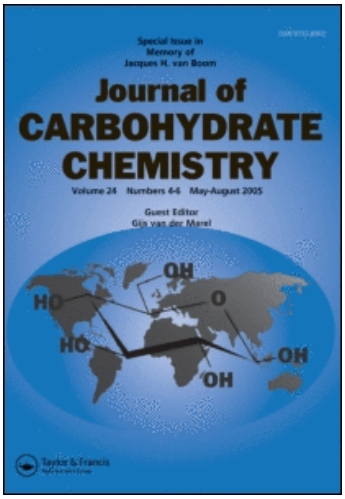

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REVIEW ARTICLE

ENANTIOMERICALLY PURE INSECT PHEROMONES: THE CARBOHYDRATE SYNTHETIC APPROACH *

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*) Dedicated to the memory of Prof. J. R. Pougny (*1947-1988*)

1. Introduction

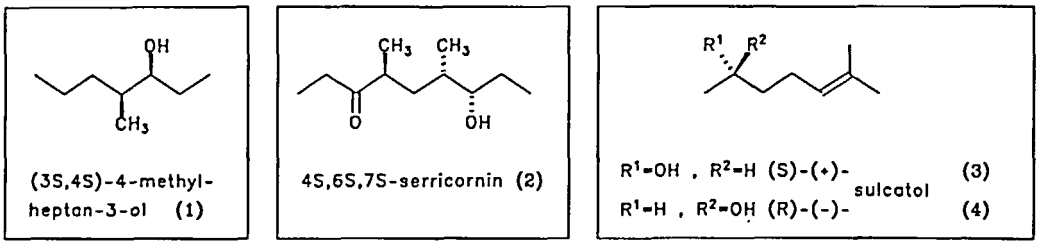
During the past two decades, there has been a rapidly growing interest in the field of intra- and interspecific chemical communication. Insect pheromones in particular have been intensely studied with respect to their potential use as a component of integrated pest management.[1] Structural identification and chemical synthesis of these so-called "semiochemicals" have developed in harmony with the biological research evaluating structure-activity relationships. Most of the pheromones identified, studied, and synthesized come from the order *Lepidoptera*: very often these pheromones consist of long-chain olefinic compounds in which regio- and *cis/trans*-isomerism determine their biological activity. Several well documented reviews have appeared, emphasizing both coupling of alkyl halides or similar electrophilic substrates with metallo-organic reagents ("Wurtz-chemistry") and carbonyl olefination, such as the Wittig reaction and its huge variety of modifications for regio- and stereoselective *C-C* bond formation.[2-8] The importance of chirality in pheromone perception by insects has been recognized and the role of optical isomerism and diastereoisomerism in behavioral discrimination has been firmly established through the combination of synthesis and bioassay. Some reviews bring good insight into the diverse strategies employed in synthesizing chiral pheromones,[8,9] originating principally from the orders *Coleoptera* and *Hymenoptera*. In spite of the increasing efficiency of asymmetric synthesis in the semiochemical field,[10] only few methods afford highly optically pure compounds with known absolute configuration. On the other hand, optical resolution is not always satisfactory and the absolute configuration of the resolved material has to be determined by some means.[11] Enantiospecific synthesis starting from naturally occuring chiral molecules such as amino or hydroxy acids, terpenes and sugars appears to be the safest path leading to highly optically pure pheromones. The prominent role of readily available carbohydrate starting materials within this "chiral synthon approach" has been clearly demonstrated.[12] The present review offers a 1976 to 1990 literature survey of the use of hexoses (mainly D-glucose and derivatives) and pentoses for the enantiospecific synthesis of chiral pheromones, issuing principally from the order *Coleoptera*.[13]

2. Noncyclic pheromones

2.1. (-)-(3*S*,4*S*)-4-Methylheptan-3-ol (1)

The pheromone produced by the smaller European elm bark beetle *Scolytus multistriatus Marsham* (*Coleoptera, Scolytidae*), has been synthesized from D-glucose as depicted in scheme 2 in a 35% overall yield by Sinaÿ et al..[14]

A nucleophilic attack of the Grignard reagent methylmagnesium chloride on methyl 2,3-anhydro-α-D-*manno*-pyranoside (**5**) yielded the *trans*-configurated product **6** which is in



Scheme 1: Linear pheromones

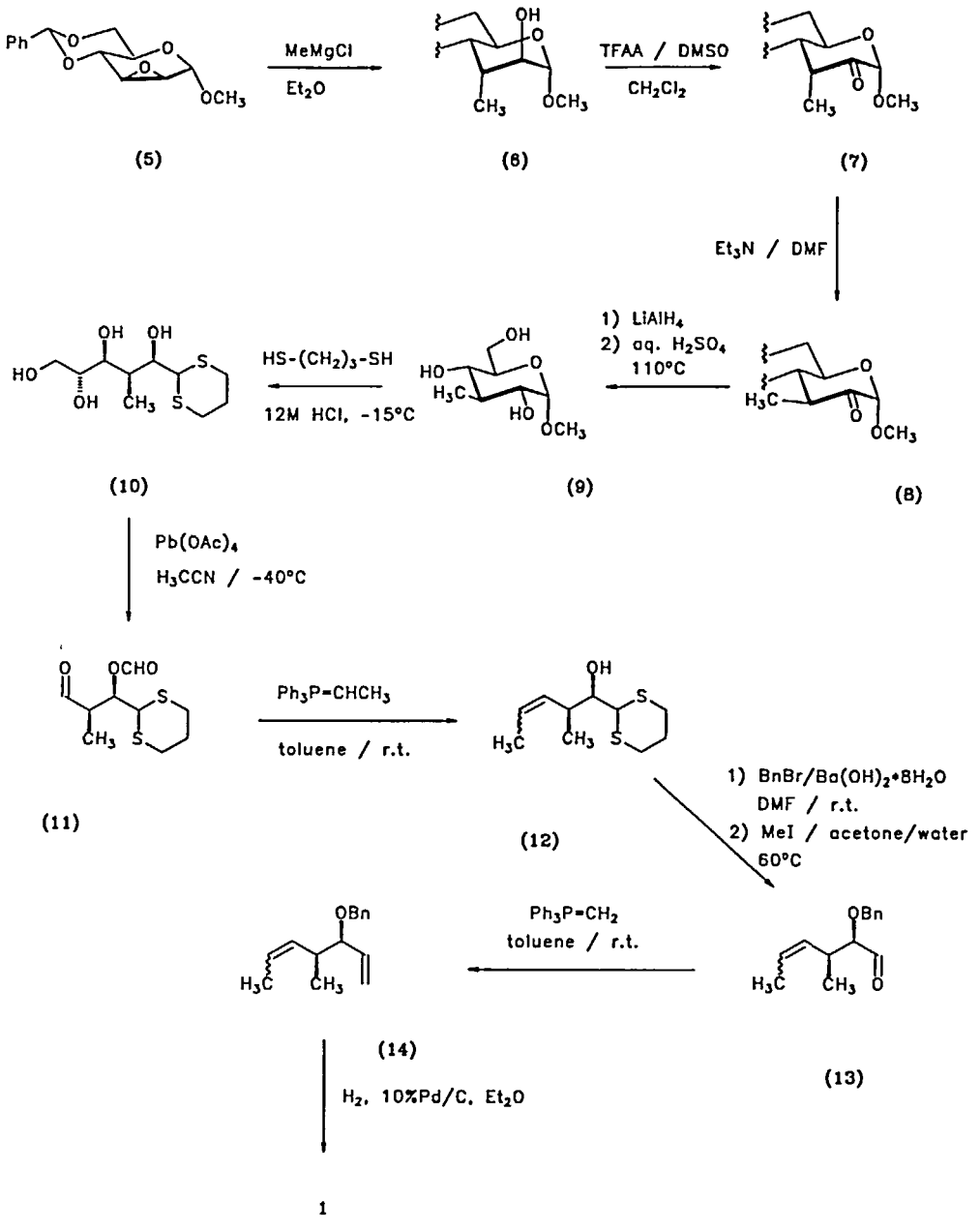
strict accordance with Fürst-Plattner's rule.[15] After oxidation of **6**, the 3-*C*-methyl group of the 2-uloside **7** was inverted under basic conditions to the equatorial product **8**. Reduction by lithium aluminum hydride of the carbonyl group and acidic cleavage of the 4,6-*O*-benzylidene acetal yielded methyl 3-deoxy-3-*C*-methyl-α-D-*gluco*-pyranoside (**9**), which was transformed into the corresponding dithioacetal **10** and subjected to lead tetraacetate diol cleavage to give **11**. The carbonyl olefination towards **12**, followed by benzylation and deblocking of the thioacetal set the stage for the second chain extension on compound **13**. A defined stereochemical outcome of both Wittig reactions was not necessarily required, as the final double hydrogenation step of the diene **14** yielded the saturated pheromone **1**.

2.2. Serricornin (2)

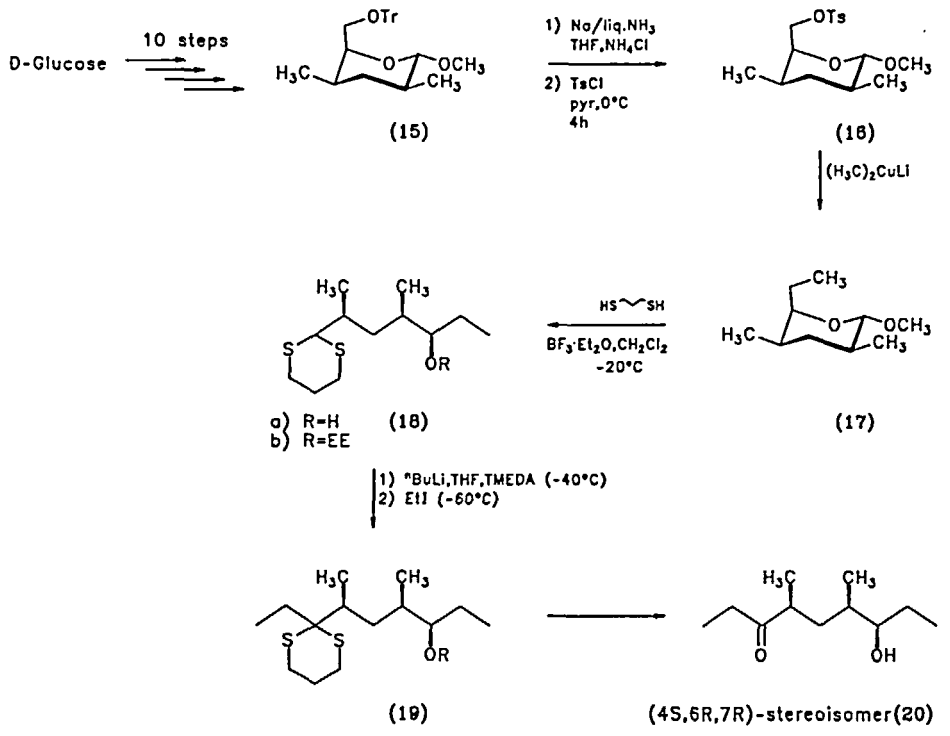
Serricornin, (4*S*,6*S*,7*S*)-4,6-dimethyl-7-hydroxynonan-3-one (**2**),[16] the second example in the class of acyclic chiral pheromones, is produced by the female cigarette beetle *Lasioderma serricorne F.* (*Coleoptera, Anobiidae*). In a synthesis carried out by Mori et al.,[17] D-glucose was transformed into a key carbohydrate synthon **15** , which was also usefully involved in the synthesis of multistriatin (cf. § 5.2). The trityl derivative **15** was deblocked and tosylated, yielding an acceptor (**16**) for the attachment of a methyl group at *C*-6 by lithium dimethylcuprate. Cleavage of the anomeric methoxy group of **17** and "Umpolung" of *C*-1 into a *C*-nucleophilic center gave dithioacetal **18a**, which after hydroxyl protection, gave **18b**. The latter compound was in turn converted to the dithioketal **19**, which after deblocking gave the (4*S*,6*R*,7*R*)-diastereomer **20** of the native serricornin (**2**).

The same authors proposed an alternative approach[18] to serricornin using levoglucosenone as the starting material and again a common intermediate with the build-up of multistriatin.

More recently, Redlich et al.[19] disclosed a new route to the target molecule starting from the D-glucose derivative **21**, which was easily obtained from 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose by a Wittig reaction.

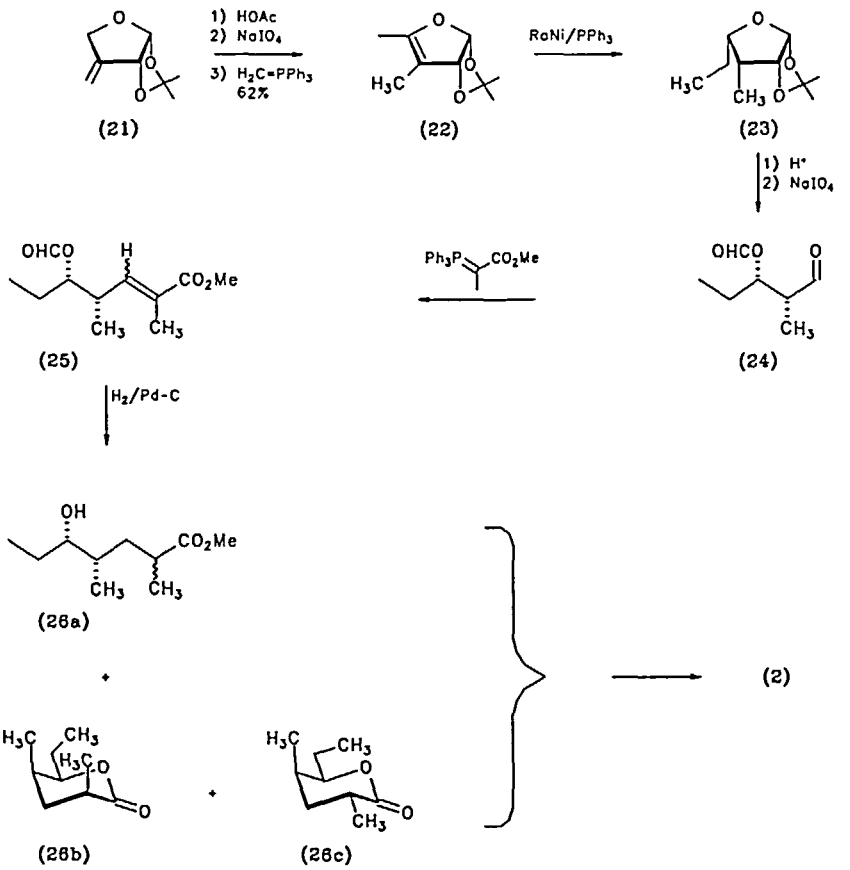


Scheme 2: Synthesis of the smaller european elm bark beetle pheromone (1) from D-glucose



Scheme 3: Synthesis of serricornin, the female cigarette beetle pheromone, from D-glucose

A three step reaction sequence yielded the unsaturated furanoside **22** in 62% overall yield; cleavage of the 5,6-*O*-isopropylidene group followed by sodium periodate oxidation and carbonyl olefination, then isomerization of the exocyclic double bond gave the shown conjugated endocyclic system. In order to protect the diene from addition of methanol, which served as solvent for the hydrogenation, a partially complexed Raney nickel catalyst was used to provide the saturated mono-isopropylidene compound **23** in 72% yield. The straightforward synthesis for the key intermediates **26a**, **b**, and **c** required deacetalization and then periodate cleavage, in order to allow the Wittig reaction of α-(carbomethoxyethylidene)triphenylphosphorane on aldehyde **24** to yield **25**. After hydrogenation a mixture of the above mentioned products was obtained due to the new, undefined α-carboxylic center and to partial deesterification. The mixture, however, was treated under basic conditions to give a simplified mixture of lactones **26b** and **26c** (1:20), ready to be converted into pure pheromone **2**, as previously described by Bartlett and coll. [20]

