despite exposure to strong bases (e.g. n-butyllithium, LDA), Lewis acids (TMSCI) and oxidants (sodium periodate and osmium tetroxide).
The overall yield of this procedure was aided by the high overall recovery of the byproducts 232 and 235. As these compounds were readily separable from the desired monoacetal 231, they could be converted into further quantities of the target compound. For instance, partial hydrolysis of the bis-acetal 235 catalyzed by p-toluenesulfonic acid in benzene again afforded after 4 h at reflux a nearly statistical mixture of the three products 231, 232 and 235 (Scheme 47).

**Scheme 47 - Partial hydrolysis of the bis-acetal (235)**

![Scheme 47](image)

Reagents and conditions: (a) H2O (1 equiv.), p-TsOH (cat.), PhH, reflux, 4 h.

In an iterative manner, multi-gram quantities of the desired monoacetal 231 were elaborated from the dione 232. The monoacetal 231 was obtained in a 62% overall yield following protection of the dione 232, recovery of the bis-acetal 235 and partial hydrolysis of this side product.

### 2.3 Oxidation of the Monoacetal (231) to the Enone (230)

With the monoacetal 231 in hand, the focus shifted to its conversion to the known enone 230 in preparation for the installation of the C-10 quaternary centre by means of a conjugate addition reaction (Scheme 48). The dehydrogenation of ketones to their α,β-unsaturated analogues is an often problematic
transformation and many methods for its execution have been developed. This section details several preparations and attempted preparations of this key enone intermediate from its saturated precursor.

**Scheme 48 - Oxidation of the monoacetal (231) to the enone (230)**

2.3.1 **Saegusa reaction via the enol silane (238)**

The most straightforward and highest yielding method for achieving this transformation involved treating the monoacetal 231 with LDA and trapping the resultant lithium enolate with trimethylsilyl chloride to afford the corresponding enol silane 238 (Scheme 49). The crude enol silane so obtained was then dissolved in dry acetonitrile and treated with a stoichiometric amount of palladium (II) acetate.

**Scheme 49 - Stoichiometric Saegusa oxidation reaction of the monoacetal (231)**

Reagents and conditions: (a) LDA, THF, -78 °C, 30 min then TMSCl, -78 °C to rt, 1.5 h; (b) Pd(OAc)$_2$, MeCN, 0 °C to rt, 16 h, 91%.

During the course of this oxidation, a palladium mirror was deposited on the walls of the reaction flask. The process was amenable to scale-up and was performed on a ~7 g scale in high (91%) yield. The obvious drawback to this
method is the stoichiometric use of palladium (II) acetate. As of this writing, the
cost of this reagent is approximately $80/g. Given that palladium (II) acetate and
the monoacetal starting material 231 have similar molecular weights, the
preparation of multi-gram quantities of the enone 230 by this method, despite the
high overall yield, remains an expensive proposition.

It has been reported that in these transformations employment of a sub-
stoichiometric amount of palladium (II) acetate in conjunction with a co-oxidant
whose function is to re-oxidize Pd$^0$ species to Pd$^{II}$ can be efficacious.$^{129,130}$
However, the previous results obtained with this approach are typically uneven,
ranging from no reaction to nearly quantitative conversion. Commonly employed
co-oxidants include chloranil,$^{129}$ p-benzoquinone$^{130}$ and molecular oxygen.$^{131}$
When the enol silane 238 was treated with 0.5 equiv. of palladium (II) acetate
along with 0.5 equiv. of p-benzoquinone instead of a full equivalent of palladium
(II) acetate, the yield of the reaction dropped from 91% to 27% (Scheme 50).
Had the p-benzoquinone merely been ineffective, one would have anticipated a
yield of slightly lower than 50%. This result suggests that in this system, either
the co-oxidant was actually impeding the ability of palladium (II) acetate to
perform the conversion of 238 to 230 or else the background hydrolysis of the
enol silane 238 to the monoacetal 231 became more prominent under these
reaction conditions.
**Scheme 50 - Sub-stoichiometric Saegusa reaction of the monoacetal (231)**

![Diagram of Scheme 50](image)

Reagents and conditions: (a) LDA, THF, -78 °C, 30 min then TMSCI, -78 °C to rt, 1.5 h; (b) Pd(OAc)$_2$ (0.5 equiv.), p-benzoquinone (0.5 equiv.), MeCN, 0 °C to rt, 16 h, 27%.

Finally, in a related attempt, changing the loading of p-benzoquinone from 0.5 equiv. to 1.0 equiv. had little effect, affording the enone 230 in 29% yield.

Irrespective of the approach employed, the enone 230 was purified by flash chromatography and recrystallized from hot hexanes. Of note, the recrystallization itself was quite exothermic. Seeding of a room temperature supersaturated hexane solution of this compound led to a rapid crystallization with evolution of heat such that the solvent boiled. Key spectral data for this compound include the C-2 enone proton resonance at $\delta = 5.72$ ppm in benzene-$d_6$, the C-2 carbon resonance at $\delta = 125.8$ ppm in benzene-$d_6$ and the enone carbonyl C=O stretching IR bands at 1699 and 1628 cm$^{-1}$. As well, all proton and carbon NMR resonances were assigned by means of COSY and HMQC experiments.

**2.3.2 Attempted DDQ oxidation of the enol silane (238)**

Fleming and Paterson have reported that, in a related bicyclic system, treatment of an enol silane with DDQ in the presence of 2,4,6-collidine in benzene at room temperature afforded the corresponding enone in 73% yield.$^{132}$ When the enol silane 238 was subjected to these reaction conditions, no reaction
was evident after 16 h, and the enol silane was almost completely recovered (Scheme 51). The reaction site is likely too hindered to allow proper formation of the charge-transfer complex between the substrate and DDQ.\textsuperscript{133,134}

**Scheme 51 - Attempted DDQ oxidation of the enol silane (238)**

\[
\begin{align*}
231 & \xrightarrow{(a)} 238 & 238 & \xrightarrow{(b)} 230
\end{align*}
\]

Reagents and conditions: (a) LDA, THF, -78 °C, 30 min then TMSCI, -78 °C to rt, 1.5 h; (b) DDQ (1.6 equiv.), 2,4,6-collidine (1.7 equiv.), PhH, rt, 16 h, no reaction.

2.3.3 Attempted α-bromination of the monoacetal (231)

In another related cyclic system, Hua and co-workers carried out a ketone to enone transformation in two steps by first brominating at a position α to the ketone with NBS, then performing an elimination reaction of the brominated intermediate with lithium carbonate in DMF to yield the desired enone.\textsuperscript{135} This approach was attractive due to the reported lack of dibromination products, the molecular symmetry which renders C-2 and C-4 equivalent and the low cost of reagents.

**Scheme 52 - Attempted preparations of the α-bromoketone (239)**

\[
\begin{align*}
231 & \xrightarrow{(a)} 239 & 239 & \rightarrow 230
\end{align*}
\]

Reagents and conditions: (a) see Table 2.
Unfortunately, in the system under study, conditions for the efficient preparation of the bromoketone 239 could not be found, and this intermediate could not be prepared other than in trace amounts. The reaction conditions corresponding to these attempts are outlined below (Table 2).

**Table 2 - Reaction conditions corresponding to Scheme 52**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NBS (1 equiv.), CCl₄, reflux, o/n</td>
<td>no reaction</td>
</tr>
<tr>
<td>2</td>
<td>NBS (1.3 equiv.), CCl₄, reflux, 24 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>3</td>
<td>NBS (3.0 equiv.), CCl₄, reflux, 24 h</td>
<td>trace of product by ¹H NMR</td>
</tr>
<tr>
<td>4</td>
<td>LDA, THF, 0 ºC, 30 min, then NBS (1.3 equiv.), THF, rt, 8 h</td>
<td>trace of product by ¹H NMR</td>
</tr>
<tr>
<td>5</td>
<td>LDA, THF, 0 ºC, 30 min, then Br₂ (1 equiv.), THF, rt, 30 min</td>
<td>complex mixture of products</td>
</tr>
</tbody>
</table>

Attempts to carry out the bromination reaction of the monoacetal 231 with NBS failed to produce anything other than a trace of product that was visible by ¹H NMR, and this was observed only when a three-fold excess of NBS was employed (Entries 1-3). Formation of the corresponding lithium enolate with LDA and attempted trapping with NBS was likewise unproductive (Entry 4). Finally, generation of the corresponding enolate and trapping with molecular bromine led to a complex mixture of products (Entry 5).
2.3.4 *Methods based on o-iodoxybenzoic acid (IBX) (241)*

Nicolaou has pioneered the use of o-iodoxybenzoic acid (IBX) as a reagent for the direct dehydrogenation of ketones to the corresponding enones.\(^{136}\) This reagent had previously been employed as a selective oxidant for alcohols.\(^{137}\) In Nicolaou's work, heating a variety of cyclic and acyclic ketones with 1.0 to 4.0 equiv. of IBX in a mixture of toluene (or in some cases fluorobenzene) and DMSO (2:1) afforded the corresponding enones in 52-89% yield. The mechanistic rationale for this transformation is presented below (Scheme 53).

**Scheme 53 - Mechanistic rationale for the IBX oxidation of ketones to enones**

IBX undergoes nucleophilic attack on the iodine atom by the enol tautomer of the substrate ketone to form the intermediate \(\text{242}\), which then eliminates the reduced iodine species \(\text{244}\) along with an allylic hydrogen to form the desired enone.
IBX was freshly prepared according to a literature procedure and was employed in the oxidation reaction of the monoacetal 231 under a variety of conditions (Scheme 54). These results are summarized below (Table 3).

**Scheme 54 - Attempted IBX oxidations of the monoacetal (231)**

![Scheme 54](image)

Reagents and conditions: (a) see Table 3.

**Table 3 - Reaction conditions corresponding to Scheme 54**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IBX (1.1 equiv.), PhMe:DMSO (2:1), 70 °C, o/n</td>
<td>no reaction</td>
</tr>
<tr>
<td>2</td>
<td>IBX (2.0 equiv.), PhMe:DMSO (2:1), 70 °C, o/n</td>
<td>complex mixture of products, extensive acetal loss</td>
</tr>
<tr>
<td>3</td>
<td>IBX (2.0 equiv.), NaHCO₃ (2.2 equiv.), PhMe:DMSO (2:1), 70 °C, o/n</td>
<td>complex mixture of products, no acetal loss, much starting material remained</td>
</tr>
<tr>
<td>4</td>
<td>IBX (5.0 equiv.), NaHCO₃ (5.2 equiv.), PhMe:DMSO (2:1), 70 °C, o/n</td>
<td>complex mixture of products, no acetal loss</td>
</tr>
<tr>
<td>5</td>
<td>IBX (1.1 equiv.), PhMe:DMSO (2:1), rt, o/n</td>
<td>no reaction</td>
</tr>
<tr>
<td>6</td>
<td>IBX (1.1 equiv.), DMSO, 70 °C, o/n</td>
<td>extensive decomposition</td>
</tr>
</tbody>
</table>

A first attempt employing the original literature conditions (Entry 1) led to no reaction. Increasing the amount of IBX employed from 1.1 to 2.0 equiv. (Entry
2) led to a complex mixture of products, including a trace of the desired enone 230, as observed by \(^1\)H NMR. Loss of the acetal protecting group was extensive under these reaction conditions. Since IBX is known to be mildly acidic,\(^{138}\) attempts were made to buffer the reaction with sodium bicarbonate. Repeating the reaction with 2.0 equiv. of IBX in the presence of 2.2 equiv. of sodium bicarbonate prevented the loss of the acetal, but again gave a complex mixture of products along with recovered starting material (Entry 3). Increasing both the loading of IBX and that of sodium bicarbonate to 5.0 and 5.2 equiv., respectively, had little effect (Entry 4). Carrying out the unbuffered reaction at room temperature led to no reaction (Entry 5), while eliminating the toluene component of the solvent mixture led to extensive decomposition (Entry 6).

In a subsequent study, Nicolaou and co-workers reported an extension of their original method.\(^{139}\) In this case, it was found that treatment of enol silanes (rather than their corresponding ketones) with the complex formed from IBX and 4-methoxypyridine-\(N\)-oxide (MPO) in DMSO at room temperature afforded the corresponding enones in moderate to high yields. In this system, conversion of the monoacetal 231 to the analogous enol silane followed by treatment with IBX and MPO in DMSO afforded the desired enone 230, albeit in low (30\%) yield (Scheme 55). A large proportion of the starting material was recovered. This approach was more promising than the direct IBX oxidation of ketones, but proved less satisfactory than other methods.
Scheme 55 - IBX oxidation of the enol silane (238)

Reagents and conditions: (a) LDA, THF, -78 °C, 30 min, then TMSCI, -78 °C to rt, 1.5 h; (b) IBX (4 equiv.), MPO (4 equiv.), DMSO, rt, o/n, 30% (73% BRSM)

2.3.5 Selenoxide eliminations\textsuperscript{140}

In this approach, the lithium enolate of the monoacetal 231 was trapped with phenylselenyl bromide. The crude \( \alpha \)-phenylselenide so obtained was then, without purification, oxidized to the corresponding selenoxide. In turn, this intermediate underwent a syn-elimination reaction of phenylselenol to afford the desired enone 230 (Scheme 56). The phenylselenide 245 was readily obtained and a series of oxidants (hydrogen peroxide,\textsuperscript{141} Oxone\textsuperscript{\textregistered} 142 and sodium periodate\textsuperscript{143}) were screened in order to optimize this process (Table 4).

Scheme 56 - Selenide formation and selenoxide elimination

Reagents and conditions: (a) LDA, THF, -78 °C, 30 min, then PhSeBr, -78 °C to rt, 1 h; (b) see Table 4.

Table 4 - Reaction conditions corresponding to Scheme 56

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Oxone\textsuperscript{\textregistered} (2.5 equiv.), MeOH:H\textsubscript{2}O, 0 °C to rt, o/n</td>
<td>complex mixture of products</td>
</tr>
<tr>
<td>Entry</td>
<td>Conditions</td>
<td>Result</td>
</tr>
<tr>
<td>-------</td>
<td>------------</td>
<td>--------</td>
</tr>
<tr>
<td>2</td>
<td>NaIO₄ (2.25 equiv.), MeOH, 0 °C to rt, o/n</td>
<td>19% yield of enone 230 (over two steps)</td>
</tr>
<tr>
<td>3</td>
<td>H₂O₂ (7 equiv.), py (2 equiv.), H₂O:DCM (1:12), 0 °C to rt, 1.25 h</td>
<td>57% yield of enone 230 (over two steps)</td>
</tr>
</tbody>
</table>

Oxone® failed to effect the desired transformation, sodium periodate was marginally effective, while hydrogen peroxide afforded the desired enone 230 in fair yield. The latter reaction also performed well on a multi-gram scale. In summary, the only practical alternative to the stoichiometric Saegusa oxidation method which could be found was the selenoxide elimination reaction which arose upon oxidation of the α-phenylselenide 245 with hydrogen peroxide in the presence of pyridine.

2.4 Tandem Conjugate Addition/Allylation

The key step in the conjugate addition route was a conjugate addition reaction of an organocuprate reagent to the enone 230 followed by alkylation of the resultant enolate by allyl bromide. This conjugate addition to the enone 230 would establish the quaternary centre at C-1, installing what would ultimately become the centro-substituent in the corresponding triquinacene derivative. Furthermore, the allylation at C-2 would provide the necessary carbon fragment for the elaboration of the third 5-membered ring of the triquinane skeleton. As a proof of principle for the conjugate addition route, organocuprates derived from
phenyl organometallics (i.e. from phenylmagnesium bromide or phenyllithium) were selected.

Initially, the conjugate addition reaction was carried out without attempting to alkylate the resultant enolate (Scheme 57, Table 5). Since a quaternary centre is formed in this reaction, it was anticipated that relatively forcing reaction conditions would be required. An excess of the organocuprate reagent was employed, along with TMSCl as a promoter and HMPA as a co-solvent in order to diminish the extent of enolate aggregation.\textsuperscript{144,145} The desired conjugate adduct 246 was obtained under a variety of conditions, along with the corresponding enol silane 247. The latter compound was found to be unstable to silica gel chromatography and in order to obtain a single reaction product, the crude products were treated with 1 equiv. of tetra-n-butylammonium fluoride in THF in order to completely convert the silane 247 to the conjugate adduct 246.

\textit{Scheme 57 - Conjugate additions to the enone (230)}

\[
\begin{align*}
\text{230} & \quad \xrightarrow{(a)} \quad \text{246} \quad + \quad \text{TMSO} \quad \text{247} \quad \xleftarrow{(b)} \\
& \text{Reagents and conditions: (a) see Table 5; (b) TBAF (1 equiv.), THF, 0 \degree C, 30 min}
\end{align*}
\]
Table 5 - Reaction conditions corresponding to Scheme 57

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Combined yield of 246 + 247</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhMgBr (5 equiv.), CuBr•Me₂S (1 equiv.), TMSCl (5 equiv.), THF, -78 °C to rt, 4 h</td>
<td>60%</td>
</tr>
<tr>
<td>2</td>
<td>PhMgBr (4 equiv.), Cul (2.2 equiv.), THF, -78 °C to rt, 6 h</td>
<td>80%</td>
</tr>
<tr>
<td>3</td>
<td>PhMgBr (4 equiv.), Cul (2.2 equiv.), THF, 0 °C to rt, 5 h</td>
<td>82%</td>
</tr>
<tr>
<td>4</td>
<td>PhMgBr (4 equiv.), Cul (2.2 equiv.), TMSCl (5 equiv.), THF, 0 °C to rt, 5 h</td>
<td>78%</td>
</tr>
</tbody>
</table>

From the above, it was determined that promotion of the reaction with TMSCl was neither essential in this system nor detrimental to the reaction's outcome. The very cold (-78 °C) conditions necessary for the stability of some organocuprate reagents were not required here. Furthermore, the standard 2:1 ratio between the Grignard reagent and the Cu¹ source afforded superior results to conditions having a higher ratio of Grignard reagent to copper source.¹⁴⁶

With conditions for efficient conjugate addition established, the focus then shifted to performing the tandem conjugate addition-enolate alkylation sequence. Conditions suitable for accomplishing both the conjugate addition reaction of a phenyl organocuprate as well as the regiospecific alkylation of the resultant enolate at C-2 were sought (Scheme 58, Table 6).
Scheme 58 - Tandem conjugate addition - alkylation reactions of the enone (230)

Reagents and conditions: (a) see Table 6

Table 6 - Reaction conditions corresponding to Scheme 58

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield of 246</th>
<th>Yield of 229</th>
<th>Yield of 248</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1) PhMgBr (4 equiv.), Cul (2.2 equiv.), 0 °C, 1 h. 2) allyl bromide (5 equiv.), THF, o/n</td>
<td>83</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1) PhLi (4 equiv.), Cul (2.2 equiv.), 0 °C, 1 h. 2) allyl bromide (4 equiv.), THF, o/n</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>1) PhLi (4 equiv.), Cul (2.2 equiv.), -78 °C to rt, 2 h. 2) allyl bromide (5 equiv.), THF, -78 °C to rt, o/n</td>
<td>76</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>1) PhLi (4 equiv.), Cul (2.2 equiv.), -78 °C to rt, 2 h. 2) allyl bromide (5 equiv.), HMPA/THF, -78 °C to rt, o/n</td>
<td>46</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>1) PhMgBr (4 equiv.), Cul (2.2 equiv.), 0 °C, 1 h. 2) allyl bromide (5 equiv.), HMPA/THF, o/n</td>
<td>79</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>1) PhMgBr (5 equiv.), Cul (2.5 equiv.), TMSCl (5 equiv.), 0 °C, 3 h 2) NEt₃ quench 3) MeLi, THF, 0 °C, 30 min 4) allyl bromide (5 equiv.), HMPA/THF, 0 °C to rt, 16 h</td>
<td>15</td>
<td>10</td>
<td>55</td>
</tr>
</tbody>
</table>

Initially (Entry 1), the enone 230 was treated with the cuprate derived from phenylmagnesium bromide under conditions which were known to be suitable for
efficient conjugate addition. Indeed, the desired conjugate addition reaction took place, affording the conjugate adduct 246 in high yield. However, no allylated products were obtained. Switching to the phenyl cuprate derived from phenyllithium (as opposed to phenylmagnesium bromide) under similar conditions (Entry 2) not only failed to afford the desired allylated products, but also failed to effect the conjugate addition reaction. Instead, a side-product having NMR spectra consistent with the diallyl ketone 249 was obtained in 42% yield (Scheme 59).

Scheme 59 - Unexpected byproduct formation corresponding to Table 6, Entry 2.

![Scheme 59](image)

Reagents and conditions: PhLi (4 equiv.), Cul (2.2 equiv.), 0 °C, 1 h, then allyl bromide (5 equiv.), HMPA/THF, o/n.

It is evident that, unlike that derived from phenylmagnesium bromide, the organocuprate reagent obtained from phenyllithium is not stable at 0 °C. As a consequence of this instability, the phenyllithium acted as a base rather than as a nucleophile, abstracting in sequence both C-4 protons with concomitant alkylation of the resultant anions by the excess allyl bromide present in the reaction mixture.

In an effort to overcome the instability of the lithium organocuprate (Entry 3), the conditions presented in Entry 2 were repeated with both the cuprate formation and conjugate addition steps being carried out at -78 °C rather than at
0 °C. In this instance, the desired organocuprate reagent did form, as evidenced by the 76% yield of the conjugate adduct 246. However, in parallel with the reaction conditions attempted earlier (Entry 1), the enolates formed by the conjugate addition reaction were completely unreactive towards allyl bromide; no allylated products could be detected.

At this point, it was thought that the unreactive nature of these enolates towards electrophiles might be a consequence of their aggregation. In order to test this hypothesis, hexamethylphosphoramide (HMPA), a highly coordinating solvent, was employed as a co-solvent during the alkylation step. It was hoped that the presence of this solvent would induce the dissociation of the aggregated enolate ions. Indeed, the use of THF:HMPA (5:1) as the solvent system for the alkylation step (Entry 4) under conditions otherwise identical to those described in Entry 3, led to the formation of not only the conjugate adduct 246 (46%) but also to the O-allylated adduct 248 (20%) as well as the desired C-allylated isomer 229 (15%). Thus, it was determined that the use of HMPA as a co-solvent was, under these conditions, essential for the reaction of these enolates with allyl bromide.

In light of the promise shown in the above experiment, a similar approach was taken with the cuprate derived from phenylmagnesium bromide. Repeating the conditions presented in Entry 1 along with the use of THF:HMPA (5:1) as the solvent system for the alkylation step (Entry 5) did not, however, favour the alkylation reaction as was the case with the phenyllithium-derived cuprate. The
conjugate adduct 246, which was obtained in 79% yield, was the sole product of this reaction.

At this stage, an explanation was sought for the recalcitrance of these enolate ions with respect to their reaction with allyl bromide, which is generally regarded as a rather reactive electrophile.\textsuperscript{148} A literature search revealed a study by Coates and Sandefur which reported that the copper enolates obtained as the products of similar conjugate addition reactions either reacted very slowly or not at all with a range of electrophiles in either ether or THF.\textsuperscript{149} Furthermore, in contrast to more reactive lithium enolates, the poor reactivity of these copper enolates was attributed to the higher degree of covalent character present in the enolate oxygen-copper bond as opposed to the oxygen-lithium bond found in lithium enolates. In order to circumvent this problem, the authors recommended the use of DME as solvent, which offered some improvement. However, given that conditions for the efficient conjugate addition of phenylcuprates to the enone 230 had already been established and given the strong solvent dependence of organocuprate formation, stability and reactivity,\textsuperscript{150} this suggestion was not implemented. Rather, a means of converting a copper enolate to a lithium enolate was sought.

It was envisaged that carrying out the conjugate addition reaction under the previously optimized conditions in the presence of TMSCl as a promoter would initially lead to the formation of a copper enolate, which would rapidly be silylated on the enolate oxygen atom by the excess TMSCl present in the reaction mixture (Table 6, Entry 6; Scheme 60). If the enol silane so obtained
could be isolated without having it undergo hydrolysis to the conjugate adduct 246, it was hoped that it could be freed of copper salts and redissolved in THF. Subsequent treatment of the enol silane with methyllithium was expected to result in a nucleophilic attack of methyllithium on the silicon atom,\textsuperscript{151} liberating tetramethylsilane and generating a lithium enolate which, in the presence of HMPA, could be made to react at C-2 with allyl bromide.

\textit{Scheme 60 - Optimized conditions for the tandem conjugate addition-allylation reaction to the enone (230)}

Reagents and conditions: (a) PhMgBr (5 equiv.), Cul (2.5 equiv.), TMSCl (5 equiv.), 0 °C, 3 h; (b) MeLi, THF, 0 °C, 30 min, then allyl bromide (5 equiv.), HMPA/THF, 0 °C to rt, 16 h.

In fact, the above sequence was successful in delivering the requisite allylated products. The sensitive enol silane intermediate 247 was isolated by quenching the conjugate addition reaction with freshly distilled triethylamine instead of water, followed by removal of volatiles \textit{in vacuo}. The residue was then taken up in pentane, mixed vigorously, and carefully filtered. The enol silane 247 was soluble in pentane, as was a small quantity of biphenyl, a byproduct which arose by means of a copper-catalyzed Wurtz coupling reaction of the excess phenylmagnesium bromide.\textsuperscript{152} All salts, including the undesirable copper species, were removed by filtration. Generation of the desired lithium enolate upon treatment of the enol silane 247 with methyllithium proceeded smoothly,
with no enol silane detectable by TLC after 30 min at 0 °C. Following alkylation with allyl bromide in THF/HMPA, the product of O-allylation, the allyl enol ether 248, was obtained in 55% yield, along with the desired C-2-allylated ketone 229 (10%) and the non-allylated conjugate adduct 246 (15%). The 65% overall yield of the allylated products was deemed satisfactory and no further optimization attempts were made.

The O- and C-allyl regioisomers could easily be differentiated on the basis of their NMR and IR spectra. For instance, the C-allyl regioisomers 229 exhibited a carbonyl C=O stretching band at 1738 cm⁻¹ which was absent in the O-allyl compound; rather, in the latter isomer a C=C stretching absorption was seen at 1642 cm⁻¹. Furthermore, the ¹³C NMR spectrum (benzene-d₆) of the C-allyl epimeric pair contained carbonyl resonances at δ = 215.0 and 215.4 ppm corresponding to C-3 for each epimer whereas carbonyl resonances were absent in that of the O-allyl regioisomer 248.

Of interest, the C-2 allylated products 229 were obtained as a 1:1 mixture of C-2 epimers, as determined by ¹H NMR. This implies that there was little, if any, stereochemical preference in the alkylation reaction for either the concave or the convex faces of the 1-phenylbicyclo[3.3.0]octane ring system. As one would generally expect there to be at least a modest preference for alkylation on the less-hindered (in the parent system) convex face, it may be postulated that the phenyl substituent, positioned over the convex face, hindered this face to an appreciable extent. Furthermore, with both faces in this system significantly
hindered, it was not surprising that O-allylation predominated at the expense of allylation at C-2.

Conversion of the O-allylated adduct 248 to the desired C-2-allylated ketone 229 was easily accomplished by means of a Claisen rearrangement reaction (Scheme 61). Heating this material at reflux for 3 days in toluene afforded the desired compound in 98% yield. Again, this material was obtained as a 1:1 mixture of C-2 epimers, a further indication of there being little if any difference in the steric demands presented by the convex and concave faces of this phenyl-substituted ring system.

Scheme 61 - Claisen rearrangement reaction of the allyl enol ether (248) to the C-allylated ketone (229).

Reagents and conditions: (a) PhMe, reflux, 3 days, 98%

The overall process (conjugate addition, allylation and Claisen rearrangement) was quite efficient, affording the C-allylated adduct 229 in 63% overall yield from the enone 230. The process worked well on small (~200 mg) and moderate (~ 2 g) scales, but the yield dropped to 42% when this sequence was carried out on a 5 g scale.

In summary, efficient conditions for the introduction of the eventual centro-substituent by means of a conjugate addition reaction had been established.
Initial attempts at combining this process with an allylation reaction at C-2 in order to allow for the elaboration of the third ring of the triquinacene ring system were met with resistance. These problems were circumvented by the use of HMPA as a co-solvent in order to diminish the extent of enolate aggregation combined with the conversion of an unreactive copper enolate to a more reactive lithium enolate.

2.5 Oxidative Cleavage and Aldol Condensation

Having developed an efficient means for introducing both the eventual centro-substituent as well as the C-2 allyl moiety, the next task was to cleave the allyl group oxidatively to afford the corresponding aldehyde, which after removal of the C-7 acetal protecting group, could undergo an intramolecular aldol condensation reaction to form the third ring of triquinacene.

Initial studies aimed at achieving the conversion of the C-allyl ketone 229 to the corresponding keto aldehyde 228 consisted of attempts to cleave the terminal olefin moiety by means of an ozonolysis reaction with a reductive (dimethyl sulfide) workup. Unfortunately, in this system these conditions failed to effect the desired transformation. Treatment of the C-allyl ketone 229 with an excess of ozone at -78 °C in dichloromethane led to extensive decomposition, as did a similar attempt employing ethyl acetate as solvent. The decomposition occurred rapidly on exposure to ozone and was extensive even before the solution had become saturated with ozone and had taken on its characteristic blue colour. The Lemieux dihydroxylation/oxidative cleavage reaction was then
investigated. In this process, treatment of an olefin with a catalytic amount of osmium tetroxide effects a syn dihydroxylation reaction via an osmate ester intermediate. The resultant diol is oxidatively cleaved via a periodate ester intermediate to two carbonyl compounds by sodium periodate, which is present in excess. The reduced osmium species is then re-oxidized to osmium tetroxide by periodate and the cycle begins anew.

Treatment of the C-allyl ketone 229 with a catalytic amount of osmium tetroxide in aqueous p-dioxane, followed by the addition of 2.5 equiv. of sodium periodate, afforded the aldehyde 228 in 85% yield. The aldehyde did not appear to be appreciably hydrated by $^1$H NMR. As expected, the aldehyde 228 was obtained as a 1:1 mixture of C-2 epimers.

**Scheme 62 - Synthesis of the aldehyde (228) by Lemieux oxidative cleavage**

![Scheme 62](image)

Reagents and conditions: (a) OsO$_4$ (cat.), NaIO$_4$ (2.5 equiv.), p-dioxane:H$_2$O (4:3), rt, 6 h, 85%

As the reaction performed satisfactorily on a larger scale, no further optimizations were carried out. Although the material was obtained as an epimeric mixture, this was not expected to be problematic in the following steps. The intention was to carry out a tandem acetal hydrolysis/aldol condensation sequence under acidic conditions. Following deprotection, even though only the *anti* diastereomer 253 should be capable of undergoing a productive aldol
condensation reaction to form the tricyclic diketo alcohol 227, under the reaction conditions, it was anticipated that the syn and anti diastereomers 251 and 253 would be readily interconverted through the formation of the enol 252 and subsequent reprotonation at C-2 from either face of this planar intermediate (Figure 8).

Figure 8 - Mechanistic rationale for the tandem acetal hydrolysis/aldol condensation sequence

A series of studies was then carried out with the goal of determining suitable reaction conditions to effect the desired transformations. In the synthesis of the parent triquinacene 1 by Deslongchamps and co-workers, a similar sequence was carried out by treating a related protected keto-aldehyde with dilute aqueous hydrochloric acid in acetone solution. Furthermore, Cook and co-workers in their synthesis, again of the parent triquinacene 1, reported
that an analogous transformation could be carried out in a mixture of THF and 2 M aqueous hydrochloric acid (2:1).\textsuperscript{47} However, in this case, these conditions failed to effect either the deprotection or the aldol condensation; more than 95% of the starting material was recovered after 5 days at room temperature. In contrast with the parent system, the presence of the additional phenyl substituent may have affected the overall degree of steric hindrance and/or the water solubility of the starting material, rendering the established conditions unsuitable. In a second attempt, heating an identical reaction mixture at reflux led to extensive decomposition after 1 h.

Next, a system consisting of a catalytic amount of \textit{p}-toluenesulfonic acid in reagent grade acetone was investigated. It was hoped that the use of a strong, organic-soluble catalyst would be more effective in this case; moreover, it was expected that the water present in the acetone would be sufficient to facilitate the transacetalization (deprotection) reaction whereby the neopentyl glycol moiety would be transferred to the acetone solvent.

After stirring the aldehyde 228 at room temperature for 5 days in reagent grade acetone along with a catalytic amount of \textit{p}-toluenesulfonic acid, the product resulting from the intermolecular aldol condensation without deprotection of the acetal moiety was isolated in high yield (75%) (Scheme 63).
Scheme 63 - Synthesis of 10-phenyltricyclo[5.2.1.0\textsuperscript{4,10}]deca-3,8-dione-6-ol, 8-(2',2'-dimethylpropyldiene acetal) (255)

![Chemical structure](image)

Reagents and conditions: (a) \( p\text{-}TsoH \) (cat.), reagent grade acetone, rt, 5 days, 75%

This product could have, in principle, arisen either by (a) deprotection of the acetal moiety, aldol condensation and subsequent reprotection or (b) via opening of the cyclic acetal, aldol condensation and subsequent acetal ring closure (Figure 9).\textsuperscript{154}

![Mechanistic rationale](image)

Figure 9 - Mechanistic rationale for the formation of the tricyclic acetal (255)

However, scenario (a) could most probably be ruled out since no transfer of the neopentyl glycol moiety between C-3 and C-7 was observed. If complete
deprotection prior to aldol condensation were to have taken place, upon reprotuction, one would expect a nearly statistical mixture of the regioisomeric C-3 and C-7 acetals to be formed. However, no such "scrambling" of the acetal group's location was observed by $^1$H NMR. Moreover, the yield (75%) of this process indicated that the two C-2 epimers (initially present in a 1:1 ratio) of the starting material 228 were efficiently interconverted under the reaction conditions. Had this not been the case, the maximum yield would have been $\sim$50% (vide supra).

The tricyclic acetal 255 was obtained as a crystalline solid consisting of a 5:1 mixture of C-6 diastereomers. This ratio was determined by integration of the H-6 proton resonances (at $\delta = 4.15$ ppm for the major epimer and 4.56 for the minor epimer) in the $^1$H NMR spectrum of the mixture (Figure 10). These resonances were suitably diagnostic, as they were well-removed from the other signals in the spectrum. The diastereomers were co-polar and could not be separated by flash chromatography; however, this was not a concern since the centre in question was to be later subjected to an elimination reaction which would eliminate this stereogenic centre.
Next, a series of small scale studies was undertaken in order to determine more suitable reaction conditions. In a first instance (Scheme 64), the aldehyde 228 was stirred in a mixture of acetone and water (2:1) in the presence of a catalytic amount of p-toluenesulfonic acid. After 6 days, an intermediate having a $^1$H NMR spectrum consistent with the tricarbonyl compound 250 was formed. This compound was unstable to silica gel chromatography and could not be isolated. Having achieved the deprotection reaction, this intermediate was immediately subjected to the previously determined conditions for aldol condensation. Treatment of this intermediate with the same acid catalyst in

*Figure 10 - Detail from the $^1$H NMR spectrum (CDCl$_3$, 400 MHz) of the tricyclic acetal (255)*
reagent-grade acetone afforded, after 7 days, the desired tricyclic diketo alcohol 227 in a 70% overall yield.

**Scheme 64 - Stepwise acetal hydrolysis/aldol condensation reactions of the aldehyde (228)**

Reagents and conditions: (a) p-TsOH (cat.), acetone:H2O (2:1), rt, 6 days; (b) p-TsOH (cat.), acetone, rt, 7 days 70% over two steps or THF:2 M aq. HCl (2:1), rt, 5 days, 55% over two steps.

This study was followed up, in an analogous manner, by preparing the tricarbonyl intermediate 250 and subsequently subjecting it to the conditions (THF:2 M aqueous HCl) reported for the preparation of the corresponding tricyclic compound in the parent series. In this instance, the aldol condensation reaction was complete after 5 days and afforded the diketo alcohol 227 in a 55% overall yield from the aldehyde 228.

Next, having achieved the preparation of the diketo alcohol 227 in a stepwise manner (deprotection followed by aldol condensation), the analogous sequence with the order of the steps reversed was carried out. The keto hydroxy acetal 255 was prepared in a manner analogous to that shown earlier (Scheme 63). This intermediate was isolated and purified, then stirred in a mixture of acetone and water (2:1) under p-toluenesulfonic acid catalysis (Scheme 65). In this case, deprotection occurred after 5 days, affording the tricyclic diketo alcohol 227 in 61% yield over two steps. Alternatively, treatment of the intermediate 255
with a mixture of THF and 2 M aqueous HCl (2:1) afforded the alcohol 227 after 6 days but in a much lower yield (25%, 18% from the aldehyde 228) with considerable decomposition taking place.

Scheme 65 - Stepwise aldol condensation/acetal hydrolysis reactions of the aldehyde (228)

Reagents and conditions: (a) p-TsOH (cat.), reagent grade acetone, rt, 5 days, 73%; (b) p-TsOH (cat.), acetone:H₂O (2:1), rt, 5 days, 84% or THF:2 M aq. HCl (2:1), rt, 6 days, 25%.

Finally, as the results of the above studies indicated that the most efficient approach was to perform the aldol condensation reaction in reagent grade acetone and then to carry out the acetal hydrolysis in aqueous acetone (under p-toluenesulfonic acid catalysis), a modified sequence was investigated whereby the tricyclic acetal intermediate 255 was not isolated. Here, the aldehyde 228 was stirred for 5 days in reagent grade acetone, then sufficient water was added to duplicate the conditions for acetal hydrolysis (Scheme 66). This proved to be the most practical and high-yielding route to the target diketo alcohol 227. After 2 days, the desired compound was obtained in 79% yield, along with a 14% yield of the intermediate 255, which could be "recycled" by subjecting it to similar reaction conditions in order to afford further quantities of the diketo alcohol 227.
Scheme 66 - Synthesis of the diketo alcohol (227)

Reagents and conditions: (a) p-TsOH (cat.), acetone, rt, 5 days; (b) p-TsOH (cat.), acetone:H₂O (2:1), rt, 2 days, 92%.

As was the case with the tricyclic acetal 255, the diketo alcohol 227 was obtained as a mixture of C-6 epimers. The diastereomeric ratio was again determined by integration of the H-6 resonances in the ¹H NMR spectrum (Figure 11).

Interestingly, upon acetal hydrolysis, the diastereomeric ratio changed from the 5:1 mixture observed in the starting material 255 to a 7:3 mixture in the diketo alcohol product 227. This suggests that under the reaction conditions, the acetal hydrolysis reaction was accompanied by a retro-aldol condensation process which, in conjunction with the analogous forward process, allowed an equilibrium mixture of epimers to be formed.

Having identified the one-pot stepwise aldol condensation/acetal hydrolysis process to be the most effective approach, the bulk of the material at hand, the aldehyde 228, was transformed to the tricyclic diketo alcohol 227 by this method.
Figure 11 - Detail from the $^1$H NMR spectrum (CDCl$_3$, 400 MHz) of the diketo alcohol (227)

2.6 Completion of Synthesis

In order to convert the diketo alcohol 227 to the corresponding triquinacene derivative 84, the two carbonyl moieties had to be reduced to form the corresponding triol. Elimination of the three hydroxyl groups would then lead to the desired hydrocarbon. The approach chosen was based on the syntheses of the parent triquinacene by the groups of Deslongchamps$^{41}$ and Cook$^{47}$. In these approaches, which were virtually identical, the reductions were accomplished with either borane or DIBAL-H and the elimination reaction was effected by activation of the triol to the corresponding trimesylate followed by stirring over highly activated alumina in dichloromethane.
Based on literature precedent in the parent triquinacene system, borane-THF complex was chosen to reduce the diketo alcohol 227 to the triol 261. This Lewis acid-mediated reduction with borane-THF proceeded smoothly, yielding the triol 261 as a complex mixture of stereoisomers in good yield. It had been reported that hydride reducing agents such as sodium borohydride and lithium aluminum hydride were unsuitable for use in this system. As these reagents are somewhat basic, treatment of the analogous diketo alcohol in the parent series led to a retro-aldol condensation reaction followed by reduction of the three carbonyl groups to form the corresponding ring-opened triol.

Scheme 67 - Synthesis of the triol (261)

Reagents and conditions: (a) BH$_3$•THF complex, THF, 0 °C to rt, 16 h, 77%

In theory, as many as eight stereoisomers could have been formed in this reaction and so this compound was not fully characterized. However, the IR spectrum of the crude product showed no carbonyl C=O stretching resonances, and the mixture exhibited a satisfactory mass spectral analysis.

Cook and co-workers have reported that, in the parent triquinacene system, heating the analogous triol at reflux in HMPA for 48 h directly afforded triquinacene in good yield. As these conditions were somewhat harsh, activation of the triol 261 to the trimesylate 262 was investigated. Both Cook and
Deslongchamps had achieved this transformation in the parent series by treating the corresponding triol with methanesulfonyl chloride and pyridine for several days in a freezer without stirring. Rather, an alternative procedure (treatment with methanesulfonyl chloride and triethylamine in dichloromethane solution at room temperature) was employed (Scheme 68).\textsuperscript{155} No starting material could be detected by TLC after 2 h. Again, on account of the number of stereoisomers present, this compound was not fully characterized and was used in the following step without purification. However, no hydroxyl O-H stretching bands could be seen in the IR spectrum of the crude material, indicating that the activation reaction had gone to completion.

**Scheme 68 - Synthesis of the trimesylate (262)**

\[
\begin{align*}
261 & \quad \text{OH} \\
& \quad \text{HO} \quad \text{Ph} \\
& \quad \text{HO} \\
\end{align*}
\]

\[
\begin{align*}
\rightarrow (a) & \quad \text{MsO} \quad \text{OMs} \\
262 & \quad \text{Ph} \\
& \quad \text{OMs} \\
\end{align*}
\]

Reagents and conditions: (a) MsCl, NE\textsubscript{3}, DCM, 0 °C to rt, 2 h.

The synthesis of 10-phenyltriquinacene 84 was carried out by stirring the crude trimesylate 262 with a slurry of highly activated neutral alumina in dichloromethane (Scheme 69).\textsuperscript{41} It was found to be imperative that the alumina be as anhydrous as possible and freshly activated.
Scheme 69 - Synthesis of 10-phenyltriquinacene (84)

\[ 
\text{MsO} \quad \text{OMs} \\
\text{MsO} \quad \text{OMs} \\
\begin{array}{c}
\text{Ph} \\
262 \\
\end{array} \\
\text{(a)} \\
\begin{array}{c}
\text{Ph} \\
84 \\
\end{array} \\
\text{Reagents and conditions: (a) activated neutral Al}_2\text{O}_3, \text{ DCM, rt, 3 days, 44% over two steps from the triol 261.}
\]

10-Phenyltriquinacene 84 was obtained as a colourless amorphous solid with a melting point of 62-63 °C. This compound was obtained in a 5% overall yield over twelve steps from glyoxal 69 and dimethyl 1,3-acetonedicarboxylate 233. The material obtained had spectral and physical properties consistent with literature values.\(^5\) The compound was purified by flash chromatography in neat pentane, in which it had a TLC \(R_f\) of 0.90.

On account of its \(C_3\) symmetry, 10-phenyltriquinacene 84 had remarkably simple NMR spectra. For instance, the \(^1\)H NMR spectrum (Figure 12) showed only two non-aryl resonances: a singlet at \(\delta = 3.84\) ppm (CDCl\(_3\)) assigned to the three equivalent bridgehead methane protons and another singlet at \(\delta = 5.70\) ppm corresponding to the six equivalent alkene protons. The five aryl proton resonances appeared in the range of \(\delta = 7.14\) to 7.36 ppm as a complex multiplet.
Figure 12 - Detail from the $^1$H NMR spectrum (CDCl$_3$, 400 MHz) of 10-phenyltriquinacene (84)

The $^{13}$C NMR spectrum (CDCl$_3$) contained the resonance for the centro (C-10) carbon at $\delta = 65.7$ ppm, that for the three equivalent bridgehead methine carbons (C-1, C-4 and C-7) at $\delta = 65.8$ ppm, that for the six sp$^2$ carbons (C-2, C-3, C-5, C-6, C-8 and C-9) at $\delta = 132.1$ ppm as well as four aryl carbon signals at $\delta = 124.7$, 125.6, 128.7 and 149.1 ppm, the latter being attributed to the aryl ipso carbon.
Figure 13 - Detail from the $^{13}$C NMR spectrum (CDCl$_3$, 400 MHz) of 10-phenyltriquinacene (84)

2.7 Attempted Extension to Other Derivatives

2.7.1 Attempted conjugate addition of [(4-methoxybenzyloxy)methyl]tributylstannane (270) to the enone (230)

In light of the success of the conjugate addition route in preparing 10-phenyltriquinacene 84 and given the interest in preparing triquinacene-10-carboxylic acid 226 for molecular recognition studies, a literature search was carried out which targeted reagents capable of effecting a conjugate addition reaction of a protected hydroxymethyl anion equivalent. Formally, such a reaction would be the synthetic equivalent of a conjugate addition reaction of methanol through the carbon atom, i.e. the addition of "CH$_2$OP" where P is a
suitable protecting group (Scheme 70). Should the conjugate adduct 263 be obtainable, the triquinacene framework would be elaborated in a manner similar to that employed in the preparation of 10-phenyltriquinacene 84. Finally, deprotection would afford 10-hydroxymethyltriquinacene 265, which would then be oxidized to the desired carboxylic acid derivative 226.

Scheme 70 - Planned synthesis of triquinacene-10-carboxylic acid (226) via a conjugate addition approach.

The most promising candidates appeared to be protected derivatives of tri-n-butylstannylmethanol, i.e. n-Bu₃SnCH₂OP where P is a protecting group. Using transmetallation chemistry, these stannanes could be transmetallated to their corresponding organolithium derivatives, which in turn could be used to form the analogous organocuprate reagents. Several such derivatives were known, including four [where P = 2-(trimethylsilyl)ethoxymethyl (SEM), methoxymethyl (MOM), benzyl (Bn) or p-methoxybenzyl (PMB)] which were identified as potentially useful protecting groups. Of note, simple silyl ether derivatives such as those where P = trimethylsilyl (TMS), t-butyldimethylsilyl (TBS) or t-butyldiphenylsilyl (TBDPS) were deemed unsuitable for this purpose, as it has
been reported that they undergo a rapid *retro*-Brook rearrangement (*i.e.* silicon group transfer from oxygen to carbon) upon transmetallation.\textsuperscript{160,161} From these four candidates, the *p*-methoxybenzyl analogue was chosen on account of its stability towards the conditions employed during the elaboration of the triquinacene ring system and its relative ease of deprotection (for instance, these ethers may be cleaved with DDQ at room temperature).\textsuperscript{162} In contrast, the MOM and SEM protecting groups are acid-labile and hence incompatible with the acid-catalyzed aldol condensation reaction, and the cleavage of benzyl ethers requires hydrogenolytic conditions which may affect the three double bonds in the triquinacene ring.\textsuperscript{47}

(Chloromethyl)-tri-\textit{n}-butylstannane \textbf{269} was first prepared according to a literature method.\textsuperscript{163} In this one-pot procedure, deprotonation of tri-\textit{n}-butyltin hydride \textbf{266} with LDA followed by trapping with *p*-formaldehyde afforded the corresponding primary alcohol, which was then treated with methanesulfonyl chloride to prepare the corresponding mesylate. The methanesulfonyl moiety was then displaced by chloride ion to afford the desired chloride in excellent yield (Scheme 71). Multi-gram quantities of this reagent could be prepared \textit{via} this method, and purification was readily achieved by distillation under reduced pressure.
Scheme 71 - Synthesis of (chloromethyl)tri-n-butylstannane (269)

\[
\begin{align*}
\text{n-Bu}_3\text{SnH} & \xrightarrow{(a)} \quad \text{n-Bu}_3\text{SnLi} \\
266 & \quad 267 \\
\text{n-Bu}_3\text{Sn} & \xrightarrow{\text{Cl}} \quad \text{n-Bu}_3\text{SnLi} \\
268 & \quad 269
\end{align*}
\]

Reagents and conditions: (a) LDA, THF, 0 °C, 25 min, then (CH₂O)_₃, 0 °C to rt, 3 h, then MsCl, -78 °C to rt, 16 h, 93%.

Deprotonation of p-methoxybenzyl alcohol with potassium t-butoxide in THF followed by heating of the resultant alkoxide with the chloromethylstannane 269 and a catalytic amount of tetra-n-butylammonium iodide afforded the benzyloxystannane 270 in good yield (Scheme 72). The literature preparation of the benzyloxyethyl stannane 270 called for conversion of the chloromethyl derivative 269 to the iodomethyl analogue by treatment with sodium iodide in acetone, followed by purification (distillation) and then coupling with an alkoxide.¹⁵⁹ This step was obviated by conversion of the chloride 269 to the corresponding iodide in situ by the addition of a catalytic amount of the aforementioned quaternary ammonium salt to the coupling reaction.

Scheme 72 - Synthesis of [(4-methoxybenzyloxy)methyl]tri-n-butylstannane (270)

\[
\begin{align*}
\text{n-Bu}_3\text{Sn} & \xrightarrow{(a)} \quad \text{n-Bu}_3\text{Sn} \\
269 & \quad 270 \\
\text{OCH₃}
\end{align*}
\]

Reagents and conditions: (a) p-(MeO)C₆H₄CH₂OH, t-BuOK, n-Bu₄NI, THF, 45 °C, 17 h, 77%.

This modification represents a practical improvement to the existing literature synthesis of tributylstannylmethanol derivatives, as no loss in overall yield occurs on replacement of the iodomethyltributyltin synthesis and purification.
with an *in situ* preparation. Moreover, it was found that replacing the distillation of (chloromethyl)tri-n-butyl stannane 269 with a convenient filtration through a short pad of silica gel had no deleterious effect on the overall yield of the stannane 270. The presence of residual tributyltin hydride did not diminish the yield of the subsequent $S_N2$ reaction with the potassium alkoxide of $p$-methoxybenzyl alcohol. Overall, the stannane 270 was prepared on a multi-gram scale in 72% yield by this two-pot procedure from tributyltin hydride 266. This yield was better than that reported in the literature, wherein the same stannane was prepared in 60% yield over three separate steps.

In order to determine the efficiency of the tin-lithium transmetallation reaction of the stannane 270 with n-butyllithium, a model reaction was carried out (Scheme 73). Treatment of the stannane 270 with a slight excess of n-butyllithium in THF, followed by trapping with cyclopentanone afforded the cyclopentyl carbinol 271 in high yield, confirming that the transmetallation reaction had proceeded smoothly under these conditions.

**Scheme 73 - Transmetallation of stannane (270) and addition to cyclopentanone**

![Scheme 73](image)

Reagents and conditions: (a) $n$-BuLi, THF, $-78$ °C, 30 min, then cyclopentanone, $-78$ °C to rt, 16 h, 84%.

Having confirmed the success of the above transmetallation procedure, a second model reaction was carried out in order to determine whether a suitable
organocuprate reagent could be prepared from the stannane 270 via the corresponding organolithium species (Scheme 74).

Scheme 74 - Transmetallation of the stannane (270), cuprate formation and conjugate addition to cyclohex-2-en-1-one.

Reagents and conditions: (a) n-BuLi, THF, -78 °C, 30 min, then CuBr•Me2S, -78 °C, 1 h, then cyclohex-2-en-1-one, TMSCl, -78 °C to rt, 4 h, 87%.

Here, the tin-lithium transmetallation reaction was performed in a similar manner and cuprous bromide-dimethyl sulfide complex was treated with the organolithium species to form the corresponding organocuprate reagent. Cyclohex-2-en-1-one was then added along with TMSCl as a promoter and after 4 h at -78 °C, no more starting material was observed by TLC. Any enol silane present was hydrolyzed on work-up with buffered aqueous ammonium chloride and the conjugate adduct 272 was obtained in very high yield. No products of 1,2-addition were observed, confirming that formation of the desired organocuprate reagent was essentially complete after 1 h at -78 °C.

Encouraged by these results, the analogous conjugate addition reaction to the enone 230 was attempted (Scheme 75).
Scheme 75 - Attempted conjugate addition reactions of cuprates derived from the stannane (270) to the enone (230)

Reagents and conditions: (a) see Table 7

Table 7 - Reaction conditions corresponding to Scheme 75

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>stannane 270 (2.4 equiv.), n-BuLi (2.5 equiv.), -78 °C, 30 min, then CuBr • Me2S (1.2 equiv.), -78 °C, 30 min., then enone 230 (1 equiv.), TMSCl (5 equiv.), -78 °C to 0 °C, 6 h</td>
<td>no reaction, enone 230 recovered</td>
</tr>
<tr>
<td>2</td>
<td>stannane 270 (4.8 equiv.), n-BuLi (4.9 equiv.), -78 °C, 30 min, then CuBr • Me2S (2.5 equiv.), -78 °C, 30 min, then enone 230 (1 equiv.), TMSCl (12 equiv.), -78 °C to 0 °C, 8 h</td>
<td>no reaction, enone 230 recovered</td>
</tr>
<tr>
<td>3</td>
<td>stannane 270 (4.8 equiv.), n-BuLi (4.9 equiv.), -78 °C, 30 min, then CuBr • Me2S (2.5 equiv.), -78 °C, 30 min, then enone 230 (1 equiv.), TMSCl (12 equiv.), -78 °C to rt, 7 h</td>
<td>no reaction; enone decomposition on warming to rt</td>
</tr>
<tr>
<td>4</td>
<td>stannane 270 (4.8 equiv.), n-BuLi (4.9 equiv.), -78 °C, 30 min, then CuBr • Me2S (2.5 equiv.), -78 °C, 30 min, then enone 230 (1 equiv.), TMSCl (12 equiv.), 0 °C to rt, 7 h</td>
<td>complex mixture</td>
</tr>
</tbody>
</table>

In the first instance, conditions similar to those for the successful addition of the desired organocuprate reagent to the model enone were employed (Entry 1). Despite confirmation of successful tin-lithium transmetallation by TLC, the enone starting material 230 was recovered unchanged after 6 h. More forcing
conditions (Entry 2) were then employed, with the amounts of the organocuprate reagent and the TMSCl promoter doubled. Again, the desired reaction did not take place, and the enone 230 was again recovered. In a third attempt (Entry 3), the reaction mixture was allowed to warm from -78 °C to room temperature. While no reaction took place at the lower temperature, extensive decomposition of both the enone starting material and the organocuprate reagent was noticed upon warming. Finally (Entry 4), the conjugate addition step was carried out at 0 °C rather than at -78 °C. This led to a complex mixture of products and there was no evidence that a successful conjugate addition reaction had occurred by inspection of the 'H NMR spectrum of the crude reaction mixture.

Although the successful formation of the requisite organocuprate reagent was confirmed by the conjugate addition reaction in a model system, reaction conditions suitable for accomplishing the analogous addition to the enone 230 could not be identified. Unlike the conjugate addition to the model system, the latter reaction involves the formation of a quaternary centre. The results presented in Table 7 indicate that the organocuprate reagent in question is insufficiently reactive to accomplish this transformation at low temperature (-78 °C) and decomposes when warmed. The steric demands inherent in the formation of quaternary centres likely contributed to the failure of this study.

2.7.2 Attempted conjugate addition reactions of 4-carbethoxyphenylzinc iodide (274)

A second approach involved the study of the conjugate addition reaction of commercially-available 4-carbethoxyphenylzinc iodide 274 to the enone 230.
It was hoped that following the conjugate addition/allylation step, the triquinacene ring system could again be elaborated in a manner similar to that employed for the synthesis of 10-phenytriquinacene 84. In this manner, triquinacene-10-benzoic acid 276 could be prepared.

