

CHIRAL SYNTHESIS
OF
INSECT PHEROMONES

by

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ABSTRACT

The enantiomers of 9-hydroxy-(E)-2-decenoic acid I-1, a pheromone of the honeybee, Apis mellifera (Linnaeus), have been synthesized by organocuprate-catalyzed opening of S-(-), R-(+), and racemic methyloxirane. The very high regioselectivity and consequent stereoselectivity exhibited by these reagents on methyloxirane provided an excellent entry into the chiral 2-ol functionality. Further elaboration of the α,β -unsaturated acid functionality was completed without any racemization of the chiral center. The final products were subjected to biological testing by other investigators and it was concluded that the R-(-)-isomer was substantially more active in the settling of queenless swarms than its enantiomer.

Lineatin, an aggregation pheromone of Trypodendron lineatum (Olivier), has been shown to be (+)-(1_R,4_S,5_R,7_R)-3,3,7-trimethyl-2,9-dioxatricyclo [3.3.1.0^{4,7}]nonane, (+)-II-1, by the first stereospecific chiral synthesis involving a sixteen step sequence. D-Ribonolactone was used to prepare (2_S,3_R)-2,3-isopropylidenedioxy-4-methyl-4-[(2-trimethylsilylethoxy)methoxy]pentanal II-13. Condensation with diethyl-(3-cyano-1,1-dimethoxypropyl) phosphonate, II-8, provided 2-isomeric α,β -unsaturated nitriles II-14. Magnesium in methanol reduction of this ene-nitrile led to the expected reduction of the ene-bond with unexpected reductive elimination of γ -isopropylidene group.

Catalytic reduction, however, furnished the necessary (3R&S,5R,6R)-3-cyano-5,6-isopropylidenedioxy-7-methyl-7-[(2-trimethylsilylethoxy)methoxy]-1,1-dimethoxyoctane II-15. The 2,9dioxabicyclo[3.3.1]nonane skeleton was achieved by blocking the hemiacetal derivative II-18 with the tert-butyldimethylsilyl group. Reaction with methanesulfonyl chloride, followed by acid treatment gave (1R,4R,5R,7S)-7-cyano-3,3-dimethyl-4-methylsulfonyloxy-2,9-dioxabicyclo[3.3.1]nonane II-21. The formation of the tricyclic acetal skeleton was accomplished by nucleophilic ring closure to provide (1R,4S,5R,7S)-7-cyano-3,3-dimethyl-2,9-dioxatricyclo[3.3.1.0^{4,7}]nonane II-26. The conversion of the cyano group to a methyl was achieved by reduction first with di-isobutylaluminum hydride followed by anhydrous hydrazine in base to provide (+)-lineatin, (+)-(1R,4S,5R,7R)-3,3,7-trimethyl-2,9-dioxatricyclo[3.3.1.0^{4,7}]nonane in 2.7% overall yield.

IN MEMORY OF MY PARENTS

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Introduction

Insect pheromones were defined by Karlson and Luscher¹ as chemicals released by one member of a species that cause specific behavioral responses or physiological changes in other members of the same species. They are the agents of a chemical communication system, and as such they may serve, for example, to attract and excite members of the opposite sex, to aggregate both sexes, to signal alarm or to mark trails leading to a food source². Recently, the study of insect pheromones has attracted a great deal of attention, not only because of their purely scientific interest, but most importantly, because of their potential for controlling insect pest populations^{3,4}. The use of pheromone-baited traps to monitor regions of suspected infestation and to saturate the area with pheromone to confuse the normal response appear most promising.

Recent studies have revealed that pheromonal communication often involves several compounds. Linear olefinic alcohols, esters and aldehydes derived from fatty acid precursors are common in Lepidopteran species^{5,6,7}. Alicyclic or heterocyclic pheromones, often chiral and apparently derived from host plant terpenoid materials, are utilized by many Coleopteran pests^{7,8,9}. These insects often utilize one enantiomer or a specific ratio of enantiomers in their pheromone signal. Since these species show the ability to discriminate between and respond differently to enantiomeric pheromones, meaningful bio-

assays and evaluation of such responses must be carried out using enantiomerically as well as chemically pure substances. It is only in the last few years that stereospecific syntheses of some pheromones have provided pure enantiomers in sufficient quantities for laboratory and field studies.

One approach to the synthesis of chiral pheromones requires either resolution of a relatively simple intermediate early in the synthetic scheme or removal of the unwanted antipode near the end of the sequence by resolution of diastereoisomers¹⁰. This methodology leads to a maximum theoretical yield of 50% of the desired enantiomer from a racemic precursor and such low recovery cannot be tolerated economically. Either the enantiomer of the wrong configuration must be recycled by racemization and the racemic modification once again resolved, or the desired chiral material must be synthesized asymmetrically in the first instance.

Asymmetric synthesis is the method of choice for obtaining chiral molecules since it permits conversions up to 100%, depending on the degree of asymmetric induction, of a prochiral substrate to a chiral product^{11,12}. In practice, the use of one chiral molecule to create another can be effected in several ways, which vary in efficiency depending on how the original chiral substrate is affected. In general, the least efficient reactions are those in which one chiral center is destroyed while another is created. Reactions in which the original chiral

reagent is recovered are more efficient and those reactions in which the chiral reagent is used catalytically are the most efficient. Unfortunately, only relatively few examples of this latter class have been reported as yet and the most effective of these reagents appear to be those that asymmetrically hydrogenate prochiral olefins to chiral molecules^{13,14}.

In spite of the recent developments in asymmetric synthesis^{15,16}, the control of absolute stereochemistry and the regiospecific introduction of functionality at predetermined sites remain as crucial problems in the construction of even moderately functionalized chiral compounds. Over the years, carbohydrates have provided the source of relatively cheap, polyfunctional molecules containing several sites of known stereochemistry and conformation¹⁷. This has led to the use of carbohydrates as chirally pure starting materials in the total synthesis of natural products^{18,19} and insect pheromones²⁰⁻²³. For example, the synthesis of (-)- α -multistriatin, an aggregation pheromone of the European elm bark beetle Scolytus multistriatus, was accomplished starting with D-mannitol²⁰ and D-glucose²¹. Sulcatol, the aggregation pheromone of the two sympatric northwestern timber pests, Gnathotrichus retusus and G. sulcatus, was prepared from L-fucose and 2-deoxy-D-ribose²², and recently D-glucose was utilized to prepare (R,Z)-4-hydroxy-5-tetradecenoic acid lactone, the sex pheromone of the Japanese beetle, Popillia japonica²³.

For a viable total synthesis of chiral insect pheromones, several requirements must be considered. First, the synthesis of both enantiomers must start from a compound of known absolute configuration and optical purity so that the relationship between the stereochemistry and biological activity can be established and compared with those of the natural product²⁴. Second, throughout the synthetic sequence, reactions that may cause epimerization must be avoided. The optical purity of the final product or an intermediate very near to the target molecule should be carefully determined whenever possible²⁵. Third, chirality is preferred to be introduced as late as possible, by combining two fairly well-developed portions of the target molecule at a late stage in the synthetic scheme. This concurrent approach affords substantial cost, yield and logistical advantages relative to a linear approach in which a single fragment is continually elaborated²⁶. Moreover, the late introduction of chirality reduces the possibility of racemization during the reaction sequence.

Objectives

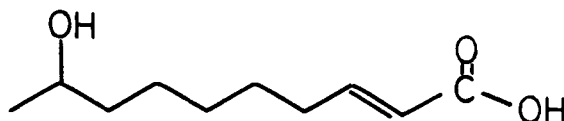
The major objective of this research was to utilize readily available chiral precursors in the synthesis of high-purity chiral pheromones. This involves the utilization of the inherent molecular features of natural products and transforms them into chirally pure synthetic intermediates. The first chapter describes the use of commercially available ethyl S-(-)-lactate, to synthesize both enantiomers of a known queen honeybee pheromone, 9-hydroxy-(E)-2-decenoic acid I-1. The second chapter discusses the first stereospecific total synthesis of (+)-(1R,4S,5R,7R)-3,3,7-trimethyl-2,9-dioxatricyclo[3.3.1.0^{4,7}]nonane (+)-II-1, an aggregation pheromone of Trypodendron lineatum, starting from commercial D-ribonolactone.

CHAPTER I

Enantiomeric Synthesis of 9-Hydroxy-(E)-2-Decenoic Acid

Background

Honeybee queens, *A. mellifera*, produce a number of pheromones which influence the behavior and physiology of worker bees. One of these is 9-hydroxy-(E)-2-decenoic acid I-1, which, like the better-known queen substance 9-oxo-(E)-2-decenoic acid I-2, is produced in the queen's mandibular gland²⁷. There has been some controversy, however, concerning the activity of 9-hydroxy-(E)-2-decenoic acid I-1.

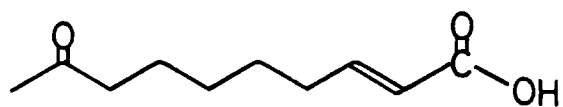


I-1

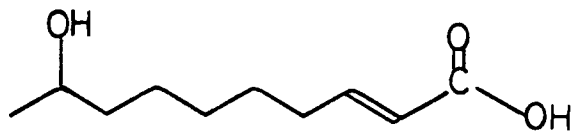
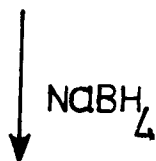
In some studies it has been shown to be active either alone or synergistically with 9-oxo-(E)-2-decenoic acid I-2 in attracting workers to swarm clusters²⁸, inhibiting queen rearing²⁹, and attracting drones²⁷. In contrast, other studies have shown little or no activity of 9-hydroxy-(E)-2-decenoic acid I-1 in attracting workers to swarms³⁰, inhibiting queen rearing³¹, and attracting drones³⁰.

The conflicting nature of these results has been further compounded by the disclosure that the purity of 9-hydroxy-(E)-2-decenoic acid I-1 used in some of these experiments was questionable³⁰. The first preparation of 9-hydroxy-(E)-2-decenoic acid I-1, reported by Eiter³², involved sodium borohydride reduction of 9-oxo-(E)-2-decenoic acid I-2 (Scheme 1). A melting point of 43-45 °C was reported for this product. Boch et.al.³⁰ repeated this preparation and concluded that the procedure adopted by Eiter resulted in incomplete reduction of biologically active 9-oxo-(E)-2-decenoic acid I-2, m.p. 53-54 °C (Scheme 1).

Chirality of the 9-hydroxyl group may further complicate the recognition of this material by workers bees. Inhibition of pheromonal response by the opposite enantiomers has been documented in several insects³³. Thus, the racemic 9-hydroxy-(E)-2-decenoic acid (+)-I-1 produced and used in previous studies might be a poor substitute for the natural pheromone.



I-2



(±)-I-1

Scheme 1

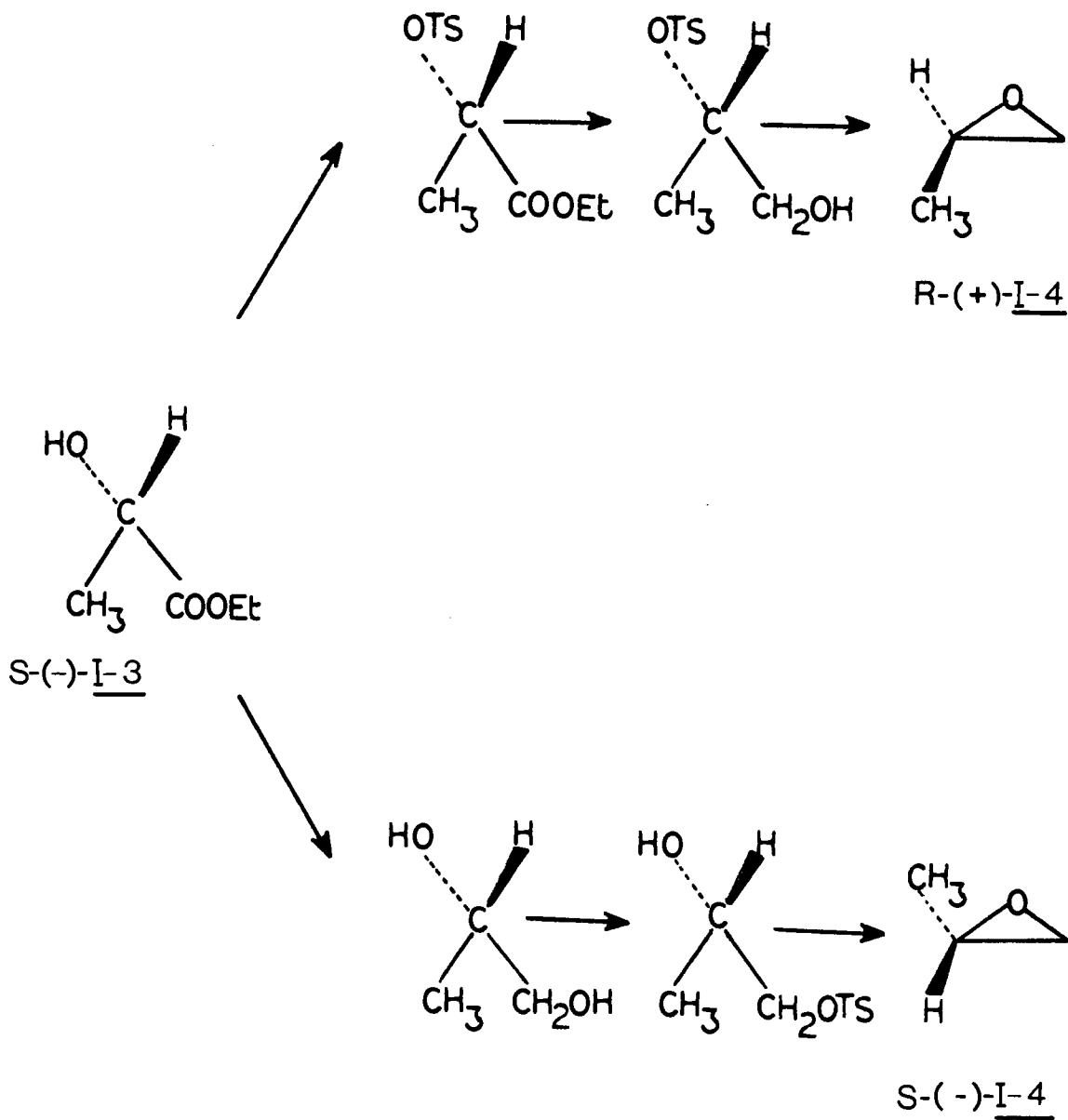
Approach

The aim of this research project was to synthesize 9-hydroxy-(E)-2-decenoic acid I-1, the queen honeybee pheromone, in racemic and enantiomeric form without the intermediacy of the biologically active 9-oxo-(E)-2-decenoic acid I-2. Advantage was taken of the CuI-catalyzed opening of chiral methyloxiranes³⁴, both readily derived from commercially available ethyl S-(-)-lactate. With an appropriately functionalized alkylating agent, stereospecific opening of methyloxirane provided a direct route to the desired chiral 2-ol functionality. The incompatibility of the α,β -unsaturated ester functionality in the alkylating Grignard reagent necessitated the early introduction of the chiral center. Chemical transformations which did not affect the chiral center were employed to elaborate the complete functionality of the natural product in very high enantiomeric purity.

Results and Discussion

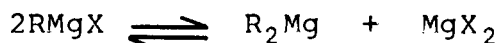
Both enantiomers of methyloxirane I-4 of high chiral purity were prepared from commercially available ethyl S-(-)-lactate I-3, $[\alpha]_D^{20} -12^\circ$ (neat), via a crystalline intermediate to ensure high enantiomeric purity^{34,35} (Scheme 2). A protected 5-bromopentan-1-ol I-6 was used as the alkylating agent. The precursor 5-bromopentan-1-ol I-5, was prepared by the action of lithium aluminum hydride and aluminum chloride on 5-bromovaleric acid³⁶. This modified method to prepare 5-haloalkanols is more effective than treating 1,5-pentane diol with hydrogen halide in refluxing heptane, due to ease of cyclization of 5-halopentan-1-ol under these reaction conditions to tetrahydropyran³⁷.

Difficulty was experienced in promoting the formation of Grignard reagent when tetrahydropyranyl ether was utilized as a blocking group. Trimethylsilyl ether was found to be labile under the required coupling conditions, but the tert-butyl dimethylsilyloxy group was found to be stable under these conditions and could be readily removed with either dilute aqueous acid or fluoride ion in an aprotic solvent³⁸. Reaction of I-5 with tert-butyl dimethylsilyl chloride in the presence of imidazole, produced I-6 in 85% yield, which exhibited all the expected spectral properties.



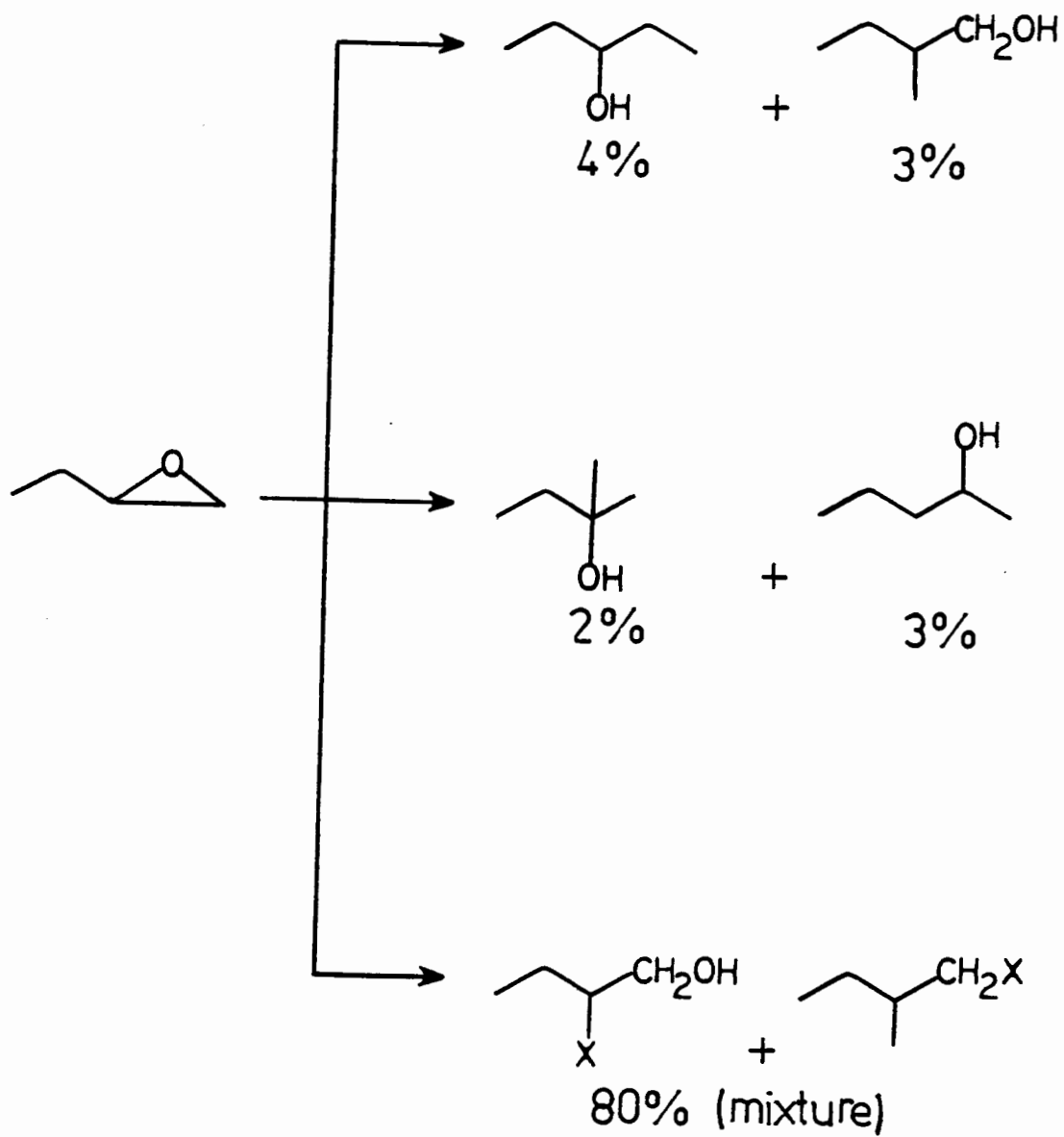
Scheme 2

The reaction of Grignard reagent prepared from I-6 with (+)-methyloxirane I-4 produced a complex mixture caused by the chemical nature of Grignard reagent. Alkyl magnesium halides are in equilibrium with two other species, a dialkylmagnesium compound and magnesium dihalide, both of which can undergo reaction with the epoxide³⁹. The magnesium dihalide can act as a Lewis acid and cause prior isomerization of the epoxide to form



a carbonyl compound which can further react with the Grignard reagent. The major side reaction is the addition of halide to the epoxide to form a halohydrin. This is in accord with Wilbur Herr and Johnson's observations⁴⁰ on the products from the reaction of metallomethyl reagents with 1,2-epoxybutane (Scheme 3).

The product distribution of the reaction of (+)-I-4 with Grignard reagent derived from I-6 prompted the use of catalytic copper reagents formed from a Grignard reagent and catalytic amount of copper (I) iodide⁴¹. These catalytic reactions are far superior to those obtained with Grignard reagents with respect to both the yield of nucleophilic ring-opening product and the suppression of side reactions due to the Lewis acidity of Grignard reagent complex. Huynh et. al.⁴¹ developed an efficient

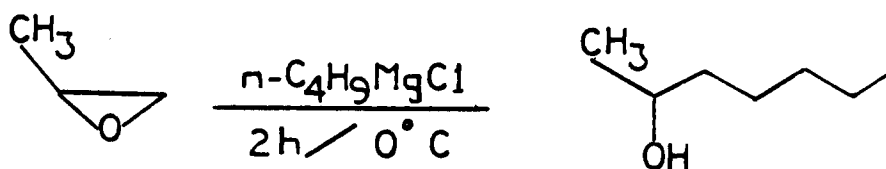


Scheme 3

copper catalyzed reaction of Grignard reagents with epoxides, which proceeds in high yield under very mild conditions (Scheme 4). With these conditions to open the oxirane (+)-I-4 in a stereoselective manner, the synthesis of (+)-9-hydroxy-(E)-2-decenoic acid I-1 was accomplished as outlined in Scheme 5.

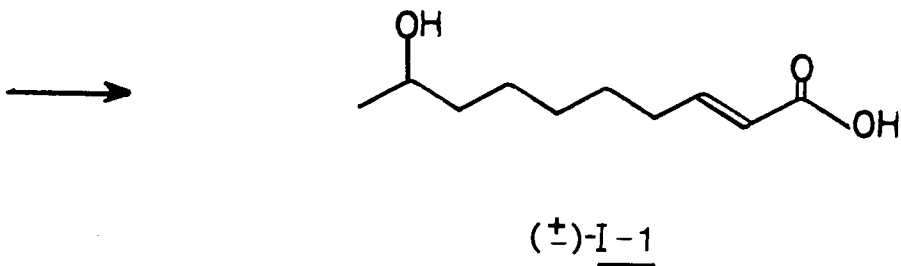
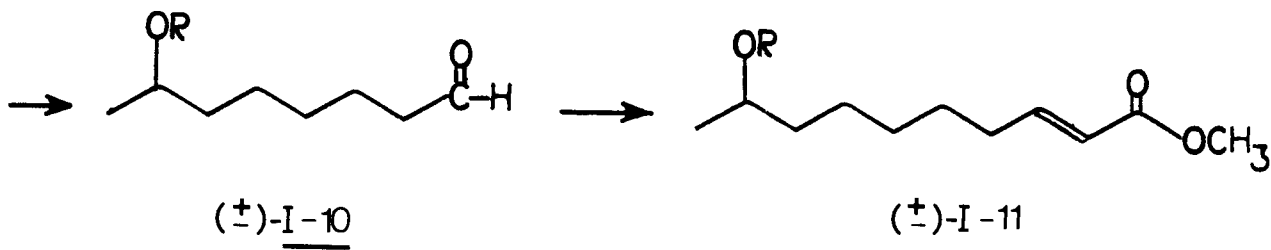
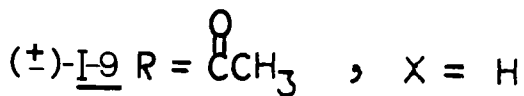
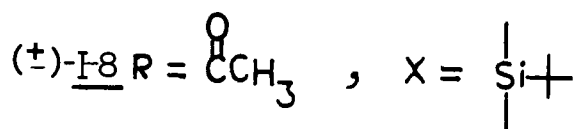
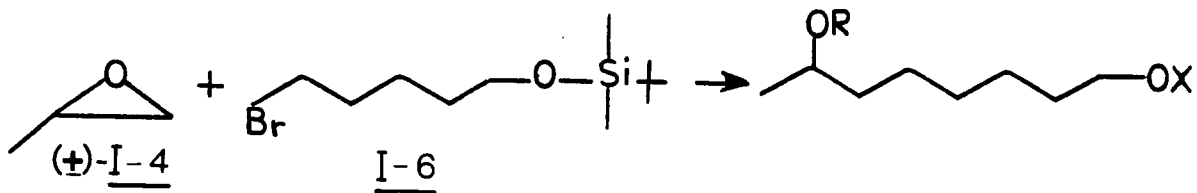
The nucleophilic ring opening of (+)-I-4, in the presence of freshly purified CuI^{42} , with the Grignard reagent prepared from I-6, provided the silyl ether derivative (+)-I-7 in 84% yield. The proton magnetic resonance spectrum⁴³ (^1H NMR) of (+)-I-7 showed a doublet at $\delta 1.21$ assigned to $\text{CH}_3\text{-CH-}$ ($J=6$ Hz), and two singlets at $\delta 0.86$ and 0.00 corresponding to tert-butyl-dimethylsilyloxy group. In addition, infrared absorption spectrum (IR) showed a broad band at 3316 cm^{-1} corresponding to hydroxyl stretching vibration. Acetylation of the hydroxy silylether (+)-I-7 with acetic anhydride and pyridine for 12 h produced (+)-1-tert-butyldimethylsilyloxy-7-acetoxy-octane I-8 in nearly quantitative yield. The spectral data of (+)-I-8 was in agreement with the expected structure; the IR showed an absorption at 1747 cm^{-1} and the ^1H NMR showed a sharp singlet at 1.94 ppm corresponding to $(\text{CH}_3\text{CO-})$.

The removal of tert-butyldimethylsilyl blocking group was achieved using a mixture of acetic acid:water:tetrahydrofuran³⁸ (3:1:1) to give (+)-7-acetoxy-octan-1-ol I-9 in 84% yield.



		yield
with	10% CuI catalyst	93%
without	CuI catalyst	26%

Scheme 4



Scheme 5

Oxidation of (+)-I-9 was accomplished using approximately two molar equivalents of pyridinium chlorochromate⁴⁴ in dichloromethane to yield the acetoxyoctanal (+)-I-10 in 96% yield. This compound was characterized by its IR spectrum 2735, 1752 and 1728 cm^{-1} , and the ^1H NMR spectrum which showed a triplet at $\delta 9.83$ ($J=2$ Hz) corresponding to (-CHO). Difficulty was experienced obtaining consistent carbon and hydrogen analyses for the derived aldehyde (+)-I-10 and its chiral analogues (+)-I-10 and (-)-I-10, which may have been due to either hydration or decomposition of the aldehyde functionality. High resolution mass spectrometry⁺ exhibited a consistent but weak $(M-1)^+$ and a strong $(M-\text{COCH}_3)^+$.