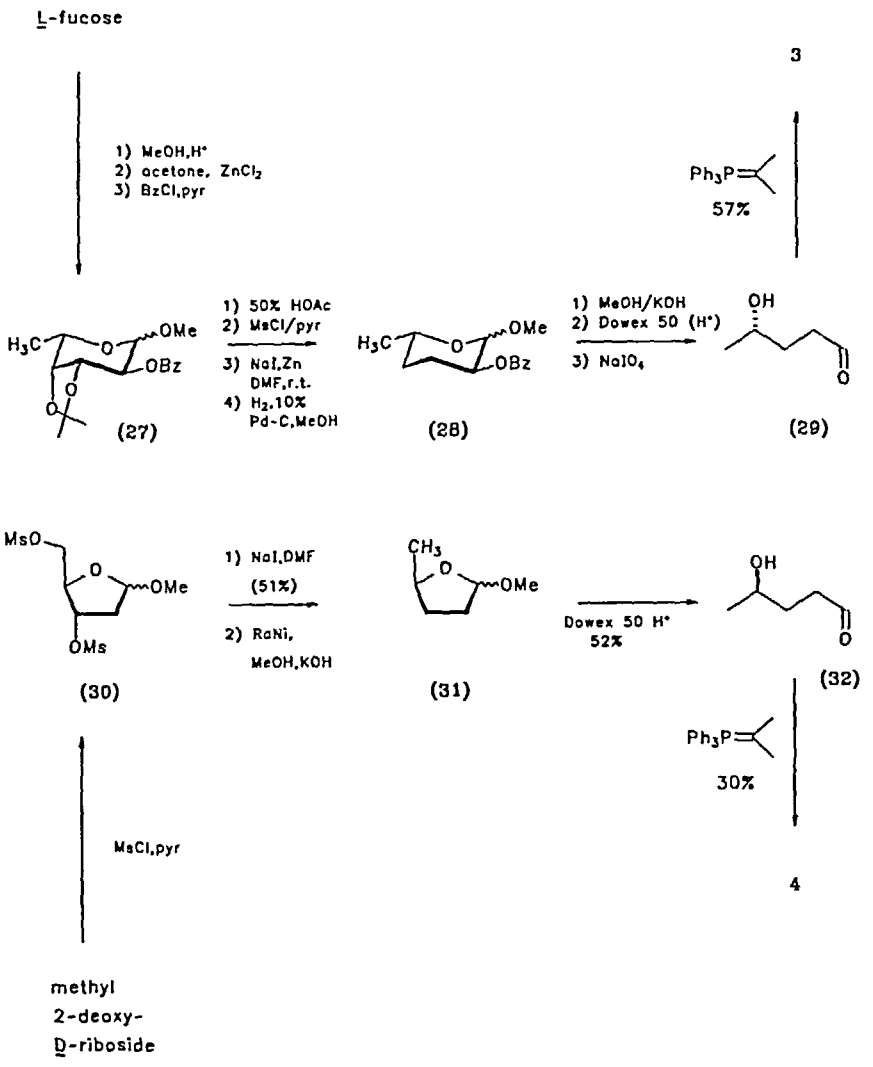


Scheme 4: Synthesis of serricornin from 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose

2.3. Sulcatol (6-methylhept-5-en-2-ol) (3) and (4)

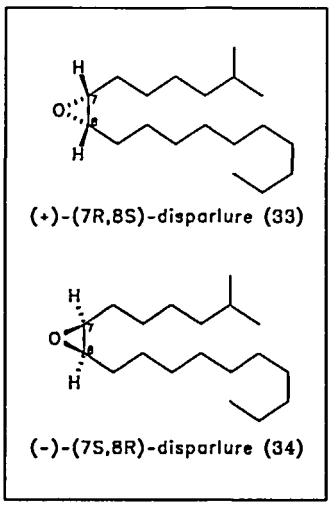
The aggregation pheromone of the ambrosia beetle, *Gnathotricus sulcatus* (*Coleoptera, Scolytidae*) was shown to consist of a 65:35 mixture of the (*S*)-(+) and the (*R*)-(-)-enantiomers of sulcatol, both of which have been synthesized by Slessor and co-workers.[21]

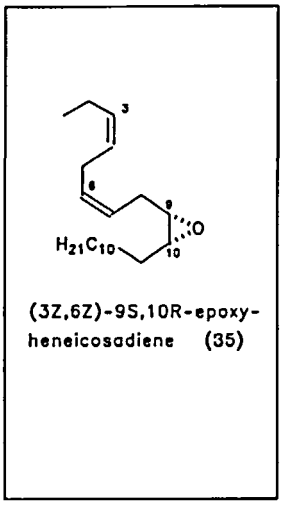
The entire synthesis was based on the somewhat extravagant rationale to convert either *C*-5 of L-fucose, or *C*-4 of 2-deoxy-D-ribose into the solitary chiral carbon, *C*-2 of sulcatol. However, it was the ease of simultaneous access to *C*-3 and *C*-5 through the isopropylidene derivative **27**, which was taken advantage of in this synthesis, with L-fucose already showing the correct absolute (*S*)-configuration at *C*-5. The bis-(methanesulfonyl)

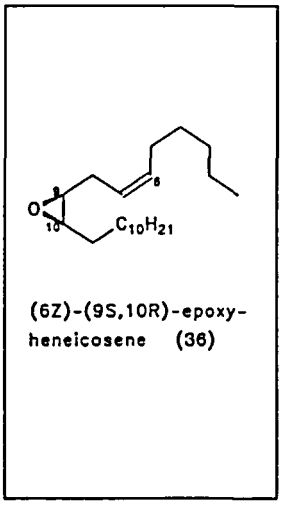


Scheme 5: Synthesis of the ambrosia beetle pheromone sulcatol (3) and (4)

ester was then transformed into a 3-enopyranoside in 52% yield, following the well established Tipson-Cohen reaction.[22] The methyl-2-*O*-benzoyl pyranoside **28** was deblocked and deglycosylated, and upon treatment with sodium periodate, the chain length was reduced to the trideoxypentose **29**. Its counterpart, enantiomeric **32**, was prepared from 2-deoxy-D-ribose, which was readily converted into the glycosylated bis methanesulfonate **30**. Nucleophilic replacement by iodide and its catalytic removal results in deoxygenation at both positions, *C*-3 and *C*-4, to give compound **31**, which was







Scheme 6: Pheromones bearing the anhydro-function

deglycosylated to the desired intermediate **32**. Final Wittig reaction of **29** and **32** with an isopropylidene triphenylphosphorane yielded the (*S*)- and (*R*)-sulcatols **3** and **4**, respectively. The poor yield of the di-iodide obtained from the corresponding sulfonate **30** may be considered the major pitfall in the synthesis of **4**, thus being responsible for the low (5%) overall yield.

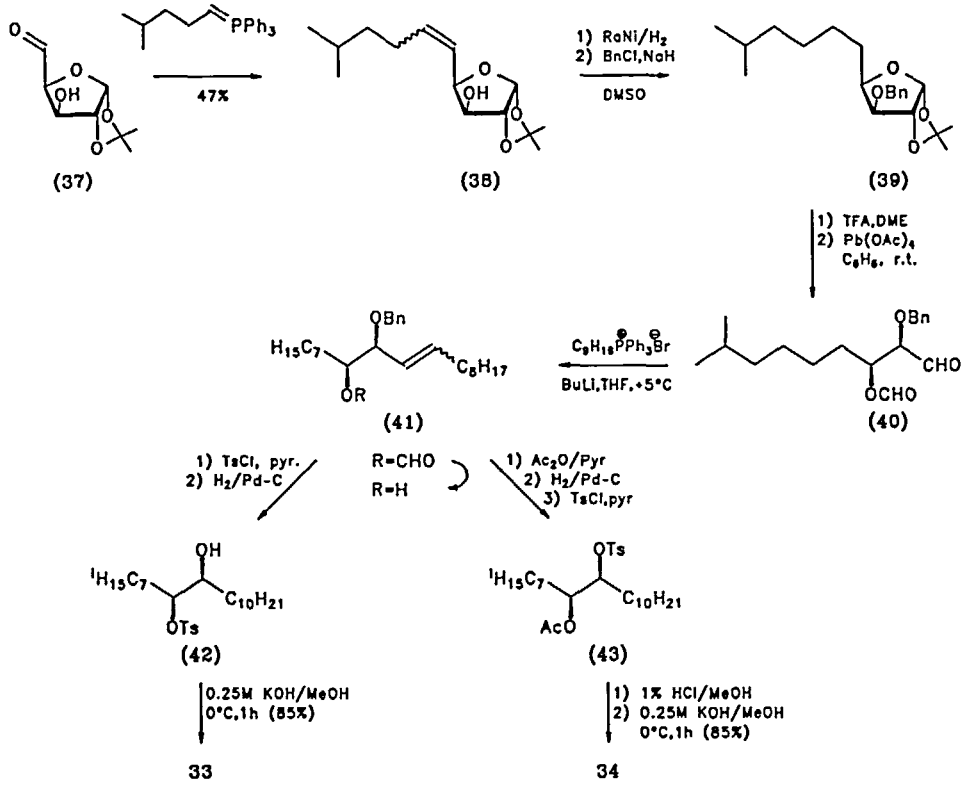
3. Epoxides

Several chiral oxirane structures closely related to the corresponding mono- or polyenes have been identified among the semiochemicals of *Lepidoptera*.

3.1. Disparlure: (+)-(7*R*,8*S*)-7,8-epoxy-2-methyl octadecane (33)

Disparlure was identified as the principal sex attractant of the female gypsy moth *Porthetria (Lymantria) dispar L.* (*Lepidoptera, Lymantriidae*). The molecule consists of a chiral *cis*-epoxide bearing two saturated substituents. The synthesis applied by Achmatowitcz et al.[23] yielded both enantiomers, **33** and **34**, in pure form.

The pentodialdo furanose **37**, readily available from D-glucose, was subjected to a Wittig reaction to yield the olefin **38** in 47%. After hydrogenation the hydroxyl group located at *C*-3 was protected as its benzyl ether **39**. Lead tetraacetate cleavage, which was carried out right after deisopropylidenation of **39**, left retained stereochemistry at *C*-3 and *C*-4, represented as *C*-2 and *C*-3, respectively, in the aliphatic aldehyde **40**. The newly



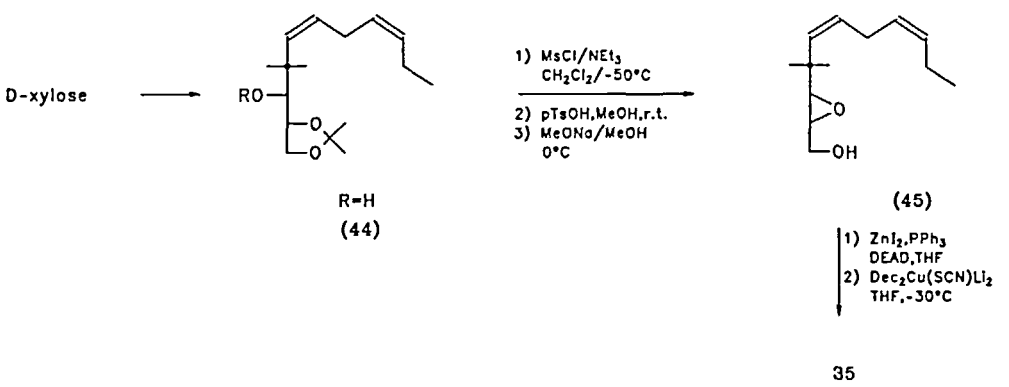
Scheme 7: Synthesis of the disparlure enantiomers 33 and 34

formed carbonyl group provided a reactive site for chain elongation, which yielded the key intermediate **41**. The latter compound was converted into either the toluenesulfonate at *C*-8,(**42**) or *C*-9, (**43**), after several specific steps designed to discriminate between the *C*-8 and *C*-9 hydroxy groups.

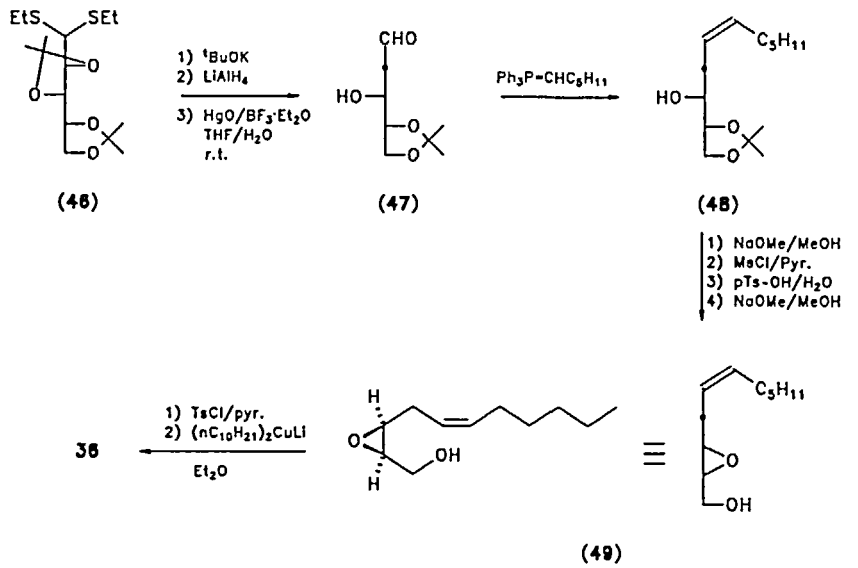
Thus, oxirane ring formation lead to either (+)- (**33**) or (-)-disparlure (**34**) in 85% yield based on the last step. Another synthesis of (+)-disparlure from D-ribose has been reported.[24]

3.2. (+)-(3*Z*,6*Z*)-9*S*,10*R*-Epoxyheneicosadiene (35) and (+)-(6*Z*)-9*S*,10*R*-epoxyheneicosene (36)

The salt marsh caterpillar moth *Estigmene acrea Drury* (*Lepidoptera, Arctiidae*) as well as another member of the *Arctiidae* family, *Hyphantria cunea Drury*, produce an unsaturated epoxide-type pheromone, the synthesis of which was accomplished by Pougny et al..[25]



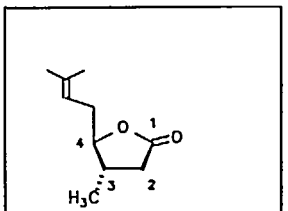
Scheme 8: Synthesis of the salt marsh caterpillar moth pheromone **35** from D-xylose



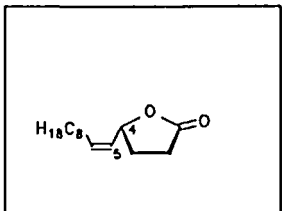
Scheme 9: Synthesis of the (+)-enantiomer **36**

Starting from a suitably protected open chain D-xylose, Wittig olefination yielded stereoselectively the (*Z*,*Z*)-unsaturated alcohol **44**, which upon mesylation, de-*O*-isopropylidenation and basic treatment yielded the epoxide **45**.

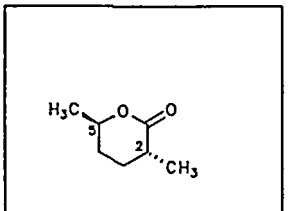
The chemical modification of the primary hydroxyl group via a zinc salt modified Mitsunobu reaction [26] provided the corresponding iodide representing an electrophilic



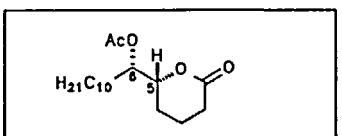
(+)-eldanolide (50)



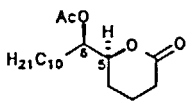
(-)-(4R,5Z)-tetradec-5-en-4-olide (51)



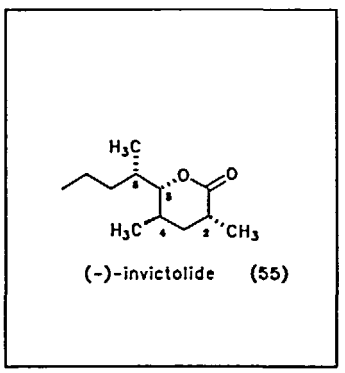
(+)-(2R,5R)-5-hydroxy-2-methyl-hexanolide (52)



(-)-(5R,6S)-erythro-6-acetoxy-5-hexadecanolide (53)



(+)-(5S,6R)-erythro-6-acetoxy-5-hexadecanolide (54)



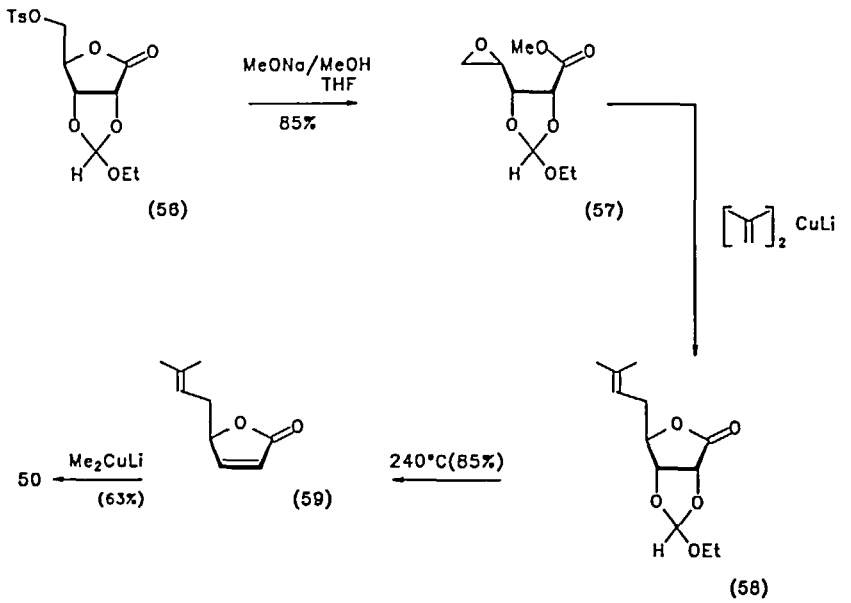
(-)-invictolide (55)

Scheme 10: Lactonic pheromones

acceptor. This was treated with the higher-order thiocyanato cuprate reagent to afford the target molecule **35** in 81% yield.

