NEW SYNTHETIC APPROACHES TO SELECTED INSECT PHEROMONES

by

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Title of Thesis/Project/Extended Essay

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Abstract

The species-specific response of insects to chemical messages or pheromones has been extensively studied as a possible alternative to the use of traditional, but often toxic, broad-spectrum insecticides. Application of pheromones in the monitoring of insect infestation, or for use as mating disruption and mass trapping agents, depends on the availabilty of synthetic materials.

Exo-brevicomin (*exo*-7-ethyl-5-methyl-6,8-dioxabicyclo-[3.2.1]octane) and frontalin (1,5-dimethyl-6,8-dioxabicyclo-[3.2.1]octane) are major components in the pheromone complexes of several species of *Dendroctonus* bark beetles. The enantiomers of *exo*-brevicomin were synthesized in high chiral purity and moderate overall yield. Sharpless asymmetric epoxidation of (*Z*)-2-octen-7-one-1-ol yielded the chiral isomers of 7-hydroxymethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane which were converted to (+)- or (-)-*exo*-brevicomin. Similarly, (+)- and (-)-frontalin were prepared in six steps from (*E*)-2-methyl-2,6-heptadiene-1-ol using asymmetric epoxidation to induce chirality.

Lineatin (3,3,7-trimethyl-2,9-dioxatricyclo[3.3.1.$0^{4,7}$]-nonane), another bark beetle pheromone, was synthesized in four steps from 2,2,4-trimethyl-5,6-dihydro-2*H*-pyran. The key reaction was a dichloroketene [2+2] cycloaddition. Modification of the standard method for dichloroketene generation was necessary in order to avoid a rearrangement reaction. The scope of this modified procedure was briefly investigated.

Spectroscopic analysis of the aggregation pheromone isolated from the square-neck grain beetle (*Cathartus quadricollis*) indicated the structure to be a geometric isomer of either 3-methyl or 4-methyl-7-acetoxy-3-nonene. Synthesis of (*E,Z*) mixtures confirmed the pheromone to be (*E*)-3-methyl-7-acetoxy-3-nonene. A stereoselective synthesis of the racemic pheromone preceded an eight-step, sterospecific synthesis of the 3-(*S*) enantiomer from (*S*)-(+)-ethyloxirane. The 3-(*R*) enantiomer was obtained by inversion.

In summary, synthetic methods were designed which yielded four insect pheromones. Three of these sequences yielded either enantiomer with high enantiomeric excess. The racemic synthesis of lineatin was competitive with, or superior to, other published methods.

To my wife, Janet S. Martini

ACKNOWLEDGEMENTS

I would like to thank Dr. K.N. Slessor for introducing me to organic synthesis and for teaching me research fundamentals of attitude, execution and design which have proven invaluable over the years. I would also like to thank Dr. A.C. Oehlschlager for providing ideas, enthusiasm, excellent equipment and a stimulating research environment.

Many others also deserve my gratitude. M. Tracey and G. Owen gave excellent spectroscopy service. P. Saunders, S. Liang, J. Millar, S. Pillay, M. Pinto, M. Dombsky, and R. Pomeroy provided many memorable occasions. A special couple, Leslie and William Romines, both good friends, helped make the last few years enjoyable and interesting.

TABLE OF CONTENTS

LIST OF SYNTHETIC SCHEMES

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1

SYNTHESIS OF THE ENANTIOMERS OF *exo*-BREVICOMIN

Introduction

exo-Brevicomin (7-ethyl-5-methyl-6,8-dioxabicyclo-[3.2.1]octane) (**1**) is produced by three species of *Dendroctonus* beetles as part of their pheromone complex.[1-3] Two of the species, *D. brevicomis* (western pine beetle) and *D. ponderosae* (mountain pine beetle), are of major economic importance in western North America. Racemic *exo*-brevicomin is attractive in the field to *D. brevicomis* although it is known that the (1*R*,7*R*)-(+)-isomer is naturally produced by these beetles. The effects of racemic *exo*-brevicomin on *D. ponderosae* vary from antiaggregation to attraction, apparently depending on the release rate of the pheromone, as well as the host and location of the population being tested.[3] This variation raises the possibility that different populations of *D. ponderosae* discriminate between different enantiomers of *exo*-brevicomin. In order to examine the field response of *D. ponderosae* to the enantiomers of *exo*-brevicomin and to determine the chirality of *exo*-brevicomin in *D. ponderosae*, we required efficient syntheses of both chiral forms of this bicyclic ketal.

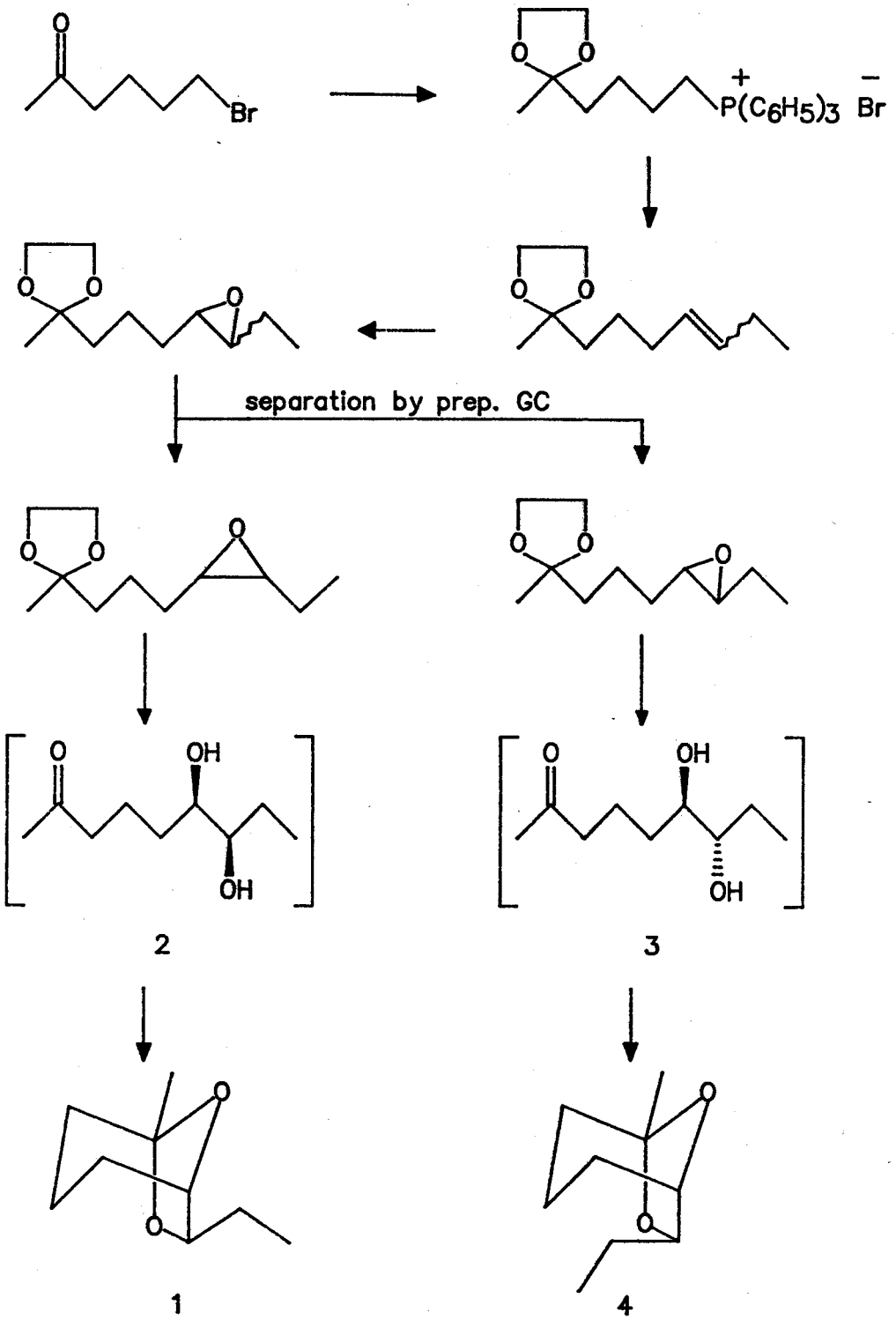
The synthesis of racemic *exo*-brevicomin has been the subject of numerous reports in the literature. Most of the synthetic approaches have followed the lead of the original synthesis by Silverstein *et al.*,[4] who recognized that the intramolecular ketal structure could be assembled by cyclization of *threo*-6,7-

dihydroxy-2-nonanone **2** (Scheme 1). The cyclization of the *erythro* dihdroxy compound **3** (Scheme 1) leads to an isomer of **1**, *endo*-brevicomin (**4**), which has also been shown to be present in *D. brevicomis*. Although inactive as a pheromone for this insect, recent studies have implicated **4** as an important component of the pheromone blend of a related species, *D. frontalis*, the southern pine beetle.[5] Silverstein's original synthesis[4] (Scheme 1) involved a non-stereoselective Wittig reaction which subsequently necessitated preparative GC separation of *cis* and *trans* epoxide intermediates. A key precursor to **1**, the ethylene ketal of (*Z*)-6-nonen-2-one (**6**) was then prepared in a stereoselective manner via P-2 nickel catalyzed semi-hydrogenation of alkyne intermediate **5** (Scheme 2).[4] This synthesis produced **1** with <2% contamination by **4**.

Wasserman and Barber[6] have reported that thermal cyclization of epoxy-ketone **7** is an effective alternative to acid catalyzed ketal formation for the preparation of **1** (Scheme 3). Various other methods[7-18] involving intermediates **2**, **5**, **6** and **7** or their synthetic equivalents were subsequently developed (Scheme 3). Of these the methods of Silverstein *et al.*[7] and Normant *et al.*[12] are particularly noteworthy for their simplicity and selectivity.

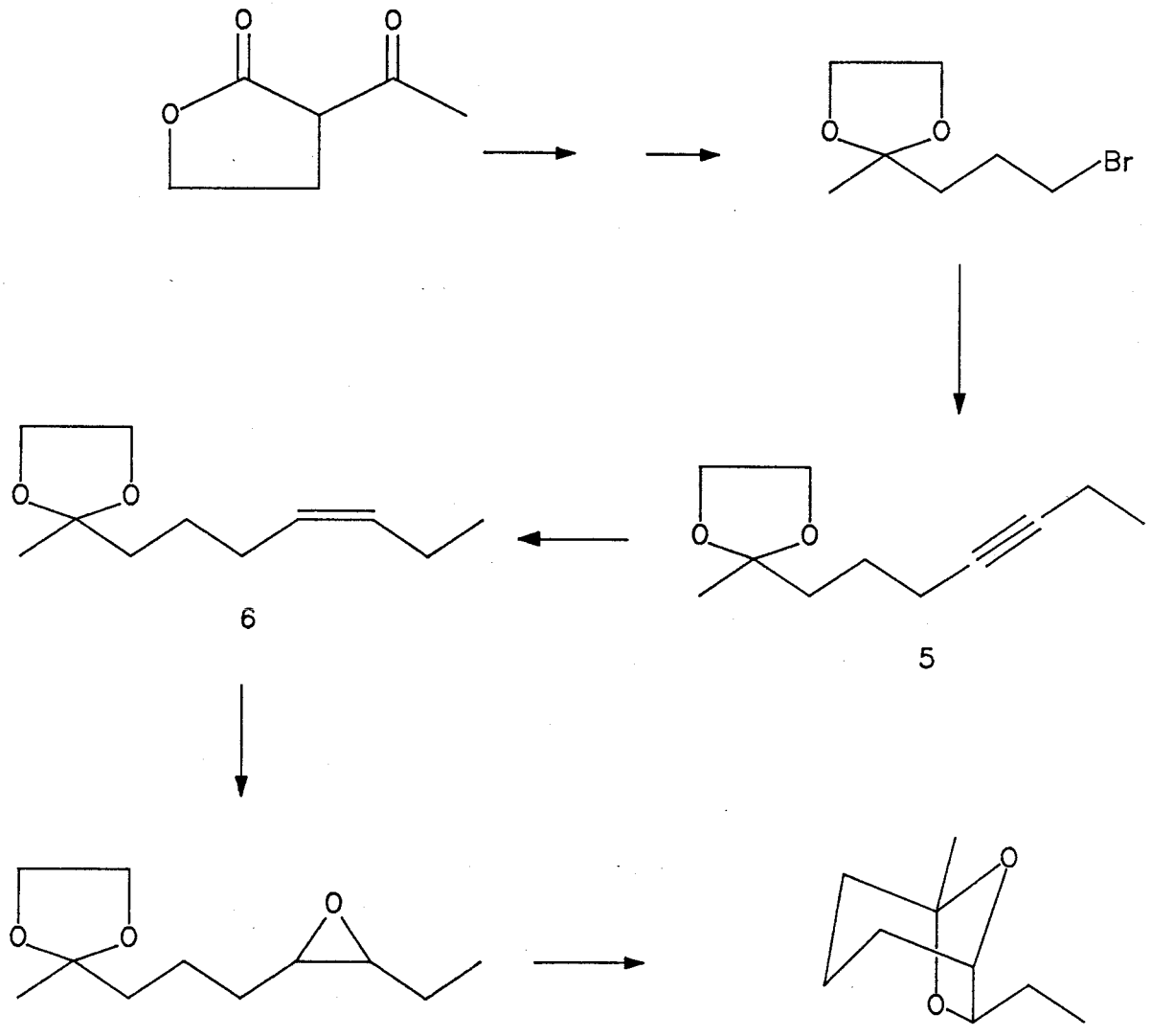
In an attempt to shorten the number of steps required, several groups[19-21] have investigated an alternative approach utilizing the Diels-Alder dimers of methyl vinyl ketone or acrolein (Scheme 4). Unforunately, each of these syntheses suffered either from one or more very low-yielding steps, or from the production of mixtures of *endo* and *exo* isomers.

Scheme 1
reference 4



Scheme 2

reference 4



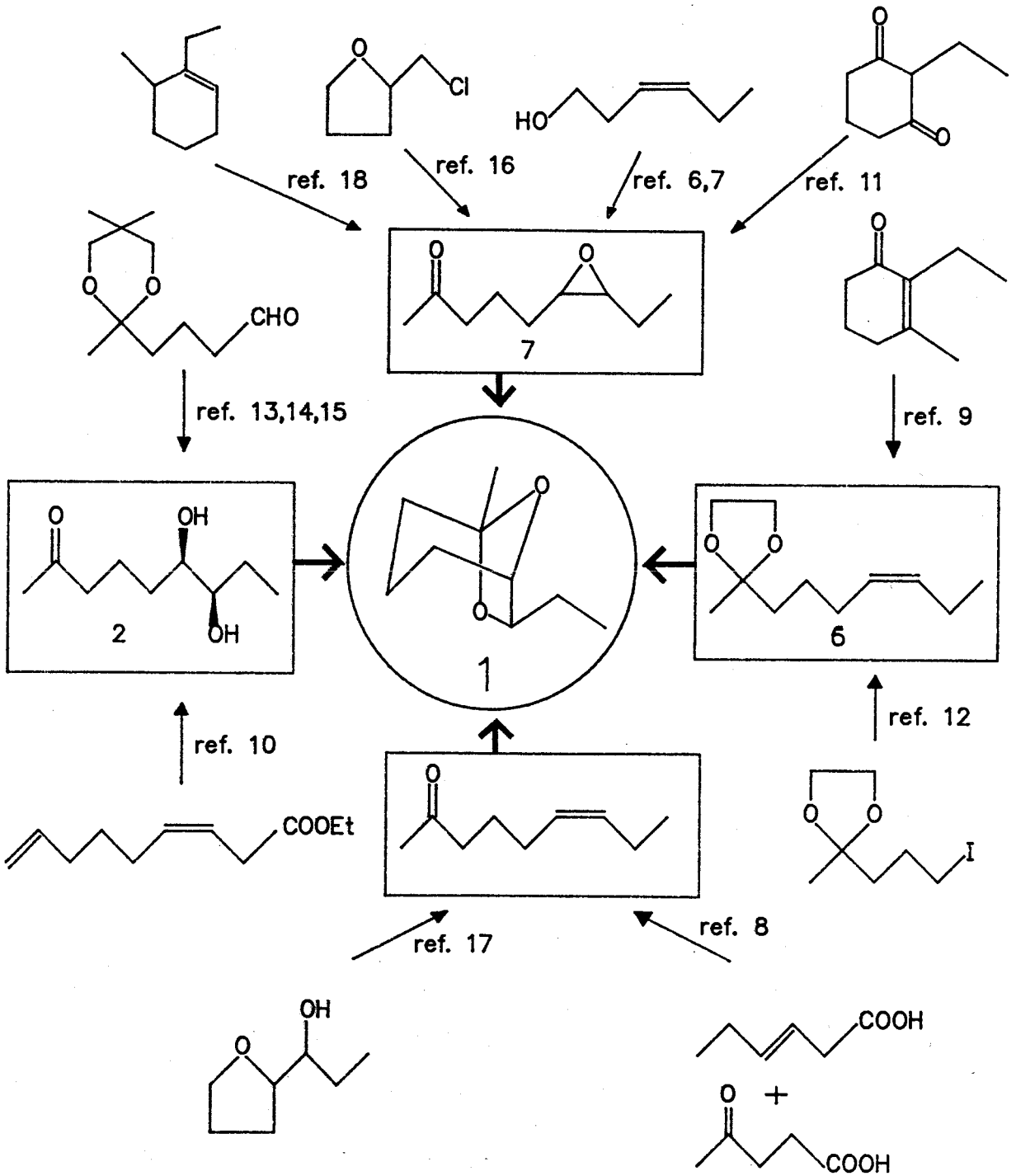
6

5

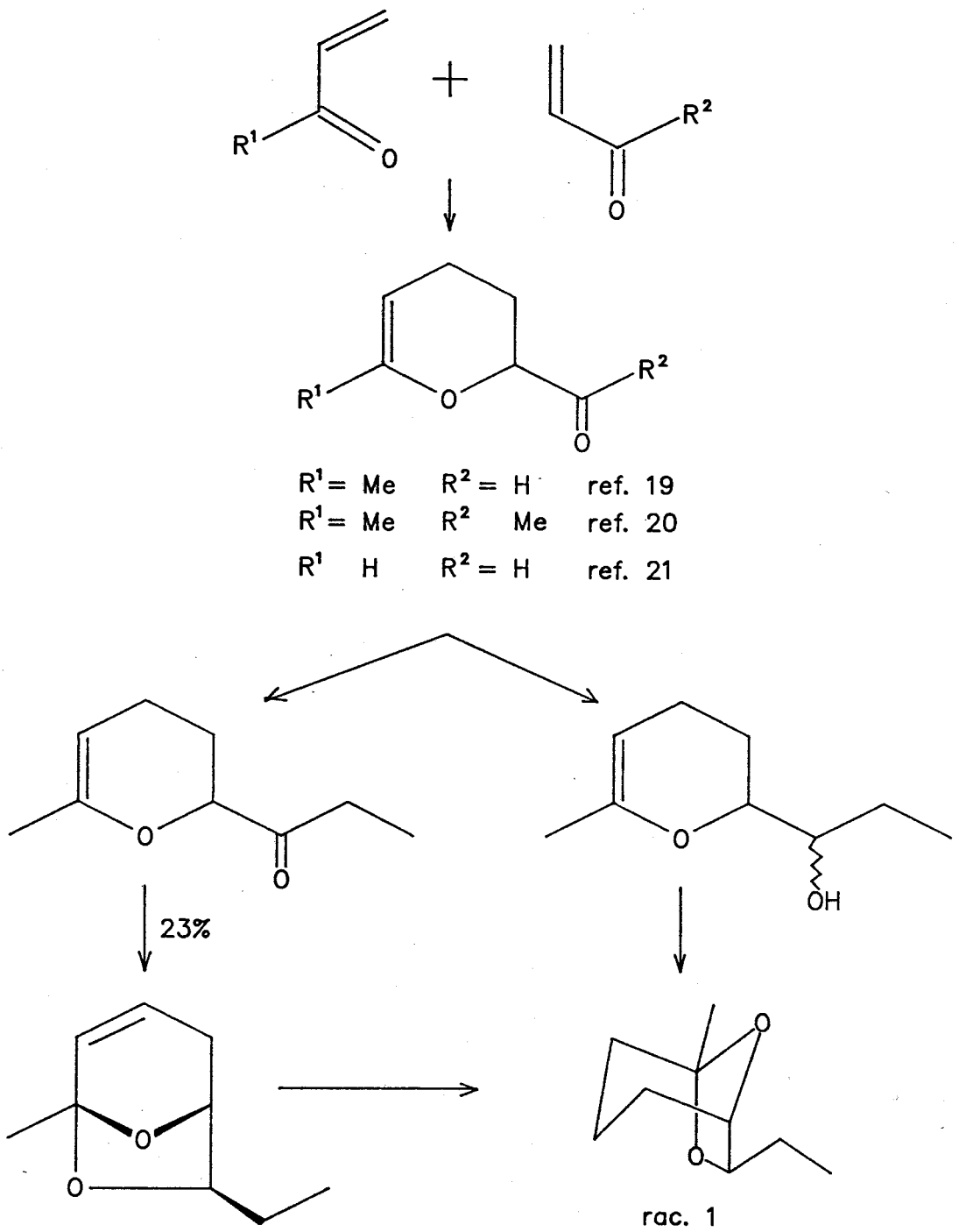
rac. 1 (<2% 4)

Scheme 3

SUMMARY OF exo-BREVICOMIN SYNTHESES



Scheme 4



R^1 = Me R^2 = H ref. 19
R^1 = Me R^2 Me ref. 20
R^1 H R^2 = H ref. 21

rac. 1

Very recently, an unsaturated analog of *exo*-brevicomin (*exo*-7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]oct-3-ene) has been identified as a multi-purpose pheromone for the species *Mus musculus* (the common house mouse).[22(a)] This finding attracted immediate synthetic interest and a number of preparations were quickly reported.[22] Each of these methods can be considered as a formal synthesis of exo-brevicomin, since it has been shown that the mouse pheromone can be reduced by catalytic hydrogenation in high yield to *exo*-brevicomin.[20]

Consideration of the acyclic keto-diol precursors to the *exo*-brevicomin enantiomers makes it apparent that an asymmetric synthesis, involving intramolecular ketal formation as the final step, requires synthesis of a suitable *threo* diol of known absolute stereochemistry. Mori[23] employed the *threo* diol unit present in enantiomerically pure tartaric acids for the construction of the *exo*-brevicomin enantiomers. This energetic synthesis of fourteen steps proved that the biologically active (+)-*exo*-brevicomin isomer derived from (2*S*,3*S*)-tartaric acid had the 1*R*,7*R* absolute configuration (Scheme 5). A similar general approach was also used by Meyer[24] to synthesize the (-)-isomer starting from the (2*R*,3*R*)-tartrate derivative (Scheme 6). The use of the more easily cleaved isopropylidene group for diol protection (rather than the methyl ethers required in Mori's synthesis) provided a better overall yield. The tartrate approach has been refined even further by Masaki *et al.*[25] who made use of the C_2 symmetry of diethyl tartrate in an elegant, relatively short synthesis involving intramolecular carbon-carbon

bond formation (Scheme 7).

Other investigators have preferred to begin with alternate natural chiral-pool starting materials. Fraser-Reid[26] has demonstrated the utility of carbohydrate starting materials for asymmetric synthesis by incorporating the *threo* C-3,C-4 hydroxyl substituents of *D*-glucose into (+)-*exo*-brevicomin (Scheme 8). This synthesis required deoxygenation reactions and a Wittig chain extension. A modified version of this synthesis was developed by Ferrier[27] to give higher overall yields (Scheme 9). In addition, this group[28] developed a method for inversion at C-3 and C-4 of *D*-glucose, utilizing the 3,4-anhydro-derivative, in order to prepare the enantiomer [(-)-*exo*-brevicomin] (Scheme 10). Finally, a synthesis of (+)-*exo*-brevicomin from glutamic acid has very recently been reported.[29] This synthesis employed the diastereoselective reduction of a chiral acetyl lactone derivative for the production of the *threo* dihydroxy derivative (Scheme 11).

The use of small, highly functionalized chiral synthons derived from natural sources, or from asymmetric induction reactions using naturally occurring chiral auxiliaries, has been demonstrated in several other syntheses of the brevicomin enantiomers. Two groups have developed different approaches to (*R*) or (*S*)-2-benzyloxybutanal. Asami and Mukaiyama[30] synthesized the (*R*)-hydroxy-aldehyde derivative in high enantiomeric excess using a chiral auxiliary derived from *L*-proline (Scheme 12) while Bernardi *et al.*[31] prepared the (*S*)-aldehyde through an involved sequence which initially made use of yeast culture asymmetric

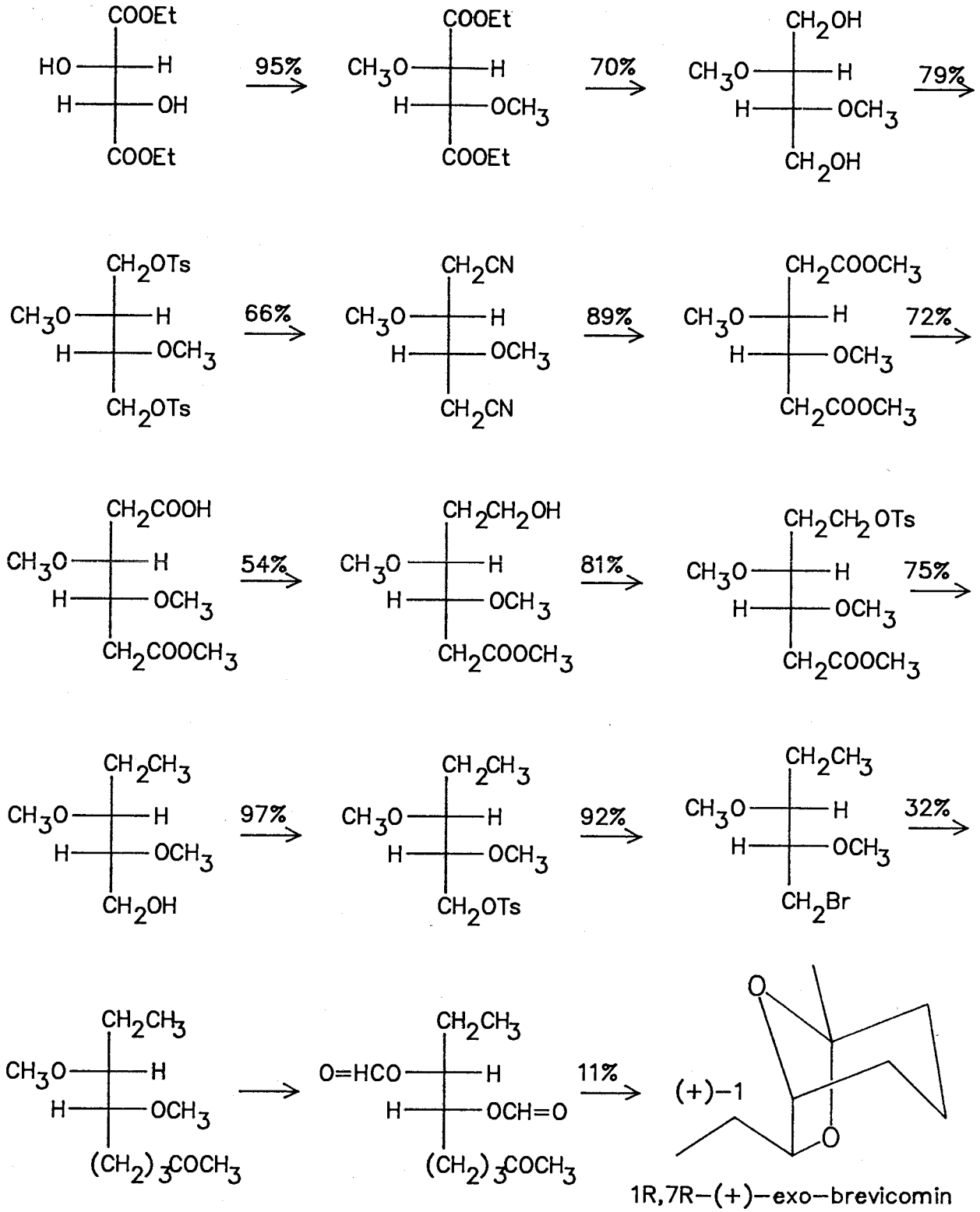
reduction of cinnamaldehyde (Scheme 13). Both groups converted their 2-hydroxybutanal derivatives to (+) or (-)-*exo*-brevicomin by *threo* diastereoselective alkylation with Grignard reagents. The Japanese chemists[30] obtained much greater selectivity than the Italian chemists[31] in this reaction. A subsequent paper by the Italian group[32] claimed inverse selectivity for the reaction of allyl Grignard reagents with α-hydroxy aldehyde derivatives and the synthesis of (+)-*exo*-brevicomin was performed via a tortuous route (Scheme 14).

