

STUDIES OF THE SEX PHEROMONE OF A BLUEBERRY LEAFROLLER (Cheimophila  
salicella (HUBNER)) AND ON THE SYNTHESIS OF CHIRAL PHEROMONES  
FROM CARBOHYDRATES

by

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(Cheimophila salicella (Hubner)) and on the Synthesis of  
Chiral Pheromones from Carbohydrates"

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"Studies of the Sex Pheromone of A Blueberry Leafroller (*Cheimophila*

salicella (Hubner)) and on the Synthesis of Chiral Pheromones from

Carbohydrates"

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ABSTRACT

This thesis describes the identification of the sex pheromone of Cheimophila salicella (Hubner) (Lepidoptera:Oecophoridae), a pest of high-bush blueberry in the lower Fraser Valley of British Columbia. The pheromone components have been identified as (E)-11-tetradecenyl acetate (I-1), (E)-11-tetradecenol (I-2), tetradecyl acetate (I-3) and (E)-11-tetradecenal (I-4), by capillary gas-liquid chromatography, gas chromatography-mass spectrometry and chemical derivative formation. Individual female abdominal tip washes indicated I-1-I-4 to be in the relative ratios of 100:15:10:2. Field trapping experiments showed compound I-1 to be weakly attractive to male moths and therefore was the primary pheromone component. None of the other components, I-2-I-4, were attractive to males when dispensed separately but the aldehyde I-4, in combination with the other three components, improved the capture of male moths, making this lure more attractive than virgin females.

The use of commercially available carbohydrates as precursors for specific chiral pheromones was investigated. Through deoxygenation and modification of a D-glucofuranose derivative, the chiral synthesis of (-)-(R,Z)-5-(1-decenyl)-dihydro-2(3H)-furanone ((-)-II-1), the sex pheromone of the Japanese beetle, Popillia japonica (Newman), was accomplished in an overall yield of 1%. A synthesis of (+)-(S,Z)-5-(1-decenyl)-dihydro-2(3H)-furanone ((+)-II-1), the inhibitory enantiomer of (-)-II-1, was attempted by a route paralleling that described for (-)-II-1. All attempts at deoxygenation at carbon 2, successful with the threo-furanoside (II-8) in the preparation of (-)-II-1, failed when applied to the erythro-furanoside (II-17). Successful deoxygenation at both carbons 2 and 3 of

D-ribonolactone (II-24) was achieved. However, this route was ineffective in preparing (+)-II-1, as the primary hydroxyl could not be oxidized to the essential intermediate aldehyde (II-36). This study has shown that a lack of effective and specific deoxygenation procedures make carbohydrates ineffective precursors for these chiral pheromones.

To my wife, Gabriela, for her love and courage  
and to my parents.

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**CHAPTER I - SEX PHEROMONE OF A BLUEBERRY LEAFROLLER,****Cheimophila salicella (Hubner)****I. INTRODUCTION**

Pheromones, as defined by Karlson and Butenandt<sup>1</sup> and Karlson and Luscher<sup>2</sup>, include sex attractants, warning substances and aggregation pheromones. Most of the identified female sex pheromones of the order Lepidoptera present a structural uniformity consisting of one or more mono- or polyolefinic alcohols, acetates or aldehydes<sup>3</sup>. In comparison to Lepidoptera, far fewer sex pheromones have been identified in other orders. The complexity of chemosensory communication in insect behaviour has been shown to be regulated by chemical stimuli<sup>4</sup>. Structural modification of the sex pheromone components of several species have resulted in dramatic reduction or loss of activity<sup>4</sup>. It is now well established that the vast majority of species produce more than one compound. In typical cases, two primary components are used, their ratio often being critical for optimum response of the males. Commonly, one or more secondary compounds are present which mediate behaviour of the male when in the immediate vicinity of the female<sup>5</sup>.

Identification and structural determination of sex pheromone components utilizes capillary gas chromatography, gas chromatography-mass spectrometry of the components and their derivatives, and specificity and effectiveness of synthetic blends under field conditions. Factors such as the volatile nature and sub-microgram amounts of pheromone components present in female extracts make splitless gas chromatography the analytical technique of choice. Furthermore, capillary gas chromatography provides

high resolving power, reproducibility of retention parameters through microprocessor control and speed of analysis. Such reproducible retention data, in conjunction with column performance as determined by such techniques as retention indices<sup>6</sup>, allow chain length and functional group assignments to be made. Unsaturation presents a more difficult problem in that even the high resolving power of the capillary column is incapable of separating all the possible positional and geometric isomers. Bierl et al. summarized methods of identifying the position and stereochemistry of unsaturation through epoxide formation and subsequent gas chromatography<sup>7</sup>, and gas chromatography-electron impact mass spectrometry of the epoxide derivatives<sup>8</sup>. Preferential cleavage  $\alpha$  to the epoxy group produces identifiable fragments that indicate the position of the epoxy group and thus the position of the double bond in the original compound.

For female Lepidoptera producing sufficient material to be monitored by flame ionization detection, the techniques described would provide for initial identification of the major pheromone components. Proof of the ability of such materials to attract the opposite sex must rely on field trapping experiments.

The economic and environmental importance of biological pest control through the use of natural insect pheromones has been reported by several groups<sup>4</sup>. The reduction of pest populations, by employing pheromone-baited traps and the use of confusion techniques to disrupt mating behaviour with synthetic sex pheromones, minimizes the possibility of environmental pollution and all its risks.

### Objective

The objective of this research was to identify the sex pheromone of Cheimophila salicella (Hbn) (Lepidoptera:Oecophoridae), and to develop an effective synthetic pheromone blend for the attraction of male moths. To date, no work has been reported on pheromones for C. salicella. Preliminary trapping with virgin females indicated the presence of a female-produced sex pheromone in this species (private communication, D.R. Gillespie). C. salicella is a Palearctic species that occurs from England to eastern Siberia<sup>9</sup>. In North America, C. salicella occurs only in the lower Fraser Valley of British Columbia, where it is a common and often troublesome pest of highbush blueberry<sup>10,11</sup>. The larvae also feed on species of Spiraea, Salix, Alnus, Betula, Acer and other shrubs<sup>10</sup>. The life history of C. salicella has been described by Raine<sup>10</sup>. The pupae overwinter in leaf shelters on or beneath host plants and adults emerge in March and April. The brachypterous females crawl up the host plant, where they can often be seen at mid-day, and are mated by the day-flying males. Eggs are laid on the rough bark of old stems and around the axils of buds and hatch in early- to mid-May. Larvae feed throughout the summer and pupate in August and September.

## II. EXPERIMENTAL METHODS

### A. Rearing of *C. salicella*

Larvae of *C. salicella* were collected in July and August, 1980 and 1982, from blueberry plants in Pitt Meadows and Richmond, B.C. These were reared to pupation on fresh blueberry foliage. Pupae were extracted from the foliage, held individually in snap-cap vials (3 × 10 cm) with moistened cheesecloth inside to maintain humidity, and overwintered outside at ambient temperatures. Larvae and adults were identified as *C. salicella* using characteristics given by Raine<sup>10</sup> and Hodges<sup>11</sup>.

Freshly-emerged adult females were placed in individual capped vials (3 × 10 cm), containing a short stick as a twig substitute. Behaviour associated with calling, i.e. extrusion of the ovipositor and rhythmic pumping of the abdomen, was obtained with a 16-hour photophase at 24 ± 4°C, followed by an 8-hour scotophase at 5 ± 1°C. This behaviour was normally initiated 1-2 hours into the photophase.

### B. Extraction of the Insect Volatiles

The abdominal tips of 1-3 day old females were excised and washed individually in separate aliquots of redistilled spectral-grade heptane, as described by Klun et al.<sup>12</sup>. Washes (3-5 µL) were prepared by rinsing the abdominal tip of a female two or three times. Extracts were prepared by covering several excised abdominal tips with heptane (10-20 µL) and storing these for 6 days in a sealed ampoule at room temperature.

### C. General Experimental Procedures

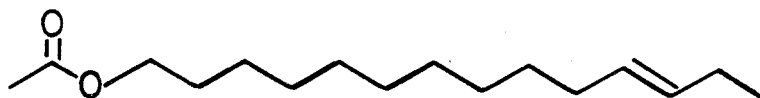
Splitless capillary gas chromatography was performed on a Hewlett-Packard 5880A instrument. Columns used in this study were 25 and 50 m



long, 0.2 mm i.d. and made of flexible fused silica coated with either Carbowax 20M or apolar methyl silicone. These were operated in a splitless mode at 40°C for 2 min, 30°C/min to 150°C, then 2°C/min to 210°C, with an injector temperature of 250°C and a helium carrier gas flow of 1 mL/min. A flame ionization detector was used at a detector temperature of 250°C. Synthetic standards were injected immediately after positive responses. Under these gas chromatograph conditions, the lower limit of Z-isomer detection was 5% Z in 95% E for  $\Delta$ -11-14:OAc on the Carbowax 20M column. Mass spectral analysis was performed on combined washes and on combined extracts by splitless injection into a Hewlett-Packard 5985 gc-ms, fitted with a 15 m Durabond-1, 0.2 mm i.d. capillary column, using electron impact ionization. Double bond position in compounds I-1, I-2 and I-4 (Fig. 1) was established by gc-electron impact mass spectrometry, as described by Bierl-Leonhardt et al.<sup>8</sup>, using a concentrated extract from 32 female abdominal tips dissolved in methylene chloride (50  $\mu$ L) containing m-chloro-perbenzoic acid (30  $\mu$ g), sealed in a glass ampoule for 2 days at 25°C. The mixture was then washed with 1% aqueous sodium bicarbonate (50  $\mu$ L) and twice with water (50  $\mu$ L). A small aliquot (typically 3  $\mu$ L) was chromatographed on the 50 m Carbowax 20M and the remainder analyzed by gc-ms. A 6-day extract of 13 female tips and samples of standards (10  $\mu$ g/50  $\mu$ L) were analyzed in an identical fashion. Untreated and epoxidized extracts were also chromatographed on the Hewlett-Packard 5880A instrument with a 30 m, 0.2 mm i.d. DB-1 column and a column temperature of 80°C for 2 min, 10°C/min to 180°C, then 2°C/min to 240°C. With these conditions, the lower limit of Z detection for untreated extracts was 1% Z in 99% E for  $\Delta$ -11-14:OAc.

Figure 1

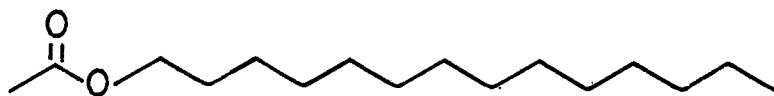
Structures of compounds I-1-I-4.



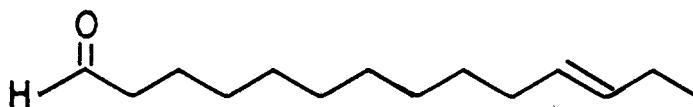
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1 - 3



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### III. SYNTHESIS OF TETRADECENYL STANDARDS

#### A. Introduction

Among the many methods available for the synthesis of monounsaturated compounds, alkynes are very often used as starting materials since they provide a precursor for the stereoselective synthesis of both geometric isomers by either catalytic partial hydrogenation to Z-olefins or dissolving metal reduction to E-olefins. Methods for carbon-carbon double bond formation without using alkynes as starting materials are available but less attractive. The acetylenic approach has included both solid phase<sup>13</sup> and solution methods. Solid phase synthetic routes<sup>14-16</sup> have led, for example, to the synthesis of (Z)-11-tetradecenyl acetate, a major component of the sex pheromone of Argyrotaenia velutinana (Walker) and many other Tortricidae. Leznoff and Fyles<sup>14-16</sup> studied the use of polymer-bound diols as initiating centres for such transformations. Carbon skeletons have been usually prepared using solution phase methods. Coupling reactions of protected or unprotected  $\omega$ -hydroxy-1-alkynes have led to positional acetylenic precursors from which both E- and Z-olefinic derivatives have been obtained. Henrick<sup>17</sup> and Rossi<sup>18</sup> have reviewed the synthesis of achiral components of insect pheromones, its many variations, limits and extensions.

The Wittig reaction<sup>19-20</sup>, in its original form, allowed little steric control but subsequent studies have revealed ways for controlling the stereochemistry of the reaction<sup>21,22-26</sup>. The reaction of saturated aliphatic nonstabilized triphenylphosphonium ylides with primary aliphatic aldehydes in non-polar solvents at 0°C in the absence of inorganic ions gives predominantly Z-olefins<sup>22-26</sup>. The same result is obtained with

nonstabilized alkylides and aliphatic aldehydes, in the presence or absence of lithium salts if the reaction is carried out in a dipolar aprotic solvent such as N,N-dimethylformamide<sup>27</sup>, dimethylsulfoxide<sup>28</sup> or hexamethylphosphoramide<sup>29-31</sup>.

Several other sets of conditions, such as potassium tert-butoxide in tetrahydrofuran at room temperature<sup>32</sup> and also sodium hydride in N,N-dimethylformamide, give the Z-olefin. Schlosser's<sup>33-34</sup> modification of the Wittig reaction involves the addition of lithium salts to the primary Wittig intermediate, with predominantly erythro configuration, generating a new intermediate,  $\beta$ -oxidophosphorous ylide. In contrast, protonation with tert-butyl alcohol generates the Wittig intermediate with the threo configuration, which then gives almost pure E-olefins. Polymer-bound aldehydes or Wittig reagents<sup>15</sup> have also been used for the synthesis of, for example, (Z)-10-tetradecenyl acetate, the sex attractant of Archips semiferanus (Walker), in high stereoselectivity. A method which constitutes an alternative to the E-stereoselective Wittig reaction, starting from  $\gamma$ -substituted allyl phosphonates, stereochemically pure or in mixtures, and alkyl halides, also affords stereochemically pure E-alkenes<sup>35</sup>.

The iodine-induced migration of dialkylvinylboranes, obtained via controlled monohydroboration of terminal alkynes, in which the migrating group from boron becomes attached to the double bond cis to the alkyl group of the original alkyne, has been used by Brown and co-workers<sup>36</sup> for the stereospecific synthesis of (Z)-7-alken-1-ols, providing another entry to the synthesis of insect sex pheromones. (Z)-7-Dodecenol, (Z)-7-dodecenyl acetate and (Z)-7-tetradecenyl acetate, pheromone of the male moth, Raphia frater (Grt) (Noctuidae)<sup>37</sup>, sex pheromone of soybean loopers, Pseudoplusia

includens (Walker)<sup>38</sup>, the cabbage looper, Trichoplusia ni (Hbn)<sup>39</sup>, and the pheromone of the Amathes c-nigrum<sup>40,41</sup>, respectively, were synthesized by this approach.

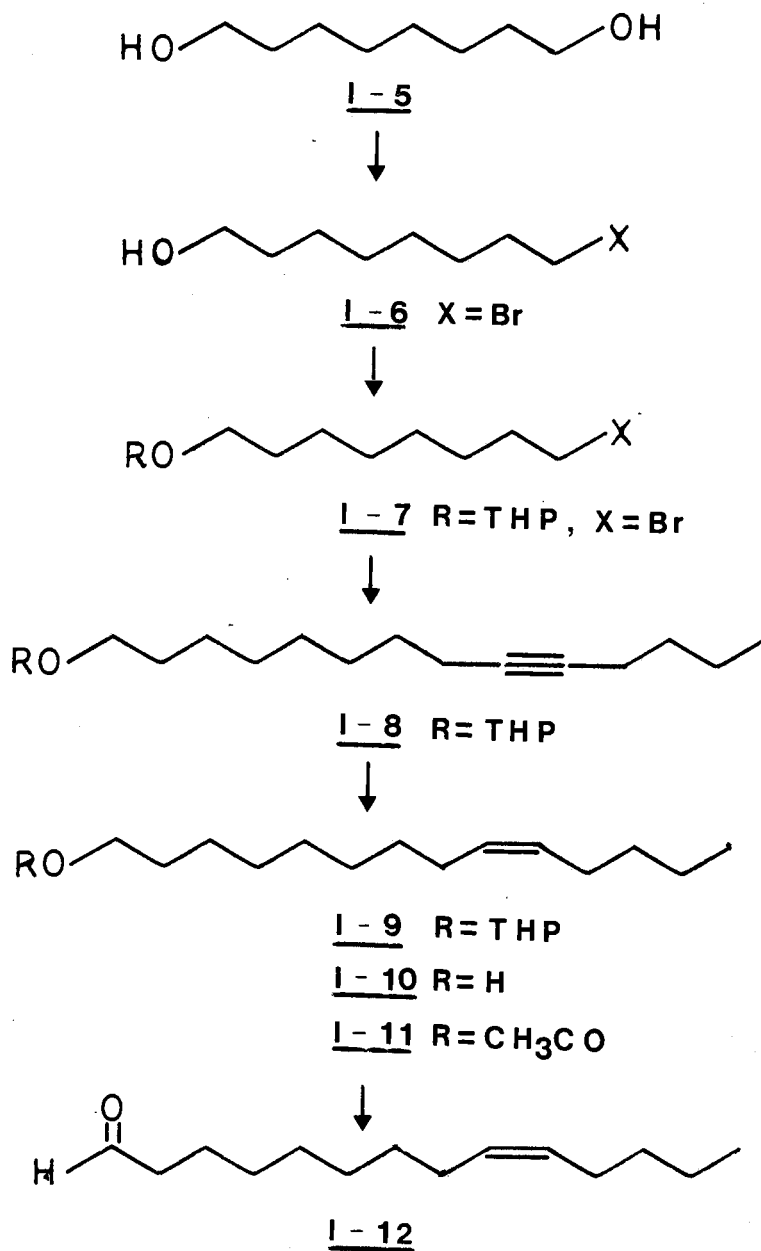
The carbometallation of acetylene by organocopper reagents allows the stereospecific synthesis of disubstituted alkenes<sup>42</sup>. The most efficient reagents for carbometallation of acetylene (and alkynes in general) are those derived from copper, either as  $\text{RCu}\cdot\text{MgX}_2$  species (or  $\text{RCuX}\cdot\text{MgX}$ , according to the solvent), homocuprates,  $\text{R}_2\text{Cu}\cdot\text{MgX}$  (or  $\text{R}_2\text{CuLi}$ ) or  $\text{RR}'\text{CuM}$ , or heterocuprates,  $\text{RCuXM}$  ( $\text{X} = \text{O-tert-C}_4\text{H}_9, \text{S-C}_6\text{H}_5$ ). Addition occurs purely in a syn fashion and in the Markovnikov way. Thus, a large array of ethylenic synthons ( $\beta$ -monosubstituted) are now readily available and behave as powerful building blocks of disubstituted olefins. Utilizing this new alkenyl metal species, in situ transformations can result in the positioning of two substituents in a Z manner. Since the vinylic copper species is reactive towards many electrophiles with complete retention of configuration, the overall stereoselectivity makes this method particularly attractive. Iodinolysis of vinylcopper reagents also affords vinyl iodides with complete retention of configuration<sup>43-45</sup>. (Z)-9-Dodecenyl acetate, the pheromone of Eupoecilia (Clysia) ambiguella (Hbn), has been synthesized using this method. The main limitation in the use of vinylcopper species is their thermal lability<sup>42</sup>. Although the synthesis of sex pheromones using organoboron and organocopper compounds allows a high stereo- and chemo-selectivity, the syn addition limits the applicability to synthetic targets of Z-configuration.

The goal in the synthesis of the standards was to prepare hundred milligram quantities of several stereochemically pure, 14-carbon straight

chain unsaturated (E and Z) alcohols, aldehydes and acetates to aid in the determination of the sex pheromone components of insects belonging to Lepidoptera species. The synthetic compounds would be used as standards in splitless capillary gas chromatography and mass spectral analyses, electroantennogram (EAG)<sup>46</sup> profiles and field trapping. Sex pheromone components including inhibitors and synergists elicit definite antennal responses in accordance with a proposed protein receptor model for pheromone perception<sup>47</sup>. Electroantennogram profiles have been used to aid in determining the double bond position and geometry of potential sex pheromones. The stereochemical purity of these compounds may be critical as the presence of the opposite geometrical isomers may inhibit attraction to the pheromone in field tests<sup>4</sup>. Impure commercial samples have resulted in erroneous implications as to potential sex pheromone components from field trap catch data (G.G. Grant and K.N. Slessor, unpublished data).

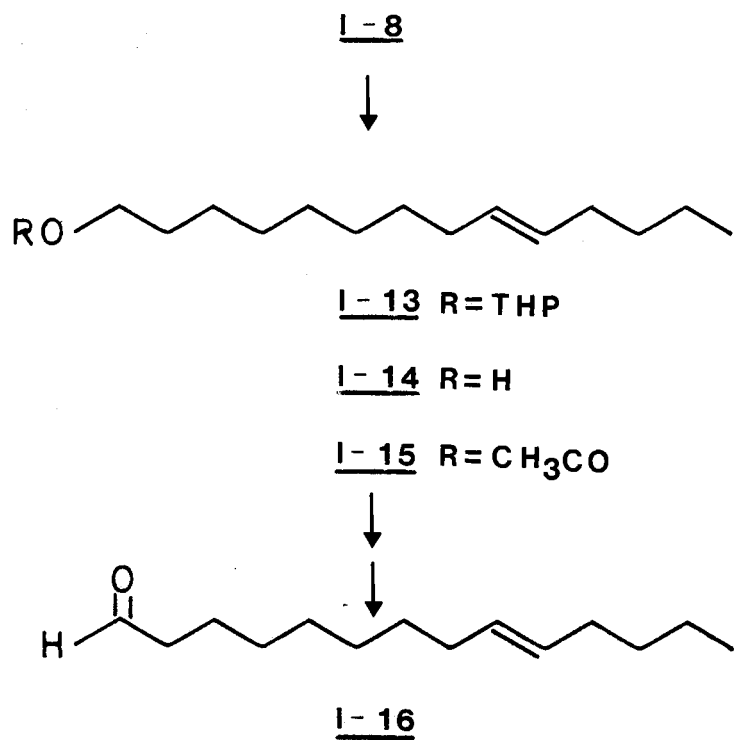
## B. Results and Discussion

At the time this work was initiated, a small number of tetradecenyl compounds of undetermined purity were available commercially. It seemed worthwhile, considering the small time investment for these extra few compounds, to prepare a comprehensive set of compounds of known positional and geometrical isomeric purity. As a result, the unsaturated E and Z tetradecenyl alcohols, acetates and aldehydes were synthesized (Table 1). The synthetic route utilized for the synthesis of the tetradecenyl standards, exemplified with  $\Delta$ -9-tetradecenyl compounds (Scheme 1), was similar to general routes often used to prepare this type of compound as far as intermediate I-8. Thus, 1,8-octanediol (I-5) was converted to 8-bromo-1-octanol (I-6) by reaction with 48% aqueous HBr, with continuous extraction with hot

Scheme 1

THP = Tetrahydropyran - 2 - yl



Scheme 1 (Cont'd)

heptane. The hydroxyl function of I-6 was then protected as the tetrahydropyranyl ether<sup>48</sup> by treatment with dihydropyran in hexane in the presence of Amberlyst H-15 resin as the catalyst for 2 hours to give I-7. Reaction of the resulting bromide (I-7) with the lithium salt of 1-hexyne, in anhydrous tetrahydrofuran-hexamethylphosphoramide at  $-30^{\circ}\text{C}$ , gave I-8 in good yield<sup>17</sup>. Stereoselective cis-reduction of I-8 with hydrogen and P-2 Nickel<sup>49</sup> catalyst gave an excellent yield of olefin I-9, with no detectable E-isomer. Cleavage of the tetrahydropyranyl ether<sup>48</sup> using Amberlyst H-15 resin in methanol at  $45^{\circ}\text{C}$  for 1 hour gave alcohol I-10 almost quantitatively. Oxidation of I-10 was initially attempted with dimethylsulphoxide activated with oxalyl chloride below  $-30^{\circ}\text{C}$ , but low yields were obtained<sup>50</sup>. Instead, use of pyridinium chlorochromate<sup>51</sup> at room temperature in methylene chloride afforded I-12 in greater than 95% yield. Acetylation of I-10, using a mixture of acetic anhydride and pyridine, gave I-11. The preparation of the corresponding E-tetrahydropyranyl ether (I-13) from I-8 was conveniently accomplished by adding the alkyne to a mixture of sodium in an excess of liquid ammonia<sup>52</sup>. Deprotection of I-13 by conventional procedures<sup>48</sup> afforded I-14 which, by acetylation and oxidation, gave I-15 and I-16, respectively. The continuous extraction method for the conversion of a polymethylene glycol to a  $\omega$ -halo-1-alkanol was not used in the case of 5-halo-1-pentanol and 4-halo-1-butanol due to competitive cyclization to tetrahydropyran and tetrahydrofuran, respectively. 5-Bromo-1-pentanol was prepared in good yield by the opening of tetrahydropyran with acetyl bromide and zinc bromide as a catalyst, followed by selective reduction with lithium aluminum hydride and aluminum chloride at low temperature<sup>53-54</sup>. Selective reduction of 4-bromo-butyric acid<sup>53-54</sup>

gave the desired 4-bromo-1-butanol. All compounds were purified by flash chromatography<sup>55</sup> on silica gel and shown to be greater than 98% pure by capillary gas chromatography. The reversible formation of complexes between silver ions and olefins has been used to advantage for the final purification of olefinic compounds, either on silver loaded cation exchange resins<sup>56</sup> or silver nitrate coated silica gel. This argentation chromatography technique has allowed the separation of saturated, mono- and di-unsaturated compounds as well as E and Z isomers, affording products of high geometric purity. Positional purity was ensured mainly by the purity of the alkyne employed in the acetylide-alkyl halide coupling reaction, providing no isomerization occurred<sup>17</sup>. Plots of retention behaviour versus double bond position, as shown in Figs. 2 and 3, illustrate the difficulty associated with attempting to simultaneously assign geometry and position from retention data alone. The overall yields and chromatographic retention times of the synthetic standards, gas liquid chromatography capillary column and conditions, were as described in Table 1.