With the appropriate aldehyde functionality in the eight carbon chain, a stereoselective introduction of a two-carbon, (E)- α,β -unsaturated ester was necessary. There are several routes that have been devised to enable the controlled introduction of carbon-carbon double bonds⁴⁵. The most widely used method is the Horner-Emmons modification of the Wittig reaction⁴⁶, in which a stabilized phosphonate is employed in the condensation instead of ordinary phosphonium ylide.

The phosphonate route to the olefins offers some advantages over the conventional Wittig reaction in that ylides derived from phosphonates are known to be more nucleophilic than phos-

phonium ylides⁴⁷. The water-soluble phosphate ion formed from phosphonates allows for the much easier separation of the olefin from the reaction mixture. More importantly, phosphonate carbanions stereoselectively produce (E)-isomer⁴⁸. The condensation of (+)-I-10 with trimethylphosphonoacetate in the presence of sodium hydride went smoothly to give (+)-methyl-9-acetoxy-(E)-2-decenoate I-11 in 70% yield, whose IR spectrum exhibited all the anticipated absorptions. The ¹H NMR showed a doublet of triplets at δ 6.85 with J=15 Hz and J=6 Hz and a doublet at 5.65 with J=15 Hz corresponding to $-\text{CH}_2-\text{CH}=\text{CH}-\text{COOR}$ and $-\text{CH}_2-\text{CH}=\text{CH}-\text{COOR}$ respectively. The acetoxy ester (+)-I-11 was hydrolyzed with 5% sodium hydroxide in methanol-water (1:1) to afford racemic 9-hydroxy-(E)-2-decenoic acid (+)-I-1 in 68% yield. The spectral data obtained for (+)-I-1 were in agreement with those reported³⁰.

The identity of the final product was verified by the formation of the known racemic p-bromophenacyl ester. Reaction of the hydroxy acid (+)-I-1 with 5% aqueous sodium hydroxide followed by 3 h reflux in the presence of p-bromophenacyl bromide provided the ester⁴⁹ (+)-I-12 in 56% yield (Scheme 6).

The S-(+)-9-hydroxy-(E)-2-decenoic acid I-1 was prepared from S-(-)-methyloxirane as described for the racemic material, except for the substitutions of anhydrous 1,2-dimethoxyethane as the solvent in the Wittig-Horner condensation. All physical

properties of the intermediate enantiomeric materials were identical to those observed for the racemate (+)-I-1, with the exception of optical rotations and melting points of the derivatives. R-(-)-9-hydroxy-(E)-2-decenoic acid I-1 was prepared from R-(+)-methyloxirane in a manner identical to the racemate.

Conclusion

This research has led to preparation of both enantiomers and racemate of 9-hydroxy-(E)-2-decenoic acid I-1, via a nucleophilic ring opening of chiral and racemic methyloxirane, by a Grignard reagent derived from 1-tert-butyldimethylsilyloxy-5-bromopentane I-6. These ring openings provide an excellent entry into molecules containing a chiral 2-ol functionality with very high regioselectivity. Protection of the secondary alcohol (+)-I-7, as an acetate using acetic anhydride in pyridine followed by removal of the silyl blocking group gave 7-acetoxy-octan-1-ol (+)-I-9. Oxidation of the primary hydroxyl group to an aldehyde with pyridinium chlorochromate, followed by a Wittig-Horner condensation with trimethylphosphonoacetate provided methyl 9-acetoxy-(E)-2-decenoate (+)-I-11 in very high stereoselectivity. Base hydrolysis of the esters followed by acidification furnished (+)-9-hydroxy-(E)-2-decenoic acid I-1. These chiral syntheses have been reported in the literature^{50a}.

Biological testing of the racemic and enantiomeric acids has shown that 9-hydroxy-(E)-2-decenoic acid I-1 was indeed effective in swarm settling, with the R-(-)-isomer substantially more active than the racemic or the dextrorotatory enantiomer S-(+)-I-1^{50b}.

CHAPTER II

Chiral synthesis of (+)-(1R,4S,5R,7R)-3,3,7-trimethyl-2,9-dioxatricyclo[3.3.1.0^{4,7}]nonane

Background

Lineatin II-1, an aggregation pheromone obtained from the frass of the female ambrosia beetle Trypodendron lineatum (Olivier)⁵¹, has been shown to elicit powerful secondary attraction in laboratory⁵² and field trials⁵³. The extensive damage to fallen and sawn timber, especially Douglas fir, caused by T. lineatum lends particular significance to this pheromone as a possible means for controlling this pest^{54,55,56}. The bioactive enantiomer of the pheromone was demonstrated by field testing to be (+)-lineatin II-1⁵⁵. Entomological investigations have demonstrated, not only that (+)-lineatin II-1 is the active pheromone⁵⁵, but shown that both its enantiomer (-)-II-1 and its regioisomer II-2 were neither attractive nor inhibitory. Consequently, all efforts aimed at a large scale syntheses have been directed toward production of racemic lineatin (+)-II-1.

Originally formulated as either II-1 or II-2⁵¹ (Fig. 1), lineatin was subsequently shown to be 3,3,7-trimethyl-2,9-dioxatricyclo[3.3.1.0^{4,7}]nonane II-1, via three syntheses by Borden et. al.⁵⁶ (Scheme 7). These routes provided microgram quantities of (+)-lineatin II-1 and were not attractive routes because of the low yield and the extensive manipulation of the

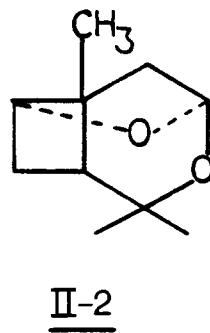
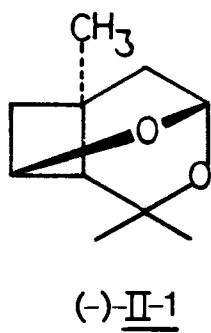
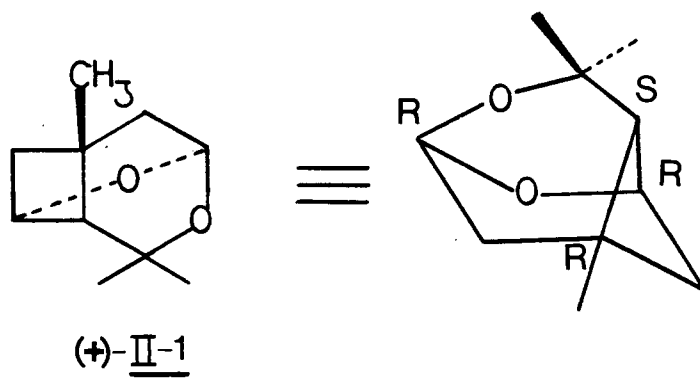
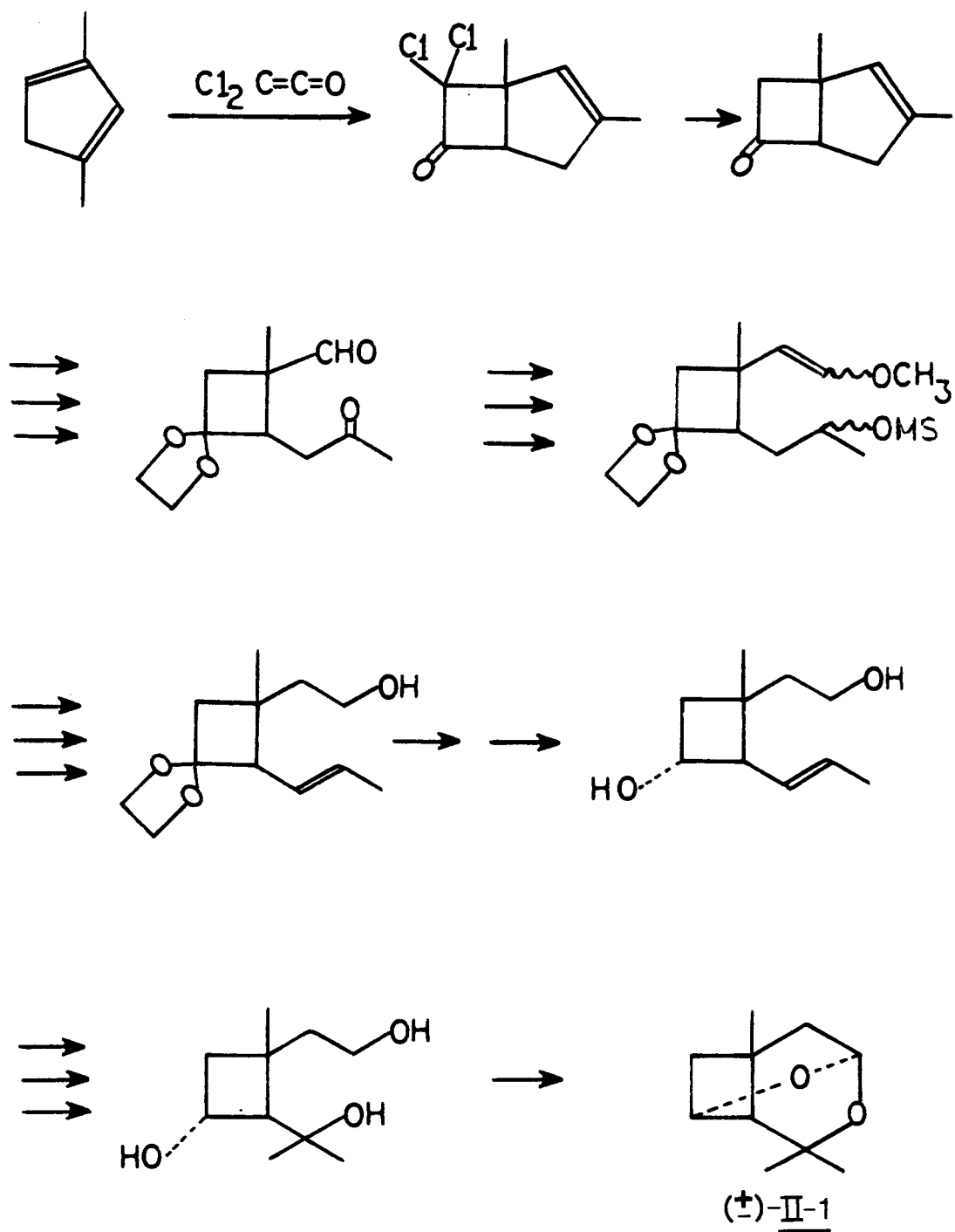


Fig. 1

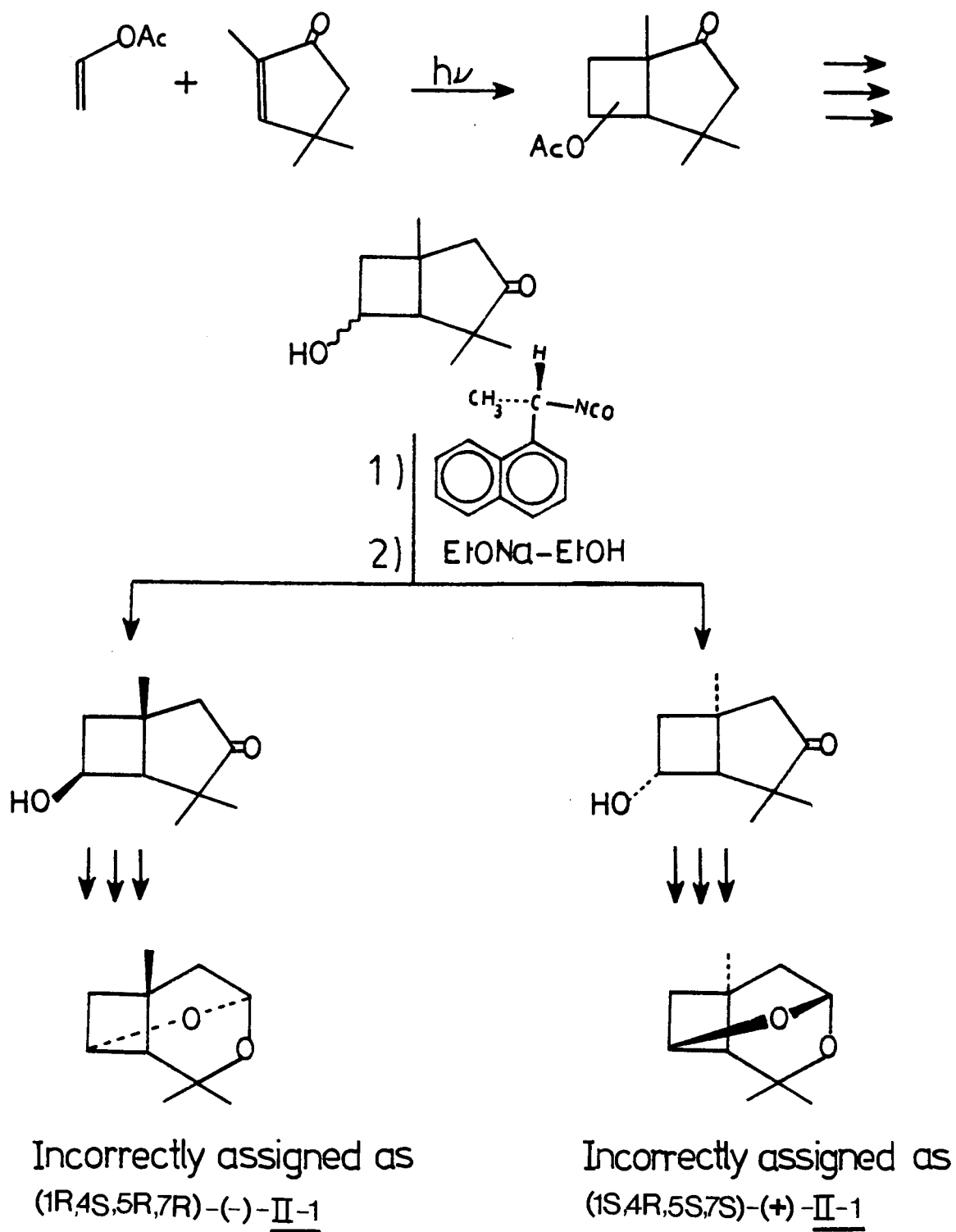


Scheme 7

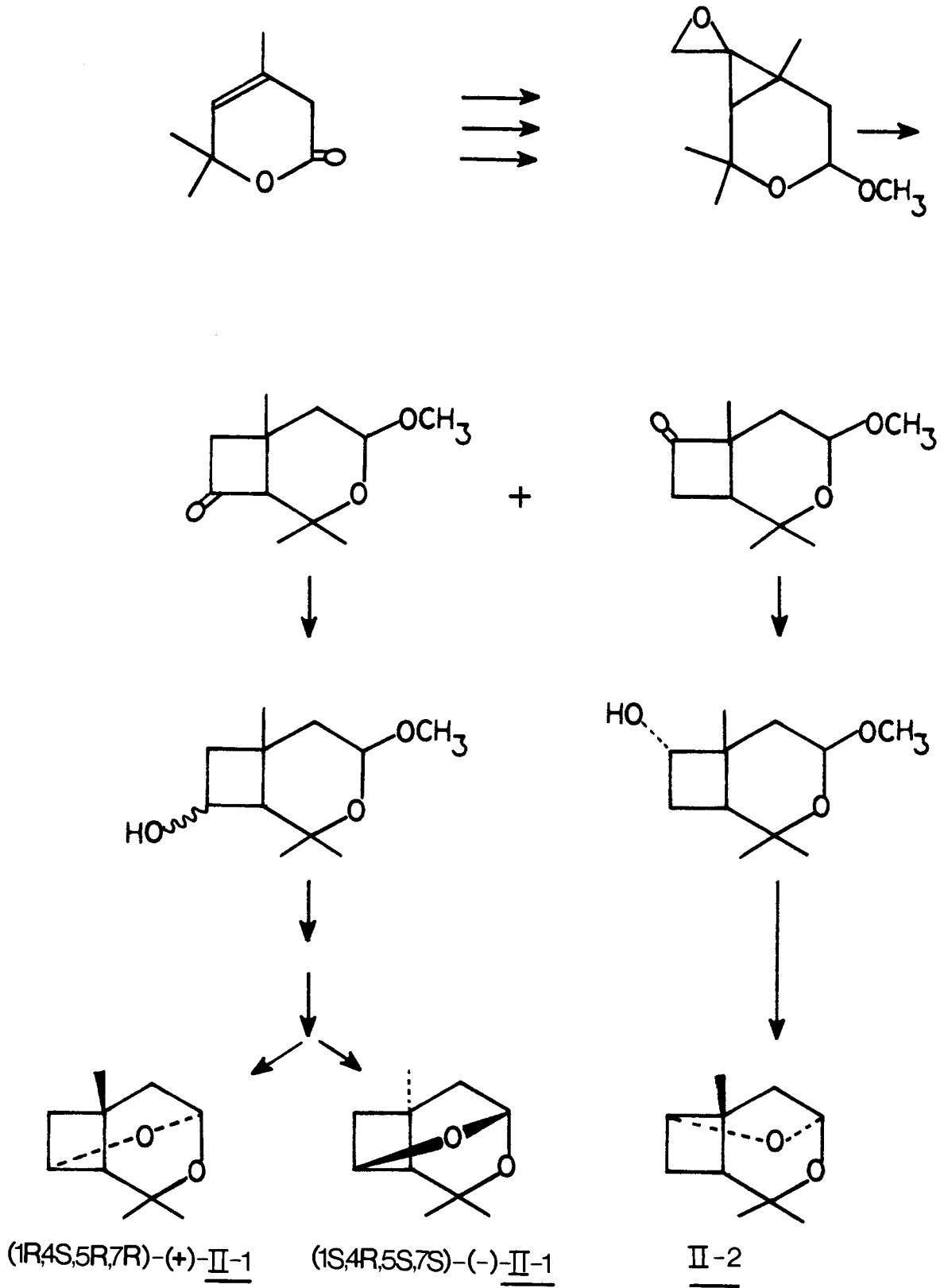
mediated cycloaddition of vinyl acetate and 2,4,4-trimethylcyclopent-2-en-1-one. This synthesis enabled isolation of both enantiomers of lineatin II-1, via an optical resolution of diastereoisomeric carbamates as outlined (Scheme 8). Mori and Sasaki incorrectly assigned the (1S,4R,5S,7S)-absolute stereochemistry to (+)-lineatin II-1, $[\alpha]_D^{22} + 36'$ and the (1R,4S,5R,7R)-to (-)-lineatin II-1, $[\alpha]_D^{22} -40'$.

Slessor et. al.⁵⁸ achieved another synthesis of lineatin II-1, via an eight step synthesis commencing from 5-hydroxy-3,5-dimethyl-3-hexenoic acid lactone (Scheme 9). This approach, which is based on ring expansion of oxaspiropentane according to the method described by Aue⁵⁹, provided a mixture of ketones, wherein the desired regioisomer predominated in a ratio of 4:1. The stereoselective reduction of cyclobutanones, followed by resolution via chiral carbamate afforded two diastereoisomeric products. Hydrolysis of the carbamate derivatives, followed by acid-catalyzed cyclization provided (+)-lineatin II-1 and (-)-lineatin II-1, in 2.8% overall yield.

In contrast to Mori's results⁵⁷, Slessor et. al. assigned (1R,4S,5R,7R)-configuration to the dextrorotatory enantiomer for (+)-lineatin II-1 $[\alpha]_D^{24} + 66.3'$ based on the chromatographic functionalities attached to the cyclobutyl ring that were



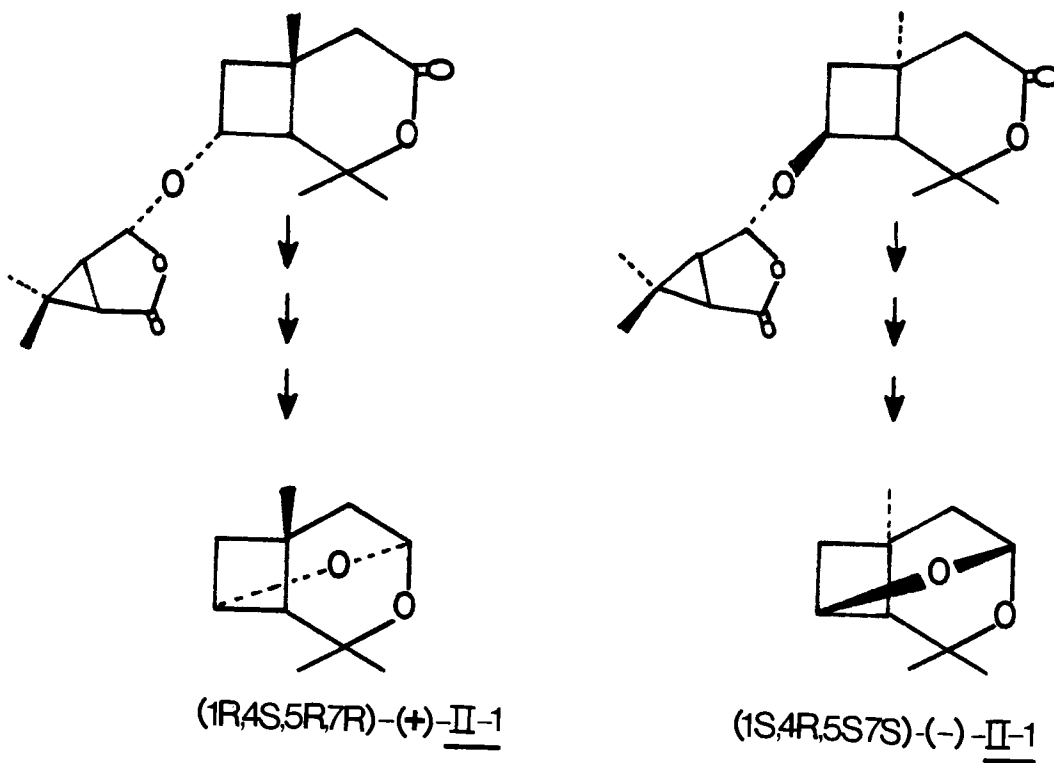
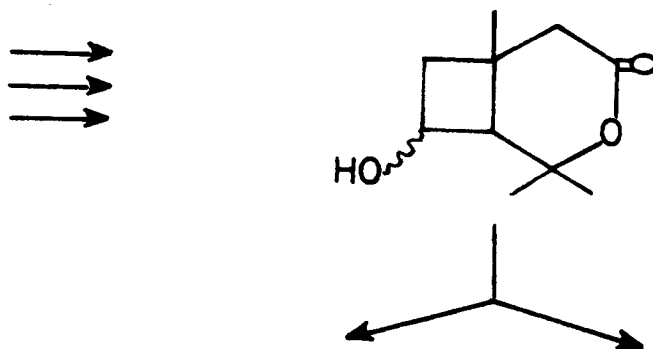
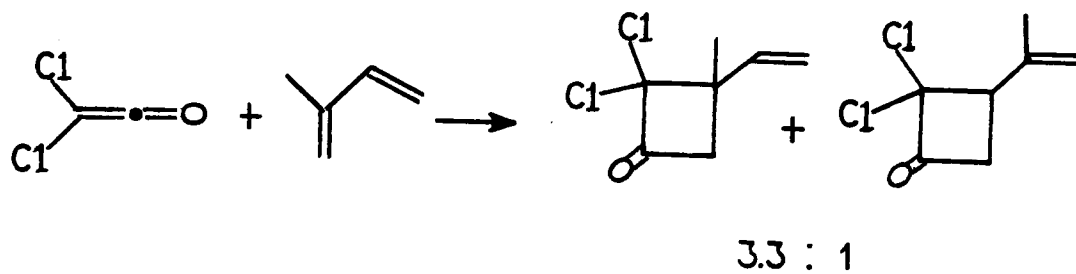
Scheme 8



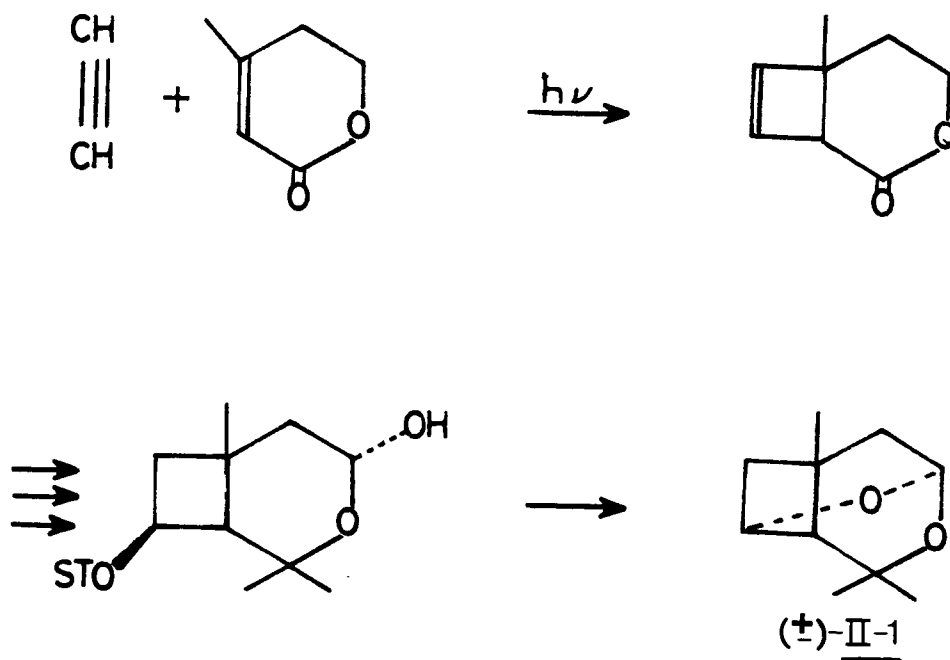
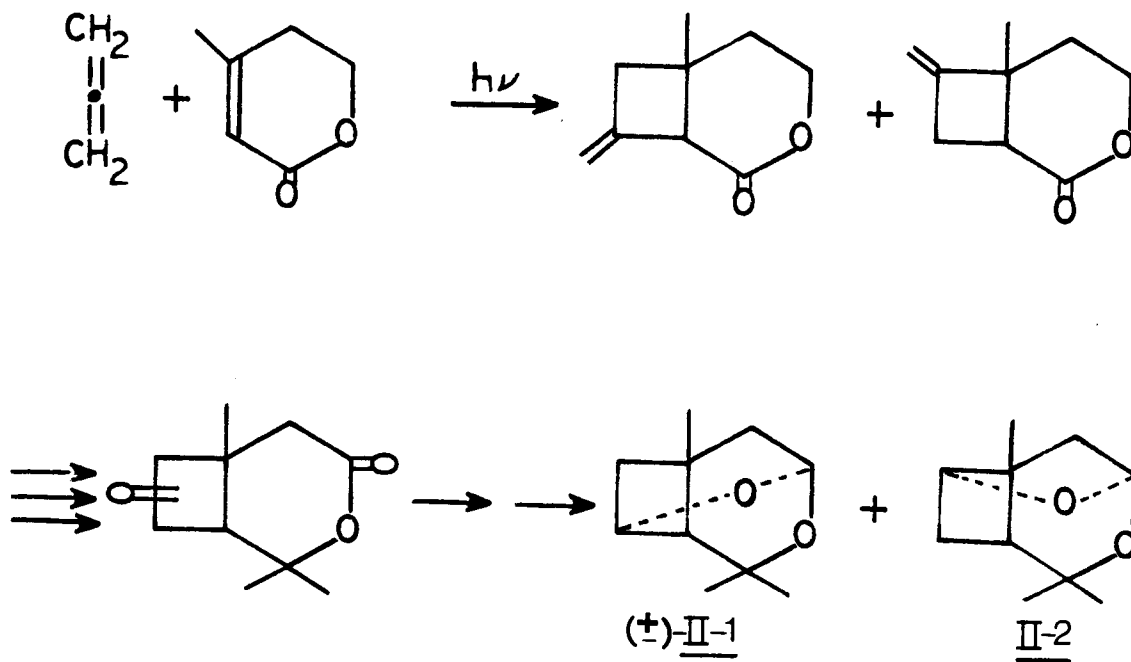
Scheme 9

required. Another approach invoking a (2+2) cycloaddition was reported by Mori and Sasaki⁵⁷ employing a photochemically properties and ¹H NMR data of the diastereoisomeric carbamates as well as optical rotatory power of the chiral centers of lineatin (+)-II-1. Later, Mori et. al.^{60,61} utilized dichloroketene and isoprene in a thermal (2+2) cycloaddition to afford a mixture of isomeric cyclobutyl derivatives. Reduction followed by alkylation of the desired regioisomer afforded lineatin II-1 (Scheme 10). This synthesis which provided an optically active acetal intermediate for a single-crystal X-ray analysis, enabled them to revise their assignment of the absolute stereochemistry of (+)-lineatin II-1 to (1R,4S,5R,7R)-(+)-II-1, $[\alpha]_D^{21.5} +85.8'$.

