Synthesis of the pheromone components of the milkweed bug, *Oncopeltus fasciatus* and the spring hemlock looper, *Lambdina athasaria*

by

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Abstract

The syntheses of the potential sex and aggregation pheromone components of the milkweed bug, *Oncopeltus fasciatus,* and the chiral isomers of the sex pheromone component of the spring hemlock looper, *Lambdina athasaria*, are described.

A potential sex pheromone component of the milkweed bug, (E)-2, 7-octadienyl acetate was synthesized from lithium tetrahydropyranyloxypropynide coupling with 5-bromo-1-pentene, followed by removal of the protecting group and reduction of the triple bond and acetylation with acetic anhydride in pyridine.

(Z)-2-Octenal, (Z)-4-oxo-2-octenal, and (E)-4-oxo-2-octenal were found to be the potential aggregation pheromone components of milkweed bug. (Z)-2-Octenal was synthesized from lithium tetrahydropyranyloxypropynide coupling with 1-bromopentane followed by removal of the protecting group and reduction of the triple bond and oxidation with pyridinium dichromate. (E)-4-Oxo-2-octenal was synthesized from lithium tetrahydropyranyloxypropynide coupling with pentanal followed by removal of the protecting group and reduction of the double bond and oxidation with pyridinium dichromate. (Z)-4-Oxo-2-octenal was synthesized from Friedel-Crafts acylation of furan followed by Wolff-Kishner reduction to remove the carbonyl group. Treatment with bromine in methanol and dilute sulphuric acid gave (Z)-4-oxo-2-octenal.

The synthesis of the sex pheromone component of spring hemlock looper required all stereoisomers of 7,11-dimethylheptadecane to further explore the relation between chirality and bioactivity. The synthesis is closely related to the synthesis of natural products which contain chiral methyl branch units. In the synthesis of (7R)-(11R)- 7,11-dimethylheptadecane, the hydroxyl group of (2S)-methyl 3-hydroxyl-2-methylpropionate was first protected by a silyl ether. After reduction of the ester group and conversion of the resulting alcohol to a mesylate, it was coupled to 1-pentyl magnesium bromide to give a five carbon chain extension. The silyl protecting group was removed and the resulting alcohol was converted to (2R)-2-methyloctyl mesylate. Treatment with sodium cyanide gave a single carbon extension, the nitrile group was first reduced to the aldehyde and then to an alcohol which was converted to the mesylate. p-Chlorothiolphenol reacted with the mesylate to yield (3R)-3-methyl-1-p-chlorophenylthiononane which was oxidized to the sulphone. Coupling with (2R)-2-methyl-1-bromooctane, synthesized from (2R)-2-methyloctanyl mesylate, afforded (7R)-(11R)-7,11-dimethyl-9-p-chlorophenylsulphonylheptadecane. Desulphonation yielded the final product (7R)-(11R)-7,11-dimethylheptadecane. The synthesis of the other stereoisomers followed the same route using the enantiomeric starting material.

To my parents
for their love, understanding and support

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M. Tracey for NMR spectroscopic analysis.

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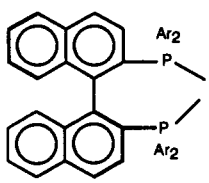
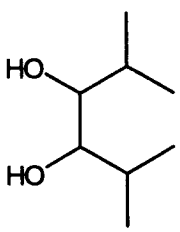
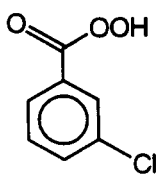
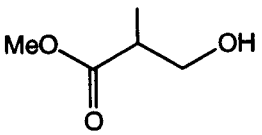
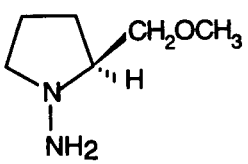
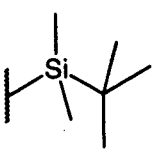
List of Abbreviations

Angiotensin converting enzyme	ACE
2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl	BINAP 
Butyl lithium	BuLi
Chiral methyl branch	CMB
Diastereomeric excess	*de*
1,2-Diisopropylethanediol	DIPED 
Dimethylsulfoxide	DMSO
Electroantennographic detector	EAD
Enantiomeric excess	*ee*
Eastern hemlock looper	EHL
Gas chromatography	GC
Hexamethylphosphoramide	HMPA
High resolution mass spectroscopy	HRMS
Lithium diisopropylamide	LDA

Lithium hexamethyldisilazide	LiHMDS
3-Chloroperoxybenzoic acid	MCPBA 
Methyl 3-hydroxy-2-methyl propionate	MHMP 
Mass spectroscopy	MS
Methanesulfonyl	Ms
Nuclear magnetic resonance	NMR
Non-steroidal antiinflammatory drugs	NSAIDs
Pyridinium dichromate	PDA
(S)-1-Amino-2-methoxymethyl-pyrrolidine	(S)-AMP 
Spring hemlock looper	SHL
t-Butyldimethylsilyl	TBDMS 
Tetrahydrofuran	THF
Thin layer chromatography	TLC
Western hemlock looper	WHL

Chapter 1. Introduction

1.1 Pheromones

Pheromones are the agents of chemical communication between organisms of the same species[1]. During the last 30 years, there has been a major advance in our understanding of the function of pheromones in insect communication. These advances will not only enrich our knowledge of insect communication, but can also have a very significant impact on insect control[2]. Monitoring and disruption of mating of pest populations, and facilitation of apiculture and pollination for honey bees, are examples of pheromone-based insect control and manipulation.

Pheromones are chemicals released by one insect to signal a certain meaning to other insects of the same species and thus cause a specific behavioral or physiological response[3]. Three steps are necessary to establish the identity of a pheromone-based communication system. First, a bioassay method is needed to demonstrate the presence of pheromone communication. Second, the potential pheromone must be isolated and identified. Third, the pheromone candidate is tested to prove the synthetic pheromone initiates a response identical to that observed for the natural material. This thesis focuses on a portion of the second step, the confirmation of the pheromone identification by synthesis of pheromone candidates for two insect species.

1.2 Identification of pheromones

The biggest challenge to pheromone identification has been the minute amount of pheromone available for analysis. Insects typically contain micro to femtogram (10^{-6}-10^{-15} g) amounts of pheromone. A crude extract containing the pheromone is typically a complex mixture of chemicals which complicates the structural identification of minor pheromonal compounds. Some components may be pheromone candidates, but more are not, they are often culticular hydrocarbons, biosynthetic precursors and other chemicals that involv other functions. Instrumental analysis, such as IR, NMR, and UV generally requires a pure sample in the milligram range, so analysis of dilute crude extracts by these methods is not useful. Coupled GC-mass spectrometry (GC-MS) is a highly sensitive method that separates and provides useful information on the components of a pheromone extract. To identify all the chemicals in an extract and test them on the insect would be inefficient and time consuming. The GC-EAD (electroantennographic detector) method[4] simplifies this problem by using a GC to separate the mixture and using the live insect's antenna as a detector to determine that the insect does indeed respond to a particular constituent. The EAD response limit can be as low as 10^{-15} gram and this can provide a very powerful tool in identification of a component as a pheromone in a crude extract.

1.3 The contribution of synthesis to pheromone identification.

By application of GC-EAD and GC-MS, considerable information about the pheromone candidate structure can be obtained. A pheromone must cause a specific response

by insect's antenna, so pure synthetic pheromone candidates are necessary for the full identification of a pheromone. For those substances that have not been previously identified, or those that are not commercially available, organic synthesis is necessary. The synthetic work reported in this thesis is related to two insects, the milkweed bug, *Oncopeltus fasciatus,* and the spring hemlock looper, *Lambdina athasaria*. The synthesis of components of the potential sex and aggregation pheromones of the milkweed bug will be discussed in Chapter 2. Methods available to synthesize chiral methyl branches and their application to the synthesis of the sex pheromone of the spring hemlock looper will be examined in Chapter 3. Chapter 4 describes a route for the synthesis of the chiral dimethyl alkanes that function as a component of the sex pheromone of the spring hemlock looper in order to investigate which stereoisomer is responsible for the pheromonal action.

Chapter 2. Synthesis of components of the potential aggregation and sex pheromones of the milkweed bug

2.1 Introduction

The milkweed bug, *Oncopeltus fasciatus,* belongs to the same taxonomic family as the lygus bug, *Lygus lineolaris*, a serious pest that has been recorded on 169 different plant species[5]. Lygus bugs are difficult to rear in large numbers as a prerequisite for a pheromone study, however, milkweed bugs are relatively easy to rear and a study of the pheromone system of the closely related milkweed bug could provide some valuable information on the chemical communication system of the lygus bug.

The milkweed bug is found throughout the western hemisphere from Canada to Central America[6]. It has been observed that nymphs and young adults of the milkweed bug tend to form large aggregations which break apart approximately 8 days after adult eclosion. The adult male milkweed bugs were found to produce a fruity aroma to attract the female milkweed bug during mating season.

Potential aggregation pheromone extracts from the milkweed bug nymphs were obtained by B. Cinel at SFU in two ways: aeration and body wash methods. Volatiles from 2nd and 4th instar nymphs of milkweed bugs were collected on Porapak Q[7]. Approximately 1500 milkweed bugs nymphs were placed in one chamber and the

volatiles captured on Porapak Q during 9 days of aeration. The extract was eluted from the Porapak Q with pentane.

Prior to obtaining body washes, 1500 milkweed bug nymphs were placed in a freezer for 10 minutes in order to decrease their activity and reduce the possible secretion of defensive chemicals. The insects were then completely submersed and kept in pentane at room temperature for 10 minutes. The pentane extract was then evaporated and steam distilled to obtain a sample free of high molecular weight and non-volatile substances.

2.2 Synthesis of a potential sex pheromone component of the milkweed bug

The potential sex pheromone extracts were obtained by aeration of adults as described above for nymphs. The adult extracts were subjected to GC-MS and GC-EAD analysis and bioassays of the extract indicated the following compounds as potential sex pheromone components of the milkweed bug[8] (Fig. 1).

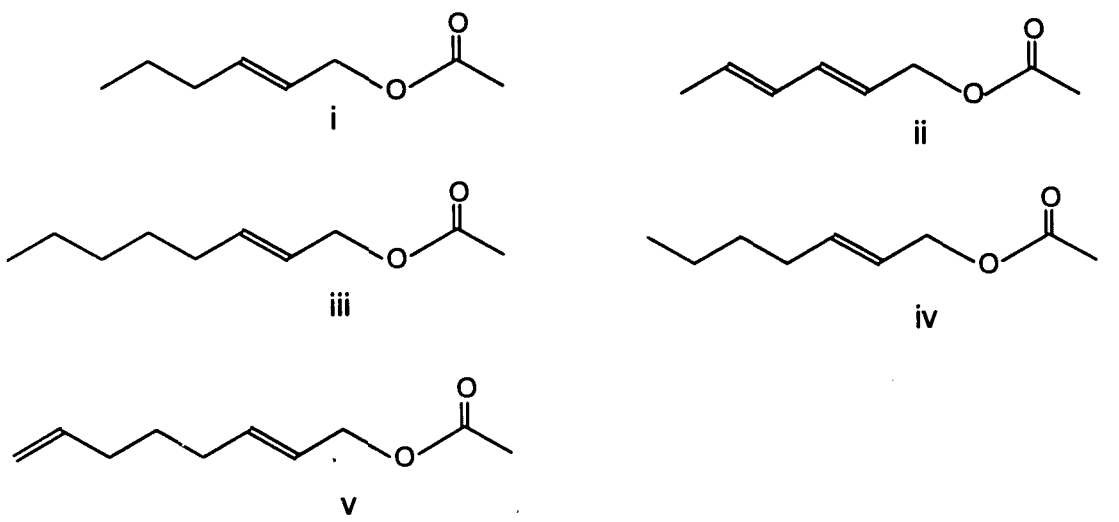
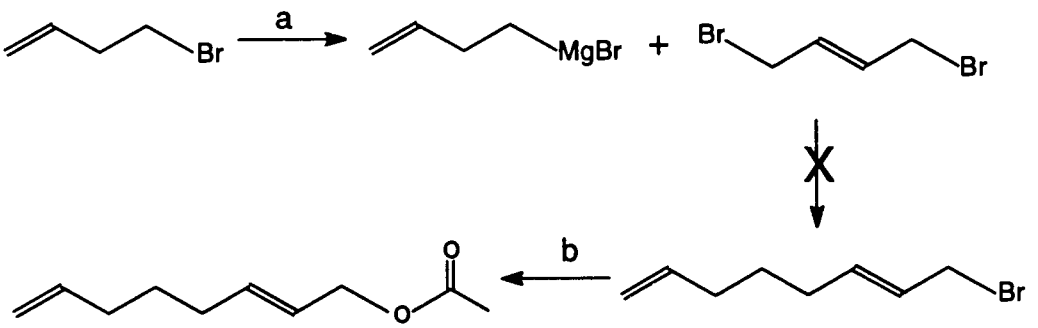


Figure 1. Potential sex pheromone components of the milkweed bug.

Among these acetates, compounds (i) to (iv) were commercially available, but compound (v) (E)-2, 7-octadienyl acetate, required synthesis. The first synthetic approach to this compound was to react 1-bromo-4-butene with magnesium and then couple it with 1,4-dibromo-2-butene to yield 2,7-octadienyl bromide. Potassium acetate would then be expected to convert the bromide into the desired acetate. (Scheme 1)

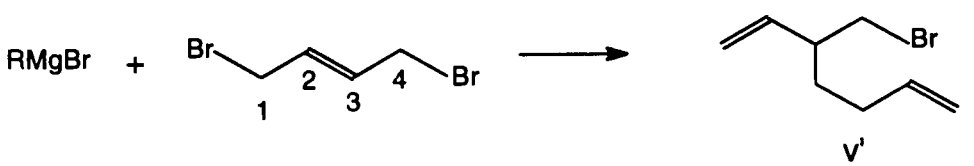
Scheme 1: First synthesis design for (E)-2, 7-octadienyl acetate



(a). Mg, THF. (b). AcOK, DMF.

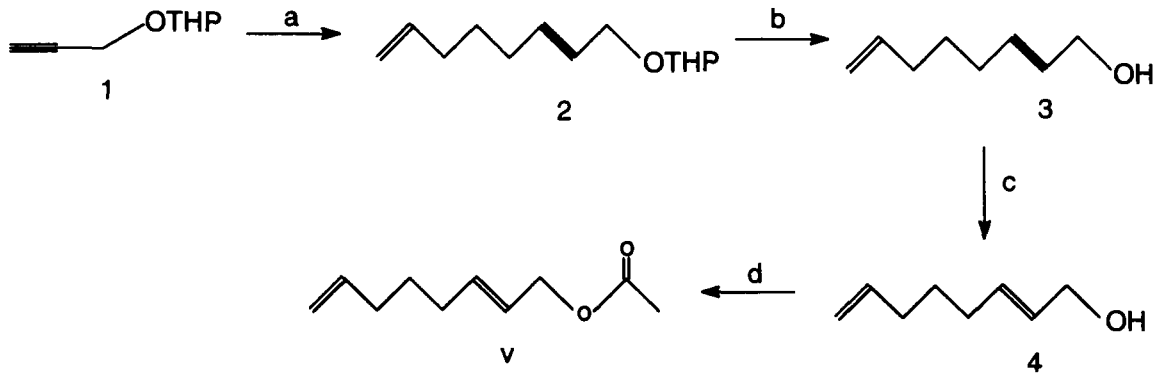
The coupling step in this short synthesis did not go as reported in the literature[9]. Instead of nucleophilic attack at carbon one, the Grignard reagent mainly attacked carbon three to yield compound v' as the major product. (Scheme 2)

Scheme 2: Rearrangement of 1,4-dibromo-2-butene



According to the literature, this only occurs when 1 mole% cuprous iodide was added to form a metal-complex with the Grignard reagent[9].

Scheme 3: Second synthesis design for (E)-2, 7-octadienyl acetate



(a). n-BuLi, THF, -78 ^{0}C, 1-bromo-4-pentene, HMPA. (b).CH_3OH, CF_3COOH. (c). $LiAlH_4$, ether. (d). Acetic anhydride, pyridine.

A second synthetic scheme (Scheme 3) using a lithio acetylide as the nucleophile, instead of the Grignard reagent was tried. Treatment of 1-(tetrahydropyran-2'-yloxy)-2-propyne with n-butyl lithium in THF gave the lithio acetylide, which was then coupled with 1-bromo-4-pentane in HMPA at -78 ^{0}C to yield 1-(tetrahydropyran-2'-yloxy)-oct-2-yn-7-ene ***2***. The tetrahydropyranyloxy protecting group was removed by CF_3COOH in methanol, and the triple bond in 2-octyn-7-en-1-ol ***3*** was reduced with lithium aluminium hydride in ether to form mainly the (E) double bond. The (Z) double bond isomer was separated from (E) isomer using a silica gel column with silica gel pretreated with silver ion. Treatment of (E)-2, 7-octadien-1-ol ***4*** with acetic anhydride in pyridine yielded the final (E)-2, 7-octadienyl acetate. The synthetic acetate was identical to that found in the crude insect extract by NMR and GC-MS analysis.

2.3 Synthesis of the potential aggregation pheromone components of the milkweed bug

The bioassay results, GC-EAD analysis and GC-MS and NMR suggested that the following compounds constituted the potential aggregation pheromone of milkweed bug[8]. (Fig. 2)

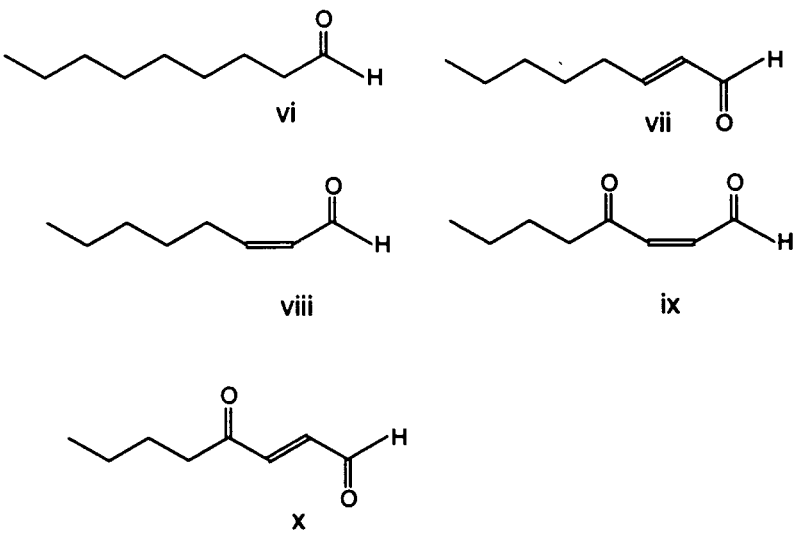


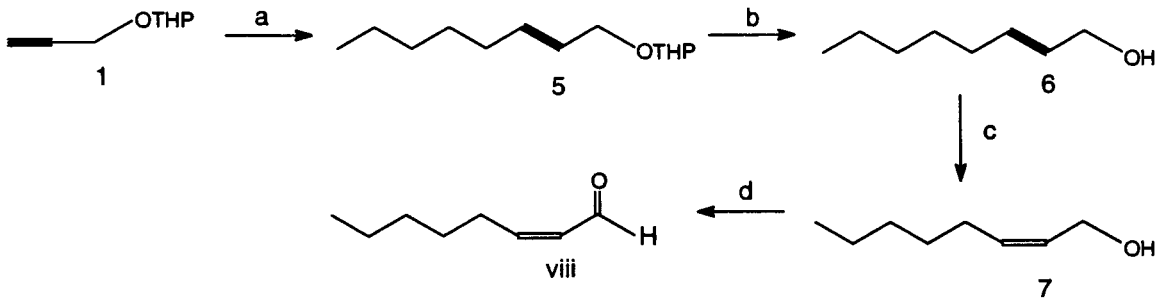
Figure 2. Potential aggregation pheromone of the milkweed bug.