Scheme 76 - Proposed synthesis of triquinacene-10-benzoic acid (276) via a conjugate addition approach

In a comprehensive study, Knochel and co-workers carried out similar conjugate addition reactions of organozinc-derived organocuprate reagents to a wide range of Michael acceptors such as cyclohexenones, propargyl esters, \(\alpha,\beta\)-unsaturated sulfones and \(\alpha,\beta\)-unsaturated nitro compounds with good results.\(^{164}\) In light of these findings, conjugate addition reactions of the organozinc reagent 274 to the enone 230 were attempted (Scheme 77).
Scheme 77 - Attempted conjugate addition reactions of cuprates derived from the organozinc reagent (274) to the enone (230)

Reagents and conditions: (a) see Table 8

Table 8 - Reaction conditions corresponding to Scheme 77

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>274 (3 equiv.), CuCN (3 equiv.), LiCl (6 equiv.), THF, -20 °C to 0 °C, 10 min, then TMSCl (3 equiv.), enone 230 (1 equiv.), -78 °C to rt, 16 h</td>
<td>no reaction, enone 230 recovered</td>
</tr>
<tr>
<td>2</td>
<td>274 (5 equiv.), CuCN (2.5 equiv.), -78 °C to 0 °C, 1 h, then TMSCl (5 equiv.), enone 230 (1 equiv.), -78 °C to rt, 6 h</td>
<td>no reaction, enone 230 recovered</td>
</tr>
<tr>
<td>3</td>
<td>274 (5 equiv.), Cul (2.5 equiv.), -78 °C to 0 °C, 1 h, then TMSCl (5 equiv.), enone 230 (1 equiv.), -78 °C to rt, 6 h</td>
<td>no reaction, enone 230 recovered</td>
</tr>
<tr>
<td>4</td>
<td>274 (5 equiv.), CuCN (2.5 equiv.), 0 °C, 1 h, then TMSCl (5 equiv.), enone 230 (1 equiv.), 0 °C to rt, 7 h</td>
<td>no reaction, enone 230 recovered</td>
</tr>
</tbody>
</table>

In all cases, the corresponding organocuprate reagent proved to be unreactive towards the enone 230. After first duplicating the conditions reported by Knochel (Entry 1), formation of the corresponding higher-order cuprate under standard conditions\textsuperscript{145} (Entry 2) with TMSCl promotion proved to be equally ineffective. Neither switching the copper source from cuprous cyanide to cuprous iodide (Entry 3) nor performing both the cuprate formation and the
conjugate addition reactions at 0 °C rather than at -78 °C (Entry 4) effected the desired reaction. Again, possibly on account of the hindered nature of the enone 230, it was determined that organocuprate reagents derived from 4-carbethoxyphenylzinc iodide 274 were insufficiently reactive, even under rather forcing conditions (e.g. organocuprate reagents used in excess, elevated reaction temperatures, TMSCI promotion), to undergo conjugate addition in this system.

2.8 Summary and Conclusions

The concept of preparing centro-substituted triquinacene derivatives by the above conjugate addition approach, with the centro substituent introduced regioselectively via a conjugate addition reaction to the enone 230, was realized by completing the synthesis of 10-phenyltriquinacene 84. The entire synthesis is summarized below (Scheme 78).

The preparation of the monoacetal 231 was readily accomplished from neopentyl glycol and the dione 232. Even though this desymmetrization step inherently led to a statistical mixture of three compounds, the byproducts could be effectively “recycled” to furnish further quantities of this intermediate.

Dehydrogenation of the monoacetal 231 to afford the key enone intermediate 230 was accomplished in high yield via oxidation of the corresponding enol silane with a stoichiometric amount of palladium (II) acetate. A more economical, but somewhat lower yielding, alternative preparation was
developed in which this transformation was accomplished by an oxidative elimination reaction of the corresponding α-phenylselenide.

A conjugate addition/enolate alkylation sequence, in which both the centro phenyl substituent and the allyl moiety were installed, was developed. Rather forcing conditions were required for efficient conjugate addition and the resultant copper enolates were found to be very unreactive towards allyl bromide. This was circumvented by trapping the enolate produced in the conjugate addition reaction as the corresponding enol silane, followed by isolation of this intermediate and generation of the more reactive lithium enolate. O-alkylation predominated in this system, as both the inherently hindered concave face and the convex face (hindered by the phenyl substituent) were significantly blocked, retarding electrophilic attack at the enolate carbon atom. Fortunately, the product of O-alkylation 248 could be smoothly converted to the desired C-allyl derivative 229 by means of an efficient Claisen rearrangement reaction.

The phenyl substituent exerted a profound influence on the tandem acetal hydrolysis/aldol condensation reaction which was used to elaborate the third five-membered ring of the triquinacene ring system. The straightforward and standard conditions suitable for effecting this process in the parent system were unsuitable and an alternative set of reaction conditions were developed.
Scheme 78 - Summary for the synthesis of 10-phenyltriquinacene (84) via the conjugate addition route

Reagents and conditions: (a) (i) NaOH, MeOH, H₂O, rt, 16 h; (ii) aq. HCl, AcOH, reflux, 3 h, 59%; (b) neopentyl glycol, p-TsOH (cat.), PhH, reflux, Dean-Stark apparatus, 4 h, 52%; (c) (i) LDA, THF, -78 °C, 30 min, then TMSCl, THF, -78 °C to rt, 2 h; (ii) Pd(OAc)₂, MeCN, 0 °C to rt, 14 h, 91%; (d) (i) PhMgBr, Cul, TMSCl, THF, 0 °C, 3 h; (ii) MeLi, THF, 0 °C, 30 min, then allyl bromide, HMPA, 0 °C to rt, 16 h, 65% (248 + 229, 5.5:1); (e) PhMe, reflux, 3 days, 96%; (f) OsO₄ (cat.), NaIO₄, p-dioxane:H₂O (13:9), rt, 6 h, 85%; (g) p-TsOH (cat.), acetone, rt, 5 days, then H₂O, 2 d, 14% (255) and 79% (227); (h) p-TsOH (cat.), acetone:H₂O (2:1), rt, 2 days, 92%; (i) BH₃•THF, THF, 0 °C to rt, 16 h, 77%; (j) MsCl, NEt₃, DCM, 0 °C to rt, 2 h; (k) activated neutral Al₂O₃, DCM, rt, 3 days, 44% (over two steps).
Finally, the diketo alcohol 227 was converted to the final product by a series of functional group interconversion reactions (reduction, activation and elimination). 10-Phenyltriquinacene 84 was prepared in 5% yield over twelve steps.

Attempts to perform two analogous conjugate addition reactions in order to obtain triquinacene derivatives suitable for molecular recognition and reactivity studies were unsuccessful. The requisite organocuprate reagents were insufficiently reactive under a range of reaction conditions to install the quaternary centre. Despite these limitations, the successful preparation of 10-phenyltriquinacene 84 by this conjugate addition approach confirmed the validity of this synthetic strategy.

In the chapters which follow, alternative preparations of these derivatives, which do not rely on conjugate addition chemistry for the formation of the quaternary centre, are described.
3.1 Overview and Retrosynthetic Analysis

This chapter is concerned with the synthesis of 1-(4'-bromophenyl)triquinacene 278 and 10-(4'-bromophenyl)triquinacene 279. Triquinacene-10-benzoic acid 276 is a derivative of interest for the proposed triquinacene dimerization studies discussed in the Introduction, and should be available from 10-(4'-bromophenyl)triquinacene 279 by a metal-halogen exchange reaction of the aryl bromide moiety followed by treatment with carbon dioxide. Moreover, as aryl bromides are versatile synthetic intermediates, the bromide 279 could also serve as a precursor for related triquinacene derivatives also capable of engaging in non-covalent bonding interactions. The corresponding C-1-substituted derivatives could also be employed for the dimerization studies outlined in the Introduction (c.f. Section 1.8.1).

In some respects, the proposed synthetic route resembled the conjugate addition route presented in Chapter 2. However, the primary difference between these two approaches was that, in the substituted glyoxal route, the eventual centro substituent was installed at the beginning of the synthesis rather than by a conjugate addition reaction at a later stage in the synthetic route. The early elaboration of the quaternary centre was accomplished by using a substituted glyoxal (in this case, 4-bromophenylglyoxal 284) rather than glyoxal 69 in the
Weiss-Cook condensation reaction which forms the bicyclo[3.3.0]octan-3,7-dione ring system. A retrosynthetic analysis of these regioisomeric triquinacene derivatives is presented below (Scheme 79).

**Scheme 79 - Retrosynthetic analysis of 1-((4'-bromophenyl)triquinacene (278) and 10-((4'-bromophenyl)triquinacene (279)**

After performing the Weiss-Cook condensation reaction between 4-bromophenylglyoxal 284 (derived from 4-bromoacetophenone 283) and 1,3-dimethyl acetonedicarboxylate 233 followed by protection of one of the ketone moieties of the resultant bicyclo[3.3.0]octan-3,7-dione derivative 282, the key step of this sequence would be attempted. At this stage, the allyl moiety required for the elaboration of the third ring of the triquinacene ring system would be installed by deprotonation of the corresponding ketone followed by treatment with allyl bromide. The critical issue here was one of regioselectivity, as allylation at C-2 would ultimately lead to 10-(4'-bromophenyl)triquinacene 279 whereas
allylation at C-4 would afford the analogous 1-substituted triquinacene derivative 278.

In the conjugate addition route, the allylation reaction was regiospecific as the corresponding enolate was generated by a conjugate addition reaction rather than by a ketone enolization. In the substituted glyoxal route, it was hoped that reaction conditions which would offer some regioselectivity for the C-2 allylation product (or, failing this, that conditions not highly selective for C-4 allylation) could be identified. However, the 1-substituted derivative 278 would also be of interest, as only four triquinacene derivatives (those bearing methyl, t-butyl, bromo and dimethylamino substituents) with this substitution pattern have been reported.

3.2 Weiss-Cook Condensation and Monoprotection

In order to prepare the requisite p-bromophenylglyoxal 284 for the subsequent Weiss-Cook condensation reaction, p-bromoacetophenone 283 was subjected to a Riley oxidation reaction (Scheme 80). Heating a solution of this ketone in aqueous p-dioxane in the presence of 1.4 equiv. of selenium dioxide afforded p-bromophenylglyoxal 284 as its monohydrate.

\textit{Scheme 80 - Synthesis of p-bromophenylglyoxal monohydrate (284)}

\[
\begin{align*}
\text{Br} & \quad \text{O} \\
\text{283} & \quad \text{O} \\
\text{Br} & \quad \text{OH} \\
\text{284} & \quad \text{OH} \\
\text{OH}
\end{align*}
\]

Reagents and conditions: (a) SeO$_2$ (1.4 equiv.), p-dioxane:H$_2$O (30:1), reflux, 4 h, 44\%.
Upon shaking the crude product in a mixture of dichloromethane and water, the glyoxal hydrated readily and precipitated as an off-white crystalline mass, which was then treated with activated charcoal in order to remove colloidal selenium species and was then recrystallized from boiling water. This reaction was performed on a relatively large (27 g) scale and the pure product was obtained in 44% yield. Examination of the $^1$H NMR spectrum (MeOH-d$_4$) of this material revealed that the glyoxal was completely hydrated. No resonances above $\delta = 8.0$ ppm were observed. The two equivalent hydroxyl proton resonances were observed as a 2H doublet ($\delta = 6.87$ ppm) and the $CH(OH)_{2}$ proton resonance was observed as a 1H triplet ($\delta = 5.62$ ppm). These protons were coupled with a coupling constant of 7.1 Hz.

The substituted glyoxal 284 was then used in the Weiss-Cook condensation reaction (Scheme 81). Treatment of an aqueous solution of this glyoxal with dimethyl 1,3-acetonedicarboxylate 233 in the presence of sodium bicarbonate afforded, after 2 days of stirring at room temperature, an orange resinous precipitate assumed to be the tetraester intermediate 285. In contrast with the analogous reaction employing the parent glyoxal (c.f. Section 2.2), this intermediate did not precipitate as a crystalline solid. A small amount of methanol was added in order to solubilize this resin, and stirring was continued for a further 2 days, after which time the reaction mixture had reached a steady state by TLC. The water and methanol were then removed in vacuo and the orange resinous tetraester 285 was directly subjected to the ester hydrolysis/decarboxylation reaction. This intermediate, unlike the tetraester 234,
was incompletely soluble in hot 1 M aqueous hydrochloric acid solution, and the addition of glacial acetic acid was necessary in order to achieve homogeneity. The ester hydrolysis/decarboxylation reaction was complete after 2.5 h at reflux.

Scheme 81 - Synthesis of 1-(4'-bromophenyl)-cis-bicyclo[3.3.0]octan-3,7-dione (282)

![Scheme 81 - Synthesis of 1-(4'-bromophenyl)-cis-bicyclo[3.3.0]octan-3,7-dione (282)](image)

Reagents and conditions: (a) NaHCO₃, MeOH:H₂O, rt, 4 days; (b) aq. HCl, AcOH, reflux, 2.5 h, 27% over two steps.

The crude material from the decarboxylation step was purified by flash chromatography followed by recrystallization from ether/hexanes to afford the desired bicyclo[3.3.0]octane derivative 282 in 27% yield over two steps. While the yield was lower than that obtained for the unsubstituted analogue 232, the C-1 quaternary centre (which would become the eventual C-1 and C-10 substituents in the corresponding triquinacene derivatives) was efficiently installed by this approach. Moreover, this process could be carried out on a 10 g scale without any decrease in yield.

In light of the presence of two symmetry-equivalent ketone moieties in the dione 282, as was the case with the unsubstituted system (c.f. Section 2.2), protection of one of these carbonyl groups was required. If both groups were left
unprotected, the subsequent enolate alkylation reaction could lead to undesired *bis*-alkylation products. Hence, the dione 282 was protected with neopentyl glycol (1 equiv.) to afford a mixture of the desired monoacetal 286, the *bis*-acetal 287 and the dione starting material 282 (Scheme 82).

*Scheme 82 - Synthesis of the monoacetal (286)*

Reagents and conditions: (a) neopentyl glycol (1 equiv.), *p*-TsOH (cat.), PhH, reflux, Dean-Stark apparatus, 16 h.

The ratio of products obtained (282:286:287 = 23:48:29) was close to the expected statistical ratio of 25:50:25. The three compounds were separable by flash chromatography. Moreover, after separation, further quantities of the desired monoacetal 286 were available from the dione 282 and the *bis*-acetal 287 by heating these derivatives in benzene under acid catalysis.
3.3 Alkylation and Oxidative Cleavage

The next task was the introduction of the allyl moiety necessary for the elaboration of the third five-membered ring of triquinacene. In this system, the formation of both of the regioisomeric enolates 288 and 289, corresponding to proton abstraction at either C-2 or C-4, was expected (Scheme 83). If this were the case, the synthetic route would diverge at this step. The alkylation products of the enolate 288 would be suitable for conversion to 10-(4'-bromophenyl)triquinacene 281 whereas those of the enolate 289 could be transformed into the 1-substituted triquinacene derivative 280.

Scheme 83 - Formation of the regioisomeric enolates (288) and (289)

In order to probe the regioselectivity of the enolate formation and trapping process, the monoacetal 282 was deprotonated with 1.1 equiv. of LDA at -78 °C
for 30 min and reacted with $t$-butyldimethylsilyl chloride. This afforded an inseparable mixture of the enol silanes 290 and 291 (Scheme 84).

**Scheme 84 - Synthesis of the enol silanes (290) and (291)**

![Diagram of Scheme 84](image)

Reagents and conditions: (a) LDA (1.1 equiv.), THF, -78 °C, 30 min, then TBSCI (3 equiv.), -78 °C to rt, 2.5 h, 70% (290:291 = 3:2).

The ratio of the regioisomeric products 290 and 291 was determined by inspection of the $^1$H NMR spectrum of the crude reaction mixture (Figure 14). In the case of the enol silane 290, the C-2 vinylic proton resonance appeared as a singlet at $\delta = 4.83$ ppm. The C-4 vinylic proton resonance of the regioisomer 291 appeared as a broadened doublet ($J = 2.9$ Hz) at $\delta = 4.74$ ppm. This splitting was attributed to coupling between H-4 and the bridgehead methine proton (H-5). The poorly resolved “shoulders” of this doublet were likely due to long-range coupling. Molecular modeling predicted a dihedral angle of $\sim 70^\circ$ between these two nuclei and the small magnitude of the vicinal coupling constant was consistent with the Karplus correlation.\(^{169}\) On the other hand, such coupling was absent in the major diastereomer 290. The ratio of 290:291 = 3:2 was determined by integration of the above signals.
Figure 14 - Detail from the $^1$H NMR spectrum (CDCl$_3$, 400 MHz) of the TBS derivatives (290) and (291)

Treatment of the monoacetal 282 with 1.1 equiv. of LDA, followed by excess allyl bromide in the presence of HMPA, led to the formation of a complex mixture of products (Scheme 85). Separation of this mixture by flash chromatography first afforded the two regioisomeric allyl enol ethers 292 and 293. These products of O-allylation were contaminated with some non-polar impurities. Thus, this material was subjected to the Claisen rearrangement reaction conditions (vide infra). Secondly, the epimeric pairs of the regioisomeric ketones 294 and 295 (13%) were eluted from the column. Although this mixture,
as a whole, was analytically pure, these four C-allyl isomers were chromatographically inseparable and were carried through the next few steps as a mixture. Finally, a significant amount of pure unreacted monoacetal starting material 282 (28%) was recovered and resubjected to the same reaction conditions in order to obtain further quantities of allylated products.

**Scheme 85 - Enolization and allylation of the monoacetal (282)**

![Chemical diagram]

Reagents and conditions: (a) LDA, THF, -78 °C, 1 h, then allyl bromide (5 equiv.), THF/HMPA, -78 °C to rt, 16 h, 68% (96% BRSM)

The Claisen rearrangement reaction of the impure allyl enol ethers 292 and 293 proceeded smoothly to afford after 3 days at reflux in toluene the C-allyl ketones 294 and 295, which were easily separated from the non-polar impurities produced in the enolization/allylation reaction (Scheme 86). Overall, a 68% yield (96% based on recovered starting material) of the requisite C-allyl ketones 294 and 295 was achieved through the allylation and subsequent Claisen rearrangement reactions. No diallylation products were observed. As was the
case in the conjugate addition route, O-allylation was favoured over C-allylation, with the former predominating by a ratio of 4:1.

**Scheme 86 - Claisen rearrangement reaction of the allyl enol ethers (292) and (293)**

Reagents and conditions: (a) PhMe, reflux, 3 days (for yield, see text).

In preparation for closure of the third five-membered ring of the triquinacene ring system, the mixture of C-allyl ketones 294 and 295 was subjected to the Lemieux oxidative cleavage reaction (Scheme 87).

Attempts at performing this transformation by an ozonolysis reaction were unsuccessful and led to extensive decomposition of the starting material. However, treatment with a catalytic amount of osmium tetroxide and excess sodium periodate afforded the epimeric pairs of the aldehydes 296 and 297, as an inseparable mixture, in 63% yield.
Scheme 87 - Synthesis of the aldehydes (296) and (297)

![Scheme 87](image)

Reagents and conditions: (a) OsO₄ (cat.), NaIO₄ (2.5 equiv.), p-dioxane:H₂O (10:7), rt, 6.5 h, 63%.

The mixture of the isomeric aldehydes 296 and 297 was rendered analytically pure by flash chromatography. These aldehydes were not found to be appreciably hydrated by ¹H NMR analysis.

3.4 Aldol Condensation and Separation of Regioisomers

Having obtained the aldehydes 296 and 297, the next step of the synthetic route was to effect an acid-catalyzed acetal hydrolysis/aldol condensation sequence. This sequence, which elaborated the third five-membered ring of the triquinacene ring system, had precedence in the conjugate addition route (c.f. Section 2.5) and the initial reaction conditions chosen were those which had been successfully employed in the phenyl-substituted system.
In a small-scale attempt to effect the acetal hydrolysis/aldol condensation sequence, a solution of the aldehydes 296 and 297 in reagent grade acetone was treated with a catalytic amount of p-toluenesulfonic acid. After stirring at room temperature for 6 days followed by purification by flash chromatography, the major products were the epimeric tricyclic hydroxy acetals 298 (47%). Traces of other isomeric products were detected in the $^1$H NMR spectrum of the crude reaction mixture, but were not characterized at this stage owing to the small amount of material at hand. Multiple recrystallizations of this major product from hexanes/ether afforded a single C-5 epimer of the acetal 298 as colourless needles.

Scheme 88 - Synthesis of 1-(4'-bromophenyl)tricyclo[5.2.1.0$^{4,10}$]deca-3,8-dione-5-ol-3-(2',2'-dimethylpropyldiene acetal) (298)

![Scheme 88](image)

Reagents and conditions: (a) p-TsOH (cat.), reagent grade acetone, rt, 6 days, 47%
The structure of the single epimer obtained by recrystallization was used to determine the structure of the acetal 298 by means of a series of 2-D NMR experiments. This characterization was necessary as the $^1$H and $^{13}$C NMR spectra alone did not allow for the acetal 298 to be distinguished from its 10-(4'-bromophenyl) regioisomer.

Figure 15 - Detail from the $^1$H-$^1$H COSY (CDCl$_3$, 400 MHz) spectrum of the tricyclic acetal (298)

The structure determination began with the assignment of H-5 to the resonance at $\delta = 4.62$ ppm. This signal was diagnostic as it was well-removed from the other resonances on account of the hydroxyl group. The COSY spectrum revealed coupling of H-5 to both H-6 and H-6', each of which in turn
was coupled to the bridgehead methine proton H-7. This allowed for the key structural determination to be performed, as coupling of H-7 to the centro proton H-10 was observed, along with a coupling between H-10 and the H-4 bridgehead methine proton at the other end of the ring system. Further evidence in support of this structural assignment included the absence of any resonances attributable to H-1 as well as the lack of any coupling other than the geminal coupling with a coupling constant of 18.9 Hz, observed for the signals corresponding to H-9 and H-9' (i.e. no coupling with H-1 was detected).

This assignment was consistent with the corresponding HMQC spectrum (Figure 16), in which the carbon resonances for the bridgehead carbons C-4 and C-7 were assigned to the signals at \( \delta = 42.9 \) and 50.5 ppm, respectively. The signal corresponding to the C-1 quaternary centre was observed at \( \delta = 49.0 \) ppm. Finally, the centro (C-10) carbon was assigned to the resonance appearing at \( \delta = 49.7 \) ppm.
Having determined the structure of the tricyclic acetal 298, the acetal moiety was hydrolyzed by heating a solution of this compound for 1 h at reflux in a mixture of p-dioxane and aqueous hydrochloric acid (2:1) (Scheme 89). Of note, attempts to employ the acetal hydrolysis reaction conditions (p-TsOH (cat.), acetone:H₂O (2:1), rt) which had been successful in the conjugate addition route (c.f. Section 2.5) failed in this instance to effect the desired transformation, even after 5 days of stirring at room temperature. Under these more vigorous hydrolysis conditions, the diketo alcohol 280 was obtained in 80% yield.
Scheme 89 - Synthesis of 1-(4'-bromophenyl)tricyclo[5.2.1.0^{5,8}]deca-3,8-dione-5-ol (280)

Reagents and conditions: (a) p-dioxane:2 M aq. HCl (2:1), reflux, 1 h, 80%.

This material was obtained as a 3:2 mixture of C-5 epimers, as determined by integration of the H-5 resonances in the $^1$H NMR spectrum at $\delta = 4.50$-4.55 for the major diastereomer and at $\delta = 4.56$-4.62 for the minor isomer. The relatively small amount of material obtained in this experiment was fully characterized in order to provide a reference sample for a subsequent reaction.

Subjection of the mixture of aldehydes 296 and 297 to conditions suitable for aldol condensation, followed by heating the crude products from this step in a mixture of p-dioxane and aqueous hydrochloric acid, afforded the desired regioisomeric tricyclic diketo alcohols 280 (40%) and 281 (35%) (Scheme 90).
Scheme 90 - Synthesis of the regioisomeric diketo alcohols (280) and (281)

Reagents and conditions: (a) p-TsOH (cat.), reagent grade acetone, rt, 4 days; (b) p-dioxane : 2 M aq. HCl (2:1), reflux, 1 h.

Since these two regioisomers were readily separable by flash chromatography, this stage was chosen for the separation of the 1-(4'-bromophenyl) series from the 10-(4'-bromophenyl) regiosomers. These isomers had been carried through and characterized as mixtures from the alkylation reaction step. The 1-(4'-bromophenyl) isomer 280 obtained in this step had physical and spectral properties identical to those of the material obtained in the earlier small-scale trial. The 10-(4'-bromophenyl) compound 281 was initially obtained as a mixture of C-5 epimers. Recrystallization of a sample of this material from ether/dichloromethane/hexanes yielded a single epimer, which was
extensively characterized using, *inter alia*, COSY, HMQC and NOESY experiments.

Figure 17 - Detail from the $^1$H-$^1$H COSY spectrum (CDCl$_3$, 400 MHz) of the tricyclic diketo alcohol (281)

The COSY spectrum (Figure 17) of this isomer was consistent with the structural assignment. Coupling was observed between the diagnostic H-5 proton at $\delta = 4.20$ ppm and both H-6 and H-6', as well as with the bridgehead methine proton, H-4. Furthermore, correlations of both H-6 and H-6' with bridgehead methine proton H-7 were detected. Long-range correlations between both H-4 and H-7 to H-1 were observed; however, no such interaction between
H-4 and H-7 was noticed on account of the intervening quaternary centre at C-10. Geminal couplings between H-2 and H-2' as well as between H-9 and H-9' were also observed.

Figure 18 - Detail from the HMQC spectrum (CDCl₃) of the tricyclic diketo alcohol (281)

In the HMQC spectrum of the isomer 281 (Figure 18), the quaternary carbon resonance for C-10 was observed at δ = 52.5 ppm. The bridgehead methine carbon resonances for C-1, C-4 and C-7 were assigned to the signals at δ = 43.7, 61.0 and 50.7 ppm, respectively. Finally, the methylene carbons C-2, C-6 and C-9 were observed at δ = 48.4, 31.6 and 37.9 ppm.
Although both C-5 epimers of the tricyclic diketo alcohol 281 were formed from the aldehyde 296, a single diastereomer was isolated by recrystallization. As the above COSY and HQMC spectra permitted the assignment of each proton and carbon resonance, the configuration at C-5 for this epimer could be determined in this instance. On the basis of the NOESY spectrum of this material, it was determined that the 5α-OH epimer had been isolated. NOE contacts were observed between H-5 and H-7, as well as between H-7 and the (coincident) aryl protons H-12 and H-16 (Figure 19). Moreover, contacts were observed between H-5 and H-2', H-2' and H-9' as well as between H-9' and the H-12/H-16 aryl protons. As these protons all lie on the convex (β) face of the triquinacene ring system, the C-5 hydroxyl group lies on the concave (α) face.

Figure 19 - Contacts observed in the NOESY spectrum of the tricyclic diketo alcohol epimer (281)

3.5 Completion of Syntheses

Having achieved the separation and characterization of the two regioisomeric tricyclic diketo alcohols 280 and 281, these compounds were separately converted to their corresponding triquinacene derivatives. The
approach chosen was analogous to that employed in the conjugate addition route (i.e. reduction of the diketo alcohols to their corresponding triols, activation of the triols to the trimesylates followed by elimination to install the three double bonds).\textsuperscript{41,47}

3.5.1 1-(4'-Bromophenyl)triquinacene (278)

Reduction of the tricyclic diketo alcohol 280 with excess borane-tetrahydrofuran complex proceeded smoothly (Scheme 91). The IR spectrum of the crude triols 299 showed no carbonyl C=O absorptions and this material was carried on to the next step without further purification. Activation of the three hydroxyl groups of the triols 299 as their corresponding mesylates was accomplished with methanesulfonyl chloride and triethylamine in dichloromethane. The IR spectrum of the trimesylates 300 showed no O-H stretching absorptions and was, without further purification, dissolved in dichloromethane and stirred for 5 days at room temperature in the presence of highly activated neutral alumina. This procedure afforded 1-(4'-bromophenyl)triquinacene 278 in 38% yield over these three steps.
Scheme 91 - Synthesis of 1-(4'-bromophenyl)triquinacene (278)

Reagents and conditions: (a) BH$_3$ •THF, THF, 0 °C to rt, 15 h; (b) MsCl, NEt$_3$, DCM, 0 °C to rt, 50 min.; (c) activated neutral Al$_2$O$_3$, DCM, rt, 5 days, 38% over three steps.

This triquinacene derivative was obtained as a waxy colourless amorphous solid and was purified by flash chromatography on silica gel using hexanes as eluant ($R_t = 0.50$). Although material of good purity (> 90% by $^1$H NMR) was obtained, this compound co-eluted with some non-polar impurities from which it could not be separated. However, a satisfactory high-resolution mass spectral analysis was obtained.
In the $^1$H NMR spectrum of the triquinacene derivative 278 (Figure 20), the centro proton (H-10) was observed as an apparent triplet (coupled to both H-4 and H-7) at $\delta = 3.46$ ppm. The bridgehead methine protons H-4 and H-7, in turn, were observed as an apparent doublet of triplets at $\delta = 3.87$ ppm. Here, analysis of the coupling constants showed that the signal was split into a doublet by H-10 and thereafter into an apparent triplet by each of two neighbouring alkene protons. The six alkene protons appeared as three distinct resonances, each integrating to two protons. Analysis of the COSY and HMQC spectra of this compound suggested that the slightly broadened singlet at $\delta = 5.67$ ppm was due to H-2 and H-9, which are only coupled to H-3 and H-8, respectively.
magnitude of this small (~1 Hz) coupling constant could not be determined accurately. The other two alkene resonances (due to H-3, H-5, H-6 and H-8) both appeared as doublets of doublets at $\delta = 5.71$ and $\delta = 5.80$ ppm. Each signal was split into a doublet by its neighbouring alkene proton and was then further split by long-range interactions. Finally, the H-13 and H-15 aryl protons were observed at $\delta = 7.14$ ppm, whereas the resonance corresponding to H-12 and H-16 was seen at $\delta = 7.42$ ppm.

The $^{13}$C NMR spectrum of this derivative (Figure 21) contained a signal at $\delta = 57.7$ ppm which corresponded to the bridgehead carbons C-4 and C-7, and the centro (C-10) carbon was assigned to the resonance at $\delta = 58.9$ ppm. The quaternary C-1 resonance appeared at $\delta = 71.1$ ppm. The alkene carbon signals were seen at $\delta = 132.3, 133.4$ and $134.9$ ppm, whereas the aryl resonances appeared at $\delta = 119.9, 128.0, 131.3$ and $147.0$ ppm.
The corresponding 10-(4'-bromophenyl) triquinacene derivative was elaborated by the same series of functional group interconversion reactions from the tricyclic diketo alcohol 281 (Scheme 92). This derivative was obtained in a 38% overall yield following Lewis acid-mediated reduction with borane-tetrahydrofuran complex, activation with methanesulfonyl chloride and subsequent elimination with activated neutral alumina.
Reagents and conditions: (a) BH₃•THF, THF, 0 °C to rt, 16 h; (b) MsCl, NEt₃, DCM, 0 °C to rt, 1 h; (c) activated neutral Al₂O₃, DCM, rt, 4 days, 38% over three steps.

This derivative, like the 1-substituted homologue 278, was obtained as a colourless, waxy amorphous solid. The compound was purified by flash chromatography using hexanes as eluant (Rₛ = 0.30), and was obtained along with a small amount of non-polar impurities. A satisfactory high-resolution mass spectral analysis was obtained.

The ¹H NMR spectrum of this compound was, in light of its C₃ symmetry, much simpler than that of the 1-substituted isomer 278. The resonance attributable to the three bridgehead methine protons H-1, H-4 and H-7 was observed as a singlet at δ = 3.80 ppm. The signal for the six alkene protons appeared at δ = 5.69 ppm and the two sets of aryl proton resonances were observed as doublets at δ = 7.17 and 7.44 ppm.
Likewise, the $^{13}$C NMR spectrum of 10-(4'-bromophenyltriquinacene) 279 was consistent with the assigned structure (Figure 23). The bridgehead carbon resonances (C-1, C-4 and C-7) were observed at $\delta = 65.9$ ppm, while that corresponding to the quaternary centro carbon (C-10) was seen at $\delta = 68.5$ ppm. The signal for the six symmetry-equivalent alkene carbons was observed at $\delta = 132.3$ ppm, while the four aryl carbon resonances appeared at $\delta = 119.6$, 126.9, 131.8 and 148.5 ppm.
Figure 23 - Detail from the $^{13}$C NMR spectrum (CDCl$_3$, 101 MHz) of 10-(4'-bromophenyltriquinacene) (279)

The conversions of the regioisomeric triquinacene derivatives 278 and 279 to their corresponding benzoic acid derivatives 303 and 304 using Suzuki coupling methodology were also attempted (Scheme 93).\textsuperscript{170} Heating each of the triquinacene derivatives 278 and 279 with excess 4-carboxyphenylboronic acid and sodium carbonate along with catalytic amounts of palladium (II) acetate and triphenylphosphine in aqueous $n$-propanol in both cases afforded complex mixtures of products.
Scheme 93 - Attempted Suzuki coupling reactions of the triquinacenes (278) and (279)

Reagents and conditions: (a) p-B(OH)_2C_6H_4CO_2H (2.5 equiv.), Pd(OAc)_2 (cat.), PPh_3 (cat.), 2 M aq. Na_2CO_3 (10 equiv.), n-PrOH:H_2O (5:1), reflux, 1 h.

Although the reaction conditions employed had been reported to effect the cross-coupling reactions between 4-carboxyphenylboronic acid and p-bromobenzaldehyde as well as o-chloroanisole, in neither case could the desired benzoic acid derivatives 303 and 304 be isolated from the complex mixture obtained.\textsuperscript{171}

3.6 Summary and Conclusions

The p-bromophenyl substituent was successfully incorporated into the bicyclo[3.3.0]octa-3,7-dione framework by the use of p-bromophenylglyoxal 284 in the Weiss-Cook condensation reaction with the keto diester 233 (Scheme 94). The resultant dione 282 was desymmetrized by monoprotection of one of its ketone moieties to afford the corresponding 2,2-dimethylpropylidene acetal 286.
Scheme 94 - Overview of the synthesis of the monoacetal (286)

Reagents and conditions: (a) SeO₂ (1.4 equiv.), p-dioxane:H₂O (30:1), reflux, 4 h, 44%; (b) NaHCO₃, MeOH:H₂O, rt, 4 days; (c) aq. HCl, AcOH, reflux, 2.5 h, 27% over two steps; (d) neopentyl glycol (1 equiv.), p-TsOH (cat.), PhH, reflux, Dean-Stark apparatus, 16 h, 52%.

Treatment of the monoacetal 286 with LDA followed by allyl bromide afforded a mixture of the C-2 and C-4 allylated ketones 294 and 295, along with the corresponding O-allylation products 292 and 293 (Scheme 95). The latter pair of compounds were converted to their C-allylated isomers by means of a Claisen rearrangement reaction. The two regioisomeric series were carried through the oxidative cleavage, acetal hydrolysis and aldol condensation steps as a mixture. At the tricyclic diketo alcohol stage, the two triquinacene derivative precursors were separated by flash chromatography.
Scheme 95 - Overview of the synthesis of the tricyclic diketo alcohols (280) and (281)

Reagents and conditions: (a) LDA, THF, -78 °C, 1 h, then allyl bromide, THF/HMPA, -78 °C to rt, 16 h; (b) PhMe, reflux, 3 days, 68% (96% BRSM) over two steps; (c) OsO₄ (cat.), NaIO₄ (2.5 equiv.), p-dioxane:H₂O (10:7), rt, 6.5 h, 63%; (d) p-TsOH (cat.), reagent grade acetone, rt, 4 days; (e) p-dioxane : 2 M aq. HCl (2:1), reflux, 1 h, 40% (280) + 35% (281).
1-(4'-bromophenyl)triquinacene 278 and 10-(4'-bromophenyl)triquinacene 279 were elaborated from the tricyclic diketo alcohols 280 and 281, respectively, through a series of functional group interconversion reactions (Scheme 96).

Scheme 96 - Overview of the synthesis of 1-(4'-bromophenyl)triquinacene (278) and 10-(4'-bromophenyl)triquinacene (279)

Reagents and conditions: (a) BH₃ • THF, THF, 0 °C to rt, 15 h; (b) MsCl, NEt₃, DCM, 0 °C to rt, 50 min; (c) activated neutral Al₂O₃, DCM, rt, 5 days, 38% over three steps; (d) BH₃ • THF, THF, 0 °C to rt, 16 h; (e) MsCl, NEt₃, DCM, 0 °C to rt, 1 h; (f) activated neutral Al₂O₃, DCM, rt, 4 days, 38% over three steps.

These triquinacene derivatives were each prepared in 2% yield over thirteen steps from commercially-available p-bromoacetophenone 283 and 1,3-
dimethylacetone dicarboxylate 233. The attempted conversion of these derivatives to their corresponding benzoic acid derivatives 303 and 304 via Suzuki coupling methodology was unsuccessful.

Unlike the conjugate addition route presented in Chapter 2, the substituted glyoxal approach was not regioselective in that 1-substituted triquinacene derivatives were also obtained. However, with the early introduction of the centro-substituent, a greater range of centro-substituents may in principle be installed by this approach, as one is not limited to species capable of forming stable, yet sufficiently reactive, organocuprate reagents. Moreover, this route has also allowed for the synthesis of a novel C-1-substituted triquinacene derivative.
CHAPTER FOUR: RESULTS AND DISCUSSION - SUBSTITUTED GLYOXAL ROUTE II (HYDROXYMETHYL DERIVATIVES)

4.1 Overview and Retrosynthetic Analysis

In this chapter, the second implementation of the substituted glyoxal route (c.f. Chapter 3) is presented. In this case, the target compounds were the regioisomeric 1- and 10-(hydroxymethyl)triquinacenes 308 and 265. These substituted triquinacene derivatives are of interest in connection with the proposed structural and dimerization studies as well as the approach to the triquinacene dimerization problem outlined in the Introduction (c.f. Section 1.8.1).

The hydroxymethyl substituent was chosen in light of the diverse range of derivatives which could be accessed from the triquinacene derivatives 265 and 308 by means of functional group interconversion reactions. For instance, 10-(hydroxymethyl)triquinacene 265 could, upon oxidation of its primary alcohol moiety, afford triquinacene-10-carboxylic acid 226, a derivative of interest for the dimerization studies (Figure 24). Moreover, radical decarboxylation of this carboxylic acid in the presence of bromotrichloromethane would then afford 10-bromotriquinacene 218, from which the C-10-centred triquinacetyl radical 219 and anion 221 could be prepared. Also, conversion of 10-bromotriquinacene 218 to 10-hydroxytriquinacene 306 would allow for the preparation of the corresponding triquinacetyl cation 224 via the tosylate 307. Other derivatives of interest for the dimerization studies, such as 10-aminotriquinacene 305, could
also be accessed through functional group interconversion reactions. This route
would also be expected to afford the 1-substituted analogues of these
derivatives.

Figure 24 - Potential functional group interconversion reactions of (hydroxy-
methyl)triquinacene derivatives

Retrosynthetic analyses of the hydroxymethyl triquinacene derivatives 265
and 308 are presented below (Scheme 97).
The retrosynthetic analysis of the hydroxymethyl triquinacene derivatives 265 and 308 closely resembled that of the 1- and 10-(4'-bromophenyl)triquinacenes 278 and 279 (c.f. Section 3.1). cis-1-(Methoxymethyl)bicyclo[3.3.0]octan-3,7-dione 311 could be obtained by the Weiss-Cook condensation reaction between hydroxypyruvaldehyde 312 and two equivalents of 1,3-dimethylacetone dicarboxylate 233, followed by protection of the angular hydroxymethyl group as its corresponding methyl ether. Monoprotection of one of the carbonyl groups of the dione 311 followed by enolate formation, alkylation with allyl bromide in THF/HMPA and Claisen rearrangement would then afford the regioisomeric 2- and 4-allyl analogues of the dione 311. Oxidative cleavage of the allyl moieties followed by acid-catalyzed acetal hydrolysis and aldol condensation would lead to the tricyclic diketo alcohols 309 and 310. In turn, these alcohols would be converted into their corresponding triquinacene derivatives by reduction with borane-
tetrahydrofuran complex, activation of the resultant triols with methanesulfonyl chloride and three-fold elimination of the mesylate moieties by stirring with activated alumina. The 1- and 10-(hydroxymethyl)triquinacenes 308 and 265 could then be obtained by deprotection of the primary alcohol function with, for instance, boron tribromide, which has been shown to cleave methyl ethers in the presence of alkenes without affecting the latter moieties.¹⁷³

4.2 Weiss-Cook Condensation

4.2.1 Preparation of hydroxypyruvaldehyde (312)

The first task in this synthetic route was the preparation of hydroxypyruvaldehyde 312, which would serve as the 1,2-dicarbonyl component in the subsequent Weiss-Cook condensation reaction. This substituted glyoxal was reported by Evans and Waring to exist in the solid state as a trimer which, in aqueous solution, reverted slowly to its monomer.¹⁷⁴ As no attempt to employ the substituted glyoxal 312 in a Weiss-Cook condensation reaction had been reported, it was hoped that not only would it be sufficiently reactive to undergo the aforementioned condensation reaction but also that the monomeric form of this compound would be present in sufficient concentrations to allow the reaction to proceed at an appreciable rate.

The approach chosen for the preparation of hydroxypyruvaldehyde 312 was a modification of a literature method.¹⁷⁴ Oxidation of dihydroxyacetone 313 (which exists in the solid state as a dimer) with cupric acetate was performed in aqueous solution at room temperature. After removal of excess cupric ion as
cupric oxalate by treatment with an aqueous solution of oxalic acid and filtration through diatomaceous earth, the resultant blue-green solution was concentrated to near dryness. The residue was dissolved in ethanol and concentrated to dryness, then dissolved again in ethanol. Upon adding ether, hydroxypyruvaldehyde 312 precipitated as its trimeric ethanolate.

Scheme 98 - Synthesis of hydroxypyruvaldehyde (312)

Reagents and conditions: (a) Cu(OAc)$_2$, H$_2$O, rt, 6 days, 94%.

After drying in vacuo, the trimeric ethanolate of aldehyde 312 was obtained as an amorphous pale yellow solid in very high yield. This compound could not be fully characterized by $^1$H NMR on account of the tendency of the trimer to partially and reversibly dissociate in solution. However, the spectra were free of resonances attributable to the dihydroxyacetone starting material 313. The material was used in the following step without further purification.

4.2.2 Weiss-Cook condensation reactions of hydroxypyruvaldehyde

The condensation reaction between hydroxypyruvaldehyde 312 and two equivalents of 1,3-dimethylacetone dicarboxylate 233 reached a steady state (by TLC) after 4 days at room temperature (Scheme 99). Unlike the analogous reaction with $p$-bromophenylglyoxal 284 (c.f. Section 3.2), the reaction mixture was nearly homogeneous and only a small amount of a red-brown resinous
precipitate had formed toward the end of the reaction. After removal of most of the water, the corresponding crude tetraester intermediate was obtained as an orange-red oil. This oil was only sparingly soluble in hot 1 M aqueous hydrochloric acid and the addition of glacial acetic acid was required for its complete dissolution. The ester hydrolysis/decarboxylation reaction was complete after 4 h at reflux.

Scheme 99 - Synthesis of cis-1-(hydroxymethyl)bicyclo[3.3.0]octan-3,7-dione (314) and cis-1-(acetoxymethyl)bicyclo[3.3.0]octan-3,7-dione (315)

Reagents and conditions: (a) NaHCO₃, H₂O, rt, 4 days; (b) 1 M aq. HCl:AcOH (3:1), reflux, 4 h, 18% (314) and 10% (315) over two steps; (c) LiOH, THF:H₂O (3:1), rt, 40 min, 97%.

This two-step procedure afforded the hydroxydione 314 (18%) as well as the acetylated dione 315 (10%) from the Weiss-Cook precursors 233 and 312. The acetylated dione 315 was presumably formed from the hydroxydione 314 during the ester hydrolysis/decarboxylation by condensation of the hydroxydione's angular hydroxymethyl group with the acetic acid co-solvent. However, it was possible to convert this compound to the hydroxydione 314 on hydrolysis of the acetate moiety under basic conditions.
The Weiss-Cook condensation reaction depicted above was repeated without the acetic acid co-solvent (Scheme 100). Although complete dissolution of the impure tetraester intermediate in aqueous hydrochloric acid was not observed in this case, the vast majority of this material dissolved over the course of the reaction. The decarboxylation reaction was complete after 3 h at reflux and the hydroxydione 314 was obtained as the sole product in 19% yield.

Scheme 100 - Synthesis of cis-1-(hydroxymethyl)bicyclo[3.3.0]octan-3,7-dione (314)

Reagents and conditions: (a) NaHCO₃, H₂O, 6 days, rt; (b) 1 M aq. HCl, reflux, 3 h, 19%.

This Weiss-Cook reaction was novel in that it was the first instance that an angular hydroxymethyl group has been introduced into a diquinane framework by this method. Furthermore, the presence of a hydroxyl substituent on the 1,2-dicarbonyl component did not seem to impede the progress of the reaction and the yield was comparable to that obtained with p-bromophenylglyoxal 284. Even though hydroxypyrvaldehyde 312 was originally isolated as its trimer, both the rate and the extent of the trimer’s dissociation under the Weiss-Cook reaction conditions were sufficient to allow the desired condensation reaction to occur.
4.3 Protection of the Angular Hydroxymethyl Group and Desymmetrization

In order to facilitate the elaboration of the third five-membered ring of the triquinacene framework, protection of one of the ketone moieties and of the hydroxyl group of the hydroxymethyl dione 314 was required. By analogy with the syntheses presented in Chapters 2 and 3, it was envisaged that one of the carbonyl groups could be protected as the corresponding 2,2-dimethylpropylidene acetal. In view of the proposed synthetic route, the protecting group chosen for the primary alcohol needed to be stable to the reducing agent borane-tetrahydrofuran complex (which is also a mild Lewis acid), Brønsted acids (p-toluenesulfonic acid) as well as bases (LDA, triethylamine), electrophiles (methanesulfonyl chloride, allyl bromide) and oxidants (ozone or sodium periodate). Thus, protection of the hydroxyl group as its corresponding methyl ether was selected. This protecting group could be carried through the entire synthesis and removed once the triquinacene derivatives were in hand. In other words, (methoxymethyl)-substituted triquinacene derivatives would be prepared by this route and subsequently converted to the corresponding (hydroxymethyl)-substituted compounds.

4.3.1 Attempted protection of the hydroxyl group of the hydroxydione (314)

In a first instance, the installation of the methyl ether group prior to protection of the ketone moieties of the dione 314 was attempted. These experiments are summarized below (Table 9).
Scheme 101 - Attempted hydroxyl group protection of the hydroxydione (314)

Reagents and conditions: (a) see Table 9

Table 9 - Reaction conditions corresponding to Scheme 101

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaH, THF:DMF (5:3), 0 °C, 30 min, then Mel, 0 °C to rt, 16 h</td>
<td>extensive decomposition of dione 314 upon deprotonation</td>
</tr>
<tr>
<td>2</td>
<td>Me₂SO₄, NaOH, H₂O/DCM, n-Bu₄NI (5 mol %), rt, 3 h</td>
<td>reaction complete by TLC, extensive emulsification</td>
</tr>
<tr>
<td>3</td>
<td>Me₂SO₄, NaOH, H₂O/DCM, n-Bu₄NI (1 mol %), rt, 3 h</td>
<td>reaction complete by TLC, extensive emulsification</td>
</tr>
<tr>
<td>4</td>
<td>Me₂SO₄, K₂CO₃, acetone, 0 °C to rt</td>
<td>rapid and extensive decomposition of dione 314</td>
</tr>
<tr>
<td>5</td>
<td>KOH, Mel, DMSO, rt</td>
<td>rapid and extensive decomposition of dione 314</td>
</tr>
</tbody>
</table>

Subjection of the hydroxydione 314 to Williamson ether synthesis conditions led to rapid and extensive decomposition of the starting material upon treatment with sodium hydride (Entry 1). Formation of the methyl ether under phase-transfer conditions was also attempted (Entry 2). The reaction proceeded to completion (as determined by TLC analysis) without evidence of decomposition. However, upon work-up, extensive emulsification took place regardless of the choice of extraction solvent. Only trace amounts of the
methylated dione 311 could be obtained by this procedure. These practical
difficulties persisted even when the loading of the tetra-n-butylammonium iodide
phase transfer catalyst was dropped from 5 mol % to 1 mol % (Entry 3). This
approach, although apparently successful in forming the methylated dione 311,
was rendered impractical by the aforementioned emulsification and other
reaction conditions were sought. Treatment of the hydroxydione 314 with
dimethyl sulfate and potassium carbonate in acetone (Entry 4) rapidly led to
extensive decomposition of the starting material.177 Finally, treatment of the
hydroxydione 314 with potassium hydroxide and methyl iodide in DMSO (Entry 5)
also led to extensive decomposition of the starting material.178

4.3.2 Carbonyl group protection of the hydroxydione (314)

In light of the results presented in Table 9, protection of the carbonyl
groups was carried out prior to the installation of the methyl ether moiety.
Condensation of the hydroxydione 314 with neopentyl glycol (1 equiv.) in the
presence of a catalytic amount of p-toluenesulfonic acid at reflux in benzene was
attempted. However, these reaction conditions caused, after 2 h, extensive
decomposition of the starting material. This unexpected result was attributed to
the incompatibility of the hydroxydione 314 and the strongly acidic catalyst
employed. However, use of the far less acidic pyridinium p-toluenesulfonate,
under otherwise identical reaction conditions, afforded a mixture of the dione
314, the monoacetal 316 and the bis-acetal 317 (Scheme 102).
Scheme 102 - Synthesis of the hydroxymonoacetal (316) and hydroxybisacetal (317)

Reagents and conditions: (a) neopentyl glycol (1 equiv.), PPTS (cat.), PhH, reflux, Dean-Stark, 2 h.

With the monoacetal 316 in hand, installation of the methyl ether moiety was attempted. However, this transformation could not be realized under Williamson ether synthesis or phase-transfer conditions (c.f. Table 9, Entries 1-3). Again, decomposition of the starting material, monoacetal 316, arose on treatment with sodium hydride, and the phase-transfer conditions led to extensive emulsification. Hence, it was determined that protection of both carbonyl moieties would be required. Complete conversion of the hydroxydione 314 to the bis-acetal 317 was carried out by employing an excess (4 equiv.) of neopentyl glycol (Scheme 103).

Scheme 103 - Condensation of the hydroxydione (314) with excess neopentyl glycol

Reagents and conditions: (a) neopentyl glycol (4 equiv.), PPTS (cat.), PhH, reflux, Dean-Stark, 90 min, 95%.
This reaction afforded the bis-acetal 317 in excellent yield from the hydroxydione 314.

4.3.3  **Methylation of the bis-acetal (317)**

At this stage of the synthesis, with both carbonyl moieties protected, it was hoped that the installation of the methyl ether moiety would be more straightforward. Indeed, treatment of the bis-acetal 317 with sodium hydride in THF/DMF, followed by alkylation of the resultant alkoxide with methyl iodide, smoothly afforded the methoxymethyl derivative 318 (Scheme 104).

**Scheme 104 - Synthesis of cis-1-(methoxymethyl)bicyclo[3.3.0]octan-3,7-dione-3,7-bis-(2',2'-dimethylpropylidene) acetal (318)**

Reagents and conditions: (a) NaH, THF:DMF (5:3), 0 °C, 30 min, then Mel, 0 °C to rt, 17 h, 95%.

4.3.4  **Preparation of the (methoxymethyl)-monoacetal (319)**

In order to effect the conversion of the methylated bis-acetal 318 to the corresponding monoacetal 319 in preparation for the allylation step, two different strategies were employed. The first strategy involved a monodeprotection under hydrolytic reaction conditions whereas in the second approach, both acetal moieties were hydrolyzed and the resultant dione 311 was then condensed with neopentyl glycol (1 equiv.) to afford a mixture of the dione 311, the bis-acetal 318 and the monoacetal 319.
Heating a solution of the bis-acetal 318 in a mixture of benzene and water (100:1) at reflux with PPTS catalysis afforded the desired monoacetal 319 in moderate yield (Scheme 105). The balance of the crude reaction material consisted primarily of recovered bis-acetal 318 along with a small amount of the corresponding dione 311. These three compounds were readily separable by flash chromatography and further amounts of the monoacetal 319 could be obtained from the recovered starting material under identical reaction conditions.

Scheme 105 - Monodeprotection of the methylated bis-acetal (318)

Reagents and conditions: (a) PPTS (cat.), PhH:H₂O (100:1), reflux, 17 h

In the second approach, a solution of the bis-acetal 318 in a mixture of THF and 1 M aqueous hydrochloric acid (2:1) was stirred for 4 h at room temperature to afford the methylated dione 311 in nearly quantitative yield (Scheme 106). Condensation of this dione with neopentyl glycol (1 equiv.) afforded a mixture of the recovered dione 311, the desired monoacetal 319 as well as the corresponding bis-acetal 318 (26:30:44). As was the case with the p-bromophenyl series (c.f. Section 3.2), the dione and bis-acetal could again be recovered and converted to further quantities of the monoacetal 319.
**Scheme 106 - Synthesis of the monoacetal (319) by total deprotection/monoprotection**

![Chemical structure](image)

Reagents and conditions: (a) THF:1 M aq. HCl (2:1), rt, 4 h, 98%; (b) neopentyl glycol (1 equiv.), PPTS (cat.), PhH, reflux, Dean-Stark, 5.5 h

4.4 Allylation and Oxidative Cleavage

After preparing multi-gram quantities of the monoacetal 319, the next task consisted of alkylation of this compound with allyl bromide. Conditions identical to those employed in the analogous reaction in the p-bromophenyl series (c.f. Section 3.3) were chosen. Of particular interest were what effects, if any, the replacement of a p-bromophenyl substituent for a methoxymethyl substituent at C-1 would have on: (a) the overall yield of the reaction; (b) the ratio of O-allylation to C-allylation and (c) the regioselectivity (C-2 vs. C-4) of the alkylation reaction.

Deprotonation of the monoacetal 319 with LDA followed by alkylation with excess allyl bromide in the presence of HMPA afforded, in 79% yield, a mixture of the regioisomeric allyl enol ethers 320 and 321 as well as the regioisomeric C-2 and C-4 allylated ketones 322 and 323 (Scheme 107).
**Scheme 107 - Alkylation of the monoacetal (319)**

Reagents and conditions: (a) LDA, THF, -78 °C, 30 min, then allyl bromide, HMPA/THF, -78 °C to rt, 16 h, 79% (97% BRSM).

Several significant differences in the outcome of this reaction as compared to the analogous reaction in the p-bromophenyl series were apparent. The overall yield in the allylated products 320, 321, 322 and 323 of 79% (97% BRSM) was slightly higher than that obtained for the p-bromophenyl series (68%, 96% BRSM). The ratio of the O-allylated products 320 and 321 to the C-allylated products 322 and 323 was 1:3, whereas in the p-bromophenyl series O-allylation predominated in a ratio of 4:1. This reversal in selectivity was possibly due to the reduced steric hindrance (especially at C-2) that was exerted by the less bulky methoxymethyl C-1 substituent. Another potential explanation was that the coordinating oxygen atom in the C-1 substituent could (along with the C-3 carbonyl oxygen) chelate the lithium counterion and thus reduce the extent of aggregation of the relevant lithium enolates. This reduced tendency for aggregation would render the carbon centres C-2 and C-4 more accessible to the electrophile, allyl bromide.
The ratio of the inseparable C-allylated ketones \(322\) and \(323\) could not be determined. The \(^1\)H NMR spectrum of this mixture was quite complex, as each C-allyl regioisomer consisted of an epimeric pair. The C-allylated material from this reaction was characterized as a mixture the epimeric pairs of these isomers.

Figure 25 - Detail from the \(^1\)H NMR spectrum (CDCl\(_3\), 400 MHz) of the mixture of regioisomeric allyl enol ethers (320) and (321)

The ratio of the regioisomeric allyl enol ethers \(320\) and \(321\) was determined by inspection of the \(^1\)H NMR spectrum of the crude reaction mixture (Figure 25).
The doublet at $\delta = 4.24$ ppm was assigned to the H-4 enol ether proton resonance of the regioisomer 321. This resonance was split into a doublet ($J = 5.8$ Hz) by the bridgehead methine proton, H-5. In contrast, the singlet appearing at $\delta = 4.50$ ppm was attributed to the H-2 enol ether proton of regioisomer 320. Integration of these signals indicated that the ratio of isomers 320 and 321 was 1:5.