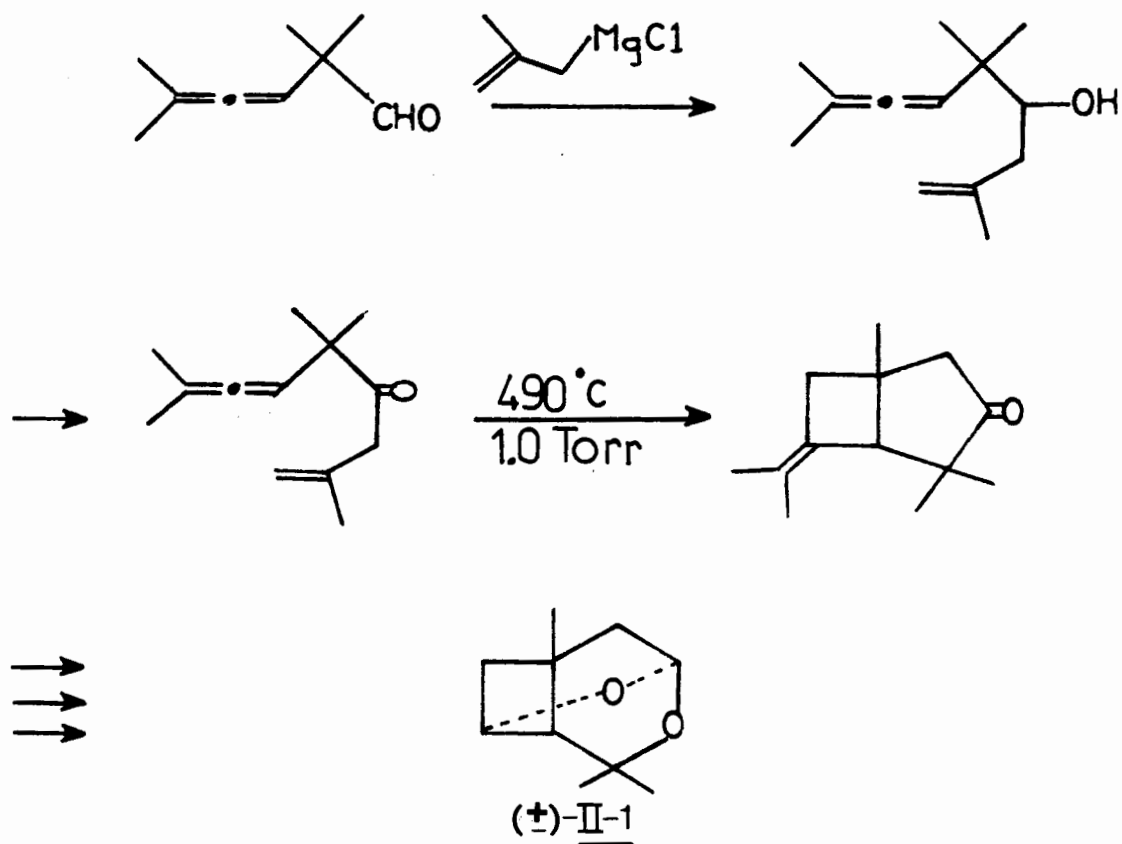
Another photochemical (2+2) cycloaddition was employed to synthesize (+)-lineatin II-1, in five-steps from anhydromevalonolactone and allene⁶² (Scheme 11). The photolysis products produced two regioisomers (ca 3:2), and efforts to improve the regioselectivity of the addition products by varying the photolysis conditions or substituents on the allene were unsuccessful. An alternate use of anhydromevalonolactone as a substrate for a photochemical (2+2) cycloaddition was initiated by White et. al.⁶³. The anticipated regioselectivity of the hydroboration of the cycloadduct was not achieved and the desired regioisomer was separated as a tosylate, which underwent intramolecular displacement to produce (+)-lineatin in 14% overall yield (Scheme 12).



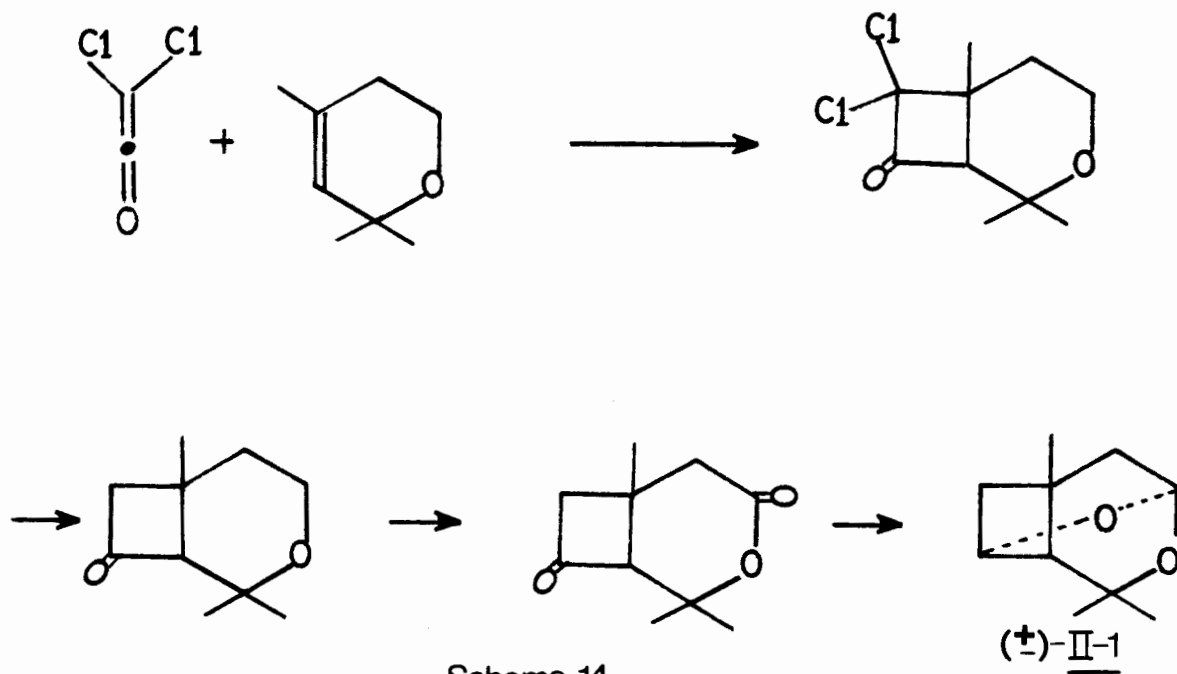
Scheme 10



In contrast to the previously reported syntheses of lineatin II-1, Skattebol and Stenstrom⁶⁴ employed a thermally induced intramolecular cyclization of an allenic ketone to yield a bicyclic ketone intermediate. The derived ketolactone was converted to (+)-lineatin in 30% overall yield (Scheme 13). Recently, Johnston et. al.⁶⁵ have synthesized (+)-lineatin II-1 by a four-step sequence starting from 2,2,4-trimethyl-5,6-dihydro-2H-pyran. The key step involved the formation of a dichlorocyclobutanone using dichloro ketene cycloaddition. The conversion of the cycloadduct to (+)-lineatin II-1 was carried out using standard synthetic techniques to provide (+)-II-1, in 10-12% overall yield (Scheme 14).



Scheme 13

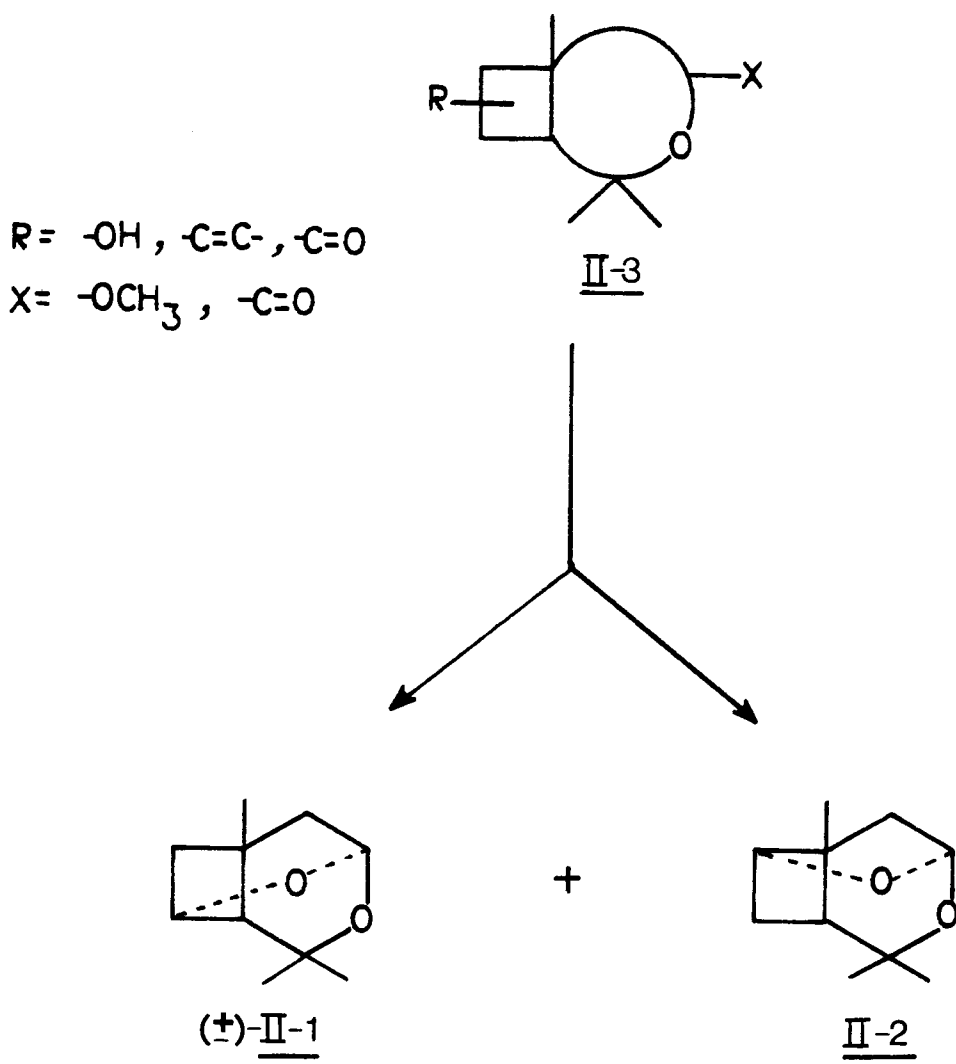


Scheme 14

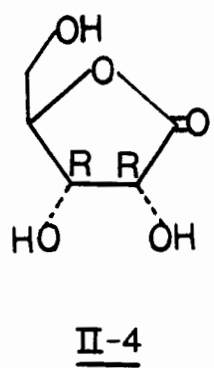
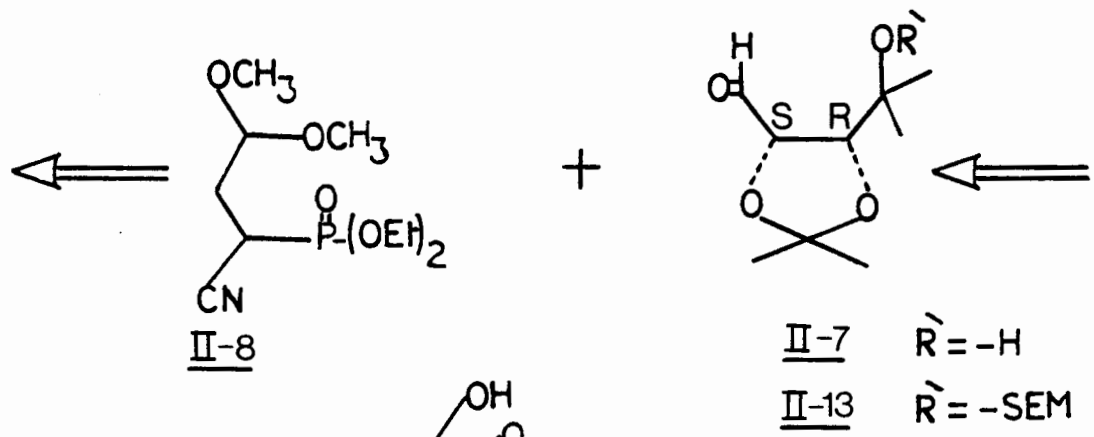
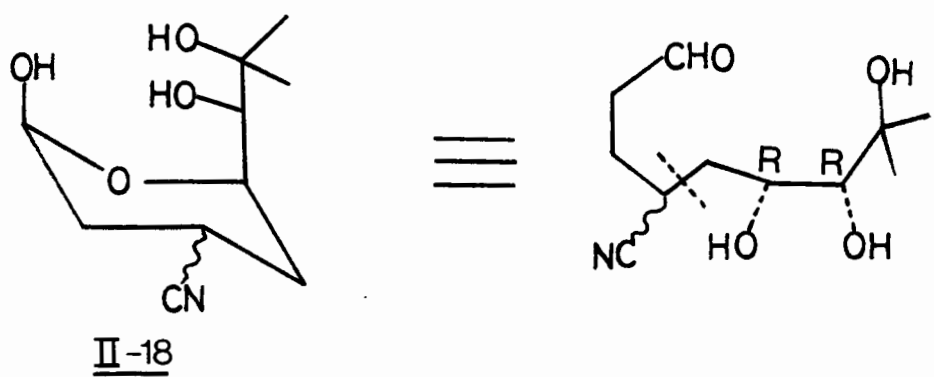
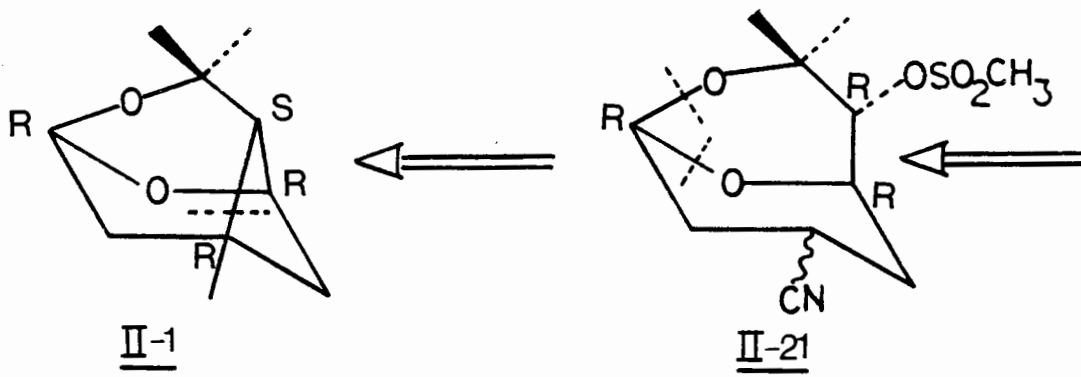
Approach

All the efforts that have been described to prepare (+)-II-1, utilized either a (2+2) cycloaddition or rearrangement to construct the cyclobutane ring derivatives, II-3, which with appropriate modification furnished (+)-lineatin II-1 and iso-lineatin II-2^{51,57,58,60-63} (Scheme 15). In several of these synthetic projects both enantiomers of lineatin II-1 were produced by resolution of diastereoisomeric derivatives of intermediates^{57,58,60,61}. In spite of these efforts, the regiospecific introduction of functionality at predetermined sites precluded the construction of (+)-II-1 in a chiral manner. The need for a stereospecific total synthesis of (+)-lineatin II-1, coupled with the fact that previous preparations have yielded (+)-II-1 with disputed absolute stereochemistry, prompted us to consider a different approach.

The strategy adopted was to utilize D-ribonolactone⁶⁷ II-4, as a "Chiral Template"¹⁸ in the synthesis (+)-II-1, based on the systematic and stereocontrolled introduction of functional groups. The major challenge in the synthesis of (+)-(1R,4S,5R,7R)-3,3,7-trimethyl-2,9-dioxatricyclo[3.3.1.0^{4,7}]nonane, (+)-II-1, is the stereospecific construction of the tricyclic acetal skeleton. A retrosynthetic analysis of the problem is outlined (Scheme 16).



Scheme 15



Scheme 16

The tricyclic compound (+)-II-1 is an intramolecular acetal derived from the cyano mesylate of 2,9-dioxabicyclo[3.3.1]nonane II-21. This is in turn derived from the trihydroxy cyanoaldehyde II-18. Compound II-18 is obtainable from the condensation of II-8 and II-7, whereas the chiral framework of II-7 is derived from D-(+)-ribonolactone II-4.

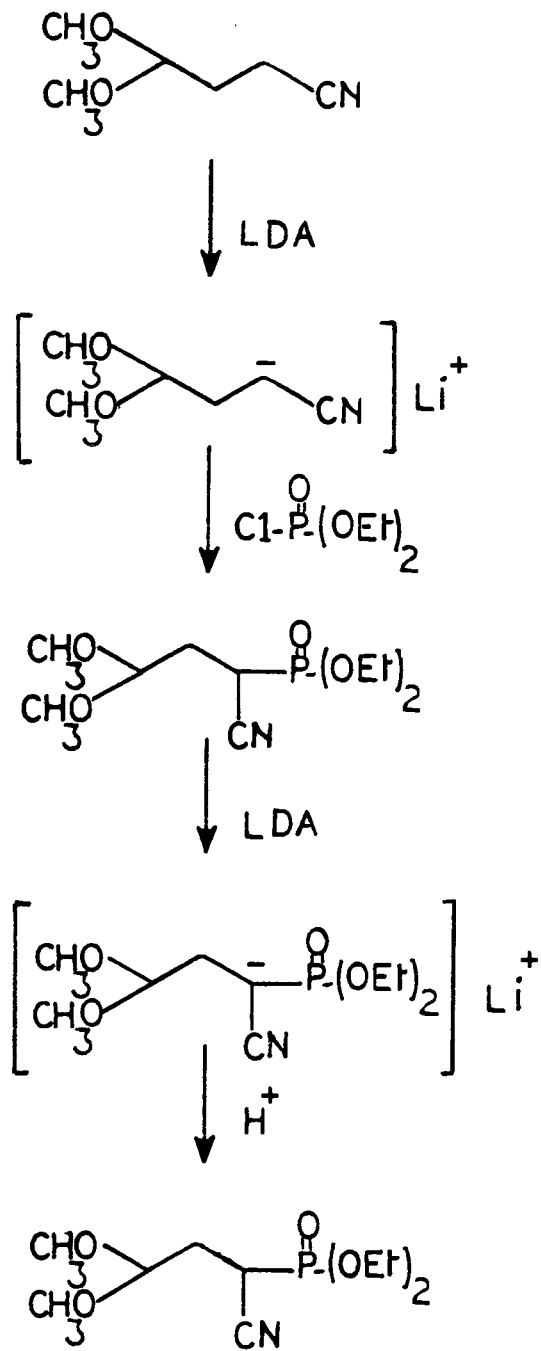
In the course of the chiral synthesis, II-21 must be prepared with an absolute stereochemistry of (1R,4R,5R). II-21 will undergo an intramolecular nucleophilic displacement of the leaving group at position-4, thus inverting the configuration of C₄ from (4R) → (4S), and establishing a new chiral centre at C₇ with an (S)-absolute stereochemistry. This is an favoured 4-Exo-Tet ring closure following Baldwin's rules⁶⁶ for ring forming reactions which will produce the tricyclic acetal with the required stereochemistry. Chemical transformations of the nitrile moiety to methyl will produce (+)-(1R,4S,5R,7R)-3,3,7-trimethyl-2,9-dioxatricyclo[3.3.1.0^{4,7}]nonane, (+)-II-1.

Results and Discussion

1) Preparation of diethyl-(3-cyano-1,1-dimethoxypropyl) phosphonate II-8

The preparation of intermediate II-18 or its precursor, required the condensation of II-8 and II-7. This process, which will lead eventually to a carbon-carbon bond formation, was approached using the Horner-Emmons modification⁴⁶ of the Wittig reaction utilizing the phosphonate of β -cyanopropionaldehydedimethyl acetal⁶⁸.

The phosphonate II-8 was prepared by the reaction of the anion derived from β -cyanopropionaldehydedimethyl acetal and diethyl chlorophosphate⁶⁸. The anion was generated using two-mole equivalents of lithium diisopropylamide⁶⁹ (LDA) at -78°C , followed by a dropwise addition of diethyl chlorophosphate to afford II-8 in 89% yield upon workup (Scheme 17). However, when β -cyanopropionaldehydedimethyl acetal was treated with one-mole equivalent of lithium diisopropylamide at -78°C , followed by the addition of diethyl chlorophosphate, the required phosphonate was not produced. The failure of this reaction under these conditions was not unexpected as the relatively high acidity of the phosphonate product liberates free cyanoacetal which then condenses with the anion derived from β -cyanopropionaldehyde-



II-8

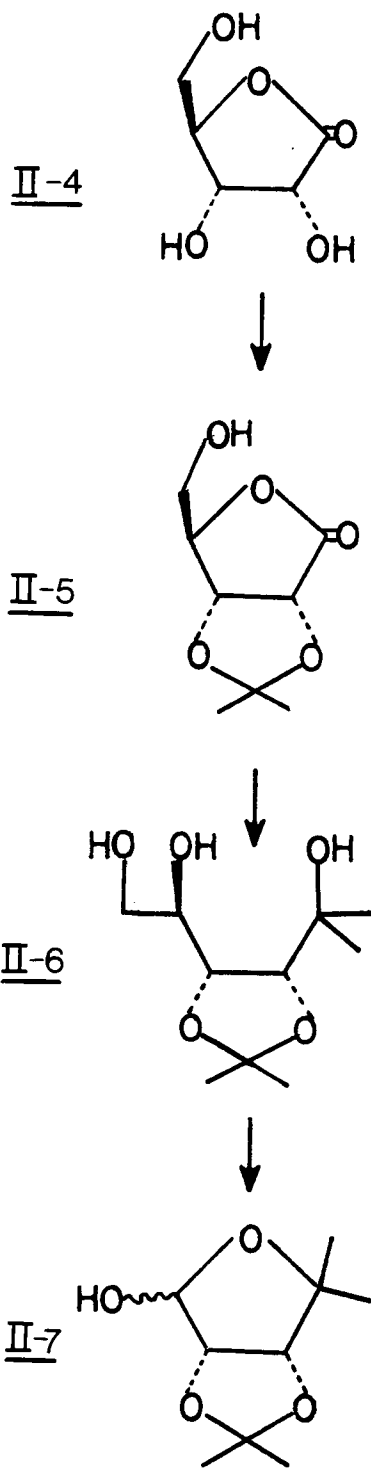
Scheme 17

dimethyl acetal leading to either self-condensation or inhibition of the reaction⁷⁰.

- 2) Conversion of D-(+)-ribonolactone II-4 to (2S,3R)-2,3-isopropylidenedioxy-4-methyl-4-[(2-trimethylsilylethoxy)methoxy]pentanal II-13

The first target in the synthesis was the chiral intermediate II-7. The synthetic sequence to furnish II-7 is outlined (Scheme 18). Treatment of D-(+)-ribonolactone⁶⁷, II-4, $[\alpha]_D^{25} +17.8^\circ$ with anhydrous acetone and concentrated sulphuric acid for 5 h afforded the known 2,3-O-isopropylidene D-(-)-ribonolactone⁷¹ II-5 in 80% yield. The introduction of the gem-dimethyl group at position 1 of 2,3-O-isopropylidene-D-(-)-ribonolactone II-5, was readily accomplished via Grignard reaction using excess methylmagnesium iodide⁷². The IR spectrum of the product II-6 showed a broad hydroxyl band at 3320 cm^{-1} , and no lactonic band in the region of 1780 cm^{-1} . ¹H NMR indicated an absorption peak at 1.44 ppm (3H), 1.31 ppm (3H) and 1.39 ppm (6H) corresponding to gem-dimethyl and isopropylidene respectively.