Compounds (vi, vii) were available, but compounds (viii) (Z)-2-octenal, (ix) (Z)-4-oxo-2-octenal, and (x) (E)-4-oxo-2-octenal required synthesis.

2.3.1 Synthesis of (Z)-2-octenal

Synthesis of (Z)-2-octenal employed the same lithio acetylide that was used in Scheme 3 (Scheme 4).

Scheme 4: Synthesis of (Z)-2-octenal



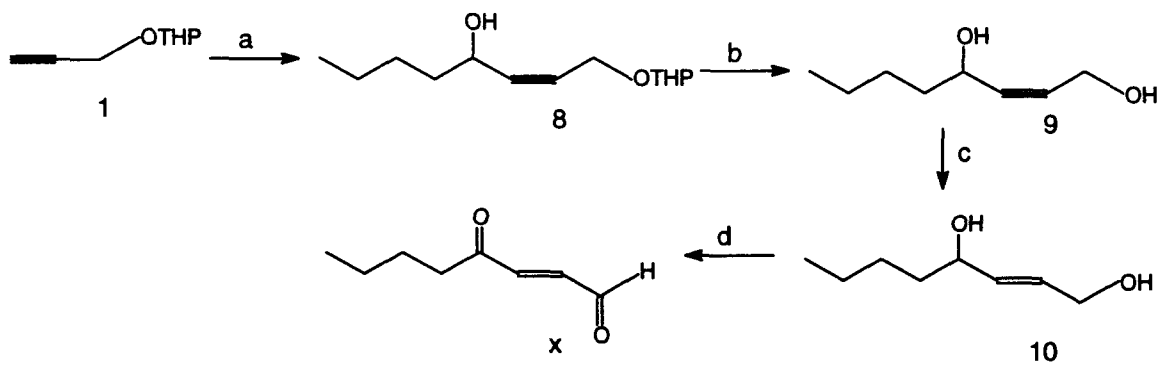
(a). BuLi, THF, -78^{0}C, 1-bromopentane, HMPA. (b). CH_3OH, CF_3COOH. (c). P-2 nickel, H_2. (d) PDC, DMF.

Deprotonation of the 1-(tetrahydropyran-2'-yloxy)-2-propyne with n-butyl lithium in THF, gave a lithio acetylide which was coupled with 1-bromopentane. The tetrahydropyranyloxy protecting group was then removed and the triple bond in 2-octynol ***6*** reduced with P-2 nickel to yield (Z)-2-octenol. Pyridinium dichromate (PDC) oxidation of the hydroxyl group to an aldehyde was accomplished without isomerization of the (Z)-double bond. However, (Z)-2-octenal was found to isomerize to (E)-2-octenal within one month in hexane solution at room temperature. These two stereoisomers could be separated on a silica column using pentane as eluant and isomerization was found to be slow below -20 ^{0}C. Synthetic (Z)-2-octenal had the same GC-MS and NMR spectra as the material found in the aggregation pheromone extracts.

2.3.2 Synthesis of (E)-4-oxo-2-octenal and (Z)-4-oxo-2-octenal

The synthetic approach to (E)-4-oxo-2-octenal also used the same lithio acetylide as a nucleophile to couple with pentanal (Scheme 5).

Scheme 5: Synthesis of (E)-4-oxo-2-octenal



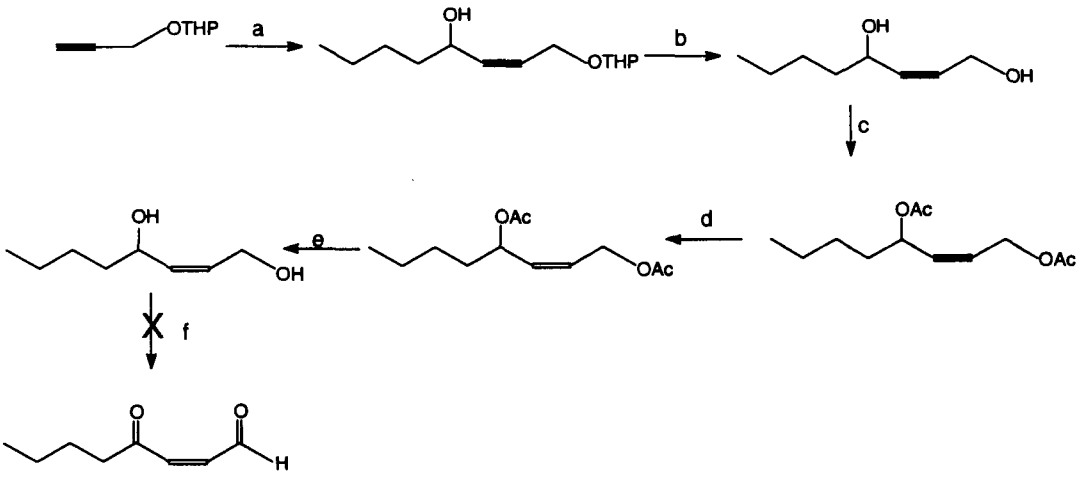
(a). BuLi, THF, -78 ^{0}C, pentanal. (b). CF_3COOH, methanol. (c).$LiAlH_4$, ether. (d). PDC, DMF.

The protecting group was removed as in Scheme 3. The product 2-octyn-1,4-diol *9* was reduced with lithium aluminum hydride to (E)-2-octene-1,4-diol. Oxidation of the diol with PDC yielded (E)-4-oxo-2-octenal which had the same GC-MS and NMR spectra as the component found in the original extract.

The synthesis of (Z)-4-oxo-2-octenal was attempted in a similar way to the successful synthesis of (E)-4-oxo-2-octenal. However, both the P-2 nickel and Lindlar (palladium on calcium carbonate, poisoned with lead) reducing methods failed to reduce 2-octyn-1,4-diol to (Z)-2-octene-1,4-diol. The two hydroxy groups in 2-octyn-1,4-diol are possibly too close to the triple bond and interfere with the catalyst activity. To test this hypothesis the hydroxyl groups were first converted to acetate groups after which

reduction of the 2-octyn-1,4-diacetate with Lindlar catalyst proceeded smoothly to form (Z)-2-octene-1,4-diacetate (Scheme 6).

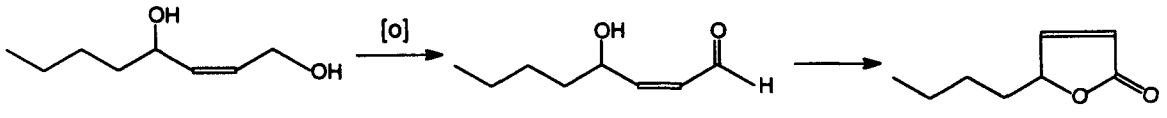
Scheme 6: First synthesis design for (Z)-4-oxo-2-octenal



(a). BuLi, THF, -78 ^{0}C, pentanal. (b). CF_3COOH, methanol. (c). acetic anhydride, pyridine. (d) Lindlar catalyst. (e). $LiAlH_4$, ether. (f). PDC, DMF.

The acetate groups were then removed with lithium aluminum hydride in ether without isomerizing the (Z) double bond. However, trials to oxidize the (Z)-2-octene-1,4-diol to (Z)-4-oxo-2-octenal with PDC failed. It appears that in the process of oxidation, the intermediate may possibly form a five-membered ring that resists further oxidation (Scheme 7).

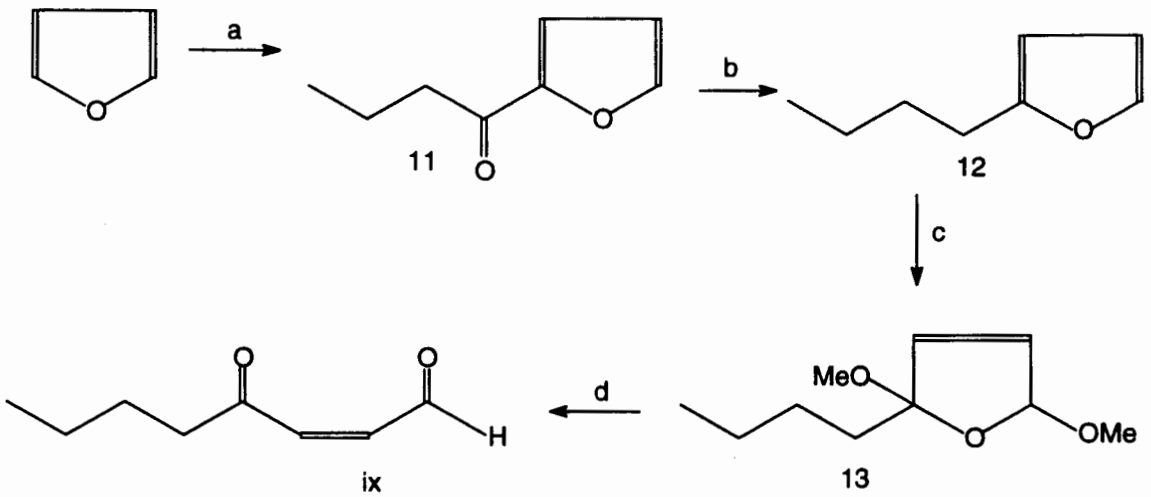
Scheme 7: Cyclization of (Z)-2-octene-1,4-diol during oxidation



The synthetic route was redesigned, using furan as the starting material. The first step was to introduce four carbon atoms onto the furan ring using a Friedel Crafts acylation. The carbonyl group was then removed by a Wolff-Kishner reduction.

Treatment of the 2-butylfuran with bromine in methanol first results in a 1,4-addition to the furan ring followed by bromine replacement *in situ* by methanol[10] to yield 2-butyl-2,5-dimethoxy-2,5-dihydrofuran ***13*** (Scheme 8).

Scheme 8: Synthesis of (Z)-4-oxo-2-octenal



(a). $TiCl_4$, butyric anhydride. (b). diethylene glycol, KOH, N_2H_4. (c). Br_2, CH_3OH. (d). 0.005M H_2SO_4.

Treatment with 0.005 M sulphuric acid successfully opened the dihydrofuran ring to yield (Z)-4-oxo-2-octenal which had the same GC-MS and NMR spectra as the pheromone component in the original extract.

2.4 Experimental section

Gas liquid chromatography (GC) was conducted employing a Hewlett Packard 5880 gas chromatograph equipped with a fused silica column (30m x 0.25mm i.d.) coated with DB-1 (J&W Scientific, Folsom, CA). Optical rotations were measured on an Autopol II automatic polarimeter. Concentrations for optical rotation are reported in grams/100 ml of solvent. Nuclear magnetic resonance (NMR) spectra were measured in

$CDCl_3$ at 400 MHz on a Bruker AMX-400 spectrometer. Mass spectra were obtained on a Varian Saturn II ion trap mass spectrometer equipped with a fused silica column (30m x 0.25 mm i.d.) coated with DB-1. THF was distilled from Na benzophenone ketyl, HMPA was distilled from CaH_2, DMSO and DMF were dried over Molecular sieves (4A). Thin layer chromatography (TLC) plates were prepared from silica gel 60G. Detection of compounds was done by spraying with 10% aqueous sulfuric acid and heating. The solvent used for flash chromatography was a double distilled mixture of hexane and ether recovered from other chromatography experiments. Evaporations of solvent were carried out under reduced pressure (~10 mmHg) below 60 ^{0}C.

2.4.1 Synthesis of the potential sex pheromone component, (E)-2, 7-octadienyl acetate

1-(Tetrahydropyran-2'-yloxy)-oct-2-yn-7-ene (2):

To a stirred solution of ***1*** (0.84 g, 6.0 mmol) and THF (10 ml) was added BuLi (2.6 ml 2.5 M, 6.6 mmol) at -78 ^{0}C under argon. The solution was stirred for 1.5 h and 1-bromo-4-pentene (0.89 g, 6.0 mmol) and HMPA (5.0 ml) was added. The solution was stirred overnight and worked up with saturated NH_4Cl solution, then extracted with pentane (3X20 ml) and dried over Na_2SO_4 and concentrated *in vacuo*, to give 0.20 g of a colorless oil in 16% yield.

^{1}H NMR δ: 5.8 (m,1H, CH_2CH), 5.0 (m, 2H, CH_2CH), 4.8 (m,1H, CHO), 4.25 (m, 2H, CCH_2O), 3.85 3.54 (m, 2H, CH_2O), 2.40 (t, J=2.5 Hz, 2H, CH_2CH_2C), 2.25 (m, 2H, $CHCH_2CH_2$), 2.15 (m, 2H, $CH_2CH_2CH_2$), 2.0-1.5 (m, 6H, CH_2 of THP).

EIMS: 165(6%), 91(28%), 85(100%, M^+ -OTHP), 79(31%), 67(18%), 55(12%), 41(27%).

*(E)-2, 7-octadien-1-ol (**4**):*

To a solution of ***2*** (0.17 g, 1.0 mmol) in methanol (20 ml) was added CF_3COOH (0.50 ml). The solution was stirred at room temperature overnight. After removal of methanol *in vacuo*, water was added and the mixture was extracted with ether and washed with 10% $NaHCO_3$ and brine. The crude product was purified on a silica column using ether:pentane (1:1) as eluant. To a solution of purified ***3*** (60 mg, 0.50 mmol) and ether (20 ml) was added $LiAlH_4$ (38 mg, 0.50 mmol) at 0 ^{0}C. The reaction mixture was refluxed overnight. The reaction was quenched by slowly adding 5%NaOH (2.0 ml) and silica gel (5.0 g) followed by filtering the mixture through a small silica column. Concentration of the solution gave 58 mg of a colorless product (92% yield).

^{1}H NMR of ***3*** δ: 5.77 (m, 1H, CH_2CH), 5.00(m, 2H, CH_2CH), 4.25 (t, J=2Hz, 2H, CH_2OH), 2.22 (tt, J= 7Hz, 2Hz, 2H, CH_2CCCH_2), 2.14 (m, 2H, $CHCH_2CH_2$),1.60 (m, 2H, $CH_2CH_2CH_2$).

^{1}H NMR of ***4*** δ: 5.80 (m,1H, CH_2CH), 5.65 (m, 2H, CH_2CH), 5.00 (m, 2H, CHCH), 4.10 (d, J=5Hz, 2H, CH_2OH), 2.06 (m, 4H, $CHCH_2$ and CH_2CH), 1.49 (m, 2H, $CH_2CH_2CH_2$).

EIMS of ***4*** : 109(48%, M^+ - OH), 95(18%), 81(24%), 67(100%), 55(9%), 41(12%).

(E)-2, 7-octadienyl acetate (v):

Compound ***4*** (58 mg, 0.46 mmol) was mixed with acetic anhydride (2.0 ml) and pyridine (2.0 ml). The solution was stirred overnight at room temperature. Work up with water followed by 10%HCl and brine washings, drying over Na_2SO_4 and concentration of the solution to give a colorless oil (28 mg, 33% yield).

^{1}H NMR δ: 5.72 (m, 1H, CH_2CH), 5.53 (m, 2H, CH_2CH), 5.02 (m, 2H, CHCH), 4.5 (d, J=5Hz, 2H, CH_2OH), 1.90 (m, 4H, $CHCH_2$ and CH_2CH), 1.72 (s, 3H, $COCH_3$), 1.3 (m, 2H, $CH_2CH_2CH_2$).

EIMS: 125(4%, M+ - $COCH_3$), 93(19%), 79(20%), 67(32%), 54(18%), 43(100%).

2.4.2 Synthesis of the potential aggregation pheromone components

*1-(Tetrahydropyran 2'-yloxyl)-2-octyne (**5**):*

To a solution of ***1*** (3.0 g, 21 mmol) and THF (10 ml) was added BuLi (9.4 ml 2.5 M, 24 mmol) at -78 ^{0}C under argon. The solution was stirred for 1.5 hr and then 1-bromopentane (3.2 g, 21 mmol) and HMPA (5.0 ml) were added. The solution was stirred overnight (-78 ^{0}C to r.t.) and saturated NH_4Cl (10 ml) was added followed by extraction with pentane (3X20 ml). The pentane extracts were dried over Na_2SO_4 and the solvent was removed *in vacuo* to give a colorless oil (2.1 g, yield 48%).

^{1}H NMR δ: 4.8 (t, J=3.2 Hz, 1H, CHO), 4.25 (qt, J=2Hz, 2H, CCH_2O), 3.85 3.50 (m, 2H, CH_2O), 2.2 (tt, J=7Hz, 2Hz, 2H, CH_2CCCH_2), 1.9-1.5 (m, 8H), 1.3 (m, 4H), 0.9 (t, J=7Hz, 3H, CH_2CH_3).

EIMS: 211(8%, M^+ + 1), 101(10%), 85 (100%), 67(9%), 55(6%), 41(9%).

*2-Octynol (**6**):*

To a solution of ***5*** (1.0 g, 5.0 mmol) and methanol (20 ml) was added CF_3COOH (0.50 ml). The solution was stirred at room temperature overnight. The methanol was removed *in vacuo* and worked up with water. Extraction with ether (3X20 ml) followed by washing with 10% $NaHCO_3$ and brine, and drying over Na_2SO_4 gave a crude product

that was purified on a silica gel column chromatography using ether:pentane (1:1) as an eluant to yield 0.51 g product (80%).

^{1}H NMR δ: 4.25 (s, 2H, CH_2O), 2.20 (tt, J=7Hz, 2Hz, 2H, CH_2CCCH_2), 1.50 (m, 2H), 1.32 (m, 4H), 0.89 (t, J=7Hz, 3H, CH_2CH_3).

(Z)-2-Octenol (7):

To $Ni(OAc)_2 \bullet 4H_2O$ (1.0 g) in ethanol (50 ml) under H_2, was added a $NaBH_4$ solution (5.0 ml) prepared by filtering the solution resulting from $NaBH_4$ (1.0 g), EtOH (24 ml), and NaOH (1.2 ml 2.0 M). After H_2 evolution had ceased, ethylene diamine (0.70 ml) and compound ***6*** (0.74 g, 5.9 mmol) were added to the solution. After 3 hours, GC analysis showed that the reaction was complete. Evaporation of the ethanol *in vacuo*, dilution with pentane:ether (1:1) gave a mixture which was filtered through a short silica column. The product was purified on a silica column to yield a colorless oil (0.61 g, 80% yield).

^{1}H NMR of ***7*** δ: 5.56 (m, 2H, CHCH), 4.19 (d, J=6Hz, 2H, $CHCH_2OH$), 2.05 (m, 2H), 1.4-1.2 (m, 6H), 0.9 (t, J=7Hz, 3H, CH_2CH_3).

EIMS of ***7***: 109(9%), 95(14%, $M^+ - CH_2OH$), 81(42%), 67(48%), 57(100%), 41(91%).

(Z)-2-Octenal (viii):

To a solution of ***7*** 128 mg (1.0 mmol) and DMF (20 ml), was quickly added pyridinium dichromate (PDC) (0.47 g, 1.2 mmol) at 0 ^{0}C. The solution was stirred for 10 minutes and quenched with water, extracted with pentane (3X20 ml) and washed with NH_4Cl (sat. aq. 10 ml). The crude product was purified on a silica gel column using ether:pentane (1:10) as eluant, and concentrated *in vacuo* to give a colorless oil (30 mg, 21% yield).