The mono-olefinic homologue of the pheromone described above, (6*Z*)-9*S*,10*R*-epoxyheneicosene (**36**), was emitted by the female ruby tiger moth, *Phragmatobia fuliginosa L.*, (*Lepidoptera, Arctiidae*). The target epoxide has been synthesized by the same group following a similar route.[27] By application of the Wong and Gray deoxygenation procedure[28] on 2,3:4,5-di-*O*-isopropylidene-D-xylose dithioacetal **46**, followed by thioacetal cleavage, the 4,5-*O*-isopropylidene-2-deoxy-D-*arabino* derivative **47** was prepared.

Reaction of **47** with the non-stabilized Wittig reagent *n*-hexylidene triphenylphosphorane, afforded the (*Z*)-olefin **48** with a 9:1 stereoselectivity in 71% yield, the ratio of which exactly meets the theoretical predictions of the Vedejs-mechanism. The unblocked epoxide **49** was prepared from the olefin **48** in a manner fully analogous to conversion of diene **44**, to the epoxide **45**. The primary alcohol function of **49** was then activated by tosylation and reacted with lithium *bis*-decylcuprate to give 62% of the desired pheromone **36**.



Scheme 11: Synthesis of (+)-eldanolide, the african sugar cane borer pheromone, starting from D-ribonolactone

4. Lactones

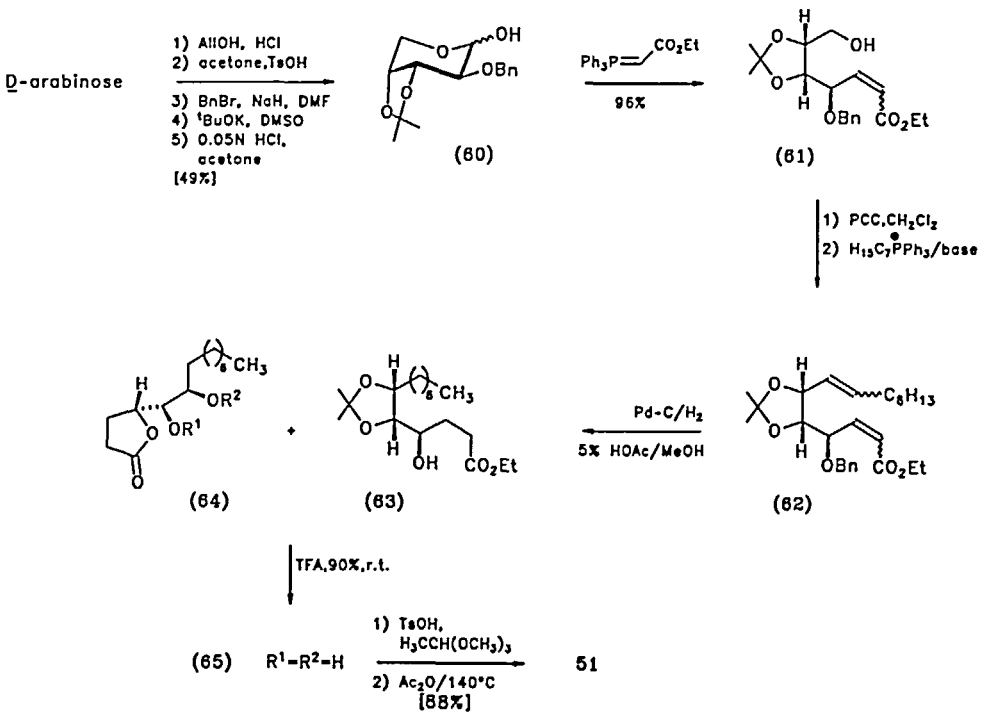
There are many different kinds of insect pheromones which contain a chiral lactonic structure, namely γ-lactones with an asymmetric *C*-4 or δ-lactones with an asymmetric *C*-5 carbon atom.

4.1. (+)-Eldanolide: (3*S*,4*R*)-3,7-dimethyloct-6-en-4-olide (50)

The African sugar cane borer, *Eldana saccharina Wlk.* (*Lepidoptera, Pyralidae*) produces an unsaturated furanoid lactonic pheromone containing two chiral centers.

Scheme 11 shows the synthesis of (+)-eldanolide (**50**) by Font et al..[29-31] The epoxide **57** was prepared from D-ribonolactone via its toluenesulfonyl ester **56** using classical techniques. Oxirane opening by di-*iso*-butenylcuprate on **57** afforded in 31% yield the unsaturated and deoxygenated lactone **58**, from which the orthoester function was eliminated thermally to give the α,β-unsaturated compound **59**.

This compound was subjected to a Michael addition with lithium dimethylcuprate to give the *trans*-branched product by a clean 1,4-addition in 63% yield. The stereochemical outcome was again in good accordance with the results obtained by Fraser-Reid and by Paulsen (vide infra, refs. 57 and 58). Compound **50** was shown to be identical with natural (+)-eldanolide.

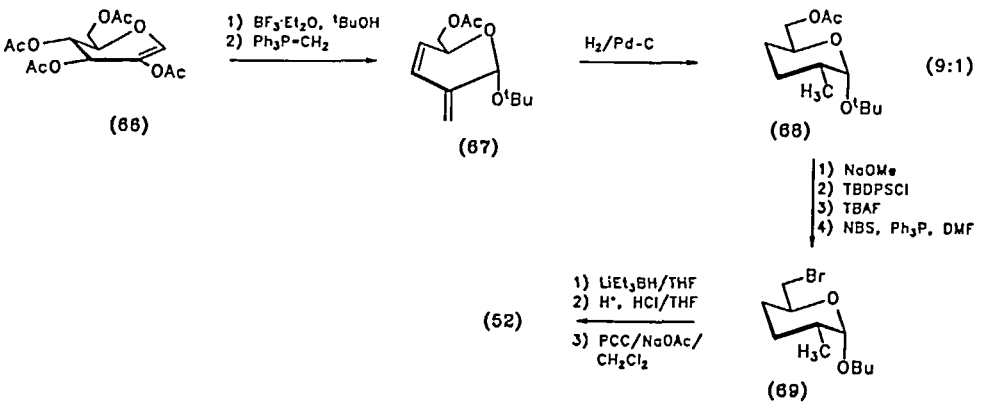


Scheme 12: Synthesis of the japanese beetle pheromone **51** from D-arabinose

4.2. (-)-(4*R*,5*Z*)-tetradec-5-en-4-olide (51)

A more general approach to chiral τ-lactones from D- and L-arabinose derivatives has been devised by Ohrui et al.[32] and applied to the synthesis of a sex pheromone of *Popillia japonica Newman* (*Coleoptera, Scarabeidae*), the Japanese beetle.

D-Arabinose was converted into its allyl glycoside, which regioselectively yielded a 3,4-isopropylidene derivative. This was easily blocked at *C*-2 by conversion into 2-*O*-benzyl-3,4-di-*O*-isopropylidene-D-arabinose (**60**). A Wittig reaction with carboethoxymethylenetriphenylphosphorane gave the alcohol **61**, already bearing the correct stereochemistry at *C*-4. Aldehyde formation at *C*-7 followed by olefination with *n*-heptyltriphenylphosphonium bromide yielded a 7:2 mixture of 7*E*:7*Z* olefins **62**. These were hydrogenated either to the saturated ester **63** or to the lactone **64**, following ethyl ester cleavage. This mixture, however, was converted to a single diol **65**, when treated with 90% trifluoroacetic acid in methanol. Thermal *cis*-elimination of a transient orthoacetate gave the desired Japanese beetle lactonic pheromone **51**.



Scheme 13: Synthesis of the carpenter bee pheromone **52** from 2-acetoxy-D-glucal (**66**)

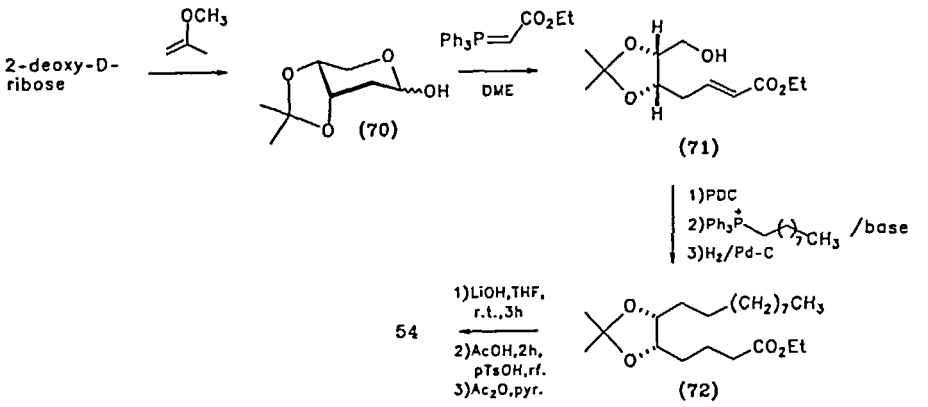
4.3. 2-Methyl-5-hexanolide (52)

The volatile component of the carpenter bee *Xylocopa hirsutissima* (*Hymenoptera, Apidae*) sex attractant was shown to be a *cis*-configurated methyl branched six-membered lactone. An easy access to this series has been worked out by Hanessian et al..[33,34]

The Lewis acid mediated addition of *t*-butyl alcohol on the readily available 3,4,6-tri-*O*-acetyl-2-acetoxy-D-glucal **66**, elaborated by Ferrier, afforded the 2-acetoxylated *t*-butyl enopyranoside. When this enol ester was reacted with methylenetriphenylphosphorane the *exo*-methylene compound **67** was formed in 72% yield. The hydrogenation yielded a 9:1 mixture in favour of the depicted *t*-butyl 6-*O*-acetyl-2-*C*-methyl-2,3,4-trideoxy-α-D-*erythro*-hexopyranoside (**68**). The preferred β-facial hydrogen attack on its precursor may be due to the bulkiness of the anomeric substituent. The mixture was then subjected to transesterification, silylation, and then purification by silica gel chromatography. Further processing included tetrabutylammonium fluoride cleavage of the bulky silyl substituent and bromination at *C*-6 by a modified Appel reaction [35,36] yielding **69**. This, in turn was converted easily into the target molecule **52** by hydride dehalogenation, acidolysis and pyridinium chlorochromate oxidation.

4.4. (-)-5*R*, 6*S*- and (+)-(5*S*,6*R*)-*erythro*-6-acetoxy-5-hexadecanolide (53) and (54)

The major component of the oviposition attractant of the mosquito *Culex pipiens fatigans Wiedemann* (*Diptera, Culicidae*) was a δ-lactone bearing an *exo*-cyclic chiral center. The synthesis of both the natural pheromone and its enantiomer has been achieved by Kang and coll.,[37,38] who made use of 2-deoxy-D-ribose as the unique starting material.



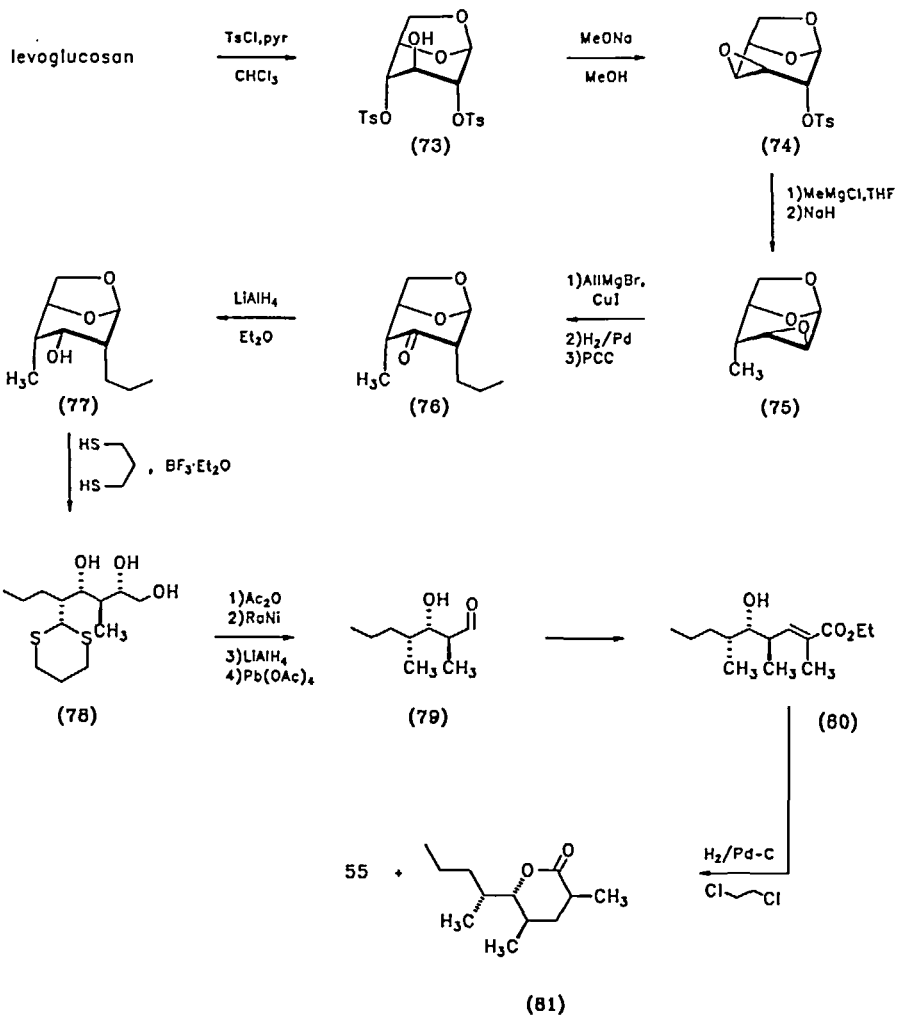
Scheme 14: Synthesis of the mosquito oviposition attractant **54** from 2-deoxy-D-ribose

After isopropylidenation (**70**) of the starting sugar a Wittig reaction furnished the α,β-unsaturated ethyl ester **71**. This was subjected to a second chain elongation sequence, here again by primary alcohol oxidation, to an aldehyde using pyridinium dichromate, followed by carbonyl olefination and hydrogenation of both double bonds. The target molecule **54** was formed in 10.5% yield, following deblocking of **72**, and acetylation.