The cleavage of the vicinal 1,2-diol to produce the required aldehyde II-7 was accomplished using aqueous solution of sodium metaperiodate⁷³. The product II-7 was isolated in 90% yield and its IR spectrum revealed a hydroxyl band at 3310 cm^{-1}

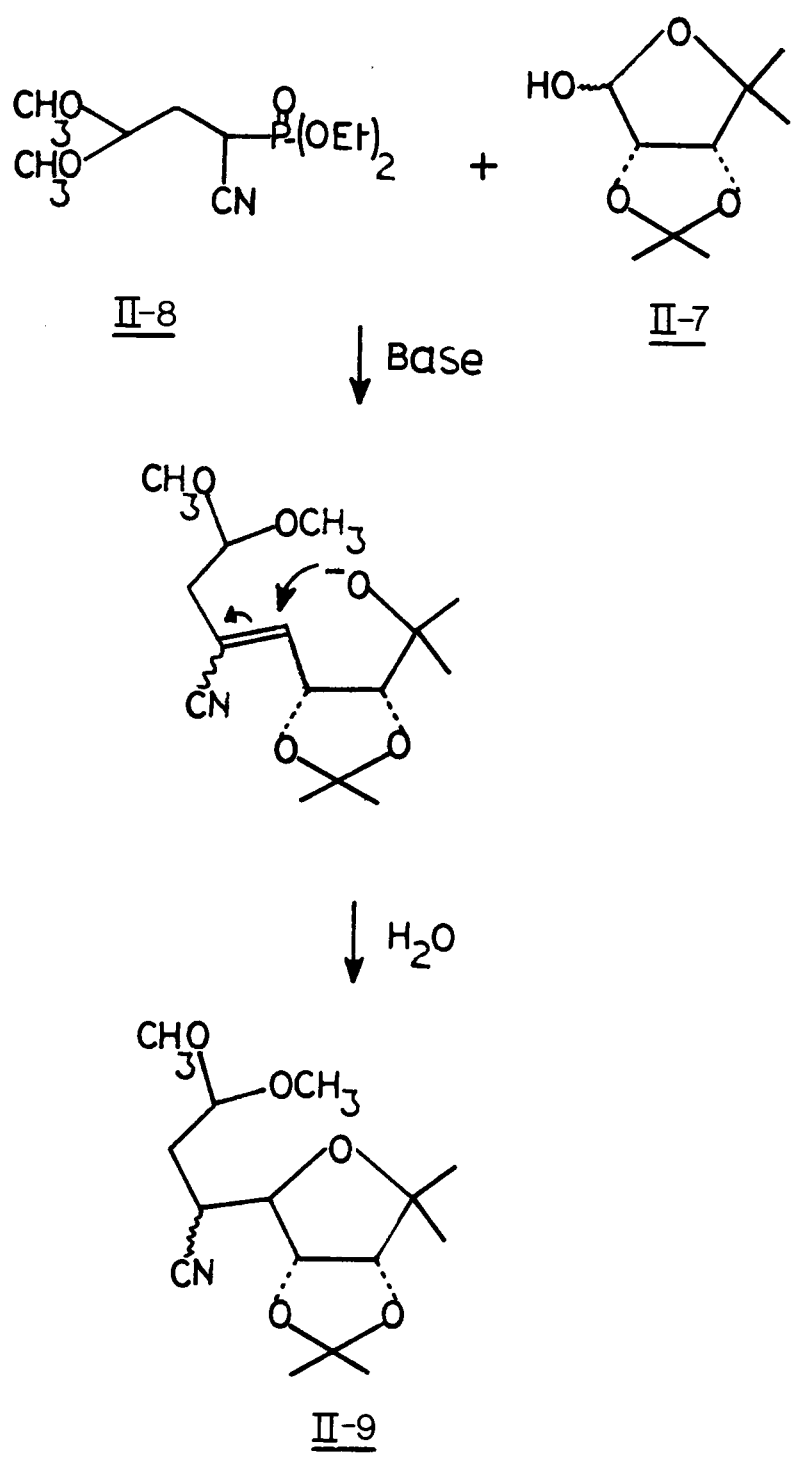


Scheme 18

and no band corresponding to aliphatic aldehyde in the ≈ 1728 cm^{-1} region. ^1H NMR showed the presence of no aldehydic proton in the ≈ 9.50 ppm region. Instead it revealed the presence of an anomeric mixture in a ratio of 1:1.

The condensation of II-7 and II-8 was performed under the conditions described by Wadsworth and Emmons⁴⁷. Although thin layer chromatography (TLC) showed only one spot, gas liquid chromatography (GC) indicated the presence of two components in the ratio of 4:1. The presence of nitrile absorption ≈ 2245 cm^{-1} and absence of a double bond stretching band demonstrated the lack of α,β -unsaturated nitrile in the mixture. These observations in addition to ^1H NMR spectrum of the reaction mixture clearly indicated the presence of II-7 as a major component in addition to a minor product tentatively identified as II-9. These results could be explained in terms of an intramolecular Michael reaction⁷⁴, in which the tertiary hydroxyl group was converted to alkoxide under the basic conditions employed to perform the condensation and this alkoxide underwent intramolecular conjugate addition to α,β -unsaturated nitrile as shown (Scheme 19).

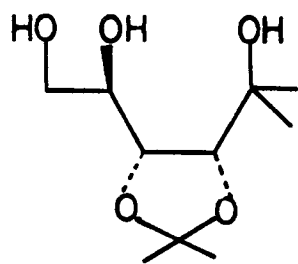
To prevent the conjugate addition it was necessary to block the tertiary hydroxyl group with a protecting group removable under very mild conditions. A wide variety of reagents have been developed specifically to protect tertiary hydroxyl



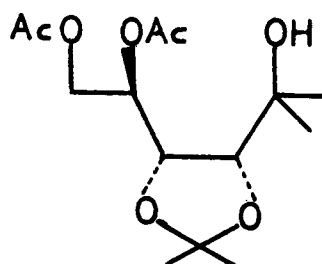
Scheme 19

groups^{75,76}. Most widely used are methoxymethyl chloride⁷⁷, β -methoxyethoxymethyl chloride⁷⁸ (MEM-Cl), methylthiomethyl chloride⁷⁹ (MTM-Cl) and β -trimethylsilylethoxymethyl chloride^{80,81} (SEM-Cl). An investigation of the literature revealed β -trimethylsilylethoxymethyl chloride (SEM-Cl) to be an excellent candidate for the protection of this tertiary hydroxyl group, since it is stable over a wide range of conditions, including dilute acids, bases, hydrogenations, and yet can be readily cleaved under aprotic conditions using a fluoride ion³⁸. The specific protection of the least reactive hydroxyl group was accomplished as indicated (Scheme 20).

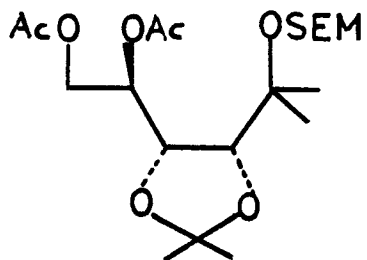
The triol II-6 was treated with a mixture of acetic anhydride-pyridine to provide the diacetate II-10 as a colourless solid, m.p. 125-6 °C, in 75% yield. Spectral data were consistent with the designated structure; IR indicated a hydroxyl absorption at 3472 cm^{-1} , in addition to a broad band at 1734 cm^{-1} corresponding to CH_3CO -groups. ^1H NMR displayed a single resonance at 2.05 ppm corresponding to (6H, 2 CH_3CO -). The cisoid nature of the 1,3-dioxolane ring was apparent from coupling constants⁸² of protons at C_3 and C_4 respectively; C_4 -H appeared as a doublet at 3.92 ppm ($J_{3,4} = 5$ Hz), whereas C_3 -H showed a doublet of doublets at 4.29 ppm ($J_{3,4} = 5$ Hz and $J_{2,3} = 6$ Hz). The blocking of the tertiary hydroxyl group proceeded



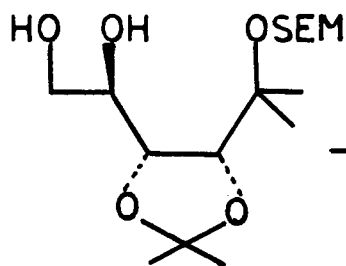
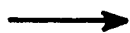
II-6



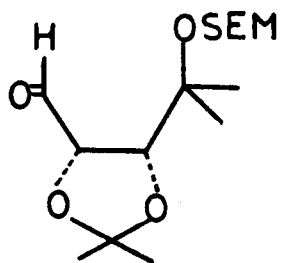
II-10



II-11



II-12



II-13

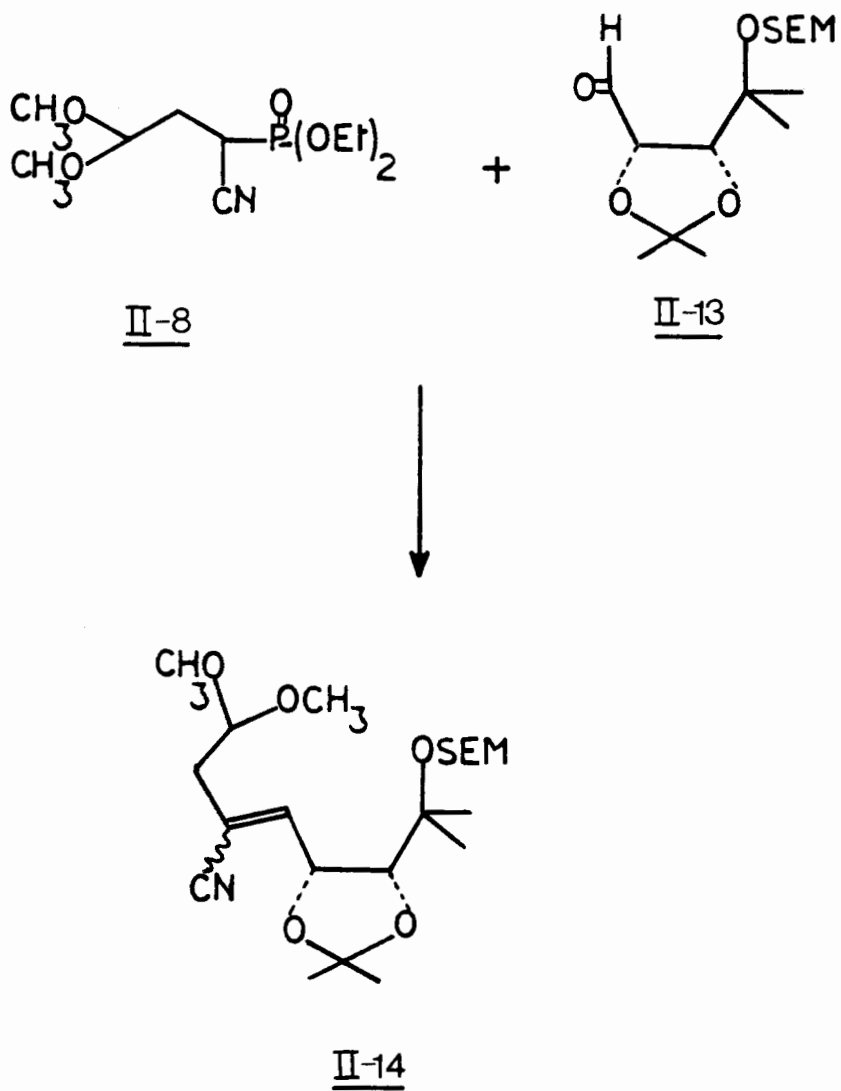
Scheme 20

smoothly using β -trimethylsilylethoxymethyl chloride^{80,81} in refluxing tetrahydrofuran containing diisopropylethyl amine to produce (2R,3R,4R)-1,2-diacetoxy-3,4-isopropylidenedioxy-5-methyl-5-[(2-trimethylsilylethoxy)methoxy]hexane II-11 in 88% yield. Compound II-11 exhibited all the anticipated spectral properties; an IR absorption band at 1755 cm^{-1} corresponding to acetyl group; ^1H NMR in (CDCl_3) displayed a single resonance at 0.00 ppm (9H, $\text{Si}(\text{CH}_3)_3$), a triplet at 0.91 ppm (2H, $-\text{CH}_2-\text{Si}(\text{CH}_3)_3$), $J = 8.4\text{ Hz}$) in addition to a pair of doublets at 4.87 and 4.67 ppm ($J = 6\text{ Hz}$) corresponding to $-\text{OCH}_2\text{O}-$ group⁸³.

The regeneration of the 1,2-diol was accomplished using 5% aqueous sodium hydroxide to furnish (2R,3R,4R)-3,4-isopropylidenedioxy-5-methyl-5-[(2-trimethylsilylethoxy)methoxy]-1,2-hexanediol II-12 in 100% yield. When II-12 was subjected to the action of aqueous sodium metaperiodate⁷³, the 1,2-vicinal diol was oxidized cleanly to the corresponding aldehyde II-13 in 95% yield. (2S,3R)-2,3-isopropylidenedioxy-4-methyl-4-[(2-trimethylsilylethoxy)methoxy]pentanal II-13 displayed an IR stretching band at 1728 cm^{-1} in addition to a shoulder at 2695 cm^{-1} . The cisoid-relationship of the hydrogens at 1,3-dioxolane ring was confirmed from their coupling constants, $\text{C}_3\text{-H}$ displayed a doublet at 4.23 ppm ($J = 6\text{ Hz}$), whereas $\text{C}_2\text{-H}$ showed a doublet of doublets at 4.39 ppm ($J_{1,2} = 2\text{ Hz}$ and $J_{2,3} = 6\text{ Hz}$), in addition a doublet at 9.54 ppm with $J_{1,2} = 2\text{ Hz}$ corresponding to aldehydic proton was observed.

3) Condensation of diethyl-(3-cyano-1,1-dimethoxypropyl) phosphonate II-8 and (2S,3R)-2,3-isopropylidenedioxy-4-methyl-4-[(2-trimethylsilylethoxy)methoxy]pentanal II-13

The carbon skeleton of II-18 leading to (+)-lineatin II-1 was constructed by condensing II-13 and ylide derived from II-8, under the conditions described by Rosenthal and Baker⁸⁴ to furnish II-14 in 90% yield. Two components were indicated by TLC which were presumably the E and Z isomers (Scheme 21). This was substantiated by both elemental analysis of the mixture and its spectral properties: IR absorption bands at 3020, 2220, 1645 cm^{-1} corresponding to olefinic hydrogen, nitrile and carbon-carbon double bond respectively. ^1H NMR indicated the presence of E:Z isomers in a ratio of 4:1 as was evident from the doublet at 6.45 ppm ($J_{2,4} = 1 \text{ Hz}$ and $J_{4,5} = 10 \text{ Hz}$) corresponding to the olefinic hydrogen of the E isomer form. The cisoid nature of the 1,3-dioxolane ring appeared to remain intact under the basic conditions employed in this condensation as indicated by the magnitude of the coupling constant between $\text{C}_5\text{-H}$ and $\text{C}_6\text{-H}$. The doublet at 5.00 ppm was assigned to $\text{C}_5\text{-H}$ with $J_{5,6} = 6 \text{ Hz}$ and $J_{4,5} = 10 \text{ Hz}$ and the doublet at 4.15 ppm ($J_{5,6} = 6 \text{ Hz}$) was assigned to $\text{C}_6\text{-H}$. Separation of the geometric isomers was not attempted since the next step was to convert the



Scheme 21

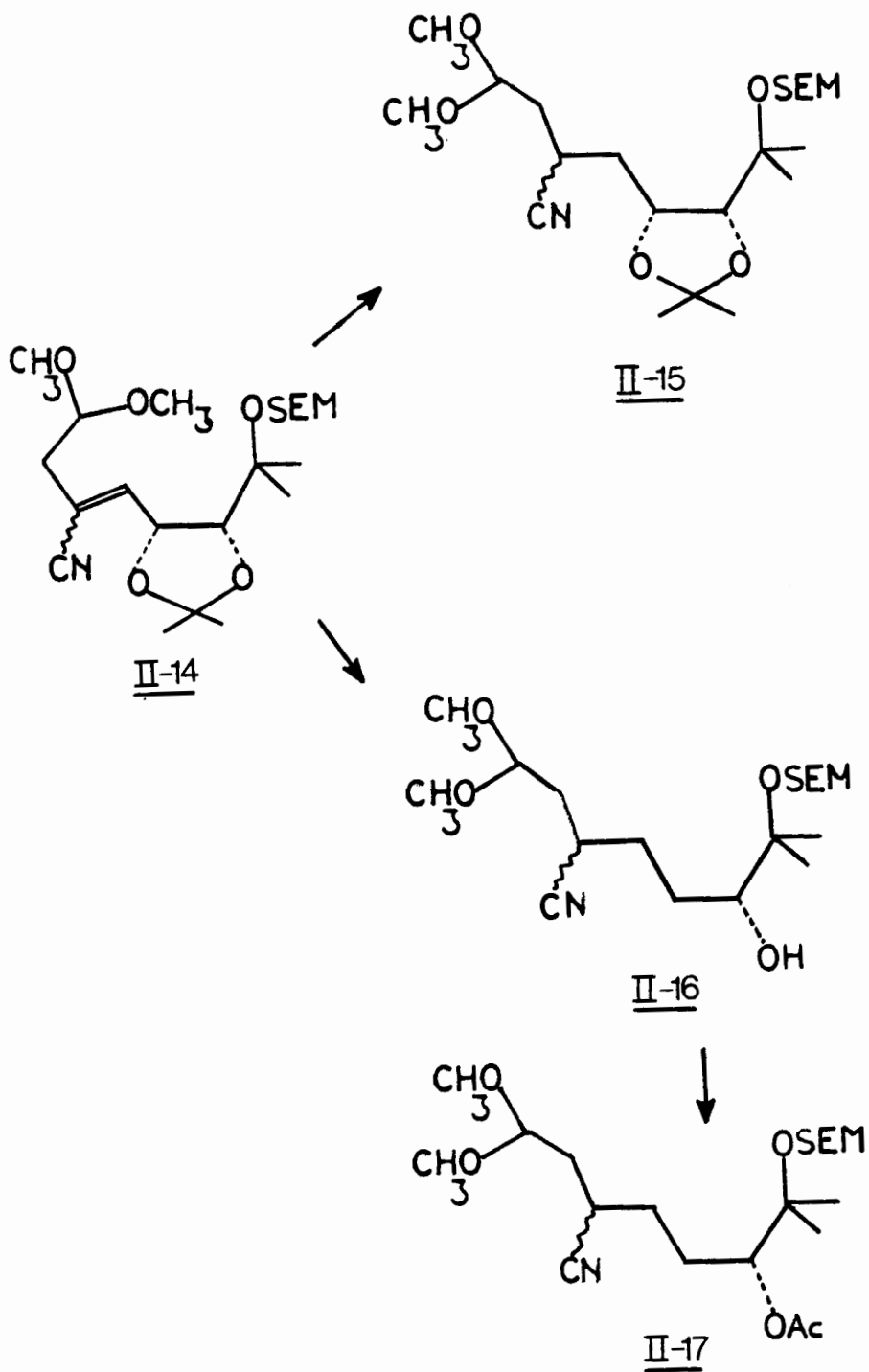
α,β -unsaturated nitrile mixture II-14 to the saturated nitrile II-15, in which the precursor identity would be lost (Scheme 22).

Corey *et. al.*⁸⁵ developed a simple, mild and selective method for the reduction of α,β -unsaturated nitriles, without concomitant reduction of the nitrile moiety⁸⁶, decyanation⁸⁷ or hydrodimerization⁸⁸. When this procedure was adopted by mixing the ene-nitrile II-14 with magnesium turnings and methanol, one product was detected which was more polar (TLC) than the starting α,β -unsaturated nitrile II-14. The reduction product II-16 was acetylated to furnish the mono-acetate (3R&S,6R)-6-acetoxy-3-cyano-7-methyl-7-[(2-trimethylsilylethoxy)methoxy]-1,1-dimethoxy-octane II-17 in 75% yield (Scheme 22). The cyano acetate II-17 exhibited all the anticipated spectral properties; IR absorption bands at 2250 and 1740 cm^{-1} corresponding to nitrile and acetate groups respectively; ^1H NMR (CDCl_3) showed a single resonance at 0.07 ppm (9H, $-\text{Si}(\text{CH}_3)_3$), a triplet at 0.91 ppm (2H, $-\text{CH}_2\text{Si}(\text{CH}_3)_3$, $J = 8.2$ Hz) in addition to a singlet at 2.14 ppm (3H, $\text{CH}_3\text{CO}-$) and a broad multiplet at 2.82 - 2.65 ppm (1H, $-\text{CH}-$).
CN

The overall reaction process of magnesium-methanol on compound II-14 can be classified into two parts:

- (a) Saturation of the α,β -unsaturated nitrile.
- (b) Reductive fission of the γ -alkoxy group.

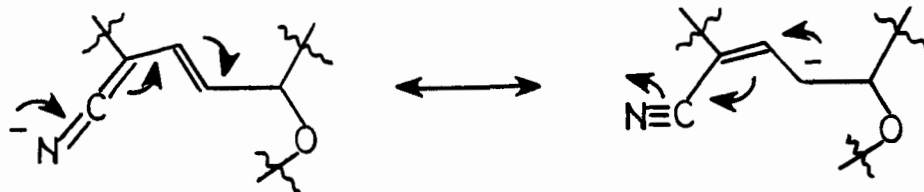
These processes can either occur separately or concurrently, but



Scheme 22

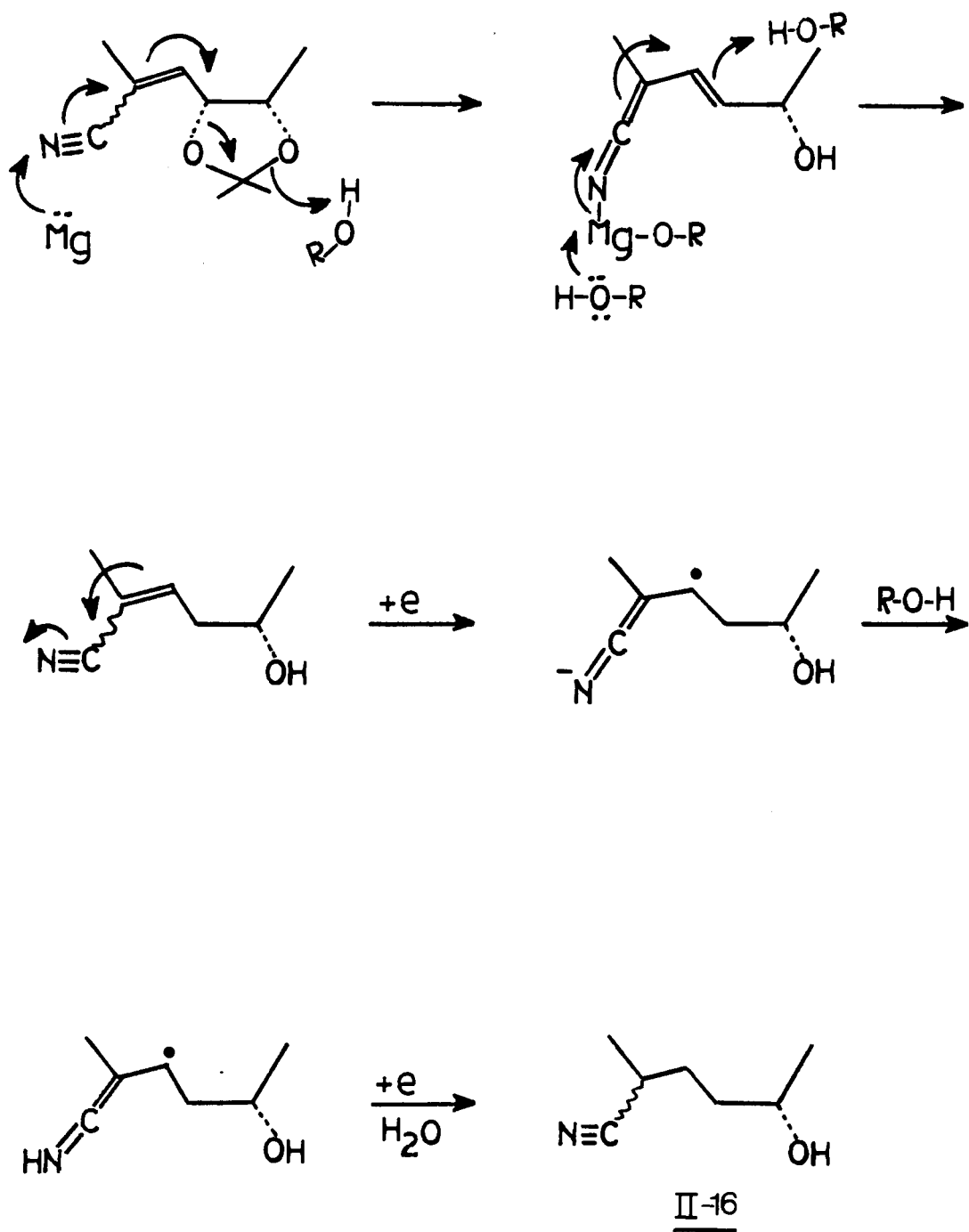
the inclusion of an acetal in the original report of the magnesium-methanol reduction⁸⁵ suggested that this reductive elimination occurs in a concurrent process. The reported acetal was isolated as the ketone, formed presumably through hydrolysis during workup. Had the acetal been cleaved in situ, the dissolving metal conditions would have reduced it to a secondary alcohol since it has been reported that dibenzylketone undergoes reduction by magnesium-methanol producing dibenzyl alcohol⁸⁹. Isolated acetals are thus likely untouched by the magnesium-methanol reducing conditions. The mechanism can be depicted in several ways. Two likely possibilities are illustrated (Schemes 23 and 24).

Both E and Z isomers of the ene-nitrile undergo reduction producing the same product. The difference between these two reaction pathways lies in the initial attack at two different sites producing reduction intermediates which can be considered resonance forms, and as such the two processes cannot be



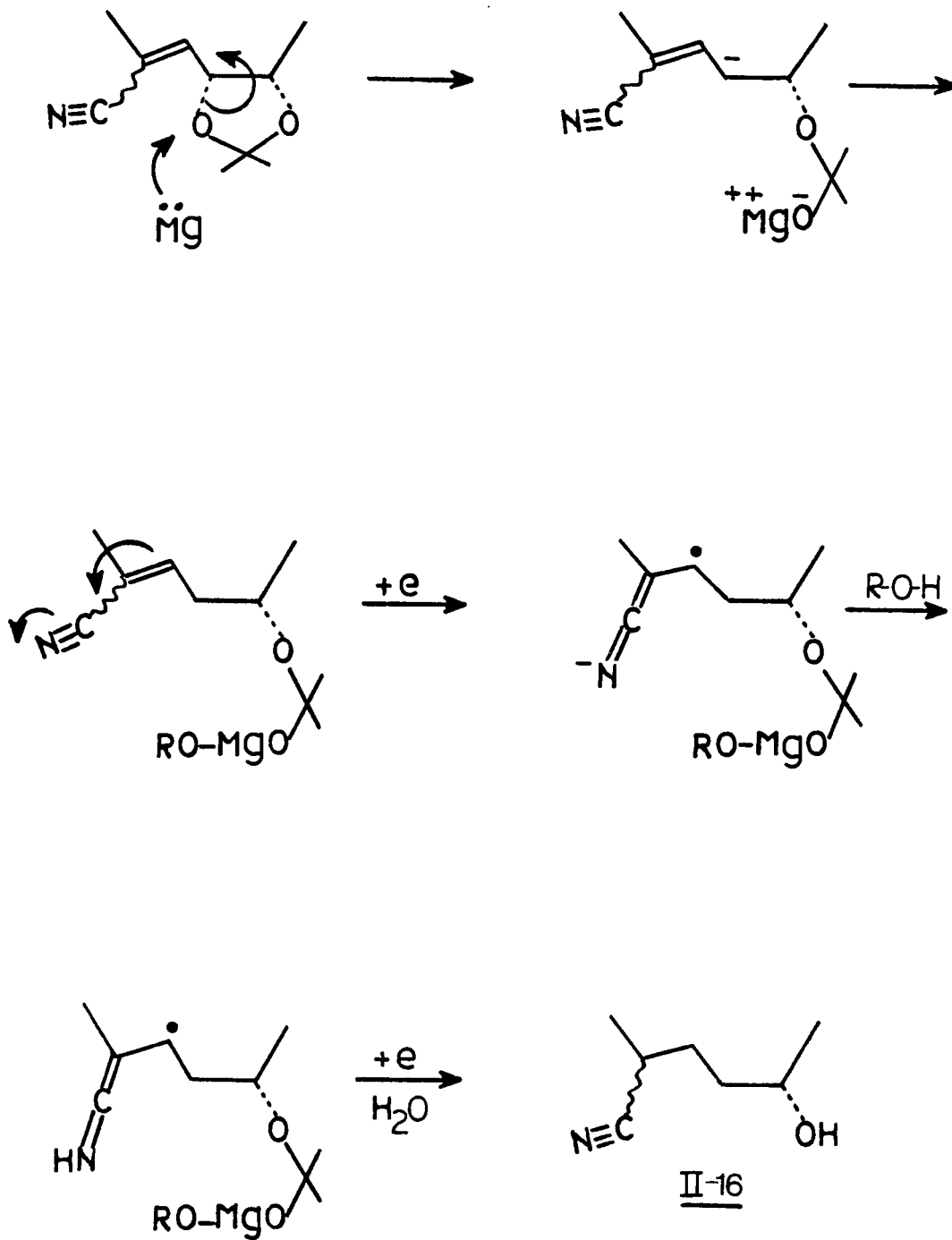
distinguished by deuteration studies or similar mechanistic probes.