The mixture of the O-allylated isomers 320 and 321 was converted to the corresponding C-allylated compounds by means of a Claisen rearrangement reaction (Scheme 108). Heating these allyl enol ethers for 3 days at reflux in toluene afforded the C-allyl ketones 322 and 323 in good yield.

**Scheme 108 - Claisen rearrangement reaction of the allyl enol ethers (320) and (321)**

\[
\begin{align*}
\text{320} & \quad + \quad \text{321} \quad \xrightarrow{(a)} \quad \text{322} \\
\text{321} & \quad + \quad \text{323}
\end{align*}
\]

Reagents and conditions: (a) PhMe, reflux, 3 days, 84%

Having achieved the synthesis of the C-allyl ketones 322 and 323 by this enolate alkylation/Claisen rearrangement sequence, the Lemieux oxidative
cleavage reaction was carried out. This procedure afforded the regioisomeric aldehydes 324 and 325 in poor yield (Scheme 109).

Scheme 109 - Synthesis of the aldehydes (324) and (325)

![Scheme 109](image)

Reagents and conditions: (a) OsO₄ (cat.), NaIO₄, p-dioxane:H₂O (13:9), rt, 6.5 h, 32%; (b) O₃, DCM, -78 °C, 15 min, then Me₂S, -78 °C to rt, 2 h, 96%.

The yield of the oxidative cleavage reaction was far lower than the analogous reactions in the 1-phenyl and 1-p-bromophenyl series, potentially on account of chelation of osmium species by the methoxymethyl substituent and a carbonyl moiety. However, ozonolysis of the C-allylated ketones 322 and 323 followed by reductive work-up with dimethyl sulfide afforded the desired aldehydes 324 and 325 in excellent yield (Scheme 109). This result was somewhat surprising, as attempts at carrying out the same reaction in both the 1-phenyl and 1-p-bromophenyl series led to rapid and extensive decomposition of the starting materials. Gram quantities of the aldehydes 324 and 325 were prepared using this ozonolysis procedure.
Unlike their counterparts in the two aforementioned series, which showed no evidence of hydration, the aldehydes 324 and 325 were found by $^1$H NMR to be extensively hydrated. No resonances above $\delta = 6.0$ ppm were observed, and only one carbonyl resonance (at $\delta = 215.7$ ppm) was seen in the $^{13}$C NMR spectrum of this mixture in CDCl$_3$. Moreover, three resonances in the $^1$H NMR spectrum, at $\delta = 5.05-5.09$, 5.15-5.19 and 5.26-5.34 ppm, were assigned to the gem-diol moiety of the hydrated aldehydes. It is possible that in this less-hindered, more oxygen-rich system, aldehyde hydration was assisted by the formation of intramolecular hydrogen bonding as depicted below (Figure 26), where a hydroxyl group of the gem-diol moiety serves as a hydrogen bond donor and the C-3 carbonyl group as acceptor.

![Figure 26 - Possible hydrogen bonding motifs in the hydrated aldehydes (324) and (325)](image)

Alternatively, the angular methoxymethyl group might also serve as a hydrogen bond acceptor site.

### 4.5 Aldol Condensation and Acetal Hydrolysis

In order to elaborate the third five-membered ring of the triquinacene ring system, the mixture of the aldehydes 324 and 325 was subjected to reaction conditions which had successfully employed in the parent system (Scheme
The 1-(methoxymethyl)-substituent in this system was less sterically demanding than either of the phenyl (c.f. Chapter 2) or the p-bromophenyl (c.f. Chapter 3) substituents. In light of this, it was hoped that the acetal hydrolysis/aldol condensation sequence would proceed under these conditions, which had failed to achieve the analogous transformation in both of the aryl-substituted analogues.

*Scheme 110 - Synthesis of the tricyclic diketo alcohols (309) and (310)*

![Reagents and conditions: (a) THF: 2 M aq. HCl (2:1), rt, 40 h, then p-dioxane: 2 M aq. HCl (2:1), reflux, 1 h, 52%.

After stirring the mixture of the aldehydes 324 and 325 for 40 h at room temperature in a mixture of THF and 2 M aqueous hydrochloric acid (2:1), a steady state was reached (as determined by TLC analysis). Purification of the crude reaction mixture by flash chromatography afforded an inseparable mixture of the desired tricyclic diketo alcohols 309 and 310. A smaller amount of a less polar byproduct having a $^1$H NMR spectrum consistent with the presence of an
acetal moiety was also obtained. This latter material was heated at reflux for 1 h in a mixture of p-dioxane and 2 M aqueous hydrochloric acid (2:1) to afford further quantities of the diketo alcohols 309 and 310. The desired compounds were obtained in an overall yield of 52% by this method.

The $^1$H NMR spectrum of this mixture was quite complex and was consistent with the presence of several isomers. As many as four isomers may have been formed in this reaction (i.e. the C-5 epimers of both of the regioisomeric diketo alcohols 309 and 310). These isomers could not be separated by flash chromatography. However, the major isomer could be isolated in low yield by repeated recrystallization of this mixture from hexanes/ether and was characterized by COSY and HMQC NMR experiments.

The COSY spectrum of the major isomer (Figure 27) showed correlations between the centro-proton (H-10) and both bridgehead methine protons (H-4 and H-7). Other correlations of interest included those between H-7 and the two adjacent methylene protons H-6 and H-6', as well as coupling between H-4 and H-5. In conjunction with HMQC spectral data, the major isomer could be assigned as one of the C-5 epimers (the C-5 stereochemistry was not determined) of the 1-(methoxymethyl)-substituted tricyclic diketo alcohol regioisomer 309.
Figure 27 - Detail from the $^1$H-$^1$H COSY spectrum (CDCl$_3$, 400 MHz) of the tricyclic diketo alcohol (309)

Full characterization data were obtained for this isomer with the exception of a satisfactory elemental analysis. The latter could not be obtained as this compound trapped traces of hexanes and ether on recrystallization. These trace amounts of solvent could not be removed even after several weeks of drying under high vacuum.

As the regioisomer 309 was the major isomer, this suggested that although O-alkylation of the monoacetal 319 (c.f. Section 4.4) was selective for the C-2 double bond isomer 320 at the expense of the C-4 double bond isomer 321, the regioselectivity was reversed for the corresponding C-allylation process.
Thus, it was likely that the C-4-allylated isomer 323 was formed preferentially over the C-2-allylated isomer 322 in the aforementioned allylation reaction.

4.6 Preparation of (Methoxymethyl)triquinacene Derivatives

As the efficient separation of the regioisomeric tricyclic diketo alcohols 309 and 310 could not be performed by chromatography or by recrystallization, these derivatives were transformed to their corresponding (methoxymethyl)triquinacene derivatives 330 and 331 as a mixture. It was hoped that the two regioisomeric compounds could be separated at this stage or on conversion to the (hydroxymethyl)triquinacene derivatives 265 and 308.

Treatment of a mixture of the diketo alcohols 309 and 310 with borane-tetrahydrofuran complex furnished a mixture of the triols 326 and 327 (Scheme 111). Inspection of the infrared spectrum of these triols revealed that the reduction reaction had gone to completion, as no carbonyl stretching bands were present. The triols 326 and 327 were converted to their corresponding mesylates 328 and 329 on treatment with excess methanesulfonyl chloride and triethylamine in dichloromethane. As no hydroxyl stretching bands were present in the infrared spectrum of the mixture of trimesylates 328 and 329, the mesylation reaction had also gone to completion.
Scheme 111 - Preparation of 1- and 10-(methoxymethyl)triquinacenes (330) and (331)

Reagents and conditions: (a) BH₃ • THF, THF, 0 °C to rt, 16 h; (b) MsCl, NEt₃, DCM, 0 °C to rt, 1.5 h; (c) activated neutral Al₂O₃, DCM, rt, 7 days, ~20% over three steps.

The elimination reactions of these trimesylates proved problematic. Under the reaction conditions which had previously been employed successfully in the preparation of 10-phenyltriquinacene 84, 1-(4′-bromophenyl)triquinacene 278 and 10-(4′-bromophenyltriquinacene) 279, the three-fold elimination reaction of the trimesylates 328 and 329 was sluggish. An early attempt at increasing the rate of this reaction by heating the reaction mixture at reflux in dichloromethane led to extensive decomposition of the starting materials. In a subsequent attempt, stirring a mixture of trimesylates 328 and 329 with highly activated neutral alumina in dichloromethane afforded, after 7 days, a complex mixture of products. Attempted purification of this reaction mixture by repeated flash chromatography afforded an oily mixture of products. ¹H NMR analysis of this mixture revealed that it consisted mainly of 1-(methoxymethyl)triquinacene 330.
along with trace amounts of 10-(methoxymethyl)triquinacene 331 and several non-polar impurities (~20% yield over three steps). The alkene proton resonances (400 MHz, CDCl₃) of the major isomer 330 were seen at δ = 5.59, 5.64 and 5.67 ppm. The first and third of these signals had a splitting pattern (apparent doublet of doublets) virtually identical to that of 1-(4'-bromophenyl)triquinacene 278 (c.f. Sections 3.5.1 and 9.3.10). The alkene proton resonances of the minor isomer 330 were overlapped with the second set of alkene resonances of the major isomer 331 at δ = 5.64 ppm. TLC analysis of this mixture of products showed only a single spot in a variety of solvent systems.

Although the aforementioned alumina-promoted elimination method had been successfully employed in the preparation of several triquinacene derivatives, this method was surprisingly ineffective in this case. Future investigations of this synthetic approach will require an evaluation of alternative methods for effecting this triple elimination reaction of the trimesylates 328 and 329 as well as repeating this route on a large scale.

4.7 Summary and Conclusions

The preparation of the key intermediate, 1-(methoxymethyl)-substituted bicyclic keto acetal 319 was achieved in five steps from hydroxypyruvaldehyde 312 and dimethyl 1,3-acetonedicarboxylate 233 (Scheme 112). Hydroxypyruvaldehyde 312 was itself prepared by cupric acetate oxidation of dihydroxyacetone 313 and was isolated as its trimeric complex with ethanol. Gratifyingly, this tendency towards oligomerization was reversible in aqueous
solution, and hydroxypyruvaldehyde served as the 1,2-dicarbonyl component in a Weiss-Cook condensation reaction, which afforded the dione 314. This is the first reported example of a Weiss-Cook condensation reaction employing a glyoxal which possessed a free hydroxyl group. Protection of both carbonyl moieties of the dione 314 was necessary in order to efficiently protect the angular hydroxymethyl group as the corresponding methyl ether. Deprotection of one carbonyl group of the bis-acetal 318 then afforded the key intermediate 319.

Scheme 112 - Synthesis of the (methoxymethyl)-substituted bicyclic keto acetal (319) (overview)

Reagents and conditions: (a) NaHCO₃, H₂O, rt, 4 days, then 1 M aq. HCl:AcOH (3:1), reflux, 4 h, 18% (314) and 10% (315); (b) LiOH, THF:H₂O (3:1), rt, 40 min, 97%; (c) neopentyl glycol (4 equiv.), PPTS (cat.), PhH, reflux, Dean-Stark, 90 min, 95%; (d) NaH, THF:DMF (5:3), 0 °C, 30 min, then Mel, 0 °C to rt, 17 h, 95%; (e) PPTS (cat.), PhH:H₂O (100:1), reflux, 17 h, 35% (96% BRSM).

The overall yield for these five steps was 9%. However, given the ease of recovery of the bis-acetal 318 in the hydrolysis reaction leading to the keto acetal
319, this yield increased in practice to ~23% after two iterations of this selective acetal monodeprotection reaction.

Deprotonation of the keto acetal 319 with LDA followed by alkylation with allyl bromide afforded a mixture of the O-allylated regioisomers 320 and 321 along with the C-allylated isomers 322 and 323 (Scheme 113).

Unlike the analogous alkylation reactions in the 1-phenyl- and 1-(4'-bromophenyl) series, the alkylation took place predominantly at the enolate α-carbon positions rather than on the enolate oxygen. This reversal in selectivity was attributed to the reduced steric hindrance at C-1 present in this system and/or reduced lithium enolate aggregation. Claisen rearrangement of the O-allylated isomers 320 and 321 afforded the C-allylated isomers 322 and 323 in high yield. Ozonolysis of the alkene moiety of the C-allylated isomers 322 and 323 afforded the aldehydes 324 and 325 in excellent yield. This result was somewhat surprising in light of the failure of ozone to effect this oxidative cleavage reaction in the 1-phenyl- and 1-(4'-bromophenyl) series. Treatment of a mixture of the aldehydes 324 and 325 with a mixture of aqueous hydrochloric acid and THF effected the desired aldol condensation reaction; however, the concomitant acetal hydrolysis reaction did not proceed to completion under these reaction conditions. Complete deprotection of the carbonyl moieties was accomplished with more vigorous hydrolysis conditions to afford the tricyclic diketo alcohols 309 and 310.
Scheme 113 - Synthesis of 1-(methoxymethyl)triquinacene (330) and 10-(methoxymethyl)triquinacene (331) (overview)

Reagents and conditions: (a) LDA, THF, -78 °C, 30 min, then allyl bromide, HMPA/THF, -78 °C to rt, 16 h, 79% (97% BRSM), (320 + 321) : (322 + 323) = 1:3; (b) PhMe, reflux, 3 days, 84%; (c) O₃, DCM, -78 °C, 15 min, then Me₂S, -78 °C to rt, 2 h, 96%; (d) THF:2 M aq. HCl (2:1), rt, 40 h, then p-dioxane:2 M aq. HCl (2:1), reflux, 1 h, 52%; (e) BH₃ • THF, THF, 0 °C to rt, 16 h; (f) MsCl, NEt₃, DCM, 0 °C to rt, 1.5 h; (g) activated neutral Al₂O₃, DCM, rt, 7 days, ~20% over three steps.

Separation of these regioisomers proved difficult and the mixture of diketo alcohols 309 and 310 was then subjected to the reduction-activation-elimination reaction sequence. However, the reaction conditions for the elimination step...
proved to be less than satisfactory. This process afforded an inseparable mixture consisting mainly of 1-(methoxymethyl)triquinacene 330 along with a trace amount of the 10-substituted regioisomer 331 and several non-polar impurities.

The impure mixture of the (methoxymethyl)-substituted triquinacene derivatives 330 and 331 was obtained in ~10% yield over eight steps from the keto acetal 319. Although the desired 1- and 10-(hydroxymethyl)triquinacene derivatives 265 and 308 have not yet been obtained by this route, these results demonstrated the feasibility of such an approach. Once improved reaction conditions for the three-fold elimination reaction of trimesylates 328 and 329 are obtained, it is likely that this strategy will furnish the aforementioned triquinacene derivatives of interest. Moreover, the separation of the two regioisomeric series, which could not be accomplished at either of the tricyclic diketo ester or (methoxymethyl)triquinacene stages, is expected to be more facile at the (hydroxymethyl)triquinacene stage, as the primary alcohol function would offer increased polarity as well as the potential for derivatization.
CHAPTER FIVE: RESULTS AND DISCUSSION - OLEFIN METATHESIS ROUTE

5.1 Overview and Retrosynthetic Analysis

This chapter is concerned with an approach to 10-hydroxytriquinacene 306 in which the proposed key step was an olefin metathesis reaction which would be used to establish the triquinane framework. 10-Hydroxytriquinacene 306 is expected to be a versatile centro-substituted triquinacene derivative for the future studies described in the Introduction, and this approach represents a potential expedient approach to this novel class of compound. In contrast with the substituted glyoxal routes (c.f. Chapters 3 and 4), this synthetic route was expected to be regioselective and allow for the formation of the centro-substituted derivative at the expense of the corresponding 1-substituted regioisomer.

A retrosynthetic analysis of 10-hydroxytriquinacene 306 is presented below (Scheme 114). This target compound could be obtained by oxidation of the phenylselenide 332, followed by thermal selenoxide elimination. In turn, the phenylselenide 332 could be accessible via a radical decarboxylation reaction of the thiohydroxamate ester 333 in the presence of diphenyldiselenide, which acts as a radical trap. The thiohydroxamate 333 could be obtained by saponification of the tricyclic ester 334 and coupling of the resultant carboxylic acid with N-hydroxy-2-pyridinethione. The tricyclic ester 334, in turn, could be prepared by an olefin metathesis sequence of the trienyl ester 335. Formally,
this metathesis sequence would establish the triquinacene framework by ring-opening metathesis of the ring double bond, followed by stepwise ring-closing metathesis with each of the α-olefin moieties of the trienyl ester 335. In turn, this ester could be obtained by the addition of an organoindium reagent derived from pentadienyl bromide 336 to the known bicyclic keto ester 337.\textsuperscript{179}

Scheme 114 - Retrosynthetic analysis of 10-hydroxytriquinacene (306)

The bicyclic keto ester 337 could be obtained from a Diels-Alder reaction between the highly reactive, anti-aromatic cyclopentadienone 338 (generated from bromoenone 342) and ethyl acrylate 339.\textsuperscript{179,180} Furthermore, the
bromoenone 342 should be available from cyclopent-2-en-1-one 343 by means of an allylic bromination reaction.\textsuperscript{180} The addition of vinylmagnesium bromide 341 to acrolein 340 should furnish the corresponding divinylcarbinol, which could then be converted to pentadienyl bromide 336 upon treatment with aqueous hydrobromic acid.\textsuperscript{181}

5.2 Synthesis of Metathesis Precursors

5.2.1 Preparation of endo-7-oxo-bicyclo[2.2.1]hept-1-ene-2-carboxylic acid ethyl ester (337)

4-Bromocyclopent-2-en-1-one 342 was prepared by the method of Gerdil and co-workers (Scheme 115).\textsuperscript{180} Heating a solution of cyclopent-2-en-1-one 343 with N-bromosuccinimide (1 equiv.) and a catalytic amount of AIBN afforded the desired allylic bromination product 342. Normally, this material was used in the subsequent Diels-Alder reaction without further purification as these reactions were clean and were generally complete after 3 h as determined by \textsuperscript{1}H NMR analysis. Furthermore, no evidence of dibrominated products was seen. A small sample of this material was purified by flash chromatography for characterization purposes and all data were in agreement with literature values.\textsuperscript{180}
Scheme 115 - Diels-Alder reaction of cyclopentadienone (343) and ethyl acrylate

Reagents and conditions: (a) NBS, AIBN (cat.), CCl₄, reflux, 3 h; (b) CH₂=CHCO₂Et, DME, reflux, 3 days, 29% (337) + 25% (344) + 3% (345) + 8% (346) over two steps.

The bromoenone 342 is a convenient precursor for the highly reactive, anti-aromatic (4π) cyclopentadienone 338 (Scheme 116). Treatment of the bromoenone 342 with bases such as triethylamine rapidly effects the elimination of the elements of HBr. When generated in this manner, cyclopentadienone 338 reacts to form dicyclopentadienone 346 in virtually quantitative yield. Furthermore, upon heating, this dimer can be decarbonylated to produce either 1-indanone 344 or the related enone 348. However, if the bromoenone 342 is heated in the absence of base, the aforementioned elimination reaction occurs far more slowly. When prepared in this fashion, cyclopentadienone 338 may act as a Diels-Alder diene and react with other dienophiles such as ethyl acrylate and acrylonitrile, which are generally present in a large excess.
Heating a solution of the bromoenone 342 (1 equiv.) and ethyl acrylate 339 (8 equiv.) in DME at reflux for 3 days afforded a mixture of products (Scheme 115). The major product was the desired keto ester 337, which was obtained along with the formal cyclopentadienone dimer 346, 1-indanone 344 (from decarbonylation of dimer 346) as well as a small amount of 7-bromodicyclopentadienone 345. A significant amount of polymeric material was also produced in this reaction.

The keto ester 337 could be purified by repeated flash chromatography and had spectral and physical properties consistent with literature values.\textsuperscript{179} Of note, the IR spectrum of this compound contained a C=O stretching band at 1787 cm\textsuperscript{-1}, well above the typical range (~1705-1750 cm\textsuperscript{-1}) for a cyclic ketone.\textsuperscript{186} This abnormal finding can be attributed to strain, as the carbonyl group in question was located on a one-carbon bridge. The complete assignment of the \textsuperscript{1}H and
$^{13}$C NMR resonances of the product was performed by analysis of COSY and HMQC spectra.

The novel 7-bromodicyclopentadienone side product 345 was a minor component of the reaction mixture. This side product was also purified by repeated flash chromatography, followed by recrystallization from hexanes. Its structure was elucidated by, inter alia, two-dimensional NMR methods. In particular, no correlations involving the enone proton H-6 were seen in the COSY spectrum, and the key correlations between H-3 and H-4, H-8 and H-9 as well as between H-3 and H-4 were evident.

A possible explanation for the formation of this byproduct was that a small amount of molecular bromine was formed in situ during the Diels-Alder reaction. This reaction generated hydrobromic acid, which could be oxidized by dissolved oxygen present in the DME solvent, which was distilled but not deoxygenated. In turn, molecular bromine could have effected the bromination/dehydrobromination sequence of dicyclopentadienone 346, leading to the formation of this byproduct (Scheme 1 17).

Alternatively, reaction of molecular bromine with the 4-bromocyclopent-2-en-1-one starting material 342 would furnish the tribromide 350, which could then undergo an elimination reaction to afford the dibromoenone 351. Diels-Alder reaction of 3-bromocyclopentadienone 351 with 1 equiv. of cyclopentadienone 338, followed by a second elimination reaction, would then furnish 7-bromodicyclopentadienone 345 (Scheme 1 17).
It was unlikely that any molecular bromine was present in the impure bromoenone 342 employed in the Diels-Alder reaction, as the work-up procedure for this precursor involved multiple washes with sodium thiosulfate. Interestingly, even though one would expect the unconjugated, more electron-rich alkene moiety of dicyclopentadienone 346 to be preferentially attacked by bromine, no products consistent with bromination of this double bond were observed. Finally, when this reaction was repeated using DME which had been deoxygenated for 30 min with nitrogen, formation of this side product was obviated.

In a separate experiment, treatment of the bromoenone 342 with a slight excess of triethylamine afforded after 15 min at room temperature dicyclopentadienone 346 as the sole product (Scheme 118). This material had
spectral and physical properties identical to those of that obtained in the Diels-Alder reaction as a minor product (Scheme 115).

**Scheme 118 - Base-induced generation and dimerization of cyclopentadienone (338)**

![Scheme 118](image)

Reagents and conditions: (a) NEt₃, Et₂O, rt, 15 min, 78%.

### 5.2.2 Preparation of pentadienyl bromide (336)

Pentadienyl bromide 336 was synthesized in 41% yield over two steps by a literature method (Scheme 119). Addition of vinylmagnesium bromide 341 to acrolein 340 afforded 1,4-pentadien-3-ol 352, which was readily purified by distillation under reduced pressure. Stirring this alcohol in 48% aqueous hydrobromic acid for 1 h at 0 °C then afforded pentadienyl bromide 336, which was also purified by distillation and obtained as a mixture of E/Z isomers (~1:1). Multi-gram quantities of this reagent were prepared by this method.

**Scheme 119 - Synthesis of pentadienyl bromide (336)**

![Scheme 119](image)

Reagents and conditions: (a) CH₂=CHMgBr, THF, 0 °C, 4 h, 52%; (b) 48% aq. HBr, 0 °C, 1 h, 78%.
5.3 Olefin Metathesis Reactions of endo-7-Hydroxy-7-(1-vinylallyl)-bicyclo[2.2.1]hept-1-ene-4-carboxylic acid ethyl ester (335)

5.3.1 Preparation of the trienyl ester (335)

Having prepared pentadienyl bromide 336, the addition reaction of a pentadienyl organometallic reagent to the keto ester 337 was then investigated. Upon metal-halogen exchange (Scheme 120), the corresponding delocalized organometallic species can react with electrophiles at either the \( \alpha \) position (i.e. \[336 \rightarrow 353 \rightarrow 355\]) to afford conjugated products or at the \( \gamma \) position (i.e. \[336 \rightarrow 354 \rightarrow 356\]) to afford bis-allylic products.\(^{187}\) The \( \alpha/\gamma \) regioselectivity of the addition of pentadienyl organometallic reagents to aldehydes and ketones has been shown to be strongly dependent on the nature of the metal counterion, and such reactions employing lithium, zinc, boron, magnesium, tin, silicon and indium have been studied.\(^{188}\) Chan and co-workers have shown that the related allylindium species reacts exclusively at the \( \gamma \) position in water or in polar aprotic solvents such as DMF.\(^{189,190}\) Furthermore, Fallis and co-workers have demonstrated that this high regioselectivity extends to the pentadienyl system and that pentadienylindium could be added to aldehydes and ketones in good yield.\(^{188}\)
Scheme 120 - Reactions of pentadienyl organometallic species

Treatment of the keto ester 337 with pentadienyl bromide 336 and finely divided indium metal in DMF smoothly afforded the hydroxy ester 335 (Scheme 121). Even though an excess of the pentadienyl reagent was employed, no products consistent with addition of this reagent to the ester moiety of the keto ester 337 were formed.

Scheme 121 - Addition of pentadienyl indium to the keto ester (337)

Reagents and conditions: (a) pentadienyl bromide, In°, DMF, 0 °C to rt, 16 h, 82%.

This compound was extensively characterized by, *inter alia*, two-dimensional NMR experiments. In particular, the NOESY spectrum showed contacts between the alkene protons of the pentadienyl moiety and those of the ring double bond, indicating that the pentadienyl indium reagent was not only
regioselective in terms of reaction at the γ-position, but that this addition had occurred exclusively to the less-hindered si face of the keto ester 337.

5.3.2  Mechanistic considerations

The catalysts chosen for the investigation of the olefin metathesis chemistry of the triene ester 335 were the “first-generation” and “second-generation” Grubbs’ catalysts 357 and 358 (Figure 28).

![First- and second-generation Grubbs' catalysts (357) and (358)](image)

*Figure 28 - First- and second-generation Grubbs' catalysts (357) and (358)*

The triene ester 335 would be subjected to olefin metathesis conditions\(^{191,192}\) in an attempt to carry out a tandem ring-opening/ring-closing metathesis sequence (Scheme 122).\(^{193,194,195}\) One possible pathway through which this sequence could operate is depicted below (Scheme 122).
Scheme 122 - Tandem ring-opening/ring-closing metathesis sequence (α-olefin initiation)

Here, the cascade is initiated by reaction of the ruthenium catalyst with one of the diastereotopic α-olefin moieties of the trienyl ester 335 with loss of styrene. This could then followed by an intramolecular [2+2] cycloaddition reaction of the intermediate 359 to form the metallacyclobutane intermediate 360. In turn, this intermediate could undergo a retro-[2+2] process where the metallacyclobutane ring is opened and one of the cyclopentene rings is formed. Next, the intermediate 361 could undergo an analogous [2+2] process with the remaining α-olefin moiety, followed by a further retro-[2+2] process which installs the second cyclopentene ring. In this step, a methylene carbenoid species is lost, which then can react with another equivalent of the triene ester starting material 335 to form the intermediate 359 with loss of ethylene.
An alternative reaction pathway for this sequence is presented below (Scheme 123).\textsuperscript{193}

**Scheme 123 - Tandem ring-opening/ring-closing metathesis sequence (ring olefin initiation)**

In this case, the reaction is initiated by reaction of the ruthenium catalyst with the ring double bond with loss of styrene to form the intermediate 363, which then forms one cyclopentenoid ring though a [2+2]/\textit{retro-[2+2]} process. The liberated methylene carbenoid then reacts with an $\alpha$-olefin moiety of the intermediate 365 and an analogous [2+2]/\textit{retro-[2+2]} process furnishes the desired tricyclic ester 334 via the metallacyclobutane intermediate 367. Finally,
reaction of the methylene carbenoid with the starting material 335 regenerates the intermediate 363 with loss of ethylene and the catalytic cyclic begins anew.

As the rate of olefin metathesis decreases with increasing olefin substitution, the first mechanism (Scheme 122) should be expected to predominate at the expense of the second (Scheme 123), as the latter process involves initiation by metathesis between the ruthenium catalyst and the disubstituted ring double bond. However, the second mechanism could be promoted by the relief of ring strain in the initial step (by analogy with the ring-opening metathesis polymerization reactions of norbornene) and hence cannot be disregarded.

A third mechanism, which could be operative if the reaction sequence were carried out under an atmosphere of ethylene, would involve a cross-metathesis reaction between the trienyl ester starting material and ethylene (Scheme 124). As was the case with the second mechanism (Scheme 123), the reaction is initiated at the ring olefin. However, in this case, a metathesis reaction between this double bond and ethylene first takes place, leading to the tetraene intermediate 370. In turn, this intermediate reacts with the liberated methylene carbenoid, generating ethylene and furnishing the intermediate 363, which then goes on to react in a manner identical to the second mechanism (Scheme 123). The ethylene atmosphere in this case could facilitate the frequently sluggish ring-opening metathesis reaction of the ring double bond.
**Scheme 124 - Tandem ring-opening/ring-closing metathesis sequence (ring olefin initiation, ethylene atmosphere)**

5.3.3 Olefin metathesis experiments

5.3.3.1 Initial results

In an initial small-scale experiment, the trienyl ester 335 was treated with 10 mol % of first-generation Grubbs’ catalyst 357 at room temperature in dichloromethane. After 24 h, a small amount of a new product was visible by TLC, along with the starting material 335. This reaction was repeated on a somewhat larger scale with an initial catalyst loading of 25 mol % (Scheme 125). After 16 h of reaction, a significant amount of the same new product was visible by TLC, and so a second 25 mol % portion of Grubbs’ catalyst was added. After a further 16 h, the reaction had gone further towards completion. Two additional portions of catalyst (both 25 mol %) were added at 16 h intervals, such that the total amount of the ruthenium catalyst 357 added was 1 equiv. Following a
further 16 h of reaction, no more starting material could be observed. After purification by flash chromatography, the unexpected cyclopropanated product \(371\) was obtained in good yield as a 1:1 mixture of diastereomers.

**Scheme 125 - Attempted olefin metathesis of the trienyl ester (335)**

Reagents and conditions: (a) \((\text{PCy}_3\text{ Ru(=CHPh)}\text{Cl}_2\) 357 (1 equiv.), DCM, rt, 64 h, 82%.

The cyclopropanated hydroxy ester \(371\) had a mass spectral parent ion of \(m/z = 234\) amu, consistent with the loss of a methylene fragment from the trienyl ester starting material \(335\) \((m/z = 248\) amu). Moreover, the \(^1\)H NMR spectrum of this compound indicated the presence of an \(\alpha\)-olefin moiety (a 1H multiplet at \(\delta = 5.68-5.79\) ppm as well as a 2H multiplet at \(\delta = 5.14-5.26\) ppm). A 3H multiplet signal at \(\delta = 1.10-1.22\) ppm was attributed to the three cyclopropane protons H-2, H-3 and H-4. These appeared somewhat downfield from the typical range for protons on a three-membered ring (generally -0.5 to 0.8 ppm)\(^{186}\) as each of the cyclopropane carbons was also a bridgehead carbon. The ring strain in the system likely distorted the cyclopropane moiety and hence perturbed the chemical shifts of the cyclopropane protons.

Inspection of the \(^{13}\)C NMR spectrum of the cyclopropanated hydroxy ester \(371\) revealed that the majority of the carbons could each be assigned to two
nearly coincidental carbon resonances. This was consistent with
cyclopropanated hydroxy ester being formed as an approximately 1:1 mixture of
diastereomers. As most of the eight stereogenic centres present in this
compound were configurationally locked by the ring system’s geometry, it was
assumed that the epimeric centre was C-5. Finally, a satisfactory elemental
analysis was obtained for this cyclopropanated product.

This unprecedented transformation amounted to an intramolecular
cyclopropanation reaction carried out by a stoichiometric amount of first-
generation Grubbs’ catalyst 357. One possible pathway through which this
process could have taken place was initiation by the ruthenium catalyst 357 at
either diastereotopic α-olefin moiety, furnishing the ruthenium-stabilized
carbenes 359 (Scheme 126). In the corresponding olefin metathesis process
(c.f. Scheme 122), these carbenes would then react with the ring double bond in
a [2+2] cycloaddition reaction. However, the rigid bicyclic framework could be
insufficiently flexible and not allow the putative metallacyclobutane intermediates
to form. The carbenoids 359 could then have cyclopropanated the ring double
bond with loss of a ruthenium species, leading to the diastereomeric
cyclopropanated products 371. Alternatively, the metallacyclobutane
intermediates may have formed in the first instance, but a reductive elimination of
a ruthenium species could then have occurred instead of the usual retro-[2+2]
process. As no catalytic turnover was observed (i.e. a full equivalent of the
ruthenium catalyst 357 was required for complete conversion of the starting
material 335), the reduced ruthenium species lost upon cyclopropanation was incapable of further reaction under these conditions.

**Scheme 126 - Mechanistic rationale for the formation of the cyclopropanated hydroxy ester (371)**

5.3.3.2 Further investigations

In order to rule out solvent effects, the above cyclopropanation reaction was repeated using benzene (as opposed to dichloromethane) as the reaction solvent with an identical schedule of catalyst loading (i.e. 1 equiv. added in four portions). After 64 h at room temperature, the cyclopropanated hydroxy ester 371 was obtained in 79% yield, which was virtually identical to that obtained in dichloromethane.
In order to investigate the effect of catalyst loading, the trienyl ester 335 was treated (in one portion) with a full equivalent of first-generation Grubbs' catalyst 357. After 24 h at room temperature, the cyclopropanated hydroxy ester 371 was obtained in 63% yield. Hence, the cyclopropanation reaction was more effective when the ruthenium catalyst 357 was added in portions over a longer period (c.f. Scheme 125).

Next, the cyclopropanation reaction with portionwise catalyst loading was repeated. However, in this case, the reaction was conducted under an atmosphere of ethylene in an attempt to effect the olefin metathesis reaction through the ring-opening/double ring-closing metathesis mechanism depicted above (Scheme 124). Again, this modification had little effect on the outcome of the reaction, and the cyclopropanated hydroxy ester 371 was obtained in 74% yield.

The use of the “second generation” Grubbs’ catalyst 358 in the attempted olefin metathesis reaction was then performed. It was hoped that this catalyst, which generally offers greater catalytic activity at lower loadings as well as longer-lived propagating species when compared with the “first-generation” analogue, would furnish the desired metathesis product. However, this modification had no effect other than slightly increasing the rate of the cyclopropanation reaction, and the cyclopropanated hydroxy ester 371 was again obtained in good yield.

Although the ruthenium catalyst 357 was known to exhibit good functional group tolerance, the role of the tertiary alcohol moiety present in the trienyl
ester 335 in this anomalous cyclopropanation reaction was investigated (Scheme 127). Treatment of the trienyl ester 335 with sodium hydride followed by p-bromobenzylbromide furnished the corresponding p-bromobenzyl ether 373 in good yield.

**Scheme 127 - Synthesis of the p-bromobenzyl ether (373)**

Reagents and conditions: (a) NaH, THF, 0 °C, 30 min, then 4-bromobenzylbromide, THF/DMF, 0 °C to rt, 16 h, 75%.

Having protected the tertiary alcohol function of the trienyl ester 335, a small-scale TLC experiment was conducted in which a solution of the trienyl ether 373 was treated portionwise with 1 equivalent of the ruthenium catalyst 357 in dichloromethane solution. After 16 h at room temperature, the majority of the trienyl ether 373 had been converted to a single product that had a 1H NMR spectrum which indicated that cyclopropanation of the ring olefin had occurred. Hence, the tertiary alcohol function was likely not responsible for the lack of metathesis activity in this system.

A related series of experiments was then performed in order to assess whether the ethyl ester moiety was involved (either through steric shielding of the bottom face of the trienyl ester 335 or through a remote electronic effect) in this cyclopropanation reaction. Reduction of the trienyl ester 335 with lithium
aluminum hydride afforded the trienyl diol 374 (Scheme 128). This diol was treated portionwise with 1 equivalent of the ruthenium catalyst 357 to furnish the diastereomeric cyclopropane diols 375. This compound was also prepared by lithium aluminum hydride reduction of the cyclopropane hydroxy ester 371. In both cases, the cyclopropane diols 375 were obtained along with an impurity from which they could not be separated by flash chromatography. The cyclopropane diols 375 were derivatized for characterization purposes. Treatment of these materials with 3,5-dinitrobenzoyl chloride and pyridine afforded the corresponding 3,5-dinitrobenzoates 376 which were readily purified by flash chromatography.

Scheme 128 - Synthesis of the 3,5-dinitrobenzoate (376)

Reagents and conditions: (a) LiAlH₄, Et₂O, 0 °C to rt, 2 h, 90%; (b) LiAlH₄, Et₂O, 0 °C, 30 min, 84%; (c) (PCy₃)₂Ru(=CHPh)Cl₂ 357 (1 equiv.), DCM, rt, 48 h; (d) 3,5-dinitrobenzoyl chloride, py, DCM, rt, 1 h, 58% over two steps from 374.
In light of the above findings, it was unlikely that the ethyl ester moiety exerted a steric or electronic influence on the cyclopropanation reaction. Furthermore, the 3,5-dinitrobenzoate derivative 376 (a microcrystalline solid) was also obtained as a 1:1 mixture of diastereomers as determined by $^{13}$C NMR.

As every cyclopropane compound obtained up to this point was either an amorphous or microcrystalline solid or an oil, two attempts were made to obtain a crystalline derivative for X-ray crystal structure analysis. In a first experiment, the ethyl ester moiety of the cyclopropane hydroxy ester 371 was hydrolyzed under alkaline conditions to afford the carboxylic acid derivative 377 (Scheme 129).

**Scheme 129 - Synthesis of the carboxylic acid derivative (377)**

![Scheme 129 - Synthesis of the carboxylic acid derivative (377)](image)

Reagents and conditions: (a) LiOH, THF:H$_2$O (1:1), rt, 15 h, 70%.

The diastereomeric carboxylic acid derivatives 377 were obtained as an amorphous solid which, despite numerous attempts at recrystallization, did not furnish material suitable for single-crystal X-ray analysis. The cyclopropane hydroxy esters 371 were converted to the diphenyl carbinol derivatives 378 by treatment with phenyllithium (Scheme 130).
Scheme 130 - Synthesis of the diphenylcarbinol derivative (378)

Reagents and conditions: (a) PhLi, THF, 0 °C to rt, 30 min, 78%.

The product of this reaction was also obtained as an amorphous solid and attempted recrystallization from a wide variety of solvent systems afforded only amorphous or microcrystalline solids.

5.4 Olefin Metathesis Reactions of endo-7-Allyl-7-hydroxy-bicyclo[2.2.1]hept-1-ene-4-carboxylic acid ethyl ester (379)

The addition of the allylindium reagent formed from allyl bromide and indium metal²⁰² to the bicyclic keto ester 337 furnished the hydroxydienyl ester 379 in good yield (Scheme 131). As was the case with the addition of pentadienylindium to this bicyclic keto ester (c.f. Scheme 121), this addition occurred exclusively from the less-hindered face of the ketone moiety.

Scheme 131 - Addition of allylindium to the bicyclic keto ester (337)

Reagents and conditions: (a) allyl bromide, In⁰, DMF, 0 °C to rt, 16 h, 59%. 
In order to complement the investigations presented above (Section 5.3.3.2), the hydroxydienyl ester 379 was reacted with 1 equivalent of the ruthenium catalyst 35. After 68 h in benzene at room temperature, the corresponding cyclopropanated compound 380 was isolated in good yield (Scheme 132). In parallel with the analogous reaction in the vinylallyl series, no catalytic turnover was noticed, and the addition of a full equivalent of the ruthenium catalyst 357 was required for the complete consumption of the starting material 379.

Scheme 132 - Cyclopropanation of the hydroxydienyl ester (379)

![Chemical Structure](image)

Reagents and conditions: (a) (PCy₃)₂Ru(=CHPh)Cl₂ (1 equiv.), PhH, rt, 68 h, 70%.

5.5 Summary and Conclusions

Treatment of the trienyl ester 335 or the related dienyl ester 379 with the ruthenium catalysts 357 or 358 under a variety of reaction conditions failed to effect the desired olefin metathesis sequence, and in every case a novel cyclopropane product was obtained instead. This unexpected behaviour could not be attributed to either the tertiary alcohol or ethyl ester moieties present in the precursors 335 and 379, as these possibilities were ruled out by a series of derivatization experiments. Instead, the most likely explanation for this unprecedented cyclopropanation reaction was rooted in the rigid bicyclic
framework of this system. In particular, the lack of flexibility in this system could have prevented the formation of the metallacyclobutane intermediates which are involved in olefin metathesis reactions. The initially formed ruthenium-stabilized carbenes then could have cyclopropanated the ring double bond. Alternatively, the metallacyclobutane intermediates may have formed, but the reductive elimination of a ruthenium species occurred at a faster rate than the expected retro-[2+2] process. No catalytic turnover was noticed and, in the case of the cyclopropane 371, the material was obtained as a 1:1 mixture of epimers as evidenced by $^{13}$C NMR.

Of note, the tetracyclo[4.3.0.0$^{2.4}$.0$^{3.7}$]nonane ring system formed in the above cyclopropanation reactions, which has the trivial names deltacyclane or deltacyclin, has been well-studied.$^{203,204,205,206}$ This ring system, which contains eight contiguous chiral centres, is commonly accessed by homoconjugative Diels-Alder reactions (i.e. $[2\pi + 2\pi + 2\pi]$ processes) of norbornadiene 381 and dienophiles such as acrylonitrile 382, followed by functional group interconversion and decarboxylation reactions (Scheme 133).$^{205,207}$
Scheme 133 - Representative literature preparation of tetracyclo[4.3.0.0^2.4.0^3.7]nonane (deltacyclane) (385)

Reagents and conditions: (a) Cu(OAc)_2 (cat.), 200 °C, 12 h; (b) NaOH, EtOH:H_2O, reflux, 50 h; (c) SOCl_2, py, Et_2O, 0 °C, 1 h, then t-BuOOH, py, p-cymene, 0 °C, 1 h, then 145 °C, 2 h, 19% over three steps.

A search of the Chemical Abstracts and Beilstein databases revealed more than six hundred known compounds which contain this ring system. However, none of these reported derivatives contained the pattern of functionalization at C-5, C-6 and C-8 present in the cyclopropanated hydroxy ester 371. Thus, not only does this unexpected and unprecedented cyclopropanation reaction afford a novel entry to the deltacyclane ring system, but it also allows the preparation of deltacyclanes bearing the aforementioned C-5/C-6/C-8 substitution pattern.
CHAPTER SIX: RESULTS AND DISCUSSION - CIS-BICYCLO[3.3.0]OCTAN-2,8-DIONE ROUTE

6.1 Overview and Retrosynthetic Analysis

This chapter contains an approach to centro-substituted triquinacene derivatives in which the key step which would elaborate the triquinacene framework is an alternative olefin metathesis reaction. Whereas the approach outlined in Chapter 5 employed a proposed ring-opening metathesis/ring-closing metathesis strategy, the key step in this route is a ring closing metathesis reaction between two terminal olefin substituents. The quaternary centro-substituent would be installed by means of an alkylaion reaction carried out at the C-1 position of the known compound, cis-bicyclo[3.3.0]octan-2,8-dione 391. This approach would allow for the installation of a variety of centro substituents and could allow for the rapid generation of a family of these triquinacene derivatives. Furthermore, in contrast with the substituted glyoxal routes presented in Chapters 3 and 4, this approach would be completely regioselective and would exclusively afford the centro-substituted derivatives. The retrosynthetic analysis of the target compounds 386 is shown below (Scheme 134).
The centro-substituted triquinacene derivatives 386 could be obtained by thermal isomerization of the corresponding thermodynamically less stable bis-isotriquinacene derivatives 387. The bis-isotriquinacene derivatives 387 should be available by activation of both of the tertiary alcohol moieties of the tricyclic diol 388 followed by elimination. This tricyclic diol could be obtained by means of a ring-closing metathesis reaction of the bicyclic diol 389. Addition of two equivalents of a vinyl organometallic reagent to the substituted dione 390 should furnish the bicyclic diol 389. Alkylation at the \( \alpha \)-position of the known \( \beta \)-diketone, cis-bicyclo[3.3.0]octan-2,8-dione 391, would install the eventual quaternary centro-substituent. As \( \beta \)-diketones can be alkylated at the
α position with a wide range of electrophiles (including, *inter alia*, carbonyl compounds, alkyl halides, propargyl halides, halogens, esters and aryl diazonium salts), a diverse range of centro-substituents could be installed. The dione 391 is a known compound and has been prepared from cyclopent-2-en-1-one 343 and ethyl 3-nitropropionate 394 by means of a sequence of conjugate addition, elimination, reduction and Claisen condensation reactions.

6.2 Synthesis of *cis*-Bicyclo[3.3.0]octan-2,8-dione (391)

6.2.1 Synthesis of ethyl 3-nitropropionate (394)

6.2.1.1 Fischer esterification/nucleophilic displacement approach

In the first instance, ethyl 3-nitropropionate 394 was prepared by a two-step approach whereby Fischer esterification of commercially-available 3-bromopropionic acid 395 afforded ethyl 3-bromopropionate 396 (Scheme 135). This intermediate was then treated with the nitrite form of the benzytrialkylammonium-functionalized Amberlite® IRA-900 anion exchange resin in benzene. The nitrite form of this resin was prepared from the commercially-available chloride form by stirring with aqueous sodium nitrite solution (50% w/v) for 48 h, collecting the resin by filtration and washing with aqueous sodium nitrite solution (1 M) until the washings gave a negative silver test for chloride. The resin was then dried under high vacuum prior to use. Although it had been reported that this modified anion exchange resin efficiently promoted the nucleophilic displacement of alkyl bromides and iodides by nitrite and was tolerant of a wide variety of functional groups, this reaction afforded the
desired ethyl 3-nitropropionate 394 in poor yield, despite a number of attempts to optimize the reaction conditions.

Scheme 135 - Synthesis of ethyl 3-nitropropionate (394) via ethyl 3-bromopropionate (396)

\[
\begin{align*}
\text{Br} & \text{CO}_2\text{H} \quad \text{CO}_2\text{Et} \\
395 & \quad 396 \\
& \quad \text{O}_2\text{N} \text{CO}_2\text{Et} \\
394 & \quad \text{Reagents and conditions: (a) EtOH, H}_2\text{SO}_4 \text{ (cat.), reflux, 24 h, 63%}; \ (b) \text{Amberlite}^\circledR \text{ IRA-900 resin (NO}_2\text{ form), PhH, 50 }^\circ\text{C, 72 h, 11%}.}
\end{align*}
\]

6.2.1.2 Oxidation/Fischer esterification approach

In light of the poor overall yield obtained by the above route, an alternate approach was then investigated. The method of Jäger and co-workers, which involved the preparation of 3-nitropropionaldehyde 397 followed by oxidation to 3-nitropropionic acid 398 and finally Fischer esterification to furnish ethyl 3-nitropropionate 394, was then undertaken. Conjugate addition of nitrous acid (generated \textit{in situ} from sodium nitrite and acetic acid) to acrolein 340 furnished 3-nitropropionaldehyde 397 (Scheme 136). While the yield for this step (36%) was moderate, this reaction was conducted on a multi-gram scale without complications, and no purification (other than a period of drying under high vacuum in order to remove residual acrolein) was necessary.
Scheme 136 - Synthesis of ethyl 3-nitropropionate (394) via 3-nitropropion- aldehyde (398)

\[
\begin{align*}
\text{CHO} & \quad (a) \quad \text{O}_2\text{N} \quad \text{CHO} \\
340 & \quad \quad 397 \\
\text{O}_2\text{N} \quad \text{CO}_2\text{H} & \quad (b) \quad \text{O}_2\text{N} \quad \text{CO}_2\text{Et} \\
398 & \quad \quad 394
\end{align*}
\]

Reagents and conditions: (a) NaNO₂, AcOH, THF, 0 °C to rt, 3 h, 36%; (b) Jones' reagent, Me₂CO, 0 °C, 3 h, 86% or NaClO₂, H₂O₂, NaH₂PO₄, MeCN:H₂O (3:4), rt, 4 h, 83%; (c) EtOH, H₂SO₄ (cat.), reflux, 16 h, 92%.

The next step involved the oxidation of 3-nitropropionaldehyde 397 to 3-nitropropionic acid 398. Two procedures for accomplishing this transformation were evaluated. First, oxidation with Jones' reagent afforded the desired nitroacid 398 in 86% yield. However, the yield dropped to 58% when this reaction was attempted on a multi-gram scale. An alternative oxidation procedure employing the sodium chlorite/hydrogen peroxide oxidant system in buffered aqueous acetonitrile was then performed. When conducted on a preparative (~6 g) scale, this procedure furnished 3-nitropropionic acid 398 in good yield (83%). Finally, Fischer esterification of 3-nitropropionic acid 398 afforded ethyl 3-nitropropionate 394 in high yield (92%).

The second preparation of ethyl 3-nitropropionate 394, while slightly longer than the first synthesis, was far more efficient (27% over three steps as opposed to 7% over two steps).

6.2.2 Conjugate addition, reduction and Claisen condensation sequence

Having prepared multi-gram quantities of ethyl 3-nitropropionate 394, cis-bicyclo[3.3.0]octan-2,8-dione 391 was elaborated from this nitroester and cyclopent-2-en-1-one 343 by the three-step procedure reported by Duthaler and
Maienfisch. The first step involved deprotonation of ethyl 3-nitropropionate \(394\) by potassium \(t\)-butoxide followed by conjugate addition of the resultant nitro-stabilized carbanion to cyclopent-2-en-1-one \(343\) (Scheme 137). Upon adding methanol, the elimination of the elements of nitrous acid from the corresponding conjugate adduct took place, affording the acrylate \(393\).

**Scheme 137 - Synthesis of ethyl 3-(3-oxocyclopentyl)acrylate (393)**

\[
\begin{align*}
\begin{array}{c}
\text{O}_2\text{N} \\
\text{CO}_2\text{Et}
\end{array}
\end{align*}
\rightarrow
\begin{align*}
\begin{array}{c}
\text{O} \\
\text{CO}_2\text{Et}
\end{array}
\end{align*}
\]

Reagents and conditions: (a) \(t\)-BuOK, THF, \(-20\) °C, 1 h, then cyclopent-2-en-1-one \(343\), \(-20\) °C to rt, 3 h, then excess MeOH, rt, 3 days, 74%.

Of note, under these reaction conditions, a small amount (< 5%) of the corresponding methyl ester was also formed. This byproduct could only be separated from the ethyl ester \(393\) by repetitive chromatography and was generally carried through the reduction and Claisen condensation steps without ill effect, as these latter reactions also converted this byproduct to the target dione \(391\). This byproduct likely arose by means of a transesterification reaction which took place following the addition of methanol.

The acrylate ester \(393\) was then reduced to the corresponding saturated ester \(392\) with hydrogen gas (1 atm) using 10% palladium on carbon as catalyst (Scheme 138). This reduction reaction was complete after 4 h, and the ester \(392\) was obtained in nearly quantitative yield.
Scheme 138 - Synthesis of cis-bicyclo[3.3.0]octan-2,8-dione (391)

Reagents and conditions: (a) H₂ (1 atm), 10% Pd on C, EtOH, 4 h, 98%; (b) NaOMe, THF, rt, 6 h, 63%.

Finally, treatment of the ester 392 with sodium methoxide (1.2 equiv.) in THF for 6 h at room temperature afforded the target dione 391 in good yield. Over the course of this Claisen condensation reaction, the product dione 391 was precipitated as its corresponding sodium enolate. In order to obtain an acceptable yield of the dione 391, it was found to be important that a neutral pH be maintained during the ensuing work-up. To this end, the reaction was quenched with aqueous potassium dihydrogen phosphate solution and was stirred until all of the precipitate had dissolved (~20 min). On the other hand, when the reaction was quenched with water, the yield dropped considerably. Presumably, under these alkaline conditions, once the dione 391 had been formed by protonation of the corresponding enolate, this product was subject to nucleophilic attack by hydroxide ion. In turn, this process could induce cleavage of the bicyclic ring system through a retro-Claisen condensation reaction. This observation suggested that the reaction conditions for the subsequent alkylation reactions needed to be chosen with care in order to preserve the integrity of this sensitive β-diketone.
6.3 Alkylation Reactions

6.3.1 Alkylation reactions of 2-methylcyclohexane-1,3-dione (399) (model system)

In order to determine reaction conditions suitable for the alkylation of dione 391 at C-1, through which the requisite quaternary centre would be established, 2-methylcyclohexane-1,3-dione 399 was chosen as a model system. The inexpensive, commercially-available model dione 399 resembled cis-bicyclo[3.3.0]octan-2,8-dione 391 in that both are α-substituted-β-diketones. It was hoped that methods suitable for efficient alkylation at the α-position of the model dione could be applied to the bicyclic system of interest.

Initial attempts at alkylation in this model system consisted of deprotonation of the dione 399 with sodium hydride in anhydrous THF, followed by addition of a solution of either benzyl bromide or allyl bromide in DMF (Scheme 139).221
Reagents and conditions: (a) NaH, THF, rt, 30 min, then BnBr, THF/DMF, rt, 3 h, 60%; (b) NaH, THF, rt, 30 min, then allyl bromide, THF/DMF, rt, 16 h, 55%.

In this manner, the benzyl derivative 400 and the allyl derivative 401 were obtained in moderate (55-60%) yield. Next, the method of Shrout and Lightner was investigated. In this case, a DMF solution of the model dione 399 was stirred for 16 h at room temperature along with anhydrous cesium carbonate (1.5 equiv.) and an alkyl, benzyl or allyl halide (3.0 equiv.). This method was originally developed for the mild, C-selective alkylation of acidic methylene compounds such as β-diketones and β-keto esters. Presumably, chelation of cesium ion by the enolate intermediate in these reactions leads to a relatively tightly-bound ion pair; diminishing the nucleophilicity of the enolate oxygen atom and hence favouring C-alkylation over O-alkylation. These results are summarized below (Scheme 140, Table 10).
Scheme 140 - Alkylation reactions of the model dione (399) (with cesium carbonate as base)

![Scheme 140](image)

Reagents and conditions: see Table 10.

**Table 10 - Reaction conditions corresponding to Scheme 140**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R-X</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-bromobenzyl bromide</td>
<td>400 (R = p-BrC₆H₄CH₂)</td>
<td>73%</td>
</tr>
<tr>
<td>2</td>
<td>allyl bromide</td>
<td>401 (R = CH₂=CHCH₂)</td>
<td>68%</td>
</tr>
<tr>
<td>3</td>
<td>methyl iodide</td>
<td>402 (R = CH₃)</td>
<td>43%</td>
</tr>
<tr>
<td>4</td>
<td>benzyl bromide</td>
<td>403 (R = CH₂Ph)</td>
<td>65%</td>
</tr>
</tbody>
</table>

This method proved satisfactory in all four cases and furnished the derivatives 400, 401, 402 and 403 in moderate to good yield (43-73%). Moreover, these reactions produced fewer side products (e.g. products of O-alkylation) than the analogous reactions that employed sodium hydride; in all cases, the model dione starting material 399 was the only other significant component present in the final reaction mixtures.

6.3.2 Alkylation reactions of cis-bicyclo[3.3.0]octan-2,8-dione (391)

The method of Shrout and Lightner was then applied to alkylation reactions of the dione 391. These results are summarized below (Table 11).
Scheme 141 - Alkylation of cis-bicyclo[3.3.0]octan-2,8-dione (391)

\[
\begin{array}{c}
\text{391} \\
\text{Cs}_2\text{CO}_3 \text{ (1.5 equiv.), R-X (3.0 equiv.), DMF, rt, 16 h} \\
\text{404 (R = CH}_3\text{)}
\end{array}
\]

Reagents and conditions: see Table 11.