### C. Experimental Procedures

#### **General procedures**

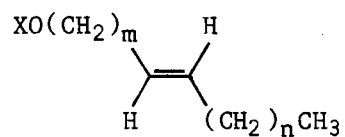
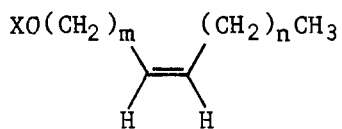
Routine gas liquid chromatography analyses were done on a Varian 1400 flame ionization gas chromatograph, with packed glass columns containing OV-17 or SE-30 on Gas Chrom Q.

Analytical (1 mm) thin layer chromatography plates were prepared from silica gel GF<sub>254</sub> (E. Merck, Darmstadt). Column chromatography was performed by the flash chromatography method, on silica gel (Kieselgel 60, 40-63  $\mu\text{m}$ , E. Merck, Darmstadt).

Chromatographic solvents were distilled before use. IR spectra were

Table 1. Chromatographic retention times of standards.

GC conditions: 50 m Carbowax 20M, 0.2 mm  
i.d., He carrier, splitless mode, 100°C for  
2 min, 30°C/min to 140°C, then 1.5°C/min to  
170°C.



	Overall Yield (%)		Retention Time (min) Carbowax 20M		Overall Yield (%)		Retention Time (min) Carbowax 20M	
	X = H	X = Ac	X = H	X = Ac	X = H	X = Ac	X = H	X = Ac
$\Delta 3$	9	8	11.01	9.59	-	-	-	-
$\Delta 4$	18	17	11.11	9.41	10	7	11.10	9.63
$\Delta 5$	16	14	11.33	9.60	13	11	11.26	9.71
$\Delta 6$	25	23	11.21	9.60	24	21	11.15	9.68
$\Delta 7$	34	30	11.13	9.64	33	30	11.11	9.68
$\Delta 8$	39	37	11.29	9.78	36	32	11.23	9.76
$\Delta 9$	36	35	11.39	9.95	28	26	11.29	9.86
$\Delta 10$	49	47	11.58	10.09	46	43	11.34	9.89
$\Delta 11$	42	40	11.80	10.28	39	41	11.54	10.08
$\Delta 12$	-	-	-	-	28	25	12.12	10.55
$\Delta 13$	-	-	-	-	17	16	11.75	10.28

Figure 2

Plot of retention time (min) versus double bond position ( $\Delta$ ) of E- and Z-tetradecenols on a Carbowax 20M column. Conditions as given in Table 1.

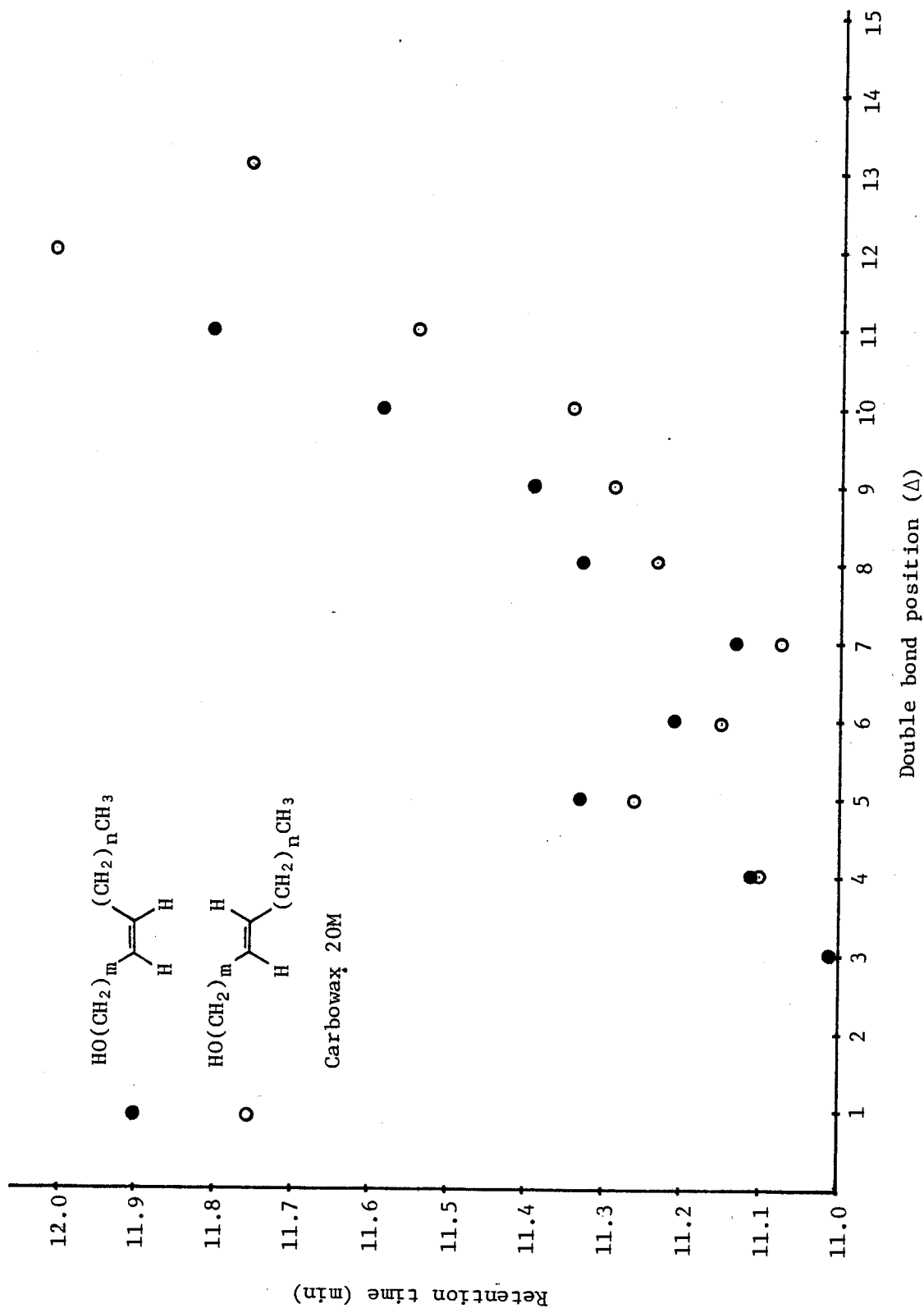
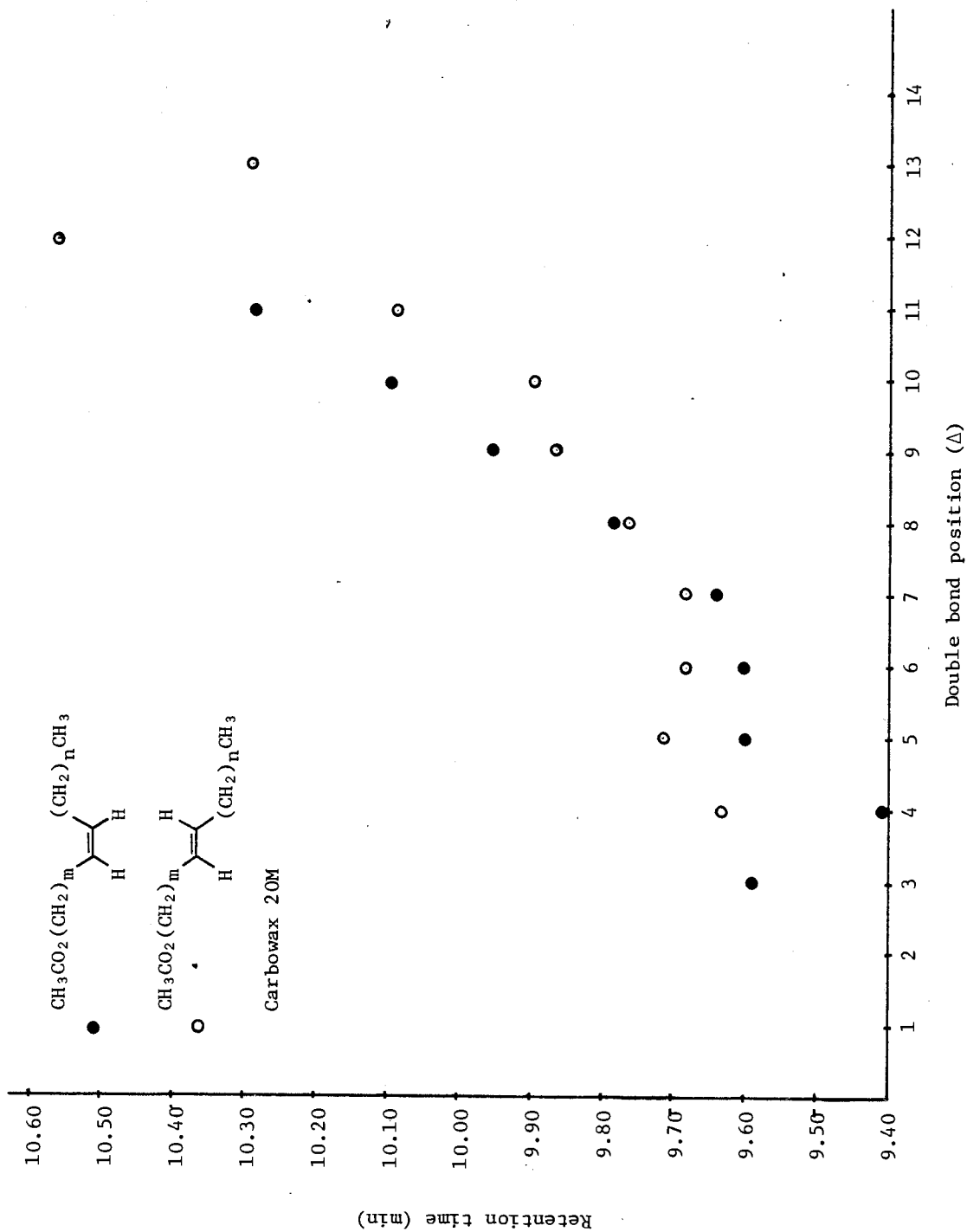


Figure 3

Plot of retention time (min) versus double bond position ( $\Delta$ ) of E- and Z-tetradecenyl acetates on a Carbowax 20M column. Conditions as given in Table 1.





determined on a Perkin-Elmer 599B spectrophotometer. Samples were run as a neat film on NaCl plates.  $^1\text{H}$  NMR spectra were recorded on a Varian EM-360 (60 MHz). Chemical shifts are reported in  $\delta$  units, referenced to an internal tetramethylsilane (TMS) standard and couplings are reported in Hertz (Hz). Splitting patterns are described as: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and combinations thereof. Low resolution mass spectra were obtained on a Hewlett-Packard 5985B coupled gas chromatograph-mass spectrometer. All samples were done using electron impact ionization (70 eV). Elemental analyses were performed on a Perkin-Elmer Model 240 elemental analyzer. All reactions requiring anhydrous and/or oxygen-free conditions were run under a positive pressure of nitrogen or argon in flame-dried glassware.

#### **8-Bromo-1-octanol (I-6)**

A mixture of 1,8-octanediol (I-5) (5 g, 34 mmol), 48% hydrobromic acid (25 mL) and  $\text{H}_2\text{O}$  (15 mL) was kept at  $90^\circ\text{C}$  and extracted continuously with hot heptane for 20 h. The heptane was then separated and washed with a 20% solution of potassium carbonate (30 mL), water ( $2 \times 30$  mL) and dried ( $\text{Na}_2\text{SO}_4$ ). The solution was concentrated in vacuo and the residue was chromatographed on silica gel with ether:petroleum ether ( $30-60^\circ$ ) (1:1) to give I-6 (6.2 g, 87%). IR (neat film)  $3340, 1055\text{ cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.10-1.50<sup>\*</sup>(m,10H), 1.60-2.0 (m,2H), 3.35 (t,2H,J=6.5), 3.52 (t,2H, J=6.0), 4.0 (s,1H,-OH, $\text{D}_2\text{O}$  exchangeable); mass spectrum, m/e (relative intensity) 164(31), 162(34), 148(39), 150(37), 83(58), 69(99), 55(100). Anal. calcd. for  $\text{C}_8\text{H}_{17}\text{OBr}$ : C, 45.95; H, 8.19. Found: C, 46.15; H, 8.39.

**8-Bromooctan-1-ol Tetrahydropyranyloxy Ether (I-7)**

A solution of I-6 (5.5 g, 26 mmol) and 3,4-dihydro-2H-pyran (2.22 g, 26.4 mmol) in hexane (20 mL) was added to a suspension of Amberlyst H-15, (H<sup>+</sup> form) (1.3 g, 5 meq) in hexane (20 mL) and the mixture was stirred for 2 h. The resin was then filtered off and the solvent removed in vacuo. The residue was chromatographed on silica gel with 1:2 ether-petroleum ether (30-60°) to yield I-7 (6.14 g, 79%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.1-2.0 (m, 18H), 3.1-4.0 (m, 6H), 4.5 (broad s, 1H).

**1-(Tetrahydropyranyloxy)-9-tetradecyne (I-8)**

To a stirred solution of 1-hexyne (1.6 g, 19 mmol) in dry tetrahydrofuran (20 mL) was added butyllithium (10 mL, 21 mmol) in hexane (15 mL) while keeping the temperature below -30°C. The bromide (5 g, 17.1 mmol) in hexamethylphosphoramide (20 mL) was added dropwise while keeping the temperature below -30°C. The reaction mixture was worked up within 3 h by pouring into a large volume of ice-water (300 mL) and extracting with hexane (2 × 30 mL). The organic layer was washed once with water (30 mL), once with brine (30 mL) and dried (Na<sub>2</sub>SO<sub>4</sub>). Evaporation of the solvent yielded an oil which was chromatographed on silica gel with 1:2 ether: petroleum ether (30-60°) to give I-8 (3.5 g, 70%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.88 (broad t, 3H, CH<sub>3</sub>-), 1.1-1.85 (m, 20H), 1.9-2.3 (m, 6H), 3.0-4.0 (m, 4H), 4.55 (broad s, 1H).

**1-(Tetrahydropyranyloxy)-(Z)-9-tetradecene (I-9)**

P-2 Nickel<sup>49</sup> was prepared via sodium borohydride reduction of Ni(C<sub>2</sub>H<sub>3</sub>O<sub>2</sub>)·4H<sub>2</sub>O (0.37 g, 1.5 mmol). The reaction flask was purged with hydrogen and ethylenediamine (0.2 mL, 3.4 mmol) was added, followed by the protected alkyne (1 g, 3.4 mmol). The reaction mixture was stirred at room

temperature under a positive hydrogen atmosphere for 2 hours, filtered through a layer of activated carbon, diluted with water and extracted with petroleum ether (30-60°) (3 × 20 mL). The combined organic extracts were washed with water (20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated under vacuum to give I-9 (0.89 g, 88%), after column chromatography on silica gel with 1:1 ether:petroleum ether (30-60°). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.7-1.0 (m, 3H, CH<sub>3</sub>-), 1.1-1.7 (m, 18H), 1.9-2.3 (m, 6H), 3.2-4.1 (m, 6H), 4.55 (broad s, 1H).

**(Z)-9-Tetradecenol (I-10)**

To a solution of tetrahydropyranyl ether (I-9) (0.8 g, 2.7 mmol) in methanol (20 mL), Amberlyst H-15 resin (0.3 g, 1 meq) was added and the mixture was stirred at 45° for 1 h. The resin was then filtered off and the solvent was removed in vacuo. The residue was then chromatographed on silica gel with 1:1 ether:petroleum ether (30-60°) to afford I-10 (0.49 g, 85%). IR (film) 3340, 3005, 1650, 1050 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.9 (broad t, 3H, CH<sub>3</sub>-), 1.1-1.6 (m, 16H), 1.7-2.1 (m, 4H), 2.65 (broad s, 1H), 3.55 (t, 2H), 5.3 (m, 2H); mass spectrum, m/e (relative intensity) 212(1), 194(33), 97(16), 96(54), 95(54), 81(100), 67(73), 55(57). Anal. calcd. for C<sub>14</sub>H<sub>28</sub>O: C, 79.18; H, 13.29. Found: C, 79.11; H, 13.59.

**(Z)-9-Tetradecenyl acetate (I-11)**

To a solution of alcohol I-10 (150 mg, 0.71 mmol) in dry pyridine (5 mL), acetic anhydride (0.3 mL, 3.6 mmol) was added and the mixture was stirred at room temperature for 2 h. The resultant mixture was quenched by pouring on ice and the mixture was extracted with hexane (3 × 10 mL). The hexane layer was washed with water (3 × 20 mL) and dried (Na<sub>2</sub>SO<sub>4</sub>). Evaporation of hexane, followed by azeotroping with toluene, afforded a residue which was chromatographed on silica gel with hexane to give I-11

(175 mg, 97%). IR (film) 3005, 1740, 1650, 1240  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.85 (broad t, 3H,  $\text{CH}_3$ -), 1.1-1.6 (m, 16H), 1.8-2.2 (m, 7H), 4.0 (t, 2H,  $J=6.5$ ), 5.35 (m, 2H); mass spectrum,  $m/e$  (relative intensity) 254(3), 211(4), 194(60), 96(60), 81(100), 67(65), 55(45), 43(40). Anal. calcd. for  $\text{C}_{16}\text{H}_{30}\text{O}_2$ : C, 75.54; H, 11.89. Found: C, 75.25; H, 12.20.

**(Z)-9-Tetradecenal (I-12)**

To a suspension of pyridinium chlorochromate (306 mg, 1.42 mmol) in anhydrous methylene chloride (10 mL), I-10 (150 mg, 0.71 mmol) in methylene chloride (5 mL) was added in one portion. The suspension was stirred for 2 h and dry ether (20 mL) was added, the supernatant was decanted from the black gum and the residue was extracted thoroughly with ether ( $3 \times 10$  mL). The combined organic layers were passed through a short pad of silica gel. Removal of the solvent in vacuo afforded pure I-12 (141 mg, 94%). IR (film) 3005, 2720, 1730, 1650  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.85 (m, 3H,  $\text{CH}_3$ -), 1.1-1.6 (m, 14H), 1.7-2.6 (m, 6H), 5.3 (m, 2H), 9.7 (t, 1H, CHO); mass spectrum,  $m/e$  (relative intensity) 210(2), 209(1), 192(11), 181(1), 135(15), 121(32), 98(59), 81(99), 67(86), 55(100), 41(57).

**1-(Tetrahydropyranyloxy)-(E)-9-tetradecene (I-13)**

To a stirred, refluxing solution of tetrahydropyranyl ether (I-8) (3 g, 10.1 mmol) in liquid ammonia (100 mL) and tetrahydrofuran (50 mL), sodium (700 mg) was added in two portions. Upon discharge of the blue colour, the ammonia was allowed to evaporate and saturated aqueous ammonium chloride (20 mL) was added cautiously. The resultant two-phase mixture was poured into hexane and washed with water (30 mL), brine (30 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo. Column chromatography on silica gel with 50% ether in petroleum ether (30-60°) gave I-13 (2.5 g, 83%).  $^1\text{H}$  NMR

(CDCl<sub>3</sub>)  $\delta$  0.7-1.0 (m, 3H, CH<sub>3</sub>-), 1.1-2.2 (m, 24H), 3.1-4.0 (m, 6H), 4.50 (broad s, 1H), 5.35 (m, 2H).

**(E)-9-Tetradecenol (I-14)**

This was prepared from I-13 in 80% yield as described for the preparation of I-10. IR (film) 3320, 3020, 965 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.83 (m, 3H, CH<sub>3</sub>-), 1.1-1.6 (m, 16H), 1.7-2.2 (m, 4H), 3.4-3.8 (m, 3H), 5.35 (m, 2H); mass spectrum, m/e (relative intensity) 212(1), 194(48), 97(18), 96(60), 95(63), 81(100), 67(70), 55(52), 41(23). Anal. calcd. for C<sub>14</sub>H<sub>28</sub>O: C, 79.18; H, 13.29. Found: C, 79.37; H, 13.54.

**(E)-9-Tetradecenyl acetate (I-15)**

This was prepared from I-14 in 92% yield as described for the preparation of I-11. IR (film) 3020, 1740, 1235, 965 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.9 (m, 3H, CH<sub>3</sub>-), 1.1-1.7 (m, 16H), 1.8-2.2 (m, 7H), 4.04 (t, 2H), 5.35 (m, 2H); mass spectrum, m/e (relative intensity) 211(4), 194(70), 96(65), 81(100), 67(65), 55(44), 43(40). Anal. calcd. for C<sub>16</sub>H<sub>30</sub>O<sub>2</sub>: C, 75.54; H, 11.89. Found: C, 75.48; H, 12.20.

**(E)-9-Tetradecenal (I-16)**

This was prepared from I-14 in 90% yield as described for the preparation of I-12. IR (film) 3020, 2720, 1720, 970 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.85 (m, 3H, CH<sub>3</sub>-), 1.1-2.7 (m, 20H), 5.35 (m, 2H), 9.7 (t, 1H, CHO); mass spectrum, m/e (relative abundance) 210(1), 209(1), 192(6), 135(13), 121(27), 98(56), 81(95), 67(87), 55(100), 41(63).

IV. ISOLATION AND IDENTIFICATION OF PHEROMONE COMPONENTS I-1-I-4 and I-17

Identification of compounds I-1-I-4 and I-17 was accomplished by chromatographic and gc-mass spectral analyses of individual female ovipositor washes and extracts of several tips with comparison to synthetic standards. Preliminary studies of a limited number of individual ovipositors of calling-females by splitless capillary gas chromatography analysis indicated the presence of several components, present only in calling-females. Three of these materials had retention times comparable to (E)-11-tetradecenyl acetate (I-1), (E)-11-tetradecenol (I-2) and tetradecyl acetate (I-3), in the ratio of 20:1:1. Further analysis of abdominal tip extracts of calling-females by splitless capillary gas chromatography showed the presence of a fourth component, in addition to the three compounds previously observed (Fig. 4). The retention parameters of this fourth component indicated the presence of (E)-11-tetradecenal (I-4). The average amounts of all four components in female tip rinses were: (E)-11-14:OAc (11 ng), (E)-11-14:OH (1.5 ng), 14:OAc (1 ng), (E)-11-14:Al (0.2 ng), corresponding to ratios of 100:15:10:2, respectively. Extracts showed enhanced aldehyde levels after several days at the expense of other components; typically, 14:Al (3 ng), (E)-11-14:Al (8 ng), (E)-11-14:OAc (1.5 ng) and (E)-11-14:OH (1.3 ng) (Fig. 5). The appropriate components in these extracts gave mass spectra identical to standard tetradecanal and (E)-11-tetradecenal on gas chromatography mass spectrometry. Mass spectra of the four components of a tip extract were consistent with assignments made on the basis of retention times. In addition, a small amount of tetradecyl alcohol was detected.

Figure 4

Gas liquid reconstructed chromatogram of a heptane wash of C. salicella tips (DB-1 capillary column). Numbers designate compounds I-1, I-2, I-3 and I-4.