A) Initial attack by magnesium metal on the nitrile nitrogen, followed by reduction of C=C-C≡N as shown in Scheme 23.



Scheme 23

B) Initial attack by magnesium metal on the acetal oxygen followed by reduction of C=C-C≡N as shown from Scheme 24.

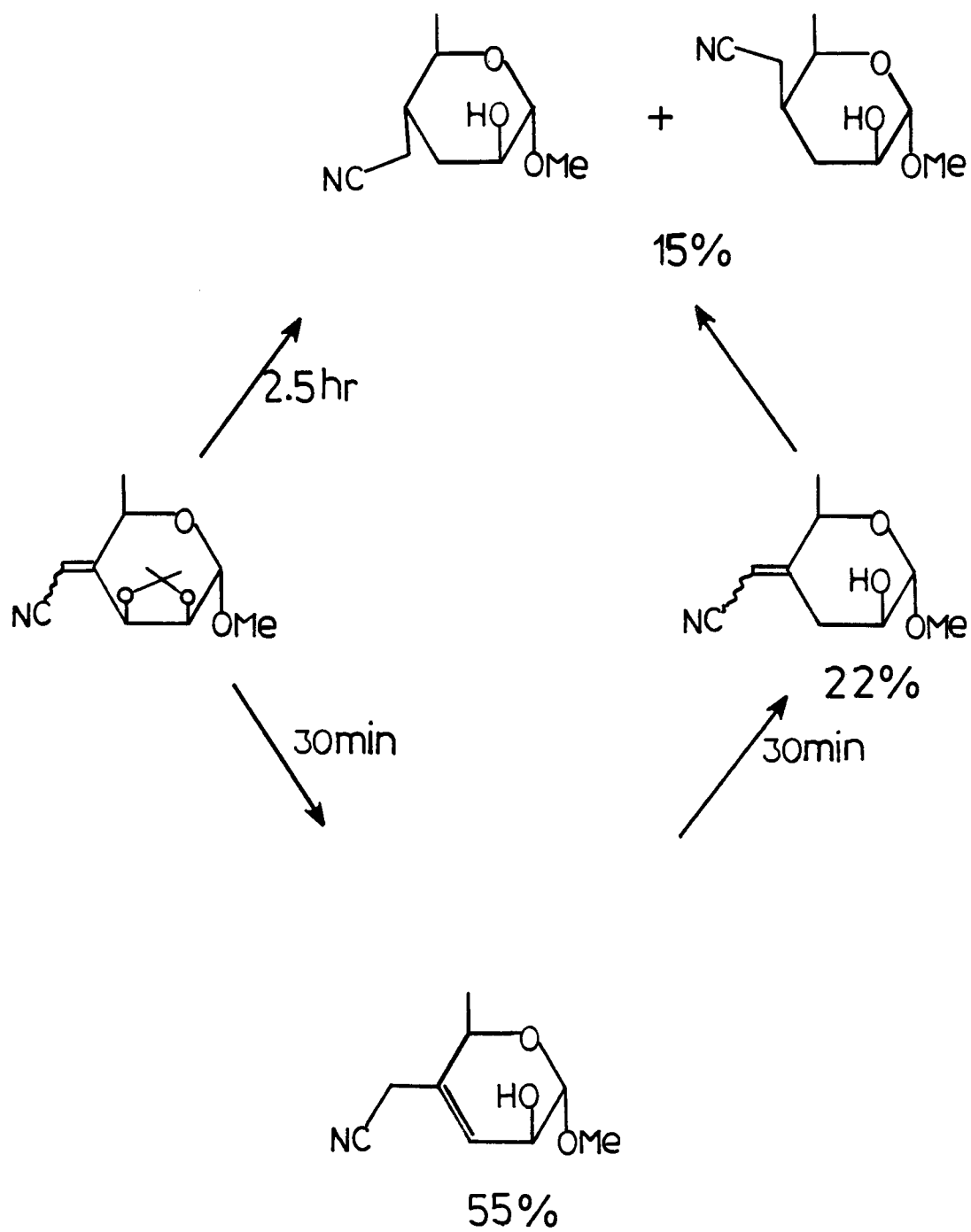


Scheme 24

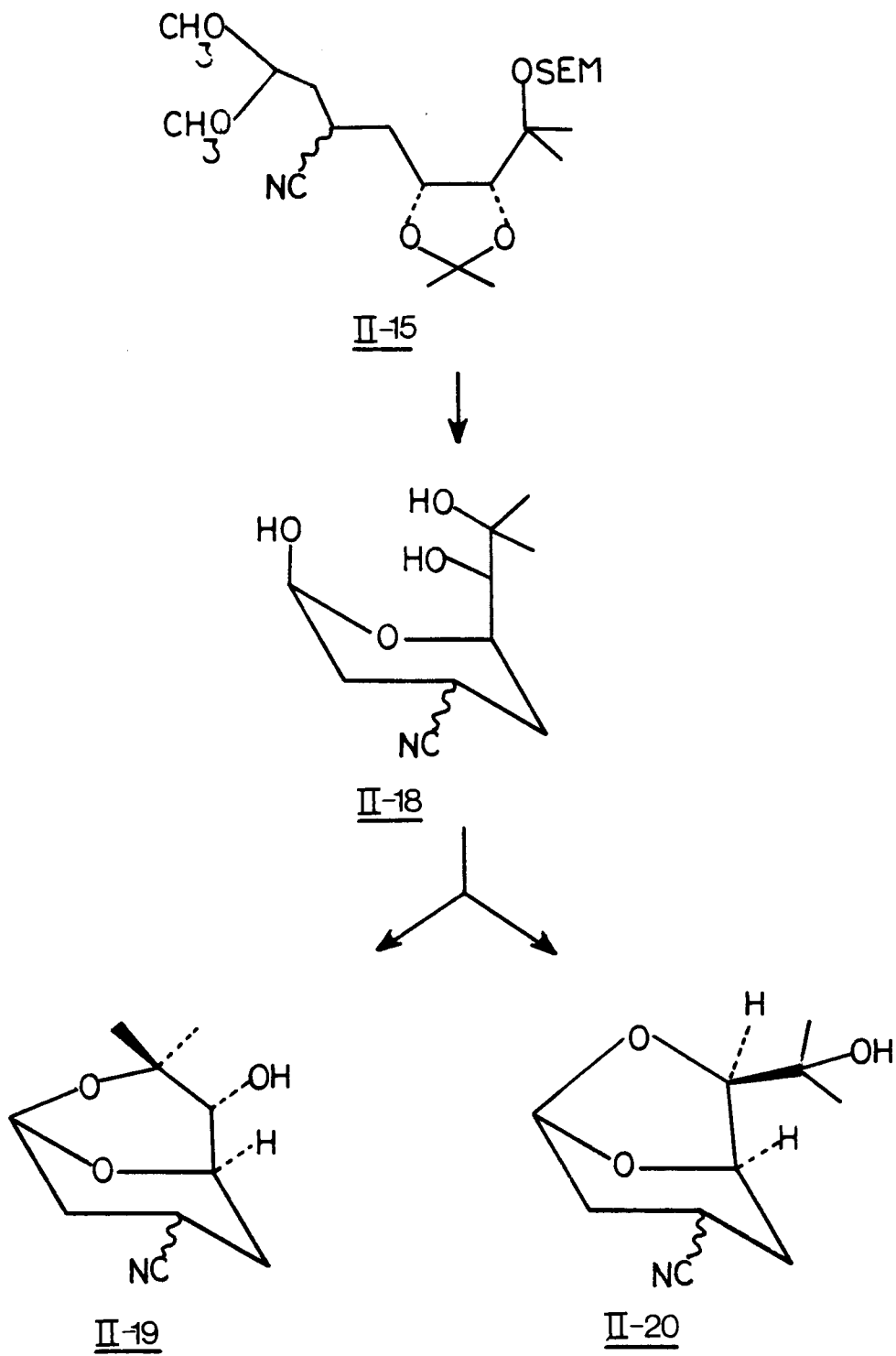
Wirrell⁹⁰ observed a similar reduction pattern when methyl 4-cyanomethylene-6-deoxy-2,3-O-isopropylidene- α -D-mannopyranoside was treated with magnesium-methanol for different reaction times (Scheme 25). The isolation of methyl 4-cyanomethyl-3,4,6-trideoxy- α -D-threopyran-3-enoside suggests that the reduction of the double bond α - to the nitrile and cleavage of the isopropylidene did not occur independently of one another, but are concurrent processes and thus both mechanisms shown in Schemes 23 and 24 are possible.

Several methods were attempted to reduce II-14, including diimide⁹¹, NaBH₄-Isopropanol⁹² and CuH⁹³ but these failed to produce any of the expected reduction product II-15. However, catalytic hydrogenation using 5% palladium on carbon⁹⁴ furnished (3R&S,5R,6R)-3-cyano-5,6-isopropylidenedioxy-7-methyl-7-[(2-trimethylsilylethoxy)methoxy]-1,1-dimethoxyoctane, II-15, in 97% yield.

An examination of molecular models suggested that II-15 would cyclize under acidic conditions to form the 2,9-dioxabicyclo[3.3.1]nonane, II-19, rather than 6,8-dioxabicyclo[3.2.1]octane II-20 via a common intermediate II-18 (Scheme 26). On this basis, cyclization was attempted under anhydrous conditions with a variety of reagents and solvent combinations, e.g. *p*-toluenesulphonic acid in acetone⁹⁵, pyridinium tosylate in acetone⁹⁶, lithium tetrafluoroborate in acetonitrile⁹⁷ and trimethylsilyl iodide in dichloromethane⁹⁸. These attempts failed



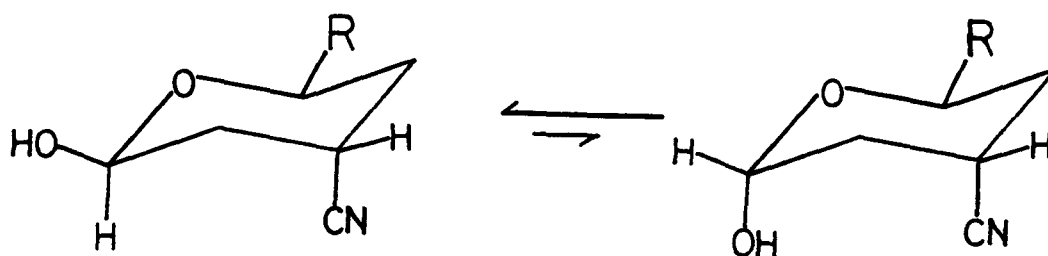
Scheme 25



Scheme 26

to bring about cyclization in good yield and TLC indicated the reaction mixture to be very complex. The inseparable products produced were presumably comprised of a mixture of partially or fully hydrolyzed products. Complete hydrolysis of II-15 to the fully unprotected precursor II-18 was found to proceed smoothly and cleanly with methanol: 1% sulphuric acid (1:1) to produce a mixture of two diastereoisomers II-18 in 90% yield. The ratio of these two diastereoisomers was found by ^1H NMR to be 3:2 in which the more polar diastereoisomer prevailed. Trituration of the mixture with dichloromethane enabled isolation of II-18a from the mixture as colourless crystals.

The structure of II-18a was deduced from its spectral data. The presence of hydroxyl and nitrile groups were apparent from the IR spectrum. The ^1H NMR spectrum revealed that both the alkyl substituted group at C_6 and the hydroxyl group at C_2 were equatorial, and the nitrile function at C_4 was axial as indicated by the analysis of the spin-spin coupling of protons at C_2 , C_4 and C_6 respectively. The C_2 -H appeared as a ddd at 5.15 ppm ($J = 2$ Hz, $J = 6$ Hz, $J = 10$ Hz), whereas the C_6 -H appeared as a ddd at 3.99 ppm with ($J = 2$ Hz, $J = 11$ Hz, $J = 6$ Hz). That the nitrile function at C_4 in II-18a was axial could be deduced from the coupling constants between C_4 -H and protons at C_3 and C_5 , which revealed a septet at 3.23 ppm with ($J = 2.5$ Hz, $J = 5$ Hz).



II-18 a

2 : 1

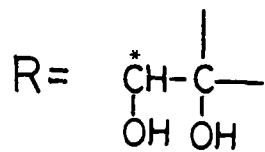


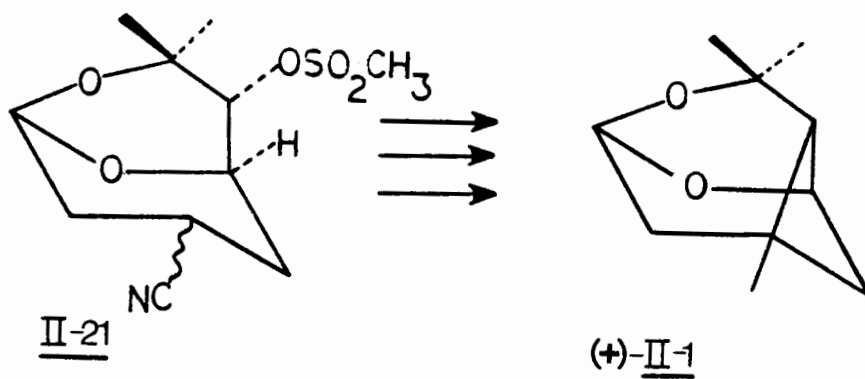
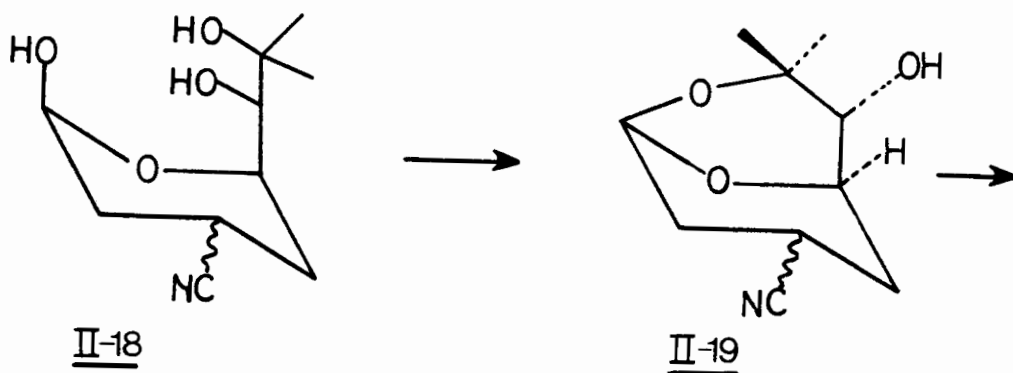
Fig. 2

In addition to the above mentioned spectral properties, II-18a was found to exist as an anomeric mixture in CDCl_3 solution in the ratio of 2:1 (Fig. 2). The remainder of the hydrolysis product failed to crystallize and attempts at further separation were not successful. The assumption that the other component in the mixture was the other epimeric nitrile with an equatorial orientation was substantiated at a later stage when the tert-butyl dimethylsilyloxy-derivatives II-23a and II-23b were separated by chromatography.

4) Formation of 2,9-dioxabicyclo[3.3.1]nonane derivative II-21

The next step in the synthetic route was the formation of an intramolecular acetal, creating a new chiral centre at C_1 , thus furnishing the (1 $\underline{\text{R}}$,4 $\underline{\text{R}}$,5 $\underline{\text{R}}$,7 $\underline{\text{R}}\&\underline{\text{S}}$)-2,9-dioxabicyclo[3.3.1]nonane derivatives, II-19. Conversion of hydroxyl group at C_4 into a leaving group, followed by an intramolecular S_{N}^2 alkylation by an anion derived from the epimeric nitrile at C_7 was expected to furnish the tricyclic cyano acetal. Reduction of the nitrile function to methyl would then furnish (+)-(1 $\underline{\text{R}}$,4 $\underline{\text{S}}$,5 $\underline{\text{R}}$,7 $\underline{\text{R}}$)-3,3,7-trimethyl-2,9-dioxatricyclo[3.3.1.0^{4,7}]nonane, (+)-II-1, (Scheme 27).

Cyclization of the diastereoisomeric mixture II-18, with p-toluenesulphonic acid in dichloromethane yielded a fast running

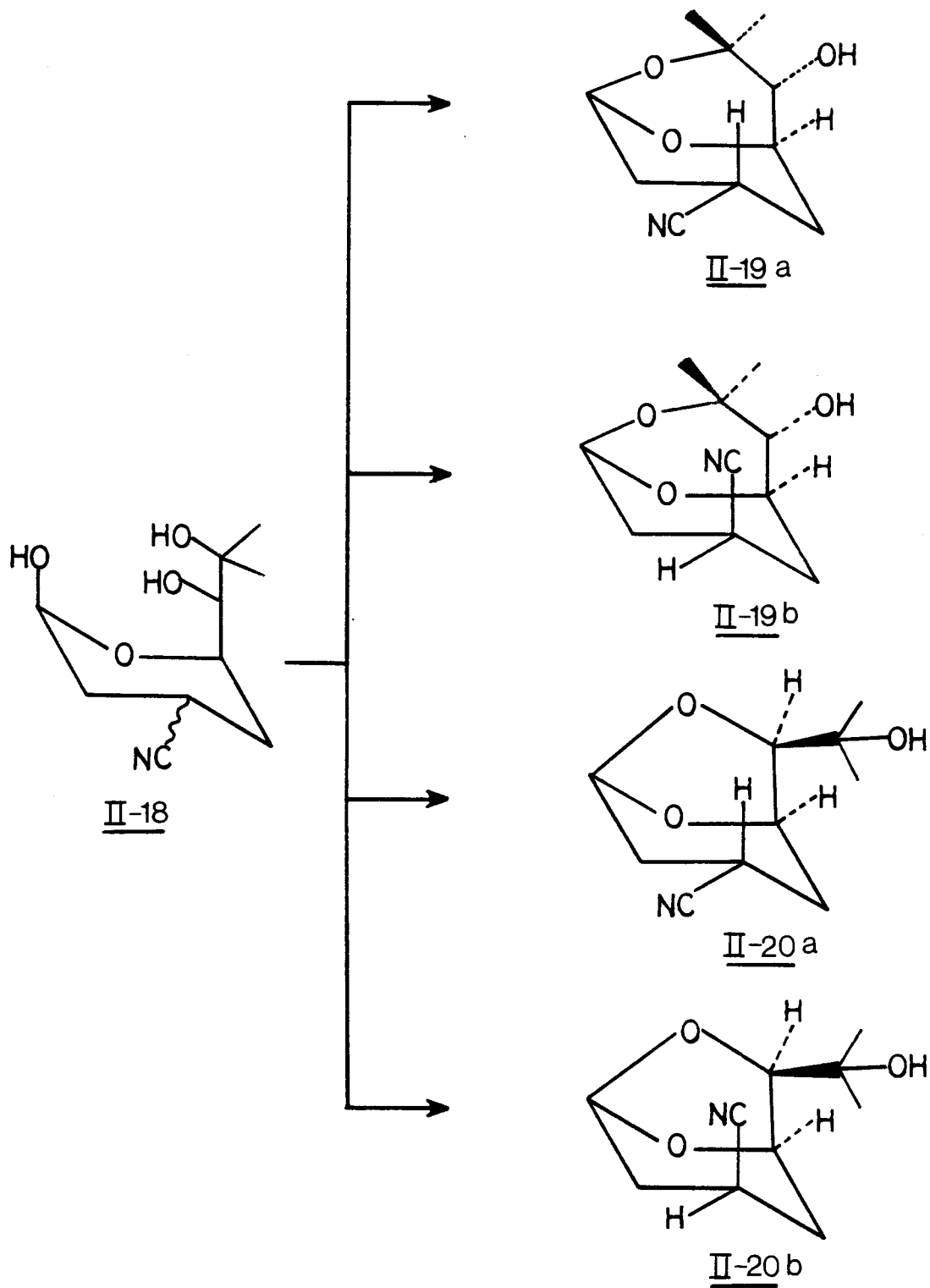


Scheme 27

component II-20 on (tlc), in addition to the unreacted triol II-18. When pure II-18a was treated in the same manner this fast running product II-20 was isolated in 65% yield, in addition to the unreacted triol II-18a.

Intramolecular acetal formation of the cyano epimers, II-18, can produce four cyclized products; two diastereoisomers resulting from cyclization between the anomeric hydroxyl group and tertiary hydroxyl group to produce 2,9-dioxabicyclo[3.3.1]nonane derivatives II-19a and II-19b, and two diastereoisomers resulting from cyclization between the anomeric hydroxyl and secondary hydroxyl group to produce 6,8-dioxabicyclo[3.2.1]octane derivatives II-20a, II-20b (Scheme 28).

The IR spectrum of the acid cyclization product of II-18, showed absorption bands at 3490 and 2252 cm^{-1} corresponding to a hydroxyl and a nitrile group respectively. A downfield shift of the NC-C-H proton signal to 3.95 ppm and the presence of two large spinspin couplings (tt, $J = 6.5 \text{ Hz}$, $J = 12 \text{ Hz}$), ruled out the two possible products in which the nitrile group would be in an axial orientation II-19b and II-20b. A Nuclear Overhauser experiment^{99,100} (NOE) allowed a decisive conclusion to be made as to the mode of cyclization. In the 2,9-dioxabicyclo[3.3.1]nonane derivative II-19a irradiation of the proton at signal $\text{C}_7\text{-H}$, should show NOE enhancement of the endo-proton at $\text{C}_4\text{-H}$, whereas in the 6,8- dioxabicyclo[3.2.1]octane derivative II-20a, irradiation of proton at $\text{C}^3\text{-H}$ should not show any NOE enhancement

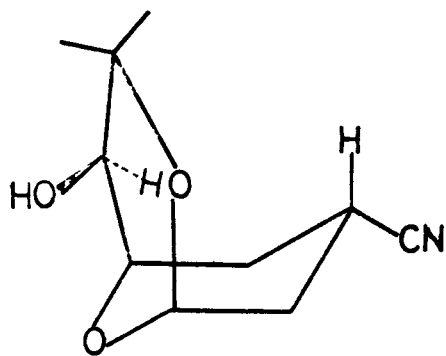


Scheme 28

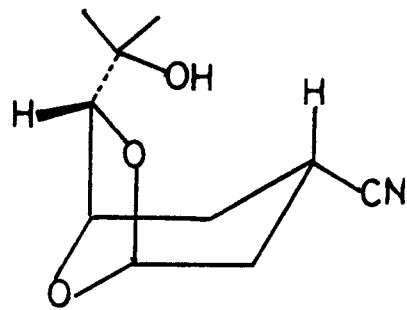
at C₇-H, but would show NOE enhancement of the endo-dimethylcarbinol. The observation that the hydroxyl hydrogen showed a NOE enhancement on saturating CH-CN provided strong evidence that II-20a was (1_R,3_S,5_R,7_R)-3-cyano-7-(dimethylcarbinol)-6,8-dioxabicyclo[3.2.1]octane, II-20a. Cyclization had preferentially produced the non-productive bicyclooctane rather than the desired bicyclononane.

Intramolecular acetal formation leading to 6,8-dioxabicyclo[3.2.1]octane derivative II-20a is expected to proceed by a disfavoured 5-Endo-Trig ring closure according to Baldwin's rules⁶⁶, whereas the formation of 2,9-dioxabicyclo[3.3.1]nonane derivative II-19a will result from a favoured 6-Endo-Trig ring closure. From a kinetic point of view, cyclization should proceed to produce II-19a in order to satisfy the stereochemical requirements of the transition state for 6-Endo-Trig ring closure.