Table 11 - Reaction conditions corresponding to Scheme 141

<table>
<thead>
<tr>
<th>Entry</th>
<th>R-X</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>methyl iodide</td>
<td>404 (R = CH$_3$)</td>
<td>43%</td>
</tr>
<tr>
<td>2</td>
<td>allyl bromide</td>
<td>405 (R = CH$_2$=CHCH$_2$)</td>
<td>82%</td>
</tr>
<tr>
<td>3</td>
<td>benzyl bromide</td>
<td>406 (R = CH$_2$Ph)</td>
<td>84%</td>
</tr>
</tbody>
</table>

This method furnished the C-1-alkylated derivatives 404, 405 and 406. In all but the case where R = CH$_3$ (where the yields were the same), the yields of these reactions were higher than those of the analogous alkylation reactions of the model dione 399. Again, these reactions were virtually free of side products, with the starting material, bicyclic dione 391, being the only other significant component of the final reaction mixtures.

6.4 Additions to C-2 and C-8

6.4.1 Attempted additions of vinyl organometallic reagents

In light of a report by Paquette and co-workers in which treatment of the dione 407 with diisobutylaluminum hydride afforded the corresponding diols 408, 409 and 410 with good stereoselectivity (408:409:410 = 7:2:1) for delivery of the
hydride nucleophile from the concave face of the cis-bicyclo[3.3.0]octane ring system (Scheme 142), a series of experiments was conducted in order to determine whether this stereoselectivity extended to nucleophiles other than hydride.\textsuperscript{224} In particular, it was hoped that the addition of vinyl organometallic reagents to the benzyl-substituted dione 406 would exhibit similar stereoselectivities, allowing for the synthesis of the required olefin metathesis precursor 389.

\textit{Scheme 142 - Stereoselective reduction of the dione (407)}

\begin{align*}
\text{Reagents and conditions:} & \quad \text{(a) DIBAL-H, THF, -78 °C, 1 h, 88\% (408:409:410 = 7:2:1).} \\
\text{Several attempts at adding vinyl organometallic reagents to the benzyl-substituted dione 406 were carried out (Scheme 143). These results are summarized below (Table 12).}
\end{align*}
Scheme 143 - Attempted additions of vinyl organometallic reagents to the benzyl-substituted dione (406)

![Scheme 143](image)

Reagents and conditions: (a) see Table 12.

Table 12 - Reaction conditions corresponding to Scheme 143

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₂=CHMgBr (4 equiv.), THF, 0 °C to rt, 5 h</td>
<td>complex mixture including starting material 406</td>
</tr>
<tr>
<td>2</td>
<td>CH₂=CHMgBr (8 equiv.), THF, 0 °C to rt, 5 h</td>
<td>complex mixture</td>
</tr>
<tr>
<td>3</td>
<td>CH₂=CHMgBr (4 equiv.), THF, -78 °C to rt, 5 h</td>
<td>complex mixture including starting material 406</td>
</tr>
<tr>
<td>4</td>
<td>CH₂=CHMgBr (4 equiv.), Et₂O, -78 °C to rt, 5 h</td>
<td>complex mixture</td>
</tr>
<tr>
<td>5</td>
<td>CH₂=CHMgBr (4 equiv.), anhydrous CeCl₃ (4 equiv.), THF, 0 °C to rt, 7 h</td>
<td>mostly recovered starting material 406 along with traces of several products</td>
</tr>
<tr>
<td>6</td>
<td>CH₂=CHSnBu₃ (3 equiv.), MeLi (3 equiv.), THF, -78 °C, 30 min, then benzyl dione 406, -78 °C to rt, 5 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>7</td>
<td>CH₂=CHSnBu₃ (3 equiv.), MeLi (3 equiv.), THF, 0 °C, 30 min, then benzyl dione 406, 0°C to rt, 5 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>8</td>
<td>CH₂=CHSnBu₃ (3 equiv.), MeLi (3 equiv.), Et₂O, -78 °C, 30 min, then benzyl dione 406, 0°C to rt, 5 h</td>
<td>no reaction</td>
</tr>
</tbody>
</table>
In a first instance (Entry 1), treatment of the benzyl dione 406 with vinylmagnesium bromide (4 equiv.) at 0 °C (with subsequent warming to room temperature) in THF solution afforded after 5 h a complex mixture of products, including some recovered starting material. Doubling the amount of vinylmagnesium bromide employed (Entry 2) also led to a complex mixture of products, although in this case no starting material remained after 5 h. Decreasing the initial reaction temperature from 0 °C to -78 °C (Entry 3) had no effect, and again a complex mixture of products, including the recovered starting material 406, was obtained. Repeating these reaction conditions in ether instead of THF (Entry 4) again led to a similar complex mixture of products.

The organocerate reagent derived from vinylmagnesium bromide and cerium (III) chloride was employed (Entry 5). The organocerate reagent was formed by stirring equimolar amounts of anhydrous cerium (III) chloride and vinylmagnesium bromide for 1 h at 0 °C in THF. A solution of the benzyl-substituted dione 406 in THF was added and after 7 h of reaction time, the majority of this starting material remained intact. Trace amounts of several side products were also formed in this reaction. However, the organocerate reagent was insufficiently reactive under these conditions, and no signals attributable to the desired diol 411 could be detected in the 1H NMR spectrum of the final reaction mixture.

The corresponding addition reactions of vinyllithium (prepared in situ by a transmetallation reaction of vinyl-tri-n-butyltin with methyllithium) were attempted. Initially, treatment of the benzyl dione 406 with vinyllithium (3
equiv.) in THF solution (Entry 6) at -78 °C with subsequent warming to room temperature afforded after 5 h only recovered starting material. Increasing the initial temperature from -78 °C to 0 °C (Entry 7), had no effect, nor did a change of solvent from THF to ether (Entry 8).

From the above results, it may be concluded that while both vinyllithium and the vinylcerate reagent derived from cerium (III) chloride were insufficiently nucleophilic under these reaction conditions to carry out the desired addition reactions, vinylmagnesium bromide was too reactive. In all cases, treatment of the benzyl dione 406 with this Grignard reagent led to a complex mixture of products. Given the strong basicity of Grignard reagents, vinylmagnesium bromide may have induced the decomposition of the benzyl dione 406. One potential pathway through which this decomposition may have taken place involved an initial addition of this Grignard reagent to one of the carbonyl moieties of the starting material. This could then be followed by a retro-aldol condensation process of the resultant β-alkoxyketone intermediate, cleaving the bicyclic ring system to furnish a monocyclic intermediate which could then undergo further reactions with the Grignard reagent, which was present in excess.

6.4.2 Additions of acetylenic organometallic reagents

In light of the above difficulties in performing the double addition of vinyl organometallic reagents to the benzyl dione 406, the next series of attempts were focused on the analogous addition reactions of acetylene organometallic reagents. It was hoped that the smaller size of these acetylene nucleophiles
when compared to the corresponding vinyl reagents would facilitate the desired addition reactions. Moreover, any acetylene adducts formed in these reactions could be transformed into their corresponding vinyl analogues upon hydrogenation over Lindlar's catalyst.231,232

Initial attempts were focused on the addition of lithium (trimethylsilyl)acetylide, generated in situ from (trimethylsilyl)acetylene and n-butyllithium, to the benzyl dione 406 (Scheme 144).233,234,235

Scheme 144 - Addition of (trimethylsilyl)acetylide to the benzyl dione (406)

Reagents and conditions: (a) (trimethylsilyl)acetylene (4 equiv.), n-BuLi (3 equiv.), THF, -78 °C to rt, 5 h, 93%; (b) TBAF, THF, 0 °C, 30 min, 90% (413 + 414).

Treatment of the benzyl dione 406 with lithium (trimethylsilyl)acetylide (3 equiv.) furnished the monoadduct 412 in excellent yield. Neither the starting material 406 nor any products of bis-addition could be detected in the ¹H NMR spectrum of the final reaction mixture. In order to facilitate the characterization of the adduct 412, the trimethylsilyl group was removed. An initial attempt at deprotection of the silyl group with potassium carbonate in methanol led to extensive decomposition.236 However, treatment of the adduct 412 with tetra-n-butylammonium fluoride in THF afforded the epimeric ethynyl carbinols 413 and 414 in excellent yield.237,238
The ethynyl carbinol was obtained as a mixture of C-8 epimers (413:414 = 7:3), as determined by integration of the furthest downfield C-11 benzylic methylene proton resonances of the two epimers. The resonances in question appeared at $\delta = 3.88$ ppm (d, $J = 13.0$ Hz) for the major epimer and at $\delta = 3.52$ ppm (d, $J = 13.0$ Hz) for the minor epimer. After repeated recrystallization of this mixture of epimers from hexanes/ether, an analytical sample of the minor epimer was obtained. The $^1$H and $^{13}$C NMR resonances for this minor epimer were completely assigned on the basis of COSY and HMQC experiments. Moreover, the NOESY spectrum of this epimer showed, inter alia, a contact between the terminal acetylene proton H-10 and the benzylic methylene proton H-11. Thus, the minor (8α-OH) epimer 414 resulted from addition of (trimethylsilyl)acetylide to the convex face of the bicyclo[3.3.0]octane ring system (i.e. syn with respect to the C-1 benzyl substituent). Conversely, the major (8β-OH) epimer 413 was the result of nucleophilic addition to the concave face. This finding was consistent with Paquette's observation (c.f. Scheme 142) that nucleophilic attack of hydride at C-2 or C-8 in this ring system occurs preferentially from the concave face. Moreover, the major epimer had the correct C-8 stereochemistry to allow for the planned olefin metathesis reaction (c.f. Section 6.1) which would establish the triquinane framework.

Alternatively, the ethynyl carbinols 413 and 414 were synthesized in one step in good yield by the addition of ethynylmagnesium bromide to the benzyl dione 406 (Scheme 145).
**Scheme 145 - Addition of ethynylmagnesium bromide to the benzyl dione (406)**

![Chemical Structure](image)

Reagents and conditions: (a) ethynylmagnesium bromide (5 equiv.), THF, -78 °C to rt, 16 h, 76% (413 + 414).

Although ethynylmagnesium bromide was present in excess, only the products of monoaddition, the ethynyl carbinols 413 and 414, was present in the crude reaction mixture. Of note, the material obtained in this manner had a ratio of C-8 epimers (8α-OH : 8β-OH = 3:7) identical to that of the material obtained via the addition of lithium (trimethylsilyl)acetylide followed by silyl group deprotection.

The mixture of the epimeric ethynyl alcohols 413 and 414 was then treated with ethynylmagnesium bromide under several different reaction conditions in an effort to achieve the addition of a second equivalent of this reagent in order to obtain the diol 415 (Scheme 146). These results are summarized below (Scheme 146, Table 13).

**Scheme 146 - Attempted addition of ethynylmagnesium bromide to the ethynyl carbinols (413) and (414)**

![Chemical Structure](image)

Reagents and conditions: (a) see Table 13.
In an initial attempt (Entry 1), the mixture of ethynyl carbinols 413 and 414 was treated with ethynylmagnesium bromide (5 equiv.) in THF. After 16 h, the starting materials were almost quantitatively recovered. No evidence of starting material decomposition (through a retro-aldol condensation pathway or otherwise) was detected. Increasing the amount of Grignard reagent employed and increasing the temperature at the point of addition (Entry 2) had no effect on the outcome of the reaction. The conditions listed in Entry 1 were then repeated at reflux (Entry 3). Again, no addition products were observed; furthermore, under these conditions some decomposition of the starting materials was detected. Finally, attempting the reaction in ether instead of THF (Entry 4) afforded only recovered starting material.
The failure to achieve the desired double addition of nucleophiles to the benzyl dione 406 was likely the result of steric hindrance, as the corresponding bis-adduct 411 would contain three contiguous quaternary centres at C-1, C-2 and C-8. In order to probe the role of the benzyl substituent of the benzyl dione 406, the addition of ethynylmagnesium bromide to both the methyl and allyl analogues 404 and 405 was then attempted (Scheme 147). In stark contrast to the corresponding addition reaction to the benzyl dione 406, which cleanly underwent mono-addition, in both of these cases extensive decomposition of the starting materials took place. Furthermore, no products corresponding to the addition of this Grignard reagent to the carbonyl moieties of the diones 404 and 405 could be observed in the $^1$H NMR spectra of these reaction mixtures.

**Scheme 147 - Attempted addition of ethynylmagnesium bromide to the methyl dione (404) and the allyl dione (405)**

Reagents and conditions: (a) ethynylmagnesium bromide (5 equiv.), THF, 0 °C to rt, 16 h.
6.5 Summary and Conclusions

A summary of the 2,8-dione route is presented below (Scheme 148). cis-Bicyclo[3.3.0]octan-2,8-dione 391 was prepared in 13% yield over six steps from acrolein 340 and cyclopent-2-en-1-one 343 according to the method of Duthaler and Maenífisch.$^{208}$ A series of \( \alpha \)-alkylation reactions were performed on the \( \alpha \)-substituted-\( \beta \)-diketone model substrate 2-methyl-1,3-cyclohexanedione 399. The method of Shrout and Lightner$^{222}$ (deprotonation with anhydrous cesium carbonate in DMF solution in the presence of organohalide electrophiles) was successful in achieving \( \alpha \)-alkylation with a variety of electrophiles of the model dione 399. The bicyclic dione 391 was then converted to the corresponding benzyl, methyl and allyl derivatives 404, 405 and 406 under these reaction conditions.

In order to obtain the requisite substrate for the intended olefin metathesis reaction which would establish the triquinacene framework, the benzyl dione 406 was then treated with vinylmagnesium bromide or vinyllithium. However, these attempted carbonyl addition reactions proved unsuccessful under a range of reaction conditions, with vinyllithium being completely unreactive towards the benzyl dione 406 and vinylmagnesium bromide causing extensive decomposition of the starting material.
Scheme 148 - Summary for cis-bicyclo[3.3.0]octan-2,8-dione route

Reagents and conditions: (a) NaN\textsubscript{3}O\textsubscript{2}, AcOH, THF, 0 °C to rt, 3 h, 36%; (b) Jones' reagent, Me\textsubscript{2}CO, 0 °C, 3 h, 86% or NaClO\textsubscript{2}, H\textsubscript{2}O\textsubscript{2}, NaH\textsubscript{2}PO\textsubscript{4}, MeCN:H\textsubscript{2}O (3:4), rt, 4 h, 83%; (c) EtOH, H\textsubscript{2}SO\textsubscript{4} (cat.), reflux, 16 h, 92%; (d) t-BuOK, THF, -20 °C, 1 h, then cyclopent-2-en-1-one 343, -20 °C to rt, 3 h, then excess MeOH, rt, 3 days, 74%; (e) H\textsubscript{2} (1 atm), 10% Pd on C, EtOH, 4 h, 98%; (f) NaOMe, THF, rt, 6 h, 63%; (g) Cs\textsubscript{2}CO\textsubscript{3} (1.5 equiv.), E (3.0 equiv.), DMF, rt, 16 h, 43% (E = CH\textsubscript{3}I, R = CH\textsubscript{3}), 82% (E = CH\textsubscript{2}=CHCH\textsubscript{2}Br, R = CH\textsubscript{2}CH=CH\textsubscript{2}) and 84% (E = PhCH\textsubscript{2}Br, R = CH\textsubscript{2}Ph); (h) ethynylmagnesium bromide (5 equiv.), THF, -78 °C to rt, 16 h, 76% (413 + 414) or (i) (trimethylsilyl)acetylene (4 equiv.), n-BuLi (3 equiv.), THF, -78 °C to rt, 5 h, 93%; (ii) TBAF, THF, 0 °C, 30 min, 90% (413 + 414).

The addition reactions of acetylene organometallic reagents to the benzyl dione 406 were also investigated, with the intention of reducing the alkynyl moieties to alkenes. Both (trimethylsilyl)acetylene and ethynylmagnesium bromide were successfully added to one of the two carbonyl moieties of the benzyl dione 406; however, no products of bis-addition could be obtained, even under forcing reaction conditions. The C-8 epimeric monoadducts 413 and 414 were in both cases obtained in a 7:3 ratio, with the major epimer 413 possessing the 8β-OH stereochemistry which was required for the planned olefin metathesis.
reaction. The corresponding addition reactions of ethynylmagnesium bromide to the methyl dione 404 and the allyl dione 405 were both unsuccessful. Moreover, treatment of a mixture of the epimeric monoadducts 413 and 414 with ethynylmagnesium bromide furnished only recovered starting material.

The intended double addition reaction of organometallic reagents to the carbonyl moieties of 1-substituted derivatives of the dione 406 required the formation of three contiguous quaternary centres in a rigid bicyclic framework. The failure of the aforementioned double addition reactions was attributed to the pronounced steric hindrance present in this system.
CHAPTER SEVEN: RESULTS AND DISCUSSION - STETTER ROUTE AND MISCELLANEOUS APPROACHES

7.1 Stetter Route

7.1.1 Overview and retrosynthetic analysis

This section concerns a novel approach to centro-substituted triquinacene derivatives based on aldol condensation and Stetter reaction chemistry. The retrosynthetic analysis is presented below (Scheme 149).

Scheme 149 - Retrosynthetic analysis of the centro-substituted triquinacene derivatives (386) (Stetter route)

The enone 423 should be available from the known, protected aldehyde 424 and the β-keto phosphonate 425 through a Horner-Wadsworth-Emmons
olefination reaction. The eventual centro-substituent could then be installed using a Stetter reaction between the enone 423 and an aldehyde 422 to afford the dione 421. The scope of the Stetter reaction is somewhat broad and this approach should allow for the introduction of a variety of centro substituents that possess appropriate functionalities for the future studies mentioned in the Introduction. In turn, after cleavage of the acetal protecting group of the dione 421, the resultant triketone could then undergo an aldol condensation/Michael addition cascade via the enone 420, leading to the C-2-allyl dione 419. This approach would be expected to provide this allylated intermediate with the same regiospecificity as was obtained in the conjugate addition route (i.e. the allyl moiety would be present only at C-2 and not at C-4, leading exclusively to 10-substituted triquinacene derivatives). The corresponding centro-substituted triquinacene derivatives 386 could then be obtained via a sequence analogous to that employed in the other routes, i.e. oxidative cleavage of the allyl moiety, closure of the third ring by an aldol condensation reaction to afford the diketo alcohol 418 and final elaboration by reduction, activation and elimination.

The proposed pathway through which the key aldol cascade step, which establishes the bicyclic framework of the allyl ketone 419 and forms the quaternary centre, could operate is depicted (for an acid-catalyzed series of reactions) below (Scheme 150).
Scheme 150 - Potential rationale for the aldol cascade

Acid-catalyzed hydrolysis of the acetal moiety of the dione 421 would lead to the trione 426, which under these reaction conditions (aqueous acid) could tautomerize to the enol 427. This intermediate should then undergo aldol condensation with the neighbouring ketone moiety in a 5-exo-trig ring closure process leading to the diketo alcohol 428. While 6-exo-trig addition to the other carbonyl group of this intermediate would also be possible, no further reaction of the product of this addition would be expected. As this ring closure could be reversible under these reaction conditions, it would be expected that any material diverted through this side pathway would eventually undergo a retro-aldol condensation reaction to return to the trione 426. Acid-catalyzed dehydration of the intermediate 428 should afford the keto enone 420.
Reversible enol formation of the unconjugated carbonyl group could occur at either α carbon; however, the Michael addition involving the regioisomeric enol 429 would be expected to be favoured as the product dione 419 should be far more stable than the analogous product of 3-endo-trig cyclization. By analogy with the Robinson annulation reaction, this cascade process could alternatively be carried out under alkaline conditions.242,243

Retrosynthetic analyses of the protected aldehyde 424 and the β-ketophosphonate 425 are presented below (Scheme 151).

Scheme 151 - Retrosynthetic analyses of the aldehyde (424) and the β-keto phosphonate (425)

Condensation of ethyl acetoacetate 432 with one equivalent of neopentyl glycol 433 should yield the protected ester 431. In turn, the desired aldehyde 424 could be obtained by reduction of the ester 431 to the corresponding primary alcohol followed by oxidation. In addition, following the conversion of commercially-available 4-pentenoic acid 434 to its corresponding ethyl ester, treatment of this ester with the phosphonate-stabilized carbanion derived from
dimethyl methyl phosphonate 435 should afford the β-keto phosphonate 425 that is required for the proposed Horner-Wadsworth-Emmons olefination reaction.

7.1.2 Synthesis of the enone (423)

7.1.2.1 Synthesis of 2-(2,5,5-trimethyl-1,3-dioxan-2-yl)acetaldehyde (424)

Condensation of ethyl acetoacetate 432 and neopentyl glycol 433 at reflux in benzene with azeotropic removal of water in a Dean-Stark apparatus afforded the acetal ester 431 in nearly quantitative yield (Scheme 152). This reaction was performed on a 160 g scale and, following aqueous work-up, material of >98% purity by 'H NMR was obtained. Reduction of this ester on a 60 g scale with lithium aluminum hydride proceeded in quantitative yield. Finally, oxidation of this alcohol with freshly prepared pyridinium dichlorochromate in dichloromethane afforded the desired aldehyde 424.

Scheme 152 - Synthesis of 2-(2,5,5-trimethyl-1,3-dioxan-2-yl)acetaldehyde (424)

Reagents and conditions: (a) neopentyl glycol, p-TsOH (cat.), PhH, reflux, Dean-Stark apparatus, 14 h, 98%; (b) LiAlH₄, THF, 0 °C, 15 min, 99%; (c) PDC, DCM, 0 °C to rt, 16 h, 38%.

7.1.2.2 Synthesis of dimethyl 2-oxohex-5-enylphosphonate (425)

Fischer esterification of commercially-available 4-pentenoic acid 434 afforded after 2 days at reflux in absolute ethanol followed by distillation through a Vigreux column the corresponding ethyl ester 437 in 70% yield (Scheme
This yield was somewhat lower than expected on account of the volatility of this compound. Deprotonation of dimethyl methylphosphonate with \(n\)-butyllithium at low temperature formed the corresponding phosphonate-stabilized carbanion that was treated with ethyl 4-pentenoate \(437\) to afford the \(\beta\)-keto phosphonate \(434\) in good yield.\(^{248}\)

**Scheme 153 - Synthesis of dimethyl-2-oxohex-5-enylphosphonate (425)**

\[
\begin{align*}
\text{434} & \xrightarrow{(a)} \text{437} & \xrightarrow{(b)} \text{425} \\
\end{align*}
\]

Reagents and conditions: (a) \(\text{H}_2\text{SO}_4\) (cat.), EtOH, reflux, 2 days, 70%; (b) \(\text{H}_3\text{CPO(OCH}_3\text{)}_2\) (2 equiv.), \(n\)-BuLi, -78 °C, 3 h, 81%.

7.1.2.3 *Horner-Wadsworth-Emmons olefination*

The coupling reaction of the aldehyde \(424\) and the \(\beta\)-keto phosphonate \(425\) to form the enone \(423\) was accomplished under Horner-Wadsworth-Emmons conditions.\(^{249}\) Stirring these precursors for 16 h at room temperature in the presence of lithium chloride and Hünig’s base afforded the desired enone \(423\) in 73% yield.
7.1.3 Attempted Stetter reactions

7.1.3.1 Overview

The Stetter reaction may be regarded as the conjugate analogue of the benzoin condensation, whereby an aldehyde 422 is first reversibly converted to a stabilized carbanion 438 by the catalytic action of cyanide or a thiazolium salt (Scheme 155). This carbanion then undergoes an irreversible conjugate addition process to an α,β-unsaturated ketone, ester or nitrile and liberates the cyanide or thiazolium catalyst. Aliphatic aldehydes generally require the use of thiazolium catalysts, whereas aromatic aldehydes generally respond well to either cyanide or thiazolium catalysis. In the case where the Michael acceptor is an α,β-unsaturated ketone, the Stetter reaction represents an expedient means to prepare the 1,4-diketones 442.
While Stetter reactions under cyanide catalysis are usually carried out in aprotic media such as DMF in order to minimize HCN formation, protic solvents may be used when the reaction is catalyzed by thiazolium salts. Some commonly employed thiazolium salt catalysts are shown below (Figure 29). When the aldehyde component is aliphatic, superior results are generally obtained with N-benzylated salts such as 3-benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride 443. On the other hand, with aromatic aldehydes, N-alkylated analogues such as 3-ethyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium bromide 444 or 5-(2-hydroxyethyl)-3,4-dimethylthiazolium iodide 445 have been successfully employed. The catalytic activity arises upon treatment of these salts with a base such as sodium acetate or triethylamine, with subsequent nucleophilic attack of the thiazolium C-2 centre on the aldehyde carbonyl group.
7.1.3.2 Attempted Stetter reactions under cyanide catalysis

Initial efforts were focused on the addition of simple aromatic aldehydes to the enone 423 using literature conditions with sodium cyanide (5 mol %) as catalyst.\(^{239}\) This reaction was attempted with benzaldehyde, p-chlorobenzaldehyde, p-bromobenzaldehyde and p-nitrobenzaldehyde. These results are summarized below (Scheme 156, Table 14).

Scheme 156 - Attempted Stetter reactions of the enone (423)

Reagents and conditions: (a) see Table 14 and Table 15.

Table 14 - Reaction conditions corresponding to Scheme 156 (cyanide catalysis)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-bromobenzaldehyde (2.6 equiv.), NaCN (cat.), DMF, 40 °C, o/n</td>
<td>no reaction; mostly recovered enone 423 with some loss of acetal group</td>
</tr>
<tr>
<td>2</td>
<td>p-bromobenzaldehyde (2.6 equiv.), NaCN (cat.), DMF, 70 °C, o/n</td>
<td>no reaction; mostly recovered enone 423 with some loss of acetal group</td>
</tr>
</tbody>
</table>
An initial attempt using the literature conditions (Entry 1) failed to effect the desired transformation. Nearly all of the enone starting material 423 was recovered, along with some product which had only undergone acetal cleavage. In a second attempt (Entry 2), the reaction temperature was raised from 40 °C to 70 °C with similar results. Substitution of p-chlorobenzaldehyde for p-bromobenzaldehyde (Entry 3) had no effect, with no products detectable by TLC even after 48 h at 70 °C. Analogous results were obtained when benzaldehyde was used as the aldehyde component (Entry 4). Finally, attempting this Stetter reaction with p-nitrobenzaldehyde, which possesses a strongly electron-withdrawing ring substituent (Entry 5), led to no reaction after 6 days at 70 °C.

7.1.3.3 Attempted Stetter reactions under thiazolium catalysis

As the above reaction conditions employing cyanide catalysis did not effect the desired Stetter reaction, the use of the commercially-available thiazolium catalyst 444 was then investigated. The results are summarized below (Table 15).
Table 15 - Reaction conditions corresponding to Scheme 156 (thiazolium catalysis)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-bromobenzaldehyde (1.5 equiv.), thiazolium catalyst 444 (10 mol %), NEt₃ (10 mol %), DMF, 70 °C, 16 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>2</td>
<td>p-bromobenzaldehyde (2 equiv.), thiazolium catalyst 444 (1 equiv.), NEt₃ (1 equiv.), DMF, 70 °C, 16 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>3</td>
<td>p-bromobenzaldehyde (5 equiv.), thiazolium catalyst 444 (1 equiv.), NEt₃ (1 equiv.), DMF, 70 °C, 16 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>4</td>
<td>p-bromobenzaldehyde (5 equiv.), thiazolium catalyst 444 (1 equiv.), NEt₃ (1 equiv.), EtOH, 45 °C, 16 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>5</td>
<td>p-chlorobenzaldehyde (5 equiv.), thiazolium catalyst 444 (1 equiv.), NEt₃ (1 equiv.), DMF, 70 °C, 16 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>6</td>
<td>p-chlorobenzaldehyde (5 equiv.), thiazolium catalyst 444 (1 equiv.), NEt₃ (1 equiv.), EtOH, 45 °C, 16 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>7</td>
<td>p-bromobenzaldehyde (5 equiv.), thiazolium catalyst 444 (1 equiv.), NEt₃ (1 equiv.), DMF, 70 °C, 7 days</td>
<td>no reaction, some SM decomposition</td>
</tr>
</tbody>
</table>

Again, the first attempt (Entry 1) following a literature procedure was unsuccessful. Increasing the amount of p-bromobenzaldehyde from 1.5 to 2.0 equiv. along with the use of stoichiometric amounts of thiazolium salt and base (Entry 2) had no effect, nor did a further increase in the loading of p-bromobenzaldehyde to 5.0 equiv. (Entry 3). Switching to a protic solvent (anhydrous ethanol) (Entry 4) did not affect the outcome of the reaction.
Employing p-chlorobenzaldehyde as the aldehyde component in these reactions led only to recovery of the enone starting material 423 in both DMF (Entry 5) and ethanol (Entry 6). Finally, repeating the reaction under the conditions listed in Entry 3 provided after 7 days only recovered starting material and some decomposition products (Entry 7).

7.1.3.4 Attempted Stetter reaction of the O-TMS cyanohydrin 447

A related attempted Stetter reaction involved the use of the O-TMS cyanohydrin 447, derived from p-bromobenzaldehyde. It was hoped than upon deprotonation at the benzylic position with LDA, this carbanion would exhibit increased reactivity towards the enone 423 (c.f. Scheme 155). The synthesis and attempted use of O-TMS cyanohydrin 447 in a Stetter reaction are depicted below (Scheme 157).

Scheme 157 - Synthesis and use of the O-TMS cyanohydrin (447)

Reagents and conditions: (a) TMSCI, KCN, ZnI₂ (cat.), MeCN, reflux, 4 h, 65%; (b) LDA, THF, -78 °C, 15 min, then enone 423, THF, -78 °C to rt, 16 h.
This sequence also failed to afford any addition products and the enone starting material 423 was recovered.

7.1.4 Summary and conclusions

The aldehyde 424 was prepared in 37% yield over three steps from ethyl acetoacetate 432 and neopentyl glycol 433. The β-ketophosphonate 425 was prepared in 57% yield over two steps from 4-pentenoic acid 434 and dimethyl methylphosphonate 435. The aldehyde 424 and the β-ketophosphonate 425 were coupled in a Horner-Wadsworth-Emmons olefination reaction which afforded the enone 423 in 73% yield.

Attempted addition of substituted benzaldehydes to the enone 423 in a Stetter reaction were unsuccessful. This reaction was attempted under cyanide and thiazolium catalysis in both protic (ethanol) and aprotic (DMF) solvents. As well, attempts at performing an analogous reaction with the O-TMS cyanohydrin 447 (derived from p-bromobenzaldehyde 446) also met with resistance. Potentially, the α,β-unsaturated moiety of the enone acetal 423 was hindered by the neighbouring neopentyl glycol-derived acetal group, inhibiting effective conjugate addition.

7.2 Miscellaneous Approaches

In a novel approach to the triquinacene ring system, the Diels-Alder reaction between cyclopentadienone (generated in situ by slow elimination of the elements of HBr from the bromoenone 342) and cyclopent-4-en-1,3-dione 449 (c.f. Chapter 5) was attempted (Scheme 158). The intent was to subject the
Diels-Alder adduct, the trione 450, to reaction conditions suitable for effecting reductive cleavage of a 1,4-dione moiety.\textsuperscript{253,254} This would then be followed by treatment of the trione 450 with base in order to investigate whether intramolecular C1-C10 bond formation between the reactive carbonyl group on the one-carbon bridge and the \( \beta \)-diketone moiety could be induced by aldol condensation chemistry, leading to the triquinane derivative 454. In turn, this intermediate could be converted to 10-hydroxytriquinacene by reduction of the carbonyl functions of this intermediate, followed by activation and elimination.

\textit{Scheme 158 - Proposed Diels-Alder, reductive cleavage and aldol condensation route to the triquinacene ring system}

However, heating a solution of 4-bromocyclopent-2-en-1-one 342 and cyclopent-4-en-1,3-dione 449 for 40 h at reflux in DME afforded only 1-indanone 344 along with dicyclopentadienone 346 (c.f. Chapter 5), indicating that the
cyclopentadienone generated reacted more rapidly with itself than with the dienophile 449. The latter compound was recovered from the reaction mixture.

In a related attempt, it was envisaged that treatment of the acetate 455 (which should be available from a Diels-Alder reaction between cyclopentadienone 338 and 3-acetoxy-3-cyclopent-2-en-1-one 459) with base (e.g. methoxide or hydroxide) could cleave the acetate moiety, leading to the alkoxide 456 (Scheme 159). This alkoxide could then undergo a retro-aldol condensation reaction, cleaving the six-membered ring to furnish the enolate 457. This enolate could then undergo equilibration to the regioisomeric enolate 453, which could in undergo an aldol condensation reaction similar to that proposed in Scheme 158, affording the triquinane derivative 458.

Scheme 159 - Proposed Diels-Alder, acetate cleavage and aldol condensation route to the triquinacene ring system

The enol acetate 459 was prepared from 1,3-cyclopentanedione 458 and then heated at reflux in DME along with 4-bromocyclopent-2-en-1-one 342 (Scheme 160).255
Scheme 160 - Attempted Diels-Alder reaction of the enol acetate (460)

Reagents and conditions: (a) AcCl, py, DCM, 0 °C to rt, 2 h, 86%; (b) 4-bromo-cyclopent-2-en-1-one 342, DME, reflux, 16 h.

As was the case with the previous attempt, the only reaction products were 1-indanone 344 and dicyclopentadienone 346, again indicating that reaction of this enol acetate dienophile with cyclopentadienone was slower than the dimerization of this reactive intermediate.
8.1 Overview

In this chapter, the results of a series of ab initio molecular modeling studies of the triquinacene ring system are presented. The first series of studies concerned a series of geometry optimizations of triquinacene 1 as well as the C-10-centred triquinacyn radical 219, anion 221 and cation 224. The second series of studies consisted of an evaluation of the energetics of the dimerization reaction of two molecules of triquinacene 1 to dodecahedrane 178. The species of interest for these studies are depicted below (Figure 30).

![Species of interest for the molecular modeling studies](image)

*Figure 30 - Species of interest for the molecular modeling studies*

All studies were carried out using the Gaussian 98 suite of programs for Linux (Revision A.11.3) on Simon Fraser University’s “Bugaboos” high-performance computing facility consisting of 192 2.8 GHz Athlon processors linked in a Beowulf architecture. Computational details are outlined in Appendix 1 (Section 10.1).
8.2 Energies and Geometries of the Triquinacyl Reactive Species

8.2.1 Relative heats of formation

The gas-phase heats of formation for the C-10-centered triquinacyl cation, anion and radical were evaluated using density functional theory at the B3LYP/6-31+G* level. In order to provide a reference, identical calculations were performed for the analogous methyl and t-butyl species. The heats of formation of these species may be compared across molecular systems as shown below:

Consider two neutral, closed-shell hydrocarbon species A and B undergoing homolysis (Z = 0) to afford the radical species A* and H* or heterolysis to furnish either the A*/H- (Z = 1) or the A+/H- (Z = -1) ion pairs. The heats of formation \( \Delta E \) for the reactive species \( A^z \) and \( B^z \) are obtained from:

\[
\text{for } A - H \rightarrow A^z + H^- \quad \Delta E_{A^z} = E_{A^z} + E_{H^-} - E_{A-H} \quad (\text{Equation 1})
\]

\[
\text{for } B - H \rightarrow B^z + H^- \quad \Delta E_{B^z} = E_{B^z} + E_{H^-} - E_{B-H} \quad (\text{Equation 2})
\]

The relative heat of formation \( \Delta \Delta E_{A^zB^z} \) of the two reactive species \( A^z \) and \( B^z \) is expressed as:

\[
\Delta \Delta E_{A^zB^z} = \Delta E_{B^z} - \Delta E_{A^z} \quad (\text{Equation 3})
\]

Substitution of Equations 1 and 2 into Equation 3 yields:
\[ \Delta \Delta E_{AB}^{z} = \Delta E_{B}^{z} - \Delta E_{A}^{z} = E_{B}^{z} + E_{H}^{z} - E_{B-H}^{z} - (E_{A}^{z} + E_{H}^{z} - E_{A-H}^{z}) \]  
(Equation 4)

Of note, the heats of formation for the hydrogen radical, anion and cation need not be evaluated, as their corresponding terms cancel in Equation 4. Furthermore, by comparing each reactive species with its corresponding closed-shell neutral hydrocarbon, this approach took into account the fact that the methane, \( i \)-butane and triquinacene molecular systems contain different numbers of particles and have different zero-point energies.

The calculated gas-phase relative heats of formation for the \( t \)-butyl and triquinacetyl cation, anion and radical with respect to the corresponding methyl species are given below (Table 16).

**Table 16 - Relative gas-phase heats of formation of the \( t \)-butyl and triquinacetyl radical, cation and anion**

<table>
<thead>
<tr>
<th>Molecular system</th>
<th>Relative heat of formation (( \Delta \Delta E )) / kcal mol(^{-1} )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>radical</td>
</tr>
<tr>
<td>methane</td>
<td>0</td>
</tr>
<tr>
<td>( i )-butane</td>
<td>-10.8</td>
</tr>
<tr>
<td>triquinacene</td>
<td>-3.7</td>
</tr>
</tbody>
</table>

The above data suggest that the energetic cost of forming the C-10-centred triquinacetyl radical 219 from triquinacene lies between those of forming
the methyl radical and the C-2-centred-t-butyl radical from methane and i-butane, respectively. The t-butyl radical, which possesses three alkyl substituents adjacent to the radical centre, is stabilized by hyperconjugative interactions between the C-H \( \sigma \) bonds of the alkyl substituents and the singly-occupied p orbital of the radical centre.\(^{262}\) The methyl radical, on the other hand, lacks such stabilizing interactions, rendering its formation more endothermic than that of the t-butyl radical. The triquinacryl radical 219, much like the t-butyl radical, also possesses three adjacent alkyl substituents. However, the geometrical constraints of the ring system preclude the achievement of the conformation most favourable for hyperconjugative stabilization: a parallel or near-parallel and planar orientation of the \( \beta \)-C-H \( \sigma \) bond and the singly occupied p orbital.\(^{263}\) As a result, the relative stability of the triquinacryl radical 219 with respect to the parent hydrocarbon is greater than that seen in the methyl radical/methane system but less than that of the t-butyl radical/i-butane system.

The results for the corresponding cationic species may be rationalized in terms of a similar hyperconjugative stabilization argument. Here, the stabilizing interactions in question are those between \( \beta \)-C-H \( \sigma \) bonds and the empty p orbital of the cationic centre. Again, the energetic cost of forming the triquinacryl cation 224 from triquinacene 1 was intermediate between those of the methyl and t-butyl systems. A further consideration for the triquinacryl cation 224 is that, in light of the cationic centre being at the junction of three fused five-membered rings, the energetic cost of sp\(^3\) to sp\(^2\) rehybridization would be expected to be greater than those of acyclic systems. The desire of cationic species to achieve
planarity at the cationic centre must in the case of the triquinacryl cation 224 be balanced by the ring strain and other destabilizing deformations engendered by this rehybridization of C-10.

On the other hand, the triquinacryl anion 221 was more stable than the corresponding methyl or t-butyl anions with respect to the parent hydrocarbons.

8.2.2 Optimized geometries

Along with their heats of formation, the optimized geometries for these species were also obtained. Detailed structural data, in Cartesian coordinates, are presented in Appendix 2 (Section 10.2).

Table 17 - Calculated geometric parameters for triquinacene (1) as well as the triquinacryl radical (219), anion (221) and cation (224)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Triquinacene 1 (crystal structure)</th>
<th>Triquinacene 1 (calculated)</th>
<th>Triquinacryl radical 219</th>
<th>Triquinacryl anion 221</th>
<th>Triquinacryl cation 224</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1-C2 bond length, Å</td>
<td>1.511</td>
<td>1.519</td>
<td>1.525</td>
<td>1.524</td>
<td>1.535</td>
</tr>
<tr>
<td>C2-C3 bond length, Å</td>
<td>1.319</td>
<td>1.338</td>
<td>1.340</td>
<td>1.340</td>
<td>1.342</td>
</tr>
<tr>
<td>C1-C10 bond length, Å</td>
<td>1.558</td>
<td>1.564</td>
<td>1.522</td>
<td>1.555</td>
<td>1.470</td>
</tr>
<tr>
<td>C1-H1 bond length, Å</td>
<td>0.982</td>
<td>1.100</td>
<td>1.103</td>
<td>1.111</td>
<td>1.108</td>
</tr>
<tr>
<td>Parameter</td>
<td>Triquinacene 1 (crystal structure)</td>
<td>Triquinacene 1 (calculated)</td>
<td>Triquinacyl radical 219</td>
<td>Triquinacyl anion 221</td>
<td>Triquinacyl cation 224</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>-----------------------------------</td>
<td>-----------------------------</td>
<td>-------------------------</td>
<td>-----------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>C2-H2 bond length, Å</td>
<td>0.951</td>
<td>1.087</td>
<td>1.087</td>
<td>1.093</td>
<td>1.084</td>
</tr>
<tr>
<td>C1-C2-C3 angle, °</td>
<td>112.8</td>
<td>112.7</td>
<td>112.5</td>
<td>111.9</td>
<td>112.1</td>
</tr>
<tr>
<td>C1-C10-C4 angle, °</td>
<td>106.5</td>
<td>106.7</td>
<td>110.8</td>
<td>105.7</td>
<td>116.0</td>
</tr>
<tr>
<td>C10-C1-C2 angle, °</td>
<td>103.9</td>
<td>103.9</td>
<td>102.1</td>
<td>105.2</td>
<td>99.6</td>
</tr>
<tr>
<td>H1-C1-C2 angle, °</td>
<td>112.8</td>
<td>110.7</td>
<td>110.6</td>
<td>108.7</td>
<td>110.5</td>
</tr>
<tr>
<td>C-10 RMS deviation from planarity, Å</td>
<td>N/A</td>
<td>0.896</td>
<td>1.939</td>
<td>0.731</td>
<td>0.337</td>
</tr>
<tr>
<td>C2-C10 distance, Å</td>
<td>N/A</td>
<td>2.427</td>
<td>2.369</td>
<td>2.445</td>
<td>2.395</td>
</tr>
</tbody>
</table>

Selected geometric parameters taken from the optimized structures of triquinacene 1 as well as the C-10-centred triquinacyl radical 219, anion 221 and cation 224 are presented above (Table 17). The geometry of the triquinacyl radical 219 largely resembled that of triquinacene 1. Aside from a few minor changes in bond angles and lengths, the main difference between these two species lay in the root-mean-squared (RMS) deviation from planarity of the three methine carbons C-1, C-4 and C-7 and the centro-carbon (C-10). This parameter served as an estimate of the planarity of each species about the centro position. The triquinacyl radical 219 was far less planar about the C-10
position (RMS deviation from planarity 1.939 Å) than was triquinacene 1 (0.896 Å). Furthermore, the distance between C-2 and C-10 did not vary appreciably between triquinacene 1 (2.427 Å) and the triquinacyl cation 224 (2.395 Å), which indicated that delocalization of the double bonds to the cationic centre in the cation 224 was likely insignificant.

Of the three reactive species 219, 221 and 224, the triquinacyl cation 224 bore the least resemblance to the parent hydrocarbon, triquinacene 1. The bonds between the bridgehead methine carbons C-1, C-4 and C-7 and the centro position (C-10) were significantly shorter (1.470 Å) in the cation 224 than in triquinacene 1 (1.564 Å). Furthermore, in the cation 224, the C1-C10-C4 angle was much larger (116.0° vs. 106.7°) and the C10-C1-C-2 angle smaller (99.6° vs. 103.9°) than in triquinacene 1. The root-mean-squared (RMS) deviation from planarity about the centro-position of the cation 224 (0.337 Å) was significantly less than that of triquinacene 1 (0.896 Å). The tendency of sp²-hybridized centres towards planarity was in this case partially balanced by ring strain.

The triquinacyl anion 221 had no major deviations in bond angles and lengths from the parent hydrocarbon. However, minor changes in these parameters combined to reduce the RMS deviation from planarity to 0.731 Å (vs. 0.896 Å in triquinacene 1).
8.3 Modeling of the Dimerization Reaction of Triquinacene (1) to Dodecahedrane (178)

The second series of molecular modeling studies consisted of modeling the dimerization reaction of two molecules of triquinacene 1 to afford dodecahedrane 178. This was accomplished by restricting the intermolecular distance between the six pairs of sp² hybridized carbon atoms which would be involved in this dimerization reaction to a fixed value, denoted r (Figure 31).

![Figure 31 - Definition of the intermolecular distance parameter r](image)

The value of this parameter was varied between 1.0 and 10.0 Å and the energy of the system was evaluated for each value of r by geometry optimization at the B3LYP/6-31G* level of theory. By fixing the intermolecular distance in this manner, the analysis is greatly simplified, as rotation of one triquinacene moiety with respect to the other (about their C₃ᵥ axes) is prevented. Hence, for all values of r, the two triquinacene moieties are always in the correct relative orientation for dimerization.

In the crystal structure of dodecahedrane 178, the lengths of the six σ bonds joining the triquinacene "halves" (analogous to the parameter r) were 1.535 ± 0.005 Å.²⁶⁴ Hence, values of r were chosen such that this bond distance was bracketed. It was expected that the profile of energy vs. r would show a minimum near 1.50-1.55 Å, with a steep rise in energy at lower values of r on
account of internuclear repulsion. At higher values of r, the energy was expected to rise until a transition state value was reached. Beyond this transition state, the energy was expected to fall again and eventually level off with the interactions between the two triquinacene moieties becoming less and less significant at higher values of r.

The energies were calculated for both the ground state and first singlet excited state electronic configurations. The calculations for the first singlet excited state were performed using the CI-Singles (CIS) method\textsuperscript{265} as implemented in Gaussian 98. The analogous calculations for the first triplet excited state were attempted; however, these optimizations failed to converge, generating premature termination errors. In light of the relatively large size (20 non-hydrogen atoms) of the molecular system in question, this was likely the result of memory and other computational limitations.

8.3.1 *Ground state energy profile*

The energy profile for the triquinacene dimerization reaction in the electronic ground state of the system is presented below (Figure 32). The position \((r = 1.55 \text{ Å})\) of the energy minimum corresponded well with the value of the equilibrium C-C bond length \((1.535 \pm 0.005 \text{ Å})\) for dodecahedrane \textbf{178} as determined from its X-ray crystal structure.\textsuperscript{264} Moreover, the estimated reaction exothermicity of 92 kcal mol\(^{-1}\) was in agreement with Paquette's estimate of 97 kcal mol\(^{-1}\), which was based on the thermodynamics of breaking six isolated C-C \(\pi\) bonds along with the formation of six C-C \(\sigma\) bonds.\textsuperscript{96} The optimized transition state structure for this reaction is given in *Appendix 3* (Section 10.3).
8.3.2 First singlet excited state energy profile

The corresponding energy profile for the triquinacene dimerization reaction in the first singlet excited state of the system is presented below (Figure 33). The energy for the lowest point on the profile, that corresponding to $r = 1.55$ Å, was assigned a relative energy of 0 kcal mol$^{-1}$. The transition state ($E = 234.98$ kcal mol$^{-1}$) was found at $r = 2.25$ Å. The energy at $r = 10.0$ Å, where interactions between the triquinacene moieties should be negligible, was 91.60 kcal mol$^{-1}$. Hence, for the gas-phase, ground state dimerization reaction of two molecules of triquinacene 1 to dodecahedrane 178, the reaction was estimated
to be exothermic by 92 kcal mol\(^{-1}\) and had a calculated activation energy of 143 kcal mol\(^{-1}\).

![Graph](attachment:image.png)

**Figure 33 - Energy vs. interatomic distance for the first singlet excited state dimerization reaction of triquinacene (1) to afford dodecahedrane (178)**

In the case of the first excited singlet state of the system, the reaction was estimated to be exothermic by 88 kcal mol\(^{-1}\), some 4 kcal mol\(^{-1}\) less exothermic than the analogous reaction in the ground state. Again, the energy minimum occurred at \(r = 1.55 \text{ Å}\). However, in this case, the activation energy was calculated to be 223 kcal mol\(^{-1}\), which was much greater than that of the ground state dimerization reaction (143 kcal mol\(^{-1}\)). The transition state was found at a value of \(r (2.20 \text{ Å})\) which was close to that of the ground state reaction (2.25 Å). The transition state geometry is given in *Appendix 3* (Section 10.3). The
tabulated energy vs. r data for the ground and first excited singlet states are found in Appendix 4 (Section 10.4).

8.3.3 Discussion

The gas-phase dimerization reaction of triquinacene 1 to dodecahedrane 178 had a larger activation barrier in the first singlet excited state (223 kcal mol\(^{-1}\)) than in the ground state (143 kcal mol\(^{-1}\)). As this reaction is a \([6+6]\) cycloaddition, the Woodward-Hoffman rules predict that the process should be photochemically allowed. However, it is possible that this reaction would take place through a triplet excited state rather than a singlet state, or that the dimerization reaction would not be concerted. Further experimental and computational studies would need to be performed in order to investigate these possibilities.

8.4 Summary and Conclusions

The C-10-centred triquinacyl radical 219, anion 221 and cation 224 were found to be more stable (with respect to the parent hydrocarbon, triquinacene 1) than the corresponding methyl species but less stable than the analogous \(t\)-butyl species. As was the case with the \(t\)-butyl species, the triquinacyl reactive species benefit from hyperconjugative stabilization. However, the geometric constraints imposed by the triquinacene ring system attenuated these stabilizing interactions (e.g. by preventing the triquinacyl cation 224 from achieving planarity). Of the three reactive species, the triquinacyl cation 224 was the most
planar about C-10 and was significantly higher in energy than the corresponding radical 221 or anion 219.

The ground state, gas-phase dimerization reaction of triquinacene 1 to dodecahedrane 178 was calculated to be exothermic by 92 kcal mol\(^{-1}\) and to have an activation energy barrier of 143 kcal mol\(^{-1}\). These values for the same reaction in the first singlet excited state of the system were 88 and 233 kcal mol\(^{-1}\), respectively. The transition states were found at an intermolecular separation of 2.25 Å (ground state) or 2.20 Å (excited state). These preliminary computational experiments will serve as a starting point for future theoretical and experimental studies of the triquinacene ring system and of the dimerization of triquinacene (1) to dodecahedrane (178).
CHAPTER NINE: EXPERIMENTAL

9.1 General Experimental

All non-aqueous reactions were performed under an atmosphere of dry nitrogen, in oven- or flame-dried glassware, unless otherwise indicated. Reaction temperatures stated were those of the external bath. Tetrahydrofuran, dimethoxyethane and diethyl ether (ether) were dried over sodium/benzophenone ketyl and distilled under an atmosphere of dry nitrogen immediately prior to use. Benzene, acetonitrile, dichloromethane, toluene, $N,N$-diisopropylamine, $N,N,N$-diisopropylethylamine (Hünig's base), trimethylsilyl chloride, $N,N$-dimethylformamide, hexamethylphosphoramide and triethylamine were dried over calcium hydride and distilled under an atmosphere of dry nitrogen immediately prior to use. Methanol was dried over its corresponding magnesium alkoxide and distilled under an atmosphere of dry nitrogen immediately prior to use. All other solvents and reagents were purified by standard techniques or used as supplied. Brine refers to a saturated aqueous solution of sodium chloride. Silica gel column chromatography ("flash chromatography") was carried out using Merck silica gel 60 (230 to 400 mesh).

Melting points (M.p.) were measured on a Gallenkamp capillary melting point apparatus and are uncorrected. All proton and carbon nuclear magnetic resonance ($^1$H NMR and $^{13}$C NMR, respectively) spectra were recorded using
either a Bruker AMX 400 FT spectrometer (operating frequencies: $^1$H, 400.13 MHz; $^{13}$C, 100.61 MHz), a Varian AS 500 spectrometer (operating frequencies: $^1$H, 499.77 MHz; $^{13}$C, 125.67 MHz) or a Bruker AMX 600 spectrometer (operating frequencies: $^1$H, 600.14 MHz; $^{13}$C, 150.92 MHz) at ambient temperature unless otherwise noted. Chemical shifts ($\delta$) for all compounds are listed in parts per million downfield from tetramethylsilane using the residual non-deuterated solvent peak as an internal reference. Infrared (IR) spectra were recorded as either neat liquids (neat), KBr discs (KBr) or evaporated films (ef) using a Perkin Elmer 599B IR spectrophotometer. Mass spectra (MS) were recorded on a Hewlett Packard 5985 GC-mass spectrometer. The modes of ionization used were electron impact (El) or chemical ionization (CI) with isobutane. High-resolution mass spectra (HRMS) using fast atom bombardment (FAB) were recorded on a Kratos Concept IH mass spectrometer. Microanalyses (Anal.) were performed on a Carlo Erba Model 1106 CHN analyzer.

Solutions of lithium $N,N$-diisopropylamide were prepared by adding $n$-butyllithium (2.5 M solution in hexanes) dropwise to a solution of freshly distilled $N,N$-diisopropylamine (1.1 equiv. with respect to $n$-butyllithium) in THF at 0 °C and stirring for 30 min at this temperature.
To a 500 mL flask fitted with a mechanical stirrer, reflux condenser and dropping funnel was added anhydrous methanol (90 mL). After cooling to 0 °C, powdered sodium hydroxide (6.38 g, 159 mmol, 2.02 equiv.) was added and stirring was continued until a clear, colourless solution was obtained. Dimethyl-1,3-acetone dicarboxylate 233 (27.4 g, 157 mmol, 2.00 equiv.) was then added dropwise over a period of 1 h. Over the course of the addition, a yellow-white precipitate was deposited. The ice-water bath was then replaced with a heating mantle and the reaction mixture was brought to reflux temperature (~65 °C) over the course of 30 min, during which time the precipitate dissolved to afford a pale yellow solution. After a further 20 min at reflux, glyoxal 69 (28.8 mL of a 40% w/v aqueous solution, 79.4 mmol, 1.00 equiv.) was added dropwise over a period of 100 min, during which time a yellow-orange precipitate was deposited. The heating was then discontinued and the resultant slurry was allowed to stir overnight. The precipitate was collected by vacuum filtration and washed with methanol (50 mL), to afford the crude disodium enolate of tetramethyl bicyclo[3.3.0]octan-3,7-dione-2,4,6,8-tetracarboxylate 234 (9.43 g) as a pale orange crystalline solid which was then dissolved in a mixture of aqueous
hydrochloric acid (1 M, 70 mL) and glacial acetic acid (7.0 mL) and then heated at reflux for 3 h. The progress of the decarboxylation reaction was monitored by means of a bubbler affixed to the top of the reflux condenser. The reaction mixture was then cooled to room temperature and extracted with chloroform (5 × 25 mL). After removal of solvent in vacuo, the residue was taken up in chloroform (150 mL) and washed repeatedly with saturated aqueous sodium bicarbonate solution (3 × 20 mL) until the aqueous phase was basic to litmus paper. The combined aqueous phases were back-extracted with chloroform (3 × 10 mL) and the combined organic phases were dried over anhydrous magnesium sulfate and concentrated in vacuo to afford a yellow-orange solid. Recrystallization of this material from methanol afforded the title compound 232 (6.47 g, 59%) as a colourless solid. Spectral data were consistent with those previously reported.\textsuperscript{126} \textit{R}_{f} 0.15 (hexanes:ether, 1:1); \textbf{M.p.} 82-84 °C, methanol (lit.\textsuperscript{126} 83-86 °C, methanol); \textbf{\textit{H} NMR} (400 MHz, CDCl\textsubscript{3}) \(\delta\) 2.12 (dd, \(J = 19.5, 4.0\) Hz, 4H), 2.55 (ddd, \(J = 19.5, 7.0, 1.8\) Hz, 4H), 2.96-3.06 (m, 2H, 2 × bridgehead CH); \textbf{\textit{13C} NMR} (101 MHz, CDCl\textsubscript{3}) \(\delta\) 36.4, 43.6, 217.8; \textbf{IR} (KBr) 2957, 1734, 1405, 1222 cm\textsuperscript{-1}; \textbf{MS} (El) \textit{m/z} (rel. intensity) 138 (M, 91), 110 (7), 95 (8), 81 (13), 69 (68), 68 (100), 55 (14).
A solution of cis-bicyclo[3.3.0]octan-3,7-dione 232 (6.00 g, 43.4 mmol, 1.00 equiv.), neopentyl glycol (4.52 g, 43.4 mmol, 1.00 equiv.), p-toluenesulfonic acid monohydrate (25 mg, catalytic amount) in benzene (125 mL) was heated at reflux with azeotrophic removal of water (Dean-Stark trap) until the evolution of water ceased (~4 h). The resultant clear, colourless solution was allowed to cool to room temperature and anhydrous potassium carbonate (50 mg) was added. After stirring for 10 min, the suspension was filtered and the solvent was removed in vacuo to afford a colourless semi-solid which was purified by flash chromatography (hexanes:ether, 3:1; crude mixture loaded in hexanes:ether:dichloromethane, 3:2:1).