^{1}H NMR δ: 10.08 (d, J=8Hz, 1H, CHO), 6.63 (dt, J=11Hz, 8Hz, 1H, CH_2CHCH), 5.95 (qt, J=11Hz, 8Hz, 2Hz, 1H, $CHCHCHO$), 2.60 (m, 2H), 1.5-1.2 (m, 6H), 0.89 (t, J=7Hz, 3H, CH_2CH_3).

EIMS: 126(11%, M^+), 109(19%), 97(11%), 83(100%), 70(39%), 55(70%), 41(72%).

1-(Tetrahydropyran 2'-yloxy)-4-hydroxy-2-octyne (8):

To a solution of compound ***1*** (3.6 g, 25 mmol) in THF (20 ml) was added BuLi (27 mmol) at -78 ^{0}C and the mixture stirred at that temperature for 1.5 hours. Pentanal (2.1 g, 25 mmol) in HMPA (10 ml) was added dropwise at -30 ^{0}C and the solution was stirred overnight, worked up with NH_4Cl (sat. 30 ml), and extracted with ether (3X50 ml). The combined ether extracts were washed with water and brine and the extract was dried over sodium sulfate. Removal of the solvent *in vacuo* and purification on a silica column yielded a colorless product (2.9 g, 51%).

^{1}H NMR δ: 5.40 (t, J=7Hz, 1H, CH_2CHOHC), 4.80 (m, 1H, CHO), 4.26 (s, 2H, CCH_2OTHP), 3.85 and 3.54 (m, 2H, CH_2O), 2.40 (t, J=2.5 Hz, 2H), 2.25 (m, 2H), 2.15 (m, 2H), 1.15-1.80 (m, 6H), 0.85 (t, J=7Hz, 3H, CH_2CH_3).

2-Octyn-1,4-diol (9):

To a solution of ***8*** (1.0 g, 4.4 mmol) in methanol (30 ml) was added CF_3COOH (0.50 ml) at room temperature and stirred overnight. The reaction was quenched with water (10 ml) and extracted with ether (30 ml) and dried over sodium sulfate. Removal of

the ether *in vacuo* and purification on a silica column yielded a colorless oil (0.58 g, 92%).

^{1}H NMR δ: 5.39 (t, J=7Hz, 1H, CH_2CHOHC), 4.69 (s, 2H, CCH_2OTHP), 1.15-1.80 (m, 6H), 0.8 (t, J=7Hz, 3H, CH_2CH_3).

*(E)-2-Octene-1,4-diol (**10**):*

To a solution of ***9*** (0.30 g, 2.1 mmol) in ether (30 ml) was added $LiAlH_4$ (0.16 g, 4.2 mmol) at 0 ^{0}C and the mixture refluxed gently overnight. A solution of 5% NaOH (1.5 ml) at 0 ^{0}C was added, the mixture was stirred for 0.5 h and sodium sulfate (3.0 g) was added. The mixture was stirred for 30 minutes and filtered through a short silica column The solvent was removed *in vacuo* and the residue was purified on a silica column to yield a colorless oil (0.27 g, 90%).

^{1}H NMR δ: 5.75 (m, 2H, CH_2CHOHC), 5.25 (q, J=7Hz, J=6.5Hz, 1H, $CHCHCH_2OH$), 4.55 (d, J=5.5Hz, 2H, $CHCHCH_2OH$), 1.10-1.80 (m, 6H), 0.85 (t, J=7Hz, 3H, CH_2CH_3).

(E)-4-oxo-2-octenal (x):

To a solution of ***10*** (0.1 g, 0.70 mmol) in CH_2Cl_2 (5.0 ml) was added PDC (0.40 g , 1.0 mmol) at 0 ^{0}C. The reaction was stirred for 0.5 h at 0 ^{0}C, quenched with water (5.0 ml) and extracted with ether (3X10 ml). The combined ether extract was dried over sodium sulfate and the solvent evaporated and purified on a silica column to yield a colorless oil (80 mg, 81%).

^{1}H NMR δ: 9.75 (d, J=8 Hz, 1H, CHO), 6.8 (d, J=16.5 Hz, 1H, CHC*H*), 6.7 (d, J=16.5 Hz, 1H, C*H*CH), 2.65, (t, 2H, CH_2CH_2CO), 1.15-1.8 (m, 4H), 0.9 (t, 3H, CH_2CH_3).

EIMS: 141 (8%, M^+), 125 (10%), 111 (52%), 97 (21%), 83 (39%), 70, (40%), 55 (100%), 41 (51%).

*2-Butanoyl-furan (**11**):*

To a solution of furan (3.4 g, 50 mmol) in CH_2Cl_2 (25 ml), was slowly added butyric anhydride (9.5 g, 60 mmol) at 0 ^{0}C. Titanium tetrachloride (19 g, 0.10 mol) in CH_2Cl_2 (10 ml) was added dropwise at the same temperature. The mixture immediately turned red and then black and was stirred for two hours. The reaction was quenched with HCl (6.0 M, 50 ml) at 0 ^{0}C and the aqueous solution was extracted with ether (3X100 ml), washed with NaOH (4.0 M, 40 ml), water and brine. The crude product was purified on a silica column to yield 3.5 g of product (51% yield). The ^{1}H NMR data matched those in the literature[11].

*2-Butylfuran (**12**):*

To a solution containing diethylene glycol (50 ml), N_2H_4 hydrate (5.0 g, 0.10 mol), and KOH (16 g, 0.28 mol) was added ***11*** (3.5 g, 25 mmol) at room temperature. The solution turned from yellow to dark green. It was then heated to 170 ^{0}C for 2 hours. The solution turned red-yellow and after cooling it down to room temperature, water (30 ml) was added and the mixture extracted with pentane (3X50 ml). Removal of the solvent yielded a colorless oil (1.7 g, 55%).

^{1}H NMR δ: 7.3 (b, 1H), 6.3 (b, 1H), 6.0 (b, 1H), 2.61 (t, 2H, CH_2CO), 1.25 (m, 4H), 0.88(t, 3H, CH_2CH_3).

*2-Butyl-2,5-dimethoxy-2,5-dihydrofuran (**13**):*

A solution of ***12*** (61 mg, 0.50 mmol), methanol (2.0 ml), ether (1.0 ml), and Na_2CO_3 (214 mg) was cooled to -5 ^{0}C, then Br_2 (0.47 M in methanol, 1.0 ml) was added dropwise to the solution. The reaction was stirred for 30 minutes and was worked up by pouring it into brine (30 ml). The mixture was extracted with ether (3X20 ml) and dried over sodium sulfate. Removal of the ether yielded a colorless oil (90 mg, 97%).The ^{1}H NMR matched those in the literature[11].

(Z)-4-oxo-2-octenal(ix):

A portion of ***13*** (0.21 g, 1.3 mmol) was mixed with H_2SO_4 (0.005 M, 2.0 ml) in a small vial and stirred for 10 min. The solution was quenched with water (1.5 ml) and extracted with ether (3X5.0 ml). The combined ether extract was dried over sodium sulfate and the solvent was removed *in vacuo* to yield a slightly yellow liquid (0.14 g, 76%).

^{1}H NMR δ: 10.2 (d, J=8 Hz, 1H, CHO), 6.95 (d, J=12 Hz, 1H, CHC*H*), 6.15 (d, J=12 Hz, 1H, C*H*CH), 2.6 (t, 2H, CH_2CH_2CO), 1.15-1.8 (m, 4H), 0.9 (t, 3H, CH_2CH_3).

EIMS: 141 (21%, M^+), 123 (8%), 111 (14%), 98 (40%), 83 (23%), 70 (21%), 55 (100%), 41 (41%).

Chapter 3. Evaluation of literature methods to synthesize compounds containing the chiral methyl branch unit

3.1 Introduction

In northeastern America the spring hemlock looper[12] (SHL), *Lambdina athasaria,* has sporadic outbreaks during which it feeds primarily on hemlock. The insect flies in the spring and overwinters as a pupa. For pheromone analysis, SHL pupae were collected at Devil's Hopyard State Park, near East Haddam, Middlesex County, Connecticut. They were reared to adults at Simon Fraser University under a 14L:10D photoperiod. Pheromone glands of 1 to 2-day-old virgin females were removed 3-4 hours into the photophase and extracted in hexane for 5 minutes by Ms. R. Gries.

3.2 Sex pheromone of SHL

Pheromone extracts from SHL were analyzed by GC-MS and GC-EAD and two methylated hydrocarbons, 7-methylheptadecane (7Me:17H) and 7,11-dimethylheptadecane (7,11diMe:17H) were identified as the potential sex pheromone of SHL. (Fig. 3)

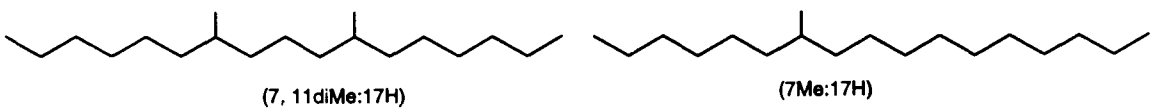


Figure 3. Sex pheromone of SHL (7Me:17H) and (7,11diMe:17H).

In field trapping experiments, (7Me:17H) and (7,11diMe:17H) by themselves were not bioattractive but in combination attracted numerous SHL. This phenomenon is called synergism, and the combination of (7Me:17H) and (7,11diMe:17H) were identified as the sex pheromone. The former (7Me:17H) has two stereoisomers and the later (7,11diMe:17H) has three stereoisomers. The (7Me:17H) and (7,11diMe:17H) used in the field were mixtures of all of these stereoisomers. From earlier pheromone work on insects of the same congeneric family of SHL, the eastern hemlock looper (EHL), *Lambdina fiscellaria fiscellaria,* and the western hemlock looper (WHL), *L.f. lugubrosa,* it was found that not all stereoisomers are attractive. The attractive stereoisomers are listed in Figure 4.

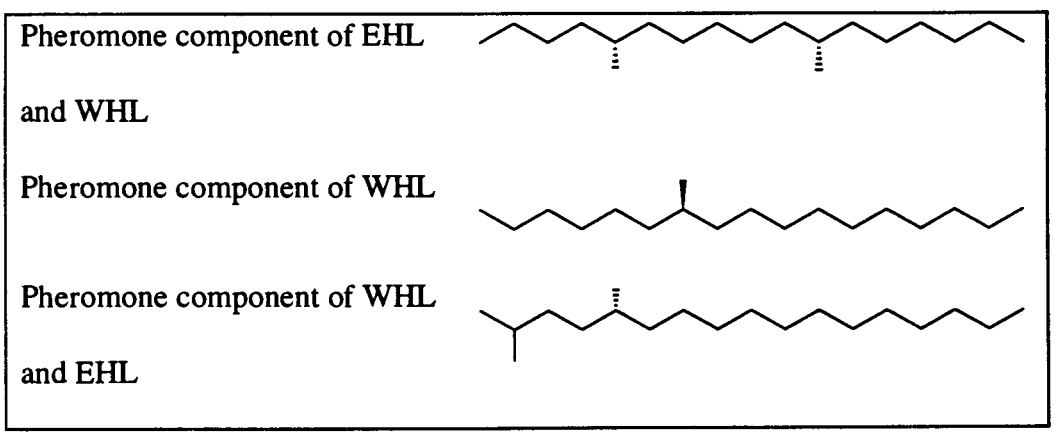


Figure 4. Bioactive stereoisomers of EHL and WHL pheromones.

All the stereoisomers.of (7Me:17H) and (7,11diMe:17H) were therefore required in order to determine which stereoisomer is bioactive. R-(7Me:17H) and S-(7Me:17H) had been previously synthesized in our group[13]. The focus of this work was to synthesize

all stereoisomers of (7,11diMe:17H), namely R, R-(7,11diMe:17H), S, S-(7,11diMe:17H) and *meso*-(7,11diMe:17H) (Figure 5).

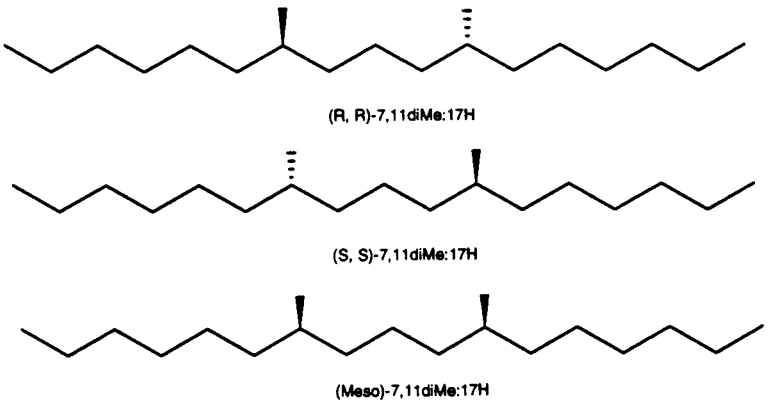
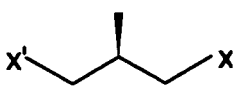


Figure 5. Stereoisomers of (7,11diMe:17H).

3.3 Compounds containing the chiral methyl branch unit

Stereoisomers of (7,11diMe:17H) and other naturally occurring compounds possess the following general formula.



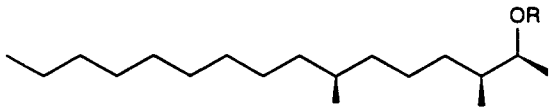
x' and x: Functional or alkyl group

Due to the difference in x' and x, the center with the methyl group is chiral, hence a chiral methyl branch unit could significantly influence bioactivity.

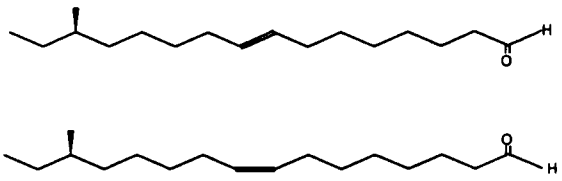
3.3.1 Pheromones containing the chiral methyl branch (CMB) unit

Female sex pheromones of SHL, WHL, and EHL contain CMB units, as do a large number of other insect pheromones. Examples include the sex pheromone of the pine sawfly *Neodiprion sertifer* (S,S,S)-3,7-dimethyl-2-pentadecyl acetate (a)[14], the sex pheromone of the dermestid beetles, *Trogoderma inclusum and T. granarium,* (Z) and (E)-14-methyl-8-hexadecenal[15] (b), the major sex pheromone component of the mountain-ash bentwing *Leucoptera scitella,* 5,9-dimethylpentadecane[16] (c), the sex pheromone of the cigarette beetle, *Lasioderma serricorne,* serricornin[17] (d), the sex pheromone of the tsetse flies *Glossina morsitans morsitans*[18](e), and *Glossina palladipes*[19] (k), the sex pheromone of the red flour beetle[20] (f), a sex pheromone component of the southern corn rootworm, *Diabrotica undecimpunctata howardi,* 10-methyl-2-tridecanone[21] (g), the aggregation pheromone of *Tribolium castaneum* (4R, 8R)-4,8-dimethyldecanal[22] (h), the sex pheromone of German cockroach *Blattella germanica* (3R, 11R)-3,11-dimethyl-2-nonacosanone[23](i), the sex attractant of the western corn rootworm, *D. virgifera virgifera,* (2R, 8R)-8-methyl-2-decyl propionate[24] (j), the sex pheromone of the peach leafminer moth *Lyonetia clerkella*[25] (l), the sex pheromone of the rice moth *Corcyra cephalonica*[26] (m), the alarm pheromone of the leaf cutting ant, *Atta texana,* (S)-4-methyl-3-heptanone[27] (n), the alarm pheromone of *Crematogaster* ants[28] (o), the sex pheromone of the banded cucumber beetle *D. balteata*[29]

(p), the aggregation pheromone of the acarid mite, *Lardoglyphus knoi*[30] (q), and the sex pheromone of the smaller tea tortrix moth, *Adoxophyes* sp[31] (r) (Figure 6).



a



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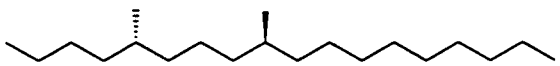

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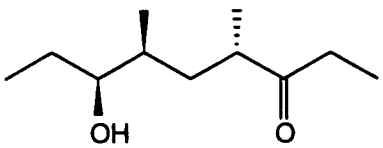

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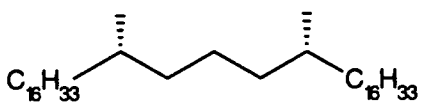

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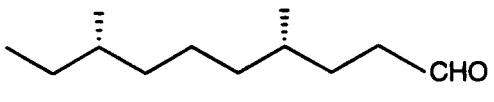

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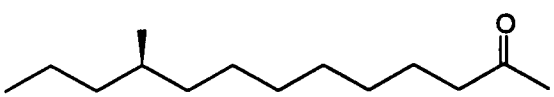

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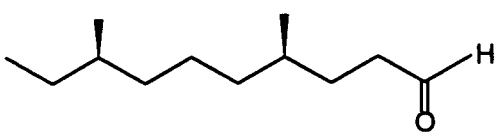

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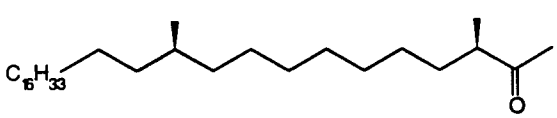

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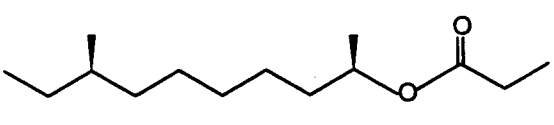

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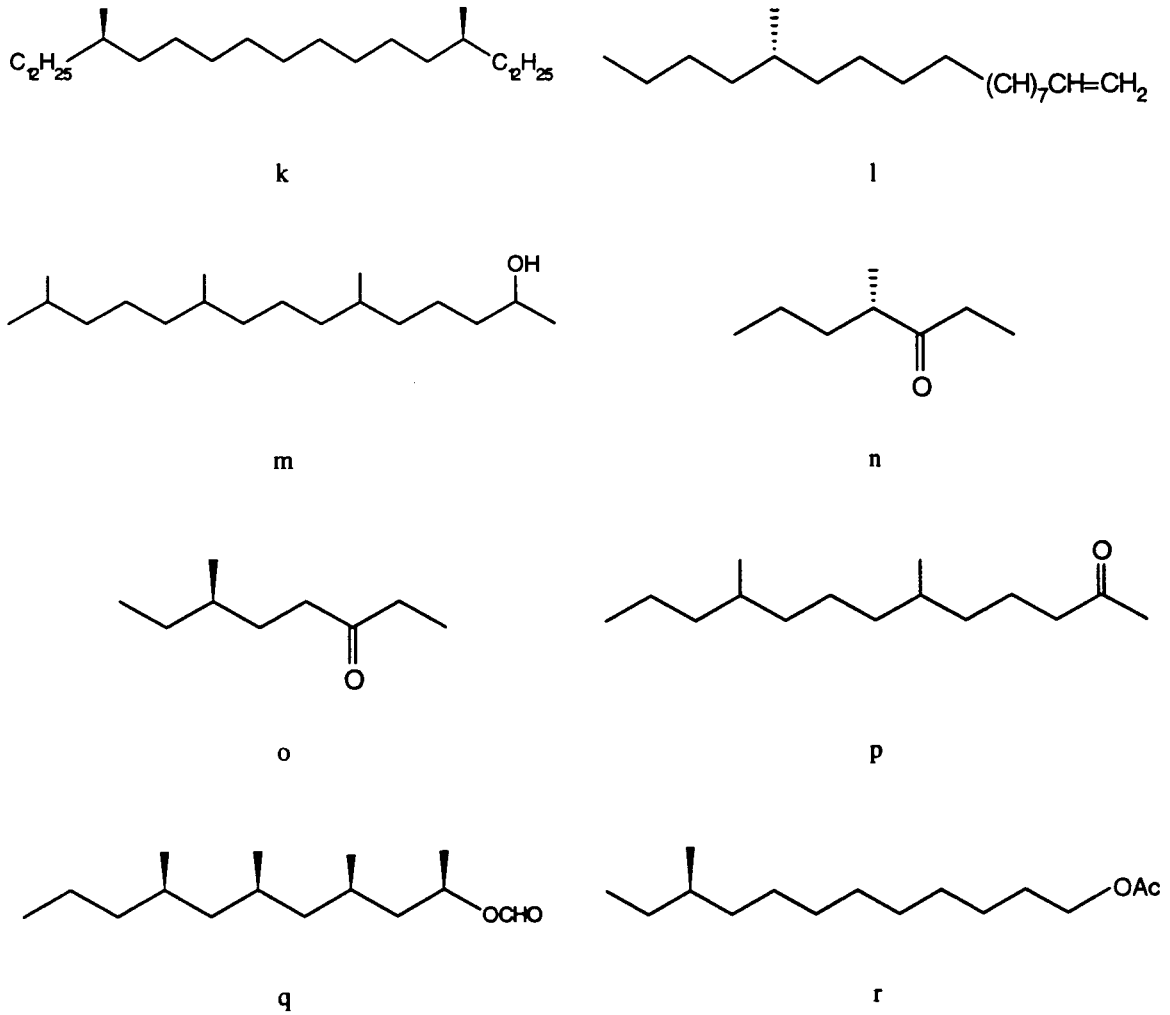
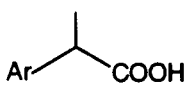


Figure 6. Pheromones that contain CMB units.