4.5. (-)-Invictolide, (2*R*,4*R*,5*S*,6*R*)-2,4,6-trimethyl-5-nonanolide (55)

The queen recognition pheromone of the red imported fire ant, *Solenopsis invicta Buren* (*Hymenoptera, Formicidae*) was a chirally complex δ-lactone which contains 4 asymmetric carbon atoms. A synthesis from levoglucosan of the active stereoisomer, (-)-invictolide [39] has been published.[40]

The tosylation of levoglucosan selectively yielded the 2,4-bis-tosylate **73**, which was then readily transformed into the 3,4-epoxytosylate **74**.[41] Grignard attack on **74** opens the oxirane stereospecifically *trans* by an axial attack. The generated hydroxyl group at *C*-3 upon basic treatment attacks *C*-2 and eliminates the tosylate to yield the migrated epoxide **75**. This epoxide is well suited for a second Grignard addition with allylmagnesium bromide in the presence of copper(I)iodide to give the branched chain alcohol, readily hydrogenated and then oxidized rendering the saturated ketone **76**. As a result of the reduction with lithium aluminum hydride, the stereochemistry was inverted in *C*-3 in the conversion of **73** to **77**. Transformation of the intramolecular acetal to a dithioacetal was achieved by the treatment of **77** with propanedithiol, boron trifluoride serving as Lewis acid. After acetylation, the dithioacetal group of **78** was reductively removed, the ester groups were cleaved and the free alcohol subjected to diol cleavage conditions. The

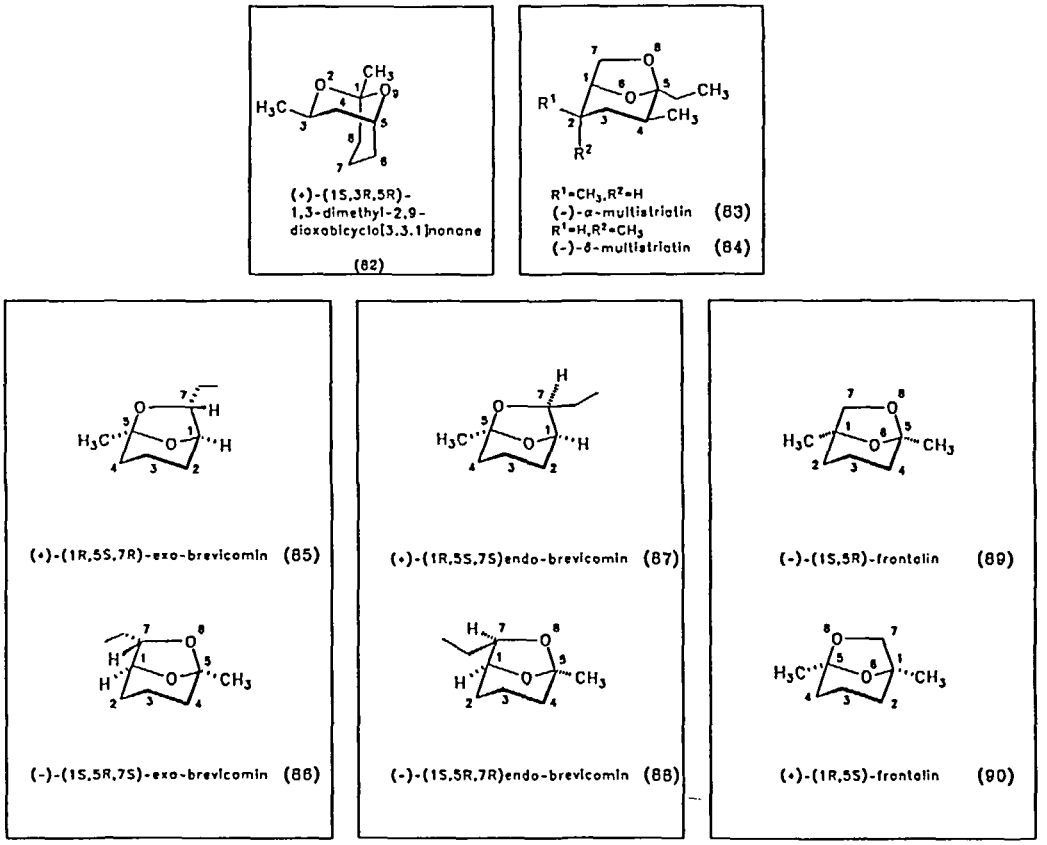


Scheme 15: Synthesis of both invictolides, the recognition pheromones of the red imported fire ant, from levoglucosan

resulting heptanal **79** was extended by carbonyl olefination, to give **80**, which after hydrogenation yielded a 3:1 mixture in favour of the desired (-)-invictolide (**55**) to its *C*-2 epimer (**81**).

5. Bicyclic ketal pheromones

Dioxabicycloalkane *Coleoptera* pheromones have been favourite targets in enantiospecific synthesis from carbohydrate precursors. This was particularly true for

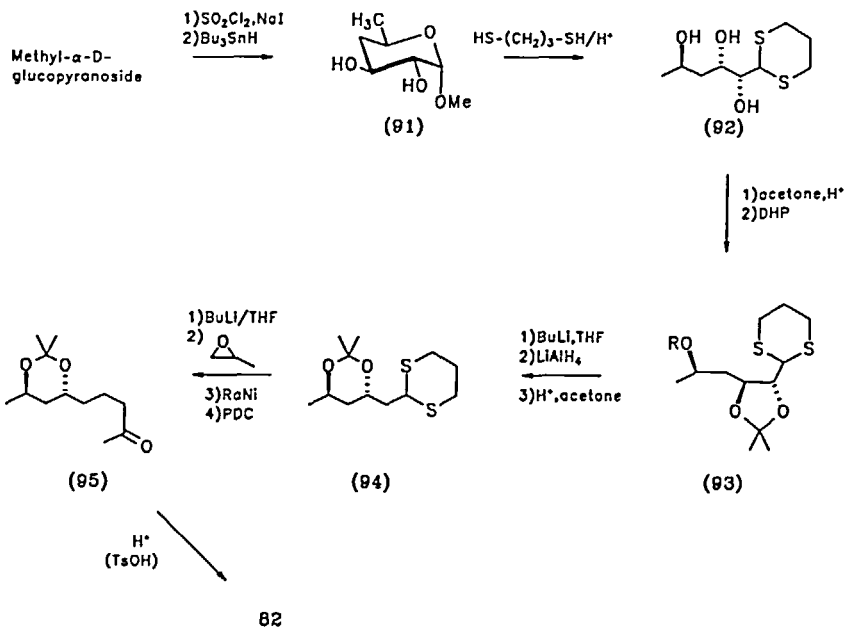


Scheme 16: Bicyclic pheromones

semiochemicals of the family *Scolytidae*, multistriatins, brevicomins, and frontalins, which possess a 6,8-dioxabicyclo[3.2.1]octyl skeleton, closely related to 1,6-anhydro-β-D-hexopyranoses.

5.1. (+)-(1*S*,3*R*,5*R*)-*exo*-1,3-Dimethyl-2,9-dioxabicyclo[3.3.1]nonane (82)

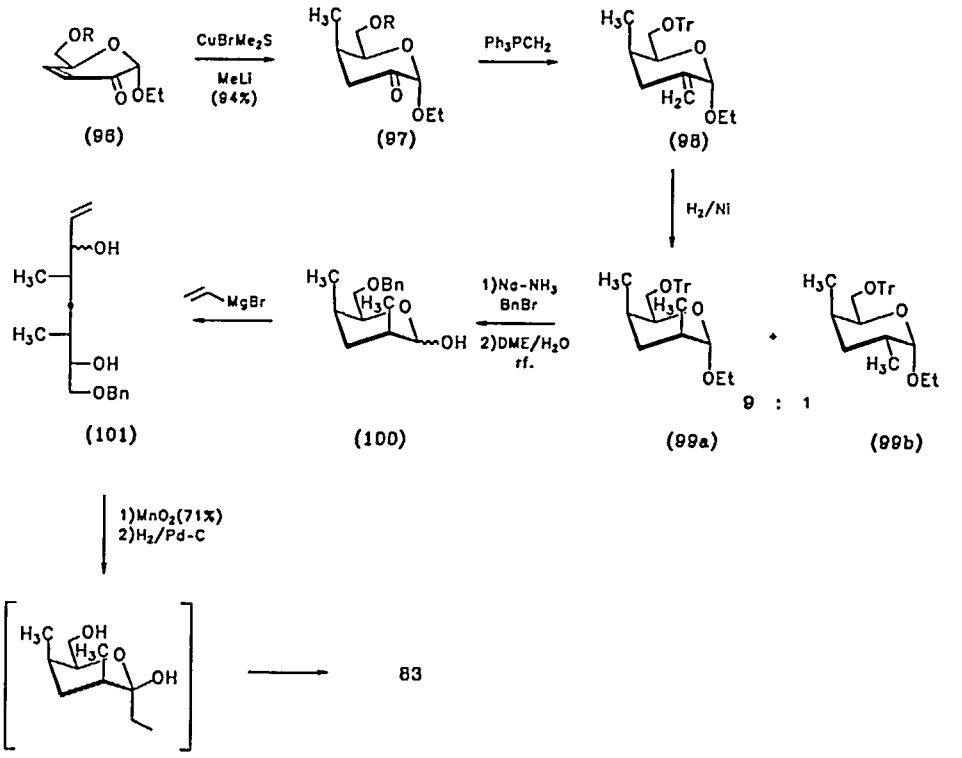
This compound was one of the host-specific molecules isolated from the Norway spruce infested by the striped ambrosia beetle *Trypodendron lineatum Olivier* (*Coleoptera, Scolytidae*). The stereochemistry at the acetalic position is a consequence of the hydroxy groups in the intermolecular cyclization, therefore, only two of the three chiral centers in this bicyclic structure have to be derived from D-glucose, simplifying the synthetic framework. This synthesis has been worked out by Redlich et al.. [42,43]



Scheme 17: Synthesis of the striped ambrosia beetle pheromone **82** from methyl α-D-glucopyranoside

Sulfuryl chloride / sodium iodide deoxygenation,[44] and subsequent dehalogenation by radical reduction, yielded the 4,6-dideoxypyranoside **91** in two steps. The dithioacetalization was carried out after deglycosylation in acidic medium to give the linear dithioacetal **92**, which in turn was protected selectively at its 2, 3 and 5 positions by isopropylidenation and tetrahydropyranylation, respectively. This protected dithioacetal **93** was deoxygenated following an electrocyclic dioxolane ring opening reaction sequence, which was induced by a favoured abstraction of the dithioacetal proton,[45] due to the "Umpolung"-effect and the charge-stabilization at *C*-1. Lithium aluminum hydride reduced the intermediate ketene dithioacetal to give the 2-deoxy-5-*O*-THP-dithioacetal **94**. Following the Corey-Seebach procedure,[46] propylene oxide addition yielded the methyl octyl ketone **95** after desulfurization and pyridinium dichromate oxidation.[47] Under acidic conditions a final transacetalization occured and the target molecule (1*S*,3*R*,5*R*)-1,3-dimethyl-2,9-dioxabicyclo[3.3.1]nonane **82** was formed.

By sequential application of the Mitsunobu reaction [48] on **92** the three remaining stereoisomers in this series of four stereoisomers have been obtained. [49]



Scheme 18: Synthesis of the smaller European elm bark beetle pheromone, α-multistriatin (83)

5.2. (-)-(1*S*,2*R*,4*S*,5*R*)-α-Multistriatin (83) and epimeric (-)-(1*S*,2*S*,4*S*,5*R*)-δ-multistriatin (84): 5-ethyl-2,4-dimethyl-6,8-dioxabicyclo[3.2.1]octanes

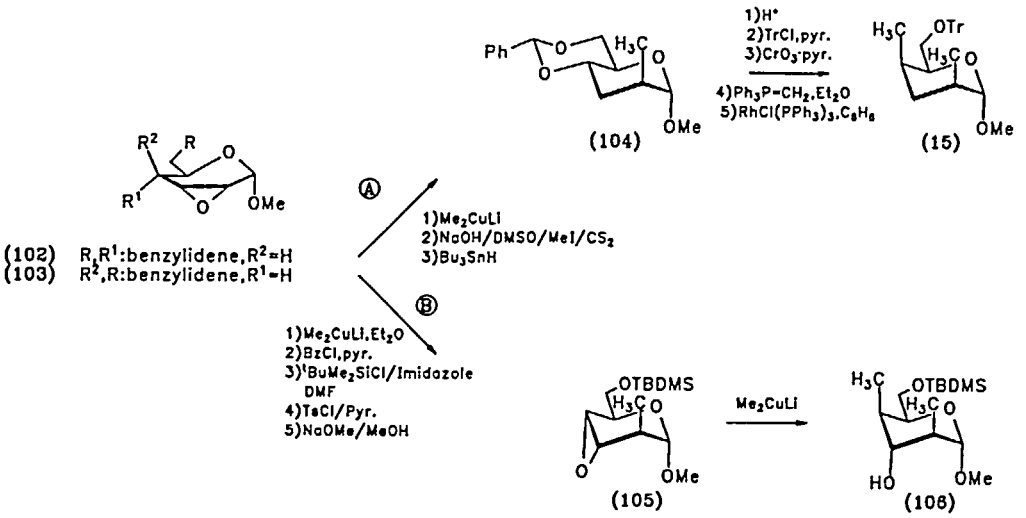
Syntheses of the European elm bark beetle (*Scolytus multistriatus Marsham*) aggregation pheromones (cf. § 2.1.) have been achieved by various groups following different approaches, starting with either enopyranosides or anhydropyranosides. The former starting materials have been obtained by chemical modifications on D-glucose, the latter being available from levoglucosenone already furnished with the 1,6-anhydro bridge.

Fraser-Reid and coll.[50] started their synthesis with the enone **96** representing a most reactive Michael acceptor system. 1,4-Addition of methyllithium in the presence of a copper reagent specifically gave the axially configurated methyl branched derivative **97** in 94% yield. Carbonyl olefination yielded the *exo*-methylene group at *C*-2 in **98**, which was subsequently hydrogenated over a nickel catalyst to give the *C*-2 methyl branched products **99a** and **99b** in a 9:1 ratio, respectively. A different approach [51] afforded the axial methyl branch at *C*-2 by addition of lithium dimethylcuprate on the corresponding hex-2-eno-4-

uloside. Olefination of the *C*-4 keto function and then hydrogenation afforded 2.3:1 mixtures of equatorial/axial *C*-4 methyl group epimers, respectively, the latter being the desired intermediate in the synthesis outline.

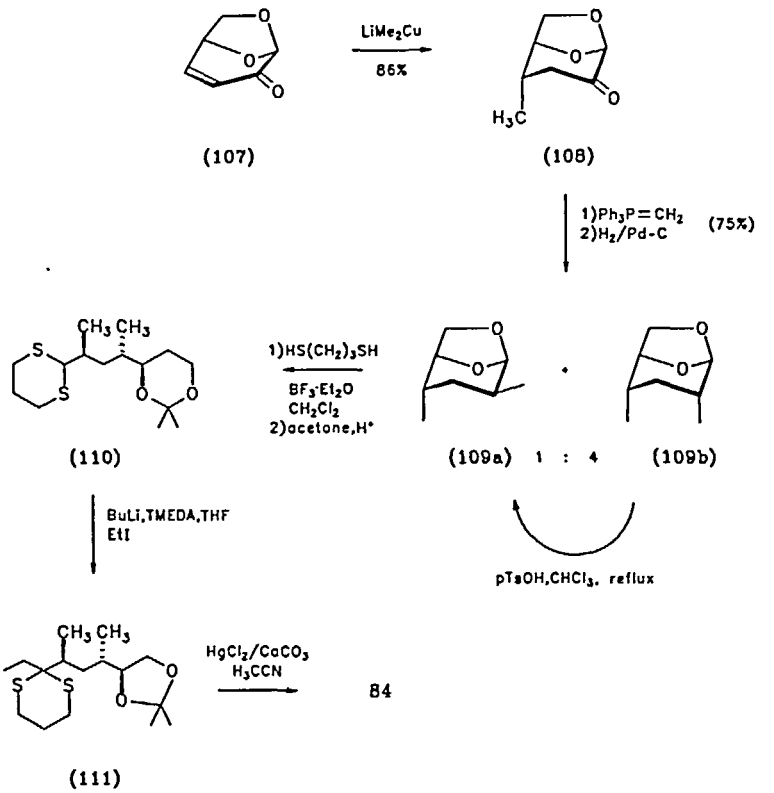
Further processing is depicted in scheme 18: detritylation and benzylation followed by deglycosylation yielded the 6-*O*-benzyl-2,3,4-trideoxy-2,4-di-*C*-methyl-D-*lyxo*-hexopyranose (**100**). After Grignard addition of vinylmagnesium bromide on the anomeric hemiacetal function, the open chain derivative **101** was subjected to an allylic oxidation with manganese dioxide to give an allyl ketone. The hydrogenation only affected the *C*=*C* bond, giving the corresponding saturated ketone which lead to the expected α-multistriatin **83** spontaneously through cyclo-ketalization.