More direct approaches to the required asymmetric *threo* diol functional group, employing chiral boronate ester derivatives, have been developed. Matteson and Sadhu[33] have demonstrated the elaboration of chiral α-chloro boronates, incorporating (-)-pinanediol as a chiral auxiliary, and the homologation of these derivatives into a suitable *threo* diol precursor for (+)-*exo*-brevicomin (Scheme 15). Wuts and Bigelow[34] used the diastereoselective coupling of an allylic boronate ester, containing a chiral tetrahydropyranyl derivative obtained from (*R*)-dihydrocarvone, with a protected keto-aldehyde to produce another *threo* diol precursor for (-)-*exo*-brevicomin (Scheme 16).

With the exception of one route[25] (Scheme 7), the above synthetic approaches to the brevicomin enantiomers suffer from one or more disadvantages. Several are inordinately lengthy while others seem applicable to production of only one enantiomer. The use of chiral auxiliaries which require chromatographic separation is another disadvantage for large scale work. More importantly, the variability in the reported

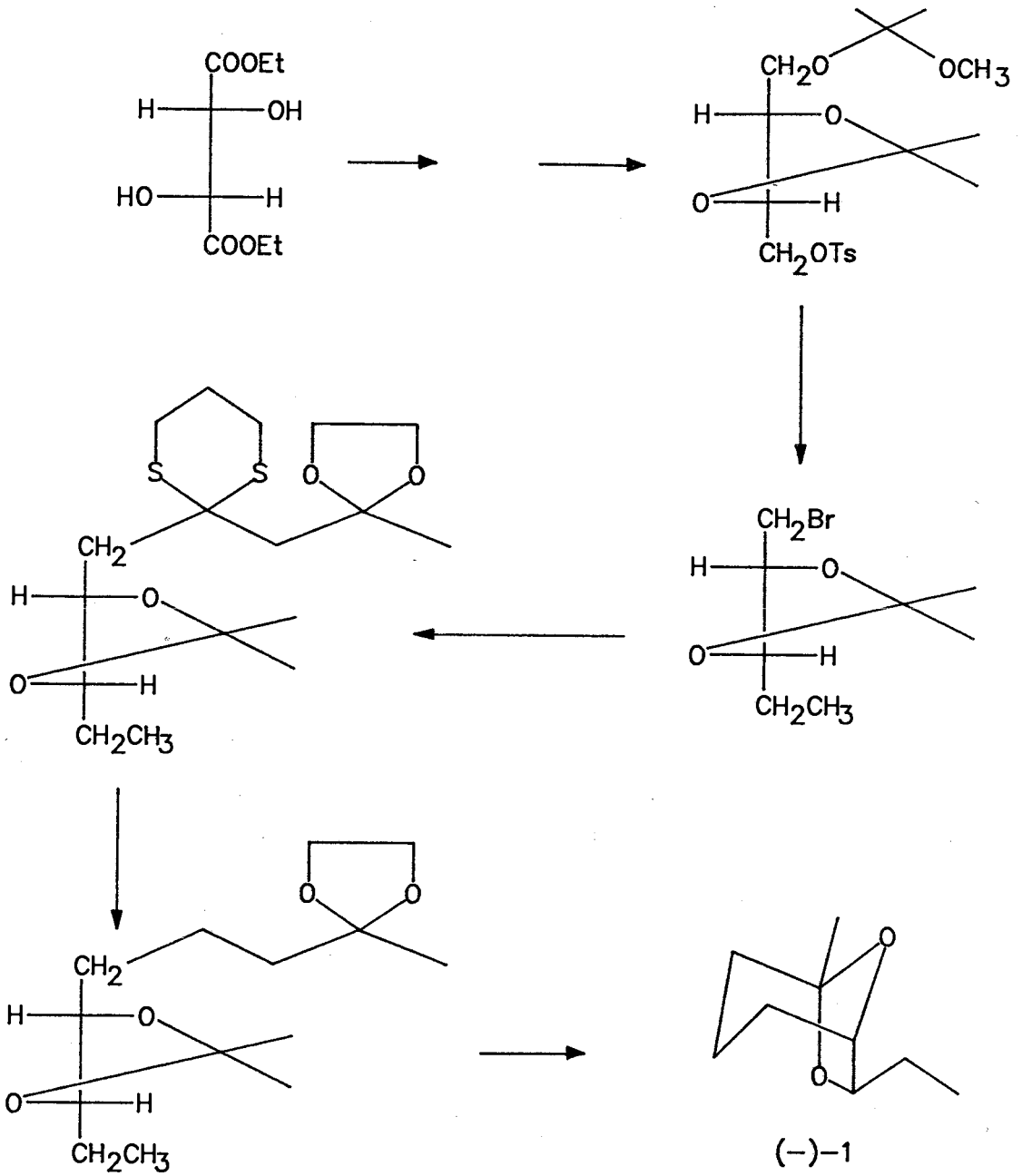
optical rotations for the brevicomin enantiomers makes the assignment of enantiomeric purity questionable for most of these synthetic schemes. Table 1 presents a summary of the published asymmetric syntheses of *exo*-brevicomin and illustrates the wide disparity in the reported optical rotations.