3.3.2 Drugs containing the CMB units

Non-steroidal antiinflammatory drugs (NSAIDs) are one of the largest class of CMB containing drugs that are of therapeutic interest, and can be viewed as α-aryl propionic acid derivatives with the following general formula[32]:



Chiral methyl branches here are very crucial to the activity of compounds, such as naproxen and ibuprofen, (Fig. 7) in which only the (S)-enantiomers are active and are marketed separately from the racemate[33].

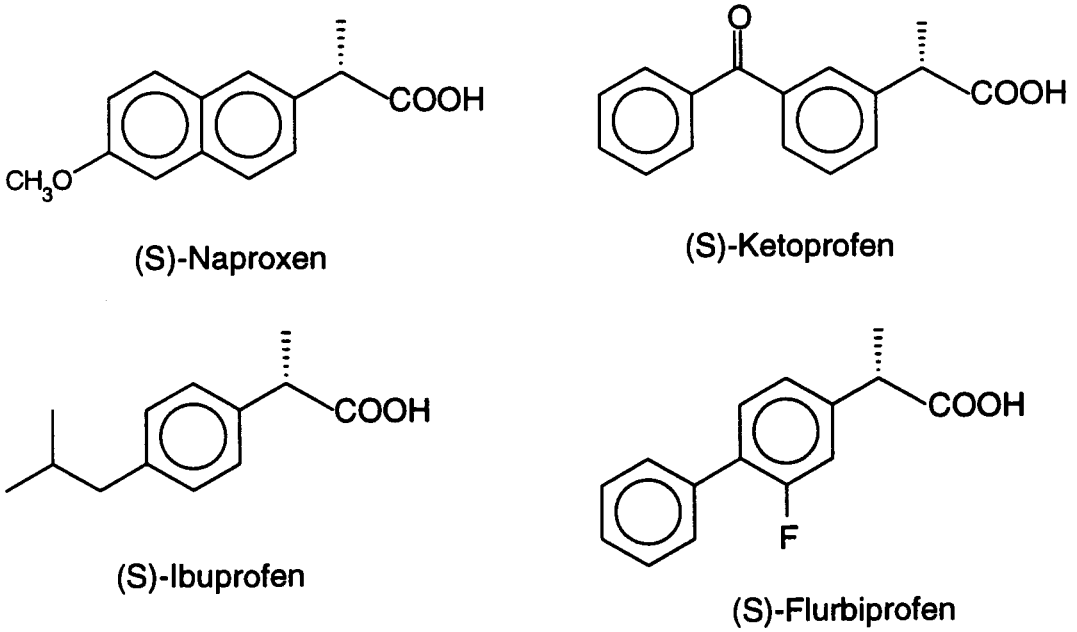
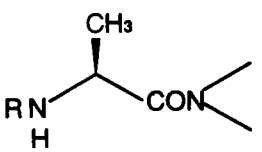
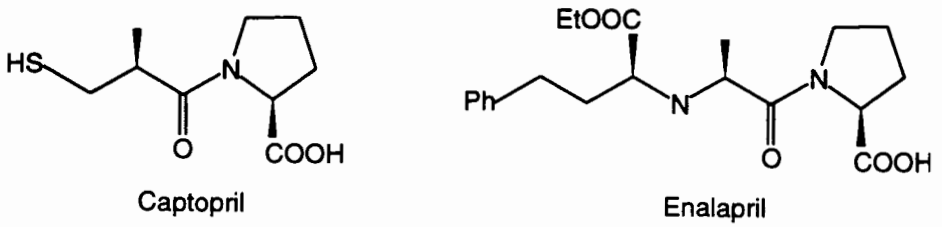


Figure 7. Structures of active NSAIDs.

Angiotensin converting enzyme (ACE) inhibitors, which belong to modern synthetic drugs, have the following general formula:



The methyl branch here is also necessary for the activity, with all methyls in ACE-inhibitors having the (S) configuration. A typical example is Captoril and Enalapril (Fig. 8), which had world-wide sales far exceeding $1000 million in 1990[33].

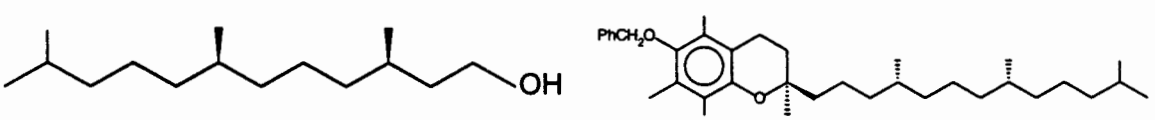


Captopril Enalapril

Figure 8. Structures of Captoril and Enalapril.

3.3.3 Other natural compounds having CMB units

Examples of other biological natural products that contain CMB units are, the precursor of the side chain of vitamins E and K (s), side chain of *α-tocopherol*[34]*(t)*, an archaebacterial macrocyclic diether lipid[35](u) and α,ω-bisphytanyl tetraethers (v) from archaebacteria occurring in sediments and petroleums[36], the side chain of phytol[37] (w), a morpholine fungicide[38] (x), the side chain of tricyclic terpene hydrocarbons occurring in sediments and petroleums[39] (y), a side chain of a alkaloid marine sponge *Niphates sp*[40] (z), a natural muskone[41] (aa), pyridine alkaloids with antimicrobial and cytostatic activity occurring in molluscs and sponges[42] (ab), and a marine sponge sesquiterpenoid[43] (ac). (Fig. 9)



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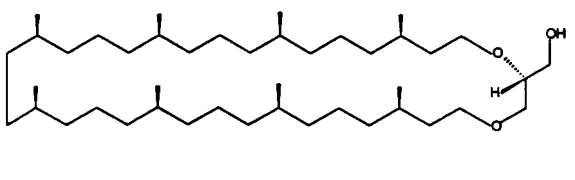

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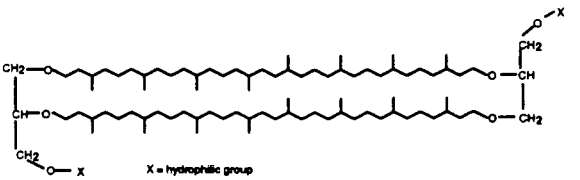
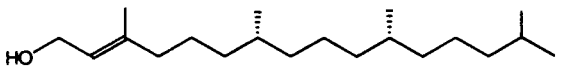


v



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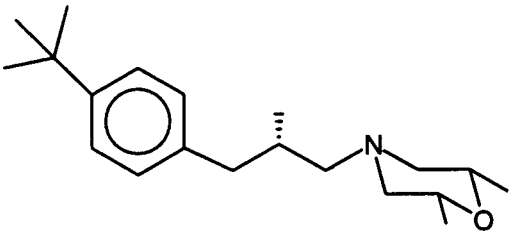

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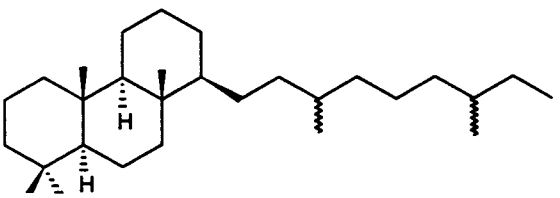

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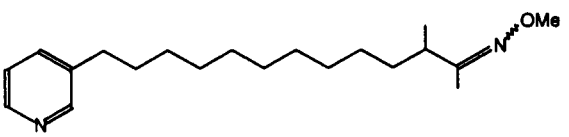

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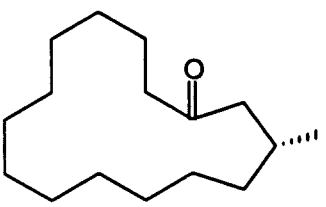
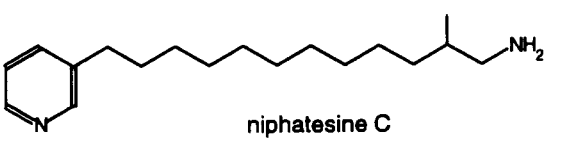
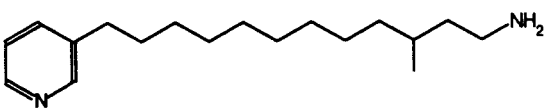


aa

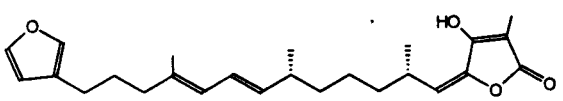


niphatesine C



niphatesine D

ab



ac

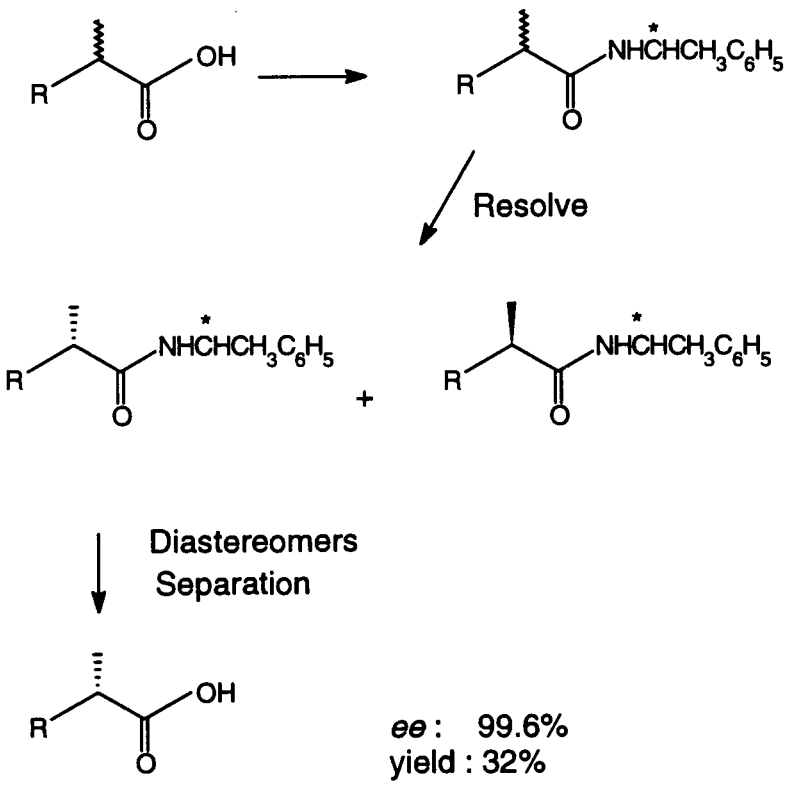
Figure 9. Other natural products containing CMB units.

3.4 Methods available to synthesize CMB units

In "Asymmetric Synthesis"[44], Scott identifies the CMB unit as one of the three most required chiral functionalities along with chiral epoxides and chiral polyhydroxylated chains. The difficulties in the synthesis of CMB units lie in the flexible nature of the chain containing a CMB unit which makes physical and chemical differences between enantiomers very small. This causes not only difficulties in synthesis and separation, but also causes major difficulties in the analysis of the chiral purity of the product. Despite the difficulties in synthesis, tremendous progress has been made in the synthesis of CMB units, especially in the area of asymmetric synthesis. In the following section, various methods for the synthesis of compounds with CMB units are described and the advantages and disadvantages of the methods are discussed.

3.4.1 Classical resolution method for CMB units

The classical method to obtain CMB compounds[45] was resolution of α-methylalkanoic acids (Scheme 9).



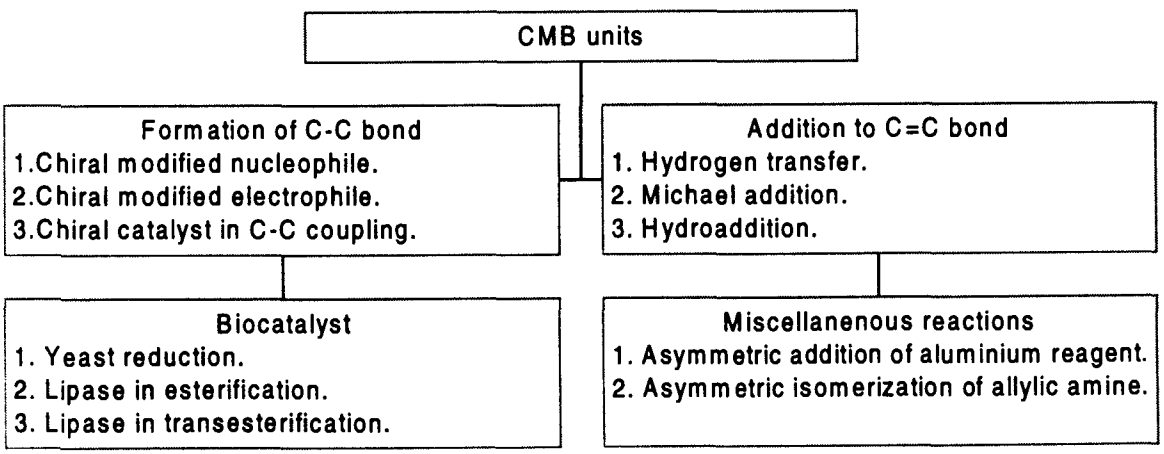
Scheme 9: Classical methods to obtain CMB

α-Methylalkanoic acids are readily prepared from alkylation of the dianion of propanoic acid with the appropriate n-alkyl bromide[46]. The acid is first converted to α-methylalkanoyl chloride and then reacted with a chiral amine such as α-methylbenzylamines, to form two diastereomeric amides. Being diastereoisomers, these two amides have different physical constants and can be separated by recrystallization.

Indeed, after four recrystallizations, compounds containing CMB units having *ee* larger than 99% could be obtained. The drawbacks of this approach are the low recovery and extensive labour required to perform the recrystallization.

3.4.2 Asymmetric synthesis approach to CMB units

As mentioned above, there has been tremendous progress in obtaining chiral molecules by employing asymmetric synthesis[47], which by definition, is a reaction in which an achiral unit in an ensemble of substrate molecules is converted by a reaction into a chiral unit in such a manner that the stereoisomeric products are produced in unequal amounts[48]. Asymmetric synthesis of CMB units can be classified into four principal groups:



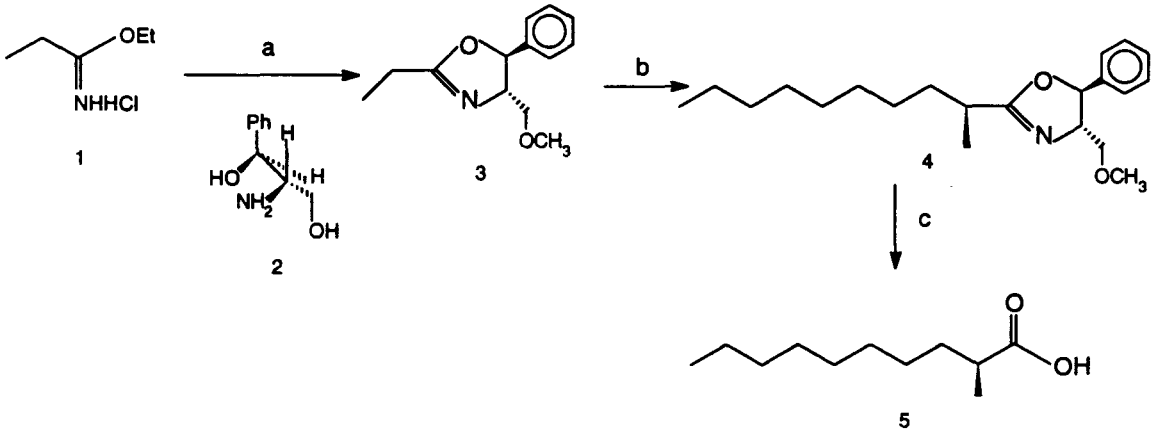
3.4.2.1 Synthesis of CMB units by formation of carbon-carbon single bonds

When forming a carbon-carbon single bond, chiral modification can be done on either the nucleophile or the electrophile. Recent advances in catalytic asymmetric reactions also make it possible to use tiny amounts of catalyst to catalyze carbon-carbon bond formation.

3.4.2.1.1 Chiral modification of the nucleophile

In synthesizing the intermediate of the sex pheromone of pine sawfly[49], (S)-2-methyldecanoic acid ***5***, chiral oxazoline[50] ***3***, a chiral modified nucleophile, which was prepared from (1S, 2S)-(+)-1-phenyl-2-amino-1,3-propanediol ***2*** and imino ether ***1*** was depronated by LDA followed by coupling with octyl iodide to yield oxazoline ***4***. This was then hydrolyzed by dilute sulfuric acid to yield (S)-2-methyldecanoic acid in 60% overall yield with 72% *ee* (Scheme 10).

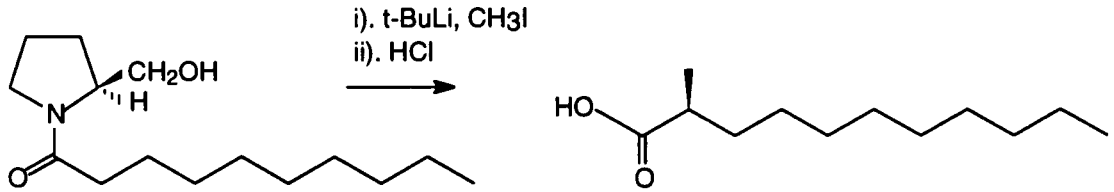
Scheme 10: Synthesis of (S)-2-methyldecanoic acid



(a). NaH, MeI. (b). LDA, n-$C_8H_{17}I$, -100 ^{0}C. (c). 4 M H_2SO_4.

Changing the chiral oxazoline to chiral amide ***6*** derived from (S)-(-)-prolinol increased the *ee* to 80%[51] (Scheme 11).

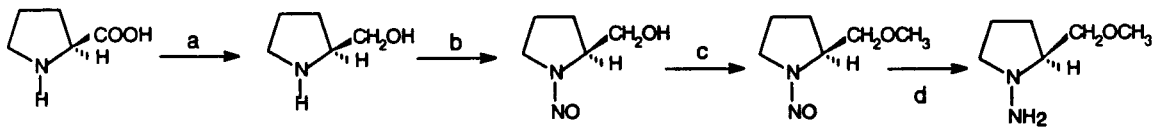
Scheme 11: Second route to (S)-2-methyldecanoic acid



6 5

A proline-derivative chiral auxiliary such as (S)-1-amino-2-methoxymethyl-pyrrolidine **8** (S)-AMP was prepared from (S)-proline ***7*** in four steps with 50% overall yield[52] (Scheme 12).