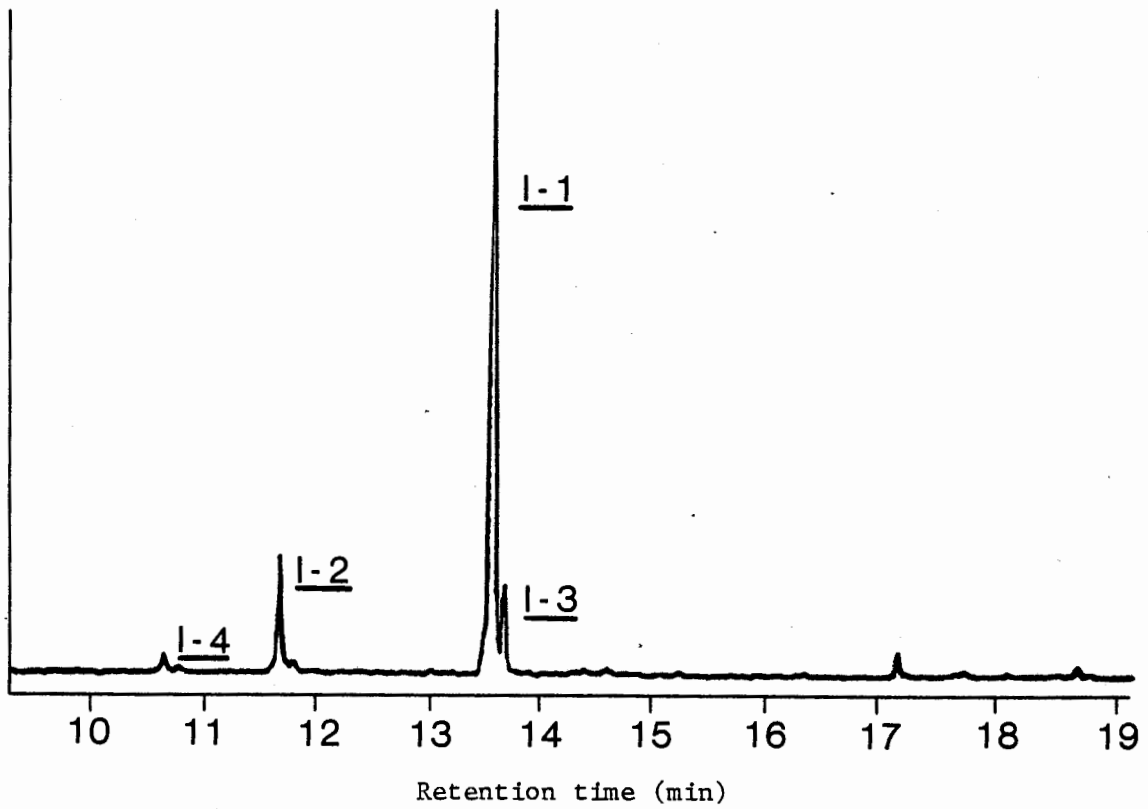
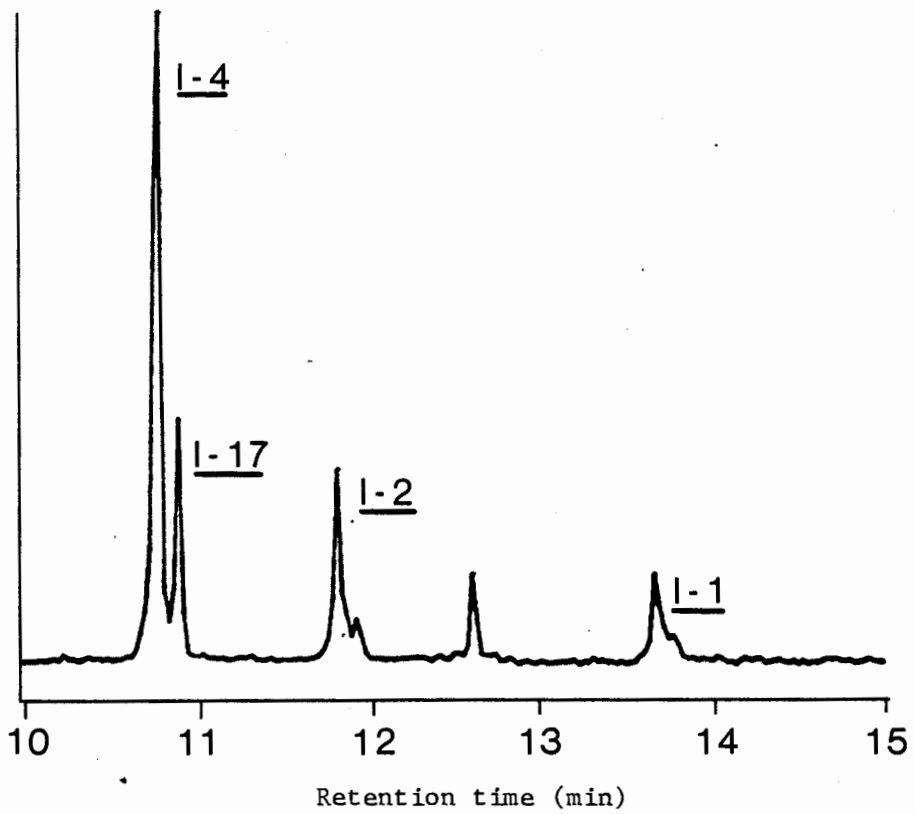




Figure 5

Gas liquid reconstructed chromatogram of a 6-day heptane extract of C. salicella tips (DB-1 capillary column). Numbers designate compounds I-1, I-2, I-3, I-4 and I-17.



A. Identification of (E)-11-Tetradecenyl Acetate (I-1)

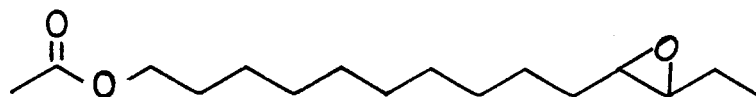
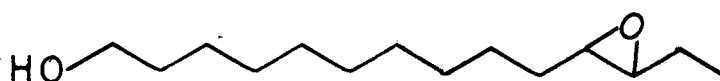
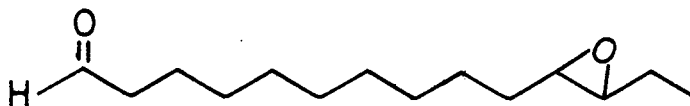
Preliminary examination of the gas chromatogram (Fig. 4) and the mass spectra of the four components of a tip wash of Cheimophila salicella revealed that the major component had a retention time and fragmentation pattern consistent with assignments made on the basis of retention times. A weak but discernible molecular ion peak at m/e 254 for a possible molecular formula of  $C_{16}H_{30}O_2$  with two sites of unsaturation was observed. Fragments at m/e 194 (M-60) and at m/e 61 (M-193) were the result of a McLafferty and a McLafferty + 1 rearrangement<sup>57</sup>, respectively, suggesting the presence of an acetate. A peak at m/e 69 (M-185) suggested allylic cleavage but the unequivocal position of the double bond of I-1 was determined by examination of the gc-ms of its epoxide (I-18) (Fig. 6). This showed the first significant fragment to be at m/e 241 (M-29), corresponding to the loss of a  $C_2H_5$  unit, characteristic of  $\alpha$ -cleavage between carbons 12 and 13. Also, a peak at m/e 71 (M-199), corresponding to the other  $\alpha$ -cleavage between carbons 10 and 11, showed elevated intensity, confirming the position of the double bond between C-11 and C-12. The spectra of I-1 and I-18 were identical in retention and fragmentation characteristics to authentic standards of these materials.

B. Identification of (E)-11-Tetradecenol (I-2)

Analysis of the gc-ms of a concentrated heptane extract of abdominal tips showed a significant fragment at m/e 194 (M-18), corresponding to the loss of water, and suggested a molecular formula of  $C_{14}H_{28}O$ , with one site of unsaturation. The position of the double bond in I-2 was ascertained by examination of the gc-ms of its epoxide (I-19) in the extract. A noticeable peak at m/e 199 (M-29), corresponding to the loss of  $C_2H_5$ , was

Figure 6

Structures of compounds I-18-I-20.

1-181-191-20

indicative of  $\alpha$ -cleavage. The other  $\alpha$ -cleavage fragment at m/e 71 (M-157) also showed elevated intensity. The peak at m/e 199 (M-29) suggested a molecular formula of  $C_{14}H_{28}O_2$  for the epoxide of (I-2), with one site of unsaturation, and confirmed an increase of 16 mass units. Comparison of the gc-ms of I-2 and I-19 with those of the standards indicated them to be identical, corroborating early assignments on the basis of retention times.

C. Identification of (E)-11-Tetradecenal (I-4)

Molecular ions of long chain aldehydes seldom give recognizable peaks, rather (M-18), corresponding to a loss of water, is most often the highest mass observed. Comparison of the gc-ms of a heptane extract of C. salicella tips showed a spectrum identical to and at the same retention time as standard (E)-11-tetradecenal, with a diagnostic peak at m/e 192 (M-18), indicative of the presence of compound I-4 in the extract. An examination of the gc-ms of an epoxidized extract showed a peak whose retention and fragmentation were identical to standard trans-11,12 epoxy tetradecanal. The first significant high mass fragment was at m/e 197 (M-29), corresponding to loss of an ethyl fragment, in accordance with the  $\alpha$ -cleavage of epoxy aldehyde I-20. A peak at m/e 71 (M-155), corresponding to the other  $\alpha$ -cleavage, confirmed the epoxide position and therefore the location of the double bond.

D. Identification of Tetradecyl Acetate (I-3)

The gc-ms of tip washes revealed a small peak whose retention was identical to tetradecyl acetate. The mass spectrum of this substance had low intensity peaks at m/e 241 (M-15), corresponding to loss of  $CH_3$ , and at m/e 213 (M-43), corresponding to loss of  $CH_3CO$ , in keeping with a molecular

formula of  $C_{16}H_{32}O_2$ , with one site of unsaturation. A peak at m/e 196 (M-60), corresponding to loss of acetic acid, and a distinct peak at m/e 61 corroborates the structure of a 14-carbon acetate. No reaction of this component was observed under epoxidation conditions. This information is consistent with tetradecyl acetate and was identical to that obtained for a standard sample of tetradecyl acetate.

E. Identification of Tetradecanal (I-17)

Splitless capillary gas chromatographic analysis of C. salicella extracts, after several days, indicated the presence of a compound with a retention time corresponding to that of standard tetradecanal. The gc-ms of this substance showed peaks at m/e 168 (M-44), due to a McLafferty rearrangement<sup>57</sup> with charge migration, and at m/e 169 (M-43), corresponding to  $\beta$ -cleavage, suggesting a molecular formula of  $C_{14}H_{28}O$ , with one site of unsaturation.

## V. RESULTS AND DISCUSSION

### A. Gas Chromatograph-Mass Spectral Analyses

Analysis of individual female abdominal tip washes and extracts of several tips by splitless capillary gas chromatography, utilizing either polar Carbowax 20M or apolar methyl silicone columns, revealed the presence of several components present only in C. salicella females. Retention characteristics of the individual components, as compared to standards, indicated the presence of E-11-14:OAc (I-1), E-11-14:OH (I-2), 14:OAc (I-3) and E-11-14:Al (I-4), in the relative ratios of 100:15:10:2, respectively. A good correspondence was obtained for retention times of the components of the epoxidized insect extracts as compared to epoxidized tetradecenyl standards (Table 2). Mass spectra of the four components of a tip wash extract were consistent with assignments made on the basis of retention times. The double bond position in the appropriate components was unequivocally established by gc-mass spectral analysis of the epoxide derivatives<sup>58,59</sup>. Analysis of untreated and epoxidized female extracts on the DB-1 column demonstrated that the Z-isomers occur at <1% of E isomers, if at all.



Standards	t (min)	Epoxidized Tip Wash	t (min)	Epoxidized 6-Day Extract	t (min)
(14:Al)	15.60			(14:Al)	15.54
(Z-11-14:Al)	16.79				
(E-11-14:Al)	16.33			(E-11-14:Al)	16.33
(14:OAc)	19.58	(14:OAc)	19.41		
(14:OH)	21.37	(14:OH)	21.18		
(E-11-epox-14:Al)	26.52			(E-11-epox-14:Al)	26.50
(Z-11-epox-14:Al)	27.19				
(E-11-epox-14:OAc)	32.47	(E-11-epox-14:OAc)	32.47	(E-11-epox-14:OAc)	32.43
(Z-10-epox-14:OAc)	33.54				
(E-11-epox-14:OH)	35.09	(E-11-epox-14:OH)	35.16	(E-11-epox-14:OH)	35.06
(Z-10-epox-14:OH)	36.12				
(Z-11-epox-14:OH)	36.66				

Table 2. Chromatographic retention times of epoxidized extracts and standards. GC conditions: 50 m Carbowax 20M, 0.2 mm i.d., He carrier, splitless mode, 40°C for 2 min, 30°C/min to 150°C, then 2°C/min to 210°C.

VI. FIELD TEST PROCEDURES

Bait mixtures were applied in heptane inside rubber septa (Arthur H. Thomas, No. 8753-D22), mounted on insect pins. Virgin females were contained singly within vials (2.8 × 7.2 cm) screened at both ends. Baits and caged females were placed inside traps, which were, in one test, 2 L milk cartons open at the ends and coated inside with Stickem Special (Michael and Pelton Ltd., Emeryville, Calif.) and were, in other tests, 15 × 30 cm cards coated similarly, folded in thirds and fastened to form a triangular tube, 10 cm on a side and 15 cm long. Traps were suspended from blueberry bushes 0.6 to 0.9 m above the ground at different sites in Pitt Meadows, B.C.

The effects of bait mixtures on trap catches of male C. salicella was tested in four separate experiments. In experiment 1, treatments were: (E)-11-tetradecenyl acetate (E-11-14:OAc) (100 µg); (E)-11-tetradecenol (E-11-14:OH) (5 µg); tetradecyl acetate (14:OAc) (5 µg):E-11-14:OAc (100 µg); and E-11-14:OH (5 µg):E-11-14:OAc (100 µg):E-11-14:OH (100 µg):a heptane control. Milk carton traps were dispersed in a 5 × 5 Latin square with 18 m between rows and 30 m between columns. Trapping was carried out from 21-23 March, 1981. In experiment 2, treatments were: E-11-14:OAc (100 µg); E-11-14:OH (15 µg); 14:OAc (10 µg); (E)-11-tetradecenol (E-11-14:Al) (2 µg):E-11-14:OAc (100 µg); E-11-14:OH (15 µg); 14:OAc (10 µg):E-11-14:OAc (100 µg); E-11-14:OH (15 µg):a single, caged virgin female; and a heptane control. Triangular traps were dispersed in a 10-replicate randomized block experiment with 30 m between traps. Trapping was carried out from 15-17 March, 1983.

The activity of minor components was compared in experiment 3. Baits

were: E-11-14:Al (100 µg); 14:OAc (100 µg):E-11-14:OAc (100 µg); E-11-14:OH (15 µg); 14:OAc (10 µg); and E-11-14:Al (2 µg):a heptane control. Triangular traps were dispersed in a 10-replicate randomized block experiment with 15 m between traps. Trapping was carried out from 17-19 March, 1983.

In experiment 4, the effect of bait loading on response of males to traps was determined using a mixture of E-11-14:OAc, E-11-14:OH:14 and OAc, in a 20:1:1 ratio. Bait loads were: 1000:50:50 µg; 100:5:5 µg and 10:0.5:0.5 µg. A bait containing E-11-14:OAc (100 µg) and E-11-14:OH (5 µg) without 14:OAc and a heptane control was also included. Triangular traps were dispersed in a 10-replicate randomized block experiment with 15 m between traps. Trapping was carried out from 26-28 March, 1981.

Constraints were imposed on the design of individual experiments by the layout of the blueberry fields. Thus, inter-trap distances varied between experiments. Trapping was carried out during brief periods of relatively clear, rain-free weather and, thus, trapping periods tend to be of short duration (2-3 days).

#### A. Field Test Results

In the first field test of compounds identified in the extracts of calling females of C. salicella (Table 3, Expt. 1), E-11-14:OAc was attractive alone. Addition of E-11-14:OH (which was not attractive alone) caused an apparent rise in response, whereas further addition of 14:OAc caused the ternary mixture to be significantly more attractive than E-11-14:OAc alone. In experiment 2 (Table 3), addition of E-11-14:Al to the attractive ternary mixture resulted in a four-component blend that was considerably more attractive than single virgin females. The relatively low trap catch

Table 3. Captures of male Chēmophila salicella in four experiments in response to various treatments at Pitt Meadows, B.C.

Experiment No.	Date	No. of Replicates	Bait ( $\mu$ g)	Mean No. Males/Trap <sup>a</sup>
1	21-23 March 1981	5	E-11-14:OAc (100)	11.8a
			E-11-14:OH (5)	
			14:OAc (5)	
			E-11-14:OAc (100)	
			E-11-14:OH (5)	
2	15-17 March 1983	10	E-11-14:OAc (100)	59.4a
			E-11-14:OH (15)	
			14:OAc (10)	
			E-11-14:Al (2)	
			E-11-14:OAc (100)	
3	17-19 March 1983	10	E-11-14:OH (15)	0.9c
			14:OAc (10)	
			E-11-14:OAc (100)	
			E-11-14:OH (15)	
			E-11-14:OAc (100)	
3	17-19 March 1983	10	E-11-14:OAc (100)	0.0a
			E-11-14:OH (15)	
			14:OAc (100)	
			E-11-14:Al (2)	
			single virgin female	
3	17-19 March 1983	10	E-11-14:OAc (100)	0.0c
			E-11-14:OH (15)	
			14:OAc (10)	
			E-11-14:Al (2)	
			control (blank)	
3	17-19 March 1983	10	E-11-14:OAc (100)	0.0a
			E-11-14:OH (15)	
			14:OAc (10)	
			E-11-14:Al (2)	
			control (blank)	
3	17-19 March 1983	10	E-11-14:OAc (100)	4.3b
			E-11-14:OH (15)	
			14:OAc (10)	
			E-11-14:Al (2)	
			control (blank)	

Table 3 (Cont'd)

Experiment No.	Date	No. of Replicates	Bait ( $\mu\text{g}$ )		Mean No. Males/Trap <sup>a</sup>
			control	(blank)	0.0a
4	26-28 March 1981	10	E-11-14:OAc	(10)	
			E-11-14:OH	(0.5)	
			14:OAc	(0.5)	9.3a
			E-11-14:OAc	(100)	
			E-11-14:OH	(5)	
			14:OAc	(5)	8.4a
			E-11-14:OAc	(100)	
			E-11-14:OH	(5)	6.2ab
			E-11-14:OAc	(1000)	
			E-11-14:OH	(50)	
			14:OAc	(50)	3.5b
			control	(blank)	0.0c

<sup>a</sup> For all experiments, ANOVA  $P < 0.05$ . Means for each experiment followed by the same letter are not significantly different, Fisher's L.S.D.,  $\alpha = 0.05$ .

of the ternary mixture, in comparison to the quaternary, emphasizes the importance of the aldehyde as a synergist. However, traps baited with the binary mixture of E-11-14:OAc plus E-11-14:OH or the ternary mixture of E-11-14:OAc, E-11-14:OH and 14:OAc captured no more males than the blank (control) traps. The E-11-14:Al and 14:OAc were inactive when tested alone (Table 3, Expt. 3). For the ternary mixture of E-11-14:OAc, E-11-14:OH and 14:OAc, high attractant loadings of 1000  $\mu\text{g}$  of E-11-14:OAc resulted in significantly fewer males captured than in traps with 10 and 100  $\mu\text{g}$  of E-11-14:OAc (Table 3, Expt. 4).

#### B. Data Analysis

Variances in all experiments were significantly heterogenic (Bartlett's and Hartley's tests,  $\alpha = 0.05$ ) and the data were in the form of counts with some 0's. Therefore, a square root plus 0.5 transformation was applied to all counts<sup>60</sup>, correcting the heterogeneity of variance. Transformed data were subjected to ANOVA. Multiple comparisons between treatment means were made using Fisher's L.S.D. ( $\alpha = 0.05$ ). Data are presented as mean number of males caught per trap.

VII. CONCLUSIONS

The results indicate that the primary component in the pheromone blend is E-11-14:OAc. Its activity is enhanced by the addition of E-11-14:OH and 14:OAc and strongly synergized by the presence of E-11-14:Al, none of which is attractive alone. Thus, the female-produced sex pheromone of C. salicella (Hbn) is a blend of E-11-14:OAc, E-11-14:OH, 14:OAc and E-11-14:Al and is found in tip rinses in the ratio of about 100:15:10:2. This blend provides an effective pheromone lure. It is possible that, as in other moths, e.g. Grapholita molesta<sup>61</sup>, the three minor components may function in aspects of sexual communication other than attraction. At present, C. salicella is restricted in North America to the lower Fraser Valley of British Columbia. A pheromone can be used to detect spread of the population, to monitor local populations in blueberry fields as part of pest management programs and to disclose introductions of this pest into other blueberry-growing areas of North America.

Attraction of male Cheimophila sp. to traps baited with E-11-14:OAc has been reported by Ando et al.<sup>40</sup>. The synergistic effect of minor components, especially the aldehyde, serves to emphasize the importance of minor components in the semiochemical communication of insects. This first investigation of the pheromone complex of a member of the Oecophoridae has implications for other members of this family; e.g., the parsnip webworm, Depressaria pastinacella (Duponchel), the brown house moth, Hofmannophila pseudopretella (Stainton), and the white-shouldered house moth, Endrosis sarcitrella (L.).

**CHAPTER II - CHIRAL SYNTHESIS OF THE SEX PHEROMONE OF THE JAPANESE BEETLE,****Popillia japonica (Newman),****(R)-(-)-(Z)-5-(1-Decenyl)-dihydro-2(3H)-furanone****I. INTRODUCTION**

The development of asymmetric syntheses of chiral lactones, to be used as synthons or as target molecules, has received increasing attention from both chemical<sup>62-65</sup> and enzymatic directions<sup>66,67</sup>.

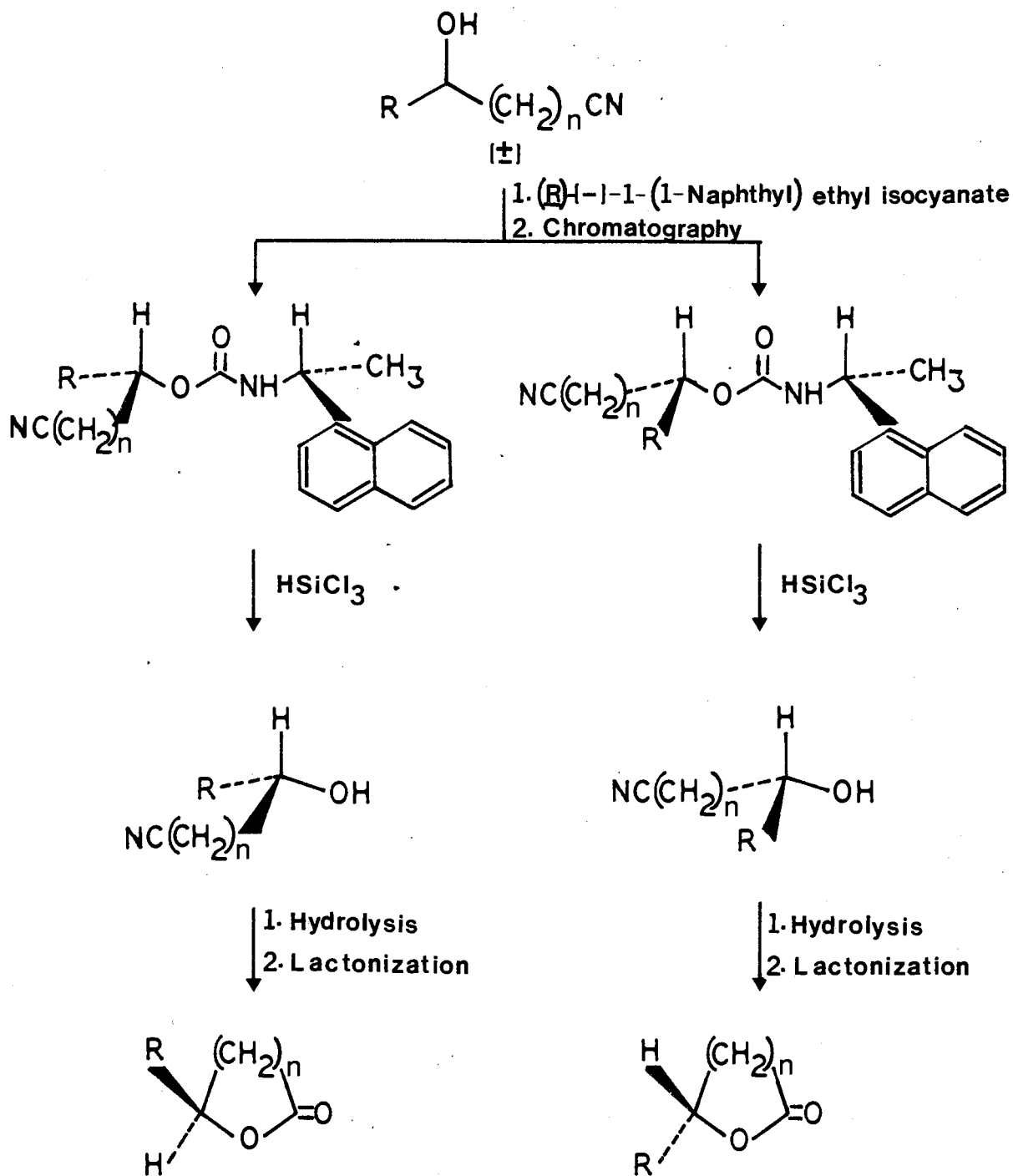
$\gamma$ -Lactones substituted at the 4-position are often found in nature as pheromonal constituents<sup>68,69</sup>. Synthetic approaches to such compounds can be grouped into four major categories: a) routes that involve chiral resolution of an appropriate intermediate; b) routes that utilize optically-active starting materials; c) asymmetric syntheses that are initiated with a suitable precursor; and d) routes that involve enzymatic approaches.