C-alkylation may also be achieved by highly regio- and stereoselective Me_2CuLi attack on sugar epoxides as it has been carried out in both the syntheses by Lukacs and coll.[52] or Sum and Weiler[53,54] as depicted in scheme 19:



Scheme 19: Synthesis of the intermediates **15** and **106**

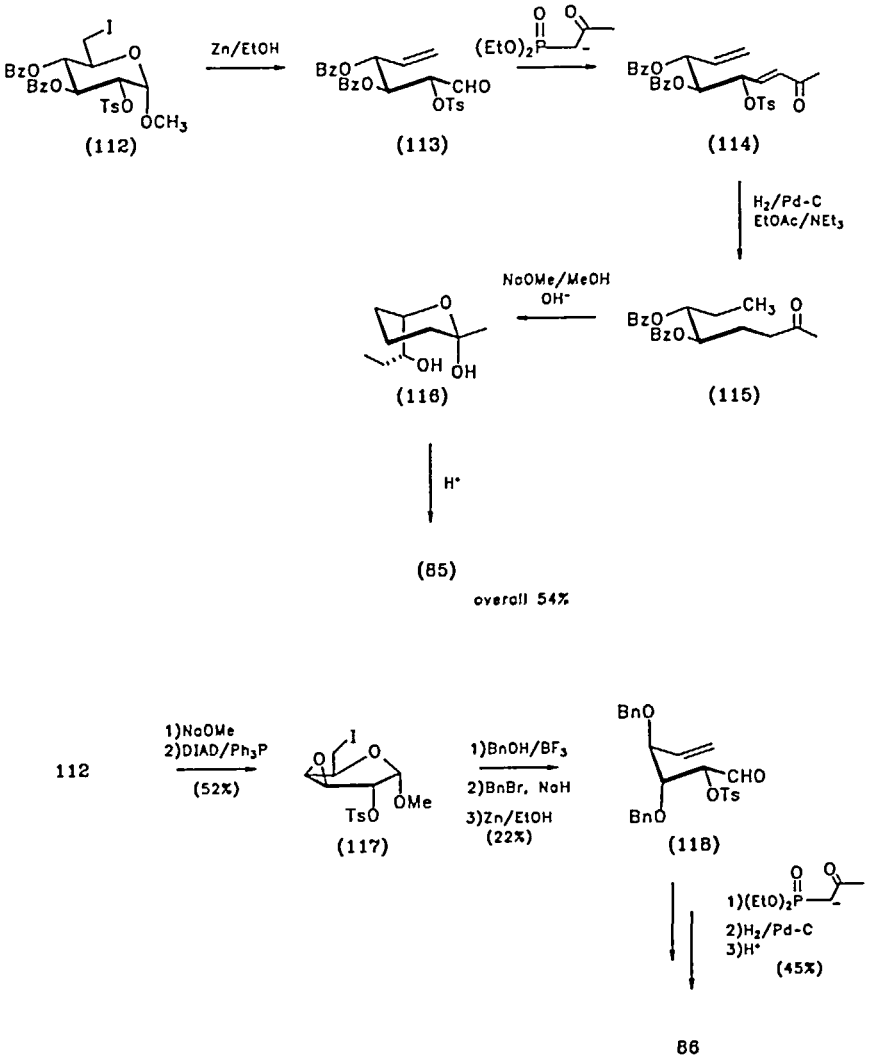
The attack on the *gulo*- and *gluco*-configurated epoxides **102** and **103** was in strict accordance with that on the *manno*-analogue **5** (cf. ref. 14, § 2.1). However, with the *gulo*- and *gluco*-epoxides **102** and **103** nucleophilic attack afforded the axial configurated *C*-2 methyl branched derivative **104** after Barton-McCombie deoxygenation. The *C*-4 position was alkylated either following path A via Wittig olefination of the corresponding 4-uloside to produce **15**,[54] or following path B, which required several extra steps for the preparation



Scheme 20: Synthesis of δ-multistriatin (**84**) from levoglucosenone

of the suitably configurated 3,4-epoxide **105** before a final cuprate addition could be applied. Protection of OH-3, deblocking of 4 and 6 positions, selective silylation at OH-6, tosylation, base catalyzed ester cleavage, and epoxidation unfavourably lengthen the reaction sequence towards the *ido*-configurated pyranoside **106**.[52] After a first approach from di-*O*-isopropylidene-D-*glycero*-triose towards α-multistriatin,[55] Mori et al.[18,56] published a short route synthesis for (-)-δ-multistriatin from levoglucosenone **107**.

In accord with the postulated rules for nucleophilic additions to some carbohydrate Michael-acceptor systems[57,58,59] lithium diethylcuprate yielded the axially methylated compound **108** as a single isomer in almost 86% yield. A Wittig reaction and subsequent hydrogenation of the exocyclic double bond gave a mixture of equatorial and axial *C*-2 epimers in a 1:4 ratio (**109a**:**109b**), respectively. The latter was isomerized under acidic conditions to the thermodynamically favoured, equatorial derivative **109a**, which in turn was subjected to a Lewis acid mediated dithio-acetalization, followed by protection to the 5,6-*O*-isopropylidene compound **110**. A two step reaction sequence from **110**, i.e. Corey-



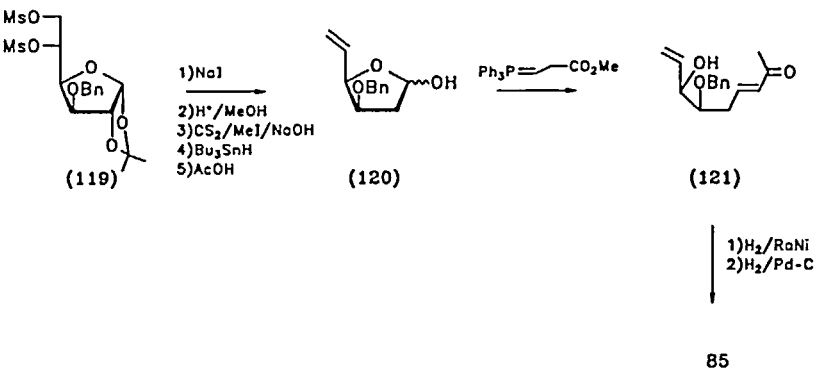
Scheme 21: Synthesis of the western pine beetle pheromones, (+)-exo-brevicomin (85) and (-)-exo-brevicomin (86)

Seebach chain elongation to **111**, and dithioacetal cleavage with transacetalation gave a 95:5 mixture of (-)-δ-multistriatin **84** and its *C*-4 epimer. Another approach to (-)-α-multistriatin has been disclosed recently by J. Stanek Jr.[60] starting with periodate cleavage of levoglucosan and including a nitromethane condensation. (cf. § 6.2, refs. 83-85)

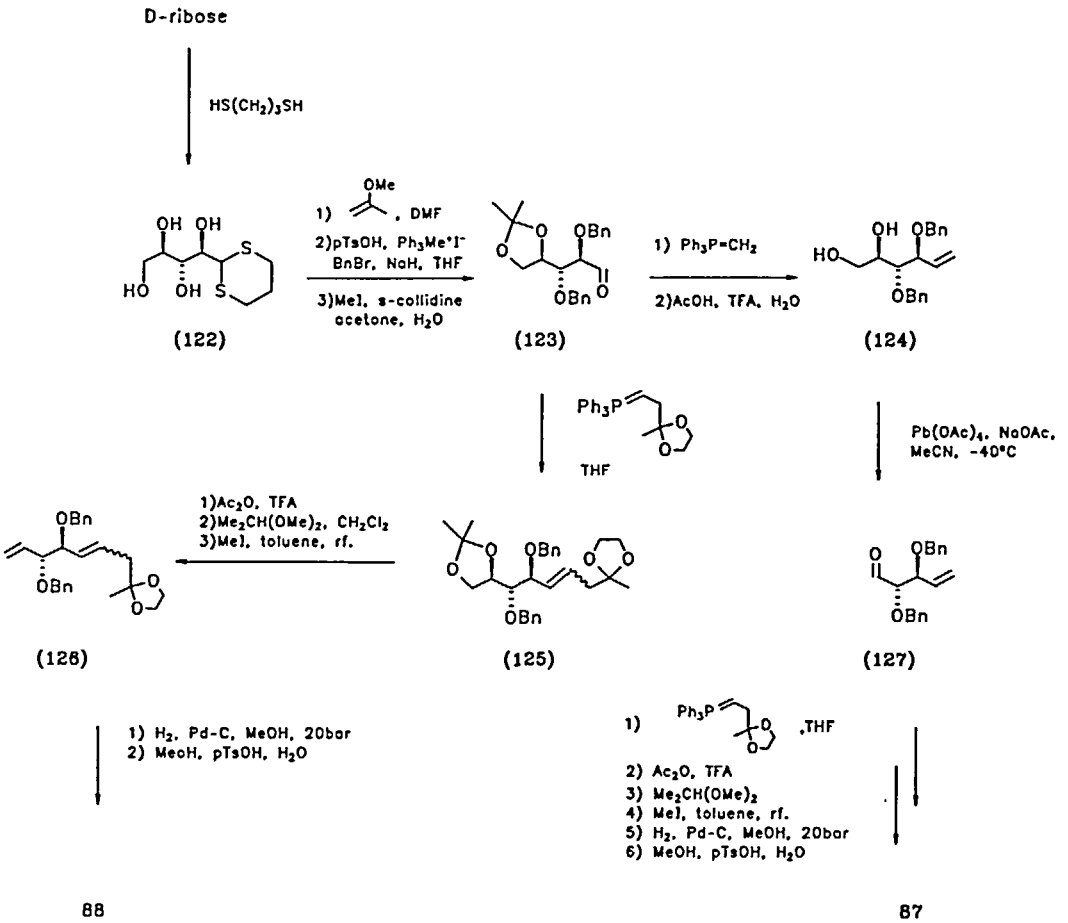
5.3.1. (+)-(1*R*,5*S*,7*R*)-*exo*-Brevicomin (85) and its (-)-(1*S*,5*R*,7*S*)-enantiomer (86): 7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1.]octanes

The western pine beetle, *Dendroctonus brevicomis Le Conte* (*Coleoptera, Scolytidae*) emits a bouquet of pheromones comprising a mixture of both (+)-, and (-)-*exo*-brevicomin enantiomers. Like the multistriatins, the brevicomins may be regarded as completely deoxygenated sugar derivatives with a 1,6-anhydro bridge; the latter, however, display an additional ethyl group located on the new chiral center *C*-7. Two major concepts have been followed for the synthesis of the brevicomins, either by making use of the stereochemistry of centers 3 and 4 in D-glucose and a chain extension at the anomeric position, or through a chain extension at the *C*-5 of D-xylose.[61] The former approach, however, includes fewer steps with a higher overall yield. Ferrier et al.[62,63] published syntheses for both enantiomers, starting from the same precursor, methyl 3,4-di-*O*-benzoyl-6-deoxy-6-iodo-2-*O*-*p*(toluenesulfonyl)-α-D-*gluco*pyranoside (**112**). The 6-iodo precursor **112** was either converted directly into the olefinic aldehyde **113** or into the epoxide **117** via de-*O*-benzoylation and a Mitsunobu type epoxidation. Subsequent Lewis acid mediated epoxide cleavage with benzyl alcohol, benzylation of the adjacent hydroxyl group and reductive dehalogenation / fragmentation gave **118**. Further conversion of both **113** and **118** was different only with respect to the ester and ether type protective groups. Compound **113** was subjected to a Wittig-Horner reaction, which utilizes a much less basic reagent than a Wittig reaction, and thus avoids olefination via the loss of benzoic acid at *C*-3. Reduction of **114** gave the saturated ketone **115** and debenzoylation by Zemplén transesterification yielded predominantly the β-pyranose **116**. Acid-catalyzed ketalization produced the anhydro bridge as shown in **85**. In contrast the enantiomeric compound **86** was formed under acidic conditions after hydrogenation of its precursor **118**.

Fraser-Reid et al.[64] report another synthesis of **85** from the 1,2-*O*-isopropylidene glucose derivative **119** as depicted in scheme 22:



Scheme 22: Alternative approach to compound **85**



Scheme 23: Synthesis of the aggregation pheromones (+)-endo- and (-)-endo-brevicomin, **87** and **88**

The generation of the exocyclic double bond via a modified Tipson-Cohen reaction[22] was followed by de-*O*-isopropylidenation, methyl glycosidation, *C*-2 deoxygenation and acidolysis to yield the eno furanose **120**. This, in turn, was extended to give the unsaturated ketone **121**, which was hydrogenated to the (+)-*exo*-brevicomin (**85**) stereoselectively and in 21% overall yield.

5.3.2. (+)-(*1R,5R,7S*)-*endo*-Brevicomin (87) and its (-)-(*1S,5R,7R*)-enantiomer (88)

These *C*-7 epimers of the *exo*-brevicomins are biologically inactive towards *Dendroctonus brevicomis*; however, they can act as an aggregation pheromone for another

scolytid, *Dryocoetes autographus Ratz* (*Coleoptera, Scolytidae*).[65] Both enantiomeric *endo*-brevicomins (**87**) and (**88**) have been synthesized by Scharf and coll. from D-glucose and L-arabinose, respectively.[66,67]

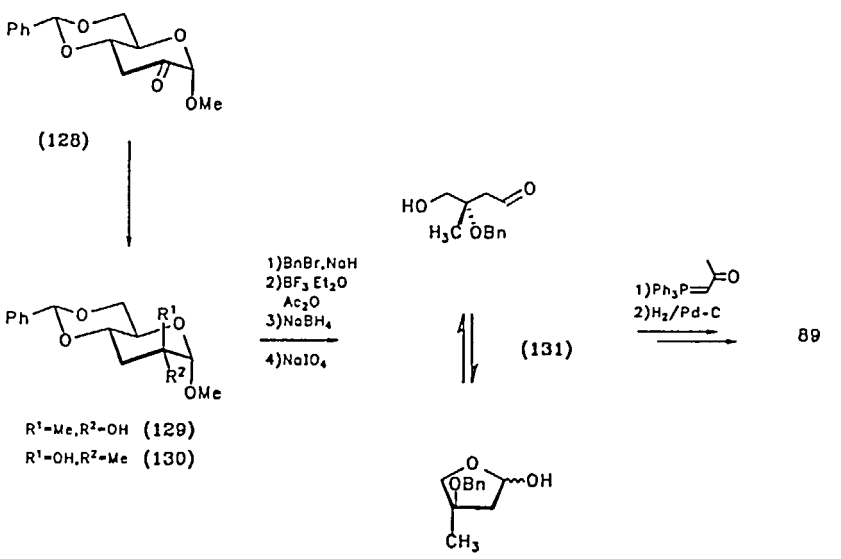
More recently, Redlich and coll.[68] described a more straightforward synthesis originating from D-ribose, offering the possibility of forming either enantiomer. D-Ribose was thus temporarily blocked as its dithioacetal **122**. As both the terminal hydroxyl groups are prone to isopropylidenation, the secondary *C*-2 and *C*-3 hydroxyl groups were protected as their benzyl ethers, before the dithioacetal was removed. It is from the intermediate **123** that the synthesis divides. The nonene acetals (**125**) were formed by a Wittig reaction with **123**, and the isopropylidene group replaced by a dimethylformamide acetal via acidolysis and reaction with DMF dimethylacetal. The resulting intermediate upon quaternization with methyl iodide, following the procedure of Hanessian and coll.[69] eliminated both the oxygen atoms to give unsaturated **126**. Hydrogenolysis cleaved the benzyl ether groups and yielded the nonane acetal, which upon acidic treatment gave the intramolecular acetal (-)-*endo*-brevicomin (**88**), overall in around 6% yield. On the other hand, when the chain of **123** was extended at *C*-1 by the reaction with methylene-triphenylphosphorane and cleaved between the former *C*-4 and *C*-5 via a deprotection / diol cleavage procedure, the pentene aldehyde **127** was formed. Applying the Wittig reaction used to convert **123** to **125**, a diene was formed.

This synthetic trick serves to produce a substrate for chain extension with inverted stereochemistry, although it is in fact a simple inversion of numbering. That benzyloxy-substituted *R*-configurated carbon alpha to the carbonyl atom served either as the *C*-5 in **88** or as *C*-1 in **87**, the opposite being true for the *S*-configurated one. Employing the conversion described above **127** lead to the (+)-*endo*-enantiomer **87**.

5.4. (-)-(*1S,5R*)- and (+)-(*1R,5S*)-frontalin (89 and 90): 1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octanes

(*S*)-(-)Frontalin **89** was the aggregation pheromone of the southern pine beetle, *Dendroctonus frontalis Zimm.* (*Coleoptera, Scolytidae*). This beetle belongs to the same genus as *D. brevicomis* does and the pheromone produced shows a close structural analogy with the *exo*-brevicomins **85** and **86**.