Scheme 5
reference 23

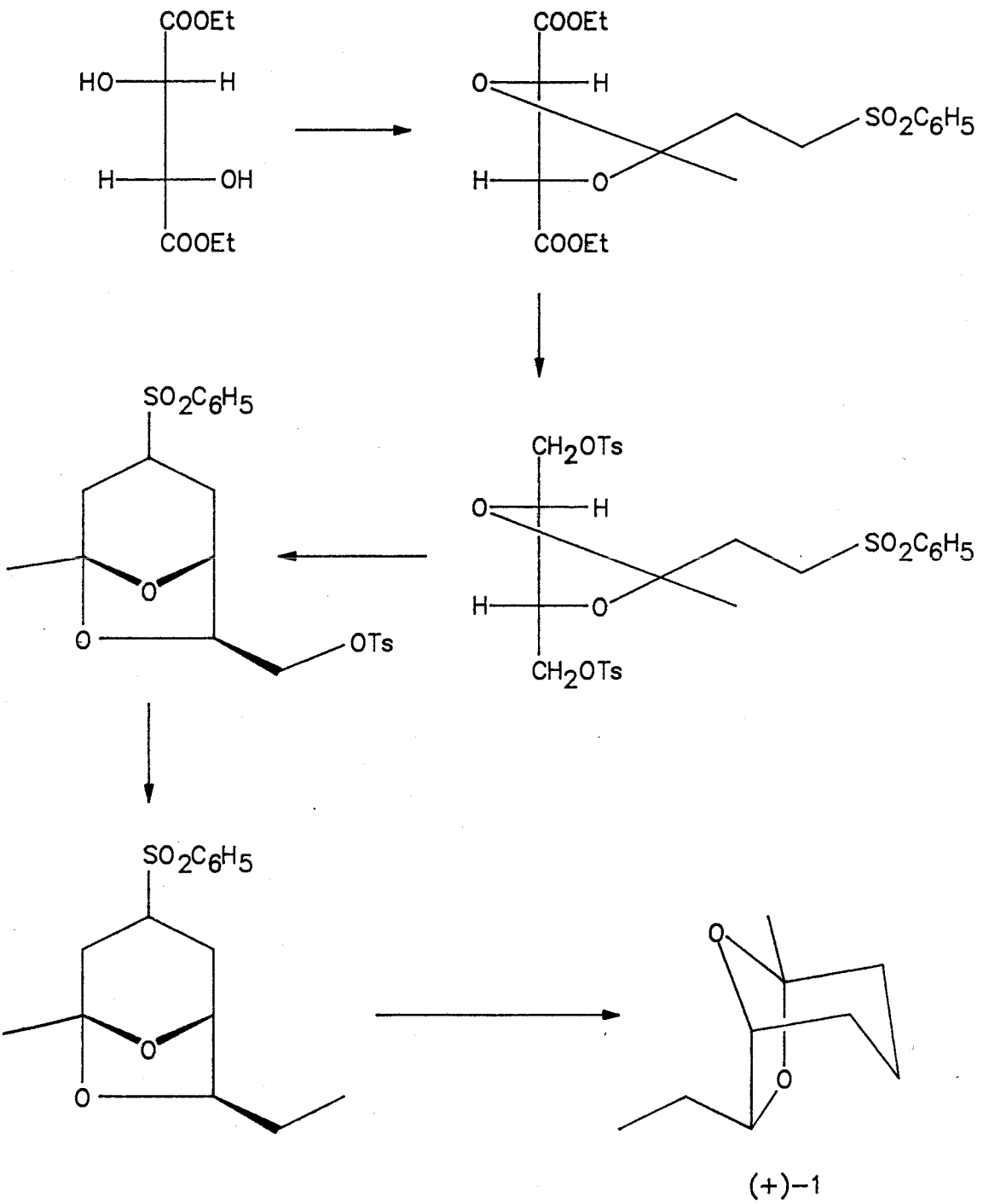


1R,7R-(+)-exo-brevicomin

Scheme 6
reference 24

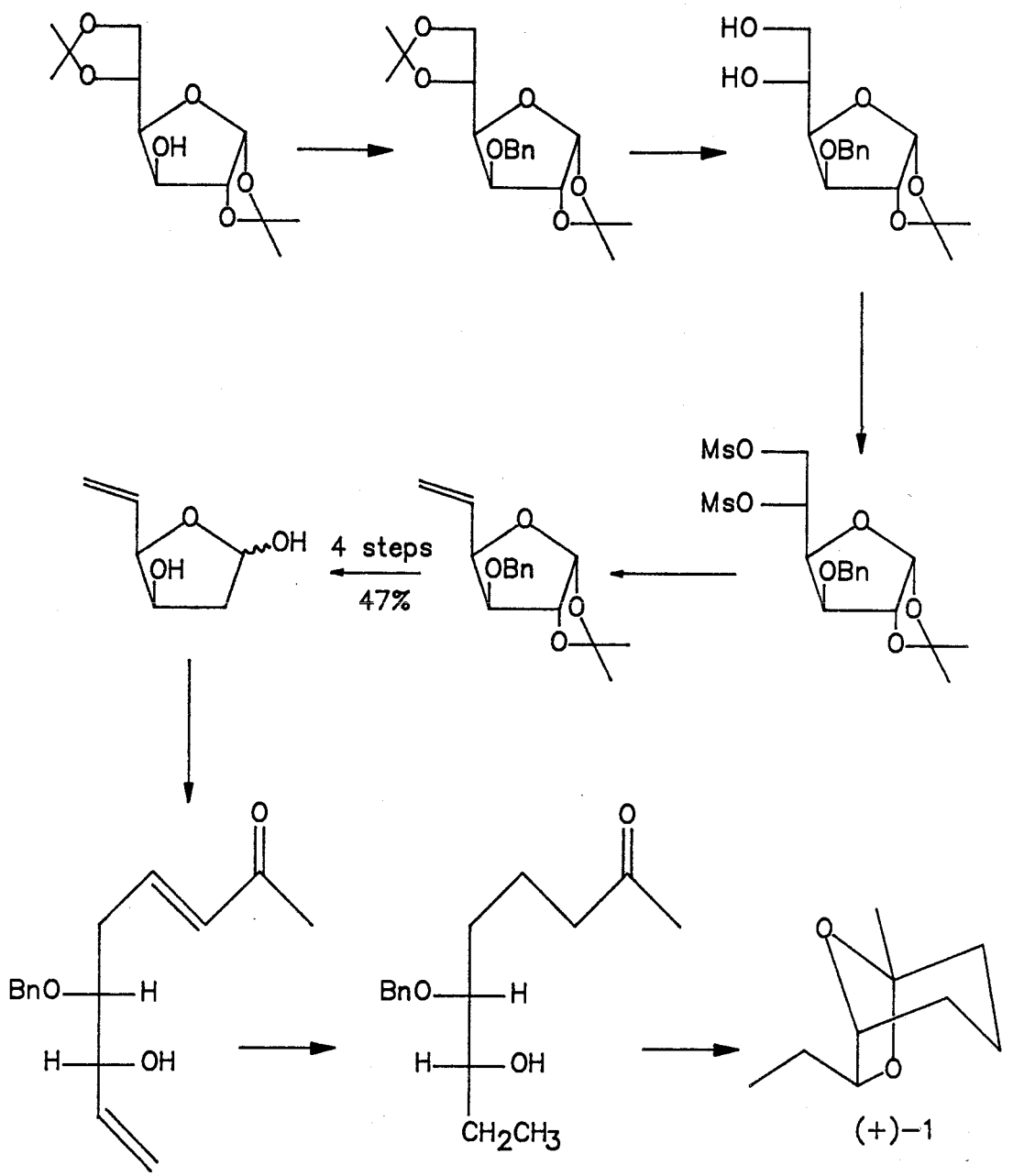


Scheme 7
reference 25

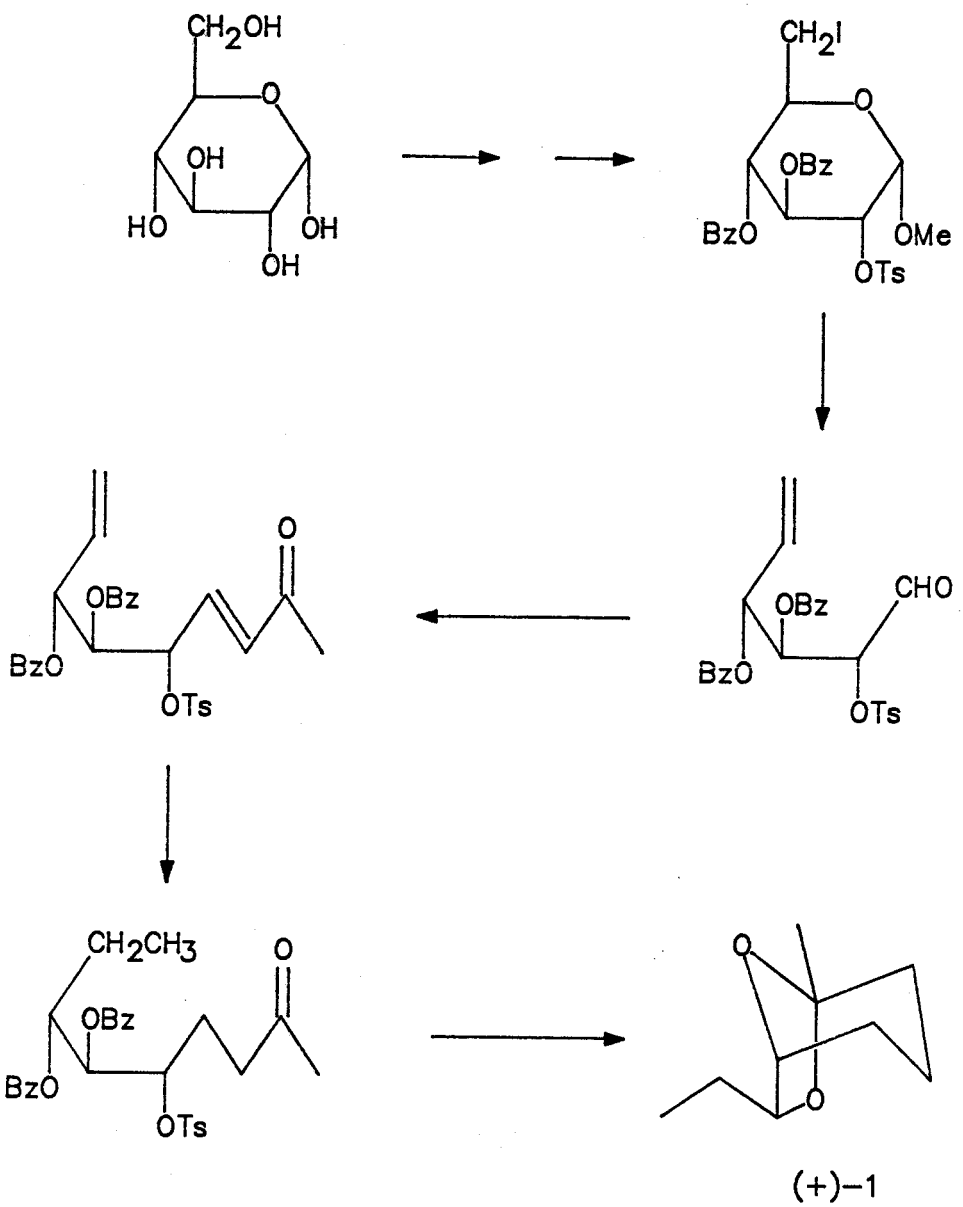


(+)-1

Scheme 8
reference 26

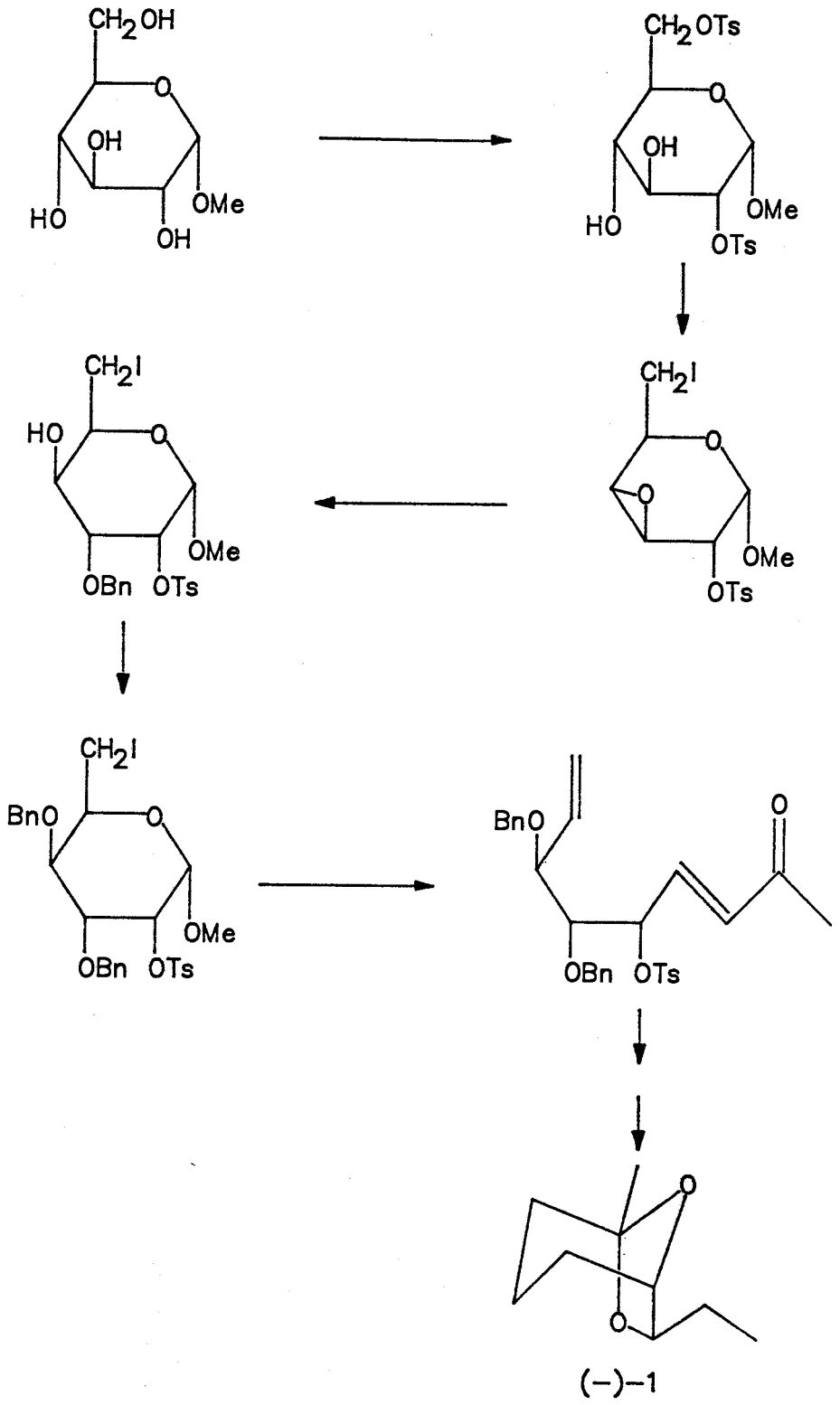


Scheme 9
reference 27

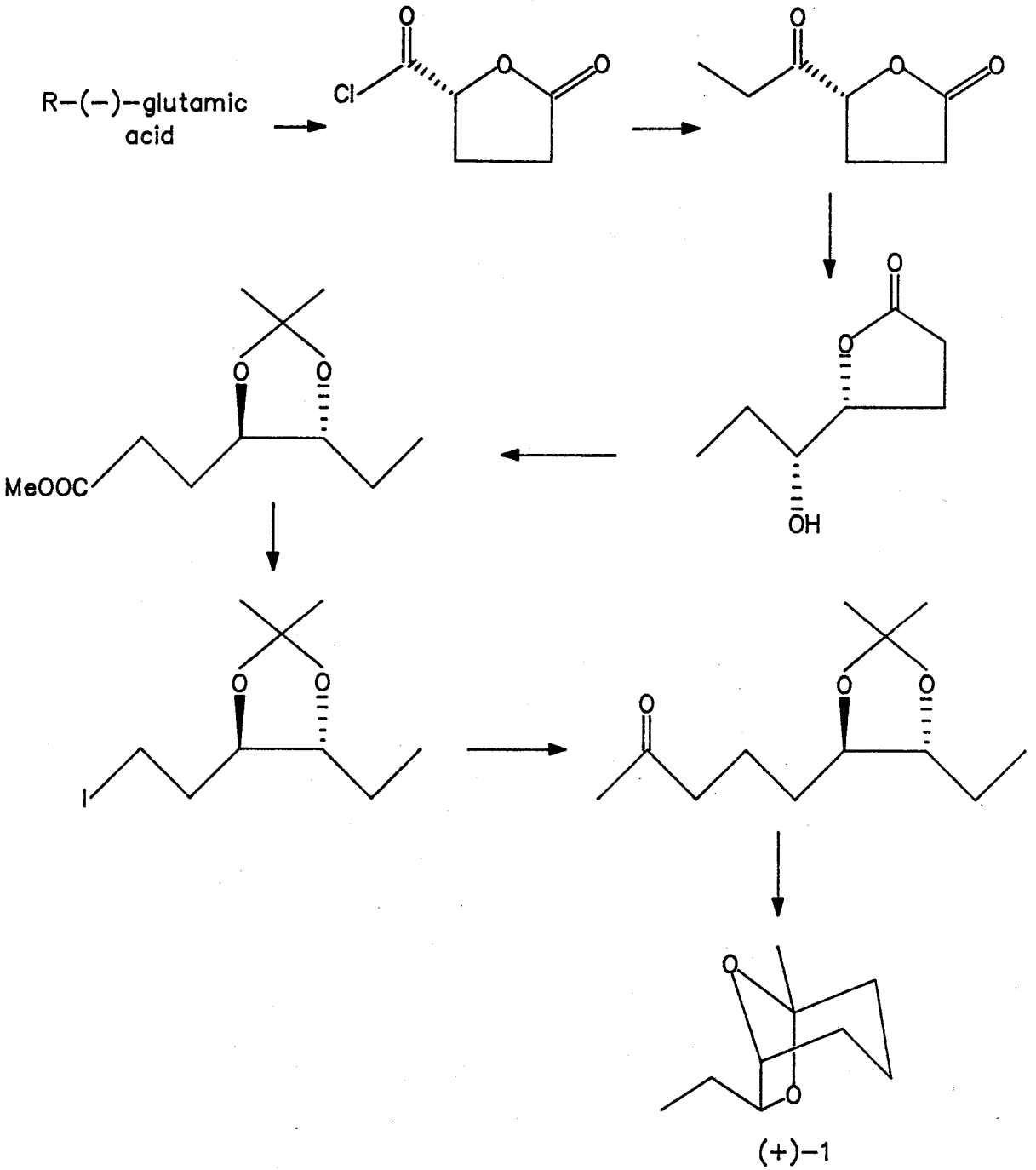


(+)–1

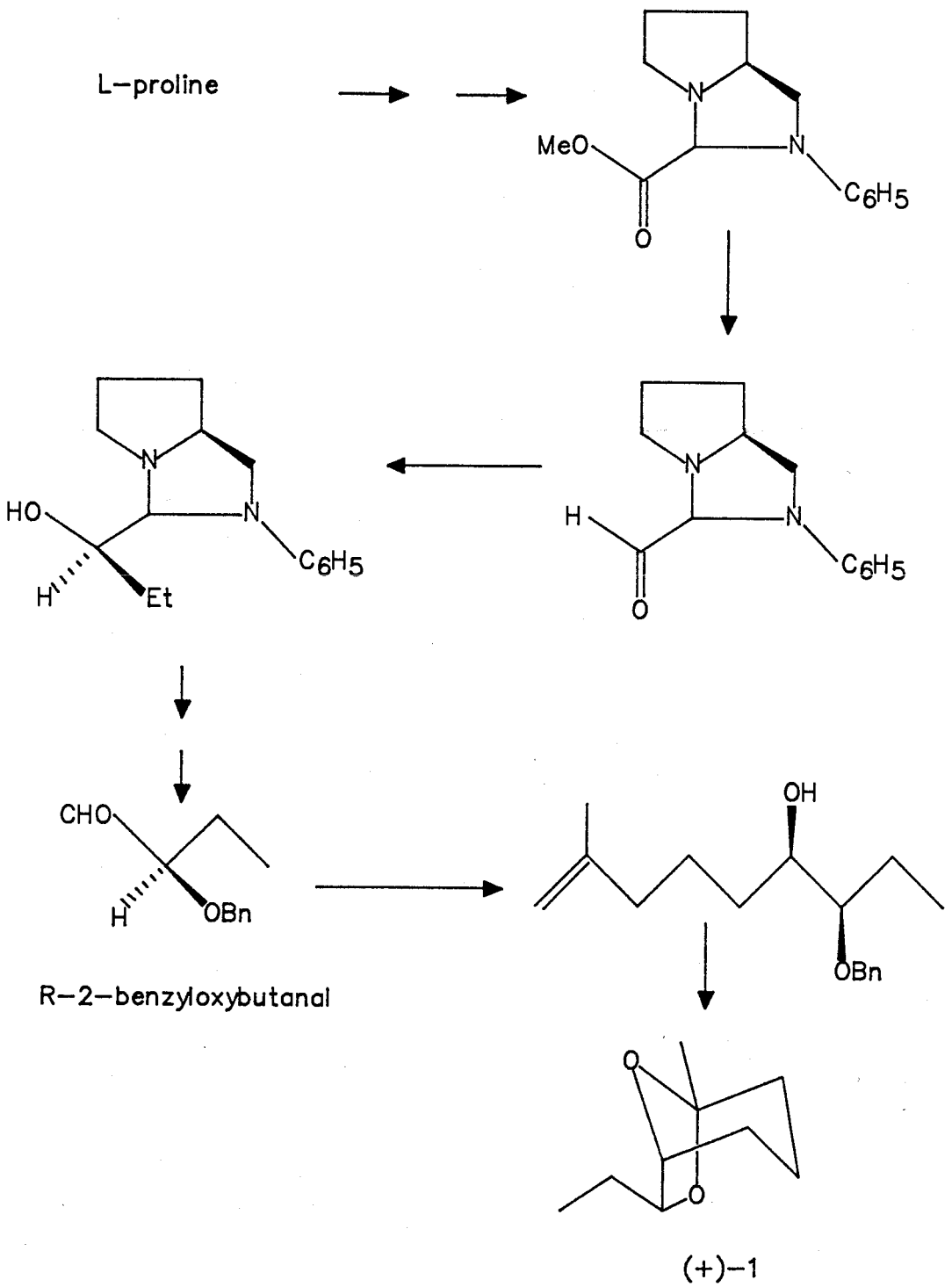
Scheme 10
reference 28



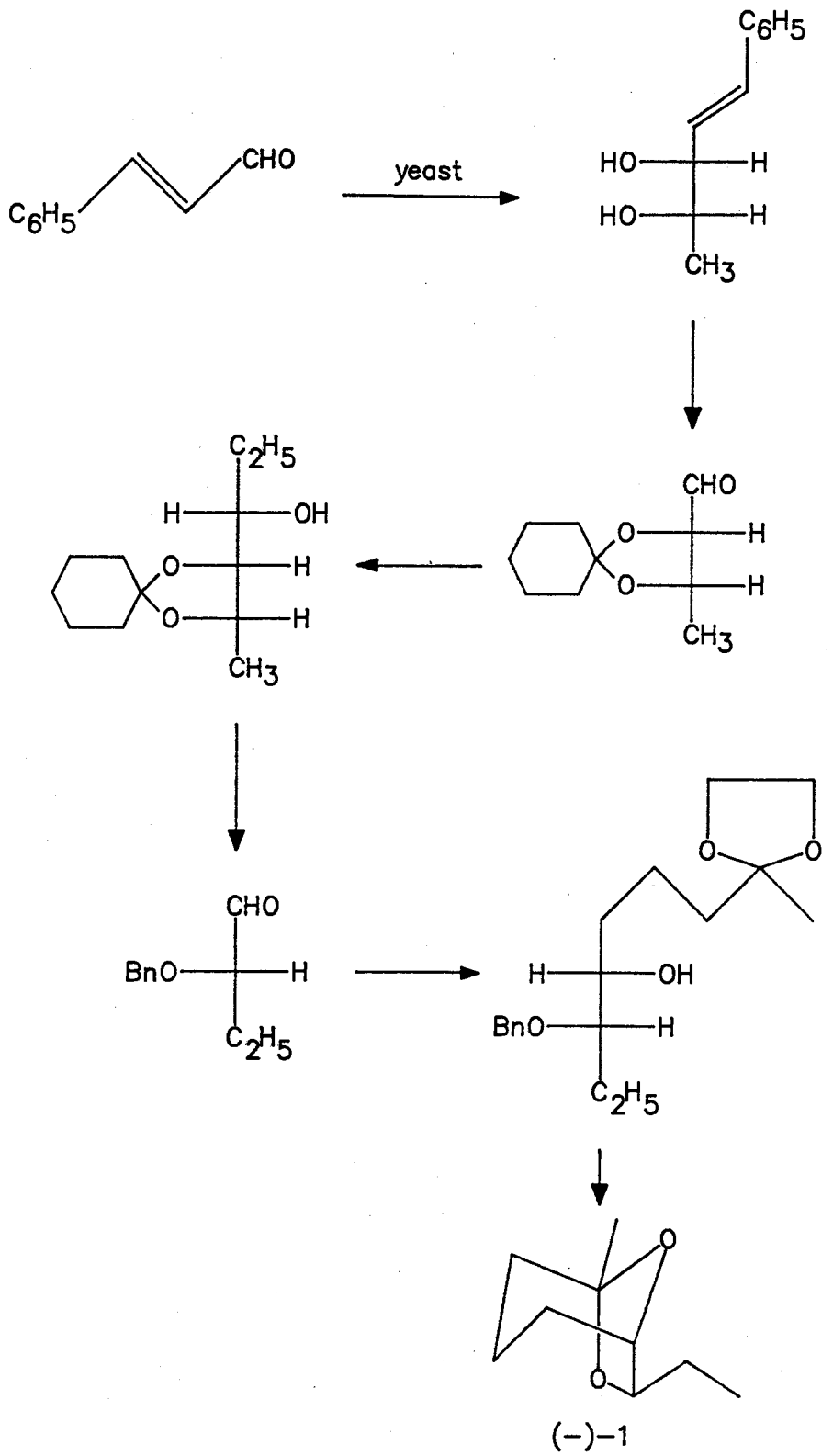
Scheme 11
reference 29



Scheme 12
reference 30

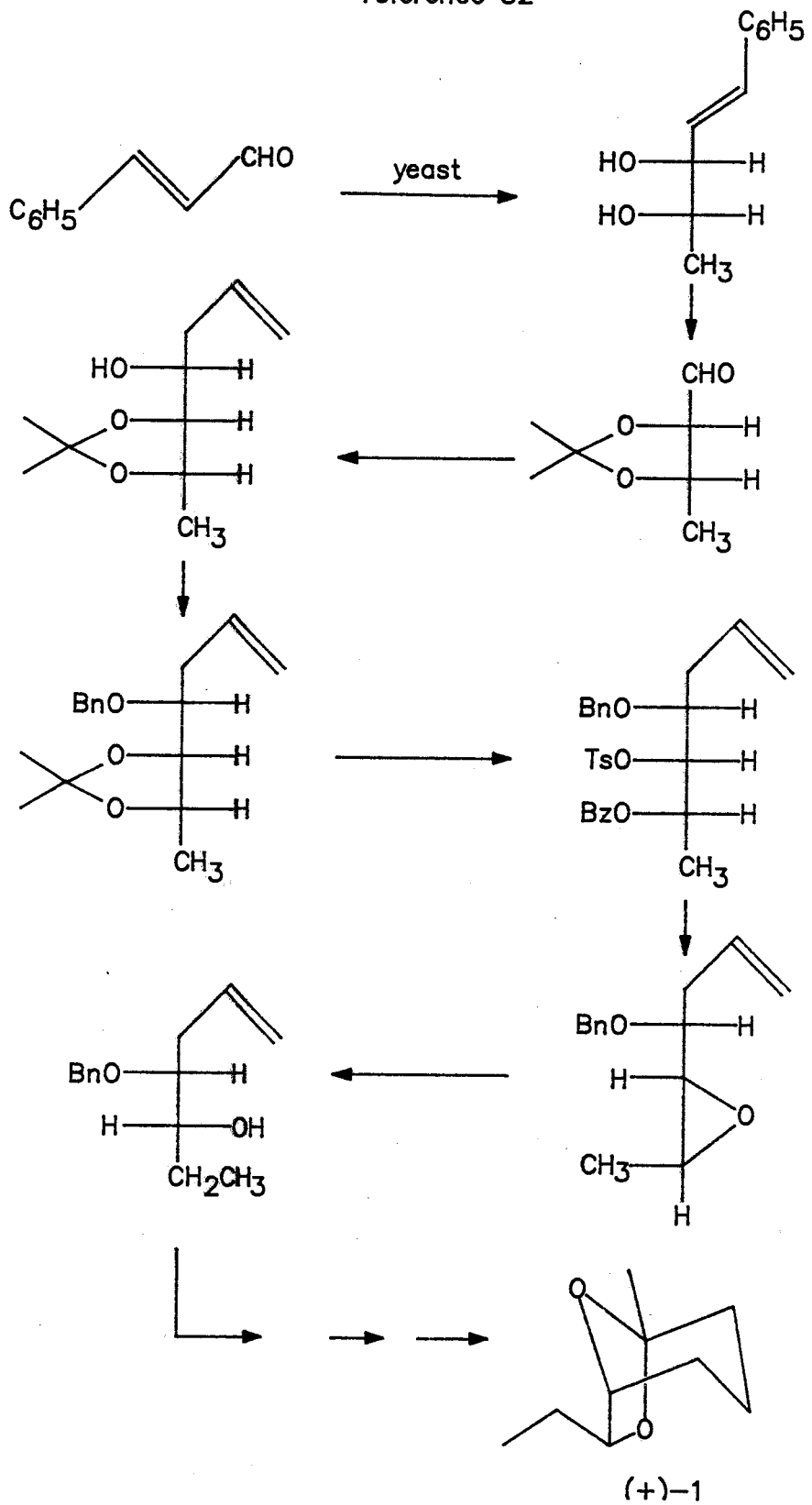


Scheme 13
reference 31



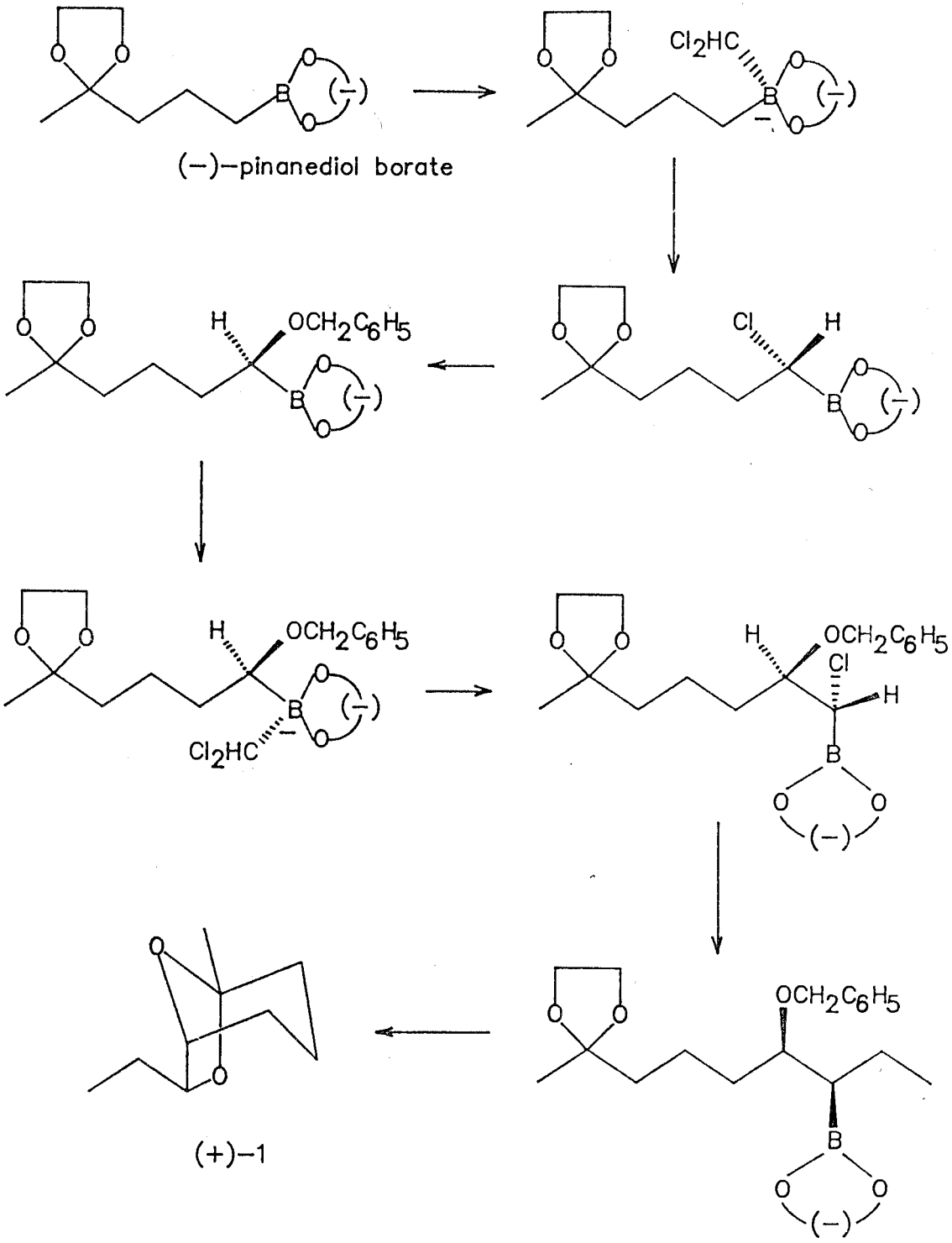
(−)−1

Scheme 14
reference 32

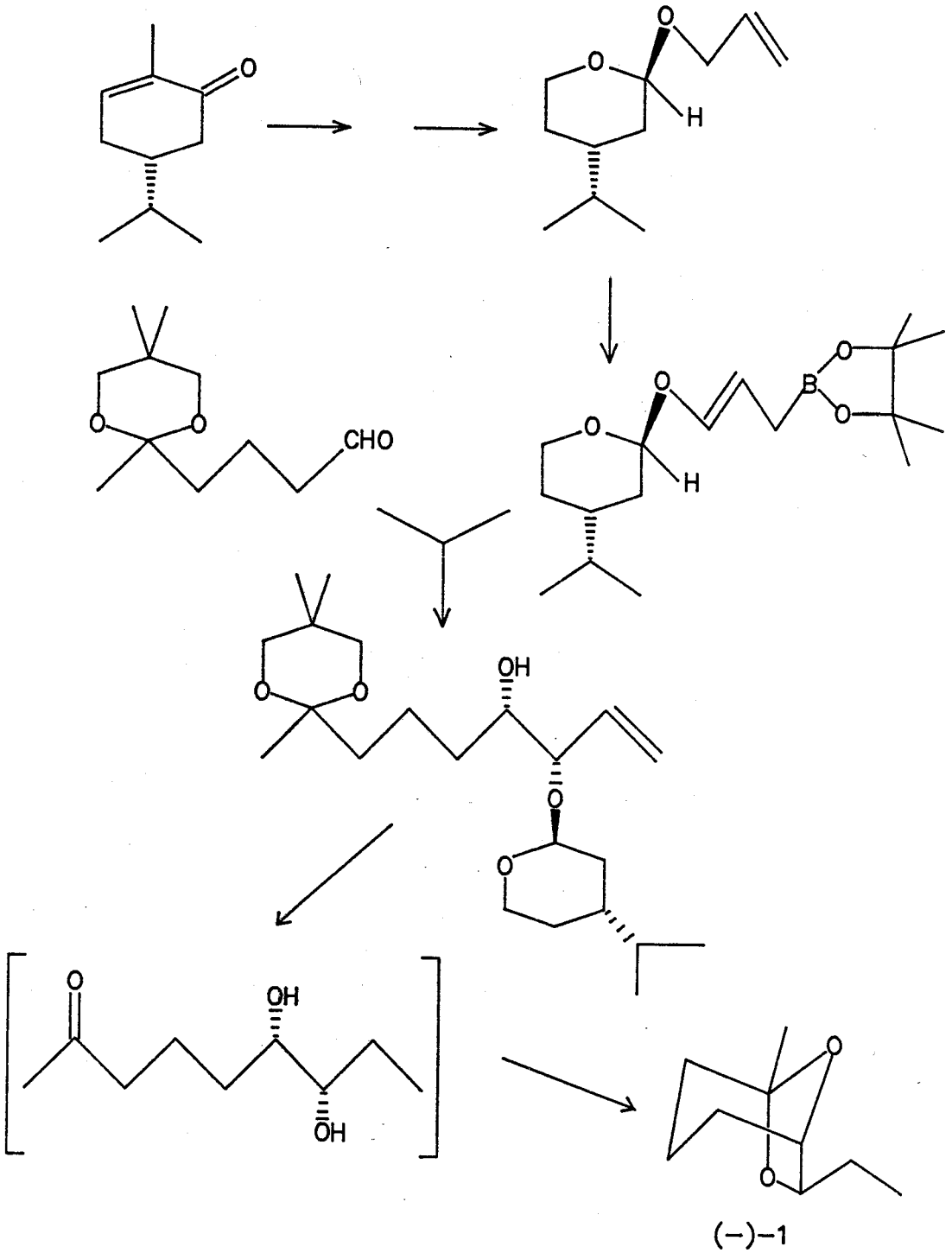


(+)-1

Scheme 15
reference 33



Scheme 16
reference 34



(−)−1

TABLE 1

Summary of Asymmetric *exo*-Brevicomin Syntheses

Scheme (enantiomer)	No. of Steps	Overall Yield	$[\alpha]_D$	Ref.
5 (+)	14	<1%	+84.1 (Et_2O)	23
(-)	"	"	-80.0 (Et_2O)	"
6 (-)	7	27%	-67.5 (Et_2O)	24
7 (+)	6	32%	+81.6 (Et_2O)	25
8 (+)	11	<20%	+81.5 (?)	26
9 (+)		<20%	+82.4 (Et_2O)	27
10 (-)	9	<10%	-73 (Et_2O)	28
11 (+)	11	37%	+64.8 ($CHCl_3$)	29
12 (+)	6	34%	+50.3 (Et_2O)	30
(+)	10	<20%	+70 (Et_2O)	31
13 (-)	"	"	-66 (Et_2O)	"
14 (+)	14	<20%	+74 (Et_2O)	32
15 (+)	6	?	+81.1 (Et_2O)	33
16 (-)	7	?	-60.0 (Et_2O)	34
(+)	6	<10%	+52 (Et_2O)	35
17 (+)	7	28%	+59.0 ($CHCl_3$)	Exp.
17 (-)	7	27%	-60.6 ($CHCl_3$)	Exp.

Results and Discussion

Our approach to the enantiomers of brevicomin was designed to meet several requirements. Firstly, the synthesis was required to yield either enantiomer with equal facility. Secondly, a synthetic route was desired which consisted of relatively few steps and would thus be amenable to the production of the pheromones in the quantities (several grams) necessary for extensive biological testing. The provision for monitoring of enantiomeric purity by direct methods both for intermediates and final products was also an important consideration.

The synthesis designed to meet these requirements commenced with the commercially available ketal of 5-chloro-2-pentanone (**8**) which was elaborated via a three-step sequence[36-37] to give **11** in 65% overall yield (Scheme 17). A large scale (0.2 mole) preparation of **11** without purification of intermediates gave an overall yield of 81%. The two-step chain extension to give **10** proved superior, in our hands, to the single step reaction of **8** with either the dianion of propargyl alcohol[38] or the lithium anion of silyl and THP protected propargyl derivatives.[39]

Asymmetric epoxidation of **11** by the Sharpless method[40,41] followed by non-acidic processing gave the enantiomers of **12** in high enantiomeric purity (95% ee)[42] but only moderate chemical yield (~30%). Treatment of chloroform solutions of each optical isomer of **12** with 5% aqueous hydrochloric acid gave the bicyclic alcohols **14** but in decreased optical purity (~80% ee).[42] Reasoning that the loss in enantiomeric purity was due to lack of

regiochemical control during the strongly acidic conditions employed for epoxide opening, we investigated the epoxidation of an intermediate (**13**) which would produce a more easily cyclized epoxide. Accordingly the protecting group was removed from **11** and the keto-allylic alcohol (**13**) was subjected to Sharpless asymmetric epoxidation for 4 days at -25°C. Standard aqueous tartaric acid processing[40] proved sufficiently acidic to promote cyclization of the intermediate epoxides to the enantiomers of **14** in high chemical (>70%) and optical (95% ee)[42] yields. A possibly related rearrangement during Sharpless oxidation of an allylic alcohol containing a carbonyl δ to the unsaturation has been noted by Corey.[41(a)]

The enantiomers of **14** were converted to (+)- and (-)-*exo*-brevicomin (**1**) by bromination[43] to give **15** followed by methylation with lithium dimethylcuprate.[44] Attempts to displace sulfonate groups[45] from the tosylate or mesylate of **14** were unsuccessful due to competing attack of the lithium dimethylcuprate at the sulfur. Presumably the bicyclic ring system partially shields the *exo*-methylene carbon from nucleophilic attack. The overall yield of *exo*-brevicomin from (**8**) was 30-40%.

The absolute configuration and stereochemistry of the *exo*-brevicomin enantiomers are those which require the intermediate oxirane of **13** to undergo acid catalyzed cyclization involving inversion of configuration at C-3 and retention at C-2. The mechanism of the cyclization step must not, therefore, involve non-selective hydrolysis of the epoxide to the 1,2,3 triol which would result in racemization. A mechanistic proposal which

explains the observed results is presented in Figure 1. This mechanism involves the retention of the original carbonyl oxygen atom in the intramolecular ketal. Although this is contrary to the generally accepted mechanism for intermolecular ketal formation, which involves the loss of the carbonyl oxygen by successive protonation steps to ultimately yield water, the fact that thermal cyclization of appropriate epoxy-ketones[6] also yields intramolecular ketals gives some basis for proposal of epoxide opening by nucleophilic attack of the carbonyl oxygen . This must be selective for attack at C-3 (6 membered-ring transition state) as opposed to attack at C-2 (7 membered-ring transition state).