**a) routes that involve chiral resolution of an appropriate intermediate**

In the first category, Pirkle et al.<sup>70,71</sup> used racemic cyano alcohols, which were easily converted to diastereomeric cyano carbamates by reaction with a suitable resolving agent (Scheme 2). Separation of the diastereomers by automated liquid chromatography and retrieval of the chiral cyano alcohols led, after appropriate manipulations, to  $\gamma$ -lactone enantiomers. The major advantage of this methodology is that both enantiomers of a substance are obtained when needed for purposes of comparison and testing. Sato et al.<sup>72</sup> resolved acetylenic alcohol half ester phthalates by recrystallization of their salts formed with chirally-pure



Scheme 2



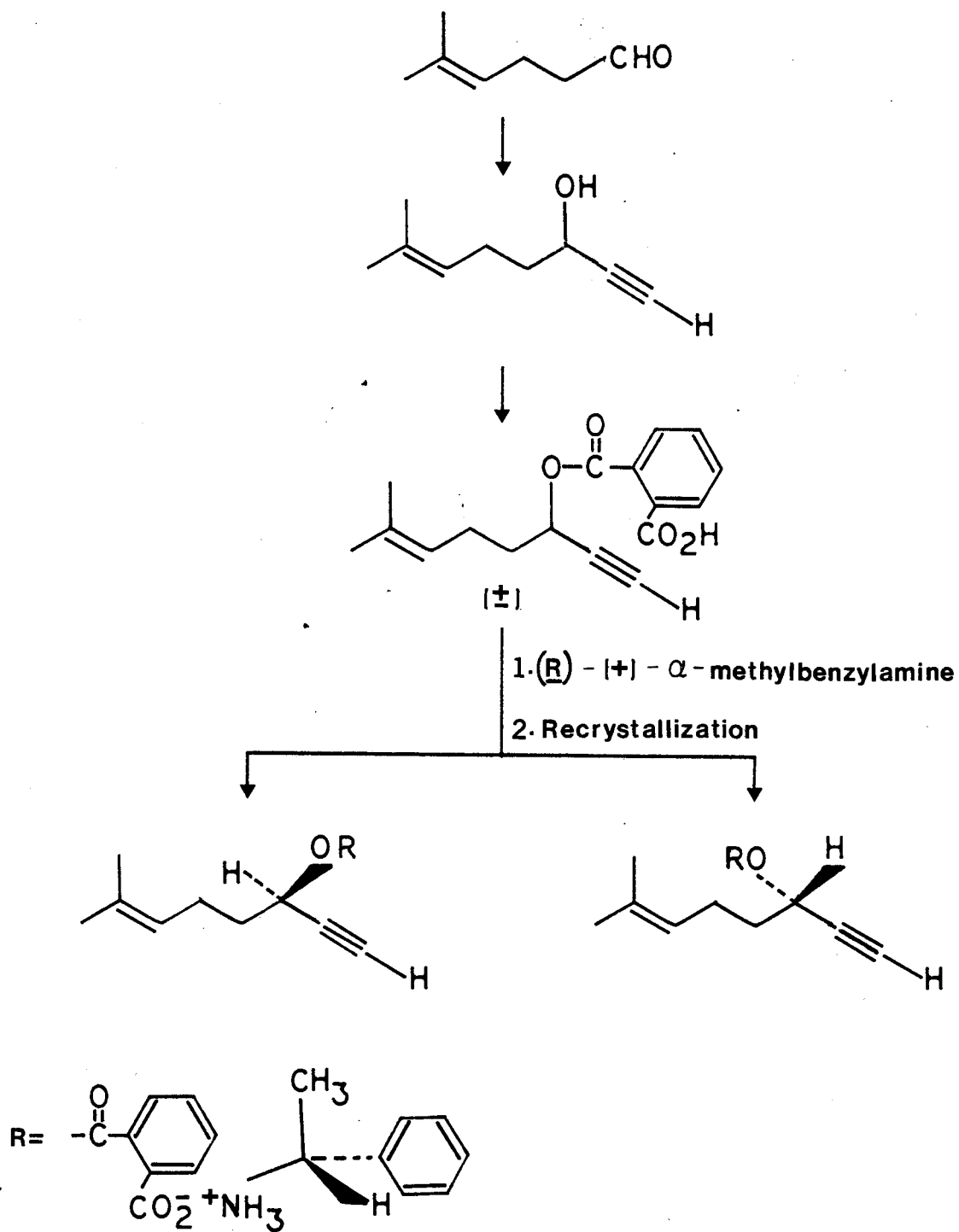
$\alpha$ -methylbenzylamine. The resolved acetylenic alcohols were used to develop a route to the pheromone of the Japanese beetle, Popillia japonica (Newman)<sup>73</sup>, (-)-(II-1), and its enantiomer, (+)-(II-1). The limited availability of both the phthalate half ester and the expensive resolving agent constitute the major drawbacks of this approach (Scheme 3).

The successful resolution of even simple organic compounds, involving crystallization techniques, is occasionally difficult to achieve. Salt-forming, acid-base reactions are central to such processes. Resolutions have been considered to be complete when crystalline enantiomers or precursor diastereomers are unchanged in melting point or rotation upon further crystallization and when the two enantiomers are obtained in states of equal optical purity. These criteria of optical purity have gained general acceptance but they are not completely reliable, as has been pointed out by Eliel<sup>74</sup> and by Raban and Mislow<sup>75</sup>.

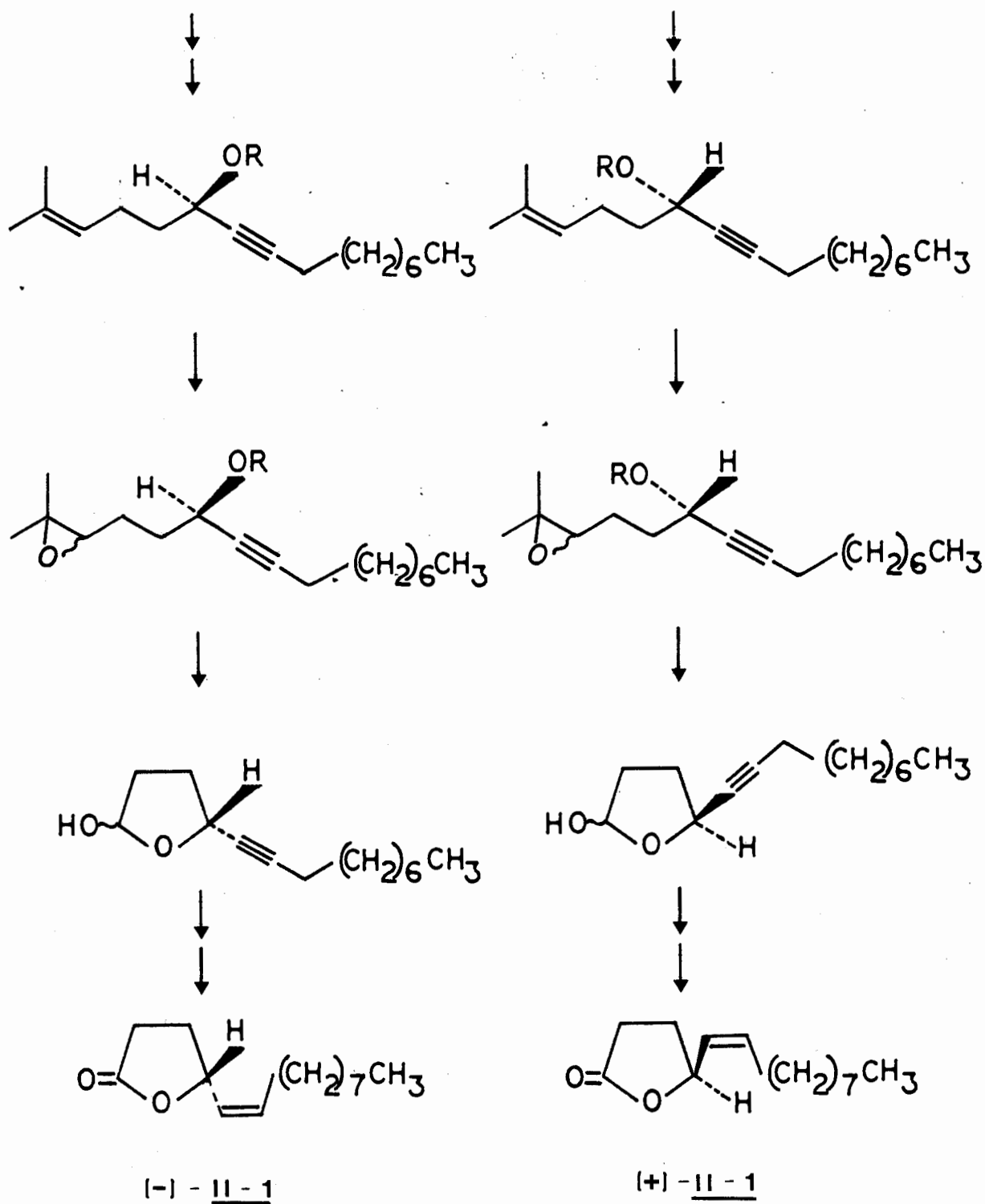
**b) routes that utilize optically-active starting materials**

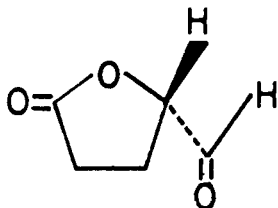
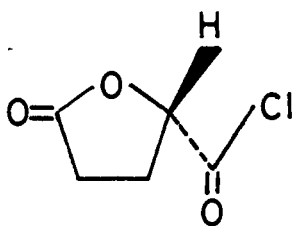
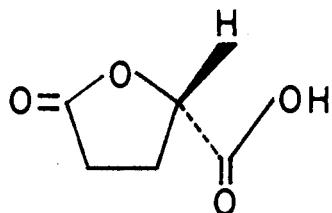
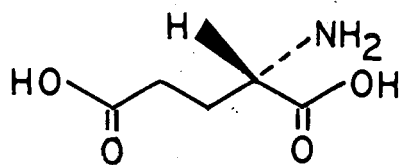
In the second category, utilizing optically-active precursors, natural (S)-(+)-glutamic acid and its enantiomer have been used by stereospecific deamination to yield the  $\gamma$ -butyrolactone- $\gamma$ -carboxylic acid intermediates<sup>76,77</sup>. The synthesis of  $\gamma$ -lactone enantiomers, e.g. the sex pheromone of the female Japanese beetle<sup>73</sup> and the pheromone components of a Dermestid beetle, Trogoderma glabrum<sup>77</sup>, has been achieved using these intermediates, as shown in Scheme 4. This approach relies on the conversion of glutamic acid to the  $\gamma$ -lactone- $\gamma$ -carboxylic acid, proceeding with complete retention of configuration<sup>78-82</sup>. Anchimeric assistance by the carboxyl group adjacent to the departing dinitrogen molecule, followed by intramolecular participation of the carboxylic acid group, has been

## Scheme 3



## Scheme 3 (Cont'd)



Scheme 4

(+) - II - 1

detailed as the mechanism for this reaction.

Optically-active  $\delta$ -hydroxy- $\gamma$ -valerolactone derivatives have also been extensively used as key chiral building blocks<sup>83</sup> in the synthesis of naturally-occurring substances such as carbohydrates, terpenes, lignans and alkaloids. Both lactone enantiomers have been obtained from glutamic acid through stereospecific deamination. The utility of natural (S)-(+)-glutamic acid as a starting material<sup>76</sup> has been expanded by the inversion reaction developed by Mitsunobu and coworkers<sup>83,84</sup>. Conversion of (S)-(+)-glutamic acid to (S)-(+)- $\delta$ -hydroxy- $\gamma$ -valerolactone, followed by protection of the  $\delta$  hydroxy group, afforded a convenient precursor for lactone hydrolysis and inversion of configuration at the  $\gamma$ -position, using diethylazodicarboxylate (DEAD) and triphenylphosphine (TPP). The use of the less available, unnatural (R)-(-)-glutamic acid can thus be avoided.

$\delta$ -Hydroxy- $\gamma$ -valerolactone intermediates have also been accessible through butenolides<sup>85</sup>. Camps et al.<sup>86</sup> have described the preparation of (S)-5-hydroxymethyl-(5H)-furan-2-one from D-ribonolactone.

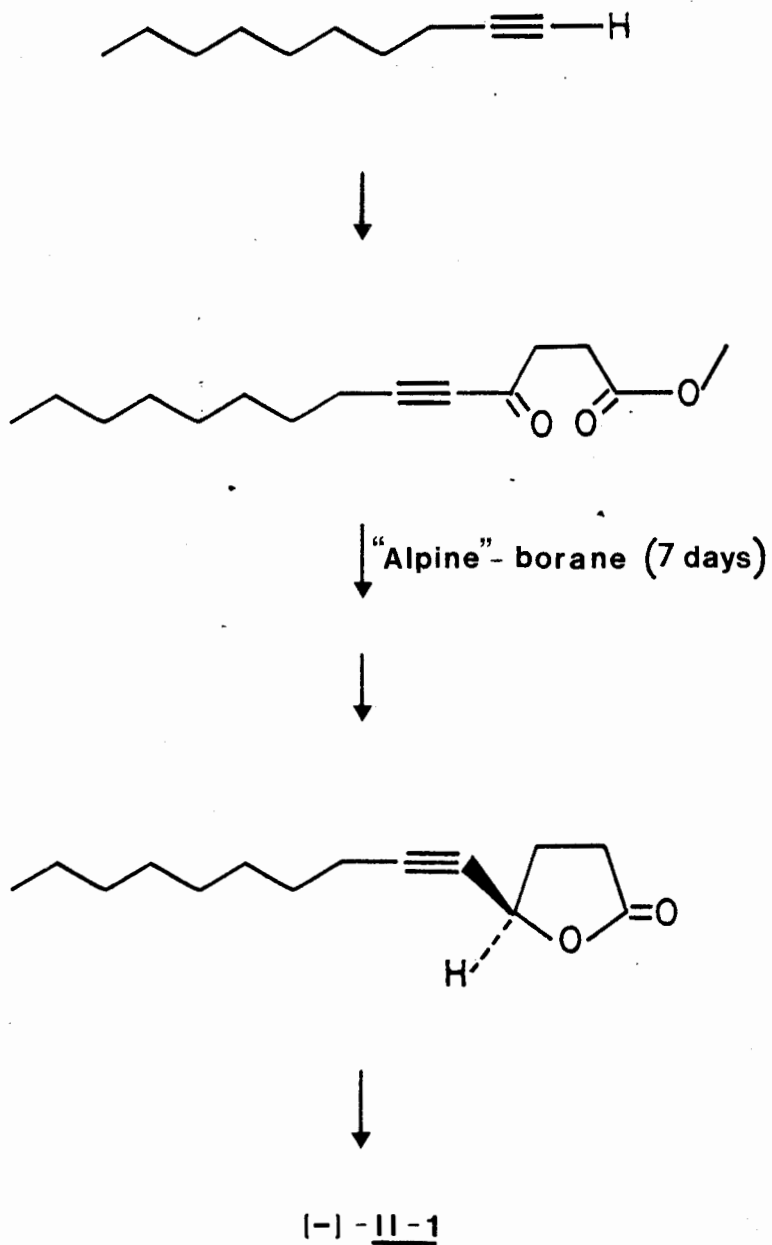
**c) asymmetric syntheses that are initiated with a suitable precursor**

In the third category, asymmetric syntheses of suitable chiral intermediates obtained by the use of asymmetric reducing agents have been employed. Vigneron and Bloy<sup>87</sup> prepared optically-active 4-alkyl- $\gamma$ -lactones from optically-active propargyl carbinols which, in turn, were prepared by asymmetric reduction of  $\alpha$ -acetylenic ketones. The chiral complex formed between lithium aluminum hydride, chiral *N*-methylephedrine and 3,5-dimethylphenol was used as the reducing agent. Carbonation of the chiral acetylenic alcohols, followed by catalytic hydrogenation and cyclization, gave the appropriate lactones. A similar approach by Midland and

coworkers<sup>88,89</sup> has been used, in which the chiral centre was introduced by asymmetric reduction of either  $\alpha,\beta$ -acetylenic ketones or 4-oxo-2-alkynoates with B-3-pinanyl-9-borabicyclo[3.3.1]nonane ("Alpine" borane). Hydrogenation of the 4-hydroxy-2-alkynoates and acid-catalyzed lactonization gave the chiral products. Alternatively, partial catalytic hydrogenation of optically-active 4-hydroxy-2-alkynoates, followed by acid-catalyzed cyclization, afforded butenolides<sup>88,89</sup>. Conjugate reduction with copper hydride<sup>90</sup> has also led to the saturated  $\gamma$ -lactones. The propargyl ketone precursors for these syntheses have been conveniently prepared by nucleophilic acyl displacement of acid chlorides with acetylides, using the procedure of Normant<sup>91</sup> or House and coworkers<sup>92</sup>. Nishizawa *et al.*<sup>93</sup> used a complex aluminum hydride, modified by chiral 2,2'-dihydroxy-1,1'-binaphthyl ("BINAL"-H), to asymmetrically reduce alkynyl ketones, which were further elaborated to chiral  $\gamma$ -lactones. The recovery of the chiral auxiliary ligand, without loss of optical purity, has been claimed for these asymmetric reductions<sup>93</sup>. The general methodology of these approaches is shown in Scheme 5, applied to the synthesis of Japonilure<sup>73</sup>, (-)-(II-1), by Midland and coworkers<sup>88,89</sup>. A very high optical purity has been claimed for this synthesis<sup>89</sup>. The disadvantages to this approach reside in the availability of the chiral ligand in high optical purity and the long reaction times necessary with this borane reagent<sup>94</sup>.

#### d) routes that involve enzymatic approaches

In the fourth category, the stereoselectivity of enzymatic reactions has been attempted, with generally poor results, to produce optically-active alkyl alkynylcarbinols from the corresponding racemic acetates. Akao and Mori<sup>95</sup> used Bacillus subtilis var. Niger to asymmetrically

Scheme 5



hydrolyze a variety of racemic alkyl alkynyl acetates. The bacterium preferentially hydrolyzes (S)-acetates, giving the corresponding alcohols in varying optical yields. This methodology appears to be limited by the size and nature of the alkyl groups in the acetates and the optical purity of the product.

The usefulness of sugars as sources of known chirality has been discussed<sup>96,97</sup> and the concept of chiral templates is well established<sup>96</sup>. Most efforts have been focused on sugars such as D-ribose and D-glucose. To date, no chiral template approach for the synthesis of the pheromone of the Japanese beetle, (-)-(II-1), and its enantiomer, (+)-(II-1), has been attempted.

The Japanese beetle is a notorious pest in the eastern part of the U.S.A.<sup>73</sup> and pheromone-baited traps offer some control possibilities. The pheromone was isolated from virgin females by Tumlinson *et al.*<sup>73</sup> and was shown to be (-)-(R,Z)-5-(1-decenyl)-dihydro-2(3H)-furanone, (-)-(II-1). The importance of chirality in the biological activity of the sex pheromone produced by the female beetle has been clearly demonstrated. As little as 1% of the (+)-(S,Z) isomer, (+)-(II-1), can significantly reduce the response of male beetles to traps baited with (-)-(R,Z) isomer<sup>73</sup>.

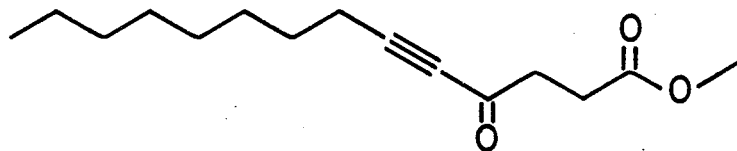
Both enantiomers of this pheromone were originally synthesized by Tumlinson *et al.*<sup>73</sup> from both glutamic acids, using a Wittig reaction to construct the olefinic linkage, as shown in Scheme 4. Sato *et al.*<sup>72</sup> prepared both enantiomers of II-1 by resolution of propargyl alcohol intermediates (Scheme 3) but the optical purity of both enantiomers was lower than that achieved in the first synthesis by Tumlinson<sup>73</sup>. Pirkle and coworkers<sup>70</sup> used resolution of cyano alcohols to prepare both enantiomers

(Scheme 2). The rotations of the final products were in agreement with those obtained by Tumlinson<sup>73</sup>. Midland et al.<sup>88,89</sup> prepared the biologically-active enantiomer in 97% optical purity using chiral  $\alpha$ -pinene<sup>98,99</sup> to generate the asymmetric reducing agent (Scheme 5). Nishizawa et al.<sup>93</sup> also reported the synthesis of the biologically-active enantiomer by asymmetric reduction of an alkynyl ketone, as shown in Scheme 6. The optical purity of the compound was reported to be 75%.

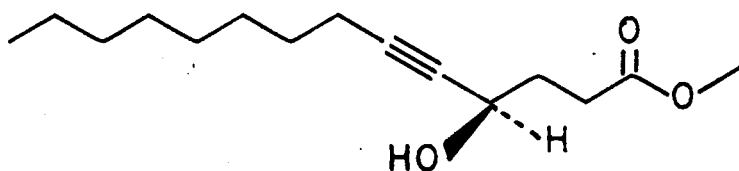
### Objective

The objective of this work was to explore the utility of commercially-available carbohydrates to synthesize the sex pheromone of the Japanese beetle, P. japonica<sup>73</sup>, (-)-(II-1), and its enantiomer, (+)-(II-1). The potential of furanoses as latent  $\gamma$ -lactones from a single sugar precursor such as 1,2:5,6-di-O-isopropylidene- $\alpha$ -D-glucofuranose for the synthesis of (-)-(II-1) and (+)-(II-1) was to be explored.

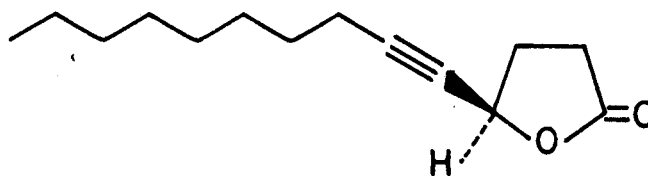
## Scheme 6



↓ (R) - "BINAL"-H



↓



↓

(-)-11-1

## II. RESULTS AND DISCUSSION

Retrosynthetic analysis of the target molecules revealed three major areas of concern: a) reactions that would allow inversion of the absolute stereochemistry at C-4 of the starting material II-3 for the synthesis of (-)-II-1; b) coupling and stereoselective introduction of the Z-stereochemistry at C-5; and c) deoxygenation reactions to remove unwanted hydroxyl groups at C-2 and C-3. The possibility of access to crystalline intermediates at an advanced stage of the synthetic route was also considered advantageous.