Scheme 12: Synthesis of (S)-1-amino-2-methoxymethylpyrrolidine

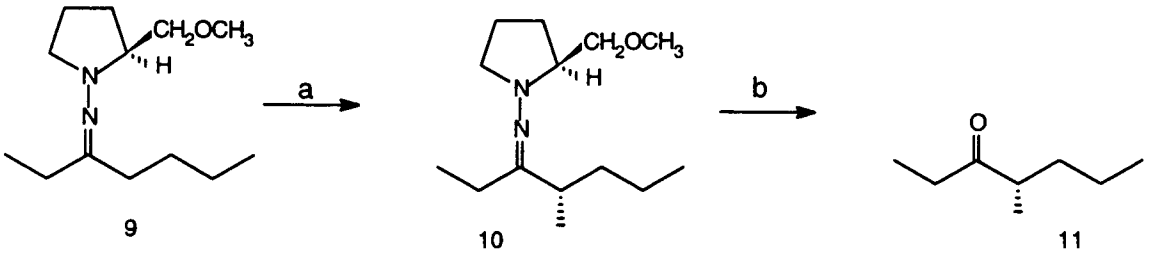


7 8

(a). $LiAlH_4$, ether. (b). RONO, THF. (c). NaH, THF, CH_3I. (d). $LiAlH_4$, THF.

Reaction of chiral hydrazine (S)-AMP **8** with diethyl ketone affords a chiral hydrazone ***9***, which was then deprotonated and coupled with propyl iodide. After hydrolysis of ***10*** in HCl, (S)-4-methyl-3-heptanone ***11*** which is the alarm pheromone of the leaf-cutting ant *Atta texana,* was obtained in 60% overall yield with 99.5% *ee* (Scheme 13).

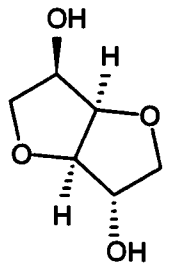
Scheme 13: Synthesis of (S)-4-methyl-3-heptanone



9 10 11

(a). LDA, ether, n-C_3H_7I, -110 ^{0}C. (b). 6N HCl/pentane.

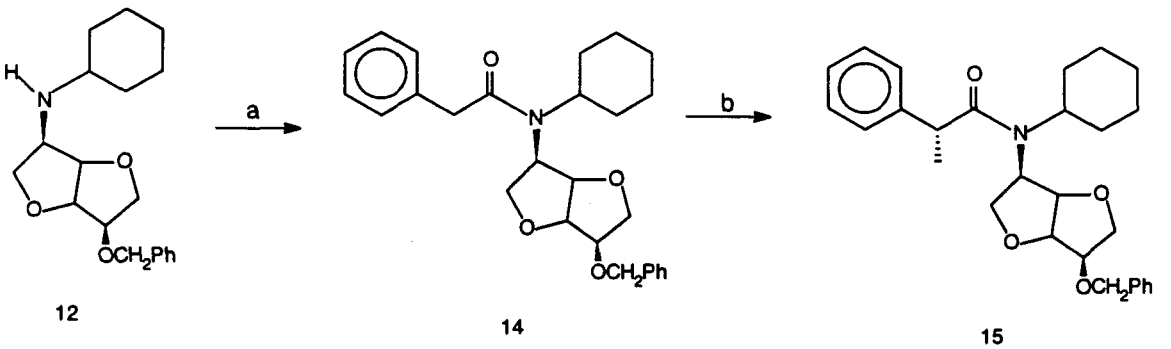
Another major source of chiral auxiliaries are from carbohydrate derivatives[53], such as aminoether ***12*** which was derived from the cheap and commercially available isosorbide, [1R, 4S, 5R, 8R]-2,6-dioxabicyclo [3. 3. 0] octan-4,8-diol ***13***, a starch derivative[54].



13

Treatment of amino-compound ***12*** with phenylacetic anhydride in pyridine yielded the corresponding phenylacetic amide ***14*** in 95% percent yield. The resulting amide was lithiated by LDA in THF-HMPA at 20 ^{0}C and then treated with methyl iodide at -78 ^{0}C to afford the chiral amide ***15*** in 82% overall yield and 82% *de*[55] (Scheme 14).

Scheme 14: Carbohydrate derivatives as chiral auxiliaries



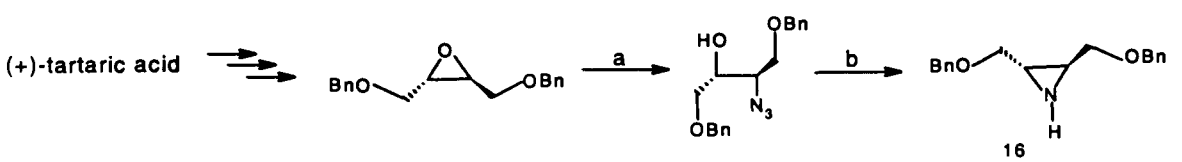
12 14 15

(a). $(PhCH_2CO)_2O$, pyridine, 80 ^{0}C. (b). LDA, HMPA, r.t., then CH_3I, -78 ^{0}C.

It was reported that the moieties on the chiral auxiliary influence the asymmetric induction and HMPA solvent plays an important role in asymmetric induction.

It is worth pointing out that all of the above chiral auxiliaries lack mirror symmetry. Recent advances in design of chiral auxiliaries indicate the importance of having a C_2 symmetry axis in order to reduce the number of possible competing diastereomeric transition states[56]. Chiral aziridines having C_2 symmetry have proven to be good chiral auxiliaries in modifying the nucleophile in asymmetric alkylations[57]. The chiral aziridine ***16*** is prepared in enantiomerically pure form from the relevant epoxide obtained from (+)-tartaric acid (Scheme 15).

Scheme 15: Synthesis of a chiral aziridine



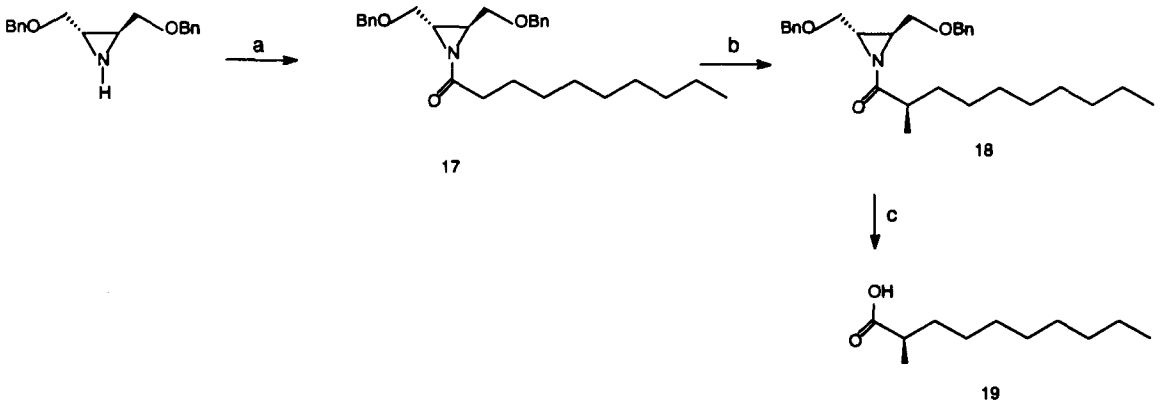
16

(a). NaN_3. (b). PPh_3.

N-Acylation of aziridine ***16*** with octanoic acid anhydride in pyridine afforded the chiral amide ***17*** which was lithiated by lithium hexamethyldisilazide (LiHMDS) in THF at -78 ^{0}C. Methyl iodide was added at that temperature to yield the chiral amide ***18*** which

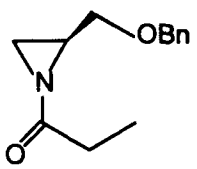
was hydrolyzed by LiOH to (R)-2-methyldecanoic acid ***19*** in 74% overall yield and 70% *ee* (Scheme 16).

Scheme 16: Synthesis of (R)-2-methyldecanoic acid



(a). $(n\text{-}C_{10}H_{21}CO)_2O$, pyridine. (b). LiHMDS, CH_3I. (c). LiOH.

It was reported that using the chiral aziridine ***20*** that lacks C_2 symmetry reduces the *ee%* by 40%.

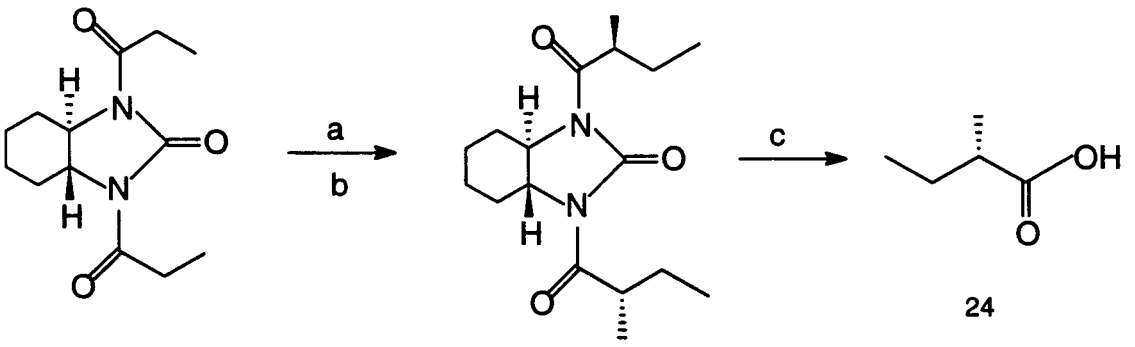


20

Another elegant use of a chiral auxiliary is called tandem asymmetric synthesis[58], in which one uses a chiral reagent or chiral catalyst to convert two prochiral centers into two chiral centers under *one-pot conditions* in a sequential way. There are several cases where tandem asymmetric synthesis is used in modifying the chiral nucleophile, such as in Davies' bifunctional chiral auxiliary series[59], using 1,3-diacylimidazolidin-2-one[60] ***22***. Deprotonation by potassium bis (trimethylsilyl) amide $KN(SiMe_3)_2$ followed by treatment with ethyl iodide at -30 ^{0}C provides ***23***. The chiral auxiliary in ***23*** was removed

by treatment with triethyl borane in AcOH to yield (S)-2-methyl-butyric acid ***24*** in 64% overall yield with 88% *ee* (Scheme 17).

Scheme 17: Synthesis of (S)-2-methylbutyric acid



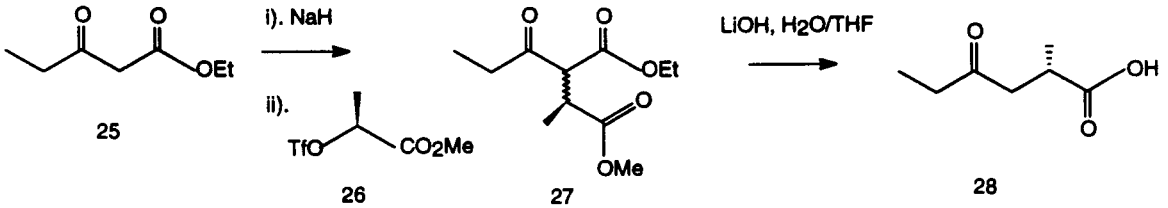
22 23 24

(a). $KN(SiMe_3)_2$. (b). EtI. (c). Et_3B, HOAc.

3.4.2.1.2 Chiral modification of the electrophile

Not only nucleophiles can be chirally modified, but also electrophiles, such as when β-ketoester ***25*** was deprotonated with sodium hydride, and then coupled with ester ***26*** which was readily prepared from lactic acid. The resulting ester ***27*** was treated with lithium hydroxide to yield the (2S)-2-methyl-4-ketobutyric acid ***28*** in 64% overall yield and 94% *ee* (Scheme 18)[61].

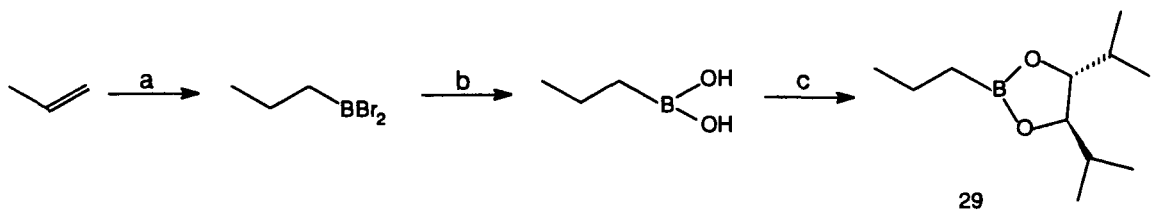
Scheme 18: Synthesis of (2S)-2-methyl-4-ketobutyric acid



25 26 27 28

Another chiral electrophile was the α-halo boronic ester ***29*** that was prepared

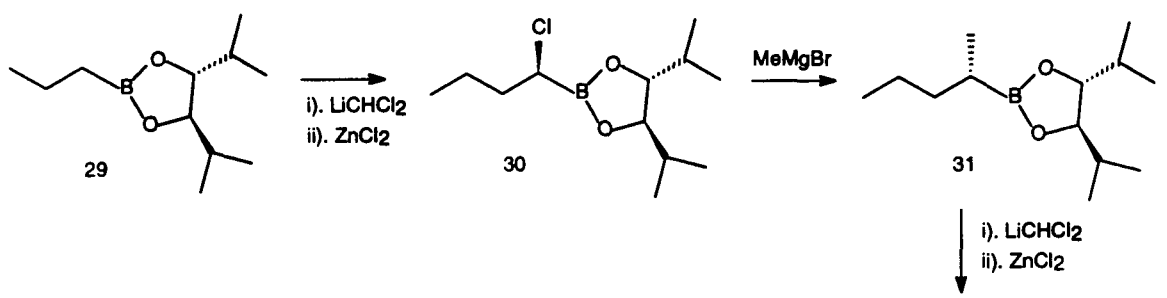
Scheme 19: Synthesis of a chiral α-halo boronic ester

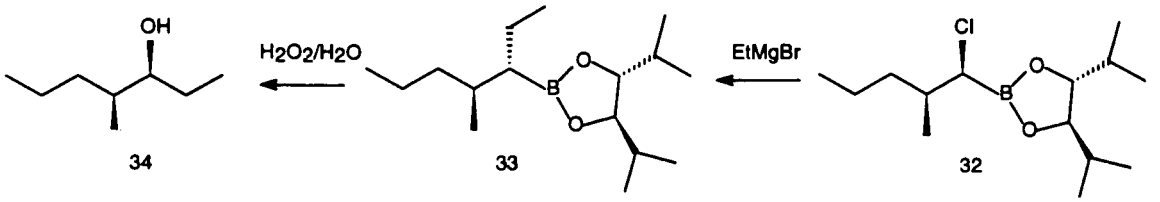


(a). $HBBr_2$, SMe_2, cat. BBr_3. (b). H_2O. (c). (R, R)-DIPED (1,2-diisopropylethanediol.

from propene in three steps (Scheme 19). The boronic ester ***29*** was then treated with dichloromethyl lithium at -100 ^{0}C in THF. Anhydrous zinc chloride was added to yield α-halo boronic ester ***30***. Methyl Grignard reagent then displaced the chloride by a methyl group. Then the first step was repeated to do another one carbon extension and generate a new α-halo boronic ester ***32***. Ethyl Grignard displaced the chloride to yield boronic ester ***33***. The chiral auxiliary was removed by H_2O_2 in water to yield the (3S, 4S)-4-methyl-3-heptanol ***34***, which is a component of the aggregation pheromone of the elm bark beetle *Scolytus multistriatus*, in 60% overall yield with 99% *ee*[62] (Scheme 20).

Scheme 20: Synthesis of (3S, 4S)-4-methyl-3-heptanol

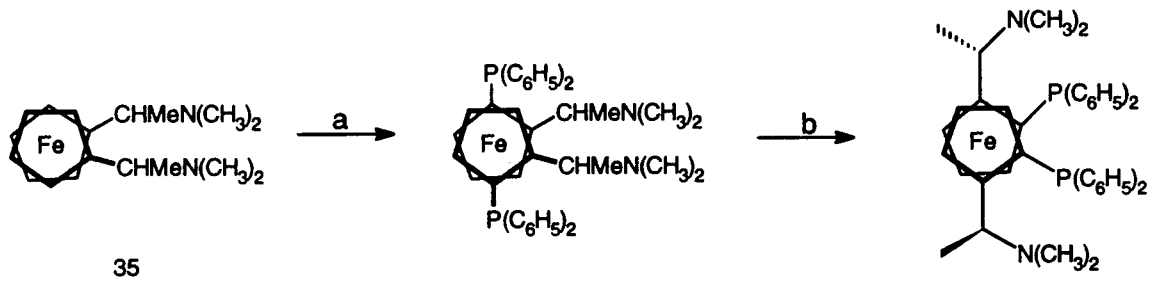




3.4.2.1.3 Asymmetric carbon carbon coupling catalyzed by a chiral catalyst

There has been a tremendous emphasis on catalytic asymmetric synthesis in recent years[63]. The chiral ferrocenylphosphine ligand ***36*** was prepared from N, N-dimethyl-1-ferrocenylethylethylamine ***35*** (Scheme 21).

Scheme 21: Synthesis of a chiral ferrocenylphosphine ligand

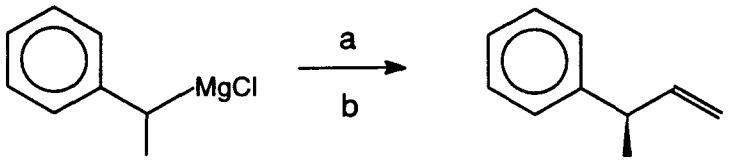


35 36

(a). n-BuLi, hexane, $ClPPh_2$. (b). (+)-tartaric acid, methanol.

In combination with the palladium complex $PdCl_2(MeCN)_2$, the complex was found to catalyze the asymmetric cross coupling of vinyl bromide with 1-phenylethylzinc chloride, which was prepared by mixing 1-phenylethylmagnesium chloride ***37*** with excess zinc chloride. The product (R)-3-phenylbut-1-ene ***38*** was prepared in quantitative yield with 93% *ee*[64] (Scheme 22).

Scheme 22: Synthesis of (R)-3-phenylbut-1-ene



37 38

(a). $ZnCl_2$. (b). CH_2=CHBr, 0.5% mol of *36* and $PdCl_2(MeCN)_2$, THF/ether.