Scheme 17

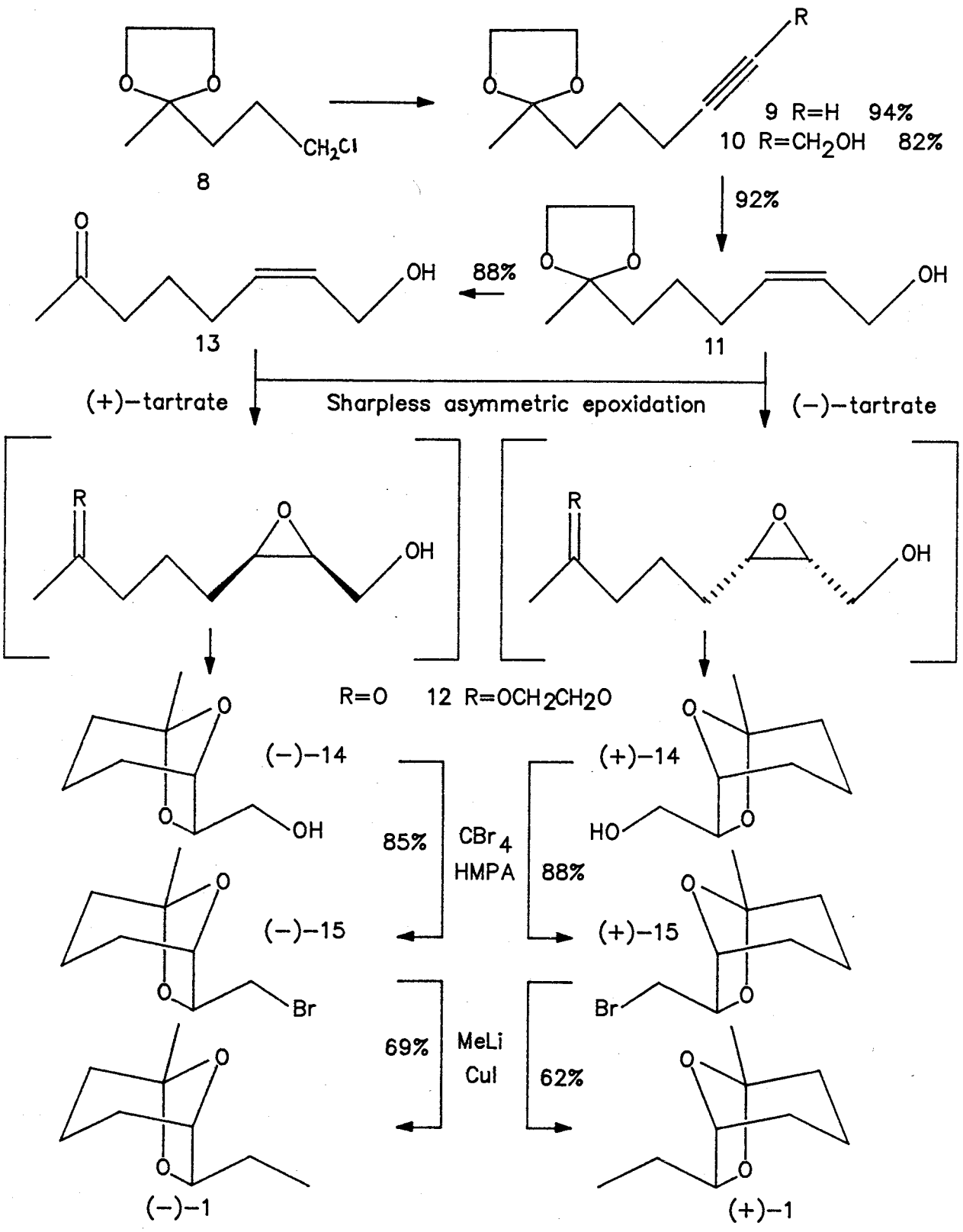
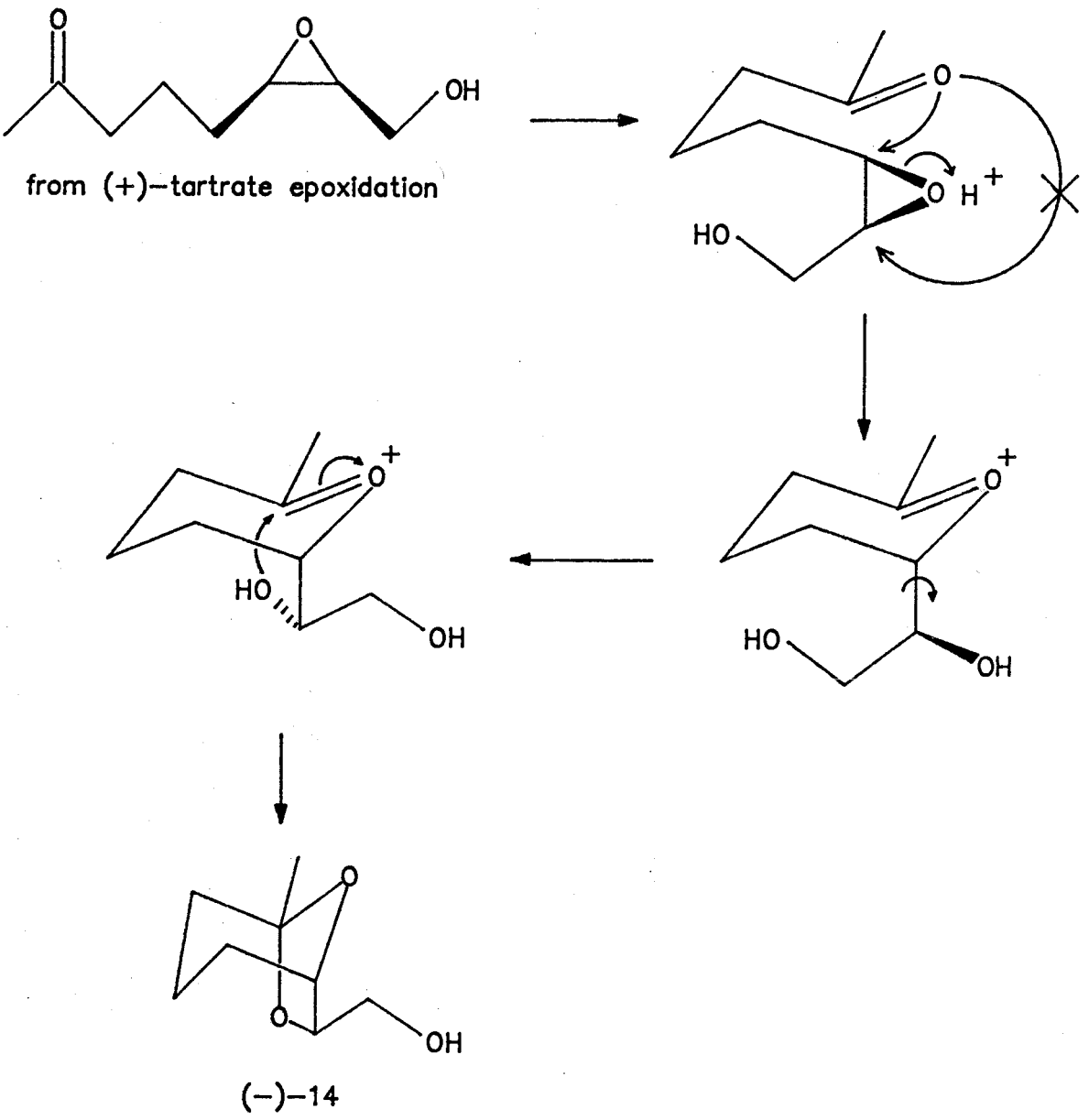

R
9 R=H 94%
10 R=CH2OH 82%
CH2Cl
8
92%
OH
88%
OH
13
11
(+)-tartrate
Sharpless asymmetric epoxidation
(-)-tartrate
R
O
OH
R=O 12 R=OCH2CH2O
(-)-14
(+)-14
OH
HO
85%
CBr4
HMPA
88%
(-)-15
(+)-15
Br
Br
69%
MeLi
CuI
62%
(-)-1
(+)-1

Figure 1



Mechanism of Cyclization to Give 14

CHAPTER 2

SYNTHESIS OF THE ENANTIOMERS OF FRONTALIN

Introduction

The succssful synthesis of both enantiomers of brevicomin (**1**) which utilized the Sharpless asymmetric epoxidation[40] in the key chiral induction step has led us to investigate the use of this reaction in the asymmetric synthesis of other natural products, particularly other chiral insect pheromones. Immediately obvious as synthetic targets were the chiral isomers of frontalin **16** which contain the 6,8-dioxabicyclo[3.2.1]octane nucleus in common with brevicomin.

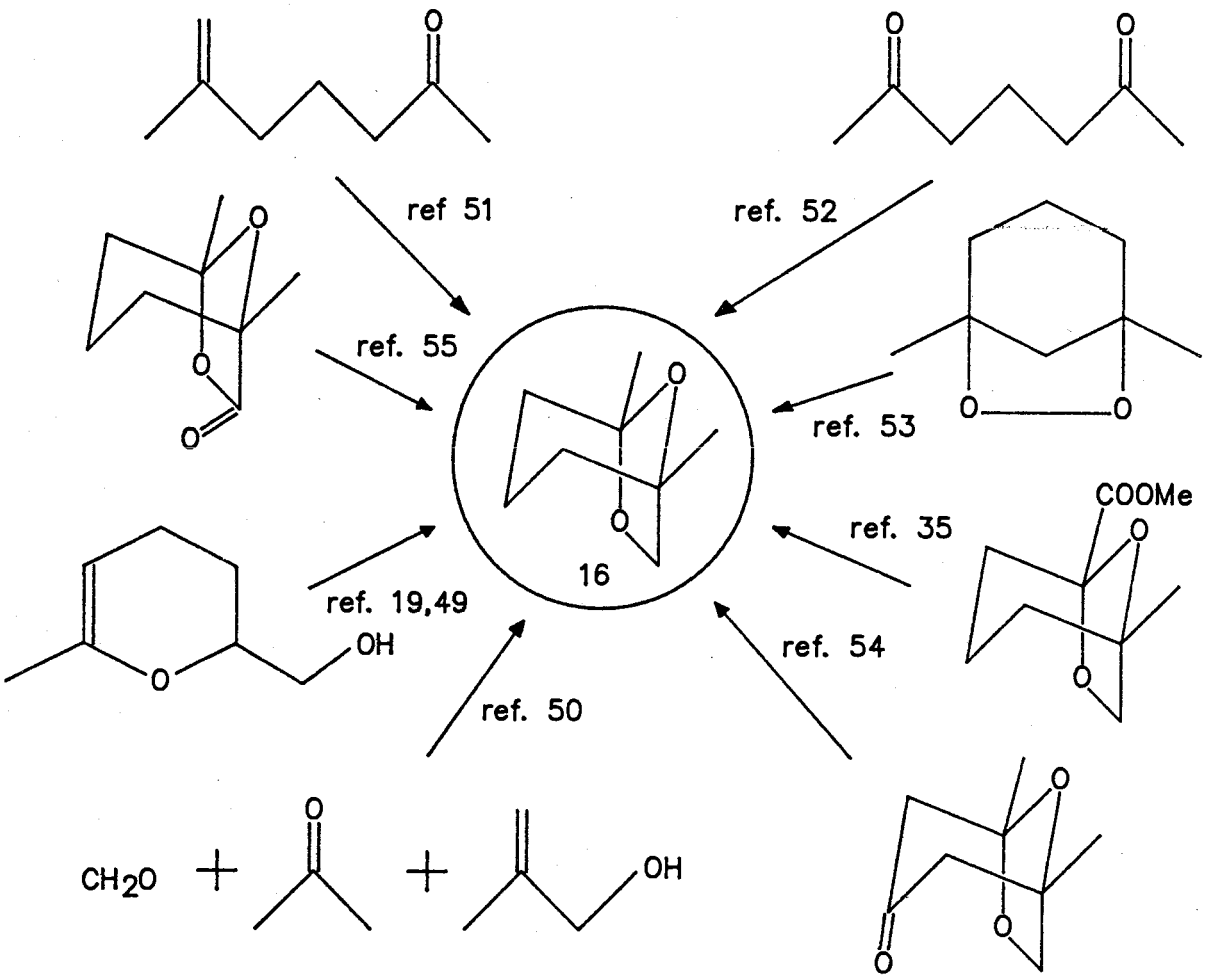
Frontalin (1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octane) has been shown to possess aggregation pheromone activity in several species of *Dendroctonus* bark beetles.[48] As part of a collaborative multidisciplinary project involving the detection, monitoring and control of bark beetle populations using pheromone baited traps, we required three to five gram amounts of each chiral isomer of frontalin in order to determine if different *Dendroctonus* species would respond with chiral recognition to the enantiomers.

Frontalin has been a popular target for synthetic chemists and there have been a number of racemic[19,35,49-55] and chiral[56-67] syntheses of the molecule. A summary of the published racemic syntheses is presented in Scheme 18. These methods range in complexity from involved, multi-step procedures to simple one or two-step methods.

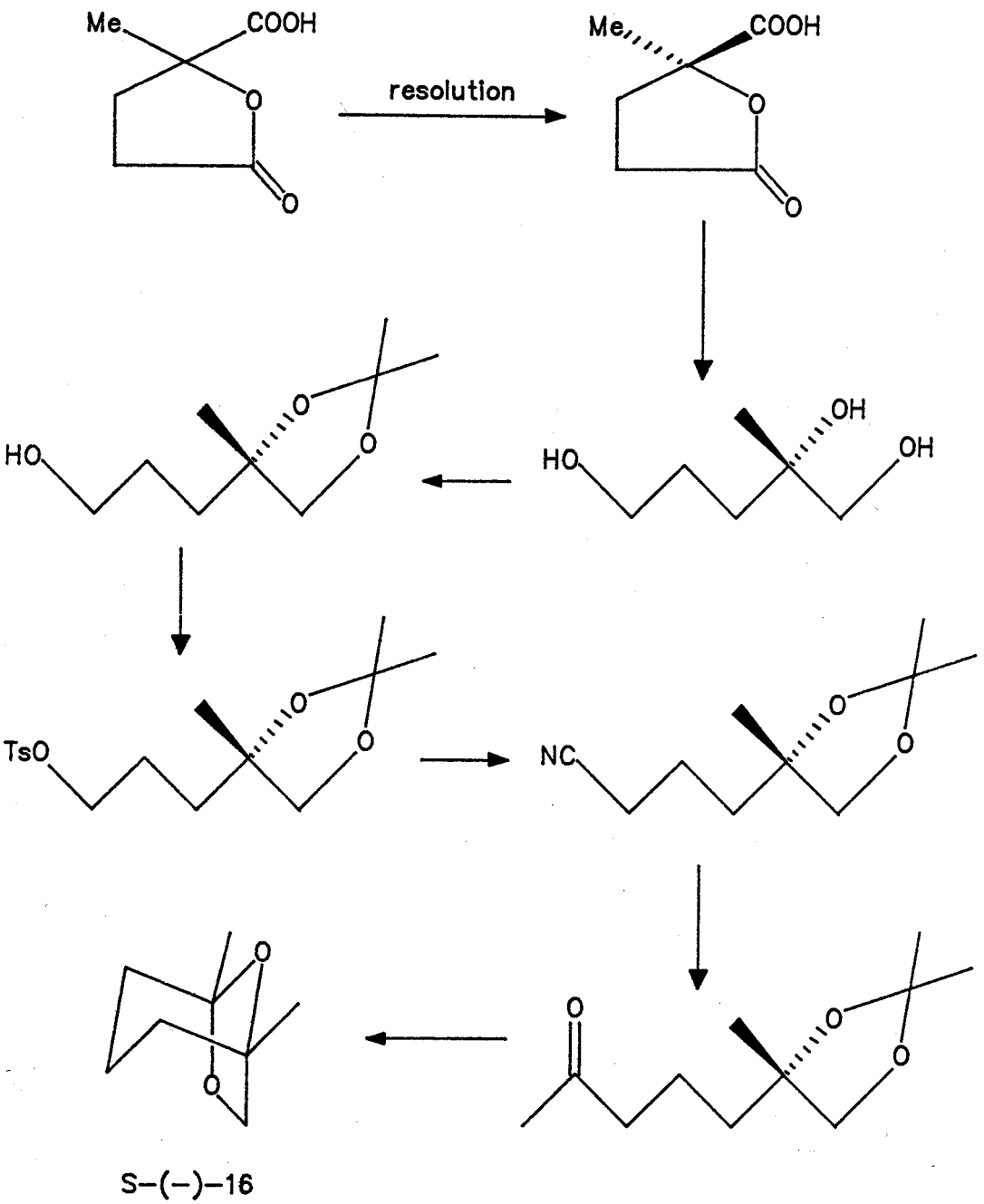
The synthesis of frontalin enantiomers was pioneered by Mori[56] (Scheme 19) who used classical methods to resolve a lactonic-acid intermediate through fractional crystallization of diastereomeric alkaloid salts. The assignment of absolute stereochemistry was made on the basis of circular dichroism studies. Later syntheses utilized the known absolute configuration of chiral, natural product starting materials in order to confirm that the assignments made by Mori were correct. There have been two such applications of *D*-glucose[57,58] (Schemes 20,21) and one for each of *S*-(+)-citramalic acid[59] (Scheme 22), *R*-(-)-linalool[60] (Scheme 23) and *S*-(+)-lactic acid[61] (Scheme 24). With the absolute configuration of the frontalin enantiomers firmly established, other syntheses which made use of chiral auxiliaries for the induction of asymmetry appeared[62-67] (Schemes 25-29). When the present work was undertaken, an examination of the published chiral synthetic routes revealed that several did not appear amenable to scale-up for the amounts we required and that the others seemed only directly applicable to production of one of the two possible enantiomers. A summary of published routes to the frontalin enantiomers is presented in Table 2.