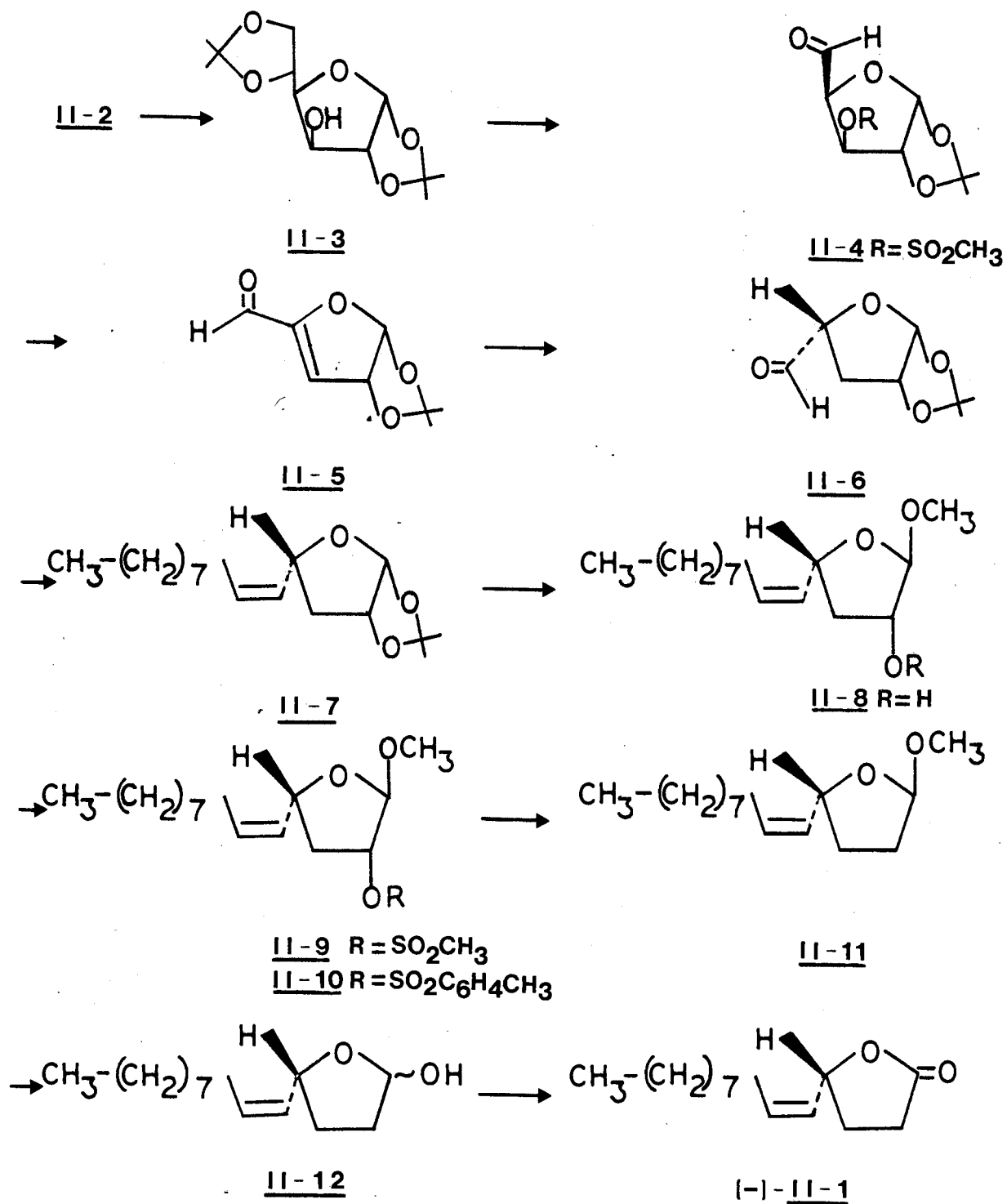
Aldehyde mesylate (II-4) (Scheme 7), which is readily obtained by standard procedures, undergoes  $\beta$ -elimination quantitatively in refluxing pyridine to give II-5. The potential of II-5 as a chiral synthon is enhanced by the fact that catalytic hydrogenation of similar systems such as 3-deoxy-1,2:5,6-di-O-isopropylidene- $\alpha$ -D-glucos-3-ene occurs stereoselectively at the less hindered face, as demonstrated by Weygand and Wolz<sup>100</sup>.

### A. Synthesis of (R)-(-)-(Z)-5-(1-Decenyl)-dihydro-2(3H)-furanone, (-)-II-1

Compound II-5, which appeared to be the ideal synthon for stereo- and regioselective transformations leading to (-)-II-1 is shown in Scheme 7. Sun and Fraser-Reid<sup>101</sup> have described the preparation of this material and Nakanishi *et al.*<sup>102</sup> have prepared it from 1,2;5,6-di-O-isopropylidene-3-O-p-toluenesulfonyl- $\alpha$ -D-glucofuranose<sup>103</sup>, by a similar route. Brown and Jones<sup>104</sup> have prepared II-5 in poor yield from the 3-tosyl precursor by treatment with sodium methoxide in dry methanol at room temperature.

1,2;5,6-Di-O-isopropylidene- $\alpha$ -D-glucofuranose (II-3) was prepared as

Scheme 7



described by Schmidt<sup>105</sup> and the aldehyde mesylate II-4<sup>101</sup> was obtained in almost quantitative yield as a mixture of the free aldehyde and its hydrated form. Refluxing of II-4 in the presence of pyridine afforded II-5 as an unstable oil<sup>101,104</sup>. This compound photodecomposes but it is stable indefinitely in the dark at low temperature.

Partially hydrated II-6 has been prepared in unspecified yield from precursor II-5 by catalytic hydrogenation over palladium on carbon<sup>104</sup>. Murray and Prokop<sup>106,107</sup> obtained this material from 3-deoxy-1,2;5,6-di-O-isopropylidene- $\alpha$ -D-galactofuranose. Attempts to hydrogenate II-5 in a suspension of 5% palladium on carbon, equilibrated with hydrogen prior to reduction, as reported by Brown and Jones<sup>104</sup>, failed repeatedly. When either methanol or ethanol was used as a solvent and hydrogenation was performed at 2080 (Torr) for periods of 4-12 hours, low yields of product resulted. Hydrogenation of II-5 was consistently achieved using ethyl acetate as the solvent, and performing the hydrogenation at 2080 (Torr) to give II-6 (in 50% purified yield).

Wittig olefination of aldehyde II-6 was carried out with high stereoselectivity in dimethylsulphoxide (DMSO) as reported by Greenwald *et al.*<sup>108</sup> giving II-7 (95% Z by glc) in 57% yield. The E,Z mixture was subjected to column chromatography upon which II-7 was obtained free of the E-isomer. Acid-catalyzed methanolysis of II-7 afforded an anomeric mixture of II-8 in good yield. The <sup>1</sup>H NMR spectrum of II-8 displayed two signals for H-1, corresponding to the two furanoside anomers produced under the acidic reaction conditions. A singlet at  $\delta$  4.87 appeared for the  $\alpha$ -anomer, overlapping with the multiplet of H-4, and a doublet at  $\delta$  4.73 ( $J_{1,2}=4.5$ ) for the  $\beta$ -anomer. In addition, the relative intensities of the two methoxyl

signals at  $\delta$  3.45 ( $\beta$ -isomer) and  $\delta$  3.35 ( $\alpha$ -isomer) indicated a ratio of  $\beta$ : $\alpha$  of 1:4.5. The acetal mixture II-8 could not be separated by column chromatography. Therefore, II-8 was methanesulfonylated (mesylated) by treatment with mesyl chloride and triethylamine in methylene chloride, using the Servis and Crossland procedure<sup>109</sup>, to afford mesylate (II-9). The <sup>1</sup>H NMR spectrum of the major component, after purification by column chromatography, showed a signal for the anomeric proton at  $\delta$  5.11 as a broad triplet ( $J_{1,2}=0.7$ ), indicating an  $\alpha$ -configuration for the anomeric carbon.

The chemoselectivity and nucleophilicity of borohydride in polar aprotic solvents is well documented<sup>110</sup>. The crystalline mesylate II-9 was deoxygenated with NaBH<sub>4</sub> in hexamethylphosphoramide (HMPA) at 80-100°C for 24 hours, giving II-11 in 43% yield. Attempts to improve yields and/or deoxygenate II-9, using the powerful lithium triethylborohydride nucleophile<sup>111</sup> (super hydride) in tetrahydrofuran (THF) under a variety of conditions, were not successful. Considerable amounts of acetal II-8 from sulfur-oxygen bond cleavage and some unreacted starting material were recovered with only traces of the expected 2-deoxy compound II-11 detected by thin layer chromatography. The 2-O-tosyl derivative was then prepared to see if tosylate displacement was more effective than the mesylate displacement had been. Treatment of the tosylate II-10 with either sodium borohydride in HMPA at room temperature and 100°C or lithium triethylborohydride in THF at reflux resulted in only oxygen-sulfur bond cleavage instead of displacement. The use of the Cu<sup>I</sup>H complex, reported by Masamune and coworkers<sup>112</sup>, in THF resulted in oxygen-sulfur bond cleavage as well. Attempted displacement of the mesylate group of II-9 with NaI and

zinc powder in 1,2-dimethoxy ethane<sup>113</sup> under reflux resulted in the recovery of unreacted starting material.

A two-step procedure, in which the free 2-hydroxy compound II-8 was reacted with TPP in dry benzene in the presence of DEAD<sup>114-116</sup> at room temperature for 24 hours, gave an oily residue assumed to be the alkoxyphosphonium salt. Treatment of this residue with methyl iodide in refluxing toluene resulted in unreacted II-8 being recovered.

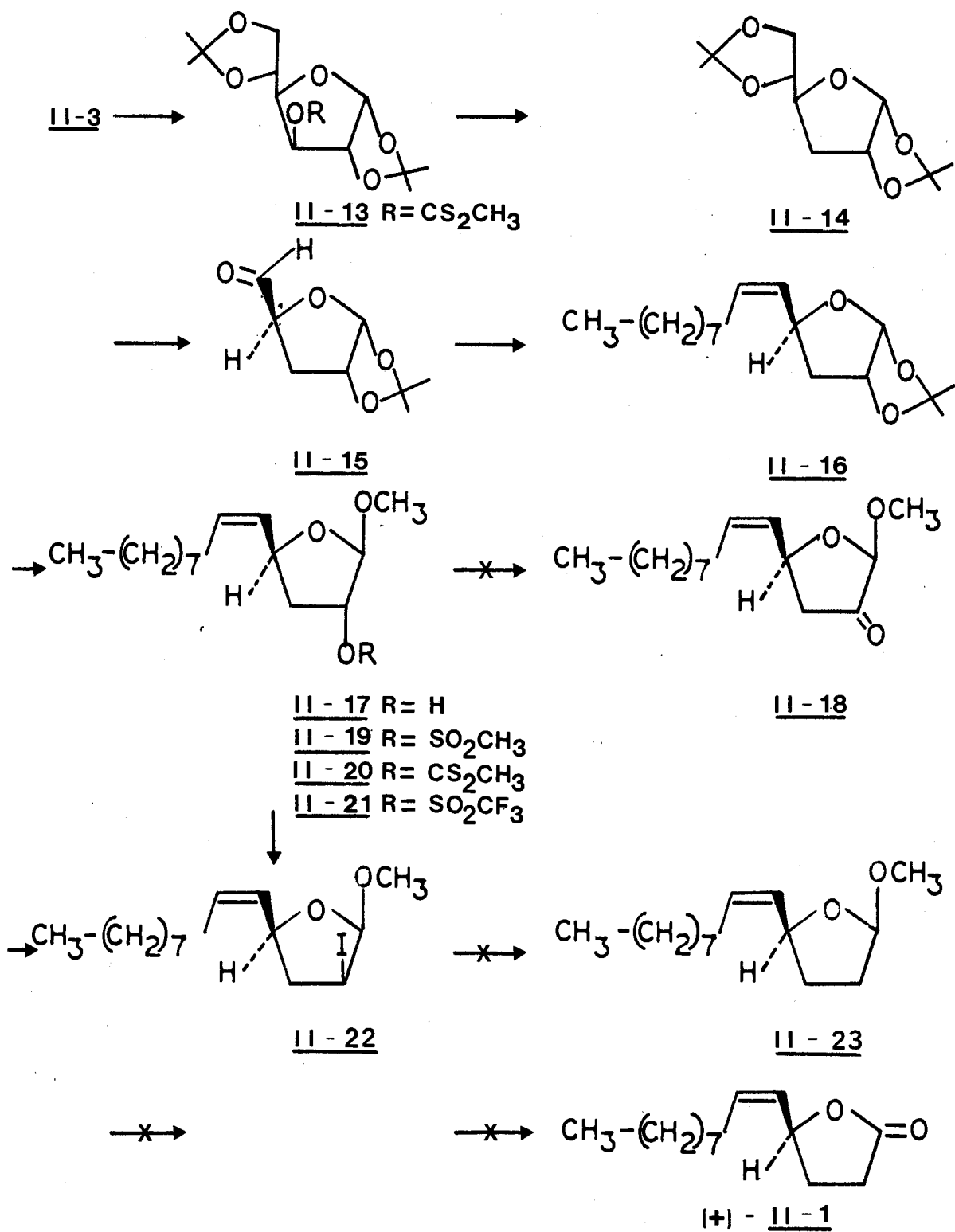
In spite of the low yield experienced in the deoxygenation reaction of II-9, conditions were established for the mild hydrolysis of II-11, using 0.01 N hydrochloric acid in THF:H<sub>2</sub>O, 1:1 at 55-60°C, which gave II-12 in good yield. The target lactone (-)-(II-1) was obtained by Collins<sup>117</sup> oxidation of II-12 and was characterized by elemental analysis and spectral data which were in good agreement with those published for (R)-(-)-(Z)-5-(1-decenyl)-dihydro-2(3H)-furanone, (-)-(II-1)<sup>70,72,73,140</sup>.

B. Attempted Synthesis of (S)-(+)-(Z)-5-(1-Decenyl)-dihydro-2(3H)-furanone, (+)-(II-1)

The synthetic route to (+)-(II-1) from II-3 (Scheme 8) followed the same successful scheme as in the synthesis of (-)-(II-1), except that II-3 possessed the correct stereochemistry at C-4 and thus inversion was unnecessary. The route to (+)-(II-1) commenced with the same starting material, 1,2:5,6-di-O-isopropylidene- $\alpha$ -D-glucofuranose, which was converted to the S-methyl dithiocarbonate II-13 quantitatively. Deoxygenation of II-13 with tri-n-butyltin hydride in refluxing toluene in the presence of  $\alpha,\alpha'$ -azobisisobutyronitrile (A.I.B.N.)<sup>132</sup>, by the Barton and McCombie method<sup>118</sup>, gave II-14 in excellent yield. Compound II-14 was converted into aldehyde II-15 by hydrolysis with dilute hydrochloric acid<sup>119</sup>,



## Scheme 8



followed by periodate oxidation of the resulting diol. Wittig olefination of II-15 was carried out as stated previously for the synthesis of II-7, giving II-16 in 55% yield. Acid-catalyzed methanolysis of II-16 gave furanoside II-17. The  $^1\text{H}$  NMR spectrum of II-17 showed a signal for the anomeric proton at  $\delta$  4.81 as a singlet. Close examination of this signal revealed a slight shoulder that could not be resolved. In addition, the methoxyl signal showed two, almost overlapping singlets at  $\delta$  3.35. These signals indicated an approximate ratio of  $\alpha$  to  $\beta$  anomer of 1:4. The anomeric mixture was converted into mesylate II-19 as indicated for the synthesis of II-9. A signal for the anomeric proton at  $\delta$  5.04 as a singlet was evidence that the  $\beta$ -configuration of H-1 predominated. The methoxyl signal at  $\delta$  3.37 also revealed a slight shoulder that could not be resolved and was presumably the  $\alpha$ -anomer. Attempts to displace the mesylate group of II-19 with  $\text{NaBH}_4$  using the same conditions as for the displacement of the mesylate group in II-9 resulted in partial decomposition of the mesylate and recovery of unreacted starting material.

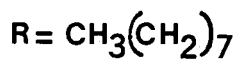
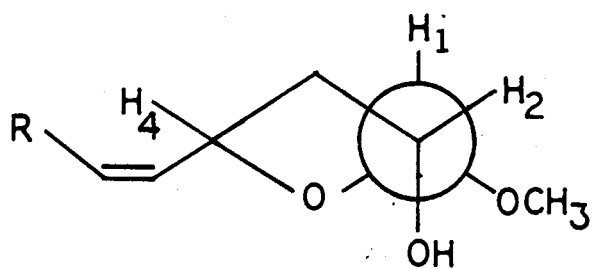
The striking difference in reactivity between trifluoromethanesulfonate (triflate) and its counterparts, *p*-toluenesulfonate (tosylate) and methanesulfonate (mesylate), as leaving groups<sup>120,121</sup>, strongly suggested the use of triflate to overcome the obstreperous deoxygenation of C-2 in II-17. Thus, II-17 was converted into triflate II-21, as reported by Hehemann and Binkley<sup>122</sup>. The  $^1\text{H}$  NMR spectrum of II-21 showed a signal at  $\delta$  5.05 as a singlet consistent with the  $\beta$ -anomer. No evidence for the  $\alpha$ -anomer was detected. Attempts to displace the triflate group of II-21 with tetrabutyl ammonium iodide in refluxing benzene resulted in very low yield (5%) of the iodo compound II-22. The  $^1\text{H}$  NMR spectrum indicated a

signal for the anomeric proton at  $\delta$  4.80 as a doublet ( $J_{1,2}=4$ ), indicating a 1,2-cis relationship in the iodo-furanoside derivative, showing nucleophilic attack had resulted in inversion at C-2.

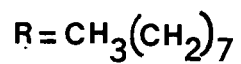
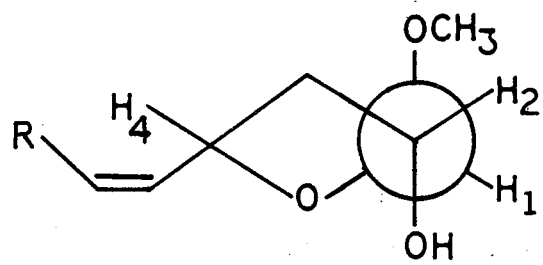
Experience shows nucleophilic displacement of a C-2 sulfonyloxy group is very difficult<sup>123</sup> but the complete lack of reactivity of mesylate II-19, when compared to mesylate II-9, was striking. A clear preference of the methyl L-furanoside II-8 for the  $\alpha$  and the methyl D-furanoside II-17 for the  $\beta$  configuration at the anomeric centre, presumably due to the more favourable 1,2-trans interaction as compared to the 1,2-gauche, was found. This trans configuration restricts access to nucleophilic substitution at C-2, as can be seen in Figure 7, and makes this process difficult. A possible explanation of the differential reactivity of these two trans compounds may be found in the conformations adopted by the two furanosides brought about by the change in configuration at C-4. Evidence from the <sup>1</sup>H NMR suggests that the conformations of mesylates II-9 and II-19 are as depicted in Figure 8. A comparison of their coupling constants clearly showed dihedral angles of approximately 90° between H<sub>1</sub> and H<sub>2</sub> ( $J_{1,2}=0.7$ ) for II-9, and between H<sub>1</sub> and H<sub>2</sub> ( $J_{1,2}=0$ ) and H<sub>2</sub> and H<sub>3'</sub> ( $J_{2,3'}=0$ ) for II-19, indicating that both furanosides adopt the twist conformation shown (Figure 8). In both conformations, C-2 is below and C-3 is above the plane defined by C-4, O and C-1, in agreement with the conformations expected on the basis of conventional conformational concepts, since they represent the most efficient way of relieving the cis-eclipsed interactions which would be present if the furanoside rings were closer to planarity. As a result, the steric control exerted by the glycosidic methoxy group being approximately the same in both glycosides, can not explain the

Figure 7

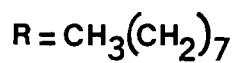
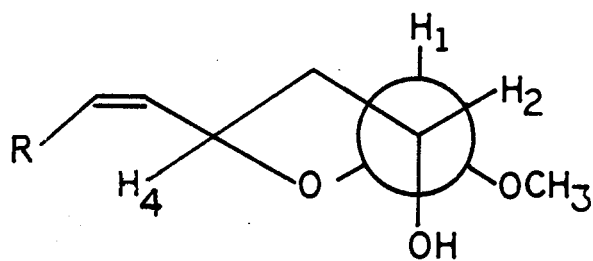
Newman projections of methylfuranosides II-8 and II-17.



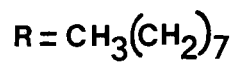
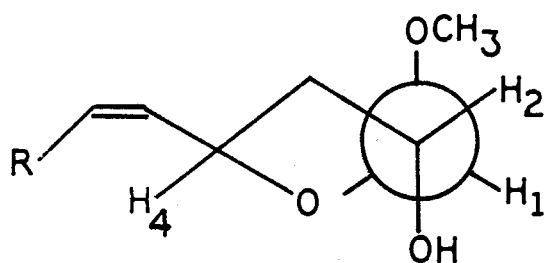
$\beta$ -11-8 gauche



$\alpha$ -11-8 trans



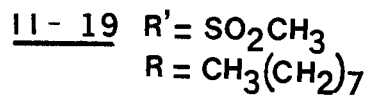
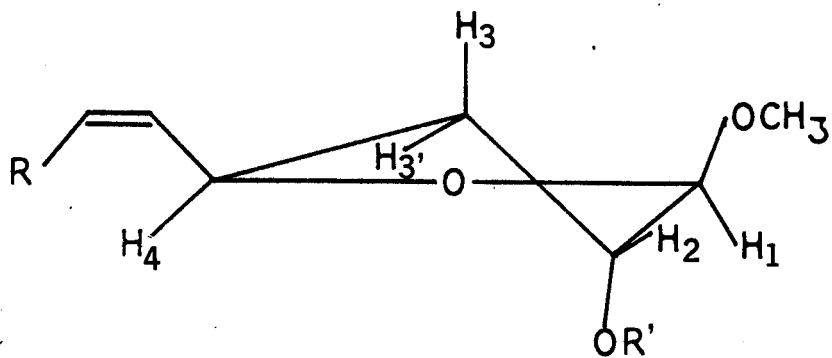
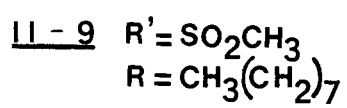
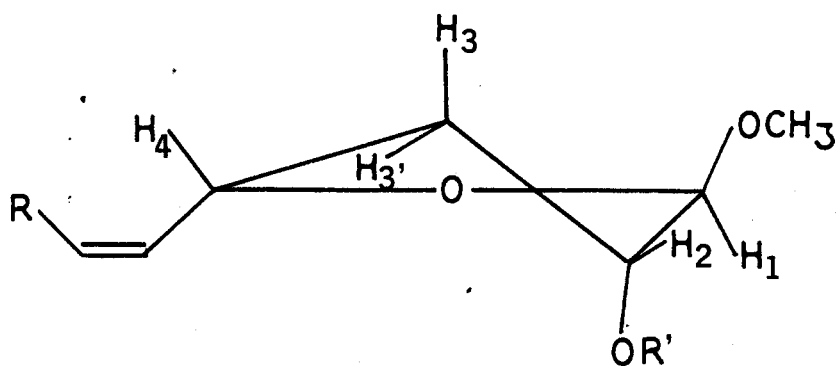
$\alpha$ -11-17 gauche



$\beta$ -11-17 trans

Figure 8

Conformations of mesylates II-9 and II-19.



greater reactivity of II-9 as compared to II-19. The reasons have to be found in the additional steric and electronic impedance introduced by the change of configuration at C-4. As has been stated<sup>124</sup>, the reactivity of a sulfonyloxy group toward direct displacement does not depend solely upon the ground state energy level of a substrate but also upon the transition state energy level achieved by the reactants. Thus, the attack of hydride on both furanosides produces ring flattening at C-2, resulting in a transition state that is more favourable in the case of mesylate II-9 than in II-19. Under the conditions studied, II-9 was reduced in low yield by hydride displacement whereas II-19 failed to react.

Two different concepts of deoxygenation of the key intermediate II-17 were then attempted to obtain deoxygenation at the C-2 position. The first one, via radical deoxygenation, offered an alternative to nucleophilic displacement reactions. Radical reactions take place under neutral conditions and radicals are generally unsolvated and therefore less susceptible to steric factors<sup>125</sup>. The radical-induced and previously successful method<sup>118</sup> (e.g., preparation of II-14), utilizing S-methyl dithiocarbonate, was applied to II-17. Surprisingly, xanthate II-20 was obtained in low yield on repeated occasions. Evidence for the  $\beta$ -configuration of II-20 was obtained from <sup>1</sup>H NMR, which showed a signal for H-1 at  $\delta$  5.04 as a singlet. Attempts to deoxygenate C-2 with tri-n-butyltin hydride failed to give any of the expected product and some unreacted II-20 was recovered.