3.4.2.2 Synthesis of CMB units by addition to a carbon carbon double bonds

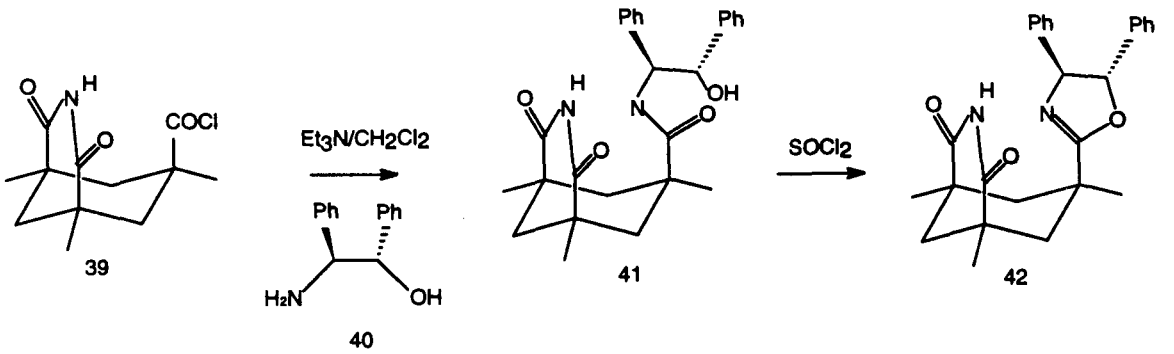
Three methods that employ addition to carbon carbon double bonds that can generate compounds containing CMB units are introduced here. These are asymmetric hydrogen transfer methods, the asymmetric Michael reaction, and asymmetric hydroaddition. In asymmetric hydrogen transfer methods, hydrogen either from a chiral proton source or hydrogen gas was introduced to either a chirally modified double bond or one under the influence of a chiral catalyst. In the asymmetric Michael reaction, methyl anions or other nucleophiles are enantioselectively added, either to chirally modified double bonds, or one under the influence of a chiral catalyst to a non-chiral double bond. All the asymmetric hydroadditions were catalyzed by chiral catalysts. Small molecules such as CO, H_2O, H_2, HCN, CH_2=CH_2, are introduced enantioselectively to the substrate. These reactions have very high potential for applications in industry.

3.4.2.2.1. Asymmetric hydrogen transfer

Enantioselective protonation of a prochiral enolate is an effective method to synthesize α-substituted carbonyl compounds. If the α-substituent is a methyl group, the

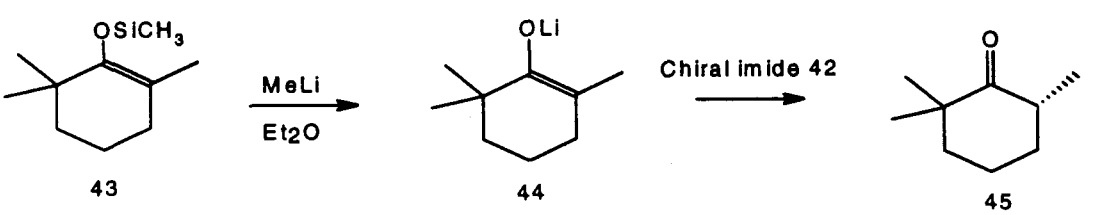
CMB unit can be obtained in a short number of steps and good *ee*. Numerous successes have been reported in the last twenty years. Chiral imide ***42*** which contains an asymmetric 2-oxazoline was found to be an excellent chiral source in enantioprotonation of lithium enolates. The chiral imide can be synthesized from Kemp's tricarboxylic acid in two steps with more than 90% overall yield. The starting imide acid chloride ***39*** was reacted with (1R, 2S)-2-amino-1,2-diphenylethanol ***40*** to afford amide ***41***. The amide was then cyclized by treatment with thionyl chloride to form a 2-oxazoline ring to yield the chiral imide ***42*** (Scheme 23).

Scheme 23: Synthesis of a chiral imide containing an asymmetric 2-oxazoline



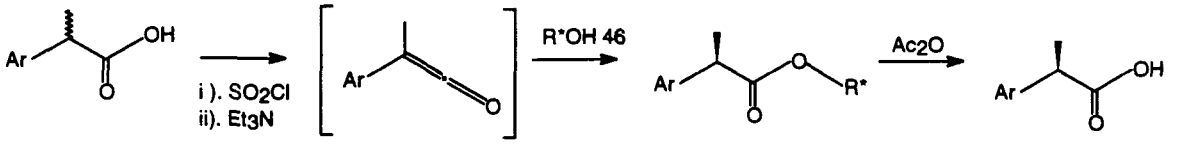
When lithium enolate ***44***, prepared from silyl enol ether ***43*** and methyl lithium at -78 ^{0}C, was reacted with chiral imide ***42***, (R)-2,2,6-trimethylcyclohexanone ***45*** was generated in 87% *ee*[65] (Scheme 24).

Scheme 24: Synthesis of (R)-2,2,6-trimethylcyclohexanone

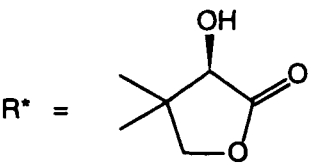


Asymmetric transformation of racemic 2-arylpropionic acids to their enantiomers by tertiary amine mediated addition of the chiral alcohol ***46***, provides a convenient method to obtain CMB units.

Scheme 25: Synthesis of a chiral 2-arylpropionate ester



47 48 49



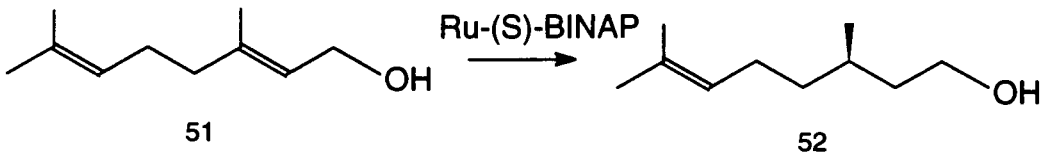
46

Treatment of racemic ibuprofen ***47*** with thionyl chloride and triethylamine afforded ketene ***48***, which was then reacted with chiral α-hydroxy ester ***46*** to give the 2-arylpropionate esters ***49*** in 99% *de*. It was reported that the diastereoselectivity of the reaction is highly dependent on solvent polarity, with nonpolar solvents, such as hexane and heptane being the most effective[66] (Scheme 25).

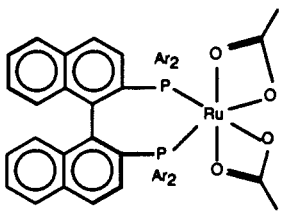
Recently, there have been tremendous improvements in asymmetric catalytic homogeneous hydrogenation. A well known catalyst is a ruthenium (II)-BINAP (2,2'-bis (diphenylphosphino)-1,1'-binaphthyl) dicarboxylate complex (Ru-(S)-BINAP)[67] ***50*** which exhibits very high catalytic activity and enantioselectivity in the hydrogenation of a wide range of substrate such as enamides[68], α-(acylamino)acrylic acid[69], alkyl and aryl-substituted acrylic acids, β-γ-unsaturated carboxylic acids[70], allylic and homoallylic

alcohols and α-amino ketones. Geraniol ***51*** treated in methanol under 100 atm hydrogen pressure at 20 ^{0}C with chiral complex ***50*** gave (R)-citronellol in 3.5 hrs in a quantitative yield and 96% *ee* (Scheme 26).

Scheme 26: Synthesis of citronellol



51 52



50

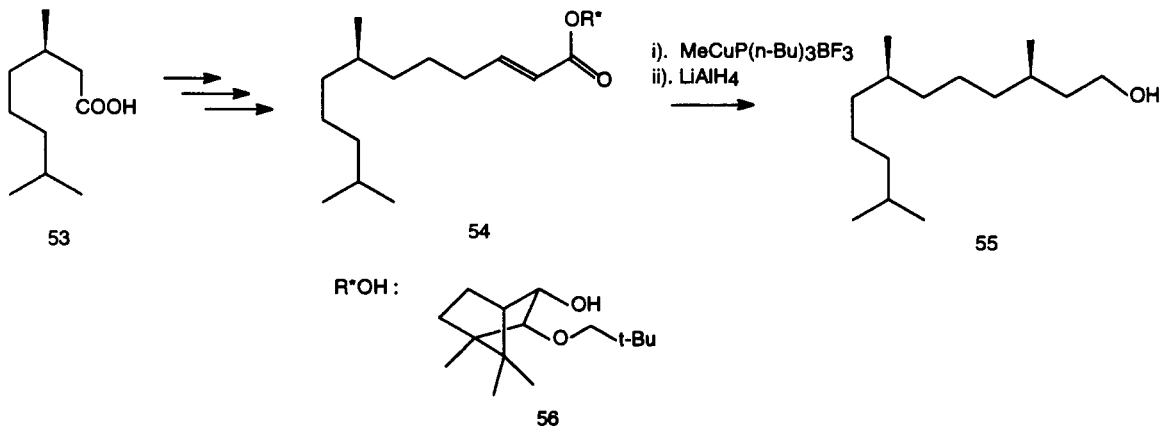
However, Ru-BINAP is a homogenous catalyst that is hard to recycle and reuse. Recently, a heterogeneous asymmetric Ru-BINAP was made successfully by immobilizing the catalyst with ethylene glycol onto a controlled-pore glass support. This heterogeneous catalyst reportedly has no detectable leaching of Ru which makes it more practical and cost-effective in asymmetric catalytic hydrogenation[71].

3.4.2.2.2. Asymmetric Michael reaction

Organocopper reagents were recently reported to give 1,4- asymmetric addition to the α,β-unsaturated carbonyl groups. When $MeCuP(n\text{-}Bu)_3 \bullet BF_3$ was added to the α,β-unsaturated ester ***54*** which was prepared from (S)-citronellic acid ***53*** and chiral auxiliary

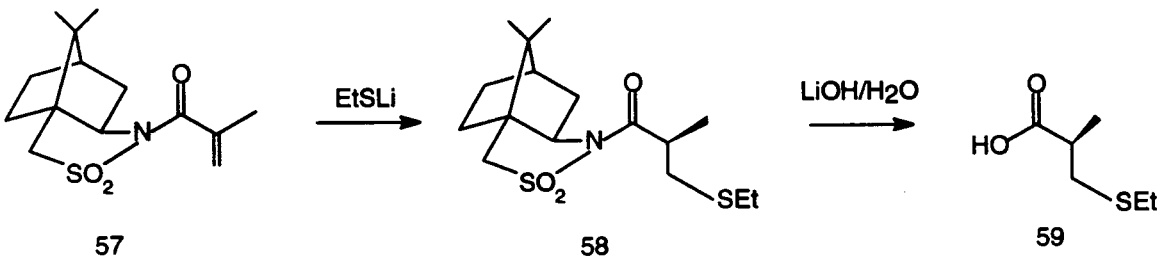
56. The side chain of Vitamin E, ***55***, was prepared from ***54*** in 87% overall yield with 98% *ee*[72] (Scheme 27).

Scheme 27: Synthesis of the side chain of vitamin E



Sulfur compounds such as ethanethiol, can behave as nucleophiles to give 1,4-additions. Reaction of the thiol with butyl lithium generates the thiolated anion EtS$^-$ which adds to N-methacryloylcamphorsultam[73] ***57*** at -78 ^{0}C to afford the amide ***58***. The chiral auxiliary was removed by treatment with LiOH in aqueous THF to afford the final product thiol ***59*** in 97% overall yield with 90% *ee*[74] (Scheme 28).

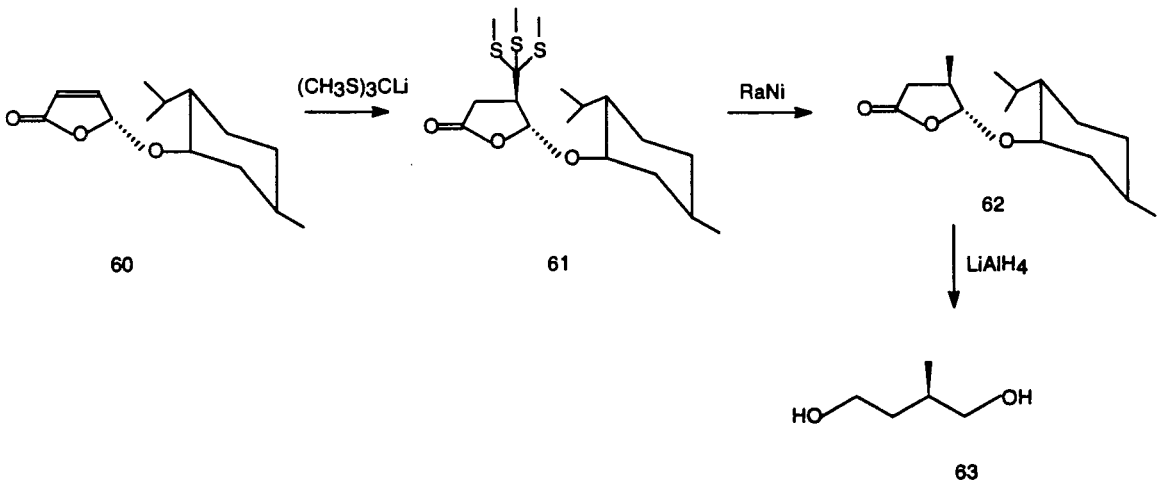
Scheme 28: Asymmetric Michael reaction using ethanethiol



Lithiated trimethylthiomethane also underwent asymmetric Michael addition to 5(R)-(1-menthyloxy)-2-[5H]-furanone ***60*** to yield lactone ***61*** which was desulfurized by

Raney nickel to lactone ***62***. After reduction by $LiAlH_4$, (R)-2-methyl-1,4-butanediol ***63*** was obtained in 76% overall yield with *ee* larger than 99%[75] (Scheme 29).

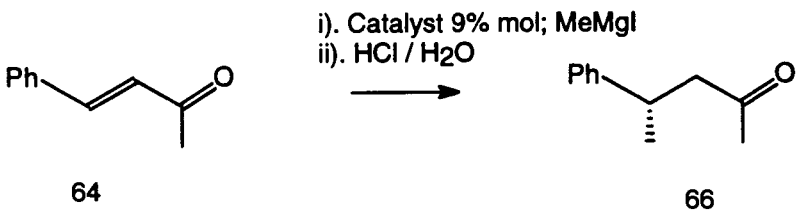
Scheme 29: Synthesis of (R)-2-methyl-1,4-butanediol



60 61 62 63

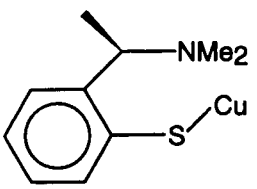
There has been also some progress in asymmetric catalytic Michael addition. Arenethiolatocopper(I) complex ***65*** was reported to catalyze methyl Grignard reagent 1,4-addition to 4-phenyl-3-buten-2-one ***64*** to afford the product (R)-4-phenyl-4-methyl-3-butan-2-one ***66*** in 97% overall yield[76] with 76% *ee* (Scheme 30).

Scheme 30: Synthesis of (R)-4-phenyl-2-pentanone



64 66

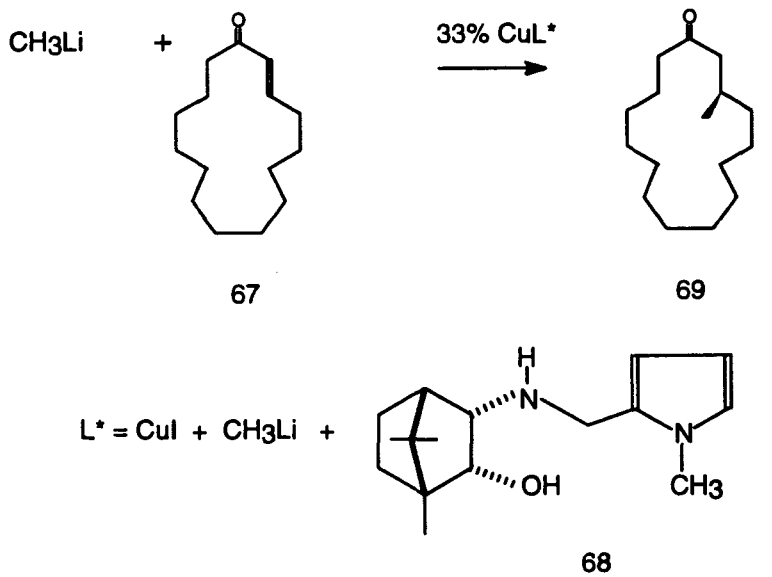
Catalyst :



65

The chiral complex CuL*, derived from (1R,2R,3S,4S)-3-[(1-methylpyrrol-2-yl)methylamino]-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-ol[77] ***68***, methyl lithium and CuI at -78 ^{0}C, was reported to catalyze MeLi enantioselective conjugate addition to (E)-cyclopentadec-2-enone ***67*** to yield the product ***69*** in 76% overall yield with 96% *ee* (Scheme 31). Methyl lithium generally is very nucleophilic, normally undergoing 1,2-addition instead of 1,4 addition to α-β-unsaturated carbonyl compounds. However, under the influence of these chiral copper compounds, only 1,4-addition was observed[78].

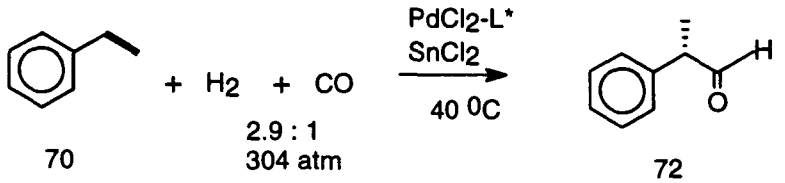
Scheme 31: Synthesis of (3S)-3-methylcyclopentadecanone



3.4.2.2.3. Asymmetric hydroaddition reaction

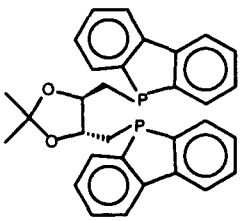
Asymmetric hydroformylation is a convenient synthetic method for obtaining chiral aldehydes from olefinic substrates. Chiral diphosphine ligand ***71*** together with palladium and tin chloride was reported to catalyze the enantioselective addition of hydrogen and CO to styrene ***70*** to yield 2-phenyl propanal ***72*** in 79.8% *ee* (Scheme 32)[79].

Scheme 32: Synthesis of 2-phenylpropanal



70 72

L* =

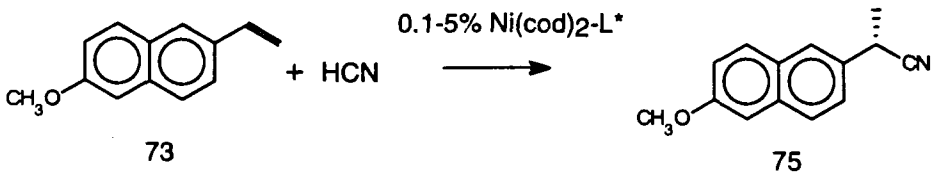


71

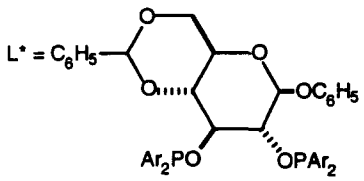
The drawbacks of the hydroformylation reaction are the requirement for high pressures of H_2 and CO gas and the ability of the aldehyde product to racemize.

A nickel (0) complex with the chiral phosphinite ligand ***74***, derived from β-phenyl glucoside was reported to catalyze the asymmetric hydrocyanation of vinylarenes ***73*** to yield ***75***, a precursor of naproxen, in 85% *ee* with 100% conversion. It was reported that electron-withdrawing substituents on phosphorus-linked aryl groups dramatically enhanced the enantioselectivity[80] (Scheme 33).