Scheme 18

SUMMARY OF RACEMIC FRONTALIN SYNTHESES

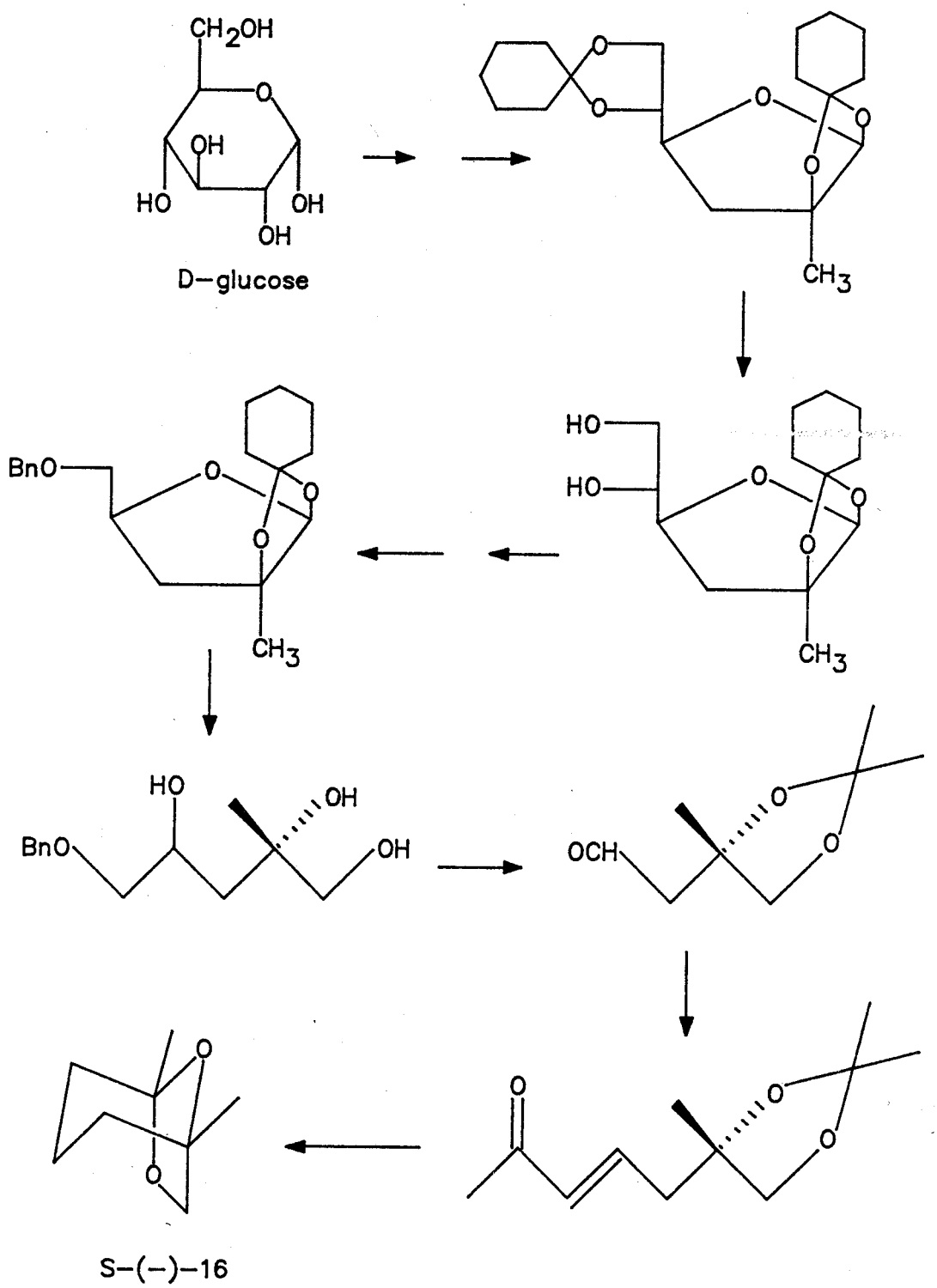


Scheme 19
reference 56

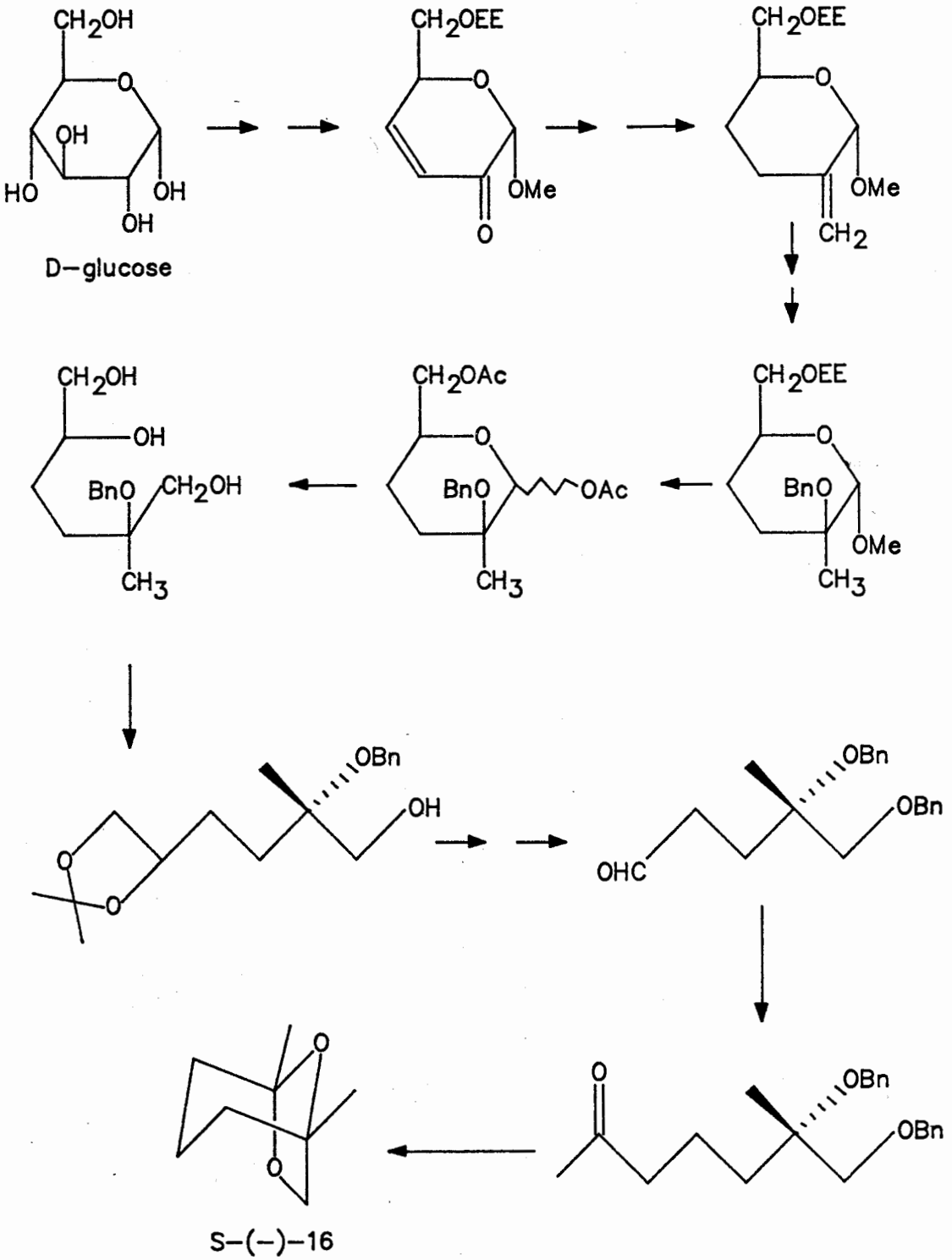


S-(-)-16

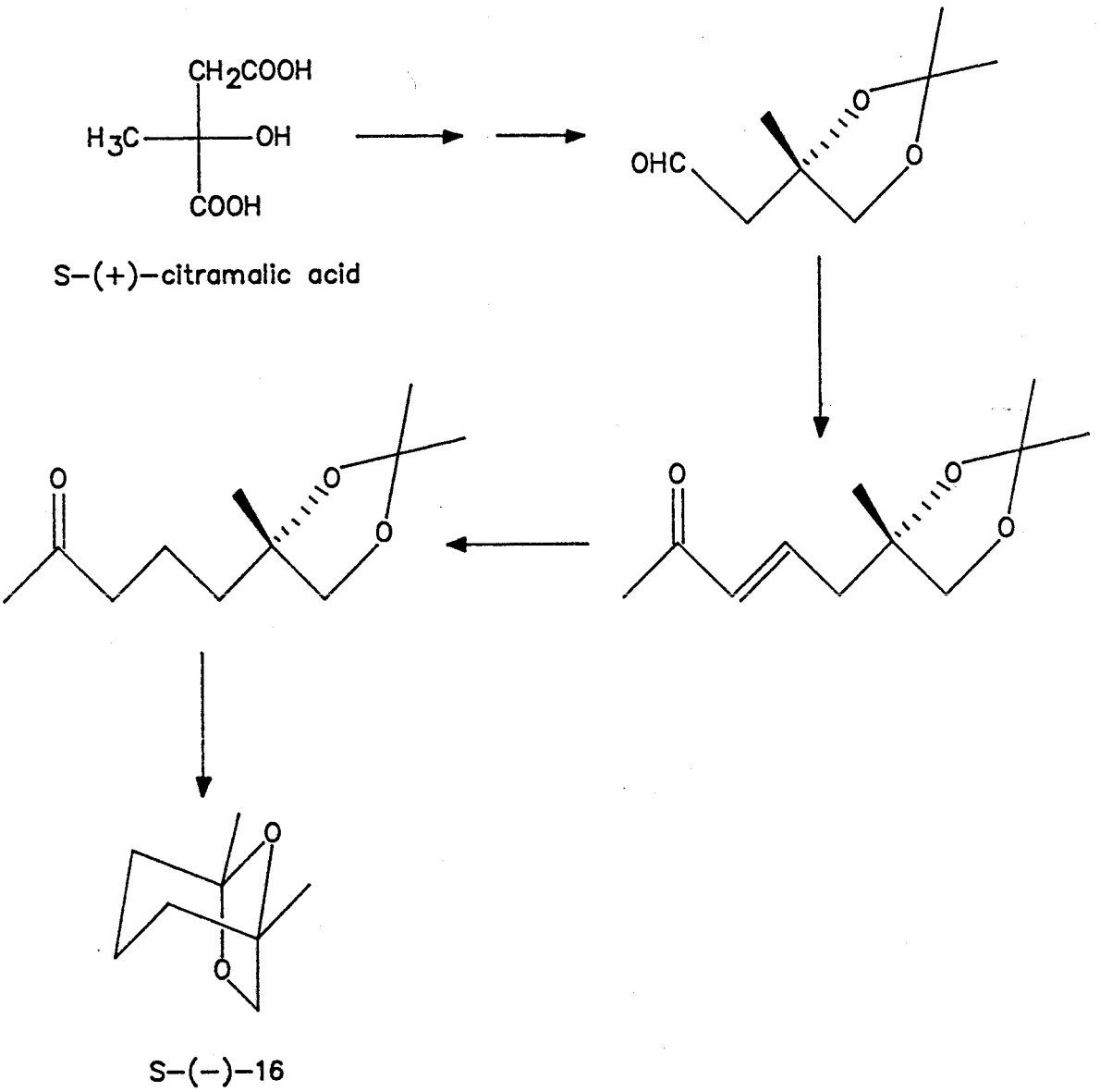
Scheme 20
reference 57



Scheme 21
reference 58



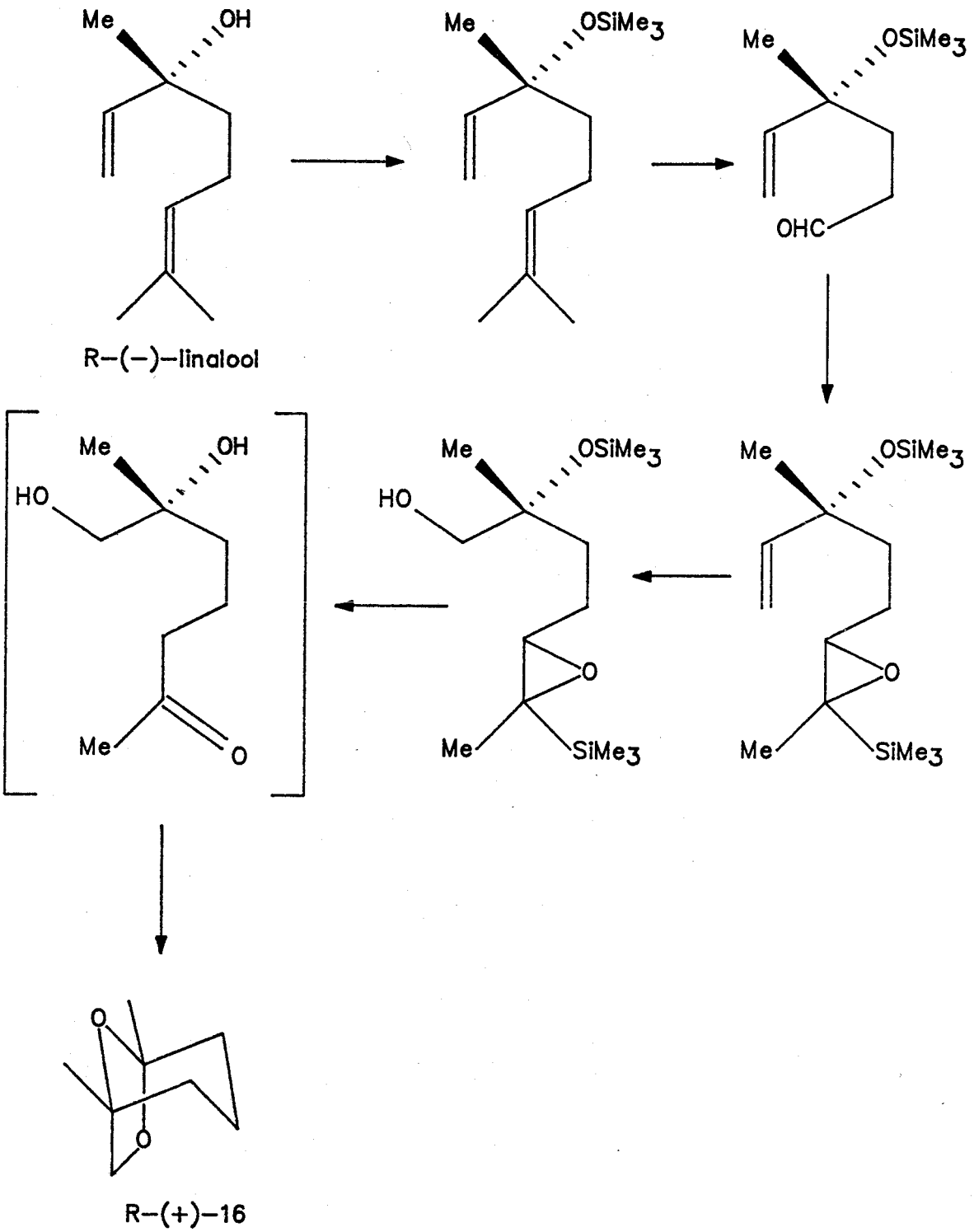
Scheme 22
reference 59



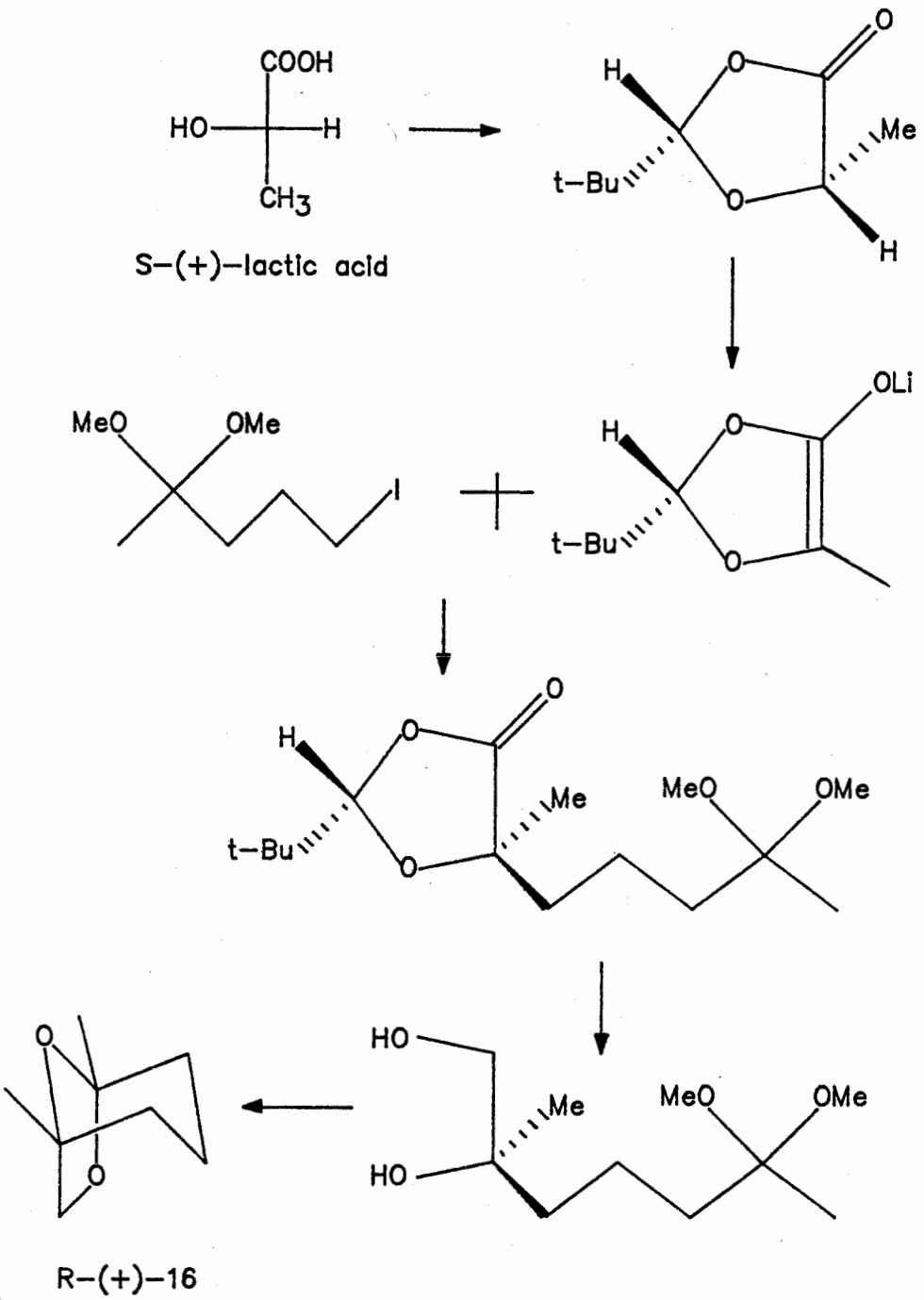
S-(+)-citramalic acid

S-(-)-16

Sheme 23
reference 60

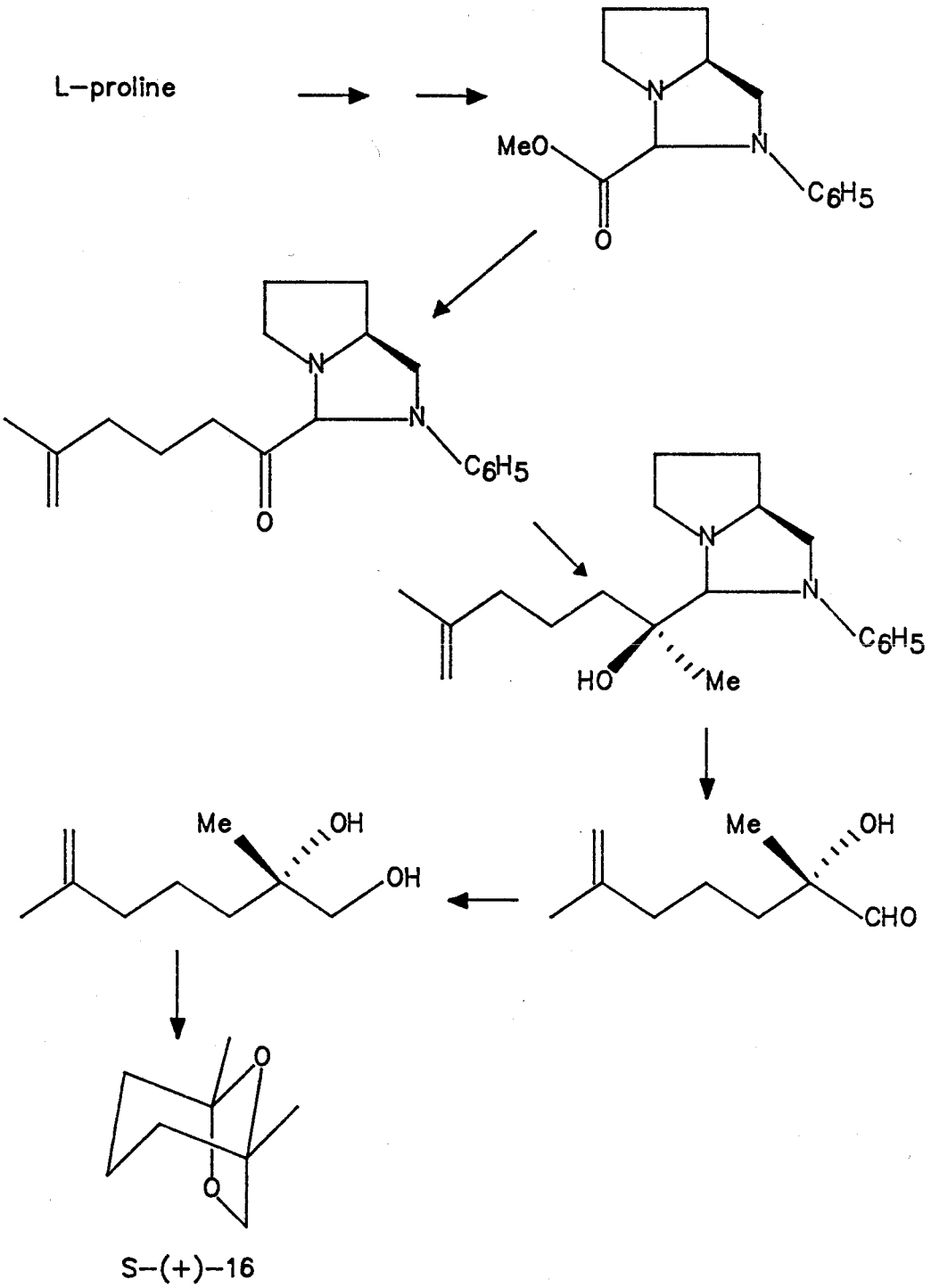


Scheme 24
reference 61



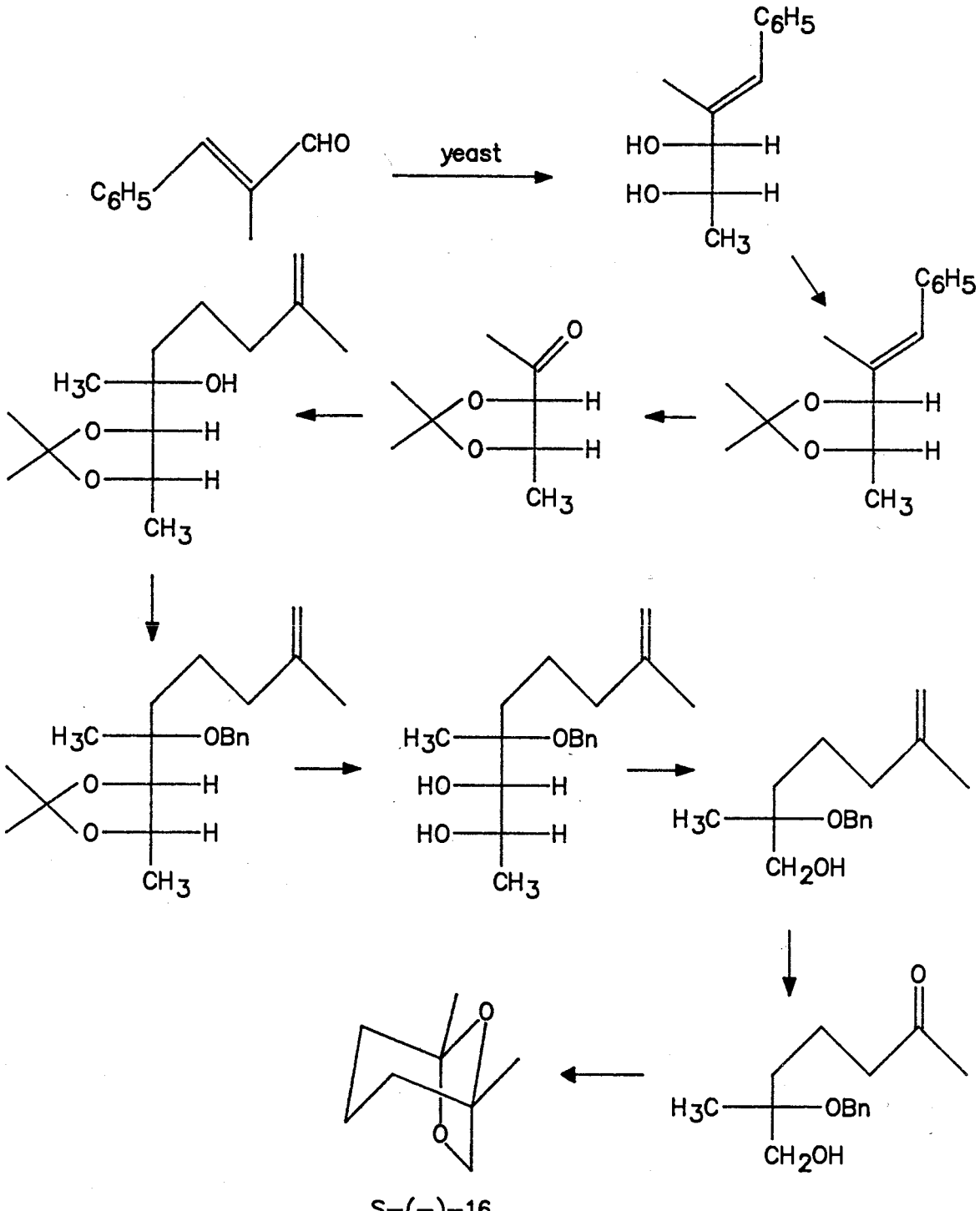
R-(+)-16

Scheme 25
reference 62



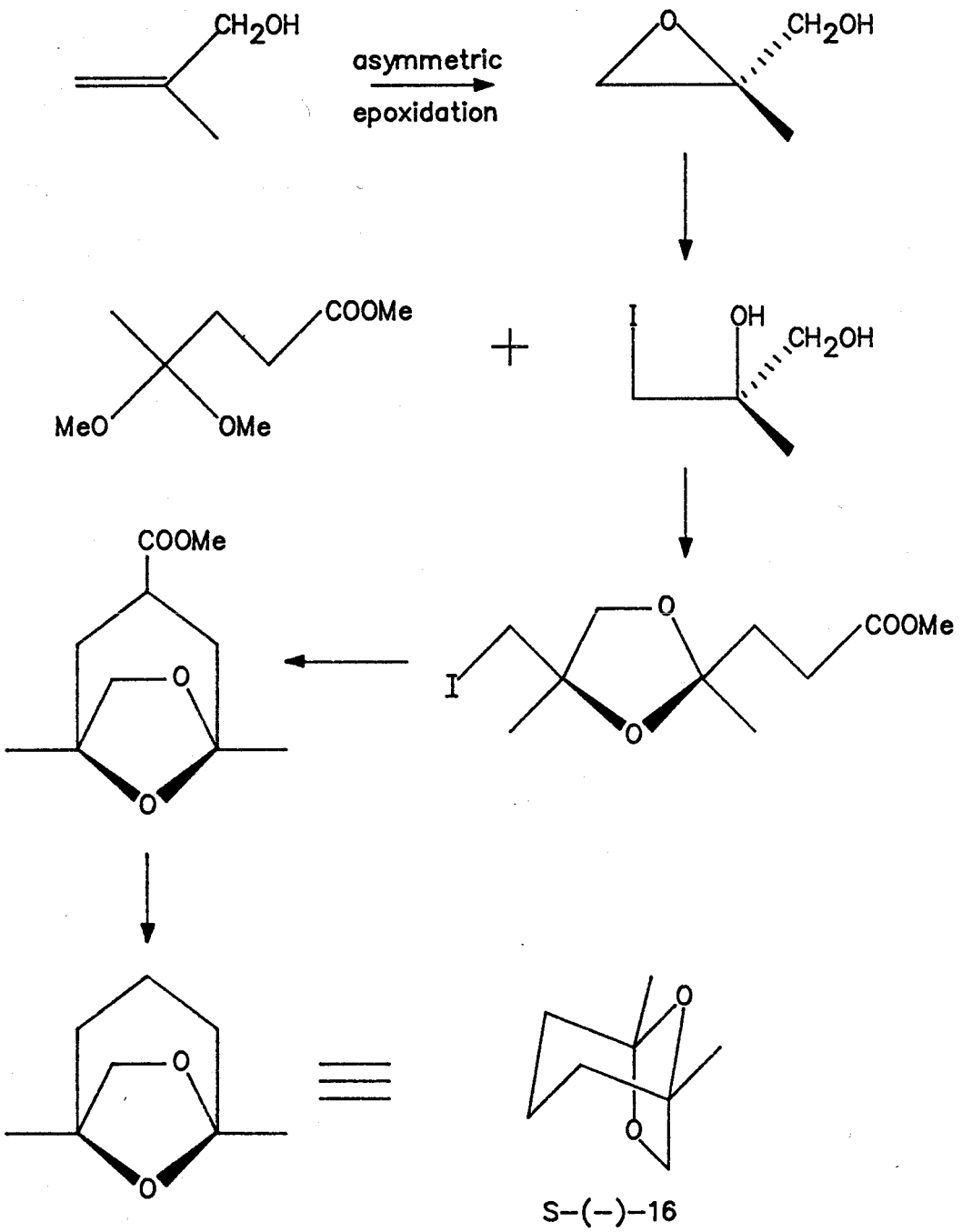
S-(+)-16

Scheme 26
reference 63

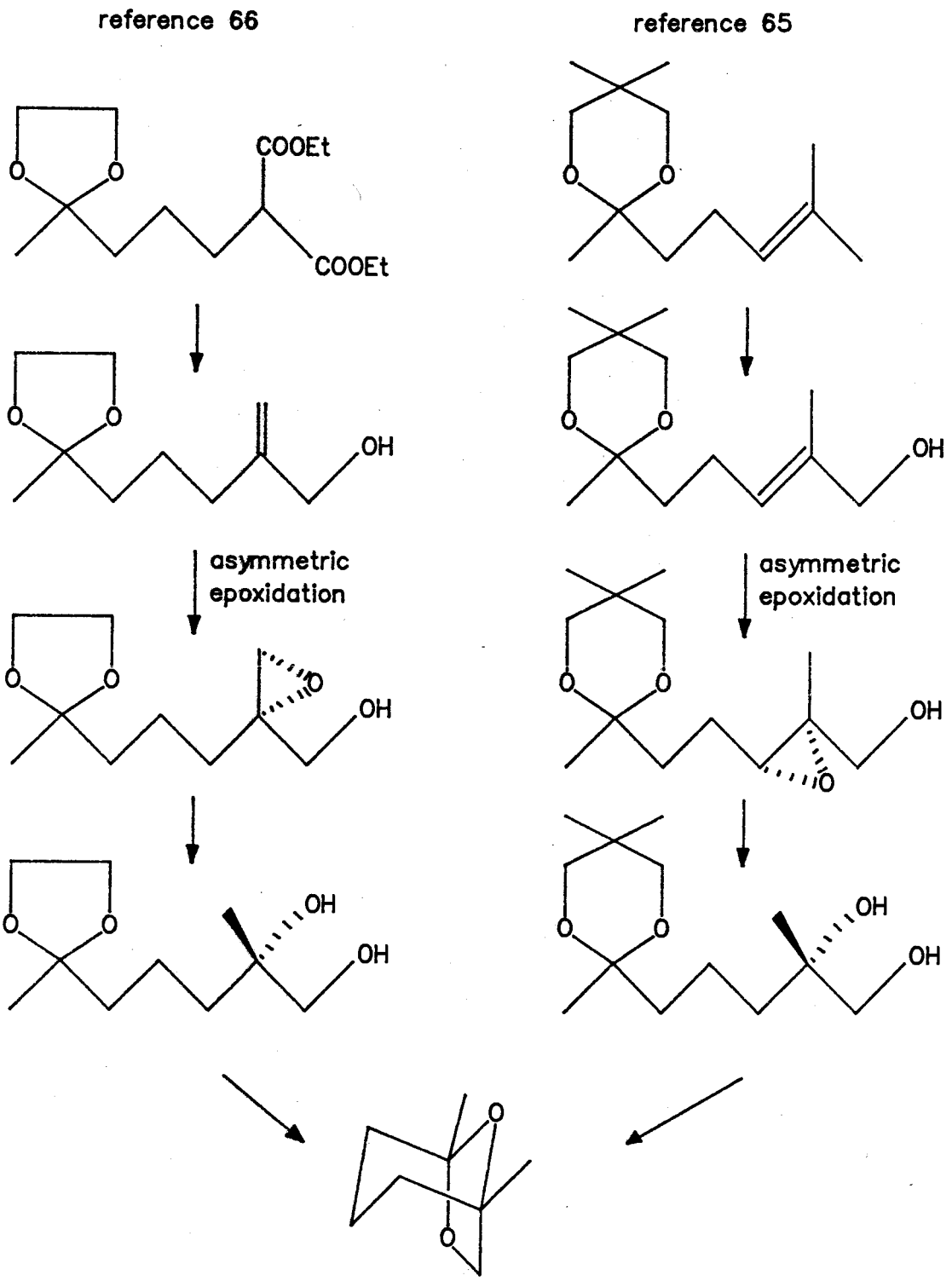


S-(-)-16

Scheme 27
reference 64

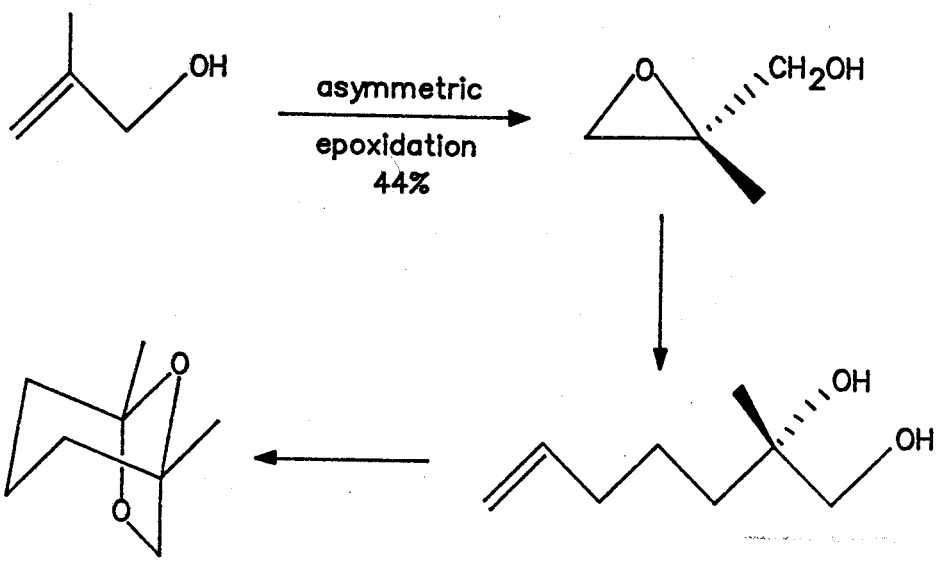


Scheme 28



S-(−)-16

Scheme 29
reference 67



S-(-)-16

TABLE 2

Summary of Asymmetric Frontalin Syntheses

Scheme (enantiomer)	No. of Steps	Overall Yield	$[\alpha]_D$	Ref.
19 (+)	6	7%	+53.4 (Et_2O)	56
19 (-)	6	6%	-52.0 (Et_2O)	56
20 (-)	14	<10%	-54.4 (Et_2O)	57
(+)	9	11%	+51.3 (Et_2O)	58
21 (-)	9	13%	-50.7 (Et_2O)	58
22 (-)	6	45%	-55.5 (Et_2O)	59
23 (+)	6	25%	+52.6 (neat)	60
24 (+)	4	73%	+53.5 (Et_2O)	61
(-)	4	40%	-53.5 (Et_2O)	61
25 (+)	6	40%	+54.3 (Et_2O)	62
(-)	6	40%	-45.5 (Et_2O)	62
26 (-)	8	8%	-45 (Et_2O)	63
27 (-)	7	<10%	-53.6 (Et_2O)	64
(+)	4	67%	+52.4 (Et_2O)	65
28 (-)	4	-	-51.8 (Et_2O)	65
28 (-)	5	42%	-51.5 (Et_2O)	66
29 (-)	3	28%	-50.9 (Et_2O)	67
32 (+)	7	56%	+50.7 (Et_2O)	Exp.
32 (-)	7	52%	-52.9 (Et_2O)	Exp.

Results and Discussion

Our initial synthetic plan was to utilize the Sharpless method in a short sequence, beginning with commercially available 6-methyl-5-hepten-2-one, **17** (Scheme 30). The ketone was protected as the ethylene ketal. Subsequent allylic oxidation[68] followed by reduction of the mixture of aldehyde **19** and alcohol **20** with $NaBH_4$ gave an acceptable yield of the *E* allylic alcohol **20**. Unfortunately, Sharpless epoxidation[40] of **20** did not yield the expected epoxide **21** but rather the interesting dioxabicyclo compound **22**. Evidently, Sharpless epoxidation conditions promote opening of both the ketal and the epoxide. After completion of this work, Sharpless reported in a review article[69] that the 2,2-dimethyltrimethylenedioxy ketal analog of **21** does not undergo this rearrangement and that this epoxide can be efficiently (74% overall) converted to frontalin. This synthesis was later published in the form of a communication by Lee[65] (Scheme 28).

Structure **22** was assigned on the basis of spectroscopic analysis. The mass spectrum indicated a molecular ion of 202, which corresponded to the expected epoxide product, but the ^1H NMR spectrum in several solvents (DMSO-d_6, benzene-d_6, $CDCl_3$) could not be reconciled with structure **21**. In particular, an AB pattern characteristic of an isolated methylene with diastereotopic hydrogens was apparent; but, under conditions where OH coupling was observed (DMSO-d_6, triplet, J=6 Hz), no extra coupling was observed in the AB pattern. This indicated that, although a primary alcohol was present, the product could

not be the expected epoxide, **21**.

Secondary and tertiary alcohol structures **23** and **24**, which were initially considered as possibilities, were also eliminated by this result. Comparison of the ^1H NMR of the acetate **25** with that of the parent alcohol **22** indicated that the AB pattern was still present but that a downfield shift of ~0.5 ppm had occurred for a second highly coupled methylene group. A partial structure of $-OCH_2CH_2OH$ which must contain methylenes with diastereotopic hydrogens was therefore deduced. A choice between structures **22** and **26** was made on the basis of ^{13}C NMR. The chemical shifts of the carbons involved in the ether linkage of **22** were indicative of an oxetane rather than an epoxide[70]. As further confirmation, attempted reduction of **22** with excess lithium aluminum hydride in ether at room teperature resulted in recovery of starting material, a result which would not be expected if an epoxide had been present.