Analysis of molecular models had suggested that II-18a would yield II-19a under acidic conditions rather than II-20a. For an equilibrium between cyclic and acyclic structures, one would expect that the main factor influencing the position of equilibrium to be the amount of strain in the resulting ring¹⁰¹. The greater stability of the six-membered ring is expected compared to the five-membered ring, since the former is stable in the preferred chair form, while the latter is less stable due to

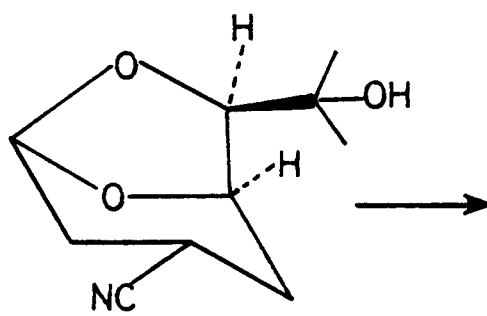


II-19 a

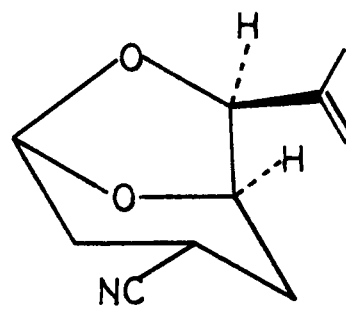


II-20 a

Fig. 3



II-20 a



II-22

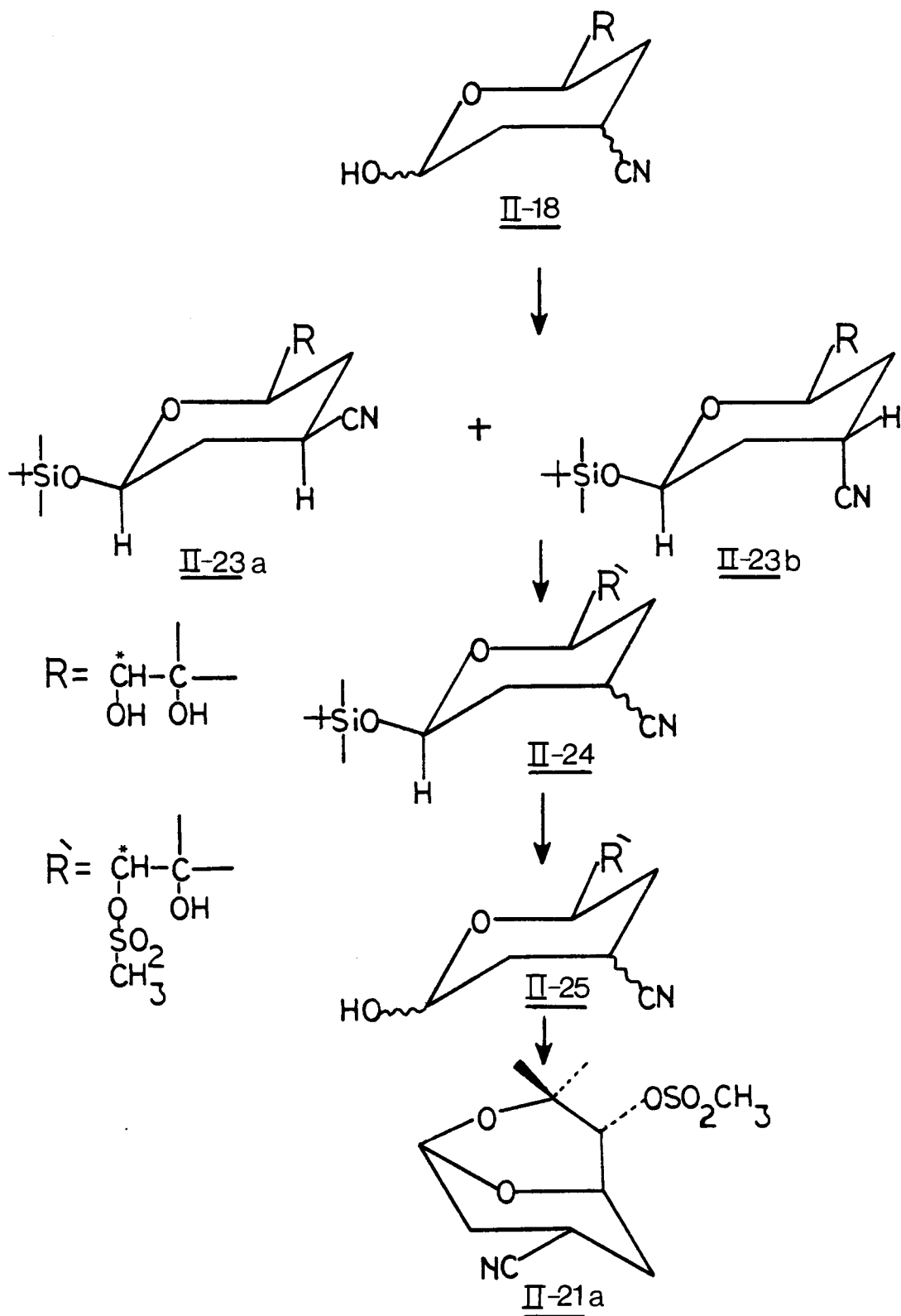
Scheme 29

strain arising from hydrogen-hydrogen repulsions. This order is also in accord with the observation that the pyranose structure is more stable than the furanose structure in simple sugars¹⁰². On the other hand, secondary hydroxyl groups have been shown to have a greater tendency to participate in the formation of intramolecular acetals as compared to primary hydroxyl groups with tertiary hydroxyl groups having an even lesser tendency^{103,104}. The conclusion was based on data relating to the relative stabilities of 1,7-anhydroheptopyranoses and 1,6-anhydroheptopyranoses, possessing an exo-hydroxymethyl substituent¹⁰⁵. However, 1,6-anhydroheptopyranoses containing an endo-hydroxymethyl substituent have been shown to be of about equal stability as 1,7-anhydroheptopyranoses¹⁰⁵. The latter system is analogous to that found in II-20a and II-19a. On the basis of these thermodynamic arguments one would expect that II-20a with a bulky endo-dimethylcarbinol might be of approximately the same stability as II-19a. However, when II-20a in chloroform was treated with p-toluenesulphonic acid for 14 days at room temperature, II-20a was recovered quantitatively.

The reluctance of II-20a to produce II-19a can be rationalized in terms of destabilization arising from the interaction between the endo-hydrogen at C₇ and endo-methyl at C₃ in II-19a, in the chair-chair conformation forcing the 1,3-dioxane ring to exist in either the boat or skew conformation. It would then appear that II-20a is the product of thermodynamic control.

When II-20a was treated with methanesulfonyl chloride (mesyl chloride) and triethyl amine¹⁰⁶, dehydration occurred through β -elimination¹⁰⁷ to furnish the olefin II-22 in 32% yield (Scheme 29).

To obtain the required 2,9-dioxabicyclo[3.3.1]nonane ring system by intramolecular acetal cyclization, the secondary hydroxyl group in the diastereoisomeric triol II-18 must be blocked by use of a suitable blocking group. The following synthetic transformations were utilized to effect this sequence (Scheme 30). Based on the relative reactivities of hydroxyl groups¹⁰¹, diastereoisomeric mixture II-18 was treated with tert-butyldimethylsilyl chloride according to the procedure described by Kraska *et. al.*¹⁰⁸ which produced II-23a and II-23b (2:3) as a readily separable mixture of diastereoisomers in 84% yield. These silyl ethers showed two singlets at 0.88 and 0.11 ppm corresponding to $(\text{CH}_3)_2\text{Si}-\text{C}(\text{CH}_3)_3$. The stereochemistry of II-23a and II-23b were assigned on the basis of coupling constants measured in their 400-MHz ¹H NMR spectra. Silyl ether II-23a showed a doublet-triplet at 2.75 ppm ($J = 4$ Hz and $J = 12.5$ Hz) corresponding to an axial C₄-H, whereas the more polar isomer II-23b displayed a doublet-triplet at 3.18 ppm with coupling constants of $J = 2.4$ Hz and $J = 5$ Hz corresponding to an equatorial C₄-H.



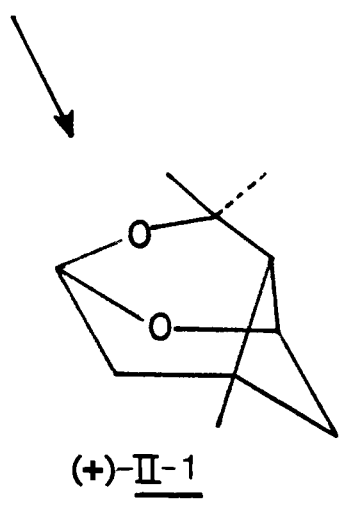
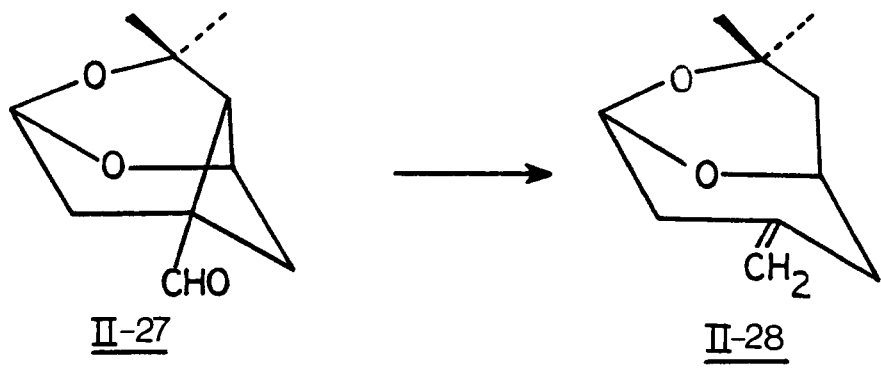
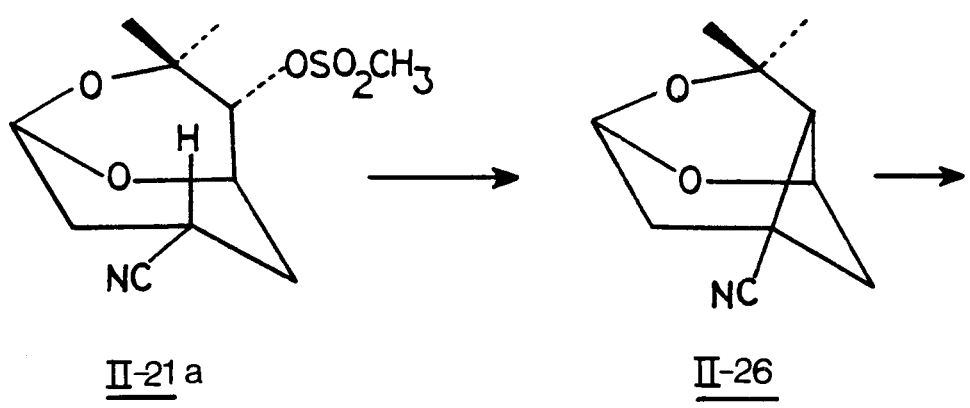
Scheme 30

The blocking of the secondary hydroxyl group was accomplished using the mesylate ester which later can be displaced in a nucleophilic manner, yet is stable to the acidic conditions required for the cyclization. The mesylate mixture II-24 was isolated in 77% yield. The regeneration of the hemiacetal portion was accomplished using 5% aqueous hydrofluoric acid¹⁰⁹ to afford a diastereoisomeric mixture of dihydroxy mesylates II-25.

This mixture II-25 was dissolved in benzene containing *p*-toluenesulphonic acid and refluxed using a Dean-Stark trap. A mixture of several products was produced in which II-21a, the major component, was isolated in 33% yield. The IR spectrum of II-21a showed a nitrile absorption at 2228 cm^{-1} . The ^1H NMR displayed a doublet-triplet at 3.30 ppm with $J = 5$ Hz and $J = 12$ Hz indicating an equatorial orientation of nitrile at C_7 . Nuclear Overhauser enhancement of C_4 -H was observed when NC-C-H was irradiated as would be expected for the postulated 2,9-dioxabicyclo[3.3.1]nonane ring system.

5) Formation of (+)-(1R,4S,5R,7R)-3,3,7-trimethyl-2,9-dioxatricyclo[3.3.1.0^{4,7}]nonane (+)-II-1

With formation of the 2,9-dioxabicyclo[3.3.1]nonane skeleton II-21a completed, the stereospecific cyclobutane formation through formation of a C_4 — C_7 bond was investigated. A $\text{S}_{\text{N}}2$ intramolecular displacement with inversion of configuration at C_4 was expected to provide the tricyclic cyano acetal II-26 (Scheme 31).



Scheme 31

Attempted cyclization of cyano mesylate II-21a using lithium diisopropylamide, lithium hexamethyldisilazide and tert-butyllithium failed to bring about the necessary ring closure. Apparently, the hindered nature of C₇-H prevented anion formation with these strong but sterically hindered bases. Treatment of II-21a with a less sterically hindered strong base, freshly prepared sodium amide in refluxing tetrahydrofuran, provided the tricyclic cyano acetal II-26 in 69% yield.

The assignment of structure II-26 relied on ¹H NMR decoupling experiments. The assignment of H_{8ax} and H_{8eq} could be made from decoupling results of H₁ and the assignment of H_{6ax} and H_{6eq} were made from their interactions with H₅ and H_{8eq}. An assignment for H₄ was obtained from the decoupling of H₅. A long range coupling (\approx 1 Hz) was observed between H₄ and H_{8ax} in accordance with their W plane conformation. The observed coupling constants were in agreement with those estimated from the Karplus relationship¹¹⁰ using dihedral angles estimated from a Dreiding model of II-26.

To effect the final conversion of the nitrile moiety to a methyl group, II-26 was treated with di-isobutylaluminum hydride in tetrahydrofuran¹¹¹ to furnish the aldehyde in 75% yield (Scheme 31). The product, II-27, showed an absorption band at 1708 cm⁻¹ in its IR spectrum and displayed a singlet at 9.58 ppm in its ¹H NMR spectrum in agreement with its expected aldehyde

structure. Sodium cyanoborohydride reduction of the tricyclic N-tosylhydrazone^{112,113} prepared in situ from the aldehyde II-27, furnished the bicyclic olefin II-28 in 22% yield (Scheme 31). The formation of bicyclic olefins during deoxygenation of hindered carbonyls has been previously reported to furnish olefins¹¹⁴.

When the aldehyde II-27 was treated with anhydrous hydrazine and potassium hydroxide in a standard Wolff-Kishner reduction^{115,116}, (+)-lineatin II-1 was obtained in 73% yield (Scheme 31). (+)-Lineatin prepared in this way was uncontaminated by any other volatile material judged by capillary gas chromatography and exhibited all the spectral properties of natural lineatin⁵¹.

Conclusion

This research has led to the first stereospecific synthesis of optically active (+)-lineatin, (1R,4S,5R,7R)-3,3,7-trimethyl-2,9-dioxatricyclo[3.3.1.0^{4,7}]nonane, (+)-II-1. Commercially available D-(+)-ribonolactone II-4 was utilized as "Chiral Template" to prepare (2S,3R)-2,3-isopropylidene-4-methyl-4-[(2-trimethylsilylethoxy)methoxy]pentanal II-13 of known absolute configuration. Condensation of II-13 with diethyl-(3-cyano-1,1-dimethoxypropyl)phosphonate II-8 provided an isomeric mixture of ene-nitriles II-14, which could be reduced with palladium on carbon to provide a diastereoisomeric mixture of saturated nitriles II-15. Acid catalyzed cyclization of II-15 produced the unproductive 6,8-dioxabicyclo[3.2.1]octane derivative II-20a. However, selective protection, blocking and deprotection protocols for the hemiacetal and secondary hydroxyl centers enabled acid catalyzed cyclization to the required 2,9-dioxabicyclo[3.3.1]nonane derivative II-21a. Stereospecific cyclobutane formation via an intramolecular nucleophilic displacement furnished the tricyclic cyano acetal II-26. Conversion of the nitrile functionality to a methyl group provided (+)-lineatin II-1 in 2.7% overall yield.

This synthetic route to (+)-lineatin clearly established the absolute configuration as 1R,4S,5R,7R on the basis of stereospecific and systematic introduction of functional groups.

It is also clear that the approach could be useful in the preparation of a large number of organic natural products as well as insect sex pheromones from carbohydrate precursors.

EXPERIMENTAL

General Conditions and Chemicals

Evaporation was carried out under reduced pressure at temperatures not exceeding 45°C. Unless otherwise specified, the following experimental methods were used. Melting points were determined on a Fisher-Johns apparatus and were uncorrected. Infrared spectra (IR) were recorded on a Perkin-Elmer 599B spectrophotometer. Samples were run as a neat film on NaCl plates or as solutions in a cell with NaCl windows. Mass spectra and gas chromatography-mass spectra were taken on a Hewlett-Packard 5985 B mass spectrometer using a SE-30 capillary column. High resolution mass spectra (HRMS) were provided by Dr. G. Eigendorf, University of British Columbia, using a Kratos DS-50 mass spectrometer. Elemental analyses were performed by Mr. M. Yang of Simon Fraser University, on a Perkin-Elmer elemental analyzer, Model 240.

Routine gas liquid chromatography (GC) analyses were run on a Varian 1400 flame ionization gas chromatograph, with glass columns containing supported OV-17 or SE-30, programmed from 80 C to 200°C at 10°C/min. Thin layer chromatography (TLC) plates were prepared from silica gel 60 and compounds were detected by spraying plates with 10% aqueous sulphuric acid and heating. Chromatographic separations were carried out as described by Still et. al.¹¹⁷ using 230-400 mesh silica gel.

Optical rotations were determined on a Rudolph Polarimeter Model 70 using 1 dm × 1.5 mm i.d. sample cell, concentrations are reported in g/100 mL of solvent. Nuclear magnetic resonance (NMR) spectra were measured in CDCl₃ or CCl₄ solutions on a Varian Associates EM-360 spectrometer using Me₄Si as an internal standard or on a Bruker WM-400 spectrometer in the Fourier transform mode with CDCl₃ internal lock. Splitting patterns are described as s (singlet), d (doublets), t (triplets), q (quartets), m (multiplets), dd (double doublets), dt (double triplets), with b designating broadening. Coupling constants are reported in Hertz (Hz).

Solvents employed for chromatography, petroleum ether (30-60 °C), pentane, and ethyl acetate were distilled prior to use. Compositions of solvent mixtures are reported as volume ratios. Tetrahydrofuran (THF) was distilled from lithium aluminum hydride, N,N-dimethylformamide (DMF) and 1,2-dimethoxyethane were distilled from calcium hydride. Ether was dried with anhydrous calcium chloride, distilled and stored over sodium wire. All reactions requiring anhydrous and/or oxygen free conditions were run under a positive pressure of nitrogen or argon.

5-Bromopentan-1-ol I-5

5-Bromopentan-1-ol, I-5 was prepared following the method described by Nystrom³⁶. A solution of 5-bromovaleric acid⁶⁸ (30.0 g, 0.16 mol) in ether (150 mL) was added to lithium aluminum hydride-aluminum chloride (1:1) (total of 27.3 g, 0.16 mol of each) in ether (300 mL), which was cooled to -75°C. Thirty minutes after the addition of acid, excess hydride was destroyed by careful addition of methanol (20 mL). The mixture was warmed to room temperature and water (100 mL) and 3 M sulphuric acid (100 mL) were added. The clear solution was extracted with ether (3 × 200 mL), washed with 5% cold aqueous sodium bicarbonate (2 × 50 mL), brine (2 × 100 mL) and dried over anhydrous sodium sulphate. Evaporation of solvent under reduced pressure followed by vacuum distillation afforded I-5 (22.4 g, 82%), b.p. 100-102°C (3 Torr), lit.¹¹⁸, b.p. 75-76°C (0.5 Torr).

1-tert-Butyldimethylsilyloxy-5-bromopentane I-6

5-Bromopentanol I-5 (5.8 g) was stirred with imidazole (5.9 g, 2.5 equiv.) and tert-butyldimethylsilyl chloride (6.2 g, 1.2 equiv.) in DMF (15 mL) at 25°C for 12 h. The mixture was poured into ice-cold water (50 mL), extracted with ether (2 × 20 mL), washed with brine (50 mL) and dried over sodium sulphate. Evaporation of the solvent under reduced pressure followed by vacuum distillation afforded I-6 (8.3 g, 85%); b.p. 68-70°C

(0.25 Torr); IR (film) 2958, 2865, 1475, 1465, 1255, 1105, 840 cm^{-1} ; ^1H NMR (CCl_4) δ 3.60 (2H, $-\text{CH}_2\text{O}-$, t, $J = 6$), 3.38 (2H, $-\text{CH}_2-\text{Br}$, t, $J = 7$), 2.00-1.30 (6H, $-(\text{CH}_2)_3-$, m), 0.82 (9H, $(\text{CH}_3)_3\text{C}-$, s), 0.00 (6H, $(\text{CH}_3)_2\text{Si}-$, s).

Anal. Calcd for $\text{C}_{11}\text{H}_{25}\text{OBrSi}$: C, 46.97; H, 8.89. Found: C, 46.95; H, 8.65.

(+)-1-tert-Butyldimethylsilyloxy-octan-1-ol (+)-I-7

A three-necked flask (50 mL), containing magnesium turnings (0.18 g, 7.5 mg-atoms) and a stirring bar was dried in an oven at 100°C for 2 h and cooled to room temperature under a stream of dry nitrogen. A portion of a solution of 1-tert-butyl-dimethylsilyloxy-5-bromopentane I-6 (1.0 g, 3.6 mmol) in anhydrous THF (5 mL) was introduced and the reaction was initiated with a small crystal of iodine, with the remaining solution added over 5 min. Stirring was continued for a further 1 h at room temperature and the mixture was cooled to -30°C . Freshly purified CuI^{42} (0.07 g, 0.36 mmol) was added and the mixture stirred for 30 min. Methyloxirane, (+)-I-4 (0.14 g, 2.4 mmol) was added dropwise over a 5 min. period, the mixture warmed to 0°C , and stirred for 3 h. The reaction was quenched by addition of saturated aqueous ammonium chloride (5 mL) and the product isolated by extraction with ether to yield a colourless liquid (0.72 g). Chromatography with ether-petroleum ether (1:1) afforded a pure product (+)-I-7 (520 mg, 84%); IR (film) 3316,

1462, 1359, 1257, 1109, 785 cm^{-1} ; ^1H NMR (CCl_4) δ 3.72 (1H, -CH-,m), 3.52 (2H, -CH₂O-,t,J = 6), 2.98 (1H,OH,bs), 1.35 (10H, - CH_2)₅-,m), 1.18 (3H,CH₃-CH,d,J = 6), 0.87 (9H,(CH₃)₃C-,S), 0.00 (6H,(CH₃)₂Si-,S).

Anal. Calcd for $\text{C}_{14}\text{H}_{32}\text{O}_2\text{Si}$: C, 64.56; H, 12.40. Found: C, 64.61; H, 12.23.

S-(+)-I-7 was prepared from the magnesium salt of I-6 and S-(-)-methyloxirane, $[\alpha]_{\text{D}}^{23}$ -14.1° (neat), prepared by the method of Seuring and Seebach³⁵ to give (+)-I-7 (94%); $[\alpha]_{\text{D}}^{23}$ +3.7° (\underline{c} 2.43, EtOH); Found: C, 64.64; H, 12.02.

R-(-)-I-7 was prepared as described above from I-6 and R-(+)-methyloxirane, $[\alpha]_{\text{D}}^{23}$ +12.1° (neat), prepared by the method of Johnston and Slessor³⁴ to give (-)-I-7 (82%); $[\alpha]_{\text{D}}^{23}$ -3.6° (\underline{c} 11.3, EtOH); Found: C, 64.65; H, 12.12.

(+)-1-tert-Butyldimethylsilyloxy-7-acetoxy-octane (+)-I-8

The hydroxy silyl ether (+)-I-7 (0.8 g, 3.2 mmol) was acetylated in pyridine (8 mL) using acetic anhydride (8 mL) at room temperature for 12 h. The solution was poured into ice water (20 mL), extracted with dichloromethane (2 × 30 mL) washed with ice-cold 1 M hydrochloric acid (2 × 5 mL), water (2 × 25 mL) and dried over anhydrous sodium sulphate. Evaporation of

the solvent afforded (+)-I-8 (0.72 g, 93%); IR (film) 1747, 1248, 1105 cm^{-1} ; ^1H NMR (CCl_4) δ 4.82 (1H, $-\overset{\text{OAc}}{\text{CH}}-$, m), 3.58 (2H, $-\text{CH}_2\text{O}-$, t, J = 5), 1.94 (3H, $\text{CH}_3\text{CO}-$, s), 1.37 (10H, $-(\text{CH}_2)_5$, m), 1.21 (3H, $\text{CH}_3-\overset{\text{OAc}}{\text{CH}}-$, d, J = 6), 0.86 (9H, $(\text{CH}_3)_3\text{C}-$, s), 0.00 (6H, $(\text{CH}_3)_2\text{Si}-$, s).

Anal. Calcd for $\text{C}_{16}\text{H}_{34}\text{O}_3\text{Si}$: C, 63.57; H, 11.35. Found: C, 63.81; H, 11.40.

S-(+)-I-8: Yield 69%; $[\alpha]_{\text{D}}^{23} +0.8^\circ$ (c 4.64, EtOH); Found: C, 63.61; H, 11.60.

R-(-)-I-8: Yield 88%; $[\alpha]_{\text{D}}^{23} -0.7^\circ$ (c 12.2, EtOH); Found: C, 63.68; H, 11.35.

(+)-7-Acetoxy-octan-1-ol (+)-I-9

A solution of (+)-I-8 (1.0 g, 3.3 mmol) in acetic acid-water-tetrahydrofuran (3:1:1, 34 mL) was stirred at 25°C for 24 h. The reaction was poured into ice water (50 mL), extracted with dichloromethane (2 \times 30 mL) and washed with cold water (2 \times 5 mL). The extract was given a final water wash (20 mL), dried over anhydrous sodium sulphate and evaporated. Chromatography using ether-petroleum ether (1:1) afforded (+)-I-9 (0.52 g, 84%); IR (film) 3405, 1742, 1262, 1248 cm^{-1} ; ^1H NMR (CCl_4) δ 4.74 (1H, $-\overset{\text{OAc}}{\text{CH}}-$, m), 3.74 (1H, OH, s), 3.53 (2H, $-\text{CH}_2\text{O}-$, t, J = 4),

1.91 (3H, CH₃CO-,S), 1.39 (10H,-(CH₂)₅-,m), 1.29 (3H,CH₃-CH-,
|
OAc
CH₃-CH-,d,J = 6).

Anal. Calcd for C₁₀H₂₀O₃: C, 63.81; H, 10.71. Found: C,
64.12; H, 10.88.

S-(+)-I-9: Yield 72%; [α]_D²³ +1.5° (c 4.53, EtOH); Found: C,
63.95; H, 10.72.

R-(-)-I-9: Yield 86%; [α]_D²³ -1.8° (c 8.79, EtOH); Found: C,
63.74; H, 10.86.

(+)-7-Acetoxy-octanal (+)-I-10

A solution of (+)-I-9 (0.28 g, 1.48 mmol) in dichloro-
methane (1 mL) was added to a stirred suspension of pyridinium
chlorochromate (0.48 g, 2.23 mmol) in dichloromethane (4 mL)
under nitrogen atmosphere. After 2 h at room temperature,
anhydrous ether (20 mL) was added and the supernatant decanted
from the black gum. The insoluble residue was washed thoroughly
with ether (3 × 50 mL) and the combined extracts filtered
through a short column of Florisil. The eluent was evaporated
to yield (+)-I-10 (0.26 g, 96%); IR (film) 2982, 2735, 1752,
1728, 1378, 1248 cm⁻¹; ¹H NMR (CCl₄) δ 9.83 (1H, -CHO,t,J = 2),
4.82 (1H,-CH-,m), 2.37 (2H,-CH₂-CHO,m), 1.93 (3H,CH₃CO-,S), 1.42
|
OAc
(10H,-(CH₂)₅-,m), 1.24 (3H, CH₃-CH,d,J = 6).
|
OAc

HRMS calcd for $C_8H_{15}O_2(M-1)^+$, 143.1072; Found, 143.1070.

S-(+)-I-10: Yield 76%; $[\alpha]_D^{23} +2.9^\circ$ (c 3.48, EtOH); Found, 143.1066.

R-(-)-I-10: Yield 86%; $[\alpha]_D^{23} -3.1^\circ$ (c 5.88, EtOH); Found, 143.1072.