Scheme 33: Asymmetric hydrocyanation



73 75

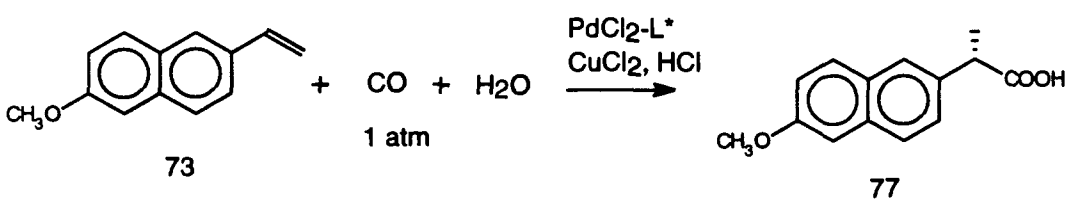


74

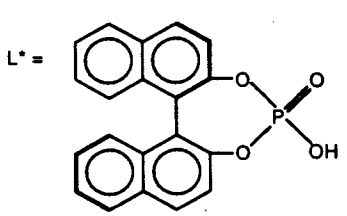
Ar = 3,5-$(CF_3)_2C_6H_3$

Palladium catalyzed asymmetric hydrocarboxylation provided another option for the synthesis of naproxen. The chiral catalyst which was derived from $PdCl_2$ and (R)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate ***76*** catalyzed the addition of CO and water to 2-vinyl-6-methoxynaphthalene ***73*** in acidic conditions to yield naproxen [2-(6-methoxy-2-naphthyl)propionic acid] ***77*** in 64 % yield with 91% *ee* (Scheme 34).

Scheme 34: Synthesis of naproxen



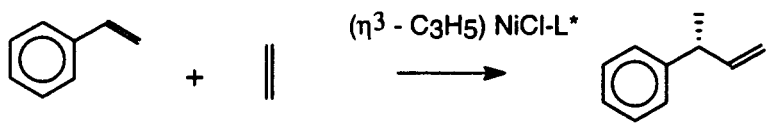
73 77

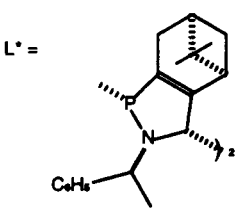


76

The nickel complex of ligand ***78,*** which was derived from (R)-myrtenal and (S)-1-phenylethylamine, was reported to catalyze the enantioselective hydrovinylation of styrene to produce chiral 2-phenyl-1-butene in 95.2% *ee* on a 10 kg scale[81] (Scheme 35).

Scheme 35: Synthesis of 2-phenyl-1-butene



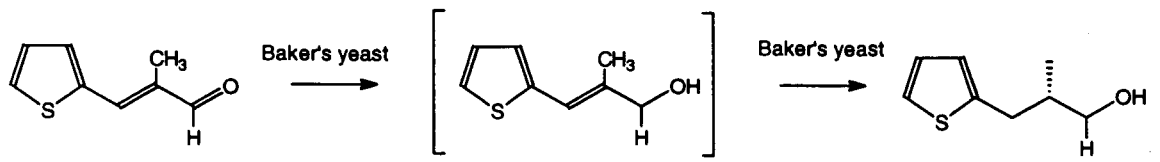


78

3.4.2.3 Biocatalyst approach to CMB units

Since most biocatalysts, such as enzymes, are inherently chiral, the transformations under these catalysts are also enantioselective or diastereoselective. There has been enormous progress in this area recently[82]. For example, baker's yeast[83] was reported to enantioselectively reduce the (E)-2-methyl-3-(2-thiophene)propenal ***79*** to afford (S)-(-)-2-methyl-3-(2-thiophene)-1-propanol ***80*** in 70% with 98% *ee* (Scheme 36).

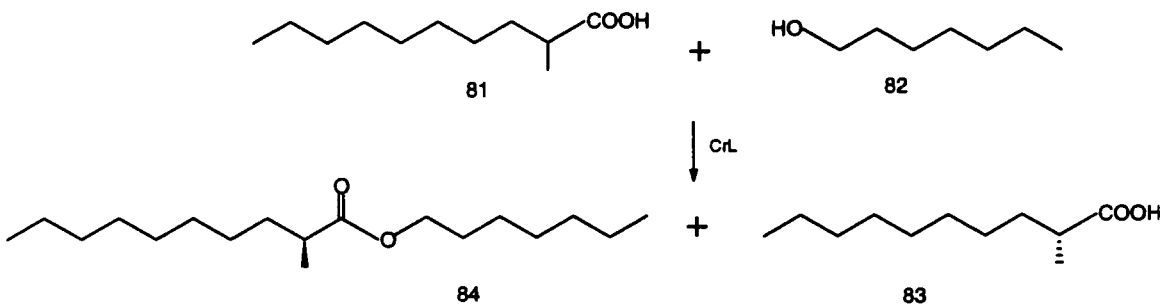
Scheme 36: Synthesis of (S)-(-)-2-methyl-3-(2-thiophene)-1-propanol



79 80

Lipase from *Candida rugosa* was reported to catalyze the esterification of racemic 2-methyldecanoic acid ***81*** with 1-heptanol to yield (R)-2-methyldecanoic acid ***83*** (87% *ee* at 54% conversion) and heptanol ester of (S)-2-methyldecanoic acid ***84*** (76% ee at 49% conversion)[84] (Scheme 37).

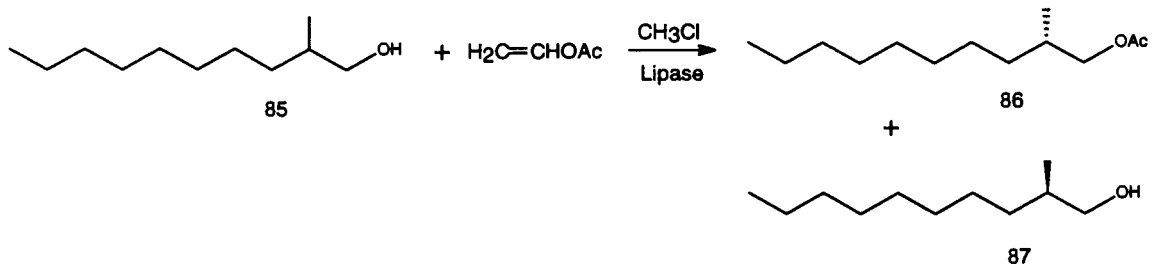
Scheme 37: Synthesis of (S)-2-methyldecanoic acid



81 82 84 83

Lipases from *Pseudomonas* were reported to catalyze the enantioselective transesterification of racemic 2-methyl-1-decanol ***85*** with vinyl acetate to yield (S)-2-methyl-1-decanol acetate ***86*** (98% *ee* at 40% conversion) and (R)-2-methyl-1-decanol ***87*** (98% *ee* at 60% conversion)[85] (Scheme 38).

Scheme 38: Synthesis of (R)-2-methyl-1-decanol

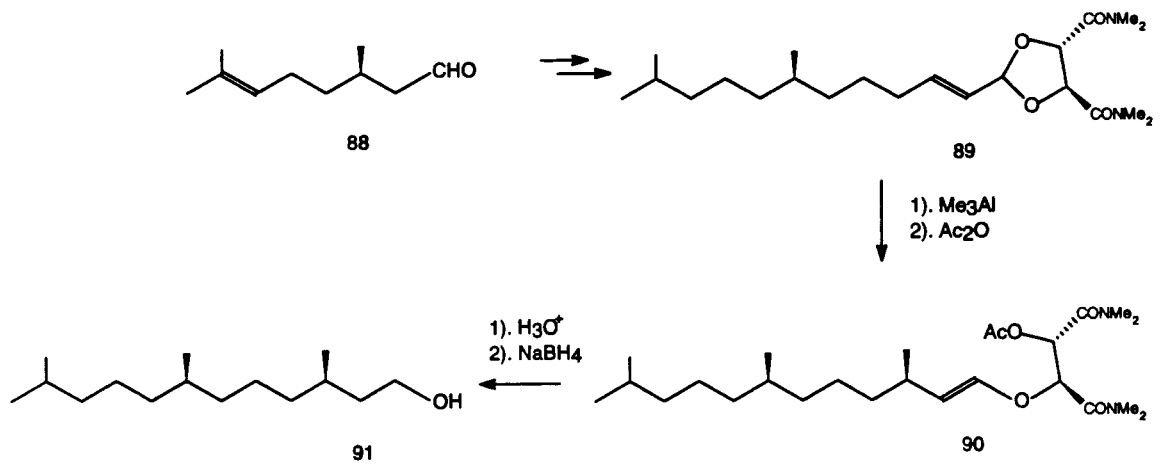


85 86 87

3.4.2.4 Miscellaneous reactions that afford CMB units

Trimethylaluminum was reported to undergo asymmetric addition to α,β-unsaturated chiral acetal ***89*** which was derived from chirally pure tartaric acid diamide to afford chiral acetal ***90***. After hydrolysis and reduction, the side chain ***91*** of vitamins E and K was obtained in 53% overall yield[86] with 96% *ee* (Scheme 39).

Scheme 39: Synthesis of components of vitamins E and K

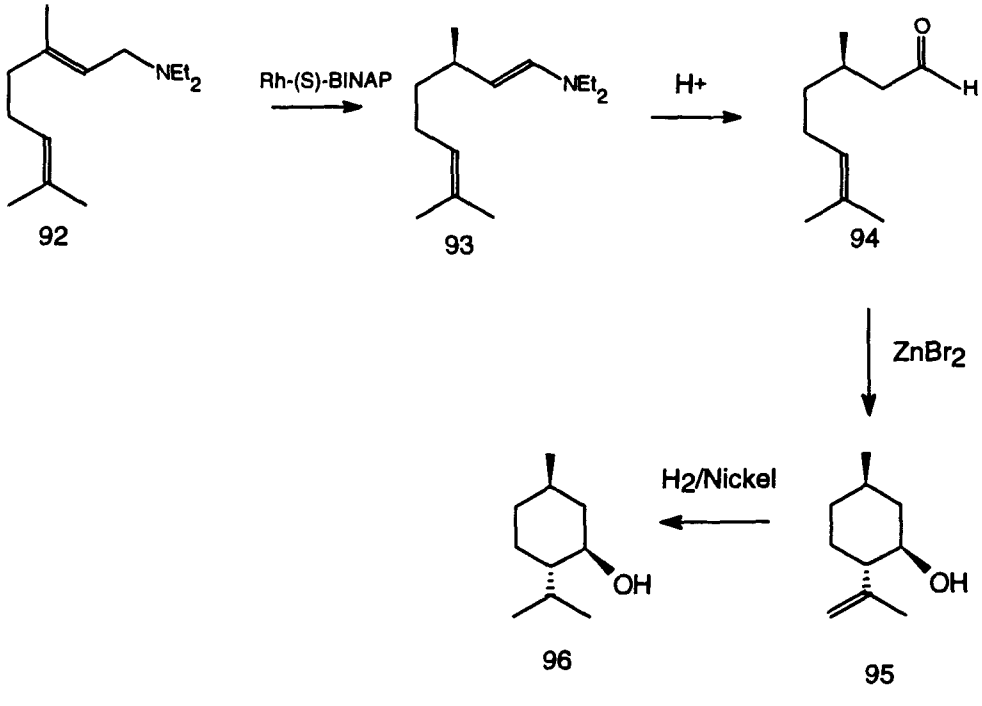


88 89 90 91

Under the influence of a chiral Rh-BINAP complex, allylamines such as N-diethylgeranylamine ***92,*** isomerized to the corresponding enamine ***93*** which was

hydrolyzed to afford (R)-citronellal ***94*** with *ee* higher than 98% at quantitative conversion. In two more steps (+)-citronellal could be converted to (-)-menthol ***96*** almost quantitatively. This process has been applied by the Takasago International Corporation to the manufacturing of (-)-menthol on a ~1500t/year scale (Scheme 40).

Scheme 40: Commercial Synthesis of (-)-menthol



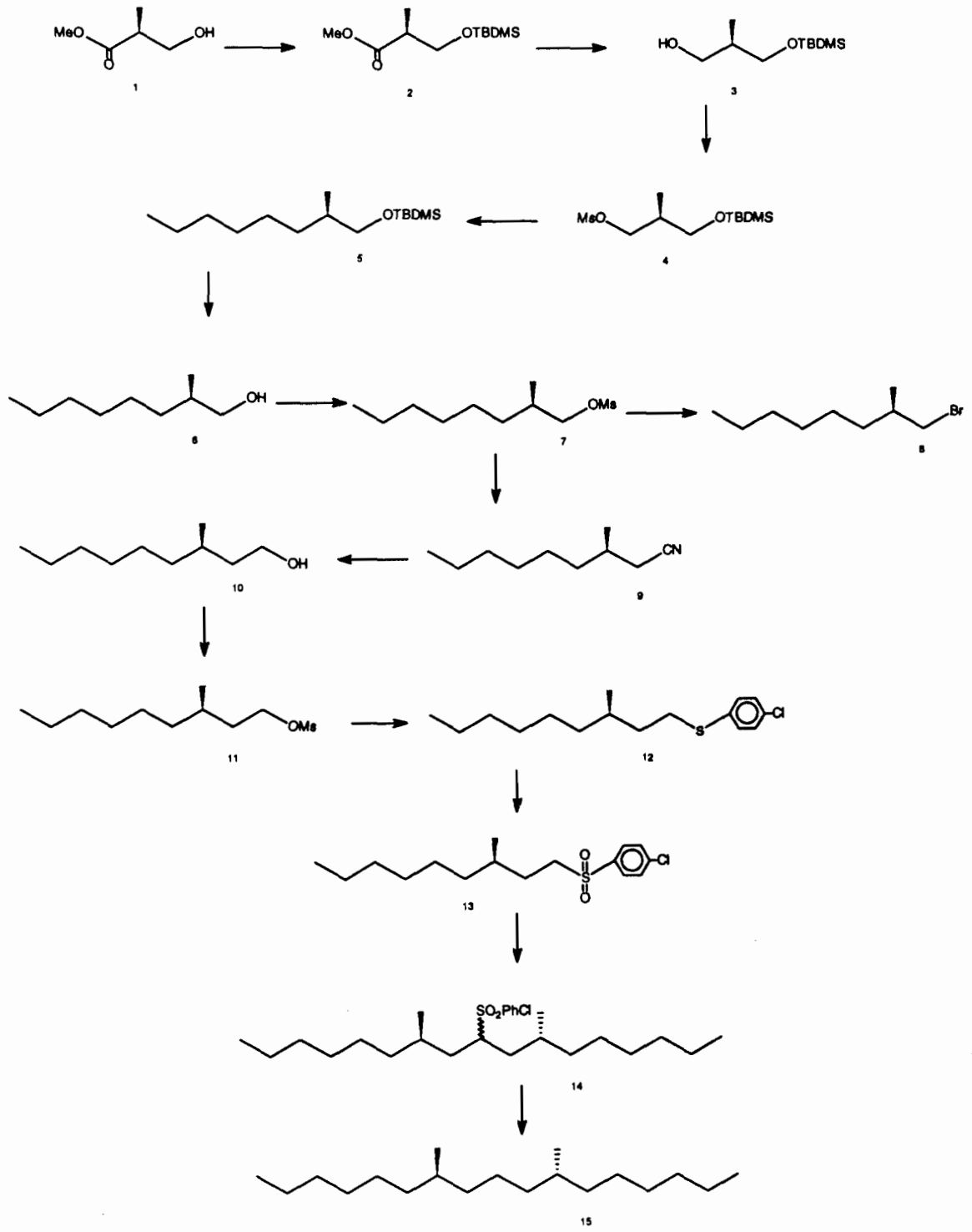
Chapter 4. Synthesis of components of the sex pheromone of the spring hemlock looper

4.1 Synthesis of all stereoisomers of 7,11-dimethylheptadecane

The synthesis of all stereoisomers of 7,11-dimethylheptadecane was started from the chiral building block (S) or (R)-methyl 3-hydroxy-2-methyl propionate (MHMP). Both (R) and (S)-MHMP units are commercially available in high chiral purity (>98%). The synthesis of (7R)-(11R)-7,11-dimethylheptadecane (R, R-7,11diMe:17H) (Scheme 41) began with (S)-MHMP units. The synthesis of (7S)-(11S)-7,11-dimethylheptadecane (S, S-7,11diMe:17H) was synthesized in the same way except from the (R)-MHMP starting unit. The synthesis of meso-7,11-dimethylheptadecane (meso-7,11diMe:17H) was synthesized from (3R)-3-methyl-1-p-chlorophenylsulphonylnonane (**13**) by a coupling with (2S)-2-methyl-1-bromooctane, followed by desulphonation.

(S)-MHMP was reacted with tert-butyldimethylsilyl chloride to protect the hydroxyl group to give (2S)-2-methyl-3-[(tert-butyldimethylsilyl)oxy]-2-methyl propionate[87] (**2**). The ester group of **2** was reduced to give (2R)-3-[(tert-butyldimethylsilyl) oxy]-2-methyl-propanol[88] (**3**) by borane in THF.

Scheme 41: Synthesis of (7R)-(11R)-7,11-dimethylheptadecane



Treatment of **3** with methanesulfonyl chloride in dichloromethane yielded (2S)-3-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl mesylate[86] (**4**) which was then coupled with 1-pentyl magnesium bromide with CuI as a catalyst to give (2R)-3-[(tert-butyldimethylsilyl)oxy]-2-methyloctanol (**5**). The silyl protecting group of **5** was then removed with 10% HF in acetonitrile to afford (2R)-2-methyloctanol[89] (**6**)* . Treatment of **6** with methanesulfonyl chloride in dichloromethane yielded (2R)-2-methyloctyl mesylate (**7**). Refluxing a mixture of **7** with tetradecyltrimethyl ammonium bromide in acetone gave (2R)-2-methyl-1-bromooctane (**8**) that was ready for coupling. Another portion of **7** was treated with sodium cyanide in DMSO to afford (2R)-1-cyano-2-methyloctane (**9**). DIBAL in pentane reduced **9** to (3R)-3-methylnonanal which was further reduced by sodium borohydride in ethanol to (3R)-3-methylnonanol[90] (**10**). Treatment of **10** with methanesulfonyl chloride in dichloromethane yielded (3R)-3-methylnonanyl mesylate (**11**) which was then coupled with p-chlorothiophenol in DMF to afford (3R)-3-methyl-1-p-chlorophenylthiononane (**12**). Oxidation of **12** by MCPBA yielded (3R)-3-methyl-1-p-chlorophenylsulphonylnonane (**13**). Treatment of **13** with n-BuLi in THF and then coupling with (2R)-2-methyl-1-bromooctane (**8**) afforded (7R)-(11R)-7,11-dimethyl-9-p-chlorophenylsulphonylheptadecane (**14**). The final desulphonation was carried out in liquid ammonia with lithium metal to yield (7R)-(11R)-7,11-dimethylheptadecane (**15**).

* The chiral purity of **6** was found unchanged as determined by chiral column GC.

(7R)-(11R)-7,11-dimethylheptadecane, (7S)-(11S)-7,11-dimethylheptadecane and meso-7,11-dimethylheptadecane are new compounds that have not been synthesized before. They will be field tested in the spring of 1996.

4.2 Experimental section

Coupled GC-high resolution MS was done in a Kratos MS80RFA fitted with a DB-5-coated, fused silica column (30m X 0.25 mm ID J&W Scientific) in EI mode. Elemental analysis was carried out on a Carlo Erba Model-1106 Elememtal Analyzer by Mr. M.Yang. Other experimental details were the same as reported in section 2.4.

(2S)-Methyl 3-[(tert-butyldimethylsilyl)oxy]-2-methyl propionate (2):

To a solution of *tert*-butyldimethylsilyl chloride (14.0 g, 93.2 mmol), triethylamine (8.55 g, 84.7 mmol) and 4-dimethylaminopyridine (1.03 g, 8.47 mmol) in CH_2Cl_2 (150 ml) was added (S)-methyl 3-hydroxyl-2-methylpropionate (10.1 g, 84.7 mmol). The reaction mixture was kept at 0 ^{0}C overnight, water (50.0 ml) was added and the mixture extracted with CH_2Cl_2 (3X100 ml). Drying over sodium sulfate and purification on a silica column afforded a colorless oil (19.0 g, 97% yield). $[\alpha]^{25}_D$ +15.9 (*c* 0.09, $CHCl_3$). For (R)-isomer, $[\alpha]^{25}_D$ -16.5 (*c* 0.12, $CHCl_3$). Lit[91]. $[\alpha]^{25}_D$ -20.5 (*c* 3.21, CH_2Cl_2) for (R)-isomer.