The first compound to elute was cis-bicyclo[3.3.0]octan-3,7-dione-3,7-bis-(2',2'-dimethylpropylidene) acetal 235 (2.83 g, 21%) which was obtained as a colourless crystalline solid. Spectral data were consistent with those previously reported.\textsuperscript{126} \textit{Rf} 0.35 (hexanes:ether, 1:1); \textbf{M.p.} 137-139 °C, hexanes/ether (lit.\textsuperscript{126} 140-142 °C, ethanol); \textit{^1}H NMR (400 MHz, CDCl\textsubscript{3}) \textit{δ} 0.94 (s, 12 H, 4 × acetal 232 (22%) + 235 (21%)
CH₃), 1.71 (dd, J = 13.2, 6.0 Hz, 4 H), 2.19 (dd, J = 13.2, 8.7 Hz, 4H), 2.50-2.60 (m, 2H, bridgehead CH), 3.45 (s, 4H, acetal OCH₂), 3.46 (s, 4H, acetal OCH₂); ¹³C NMR (101 MHz, C₆D₆) δ 22.6, 30.0, 37.6, 40.2, 71.7, 72.3, 110.2; IR (KBr) 2953, 2858, 1471, 1306, 1115 cm⁻¹; MS (El) m/z (rel. intensity) 310 (M, 42), 267 (44), 225 (11), 207 (18), 182 (12), 155 (31), 141 (29), 139 (31), 128 (24), 111 (15), 95 (11), 81 (11), 69 (100), 55 (31).

The second compound to elute was cis-bicyclo[3.3.0]octan-3,7-dione-7-(2',2'-dimethylpropylidene) acetal 231 (5.07 g, 52%), which was obtained as a colourless solid and then recrystallized from hexanes. Spectral data were consistent with those previously reported.¹²⁶ Rf 0.30 (hexanes:ether, 1:1); M.p. 45-46 °C, hexanes (lit.¹²⁶ 48 °C); ¹H NMR (400 MHz, C₆D₆) δ 0.74 (s, 6H, acetal CH₃), 1.57 (dd, J = 13.3, 3.9 Hz, 2H), 1.85-2.10 (m, 6H), 2.21-2.32 (m, 2H), 3.12 (s, 2H, acetal OCH₂), 3.21 (s, 2H, acetal OCH₂); ¹³C NMR (101 MHz, C₆D₆) δ 22.4, 22.5, 29.8, 36.7, 41.3, 44.4, 71.8, 72.0, 109.8, 217.0; IR (KBr) 2952, 2865, 1750, 1394, 1117 cm⁻¹; MS (El) m/z (rel. intensity) 224 (M, 48), 181 (27), 155 (31), 154 (30), 141 (16), 139 (10), 128 (12), 81 (8), 69 (100), 68 (27), 55 (19).

The third compound to elute was the starting material, dione 232 (1.28 g, 22%), which was recovered as a colourless solid.
9.2.3  *Re-equilibration ("recycling") of the bisacetal (235)*

A solution of cis-bicyclo[3.3.0]octan-3,7-dione-3,7-bis-(2',2'-dimethylpropylidene) acetal 235 (7.50 g, 24.2 mmol, 1.00 equiv.), water (435 µL, 24.2 mmol, 1.00 equiv.) and p-toluenesulfonic acid monohydrate (25 mg, catalytic amount) in anhydrous benzene (125 mL) was heated at reflux for 24 h. The resultant clear, colourless solution was allowed to cool to room temperature and anhydrous potassium carbonate (50 mg) was added. After stirring for 10 min, the suspension was filtered and the solvent removed *in vacuo* to afford a colourless semi-solid. Separation of the mixture by flash chromatography (hexanes:ether, 3:1) afforded the starting material, cis-bicyclo[3.3.0]octan-3,7-dione-3,7-bis-(2',2'-dimethylpropylidene) acetal 235 (1.73 g, 23%), as well as cis-bicyclo[3.3.0]octan-3,7-dione-7-(2',2'-dimethylpropylidene) acetal 231 (2.49 g, 46%) and cis-bicyclo[3.3.0]octane-3,7-dione 232 (800 mg, 24%). All three compounds had spectral and physical properties identical to those of the materials which were obtained by *Procedure 9.2.2*. 
9.2.4 cis-Bicyclo[3.3.0]oct-1-en-3-one-7-(2',2'-dimethylpropylidene) acetal (230)*

9.2.4.1 Procedure A - Saegusa reaction

To a freshly prepared solution of LDA (36.8 mmol, 1.20 equiv.) in dry THF (100 mL) at -78 °C was added a solution of cis-bicyclo[3.3.0]octan-3,7-dione-7-(2',2'-dimethylpropylidene) acetal 231 (6.89 g, 30.7 mmol, 1.00 equiv.) in dry THF (20 mL) via a cannula. After stirring for 30 min at -78 °C, the resultant pale yellow solution was allowed to warm to 0 °C. The solution was then re-cooled to -78 °C and freshly distilled trimethylsilyl chloride (5.25 mL, 41.4 mmol, 1.35 equiv.) was added. The reaction mixture was allowed to warm to room temperature over a period of 1.5 h and then recooled to -78 °C. The reaction was quenched with a saturated aqueous solution of sodium bicarbonate (25 mL) and was again allowed to warm to room temperature. The phases were then separated and the aqueous phase was extracted with distilled dichloromethane (3 × 50 mL). The combined organic phases were dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford the corresponding crude enol silane, which was immediately dissolved in dry acetonitrile (50 mL) and cooled to 0 °C. Palladium (II) acetate (6.89 g, 30.7 mmol, 1.00 eq) was added with stirring and the reaction was allowed to warm to room temperature overnight. The reaction mixture was then filtered through a pad of silica gel topped with a layer of sand.
and washed repeatedly with ether (400 mL). The amber coloured filtrate was concentrated in vacuo to afford a pale yellow crystalline solid which was purified by flash chromatography (hexanes:ether, 1:1) and finally by recrystallization from hexanes to afford the title compound 230 (6.23 g, 91%) as a white crystalline solid. \( R_f \) 0.15 (hexanes:ether, 1:1); \textbf{M.p.} 81-82 °C, hexanes (lit.\textsuperscript{128} 84-86 °C). \( ^1\text{H} \) NMR (400 MHz, C\textsubscript{6}D\textsubscript{6}, assignments by COSY and HMQC experiments) \( \delta \) 0.73 (s, 3H, 3 \times H\textsubscript{12} or H\textsubscript{13}), 0.84 (s, 3H, 3 \times H\textsubscript{12} or H\textsubscript{13}), 1.06 (t, \( J = 12.3 \) Hz, 1H, H\textsubscript{6}), 1.74 (dd, \( J = 17.5, 3.6 \) Hz, 1H, H\textsubscript{8}), 2.26-2.33 (m, 2H, H\textsubscript{6} and H\textsubscript{8}), 2.42-2.62 (m, 2H, 2 \times H\textsubscript{4}), 2.65-2.75 (br m, 1H, H\textsubscript{5}), 3.10-3.25 (m, 4H, 2 \times H\textsubscript{9} and 2 \times H\textsubscript{11}), 5.72 (s, 1H, H\textsubscript{2}); \( ^{13}\text{C} \) NMR (101 MHz, C\textsubscript{6}D\textsubscript{6}) \( \delta \) 21.9 (C\textsubscript{12} or C\textsubscript{13}), 22.0 (C\textsubscript{12} or C\textsubscript{13}), 30.0 (C\textsubscript{10}), 38.2 (C\textsubscript{4}), 41.8 (C\textsubscript{6}), 42.0 (C\textsubscript{8}), 43.2 (C\textsubscript{5}), 71.5 (C\textsubscript{9} or C\textsubscript{11}), 72.3 (C\textsubscript{9} or C\textsubscript{11}), 105.8 (C\textsubscript{7}), 125.8 (C\textsubscript{2}), 183.5 (C\textsubscript{1}), 207.1 (C\textsubscript{3}); \textbf{IR} (KBr) 2974, 2865, 1699, 1628, 1467, 1287, 1094 cm\textsuperscript{-1}; \textbf{MS} (Cl) \textit{m/z} (rel. intensity) 223 (M, 100), 155 (3), 137 (2), 128 (2), 108 (1), 95 (1), 85 (4); \textbf{Anal.} Calcd. for C\textsubscript{13}H\textsubscript{18}O\textsubscript{3}: C, 70.24; H, 8.16; Found: C, 70.24; H, 8.32.

9.2.4.2 \textit{Procedure B - Selenoxide elimination}

\begin{align*}
\text{cis-bicyclo[3.3.0]octan-3,7-dione-7-(2',2'-dimethyl-propylidene) acetal 231} \quad & \quad \text{1. LDA, THF, -78 °C, 30 min then PhSeBr, -78 °C to rt, 2 h} \quad \text{231} \\
& \quad \text{2. H\textsubscript{2}O\textsubscript{2}, py, DCM, 0 °C to rt, 75 min} \\
& \quad \text{57%} \quad \text{230} 
\end{align*}

A solution of \textit{cis-bicyclo[3.3.0]octan-3,7-dione-7-(2',2'-dimethyl-propylidene) acetal 231} (3.00 g, 13.4 mmol, 1.0 equiv.) in THF (10 mL) was added to a solution of LDA (16.0 mmol, 1.2 equiv.) in THF (50 mL) at -78 °C via a cannula. The resultant yellow solution was stirred for 30 min at -78 °C and was
allowed to warm to 0 °C over 15 min. The reaction mixture was re-cooled to -78 °C and phenylselenium bromide (3.78 g, 16.0 mmol, 1.2 equiv.) was added. After 30 min at -78 °C, the solution was allowed to warm to room temperature over 2 h. The reaction mixture was cooled to -78 °C and a saturated aqueous sodium bicarbonate solution (5 mL) was added. The yellow solution was allowed to warm to room temperature and the THF was removed in vacuo. The residue was diluted with water (10 mL) and extracted with dichloromethane (5 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous magnesium sulfate and filtered. The resultant orange solution of the crude phenylselenide was cooled to 0 °C and pyridine (2.2 mL, 27 mmol, 2.0 equiv.) was added. After stirring for 10 min, hydrogen peroxide (30% w/w aqueous solution, 11 mL, 94 mmol, 7.0 equiv.) was added dropwise over 5 min. The resultant orange biphasic mixture was allowed to warm to room temperature and was stirred for 75 min, during which time the orange colour faded to pale yellow. The reaction mixture was diluted with water (15 mL) and the phases were separated. The organic phase was washed with aqueous hydrochloric acid solution (1 M, 3 × 15 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography (hexanes:ether, 1:1) to afford the title compound 230 (1.69 g, 57%) as a colourless solid. The spectral and physical properties of the product were identical to those of the material which was obtained by Procedure A.
A dry 2-necked flask was charged with cuprous iodide (377 mg, 1.98 mmol, 2.2 equiv.). The cuprous iodide was briefly flame-dried and allowed to cool under a stream of N₂. The drying process was repeated four times in total. THF (10 mL) was then added and the resultant suspension was cooled to 0 °C. Phenylmagnesium bromide (1.20 mL of a 3 M solution in ether, 3.60 mmol, 4.0 equiv.) was added dropwise and the suspension was stirred for 1 h at 0 °C. A solution of cis-bicyclo[3.3.0]oct-1-en-3-one-7-(2',2'-dimethylpropylidene) acetal 230 (200 mg, 0.90 mmol, 1.00 equiv.) in THF (10 mL) was added via a cannula to the pale brown organocuprate suspension and the reaction mixture was stirred for 5 h at 0 °C and then allowed to warm to room temperature over 30 min. The reaction mixture was cooled to -78 °C and a saturated solution of ammonium chloride that had been adjusted to pH 9 by the addition of 5% v/v concentrated aqueous ammonium hydroxide solution (10 mL) and ether (10 mL) were added. The resultant biphasic mixture was allowed to warm to room temperature open to the air with vigorous stirring until the aqueous layer had turned an intense blue colour (1 h). The phases were separated and the aqueous phase was extracted with ether (3 × 10 mL). The combined organic extracts were washed with water.
(3 × 10 mL) and brine (10 mL), then dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The crude product was purified by flash chromatography (hexanes:ether, 1:1) to afford the *title compound 246* (223 mg, 82%) as a colourless oil. \( R_f \) 0.55 (hexanes:ether, 1:1); \(^1\)H NMR (400 MHz, C\(_6\)D\(_6\), assignments by COSY and HMQC experiments) \( \delta \) 0.70 (s, 3H, 3 × H\(_{12}\) or 3 × H\(_{13}\)), 0.77 (s, 3H, 3 × H\(_{12}\) or 3 × H\(_{13}\)), 1.69 (apparent dq, \( J = 7.0, 1.2 \) Hz, 1H, H\(_4\)), 2.03 (dd, \( J = 18.6, 3.2 \) Hz, 1H, H\(_6\)), 2.14-2.23 (m, 2H, H\(_{4}'\) and H\(_{6}'\)), 2.33 (apparent dq, \( J = 12.1, 1.0 \) Hz, 2H, 2 × H\(_2\)), 2.57 (dd, \( J = 4.0, 1.2 \) Hz, 2H, 2 × H\(_6\)), 2.64-2.70 (m, 1H, H\(_5\)), 3.16 (s, 2H, 2 × H\(_9\) or 2 × H\(_{11}\)), 3.20 (s, 2H, 2 × H\(_9\) or 2 × H\(_{11}\)), 6.97-7.25 (m, 5H, aryl); \(^{13}\)C NMR (101 MHz, C\(_6\)D\(_6\)) \( \delta \) 22.2 (C\(_{12}\) or C\(_{13}\)), 22.3 (C\(_{12}\) or C\(_{13}\)), 29.8 (C\(_{10}\)), 42.2 (C\(_4\)), 44.0 (C\(_6\)), 44.8 (C\(_5\)), 49.7 (C\(_2\)), 52.1 (C\(_8\)), 52.3 (C\(_1\)), 71.8 (C\(_9\) or C\(_{11}\)), 72.0 (C\(_9\) or C\(_{11}\)), 108.9 (C\(_7\)), 125.9 (C\(_{17}\)), 126.3 (C\(_{15}\) and C\(_{19}\)), 128.8 (C\(_{16}\) and C\(_{18}\)), 148.52 (C\(_{14}\)), 215.3 (C\(_3\)); IR (ef) 3034, 2953, 2866, 1741, 1113 cm\(^{-1}\); MS (Cl) m/z (rel. intensity) 301 (M + H, 100), 215 (10), 155 (2); Anal. Calcd. for C\(_{19}\)H\(_{24}\)O\(_3\): C, 75.97; H, 8.05; Found: C, 75.86; H, 8.09.
To a dry 2-necked flask was added cuprous iodide (2.32 g, 11.3 mmol, 2.50 equiv.). The cuprous iodide was briefly flame-dried and allowed to cool under a stream of N₂. The drying process was repeated four times in total. Freshly distilled THF (40 mL) was then added and the resultant suspension was cooled to 0 °C. Phenylmagnesium bromide (3 M solution in ether, 7.50 mL, 22.5 mmol, 5.00 equiv.) was added dropwise and the pale brown suspension was stirred for 1 h at 0 °C. A solution of cis-bicyclo[3.3.0]oct-1-en-3-one-7-(2',2'-dimethylpropylidene) acetal 230 (1.00 g, 4.50 mmol, 1.00 equiv.) and freshly distilled trimethylsilyl chloride (2.85 mL, 22.5 mmol, 5.00 equiv.) in THF (10 mL) was added via a cannula to the organocuprate suspension. The reaction mixture was then stirred for 2.5 h at 0 °C and allowed to warm to room temperature over 30 min. The reaction mixture was cooled to 0 °C, freshly distilled triethylamine (3.30 mL, 23.4 mmol, 5.20 equiv.) was added and the reaction mixture was
allowed to warm to room temperature over 30 min. After removal of solvents in vacuo, the green-brown residue was suspended in pentane (50 mL), mixed thoroughly (vortex mixing and ultrasonication) and filtered. The pentane was removed in vacuo and the resultant crude enol silane was immediately dissolved in THF (20 mL) and cooled to 0 °C. Methyllithium (3.5 mL of a 1.4 M solution in ether, 4.9 mmol, 1.1 equiv.) was added dropwise and after stirring for 30 min at 0 °C, allyl bromide (1.95 mL, 22.5 mmol, 5.00 equiv.) that had been purified by passage through a pad of neutral Brockman Grade I alumina and dry hexamethylphosphoramide (8.0 mL) were added. The resultant yellow solution was allowed to warm to room temperature and was stirred overnight. The reaction mixture was diluted with water (20 mL) and ether (30 mL) and the phases were separated. The aqueous phase was extracted with ether (3 × 15 mL) and the combined organic phases were washed with water (3 × 10 mL), brine (10 mL), dried over anhydrous magnesium sulfate and then concentrated in vacuo. The crude product was purified by flash chromatography (hexanes:ether, 9:1).

The first compound to elute was 1-phenyl-3-(2'-propenoxy)-cis-bicyclo[3.3.0]oct-2-en-3-one-7-(2',2'-dimethylpropylidene) acetal 248 (872 mg, 55%) which was obtained as a white crystalline solid and then recrystallized from hexanes. Rf 0.85 (hexanes:ether, 1:1); M.p. 123-124°C, hexanes; ^1H NMR (400 MHz, C₆D₆, assignments by COSY and HMQC experiments): δ 0.80 (2 x s, 6H, 3 x H₁₂ and 3 x H₁₃), 1.87 (dd, J = 13.0, 8.9 Hz, 1H, H₆), 2.09 (d, J = 14.6 Hz, 1H, H₈), 2.37 (d, J = 13.9 Hz, 1H, H₄), 2.45 (ddd, J = 13.0, 7.3, 2.0 Hz, 1H, H₆'), 2.60-
2.70 (m, 2H, H₅ and H₆'), 2.78 (dd, J = 13.9, 2.0 Hz, 1H, H₄'), 3.27 (s, 2H, 2 × H₉ or 2 × H₁₁), 3.38 (s, 2H, 2 × H₉ or 2 × H₁₁), 4.05-4.11 (m, 2H, 2 × H₁₄), 4.52 (s, 1H, H₂), 5.02 (ddd, J = 10.6, 1.6, 1.2 Hz, 1H, H₁₆), 5.22 (dq, J = 17.0, 1.6 Hz, 1H, H₁₆'), 5.80-5.90 (m, 1H, H₁₉ and H₂₁), 7.11 (dt, J = 7.3, 0.8 Hz, 1H, H₂₀), 7.25-7.30 (m, 2H, H₁₉ and H₂₁), 7.61 (dd, J = 7.3, 0.8 Hz, 2H, H₁₈ and H₂₂); ¹³C NMR (101 MHz, C₆D₆) δ 22.2 (C₁₂ or C₁₃), 22.4 (C₁₂ or C₁₃), 30.0 (C₁₀), 37.7 (C₈), 42.0 (C₆), 46.9 (C₅), 49.3 (C₄), 58.2 (C₁), 70.0 (C₁₄), 71.1 (C₉ or C₁₁), 72.3 (C₉ or C₁₁), 103.7 (C₂), 108.9 (C₇), 116.6 (C₁₆), 125.6 (C₂₀), 126.4 (C₁₈ and C₂₂), 128.1 (C₁₉ and C₂₁), 134.0 (C₁₅), 151.1 (C₁₇), 157.9 (C₃); IR (KBr) 2953, 2847, 1642, 1114, 1011 cm⁻¹; MS (Cl) m/z (rel. intensity) 341 (M + H, 100), 321 (3), 299 (2), 129 (5); Anal. Calcd. for C₂₂H₂₈O₃: C, 77.61; H, 8.29; Found: C, 77.73; H, 8.23.

The second compound to elute was 1-phenyl-2-(2'-propenyl)-cis-bicyclo[3.3.0]octan-3,7-dione-7-(2',2'-dimethylpropylidene) acetal 229 as a colourless oil (~1:1 mixture of diastereomers, diastereomeric at C₂, 158 mg, 10%). Rf 0.75 (hexanes:ether, 1:1); ¹H NMR (400 MHz, C₆D₆) δ 0.64 and 0.75 (2 × s, 3H overall, acetal CH₃), 0.78 and 0.81 (2 × s, 3H overall, acetal CH₃), 1.70-1.85 (m, 1H), 1.92-2.09 (m, 1H), 2.18-2.61 (m, 4H), 2.65-2.95 (m, 2H), 3.15-3.35 (m, 4H, acetal -OCH₂), 4.79-4.98 (m, 2H, -CH=CH₂). 5.72-5.96 (m, 1H, -CH=CH₂), 6.95-7.35 (m, 5H, aryl); ¹³C NMR (101 MHz, C₆D₆) δ 22.1, 22.4, 29.7, 29.8, 31.1, 31.5, 38.7, 41.6, 41.7, 42.3, 43.0, 43.7, 45.3, 46.7, 55.9, 57.3, 58.6, 61.9, 71.7, 71.8, 72.1, 72.3, 109.0, 110.0, 115.4, 116.0, 126.4, 126.9, 127.0, 128.4, 137.1, 137.2, 145.6, 146.1, 215.0, 215.4; IR (ef) 3064, 2953, 2865, 1738, 1641, 1114 cm⁻¹; MS (Cl) m/z (rel. intensity) 341 (M + H, 100), 297 (3), 255 (5), 285.
129 (1), 85 (1); Anal. Calcd. for C\textsubscript{22}H\textsubscript{28}O\textsubscript{3}: C, 77.61; H, 8.29; Found: C, 77.33; H, 8.44.

The third compound to elute was 1-phenyl-cis-bicyclo[3.3.0]octan-3,7-dione-7-(2',2'-dimethylpropylidene) acetal 246 (231 mg, 15%) which was obtained as a colourless oil. This material had spectral and physical properties identical to those of the material obtained by Procedure 9.2.5.

9.2.7 1-Phenyl-2-(2'-propenyl)-cis-bicyclo[3.3.0]octan-3,7-dione-7-(2',2'-dimethyl-propylidene) acetal (229) by Claisen rearrangement of 1-phenyl-3-(2'-propenoxy)-cis-bicyclo[3.3.0]oct-2-en-3-one-7-(2',2'-dimethylpropylidene) acetal (248)

A solution of 1-phenyl-3-(2'-propenoxy)-cis-bicyclo[3.3.0]oct-2-en-3-one-7-(2',2'-dimethylpropylidene) acetal 248 (630 mg, 1.85 mmol, 1.00 equiv.) in toluene (100 mL) was deoxygenated with dry N\textsubscript{2} for 30 min at room temperature. The clear, colourless solution was then heated at reflux for 68 h and then allowed to cool to room temperature. After removal of the solvent in vacuo, flash chromatography (hexanes:ether, 4:1) afforded the title compound 229 (~3:2 mixture of diastereomers, diastereomeric at C-2, 605 mg, 96%) as a colourless oil. This material had spectral and physical properties identical to those of the material obtained by Procedure 9.2.6.
To a solution of 1-phenyl-2-(2'-propenyl)-cis-bicyclo[3.3.0]octan-3,7-dione-7-(2',2'-dimethylpropyldiene) acetal 229 (220 mg, 0.647 mmol, 1.00 equiv.) in p-dioxane (4.4 mL) and water (3.1 mL) at room temperature was added osmium tetroxide (~5 mg, catalytic amount). The reaction vessel was wrapped in aluminum foil to protect it from light and the reaction mixture was stirred for 45 min, over which time an intense purple-brown colour developed. Sodium periodate (346 mg, 1.62 mmol, 2.50 equiv.) was then added in small portions over a period of 4 hours. After stirring for 1 h, the resultant brown reaction mixture was filtered to remove inorganic salts and the filter cake was washed with ethyl acetate (10 mL). The phases were separated and the aqueous phase was extracted with ethyl acetate (5 x 5 mL). The combined organic phases were passed through a pad of neutral alumina (Brockman Grade I) to remove residual osmium species with ethyl acetate (75 mL). The resultant yellow solution was dried over anhydrous magnesium sulfate and filtered. After removal of solvents in vacuo, flash chromatography (hexanes:ether, 3:1) afforded the title compound 228 (187 mg, 85%) as a pale yellow oil (1.6:1 mixture of diastereomers). This material was used in the next step without further purification.
An analytical sample of the major diastereomer was obtained by repeated flash chromatography (hexanes:ether, 4:1). \( R_f \) 0.30 (hexanes:ether, 1:1); \(^1^H\) NMR (400 MHz, C\(_6\)D\(_6\)) \( \delta \) 0.72 (s, 3H, acetal CH\(_3\)), 0.89 (s, 3H, acetal CH\(_3\)), 1.51 (dd, \( J = 18.2, 6.4 \) Hz, 1H), 1.79 (ddd, \( J = 13.8, 5.9, 1.5 \) Hz, 1H), 2.18-2.42 (m, 5H), 2.62-2.72 (m, 1H, bridgehead CH), 3.07 (dd, \( J = 13.8, 1.5 \) Hz, 1H), 3.20-3.25 (m, 3H), 3.53-3.57 (m, 1H), 3.60 (d, \( J = 11.2 \) Hz, 1H), 6.73-6.77 (m, 2H), 6.94-7.06 (m, 3H), 9.14 (s, 1H, CHO); \(^{13}\)C NMR (101 MHz, C\(_6\)D\(_6\)) \( \delta \) 22.3, 22.6, 29.9, 41.4, 41.8, 43.9, 44.0, 44.5, 53.2, 55.4, 71.9, 72.3, 108.8, 126.5, 126.7, 126.8, 127.2, 128.7, 146.2, 199.5, 215.3; IR (ef) 2953, 2859, 2721, 1738, 1722, 1126 cm\(^{-1}\); MS (Cl) \( m/z \) (rel. intensity) 343 (M + H, 100), 325 (10), 257 (33), 239 (6), 154 (3), 129 (7). \textbf{Anal.} Calcd. for C\(_{21}\)H\(_{26}\)O\(_4\): C, 73.66; H, 7.65; Found: C, 73.46; H, 7.78.

9.2.9 \( \text{10-Phenyltricyclo[5.2.1.0\(^{4.10}\)]deca-3,8-dione-6-ol, 8-(2',2'-dimethylpropyliendene acetal) (255) and 10-Phenyltricyclo-[5.2.1.0\(^{4.10}\)]deca-3,8-dione-6-ol (227) } \)

\[ \begin{align*}
\text{228} & \xrightarrow{p-$\text{TsOH}$ (cat.), Me\(_2\)CO, rt, 5 days then H\(_2\)O, 2 days} \text{255 (14%) + 227 (79%)} \\
\end{align*} \]

To a solution of aldehyde \textbf{228} (222 mg, 0.648 mmol, 1.00 equiv.) in reagent grade acetone (10 mL) was added \( p \)-toluene sulfonic acid monohydrate (~5 mg, catalytic amount). After stirring for 5 days at room temperature, water (5 mL) was added and the reaction mixture was stirred at room temperature for a further 2 days. Solid sodium bicarbonate (100 mg) was added and the resultant
mixture stirred for a further 5 min. The solvent was removed in vacuo and the aqueous residue was diluted with water (5 mL) and extracted with dichloromethane (5 × 10 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography (hexanes:ether, 2:1 followed by neat ether).

The first compound to elute was 10-phenyltricyclo[5.2.1.04\,4.10]deca-3,8-dione-6-ol, 8-(2',2'-dimethylpropyldene acetal) 255 (31 mg, 14%) which was obtained as a colourless solid (~5:1 mixture of diastereomers). Rf 0.80 (ether); M.p. 69-70 °C, ether/hexanes; ¹H NMR (400 MHz, CDCl₃, integration refers to the apparent number of protons in the diastereomeric mixture) δ 0.57 (s, 2.5 H, acetal CH₃ of major diastereomer), 0.68 (s, 0.5 H, acetal CH₃ of minor diastereomer), 1.04 (s, 2.5 H, acetal CH₃ of major diastereomer), 1.11 (s, 0.5 H, acetal CH₃ of minor diastereomer), 1.30-1.40 (m, 0.1 H), 1.41-1.49 (m, 0.8 H), 1.96-2.55 (m, 4.5 H), 2.64-3.20 (m, 5.5 H), 3.22-3.31 (m, 0.9 H), 3.32-3.46 (m, 1.9 H), 3.50-3.58 (m, 0.3 H), 4.14 (t, J = 5.8 Hz, 0.8 H, CHO of major diastereomer), 4.59 (apparent q, J = 3.3 Hz, 0.2 H, CHO of minor diastereomer), 7.07-7.44 (m, 5 H, aryl); ¹³C NMR (101 MHz, CDCl₃) δ 23.0, 30.9, 31.8, 39.4, 42.0, 42.7, 43.0, 43.4, 43.9, 46.0, 50.2, 53.2, 55.0, 56.0, 76.8, 76.9, 77.1, 99.0, 99.4, 125.9, 126.6, 127.1, 128.8, 128.9, 142.3, 215.9; IR (KBr) 3630-3200 (broad), 2968, 2928, 2843, 1734 (s), 1140, 1087 cm⁻¹; MS (Cl) m/z (rel. intensity) 343 (M + H, 100), 341 (2), 244 (5), 239 (5) 128 (7); Anal. Calcd. for C₂₁H₂₆O₄: C, 73.66; H, 7.65; Found: C, 73.39; H, 7.64.
The second compound to elute was 10-phenyltricyclo[5.2.1.0\textsuperscript{4,10}]deca-3,8-dione-6-ol \textbf{227} (131 mg, 79\%) which was obtained as a colourless semi-solid (~7:3 mixture of diastereomers). $R_f$ 0.55 (ether); $^1\text{H NMR}$ (400 MHz, CDCl\textsubscript{3}, integration refers to apparent number of protons in the diastereomeric mixture) $\delta$ 1.77 (s, ~0.3 H, CHOH), 2.03-2.11 (m, 0.3 H), 2.23-2.67 (m, 4.7 H), 2.84-2.97 (m, 2.0 H), 3.10-3.28 (m, 2.6 H), 3.36 (t, $J = 7.9$ Hz, 0.3 H), 4.43-4.49 (m, 0.3 H, CHOH of minor diastereomer), 4.64-4.69 (m, 0.7 H, CHOH of major diastereomer), 7.23-7.42 (m, 5H, aryl); $^{13}\text{C NMR}$ (101 MHz, CDCl\textsubscript{3}) $\delta$ 39.9, 41.1, 41.4, 43.7, 46.1, 46.3, 48.8, 58.8, 60.1, 63.2, 63.8, 66.8, 69.3, 75.6, 77.9, 124.7, 125.3, 126.8, 126.9, 129.1, 129.2, 146.5, 147.3, 217.5, 218.7, 219.0, 221.3; IR (ef) 3630-3150 (broad), 2931, 1731, 1498, 1444, 1408, 1277, 1175 cm\textsuperscript{-1}; MS (Cl) m/z (rel. intensity) 257 (M + H, 46), 240 (18), 239 (100), 213 (1), 171 (1), 158 (1), 146 (1); Anal. Calcd. for C\textsubscript{16}H\textsubscript{16}O\textsubscript{3}: C, 74.98; H, 6.29; Found: C, 74.77; H, 6.32.

\textbf{9.2.10 10-Phenyltricyclo[5.2.1.0\textsuperscript{4,10}]deca-3,8-dione-6-ol (227) by hydrolysis of 10-phenyltricyclo[5.2.1.0\textsuperscript{4,10}]deca-3,8-dione-6-ol, 8-(2',2'-dimethylpropylidene acetal) (255)}

\begin{center}
\begin{tikzpicture}
\node (255) at (0,0) {\includegraphics[scale=0.5]{255}}; \node (227) at (2,0) {\includegraphics[scale=0.5]{227}};
\draw[->,thick] (255) to node[anchor=south] {92\%} node[anchor=north] {$p$-TsOH (cat.), Me\textsubscript{2}CO: H\textsubscript{2}O (2:1), rt, 2 days} (227);
\end{tikzpicture}
\end{center}

A solution of 10-phenyltricyclo[5.2.1.0\textsuperscript{4,10}]deca-3,8-dione-6-ol, 8-(2',2'-dimethylpropylidene acetal) \textbf{255} (25 mg, 0.073 mmol, 1.0 equiv.) and $p$-toluenesulfonic acid monohydrate (2 mg, catalytic amount) in a mixture of reagent grade acetone (3 mL) and water (1.5 mL) was stirred for 2 days at room
temperature. Solid sodium bicarbonate (5 mg) was added and the resultant mixture stirred for a further 10 min. The solvent was removed in vacuo and the aqueous residue was diluted with water (2 mL) and extracted with dichloromethane (5 x 2 mL). The combined organic extracts were washed with water (2 mL) and brine (2 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography (hexanes:ether, 1:1) to afford the title compound 227 (17 mg, 92%) as a colourless solid having spectral and physical properties identical to those of the material obtained by Procedure 9.2.9.

9.2.11 10-Phenyltricyclo[5.2.1.0^4.10]deca-2,5,8-triene (10-phenyltriquinacene) (84)^50

9.2.11.1 10-Phenyltricyclo[5.2.1.0^4.10]deca-3,5,8-triol 261

To a solution of 10-phenyltricyclo[5.2.1.0^4.10]deca-3,8-dione-6-ol 227 (90 mg, 0.35 mmol, 1.0 equiv.) in anhydrous THF (5 mL) at 0 °C was added dropwise borane-tetrahydrofuran complex (0.70 mL of 1 M solution in THF, 0.70 mmol, 2.0 equiv.). The reaction was then allowed to warm to room temperature and was stirred for 16 h. Methanol (5 mL) was added and the resultant solution was concentrated in vacuo. The addition and removal of methanol was repeated four times in total to remove the borate residues as trimethylborate. Flash chromatography (ether followed by ethyl acetate) afforded the title compound.
261 (70 mg, 77%) as a colourless solid and as a complex mixture of
diastereomers. M.p. 63-66 °C. The infrared spectrum of the triol showed no
carbonyl stretching bands. This material was used in the next step without
further purification.

9.2.11.2 10-Phenyl-3,5,8-trimesyloxytricyclo[5.2.1.0^4,10]deca-3,5,8-triol 262

To a solution of 10-phenyltricyclo[5.2.1.0^4,10]deca-3,5,8-triol 261 (55 mg,
0.21 mmol, 1.0 equiv.) in anhydrous dichloromethane (5 mL) at 0 °C was added
triethylamine (295 µL, 2.11 mmol, 10 equiv.) and methanesulfonyl chloride (165
µL, 2.14 mmol, 10 equiv.). The reaction mixture was allowed to warm to room
temperature and was stirred for 2 h, after which time a saturated aqueous
solution of sodium bicarbonate (1 mL) was added. The phases were separated,
the aqueous phase was extracted with dichloromethane (2 × 2 mL) and the
combined organic phases were washed with water (2 × 5 mL), dried over
anhydrous sodium sulfate and concentrated in vacuo to afford the title compound
262 (134 mg) as a yellow oil. No absorptions corresponding to hydroxyl groups
were observed by infrared spectroscopy. This material was used in the next step
without further purification.
9.2.11.3 10-Phenyltriquinacene 84

The product from the previous reaction, 10-phenyl-3,5,8-trimesyloxytricyclo[5.2.1.0^4,10]decane 262 (134 mg), was dissolved in dry dichloromethane (20 mL) and highly activated (by heating for 8 h at 300 °C) alumina (4.00 g) was added. The resultant suspension was stirred vigorously for 72 h at room temperature. The alumina was removed by filtration and washed with dichloromethane (100 mL). The filtrate was concentrated in vacuo and the crude product was purified by flash chromatography (pentane) to afford 10-phenyltriquinacene 84 (19 mg, 44% from 227) as a colourless solid. All spectral data for this compound were consistent with literature values.\(^5\) \(R_f\) 0.90 (pentane); \(\text{M.p.}\) 62-63 °C, pentane (lit.\(^5\) 64 °C); \(^1\text{H NMR} (400 \text{ MHz, CDCI}_3) \delta\) 3.84 (s, 3H, bridgehead CH), 5.70 (s, 6H, vinylic), 7.14-7.36 (m, 5H,aryl); \(^{13}\text{C NMR} (101 \text{ MHz, CDCI}_3) \delta\) 65.7 (C\(_{10}\)), 65.8 (C\(_1\), C\(_4\) and C\(_7\)), 124.7, 125.6, 128.7, 132.1 (C\(_2\), C\(_3\), C\(_5\), C\(_6\), C\(_8\) and C\(_9\)), 149.1 (aryl C\(_{ipso}\)); \(\text{IR (KBr)}\) 3050 cm\(^{-1}\); \(\text{MS (Cl)}\) \(m/z\) (rel. intensity) 207 (M + H, 100), 153 (11), 152 (85), 151 (41).
9.2.12  \((\text{Chloromethyl)}\text{tri-n-butylstannane (269)}^{163}\)

\[ \text{n-Bu}_3\text{SnH} \xrightarrow{\text{LDA, THF, 0 °C, 25 min then (CH}_2\text{O})_n, 0 \text{ °C to rt, 3 h}} \text{n-Bu}_3\text{Sn} \xrightarrow{\text{then MsCl, -78 °C to rt, 16 h}} \text{n-Bu}_3\text{SnCl} \]

93%

To a solution of LDA (18.1 mmol, 1.05 equiv.) in THF (45 mL) at 0 °C was added tributyltin hydride 266 (4.62 mL, 17.2 mmol, 1.0 equiv.) dropwise over 5 min. The resultant solution was stirred for a further 25 min and then anhydrous paraformaldehyde (567 mg, 18.9 mmol, 1.1 equiv.) was added. The reaction mixture was allowed to warm to room temperature over 20 min and was then stirred for 3 h. The yellow solution was cooled to -78 °C and methanesulfonyl chloride (1.7 mL, 22 mmol, 1.3 equiv.) was added. The reaction mixture was allowed to warm to room temperature and was stirred for 16 h. Water (20 mL) and hexanes (35 mL) were then added. The phases were separated and the aqueous phase was extracted with hexanes (3 x 35 mL). The combined organic extracts were washed with water (15 mL), dried over anhydrous magnesium sulfate and concentrated \textit{in vacuo}. The crude product was filtered through a pad of silica gel with hexanes (200 mL) and the combined filtrates were concentrated \textit{in vacuo}. Distillation of the residue through a Vigreux column under reduced pressure afforded the \textit{title compound} 269 (5.42 g, 93%) as a colourless oil. \textbf{R}_f 0.80 (hexanes); \textbf{B.p.} 124-127 °C/5 mmHg (lit.$^{163}$ 119-120 °C/2 mmHg); $^1\text{H}$ \textbf{NMR} (CDCl$_3$, 400 MHz) $\delta$ 0.90 (t, $J = 7.3$ Hz, 9H, 3 x CH$_3$), 0.97-1.03 (m, 6H, 3 x CH$_2$), 1.27-1.37 (m, 6H, 3 x CH$_2$), 1.48-1.59 (m, 6H, 3 x CH$_2$), 3.06 (s, 2H, SnCH$_2$Cl); $^{13}\text{C}$ \textbf{NMR} (CDCl$_3$, 101 MHz) $\delta$ 9.6, 13.8, 24.6, 27.4, 29.0; \textbf{IR} (neat)
To a suspension of potassium t-butoxide (2.59 g, 23.1 mmol, 1.5 equiv.) in THF (80 mL) at 0 °C was added 4-methoxybenzyl alcohol (3.8 mL, 31 mmol, 2.0 equiv.) and the resultant solution was stirred for 10 min. (Chloromethyl)-tri-n-butyllstannane 269 (5.22 g, 15.4 mmol, 1.0 equiv.) and tetra-n-butylammonium iodide (569 mg, 1.54 mmol, 0.1 equiv.) were added and the reaction mixture was heated at 45 °C for 17 h. After allowing the reaction mixture to cool to room temperature, it was opened to the air, stirred for 30 min, diluted with hexanes (200 mL) and then washed with aqueous hydrochloric acid (1 M, 50 mL) and brine (50 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography (hexanes:ether, 49:1) to afford the title compound 270 (5.23 g, 77%) as a colourless oil. Rf 0.70 (hexanes:ether, 19:1); $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 0.85-0.93 (m, 15H, 3 x CH$_3$ and 3 x CH$_2$), 1.24-1.35 (m, 6H, 3 x CH$_2$), 1.45-1.53 (m, 6H, 3 x CH$_2$), 3.71 (s, 2H, SnCH$_2$O-), 3.80 (s, 3H, Ar-OCH$_3$), 4.34 (s, 2H, -CH$_2$OAr), 6.87 (d, J = 8.2 Hz, 2H, ArH), 7.23 (d, J = 8.2 Hz, 2H, ArH); $^{13}$C NMR
(CDCl₃, 101 MHz) δ 9.2, 13.9, 27.5, 29.3, 55.4, 61.2, 113.7, 129.2, 131.1, 159.1; IR (neat) 3063, 2955, 2926, 2870, 2850, 1613, 1513, 1247, 1171, 1067, 1040 cm⁻¹; MS (Cl) m/z (rel. intensity) 442 (M + H, 2), 389 (12), 387 (10), 386 (16), 385 (81), 384 (33), 383 (59), 382 (24), 381 (27), 295 (20), 293 (18), 292 (13), 291 (100), 290 (37), 289 (81), 288 (35), 287 (43), 279 (45), 278 (65), 277 (22), 276 (14), 275 (30), 261 (9), 235 (13), 120 (94).

9.2.14 1-[(4'-Methoxybenzyloxy)methyl]cyclopentanol (271)

To a solution of [(4-methoxybenzyloxy)methyl]tri-n-butylstannane 270 (242 mg, 0.55 mmol, 1.1 equiv.) in THF (1 mL) at -78 °C was added n-butyllithium (220 μL of a 2.5 M solution in hexanes, 0.50 mmol, 1.0 equiv.) and the resultant bright yellow solution was stirred for 30 min. Freshly distilled cyclopentanone (44 μL, 0.50 mmol, 1.0 equiv.) was added, the reaction mixture was allowed to warm to room temperature over 1 h and was stirred for a further 15 h. Water (2 mL) and ether (5 mL) were added and the phases were separated. The aqueous phase was extracted with ether (3 × 5 mL) and the combined organic extracts were washed with water (3 × 5 mL) and brine (5 mL), then dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography (hexanes:ether, 3:1, then hexanes:ether, 2:1) to afford the title compound 271 (99 mg, 84%) as a colourless oil. Rₜ 0.15 (hexanes:ether,
3:1); \textbf{\textsuperscript{1}H NMR} (CDCl\textsubscript{3}, 400 MHz) \(\delta\) 1.53-1.87 (m, 8H, 4 \times \text{aliphatic ring CH}_2), 3.39 (s, 2H, ArCH\textsubscript{2}OCH\textsubscript{2}H), 3.80 (s, 3H, ArOCH\textsubscript{3}), 4.51 (s, 2H, ArCH\textsubscript{2}OCH\textsubscript{2}H), 6.89 (d, \(J = 8.7\) Hz, 2H, ArH); \textbf{\textsuperscript{13}C NMR} (CDCl\textsubscript{3}, 101 MHz) \(\delta\) 24.5, 37.6, 55.5, 73.4, 77.6, 81.8, 114.0, 129.5, 130.6, 159.5; \textbf{IR} (neat) 3610-3160 (broad), 2953, 2859, 1612, 1513, 1464, 1302, 1248, 1091, 1035 cm\textsuperscript{-1}; \textbf{MS} (Cl) \(m/z\) (rel. intensity) 236 (M, 28), 235 (17), 163 (22), 157 (30), 152 (35), 151 (40), 137 (96), 136 (23), 135 (100); \textbf{Anal.} Calcd. for C\textsubscript{14}H\textsubscript{20}O\textsubscript{3}: C, 71.16; H, 8.53; Found: C, 71.37; H, 8.65.

9.2.15 3-[(4'-Methoxybenzyloxy)methyl]cyclohexanone (272)

![Chemical structure](image)

To a solution of [(4-methoxybenzyloxy)methyl]tri-n-butylstannane 270 (477 mg, 1.08 mmol, 2.40 equiv.) in THF (2 mL) at -78 °C was added n-butyllithium (440 \(\mu\)L of a 2.5 \textit{M} solution in hexanes, 1.10 mmol, 2.45 equiv.) and the resultant yellow solution was stirred at -78 °C for 30 min. In a separate flask, cuprous bromide-dimethyl sulfide complex (117 mg, 0.572 mmol, 1.25 equiv.) was briefly flame-dried under high vacuum and allowed to cool under an atmosphere of nitrogen. This process was repeated four times in total and the complex was suspended in THF (2 mL). The organolithium solution was added to the cuprous bromide suspension via a cannula and the resultant yellow suspension was
stirred for 1 h at -78 °C, during which time an intense brown colour developed. Freshly distilled cyclohex-2-en-1-one (43 μL, 0.45 mmol, 1.0 equiv.) was added, followed by freshly distilled trimethylsilyl chloride (340 μL, 2.70 mmol, 6.00 equiv.). The reaction mixture was stirred for 4 h at -78 °C and was then allowed to warm to room temperature over 30 min, during which time the brown colour faded. A saturated solution of ammonium chloride which had been adjusted to pH 9 by the addition of 5% v/v concentrated aqueous ammonium hydroxide solution (10 mL) and ether (10 mL) were added. The resultant biphasic mixture was stirred vigorously while open to the air until an intense blue colour developed in the aqueous layer (1 h). The phases were separated and the aqueous phase was extracted with ether (3 x 10 mL). The combined organic extracts were washed with water (3 x 10 mL) and brine (10 mL), then dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography (hexanes:ether, 3:1 followed by hexanes:ether, 2:1) to afford the title compound 272 (89 mg, 87%) as a colourless oil. \( R_f \) 0.40 (hexanes:ether, 1:1); \(^1\)H NMR (CDCl₃, 400 MHz) \( \delta \) 1.42-1.71 (m, 2H), 1.89-2.44 (m, 7H), 3.35 (d, \( J = 5.5 \) Hz, 2H, -CH₂OCH₂Ar), 3.81 (s, 3H, ArOCH₃), 4.43 (s, 2H, CH₂Ar), 6.88 (d, \( J = 8.7 \) Hz, 2H, ArH), 7.24 (d, \( J = 8.7 \) Hz, 2H, ArH); \(^{13}\)C NMR (CDCl₃, 101 MHz) \( \delta \) 25.1, 28.3, 39.4, 41.6, 45.0, 55.4, 72.9, 74.0, 113.9, 129.3, 130.5, 159.3, 211.6; IR (neat) 2939, 2867, 1713, 1606, 1513, 1247, 1095, 1034 cm⁻¹; MS (Cl) \( m/z \) (rel. intensity) 249 (M + H, 6), 248 (12), 241 (54), 163 (1), 122 (43), 121 (100); Anal. Calcd. for C₁₅H₂₀O₃: C, 72.55; H, 8.12; Found: C, 72.84; H, 8.26.
A suspension of selenium dioxide (40.5 g, 365 mmol, 1.4 equiv.) in a mixture of p-dioxane (300 mL) and water (10 mL) was heated at 55 °C until the selenium dioxide had dissolved (~45 min). 4-Bromoacetophenone 283 (52.0 g, 261 mmol, 1.0 equiv.) was then added portionwise over 30 min and the resultant pale yellow-green solution was heated at reflux for 4 h. A small amount of black precipitate was gradually deposited. The mixture was filtered while still hot and the filtrate was concentrated in vacuo. The residue was taken up in dichloromethane (~100 mL) and filtered. Water (100 mL) was added and the mixture was shaken vigorously in order to precipitate the crude product. The suspension was allowed to stand overnight at room temperature and the crude product was collected by filtration. The product was purified by recrystallization from boiling water (1.2 L). The hot aqueous solution was also treated with activated carbon (Norit A). This afforded the title compound 284 (26.6 g, 44%) as a slightly off-white crystalline solid. M.p. 127-130 °C, water (lit. 269 134-136 °C, water); $^1$H NMR (DMSO-d$_6$, 400 MHz) δ 5.62 (t, $J$ = 7.1 Hz, 1H, -CH(OH)$_2$), 6.87 (d, $J$ = 7.1 Hz, 2H, -CH(OH)$_2$, 7.74 (d, $J$ = 8.4 Hz, 2H, ArH), 7.99 (d, $J$ = 8.4 Hz, 2H, ArH); $^{13}$C NMR (MeOH-d$_4$, 101 MHz) δ 97.0, 129.7, 131.2, 131.8, 132.3, 133.0, 134.0, 194.9; IR (ef) 3530-3100 (broad), 1694, 1645, 1400, 1026 cm$^{-1}$;
MS (Cl) m/z (rel. intensity) 215 (M + H for $^{81}$Br, 98), 213 (M + H for $^{79}$Br, 100), 185 (5), 183 (5).

9.3.2 1-(4'-Bromophenyl)-cis-bicyclo[3.3.0]octan-3,7-dione (282)

A solution of 4-bromophenylglyoxal monohydrate 284 (7.78 g, 33.7 mmol, 1.0 equiv.) in water (150 mL) was cooled to 0 °C and sodium bicarbonate (2.12 g, 25.3 mmol, 0.75 equiv.) was added. After stirring for 30 min, 1,3-dimethyl acetone dicarboxylate 233 (10.0 mL, 68.0 mmol, 2.02 equiv.) was added dropwise. The reaction mixture was allowed to warm to room temperature and was stirred for 2 days. During this period, the solution became yellow and an orange resinous precipitate was deposited gradually. Methanol (20 mL) was added in order to solubilize the resin and the resultant orange solution was stirred for a further 2 days. The solution was then concentrated to near dryness in vacuo. The orange-red residue was dissolved in a mixture of glacial acetic acid (50 mL) and aqueous hydrochloric acid (1 M, 150 mL). The solution was then heated at reflux, with a bubbler affixed to the top of the reflux condenser, until the evolution of carbon dioxide ceased (2.5 h). The reaction mixture was allowed to cool to room temperature and was extracted with ether (6 x 50 mL). The organic extracts were washed with saturated aqueous sodium bicarbonate
solution (2 x 50 mL), water (50 mL) and brine (50 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was taken up in ether (50 mL) and the solution was passed through a pad of silica gel on a cintered funnel in order to remove polymeric impurities. The pad of silica was washed thoroughly with ether (200 mL) and the filtrate was concentrated in vacuo. Purification of the crude product (5.50 g) by flash chromatography (hexanes:ether, 1:1 followed by ether) and recrystallization from hexanes/ether afforded the title compound 282 (2.48 g, 27%) as a colourless crystalline solid. Rf 0.25 (ether); M.p. 93-94 °C, hexanes/ether; \(^1\)H NMR (C\(_6\)D\(_6\), 400 MHz ) \(\delta\) 1.50 (dd, \(J=19.1, 5.6\) Hz, 2H), 1.86-2.03 (m, 4H), 2.08 (d, \(J=18.7\) Hz, 2H), 2.14-2.44 (m, 1H, bridgehead CH), 6.36 (d, \(J=8.6\) Hz, 2H, ArH), 7.13 (d, \(J=8.6\) Hz, 2H, ArH); \(^{13}\)C NMR (C\(_6\)D\(_6\), 101 MHz) \(\delta\) 41.9, 43.4, 50.4, 50.6, 121.0, 127.7, 132.0, 143.9, 213.4; IR (KBr) 2953, 1740, 1491, 1403, 1247, 1160, 1007 cm\(^{-1}\); MS (Cl) m/z (rel. intensity) 295 (M + H for \(^{81}\)Br, 98), 293 (M + H for \(^{79}\)Br, 100), 231 (6), 215 (40); Anal. Calcd. for C\(_{14}\)H\(_{13}\)BrO\(_2\): C, 57.36; H, 4.47; Found: C, 57.27; H, 4.54.
9.3.3 1-(4'-Bromophenyl)-cis-bicyclo[3.3.0]octan-3,7-dione-7-(2',2'-dimethylpropylidene acetal) (286) and 1-(4'-Bromophenyl)-cis-bicyclo[3.3.0]octan-3,7-dione-3,7-bis-(2',2'-dimethylpropylidene acetal) (287)

9.3.3.1 Procedure A - Monoprotection

A solution of 1-(4'-bromophenyl)-cis-bicyclo[3.3.0]octan-3,7-dione 282 (2.48 g, 8.95 mmol, 1.0 equiv.), neopentyl glycol (932 mg, 8.95 mmol, 1.0 equiv.) and p-toluenesulfonic acid monohydrate (10 mg, catalytic amount) in benzene (100 mL) was heated overnight at reflux with azeotropic removal of water in a Dean-Stark trap. The reaction mixture was allowed to cool to room temperature and solid sodium bicarbonate (50 mg) was added. After stirring for 30 min at room temperature, the reaction mixture was concentrated in vacuo and purified by flash chromatography (hexanes:ether, 4:1, followed by hexanes:ether, 2:1 and finally hexanes:ether, 1:1).
The first compound to elute was 1-(4'-bromophenyl)-cis-bicyclo[3.3.0]octan-3,7-dione-3,7-bis-(2',2'-dimethylpropylidene acetal) 287 (1.11 g, 29%) which was obtained as an off-white crystalline solid and was then recrystallized from hexanes. $R_f$ 0.40 (hexanes:ether, 2:1); **M.p.** 128-129 °C, hexanes; $^1$H NMR (C$_6$D$_6$, 400 MHz) $\delta$ 0.71 (s, 6H, 2 $\times$ acetal CH$_3$), 0.76 (s, 6H, 2 $\times$ acetal CH$_3$), 2.11-2.22 (m, 4H), 2.44 (s, 4H), 2.75-2.84 (m, 1H, bridgehead CH), 3.09-3.16 (m, 4H, 2 $\times$ acetal CH$_2$), 3.23-3.30 (m, 4H, 2 $\times$ acetal CH$_2$), 7.06 (d, $J = 8.6$ Hz, 2H, ArH), 7.31 (d, $J = 8.6$ Hz, 2H, ArH); $^{13}$C NMR (C$_6$D$_6$, 101 MHz) $\delta$ 22.4, 22.5, 29.9, 40.9, 45.2, 49.4, 53.9, 71.6, 72.2, 109.4, 119.5, 128.6, 131.3, 149.6; IR (ef) 2953, 2857, 1491, 1394, 1325, 1113, 1007 cm$^{-1}$; **MS** (Cl) m/z (rel. intensity) 467 (M + H for $^{81}$Br, 99), 465 (M + H for $^{79}$Br, 100), 381 (5), 379 (5), 312 (6), 310 (5), 129 (25), 128 (19); **Anal.** Calcd. for C$_{24}$H$_{33}$BrO$_4$: C, 61.93; H, 7.15; Found: C, 61.68; H, 7.20.

The second compound to elute was 1-(4'-bromophenyl)-cis-bicyclo[3.3.0]octan-3,7-dione-7-(2',2'-dimethylpropylidene acetal) 286 (1.51 g, 48%) which was obtained as a semi-solid gum. $R_f$ 0.15 (hexanes:ether, 2:1); $^1$H NMR (C$_6$D$_6$, 400 MHz ) $\delta$ 0.74 (s, 6H, 2 $\times$ acetal CH$_3$), 1.64 (dd, $J = 13.7$, 6.7 Hz, 1H), 1.97-2.15 (m, 3H), 2.18 (s, 2H), 2.32-2.54 (m, 3H), 3.14-3.18 (m, 4H, 2 $\times$ acetal CH$_2$), 6.71 (d, $J = 8.6$ Hz, 2H, ArH), 7.22 (d, $J = 8.6$ Hz, 2H, ArH); **MS (Cl)** m/z (rel. intensity) 381 (M + H for $^{81}$Br,
The third compound to elute was the starting material, 1-(4'-bromophenyl)-
cis-bicyclo[3.3.0]octan-3,7-dione 282 (512 mg, 23%), which was obtained as a
colourless solid. The overall yield for this reaction, based on recovered starting
material, was 92%.