(+)-Methyl-9-acetoxy-(E)-2-decenoate (+)-I-11

Trimethylphosphonoacetate (0.46 g, 2.52 mmol) and sodium hydride (0.13 g of 50% dispersion) were stirred together in anhydrous THF (10 mL), under argon at room temperature for 40 min. A solution of (+)-I-10 (0.47 g, 2.5 mmol), in THF (2 mL) was added and the stirring continued for 1.5 h. Water (10 mL) was added to the reaction mixture and the mixture immediately neutralized with 2 M hydrochloric acid. The aqueous suspension was extracted with ether, the extract dried over anhydrous sodium sulphate and evaporated to a crude product (0.51 g). This material was subjected to chromatography and elution with ether-petroleum ether (1:4) yielded the diester (+)-I-11 (0.41 g, 70%); IR (film) 3005, 1745, 1718, 1655, 1240, 960 cm^{-1} ; 1H NMR (CCl_4) δ 6.85 (1H, $-CH_2-\underline{CH}=\underline{CH}-$, d of t, $J = 15, 6$), 5.65 (1H, $-CH_2-\underline{CH}=\underline{CH}-$, d, $J = 15$), 4.78 (1H, $-\underline{CH}-$, m), 3.92 (3H, CH_3O- , s), 2.22 (2H, $-\underline{CH}_2-\underline{CH}=\underline{CH}-$, d, $J=6$), 1.79 (3H, CH_3CO- , s), 1.38 (8H, $-(CH_2)_4$, m), 1.21 (3H, $CH_3-\underline{CH}-$, d, $J=6$).

Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.61; H, 9.51.

S-(+)-I-11: Yield 64%; $[\alpha]_D^{23} +2.1^\circ$ (c 6.16, EtOH); Found: C, 64.62; H, 9.29.

R-(-)-I-11: Yield 67%; $[\alpha]_D^{23} -1.8^\circ$ (c 7.17, EtOH); Found: C, 64.68; H, 9.30.

(+)-9-Hydroxy-(E)-2-decenoic acid (+)-I-1

The acetoxy ester (+)-I-11 (0.8 g, 3.3 mmol) was stirred with 5% sodium hydroxide in methanol-water (1:1) (8 mL) at room temperature for 12 h. Evaporation of methanol and dissolution in water (5 mL) followed by washing with dichloromethane (2 x 5 mL) yielded an aqueous solution which was acidified with ice-cold 2M hydrochloric acid (5 mL). Extraction with dichloromethane (3 x 30 mL), washing with water (2 x 10 mL) and drying over anhydrous sodium sulphate gave a solution which was evaporated to give the racemic 9-hydroxy-(E)-2-decenoic acid (+)-I-1 (0.42 g, 68%); IR (film) 3385, 3005, 1705, 1662, 1425, 1292, 965 cm^{-1} ; 1H NMR ($CDCl_3$) 7.21 (2H, OH and COOH, bs), 6.98 (1H, $-CH_2-\underline{CH}=\underline{CH}-$, d of t, $J=15,6$), 5.77 (1H, $-CH_2-\underline{CH}=\underline{CH}-$, d, $J=15$), 3.89 (1H, $-\underset{\text{OH}}{\text{CH}}-$, m), 2.24 (2H, $-\underline{CH}_2-\underline{CH}=\underline{CH}-$, d, $J=6$), 1.38 (8H, $-(CH_2)_4-$, m), 1.22 (3H, $CH_3-\underset{\text{OH}}{\text{CH}}$, d, $J=6$).

Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 65.05; H, 9.51.

S-(+)-I-1: The free acid was prepared as described for the racemic material, except for the substitution of anhydrous 1,2-dimethoxyethane as the solvent in the Wittig-Horner condensation to yield (+)-I-1 (79%); $[\alpha]_D^{23} +5.2^\circ$ (c 7.61, EtOH); Found: C, 64.58; H, 9.58.

R-(-)-I-1: The laevorotatory isomer was prepared in a manner identical to racemate to yield (-)-I-1 (91%); $[\alpha]_D^{23} -5.4^\circ$ (c 21.0, EtOH); Found: C, 64.35; H, 9.76.

p-Bromophenacyl-(+)-9-hydroxy-(E)-2-decenoic acid (+)-I-12

A sample of the hydroxy acid (+)-I-1 (186 mg) was converted into its sodium salt with 5% aqueous sodium hydroxide into which (286 mg, 0.9 mmol) of p-bromophenacyl bromide in ethanol (5 mL) was added. The solution was refluxed for 3 h, cooled, filtered, and recrystallized from hexane to give the derivative (+)-I-12 (215 mg, 56%) as colourless needles: m.p. 73-74°C; lit.⁴⁹ m.p. 73-74°C.

Anal. Calcd for $C_{18}H_{23}O_4Br$: C, 56.40; H, 6.06. Found: C, 56.69; H, 6.21.

S-(+)-I-12: Yield 53%; m.p. 96-97°C; $[\alpha]_D^{23} +6.1$ (c 5.23, EtOH); Found: C, 56.42; H, 6.22.

R-(-)-I-12: Yield 57%; m.p. 96-97°C; $[\alpha]_D^{23} -6.4$ (c 6.61, EtOH); Found: C, 56.37; H, 6.19.

2,3-O-Isopropylidene-D-ribonolactone II-5

To a suspension of D-ribonolactone⁶⁷ II-4 (25 g; 0.17 mol) in acetone (500 mL), concentrated sulphuric acid (10 mL) was added dropwise while the solution was cooled in an ice bath. The mixture was stirred for 5 h at room temperature during which time the starting material dissolved. Ammonia gas was passed through the ice-cooled solution, filtered and the filtrate was evaporated under reduced pressure. The resulting crystalline residue was recrystallized from benzene to yield the product II-5 (28.2 g, 85%) as colourless needles: m.p. 138-89°; $[\alpha]_D^{23}$ -83.2° (c 2.48, Acetone); Lit.⁷¹ m.p. 138-39° $[\alpha]_D^{23}$ -84.2° (c 0.9, Acetone).

(2R,3R,4R)-3,4-Isopropylidenedioxy-5-methyl-1,2,5-hexane triol
II-6

To a solution of methylmagnesium iodide prepared from magnesium (4.85 g, 202 mg.atoms) and methyl iodide (28.68 g, 202 mmol) in ether (200 mL), 2,3-O-isopropylidene-D-ribonolactone II-5 (9.4 g, 50 mmol) in dry THF (100 mL) was added dropwise at room temperature with stirring under argon atmosphere over a period of 0.5 h. The reaction mixture was stirred a further 0.5 h and then refluxed for 5 h. The cooled reaction mixture was treated with saturated ammonium chloride solution (100 mL) and the aqueous layer separated and evaporated to dryness under

reduced pressure. The solid was extracted with boiling ethyl acetate (4 × 100 mL) and the combined washings were dried over anhydrous sodium sulphate and evaporated to yield a yellow syrup which was chromatographed with ethyl acetate-ether (1:1) (Rf 0.51) to yield (8.2 g, 75%) of II-6; $[\alpha]_D^{24} +2.72^\circ$ (c 3.5, MeOH); IR (film) 3320, 2990, 2940, 1375, 1240, 1165, 875 cm^{-1} ; ^1H NMR (CDCl_3) δ 4.82 (1H, OH, bs), 4.01 (1H, H₃, dd, J = 5, J = 10), 3.94 (1H, H₄, d, J = 5), 3.91 (2H, H₂, H₁, m), 3.65 (1H, H₁, dd, J = 6, 10), 3.59 (1H, OH, bs), 2.88 (1H, OH, bs), 1.44 (3H, CH₃-, S), 1.39 (6H, 2CH₃-, S), 1.31 (3H, CH₃-, S).

Anal. Calcd for C₁₀H₂₀O₅: C, 54.53; H, 9.15. Found: C, 54.53; H, 9.27.

(2R&S, 3S, 4R)-5,5-Dimethyl-2-hydroxy-3,4-isopropylidenedioxy-tetrahydrofuran II-7

To a stirred solution of the triol II-6 (380 mg, 1.72 mmol) in water (2.5 mL) at 5°C, sodium metaperiodate (410 mg, 1.87 mmol) in water (2.5 mL) was added and the solution was stirred for 2 h. The reaction mixture was extracted with dichloromethane (50 mL), washed with brine (50 mL) and dried over anhydrous sodium sulphate. The solvent was evaporated and the residue was chromatographed with ether-petroleum ether (1:1) to give II-7 (290 mg, 90%); $[\alpha]_D^{24} +45.8^\circ$ (c 5.33, CHCl_3); IR (film) 3310, 2990, 2945, 1465, 1385, 1375, 1255, 1215, 1165, 1015, 880 cm^{-1} ; ^1H NMR (CDCl_3) δ 5.18 (1H, H₂, dd, J = 4, J = 12),

4.63 (1H, H₃, dd, J = 4, J = 6), 4.36 (1H, H₄, d, J = 6), 3.82 (1H, OH, d, J = 12), 1.38 (6H, (CH₃)₂, s), 1.34 (6H, (CH₃)₂, s).

Anal. Calcd for C₉H₁₆O₄: C, 57.43; H, 8.57. Found: C, 57.70; H, 8.69.

Diethyl-(3-cyano-1,1-dimethoxypropyl)phosphonate II-8

To a solution of lithium diisopropylamide (834 mmol from equimolar amounts of n-butyllithium and diisopropylamine at 0°C) in anhydrous THF (800 mL), cooled to -78°C under argon, β-cyanopropionaldehydedimethyl acetal (53.8 g, 417 mmol) in anhydrous THF was added dropwise over a period of 1 h. The mixture was stirred for 1.5 h and a solution of diethyl chlorophosphate (71.96 g, 417 mmol) in THF (100 mL) was added dropwise over a period of 0.5 h and stirring was continued for an additional 3 h. The solution was warmed to -40°C and stirred for an additional 2 h. The reaction mixture was poured into water (600 mL) and the aqueous layer was extracted with dichloromethane (3 × 200 mL). The combined organic layers were washed with brine (2 × 200 mL), dried over anhydrous sodium sulphate and concentrated to give a pale orange oil. This product was subjected to column chromatography using ether to afford II-8 (98.2 g, 89.0%) of a pale orange oil; IR (film) 2978, 2830, 2238, 1440, 1385, 1365, 1255, 1030, 960, 830, 790, 745 cm⁻¹; ¹H NMR (CDCl₃) δ 4.57 (1H, -OCHO-, dd, J = 4, J = 7), 4.22 (4H, 2(-OCH₂CH₃), m), 3.38

(6H, (CH₃O)₂-, S), 3.08 (1H, CHCN, ddd, J = 4, J = 11, J = 23), 2.01 (2H, -CH₂-CH-, m), 1.38 (6H, (CH₃)₂-, t, J = 7).

Anal. Calcd for C₁₀H₂₀NO₅P: C, 45.28; H, 7.54; N, 5.28.

Found: C, 44.90; H, 7.90; N, 5.18.

Condensation of II-7 and II-8

Diethyl-(3-cyano-1,1-dimethoxypropyl)phosphonate II-8 (3.08 g, 1.16 mmol) and sodium hydride (0.50 g of 50% dispersion in mineral oil) were stirred together in anhydrous THF (20 mL) under argon at room temperature until hydrogen gas evolution had subsided (10 min). A solution of aldehyde II-7 (1 g, 5.3 mmol) in THF (10 mL) was added and stirring continued for 3 h. Water (30 mL) was added to the reaction mixture. The aqueous suspension was extracted with dichloromethane (3 × 20 mL) and the extract was dried over anhydrous sodium sulphate. Evaporation of the solvent afforded an oil (3.82 g) which was subjected to column chromatography with ether-petroleum ether (1:1) to give an unseparable mixture of (1 g) of unreacted aldehyde II-7 and a Michael-type product in a ratio of ≈ 10:1.7 judged from capillary GC.

(2R,3R,4R)-1,2-Diacetoxy-3,4-isopropylidenedioxy-5-methylhexane-5-ol II-10

Triol II-6 (10.0 g, 45.3 mmol) was acetylated with acetic anhydride (50 mL) in pyridine (50 mL) at room temperature for 12

h. The solution was poured into ice-cold water (100 mL), extracted with dichloromethane (2 × 100 mL), washed with ice-cold 1M hydrochloric acid (2 × 25 mL), water (2 × 50 mL), and dried over anhydrous sodium sulphate. Evaporation of the solvent afforded solid II-10 (10.2 g, 75%). Recrystallization from petroleum ether (60-80°C) and dichloromethane (5:2) gave II-10 as colourless crystals: m.p. 125-6°C; $[\alpha]_D^{24} +51.3^\circ$ (c 7.33, MeOH); IR (KBr) 3472, 2970, 2940, 2865, 1735, 1380, 1238 cm^{-1} ; ^1H NMR (CDCl_3) δ 5.29 (1H, H_2 , m); 4.59 (1H, H_1 , dd, $J = 3$ Hz, $J = 11$), 4.29 (1H, H_3 , dd, $J = 5$, $J = 6$), 4.15 (1H, H_1 , dd, $J = 5$, $J = 11$), 3.92 (1H, H_4 , d, $J = 5$), 2.05 (6H, $2\text{CH}_3\text{CO}-$, s), 1.86 (1H, OH, bs), 1.50 (3H, CH_3- , s), 1.35 (9H, 3CH_3- , s).

Anal. Calcd for $\text{C}_{14}\text{H}_{24}\text{O}_7$: C, 55.25; H, 7.95. Found: C, 55.35; H, 8.15.

(2R,3R,4R)-1,2-Diacetoxy-3,4-isopropylidenedioxy-5-methyl-5-[(2-trimethylsilylethoxy)methoxy]hexane II-11

The diacetate II-10 (12.16 g, 40 mmol) was refluxed with diisopropyl ethylamine (25.8 g, 200 mmol) and β -(trimethylsilylethoxy)methyl chloride (19.9 g, 120 mmol) in THF (40 mL) under argon atmosphere for 3 h. The mixture was poured into ice-water (200 mL), extracted with dichloromethane (2 × 100 mL),

washed with brine (100 mL), and dried over anhydrous sodium sulphate. Evaporation of the solvent under reduced pressure gave a yellow syrup, which was chromatographed with ether-petroleum ether (1:1) (Rf 0.75) to give the silyl ether II-11 (15.20 g, 88%); $[\alpha]_D^{24} +9.9^\circ$ (c 18.4, CHCl_3); IR (film) 3120, 3120, 2980, 2920, 1755, 1385, 1255, 1235, 870, 850 cm^{-1} ; ^1H NMR (CDCl_3) δ 5.35 (1H, H_2 , m), 4.87 (1H, $-\text{OCH}_2\text{O}-$, d, $J = 6$), 4.67 (1H, $-\text{OCH}_2\text{O}-$, d, $J = 6$), 4.55 (1H, H_1' , dd, $J = 2$, $J = 11$), 4.28 (1H, H_3 , t, $J = 5$), 4.21 (1H, H_1 , dd, $J = 5$, $J = 11$), 3.90 (1H, H_4 , d, $J = 5$), 3.58 (2H, $-\text{OCH}_2\text{CH}_2-$, m), 2.05 (6H, $2\text{CH}_3\text{CO}-$, s), 1.48 (3H, CH_3- , s), 1.42 (3H, CH_3- , s), 1.36 (3H, CH_3 , s), 1.33 (3H, CH_3 , s), 0.91 (2H, $-\text{CH}_2-\text{Si}-$, t, $J = 8.4$), 0.00 (9H, $-\text{Si}(\text{CH}_3)_3$, s).

Anal. Calcd for $\text{C}_{20}\text{H}_{38}\text{O}_8\text{Si}$: C, 55.29; H, 8.75. Found: C, 55.50; H, 9.01.

(2R,3R,4R)-3,4-Isopropylidenedioxy-5-methyl-5-[(2-trimethylsilylethoxy)methoxy]-1,2-hexanediol II-12.

The diacetate silylether II-11 (15.21 g, 35.1 mmol) was stirred with 10% sodium hydroxide in methanol-water (1:1; 150 mL) at room temperature for 12 h. The resulting solution was evaporated, dissolved in water (100 mL) and extracted with dichloromethane (3 \times 75 mL). The combined extract was washed with brine (100 mL), dried over sodium sulphate and evaporated

under reduced pressure to give a syrup. Chromatography with ether yielded II-12 (12.3 g; 100%); $[\alpha]_D^{24} -2.1^\circ$ (c 4.02, CHCl_3); IR (film) 3450, 2992, 2960, 1385, 1372, 1252, 1218, 1160, 1102, 925, 868, 842 cm^{-1} ; ^1H NMR (CDCl_3) δ 4.96 (1H, $-\text{OCH}_2\text{O}-$, d, $J = 7$), 4.82 (1H, $-\text{OCH}_2\text{O}-$, d, $J = 7$), 4.68 (1H, OH, d, $J = 2.5$), 4.08 (1H, H_3 , dd, $J = 5.5$, $J = 9.8$), 4.02 (1H, H_2 , ddd, $J = 2.5$, $J = 5$, $J = 9.8$), 3.95 (1H, H_4 , d, $J = 5.5$), 3.85 (1H, H_1' , m), 3.56-3.69 (3H, H_1 , $-\text{OCH}_2-\text{CH}_2-$, m), 2.27 (1H, OH, t, $J = 6$), 1.48 (3H, CH_3- , s), 1.45 (3H, CH_3- , s), 1.41 (3H, CH_3- , s), 1.34 (3H, CH_3- , s), 0.94 (2H, $-\text{CH}_2\text{Si}-$, t, $J = 8.4$), 0.00 (9H, $(\text{CH}_3)_3\text{Si}$, s).

Anal. Calcd for $\text{C}_{16}\text{H}_{34}\text{O}_6\text{Si}$: C, 54.71; H, 9.71. Found: C, 54.29; H, 10.05.

(2S,3R)-2,3-Isopropylidenedioxy-4-methyl-4-[(2-trimethylsilylethoxy)methoxy]pentanal II-13

A solution of the diol II-12 (11.8 g, 33.7 mmol) in water (80 mL) was stirred at 0°C , and a solution of sodium metaperiodate (7.21 g, 33.7 mmol) in water (80 mL) was added over a period of 15 min. and stirring was continued for a further 3 h. The reaction mixture was extracted with dichloromethane (2×100 mL), washed with brine (100 mL) and dried over anhydrous sodium sulphate. Evaporation of the dichloromethane and chromatography with ether-petroleum ether (1:2) gave the aldehyde II-13 (10.0 g, 95%) (R_f 0.85); $[\alpha]_D^{24} +9.4^\circ$ (c 16.4, CHCl_3); IR (film)

2975, 2870, 2695, 1728, 1462, 1395, 1385, 1250, 1218, 1065, 915, 862, 840 cm^{-1} ; ^1H NMR (CDCl_3) δ 9.54 (1H-CHO, d, $J = 2$), 4.83 (1H, -OCH₂O-, d, $J = 6$), 4.67 (1H, -OCH₂O-, d, $J = 6$), 4.39 (1H, H₂, dd, $J = 2$, $J = 6$), 4.23 (1H, H₃, d, $J = 6$), 3.58 (2H, -CH₂-CH₂-Si, m), 1.59 (3H, CH₃, s), 1.41 (3H, CH₃-, s), 1.37 (3H, CH₃-, s), 1.30 (3H, CH₃-, s), 0.91 (2H, -CH₂Si-, t, $J = 8$), 0.00 (9H, (CH₃)₃Si-, s).

Anal. Calcd for C₁₅H₃₀O₅Si: C, 56.60; H, 9.43. Found: C, 56.78; H, 9.77.

(E,Z)-(5R,6R)-3-Cyano-5,6-isopropylidenedioxy-7-methyl-7-[(2-trimethylsilylethoxy)methoxy]-1,1-dimethoxy-octa-3-ene II-14

A suspension of 50% sodium hydride (7.0 g, 146 mmol) was washed with anhydrous hexane (2 × 10 mL) and suspended in anhydrous THF (500 mL) and cooled to 0°C under argon atmosphere. The phosphonate II-8 (38.75 g, 146 mmol) in THF (200 mL) was added over a period of 1 h. After the evolution of hydrogen gas had subsided, the mixture was stirred for an additional 0.5 h. To this cold mixture ($\approx 5^\circ\text{C}$) was added solution of aldehyde II-13 (42.6 g, 133 mmol) in THF (200 mL) over a period of 1 h and the mixture was stirred for an additional 4 h. The reaction was poured into ice-water (200 mL), extracted with dichloromethane (4 × 100 mL), the combined dichloromethane extractions were washed with brine (2 × 100 mL) and dried over anhydrous

sodium sulphate. Evaporation of the solvent gave an oil which was chromatographed with ether-petroleum ether (1:2) to afford a mixture of E/Z isomers II-14 (51.7 g, 90%):

$[\alpha]_D^{24} -8.0^\circ$ (C 7.85, $CHCl_3$); IR (film) 3020, 2900, 2220, 1645, 1455, 1380, 1250, 1125, 1065, 1035, 862, 870 cm^{-1} ;
 1H NMR ($CDCl_3$) δ 6.45 (1H, H_4 , td, $J = 1$, $J = 10$), 5.00 (1H, H_5 , dd, $J = 6$, $J = 10$), 4.85 (1H, $-OCH_2O-$, d, $J = 7$), 4.77 (1H, $-OCH_2O-$, d, $J = 7$), 4.58 (1H, $-OCHO-$, t, $J = 5$), 4.15 (1H, H_6 , d, $J = 6$), 3.61 (2H, $-OCH_2-CH_2-$, m), 3.36 (6H, $2CH_3O-$, s), 2.55 (2H, $CH_2-C=C-$, dd, $J = 1$, $J = 5$), 1.40 (3H, CH_3- , s), 1.39 (3H, CH_3- , s), 1.35 (3H, CH_3 , s), 1.28 (3H, CH_3- , s), 0.91 (2H, $-CH_2-Si-$, t, $J = 8$), 0.00 (9H, $-Si(CH_3)_3$, s).

Anal. Calcd for $C_{21}H_{39}NO_6Si$: C, 58.74; H, 9.09; N, 3.26.

Found: C, 58.53; H, 9.44; N, 3.44.

(3R&S, 6R)-6-Acetoxy-3-cyano-7-methyl-7-[(2-

trimethylsilylethoxy)methoxy]-1,1-dimethoxyoctane II-17

To the α, β -unsaturated nitrile II-14 (6.52 g, 15.15 mmol) in methanol (151.5 mL) was added magnesium turnings (14.68 g, 0.6 mol, 40 equiv). The exothermic reaction which ensued after 10 min. was moderated with an ice bath. The reaction was stir-

red for 1 h at 0°C and 5 h at 25°C. To the reaction at 0°C was added saturated aqueous ammonium chloride solution (300 mL) to afford a clear solution which was extracted with dichloromethane (3 × 150 mL). The dichloromethane solutions were combined, washed with brine (200 mL), dried over anhydrous sodium sulphate and evaporated to yield an oil. The oil was column chromatographed with ether-petroleum ether (1:1) to furnish II-16 (4.2 g, 74.0%) which showed IR absorption bands at 3400 cm⁻¹ (OH) and 2235 cm⁻¹ (CN). The oil II-16 (500 mg, 1.3 mmol) was acetylated in pyridine (5 mL) using acetic anhydride (5 mL) at room temperature for 12 h, to afford the cyano acetate II-17 (420 mg, 75%) after column chromatography with ether-petroleum ether (1:1); $[\alpha]_D^{22} -4.0^\circ$ (c 7.9, CHCl₃); IR (film) 2950, 2900, 2838, 2250, 1740, 1375, 1248, 1060, 1030, 865, 840 cm⁻¹; ¹H NMR (CDCl₃) δ 4.85 (1H, H₆, dd, J = 2.6, J = 10.1), 4.79 (1H, -OCH₂O-, d, J = 7.6), 4.72 (1H, -OCH₂O-, d, J = 7.6), 4.54 (1H, -OCHO-, dd, J=4.3, J=7.3), 3.54-3.65 (2H, -OCH₂-CH₂, m), 3.38 (3H, CH₃O-, s), 3.50 (3H, CH₃O-, s), 2.82-2.65 (1H, CHCN, m), 2.14 (3H, CH₃CO-, s), 1.98-1.55 (6H, -(CH₂)₃-, m), 1.22 (6H, (CH₃)₂-, s), 0.91 (2H, -CH₂-Si(CH₃)₃, t, J = 8.2), 0.07 (9H, (CH₃)₃Si-, s).

Anal. Calcd for C₂₀H₃₉NO₆Si: C, 57.52; H, 9.41, N, 3.35.

Found: C, 57.41; H, 9.64; N, 3.55.

Attempted Reduction of II-14

(a) A mixture of unsaturated nitrile II-14 (0.90 g, 2.1 mmol) and sodium borohydride (0.30 g, 7.9 mmol) in anhydrous isopropyl alcohol (20 mL) was refluxed for 24 h. The reaction mixture was hydrolyzed with water (10 mL), extracted with ether (3 × 20 mL), the organic extract was dried with anhydrous sodium sulphate, filtered and evaporated. The ¹H NMR of the residue (0.8 g) revealed the presence of an olefinic proton at 6.45 ppm and IR absorption bands at 3020 and 1645 cm⁻¹ corresponding to starting ene-nitrile II-14.

(b) To cuprous bromide (1.86 g, 13.0 mmol) in anhydrous THF (10 mL) cooled to 0°C under nitrogen atmosphere was added Vitride (7.4 mL, 26.0 mmol of 3.5 M solution of sodium bis(2-methoxyethoxy) aluminum hydride in benzene). The resulting dark solution was stirred at 0°C for 0.5 h and then brought to -78°C. 2-Butanol (2.3 mL, 26.0 mmol) was cautiously introduced via syringe, followed by a solution of ene-nitrile II-14 (0.56 g, 1.3 mmol) in dry THF (5 mL). After 3 h at this temperature, the reaction mixture was stirred at room temperature for 24 h, after which the mixture was treated with saturated ammonium chloride solution (10 mL). The product was extracted into dichloromethane (3 × 20 mL) and dried with anhydrous sodium sulphate. Column chromatography of the residue resulted in recovery of ene-nitrile II-14 in almost quantitative yield (0.55 g).

(c) Sodium metaperiodate (0.53 g, 2.5 mmol) in water (5 mL) was added dropwise (1 h) to a mixture of II-14 (0.21 g, 0.5 mmol), hydrazine hydrate (100%, 20 mmol), two drops of saturated aqueous copper sulphate solution and two drops of glacial acetic acid dissolved in THF (4 mL). After stirring for 48 h at room temperature the mixture was extracted with dichloromethane (2 x 10 mL), dried over anhydrous sodium sulphate and evaporated. ¹H NMR of the resulting residue (0.19 g) revealed no saturated nitrile in the mixture.