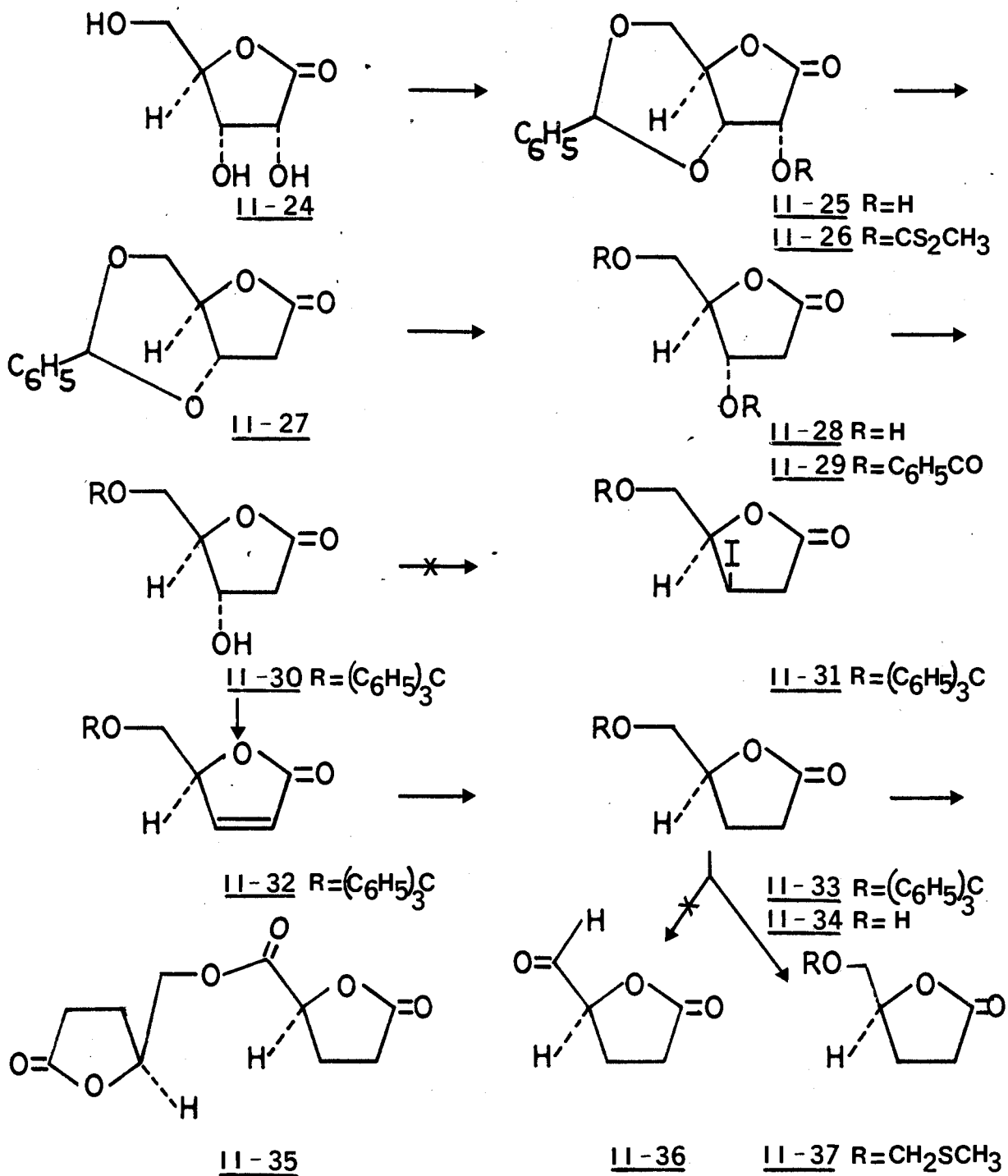
A second approach, based on the availability of mild and specific oxidation methods in carbohydrate chemistry, was considered. Literature reports<sup>126</sup> suggested that a wide variety of aldehydes and ketones could be deoxygenated via their tosylhydrazones selectively to methylene derivatives



with sodium cyanoborohydride under acidic conditions<sup>127</sup>. Therefore, attempts to deoxygenate C-2 through oxidation, tosylhydrazone formation and reductive elimination<sup>126</sup> were investigated. Oxidation of II-17, using DMSO in the presence of dicyclohexylcarbodiimide (DCC), resulted in unreacted II-17 being recovered. Chromium-based oxidations with Collins reagent<sup>117</sup> or pyridinium chlorochromate<sup>51</sup> resulted in long reaction times and decomposition of the starting material. Oxidation of a similar system by Tam and Fraser-Reid<sup>128</sup> resulted in the formation of an unstable ketone with its subsequent in situ decomposition. Due to the difficulties encountered in the deoxygenation of the C-2 hydroxyl group and the low yields achieved in the formation of precursors II-20, II-21 and II-22, this route to lactone (+)-(II-1) had to be abandoned.

A new approach was undertaken which utilized commercially-available D-ribonolactone<sup>129</sup>, II-24. Deoxygenation at both C-2 and C-3 would afford intermediate II-34. Oxidation of this chiral  $\delta$ -hydroxy- $\gamma$ -valerolactone to aldehyde II-36, followed by stereoselective Wittig olefination, was expected to lead to the target molecule. While this research was in progress, a communication<sup>130</sup> on the use of D-ribonolactone as a chiral synthon was reported, including the deoxygenation of compound II-25 through its xanthate. Treatment of II-24 (Scheme 9) with benzaldehyde and concentrated hydrochloric acid for 7 hours resulted in a quantitative yield of the known benzylidene derivative<sup>131</sup> II-25. Attempts to obtain xanthate II-26, as reported by Barton and McCombie<sup>118</sup>, resulted in low yields. The reaction of II-25 with carbon disulfide, in the presence of sodium hydride in dry N,N-dimethylformamide (DMF) at  $-60^{\circ}\text{C}$ , followed by alkylation with methyl iodide, gave xanthate II-26 in reasonable yield<sup>130</sup>. Reduction of II-26

Scheme 9



with tri-n-butyltin hydride in the presence of initiator (A.I.B.N.) gave II-27. Deprotection of the 2-deoxy compound II-27 with 50% aqueous trifluoroacetic acid in chloroform at 70°C for 10 hours gave II-28, which was characterized as the solid dibenzoyl derivative<sup>133</sup> II-29. Compound II-28 was readily converted into the 5-O-trityl ether II-30. Attempted conversion of II-30 into the 3-iodo-lactone II-31, by treatment with DEAD, TPP and methyl iodide<sup>134</sup>, as a suitable intermediate for reductive dehalogenation, afforded butenolide II-32 in good yield. The favourable position for elimination of the 3-alkoxy triphenylphosphonium salt intermediate of II-30 was demonstrated by the facility and high yield by which the elimination occurred when II-30 was subjected to the same reaction in the absence of methyl iodide. The large steric effect of the trityl group hinders nucleophilic attack at C-3 of II-30, which undergoes elimination instead of substitution. Catalytic hydrogenation of II-32, however, led to a convenient production of the required compound. Removal of the trityl ether of II-33 with p-toluene sulfonic acid in methanol gave intermediate II-34.

In order to oxidize II-34, several methods based on chromium(VI) reagents were attempted. The use of chromium trioxide-dipyridine complex<sup>117</sup> in methylene chloride produced traces of oxidation products as indicated by tlc, but the reaction times were long and the product isolation was difficult. Pyridinium chlorochromate oxidation<sup>51</sup>, resulted in very slow oxidation to ester II-35, as well as unreacted II-34, even after prolonged reaction times. The apparent low reactivity of II-34 and the inability of the aforementioned reagents to oxidize it to aldehyde II-36 lead to investigation of another oxidizing system. Stensjö and Wachtmeister<sup>135</sup> have observed the activation effect exerted by acetic acid

in oxidations performed with chromium(VI) oxide-pyridine complex. From this observation, the chromium(VI) oxide-pyridine-acetic anhydride (1:2:1) and pyridinium dichromate-acetic anhydride reagents<sup>136</sup> were developed. Their utility in the oxidations of partially protected carbohydrates has been demonstrated despite the electron-deficient nature of the carbon backbone. These reaction conditions were unsuccessfully applied to the oxidation of II-34. Some starting alcohol (II-34) was recovered and the isolation process was inefficient. The lack of reactivity of II-34 with chromium reagents prompted the use of a quite different oxidizing system. Reaction of DMSO with electrophilic activators is well documented and has proven very useful in the oxidation of alcohols to carbonyls<sup>50</sup>. Compound II-34 was treated with DMSO, oxalyl chloride and triethyl amine in methylene chloride at low temperatures<sup>50</sup>. No clear evidence of oxidation products was apparent when monitored by tlc and attempted isolation of a product by either aqueous or non-aqueous workup failed to give any of the expected product, although some unreacted II-34 and a small amount of the methylthiomethylether II-37 were recovered. The appearance of II-37 in low yield indicated nucleophilic attack by triethylamine on the sulfonium sulfur<sup>50</sup> rather than proton removal of the alkoxysulfonium salt intermediate to give the carbonyl compound II-36 was occurring. Use of a more hindered base, diisopropylethylamine, to form the sulfonium ylide intermediate was unsuccessful. *p*-Toluenesulfonyl chloride as an activating electrophile<sup>137</sup> for DMSO in the presence of HMPA was also tried unsuccessfully and attempted recovery of the starting material was unsatisfactory. The Pfitzner-Moffatt technique<sup>138</sup> utilizing DMSO, DCC and phosphoric acid on II-34 was also unsuccessful. Literature data<sup>139</sup> appeared to indicate

this method as the technique of choice for the oxidation of the primary hydroxyl of II-34. No clear evidence of oxidation products was apparent from tlc and reisolation of the starting material was difficult due to its solubility in aqueous media.

An adequate synthetic route to the inhibitory enantiomer (+)-(II-1) was not found.

III. CONCLUSIONS

The sex pheromone of the Japanese beetle, Popillia japonica (Newman), (R)-(-)-(Z)-5-(1-deceny)-dihydro-2(3H)-furanone, (-)-(II-1), was synthesized in 1% overall yield and in good optical purity (85%). The low yields experienced in deoxygenation of the methyl 3-deoxy- $\alpha$ -L-furanoside restricts the utility of this method as a favourable route to this valuable substance.

The inability to deoxygenate the methyl 3-deoxy- $\beta$ -D-furanoside in a similar manner probably originates with the additional steric and electronic barrier brought about by the change of configuration at C-4, which may severely restrict the approach of nucleophiles in an  $S_N2$  fashion. Attempts to deoxygenate by other means were not successful. (S)-(+)- $\delta$ -hydroxy- $\gamma$ -valerolactone was readily available through successful deoxygenation of D-ribonolactone. Oxidation attempts of the primary hydroxyl group by a variety of reagents were explored and found to be unsuccessful.

The carbohydrate chiral template approach, as outlined in this research, does not appear to be a viable route to chiral  $\gamma$ -lactones. The difficulties encountered in specific oxidations and deoxygenations appear to preclude these carbohydrates as effective synthons for chiral  $\gamma$ -lactones.

#### IV. EXPERIMENTAL METHODS

##### General Procedures

Routine gas liquid chromatography (gc) analyses were run on a Varian 1400 flame ionization gas chromatograph, with packed glass columns containing 3% OV-17 on Chromosorb W.

Analytical (0.25 mm) thin layer chromatography (tlc) plates were prepared from silica gel GF<sub>254</sub> (E. Merck, Darmstadt). Column chromatography was performed by the flash chromatography method<sup>55</sup>, on silica gel (Kieselgel 60, 40-63  $\mu$ m, E. Merck, Darmstadt). Chromatographic solvents were distilled before use. Low-boiling (30-60°C) petroleum ether was used for chromatography.

IR spectra were determined on a Perkin-Elmer 599B spectrophotometer. Samples were run as a neat film on NaCl plates, as KBr pellets or as solutions in a cell with NaCl windows.

<sup>1</sup>H NMR were recorded on a Varian EM-360 (60 MHz) or a Bruker 400 (400 MHz) NMR spectrometer. Chemical shifts are reported in  $\delta$  units, referenced to an internal standard (TMS) or to an internal (deuterium) lock signal. Splitting patterns are described as: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and combinations thereof. Coupling constants are reported in Hertz (Hz).

Low resolution mass spectra were obtained with direct insertion probe or gc-ms samples on a Hewlett-Packard 5985B coupled gas chromatograph-mass spectrometer. All samples were run using electron impact ionization (70 eV). Relative abundances are expressed as percentages of the abundance of the base peak. Elemental analyses were performed on a Perkin Elmer Model 240 elemental analyzer. Optical rotations were measured with a

Rudolph Model 70 polarimeter, using either a 1 dm  $\times$  4 mm i.d. sample cell or a 1 dm  $\times$  1.5 mm i.d. sample cell. Concentrations are reported in g/100 mL solvent.

All reactions requiring anhydrous and/or oxygen-free conditions were run under a positive pressure of nitrogen or argon.

**1,2;5,6-Di-O-isopropylidene- $\alpha$ -D-glucofuranose (II-3)**

This was prepared from D-glucose II-2 in 75% yield, as described by Schmidt<sup>105</sup>; m.p. 110°,  $[\alpha]_D -17.5^\circ$  (c 0.4, water); Lit.<sup>105</sup>, m.p. 110-111°,  $[\alpha]_D -18.5^\circ$  (c 5.0, water).

**1,2-O-Isopropylidene-3-O-methanesulfonyl- $\alpha$ -D-xylo-pentodialdo-1,4-furanose (II-4)**

This was prepared by the procedure of Sun and Fraser-Reid<sup>101</sup> from 1,2;5,6-di-O-isopropylidene- $\alpha$ -D-glucofuranose (II-3) as a mixture of the free aldehyde and its hydrated form in 95% yield.  $R_f$ : 0.25, ether;  $[\alpha]_D^{23} -39.1^\circ$  (c 14.3, CHCl<sub>3</sub>); Lit.<sup>101</sup>  $[\alpha]_D^{20} -38.4^\circ$  (c 4.8, CHCl<sub>3</sub>). IR (film) 3480, 2740, 1740 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>) (free aldehyde)  $\delta$  1.35 (s, 3H, CH<sub>3</sub>-), 1.52 (s, 3H, CH<sub>3</sub>-), 3.0 (s, 3H, MsO-), 4.72 (d, 1H, H<sub>2</sub>, J<sub>1,2</sub>=3.5), 4.86 (d, 1H, H<sub>4</sub>, J<sub>3,4</sub>=3.5), 5.28 (d, 1H, H<sub>3</sub>, J<sub>3,4</sub>=3.5), 6.15 (d, 1H, H<sub>1</sub>, J<sub>1,2</sub>=3.6), 9.72 (s, 1H, CHO-); mass spectrum, m/e: 251(36.5), 237(42), 179(30), 113(26), 85(100), 59(55.1), 43(58.8).

**1,2-O-Isopropylidene- $\alpha$ -D-glycero-pent-3-enodialdo-1,4-furanose (II-5)**

This was prepared by the procedure of Sun and Fraser-Reid<sup>101</sup> from II-4, in 94% yield.  $R_f$ : 0.50, ether;  $[\alpha]_D^{23} -81^\circ$  (c 4.5, CHCl<sub>3</sub>); Lit.<sup>101</sup>  $[\alpha]_D^{20} -88.6$  (c 9.7, CHCl<sub>3</sub>). IR (film) 3115, 2990, 2940, 2860, 2730, 1700, 1615 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.42 (s, 3H, CH<sub>3</sub>-), 1.45 (s, 3H, CH<sub>3</sub>-), 5.42 (dd, 1H, H<sub>2</sub>, J<sub>1,2</sub>=5.5, J<sub>2,3</sub>=2.5), 6.14 (d, 1H, H<sub>3</sub>, J<sub>2,3</sub>=2.5),



6.20 (d, 1H, H<sub>1</sub>, J<sub>1,2</sub>=5.5), 9.5 (s, 1H, CHO-); mass spectrum, m/e: 170(0.1), 169(0.1), 155(3), 141(58.2), 83(100), 43(46.9). Semicarbazone of II-5, m.p. = 182°C (dec). Anal. calcd. for semicarbazone of II-5 (C<sub>9</sub>H<sub>13</sub>N<sub>3</sub>O<sub>4</sub>): C, 47.57; H, 5.77. Found: C, 47.45; H, 5.81.

**3-Deoxy-1,2-O-isopropylidene-β-L-threo-pentodialdo-1,4-furanose<sup>104</sup>**

**(II-6)**

A solution of 1,2-O-isopropylidene-α-D-glycero-pent-3-enodialdo-1,4-furanose (II-5) (14.6 g, 0.086 mol) in ethyl acetate (30 mL) was added to a suspension of 5% palladium on carbon (1.46 g) (previously equilibrated with hydrogen) in ethyl acetate (30 mL) and hydrogenated for 4 hours. Removal of catalyst and solvent, followed by evaporation twice with chloroform, gave a mobile oil (9.9 g) which, after column chromatography using ether: petroleum ether (3:2), afforded II-6 (7.4 g, 50%). R<sub>f</sub>: 0.34, ether: petroleum ether (1:1); [α]<sub>D</sub><sup>23</sup> +15.4° (c 14.3, ethyl acetate). IR (film) 2980, 2940, 2820, 1740, 1385, 1375 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.29 (s, 3H, CH<sub>3</sub>-), 1.46 (s, 3H, CH<sub>3</sub>-), 2.26 (dddd, 1H, H<sub>3</sub>, J<sub>3,3'</sub>=14, J<sub>3,4</sub>=9, J<sub>2,3</sub>=3.5, J<sub>1,3</sub>=1), 2.58 (d, broad, 1H, H<sub>3'</sub>, J<sub>3,3'</sub>=14), 4.42 (d, broad, 1H, H<sub>4</sub>, J<sub>3,4</sub>=9), 4.72 (dd, 1H, H<sub>2</sub>, J<sub>1,2</sub>=3.5, J<sub>2,3</sub>=3.5), 5.93 (d, 1H, H<sub>1</sub>, J<sub>1,2</sub>=3.5), 9.92 (s, broad, 1H, H<sub>5</sub>); mass spectrum, m/e: 172(0.3), 157(93.8), 143(98.4), 85(100), 59(97.7), 43(80). Anal. calcd. for C<sub>8</sub>H<sub>12</sub>O<sub>4</sub>: C, 55.81; H, 7.03. Found: C, 55.87; H, 7.30.

**3,5,6-Trideoxy-1,2-O-isopropylidene-β-L-threo-tetradec-5-(Z)-eno-furanose (II-7)**

Nonylidenetriphenylphosphorane

Sodium hydride (2.28 g, 0.047 mol), as a 50% dispersion in mineral oil in a 250 mL three-necked flask, was washed with several portions of pentane

to remove the mineral oil. The flask was equipped with a reflux condenser, a pressure equalizing dropping funnel and a magnetic stirrer. Dimethylsulfoxide (50 mL) was introduced via syringe under a stream of argon and the mixture was heated at 75-80° for 45 min. The resulting solution of methylsulfinyl carbanion<sup>108</sup> was cooled in an ice-water bath and nonyltriphenylphosphonium bromide<sup>140</sup> (24.2 g, 0.052 mol) in warm dimethylsulfoxide (50 mL) was added. The resulting dark red solution of the ylide was stirred at room temperature for 20 min before use. A solution of II-6 (7.4 g, 0.043 mol) in dimethylsulfoxide (15 mL) was slowly added and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was poured into ice-water and extracted with ether (3 × 100 mL). The ether extracts were washed with water (2 × 100 mL) and brine (100 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo to yield II-7 (6.9 g, 57%) after column chromatography with ether:petroleum ether (1:1). R<sub>f</sub> = 0.45, ether:petroleum ether (1:1); [α]<sub>D</sub><sup>23</sup> -28.7° (c 8.5, CHCl<sub>3</sub>). IR (film) 2980, 2940, 2840, 1645, 1460, 1430, 1375, 1365 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.87 (t, 3H, CH<sub>3</sub>-), 1.1-1.3 (m, 12H, -CH<sub>2</sub>-), 1.31 (s, 3H, CH<sub>3</sub>-), 1.57 (s, 3H, CH<sub>3</sub>-), 1.98 (ddd, 1H, H<sub>3</sub>, J<sub>3,3'</sub>=14, J<sub>3,4</sub>=6, J<sub>2,3</sub>=8), 2.07 (m, 2H, H<sub>7</sub>), 2.29 (ddd, 1H, H<sub>3'</sub>, J<sub>3,3'</sub>=14, J<sub>2,3'</sub>=1.5, J<sub>3',4</sub>=3.5), 4.77 (ddd, 1H, H<sub>2</sub>, J<sub>2,3'</sub>=8, J<sub>1,2</sub>=4, J<sub>2,3</sub>=1.5), 4.93 (dddd, 1H, H<sub>4</sub>, J<sub>4,5</sub>=9, J<sub>3,4</sub>=6, J<sub>3',4</sub>=3.5, J<sub>4,6</sub>=1.5), 5.48 (dtd, 1H, H<sub>6</sub>, J<sub>5,6</sub>=11, J<sub>6,7</sub>=8, J<sub>4,6</sub>=1.5), 5.77 (tdd, 1H, H<sub>5</sub>, J<sub>5,6</sub>=11, J<sub>4,5</sub>=9, J<sub>5,7</sub>=1.5), 5.79 (d, 1H, H<sub>1</sub>, J<sub>1,2</sub>=4); mass spectrum, m/e: 282(2), 267(27), 111(86.9), 95(89.7), 59(100), 43(45). Anal. calcd. for C<sub>17</sub>H<sub>30</sub>O<sub>3</sub>: C, 72.30; H, 10.71. Found: C, 71.99; H, 10.98.

**Methyl-3,5,6-trideoxy- $\alpha$ -L-threo-tetradec-5-(Z)-enofuranoside (II-8)**

A solution of II-7 (6.9 g, 0.025 mol) was dissolved in methanol (50 mL), containing 7 N hydrochloric acid (1.0 mL) at 0°C (ice-water bath) and stirred at this temperature for 10 min, after which time the bath was removed and the solution was stirred at room temperature for 1 hour. The solution was then neutralized with 5% aqueous NaHCO<sub>3</sub> solution (2 × 25 mL), extracted with ether (3 × 25 mL), washed with water and dried (Na<sub>2</sub>SO<sub>4</sub>). Evaporation of the solvent in vacuo gave a yellow oil which, after column chromatography with ether:petroleum ether (1:1), yielded II-8 (4.5 g, 72%). R<sub>f</sub> = 0.35, ether:petroleum ether (1:1);  $[\alpha]_D^{23}$  -65° (c 5.1, CHCl<sub>3</sub>). IR (film) 3440, 3020, 1660, 1125-1080, 730-665 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>) ( $\alpha$ -anomer)  $\delta$  0.88 (t, 3H, CH<sub>3</sub>-), 1.1-1.4 (m, 12H, -CH<sub>2</sub>-), 1.54 (ddd, 1H, H<sub>3</sub>, J<sub>3,3'</sub> = 13.5, J<sub>3,4</sub> = 6.5, J<sub>2,3</sub> = 3), 1.90 (d, 1H, 2-OH, J<sub>2-OH,2</sub> = 6, D<sub>2</sub>O exchangeable), 2.08 (m, 2H, H<sub>7</sub>), 2.50 (ddd, 1H, H<sub>3'</sub>, J<sub>3,3'</sub> = 13.5, J<sub>3',4</sub> = 7.5, J<sub>2,3'</sub> = 6.5), 3.35 (s, 3H, CH<sub>3</sub>O-), 4.25 (m, 1H, H<sub>2</sub>), 4.87 (m, 2H, H<sub>4</sub>, H<sub>1</sub>), 5.53 (m, H<sub>6</sub>, H<sub>5</sub>); mass spectrum, m/e: 256(3.1), 238(0.8), 225(5), 157(11), 143(78.0), 111(85), 84(100), 83(87.8), 69(55), 55(70), 41(45). Anal. calcd. for C<sub>15</sub>H<sub>28</sub>O<sub>3</sub>: C, 70.28; H, 11.01. Found: C, 70.02; H, 10.96.

**Methyl-3,5,6-trideoxy-2-O-methanesulfonyl- $\alpha$ -L-threo-tetradec-5-(Z)-enofuranoside (II-9)**

To a mixture of acetal II-8 (5.78 g, 0.023 mol) and triethylamine (2.83 g, 0.028 mol) in methylene chloride (40 mL) at -10°C was added a 10% excess of methanesulfonyl chloride over a period of 5-10 min. The reaction was stirred for a further 2 hours, after which the reaction mixture was transferred to a separatory funnel with the aid of more methylene chloride (20 mL). The mixture was first extracted with ice-water (40 mL), followed

by cold 10% hydrochloric acid (30 mL), saturated sodium bicarbonate solution (30 mL) and brine (30 mL). The methylene chloride solution was dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent removed to give an oil which, after column chromatography with ether:petroleum ether (1:1), gave II-9 as a crystalline solid (3.84 g, 51%).  $R_f = 0.4$ , ether:petroleum ether (1:1); m.p. = 44-46°C;  $[\alpha]_D^{23} -45^\circ$  ( $c$  3.9,  $\text{CHCl}_3$ ). IR (film) 3100, 1615, 1400-1300, 1200-1150  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.88 (t, 3H,  $\text{CH}_3$ -), 1.20-1.40 (m, 12H,  $-\text{CH}_2-$ ), 1.83 (dddd, 1H,  $\text{H}_3$ ,  $J_{3,3'}=14.2$ ,  $J_{3,4}=6.8$ ,  $J_{2,3}=6.6$ ), 2.08 (m, 2H,  $\text{H}_7$ ), 2.62 (ddd, 1H,  $\text{H}_3'$ ,  $J_{3,3'}=14.2$ ,  $J_{2,3'}=3$ ,  $J_{3',4}=3$ ), 3.05 (s, 3H,  $\text{MsO}-$ ), 3.37 (s, 3H,  $\text{CH}_3\text{O}-$ ), 4.92 (q, broad, 1H,  $\text{H}_4$ ), 5.02 (ddd, 1H,  $\text{H}_2$ ,  $J_{2,3}=6.6$ ,  $J_{2,3'}=3$ ,  $J_{1,2}=0.7$ ), 5.11 (t, broad, 1H,  $\text{H}_1$ ,  $J_{1,2}=0.7$ ), 5.58 (tdd,  $\text{H}_5$ ,  $J_{5,6}=10.9$ ,  $J_{4,5}=8.6$ ,  $J_{5,7}=1.4$ ), 5.61 (dtd, 1H,  $\text{H}_6$ ,  $J_{5,6}=10.8$ ,  $J_{6,7}=7.4$ ,  $J_{4,6}=1$ ); mass spectrum, m/e: 334(1.0), 167(33.9), 125(100), 95(32.8), 87(40.7). Anal. calcd. for  $\text{C}_{16}\text{H}_{30}\text{O}_5\text{S}$ : C, 57.46; H, 9.04. Found: C, 57.30; H, 9.08.