Reasoning that protection of the ketone as outlined in Scheme 30 might not be required, we undertook the alternate synthesis outlined in Scheme 31. The ethylene ketal protecting group was removed from allylic alcohol **20** to yield **27** which was subjected to Sharpless epoxidation. Again, the expected epoxide **28** could not be isolated due to epoxide hydrolysis and intramolecular ketal formation during processing. In order to determine if **28** was a stable, isolable compound, the epoxidation was performed using *meta*-chloroperoxybenzoic acid to give racemic **28**. The epoxide (±)-**28** could be obtained in satisfactory yield with a non-aqueous workup[71] but proved to be unstable and slowly

cyclized to **29** (the same structure as obtained from Sharpless epoxidation) over a period of several days. The tendency of *gamma* keto-epoxides to undergo thermal rearrangement to intramolecular ketals is well documented.[6,72,73]

The dioxabicyclo alcohol **29** corresponds to frontalin if the alcohol function is replaced with hydride. Towards this end, racemic **29** was converted to mesylate **30**. Unfortunately, reduction of this hindered, neo-pentyl-like mesylate was unsuccessful using either $LiAlH_4$ in Et_2O (no reaction) or $LiBHEt_3$ in refluxing THF (complex mixture of ring-opened products).

A further attempt to convert **29** to frontalin was also made. With the aim of deoxygenation through reduction of the dithiolane **32**, racemic **29** was oxidized with pyridinium chlorochromate to ketone **31**. Conversion of **31** to the dithiolane derivative **32** using 1,2-ethanedithiol and BF_3:Et_2O was, however, unsuccessful, leading to a complex mixture of sulfur-containing products.

The problems encountered in Schemes 30 and 31 appear to center around the presence of a ketone in either its free or protected form in the substrate during Sharpless epoxidation. We therefore decided to postpone introduction of the ketone to a later stage. Reasoning that a terminal alkene is synthetically equivalent to a methyl ketone, the diene alcohol **33** was prepared by the literature method.[74] Sharpless epoxidation of **33** gave good yields of the expected chiral epoxides **34**. The enantiomeric excess of each chiral isomer was determined by integration of the ^{1}NMR signals for the diastereotopic hydrogens of the $-OCH_2-$ group in the (+)-α-methoxy-α-trifluoromethylphenyl acetate

derivatives[56] to be 95% ee for (-)-**34** and 96% ee for (+)-**34**.

Lithium aluminum hydride reduction of the chiral isomers of **34** using non-acidic processing with limited amounts of water gave excellent yields of the chiral diols **35**. Two different methods for completion of the synthesis were investigated. Initially, we employed a Wacker-type oxidation to obtain frontalin directly from diol **35**. This method has been employed by Grigg,[11] albeit in low yield, in a synthesis of racemic brevicomin. In an attempt to improve upon the original Wacker conditions ($CuCl_2$, O_2, Pd^{+2}) used by Grigg, we chose the modified conditions (H_2O_2, Pd^{+2}) developed by Mimoun.[75] Several attempts at this method using various reaction conditions and workup procedures gave dismally low yields of frontalin (10-12%) and the chemical purity of the final product could not be improved above 85% by simple fractional distillation.

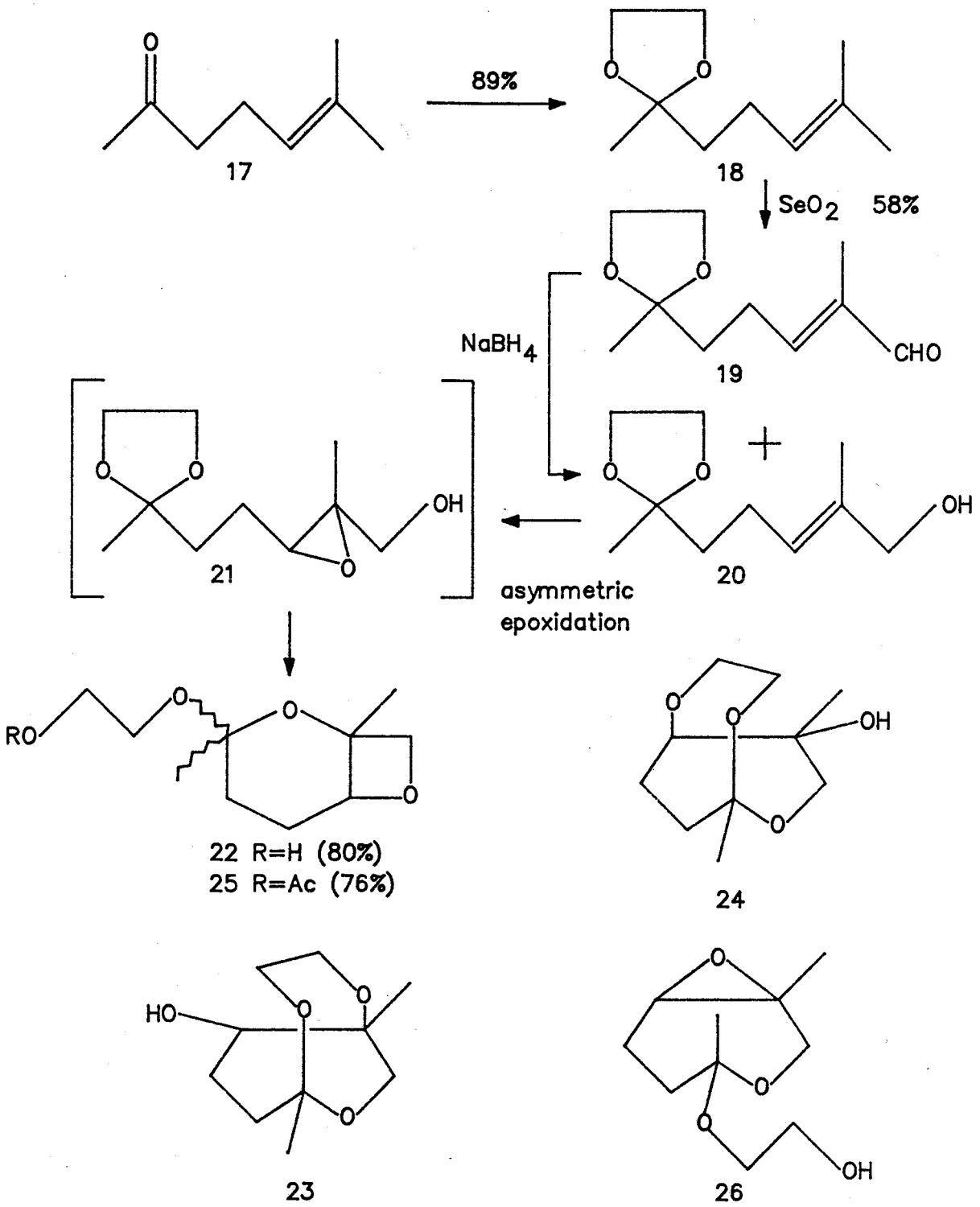
The synthesis was completed in a satisfactory manner using the route from **35** outlined in Scheme 32. This relatively lengthy, but nevertheless high yield, sequence began by protection of the diol **35** containing the sensitive chiral tertiary alcohol function as the acetone ketal **36**. Peracid oxidation of the terminal double bond gave epoxide **37** as a mixture of diastereomers. Lithium aluminum hydride reduction of **37** afforded excellent yields of secondary alcohol **38**, again as a mixture of diastereomers. Sodium hypochlorite oxidation in acetic acid gave the methyl ketone **39** which, although it could be detected by GC analysis of the crude reaction mixture, was not isolated due to slow *in situ* hydrolysis of the ketal and

spontaneous cyclization to cleanly give frontalin **16** in 75% yield.

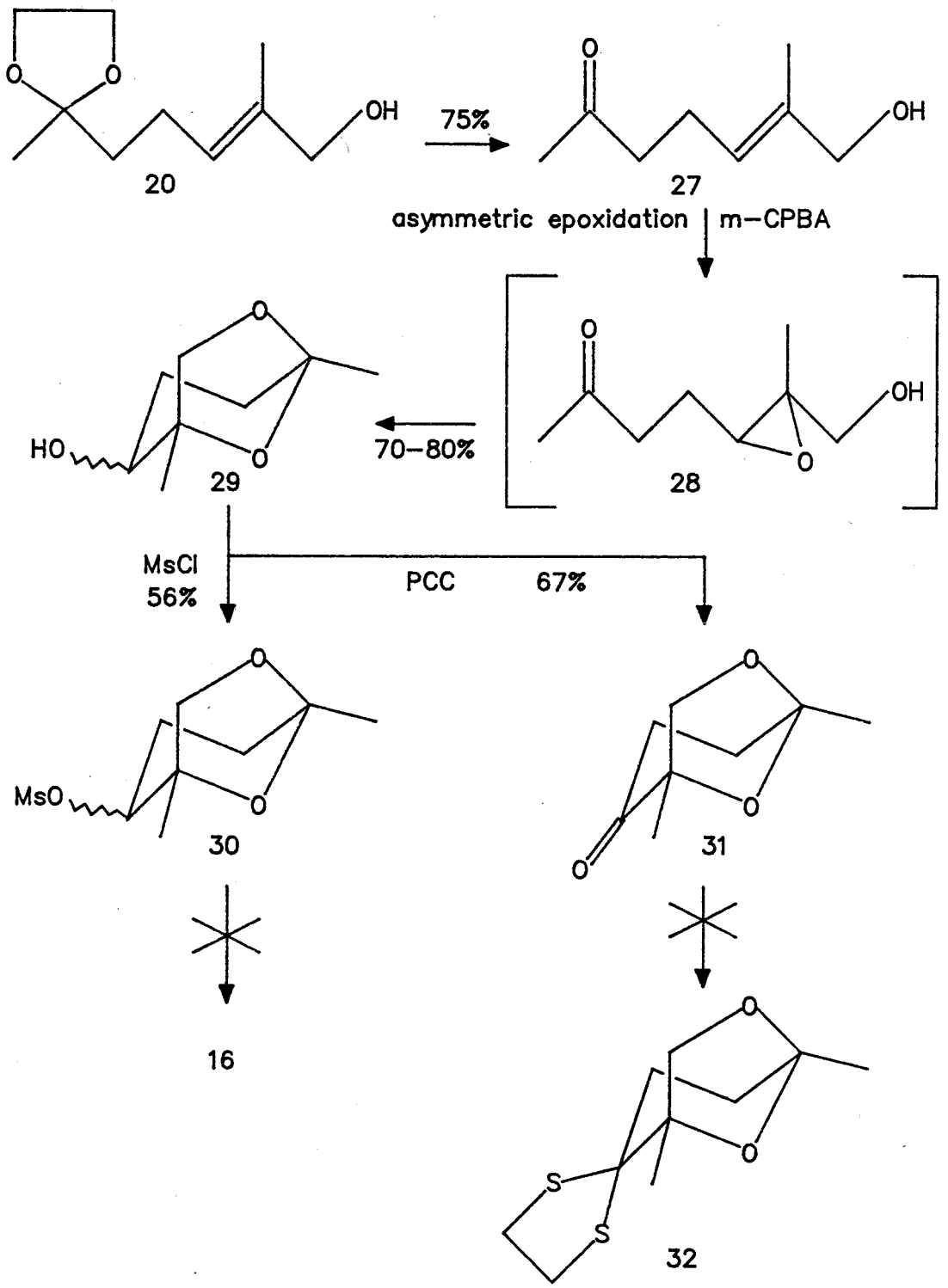
The optical purity of the frontalin enantiomers as determined by a combination of optical rotation measurements and NMR integration in the presence of the chiral shift reagent tris-[3-(trifluoromethylhydroxymethylene)-d-camphorato]- europium(III) indicated 89-93% ee for (+)-frontalin and 97% ee for (-)-frontalin. In the case of (+)-frontalin, we speculate that the decrease in optical purity from the initial Sharpless epoxidation product may be due to a small amount of acid-catalyzed racemization of one of the tertiary alcohol inter-mediates.

In summary, the application of the Sharpless asymmetric epoxidation reaction to an appropriate acyclic allylic alcohol precursor has been shown to afford both frontalin enantiomers (>90% ee) in overall chemical yields of ~50% (from **33**). The synthetic sequence is suitable for the production of multi-gram quantities of the frontalin enantiomers and proceeds entirely without the necessity for chromatographic purification of intermediates.

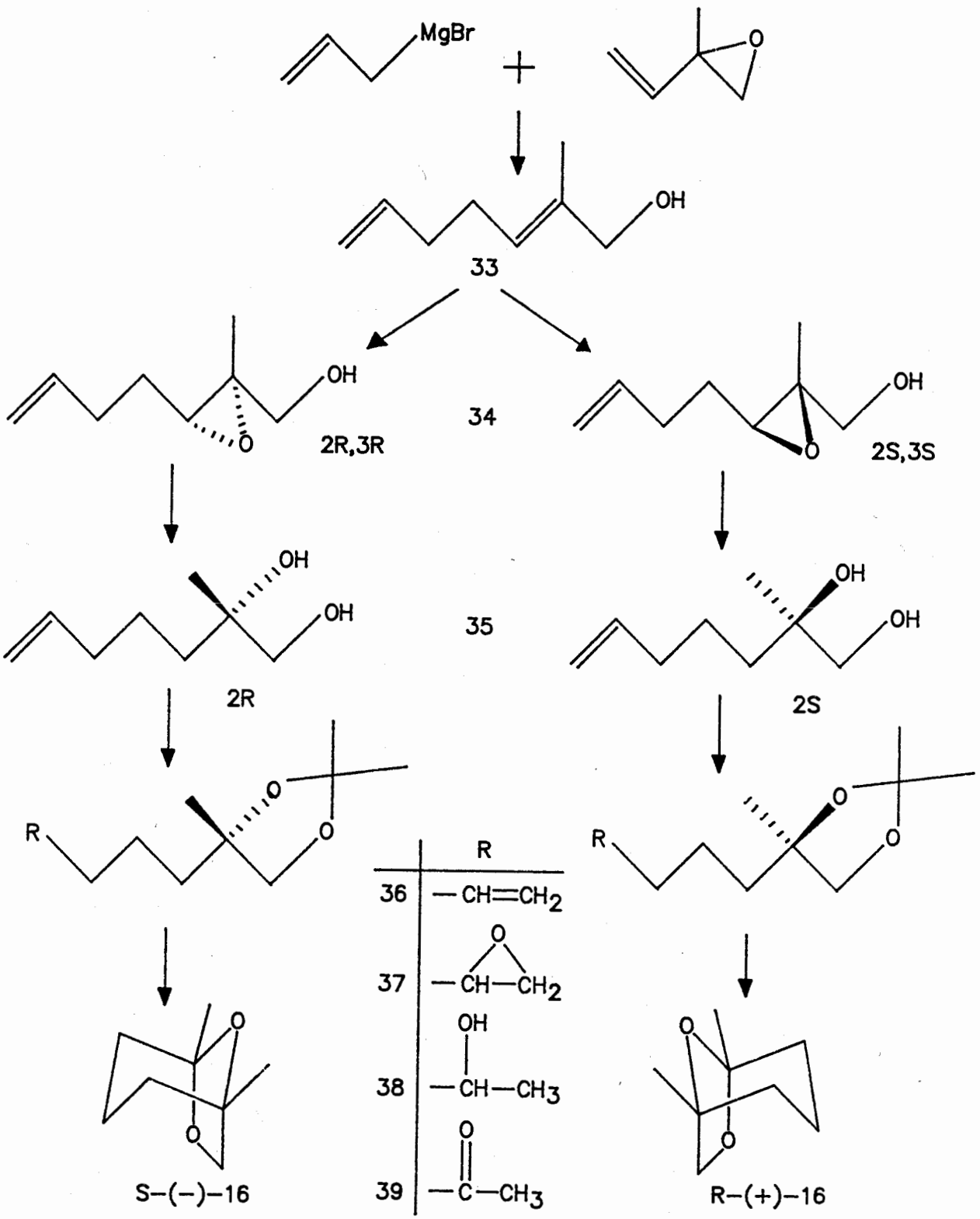
Scheme 30


89%
17
18
SeO_2 58%
19
CHO
$NaBH_4$
OH
21
20
OH
asymmetric
epoxidation
RO
22 R=H (80%)
25 R=Ac (76%)
24
OH
HO
23
26
OH

Scheme 31


20
75%
27
asymmetric epoxidation | m-CPBA
28
70-80%
29
MsCl
56%
PCC
67%
30
31
16
32

Scheme 32


MgBr
O
OH
33
OH
O
2R,3R
34
OH
O
2S,3S
OH
OH
2R
35
OH
OH
2S
R
O
O
R
O
O
R
O
O
S-(-)-16
R-(+)-16
R
36 —CH=CH2
37 —CH—CH2
38 —CH—CH3
39 —C—CH3

CHAPTER 3

SYNTHESIS OF RACEMIC LINEATIN

Introduction

Lineatin (3,3,7-trimethyl-2,9-dioxatricyclo[3.3.1.$0^{4,7}$]-nonane, (**40**) has been shown to be an aggregation pheromone for the bark beetle *Trypodendron lineatum* (Oliver), an economically important forest pest which is responsible for significant damage to fallen and cut timber.[81] The unusual tricyclic acetal structure of **40** has attracted synthetic interest and there have been a number of syntheses reported[82-89] (Schemes 33-40).

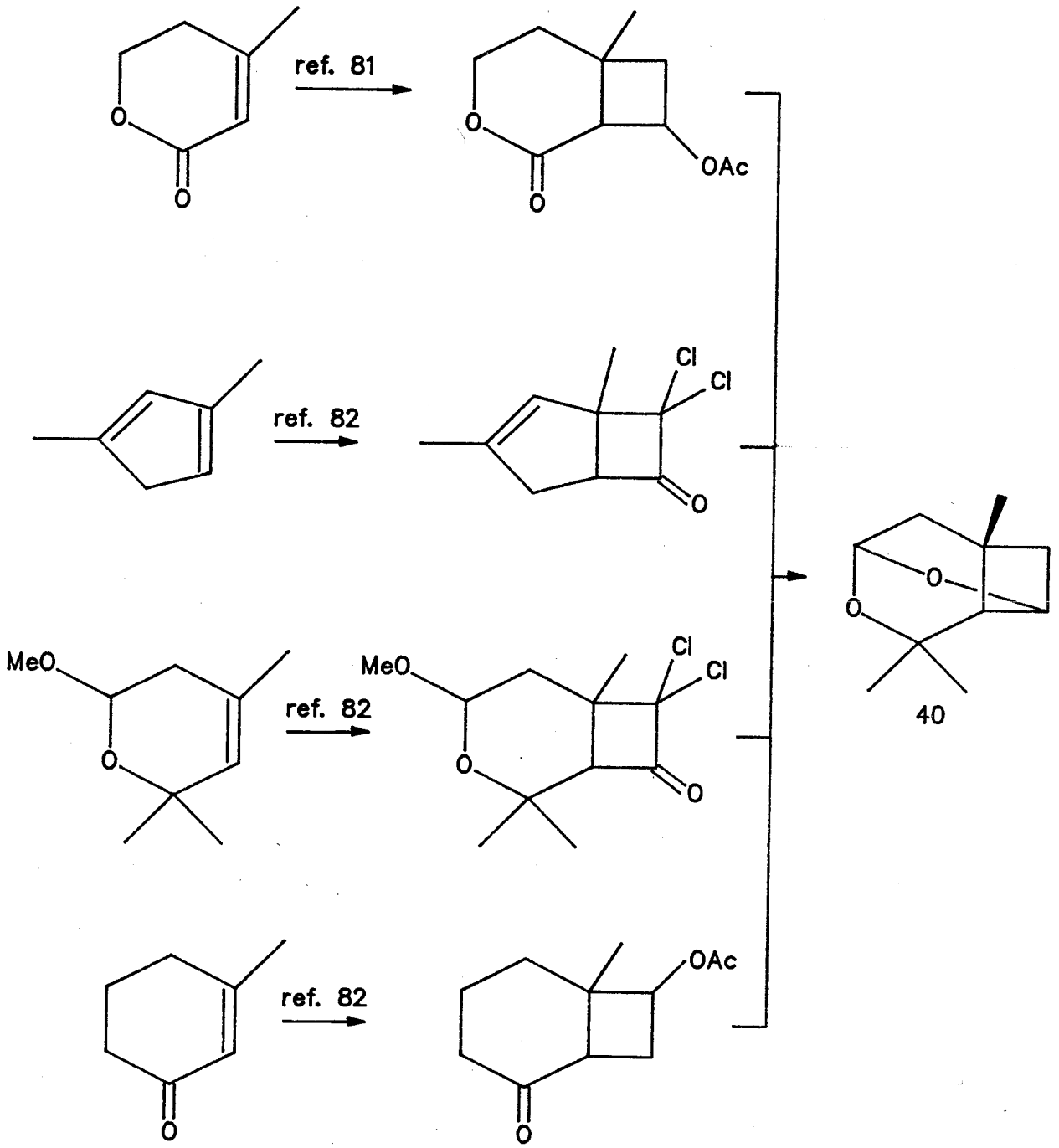
Two early papers[81,82] gave brief outlines for four different approaches to (±)-lineatin, based upon thermal or photochemical [2+2] cycloadditions (Scheme 33). Apparently, none of these methods was ever developed beyond the stage of providing miniscule amounts of impure material. The first completely documented lineatin synthesis[83] also involved a photochemical [2+2] cycloaddition and established the gross structure of the pheromone as **40** rather than **41** (Scheme 34). In addition, this synthetic scheme provided an intermediate suitable for resolution to produce the lineatin enantiomers. The absolute configuration of the enantiomers was inferred from CD and ORD studies. These assignments were subsequently placed in doubt by Slessor *et al.*[84] who prepared racemic lineatin by a ring expansion method and also resolved an intermediate to produce small amounts of the lineatin enantiomers (Scheme 35). The absolute configurations, inferred through a combination of arguments based upon the chromatographic

behavior and NMR chemical shift data for diastereomeric derivatives and by analogy with other chiral intramolecular acetals and ketals, were opposite to those advanced by Mori.[83]

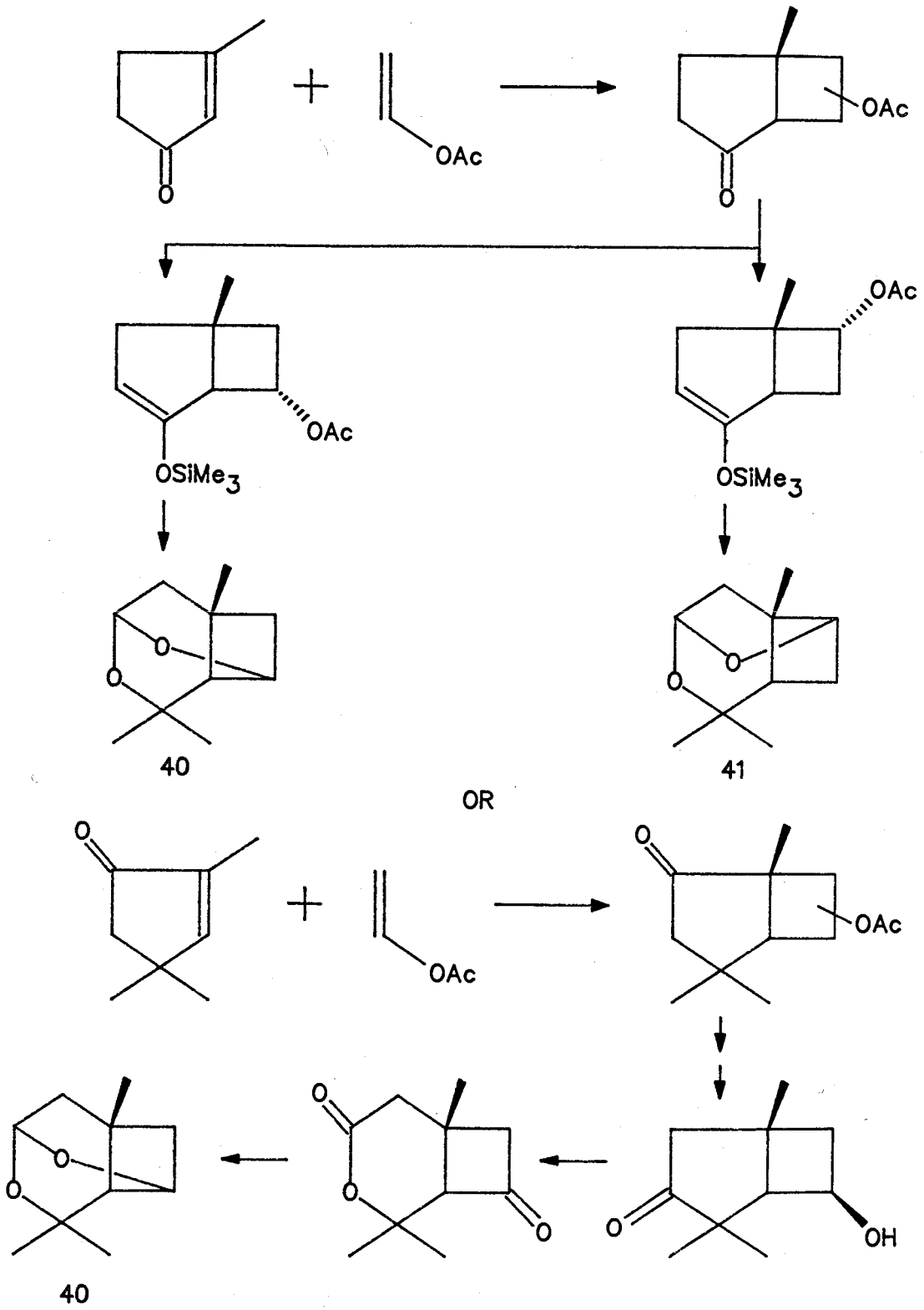
Mori[85] then developed an alternate synthesis of racemic lineatin based on dichloroketene [2+2] cycloaddition with isoprene (Scheme 36). The penultimate cyclobutanol intermediate was resolved by diastereomeric acetal formation with a chrysanthemic acid derivative. X-ray crystallography of this intermediate allowed Mori to resolve the controversy in favor of the assignments made by Slessor *et al.* Very recently a stereospecific synthesis of the natural (+)-lineatin enantiomer from *D*-ribonolactone has been completed by Kandil and Slessor[86] (Scheme 37). This synthesis unequivocally determines the absolute configuration of (+)-lineatin to be (1*R*,4*S*,5*R*,7*R*).