^{1}H NMR δ: 3.76 (dd, J=10, 7 Hz, 1H, CHOTBDMS), 3.68 (s, 3H, OCH_3), 3.64 (dd, J=10, 6 Hz, 1H, CHOTBDMS), 2.64 (m, 1H, C*H*CH_3), 1.12 (d, J=7 Hz, 3H, CHC*H*$_3$), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.04 (s, 6H, $Si(CH_3)_2$).

*(2R)-3-[(tert-Butyldimethylsilyl)oxy]-2-methyl-1-propanol(**3**):*

To a solution of **2** (15 g, 65 mmol) in THF (100 ml) was added BH_3•SMe_2 (10 ml, 100 mmol) at room temperature. The mixture was stirred at room temperature for 3 days and quenched with 5% NaOH (25 ml) at 0 ^{0}C. The mixture was extracted with ether (3X50 ml), dried over sodium sulfate and evaporated *in vacuo*. Purification on a silica column yielded a colorless oil (12 g, 88%). $[\alpha]^{25}_D$ +9.02 (*c* 0.10, $CHCl_3$). For (S)-isomer, $[\alpha]^{25}_D$ -8.78 (*c* 0.09, $CHCl_3$). Lit[86]. $[\alpha]^{25}_D$ +9.44 (*c* 1.97, CH_2Cl_2) for (R)-isomer.

^{1}H NMR δ: 3.50-3.80 (m, 4H), 2.86 (brs, 1H, OH), 1.93 (m, 1H, C*H*CH_3), 0.9 (s, 9H, $SiC(CH_3)_3$), 0.81 (d, J=7 Hz, 3H, CHC*H*$_3$), 0.09 (s, 6H, , $Si(CH_3)_2$).

*(2S)-3-[(tert-Butyldimethylsilyl)oxy]-2-methylpropyl 1-mesylate(**4**):*

To a solution of **3** (9.0 g, 44 mmol) and triethylamine (8.9 g, 88 mmol) in CH_2Cl_2 (50 ml) was added methanesulfonyl chloride (6.6 g, 57 mmol) at 0 ^{0}C. After 15 min, water (10 ml) was added and the reaction mixture was extracted with ether (3X50 ml). Drying over sodium sulfate and purification on a silica column gave a colorless oil (12 g, 96%). $[\alpha]^{25}_D$ +6.80 (*c* 0.11, $CHCl_3$). For (R)-isomer, $[\alpha]^{25}_D$ -7.21 (*c* 0.12, $CHCl_3$).

^{1}H NMR δ: 4.22 (dd, J=10, 6 Hz, 1H), 4.14 (dd, J=9.5, 5.5 Hz, 1H), 3.61 (dd, J=10.5, 5 Hz, 1H), 3.48 (dd, J=10, 6.5 Hz, 1H), 3.0 (s, 3H, SO_2CH_3), 2.04 (m, 1H, C*H*CH_3), 0.99 (d, J=7 Hz, 3H, CHC*H*$_3$), 0.89 (s, 9H, SiC$(CH_3)_3$), 0.01 (s, 6H, Si$(CH_3)_2$).

EIMS: 187(58%, M^+ - MsO), 153(100%, M^+ - OTBDMS), 89(12%), 75(20%).

(2R)-3-[(tert-butyldimethylsilyl)oxy]-2-methyloctan-1-ol(5):

1-Bromopentane (3.0 g, 20 mmol) was added dropwise to magnesium turnings (0.96 g, 40 mmol) in 15ml freshly distilled THF, and then the solution refluxed for 1 h. Grignard reagent was then added to a solution of **4** in THF (60 ml) and CuI (0.66 g, 3.5 mmol) at -30 ^{0}C. The reaction was kept at -30 ^{0}C for 2 h and then slowly warmed to room temperature overnight. NH_4Cl (Sat. 50 ml) and H_2O (20 ml) were added and the mixture stirred until a dark blue solution formed. Extraction with hexane(3X50 ml) followed by drying over sodium sulfate and purification on a silica column afforded a colorless oil (1.3 g, 72%). $[\alpha]^{25}_D$ +8.82 (*c* 0.13, $CHCl_3$). For (S)-isomer, $[\alpha]^{25}_D$ -9.03 (*c* 0.09, $CHCl_3$).

^{1}H NMR δ: 3.45 (dd, J=6, 5.5 Hz, 1H, CHOTBDMS), 3.34 (dd, J= 7, 7 Hz, 1H, CHOTBDMS), 1.51 (m, 1H, C*H*CH_3), 1.25 (m, 10H), 0.89 (m, 12H), 0.05(s, 6H, Si$(CH_3)_3$). Anal. Calcd. for $C_{15}H_{34}OSi$: C, 69.77%; H, 13.18%. Found: C, 69.70%; H, 13.05%. EIMS: 201(31%, M^+ - C$(CH_3)_3$), 75(100%), 69(14%), 57(11%), 41(22%).

(2R)-2-methyl-1-octanol(6):

To a solution of **5** (2.0 g, 7.7 mmol) in acetonitrile (30 ml) was added 10% HF (1.0 ml) at room temperature and the solution stirred for 2 h, and water (30 ml) was added. The solution was extracted with ether:hexane(1:1) (3X30 ml). Purification on a silica column afforded a colorless oil (1.0 g, 91%). $[\alpha]^{25}_{D}$ +10.1 (*c* 0.11, $CHCl_3$). For (S)-isomer,

$[\alpha]^{25}_{D}$ -9.88 (*c* 0.08, $CHCl_3$). Lit[92]. $[\alpha]^{20}_{D}$ -7.07 (neat) for (S)-isomer.

^{1}H NMR δ: 3.5 (dd, J= 5.5, 6Hz, 1H, CHOTBDMS), 3.4 (dd, J=7, 6.5Hz, 1H, CHOTBDMS), 1.65-1.20 (m, 11H), 0.92 (d, J= 7Hz, 3H, $CHCH_3$), 0.87 (t, J= 7Hz, 3H, CH_2CH_3).

EIMS: 97(22%), 83(29%, M^+ - $HOCH_2CHCH_3$), 71(61%), 57(72%), 41(100%).

(2R)-2-methyloctanyl-1-mesylate(7):

To a solution of **6** (1.0 g, 7.0 mmol) and triethylamine (3.9 ml, 28 mmol) in CH_2Cl_2 (15 ml) was added methanesulfonyl chloride (1.6 ml, 14 mmol) at 0 ^{0}C. The reaction was kept at 0 ^{0}C for 15 minutes, water (15 ml) was added and the reaction mixture was extracted with ether (3X15 ml). The extract was dried over sodium sulfate and purified on a silica column to give a colorless oil (1.4 g, 90%). $[\alpha]^{25}_{D}$ +6.5 (*c* 0.10, $CHCl_3$). For (S)-isomer, $[\alpha]^{25}_{D}$ -4.6 (*c* 0.17, $CHCl_3$).

^{1}H NMR δ: 4.1 (dd, J= 6, 5.5 Hz, 1H, CHOTBDMS), 4.0 (dd, J= 7, 7 Hz, 1H, CHOTBDMS), 3.0 (s, 3H, OMs), 1.85 (m, 1H, C*H*CH_3), 1.4-1.2 (m, 10H), 0.98 (d, J= 7 Hz, 3H, CHC*H*$_3$), 0.88 (t, J=7Hz, 3H, CH_2C*H*$_3$).

EIMS: 126(8%, M^+ - OMs), 111(11%, M^+ - CH_2OMs), 97(32%), 85(98%), 71(100%), 57(58%), 41(83%).

(2R)-2-methyl-1-bromooctane(8):

To a solution of **7** (1.0 g, 4.5 mmol) in acetone (100 ml) was added tetradecyltrimethyl ammonium bromide (6.7 g, 20 mmol). The reaction was refluxed for 3 days, the acetone was removed *in vacuo* and hexane (30 ml) was added. The solution was then filtered and dried over sodium sulfate and purified on a silica column to give a colorless oil (0.90 g, 96%). $[\alpha]^{25}_D$ +7.10 (*c* 0.12, $CHCl_3$). For (S)-isomer, $[\alpha]^{25}_D$ -6.20 (*c* 0.13, $CHCl_3$).

^{1}H NMR δ: 3.4 (dd, J=5, 5Hz, 1H, CHBr), 3.32(dd, J=6, 6Hz, 1H, CHBr), 1.8 (m, 1H, C*H*CH_3), 1.5-1.2 (m, 10H), 1.0 (d, J= 7Hz, 3H, CHC*H*$_3$), 0.89 (t, J= 7Hz, 3H, CH_2C*H*$_3$).

Anal. Calcd. for $C_9H_{19}Br$: C, 52.20%; H, 9.18%. Found: C, 52.48%; H, 9.40%.

EIMS: 151 (19%, M^+ - C_4H_9), 149 (20%), 85 (31%), 71 (72%), 57 (56%), 41 (100%).

(2R)-1-cynano-2-methyloctane(9):

To a solution of **8** (1.0 g, 4.5 mmol) in DMSO (100 ml) was added sodium cyanide (1.2 g, 20 mmol) at room temperature. After stirring for five days, water (100 ml)

was added at 0 ^{0}C and the solution extracted with pentane (3X60 ml), dried over sodium sulfate and purified on a silica column to give a colorless oil (0.60 g, 87%). $[\alpha]^{25}_D$ +5.1 (*c* 0.11, $CHCl_3$). For (S)-isomer, $[\alpha]^{25}_D$ -4.2 (*c* 0.09, $CHCl_3$).

^{1}H NMR δ: 2.3 (dd, J=6, 6 Hz, 1H, CHOTBDMS), 2.22 (dd, J=7, 7Hz, 1H, CHOTBDMS), 1.84 (m, 1H, C*H*CH_3), 1.4-1.2 (m, 12H), 1.05 (d, J=7Hz, 3H, CHC*H*$_3$), 0.89 (t, J=7 Hz, 3H, CH_2C*H*$_3$).

EIMS: 154 (6%, M^++1), 138 (8%, M^+ - CH_3), 124 (11%, M^+ - C_2H_5), 110 (30%), 96 (46%), 82 (25%), 68 (31%), 57 (39%), 41 (100%).

*(3R)-3-methylnonanol (**10**):*

To a solution of **9** (0.60 g, 3.9 mmol) in pentane (20 ml) was added DIBAL (5.0 ml, 5.0 mmol) at -70 ^{0}C. After 2 h, water (5.0 ml) was added to hydrolyze the aluminum complex. The mixture was extracted with pentane (3X20 ml) and then evaporated to remove the pentane. To the crude aldehyde was added ethanol (15 ml) and $NaBH_4$ (0.20 g, 5.2 mmol). and reacted at room temperature for 2 h. Water (15 ml) was added to remove the unreacted $NaBH_4$ and the mixture extracted with pentane (3X10 ml), dried over sodium sulfate and purified on a silica column to give a colorless oil (0.40 g, 65%). $[\alpha]^{25}_D$ +5.5 (*c* 0.11, $CHCl_3$). For (S)-isomer, $[\alpha]^{25}_D$ -4.2 (*c* 0.09, $CHCl_3$). Lit[89]. $[\alpha]^{35}_D$ +3.62 (neat).

^{1}H NMR δ: 3.7 (m, 2H, C*H*$_2$OH), 1.7-1.1 (m, 13H), 0.89 (m, 6H, CHC*H*$_3$ and CH_2C*H*$_3$).

EIMS: 110 (28%, M^+ - C_2H_4OH), 97 (19%), 83 (41%), 70 (58%), 55 (62%), 41 (100%).

*(3R)-3-methylnonanyl mesylate (**11**):*

To a solution of **10** (0.60 g, 3.8 mmol) in CH_2Cl_2 (15 ml) and triethylamine (1.2 ml, 7.6 mmol) was added methanesulfonyl chloride (0.40 ml, 4.2 mmol) at 0 ^{0}C. The reaction was quenched with water after 15 minutes at 0 ^{0}C and extracted with hexane (3X10 ml). The hexane extract was dried over sodium sulfate and purified on a silica column to give a colorless oil (0.75 g, 85%). $[\alpha]^{25}_D$ +6.02 (*c* 0.09, $CHCl_3$). For (S)-isomer, $[\alpha]^{25}_D$ -5.05 (*c* 0.13, $CHCl_3$).

^{1}H NMR δ: 4.25 (m, 2H, CH_2OMs), 3.0 (s, 3H, OMs), 1.7-1.1 (m, 13H), 0.9(m, 6H, $CHCH_3$ and CH_2CH_3).

EIMS: 110 (12%, M+ - C_2H_4OMs), 97 (26%), 83 (41%), 70 (100%), 55 (91%), 41 (99%).

*(3R)-3-methyl-1-p-chlorophenylthiononane (**12**):*

To a solution of p-chlorothiolphenol (0.58 g, 4.0 mmol) in DMF (30 ml) was added NaH (0.22 g, 6.0 mmol) at 0 ^{0}C and the mixture stirred for 0.5 h prior to adding **11** (0.70 g, 3.0 mmol) at 0 ^{0}C. After 2 h, the reaction was worked up by quenching with water (30 ml), extracted with hexane (3X20 ml) and purified on a silica column to give a colorless oil (0.75 g, 88%). $[\alpha]^{25}_D$ +8.75 (*c* 0.14, $CHCl_3$). For (S)-isomer, $[\alpha]^{25}_D$ -9.05 (*c* 0.08, $CHCl_3$).

^{1}H NMR δ: 7.25 (s, 4H, C_6H_4), 2.8 (m, 2H, $CH_2SC_6H_4Cl$), 1.7-1.2 (m, 12H), 0.89 (m, 6H). EIMS: 203 (12%,), 177 (26%), 111 (81%), 83 (10%), 70 (49%), 55 (50%), 41 (100%).*

*(3R)-3-methyl-1-p-chlorophenylsulphonylnonane (**13**):*

To a solution of **12** (0.70 g, 2.5 mmol) in ether (20 ml) was added MCPBA (4.1 g, 12 mmol) at 0 ^{0}C and stirred for 0.5 h, NaOH (5.0 %, 40 ml) was added to the reaction mixture and the mixture extracted with ether (3X30 ml), dried over sodium sulfate and purified on a silica column to give a colorless oil (0.75 g, 95%). $[\alpha]^{25}_D$ +8.52 (*c* 0.11, $CHCl_3$). For (S)-isomer, $[\alpha]^{25}_D$ -7.05 (*c* 0.09, $CHCl_3$).

^{1}H NMR δ: 7.7 (m, 4H), 3.1 (m, 2H), 1.8-1.1 (m, 12H), 0.89 (m, 6H, $CHCH_3$ and CH_2CH_3). Anal. Calcd. for $C_{15}H_{25}SO_2Cl$: C, 60.66%; H, 7.90%. Found: C, 60.82%; H, 7.81%.

*(7R)-(11R)-7,11-dimethyl-9-p-chlorophenylsulphonylheptadecane(**14**):*

To a solution of **13** (0.41 g, 1.3 mmol) in THF (15 ml) was added n-BuLi (0.75 ml, 1.9 mmol) at -70 ^{0}C. The reaction temperature was kept at -40 ^{0}C for 2 h and **8** (0.33 g, 1.5 mmol) in HMPA (4.0 g) was added at -70 ^{0}C. The reaction was stirred overnight and worked up by addition of sat. aq. NH_4Cl (10 ml) at 0 ^{0}C and extracted with hexane

* CH analysis yielded an unsatisfactory result.

(3X10 ml). Drying over sodium sulfate and purification on a silica column afforded a colorless oil (0.31 g, 53%).

^{1}H NMR δ: 7.7 (m, 4H), 3.05 (m, 1H), 1.9-1.2 (m, 24H), 0.89 (m, 6H), 0.78 (d, J=7 Hz, 6H, CHC*H*$_3$). Anal. Calcd. for $C_{25}H_{43}SO_2Cl$: C, 67.80%; H, 9.72%. Found: C, 67.83%; H, 9.68%.

*(7R)-(11R)-7,11-dimethylheptadecane(**15**):*

To liquid NH_3 (0.10 l) at -40 ^{0}C was added Li metal (0.20 g). A dark blue color formed instantly, **14** (0.31 g, 0.70 mmol) in THF (3.0 ml) was added dropwise after 0.5 h. The reaction was kept at -40 ^{0}C for 3 h, and sat. aq. NH_4Cl (10 ml) was added slowly to work up the reaction. The crude solution was left in fumehood overnight to let the NH_3 evaporate. The residue was extracted with pentane (3X10 ml), dried over sodium sulfate and purified on a silica column to give a colorless oil (0.10 g, 54%). $[\alpha]^{25}_D$ +4.5 (*c* 0.02, $CHCl_3$).

^{1}H NMR δ: 1.3 (b, 28H), 0.89 (t, J=7Hz, 6H, CH_2CH_3), 0.83 (d, J=7Hz, 6H, CHC*H*$_3$). EIMS: 207 (6%), 111 (12%) , 97 (10%), 85 (38%, $C_6H_{13}^+$), 71 (90%), 57 (100%), 41 (73%). HRMS: 268.3123, Calculated result for $C_{19}H_{40}$: 268.3130.

(7S)-(11S)-7,11-dimethylheptadecane:

To liquid NH_3 (80 ml) at -40 ^{0}C was added Li metal (0.18 g). A dark blue color formed instantly, (7S)-(11S)-7,11-dimethyl-9-p-chlorophenylsulphonylheptadecane (0.10

g, 0.30 mmol) in THF (3.0 ml) was added dropwise after 0.5 h. The reaction was kept at -40 ^{0}C for 3 h, and sat. aq. NH_4Cl (10 ml) was added slowly to work up the reaction. The crude solution was left in fumehood overnight to let the NH_3 evaporate. The residue was extracted with pentane (3X10 ml), dried over sodium sulfate and purified on a silica column to give a colorless oil (40 mg, 52%). $[\alpha]^{25}_D$ -5.65 (*c* 0.04, $CHCl_3$).

^{1}H NMR δ: 1.3 (b, 28H), 0.89 (t, J=7Hz, 6H, CH_2CH_3), 0.83 (d, J=7Hz, 6H, $CHCH_3$).

EIMS: 207 (6%), 111 (12%) , 97 (10%), 85 (38%, $C_6H_{13}^+$), 71 (90%), 57 (100%), 41 (73%). HRMS: 268.3131, Calculated result for $C_{19}H_{40}$: 268.3130.

Meso-7,11-dimethylheptadecane:

To liquid NH_3 (80 ml) at -40 ^{0}C was added Li metal (0.18 g). A dark blue color formed instantly, (7R)-(11S)-7,11-dimethyl-9-p-chlorophenylsulphonylheptadecane (80 mg, 0.20 mmol) in THF (3.0 ml) was added dropwise after 0.5 h. The reaction was kept at -40 ^{0}C for 3 h, and sat. aq. NH_4Cl (10 ml) was added slowly to work up the reaction. The crude solution was left in fumehood overnight to let the NH_3 evaporate. The residue was extracted with pentane (3X10 ml), dried over sodium sulfate and purified on a silica column to give a colorless oil (20 mg, 37%).

^{1}H NMR δ: 1.32 (b, 28H), 0.90 (t, J=7Hz, 6H, CH_2CH_3), 0.85 (d, J=7Hz, 6H, CH_2CH_3).

EIMS: 207 (8%), 111 (15%) , 97 (13%), 85 (38%, $C_6H_{13}^+$), 71 (90%), 57 (100%), 41 (73%). HRMS: 268.3126, Calculated result for $C_{19}H_{40}$: 268.3130.

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