**Methyl-3,5,6-trideoxy-2,0-p-toluenesulfonyl- $\alpha$ -L-threo-tetradec-5-(Z)-enofuranoside (II-10)**

To a solution of acetal II-8 (180 mg, 0.7 mmol) in pyridine (5 mL) was added p-toluenesulfonyl chloride (400 mg, 2.1 mmol) and the reaction mixture was stirred at room temperature for 24 hours. The mixture was then poured into ice-water (40 mL) and extracted with methylene chloride (3  $\times$  10 mL). The combined organic layers were washed with 10% aqueous sodium bicarbonate solution (15 mL), water (15 mL) and brine (15 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo. Final traces of solvent were removed by evaporation with toluene. The oily residue was purified by chromatography on silica gel, eluting with methylene chloride to give II-10

(165 mg, 57%) as an oil.  $R_f$ : 0.21, 15% ether:petroleum ether;  $[\alpha]_D^{24} +108^\circ$  ( $c$  5.0,  $\text{CHCl}_3$ ). IR (film) 3110, 3080, 1610, 1505, 1420-1330, 1200-1145, 850-800  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.87 (t, 3H,  $\text{CH}_3$ -), 1.1-1.4 (m, 12H,  $-\text{CH}_2$ -), 1.70 (ddd, 1H,  $\text{H}_3$ ,  $J_{3,3'}=14$ ,  $J_{2,3'}=3$ ,  $J_{3,4}=6.75$ ), 2.04 (m, 2H,  $\text{H}_7$ ), 2.45 (s, 3H,  $\text{CH}_3$ -), 2.45 (m, 1H,  $\text{H}_3'$ ), 3.25 (s, 3H,  $\text{CH}_3\text{O}$ -), 4.82 (dd, 1H,  $\text{H}_2$ ,  $J_{2,3}=6.5$ ,  $J_{2,3'}=3$ ), 4.85-4.90 (m, 1H,  $\text{H}_4$ ), 5.30 (s, 1H,  $\text{H}_1$ ), 5.45 (tdd, 1H,  $\text{H}_5$ ,  $J_{5,6}=11$ ,  $J_{4,5}=8.5$ ,  $J_{5,7}=1$ ), 5.55 (dtd, 1H,  $\text{H}_6$ ,  $J_{5,6}=11$ ,  $J_{6,7}=7$ ,  $J_{4,6}=1$ ), 7.2-7.4 (m, 2H,  $-\text{C}_6\text{H}_4$ -), 7.7-7.9 (m, 2H,  $-\text{C}_6\text{H}_4$ -); mass spectrum,  $m/e$ : 410(1.7), 409(0.2), 379(2), 311(0.5), 255(1.2), 239(2.5), 238(10), 206(8.8), 190(28), 155(68), 91(100), 65(33).

**(2R,5R)-(Z)-5-(1-Decenyl)-dihydro-2(3H)-methoxy-furan (II-11)**

A mixture of mesylate II-9 (2.3 g, 6.9 mmol) and  $\text{NaBH}_4$  (1.05 g, 27.6 mmol) in hexamethylphosphoramide (20 mL) was heated at  $100^\circ$  (oil bath) for 24 hours. After the reaction mixture was cooled, water (20 mL) was added to quench the reaction. The aqueous mixture was extracted with ether (3  $\times$  20 mL) and the combined extracts were dried ( $\text{Na}_2\text{SO}_4$ ). The solvent was removed on the rotary evaporator to give a yellow oil. Column chromatography, using ether:petroleum ether (1:1) as an eluant, afforded II-11 (0.71 g, 43%) as a colourless oil.  $R_f$ : 0.45, 20% ether:petroleum ether;  $[\alpha]_D^{23} -100^\circ$  ( $c$  5.7°,  $\text{CHCl}_3$ ). IR (neat) 3020, 1660, 1465-1440, 1100, 1040, 730  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.88 (t, 3H,  $\text{CH}_3$ -), 1.1-1.4 (m, 12H,  $-\text{CH}_2$ -), 1.50 (m, 1H,  $\text{H}_3$ ), 1.87, (m, 1H,  $\text{H}_2$ ), 2.10 (m, 4H,  $2\text{H}_7, \text{H}_2', \text{H}_3'$ ), 3.36 (s, 3H,  $\text{CH}_3\text{O}$ -), 4.82 (q, broad,  $\text{H}_4$ ), 5.06 (dd, 1H,  $\text{H}_1$ ,  $J_{1,2'}=5.25$ ,  $J_{1,2}=2$ ), 5.41 (tdd, 1H,  $\text{H}_5$ ,  $J_{5,6}=11$ ,  $J_{4,5}=8$ ,  $J_{5,7}=1.5$ ), 5.55 (dtd, 1H,  $\text{H}_6$ ,  $J_{5,6}=11$ ,  $J_{6,7}=7.5$ ,  $J_{4,6}=1$ ); mass spectrum,  $m/e$ : 240(2.8), 239(0.2), 209(5), 141(28), 127(91.7), 95(44.8), 72(100), 71(57.6). Anal. calcd. for  $\text{C}_{15}\text{H}_{28}\text{O}_2$ : C,

74.95; H, 11.74. Found: C, 74.84; H, 11.73.

**(-)-(R-Z)-5-(1-Decenyl)-dihydro-2(3H)-furanone (II-1)**

Acetal II-11 (180 mg, 0.75 mmol), dissolved in a 1:1 mixture of THF: H<sub>2</sub>O (10 mL), was treated with 0.01 N hydrochloric acid solution (1 mL) and the reaction mixture was heated at 55-60°C for 3 hours with stirring. The solution was cooled and was extracted with ether (3 × 10 mL), washed with 10% aqueous NaHCO<sub>3</sub> solution (10 mL), brine (10 mL) and dried (Na<sub>2</sub>SO<sub>4</sub>). Removal of the solvent in vacuo gave II-12 (130 mg, 76%) as an oil, which was chromatographically homogeneous and was used directly. Oxidation of II-12 was accomplished with the Collins reagent, dipyridine-chromium(VI)-oxide (1.4 g, 8.8 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL), prepared as described<sup>117</sup>. The mixture was stirred at room temperature for 2 hours, filtered through a short pad of silica gel and the solvent removed to give a residue which, after column chromatography with ether:petroleum ether (1:3), afforded II-1 (40 mg, 30%). R<sub>F</sub>: 0.35 ether:petroleum ether (1:3);  $[\alpha]_D^{25} -51.6^\circ$  (c 1.6, CHCl<sub>3</sub>); Lit.<sup>140</sup>  $[\alpha]_D^{25} -70.0^\circ$  (c 5.0, CHCl<sub>3</sub>). IR (film), 3020, 1780, 1660, 1180 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.89 (t, 3H, CH<sub>3</sub>-), 1.1-1.5 (m, 12H, -CH<sub>2</sub>-), 1.95 (tdd, 1H, H<sub>3</sub>, J<sub>3,3'</sub>=13, J<sub>3,4</sub>=8.5, J<sub>2',3</sub>=3.25), 2.13 (m, 2H, H<sub>7</sub>), 2.38 (tddd, 1H, H<sub>3'</sub>, J<sub>3,3'</sub>=13, J<sub>2',3'</sub>=6.5, J<sub>3',4</sub>=6.5, J<sub>2,3'</sub>=1), 2.56 (dd, 1H, H<sub>2'</sub>, J<sub>2,2'</sub>=9.75, J<sub>2',3</sub>=3.25), 2.58 (dd, 1H, H<sub>2</sub>, J<sub>2,2'</sub>=9.75, J<sub>2,3'</sub>=1.25), 5.26 (dddd, 1H, H<sub>4</sub>, J<sub>4,5</sub>=8.5, J<sub>3,4</sub>=8.5, J<sub>3',4</sub>=6.5, J<sub>4,6</sub>=1), 5.65 (tdd, 1H, H<sub>5</sub>, J<sub>5,6</sub>=10.75, J<sub>4,5</sub>=8.5, J<sub>5,7</sub>=1.5), 5.7 (dtd, 1H, H<sub>6</sub>, J<sub>5,6</sub>=10.75, J<sub>6,7</sub>=7.75, J<sub>4,6</sub>=1); mass spectrum, m/e: 224(2.9), 126(31.7), 125(24.5), 111(100), 81(37.3). Anal. calcd. for C<sub>14</sub>H<sub>24</sub>O<sub>2</sub>: C, 74.96; H, 10.78. Found: C, 75.07; H, 11.07.

**1,2;5,6-Di-O-isopropylidene-3-O-[(methylthio)-thiocarbonyl]- $\alpha$ -D-glucofuranose<sup>119</sup> (II-13)**

A mixture of II-3 (20 g, 0.077 mol), sodium hydride (4.1 g, 0.085 mol, 50% dispersion in mineral oil), imidazole (0.2 g) and dry tetrahydrofuran (50 mL) was stirred for 45 min at room temperature. Carbon disulphide (6.5 g, 0.085 mol) was added and the stirring continued for 1 hour. Methylation with MeI (12 g, 0.085 mol) for 30 min was followed by dilution with water (50 mL) and extraction with CH<sub>2</sub>Cl<sub>2</sub> (3  $\times$  50 mL). The combined organic extracts were washed with 10% hydrochloric acid solution (50 mL), sodium bicarbonate solution (50 mL) and water and dried (Na<sub>2</sub>SO<sub>4</sub>). Removal of the solvent gave a yellow oil which, after column chromatography with ether:petroleum ether (1:3), afforded II-13 (26.1 g, 100%). R<sub>f</sub>: 0.41, ether:petroleum ether (1:3);  $[\alpha]_D^{23}$  -14.7° (c 13.71, CHCl<sub>3</sub>); Lit.<sup>141</sup>  $[\alpha]_D^{20}$  -19.3° (c 1.4, CHCl<sub>3</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.32 (s, 3H, CH<sub>3</sub>-), 1.33 (s, 3H, CH<sub>3</sub>-), 1.42 (s, 3H, CH<sub>3</sub>-), 1.55 (s, 3H, CH<sub>3</sub>-), 2.60 (s, 3H, CH<sub>3</sub>S-), 4.06 (dd, 1H, H<sub>6</sub>', J<sub>6,6'</sub>=8.5, J<sub>5,6'</sub>=5), 4.15 (dd, 1H, H<sub>6</sub>', J<sub>6,6'</sub>=8.5, J<sub>5,6'</sub>=6), 4.31 (ddd, 1H, H<sub>5</sub>, J<sub>4,5</sub>=7.5, J<sub>5,6</sub>=6, J<sub>5,6'</sub>=5), 4.34 (dd, 1H, H<sub>4</sub>, J<sub>4,5</sub>=7.5, J<sub>3,4</sub>=2.75), 4.68 (d, 1H, H<sub>2</sub>, J<sub>1,2</sub>=4), 5.91 (d, 1H, H<sub>3</sub>, J<sub>3,4</sub>=2.75), 5.91 (d, 1H, H<sub>1</sub>, J<sub>1,2</sub>=4); mass spectrum, m/e: 335(20), 317(30.1), 303(33.9), 101(100), 43(42). Anal. calcd. for C<sub>14</sub>H<sub>22</sub>O<sub>6</sub>S<sub>2</sub>: C, 47.99; H, 6.33. Found: C, 48.01; H, 6.56.

**1,2;5,6-Di-O-isopropylidene-3-deoxy- $\alpha$ -D-glucofuranose (II-14)**

This was prepared from II-13 by the method of Barton and McCombie<sup>118</sup>. R<sub>f</sub>: 0.28, ether:petroleum ether (1:3);  $[\alpha]_D^{23}$  -4.1° (c 24.7, CHCl<sub>3</sub>); Lit.<sup>119</sup>  $[\alpha]_D^{18}$  -5.8 (c 4.2, ethanol). <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.33 (s, 3H, CH<sub>3</sub>-), 1.37 (s, 3H, CH<sub>3</sub>-), 1.43 (s, 3H, CH<sub>3</sub>-), 1.52 (s, 3H, CH<sub>3</sub>-), 1.78 (ddd, 1H, H<sub>3</sub>,

$J_{3,3'}=13.5, J_{3,4}=10, J_{2,3}=5$ ), 2.19 (dd, 1H,  $H_{3'}$ ,  $J_{3,3'}=13.5, J_{3',4}=4$ ), 3.82 (m, 1H,  $H_4$ ), 4.05-4.25 (m, 3H,  $H_5, H_6$ ), 4.77 (dd, 1H,  $H_2, J_{1,2}=4, J_{2,3}=4$ ), 5.83 (d, 1H,  $H_1, J_{1,2}=4$ ); mass spectrum, m/e: 229(30), 143(56.3), 111(52.8), 101(42), 85(100), 59(50), 43(68). Anal. calcd. for  $C_{12}H_{20}O_5$ : C, 59.01; H, 8.25. Found: C, 58.81; H, 8.50.

**3-Deoxy-1,2-O-isopropylidene- $\alpha$ -D-erythro-pentodialdo-1,4-furanose<sup>104</sup>**  
**(II-15)**

Compound II-14 (5 g, 0.021 mol) was dissolved in 0.02 N hydrochloric acid solution (200 mL) with stirring. After 2 hours at room temperature, the solution was cooled in an ice-water bath and sodium hydrogen carbonate was added to neutralize the acid. A solution of sodium metaperiodate (4.82 g, 0.023 mol) in water (50 mL) was added slowly, over a period of 1.5 hours, and the mixture was stirred vigorously for a further 30 min. The aqueous solution was then extracted with  $CH_2Cl_2$  (5  $\times$  20 mL), washed with brine (50 mL), dried ( $Na_2SO_4$ ) and concentrated. Column chromatography of the oily residue with ethyl acetate as an eluant gave II-15 (2.6 g, 74%).  $R_f$ : 0.3, ether:petroleum ether (1:3);  $[\alpha]_D^{23} -93.3^\circ$  (c 13.0, ethyl acetate). IR (film) 3450, 2730, 1735, 1380  $cm^{-1}$ .  $^1H$  NMR ( $CDCl_3$ )  $\delta$  1.34 (s, 3H,  $CH_3^-$ ), 1.52 (s, 3H,  $CH_3^-$ ), 1.82 (ddd, 1H,  $H_3, J_{3,3'}=14, J_{3,4}=11.6, J_{2,3}=5$ ), 2.34 (dd, 1H,  $H_{3'}, J_{3,3'}=14, J_{3',4}=5.8$ ), 4.57 (ddd, 1H,  $H_4, J_{3,4}=11.6, J_{3',4}=5.8, J_{4,5}=1.8$ ), 4.79 (t, 1H,  $H_2, J_{2,3}=5, J_{1,2}=3.68$ ), 5.95 (d, 1H,  $H_1, J_{1,2}=3.68$ ), 9.7 (d, 1H,  $H_5, J_{4,5}=1.8$ ); mass spectrum, m/e: 157(10), 143(15), 85(46.9), 59(66.3), 43(100). Anal. calcd. for  $C_8H_{12}O_4$ : C, 55.81; H, 7.03. Found: C, 55.61; H, 7.22.



**3,5,6-Trideoxy-1,2-O-isopropylidene- $\alpha$ -D-erythro-tetradec-5-(Z)-  
enofuranose (II-16)**

Compound II-16 was prepared in 55% yield, following the procedure described for the preparation of II-7. R<sub>f</sub>: 0.5, ether:petroleum ether (2:3);  $[\alpha]_D^{23}$  -10° (c 6.3, CHCl<sub>3</sub>). IR (film) 1660 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.88 (t, 3H, CH<sub>3</sub>-), 1.1-1.4 (m, 15H, -CH<sub>2</sub>-, CH<sub>3</sub>-), 1.5-1.6 (m, 4H, H<sub>3</sub>, CH<sub>3</sub>-), 2.10 (m, 3H, H<sub>3</sub>', 2H<sub>7</sub>), 4.74 (dd, 1H, H<sub>2</sub>, J<sub>1,2</sub>=4, J<sub>2,3</sub>=4), 4.95 (ddd, broad, 1H, H<sub>4</sub>, J<sub>3,4</sub>=11, J<sub>4,5</sub>=8, J<sub>3',4</sub>=4), 5.35 (tdd, 1H, H<sub>5</sub>, J<sub>5,6</sub>=11, J<sub>4,5</sub>=8, J<sub>5,7</sub>=1.5), 5.75 (ddd, 1H, H<sub>6</sub>, J<sub>5,6</sub>=11, J<sub>6,7</sub>=8, J<sub>4,6</sub>=1), 5.85 (d, 1H, H<sub>1</sub>, J<sub>1,2</sub>=4); mass spectrum, m/e: 282(2.2), 267(10), 84(65.4), 83(57.3), 59(100), 43(95.2). Anal. calcd. for C<sub>17</sub>H<sub>30</sub>O<sub>3</sub>: C, 72.30; H, 10.71. Found: C, 71.85; H, 10.81.

**Methyl-3,5,6-trideoxy- $\beta$ -D-erythro-tetradec-5-(Z)-enofuranoside  
(II-17)**

Compound II-17 was prepared in 61% yield from II-16, as described for the preparation of II-8. R<sub>f</sub>: 0.31, ether:petroleum ether (1:1);  $[\alpha]_D^{23}$  -24.5° (c 8.50, methanol). IR (film) 3350, 3060, 1650 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>) ( $\beta$ -anomer)  $\delta$  0.88 (t, 3H, CH<sub>3</sub>-), 1.1-1.5 (m, 12H, -CH<sub>2</sub>-), 1.76 (d, 1H, 2-OH, J<sub>2-OH,2</sub>=5, D<sub>2</sub>O exchangeable), 1.91 (ddd, 1H, H<sub>3</sub>, J<sub>3,3'</sub>=13.5, J<sub>3,4</sub>=9.5, J<sub>2,3</sub>=4.5), 2.04 (dd, 1H, H<sub>3</sub>', J<sub>3',3</sub>=13.5, J<sub>3',4</sub>=6.5), 2.1 (m, 2H, H<sub>7</sub>), 3.35 (s, 3H, CH<sub>3</sub>O-), 4.27 (dd, 1H, H<sub>2</sub>, J<sub>2,2-OH</sub>=5, J<sub>2,3</sub>=4.5), 4.81, (s, 1H, H<sub>1</sub>), 5.14 (dd, 1H, H<sub>4</sub>, J<sub>3,4</sub>=9.5, J<sub>4,5</sub>=9, J<sub>3',4</sub>=6.5), 5.38 (tdd, 1H, H<sub>5</sub>, J<sub>5,6</sub>=11, J<sub>4,5</sub>=9, J<sub>5,7</sub>=1.5), 5.52 (dtd, 1H, H<sub>6</sub>, J<sub>5,6</sub>=11, J<sub>6,7</sub>=7, J<sub>4,6</sub>=1); mass spectrum, m/e: 256(1), 241(0.2), 225(0.5), 143(77.2), 111(90.7), 84(100), 83(100). Anal. calcd. for C<sub>15</sub>H<sub>28</sub>O<sub>3</sub>: C, 70.28; H, 11.01. Found: C, 70.08; H, 11.30.

**Methyl-3,5,6-trideoxy-2-O-methanesulfonyl- $\beta$ -D-erythro-tetradec-5-(Z)-  
enofuranoside (II-19)**

Compound II-19 was prepared from acetal II-17 in 66% yield, as described for the preparation of II-9.  $R_f$ : 0.51, ether:petroleum ether (1:1);  $[\alpha]_D^{23}$   $-31^\circ$  ( $c$  5.0,  $CHCl_3$ ).  $^1H$  NMR ( $CDCl_3$ )  $\delta$  0.9 (t, 3H,  $CH_3-$ ), 1.1-1.5 (m, 12H,  $-CH_2-$ ), 2.05 (ddd, 1H,  $H_3$ ,  $J_{3,3'}=14$ ,  $J_{3,4}=9.5$ ,  $J_{2,3}=4.75$ ), 2.07 (m, 2H,  $H_7$ ), 2.31 (dd, 1H,  $H_{3'}$ ,  $J_{3,3'}=14$ ,  $J_{3',4}=6.5$ ), 3.07 (s, 3H,  $MsO-$ ), 3.37 (s, 3H,  $CH_3O-$ ), 5.04 (s, 1H,  $H_1$ ), 5.05 (d, 1H,  $H_2$ ,  $J_{2,3}=4.5$ ), 5.13 (ddd, 1H,  $H_4$ ,  $J_{3,4}=9.5$ ,  $J_{4,5}=9$ ,  $J_{3',4}=6.5$ ), 5.35 (tdd, 1H,  $H_5$ ,  $J_{5,6}=11$ ,  $J_{4,5}=9$ ,  $J_{5,7}=1$ ), 5.56 (dtd, 1H,  $H_6$ ,  $J_{5,6}=11$ ,  $J_{6,7}=7.5$ ,  $J_{4,6}=1$ ); mass spectrum,  $m/e$ : 334(0.5), 303(0.1), 167(64.8), 125(100), 79(66.2), 67(64.7), 55(68), 41(60). Anal. calcd. for  $C_{16}H_{30}O_5S$ : C, 57.46; H, 9.04. Found: C, 57.77; H, 9.15.

**Methyl-3,5,6-trideoxy-2-O-[(methylthio)-thiocarbonyl]- $\beta$ -D-erythro-  
tetradec-5-(Z)-enofuranoside (II-20)**

Compound II-20 was prepared from II-17 in 13% yield, as described for the preparation of II-13.  $^1H$  NMR ( $CDCl_3$ )  $\delta$  0.9 (t, 3H,  $CH_3-$ ), 1.1-1.4 (m, 12H,  $-CH_2-$ ), 2.10 (m, 3H, 2H $_7$ ,  $H_3$ ), 2.31 (dd, 1H,  $H_{3'}$ ,  $J_{3',3}=14$ ,  $J_{3',4}=6.5$ ), 2.58 (s, 3H,  $CH_3S-$ ), 3.38 (s, 3H,  $CH_3O-$ ), 5.04 (s, 1H,  $H_1$ ), 5.12 (ddd, 1H,  $H_4$ ,  $J_{4,5}=9$ ,  $J_{3,4}=8.5$ ,  $J_{3',4}=6.5$ ), 5.40 (tdd, 1H,  $H_5$ ,  $J_{5,6}=10.5$ ,  $J_{4,5}=9$ ,  $J_{5,7}=1$ ), 5.54 (dtd, 1H,  $H_6$ ,  $J_{5,6}=10.5$ ,  $J_{6,7}=7.5$ ,  $J_{4,6}=1$ ), 5.81 (d, 1H,  $H_2$ ,  $J_{2,3}=4.5$ ).

**Methyl-3,5,6-trideoxy-2-O-trifluoromethanesulfonyl- $\beta$ -D-erythro-  
tetradec-5-(Z)-enofuranoside (II-21)**

Triflic anhydride (234 mg, 0.60 mmol) in dichloromethane (5 mL) was added to a solution of pyridine (69 mg, 0.87 mmol) in dichloromethane

(10 mL) maintained at  $-15^{\circ}\text{C}$ . To this solution was added methyl furanoside II-17 (170 mg, 0.66 mmol) in dichloromethane (5 mL) and the reaction mixture was stirred for 1.5 hours at  $-15^{\circ}\text{C}$  before being poured into sodium bicarbonate solution (20 mL). The organic layer was separated and dried (anhydrous  $\text{Na}_2\text{SO}_4$ ) and the solvent was evaporated to give an oil which, after column chromatography with 20% ether in petroleum ether, afforded II-21 (150 mg, 65%) as a colourless oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.88 (t, 3H,  $\text{CH}_3$ -), 1.2-1.5 (m, 12H,  $-\text{CH}_2$ -), 2.1 (m, 2H,  $\text{H}_7$ ), 2.14 (ddd, 1H,  $\text{H}_3$ ,  $J_{3,3'}=14$ ,  $J_{2,3}=4$ ,  $J_{3,4}=9.5$ ), 2.35 (dd, 1H,  $\text{H}_3'$ ,  $J_{3,3'}=14$ ,  $J_{3',4}=6.5$ ), 3.37 (s, 3H,  $\text{CH}_3\text{O}$ -), 5.05 (s, 1H,  $\text{H}_1$ ), 5.15 (m, 1H,  $\text{H}_4$ ,  $J_{4,5}=9$ ), 5.23 (d, 1H,  $\text{H}_2$ ,  $J_{2,3}=4$ ), 5.33 (tdd, 1H,  $\text{H}_5$ ,  $J_{5,6}=11$ ,  $J_{4,5}=9$ ,  $J_{5,7}=1$ ), 5.6 (dtd, 1H,  $\text{H}_6$ ,  $J_{5,6}=11$ ,  $J_{6,7}=7.5$ ,  $J_{4,6}=1$ ); mass spectrum, m/e: 388(10), 289(15), 275(10), 149(5), 113(5), 55(100).