(3R&S,5R,6R)-3-Cyano-5,6-isopropylidenedioxy-7-methyl-7-[(2-trimethylsilylethoxy)methoxy]-1,1-dimethoxyoctane II-15

A solution of the unsaturated nitrile II-14 (40.0 g, 72.2 mmol) in 100% ethanol (400 mL) containing 5% palladium on charcoal (4.0 g) was stirred under hydrogen at one atmosphere and room temperature for 12 h. The mixture was filtered, evaporated and chromatographed using ether-petroleum ether (1:1) as eluent to give an oil (39.2 g, 97%). The saturated nitrile II-15 exhibited a double spot on TLC with Rf's 0.78 and 0.80 corresponding to the two diastereoisomers; $[\alpha]_D^{24} +14.0^\circ$ (C 11.4, CHCl₃); IR (film) 2992, 2960, 2907, 2840, 2242, 1462, 1439, 1382, 1375, 1255, 1220, 1168, 1061, 940, 925 cm⁻¹; ¹H NMR

(CDCl₃) δ 4.84 (1H, -OCH₂O-, d, J = 7.4), 4.73 (1H, -OCH₂O-, d, J = 7.4), 4.60 (1H, -OCHO-, dd, J = 4.5, J = 7.3), 4.23 (1H, H₅, ddd, J = 5, J = 6, J = 9), 3.88 (1H, H₆, d, J = 6), 3.58-3.69 (2H, -OCH₂-, m), 3.37 (3H, CH₃O-, s), 3.36 (3H, CH₃O-, s), 2.92-2.15 (1H, CHCN, m), 1.85-2.15 (4H, 2H₂, 2H₄, m), 1.33 (9H, 3 CH₃-, s), 1.28 (3H, CH₃-, s), 0.91 (2H, -CH₂Si-, t, J = 8.5), 0.00 (9H, (CH₃)₃Si-, s).

Anal. Calcd for C₂₁H₄₁NO₆Si: C, 58.46; H, 9.51; N, 3.24.

Found: C, 58.11; H, 9.80; N, 3.38.

(1'R, 2S, 4S, 6R)-4-Cyano-2-hydroxy-6-(1', 2'-dihydroxy-2'-methylpropyl)tetrahydropyran II-18a

A solution of the nitrile II-15 (21.0 g, 48.7 mmol) in methanol (210 mL) and 1% aqueous sulphuric acid (210 mL) was stirred at room temperature. The hydrolysis was monitored by TLC (ethyl acetate) which indicated after 36-48 h, the appearance of two slow running components (R_f 0.33, R_f 0.25) and disappearance of II-15. After hydrolysis, the solution was cooled to 0°C, and neutralized with 6 M ammonium hydroxide (13 mL). The solution was evaporated to yield a syrup which was subjected to column chromatography using ethyl acetate to furnish 9.3 g (90%) of a colourless syrup. The syrup was diluted with dichloromethane whereupon a solid II-18a was crystallized out (3.8 g) (R_f 0.25); m.p. 144 - 7° C from ethyl acetate; $[\alpha]_D^{24}$ -0.5° (c 1.99, MeOH). The remaining solution failed to

crystallize further and was used for next reaction as a mixture of diastereoisomers. The slower eluting nitrile (major) II-18a exhibited the following spectral characteristics: IR (Nujol) 3400, 2950, 2910, 2845, 2230, 1450, 1201, 1190, 1170, 1038, 1005, 955, 907, 885, 855 cm^{-1} ; ^1H NMR (CDCl_3) δ 5.15 (1H, H_2 , ddd, $J = 2, J = 6, J = 10$), 3.99 (1H, H_6 , ddd, $J = 2, J = 11, J = 6$), 3.55 (1H, H_1' , dd, $J = 5_{\text{eq},6}, J = 6$), 3.23 (1H, CHCN , septet, $J = 2.5, J = 5$), 3.19 (1H, OH, d, $J = 6$), 2.81 (1H, OH, bs), 1.61-2.5 (5H, $\text{H}_{3\text{eq}}, \text{H}_{3\text{ax}}, \text{H}_{5\text{ax}}, \text{H}_{5\text{eq}}, \text{OH}$, m), 1.33 (3H, CH_3 -, s), 1.25 (3H, CH_3 -, s).

Anal. Calcd for $\text{C}_{10}\text{H}_{17}\text{NO}_4$: C, 55.80; H, 7.96; N, 6.51.

Found: C, 55.45; H, 8.19; N, 6.70.

(1R,3S,5R,7R)-3-Cyano-7-(dimethylcarbinol)-6,8-dioxabicyclo
[3.2.1]octane II-20a

A suspension of II-18a (200 mg, 0.92 mmol) in dichloromethane (10 mL) containing p-toluenesulphonic acid (1 mg) was stirred at room temperature for 4 h. The solution was diluted with dichloromethane (20 mL), washed with cold 5% sodium bicarbonate (5 mL), brine (20 mL) and dried over anhydrous sodium sulphate. Column chromatography using ether-petroleum ether (2:1) afforded the bicyclic alcohol II-20a (120 mg, 65%) (R_f 0.40); $[\alpha]_D^{24} +78.4^\circ$ (c 12.42, CHCl_3); IR (film) 3490, 2980, 2948, 2890, 2252, 1472, 1447, 1385, 1362, 1300, 1268, 1248, 1230, 1183, 1168, 1125, 1075, 1038, 1015, 996, 980, 960, 917,

895, 882, 835, 805 cm^{-1} ; ^1H NMR (CDCl_3) δ 5.58 (1H, H_5 , bs), 4.27 (1H, H_1 , t, $J_{1,7} = 3.5$), 3.95 (1H, CHCN, tt, $J = 6.5$, $J = 12$), 3.68 (1H, H_7 , d, $J_{1,7} = 3.5$), 2.32 (1H, $\text{H}_{2\text{eq}}$, dd, $J_{2\text{eq},3} = 6.5$, $J_{2\text{eq},2\text{ax}} = 13$) 2.13 (2H, $\text{H}_{4\text{eq}}$, $\text{H}_{2\text{ax}}$, m), 1.98 (1H, $\text{H}_{4\text{ax}}$, dt, $J_{4\text{ax},5} = 1$, $J_{4\text{ax},4\text{eq}} = 12$) 1.79 (1H, OH, bs), 1.42 (3H, CH_3 -, s), 1.23 (3H, CH_3 -, s).

Anal. Calcd for $\text{C}_{10}\text{H}_{15}\text{NO}_3$: C, 60.90; H, 7.67; N, 7.10.

Found: C, 60.71; H, 7.98; N, 7.18

(1R,3S,5R,7R)-3-Cyano-7-isopropenyl-6,8-dioxabicyclo[3.2.1]octane II-22

To a solution of the hydroxynitrile II-20a (120 mg, 0.61 mmol) and triethylamine (250 mg, 2.52 mmol) in dichloromethane (3 mL) at 0°C under argon, methansulfonyl chloride (140 mg, 1.23 mmol) was added dropwise. After 15 min the ice bath was removed, and the reaction stirred for 2 h at room temperature. The reaction mixture was transferred to a separatory funnel with the aid of more dichloromethane (50 mL), and was extracted first with ice-water (50 mL), followed by cold 10% aqueous hydrochloric acid (20 mL), saturated aqueous sodium bicarbonate solution (20 mL) and brine (2 \times 30 mL). Column chromatography of the crude product using ether-petroleum ether (1:1) yielded the olefin II-22 (35 mg, 32%, R_f 0.63) and unreacted alcohol II-20a (50 mg); $[\alpha]_D^{24} +78.2^\circ$ (c 2.08, CHCl_3); IR (film) 3090, 2970, 2938, 2860, 2245, 1658, 1445, 1355, 1335, 1158, 1125,

1108, 975 cm^{-1} ; ^1H NMR (CDCl_3) δ 5.64 (1H, H_5 , bs), 5.33 (1H, H_7 , dt, $J = 1$, $J = 3$), 5.16 (1H, H_{10a} , dd, $J = 1.5$, $J = 5$), 4.42 (2H, H_{10b} , H_1 , m), 3.44 (1H, CHCN, tt, $J = 6$, $J = 12$), 2.13 (1H, H_{4eq} , ddd, $J = 1$, $J = 6$, $J = 13$), 2.07 (1H, H_{2ax} , m), 1.98 (1H, H_{4ax} , ddd, $J = 1.5$, $J = 12$, $J = 13$), 1.92 (1H, H_{2eq} , ddd, $J = 1.0$, $J = 2.5$, $J = 6$, $J = 14$), 1.75 (3H, CH_3 -, dt, $J = 1$, $J = 2.5$).

Anal. Calcd for $\text{C}_{10}\text{H}_{13}\text{NO}_2$: C, 67.02; H, 7.31; Found: C, 67.49; H, 7.62.

(1'R, 2R, 4R, 6R)-4-Cyano-2-(tert-butyldimethylsilyloxy)-6-(1', 2'-dihydroxy-2'-methylpropyl)tetrahydropyran II-23a and (1'R, 2R, 4S, 6R)-4-cyano-2-(tert-butyldimethylsilyloxy)-6-(1', 2'-dihydroxy-2'-methylpropyl)tetrahydropyran II-23b

A mixture of the two diastereoisomers II-18 (4.0 g, 18.6 mmol) was stirred with imidazole (3.16 g, 46.4 mmol) and tert-butyldimethylsilyl chloride (3.37 g, 22.3 mmol) in DMF (10 mL) at 25°C for 24 h. The major components appeared on TLC with ether-petroleum ether (1:1) as two spots with R_f values of (0.48) and (0.38), as well as several minor fast running products. The mixture was poured into ice-water (50 mL), extracted with dichloromethane (3 x 50 mL), washed with brine (100 mL) and dried over anhydrous sodium sulphate. The two major components were separated by column chromatography using

ether-petroleum ether (1:1). The faster eluting nitrile yielded II-23a (2.0 g; R_f 0.48) and the slower eluting nitrile yielded II-23b (3.1 g; R_f 0.38) on solvent exaporation to give a total of 5.1 g (84%).

Nitrile II-23a exhibited the following characteristics:

$[\alpha]_D^{22} +12.7^\circ$ (c 4.7, $CHCl_3$); IR (film) 3460, 2960, 2935, 2860, 2245, 1465, 1390, 1255, 1165, 1060 cm^{-1} ; 1H NMR ($CDCl_3$) δ 4.72 (1H, H_2 , dd, $J = 2.1, J = 9.4$), 3.52 (1H, H_6 , ddd, $J = 1.9, J = 6, J = 11$), 3.47 (1H, H_1' , dd, $J = 4, J = 6$), 2.75 (1H, CHCN, dt, $J = 4, J = 12$), 2.60 (1H, OH, bs), 2.42 (1H, OH, d, $J = 4, J = 12$), 2.07-2.35 (2H, H_5 , H_3 , m), 1.78-1.62 (2H, H_5 , H_3 , m), 1.29 (3H, CH_3 -, S), 1.22 (3H, CH_3 -, S), 0.88 (9H, $(CH_3)_3C$ -, S), 0.11 (6H, $(CH_3)_2Si$ -, S).

Anal. Calcd for $C_{16}H_{31}NO_4Si$: C, 58.36; H, 9.42; N, 4.25.

Found: C, 58.61; H, 9.42; N, 4.25.

Nitrile II-23b exhibited the following characteristics:

$[\alpha]_D^{24} +30.8^\circ$ (c 2.25, $CHCl_3$); IR (film) 3420, 2950, 2840, 2230, 1455, 1435, 1378, 1362, 1305, 1245, 1160, 1035 cm^{-1} ; 1H NMR ($CDCl_3$) δ 5.11 (1H, H_2 , dd, $J = 2.1, J = 9.4$), 3.94 (1H, H_6 , ddd, $J = 1.9, J = 5.4, J = 11.4$), 3.48 (1H, H_1' , bd, $J = 5.4$), 3.18 (1H, CHCN, tt, $J = 2.4, J = 5$), 2.55 (1H, OH, bs), 2.35 (1H, OH, bs), 2.18 (1H, H_5 , ddd, $J = 1.9, J = 5, J = 14$), 2.01 (1H, H_3 , ddd, $J = 2.1, J = 5$), 1.61-1.73 (2H, H_3 , H_5 , m), 1.31 (3H, CH_3 -, S), 1.23 (3H, CH_3 -, S).

(3H,CH₃-,S), 0.89 (9H,(CH₃)₃C-,S), 0.13 (6H,(CH₃)₂Si-,S).

Anal. Calcd for C₁₆H₃₁NO₄Si: C, 58.36; H, 9.42; N, 4.25.

Found: C, 58.21; H, 9.80; N, 4.39.

(1'R,2R,4R&S,6R)-4-Cyano-2-(tert-butyltrimethylsilyloxy)-6-(1'-methylsulfonyloxy-2'-hydroxy-2'-methylpropyl)tetrahydropyran

II-24

To a solution of the silylether II-23a&b (1.0 g, 3.03 mmol) in anhydrous pyridine (5 mL) at 0°C under argon was added distilled methanesulfonyl chloride (0.52 g, 4.55 mmol) over a period of 10 min and the reaction mixture was stirred at 0°C for 4 h followed by further stirring at room temperature for 24 h. Ice (10 g) was added and the mixture was stirred for 10 min after which the mixture was diluted with dichloromethane (50 mL), washed successively with saturated aqueous copper sulphate solution (3 × 25 mL) water (2 × 10 mL), brine (2 × 25 mL) and dried with anhydrous sodium sulphate. The solvent was evaporated to give an oil which was chromatographed with ether. A fraction was collected (R_f 0.47 - 0.49) to yield a mixture of silyl monomesylates II-24 (0.95 g, 75%): [α]_D²⁴ +39.5° (c 2.29, CHCl₃); IR (film) 3520, 2960, 2958, 2860, 2240, 1475, 1465, 1448, 1360, 1350, 1258, 1175, 1048 cm⁻¹; ¹H NMR (CDCl₃) δ 3.21 (3H,CH₃SO₂-,S), 1.39 (3H,CH₃-,S), 1.33 (3H,CH₃-,S), 0.89 (9H,(CH₃)₃C-,S).

(1'R,2R&S,4R&S,6R)-4-Cyano-2-hydroxy-6-(1'-methylsulfonyloxy-2'-hydroxy-2'-methylpropyl)tetrahydropyran II-25

A solution of silylmesylate II-24 (10 g, 24.6 mmol) in acetonitrile (120 mL) and 49% hydrofluoric acid (12 mL) was stirred at room temperature for 24 h. The mixture was extracted with dichloromethane (3 × 100 mL) washed with water (2 × 50 mL), brine (2 × 100 mL) and dried over anhydrous sodium sulphate and evaporated. Column chromatography using ethyl acetate afforded a mixture of isomers II-25 (6.4 g, 89%) (R_f 0.23, R_f 0.18; ether); $[\alpha]_D^{24}$ -24.7° (c 5.69, $CHCl_3$); IR (film) 3480, 2990, 2948, 2252, 1450, 1418, 1355, 1338, 1178, 965, 915 cm^{-1} ; 1H NMR ($CDCl_3$) δ 5.42 (1H, H₂, bt), 3.16 (3H, CH₃SO₂-, S).

(1R,4R,5R,7S)-7-Cyano-3,3-dimethyl-4-methylsulfonyloxy-2,9-dioxabicyclo[3.3.1]nonane II-21

The mixture II-25 (9.5 g, 32.4 mmol) was dissolved in dichloromethane (95 mL), dry benzene (90 mL) and *p*-toluenesulphonic acid (0.95 g) were added. The solution was refluxed for 3 h using a Dean-Stark trap. The product was diluted with dichloromethane (50 mL), washed with ice-cold 5% aqueous sodium bicarbonate solution (2 × 10 mL), water (2 × 50 mL), brine (2 × 25 mL) and then dried over anhydrous sodium sulphate. Chromatography of the crude material allowed isolation of the major component II-21 (R_f 0.66) which was crystallized by dissolving

in dichloromethane (1 mL) and diluting with petroleum ether (60-80°C) (20 mL) to give colourless crystals, (2.91 g, 33%), m.p. 95-6°C; $[\alpha]_D^{24} +31.1^\circ$ (c 3.09, CHCl_3); IR (film) 3000, 2968, 2928, 2228, 1442, 1353, 1328, 1219, 1190, 1170, 1117, 1021 cm^{-1} ; ^1H NMR (CDCl_3) δ 5.32 (1H, H_1 , t, $J = 2$), 4.38 (1H, H_4 , d, $J = 2$), 4.32 (1H, H_5 , dd, $J = 2$, $J = 5$), 3.30 (1H, H_7 , tt, $J = 5$, $J = 12$), 3.09 (3H, CH_3SO_2 -, S), 2.21 (1H, H_6 , ddd, $J = 2$, $J = 5$, $J = 13$), 2.01-2.13 (2H, H_8 , m), 1.84 (1H, H_8 , ddd, $J = 2$, $J = 12$, $J = 13$), 1.49 (3H, CH_3 -, S), 1.35 (3H, CH_3 -, S).

Anal. Calcd for $\text{C}_{11}\text{H}_{17}\text{NO}_5\text{S}$: C, 48.00; H, 6.18; N, 5.09.

Found: C, 47.96; H, 6.13; N, 5.13.

(1R,4S,5R,7S)-7-Cyano-3,3-dimethyl-2,9-dioxatricyclo

[3.3.1.0^{4,4}]nonane II-26

Dry ammonia (20 mL) was condensed in a 100 mL 3-necked flask equipped with a gas inlet tube and a cold-finger condenser charged with dry ice-acetone. Potassium metal (50 mg, 1.2 mg-atoms) in small pieces and a crystal of ferric nitrate were added and the mixture was stirred until the blue colour had disappeared. Anhydrous THF (20 mL) was added to the mixture and excess ammonia was allowed to evaporate at room temperature. The bicyclic nitrile II-21 (100 mg, 0.36 mmol) in THF (5 mL) was

added over a period of 5 min under argon, and the mixture was refluxed for 3 h. The mixture was cooled and quenched by addition of ice-water (10 mL). The aqueous layer was extracted several times with dichloromethane (3 × 20 mL) and dried over anhydrous sodium sulphate. The crude product was chromatographed with ether (R_f 0.76) to afford II-26 (45 mg, 69%).

Capillary GC indicated no other volatile compound was present.

The tricyclic nitrile exhibited the following characteristics:

$[\alpha]_D^{24} +69.1^\circ$ (c 0.74, pentane); IR (film) 2972, 2940, 2865, 2232, 1465, 1452, 1385, 1365, 1345, 1315, 1228, 1180, 1155, 1082, 1045, 968 cm^{-1} ; ^1H NMR (CDCl_3) δ 5.14 (1H, H, bd, $J = 2.5$), 4.53 (1H, H₅, t, $J = 4.$), 2.72 (1H, H₄, dd, $J = 1$, $J = 4$), 2.48 (1H, H₈_{eq}, ddd, $J = 1.3$, $J = 2.5$, $J = 13$), 2.47 (1H, H₆_{eq}, ddd, $J = 2.5$, $J = 4$, $J = 10.4$), 2.45 (1H, H₈_{ax}, ddd, $J = 1$, $J = 2.5$, $J = 13.0$), 2.07 (1H, H₆_{ax}, d, $J = 10.4$), 1.34 (3H, CH₃-, S), 1.31 (3H, CH₃-, S); Ms (70 ev):

m/e (relative intensity); 179.2 (M^+ , 4), 164(8), 152(2), 151(17), 136(18), 120(100), 113(25), 112(52), 108(53.4), 85(78.0), 83.1(59), 81.1(32), 80(28). HRMS Calcd for $\text{C}_{10}\text{H}_{13}\text{NO}_2$: 179.0947.

Found: 179.0983.

(1R,4S,5R,7S)-3,3-Dimethyl-7-formyl-2,9-dioxatricyclo
[3.3.1.0^{4,7}]nonane II-27

To a solution of the nitrile II-26 (600 mg, 3.5 mmol) in anhydrous THF (50 mL) at -78° C under argon atmosphere was added 1M di-isobutylaluminum hydride in hexane (6.7 mL, 6.0 mmol). The solution was stirred for 0.5 h at -78° C and allowed to warm to room temperature. The reaction was stirred for a total of 5 h, whereupon 6M hydrochloric acid (40 mL) was added at 0°C, and the two-phase system was stirred vigorously for 1 h. The mixture was extracted with dichloromethane (3 × 50 mL). The combined extracts were washed with brine (40 mL), and dried over anhydrous sodium sulphate. Column chromatography with ether (R_F 0.6) afforded II-27 (460 mg, 75%); $[\alpha]_D^{24} +61.5^\circ$ (c 2.21, pentane); IR (film) 2962, 2920, 2858, 2708, 1708, 1460, 1445, 1380, 1360, 1336, 1338, 1218, 1172, 1108, 1075, 1035, 960 cm⁻¹; ¹H NMR (CDCl₃) δ 9.58 (1H, CHO, S), 5.23 (1H, H₁, bd, J = 3.3), 4.58 (1H, H₅, t, J = 3.9), 2.57 (1H, H₄, dd, J = 1.3, J = 3.9), 2.56 (1H, H₈_{eq}, ddd, J = 0.8, J = 2.4, J = 13), 2.35 (1H, H₆_{eq}, ddd, J = 2.4, J = 3.3, J = 10.4), 2.21 (1H, H₈_{ax}, ddd, J = 1.3, J = 3.3, J = 13), 1.80 (1H, H₆_{ax}, d, J = 10.4, H₂), 1.29 (3H, CH₃-, S), 1.09 (3H, CH₃-, S); Ms (70 eV): m/e (relative intensity); 183.2(0.4), 182.2(M⁺, 04), 168(12), 167(100), 164(5), 154(11), 153(14), 139(31), 123(42), 121(44), 83.1(78), 55.1(65), 43.1(70); HRMS Calcd for C₁₀H₁₄O₃: 182.0943. Found: 182.0937.

(1R,4S,5R,7R)-3,3,7-Trimethyl-2,9-dioxatricyclo[3.3.1.0^{4,7}]

nonane II-1

Hydrazine hydrate (100%; 0.1 g) was added to a solution of the tricyclic aldehyde II-27 (60 mg, 0.33 mmol) and potassium hydroxide (0.1 g, 2.5 mmol) in triethylene glycol (5 mL) and the mixture was heated at 135°C for 1 h. The reaction temperature was gradually raised to 210–230°C, distilling off the excess N₂H₄ and some of the product. The remaining mixture was then refluxed for 3 h at 210°C. The mixture was cooled, diluted with water (10 mL) and extracted with dichloromethane (2 × 50 mL). The extracts and distillate were combined and washed with 1M hydrochloric acid (5 mL), water (20 mL) and brine (2 × 20 mL). The crude product in dichloromethane was dried with anhydrous sodium sulphate and was subjected to column chromatography using pentane-ether (3:1) to afford II-1 (40 mg, 73%). Bulb to bulb vacuum distillation of a portion of this product (14 mg) provided (+)-II-1 (4 mg), bp 68°C (5 Torr). Analysis by capillary GC revealed no other volatile material other than II-1 was present and its retention time was identical to racemic lineatin; $[\alpha]_D^{24} +79^\circ$ (c 0.21, CHCl₃) lit. $[\alpha]_D^{24} +66.3^\circ + 3.5^\circ$ (c 3.1, CHCl₃)⁵⁸, $[\alpha]^{21.5} +85.5^\circ$ (c 1.1, CHCl₃); IR (film) 2980, 2938, 2878, 1470, 1435, 1378, 1375, 1368, 1348, 1318, 1245, 1225, 1210, 1185, 1172, 1125, 1102, 1078, 1018, 1004, 965, 908, 872, 837 cm⁻¹; ¹H NMR (CDCl₃) δ 5.11 (1H, H₁, bd, J = 3.2), 4.51 (1H, H₅, dd, J = 3.1, J = 4.2), 2.11 (1H, H_{8ax}, 1,8_{ax}, 5,6_{eq}, 4,5

ddd, J = 1.2, J = 3.4, J = 12.8), 1.97 (1H, H₈^{eq}, ddd, J = 0.8, J = 2.4, J = 12.8), 1.91 (1H, H₄, dd, J = 1.2, J = 4.2), 1.75 (1H, H₆^{eq}, dt, J = 3.1, J = 10.2), 1.66 (1H, H₆^{ax}, d, J = 10.2), 1.26 (3H, CH₃⁻, S), 1.19 (3H, CH₃⁻, S), 1.18 (3H, CH₃, S); Ms (70 eV): m/e (relative intensity); 168 (M⁺, .04), 153(1.9), 140(1.6), 126(12.6), 125(17.2), 113(10.7), 111(36.7), 109(30.8), 107(27.2), 97(19.9), 96(37.9), 91(10.3), 85(100.0), 84(20.4) 83(55.9), 81(26.2), 79(21.3), 69(45.5), 67(20.7), 57(27.3), 56(45.5), 55(87.1), 53(20.4), 43(76.5), 42(10.0), 41(90.0); HRMS Calcd for C₁₀H₁₆O₂: 168,1151. Found: 168.1136.

(1R,5R)-3,3-Dimethyl-7-methylene-2,9-dioxabicyclo[3.3.1]nonane

II-28

To a solution of the aldehyde II-27 (400 mg, 2.19 mmol) and p-toluenesulfonylhydrazine (520 mg, 2.79 mmol) in a 1:1 mixture of DMF-sulfolane (10 mL) containing p-toluenesulfonic acid (54 mg, 0.28 mmol) at 100°C was added sodium cyanoborohydride (553 mg, 8.8 mmol) and cyclohexane (5 mL) and the solution was heated at 100-105°C for 2 h. The reaction was then diluted with water (35 mL) and extracted with cyclohexane (3 × 40 mL). The cyclohexane solution was washed twice with water (2 × 15 mL), dried and concentrated. Column chromatography of the residue using ether-pentane (1:9) afforded II-28 (80 mg, 22%); [α]_D²⁴ +108.6°

(c 1.69, CHCl₃); IR (film) 3080, 3022, 2978, 2932, 1665, 1368, 1328, 1254, 1218, 1139, 1125, 1060, 1012, 988, 932, 895, 755 cm⁻¹; ¹H NMR (CDCl₃) δ 5.39 (1H, H₁, bs), 4.92 (1H, H, dd, J = 2, J = 4), 4.88 (1H, H, dd, J = 2, J = 4), 4.36 (1H, H₅, dt, J = 4, J = 10.4), 2.61 (1H, H_{6eq}, ddd, J = 2, 5, 6eq⁻⁴endo, 5⁴exo, 5^{6eq,8eq}), 2.35 (1H, H_{8eq}, tddd, J = 2, J = 2, 5, 6eq^{6eq,6ax}), 2.29 (1H, H_{8ax}, dd, J = 1, J = 14), 2.00 (1H, H_{1,8eq}, 8eq^{8ax}, 1,8ax^{8ax,8eq}), 1.97 (1H, H_{6ax}, bd, J = 13.4, 4exo, 5^{4exo,4endo}), 1.64 (1H, H_{4endo}, dd, J = 4.0, J = 13.4), 1.45 (3H, CH₃-, S), 1.15 (3H, CH₃-, S); Ms (70 eV): m/e (relative intensity); 169 (M+1, 1.7), 168 (M⁺, 10.4), 153(1.0), 113(27.8), 111(0.5), 109(1.8), 107(100.0), 97(0.3), 96(1.6), 95(13.1), 85(54.9), 83(4.9), 82(25.6), 81(13.5), 80(16.0), 79(45.6), 69(11.4), 57(17.3), 56(16.0), 55(13.1), 43(22.0), 41(22.9); HRMS . Calcd for C₁₀H₁₆O₂: 168.1151. Found: 168.1116.

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