Other recent syntheses have concentrated on the production of racemic lineatin, since it is known that the response of *Trypodendron* insects to the natural (+)-enantiomer is not inhibited by the presence of the (-)-enantiomer.[87] These syntheses have again made use of [2+2] cycloadditions as the key reactions to form the four membered ring. Photochemical methods include the cycloaddition of acetylene[88] or allene[89] to anhydro-mevalonolactone (Schemes 38,39). The high-temperature thermal intramolecular cycloaddition of an allene with an alkene has also been applied (Scheme 40).[90] A summary of published syntheses of racemic lineatin is presented in Table 3.

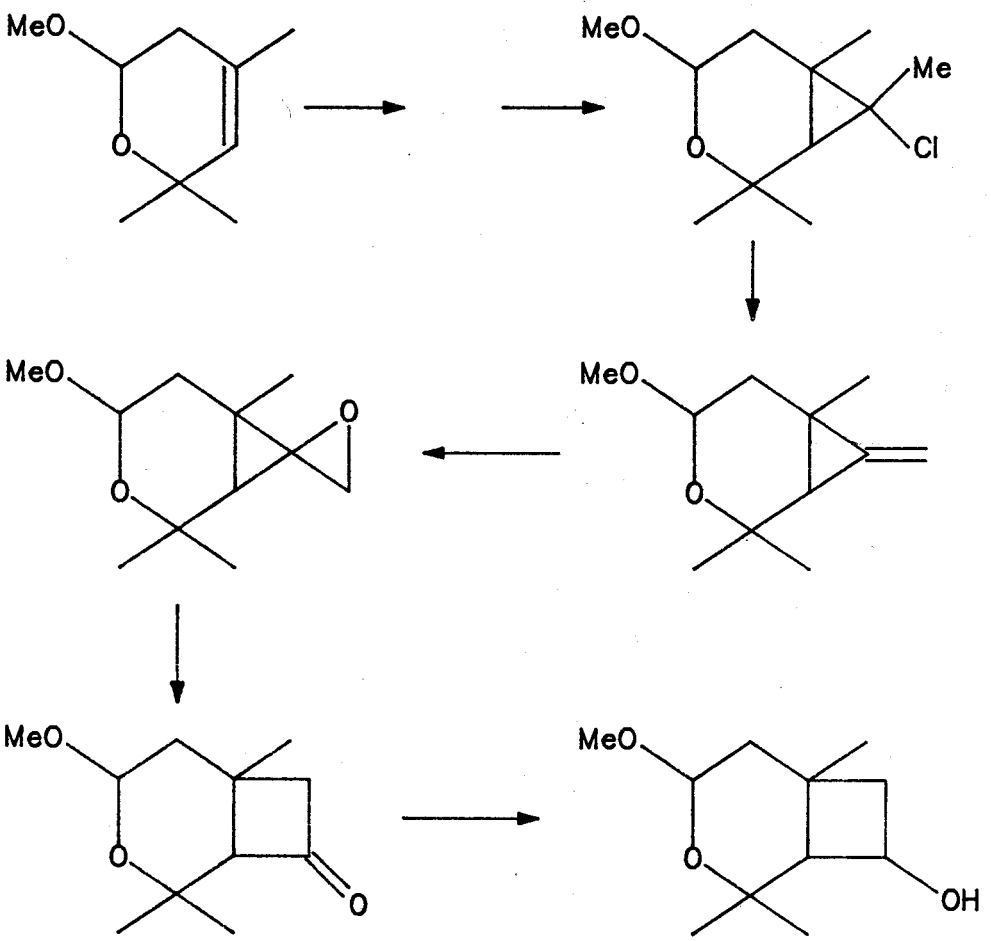
Scheme 33



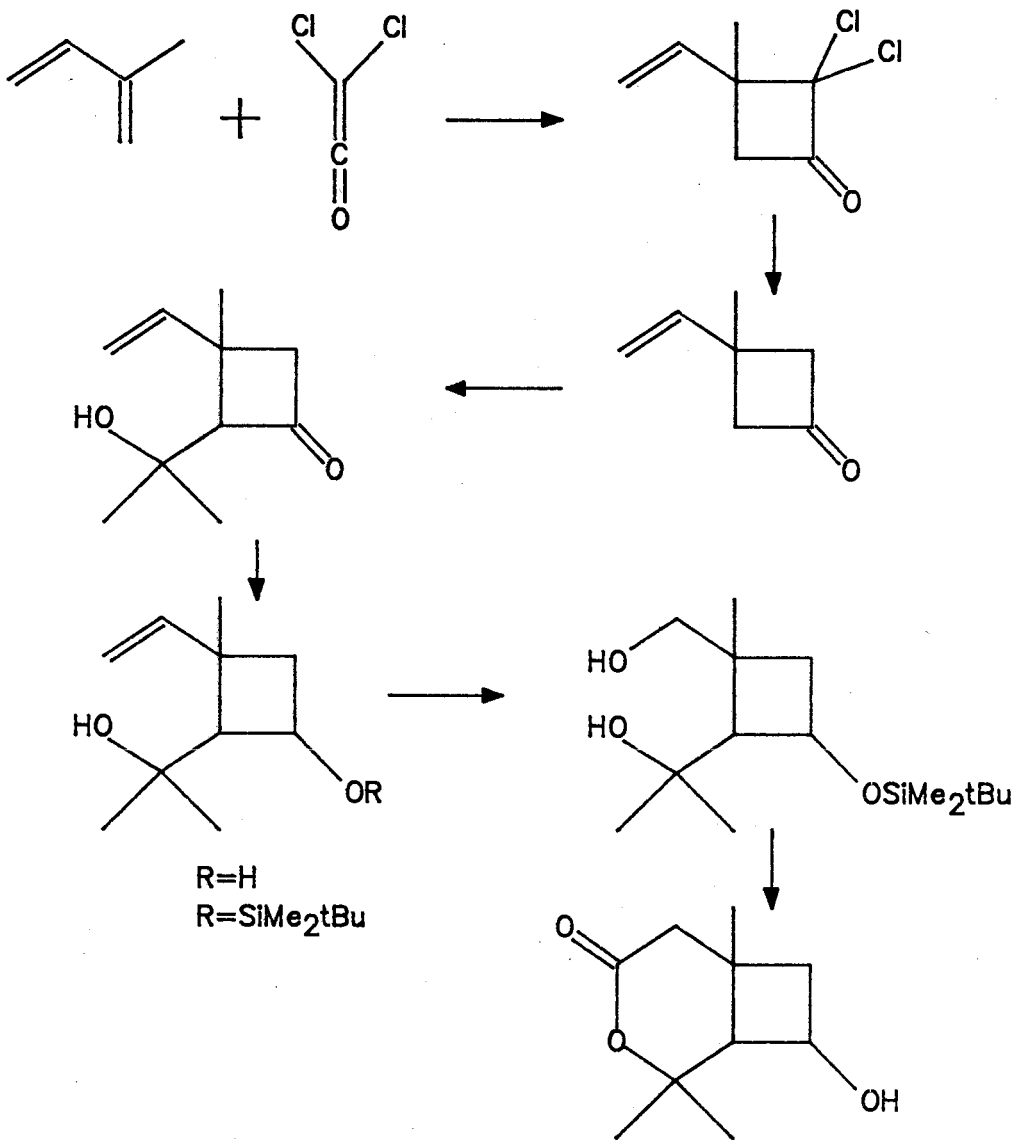
Scheme 34
reference 83



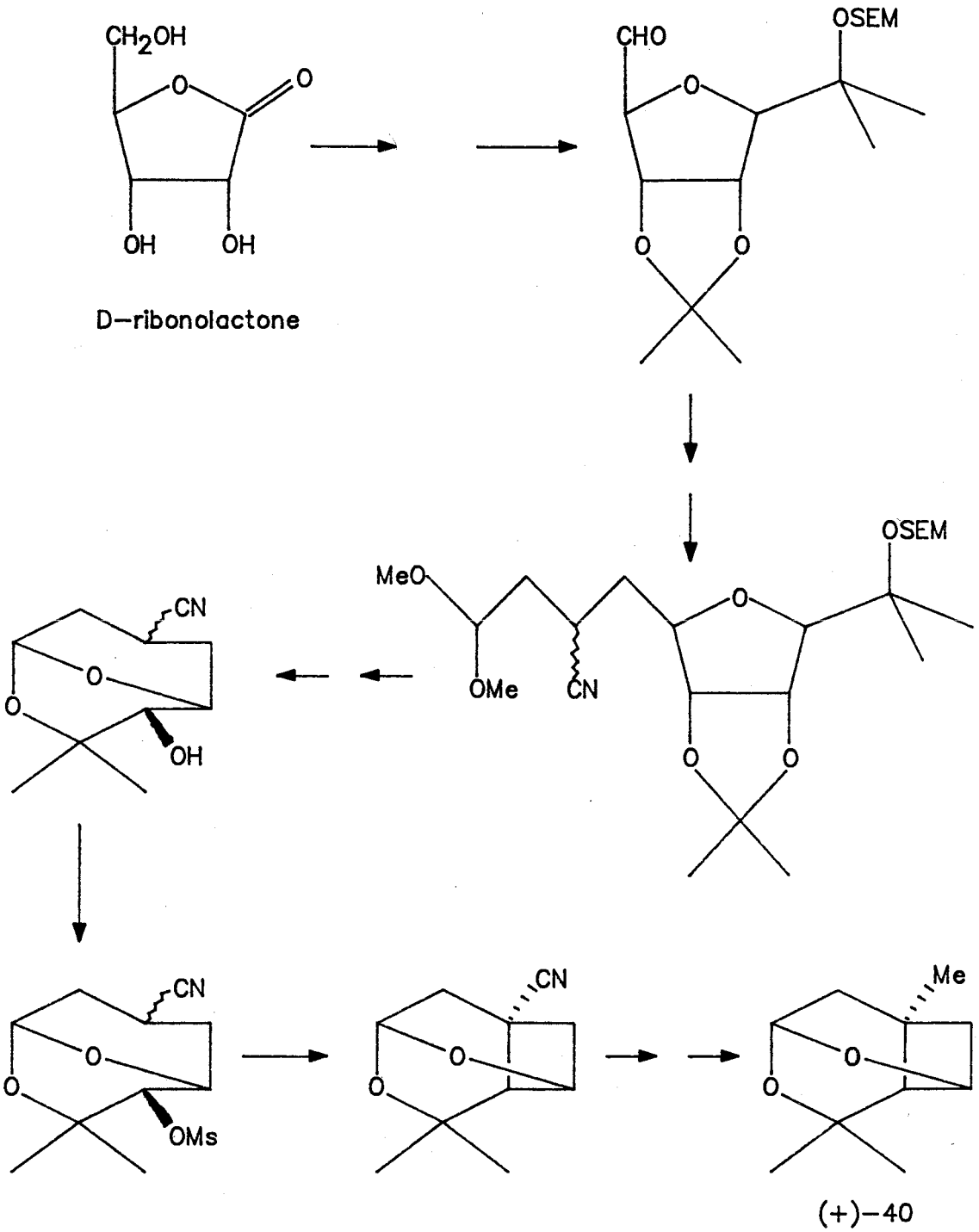
Scheme 35
reference 84



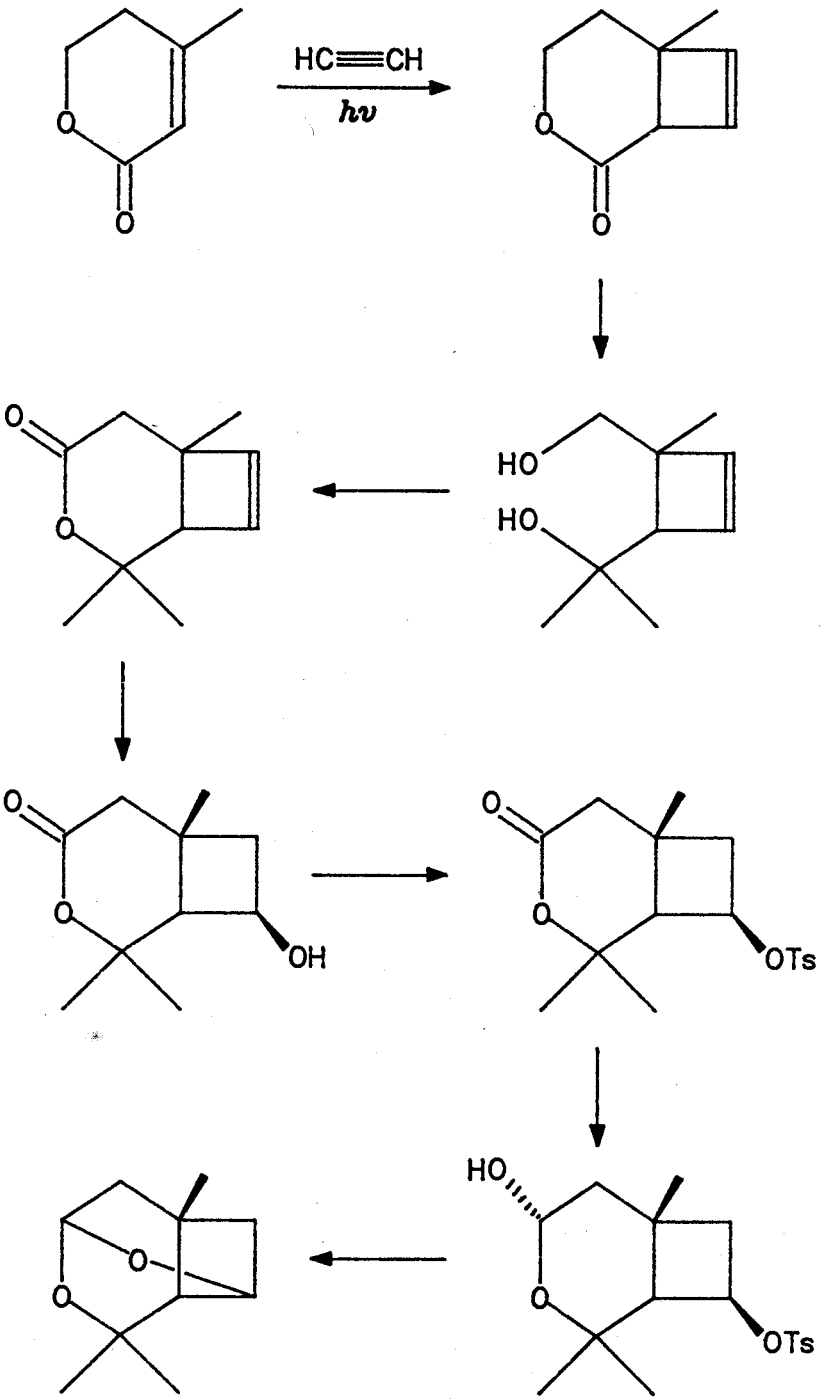
Scheme 36
reference 85



Scheme 37
reference 86

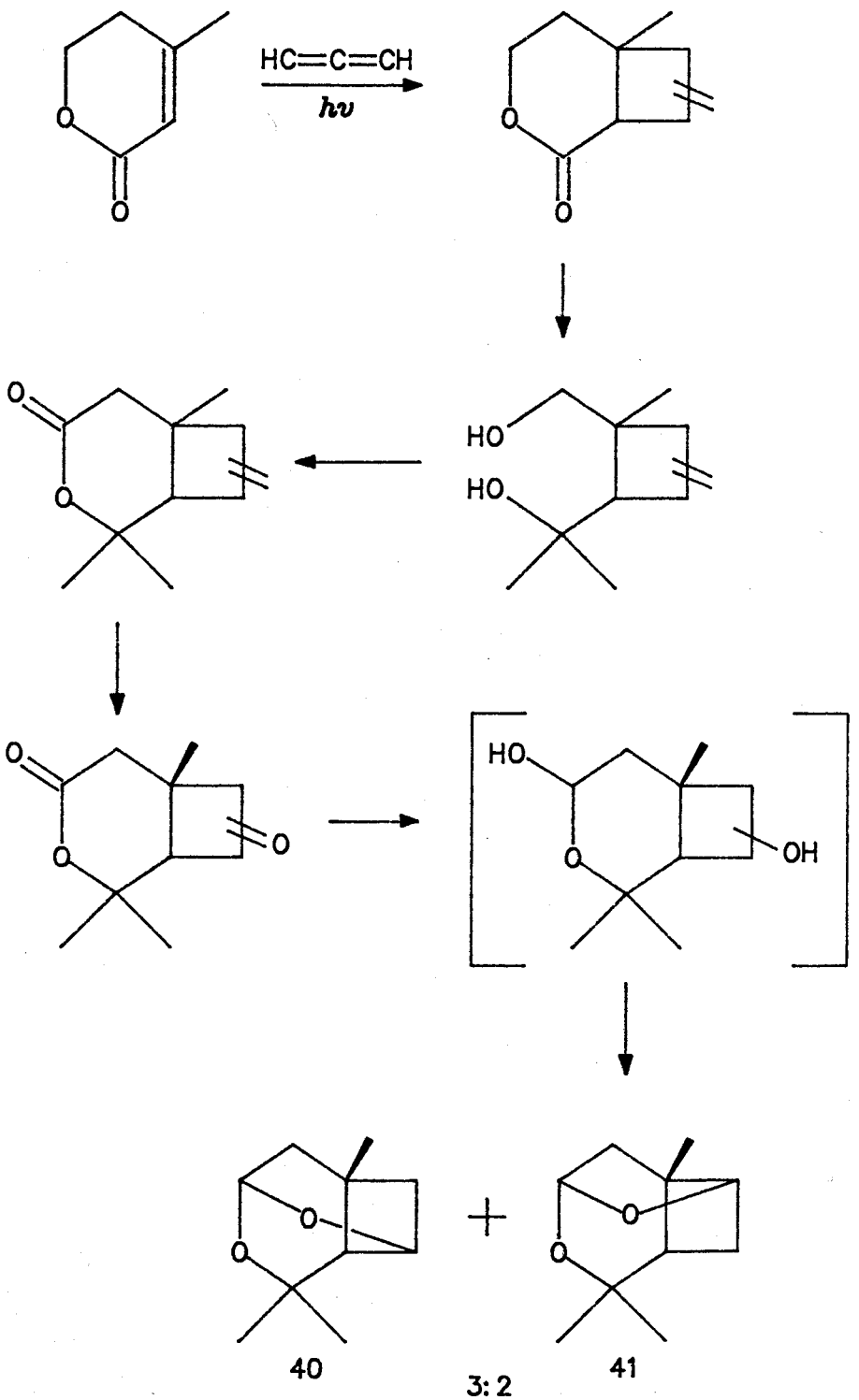


Scheme 38
reference 88



rac. 40

Scheme 39
reference 89



Scheme 40
reference 90

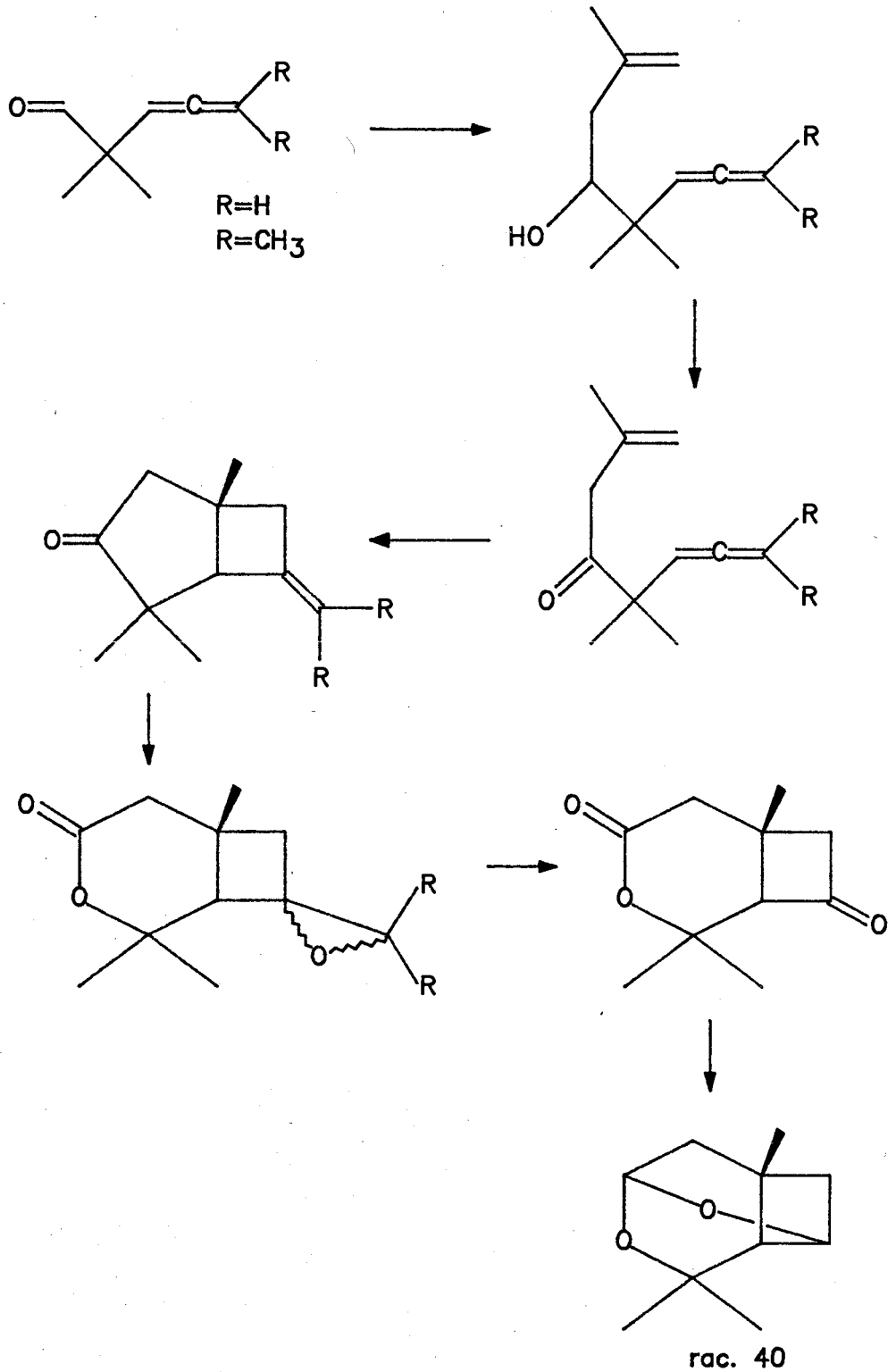


TABLE 3

Summary of Racemic Lineatin Syntheses

Scheme	No. of Steps	Overall Yield	Ref.
34	7	<1%	83
35	9	2%	84
36	9	3%	85
38	9	9%	87
39	5	11%	88
40	6	23-27%	89
43	5	10-12%	Exp.

Results and Discussion

Our recent efforts have been directed at development of a relatively simple synthetic scheme for the production of multi-gram amounts of the pheromone without the co-production of isolineatin (3,3,7-trimethyl-2,9-dioxatricyclo[4.2.1.$0^{4,7}$]-nonane, **41**) which has been a co-product in several previous syntheses (Schemes 34,39). Disconnection of the intramolecular ketal (Scheme 41) makes it apparent that a selective synthesis of **40** would require a protocol for the production of a functional-ized cyclobutane precursor with the correct regiochemistry (**42** rather than **43**).

One approach would be to utilize the well known regioselect-ivity of dichloroketene cycloadditions with unsymmetric tri-substituted alkenes.[91] Initially, this approach was frustrated by the extreme reluctance of dichloroketene to participate in [2+2] cycloaddition reactions with the required alkene substrates. Less than 5% yield of the desired cycloadduct **45** could be isolated from the reaction of **44** with dichloroketene[92] (Scheme 41). Compound **44** was eventually abandoned as a precursor to lineatin in part due to the extreme acid sensitivity of cyclo-adduct **45**.

Recent reports[92,93] emphasize that the reaction of dichloroketene with allyl ethers and allyl sulfides typically results in rearrangement rather than [2+2] cycloaddition (Scheme 42). The proposed mechanism[92] for the formation of the rearrangement product (**47**) was a [3,3]-sigmatropic rearrangement

of the initially formed dipolar intermediate **46**. In this study, dichloroketene was generated by the zinc dehalogenation of trichloroacetyl chloride with concomitant production of $ZnCl_2$. Nucleophilic attack at the carbonyl of dichloroketene leading to intermediate **46** could be facilitated by complexation of $ZnCl_2$ at the carbonyl oxygen.

Since it seemed that the most direct route to lineatin utilizing dichloroketene would involve a [2+2] cycloaddition reaction with an appropriately substituted allyl ether (e.g., **48**), ways to circumvent the rearrangement reaction were considered. Krepski and Hassner[94] have reported that the use of phosphorus oxychloride as a sequestering agent for $ZnCl_2$ gives increased yields of [2+2] cycloadduct in the reaction of dichloroketene with hindered olefins. Application of this method to the cyclic allylic ether **48** gave, in addition to unreacted starting material, two products separable by chromatography on silica gel. The desired cycloadduct **49** was obtained in only 7% isolated yield while the eight-membered ring compound **50** was the major product (26%) of the reaction. None of the expected [3,3]-sigmatropic product **51** could be isolated from the reaction mixture (Scheme 42).

Substitution of 1,2-dimethoxyethane for phosphorus oxychloride efficiently suppressed the formation of **50** and a 50 to 60% yield of **49** could be realized. Optimum conditions appeared to be 4 to 6 equivalents of 1,2-dimethoxyethane for each equivalent of trichloroacetyl chloride with the reaction carried out in refluxing ether for extended periods of time (4-5 days).

Although simple distillation of **49** resulted in only 85-90% purity by GC, this material proved suitable for use in the subsequent steps to form lineatin (Scheme 43).

Dechlorination of **49** (58%) was effected by treatment with Zn in methanol saturated with ammonium chloride.[95] Oxidation of cyclobutanone-ether **52** with catalytic amounts of RuO_4[96] in a two-phase (CCl_4/H_2O) system containing $NaIO_4$ as the co-oxidant resulted in formation of crystalline cyclobutanone-lactone **53** (61%) which could be recrystallized to a state of high purity. Use of NaOCl (commercial bleach) as a co-oxidant[97] for RuO_4 resulted in only Baeyer-Villiger type products (*i.e.*, **54**, **55**) from either cyclobutanone **52** or dichlorocyclobutanone **49**. Finally, reduction of **53** with diisobutylaluminum hydride (DIBAL) in hexane/ether[93,88,89], followed by acidic processing, yielded lineatin. The overall yield of lineatin from **48** was 10-12%.

With the successful completion of the lineatin synthesis, the question of the general utility of the modified procedure for dichloroketene generation arose. A limited set of acyclic allyl ethers and allyl sulfides was then subjected to dichloroketene cycloaddition using dimethoxyethane as a co-solvent. Several of these compounds had been previously shown to yield predominantly, if not entirely, Claisen-type rearrangement products when dichoroketene was generated using the standard trichloroacetyl cloride/zinc method.