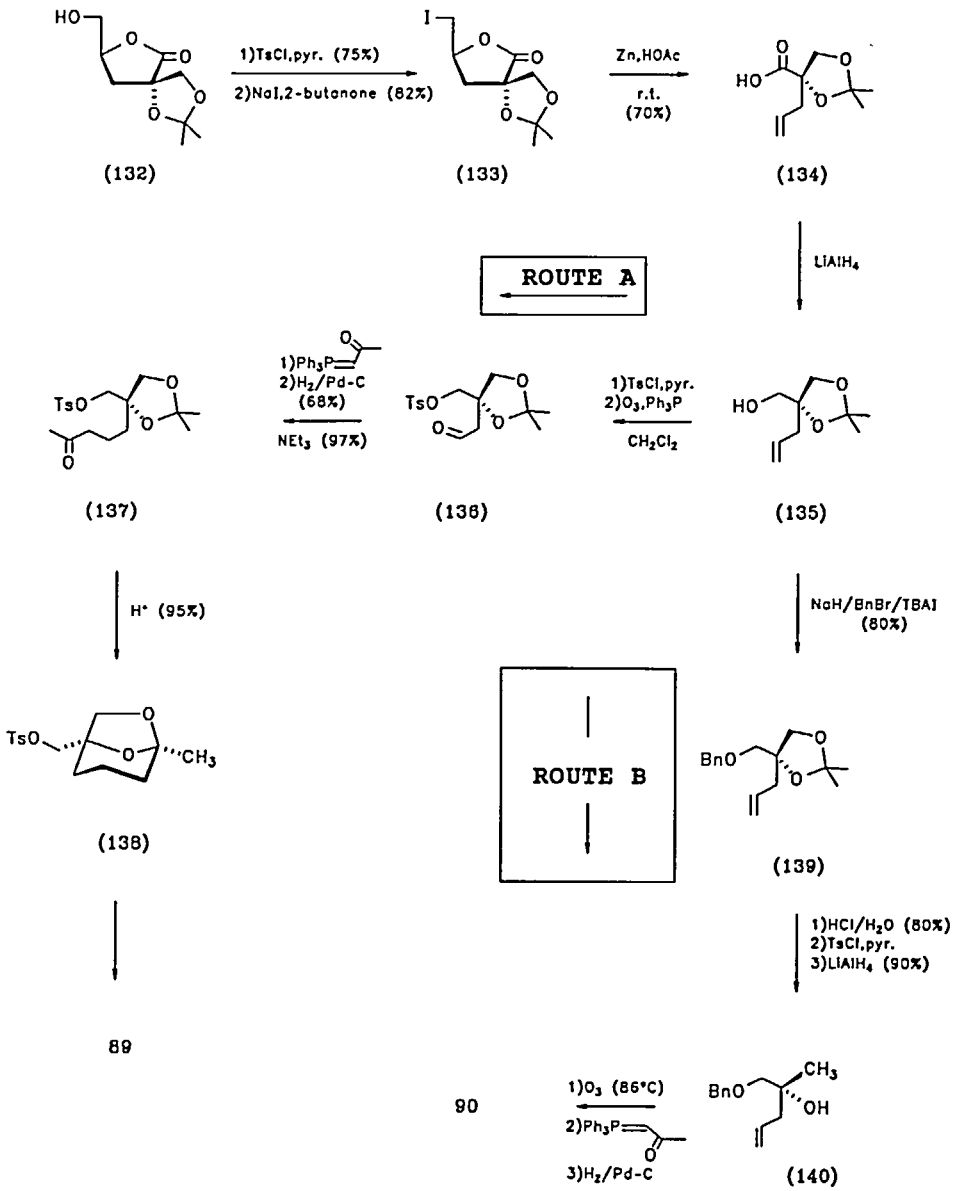
The approaches taken by Fraser-Reid et al.[70,71] (scheme 24) were designed to start from methyl 4,6-di-*O*-benzylidene-3-deoxy-α-D-*erythro*-hexopyranoside-2-ulose (**128**). Various methods gave different ratios of either the axial **129** or equatorial **130** epimer; as the former was the exclusive product of a Grignard reaction the latter was obtained as the only product by oxymercuration - demercuration on the exocyclic olefin derived from **128**. The capability of synthesizing either one, or the other enantiomer of frontalin was at hand. Scheme 24 outlines the route in general, here shown for **89**, the (-)-(*1S,5R*)-enantiomer: without purification the tertiary alcohol **130** was benzylated, the acetalic positions were cleaved, acetylation followed by sodium borohydride reduction and sodium periodate cleavage yielded e.g., **131**. A Wittig reaction was performed on this τ-hydroxy aldehyde



Scheme 24: Synthesis of (*S*)-(-)-frontalin, the southern pine beetle pheromone, from a 3-deoxy-2-uloside (**128**)

and subsequent hydrogenation / hydrogenolysis resulted in the formation of the target molecule **89**, shown to be (-)-(*1S,5R*)frontalin.

Taking advantage of the well known alkaline degradation of lactose, Monneret et al.[72,73] developed the use of an original carbohydrate precursor, α-D-isosaccharino-1,4-lactone **132** in enantiospecific synthesis. Like Fraser-Reid these workers prepared both the enantiomers **89** and **90**, the precursors of which were obtained in four steps and in 30% yield. By a tosylation / halogenation step, the iodo compound **133** was obtained and served as the key intermediate for the non-cyclic derivative **134**, which was available by following a reductive fragmentation procedure described by Bernet and Vasella.[74] This allowed the transformation of lactones bearing terminal halogen substituents into unsaturated carboxylic acids. Reduction by lithium aluminum hydride afforded a suitably configurated primary alcohol **135**. Following route A, tosylation and ozonolysis gave a 64% yield of **136** after reductive work-up in the presence of triphenylphosphine. Although this compound, as its non-tosylated analog, (*3R*)-3,4-*O*-isopropylidene-3,4-dihydroxy-3-hydroxymethylbutanal, was available in just a handful of steps by simple hydride reduction and sodium periodate cleavage from **132**, this approach was not followed further on by the authors, possibly due to difficulties in the hydride reduction and possible isomerizations at *C*-2 during the following steps. The Wittig reaction on **136**, and subsequent hydrogenation gave the methyl pentyl ketone **137** in 66% yield. After acid-catalyzed deprotection,

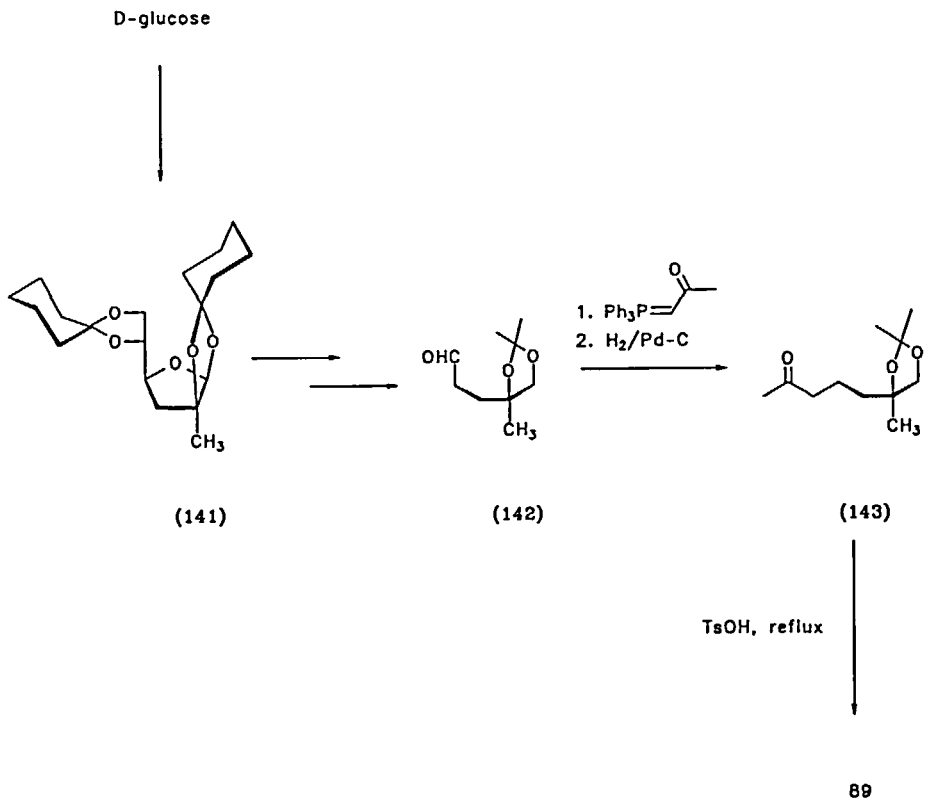


Scheme 25: Synthesis of (+)-frontalin from α-D-isosaccharino-1,4-lactone

intramolecular cyclization was observed and thus, after deoxygenation via hydride attack on the tosylate **138**, the target molecule was attained. The corresponding (*1R,5S*)-enantiomer **90** was obtained following route B, depicted in Scheme 25. Here, acetalization and ring closure ultimately occur by attack of the primary hydroxy group. Thus,

benzylation of **135** yielded the ether **139**, then de-*O*-isopropylidenation and a tosylation/reduction step on the primary hydroxy group generated the methyl branch. Further processing of **140** was similar to that employed for **136**, however cyclic ketal formation occured subsequently after hydrogenation to yield (*R*)-(+)-frontalin in three steps (69%).

Starting from D-glucose another synthesis of (*S*)-(-)-frontalin has been published by Ohrui and coll.[75] which was briefly outlined in Scheme 26:

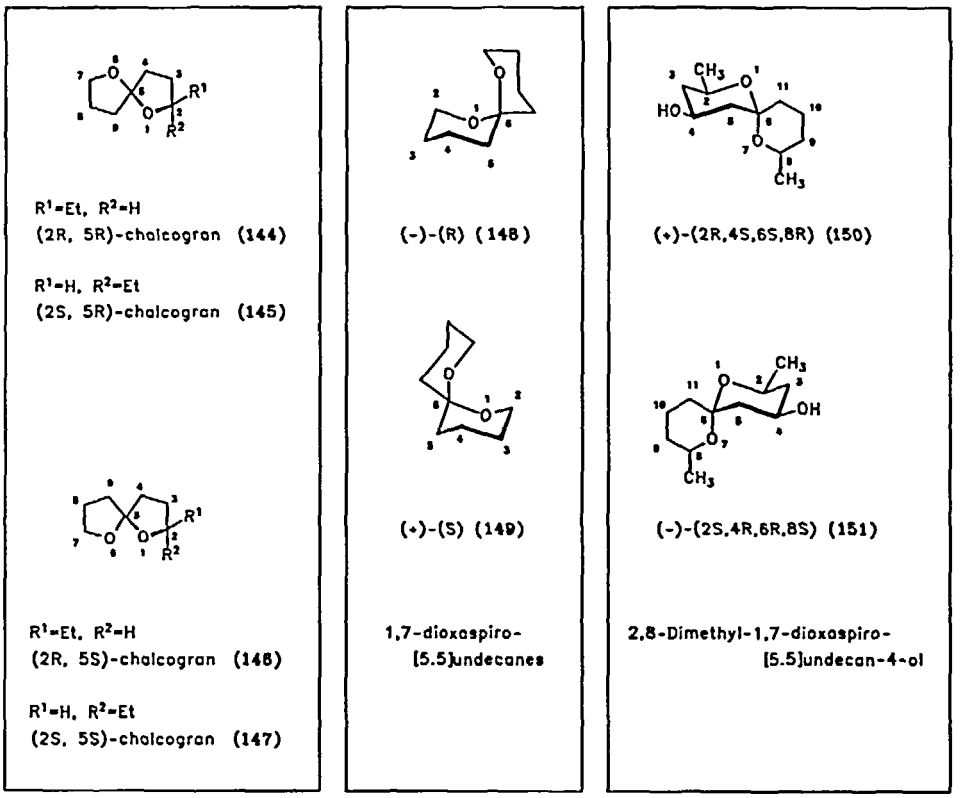


Scheme 26: Alternative route towards (*S*)-(-)-frontalin from D-glucose

Key intermediate **141** was degraded by classical methods to aldehyde **142**, which in turn was elongated and hydrogenated to give **89** after 12 steps from **143**.

6. Spiro compounds

Spiroketals have been identified as components of insect pheromones: such chiral targets have raised important synthetic efforts in the carbohydrate field.

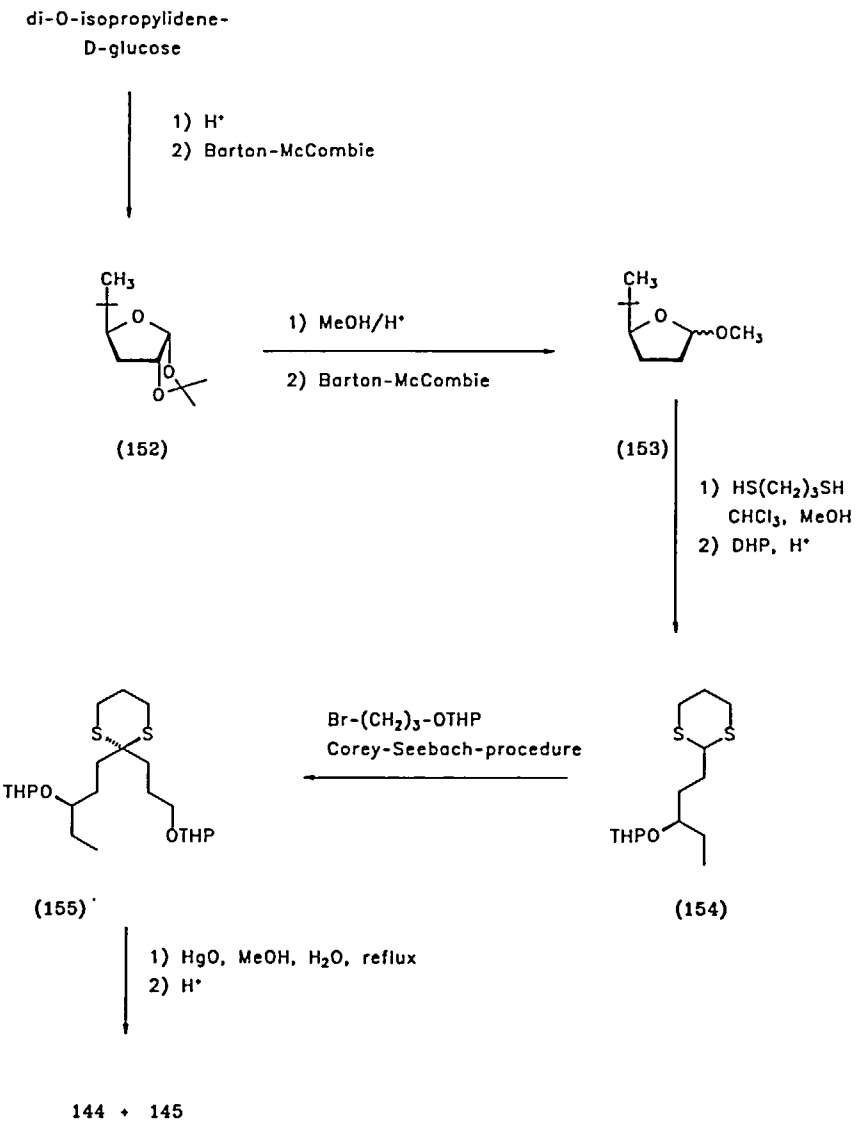


Scheme 27: Spiroketal pheromones

6.1. Chalcograns (2-Ethyl-1,6-dioxaspiro[4.4]nonanes) 144 - 147

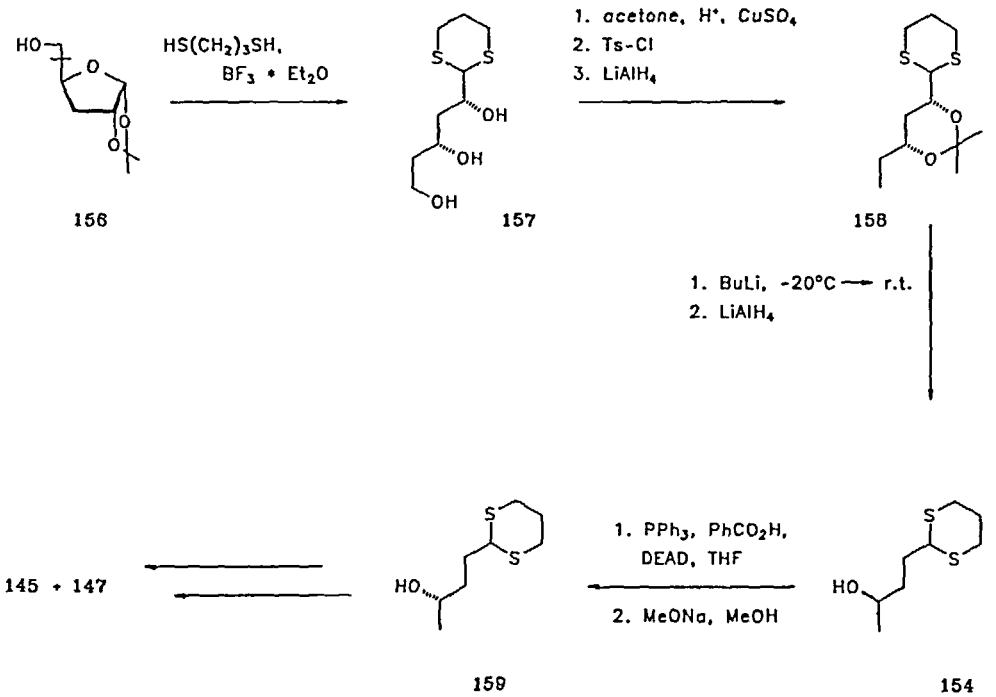
The aggregation pheromone of the bark beetle *Pityogenes chalcographus L. (Coleoptera, Scolytidae)* was a mixture of four naturally occuring stereoisomers **144 - 147.** All of these have been synthesized from a unique precursor, 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose by Redlich.[76,77] The basic idea in the synthetic plan recognizes that only two chiral centers are present in the chalcogran series, the spiro carbon atom being established automatically by ketalization. Thus, all syntheses in this series produced a diastereomeric mixture, the ratio of which was due to a marked anomeric or "double anomeric" effect,[78] forcing the oxygen atoms of each ring into a preferred axial configuration.