9.3.3.2 Procedure B - Re-equilibration

A solution of 1-(4'-bromophenyl)-cis-bicyclo[3.3.0]octan-3,7-dione-3,7-bis-
(2',2'-dimethylpropylidene acetal) 287 (1.12 g, 2.41 mmol, 0.24 equiv.), 1-(4'-
bromophenyl)-cis-bicyclo[3.3.0]octan-3,7-dione 282 (2.81 g, 10.1 mmol, 1.00
equiv.), neopentyl glycol (801 mg, 7.69 mmol, 0.75 equiv.) and p-toluenesulfonic
acid monohydrate (10 mg, catalytic amount) in benzene (125 mL) was heated at
reflux for 16 h. The solution was cooled to room temperature and sodium
bicarbonate (50 mg) was added. After stirring for 30 min at room temperature,
the solution was concentrated in vacuo and purified by flash chromatography (hexanes:ether, 4:1, followed by hexanes:ether, 2:1 and finally hexanes:ether, 1:1).

The first compound to elute was 1-(4'-bromopheny1)-cis-bicyclo[3.3.0]octan-3,7-dione-3,7-bis-(2',2'-dimethylpropylidene acetal) 287 (1.62 g, 30%) which was obtained as an off-white crystalline solid.

The second compound to elute was 1-(4'-bromopheny1)-cis-bicyclo[3.3.0]octan-3,7-dione-7-(2',2'-dimethylpropylidene acetal) 286 (1.64 g, 38%) which was obtained as a semi-solid gum.

The third compound to elute was 1-(4'-bromopheny1)-cis-bicyclo[3.3.0]octan-3,7-dione 282 (1.03 g, 32%) which was obtained as a colourless solid. The three products 282, 286 and 287 had physical and spectral properties identical to those of the materials which were obtained by Procedure A.
9.3.4 1-(4'-Bromophenyl)-2-(2'-propenoxy)-cis-bicyclo[3.3.0]oct-2-en-3,7-dione-7-(2',2'-dimethylpropylidene) acetal (292), 1-(4'-Bromophenyl)-3-(2'-propenoxy)-cis-bicyclo[3.3.0]oct-3-en-3,7-dione-7-(2',2'-dimethylpropylidene) acetal (293), 1-(4'-Bromophenyl)-2-(2'-propenyl)-cis-bicyclo[3.3.0]octan-3,7-dione-7-(2',2'-dimethylpropylidene) acetal (294) and 1-(4'-Bromophenyl)-4-(2'-propenyl)-cis-bicyclo[3.3.0]octan-3,7-dione-7-(2',2'-dimethylpropylidene) acetal (295)

\[
\text{LDA, THF, -78 °C, 1 h then allyl bromide, THF/HMPA, -78 °C to rt, 16 h} \quad \text{68%, 96% BRSM}
\]

9.3.4.1 Alkylation

To a solution of LDA (3.30 mmol, 1.1 equiv.) in THF (10 mL) at -78 °C was added dropwise a solution of 1-(4'-bromophenyl)-cis-bicyclo[3.3.0]octan-3,7-dione-7-(2',2'-dimethylpropylidene acetal) 286 (1.14 g, 3.00 mmol, 1.0 equiv.) in THF (10 mL) via a cannula. The resultant yellow solution was stirred for 1 h at -78 °C. Allyl bromide (1.30 mL, 15.0 mmol, 5.0 equiv.), which had been filtered through a pad of activated neutral alumina, was then added, followed by dry hexamethylphosphoramide (8.0 mL). The reaction mixture was allowed to warm to room temperature and was stirred for 16 h. Water (10 mL) and ether (10 mL) were added and the phases were separated. The aqueous phase was extracted
with ether (3 × 10 mL). The combined organic phases were washed with water (10 × 5 mL) and brine (10 mL), then dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography (hexanes:ether, 9:1, followed by hexanes:ether, 4:1 and finally ether).

The first compounds to elute were the allyl enol ethers 292 and 293 (~750 mg). These compounds (Rf 0.80, hexanes:ether, 2:1) co-eluted with several non-polar impurities and were used in the subsequent Claisen rearrangement reaction (vide infra).

The second compounds to elute were the epimeric and regioisomeric C-allyl ketones 294 and 295 (168 mg, 13%), which were obtained as a pale yellow oil. Rf 0.25 (hexanes:ether, 2:1); \(^1\)H NMR (CDCl\(_3\), 400 MHz ) \(\delta\) 0.90-1.03 (m, 6H, 3 × acetal CH\(_3\)), 1.49-1.58 (m, 1H), 1.80-2.18 (m, 2H), 2.28-2.81 (m, 5H), 2.85-2.92 (m, 1H), 2.84-3.01 (m, 1H, bridgehead CH), 3.40-3.51 (m, 4H, 2 × acetal CH\(_2\)), 4.75-4.94 (m, 2H, -CH=CH\(_2\)), 5.44-5.77 (m, 1H, -CH=CH\(_2\)), 6.94 (d, J = 8.6 Hz, 2H, ArH), 7.40 (d, J = 8.6 Hz, 2H, ArH); \(^13\)C NMR (CDCl\(_3\), 101 MHz) \(\delta\) 22.3, 22.6, 29.8, 30.1, 30.6, 31.1, 38.5, 41.4, 41.5, 42.5, 43.1, 43.8, 45.2, 46.3, 55.6, 58.3, 61.7, 72.0, 72.3, 72.6, 108.7, 109.5, 115.9, 116.5, 120.5, 128.5, 128.7, 131.5, 136.2, 136.3, 144.1, 217.3, 217.4; IR (ef) 3079, 2954, 2858, 1738, 1640, 1472, 1115, 1007 cm\(^{-1}\); MS (Cl) m/z (rel. intensity) 421 (M + H for \(^{81}\)Br, 99), 419 (M + H for \(^{79}\)Br, 100), 391 (9), 371 (36), 243 (23), 129 (15), 128 (17), 105 (12); Anal. Calcd. for C\(_{22}\)H\(_{27}\)BrO\(_3\): C, 63.01; H, 6.49; Found: C, 63.25; H, 6.69.
The third compound to elute was the starting material, 1-(4'-bromophenyl)-
cis-bicyclo[3.3.0]octan-3,7-dione-7-(2',2'-dimethylpropylidene acetal) 286 (323 mg).

9.3.4.2 *Claisen rearrangement*

![Chemical structures](image-url)

A solution of the impure allyl enol ethers 292 and 293 (750 mg) in toluene (80 mL) was deoxygenated for 30 min with a stream of nitrogen gas. The solution was then heated at reflux for 3 days. The reaction mixture was then allowed to cool to room temperature, was concentrated *in vacuo* and purified by flash chromatography (hexanes:ether, 9:1 followed by hexanes:ether, 6:1) to afford a further 687 mg (54% from 286) of the C-allyl ketones 294 and 295 which were obtained as a pale yellow oil.

The overall yield of the C-allyl ketones 294 and 295 from the monoacetal 286 over two steps was 855 mg (68%, 96% based on recovered starting material).
A solution consisting of a mixture of 1-(4'-bromophenyl)-2-(2'-propenyl)-cis-bicyclo[3.3.0]octan-3,7-dione-7-(2',2'-dimethylpropylidene) acetal 294 and 1-(4'-bromophenyl)-4-(2'-propenyl)-cis-bicyclo[3.3.0]octan-3,7-dione-7-(2',2'-dimethylpropylidene) acetal 295 (700 mg, 1.67 mmol, 1.0 equiv.) in p-dioxane (20 mL) and water (14 mL) was treated with osmium tetroxide (~10 mg, catalytic amount). The reaction mixture was covered with aluminum foil to protect the reaction mixture from light and was stirred at room temperature for 1 h, during which time an intense brown colour developed. Sodium periodate (892 mg, 4.17 mmol, 2.5 equiv.) was then added in four equal portions at 1 h intervals. Over the course of these additions, a white precipitate of sodium iodate was deposited. The reaction mixture was stirred for a further 2.5 h and the suspension was filtered. The filter cake was then washed with ethyl acetate (30 mL). The phases were
The aqueous phase was extracted with ethyl acetate (4 × 30 mL). The combined organic extracts were passed through a pad of neutral alumina to remove residual osmium species and were dried over anhydrous sodium sulfate and concentrated in vacuo. The crude products were purified by flash chromatography (hexanes:ether, 1:1) to afford a mixture of the title compounds \( \text{296} \) and \( \text{297} \) (443 mg, 63%) as a yellow oil. \( R_f \) 0.45 (hexanes:ether, 1:2); \( ^1\text{H NMR} \) (CDCl\(_3\), 400 MHz) \( \delta \) 0.89-1.02 (m, 6H, \( 2 \times \) acetal CH\(_3\)), 2.20-3.03 (m, 10H), 3.41-3.55 (m, 4H, \( 2 \times \) acetal CH\(_2\)), 7.19-7.25 (m, 2H, ArH), 7.43-7.49 (m, 2H, ArH), 9.73 (s, 0.6 H, CHO for major isomer), 9.82 (s, 0.4 H, CHO for minor isomer); \( ^{13}\text{C NMR} \) (CDCl\(_3\), 101 MHz) \( \delta \) 22.5, 22.6, 22.8, 30.2, 37.8, 39.8, 40.2, 41.3, 42.1, 44.5, 44.8, 46.4, 47.5, 48.5, 48.8, 49.9, 50.2, 50.6, 50.9, 52.0, 52.5, 56.4, 72.0, 72.2, 72.4, 72.6, 107.8, 109.6, 120.4, 120.6, 127.7, 127.9, 128.2, 131.8, 131.9, 132.0, 146.1, 146.3, 199.8, 200.0, 216.2, 217.2; \( \text{IR (ef)} \) 2953, 2866, 2729, 1739, 1710, 1491, 1395, 1335, 1112, 1007 cm\(^{-1}\); \( \text{MS (Cl)} \) m/z (rel. intensity) 423 (M + H for \(^{81}\text{Br}\), 100), 421 (M + H for \(^{79}\text{Br}\), 98), 129 (4), 128 (2), 105 (2); \( \text{Anal. Calcd. for C}_{21}\text{H}_{25}\text{BrO}_{4}: \text{C}, 59.86; \text{H}, 5.98; \text{Found: C}, 59.92; \text{H}, 6.14. \)
A solution of (4′-bromophenyl)-2-(2-oxoethyl)-cis-bicyclo[3.3.0]octan-3,7-dione-7-(2′,2′-dimethylpropylidene) acetal 296 and 1-(4′-bromophenyl)-4-(2-oxoethyl)-cis-bicyclo[3.3.0]octan-3,7-dione-7-(2′,2′-dimethylpropylidene) acetal 297 (146 mg, 0.347 mmol, 1.0 equiv.) and p-toluenesulfonic acid monohydrate (10 mg, catalytic amount) in reagent grade acetone (10 mL) was stirred at room temperature for 6 days. The reaction was quenched with saturated aqueous sodium bicarbonate solution (2 mL). After stirring for 10 min, the acetone was removed in vacuo. The residue was taken up in a mixture of dichloromethane (5 mL) and water (5 mL) and the phases were separated. The aqueous phase was extracted with dichloromethane (5 × 5 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography (hexanes:ether, 1:2 followed by ether).
The first compound to elute was the title compound 298 (69 mg, 47%). Recrystallization from hexanes/ether afforded a single C-5 epimer (27 mg) as colourless needles. \( R_f \) 0.90 (ether); M.p. 178-179 °C (hexanes/ether); \(^1\)H NMR (CDCl\(_3\), 400 MHz, assignments by COSY and HMQC experiments) \( \delta \) 0.71 (s, 3H, 3 × H\(_{14}\) or 3 × H\(_{15}\)), 1.14 (s, 3H, 3 × H\(_{14}\) or 3 × H\(_{15}\)), 1.79 (ddd, \( J = 14.2, 7.2, 1.5 \) Hz, 1H, H\(_6\)), 2.18 (apparent dt, \( J = 14.2, 5.0 \) Hz, 1H, H\(_6'\)), 2.32-2.39 (m, 1H, H\(_7\)), 2.48 (d, \( J = 18.7 \) Hz, 1H, H\(_2\)), 2.53-2.57 (m, 2H, H\(_4\) and -OH), 2.70 (d, \( J = 18.9 \) Hz, 1H, H\(_9\)), 2.91 (dd, \( J = 18.9, 6.3 \) Hz, 2H, H\(_2\)' and H\(_9'\)), 2.98-3.05 (m, 1H, H\(_{10}\)), 3.39 (d, \( J = 10.8 \) Hz, 2H, 2 × H\(_{11}\) or 2 × H\(_{13}\)), 3.58 (d, \( J = 10.8 \) Hz, 2H, 2 × H\(_{11}\) or 2 × H\(_{13}\)), 4.62 (t, \( J = 4.9 \) Hz, 1H, H\(_5\)), 7.16 (d, \( J = 8.6 \) Hz, 2H, H\(_{17}\) and H\(_{21}\)), 7.48 (d, \( J = 8.6 \) Hz, 2H, H\(_{18}\) and H\(_{20}\)); \(^{13}\)C NMR (CDCl\(_3\), 101 MHz) \( \delta \) 21.9 (C\(_{14}\) or C\(_{15}\)), 23.2 (C\(_{14}\) or C\(_{15}\)), 30.2 (C\(_{12}\)), 35.0 (C\(_6\)), 42.9 (C\(_4\)), 49.0 (C\(_1\)), 49.7 (C\(_{10}\)), 50.5 (C\(_7\)), 50.7 (C\(_2\)), 51.8 (C\(_9\)), 77.2 (C\(_{11}\) or C\(_{13}\)), 77.3 (C\(_{11}\) or C\(_{13}\)), 99.8 (C\(_3\)), 99.9 (C\(_5\)), 121.1 (C\(_{19}\)), 127.6 (C\(_{17}\) and C\(_{21}\)), 132.2 (C\(_{18}\) and C\(_{20}\)), 144.0 (C\(_{16}\)), 216.3 (C\(_8\)); IR (ef) 3560-3180 (broad), 2956, 2860, 1734, 1400, 1250, 1126 cm\(^{-1}\); MS (Cl) m/z (rel. intensity) 423 (M + H for \(^{81}\)Br, 92), 421 (M + H for \(^{79}\)Br, 94), 343 (20), 163 (32), 145 (14), 129 (37), 128 (100), 103 (19); Anal. Calcd. for C\(_{21}\)H\(_{25}\)BrO\(_4\): C, 59.86; H, 5.98; Found: C, 59.96; H, 5.88.

The slower-running fractions contained traces of other isomers, as determined by NMR.
A solution of 1-(4'-bromophenyl)tricyclo[5.2.1.0^{4,10}]deca-3,8-dione-5-ol, 3-(2',2'-dimethylpropylidene acetal) \( \text{298} \) (50 mg, 0.12 mmol, 1.0 equiv.) in \( p \)-dioxane (3 mL) and aqueous hydrochloric acid (2 \( M \), 1.5 mL) was heated at reflux for 1 h. The solution was allowed to cool to room temperature and was neutralized with a saturated aqueous solution of sodium bicarbonate. The reaction mixture was extracted with dichloromethane (5 × 5 mL), dried over anhydrous sodium sulfate and concentrated \textit{in vacuo}. Flash chromatography (ether) followed by recrystallization from hexanes/ethyl acetate afforded the title compound \( \text{280} \) (40 mg, 80%) as a colourless crystalline solid consisting of a \( \sim 6:4 \) mixture of C-5 epimers. \( \text{Rf} \) 0.40 (ether); \( \text{M.p.} \) 102-104 °C, hexanes/ethyl acetate; \( ^1\text{H NMR} \) (CDCl\(_3\), 400 MHz, integration refers to apparent number of protons in the diastereomeric mixture) \( \delta \) 1.87-1.95 (m, 0.6 H), 2.10 (br s, 0.4 H, \(-\text{OH of minor isomer} \)), 2.16-2.23 (m, 1.2 H), 2.29-2.40 (m, 0.8 H), 2.51 (d, \( J = 18.6 \) Hz, 0.6 H), 2.65 (d, \( J = 18.6 \) Hz, 0.4 H), 2.74-2.81 (m, 1.2 H), 2.90-3.01 (m, 1.6 H), 3.05 (d, \( J = 18.6 \) Hz, 0.4 H), 3.08-3.15 (m, 0.8 H), 3.31 (ddd, \( J = 11.3, 6.2, 0.8 \) Hz, 0.4 H), 3.42 (q, \( J = 9.6 \) Hz, 0.6 H), 3.72 (dd, \( J = 11.7, 9.2 \) Hz, 0.4 H), 3.87 (t, \( J = 9.2 \) Hz, 0.6 H), 4.50-4.55 (m, 0.6 H, \( \text{CHOH of major isomer} \)), 4.56-4.62 (m, 0.6 H, \( \text{CHOH of major isomer} \)).
0.4 H, CHOH of minor isomer), 7.08-7.12 (m, 2H, ArH), 7.47-7.51 (m, 2H, ArH);

\[ ^{13}C \text{ NMR (CDCl}_3, 101 \text{ MHz}) \delta 38.6, 43.4, 47.6, 47.8, 52.0, 52.8, 53.1, 53.3, 53.7, 53.8, 55.1, 55.4, 59.9, 63.2, 74.3, 78.5, 120.8, 121.1, 126.9, 127.0, 132.3, 132.4, 145.9, 147.2, 216.3, 216.8, 217.6, 220.0; \]

\[ \text{IR (ef) 3650-3140 (broad), 3058, 2963, 2847, 1732, 1490, 1395, 1007 \text{ cm}^{-1}; \]

\[ \text{MS (Cl) m/z (rel. intensity) } 337 \text{ (M + H for } ^{81}\text{Br, 100), 335 (M + H for } ^{79}\text{Br, 99), 319 (5), 317 (5), 259 (11), 257 (62), 239 (29), 151 (4), 113 (8); \]

\[ \text{Anal. Calcd. for } C_{16}H_{15}BrO_3: C, 57.33; H, 4.51; \]

Found: C, 57.48; H, 4.68.

9.3.8 10-(4'-Bromophenyl)tricyclo[5.2.1.0^{4,10}]deca-3,8-dione-5-ol (281)

\[
\begin{align*}
\text{Br} & \quad \text{O} \\
\text{296} & \quad + \\
\text{p-TsOH (cat.), Me}_2\text{CO, rt, 4 days then } \\
\text{p-dioxane:2 M HCl (2:1), reflux, 1 h} & \quad \text{281 (35%)} \\
\text{Br} & \quad \text{O} \\
\text{297} & \quad \text{280 (40%)} \\
\text{O} & \quad \text{CO} \\
\text{280 (40%)} & \quad \text{OH}
\end{align*}
\]

A solution of (4'-bromophenyl)-2-(2-oxoethyl)-cis-bicyclo[3.3.0]octan-3,7-dione-7-(2',2''-dimethylpropylidene) acetal 296, 1-(4'-bromophenyl)-4-(2-oxoethyl)-cis-bicyclo[3.3.0]octan-3,7-dione-7-(2',2''-dimethylpropylidene) acetal 297 (310 mg, 0.735 mmol, 1.0 equiv.) and p-toluenesulfonic acid monohydrate
(10 mg, catalytic amount) in reagent grade acetone (25 mL) was stirred at room temperature for 4 days. The reaction was quenched with sodium bicarbonate (50 mg). After stirring at room temperature for 45 min, the acetone was removed in vacuo. The residue was taken up in a mixture of dichloromethane (10 mL) and water (10 mL) and the phases were separated. The aqueous phase was extracted with dichloromethane (5 × 10 mL) and the combined organic phases were washed with water (2 × 10 mL) and brine (10 mL), then dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product (301 mg) was dissolved in a mixture of p-dioxane (20 mL) and aqueous hydrochloric acid (2 M, 10 mL) and the resultant solution was heated at reflux for 1 h. The reaction mixture was allowed to cool to room temperature and was neutralized with a saturated aqueous solution of sodium bicarbonate. The phases were separated and the aqueous phase was extracted with dichloromethane (5 × 10 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography (ether).

The first compound to elute was title compound 280 (92 mg, 40%), which was obtained as a colourless crystalline solid that had spectral and physical properties identical to those of the material which was obtained by Procedure 9.3.7.

The second compound to elute was the title compound 281 (81 mg, 35%) which was obtained as a colourless crystalline solid. Recrystallization from ether/dichloromethane/hexanes afforded the pure (5α-OH)-epimer (37 mg) as a
colourless crystalline solid.  \( R_f \) 0.25 (ether); \( M.p. \) 187-188 °C, ether/dichloromethane/hexanes; \( ^1H \) NMR (CDCl₃, 400 MHz, assignments by COSY, HMQC and NOESY experiments) \( \delta \) 1.61 (ddd, \( J = 11.7, 4.1, 1.9 \) Hz, 1H, H₆), 2.21 (ddd, \( J = 11.7, 6.4, 4.1 \) Hz, 1H, H₆'), 2.30 (d, \( J = 19.6 \) Hz, 1H, H₉), 2.40-2.50 (m, 2H, H₂ and H₉'), 2.76-2.80 (m, 1H, H₇), 2.84 (d, \( J = 19.6 \) Hz, 1H, H₂'), 3.09 (d, \( J = 4.1 \) Hz, 1H, H₄), 3.20 (t, \( J = 6.0 \) Hz, 1H, H₁), 4.20 (m, 1H, H₅), 7.16 (d, \( J = 8.6 \) Hz, 2H, H₁₃ and H₁₅), 7.50 (d, \( J = 8.6 \) Hz, 2H, H₁₂ and H₁₆); \( ^{13}C \) NMR (CDCl₃, 101 MHz) \( \delta \) 31.6 (C₆), 37.9 (C₉), 43.7 (C₁), 48.4 (C₂), 50.7 (C₇), 52.5 (C₁₀), 61.0 (C₄), 66.4 (C₆), 121.7 (C₁₁), 127.6 (C₁₂ and C₁₆), 132.5 (C₁₃ and C₁₅), 141.0 (C₁₄), 215.3 (C₃ or C₈), 215.6 (C₃ or C₈). IR (ef) 3630-3140 (broad), 2949, 1740, 1493, 1398, 1073, 1040 cm⁻¹; MS (Cl) m/z (rel. intensity) 337 (M + H for \(^{81}\)Br, 100), 335 (M + H for \(^{79}\)Br, 98), 319 (63), 317 (65), 257 (19), 239 (10), 107 (4), 81 (8); Anal. Calcd. for C₁₆H₅BrO₃: C, 57.33; H, 4.51; Found: C, 57.23; H, 4.66.
A solution of 1-(4'-bromophenyl)tricyclo[5.2.1.0\(^{4,10}\)]deca-3,8-dione-5-ol 280 (175 mg, 0.522 mmol, 1.0 equiv.) in THF (25 mL) was cooled to 0 °C. Borane-THF complex (1.6 mL of a 1 M solution in THF, 1.6 mmol, 3.0 equiv.) was added dropwise and the reaction mixture was allowed to warm to room temperature and was then stirred for 15 h. The reaction was quenched with methanol (5 mL) and concentrated in vacuo. The addition and removal of methanol was repeated five times in total in order to remove most of the borate residues as trimethylborate. The residue was purified by flash chromatography (ether:ethyl acetate, 1:1) to afford the title compound 299 (134 mg, 76%) as a waxy white solid. \( R_f \) 0.25 (ethyl acetate); IR (ef) 3660-3120 (broad), 2930, 1489, 1031, 1007 cm\(^{-1}\). The absence of a carbonyl absorption in the IR spectrum of this material indicated that the reduction reaction had gone to completion.

A suspension of 1-(4'-bromophenyl)tricyclo[5.2.1.0\(^{4,10}\)]deca-3,5,8-triol 299 (134 mg, 0.400 mmol, 1.0 equiv.) in dichloromethane (10 mL) was cooled to 0 °C. Triethylamine (560 \( \mu \)L, 4.0 mmol, 10.0 equiv.) was added, followed by methanesulfonyl chloride (310 \( \mu \)L, 4.0 mmol, 10.0 equiv.). The reaction mixture
was allowed to warm to room temperature and was stirred for 50 min. The reaction mixture was transferred to a separatory funnel and was washed with water (2 × 10 mL), dried over anhydrous sodium sulfate and concentrated in vacuo to afford the crude title compound 300 (273 mg) as a yellow oil. Rf 0.80 (ethyl acetate); \textbf{IR (ef)} 3101, 3000, 2937, 1492, 1352, 1172, 1007, 969 cm\(^{-1}\). The absence of an O-H stretching band in the IR spectrum indicated the reaction had gone to completion. This material was used in the following step without further purification.

\section*{9.3.10 1-(4'-Bromophenyl)tricyclo[5.2.1.0\(^{4,10}\)]deca-3,5,8-triene (1-(4'-bromophenyl)triquinacene) (278)}

\begin{center}
\begin{tikzpicture}
\node at (0,0) {300}; \node at (3,0) {278};
\node at (1.5,0) {\textbf{Al}_2\text{O}_3, DCM, rt, 5 days};
\draw[->] (0,0) -- (3,0);
\end{tikzpicture}
\end{center}

A suspension of highly activated neutral alumina (60-325 mesh, ~2.0 g) in dichloromethane (10 mL) was stirred for 5 min. A solution of crude 1-(4'-bromophenyl)-3,5,8-tri(methanesulfonyloxy)tricyclo[5.2.1.0\(^{4,10}\)]decane 300 (273 mg) in dichloromethane (5 mL) was added and the resultant yellow slurry was stirred for 5 days at room temperature. The alumina was removed by filtration and the filter cake was washed with dichloromethane (100 mL) and chloroform (50 mL). The filtrate was concentrated in vacuo and the crude product was purified by flash chromatography (hexanes) to afford the title compound 278 (43
mg, 38% from triol 280) as a colourless waxy solid. **Rf 0.50** (hexanes); **1H NMR** (CDCl₃, 500 MHz, assignments by COSY and HMQC experiments) δ 3.46 (t, J = 8.7 Hz, 1H, H₁₀), 3.87 (apparent dt, J = 8.7, 1.9 Hz, 2H, H₄ and H₇), 5.67 (s, 2H, H₅ and H₆), 5.71 (apparent dd, J = 5.6, 1.9 Hz, 2H, H₃ and H₈ or H₂ and H₉), 5.80 (apparent dd, J = 5.6, 1.9 Hz, 2H, H₃ and H₈ or H₂ and H₉), 7.14 (d, J = 8.6 Hz, 2H, H₁₃ and H₁₅), 7.42 (d, J = 8.6 Hz, 2H, H₁₂ and H₁₆); **13C NMR** (CDCl₃, 101 MHz) δ 57.7 (C₄ and C₇), 58.9 (C₁₀), 71.1 (C₁), 119.9 (C₁₄), 128.0 (C₁₃ and C₁₅), 131.3 (C₁₂ and C₁₆), 132.3 (C₂ and C₉), 133.4 (C₃ and C₈ or C₅ and C₆), 134.9 (C₃ and C₈ or C₅ and C₆), 147.0 (C₁₁). **IR** (ef) 3029, 1491, 1417 cm⁻¹; **MS** (Cl) m/z (rel. intensity) 287 (M + H for ⁸¹Br, 23), 285 (M + H for ⁷⁹Br, 25), 165 (14), 129 (100); **HRMS** (FAB, m/z) Calcd. for C₁₆H₁₃Br: 284.0201; Found: 284.0201.

### 9.3.11 10-(4'-Bromophenyl)tricyclo[5.2.1.0⁵.¹⁰]deca-3,5,8-triol (301) and 10-(4'-Bromophenyl)-3,5,8-tri(methanesulfonyloxy)tricyclo[5.2.1.0⁴.¹⁰]decane (302)

![Reaction Scheme]

A solution of 10-(4'-bromophenyl)tricyclo[5.2.1.0⁴.¹⁰]deca-3,8-dione-5-ol 281 (83 mg, 0.25 mmol, 1.0 equiv.) in THF (5 mL) was cooled to 0 °C. Borane-THF complex (750 µL of a 1 M solution in THF, 0.75 mmol, 3.0 equiv.) was then added dropwise. The reaction mixture was allowed to warm to room temperature and was stirred for 16 h. The reaction was quenched with methanol (3 mL) and
concentrated in vacuo. The addition and removal of methanol was repeated five times in total in order to remove most of the borate residues as trimethylborate. The crude product was purified by flash chromatography (ether:ethyl acetate, 1:1) to afford the title compound 301 (80 mg, 95%) as a waxy white solid. Rf 0.15 (ethyl acetate); IR (ef) 3640-3160 (broad), 2929, 1483, 1059, 1009 cm⁻¹. The absence of a carbonyl absorbance in the IR spectrum of this material indicated that the reduction reaction had proceeded to completion.

A suspension of 10-(4'-bromophenyl)tricyclo[5.2.1.0⁴.⁷¹⁰]deca-3,5,8-triol 301 (80 mg, 0.24 mmol, 1.0 equiv.) in dichloromethane (10 mL) was cooled to 0 °C. Triethylamine (330 µL, 2.4 mmol, 10.0 equiv.) was added, followed by methanesulfonyl chloride (190 µL, 2.4 mmol, 10.0 equiv.). The reaction mixture was allowed to warm to room temperature and was stirred for 1 h. The solution was transferred to a separatory funnel and was washed with water (2 x 5 mL), dried over anhydrous sodium sulfate and concentrated in vacuo to afford the crude title compound 302 (249 mg) as a yellow oil. Rf 0.85 (ethyl acetate); IR (ef) 3105, 2937, 1492, 1352, 1175, 1008 cm⁻¹. The absence of an O-H stretching band in the IR spectrum indicated that the mesylation reaction had proceeded to completion. This material was used in the following step without further purification.
A suspension of highly activated neutral alumina (60-325 mesh, ~2.0 g) in dichloromethane (10 mL) was stirred for 5 min. A solution of crude 10-(4'-bromophenyl)-3,5,8-tri(methanesulfonyloxy)tricyclo[5.2.1.04,10]decane 302 (249 mg) in dichloromethane (5 mL) was then added and the resultant pale yellow slurry was stirred for 4 days at room temperature. The alumina was removed by filtration and the filter cake was washed with dichloromethane (100 mL) and chloroform (50 mL). The filtrate was concentrated in vacuo and the crude product was purified by flash chromatography (hexanes) to afford the title compound 279 (27 mg, 38% from triol 281) as a colourless waxy solid. $R_f$ 0.30 (hexanes); $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 3.80 (s, 3H, H$_1$, H$_4$ and H$_7$), 5.69 (s, 6H, H$_2$, H$_3$, H$_5$, H$_6$, H$_8$ and H$_9$), 7.17 (d, $J = 8.6$ Hz, 2H, H$_{13}$ and H$_{15}$), 7.44 (d, $J = 8.6$ Hz, 2H, H$_{12}$ and H$_{16}$); $^{13}$C NMR (CDCl$_3$, 101 MHz) $\delta$ 65.9 (C$_1$, C$_4$ and C$_7$), 68.5 (C$_{10}$), 119.6 (C$_{14}$), 126.9 (C$_{12}$ and C$_{16}$), 131.8 (C$_{13}$ and C$_{15}$), 132.3 (C$_2$, C$_3$, C$_5$, C$_6$, C$_8$ and C$_9$), 148.5 (C$_{11}$) IR (ef) 3047, 2955, 1488, 1394, 1007 cm$^{-1}$; MS (Cl) m/z (rel. intensity) 287 (M + H for $^{81}$Br, 98), 285 (M + H for $^{79}$Br, 100), 283 (40), 205 (8), 129 (13); HRMS (FAB, m/z) Calcd. for C$_{16}$H$_{13}$Br: 284.0201; Found: 284.0200.
9.4 Experimental Concerning Chapter Four

9.4.1 *Hydroxypyruvaldehyde trimer ethanolate* (312)*^270*

\[
\text{HO} \quad \begin{array}{c}
\text{O} \\
\text{O} \\
\text{OH}
\end{array} \quad \begin{array}{c}
\text{O} \\
\text{OH}
\end{array} \quad \text{Cu(OAc)}_2, \text{H}_2\text{O}, \text{6 days} \quad 94\% \quad \begin{array}{c}
\text{HO} \\
\text{O} \\
\text{CH}_2
\end{array} \quad \text{EtOH}
\]

A solution of dihydroxyacetone dimer 313 (10.0 g, 55.6 mmol, 1.0 equiv.) in distilled water (20 mL) was treated with cupric acetate monohydrate (49.9 g, 250 mmol, 4.5 equiv.) which had been previously recrystallized from aqueous acetic acid (1 %) and dried under high vacuum for 72 h. The resultant thick blue-green suspension was stirred vigorously at room temperature. After 2 h, a brick red precipitate of cuprous oxide began to be deposited. Stirring was continued for 6 days, after which time a grey precipitate of cupric oxalate formed. The reaction mixture was treated with a solution of oxalic acid dihydrate (3.50 g, 27.8 mmol, 0.5 equiv.) in water (20 mL) in order to precipitate excess cupric salts as cupric oxalate. After stirring for 1 h, the thick pale red suspension was filtered through diatomaceous earth on a Büchner funnel using glass filter paper. The filter cake was washed with water (100 mL) and the blue-green filtrate was concentrated *in vacuo* to a volume of ~20 mL. Absolute ethanol (20 mL) was added, causing the solution to take on a green colour. The solution was reduced to dryness *in vacuo* and the addition and removal of ethanol was repeated four times in total. The green residue was taken up in boiling absolute ethanol (100 mL) and was filtered. The filtrate was concentrated *in vacuo* and the residue dissolved in a minimum amount of absolute ethanol (~10 mL). Ether (50 mL)
was added, causing a pale yellow precipitate to form. The precipitate was collected by filtration and was washed with ether (30 mL). The filtrate was concentrated in vacuo and the precipitation procedure was repeated twice more. The combined precipitates were air-dried, dissolved in water (100 mL) and filtered. The filtrate was then concentrated in vacuo, dissolved in absolute ethanol (50 mL) and filtered. The nearly colourless filtrate was concentrated in vacuo and dried for 2 days under high vacuum to afford the title compound 312 (10.83 g, 94%) as a pale yellow amorphous solid. M.p 120-125 °C (ethanol) (lit.270 155-160 °C). The compound could not be fully characterized on account of its instability as well as its tendency towards reversible oligomerization;270 this material was used in the next step without further purification.

9.4.2 cis-1-(Hydroxymethyl)bicyclo[3.3.0]octan-3,7-dione (314) and cis-1-(Acetoxyethyl)bicyclo[3.3.0]octan-3,7-dione (315)

9.4.2.1 Procedure A - Decarboxylation in the presence of acetic acid

To a solution of the trimeric ethanolate of hydroxypyruvaldehyde 312 (3.15 g, 35.8 mmol of the monomer, 1.0 equiv.) and sodium bicarbonate (2.25 g, 26.8 mmol, 0.75 equiv.) in water (150 mL) at 0 °C was added 1,3-dimethyl...
acetonedicarboxylate 233 (10.6 mL, 72.3 mmol, 2.02 equiv.) dropwise. The solution was allowed to warm to room temperature and was stirred for 4 days, over which time a red-brown resinous precipitate formed. The reaction mixture was concentrated in vacuo and the residue was dissolved in aqueous hydrochloric acid (1 M, 150 mL) and glacial acetic acid (50 mL). The flask was fitted with a reflux condenser attached to a bubbler and was heated at reflux until carbon dioxide evolution ceased (4 h). The red solution was cooled to room temperature, was saturated with solid sodium chloride and was extracted with dichloromethane (6 × 50 mL). The combined extracts were washed with brine (25 mL), dried over anhydrous magnesium sulfate and were concentrated in vacuo to afford a thick red oil which was purified by flash chromatography (ether, followed by ether:ethyl acetate, 1:1 and finally ethyl acetate).

The first compound to elute was cis-1-(acetoxymethyl)bicyclo[3.3.0]octan-3,7-dione 315 (752 mg, 10%), which was obtained as a pale yellow crystalline solid and was then recrystallized from ether/ethyl acetate. \( R_f \) 0.70 (ethyl acetate); M.p. 67-68 °C (ether/ethyl acetate); \(^1\text{H NMR} \) (400 MHz, CDCl\( _3 \)) \( \delta \) 2.05 (s, 3H, acetate CH\( _3 \)), 2.16 (dd, \( J = 19.0, 5.7 \text{ Hz} \), 2H), 2.28-2.44 (m, 4H), 2.71 (ddd, \( J = 19.0, 8.7, 5.7 \text{ Hz} \), 2H), 2.80-2.86 (m, 1H, bridgehead CH), 4.11 (s, 2H, -CH\( _2\)OAc); \(^{13}\text{C NMR} \) (101 MHz, CDCl\( _3 \)) \( \delta \) 20.8, 39.1, 44.4, 46.5, 47.1, 69.0, 170.7, 215.6; IR (KBr) 2953, 1736, 1649, 1447, 1240, 1042 cm\(^{-1} \); MS (Cl) \( m/z \) (rel. intensity) 211 (M + H, 38), 151 (100), 139 (5), 131 (5); Anal. Calcd. for C\( _{11} \)H\( _{14} \)O\( _4 \): C, 62.85; H, 6.71; Found: C, 62.62; H, 6.42.
The second compound to elute was cis-1-(hydroxymethyl)-bicyclo[3.3.0]octan-3,7-dione 314 (1.06 g, 18%) which was obtained as a pale yellow solid. \( R_f \) 0.30 (ethyl acetate); \textbf{M.p.} 93-94 °C (ether/ethyl acetate); \textbf{\( ^1 \)H NMR} (400 MHz, CDCl\(_3\), assignments by COSY experiment) \( \delta \) 1.81 (br s, 1H, -OH), 2.15 (ddd, \( J = 19.2, 5.7, 1.2 \) Hz, 2H, H\(_4\) and H\(_6\)), 2.27 (dd, \( J = 19.0, 1.0 \) Hz, 2H, H\(_2\) and H\(_6\)), 2.45 (dd, \( J = 19.0, 1.1 \) Hz, 2H, H\(_2'\) and H\(_8'\)), 2.75 (ddd, \( J = 18.8, 8.8, 1.4 \) Hz, 2H, H\(_4'\) and H\(_6'\)), 2.89-2.97 (m, 1H, H\(_5\)), 3.70 (s, 2H, 2 \( \times \) H\(_8\)); \textbf{\( ^{13} \)C NMR} (101 MHz, CDCl\(_3\)) \( \delta \) 38.7, 44.7, 46.4, 49.9, 68.1, 217.5; \textbf{IR} (KBr) 3690-3120 (broad), 2953, 1735, 1427, 1407, 1244, 1205, 1166, 1052 cm\(^{-1}\); \textbf{MS} (CI) \( m/z \) (rel. intensity) 169 (M + H, 100), 151 (2); \textbf{Anal.} Calcd. for C\(_9\)H\(_{12}\)O\(_3\): C, 64.27; H, 7.19; Found: C, 64.55; H, 7.23.

\textbf{9.4.2.2 Procedure B - Decarboxylation in the absence of acetic acid}

\[
\begin{align*}
\text{HO-} & \quad \text{NaHCO}_3, \text{H}_2\text{O, rt, 6 days} \\
\text{COH} & \text{then 1 M aq. HCl, reflux, 3 h} \\
\text{312} & \quad \text{19\%} \\
+ & \\
2 \times \text{MeO-} & \quad \text{314} \\
\text{233} & \quad \text{O-}
\end{align*}
\]

To a solution of the trimeric ethanolate of hydroxypyruvaldehyde 312 (8.25 g, 93.7 mmol of the monomer, 1.0 equiv.) and sodium bicarbonate (5.91 g, 70.3 mmol, 0.75 equiv.) in water (250 mL) at 0 °C was added dropwise 1,3-dimethyl acetonedicarboxylate 233 (27.8 mL, 189 mmol, 2.02 equiv.). The solution was
allowed to warm to room temperature and was stirred for 6 days, over which time a red-brown resinous precipitate formed. The reaction mixture was concentrated in vacuo and the residue was dissolved in aqueous hydrochloric acid (1 M, 200 mL). The flask was fitted with a reflux condenser attached to a bubbler and was heated at reflux until carbon dioxide evolution ceased (3 h). The red solution was cooled to room temperature, was saturated with solid sodium chloride and was extracted with dichloromethane (6 × 100 mL). The combined extracts were washed with brine (25 mL), dried over anhydrous magnesium sulfate and were concentrated in vacuo to afford a thick red oil which was purified by flash chromatography (ether, followed by ether:ethyl acetate, 1:1 and finally ethyl acetate). The crude product was recrystallized from ethyl acetate to afford cis-1-(hydroxymethyl)bicyclo[3.3.0]octan-3,7-dione 314 (2.91 g, 19%) as a pale yellow solid that had spectral properties identical to those of the material which was obtained by Procedure A.

9.4.3 cis-1-(Hydroxymethyl)bicyclo[3.3.0]octan-3,7-dione (314) by hydrolysis of cis-1-(acetoxymethyl)bicyclo[3.3.0]octan-3,7-dione (315)

To a solution of cis-1-(acetoxymethyl)bicyclo[3.3.0]octan-3,7-dione 315 (673 mg, 3.20 mmol, 1.0 equiv.) in a mixture of THF (32 mL) and water (11 mL) was added lithium hydroxide monohydrate (402 mg, 9.60 mmol, 3.0 equiv.).
After stirring at room temperature for 40 min, the reaction mixture was neutralized with aqueous hydrochloric acid (10% v/v) and was extracted with dichloromethane (5 x 15 mL). The combined extracts were dried over anhydrous sodium sulfate, concentrated in vacuo and purified by flash chromatography (ether:ethyl acetate, 1:1 followed by ethyl acetate) to afford the title compound 314 (523 mg, 97%) as a pale yellow crystalline solid that had spectral properties identical to those of the material which was obtained by Procedure A.

9.4.4 cis-1-(Hydroxymethyl)bicyclo[3.3.0]octan-3,7-dione-7-(2',2'-dimethylpropylidene) acetal (316) and cis-1-(Hydroxymethyl)bicyclo[3.3.0]octan-3,7-dione-3,7-bis-(2',2'-dimethylpropylidene) acetal (317)

9.4.4.1 Monoprotection

\[
\begin{align*}
\text{OH} & \quad \text{314} \\
\text{neopentyl glycol (1 equiv.), PPTS (cat.), PhH, reflux, Dean-Stark, 2 h} & \rightarrow \\
& \quad \text{316 (36\%)} + \text{314 (20\%)} + \text{317 (44\%)}
\end{align*}
\]

A solution of cis-1-(hydroxymethyl)bicyclo[3.3.0]octan-3,7-dione 314 (315 mg, 1.87 mmol, 1.0 equiv.), neopentyl glycol (195 mg, 1.87 mmol, 1.0 equiv.) and pyridinium p-toluene sulfonate (5 mg, catalytic amount) in benzene (30 mL) was heated at reflux for 2 h with azeotropic removal of water in a Dean-Stark trap. The reaction mixture was allowed to cool to room temperature and was
concentrated in vacuo. The crude product was purified by flash chromatography (ether followed by ether:ethyl acetate, 8:1 and finally ether:ethyl acetate, 1:1).

The first compound to elute was cis-1-(hydroxymethyl)bicyclo[3.3.0]octan-3,7-dione-3,7-bis-(2',2'-dimethylpropylidene) acetal 317 (212 mg, 44%), which was obtained as a pale yellow solid and subsequently recrystallized from ether. 

\[ R_f \] 0.75 (ether:ethyl acetate, 1:1); M.p. 87-89 °C (ether); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 0.92 (s, 6H, 2 × acetal CH\(_3\)), 0.94 (s, 6H, 2 × acetal CH\(_3\)), 1.90 (dd, \(J = 6.9, 6.3\) Hz, 2H), 1.94-2.06 (m, 4H), 2.19 (dd, \(J = 12.4, 9.0\) Hz, 2H), 2.30-2.39 (m, 1H, bridgehead CH), 2.88 (br s, 1H, -OH), 3.40-3.48 (m, 10 H, 4 × acetal CH\(_2\) and angular CH\(_2\)OH); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 22.5, 22.6, 30.1, 39.6, 40.0, 44.7, 50.6, 70.6, 71.9, 72.3, 109.3; IR (ef) 3600-3150 (broad), 2952, 2874, 1473, 1395, 1304, 1109, 1037, 1008 cm\(^{-1}\); MS (Cl) m/z (rel. intensity) 341 (M + H, 13), 256 (17), 255 (100), 169 (43), 105 (30); Anal. Calcd. for C\(_{19}\)H\(_{32}\)O\(_5\): C, 67.03; H, 9.47; Found: C, 67.08; H, 9.62.

The second compound to elute was cis-1-(hydroxymethyl)bicyclo[3.3.0]octan-3,7-dione-7-(2',2'-dimethylpropylidene) acetal 316 (129 mg, 36%) which was obtained as a colourless oil. 

\[ R_f \] 0.45 (ether:ethyl acetate, 1:1); \(^1\)H NMR (500 MHz, C\(_6\)D\(_6\)) \(\delta\) 0.73 (s, 3H, acetal CH\(_3\)), 0.76 (s, 3H, acetal CH\(_3\)), 1.60 (ddd, 13.7, 6.0, 1.3 Hz, 1H), 1.87 (dq, \(J = 13.9, 1.8\) Hz, 2H), 2.00-2.11 (m, 2H), 2.19 (dd, \(J = 18.4, 1.6\) Hz, 1H), 2.28-2.45 (m, 4H), 3.15 (s, 2H, -CH\(_2\)OH), 3.20-3.28 (m, 4H, 2 × acetal CH\(_2\)); \(^{13}\)C NMR (126 MHz, C\(_6\)D\(_6\)) \(\delta\) 22.3, 22.4, 29.9, 39.6, 41.5, 44.3, 45.0, 48.3, 49.7, 69.6, 71.7, 72.0, 108.9, 217.8; IR (ef) 3660-3080 (broad), 2953, 2864, 1737, 1472, 1398, 1112, 1042 cm\(^{-1}\); MS (Cl) m/z (rel.
intensity) 255 (M + H, 100), 209 (6), 169 (80), 105 (58), 87 (8); Anal. Calcd. for C\textsubscript{14}H\textsubscript{22}O\textsubscript{4}: C, 66.12; H, 8.72; Found: C, 66.28; H, 8.43.

The third compound to elute was the starting material, cis-1-(hydroxymethyl)-bicyclo[3.3.0]octan-3,7-dione 314 (51 mg, 20%), which was obtained as a pale yellow crystalline solid.

9.4.4.2 *bis*-Protection

A solution of cis-1-(hydroxymethyl)bicyclo[3.3.0]octan-3,7-dione 314 (3.78 g, 22.5 mmol, 1.0 equiv.), neopentyl glycol (9.36 g, 89.9 mmol, 4.0 equiv.) and pyridinium p-toluene sulfonate (50 mg, catalytic amount) in dry benzene (125 mL) was heated at reflux for 90 min with azeotropic removal of water in a Dean-Stark trap. The reaction mixture was cooled to room temperature and washed with water (3 × 50 mL) and brine (50 mL), then dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was purified by flash chromatography (ether) to afford the title compound 317 (7.27 g, 95%) as a pale yellow solid that had spectral and physical properties identical to those of the material which was obtained by Procedure 9.4.4.
9.4.5 cis-1-(Methoxymethyl)bicyclo[3.3.0]octan-3,7-dione-3,7-bis-(2',2'-dimethylpropylidene) acetal (318)

\[
\text{OH} \quad \text{NaH, THF:DMF (18:5), 0 °C, 30 min then Mel, 0 °C to rt, 17 h} \quad \text{95%}
\]

To a suspension of sodium hydride (60% dispersion in mineral oil, 794 mg, 19.9 mmol, 1.5 equiv.) in THF (40 mL) at 0 °C was added dropwise via a cannula a solution of cis-1-(methoxymethyl)bicyclo[3.3.0]octan-3,7-dione-3,7-bis-(2',2'-dimethylpropylidene) acetal 317 (4.52 g, 13.3 mmol, 1.0 equiv.) in THF (50 mL) and DMF (25 mL). The resultant yellow suspension was stirred at 0 °C for 30 min. Methyl iodide (4.1 mL, 66 mmol, 5.0 equiv.) was added and the reaction mixture was allowed to warm to room temperature. The reaction mixture was stirred overnight, during which time a pale yellow precipitate of sodium iodide was deposited. The reaction mixture was quenched with water (40 mL) and the phases were separated. The aqueous phase was extracted with ether (3 × 50 mL) and the combined organic extracts were washed with water (5 × 20 mL) and brine (20 mL), then dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography (hexanes:ether, 2:1 followed by hexanes:ether, 1:1) to afford the title compound 318 (4.46 g, 95%) as a pale yellow oil. \( R_f \) 0.85 (ether); \(^1\text{H NMR} \) (400 MHz, \( \text{C}_6\text{D}_6 \)) \( \delta \) 0.78 (s, 6H, 2 × acetal CH₃), 0.85 (s, 6H, 2 × acetal CH₃), 2.08-2.21 (m, 4H), 2.24-2.31 (m, 2H), 2.35-2.44 (m, 3H), 3.20 (s, 3H, OCH₃), 3.30-3.41 (m, 10H, 4 × acetal CH₂ and CH₂OCH₃); \(^13\text{C NMR} \) (101 MHz, \( \text{C}_6\text{D}_6 \)) \( \delta \) 22.5, 22.6, 29.9, 40.4, 40.9,
43.6, 50.1, 58.9, 71.7, 72.0, 80.7, 109.8; IR (ef) 2951, 2867, 1472, 1323, 1308, 1108 cm⁻¹; MS (Cl) \textit{m/z} (rel. intensity) 355 (M + H, 100), 323 (3), 309 (2), 269 (1); \textbf{Anal.} Calcd. for C₂₀H₃₄O₅: C, 67.76; H, 9.67; Found: C, 67.75; H, 9.75.

9.4.6 \textit{cis-1-}(methoxymethyl)\textit{bicyclo}[3.3.0]octan-3,7-dione-7-(2',2'-dimethylpropylidene) acetal (319) and \textit{cis-1-}(methoxymethyl)\textit{bicyclo}[3.3.0]octan-3,7-dione (311)

9.4.6.1 \textit{Procedure A - Partial deprotection}

A mixture of \textit{cis-1-}(methoxymethyl)\textit{bicyclo}[3.3.0]octan-3,7-dione-3,7-bis-(2',2'-dimethyl-propylidene) acetal 318 (3.27 g, 9.22 mmol, 1.0 equiv.) and pyridinium \textit{p}-toluene sulfonate (20 mg, catalytic amount) in benzene (100 mL) and water (1 mL) was heated at reflux for 17 h. The resultant heterogeneous mixture was cooled to room temperature. The phases were separated and the organic phase was dried over anhydrous magnesium sulfate and concentrated \textit{in vacuo}. The crude mixture of products was purified by flash chromatography (hexanes:ether, 2:1 followed by hexanes:ether, 1:1 and finally ether).

The first compound to elute was the starting material, \textit{cis-1-}(methoxymethyl)\textit{bicyclo}[3.3.0]octan-3,7-dione-3,7-bis-(2',2'-dimethylpropylidene) (318) (35%) and \textit{cis-1-}(methoxymethyl)\textit{bicyclo}[3.3.0]octan-3,7-dione (311) (61%).
acetal 318 (2.02 g, 61%), which was obtained as a yellow oil that had physical and spectral properties identical to those of the material which was obtained by Procedure 9.4.5.

The second compound to elute was cis-1-(methoxymethyl)bicyclo[3.3.0]octan-3,7-dione-7-(2',2'-dimethylpropylidene) acetal 319 (768 mg, 31%), which was obtained as a colourless oil. Rf 0.70 (ether); ¹H NMR (400 MHz, C₆D₆) δ 0.72 (s, 3H, acetal CH₃), 0.75 (s, 3H, acetal CH₃), 1.60 (dd, J = 12.6, 5.3 Hz, 1H), 1.91 (d, J = 2.9 Hz, 2H), 2.04-2.42 (m, 6H), 2.89 (apparent dd, J = 20.7, 8.5 Hz, 2H, CH₂OCH₃), 2.96 (s, 3H, OCH₃), 3.14 (s, 2H, 2 × acetal CH₂), 3.21 (s, 2H, 2 × acetal CH₂); ¹³C NMR (101 MHz, C₆D₆) δ 22.4, 29.9, 40.3, 41.4, 44.7, 45.0, 48.3, 48.5, 58.8, 71.7, 72.0, 80.2, 108.9, 216.3; IR (ef) 2953, 2867, 1740, 1396, 1115 cm⁻¹; MS (Cl) m/z (rel. intensity) 269 (M + H, 100), 223 (2), 183 (3); Anal. Calcd. for C₁₅H₂₄O₄: C, 67.14; H, 9.01; Found: C, 67.20; H, 8.98.

The third compound to elute was cis-1-(methoxymethyl)bicyclo[3.3.0]octan-3,7-dione 311 (73 mg, 4%), which was obtained as a colourless crystalline solid. Rf 0.15 (ether); M.p. 71-72 °C (hexanes/ether); ¹H NMR (400 MHz, C₆D₆) δ 1.51 (dd, J = 18.5, 5.3 Hz, 2H), 1.69 (d, J = 18.5 Hz, 2H), 1.89 (d, J = 18.5 Hz, 2H), 2.04-2.20 (m, 3H), 2.56 (s, 2H, CH₂OCH₃), 2.83 (s, 3H, OCH₃); ¹³C NMR (101 MHz, C₆D₆) δ 39.1, 44.4, 46.4, 47.3, 58.9, 78.6, 214.4; IR (ef) 2933, 2839, 1733, 1649, 1398, 1113, 1102 cm⁻¹; MS (Cl) m/z (rel. intensity) 183 (M + H, 100), 151 (2); Anal. Calcd. for C₁₉H₁₄O₃: C, 65.91; H, 7.74; Found: C, 66.17; H, 7.93.
9.4.6.2 Procedure B - Complete deprotection

A solution of cis-1-(methoxymethyl)bicyclo[3.3.0]octan-3,7-dione-3,7-bis-(2',2'-dimethylpropylidene) acetal 318 (2.53 g, 7.14 mmol, 1.0 equiv.) in a mixture of THF (100 mL) and aqueous hydrochloric acid (1 M, 50 mL) was stirred at room temperature for 4 h. Ether (75 mL) was added and the phases were separated. The aqueous phase was extracted with ether (3 × 25 mL) and the combined organic phases were washed with water (3 × 25 mL) and brine (25 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The aqueous phase was then back-extracted with dichloromethane (5 × 50 mL). The extracts were washed with brine (25 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography (ether) to afford cis-1-(methoxymethyl)bicyclo[3.3.0]octan-3,7-dione 311 (1.28 g, 98%), which was obtained as a colourless crystalline solid that had spectral and physical properties identical to those of the material which was obtained by Procedure A.
A solution of cis-1-(methoxymethyl)bicyclo[3.3.0]octan-3,7-dione 311 (1.28 g, 7.02 mmol, 1.0 equiv.), neopentyl glycol (732 mg, 7.02 mmol, 1.0 equiv.) and pyridinium p-toluene sulfonate (~10 mg, catalytic amount) in anhydrous benzene (40 mL) was heated at reflux for 5.5 h with azeotrop ic removal of water in a Dean-Stark trap. The solution was allowed to cool to room temperature and was concentrated in vacuo. The crude product was purified by flash chromatography (hexanes:ether, 2:1 followed by hexanes:ether, 1:1 and finally ether).

The first compound to elute was cis-1-(methoxymethyl)bicyclo[3.3.0]octan-3,7-dione-3,7-bis-(2',2'-dimethyl-propylidene) acetal 318 (1.08 g, 44%).

The second compound to elute was cis-1-(methoxymethyl)bicyclo[3.3.0]octan-3,7-dione-7-(2',2'-dimethyl-propylidene) acetal 319 (552 mg, 30%).