**Methyl-2-iodo-2,3,5,6-tetradecoxy- $\beta$ -D-threo-tetradec-5-(Z)-  
enofuranoside (II-22)**

Triflate II-21 (100 mg, 0.26 mmol) was dissolved in benzene (15 mL) and tetrabutylammonium iodide (480 mg, 1.3 mmol) was added. The reaction mixture was then refluxed for 24 hours, cooled and washed with water (20 mL), 5% aqueous sodium bisulfite (20 mL), saturated aqueous sodium bicarbonate (20 mL) and water and dried ( $\text{Na}_2\text{SO}_4$ ). The solvent was distilled to leave a residue which was chromatographed on silica gel with 10% ether in petroleum ether as the eluant to give II-22 (5 mg, 5%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.87 (t, 3H,  $\text{CH}_3$ -), 1.1-1.5 (m, 12H,  $-\text{CH}_2$ -), 2.07 (m, 2H,  $\text{H}_7$ ), 2.17 (ddd, 1H,  $\text{H}_3$ ,  $J_{3,3'}=12.5$ ,  $J_{2',3'}=12.5$ ,  $J_{3',4}=9$ ), 2.55 (ddd, 1H,  $\text{H}_3$ ,  $J_{3,3'}=12.5$ ,  $J_{2',3}=7.5$ ,  $J_{3,4}=6.5$ ), 3.41 (s, 3H,  $\text{CH}_3\text{O}$ -), 3.97 (ddd, 1H,  $\text{H}_2'$ ,  $J_{2',3'}=12.5$ ,  $J_{2',3}=7.5$ ,  $J_{1,2'}=4$ ), 4.80 (d, 1H,  $\text{H}_1$ ,  $J_{1,2'}=4$ ),

4.83 (m, 1H, H<sub>4</sub>), 5.39 (tdd, 1H, H<sub>5</sub>, J<sub>5,6</sub>=10.5, J<sub>4,5</sub>=9, J<sub>5,7</sub>=1), 5.53 (dtd, -1H, H<sub>6</sub>, J<sub>5,6</sub>=10.5, J<sub>6,7</sub>=7.5, J<sub>4,6</sub>=1); mass spectrum, m/e: 366(5), 365(1), 335(22), 334(97), 267(8), 253(26), 239(34), 208(14), 207(43), 71(100).

**3,5-O-Benzylidene-D-ribo- $\gamma$ -lactone<sup>131</sup> (II-25)**

A mixture of (D)-(+)-ribonolactone<sup>129</sup> II-24 (30 g, 0.203 mol), freshly distilled benzaldehyde (300 mL) and concentrated hydrochloric acid (30 mL) was stirred at ambient temperature for 7 hours. Ether (350 mL) was added to precipitate the product, which was collected by filtration. The crude product was washed successively with 5% aqueous sodium bicarbonate (100 mL), water (100 mL) and petroleum ether (200 mL). The white product was dried (P<sub>2</sub>O<sub>5</sub>) and recrystallized from acetone-petroleum ether to afford II-25 as needles (47 g, 98%); m.p. 234-235°C;  $[\alpha]_D^{23}$  -171° (c 2.70, DMF); Lit.<sup>130</sup> m.p. 233-235.5°C,  $[\alpha]_D^{23}$  -174.1° (c 2.26°, DMF). IR (KBr) 3430, 3380, 2935, 2890, 1750, 1460, 1410, 1180, 1140, 1078, 1055, 1045, 1010, 952, 770, 720 cm<sup>-1</sup>. <sup>1</sup>H NMR (acetone-d<sub>6</sub>)  $\delta$  4.44 (d, 1H, H<sub>5</sub>, J<sub>5,5'</sub>=13.5), 4.48 (d, 1H, OH, J<sub>2-OH,2</sub>=7, D<sub>2</sub>O exchangeable), 4.52 (dd, 1H, H<sub>5'</sub>, J<sub>5,5'</sub>=13.5, J<sub>4,5'</sub>=3.25), 4.7 (dd, 1H, H<sub>2</sub>, J<sub>2-OH,2</sub>=7, J<sub>2,3</sub>=3.25), 4.75 (dq, 1H, H<sub>3</sub>, J<sub>3,4</sub>=8, J<sub>2,3</sub>=3.25, J<sub>3,5</sub>=1), 4.85 (ddd, 1H, H<sub>4</sub>, J<sub>3,4</sub>=8, J<sub>4,5'</sub>=3.25, J<sub>4,5</sub>=1.5), 5.8 (s, 1H,  $\phi$ CH-), 7.3-7.6 (m, 5H, C<sub>6</sub>H<sub>5</sub>-); mass spectrum, m/e: 236(31), 235(50), 218(1), 130(54), 105(93), 91(30), 89(20), 79(55), 78(48), 77(100). Anal. calcd. for C<sub>12</sub>H<sub>12</sub>O<sub>5</sub>: C, 61.02; H, 5.12. Found: C, 61.21; H, 5.03.

**3,5-O-Benzylidene-2-O-[(methylthio)-thiocarbonyl]-D-ribo- $\gamma$ -lactone (II-26)**

To a stirred solution of II-25 (30 g, 0.127 mol) in dry

N,N-dimethylformamide (200 mL), kept at  $-60^{\circ}\text{C}$ , was added sodium hydride (7.30 g, 0.152 mol, 50% dispersion in mineral oil) and the stirring was continued at  $-60^{\circ}\text{C}$  for 5 hours. Carbon disulfide (11.6 g, 0.152 mol) was added and the stirring continued for a further 2 hours between  $-30$  to  $-10^{\circ}\text{C}$ . Methyl iodide (21.6 g, 0.152 mol) was added at  $-10^{\circ}\text{C}$  and the reaction was allowed to reach room temperature in 30 min. The reaction mixture was then diluted with water (200 mL). The aqueous layer was extracted with methylene chloride ( $4 \times 50$  mL), washed with a saturated sodium chloride solution (150 mL) and dried ( $\text{Na}_2\text{SO}_4$ ). The solvent was evaporated under reduced pressure and the crude product was crystallized twice from anhydrous ethanol to give crystalline II-26 (21.5 g, 52%); m.p.  $147$ - $148.5^{\circ}\text{C}$ ,  $[\alpha]_{\text{D}}^{23} -317.0^{\circ}$  ( $c$  1.1,  $\text{CHCl}_3$ ); Lit.<sup>130</sup> m.p.  $145$ - $146^{\circ}\text{C}$ ,  $[\alpha]_{\text{D}}^{23} -314.3^{\circ}$  ( $c$  2.0,  $\text{CHCl}_3$ ). IR ( $\text{CHCl}_3$ ) 2995, 2890, 1790, 1450, 1410, 1390, 1190, 1160, 1120,  $1085\text{ cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.65 (s, 3H,  $\text{CH}_3$ -S), 4.45 (dd, 1H,  $\text{H}_5$ ,  $J_{5,5'}=13.5$ ,  $J_{4,5}=1.8$ ), 4.65 (d, 1H,  $\text{H}_5'$ ,  $J_{5,5'}=13.5$ ), 4.77 (qdd, 1H,  $\text{H}_3$ ,  $J_{3,4}=8$ ,  $J_{2,3}=2$ ,  $J_{3,5}=0.8$ ), 4.99 (ddd, 1H,  $\text{H}_4$ ,  $J_{3,4}=8$ ,  $J_{4,5}=3$ ,  $J_{4,5'}=0.8$ ), 5.83 (s, 1H,  $\phi\text{CH}$ ), 6.47 (d, 1H,  $\text{H}_2$ ,  $J_{2,3}=3$ ), 7.35-7.55 (m, 5H,  $\text{C}_6\text{H}_5$ -); mass spectrum, m/e 328(4), 327(4), 326(23), 279(8), 235(8), 233(10), 219(15), 105(82), 91(100), 89(16), 79(56), 78(30), 77(85). Anal. calcd. for  $\text{C}_{14}\text{H}_{14}\text{O}_5\text{S}_2$ : C, 51.52; H, 4.32. Found: C, 51.62; H, 4.22.

### 3,5-O-Benzylidene-2-deoxy-D-erythro-pentono- $\gamma$ -lactone (II-27)

To a solution of xanthate II-26 (7.6 g, 0.023 mol) in dry toluene (100 mL) was added tri-*n*-butyltin hydride (13.6 g, 0.047 mol) and  $\alpha,\alpha'$ -azobisisobutyronitrile (0.5 g) under an argon atmosphere. The mixture was refluxed under argon overnight. The solution was cooled to room

temperature and the insoluble product was collected by filtration. Recrystallization from toluene afforded II-27 (5.6 g, 93%) as needles; m.p. 139-141°C,  $[\alpha]_D^{24}$  -175° ( $c$  0.5, CHCl<sub>3</sub>), Lit.<sup>130,142</sup> m.p. 139-139.5°C;  $[\alpha]_D$  -172.3° ( $c$  1.7, CHCl<sub>3</sub>). IR (KBr) 2940, 2880, 1745, 1413, 1395, 1348, 1270, 1160, 1102, 1065, 1048, 1030, 975, 785, 762 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  2.65 (dd, 1H, H<sub>2</sub>, J<sub>2,2'</sub>=16, J<sub>2,3</sub>=3.8), 3.06 (dd, 1H, H<sub>2'</sub>, J<sub>2,2'</sub>=16, J<sub>2',3</sub>=2.5), 4.24 (dd, 1H, H<sub>5</sub>, J<sub>5,5'</sub>=13, J<sub>4,5</sub>=2), 4.58 (ddd, 1H, H<sub>4</sub>, J<sub>3,4</sub>=8, J<sub>4,5</sub>=2, J<sub>4,5'</sub>=1.5), 4.60 (dd, 1H, H<sub>5'</sub>, J<sub>5,5'</sub>=13, J<sub>4,5'</sub>=1.5), 4.80 (ddd, 1H, H<sub>3</sub>, J<sub>3,4</sub>=8, J<sub>2,3</sub>=3.8, J<sub>2',3</sub>=2.5), 5.76 (s, 1H,  $\phi$ CH), 7.35-7.55 (m, 5H, C<sub>6</sub>H<sub>5</sub>); mass spectrum, m/e: 220(38), 219(100), 105(97), 91(16), 79(25), 78(63), 77(73), 51(22). Anal. calcd. for C<sub>12</sub>H<sub>12</sub>O<sub>4</sub>: C, 65.45; H, 5.49. Found: C, 65.46; H, 5.60.

### **2-Deoxy-D-erythro-pentono-1,4-lactone (II-28)**

The 2-deoxy compound II-27 (5.6 g, 0.026 mol) was deprotected with 50% aqueous trifluoroacetic acid (20 mL) in chloroform (20 mL) at 70°C for 10 hours. The aqueous layer was separated and the organic layer was extracted with water (2 × 10 mL). The combined water extracts were evaporated to dryness and the residue was evaporated with toluene (5 × 10 mL) to give II-28 (3.3 g, 96% crude yield) as a viscous, colourless oil. The product, which was pure by tlc, was characterized as the di-benzoyl derivative II-29 and was used without further purification.

### **3,5-Di-O-benzoyl-2-deoxy-D-erythro-pentono-1,4-lactone (II-29)**

Compound II-29 was prepared in 40% yield, as described by Bock, Lundt and Pedersen<sup>133</sup>; m.p. 98-100°C,  $[\alpha]_D^{23}$  +19.3° ( $c$  3.0, ethyl acetate), Lit.<sup>133</sup> m.p. 99-100°C,  $[\alpha]_D^{25}$  +19° ( $c$  3.3, ethyl acetate).

**5-O-Trityl-2-deoxy-D-erythro-pentono-1,4-lactone (II-30)**

To a stirred solution of 2-deoxy-D-erythro-pentono-1,4-lactone (II-28) (1.26 g, 9.54 mmol) in pyridine (20 mL) was added freshly-prepared triphenylmethyl chloride (3.2 g, 11.45 mmol) at room temperature and stirring was continued for 24 hours. Most of the pyridine was evaporated at 50-60°C and the residue was dissolved in dichloromethane (40 mL), washed thoroughly with brine (5 × 20 mL) and dried (Na<sub>2</sub>SO<sub>4</sub>). Evaporation of the solvent under reduced pressure left a colourless oil which, after column chromatography with ether:petroleum ether (1:1), afforded II-30 as a crystalline mass (3 g, 84%); m.p. 131-133°C,  $[\alpha]_D^{23} +336^\circ$  (c 4.25; methanol). IR (KBr) 3560, 3520, 3100, 3070, 3040, 2950, 2930, 2888, 2820, 1780, 1600, 1490, 1455, 1220, 1200, 1160, 1100 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.23 (d, 1H, OH), 2.5 (dd, 1H, H<sub>2</sub>, J<sub>2,2'</sub>=18, J<sub>2,3</sub>=6.5), 3.06 (dd, 1H, H<sub>5</sub>, J<sub>5,5'</sub>=11, J<sub>4,5</sub>=3), 3.2 (dd, 1H, H<sub>2'</sub>, J<sub>2,2'</sub>=18, J<sub>2',3</sub>=2.75), 3.53 (dd, 1H, H<sub>5'</sub>, J<sub>5,5'</sub>=11, J<sub>4,5'</sub>=3.75), 4.4-4.5 (m, 2H, H<sub>3</sub>, H<sub>4</sub>), 7.2-7.5 (m, 15H, C<sub>6</sub>H<sub>5</sub>); mass spectrum, m/e: 375(12), 357(1), 259(19), 258(23), 243(78), 242(8), 166(15), 165(100), 115(13), 105(38), 91(8), 79(5), 78(10), 77(25). Anal. calcd. for C<sub>24</sub>H<sub>22</sub>O<sub>4</sub>: C, 76.99; H, 5.92. Found: C, 76.70; H, 6.17.

**(S)-5-Tritylloxymethyl-(5H)-furan-2-one (II-32)**

To a stirred solution of II-30 (1.5 g, 4 mmol) and triphenylphosphine (1.3 g, 4.8 mmol) in benzene (20 mL) under argon was added diethyl azodicarboxylate (0.83 g, 4.8 mmol) in benzene (2 mL) and the mixture was stirred at room temperature for 24 hours. The solvent was then removed under reduced pressure, leaving a yellow syrup, and was replaced by toluene (20 mL). Methyl iodide (0.68 g, 4.8 mmol) was added and, after 30 min at room temperature, the mixture was refluxed for 24 hours. The solvent was

removed in vacuo and the residue was chromatographed on silica gel by eluting with methylene chloride, yielding II-32 (0.87 g, 60%), which solidified upon standing; m.p. 155-157°C,  $[\alpha]_D^{23} -106^\circ$  ( $c$  3.01,  $\text{CHCl}_3$ ), Lit.<sup>86</sup> m.p. 152-154°C,  $[\alpha]_D^{20} -95.1^\circ$  ( $c$  3.42,  $\text{CHCl}_3$ ).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  3.41 (dd, 1H,  $\text{H}_5$ ,  $J_{5,5'}=13.5$ ,  $J_{4,5}=5$ ), 3.42 (dd, 1H,  $\text{H}_5'$ ,  $J_{5,5'}=13.5$ ,  $J_{4,5'}=5$ ), 5.1 (ttd, 1H,  $\text{H}_4$ ,  $J_{4,5}=5$ ,  $J_{4,5'}=5$ ,  $J_{3,4}=2$ ), 6.2 (dd, 1H,  $\text{H}_2$ ,  $J_{2,3}=6$ ,  $J_{2,4}=2$ ), 7.2-7.5 (m, 16H,  $\text{C}_6\text{H}_5$ ,  $\text{H}_3$ ).

**(S)-(+)- $\delta$ -Tritylxy- $\gamma$ -valerolactone (II-33)**

Catalytic hydrogenation of (S)-5-trityloxymethyl-(5H)-furan-2-one<sup>86</sup> (II-32) (3.1 g, 8.7 mmol) in ethanol (100 mL) at room temperature and atmospheric pressure (760 Torr) with 5% palladium on charcoal (310 mg) for 12 hours gave, upon filtration and evaporation of the solvent, crystalline II-33. Two recrystallizations of II-33 from boiling methanol gave the lactone derivative (1.86 g, 60%); m.p. 146-148°C,  $[\alpha]_D^{26} +24.6^\circ$  ( $c$  2.36,  $\text{CHCl}_3$ ), Lit.<sup>83</sup> m.p. 153-154°C,  $[\alpha]_D +26.6^\circ$  ( $c$  1,  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  2.05 (m, 1H,  $\text{H}_2$ ), 2.25 (m, 1H,  $\text{H}_2'$ ), 2.52 (ddd, 1H,  $\text{H}_3$ ,  $J_{3,3'}=18$ ,  $J_{2,3'}=10$ ,  $J_{2,3}=7$ ), 2.70 (ddd, 1H,  $\text{H}_3'$ ,  $J_{3,3'}=18$ ,  $J_{2',3'}=10$ ,  $J_{2,3'}=7$ ), 3.17 (dd, 1H,  $\text{H}_5$ ,  $J_{5,5'}=10.5$ ,  $J_{4,5}=4.5$ ), 3.43 (dd, 1H,  $\text{H}_5'$ ,  $J_{5,5'}=10.5$ ,  $J_{4,5'}=3.5$ ), 4.65 (m, 1H,  $\text{H}_4$ ), 7.2-7.5 (m, 15H,  $\text{C}_6\text{H}_5$ ). Anal. calcd. for  $\text{C}_{24}\text{H}_{22}\text{O}_3$ : C, 80.26; H, 6.24. Found: C, 80.01; H, 6.29.

**(S)-(+)- $\delta$ -Hydroxy- $\gamma$ -valerolactone (II-34)**

Detritylation of II-33 (2 g, 5.6 mmol) was accomplished with p-toluenesulphonic acid (200 mg) in methanol (20 mL) at room temperature for 5 hours. The reaction mixture was diluted with water (20 mL) and extracted with methylene chloride (3  $\times$  20 mL). The combined organic layers were washed with brine and dried ( $\text{Na}_2\text{SO}_4$ ). Column chromatography with 7%



ethanol in chloroform as an eluant afforded II-34 (500 mg, 77%) as a colourless oil;  $[\alpha]_D^{25} +31.8^\circ$  ( $c$  8.35, ethanol); Lit.<sup>143</sup>  $[\alpha]_D^{26} +31.3^\circ$  ( $c$  2.92, ethanol). IR (neat film) 3450, 1770  $\text{cm}^{-1}$ .  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  2.15 (m, 1H,  $\text{H}_3$ ), 2.26 (m, 1H,  $\text{H}_3'$ ), 2.45 (t, broad, 1H, OH,  $\text{D}_2\text{O}$  exchangeable), 2.5-2.7 (m, 2H,  $\text{H}_2, \text{H}_2'$ ), 3.65 (ddd, 1H,  $\text{H}_5, \text{J}_{5,5'}=12.5, \text{J}_{5,5-\text{OH}}=6, \text{J}_{4,5}=4.5$ ), 3.92 (ddd, 1H,  $\text{H}_5', \text{J}_{5,5'}=12.5, \text{J}_{5',5-\text{OH}}=6, \text{J}_{4,5'}=2.75$ ), 4.65 (dddd, 1H,  $\text{H}_4, \text{J}_{3',4}=7, \text{J}_{3,4'}=7, \text{J}_{4,5}=4.5, \text{J}_{4,5'}=2.75$ ); mass spectrum,  $m/e$ : 116(1), 85(100), 57(32), 56(12). Anal. calcd. for  $\text{C}_5\text{H}_8\text{O}_3$ : C, 51.73; H, 6.95. Found: C, 51.51; H, 7.21.

**Attempted oxidation of (S)-(+)- $\delta$ -hydroxy- $\gamma$ -valerolactone (II-34) to  $\gamma$ -carbaldehyde- $\gamma$ -butyrolactone (II-36)**

To a stirred suspension of pyridinium chlorochromate (410 mg, 1.9 mmol), in methylene chloride (20 mL), was slowly added a solution of II-34 (110 mg, 0.95 mmol) in methylene chloride (5 mL) and the mixture was stirred for 3 hours. The slow formation of non-polar component was indicated by tlc. Addition of an extra amount of oxydizing agent (6 mmol) and stirring for 24 hours completed the reaction. Removal of chromium salts by filtration through silica gel and solvent afforded an oil which, after column chromatography with 7% ethanol in chloroform, afforded II-35 (70 mg, 64%).  $R_f$ : 0.44, 7% ethanol:chloroform. IR (film) 1810-1720, 1220-1130, 1060  $\text{cm}^{-1}$ .  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ) 2.0-2.15 (m, 1H,  $\text{H}_3$ ), 2.3-2.48 (m, 2H,  $\text{H}_3, \text{H}_3'$ ), 2.5-2.8 (m, 5H,  $\text{H}_2, \text{H}_2', \text{H}_3'$ ), 4.26 (dd, 1H,  $\text{H}_5', \text{J}_{5,5'}=12, \text{J}_{4,5'}=6$ ), 4.47 (dd, 1H,  $\text{H}_5, \text{J}_{5,5'}=12, \text{J}_{4,5}=3$ ), 4.78 (m, 1H,  $\text{H}_4$ ), 5.0 (m, 1H,  $\text{H}_4$ ); mass spectrum,  $m/e$ : 228(0.5), 114(4), 100(21), 85(100), 57(10), 43(8). Anal. calcd. for  $\text{C}_{10}\text{H}_{12}\text{O}_6$ : C, 52.64; H, 5.30. Found: C, 52.33; H, 5.46.

**Attempted oxidation of  $\delta$ -hydroxy- $\gamma$ -valerolactone (II-34) to  $\gamma$ -carbaldehyde- $\gamma$ -butyrolactone (II-36)**

To a stirred suspension of the Collins complex, prepared as described<sup>117</sup>, was added a solution of II-34 (200 mg, 1.72 mmol) in methylene chloride (30 mL). After stirring for 5 hours, the presence of a second component was detected by tlc. The mixture was filtered through a short pad of silica gel and the solvent removed to give a residue which was evaporated with toluene (3  $\times$  5 mL) below 40°C. No aldehyde could be isolated. Instead, II-34 (45 mg) was recovered.

**Attempted oxidation of  $\delta$ -hydroxy- $\gamma$ -valerolactone (II-34) to  $\gamma$ -carbaldehyde- $\gamma$ -butyrolactone (II-36)**

A solution of II-34 (100 mg, 0.86 mmol) in dichloromethane:N,N-dimethylformamide (4:1) (5 mL) was added to a stirred, freshly-prepared mixture of pyridinium dichromate (237 mg, 0.63 mmol) and acetic anhydride (276 mg, 2.7 mmol) dissolved in methylene chloride:N,N-dimethylformamide (4:3) (7 mL). The mixture was boiled under reflux for 2 hours and then added to the top of a short column of silica gel with ethyl acetate to precipitate the chromium salts before elution. The eluate was concentrated to near dryness and toluene (5  $\times$  1 mL) was evaporated from the residue in order to remove any acetic acid or pyridine. Compound II-34 (20 mg) was recovered.

**Attempted oxidation of  $\delta$ -hydroxy- $\gamma$ -valerolactone (II-34) to  $\gamma$ -carbaldehyde- $\gamma$ -butyrolactone (II-36)**

a) aqueous workup

Oxalyl chloride (2.18 mg, 1.72 mmol) in methylene chloride (2 mL), was placed in a 100 mL three-necked, round-bottom flask, equipped with a

magnetic stirrer, a thermometer, a  $\text{CaCl}_2$  drying tube and two pressure-equalizing dropping funnels containing dimethylsulfoxide (268 mg, 3.44 mmol) dissolved in methylene chloride (3 mL) and lactone (II-34) (200 mg, 1.72 mmol) in methylene chloride (2 mL), respectively. The dimethylsulfoxide was added to the stirred oxalyl chloride solution at  $-60^\circ\text{C}$ . The reaction mixture was stirred for 30 min and compound II-34 was added within 5 min. Stirring was continued for an additional 30 min and triethylamine (347 mg, 3.44 mmol) was added. The reaction mixture was allowed to warm to room temperature. Water (10 mL) was added and methylene chloride was separated. The aqueous layer was re-extracted with additional methylene chloride ( $3 \times 10$  mL). The organic layers were combined, washed with saturated sodium chloride solution (10 mL) and dried ( $\text{Na}_2\text{SO}_4$ ). Removal of the solvent afforded unreacted II-34 (82 mg).

b) non-aqueous workup

The reaction was performed as above. Removal of methylene chloride gave a residue which was chromatographed on silica gel with 7% ethanol in chloroform. Removal of the solvent gave II-37 (6 mg, 2%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.1-2.15 (m, 1H,  $\text{H}_3$ ), 2.15 (s, 3H,  $\text{CH}_3\text{S}$ ), 2.3-2.4 (m, 1H,  $\text{H}_3'$ ), 2.5-2.7 (m, 2H,  $\text{H}_2, \text{H}_2'$ ), 3.66 (dd, 1H,  $\text{H}_5, \text{J}_{5,5'}=11, \text{J}_{4,5}=4.5$ ), 3.78 (dd, 1H,  $\text{H}_5', \text{J}_{5,5'}=11, \text{J}_{4,5'}=3.5$ ), 4.68 (s, 2H, S- $\text{CH}_2\text{-O}$ ), 4.7 (m, 1H,  $\text{H}_4$ ).

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