By extensive use of the Barton-McCombie reaction the highly deoxygenated furanoid system **153** was obtained via the ketal **152.** After preparation of the dithioacetal-THP-ether **154,** the molecule was suitably protected for Corey-Seebach's chain elongation to give



Scheme 28: Synthesis of the bark beetle pheromones, chalcograns **144** and **145**

the bis-THP ether **155**. This, in turn, was desulfurized by means of mercuric oxide and subjected to intramolecular ketalization to give both diastereoisomers **144** and **145**, respectively, in 30% overall yield. In order to circumvent the Barton-McCombie procedure, another approach was followed in the diastereomeric series. Direct dithioacetalization of **156** yielded the dithiane **157**, representing a D-*erythro* configuration.



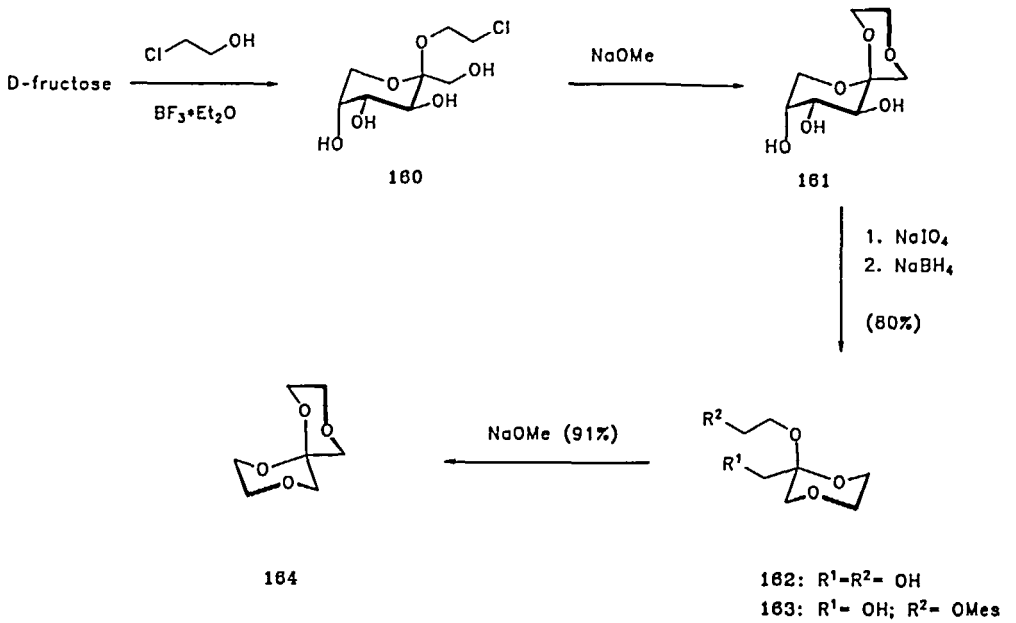
156 157 158 159 154

Scheme 29: Alternative approach towards the chalcograns **145** and **147**

Keeping thermodynamical control, the isopropylidenation afforded a 2,4-*O*-ketal **158**; this again was an ideal precursor for the ketene dithioacetal deoxygenation (cf. § 3.2.) yielding the alcohol **154** in almost 70%. Not only was the yield of **154** (R=THP) twice as high as in the synthesis through compound **153**, but avoiding the xanthate related steps was also favourable concerning environmental considerations. Further processing of **130**, which included a Mitsunobu inversion, provided easy access to the 2-(*S*) configuration, as shown in compound **159**. Finally, the diastereomers **145** and **147** were obtained in yields comparable to those of their configurational counterparts.

6.2. 1,7-Dioxaspiro[5.5]undecanes **148** and **149**

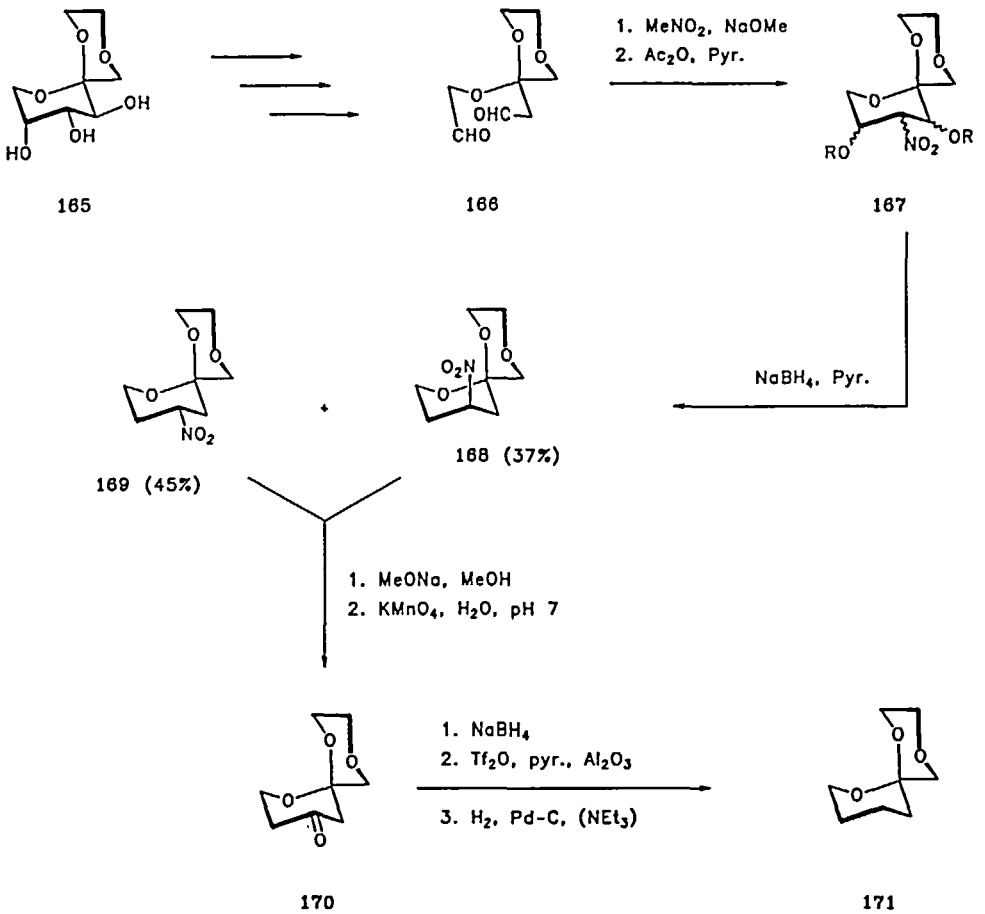
This spiroketal was the major component in the pheromone bouquet of the female olive fruit fly, *Dacus oleae Gmelin* (*Diptera, Trypetidae*). The structures display a C2 symmetry, the chirality being solely due to the spiro ring junction.[79] Stereochemical control of the spiro center was therefore the major difficulty to be encountered in such a synthesis. Approaches to a series of enantiomerically pure spiro dioxanes as model compounds have been proposed by Richardson et al.[80,81] by transducing the chirality of *C*-2 of D-fructose into the latter spiro-atom.



Scheme 30: Synthesis of the model spirobidioxane **164** from D-fructose

The β-glycoside **160** was formed in 80-90% by Lewis acid catalyzed glycosidation of D-fructose with 2-chloroethanol. This gave quantitatively the crystalline spiro-anhydride **161** after basic treatment. Subsequently sodium metaperiodate cleavage to the dialdehyde, followed by immediate reduction yielded the diol **162** with the desired chiral center (80% yield). By selective monomesitylene sulfonylation, derivative **163** was then formed and by smooth cyclisation the model spirobidioxane was at hand. A more recent route towards an enantiomerically pure trioxaspiro[5.5]undecane from D-fructose[82] takes advantage of the nitromethylation first described by Fischer and developed later by Baer et al.[83,84]

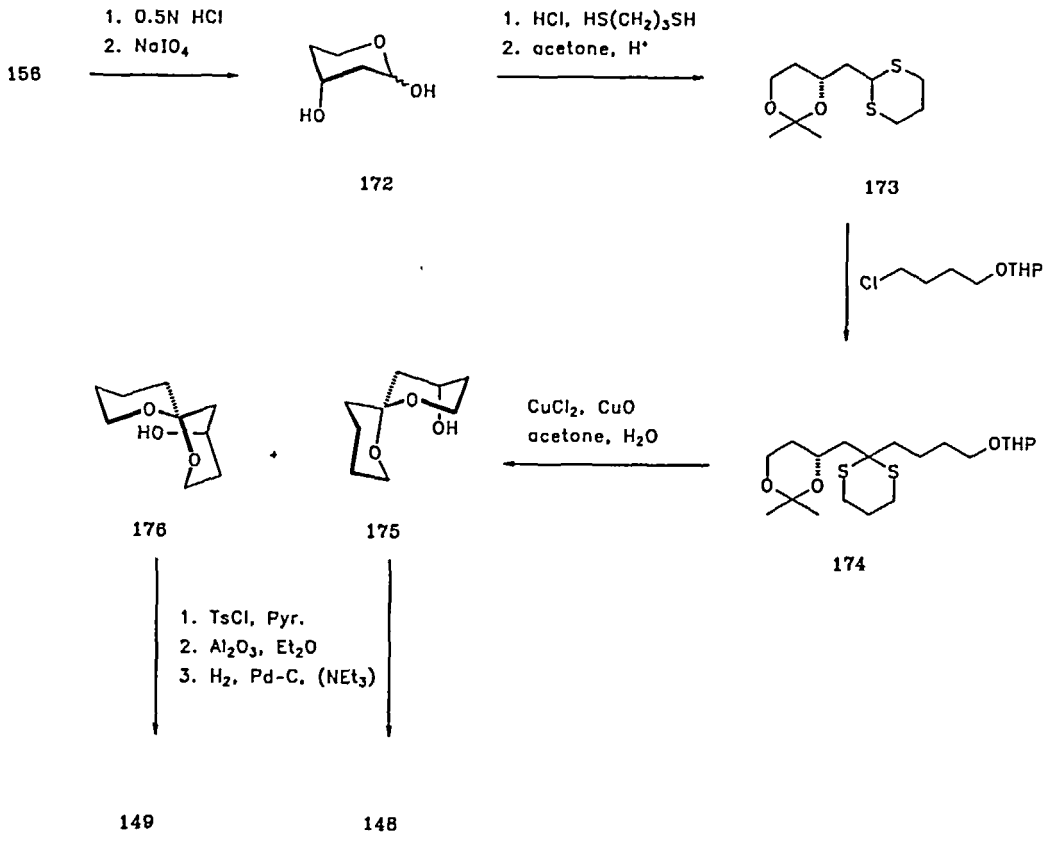
After the dialdehyde **166** was obtained from **165** in similar fashion to the method elaborated in the model synthesis, it was subjected to nitromethane condensation in the presence of sodium methoxide; the trioxaspiro-acetates **167** being formed in 30% yield. Deoxygenation with sodium borohydride at the carbon atoms neighbouring the *C*-nitro site, occured via the corresponding nitroalkenes and *aci*-nitro salts to give the bisdeoxynitro derivatives. After acidification by Amberlite IR 120 (H^+) resin a diastereomeric mixture of compounds **168** and **169** was formed, each in nearly comparable amounts. Whereas radical reduction of the nitro group by means of tributylstannane failed, the oxidative removal was accomplished by transformation by sodium methoxide into the corresponding nitronate, which underwent spontaneous oxidation in the presence of potassium permanganate to



Scheme 31: Synthesis of **171** via the nitromethane addition

give enantiomerically pure 1,4,7-trioxaspiro[5.5]undecan-10-one **170** in 75% yield. Reduction of the keto group by sodium borohydride followed by trifluoromethanesulfonylation gave a mixture of both diastereomers, which after hydrogenation afforded enantiomerically pure (-)-(*R*)-1,4,7-trioxaspiro[5.5]undecane (**171**), a 4-oxa-isoster of **148**. The sole carbohydrate based synthesis of the original pheromone was published by Redlich and Francke,[85] where the deoxygenated ketal **156** (cf. § 6.1.) was subjected after hydrolysis to sodium periodate cleavage yielding 2,4-dideoxy-D-*glycero*-pentopyranose **172**.