The third compound to elute was the starting material, cis-1-(methoxymethyl)bicyclo[3.3.0]octan-3,7-dione 311 (338 mg, 26%). All three of
these compounds had spectral and physical properties identical to those of the materials which was obtained by Procedure A.

9.4.7

1-(Methoxymethyl)-2-(2'-propenoxy)-cis-bicyclo[3.3.0]oct-2-en-3,7-dione-7-(2',2'-dimethylpropylidene) acetal (320), 1-(Methoxymethyl)-3-(2'-propenoxy)-cis-bicyclo[3.3.0]oct-3-en-3,7-dione-7-(2',2'-dimethylpropylidene) acetal (321), 1-(Methoxymethyl)-2-(2'-propenyl)-cis-bicyclo[3.3.0]octan-3,7-dione-7-(2',2'-dimethylpropylidene) acetal (322) and 1-(Methoxymethyl)-4-(2'-propenyl)-cis-bicyclo[3.3.0]octan-3,7-dione-7-(2',2'-dimethylpropylidene) acetal (323)

To a solution of LDA (9.47 mmol, 1.1 equiv.) in THF (50 mL) at -78 °C was added a solution of cis-1-(methoxymethyl)bicyclo[3.3.0]octan-3,7-dione-7-(2',2'-dimethylpropylidene) acetal 319 (2.31 g, 8.61 mmol, 1.0 equiv.) in THF (20 mL) by means of a cannula. After stirring for 30 min at -78 °C, allyl bromide (3.7 mL, 43 mmol, 5.0 equiv.) which had previously been passed through a pad of activated neutral alumina was added, followed by hexamethylphosphoramide (5 mL). The resultant orange solution was allowed to warm to room temperature and was stirred for 16 h. The reaction mixture was quenched with water (10 mL) and the phases were separated. The aqueous phase was extracted with ether (3 × 40 mL) and the combined organic phases were washed with water (7 × 40 mL)
and brine (40 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The crude products were purified by flash chromatography (hexanes:ether, 6:1 followed by hexanes:ether, 3:1 and finally hexanes:ether, 1:1).

The first compounds to elute were the two regioisomeric allyl enol ethers 320 and 321 (544 mg, 20%), which were obtained as a pale yellow oil. \( R_f \) 0.55 (hexanes:ether, 2:1); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 0.80-1.01 (m, 6H, 2 × acetal CH\(_3\)), 1.57-2.61 (m, 7H, bicyclic ring protons), 3.07-3.52 (m, 11H, 2 × acetal CH\(_2\), CH\(_2\)OCH\(_3\), OCH\(_3\) and OCH\(_2\)CH=CH\(_2\)), 4.24 (d, \( J = 5.8 \) Hz, 0.8 H, enol ether CH for isomer 321), 4.50 (s, 0.2 H, enol ether CH for isomer 320), 4.87-5.31 (m, 2H, -OCH\(_2\)CH=CH\(_2\)), 5.76-5.99 (m, 1H, -OCH\(_2\)CH=CH\(_2\)); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 22.6, 22.8, 30.1, 30.2, 38.3, 39.8, 41.1, 41.4, 42.1, 42.5, 44.7, 48.3, 50.9, 59.3, 59.5, 69.5, 70.1, 71.5, 71.7, 72.5, 72.7, 80.3, 82.1, 101.5, 108.3, 109.1, 115.0, 115.9, 116.6, 117.1, 133.5, 134.8, 136.3, 137.1, 148.1, 159.3; IR (ef) 3076, 2952, 2867, 1641, 1472, 1311, 1111 cm\(^{-1}\); MS (Cl) m/z (rel. intensity) 309 (M + H, 100), 269 (49), 223 (2).

The second compounds to elute were the two regioisomeric ketones 322 and 323 (1.58 g, 59%), which were obtained together as a colourless oil. \( R_f \) 0.25 (hexanes:ether, 2:1); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 0.82-1.02 (m, 6H, 2 × acetal CH\(_3\)), 1.76-2.68 (m, 10H), 3.15-3.48 (m, 9H, CH\(_2\)OCH\(_3\), OCH\(_3\) and 2 × acetal CH\(_2\)), 4.96-5.08 (m, 2H, -CH\(_2\)CH=CH\(_2\)), 5.51-5.88 (m, 1H, -CH\(_2\)CH=CH\(_2\)); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 22.3, 22.5, 22.7, 30.0, 30.2, 35.0, 35.1, 37.7, 40.5, 40.9, 42.8, 43.9, 45.0, 45.6, 46.8, 47.6, 48.5, 48.6, 54.5, 54.9, 59.2, 71.7, 71.9,
IR (ef) 3078, 2953, 2927, 2862, 1736, 1639, 1470, 1112 cm\(^{-1}\); MS (Cl) m/z (rel. intensity) 309 (M + H, 100), 269 (1), 266 (1), 223 (2); Anal. Calcd. for C\(_{18}\)H\(_{28}\)O\(_4\): C, 70.10; H, 9.15; Found: C, 69.86; H, 9.10.

The third compound to elute was the starting material, cis-1-(methoxymethyl)-bicyclo[3.3.0]octan-3,7-dione-7-(2',2'-dimethylpropylidene) acetal 319 (420 mg, 18%) as a colourless oil.

9.4.8 1-(Methoxymethyl)-2-(2'-propenyl)-cis-bicyclo[3.3.0]octan-3,7-dione-7-(2',2'-dimethylpropylidene) acetal (322) and 1-(Methoxymethyl)-4-(2'-propenyl)-cis-bicyclo[3.3.0]octan-3,7-dione-7-(2',2'-dimethylpropylidene) acetal (323) by Claisen rearrangement of their respective O-allyl regioisomers

A solution of the O-allyl regioisomers 320 and 321 (401 mg, 1.30 mmol, 1.0 equiv.) in dry toluene (65 mL) was deoxygenated by purging with nitrogen gas for 30 min. The reaction mixture was heated at reflux for 3 days, was allowed to cool to room temperature and was then concentrated in vacuo. The crude products were purified by flash chromatography (hexanes:ether, 5:1 followed by hexanes:ether, 3:1) to afford a mixture of the regioisomeric title compounds 322 and 323 (337 mg, 84%) as a colourless oil. The material had
spectral and physical properties identical to those of the material which was obtained by Procedure 9.4.7.

9.4.9 1-(Methoxymethyl)-2-(2-oxoethyl)-cis-bicyclo[3.3.0]octan-3,7-dione-7-(2',2'-dimethylpropylidene) acetal (324) and 1-(Methoxymethyl)-4-(2-oxoethyl)-cis-bicyclo[3.3.0]octan-3,7-dione-7-(2',2'-dimethylpropylidene) acetal (325)

9.4.9.1 Procedure A - Lemieux oxidative cleavage

A solution consisting of a mixture of 1-(methoxymethyl)-2-(2'-propenyl)-cis-bicyclo[3.3.0]octan-3,7-dione-7-(2',2'-dimethylpropylidene) acetal 322 and 1-(methoxymethyl)-4-(2'-propenyl)-cis-bicyclo[3.3.0]octan-3,7-dione-7-(2',2'-dimethylpropylidene) acetal 323 (337 mg, 1.09 mmol, 1.0 equiv.) in p-dioxane (26 mL) and water (18 mL) was treated with osmium tetroxide (~5 mg, catalytic amount). The flask was covered with aluminum foil to protect the reaction mixture from light and the reaction mixture was stirred at room temperature for 45 min, during which time an intense brown colour developed. Sodium periodate (584 mg, 2.73 mmol, 2.5 equiv.) was then added in four portions at 1 h intervals. Over the course of these additions, a white precipitate of sodium iodate was deposited. The reaction mixture was then stirred for a further 2 h. The suspension was
filtered and the filter cake was washed with ethyl acetate (20 mL). The phases were separated and the aqueous phase was extracted with ethyl acetate (4 × 20 mL). The combined organic extracts were passed through a pad of neutral alumina to remove osmium residues and were dried over anhydrous sodium sulfate and concentrated in vacuo. The crude products were purified by flash chromatography (hexanes:ether, 1:1 followed by hexanes:ether, 1:2 and finally ether) to afford the title compounds 324 and 325 (108 mg, 32%) as a yellow oil. \(^{271}\) \(R_f\) 0.15 (hexanes:ether, 1:1); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 0.91-0.96 (m, 6H, 2 × acetal CH\(_3\)), 1.61-2.55 (m, 10H), 3.17-3.49 (m, 9H, -CH\(_2\)OCH\(_3\), -OCH\(_2\)OCH\(_3\) and 2 × acetal CH\(_2\)), 5.05-5.09 (m, 1H, -CH(OH)\(_2\) or -CH(OH)\(_2\)), 5.15-5.19 (m, 1H, -CH(OH)\(_2\) or -CH(OH)\(_2\)), 5.26-5.34 (m, 1H, -CH(OH)\(_2\) or -CH(OH)\(_2\)\); \(^{13}\)C NMR (101 MHz, C\(_6\)D\(_6\)) \(\delta\) 22.3, 22.4, 29.8, 32.7, 33.2, 40.1, 40.4, 44.3, 44.5, 46.4, 46.8, 47.1, 48.3, 50.9, 51.1, 58.8, 71.6, 72.2, 79.9, 80.3, 93.8, 94.0, 102.8, 103.0, 139.3, 215.7; IR (ef) 3630-3150 (broad), 2954, 2869, 2732, 1739, 1474, 1396, 1112 cm\(^{-1}\); MS (Cl) \(m/z\) (rel. intensity) 311 (M + H, 100), 282 (3), 225 (16), 207 (13), 205, (17), 107 (42), 105 (23), 89 (30).
A solution consisting of a mixture of 1-(methoxymethyl)-2-(2'-propenyl)-
cis-bicyclo[3.3.0]octan-3,7-dione-7-(2',2'-dimethylpropylidene) acetal 322 and 1-
(methoxymethyl)-4-(2'-propenyl)-cis-bicyclo[3.3.0]octan-3,7-dione-7-(2',2'-dimethyl-
propylidene) acetal 323 (413 mg, 1.34 mmol, 1.0 equiv.) in dichloromethane (25
mL) was placed in a two-necked flask affixed with an oxygen/ozone inlet line and
a calcium chloride drying tube. The solution was cooled to -78 °C and ozone
was bubbled through the solution until a deep blue colour developed (15 min).
The solution was purged with oxygen for 10 min and then dimethyl sulfide (2.0
mL) was added. The resultant pale yellow solution was allowed to warm to room
temperature and was stirred for a further 2 h. The reaction mixture was
concentrated in vacuo and was purified by flash chromatography (hexanes:ether,
3:2 followed by hexanes:ether, 1:1) to afford the title compounds 324 and 325
(398 mg, 96%) as a yellow oil that had spectral properties identical to those of
the material which was obtained by Procedure A.
A solution of the aldehydes 324 and 325 (1.01 g, 3.25 mmol, 1.0 equiv.) in a mixture of THF (25 mL) and aqueous hydrochloric acid (2 M, 12 mL) was stirred for 40 h at room temperature. The reaction mixture was then diluted with ethyl acetate (50 mL) and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 × 20 mL) and the combined organic extracts were washed with water (3 × 15 mL) and brine (15 mL). The combined aqueous phases were back-extracted with ethyl acetate (3 × 10 mL) and the combined organic phases were washed with brine (15 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The crude products were purified by flash chromatography (hexanes:ethyl acetate, 1:2 followed by ethyl acetate).

The first compound to elute (188 mg, Rf 0.70 in ether) had a ¹H NMR spectrum consistent with the presence of an acetal moiety. After drying in vacuo, this material was dissolved in a mixture of p-dioxane (10 mL) and aqueous hydrochloric acid (2 M, 5 mL) and was heated at reflux for 1 h. The reaction
mixture was allowed to cool to room temperature and was worked up as described above. This procedure afforded the impure title compounds 309 and 310 (135 mg) as an amorphous solid.

The second compounds to elute from the column were the impure title compounds 309 and 310 (371 mg) as an amorphous solid.

The material which was obtained by the above procedures was combined (506 mg) and purified by flash chromatography (ether:ethyl acetate, 1:1) to afford the title compounds 309 and 310 (380 mg, 52%) as an amorphous solid.

These compounds were obtained as a mixture of regioisomeric C-5 epimers which were inseparable by flash chromatography. Repeated recrystallization of this material from hexanes/ether afforded a single diastereomer of 1-(methoxymethyl)tricyclo[5.2.1.0^4^10]deca-3,8-dione-5-ol 309 (~40 mg) as a crystalline solid. \( R_f \) 0.15 (ether); \( \text{M.p.} \) 86-88 °C (ether/hexanes);

\(^1\text{H NMR} \) (400 MHz, CDCl\(_3\), assignments by COSY and HMQC experiments) \( \delta \)

2.09 (ddd, \( J = 13.5, 8.9, 4.0 \) Hz, 1H, \( H_6 \)), 2.21-2.28 (m, 2H, -OH and \( H_6' \)), 2.39-2.68 (m, 4H, \( H_2, H_2', H_9 \) and \( H_9' \)), 2.90 (tt, \( J = 9.0, 1.6 \) Hz, 1H, \( H_7 \)), 3.05 (dd, \( J = 10.6, 6.0 \) Hz, 1H, \( H_4 \)), 3.31-3.40 (m, 6H, \( 2 \times H_{11} \) and \( 3 \times H_{12} \)), 4.47-4.50 (m, 1H, \( H_5 \)); \(^{13}\text{C NMR} \) (101 MHz, CDCl\(_3\)) \( \delta \) 43.3 (C\(_6\)), 45.1 (C\(_1\)), 48.5 (C\(_2\)), 51.4 (C\(_{10}\)), 51.6 (C\(_9\)), 53.0 (C\(_7\)), 59.5 (C\(_{12}\)), 59.9 (C\(_4\)), 74.9 (C\(_5\)), 80.3 (C\(_{11}\)), 218.5 (C\(_3\) or C\(_8\)), 221.4 (C\(_3\) or C\(_8\)); \( \text{IR (ef)} \) 3650-3050 (broad), 2928, 2827, 2732, 1716, 1455, 1404, 1184, 1109 cm\(^{-1}\); \( \text{MS (Cl)} \) \( m/z \) (rel. intensity) 225 (M + H, 27), 207 (M - OH, 100).
9.4.1 1-(Methoxymethyl)triquinacene (330) and 10-(Methoxymethyl)-triquinacene (331)

\[
\begin{align*}
\text{BH}_3 \cdot \text{THF, THF,} \\
\text{0°C to rt, 16 h} + \\
\text{MsCl, NEt}_3, \\
\text{DCM, 0°C to rt, 15 h} + \\
\end{align*}
\]

9.4.1.1 1-(Methoxymethyl)tricyclo[5.2.1.0^4.10]deca-3,5,8-triol 326 and 10-(Methoxymethyl)tricyclo[5.2.1.0^4.10]deca-3,5,8-triol 327

To a solution of 1-(methoxymethyl)tricyclo[5.2.1.0^4.10]deca-3,8-dione-5-ol (309) and 10-(methoxymethyl)tricyclo[5.2.1.0^4.10]deca-3,8-dione-5-ol (310) (150 mg, 0.67 mmol, 1.0 equiv.) in anhydrous THF (5 mL) at 0°C was added dropwise borane-THF complex (2.0 mL of 1 M solution in THF, 2.0 mmol, 3.0 equiv.). The reaction was then allowed to warm to room temperature and was stirred for 16 h. Methanol (5 mL) was added and the resultant solution was concentrated in vacuo. The addition and removal of methanol was repeated four times to remove the borate residues as trimethylborate. This afforded the title compounds 326
and 327 (145 mg) as a colourless solid and as a complex mixture of
diastereomers. The infrared spectrum of the triols showed no carbonyl
stretching bands. This material was used in the next step without further
purification.

9.4.11.2 1-(Methoxymethyl)-3,5,8-trimesyloxytricyclo[5.2.1.0^4^10]decane 328
and 10-(Methoxymethyl)-3,5,8-trimesyloxytricyclo[5.2.1.0^4^10]decane
329

To a solution of 1-(methoxymethyl)tricyclo[5.2.1.0^4^10]deca-3,5,8-triol (326)
and 10-(methoxymethyl)tricyclo[5.2.1.0^4^10]deca-3,5,8-triol (327) (145 mg, 0.64
mmol, 1.0 equiv.) in anhydrous dichloromethane (5 mL) at 0 °C was added
triethylamine (889 μL, 6.4 mmol, 10 equiv.) and methanesulfonyl chloride (490
μL, 6.4 mmol, 10 equiv.). The reaction mixture was allowed to warm to room
temperature and was stirred for 1.5 h, after which time the reaction a saturated
aqueous solution of sodium bicarbonate (1 mL) was added. The phases were
separated, the aqueous phase was extracted with dichloromethane (2 × 2 mL)
and the combined organic phases were washed with water (2 × 5 mL), dried over
anhydrous sodium sulfate and concentrated in vacuo to afford the title
compounds 328 and 329 (270 mg) as a yellow oil. No absorbances

9.4.11.3 1-(Methoxymethyl)triquinacene 330 and 10-(Methoxymethyl)-
triquinacene 331

A slurry of highly activated neutral alumina (60-325 mesh, 3.0 g) in
dichloromethane (10 mL) was stirred for 5 min. A solution of 1-(methoxymethyl)
3,5,8-trimesyloxytricyclo[5.2.1.0²,⁶]decane (328) and 10-(methoxymethyl)-3,5,8-trimesyloxytricyclo[5.2.1.0²,⁶]decane (329) (270 mg) in dichloromethane (5 mL) was added and the resultant yellow slurry was stirred for 7 days at room temperature. The alumina was removed by filtration and the filter cake was washed with dichloromethane (100 mL) and chloroform (50 mL). The filtrate was concentrated in vacuo. Repeated flash chromatography (hexanes, then hexanes:ether, 19:1) afforded a mixture consisting mainly of 1-(methoxymethyl)-triquinacene 330 along with traces of 10-(methoxymethyl)triquinacene 331 and of several impurities (33 mg). Rf 0.25 (hexanes:ether, 19:1).

9.5 Experimental Concerning Chapter Five

9.5.1 4-Bromocyclopent-2-en-1-one (342)\(^{180}\)

\[
\begin{align*}
\text{O} & \quad \text{NBS, AIBN (cat.), CCl}_4, \text{reflux} \\
343 & \quad \text{Br} \\
\end{align*}
\]

A solution of cyclopent-2-en-1-one 343 (3.10 mL, 37.0 mmol, 1.0 equiv.), N-bromosuccinimide (7.33 g, 40.7 mmol, 1.1 equiv.) and AIBN (619 mg, 3.70 mmol, 0.1 equiv.) in dry carbon tetrachloride (50 mL) was heated at reflux for 3 h, during which time a white precipitate was deposited. The reaction mixture was cooled in a ice-water bath for 30 min and the precipitate was removed by filtration. The filter cake was washed with ice-cold carbon tetrachloride (4 x 10 mL) and the filtrate was washed with ice-cold water (3 x 10 mL) followed by ice-cold aqueous sodium thiosulfate solution (0.1 M, 10 mL). The organic phase was
dried over anhydrous sodium sulfate and carefully concentrated *in vacuo* to afford the *title compound 342* as an orange oil (5.8 g) which was used in the next step without further purification. A small sample was purified by flash chromatography (hexanes:ether, 2:1). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 2.71 (dd, \(J = 19.6, 1.7\) Hz, 1H, \(H_5\)), 3.02 (dd, \(J = 19.6, 6.2\) Hz, 1H, \(H_5'\)), 5.10-5.14 (m, 1H, \(H_4\)), 6.23-6.29 (m, 1H, \(H_2\)), 7.67 (dd, \(J = 5.4, 2.5\) Hz, 1H, \(H_3\)); \(^{13}\)C NMR (CDCl\(_3\), 101 MHz) \(\delta\) 42.7 (C\(_4\) or C\(_5\)), 45.0 (C\(_4\) or C\(_5\)), 134.9 (C\(_2\)), 162.5 (C\(_3\)), 196.6 (C\(_1\)); IR (ef) 1721, 1680, 1650, 1578, 1402, 1341, 1177 cm\(^{-1}\); MS (Cl) m/z (rel. intensity) 162 (M + H for \(^{81}\)Br, 100), 160 (M + H for \(^{79}\)Br, 97), 81 (7).

9.5.2 endo-7-Oxo-bicyclo[2.2.1]hept-1-ene-2-carboxylic acid ethyl ester (337), \(^{179}\) 1-Indanone (344), \(^{272}\) 7-Bromodicyclopentadienone (345) and Dicyclopentadienone (346)

\[
\begin{align*}
\text{337 (29\% from 343)} & & \text{344 (25\%)} \\
\text{345 (3\%)} & & \text{346 (6\%)}
\end{align*}
\]

A solution of crude 4-bromocyclopent-2-en-1-one 342 (5.8 g, \(\sim\)37.0 mmol, 1.0 equiv.) and ethyl acrylate (32.0 mL, 296 mmol, 8.0 equiv.) in anhydrous DME (100 mL) was heated at reflux for 72 h. The resultant brown solution was allowed to cool to room temperature and the excess ethyl acrylate and the DME
were removed in vacuo to afford a resinous brown oil (18.1 g) which was purified by repeated flash chromatography (hexanes:ether, 3:1 followed by hexanes:ether, 2:1) with dry loading (silica gel).

The first compound to elute was 1-indanone 344 (1.23 g, 25% in two steps from 343), which was obtained as a colourless waxy solid. Rf 0.80 (hexanes:ether, 1:1); M.p. 39-41 °C, hexanes (lit.272 40-42 °C, hexanes); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.67-2.72 (m, 2H), 3.12-3.18 (m, 2H), 7.37 (t, $J = 7.5$ Hz, 1H), 7.48 (d, $J = 7.3$ Hz, 1H), 7.59 (t, $J = 7.4$ Hz, 1H), 7.76 (d, $J = 7.8$ Hz, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 26.0, 36.4, 123.8, 126.8, 127.4, 134.7, 137.3, 155.3, 207.2; IR (neat) 3072, 3033, 2924, 2857, 1711, 1609, 1277, 758 cm$^{-1}$; MS (El) m/z (rel. intensity) 132 (M, 95), 104 (100), 78 (23), 51 (21).

The second compound to elute was endo-7-oxo-bicyclo[2.2.1]hept-1-ene-2-carboxylic acid ethyl ester 337 (1.93 g, 29% in two steps from 343), which was obtained as a colourless oil. Rf 0.70 (hexanes:ether, 1:1); $^1$H NMR (400 MHz, CDCl$_3$, assignments by COSY, HMQC and NOESY experiments) $\delta$ 1.25 (t, $J = 7.0$ Hz, 3H, $3 \times H_{10}$), 1.71 (ddd, $J = 12.5$, 5.1, 0.8 Hz, 1H, $H_5$), 2.15-2.23 (m, 1H, $H_6$'), 2.94-2.98 (m, 1H, $H_3$), 3.10-3.16 (m, 1H, $H_4$), 3.23-3.26 (m, 1H, $H_6$), 4.07-4.19 (m, 2H, $2 \times H_9$), 6.38-6.42 (m, 1H, $H_1$), 6.60-6.64 (ddd, $J = 6.8$, 3.6, 0.9 Hz, 1H, $H_2$); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 14.3 (C$_{10}$), 26.1 (C$_4$), 38.2 (C$_5$), 46.4 (C$_3$), 48.8 (C$_6$), 61.1 (C$_9$), 130.3 (C$_1$), 134.5 (C$_2$), 172.5 (C$_8$), 202.4 (C$_7$); IR (neat) 1787, 1732, 1450, 1370, 1332, 1294, 1200, 1100, 1042, 872 cm$^{-1}$; MS (Cl) m/z (rel. intensity) 181 (M + H, 26), 133 (100).
The third compound to elute was dicyclopentadienone 346 (436 mg, 8% in two steps from 343) which was obtained as a crystalline solid. \( R_f \) 0.60 (hexanes:ether, 1:1); \textbf{M.p.} 97-98 °C, hexanes (lit.\textsuperscript{273} 98 °C, hexanes); \textbf{\( ^1H \) NMR} (400 MHz, CDCl\textsubscript{3}) \( \delta \) 2.91 (t, \( J = 5.5 \) Hz, 1H), 3.21 (t, \( J = 3.9 \) Hz, 1H), 3.40 (t, \( J = 3.9 \) Hz, 1H), 3.49-3.55 (m, 1H), 6.17 (dd, \( J = 6.8, 3.5 \) Hz, 1H), 6.32 (dd, \( J = 6.8, 3.5 \) Hz, 1H), 6.37 (dd, \( J = 5.5, 1.5 \) Hz, 1H), 7.37 (dd, \( J = 5.6, 2.7 \) Hz, 1H); \textbf{\( ^{13}C \) NMR} (101 MHz, CDCl\textsubscript{3}) \( \delta \) 41.7, 43.4, 49.3, 50.2, 129.2, 129.9, 141.5, 161.4, 199.7, 206.7; \textbf{IR} (KBr) 3060, 3018, 2928, 1776, 1703, 1354, 1204, 1113 cm\textsuperscript{-1}; \textbf{MS} (Cl) \textit{m/z} (rel. intensity) 161 (M + H, 100), 134 (5), 133 (59), 132 (2), 131 (2).

The fourth compound to elute was 7-bromodicyclopentadienone 345 (137 mg, 3% in two steps from 343) which was obtained as a colourless solid and then recrystallized from hexanes. \( R_f \) 0.55 (hexanes:ether, 1:1); \textbf{M.p.} 114-116 °C, hexanes. \textbf{\( ^1H \) NMR} (400 MHz, CDCl\textsubscript{3}, assignments by COSY and HMQC experiments) \( \delta \) 3.11 (dd, \( J = 6.2, 4.9 \) Hz, 1H, H\textsubscript{6}), 3.34-3.38 (m, 1H, H\textsubscript{8}), 3.42-3.46 (m, 1H, H\textsubscript{6}), 3.68-3.73 (m, 1H, H\textsubscript{4}), 6.30-6.35 (m, 1H, H\textsubscript{1} or H\textsubscript{2}), 6.40-6.44 (m, 1H, H\textsubscript{1} or H\textsubscript{2}), 6.53 (d, \( J = 1.8 \) Hz, H\textsubscript{6}); \textbf{\( ^{13}C \) NMR} (101 MHz, CDCl\textsubscript{3}) \( \delta \) 47.0 (C\textsubscript{8}), 48.6 (C\textsubscript{4}), 49.3 (C\textsubscript{3}), 49.9 (C\textsubscript{9}), 129.1 (C\textsubscript{1} or C\textsubscript{2}), 130.9 (C\textsubscript{1} or C\textsubscript{2}), 141.4 (C\textsubscript{7}), 159.2 (C\textsubscript{6}), 198.2 (C\textsubscript{5}), 201.8 (C\textsubscript{10}); \textbf{IR} (ef) 3068, 3011, 2952, 1886, 1796, 1778, 1699, 1575, 1260, 1177, 1167 cm\textsuperscript{-1}; \textbf{MS} (Cl) \textit{m/z} (rel. intensity) 241 (M + H for \textsuperscript{81}Br, 100), 239 (M + H for \textsuperscript{79}Br, 99), 213 (11), 211 (12), 130 (2). \textbf{Anal.} Calcd. for C\textsubscript{10}H\textsubscript{7}BrO\textsubscript{2}: C, 50.24; H, 2.95; Found: C, 50.32; H, 3.03.
To a solution of 4-bromocyclopent-2-en-1-one 342 (1.96 g, 12.2 mmol, 1.00 equiv.) in ether (20 mL) was added triethylamine (1.80 mL, 12.8 mmol, 1.05 equiv.). A white precipitate was immediately deposited. The reaction mixture was stirred for 1 h at room temperature and was then allowed to stand overnight. The triethylammonium bromide was removed by filtration and the filter cake was washed with ether (50 mL). The filtrate was concentrated in vacuo and the crude product was purified by flash chromatography (hexanes:ether, 1:1 followed by hexanes:ether, 1:2) and recrystallized from hexanes:ether, 1:4 to afford the title compound 346 (758 mg, 78%) as a colourless solid that had spectral and physical properties identical to those of the material which was obtained by Procedure 9.5.2 and consistent with literature values.273

To a dry 500 mL 2-necked flask fitted with an addition funnel and a reflux condenser was added vinylmagnesium bromide (100 mL of a 1 M solution in THF, 100 mmol, 1.0 equiv.). The red solution was cooled to 0 °C and a solution of acrolein 340 (6.70 mL, 100 mmol, 1.0 equiv.) in THF (10 mL) was added
through the dropping funnel over 1 h. The reaction mixture was stirred for 3 h while being allowed to warm to room temperature. A saturated aqueous solution of sodium bicarbonate (50 mL) was added and the resultant suspension was filtered. The yellow filtrate was extracted with pentane (3 x 100 mL), dried over anhydrous sodium sulfate and carefully concentrated in vacuo. Distillation under reduced pressure afforded the title compound 352 (4.30 g, 52%) as a colourless oil. B.p. 50-52 °C/25 mmHg; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) \textdelta 4.60-4.66 (m, 1H, H\textsubscript{3}), 5.17 (dt, J = 10.4, 1.4 Hz, 2H, H\textsubscript{1-cis} and H\textsubscript{5-cis}), 5.29 (dt, J = 17.3, 1.4 Hz, 2H, H\textsubscript{1-trans} and H\textsubscript{5-trans}), 5.86-5.95 (m, 2H, H\textsubscript{2} and H\textsubscript{4}); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 101 MHz) \textdelta 74.1 (C\textsubscript{3}), 115.4 (C\textsubscript{1} and C\textsubscript{5}), 139.3 (C\textsubscript{2} and C\textsubscript{4}); IR (neat) 3540-3170 (broad), 3088, 2982, 1558, 1540, 1507, 1115, 988, 922 cm\textsuperscript{-1}; MS (EI) m/z (rel. intensity) 83 (M - OH, 78), 69 (8), 65 (13), 57 (41), 56 (34), 55 (100), 43 (14), 42 (10).

9.5.5 5-Bromo-1,3-pentadiene (336)\textsuperscript{181}

\[
\begin{array}{c}
\text{352} \\
\text{OH} \\
\end{array}
\xrightarrow{48\% \text{aq. HBr, 0 °C, 1 h}}
\begin{array}{c}
\text{346} \\
\text{Br} \\
\end{array}
\]

To a flask containing 1,4-pentadien-3-ol 352 (4.30 g, 51.1 mmol, 1.0 equiv.) at 0 °C was added dropwise hydrobromic acid (6.4 mL of a 48% w/v aqueous solution, 56 mmol, 1.1 equiv.) and the resultant biphasic mixture was allowed to warm to room temperature over 1 h. The phases were separated and the aqueous phase was extracted with ether (20 mL). The combined organic phases were washed with ice-cold water (3 x 10 mL), dried over anhydrous
sodium sulfate, filtered and transferred to a dry flask. A Vigreux column was attached and the ether was removed over 3 h under water aspirator pressure with no heating. Distillation under reduced pressure afforded a mixture of the E/Z isomers of the title compound 336 (5.85 g, 78%) as a pale yellow oil. B.p. 41-43 °C/25 mmHg; \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta 4.01-4.05 (m, 2H)\), 5.15-5.19 (m, 1H), 5.24-5.31 (m, 1H), 5.85-5.94 (m, 1H), 6.24-6.38 (m, 2H); \(^{13}\)C NMR (CDCl\(_3\), 101 MHz) \(\delta 32.8 \text{ (C}_5\text{)}, 119.4 \text{ (C}_1\text{)}, 129.1 \text{ (C}_3\text{)}, 135.2 \text{ (C}_2 \text{ or C}_4\text{)}, 135.5 \text{ (C}_2 \text{ or C}_4\text{)};\) IR (ef) 3088, 3034, 3011, 2969, 2907, 2589, 1644, 1599, 1435, 1202 cm\(^{-1}\); MS (Cl) \(m/z\) (rel. intensity) 148 (M + H for \(^{81}\)Br, 100), 146 (M + H for \(^{79}\)Br, 98), 133 (19), 123 (8), 93 (2), 81 (3).

9.5.6 **endo-7-Hydroxy-7-(1-vinylallyl)-bicyclo[2.2.1]hept-1-ene-4-carboxylic acid ethyl ester (335)**

![Chemical Structure](image)

To a solution of endo-7-oxo-bicyclo[2.2.1]hept-1-ene-2-carboxylic acid ethyl ester 337 (665 mg, 3.69 mmol, 1.0 equiv.) and 5-bromo-1,3-pentadiene 336 (2.72 g, 18.5 mmol, 5.0 equiv.) in DMF (3 mL) at 0 °C was added indium metal (400 mesh, 1.06 g, 9.23 mmol, 2.5 equiv.) in four portions at 30 min intervals. The reaction mixture was then allowed to warm to room temperature overnight. Dichloromethane (15 mL) and ether (15 mL) were added and the resultant suspension was filtered through a pad of silica gel. The pad of silica was washed
with ether (50 mL) and the filtrate was then concentrated in vacuo and purified by flash chromatography (hexanes:ether, 3:1) to afford the title compound 335 (747 mg, 82%) as a pale yellow oil which, upon prolonged standing at -25 °C solidified to afford an off-white solid. **M.p.** 34-35 °C, hexanes/ether; **¹H NMR** (400 MHz, CDCl₃, assignments by COSY, HMQC and NOESY experiments) δ 1.22 (t, J = 7.0 Hz, 3H, 3 × H₁₀), 1.47 (dd, J = 11.7, 4.0 Hz, 1H, H₅-endo), 1.70-1.78 (br s, 1H, -OH), 2.23 (ddd, J = 11.7, 8.8, 4.0 Hz, 1H, H₅-exo), 2.25-2.29 (m, 1H, H₆), 2.90-2.94 (m, 1H, H₃), 3.29-3.34 (m, 1H, H₄), 3.52 (apparent tt, J = 7.3, 1.1 Hz, 1H, H₁₁), 4.07 (qd, J = 6.9, 2.2 Hz, 2H, 2 × H₆), 5.06 (apparent qt, J = 6.9, 1.5 Hz, 2H, 2 × H₁₃ or 2 × H₁₅), 5.15-5.21 (m, 2H, 2 × H₁₃ or 2 × H₁₅), 5.82-5.95 (m, 3H, H₁₂, H₁₄ and either H₁ or H₂), 6.16 (m, 1H, H₁ or H₂); **¹³C NMR** (400 MHz, CDCl₃) δ 14.2 (C₁₀), 27.5 (C₅), 41.9 (C₄), 47.0 (C₁₁), 48.2 (C₆), 51.3 (C₃), 60.1 (C₉), 94.0 (C₇), 117.5 (C₁₃ and C₁₅), 131.7 (C₁ or C₂), 136.7 (C₁₂ and C₁₄), 137.0 (C₁ or C₂), 174.9 (C₈); **IR** (KBr) 3550-3150 (broad), 3072, 1716, 1633 cm⁻¹; **MS** (Cl) m/z (rel. intensity) 249 (M + H, 100), 231 (53), 221 (29), 203 (31), 175 (11), 147 (3); **Anal.** Calcd. for C₁₅H₂₀O₃: C, 72.55; H, 8.12; Found: C, 72.35; H, 8.19.
A solution of the triene 335 (242 mg, 0.975 mmol, 1.0 equiv.) in dichloromethane (15 mL) at room temperature was treated with bis(tricyclohexylphosphine)benzylidene ruthenium (IV) dichloride 357 ("first generation" Grubbs' catalyst, 802 mg, 0.975 mmol, 1.0 equiv.) in four equal portions over 64 h. The solvent was removed in vacuo and the black reaction mixture was purified by flash chromatography (hexanes:ether, 1:1) to afford the title compound 371 (189 mg, 83%) as a brown oil consisting of a ~1:1 mixture of diastereomers. §H NMR (CDCl₃, 400 MHz) δ 1.10-1.22 (m, 3H), 1.27 (t, J = 7.1 Hz, 3H), 1.70 (br s, 1H, -OH), 1.90-2.10 (m, 3H), 2.20-2.28 (m, 1H), 2.52 (t, J = 8.0 Hz, 1H), 3.11 (m, 1H), 4.11-4.19 (m, 2H), 5.14-5.26 (m, 2H), 5.68-5.79 (m, 1H); §C NMR (CDCl₃, 126 MHz) δ 17.3, 17.6, 27.2, 27.3, 29.8, 42.2, 43.4, 43.5, 45.6, 45.8, 49.2, 50.2, 50.4, 60.4, 86.8, 117.7, 117.8, 137.1, 137.3; IR (ef) 3630-3120 (broad), 3058, 3025, 2928, 2853, 1731, 1448, 1370, 1180, 1156 cm⁻¹; MS (Cl) m/z (rel. intensity) 235 (M + H, 100), 189 (3), 143 (2); Anal. Calcd. for C₁₄H₁₈O₃: C, 71.77; H, 7.74; Found: C, 71.83; H, 7.71.
9.5.8 endo-7-Allyl-7-hydroxy-bicyclo[2.2.1]hept-1-ene-4-carboxylic acid ethyl ester (379)

To a solution of endo-7-oxo-bicyclo[2.2.1]hept-1-ene-2-carboxylic acid ethyl ester 337 (160 mg, 0.888 mmol, 1.0 equiv.) and allyl bromide (380 µL, 4.4 mmol, 5.0 equiv.) in DMF (400 µL) at 0 °C was added indium metal (400 mesh, 255 mg, 2.22 mmol, 2.5 equiv.) was added in four portions at 30 min. intervals. The reaction mixture was then allowed to warm to room temperature overnight. Dichloromethane (3 mL) and ether (3 mL) were added and the resultant suspension was filtered through a short pad of silica gel. The pad of silica was then washed with ether (25 mL) and the filtrate was concentrated in vacuo and purified by flash chromatography (hexanes:ether, 3:1) to afford the title compound 379 (117 mg, 59%) as a colourless oil. $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.23 (t, $J =$ 7.9 Hz, 3H), 1.46 (dd, $J =$ 11.6, 3.9 Hz, 1H), 1.91 (br s, 1H, -OH), 2.23-2.30 (m, 1H), 2.37-2.52 (m, 3H), 2.84 (t, $J =$ 3.7 Hz, 1H), 3.35 (dt, $J =$ 8.9, 3.9 Hz, 1H), 4.00-4.11 (m, 2H), 5.09-5.18 (m, 2H), 5.70-5.82 (m, 1H), 5.91-5.94 (dd, $J =$ 6.1, 3.1 Hz, 1H), 6.17 (dd, $J =$ 6.2, 3.1 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 101 MHz) $\delta$ 14.5, 27.8, 37.2, 42.1, 49.3, 52.3, 60.3, 91.9, 119.3, 132.2, 134.9, 137.2, 175.2; IR (ef) 3640-3150 (broad), 3072, 2977, 2924, 2851, 1715, 1638, 1447, 1190, 1041 cm$^{-1}$; MS (Cl) m/z (rel. intensity) 223 (M + H, 100), 205 (68), 177
9.5.9  6-Hydroxytetracyclo[4.3.0.0^{2,4}.0^{3,7}]nonane-8-carboxylic acid ethyl ester (380)

A solution of diene 379 (88 mg, 0.40 mmol, 1.0 equiv.) in benzene (30 mL) at room temperature was treated with bis(tricyclohexylphosphine)benzylidene ruthenium (IV) dichloride ("first generation" Grubbs' catalyst, 326 mg, 0.396 mmol, 1.0 equiv.) in four equal portions over 68 h. The solvent was removed in vacuo and the black reaction mixture was purified by flash chromatography (hexanes:ether, 3:1 followed by hexanes:ether 1:1) to afford the title compound 357 (58 mg, 70%) as a brown oil.  $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.08 (t, $J$ = 7.9 Hz, 2H), 1.13-1.16 (m, 1H), 1.26 (t, $J$ = 7.1 Hz, 3H, ester CH$_3$), 1.46 (br s, 1H, -OH), 1.79-1.82 (m, 2H), 1.89-1.94 (m, 1H), 1.96-2.04 (m, 1H), 2.10 (dd, $J$ = 12.7, 4.8 Hz, 1H), 2.17 (d, $J$ = 4.8 Hz, 1H), 3.10-3.18 (m, 1H), 4.10-4.22 (m, 2H, ester OCH$_2$); $^{13}$C NMR (CDCl$_3$, 101 MHz) $\delta$ 10.0, 14.3, 14.5, 17.9, 27.7, 35.4, 43.9, 45.1, 48.5, 60.4, 85.3, 175.9; IR (ef) 3560-3180 (broad), 3063, 2947, 2872, 1733, 1665, 1558, 1540, 1507, 1289, 1180, 1091 cm$^{-1}$; MS (Cl) m/z (rel. intensity) 209 (M + H, 100), 163 (3); Anal. Calcd. for C$_{13}$H$_{18}$O$_3$: C, 69.21; H, 7.74; Found: C, 68.94; H, 7.93.
A solution of 6-hydroxytetracyclo[4.3.0.0^{2.4}.0^{3.7}]nonane-8-carboxylic acid ethyl ester 371 (43 mg, 0.18 mmol, 1.0 equiv.) in THF (1 mL) was cooled to 0 °C and was treated with phenyllithium (510 μL of a 1.8 M solution in cyclohexane:ether (7:3), 0.92 mmol, 5.0 equiv.). The reaction was allowed to warm to room temperature over 30 min, then was quenched with saturated aqueous ammonium chloride (1 mL). After stirring for a further 5 min, the phases were separated. The aqueous phase was extracted with ether (3 × 5 mL) and the combined organic phases were washed with water (3 × 5 mL) followed by brine (5 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo to afford the crude product as a yellow oil. This material was then purified by flash chromatography (hexanes:ether, 3:1 followed by hexanes:ether, 2:1) to afford the title compound 378 (49 mg, 78%) as a colourless amorphous solid consisting of a ~1:1 mixture of diastereomers. M.p. 61-63 °C, hexanes/ether; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.14-1.20 (m, 1H), 1.22-1.30 (m, 2H), 1.37-1.72 (m, 4H), 1.91-2.02 (m, 2H), 2.30-2.42 (m, 1H), 3.51-3.65 (m, 1H), 5.05-5.22 (m, 2H, CH=CH$_2$), 5.47-5.76 (m, 1H, CH=CH$_2$), 7.16-7.21 (m, 2H, ArH), 7.28-7.32 (m, 4H, ArH), 7.47-7.52 (m, 2H, ArH), 7.55-7.61 (m, 2H, ArH); $^{13}$C NMR (CDCl$_3$, 101 MHz) $\delta$ 16.3, 16.5, 17.6, 17.9, 26.2, 26.4, 42.5, 44.4, 46.1, 47.4, 47.6, 48.3, 49.2,
79.7, 79.8, 86.1, 86.2, 117.8, 125.5, 125.7, 126.0, 126.2, 126.3, 126.5, 126.6,
126.7, 128.2, 128.3, 128.6, 137.3, 137.4, 147.8, 184.1; IR (ef) 3640-3130
(broad), 3057, 3026, 2945, 2871, 1637, 1598, 1492, 1447, 1284, 1065, 1033 cm⁻¹;
MS (Cl) m/z (rel. intensity) 345 (M + H, 6), 328 (29), 327 (100), 310 (6), 309
(14), 267 (41), 183 (45), 167 (17), 145 (7); Anal. Calcd. for C₂₄H₂₄O₂: C, 83.69;
H, 7.02; Found: C, 83.31; H, 7.29.

9.5.11  endo-7-(4′-Bromobenzyloxy)-7-(1-vinylallyl)-bicyclo[2.2.1]hept-1-
en-4-carboxylic acid ethyl ester (373)

To a suspension of sodium hydride (28 mg of a 60% suspension in
mineral oil, 0.68 mmol, 1.3 equiv.) in anhydrous THF (3 mL) at room temperature
was added via a cannula a solution of endo-7-hydroxy-7-(1-vinylallyl)-
bicyclo[2.2.1]hept-1-ene-4-carboxylic acid ethyl ester 335 (130 mg, 0.524 mmol,
1.0 equiv.) in anhydrous DMF (3 mL). The resultant brown solution was stirred
for 30 min. A solution of 4-bromobenzylbromide (655 mg, 2.62 mmol, 5.0 equiv.)
in THF (2 mL) was added via a cannula to afford an orange solution which was
stirred overnight at room temperature. The reaction mixture was diluted with
water (5 mL) and ether (5 mL) and then the phases were separated and the
aqueous phase was extracted with ether (3 × 5 mL). The combined organic
phases were washed with water (3 × 5 mL) followed by brine (5 mL), then dried
over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography (hexanes:ether, 7:1) to afford the title compound 373 (163 mg, 75%) as a yellow oil.  

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$

1.22 (t, $J = 7.2$ Hz, 3H, ester CH$_3$), 1.51 (dd, $J = 11.9$, 3.8 Hz, 1H), 2.12 (ddd, $J = 12.0$, 8.5, 3.8 Hz, 1H), 2.91-2.97 (m, 1H), 3.19-3.27 (m, 2H), 3.61 (apparent tt, $J = 7.3$, 1.3 Hz, 1H), 4.07 (qd, $J = 7.2$, 2.2 Hz, 2H, ester CH$_2$), 4.38-4.51 (m, 2H), 5.02 (dq, $J = 17.2$, 1.8 Hz, 2H, -OCH$_2$Ar), 5.08-5.14 (m, 2H, vinylic), 5.92-6.04 (m, 3H, vinylic), 6.20 (qd, $J = 3.4$, 0.7 Hz, 1H, vinylic), 7.17 (d, $J = 8.4$ Hz, 2H, ArH), 7.45 (d, $J = 8.4$ Hz, 2H, ArH);  

$^{13}$C NMR (CDCl$_3$, 101 MHz) $\delta$

14.4, 27.9, 42.4, 46.7, 47.2, 50.4, 60.4, 66.4, 99.7, 116.2, 121.3, 128.7, 131.6, 131.7, 132.0, 136.8, 137.9, 138.5, 138.6, 174.9;  

IR (ef) 3074, 2982, 2861, 1732, 1488, 1292, 1189, 1127, 1071, 1041, 1011 cm$^{-1}$;  

MS (Cl) m/z (rel. intensity) 419 (M + H for $^{81}$Br, 22), 417 (M + H for $^{79}$Br, 23), 401 (4), 399 (4), 391 (3), 389 (3), 373 (3), 371 (3), 345 (3), 343 (3), 231 (100), 171 (9), 169 (10);  

Anal. Calcd. for C$_{22}$H$_{25}$BrO$_3$: C, 63.31; H, 6.04; Found: C, 63.60; H, 5.95.

9.5.12  
endo-7-Hydroxy-4-(hydroxymethyl)-7-(1-vinylallyl)-bicyclo[2.2.1]-hept-1-ene (374)

A solution of triene ester 335 (83 mg, 0.34 mmol, 1.0 equiv.) in ether (3 mL) was cooled to 0 °C and treated with lithium aluminum hydride (25 mg, 0.68
mmol, 2.0 equiv.). After stirring for 2 h at 0 °C, the reaction mixture was allowed to warm to room temperature over 30 min. After cooling to 0 °C, the reaction was quenched with water (1 mL), followed by aqueous sodium hydroxide solution (10% w/v, 1 mL) and water (3 mL). The salts were removed by filtration and the filtrate was extracted with dichloromethane (3 × 10 mL). After removal of solvent \textit{in vacuo}, the crude product was purified by flash chromatography (hexanes:ether, 1:2 followed by ether) and was then recrystallized from hexanes/ether to afford the \textit{title compound 374} (62 mg, 90%) as a colourless crystalline solid. \textbf{M.p.} 93-95 °C, hexanes/ether; \textbf{\textsuperscript{1}H NMR} (CDCl\textsubscript{3}, 400 MHz) \(\delta\) 0.61 (dd, \(J = 11.6, 4.0\) Hz, 1H), 1.30 (br s, 1H, -OH), 1.81 (s, 1H, -OH), 2.11-2.18 (m, 1H), 2.50-2.54 (m, 1H), 2.64-2.73 (m, 2H), 3.34 (t, \(J = 9.3\) Hz, 1H), 3.39-3.45 (m, 1H), 3.52 (t, \(J = 7.2\) Hz, 1H), 5.04 (d, \(J = 15.9\) Hz, 2H), 5.15 (d, \(J = 10.4\) Hz, 2H), 5.84-5.93 (m, 2H), 5.95-5.99 (dd, \(J = 6.1, 3.2\) Hz, 1H), 6.07-6.13 (dd, \(J = 6.1, 3.2\) Hz, 1H); \textbf{\textsuperscript{13}C NMR} (CDCl\textsubscript{3}, 101 MHz) \(\delta\) 27.6, 39.9, 47.9, 48.1, 49.8, 65.5, 94.6, 117.3, 117.4, 132.2, 135.9, 137.4, 137.5; \textbf{IR} (ef) 3620-3120 (broad), 3101, 3066, 2972, 2938, 2864, 1630, 1407, 1279, 1121, 1036, 912 cm\textsuperscript{-1}; \textbf{MS} (Cl) \textit{m/z} (rel. intensity) 207 (M + H, 19), 189 (100), 171 (23), 161 (14), 139 (15); \textbf{Anal. Calcd. for C\textsubscript{13}H\textsubscript{18}O\textsubscript{2}: C, 75.69; H, 8.80; Found: C, 75.38; H, 9.03.
A solution of endo-7-hydroxy-4-(hydroxymethyl)-7-(1-vinylallyl)bicyclo[2.2.1]hept-1-ene 374 (37 mg, 0.18 mmol, 1.0 equiv.) in dichloromethane (2 mL) was treated with bis(tricyclohexylphosphine)benzylidene ruthenium (IV) dichloride ("first generation" Grubbs' catalyst, 147 mg, 0.18 mmol, 1.0 equiv.) in four equal portions over 72 h. The solvent was removed \textit{in vacuo} and the black reaction mixture was purified by flash chromatography (hexanes:ether, 1:1) to afford 8-hydroxymethyl-5-vinyltetracyclo[4.3.0.0\textsuperscript{2.7}]nonan-6-ol 375, along with an inseparable co-polar impurity (27 mg total). The material was used in the following step without further purification.

A solution of crude 8-hydroxymethyl-5-vinyltetracyclo[4.3.0.0\textsuperscript{2.7}]nonan-6-ol 375 (27 mg, 0.14 mmol, 1.0 equiv.) in dichloromethane (2 mL) at room temperature was treated with freshly distilled pyridine (57 \(\mu\)L, 0.70 mmol, 5.0 equiv.) followed by 3,5-dinitrobenzoyl chloride (130 mg, 0.56 mmol, 4.0 equiv.). After stirring for 1 h, the reaction was quenched with aqueous hydrochloric acid (1 \(M\), 5 mL). The phases were separated, the aqueous phase was extracted with dichloromethane (3 \times 10 mL) and the combined organic extracts were washed...
successively with saturated aqueous sodium bicarbonate (10 mL), water (10 mL) and brine (10 mL). After removal of solvents in vacuo, the residue was taken up in dichloromethane and filtered to remove 3,5-dinitrobenzoic acid. The filtrate was concentrated in vacuo and then the crude product was purified by flash chromatography (hexanes:ether 1:1) to afford the title compound 376 (40 mg, 58%) as a yellow amorphous solid consisting of a ~1:1 mixture of diastereomers. 

M.p. 112-114 °C, hexanes/ether; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.01 (td, $J = 7.0, 2.7$ Hz, 1H), 1.17-1.25 (m, 2H), 1.30-1.39 (m, 1H), 1.53-1.70 (m, 1H), 1.92-2.16 (m, 3H), 2.57 (t, $J = 7.6$ Hz, 1H), 2.71-2.86 (m, 1H), 4.56-4.65 (m, 2H), 5.13-5.27 (m, 2H, -CH=CH$_2$), 5.70-5.81 (m, 1H, -CH=CH$_2$), 9.14 (s, 2H, ArH), 9.21 (s, 1H, ArH); $^{13}$C NMR (CDCl$_3$, 101 MHz) $\delta$ 13.1, 14.9, 15.3, 17.5, 17.9, 21.1, 28.1, 28.2, 37.2, 37.3, 41.9, 44.0, 45.6, 47.7, 50.5, 69.8, 70.2, 86.3, 86.4, 117.7, 122.3, 129.4, 134.1, 136.9, 137.1, 148.7, 162.5; IR (ef) 3650-3160 (broad), 3096, 2955, 2884, 1725, 1628, 1545, 1461, 1345, 1274, 1171, 1075 cm$^{-1}$; MS (Cl) m/z (rel. intensity) 387 (M + H, 22), 177 (53), 175 (100), 157 (25), 147 (27), 97 (14); Anal. Calcd. for C$_{19}$H$_{18}$N$_2$O$_7$: C, 59.07; H, 4.70; N, 7.25; Found: C, 59.31; H, 4.72; N, 7.03.
A solution of 6-hydroxy-5-vinyltetracyclo[4.3.0.0^2.4.0^3.7]nonane-8-carboxylic acid ethyl ester 371 (103 mg, 0.440 mmol, 1.0 equiv.) in a mixture of THF (5 mL) and water (5 mL) was treated with lithium hydroxide monohydrate (55 mg, 1.3 mmol, 3.0 equiv.) and was stirred for 15 h at room temperature. The reaction mixture was acidified to pH 1 using 10% aqueous hydrochloric acid and was extracted with dichloromethane (5 × 10 mL). The combined extracts were dried over anhydrous sodium sulfate and dried in vacuo to afford the impure product as an amorphous yellow solid. This material was purified by flash chromatography (hexanes:ether, 1:2 followed by ether and finally ethyl acetate) to afford the title compound 377 (63 mg, 70%) as an amorphous white solid consisting of a ~1:1 mixture of diastereomers. **M.p. 108-110 °C, hexanes/ether;** ^1^H NMR (CDCl_3, 400 MHz) δ 1.15-1.35 (m, 4H), 1.93-2.12 (m, 3H), 2.21-2.31 (m, 1H), 2.54 (t, J = 9.5 Hz, 1H), 3.12-3.23 (m, 1H, CH-CO_2H), 5.13-5.28 (m, 2H, -CH=CH_2), 5.68-5.79 (m, 1H, -CH=CH_2); ^1^3_C NMR (CDCl_3, 400 MHz) δ 13.9, 15.0, 17.1, 27.1, 42.1, 45.7, 48.9, 50.2, 86.6, 117.8, 137.0, 181.6; IR (KBr) 3670-2510 (broad), 3075, 2956, 2856, 1704, 1639, 1414, 1283 cm^{-1}; **MS** (Cl) m/z (rel. intensity) 207 (M + H, 50), 189 (100), 179 (9), 161 (4), 133 (3).
9.6 Experimental Concerning Chapter Six

9.6.1 Ethyl 3-bromopropionate (396)\textsuperscript{274}

\[
\begin{align*}
\text{Br-} & \quad \text{H}_2\text{SO}_4 \text{(cat.}, \text{EtOH, reflux} & \quad \text{Br-} \\
\text{395} & \quad \text{CO}_2\text{H} & \quad \text{CO}_2\text{Et} \\
\text{396} & \quad \text{63\%}
\end{align*}
\]

A solution of 3-bromopropionic acid 395 (10.3 g, 67.3 mmol, 1.0 equiv.) and concentrated sulfuric acid (3 drops, catalytic amount) in anhydrous ethanol (100 mL) was heated at reflux for 24 h. The resultant yellow-brown solution was allowed to cool to room temperature and a saturated aqueous solution of sodium bicarbonate (25 mL) was added. After stirring for 10 min, the phases were separated and the aqueous phase was extracted with ether (3 x 75 mL). The combined organic extracts were washed with water (3 x 25 mL) and brine (25 mL) and were then dried over anhydrous magnesium sulfate. Most of the ether and ethanol was carefully removed in vacuo on a rotary evaporator. The crude product was purified by distillation through a Vigreux column under reduced pressure to afford the title compound 396 (7.07 g, 63%) as a pale yellow liquid.

B.p. 64-65 °C/10 mmHg (lit.\textsuperscript{274} 67-67.5 °C/12 mmHg); \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) \(\delta\) 1.27 (t, \(J = 7.3\) Hz, 3H, ester CH\textsubscript{3}), 2.91 (t, \(J = 6.8\) Hz, 2H, -CH\textsubscript{2}CO\textsubscript{2}Et), 3.58 (t, \(J = 6.8\) Hz, 2H, ICH\textsubscript{2}CH\textsubscript{2}⁻), 4.17 (q, \(J = 7.3\) Hz, 2H, ester CH\textsubscript{2}); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 101 MHz) \(\delta\) 14.3, 26.0, 37.9, 61.0, 170.5; IR (neat) 2979, 2876, 1736, 1642, 1377 cm\textsuperscript{-1}; MS (Cl) m/z (rel. intensity) 182 (M + H for \textsuperscript{81}Br, 98), 180 (M + H for \textsuperscript{79}Br, 100), 154 (19), 152 (18), 108 (1).
9.6.2 3-Nitropropanaldehyde (397)$^{219}$

\[
\text{CHO} \quad \text{NaNO}_2, \text{HOAc}, \text{THF}, 0^\circ\text{C to rt, 3 h} \quad \text{O}_2\text{N}_-\text{CHO} \\
340 \quad 36\% \quad 397
\]

A solution of freshly distilled acrolein 340 (17.9 mL, 268 mmol, 1.0 equiv.) in THF (100 mL) was cooled to 0 °C and sodium nitrite (23.1 g, 335 mmol, 1.25 equiv.) was added. The resultant suspension was stirred for 10 min and then glacial acetic acid (19.2 mL, 335 mmol, 1.25 equiv.) was added dropwise over 1 h. The resultant yellow solution was stirred for 2.5 h at 0 °C, then water (50 mL) was added and the reaction mixture was allowed to warm to room temperature. The phases were separated and the aqueous phase was extracted with dichloromethane (4 × 25 mL). The combined organic extracts were washed with saturated aqueous sodium bicarbonate solution (2 × 25 mL), brine (2 × 25 mL) and water (25 mL). The extracts were dried overnight over anhydrous magnesium sulfate and were then concentrated in vacuo to afford the title compound 397 (9.76 g, 36%) as a pale yellow liquid. $^1$H NMR (CDCl$_3$, 400 MHz) δ 3.18 (t, $J = 6.0$ Hz, 2H, -CH$_2$CHO), 4.69 (t, $J = 6.0$ Hz, 2H, CH$_2$NO$_2$), 9.81 (s, 1H, CHO); $^{13}$C NMR (CDCl$_3$, 101 MHz) δ 39.7 (C$_2$), 67.7 (C$_3$), 196.5 (C$_1$); IR (neat) 2923, 2747, 1717, 1556, 1425, 1376 cm$^{-1}$; MS (Cl) m/z (rel. intensity) 104 (M + H, 100), 75 (6).
9.6.3 3-Nitropropionic acid (398)

9.6.3.1 Procedure A - Jones oxidation

\[
\begin{align*}
\text{O}_2\text{N} & \quad \text{CHO} \\
397 & \quad \text{Jones' reagent, Me}_2\text{CO, 0 °C, 3 h} \\
86\% & \quad \text{O}_2\text{N} & \quad \text{CO}_2\text{H} \\
398 & &
\end{align*}
\]

Jones' reagent was prepared by dissolving chromium trioxide (10 g) in water (14 mL), adding concentrated sulfuric acid (8.6 mL) dropwise and then diluting the resultant orange solution with water to a total volume of 40 mL.

A solution of 3-nitropropionaldehyde 397 (330 mg, 3.20 mmol, 1.0 equiv.) in reagent grade acetone (10 mL) was cooled to 0 °C. Jones' reagent (2.25 mL) was added dropwise and the resultant orange solution was stirred for 3 h at 0 °C. Isopropanol (10 mL) was added and the resultant green suspension was allowed to warm to room temperature and was then stirred overnight. The reaction mixture was then filtered through diatomaceous earth and the filter cake was washed with ethyl acetate (50 mL). The filtrate was neutralized with solid sodium bicarbonate, which caused a precipitate to be deposited. The mixture was again filtered through diatomaceous earth and the filter cake was washed with ethyl acetate (50 mL). The filtrate was treated with decolourizing charcoal (Norit A), filtered and concentrated in vacuo. The crude product was recrystallized from chloroform to afford the title compound 398 (327 mg, 86%) as a tan coloured crystalline solid. M.p. 62.5-64 °C, chloroform (lit. 65 °C, chloroform); \(^1\)H NMR (CD\(_3\)OD, 400 MHz) \(\delta\) 2.92 (t, \(J = 5.9\) Hz, 2H, \(-\text{CH}_2\text{CO}_2\text{H}\)), 4.64 (t, \(J = 5.9\) Hz, 2H, \text{CH}_2\text{NO}_2\)); \(^{13}\)C NMR (CD\(_3\)OD, 101 MHz) \(\delta\) 31.8 (C\(_2\)), 71.1 (C\(_3\)), 173.5 (C\(_1\)); IR
(KBr) 3600-2400 (broad), 1725, 1648, 1557, 1358, 1049 cm⁻¹; MS (EI) m/z (rel. intensity) 119 (M, 5), 87 (6), 83 (11), 73 (61), 55 (18), 45 (100).

9.6.3.2 Procedure B - Sodium chlorite/hydrogen peroxide oxidation

\[
\text{O}_2\text{N} \xrightleftharpoons{\text{NaClO}_2, \text{H}_2\text{O}_2, \text{NaH}_2\text{PO}_4, \text{MeCN}:\text{H}_2\text{O} (3:4), \text{rt, 4 h}} \xrightarrow{83\%} \text{O}_2\text{N} \xrightarrow{\text{CHO}} \text{CO}_2\text{H}
\]

To a 2-necked flask fitted with a pressure-equalizing dropping funnel and a bubbler was added 3-nitropropanaldehyde 397 (5.68 g, 55.1 mmol, 1.0 equiv.), acetonitrile (45 mL) and water (60 mL). The flask was immersed in a room temperature water bath and then sodium dihydrogen phosphate (1.37 g, 6.85 mmol, 0.12 equiv.) was added, followed by hydrogen peroxide (4.30 mL of a 30% w/v aqueous solution, 44.7 mmol, 0.8 equiv.). A solution of sodium chlorite (80% technical grade, 6.88 g, 60.9 mmol, 1.1 equiv.) in water (15 mL) was added dropwise over the course of 2 h. The resultant yellow solution was then stirred at room temperature until the evolution of oxygen through the bubbler ceased (2 h). Sodium sulfite (0.5 g) was added and the reaction mixture was stirred for 15 min. The colourless solution was acidified to pH 1 with aqueous hydrochloric acid (10% w/v) and then water (30 mL) was added. The reaction mixture was extracted with ethyl acetate (3 x 50 mL). The aqueous phase was saturated with sodium chloride and was again extracted with ethyl acetate (50 mL). The combined organic extracts were concentrated in vacuo and the resultant crude product was recrystallized from chloroform to afford the title compound 398 (5.52
g, 83%) as a tan crystalline solid. This material had spectral and physical properties identical to those of the material obtained by *Procedure A*.

**9.6.4 Ethyl 3-nitropropionate (394)**

**9.6.4.1 *Procedure A* - Resin-supported nucleophilic displacement**

![Chemical reaction diagram](image)

Amberlite® IRA-900 ion exchange resin (Cl⁻ form, 4.2 mequiv/g, 100 g) was suspended in a solution of sodium nitrite (600 g) in water (1200 mL) and was stirred for 48 h. The resin beads were collected and washed with an aqueous solution of sodium nitrite (1 M) in 100 mL portions until the filtrate gave a negative silver nitrate test for chlorides (400 mL total). The resin was washed with water (500 mL), 95% aqueous ethanol (250 mL) and benzene (200 mL) and then air-dried for 30 min. The resin was dried overnight under vacuum at 45 °C and 30 mmHg and stored in a dessicator until needed.

The resin in its nitrite form (4.2 mequiv/g, 2.38 g, 10.0 mmol, 2.0 equiv.) was suspended in benzene (10 mL). Ethyl 3-bromopropionate 396 (640 μL, 5.00 mmol, 1.0 equiv.) was added and the suspension was heated at 50 °C for 72 h. After cooling to room temperature, the resin beads were removed by filtration and were washed with benzene (10 mL). The filtrate was concentrated *in vacuo* and the crude product was purified by flash chromatography (hexanes:ether, 1:1) to afford the *title compound* 394 (81 mg, 11%) as a yellow oil. 

$^{1}H$ NMR (CDCl₃, 400 MHz) $\delta$ 1.28 (t, $J = 7.1$ Hz, 3H, -CO₂CH₂CH₃), 2.98 (t, $J = 6.0$ Hz, 2H,
CH₂CH₂NO₂), 4.20 (q, J = 7.1 Hz, 2H, -CO₂CH₂CH₃), 4.65 (t, J = 6.0 Hz, 2H, CH₂CH₂NO₂); ¹³C NMR (CDCl₃, 101 MHz) δ 14.0 (ester CH₃), 31.2 (CH₂CO₂Et), 61.7 (ester CH₂), 69.9 (CH₂NO₂), 169.5 (ester C=O); IR (neat) 2985, 2942, 1731, 1556, 1381, 1256, 1194, 1023 cm⁻¹; MS (CI) m/z (rel. intensity) 148 (M + H, 100), 132 (15), 119 (1), 102 (2), 85 (2).

9.6.4.2 Procedure B - Fischer esterification of 3-nitropropionic acid 398

A solution of 3-nitropropionic acid 398 (4.89 g, 41.1 mmol, 1.0 equiv.) and concentrated sulfuric acid (3 drops, catalytic amount) in anhydrous ethanol (75 mL) was heated at reflux for 16 h. The reaction mixture was then allowed to cool to room temperature and a saturated aqueous solution of sodium bicarbonate (5 mL) was added. After stirring for 10 min, the reaction mixture was concentrated in vacuo. The residue was taken up in dichloromethane (50 mL) and filtered through a plug of diatomaceous earth. The plug was washed with dichloromethane (50 mL) and the filtrate was concentrated in vacuo to afford the title compound 394 (5.53 g, 92%) as an amber oil. This material had spectral and physical properties identical to those of the material which was obtained by Procedure A.
A solution of ethyl 3-nitropropionate 394 (3.48 g, 23.7 mmol, 1.0 equiv.) in THF (50 mL) was cooled to -20 °C. Potassium t-butoxide (2.92 g, 26.0 mmol, 1.1 equiv.) was added portionwise over 45 min and the resultant solution was stirred for a further 15 min at -20 °C. Freshly distilled cyclopent-2-en-1-one 343 (2.0 mL, 24 mmol, 1.0 equiv.) was added dropwise over 30 min. The reaction mixture was then allowed to warm to room temperature and was stirred for 3 h. Anhydrous methanol (10 mL) was added and the reaction mixture was stirred for 3 days. Aqueous hydrochloric acid (2 M, 50 mL) was added and the reaction mixture was then stirred for 30 min. The phases were separated and the aqueous phase was extracted with ether (3 × 50 mL). The combined organic extracts were washed with water (3 × 50 mL) and brine (50 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography (hexanes:ether, 1:1 followed by hexanes:ether, 2:3) to afford the title compound 393 (3.20 g, 74%) as an amber oil. Rf 0.30 (hexanes:ether, 1:1); $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.32 (t, $J$ = 7.0 Hz, 3H, ester CH$_3$), 1.76-1.87 (m, 1H), 2.10-2.42 (m, 4H), 2.45-2.63 (m, 1H), 3.21-3.30 (m, 1H), 4.24 (q, $J$ = 7.0 Hz, 2H, ester CH$_2$), 5.58 (s, 1H), 6.25 (s, 1H); $^{13}$C NMR (CDCl$_3$, 101 MHz) $\delta$ 14.3, 28.5, 38.2, 44.1, 52.1, 61.0, 123.8, 142.0,
167.1, 218.0; IR (neat) 2930, 1752, 1715, 1680, 1553, 1459 cm⁻¹; MS (Cl) m/z (rel. intensity) 169 (M + H, 100), 140 (21), 85 (12).

9.6.6 **Ethyl 3-(3-oxocyclopentyl)propanoate (392)**

![Reaction Scheme]

To a suspension of palladium on carbon (10% w/w, 500 mg) in ethanol (50 mL) was added a solution of ethyl 3-(3-oxocyclopentyl)acrylate 393 (3.00 g, 16.3 mmol, 1.0 equiv.) in ethanol (25 mL). The reaction flask was charged with hydrogen gas (~1 atm) and was then purged (water aspirator). The charging and purging process was repeated 4 times in total. The flask was then fitted with a balloon so as to maintain a slight positive pressure of hydrogen over the reaction and the reaction mixture was stirred for 4 h at room temperature. The reaction mixture was then filtered through a pad of diatomaceous earth and the filter cake was washed with ethanol (100 mL). The filtrate was concentrated *in vacuo* to afford the title compound 392 (2.99 g, 98%) as a pale yellow oil. \( \text{Rf} \) 0.20 (hexanes:ether, 1:1); \(^1\text{H} \text{NMR} \) (CDCl₃, 400 MHz) \( \delta \) 1.26 (t, \( J = 7.0 \) Hz, 3H, ester CH₃), 1.75-1.90 (m, 3H), 2.12-2.25 (m, 3H), 2.28-2.58 (m, 5H), 4.14 (q, \( J = 7.0 \) Hz, 2H, ester CH₂); \(^{13}\text{C} \text{NMR} \) (CDCl₃, 101 MHz) \( \delta \) 14.3, 29.4, 30.7, 32.8, 36.9, 38.6, 45.0, 60.6, 181.0, 218.9; IR (neat) 2929, 1741, 1712, 1644, 1553, 1460, 1435, 1376 cm⁻¹; MS (Cl) m/z (rel. intensity) 171 (M + H, 46), 132 (100), 85 (68).
A suspension of sodium hydride (659 mg of a 60% dispersion in mineral oil, 16.2 mmol, 1.2 equiv.) in ether (60 mL) was stirred for 10 min at room temperature. Freshly distilled methanol (650 µL, 16.2 mmol, 1.2 equiv.) was then added and the resultant suspension was stirred for 1 h. A solution of ethyl 3-(3-oxocyclopentyl)propanoate 392 (2.30 g, 13.5 mmol, 1.0 equiv.) in ether (10 mL) was then added dropwise by means of a cannula. The resultant solution was stirred for 6 h, over which time a yellow precipitate was deposited. The reaction mixture was then poured into an aqueous solution of potassium dihydrogen phosphate (10% w/v, 25 mL) and the resultant suspension was then stirred until the precipitate dissolved (20 min). The phases were separated and the aqueous phase was extracted with dichloromethane (3 × 25 mL). The organic extracts were washed with a saturated aqueous solution of ammonium sulfate (25 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. Flash chromatography (hexanes:ether, 3:5 followed by ethyl acetate) followed by recrystallization from hexanes/ether afforded the title compound 391 (1.18 g, 63%) as a yellow crystalline solid. Rf 0.20 (ethyl acetate); M.p. 59-60 °C, hexanes/ether (lit.277 61-61.5 °C, hexanes/benzene); $^1$H NMR (CDCl$_3$, 400 MHz) δ 1.75-1.86 (m, 2H), 2.15-2.38 (m, 6H), 3.03 (d, J = 8.3 Hz, 1H, H$_1$), 3.15-3.22 (m, 1H, H$_5$); $^{13}$C NMR (CDCl$_3$, 101 MHz) δ 26.2, 37.9, 39.4, 63.3, 209.1; IR
(ef) 2920, 1756, 1643, 1212, 1139 cm⁻¹; MS (Cl) m/z (rel. intensity) 139 (M + H, 100), 83 (4), 57 (2).

9.6.8 2-Benzyl-2-methyl-1,3-cyclohexanedione (403)²⁷⁸

9.6.8.1 Procedure A

To a suspension of sodium hydride (60% dispersion in mineral oil, 101 mg, 2.40 mmol, 1.2 equiv.) in THF (3 mL) was added portionwise over 30 min 2-methyl-1,3-cyclohexanedione 399 (252 mg, 2.00 mmol, 1.0 equiv.). After stirring the slightly cloudy solution for a further 30 min, a solution of benzyl bromide (713 µL, 6.00 mmol, 3.0 equiv.) in DMF (2 mL) was added by means of a cannula. After stirring for a further 3 h, the reaction mixture was diluted with an aqueous solution of potassium dihydrogen phosphate (10% w/v, 5 mL) and ether (5 mL). The aqueous phase was extracted with ether (3 × 10 mL) and the combined organic extracts were washed with water (3 × 5 mL) and brine (5 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. Purification of the crude product by flash chromatography (hexanes:ether, 2:1) afforded the title compound 403 (257 mg, 60%) as a colourless solid. Rf 0.55 (ether); M.p. 42-43 °C (hexanes/ether) (lit.²⁷⁸ 43 °C); ¹H NMR (CDCl₃, 400 MHz) δ 1.30 (s, 3H, 2-CH₃), 1.44-1.55 (m, 1H), 1.67-1.80 (m, 1H), 2.25-2.34 (m, 2H), 2.49-2.57 (m, 2H), 3.12 (s, 2H, CH₂Ph), 7.02 (dd, J = 7.9, 2.0 Hz, 2H, ArH), 7.18-7.25 (m, 3H, ArH);
\(^{13}\text{C} \text{NMR}\) (CDCl\(_3\), 101 MHz) \(\delta\) 16.7, 22.4, 39.5, 44.0, 65.4, 127.1, 128.5, 130.0, 136.8, 211.6; \(\text{IR}\) (ef) 3030, 2933, 2879, 1721, 1694, 1603, 1495, 1453, 1369, 1089, 1026 cm\(^{-1}\); \(\text{MS}\) (El) \(m/z\) (rel. intensity) 216 (M, 31), 173 (32), 145 (48), 117 (24), 91 (100), 77 (10), 65 (24), 55 (18), 42 (31).

9.6.8.2  \(\text{Procedure B}\)

A solution of 2-methyl-1,3-cyclohexanedione 399 (252 mg, 2.00 mmol, 1.0 equiv.) in DMF (5 mL) was treated with anhydrous cesium carbonate (976 mg, 3.00 mmol, 1.5 equiv.). After stirring the resultant suspension for 10 min, benzyl bromide (710 \(\mu\)L, 6.00 mmol, 3.0 equiv.) was added and the reaction mixture was then stirred for 16 h. The reaction mixture was diluted with brine (5 mL) and ether (5 mL). The phases were separated and the aqueous phase was extracted with ether (3 \(\times\) 5 mL). The combined organic phases were washed with water (5 \(\times\) 5 mL) and brine (5 mL), dried over anhydrous sodium sulfate and concentrated \textit{in vacuo}. Purification of the crude product by flash chromatography (hexanes:ether, 3:2) afforded the \textit{title compound} 403 (281 mg, 65%) as a colourless solid. The spectral and physical properties of this material were identical to those of the material which was obtained by \textit{Procedure A}.
A solution of 2-methyl-1,3-cyclohexanedione 399 (252 mg, 2.00 mmol, 1.0 equiv.) in DMF (5 mL) was treated with anhydrous cesium carbonate (976 mg, 3.00 mmol, 1.5 equiv.). After stirring the resultant suspension for 10 min, 4-bromobenzylbromide (750 mg, 6.00 mmol, 3.0 equiv.) was added and the reaction mixture was stirred for 16 h. The reaction mixture was diluted with brine (5 mL) and ether (5 mL). The phases were separated and the aqueous phase was extracted with ether (3 × 5 mL). The combined organic phases were washed with water (5 × 5 mL) and brine (5 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. Purification of the crude product by flash chromatography (hexanes:ether, 3:2) afforded the title compound 400 (433 mg, 73%) as a colourless viscous oil. \( R_f \) 0.30 (hexanes:ether, 1:1); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 1.29 (s, 3H, 2-CH\(_3\)), 1.45-1.56 (m, 1H), 1.73-1.84 (m, 1H), 2.25-2.34 (m, 2H), 2.51-2.60 (m, 2H), 3.06 (s, 2H, CH\(_2\)Ar), 6.90 (d, \( J = 8.3 \) Hz, 2H, ArH), 7.32 (d, \( J = 8.3 \) Hz, 2H, ArH); \(^{13}\)C NMR (CDCl\(_3\), 101 MHz) \( \delta \) 16.6, 23.1, 39.2, 42.1, 65.2, 121.0, 128.7, 131.5, 131.7, 131.9, 136.0, 211.2; IR (ef) 2961, 2933, 2961, 2933, 2961, 2933, 1725, 1698, 1592, 1488, 1454, 1406, 1370, 1320, 1073, 1025 cm\(^{-1}\); MS (Cl) m/z (rel. intensity) 297 (M + H for \(^{81}\)Br, 100), 295 (M + H for \(^{79}\)Br, 98), 260

9.6.9 2-(4'-Bromobenzyl)-2-methyl-1,3-cyclohexanedione (400)
9.6.10 2-Allyl-2-methyl-1,3-cyclohexanedione (401)

9.6.10.1 Procedure A

To a suspension of sodium hydride (60% dispersion in mineral oil, 101 mg, 2.40 mmol, 1.2 equiv.) in THF (5 mL) was added portionwise over 30 min solid 2-methyl-1,3-cyclohexanedione 399 (252 mg, 2.00 mmol, 1.0 equiv.). After stirring the slightly cloudy solution for a further 30 min, a solution of allyl bromide which had previously been passed through a pad of neutral alumina (519 μL, 6.00 mmol, 3.0 equiv.) in DMF (2 mL) was added by means of a cannula. After stirring for a further 16 h, the reaction mixture was diluted with an aqueous solution of potassium dihydrogen phosphate (10% w/v, 5 mL) and ether (5 mL). The phases were separated and the aqueous phase was extracted with ether (3 × 10 mL) and the combined organic extracts were washed with water (3 × 5 mL) and brine (5 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. Purification of the crude product by flash chromatography (hexanes:ether, 2:1) afforded the title compound 401 (184 mg, 55%) as a colourless viscous oil. \( R_f \) 0.30 (hexanes:ether, 2:1); \(^1^H\) NMR (CDCl\(_3\), 400 MHz) \( \delta \) 1.17 (s, 3H, CH\(_3\)), 1.75-1.88 (m, 1H), 1.91-2.00 (m, 1H), 2.46 (dd, \( J = 7.2, 0.8 \) Hz).
Hz, 2H), 2.52-2.65 (m, 4H), 4.95-5.03 (m, 2H, -CH=CH₂), 5.44-5.56 (m, 1H, -CH=CH₂); \(^{13}\text{C} \text{NMR}\) (CDCl₃, 101 MHz) δ 17.5, 19.5, 38.1, 41.3, 65.2, 119.1, 132.2, 209.8; \(\text{IR}\) (ef) 3079, 2966, 2943, 2874, 1725, 1694, 1640, 1455, 1428, 1320, 1255, 1130, 1026 cm\(^{-1}\); \(\text{MS}\) (CI) \text{m/z} (rel. intensity) 167 (M + H, 100), 139 (2), 127 (1).

9.6.10.2 Procedure B

![Chemical reaction diagram]

A solution of 2-methyl-1,3-cyclohexanedione 399 (252 mg, 2.00 mmol, 1.0 equiv.) in DMF (5 mL) was treated with anhydrous cesium carbonate (976 mg, 3.00 mmol, 1.5 equiv.). After stirring the resultant suspension for 10 min, allyl bromide which had previously been passed through a pad of alumina (519 µL, 6.00 mmol, 3.0 equiv.) was added and the reaction mixture was stirred for 16 h. The reaction mixture was diluted with brine (5 mL) and ether (5 mL). The phases were separated and the aqueous phase was extracted with ether (3 × 5 mL). The combined organic phases were washed with water (5 × 5 mL) and brine (5 mL), dried over anhydrous sodium sulfate and concentrated \textit{in vacuo}. Purification of the crude product by flash chromatography (hexanes:ether, 2:1) afforded the \textit{title compound} 401 (227 mg, 68%) as a colourless viscous oil. This material had spectral and physical properties identical to those of the material which was obtained by Procedure A.
A solution of 2-methyl-1,3-cyclohexanedione 399 (252 mg, 2.00 mmol, 1.0 equiv.) in DMF (5 mL) was treated with anhydrous cesium carbonate (976 mg, 3.00 mmol, 1.5 equiv.). After stirring the resultant suspension for 10 min, methyl iodide (374 μL, 6.00 mmol, 3.0 equiv.) was added and the reaction mixture was stirred for 16 h. The reaction mixture was diluted with brine (5 mL) and ether (5 mL). The phases were separated and the aqueous phase was extracted with ether (3 × 5 mL). The combined organic phases were washed with water (5 × 5 mL) and brine (5 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. Purification of the crude product by flash chromatography (hexanes:ether, 1:1) afforded the title compound 402 (173 mg, 62%) as a colourless viscous oil which upon standing in a freezer afforded a waxy colourless solid. \( R_f \) 0.25 (hexanes:ether, 1:1); \textbf{M.p.} 38-39 °C (hexanes/ether) (lit.\textsuperscript{279} 39-40 °C, toluene); \textbf{\textsuperscript{1}H NMR} (CDCl\textsubscript{3}, 400 MHz) \( \delta \) 1.29 (s, 6H, 2 × CH\textsubscript{3}), 1.89-1.97 (m, 2H), 2.67 (t, \( J = 8.6 \text{ Hz} \), 4H); \textbf{\textsuperscript{13}C NMR} (CDCl\textsubscript{3}, 101 MHz) \( \delta \) 18.0, 22.3, 37.4, 61.8, 210.5; \textbf{IR} (ef) 2966, 2940, 2874, 1728, 1697, 1427, 1316, 1135 cm\textsuperscript{-1}; \textbf{MS} (Cl) \textit{m/z} (rel. intensity) 141 (M + H, 100), 123 (1), 99 (1), 81 (1).
A solution of cis-bicyclo[3.3.0]octan-2,8-dione 391 (200 mg, 1.45 mmol, 1.0 equiv.) in DMF (7 mL) was treated with anhydrous cesium carbonate (707 mg, 2.18 mmol, 1.5 equiv.). After stirring the resultant suspension for 20 min, methyl iodide (270 μL, 4.35 mmol, 3.0 equiv.) was added and the reaction mixture was stirred for 16 h. The reaction mixture was then diluted with brine (3 mL) and ether (3 mL) and the phases were separated. The aqueous phase was extracted with ether (3 × 5 mL) and the combined organic extracts were washed with water (5 × 5 mL) and brine (5 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography (hexanes:ether, 5:4) to afford the title compound 404 (95 mg, 43%) as an off-white amorphous solid. Rf 0.30 (hexanes:ether, 1:1); M.p. 48-50 °C, hexanes/ether (lit.206 52 °C, hexanes/ether); \(^1\)H NMR (CDCl₃, 400 MHz) \(\delta\) 1.22 (s, 3H, angular CH₃), 1.73-1.82 (m, 2H), 2.15-2.24 (m, 2H), 2.33-2.45 (m, 4H), 2.69-2.76 (m, 1H, H₅); \(^13\)C NMR (CDCl₃, 101 MHz) \(\delta\) 19.3, 24.5, 36.7, 46.7, 65.3, 212.7; IR (ef) 2963, 2927, 2888, 1753, 1468, 1400, 1220, 1159, 1094, 1038 cm\(^{-1}\); MS (Cl) \(m/z\) (rel. intensity) 153 (M + H, 100), 124 (1), 109 (2).
A solution of cis-bicyclo[3.3.0]octan-2,8-dione 391 (192 mg, 1.39 mmol, 1.0 equiv.) in DMF (10 mL) was treated with anhydrous cesium carbonate (674 mg, 2.08 mmol, 1.5 equiv.). After stirring the resultant suspension for 20 min, benzyl bromide (496 µL, 4.17 mmol, 3.0 equiv.) was added and the reaction mixture was stirred for 16 h. The resultant mixture was diluted with brine (5 mL) and ether (5 mL) and the phases were then separated. The aqueous phase was extracted with ether (3 × 10 mL) and the combined organic extracts were washed with water (5 × 10 mL) and brine (10 mL), then dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography (hexanes:ether, 5:4) to afford the title compound 406 (267 mg, 84%) as a colourless crystalline solid. Rf 0.25 (hexanes:ether, 1:1); M.p. 95-96 °C, hexanes/ether; $^1$H NMR (CDCl₃, 400 MHz) δ 1.60-1.69 (m, 2H), 1.85-1.94 (m, 2H), 2.08-2.18 (m, 2H), 2.29-2.40 (m, 2H), 2.83-2.90 (m, 1H, H₅), 3.03 (s, 2H, -CH₂Ph), 7.08-7.12 (m, 2H, ArH), 7.20-7.29 (m, 3H, ArH); $^{13}$C NMR (CDCl₃, 101 MHz) δ 24.7, 37.5, 39.7, 42.8, 70.8, 127.2, 128.8, 129.9, 136.5, 211.8; IR (ef) 2964, 1756, 1619, 1142 cm⁻¹; MS (El) m/z (rel. intensity) 228 (M, 100), 200 (16), 173 (24), 172 (33), 171 (35), 156 (23), 129 (31), 128 (30), 114 (22), 105 (12), 91 (77), 77 (11), 65 (51), 51 (5); Anal. Calcd. for C₁₅H₁₆O₂: C, 78.92; H, 7.06; Found: C, 78.96; H, 7.07.
A solution of cis-bicyclo[3.3.0]octan-2,8-dione 391 (200 mg, 1.45 mmol, 1.0 equiv.) in DMF (8 mL) was treated with anhydrous cesium carbonate (707 mg, 2.18 mmol, 1.5 equiv.). After stirring the resultant suspension for 20 min, allyl bromide (376 µL, 4.35 mmol, 3.0 equiv.) which had been previously passed through a pad of neutral alumina was added and the reaction mixture was stirred for 16 h. The reaction mixture was diluted with brine (10 mL) and ether (10 mL) and the phases were then separated. The aqueous phase was extracted with ether (3 x 10 mL) and the combined organic extracts were washed with water (5 x 10 mL) and brine (10 mL), then dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography (hexanes:ether, 1:1) to afford the title compound 405 (211 mg, 82%) as a viscous colourless oil which upon standing in a freezer afforded a colourless waxy solid. 

Rf 0.35 (hexanes:ether, 1:1); M.p. 23-24 °C, hexanes/ether; \(^1\)H NMR (CDCl₃, 400 MHz) δ 1.71-1.80 (m, 2H), 2.11-2.49 (m, 8H), 2.90-2.98 (m, 1H, H₅), 5.08-5.14 (m, 2H, -CH₂CH=CH₂), 5.50-5.61 (m, 1H, -CH₂CH=CH₂); \(^13\)C NMR (CDCl₃, 101 MHz) δ 24.9, 37.5, 38.5, 42.8, 69.3, 119.7, 132.5, 211.6; IR (ef) 3083, 2953, 1754, 1635, 1410, 1139, 1084 cm⁻¹; MS (Cl) m/z (rel. intensity) 179 (M + H, 100), 150 (3), 139 (1); Anal. Calcd. for C₁₁H₁₄O₂: C, 74.13; H, 7.92; Found: C, 73.81; H, 7.95.
Procedure A

A solution of (trimethylsilyl)acetylene (475 µL, 3.36 mmol, 4.0 equiv.) in THF (15 mL) was cooled to -78 °C. n-Butyllithium (1.0 mL of a 2.5 M solution in hexanes, 2.5 mmol, 3.0 equiv.) was added dropwise and the resultant pale yellow solution was stirred for 1 h at -78 °C. A solution of cis-1-benzylbicyclo[3.3.0]octan-2,8-dione 406 (192 mg, 0.841 mmol, 1.0 equiv.) in THF (10 mL) was then added dropwise by means of a cannula. The resultant dark yellow solution was allowed to warm to room temperature over 1 h and was stirred for a further 4 h. A saturated aqueous solution of ammonium chloride (10 mL) was added and the resultant mixture was stirred for 10 min. The phases were separated and the aqueous phase was extracted with ether (3 × 10 mL). The combined organic extracts were washed with water (3 × 10 mL) and brine (10 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography (hexanes:ether, 4:1) to
afford both C-8 epimers of 1-benzyl-8-[2'-(trimethylsilyl)ethynyl]-8-hydroxy-cis-bicyclo[3.3.0]octan-2-one 412 (332 mg, 93%) as a pale yellow oil.

A solution of 1-benzyl-8-[2'-(trimethylsilyl)ethynyl]-8-hydroxy-cis-bicyclo[3.3.0]octan-2-one 412 (83 mg, 0.20 mmol, 1.0 equiv.) in THF (3 mL) was cooled to 0 °C. Tetra-n-butyl ammonium fluoride (430 μL of 1 M solution in THF, 0.43 mmol, 2.2 equiv.) was added and the resultant solution was then stirred for 30 min at 0 °C. Water (2 mL) was added and the phases were separated. The aqueous phase was extracted with ether (3 × 5 mL) and the combined organic extracts were washed with water (3 × 5 mL) and brine (5 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography (hexanes:ether, 2:1) to afford an epimeric mixture (at C-8) of 1-benzyl-8-ethynyl-8-hydroxy-cis-bicyclo[3.3.0]octan-2-one (50 mg, 90%, 413:414 = 7:3) as a colourless solid. An analytical sample of the minor (8α-OH) epimer 414 was obtained by repeated recrystallization from hexanes/ether. \( R_f \) 0.30 (hexanes:ether, 2:1); \textbf{M.p.} 105-106 °C, hexanes/ether; 

\( ^1 \text{H NMR} \) (CDCl\(_3\), 400 MHz, assignments by COSY, HMQC and NOESY experiments) \( \delta \) 1.01-1.12 (m, 1H, \text{H}_4), 1.44-1.53 (m, 1H, \text{H}_4'), 1.59-1.70 (m, 1H, \text{H}_7), 1.82 (ddd, \( J = 18.7, 9.2, 4.3 \) Hz, 1H, \text{H}_3), 1.95-2.04 (m, 1H, \text{H}_6), 2.08-2.19 (m, 2H, \text{H}_7' \text{ and } \text{H}_6'), 2.21-2.32 (m, 1H, \text{H}_3'), 2.68 (s, 1H, \text{H}_{10}), 2.71-2.76 (m, 2H, \text{H}_5 \text{ and } \text{H}_{11}), 3.00 (br s, 1H, -OH), 3.52 (d, \( J = 13.1 \) Hz, 1H, \text{H}_{11'}), 7.09-7.14 (m, 2H, o-ArH), 7.18-7.28 (m, 3H, m,p-ArH); \( ^{13} \text{C NMR} \) (CDCl\(_3\), 101 MHz) \( \delta \) 26.0 (C\(_4\)), 30.1 (C\(_7\)), 40.2 (C\(_3\)), 41.4 (C\(_{11}\)), 42.4 (C\(_6\)), 44.0 (C\(_5\)), 66.5 (C\(_1\)), 75.4 (C\(_8\)), 79.7 (C\(_{10}\)), 83.9 (C\(_9\)), 126.8 (C\(_\text{aryl}\)), 128.5 (C\(_\text{aryl}\)), 130.0 (C\(_\text{aryl}\)), 137.3 (C\(_\text{aryl}\)), 224.3
(C₂); IR (ef) 3500-3120 (broad), 3445, 3244, 2943, 2874, 2108, 1720, 1494, 1453, 1164 cm⁻¹; MS (Cl) m/z (rel. intensity) 255 (M + H, 3), 238 (15), 237 (100), 219 (3), 186 (5); Anal. Calcd. for C₁₇H₁₈O₂: C, 80.28; H, 7.13; Found: C, 80.50; H, 7.06.

9.6.15.2 Procedure B

![Chemical Structures]

A solution of cis-1-benzylbicyclo[3.3.0]octan-2,8-dione 406 (50 mg, 0.22 mmol, 1.0 equiv.) in THF (5 mL) was cooled to -78 °C. Ethynylmagnesium bromide (2.2 mL of a 0.5 M solution in THF, 1.1 mmol, 5.0 equiv.) was added dropwise and the resultant solution was allowed to warm to room temperature over 30 min. The reaction mixture was then stirred for 16 h, water (3 mL) was added and the phases were then separated. The aqueous phase was extracted with ether (3 × 10 mL) and the combined organic extracts were washed with water (3 × 10 mL) and brine (10 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography (hexanes:ether, 2:1) to afford an epimeric mixture of the 1-benzyl-8-ethynyl-8-hydroxy-cis-bicyclo[3.3.0]octan-2-ones 413 and 414 (47 mg, 76%, 413:414 = 7:3) as a colourless solid. This material had spectral and physical properties identical to those of the material which was obtained by Procedure A.
9.7 Experimental Concerning Chapter Seven

9.7.1 *Ethyl 2-(2,5,5-trimethyl-1,3-dioxan-2-yl)acetate (431)*

A solution of neopentyl glycol (160 g, 1.54 mol, 2.0 equiv.), ethyl acetoacetate 432 (98.0 mL, 768 mmol, 1.0 equiv.) and p-toluenesulfonic acid monohydrate (200 mg, catalytic amount) in benzene (400 mL) was heated at reflux for 14 h with azeotropic removal of water in a Dean-Stark trap. Over the first 30 min of heating, the neopentyl glycol dissolved to give a colourless solution. The reaction mixture was then allowed to cool to room temperature and was transferred to a separatory funnel and washed with a saturated aqueous solution of sodium bicarbonate (3 × 30 mL). The combined aqueous layers were back-extracted with ether (3 × 75 mL) and the combined organic phases were washed with water (5 × 30 mL) and brine (30 mL), then dried over anhydrous sodium sulfate and concentrated in vacuo to afford the title compound 431 (164 g, 98%) as a colourless liquid (~98% pure by $^1$H NMR). An analytical sample (~100 mg of the product) was obtained by flash chromatography (hexanes:ether, 3:1). $R_f$ 0.75 (hexanes:ether, 1:1); $^1$H NMR (C$_6$D$_6$, 400 MHz) $\delta$ 0.65 (s, 3H, acetal CH$_3$), 0.75 (s, 3H, acetal CH$_3$), 0.94 (t, $J = 7.1$ Hz, 3H, -CO$_2$CH$_2$CH$_3$), 1.68 (s, 3H, CH$_3$C(OR)$_2$CH$_2$-), 2.77 (s, 2H, -CH$_2$CO$_2$Et), 3.27 (d, $J = 11.5$ Hz, 2H, acetal CH$_2$), 3.38 (d, $J = 11.5$ Hz, 2H, acetal CH$_2$), 3.97 (q, $J = 7.1$ Hz, 2H, -CO$_2$CH$_2$CH$_3$); $^{13}$C NMR (C$_6$D$_6$, 101 MHz) $\delta$ 14.2, 22.4, 22.6, 23.3, 29.7, 41.7.
60.2, 70.5, 97.7, 117.0, 169.1; IR (neat) 2956, 2871, 1736, 1395, 1368, 1217, 1081, 1036 cm\(^{-1}\); MS (Cl) m/z (rel. intensity) 217 (M + H, 100), 203 (2), 201 (2), 131 (46), 129 (50).

9.7.2 2-(2,5,5-Trimethyl-1,3-dioxan-2-yl)ethanol (436)

\[ \text{LiAlH}_4, \text{THF, 0 }^\circ\text{C, 15 min} \]

A suspension of lithium aluminum hydride (7.88 g, 208 mmol, 0.75 equiv.) in THF (500 mL) was cooled to 0 °C. A solution of ethyl 2-(2,5,5-trimethyl-1,3-dioxan-2-yl)acetate 431 (60.0 g, 277 mmol, 1.0 equiv.) in THF (50 mL) was then carefully added over 30 min by means of a cannula. The reaction mixture was then stirred for 15 min at 0 °C. Water (8 mL) was added very carefully over 1 h, followed by an aqueous solution of sodium hydroxide (15% w/v, 8 mL) and finally water (24 mL). The white suspension was stirred overnight at room temperature and was filtered. The filter cake was washed with ether (200 mL) and the filtrate was concentrated in vacuo to afford the title compound 436 (47.6 g, 99%) as a colourless oil (~98% pure by \(^1\)H NMR). An analytical sample (~100 mg of the product) was obtained by flash chromatography (hexanes:ether, 1:1). \( R_f \) 0.65 (ether); \(^1\)H NMR (\(\text{C}_6\text{D}_6\), 400 MHz) \(\delta\) 0.37 (s, 3H, acetal \(\text{CH}_3\)), 0.95 (s, 3H, acetal \(\text{CH}_3\)), 1.15 (s, 3H, \(\text{CH}_3\)\(\text{C(OR)}_2\)), 1.86 (t, \( J = 5.6 \text{ Hz}, 2\text{H, -CH}_2\text{CH}_2\text{OH}\)), 2.86 (br s, 1H, -OH), 3.09 (d, \( J = 11.5 \text{ Hz}, 2\text{H, acetal CH}_2\)), 3.27 (d, \( J = 11.5 \text{ Hz}, 2\text{H, acetal CH}_2\)), 3.90-3.97 (m, 2H, -CH\(_2\)OH); \(^{13}\)C NMR (\(\text{C}_6\text{D}_6\), 101 MHz) \(\delta\) 19.1, 22.0, 22.8, 29.7, 42.4, 58.7, 70.2, 100.0; IR (neat) 3620-3140 (broad), 2988, 1096 cm\(^{-1}\); MS
(Cl) m/z (rel. intensity) 175 (M + H, 84), 159 (5), 157 (3), 129 (11), 117 (8), 89 (100).

9.7.3 2-(2,5,5-Trimethyl-1,3-dioxan-2-yl)acetaldehyde (424)

\[ \begin{array}{cc}
\text{436} & \text{PDC, DCM, 0 °C to rt, 16 h} \\
\text{424} & \text{38%}
\end{array} \]

A solution of 2-(2,5,5-trimethyl-1,3-dioxan-2-yl)ethanol 436 (20.0 g, 115 mmol, 1.0 equiv.) in dichloromethane (200 mL) was cooled to 0 °C. Pyridinium dichromate (56.1 g, 149 mmol, 1.3 equiv.) was added and the reaction mixture was allowed to warm to room temperature and was stirred for 16 h, then filtered through a pad of diatomaceous earth and concentrated in vacuo. The residue was taken up in ether (100 mL) and again filtered through a pad of diatomaceous earth and concentrated in vacuo. The crude material was purified by flash chromatography (hexanes:ether, 3:1) to afford the title compound 424 (7.51 g, 38%) as a colourless oil. \( R_f \) 0.55 (hexanes:ether, 1:1); \(^1\)H NMR (CDCl₃, 400 MHz) \( \delta \) 0.85 (s, 3H, acetal CH₃), 1.03 (s, 3H, acetal CH₃), 1.45 (s, 3H, CH₃C(OR)₂⁻), 2.66 (d, \( J = 3.0 \) Hz, 2H, CH₂CHO), 3.43 (d, \( J = 11.5 \) Hz, 2H, acetal CH₂), 3.61 (d, \( J = 11.5 \) Hz, 2H, acetal CH₂), 9.84 (t, \( J = 3.0 \) Hz, 1H, CHO); \(^13\)C NMR (CDCl₃, 101 MHz) \( \delta \) 20.7, 22.5, 23.1, 30.0, 52.0, 70.6, 97.6, 201.0; IR (neat) 2928, 2856, 2774, 1739, 1484, 1105 cm⁻¹; MS (Cl) m/z (rel. intensity) 173 (M + H, 3), 157 (3), 129 (100), 115 (8), 87 (53).
A solution of 4-pentenoic acid 434 (10.01 g, 100 mmol, 1.0 equiv.) and concentrated sulfuric acid (3 drops, catalytic amount) in anhydrous ethanol (150 mL) was heated at reflux for 2 days. The reaction was allowed to cool to room temperature, quenched with saturated aqueous sodium bicarbonate solution (10 mL) and was stirred for 10 min. Most of the ethanol was removed in vacuo and the resultant solution was diluted with ether (200 mL) and washed with water (5 x 20 mL). The organic phase was dried over anhydrous magnesium sulfate and was concentrated in vacuo. The crude product was purified by distillation under water aspirator pressure through a Vigreux column to afford the title compound 437 (8.97 g, 70%) as a colourless liquid. B.p. 50-51 °C/20 mmHg (lit. 144 °C/760 mmHg); \(^1\)H NMR (C\(_6\)D\(_6\), 400 MHz) \(\delta\) 0.93 (t, \(J = 7.1\) Hz, 3H, -CH\(_2\)CH\(_3\)), 2.11-2.27 (m, 4H, -CH-CH\(_2\)CH\(_2\)-), 3.92 (q, \(J = 7.1\) Hz, 2H, -CH\(_2\)CH\(_3\)), 4.87-4.95 (m, 2H, CH\(_2\)=CH-), 5.60-5.72 (m, 1H, CH\(_2\)=CH-); \(^{13}\)C NMR (C\(_6\)D\(_6\), 101 MHz) \(\delta\) 14.3, 29.2, 33.7, 60.0, 115.4, 137.1, 172.2; IR (neat) 3081, 2982, 2935, 1736, 1642, 1445, 1372, 1093, 1038 cm\(^{-1}\); MS (Cl) \(m/z\) (rel. intensity) 129 (M + H, 53), 101 (100), 83 (32).
A solution of dimethyl methylphosphonate (11.2 mL, 103 mmol, 2.2 equiv.) in THF (75 mL) was cooled to -78 °C. n-Butyllithium (41.2 mL of a 2.5 M solution in hexanes, 103 mmol, 2.2 equiv.) was added over 20 min and the resultant yellow solution was stirred for 1 h at -78 °C. A solution of ethyl 4-pentenoate 437 (6.00 g, 46.8 mmol, 1.0 equiv.) in THF (5 mL) was added by means of a cannula and the reaction mixture was stirred for 2 h at -78 °C. The reaction was then quenched with water (120 mL) and was allowed to warm to room temperature. The reaction mixture was diluted with ether (100 mL) and was acidified to pH 2 with aqueous hydrochloric acid solution (1 M, 90 mL). The phases were separated and the aqueous phase was extracted with ether (3 × 100 mL). The combined organic extracts were washed with water (100 mL) and brine (100 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography (hexanes:ethyl acetate:methanol, 6:3:1) to afford the title compound 425 (7.81 g, 81%) as a yellow oil. \( R_f \) 0.10 (hexanes:ether, 1:1); \(^1\)H NMR (CDCl₃, 600 MHz) \( \delta \) 2.29-2.35 (m, 2H), 2.71 (t, \( J = 7.2 \) Hz, 2H), 3.08 (d, \( J_{PH} = 22.7 \) Hz, 2H, -CH₂PO(OCH₃)₂), 3.77 (d, \( J_{PH} = 11.2 \) Hz, 6H, 2 × OCH₃), 4.95-5.06 (m, 2H, CH₂=CH-), 5.74-5.82 (m, 1H, CH₂=CH-); \(^{13}\)C NMR (CDCl₃, 151 MHz) \( \delta \) 27.5, 41.1, 41.9, 43.3, 53.2 (d, \( J_{CP} = 5.9 \) Hz), 115.6, 136.7, 201.2 (d, \( J_{CP} = 6.0 \) Hz); IR (neat) 3076, 2962, 2923, 2854, 1716.
Lithium chloride (248 mg, 5.86 mmol, 1.0 equiv.) was flame-dried under high vacuum and was allowed to cool under an atmosphere of nitrogen. This process was repeated 4 times in total and then acetonitrile (10 mL) was added. A solution of dimethyl 2-oxohex-5-enylphosphonate 425 (1.21 g, 5.86 mmol, 1.0 equiv.) in acetonitrile (3 mL) was added by means of a cannula and the resultant suspension was stirred for 10 min. Freshly distilled Hüning's base (1.0 mL, 5.9 mmol, 1.0 equiv.) was added and the reaction mixture was stirred for 10 min. A solution of 2-(2,5,5-trimethyl-1,3-dioxan-2-yl)acetaldehyde 424 (1.01 g, 5.86 mmol, 1.0 equiv.) in acetonitrile (3 mL) was added by means of a cannula and the reaction mixture was stirred for 16 h. The reaction was quenched with water (10 mL) and the aqueous phase was extracted with ether (3 × 10 mL). The combined organic extracts were washed with water (3 × 10 mL) and brine (10 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography (hexanes:ether, 3:1 followed by hexanes:ether, 2:1 and finally hexanes:ether, 1:1) to afford the title compound 423 (1.08 g, 73%) as a colourless oil. Rf 0.20 (hexanes:ether, 1:1); $^1$H NMR (C$_6$D$_6$, 400 MHz) $\delta$ 0.55 (s, 3H, acetal CH$_3$), 0.87 (s, 3H, acetal CH$_3$), 1.20 (s, 3H, acetal CH$_3$).
3H), 2.29-2.35 (m, 4H), 2.42 (dd, J = 7.3, 1.1 Hz, 2H), 3.18 (d, J = 11.5 Hz, 2H, acetal CH2), 3.29 (d, J = 11.5 Hz, 2H, acetal CH2), 4.88-4.99 (m, 2H, CH2=CH-), 5.67-5.78 (m, 1H, CH2=CH-), 6.02 (dt, J = 16.0, 1.3 Hz, 1H, -CO-CH=CH-), 6.90-6.98 (m, 1H, -CO-CH=CH-); 13C NMR (C6D6, 101 MHz) δ 20.1, 22.2, 22.7, 28.3, 29.8, 39.1, 42.2, 98.4, 115.0, 126.1, 133.3, 137.9, 141.2, 197.6; IR (neat) 3076, 2955, 2868, 1697, 1673, 1634, 1473, 1395, 1250, 1117, 1080 cm⁻¹; MS (CI) m/z (rel. intensity) 253 (M + H, 32), 237 (24), 217 (60), 203 (34), 167 (100), 157 (78), 149 (21); Anal. Calcd. for C15H24O3: C, 71.39; H, 9.59; Found: C, 71.11; H, 9.70.

9.7.7 3-Acetoxy cyclopent-2-en-1-one (460)

![Chemical structure](image)

A suspension of 1,3-cyclopentanedicarboxylic acid 459 (500 mg, 5.10 mmol, 1.0 equiv.) in dichloromethane (20 mL) was cooled to 0 °C. Pyridine (412 μL, 5.10 mmol, 1.0 equiv.) was added and the resultant suspension was stirred for 10 min. Acetyl chloride (435 μL, 6.12 mmol, 1.2 equiv.) was then added dropwise and the reaction mixture was allowed to warm to room temperature over 2 h. Water (15 mL) was added and the phases were separated. The organic phase was washed with aqueous hydrochloric acid (10% v/v, 15 mL) followed by a saturated aqueous solution of sodium bicarbonate (15 mL), water (15 mL) and brine (15 mL), then dried over anhydrous magnesium sulfate and concentrated in vacuo to afford the title compound 460 (620 mg, 86%) as a yellow gum which upon standing in a freezer became a pale yellow solid. No further purification was
necessary. \( R_f 0.75 \) (ether); **M.p.** 26-27 °C (dichloromethane); \(^1\text{H NMR} \) (CDCl\(_3\), 400 MHz) \( \delta 2.27 \) (s, 3H, COCH\(_3\)), 2.41-2.45 (m, 2H, 2 × H\(_4\)), 2.72-2.76 (m, 2H, 2 × H\(_5\)), 6.20 (m, 1H, H\(_2\)); \(^{13}\text{C NMR} \) (CDCl\(_3\), 101 MHz) \( \delta 21.5 \) (acetate CH\(_3\)), 28.9 (C\(_4\)), 33.4 (C\(_5\)), 116.6 (C\(_2\)), 166.3 (C\(_3\)), 179.5 (acetate C=O), 206.8 (C\(_1\)); **IR** (ef) 1790, 1709, 1600, 1437, 1372, 1337, 1196, 1147, 1010 cm\(^{-1}\); **MS** (Cl) \( m/z \) (rel. intensity) 141 (M + H, 100), 99 (32).
10.1 Appendix 1 - Computational Details

10.1.1 Evaluation of the gas-phase energies of the methyl, t-butyl and triquinacyl cation, anion and radical

These calculations were performed using the keywords \#opt rb3lyp/6-31+g(d,p) geom=connectivity (for all closed-shell species) and \#opt ub3lyp/6-31+g(d,p) geom=connectivity (for radical species) in the Gaussian input files.\(^{256}\) These geometry optimizations were performed using the Gaussian default convergence criteria until a stationary point was found.

10.1.2 Modeling of the dimerization reaction of triquinacene (1) to dodecahedrane (178)

For each value of the intermolecular distance parameter \(r\), the geometry was optimized for the ground state using the keywords \#opt=modredundant rb3lyp/6-31g* test in the Gaussian input file. In the case of the first singlet excited state, the keywords used were \#opt=modredundant CIS(direct,root=1)/6-31g* test. For the attempted modeling of the analogous reaction in the system’s first triplet excited state, the keywords \#opt=modredundant CIS(triplets,direct,root=1)/6-31g* test were employed; however, these latter optimizations terminated prematurely and hence failed to converge.
The use of the “direct” keyword was found to be necessary for the excited electronic state calculations, as omission of this keyword led to premature termination on account of disk read/write errors.

The intermolecular distance parameter \( r \) was incorporated in these calculations by the addition of the following modredundant section into the molecular specification section of each Gaussian input file, where \( d \) is the value of \( r \) in Angstroms:

\[
\begin{array}{cccc}
12 & 25 & d & F \\
13 & 22 & d & F \\
7 & 21 & d & F \\
10 & 24 & d & F \\
8 & 27 & d & F \\
11 & 26 & d & F
\end{array}
\]

The addition of this section fixed the distance between atoms 12 and 15, 13 and 22, 7 and 21, 10 and 24, 8 and 27 as well as 11 and 16 to the value of \( r \). The aforementioned atoms were the pairs of carbon atoms involved in \( \sigma \) bond formation and \( \pi \) bond breaking over the course of the dimerization reaction.

### 10.2 Appendix 2 - Optimized Geometries

The optimized geometries for triquinacene 1 as well as for the C-10-centred triquinacyl radical 219, cation 224 and anion 221 are given in Cartesian coordinates.
10.2.1 Triquinacene (1)

![Triquinacene (I)](image)

Table 18 - Optimized geometry of triquinacene (1) (Cartesian coordinates)

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10.2.2 *Triquinacetyl radical* (219)

![Structure of triquinacetyl radical (219)](image)

**Table 19 - Optimized geometry of the triquinacetyl radical (219) (Cartesian coordinates)**

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10.2.3 Triquinacly cation (224)

![Diagram of the triquinacly cation](image)

**Table 20 - Optimized geometry of the triquinacly cation (224) (Cartesian coordinates)**

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10.2.4 *Triquinacyle anion (221)*

![Image of Triquinacyle anion]

Table 21 - Optimized geometry of the triquinacyle anion (221) (Cartesian coordinates)

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10.3 Appendix 3 - Optimized Transition State Geometries for the Dimerization Reaction of Triquinacene (1) to Dodecahedrane (178)

The optimized geometries for both the ground state and first excited singlet state dimerization reactions of triquinacene 1 to dodecahedrane 178 are given in Cartesian coordinates.
10.3.1 Transition state geometry (ground state reaction)

Table 22 - Optimized geometry of the transition state for the ground state dimerization reaction of triquinacene (I) to dodecahedrane (178) (Cartesian coordinates)

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10.3.2 Transition state geometry (first excited singlet state reaction)

![Diagram of triquinacene and dodecahedrane]

Table 23 - Optimized geometry of the transition state for the first singlet excited state dimerization reaction of triquinacene (1) to dodecahedrane (178) (Cartesian coordinates)

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Table 23 - Optimized geometry of the transition state for the first singlet excited state dimerization reaction of triquinacene (1) to dodecahedrane (178) (Cartesian coordinates)
### 10.4 Appendix 4 - Tabulated Data for Dimerization Modeling

**Table 24 - Energy vs. interatomic distance (r) for the ground state dimerization reaction of triquinacene (1) to dodecahedrane (178)**

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<th>Energy (kcal mol⁻¹)</th>
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Table 25 - Energy vs. interatomic distance ($r$) for the first singlet excited state dimerization reaction of triquinacene (1) to dodecahedrane (178)

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<th>$r$ (Å)</th>
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(271) These aldehydes hydrate readily (see main text).