After thioacetalization and protection via **173** a chain extension provided the THP derivative **174**. Desulfurization with $CuCl_2/CuO$ in an acetone/water mixture initiates spiroketalization yielding **175** and **176**,[86,87] both of which can easily be separated via silica

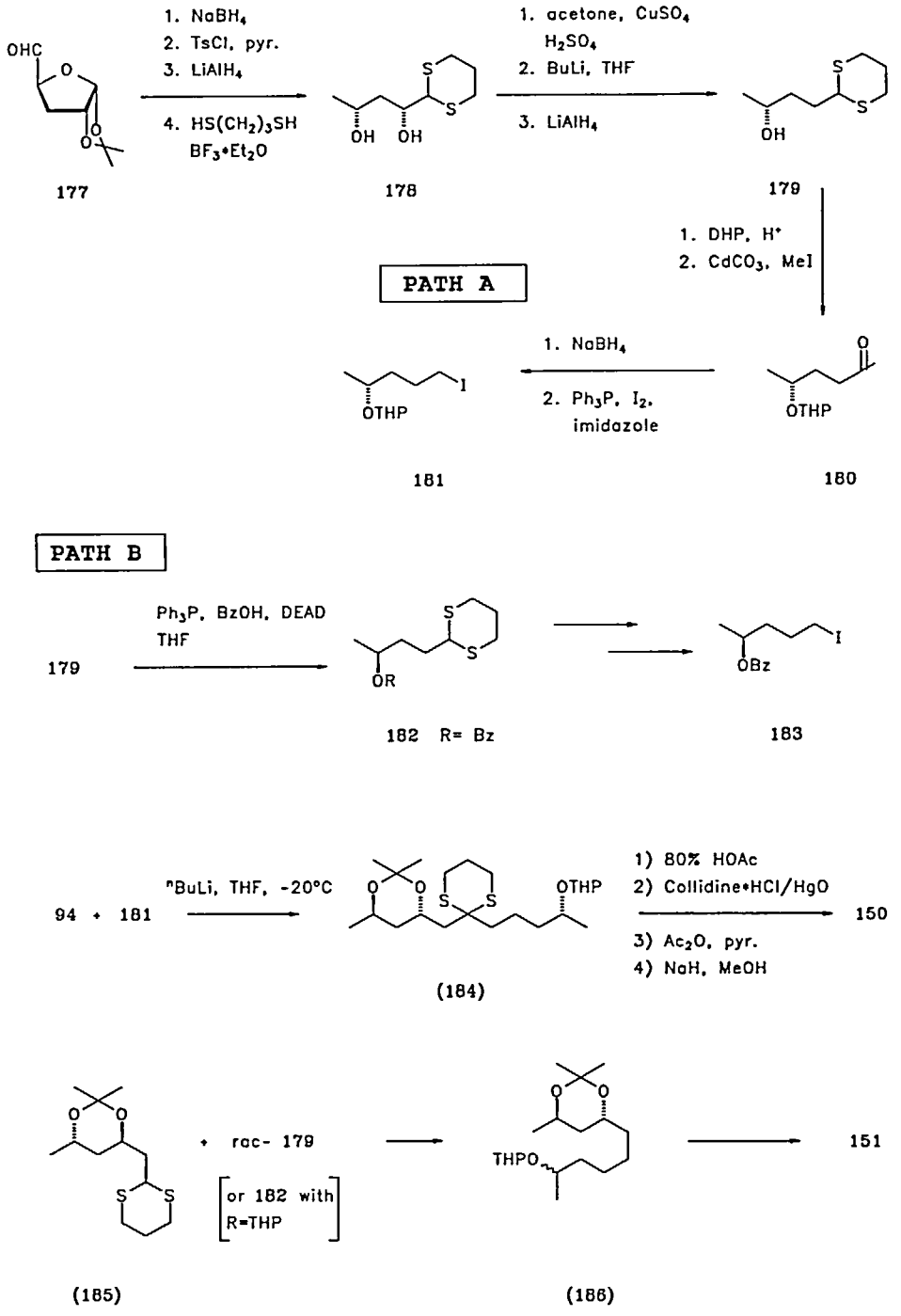


Scheme 32: Synthesis of the original pheromones of the olive fruit fly, **148** and **149**

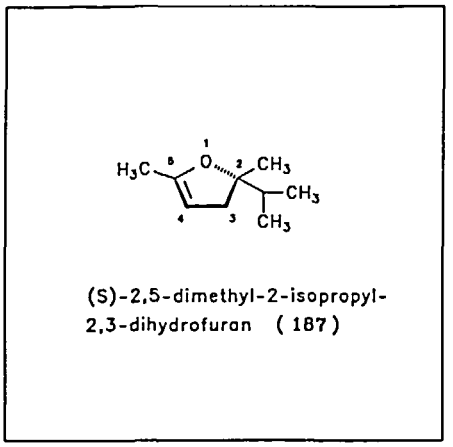
gel chromatography. The latter compounds were then converted through tosylate-induced elimination and subsequent hydrogenation into either the (*R*)- or the (*S*)- enantiomer, **148** or **149**, respectively.

6.3. (*2R,4S,6S,8R*)- and (*2S,4R,6R,8S*)-2,8-Dimethyl-1,7-dioxa-spiro[5.5]undecan-4-ol (**150** and **151**)

The sand bee *Andrena wilkella* (*Hymenoptera, Andrenidae*) emits a pheromone bouquet in which stereoisomeric 2,8-dimethyl-1,7-dioxaspiro[5.5]undecanes predominate. Among the minor constituents, hydroxylated structures, including **150** and **151**, have been identified. The rationale for picking this pair of enantiomers out of a group of eight possible stereoisomers was led by two basic assumptions; first the double anomeric effect

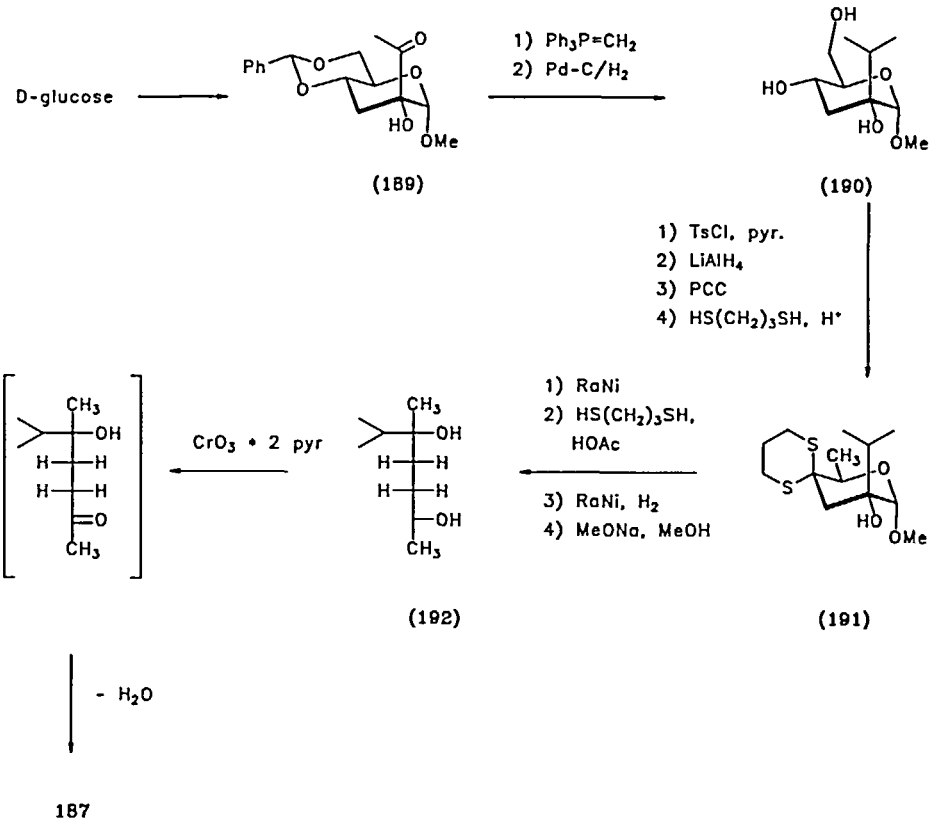


Scheme 33: Synthesis of the sand bee pheromones **150** and **151**



Scheme 34: Miscellaneous pheromones **187** and **188**

(cf. § 6.1.) directs the ring oxygens in an axial position towards each other and for this particular reason the open chain precursor has to have the *threo*-configuration. The second assumption is that the hydroxyl group at *C*-4 must be in the thermodynamically favoured, equatorial position to avoid 1,3 diaxial interactions. The synthesis by Redlich and coll.[88] makes use of synthetic equivalents already employed in the synthesis of 1,3-dimethyl-2,9-dioxabicyclo[3.3.1]nonane (**82**) (cf. § 5.1). The electrophilic counterparts have to be synthesized, to obtain racemic **179** or the pure enantiomers **181** and **183**, respectively. The aldehyde **177** was subjected to a sequence, already described in Scheme 29, in order to achieve the deoxygenation of the *C*-5 carbonyl and dithioacetalization at the anomeric position. The diol **178** was blocked and then converted in 77% yield to the deoxygenated alcohol **179**, a key intermediate; path A lead to (*R*)-configurated **181** via aldehyde **180** and included dethioketalization, carbonyl reduction and iodination through an Appel reaction. Path B led to the enantiomeric benzoate **182**, which was converted analogously to yield the (*S*)-configurated **183**. Both these blocked iodo-alcohols were appropriate precursors for a Corey-Seebach procedure, with either of the thioacetals **94** and **185**. The authors demonstrated this for the syntheses of compound **150**, of (*2R,4S,6S,8R*) configuration. The attachment of **94** to its acceptor **181** was achieved in 89% yield, the product of which, **184**, was further processed and purified via its acetate to give **150** in about 61% yield, a smooth cyclization occuring at the last step. Although there was access to the enantiomeric iodo-benzoate **181** the (*2S,4R,6R,8S*) pheromone **151** was prepared from **185** and a racemic mixture of tetrahydropyranylether derivatives of **179** and **182**, the latter easily obtained from 1,4-pentanediol. Compound **151**, derivatized as its acetate was easily separated by silica gel chromatography from the reaction mixture.



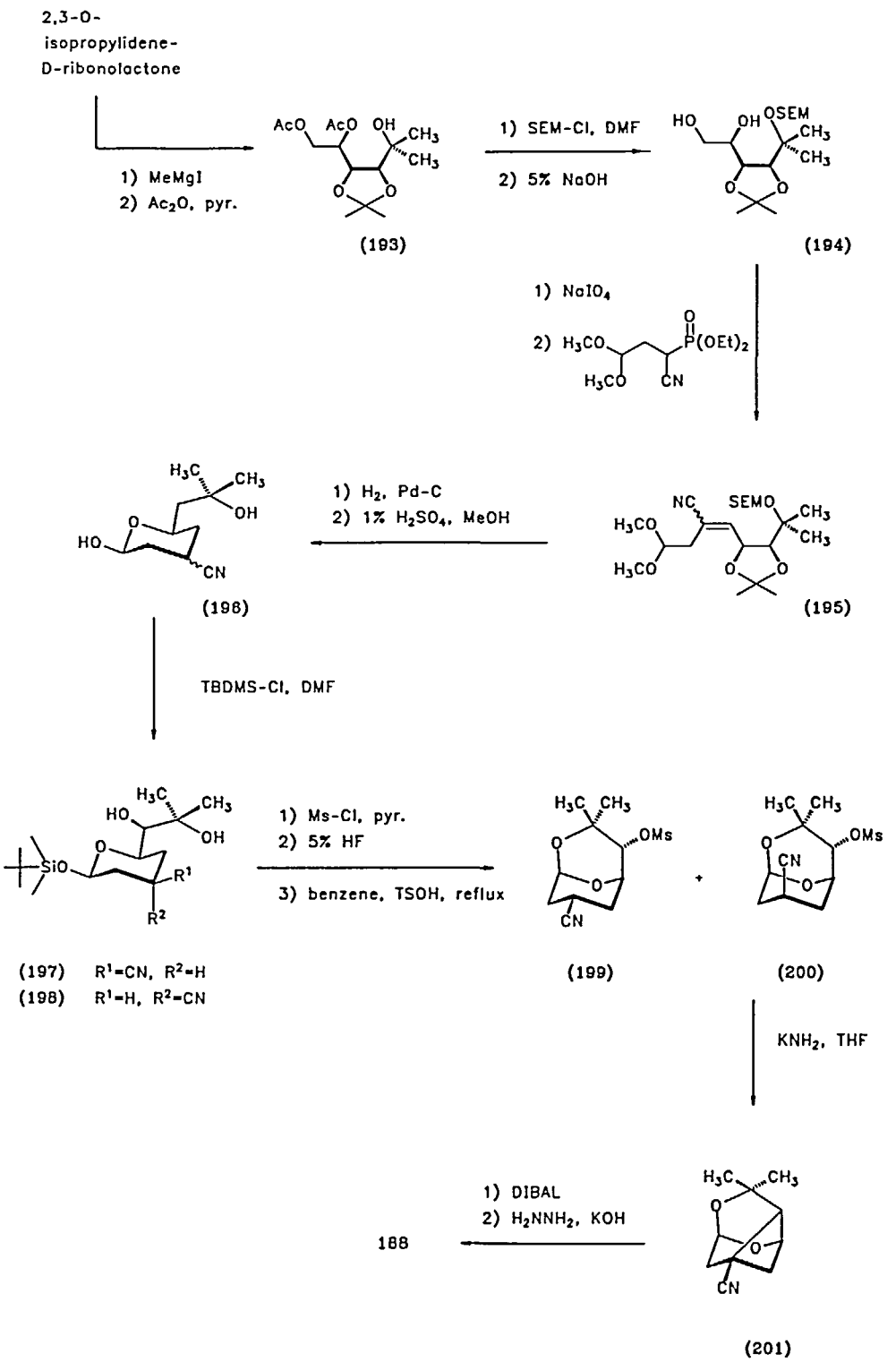
Scheme 35: Synthesis of the female wharf beetle pheromone **187**

7. Miscellaneous

7.1. (*S*)-2,5-Dimethyl-2-isopropyl-2,3-dihydrofuran (187)

With the exception of anhydroserricornin,[89] cyclic enol ether structures are rarely encountered as structural components of pheromones. The female wharf beetle *Hylecoetus dermestoides L.* (*Coleoptera, Lymexylonidae*) produces the unsaturated furanoid compound **161** which is doubly alkylated on the same carbon. An enantiospecific synthesis of this pheromone of a new type was achieved from D-glucose by Redlich et al. (cf. refs. 90a and 90b).

By application of the 1,3-dithiane procedure [90c] to a suitably protected 2-uloside, the branched chain keto derivative **189** was attained, and in turn converted by classical methods into the isopropyl side chain glycoside **190**. Selective tosylation at the primary



Scheme 36: Synthesis of (+)-lineatin (**188**), the pheromone of the female ambrosia beetle

hydroxyl group of **190** followed by hydride reduction, pyridinium chlorochromate oxidation and thioketalization of the intermediate uloside afforded the spiro-dithioketal **191** in 38% yield. Reduction of **191** with Raney nickel catalyst in ethanol, yielded the 4-deoxy compound, which was converted into the open chain dithioacetal. A second deoxygenation via the acyclic dithioacetal finally yielded the 1,3,4-trideoxydiol **192**. Cyclization to the (*S*)-2,5-dimethyl-2-isopropyl-2,3-dihydrofuran took place subsequently after dehydration of the transient hemiketal, resulting from the Cr^{VI} oxidation at *C*-5.

7.2. (+)-Lineatin: (*1R,4S,5R,7R*)-3,3,7-Trimethyl-2,9-dioxatricyclo[3.3.1.$0^{4,7}$]nonane (**188**)

(+)-Lineatin, a very unusual semiochemical that is a dioxatricyclononane with four chiral centers, is present in the aggregation pheromonal bouquet of the female ambrosia beetle, *Trypodendron lineatum Olivier*, a pest already mentioned in section 5.1. In the past decade, many syntheses of racemic lineatin have been published,[91] but very few that give the optically active form.

The first stereospecific chiral synthesis of (+)-lineatin (**188**) appeared recently [92] starting from D-ribonolactone, a precursor which provides two of the four chiral centers present in the structure. Grignard reaction on the lactone followed by acetylation yielded the tertiary alcohol **193** with the *gem*-dimethyl branch at the original *C*-1. The 3°-alcohol function was protected by silylation in order to prevent acetalization during the subsequent steps.

Thus, the terminally deblocked diol **194** was subjected to sodium periodate cleavage, establishing the aldehyde function at *C*-4, which readily coupled with the highly reactive cyano-phosphonate in a Horner-Emmons reaction. Unfortunately, no separation between the *E*- and *Z*-isomers of **195** could be achieved, and thus the mixture was hydrogenated, the isopropylidene protecting group removed, followed by cyclization to give **196**. The pyranoses **196** were the products of an intramolecular attack on the dimethylacetal by the hydroxyl group at *C*-5. Conversion of **196** into the *C*-4 (*tert*-butyldimethyl)silyl ethers **197** and **198** allowed an easy determination of their ratio (2:3) after chromatography. The entire mixture was methanesulfonylated and fluoride deblocking of the glycosidic *tert*-butyldimethylsilyl groups provided an anomeric mixture. The stereochemistry of the side chain, however, in refluxing benzene and the presence of *p*-toluenesulfonic acid directed formation of the anhydro-glycoside towards the well defined **199** as a major product in 33% yield after separation from **200**. The final cyclization to **201** between the nucleophilic carbon adjacent to the nitrile group and the mesylate was achieved in 69% yield by a favoured 4-*exo*-tet mechanism according to Baldwin's rules for ring closures.[93] Finally, the nitrile was reduced to a methyl group by a two step process; first aldehyde formation by diisobutylaluminum hydride reduction followed by a Wolff-Kishner reduction to generate the pheromone **188**. Although only two centers of chirality were maintained from the starting material, one being directed by the former *C*-3 in D-ribonolactone, the lack of stereoselectivity may be considered to be due to the hydrogenation of **195**. This, however,

constitutes the major drawback of the reaction scheme, and results in an overall yield of only 2.7%.

8. Conclusion

During the last decade, carbohydrates have proven to constitute particularly suitable starting materials for the enantiospecific synthesis of chiral pheromones for purposes of absolute structure identification and physiological assay. From this review emerges the fact that readily available common sugars have been specially used for the elaboration of the complex cyclic ketal structures mostly encountered in the harmful family of phytophagous *Scolytidae* (*Coleoptera*). However, recent synthetic efforts show that more diverse targets (including non cyclic chiral molecules) originating from other insect orders as *Diptera, Hymenoptera* and extensively studied *Lepidoptera* have been attained. One may prognosticate that significant developments will be made in this area of synthesis in years to come.

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