The results of this study are presented in Table 4. In every case, the major product was the dichlorocyclobutanone, and in most instances none of the Claisen rearrangement product could

be isolated. Yields of the [2+2] cycloadduct were, for the most part, in the range of 65-85% although certain of the products were unstable and tended to decompose during distillation or chromatography. Dechlorination with zinc proceeded smoothly to yield the corresponding cyclobutanone derivatives.

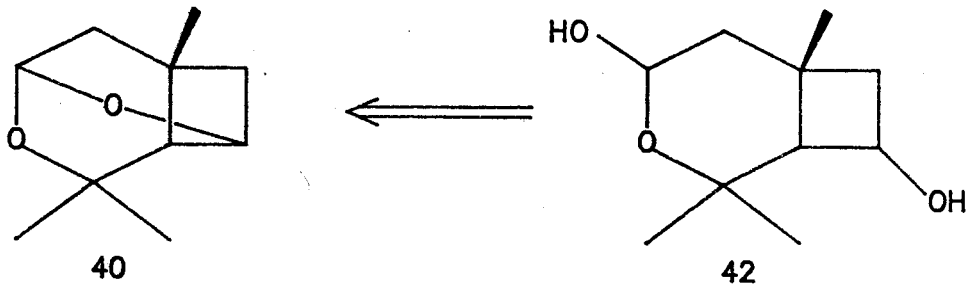
This modified procedure for dichloroketene generation, therefore, appears to have some general utility for the synthesis of cyclobutanone derivatives of allyl ethers or allyl sulfides. The method efficiently supresses the previously reported rearrangement reaction which occurs in the absence of dimethoxyethane.

It would also be of interest to study the effect of the addition of dimethoxyethane on the reaction of dichloroketene with the dithiolane derivative of an α,ß-unsaturated ketone. These substrates are known to undergo ring-expansion of the dithiolane moiety when treated with dichloroketene[93]. Addition of dimethoxyethane to this type of reaction may suppress this rearrangement in favour of [2+2] cycloaddition. An intensive investigation of this reaction is warranted since successful [2+2] cycloaddition would result in a formal, non-photochemical method for the cycloaddition of a ketene to an α,ß-unsaturated ketone. This type of ketene cycloaddition has not been achieved by thermal methods. Efforts by our group directed towards this end are in progress.

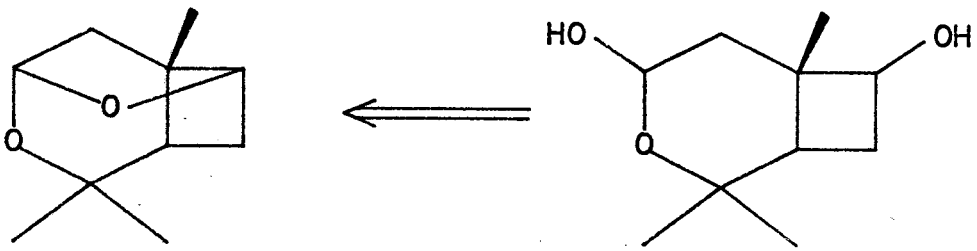
In summary, lineatin (**40**) has been prepared using a short synthetic sequence which is suitable for multigram quantities. The synthesis involves a modified procedure for dichloroketene

cycloadditions with allyl ethers to produce moderate yields of cyclobutanones which should be of value in the synthesis of similar four-membered ring systems.

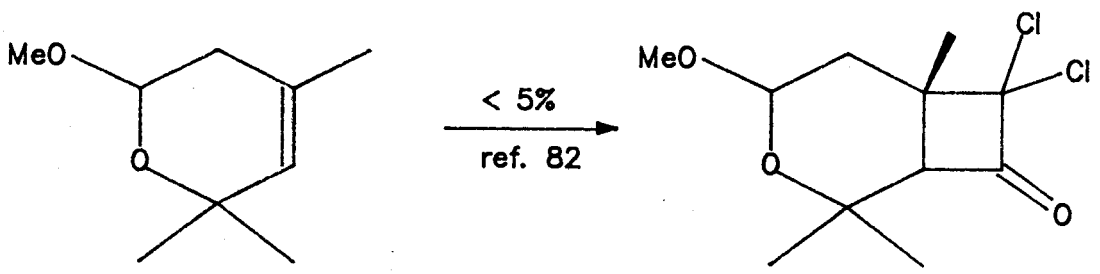
Scheme 41



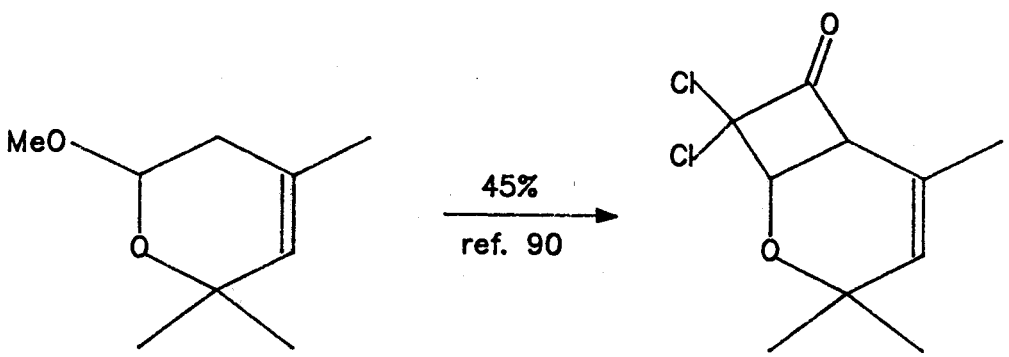
40 42



41 43

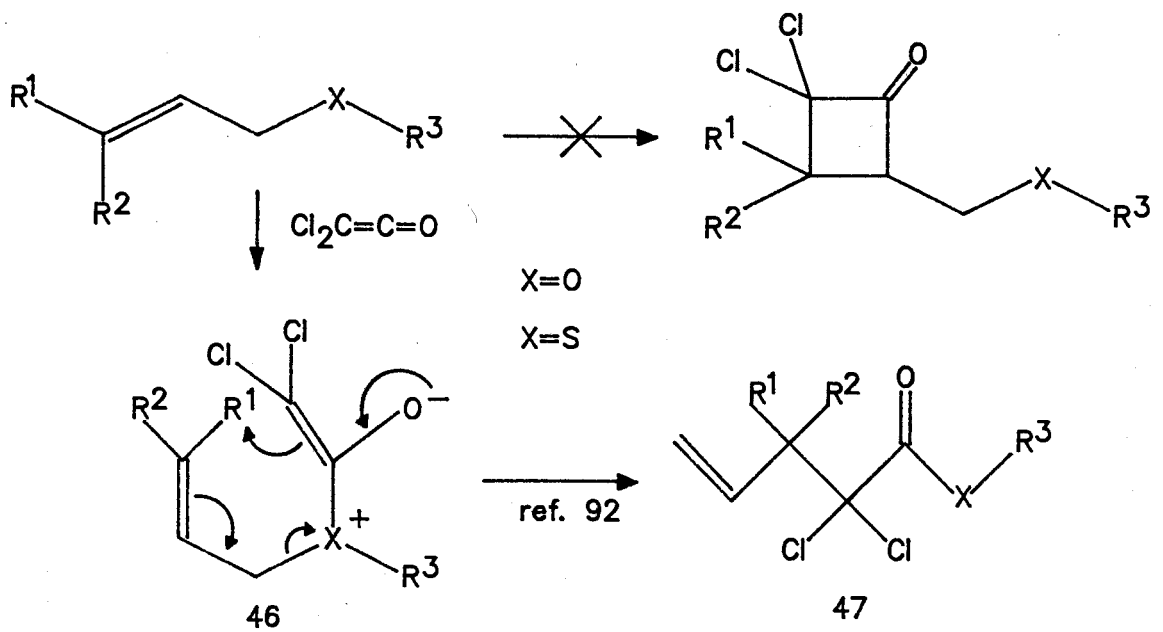


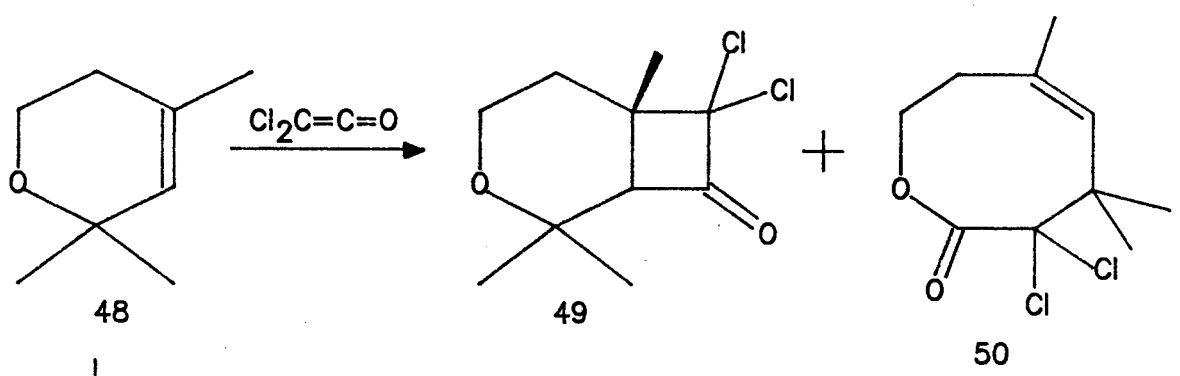
44 45

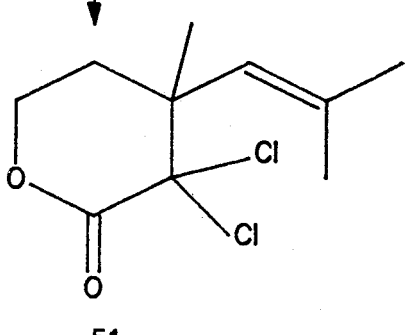


44

Scheme 42







SOLVENT	RATIO (49:50)
$Et_2O/POCl_3$	1:3.7
Et_2O/DME	>20:1

Scheme 43

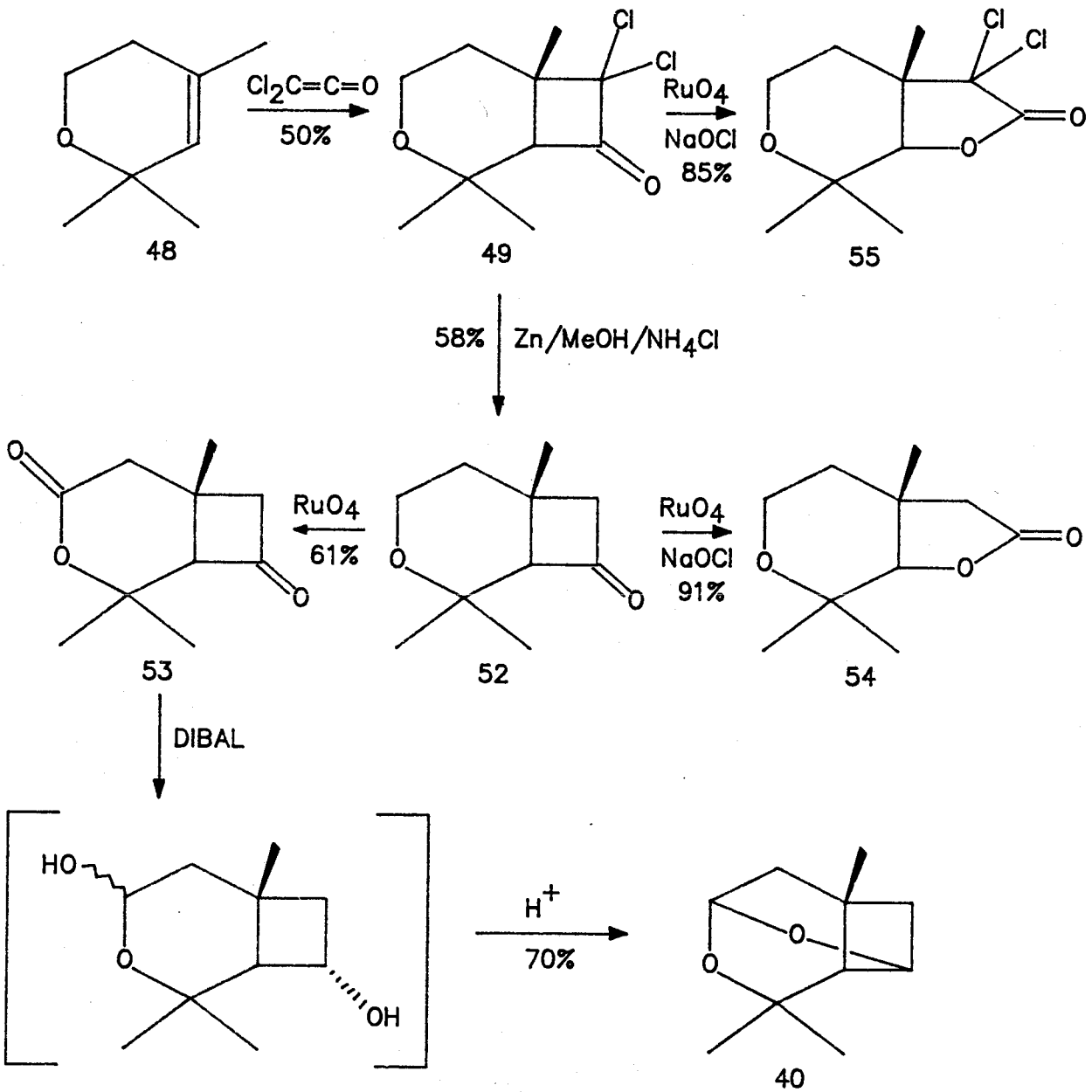
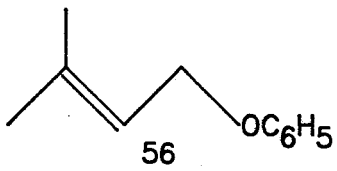
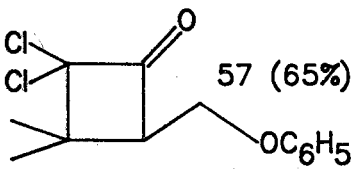
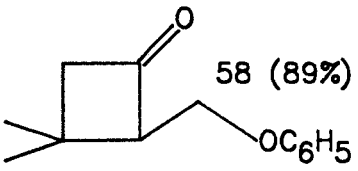
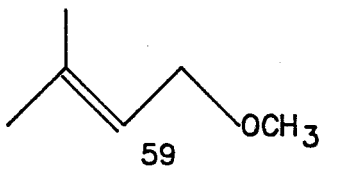
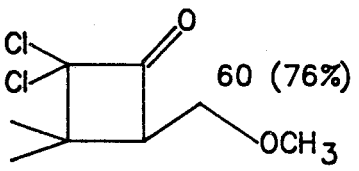
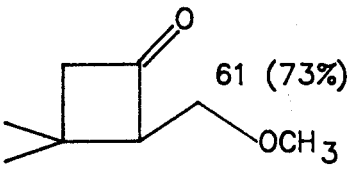
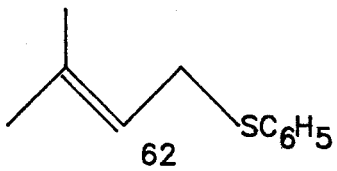
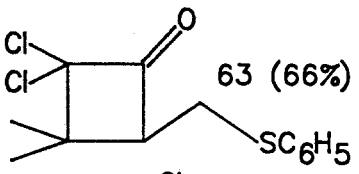
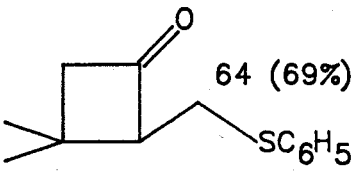
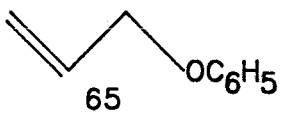
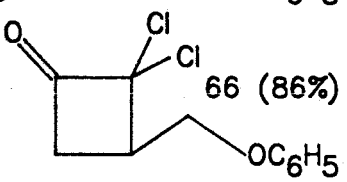
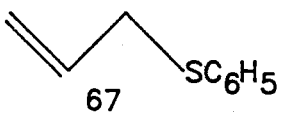
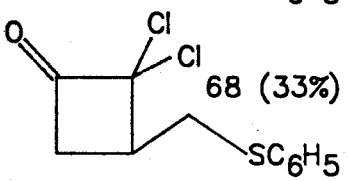
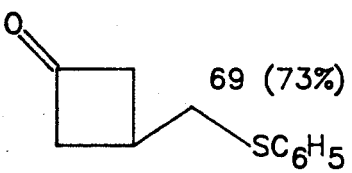
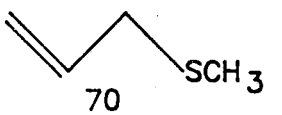
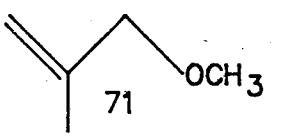
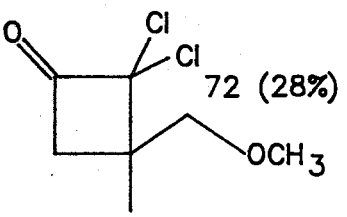
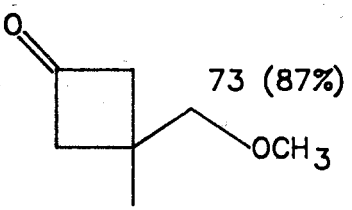
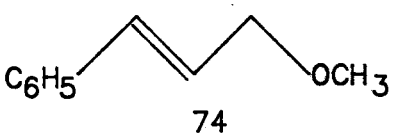

Cl2C=C=O
50%
RuO4
NaOCl
85%
58%
Zn/MeOH/NH4Cl
RuO4
61%
RuO4
NaOCl
91%
DIBAL
H+
70%
HO
OH
48
49
55
53
52
54
40

Table 4

REACTION OF DICHLOROKETENE WITH ALLYL ETHERS AND SULFIDES

Allyl Derivative	Dichlorocylobutanone (% yield)	Cyclobutanone (% yield)
 56	 57 (65%)	 58 (89%)
 59	 60 (76%)	 61 (73%)
 62	 63 (66%)	 64 (69%)
 65	 66 (86%) *	—
 67	 68 (33%) *	 69 (73%)
 70	complex mixture	—
 71	 72 (28%) *	 73 (87%)
 74	slow reaction	—

* unstable product

CHAPTER 4

SYNTHESIS OF THE AGGREGATION PHEROMONE OF THE SQUARE-NECKED GRAIN BEETLE, *CATHARTUS QUADRICOLLIS*

Introduction

The square-necked grain beetle [*Cathartus quadricollis*) (Guer.)] is one of the most common beetles found in stored corn in the southern United States.[101] In cornfields, it is almost always found on damaged or exposed ears. This beetle resembles, in morphology and habit, other grain-infesting beetles in the genera *Cryptolestes*[102-105] and *Oryzaephilus*[106,107] whose chemical communication systems have been under investigation in our laboratory. Extension of the techniques of pheromone detection and isolation utilized previously[103,108] to the square-necked beetle confirmed the presence of a pheromone.[109] Trapping of male or mixed sex volatiles and the bioassay of fractionated components led to the isolation of microgram amounts of a male-produced pheromone attractive to both sexes (aggregation pheromone).

Analysis by high field ^{1}H NMR spectroscopy and GC/MS indicated the structure to be either 4-methyl-7-acetoxy-3-nonene, **75**, or 3-methyl-7-acetoxy-3-nonene, **76**. Since the amount of isolated material was insufficient for definite structural assignment, syntheses of **75** and **76** were undertaken. Because both **75** and **76** can exist as geometric isomers, initial synthetic approaches were designed to produce mixtures of geometric isomers in order to facilitate comparison with the natural material.

Results and Discussion

The synthesis of an (*E,Z*) mixture of **75** was accomplished by the route outlined in Scheme 44. Thus, ethyl acetoacetate was converted by sequential protection of the ketone,[110] reduction of the ethyl ester[111] and bromide substitution to give 4-bromo-2-butanone ethylene ketal (**80**). The corresponding Grignard reagent reacted with propionaldehyde to produce alcohol **81**. Acetylation and removal of the protecting group gave keto-acetate **83**. Wittig reaction with the ylide derived from propyl triphenylphosphonium bromide completed the synthesis of (*E,Z*)-**75** (5:4). ^{1}H NMR spectroscopic and capillary gas chromatographic comparison of the synthetic material with the natural pheromone proved that neither geometric isomer of **75** was the natural product.

The synthesis of (*E,Z*)-**76** was performed using the procedure outlined in Scheme 45. Methyl cyclopropyl ketone (**84**) was converted via the tertiary alcohol **85** and Julia fragmentation[112] to (*E:Z*)-**86** (3:1). Grignard reaction with propionaldehyde and acetylation yielded (*E:Z*)-**76** (3:1). Comparison with the natural material by capillary GC, ^{1}H NMR spectroscopy and mass spectrometry confirmed the structure of the pheromone to be (*E*)-**76**.

A stereoselective synthesis of (*E*)-**76** outlined in Scheme 46 produced (*E*)-**76** of >97% geometric purity. The key reaction in this sequence was the coupling of allylic acetate **94** with lithium dimethyl cuprate to yield trisubstituted alkene **95**. The *E* stereoselectivity of this type of reaction has been previously demonstrated to be >95% in studies directed toward juvenile

hormone synthesis.[113] The necessary allylic alcohol precursor **93** was assembled in a series of standard synthetic procedures. Thus, alcohol **90**, the lower homolog of alcohol **87**, was synthesized by an analogous procedure from **84**. Protection of the alcohol as the silyl ether[114] and peracid epoxidation yielded epoxide **92**. Base isomerization[115] of this epoxide was selective for the formation of secondary allylic alcohol **93**. Lithium dimethyl cuprate S_N2' displacement of the acetate **94** proceeded as expected[113] to yield **95** with an (E:Z) ratio of 40:1. Removal of the protecting group and acetylation gave (E)-**76** in 50% overall yield from **90**.

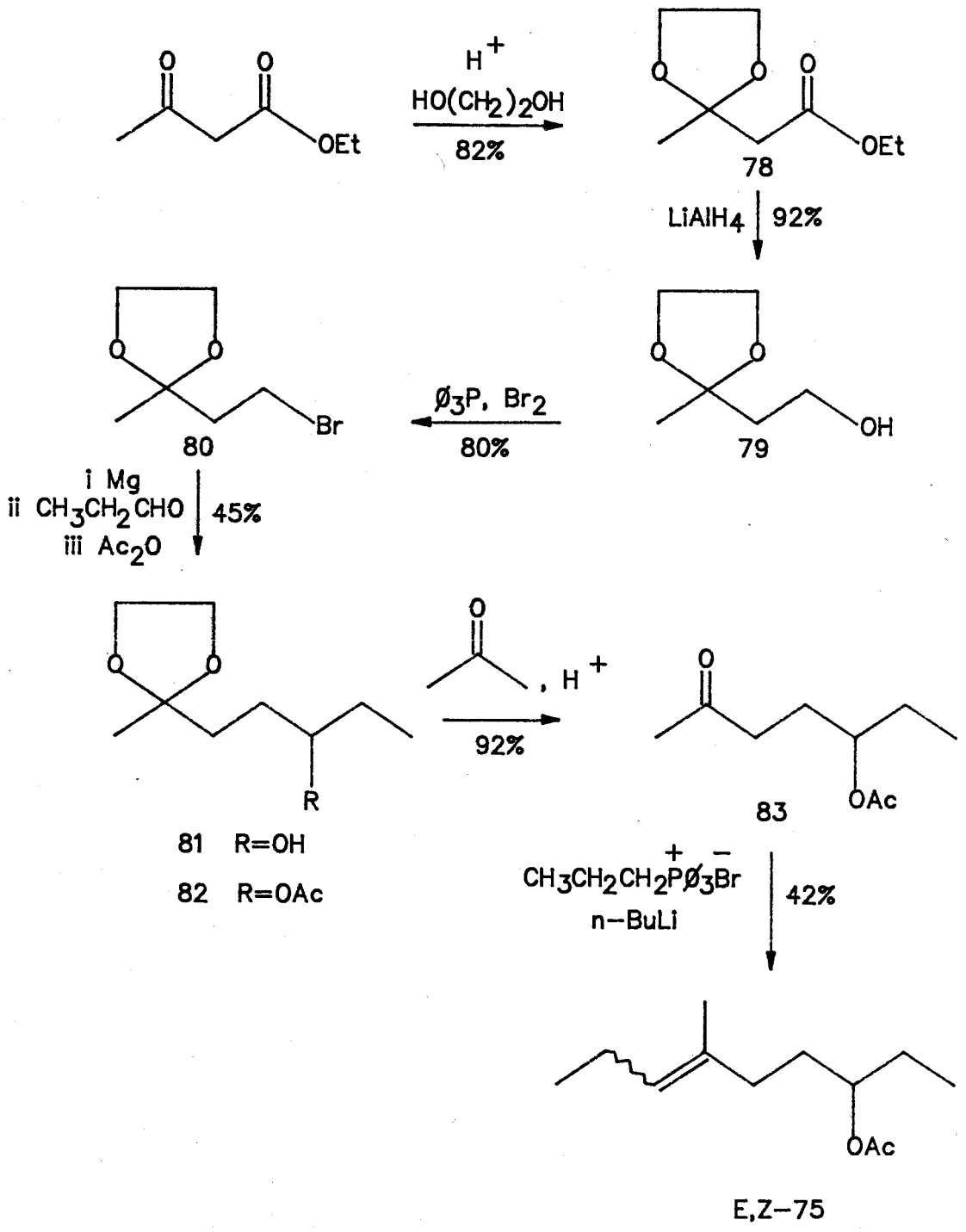
Finally, a chiral synthesis of *S*-**76** was performed as outlined in Scheme 47. (*S*)-ethyloxirane (**96**)[116] provided the chiral template. Cuprous iodide-catalyzed opening[117] of this epoxide by dimethylallyl magnesium chloride produced (*S*)-**90**. We have previously applied this reaction with (*R*)- or (*S*)-propylene oxide in the chiral synthesis of the bark beetle pheromone 6-methyl-5-hepten-2-ol (sulcatol), a lower homolog of **90**.[118] The remainder of the synthesis proceeded by the same reactions used for the racemic sequence outlined in Scheme 46. Analysis, by ^{1}H NMR spectroscopy, of the distereomeric esters of (*S*)-**90** and (*S*)-**87**, derived from reaction of the alcohols with (+)-α-methoxy-trifluoromethylphenylacetyl chloride [(+)-MTPA-Cl],[80] allowed an estimate of the chiral purity at >98% ee.

The *R* enantiomer of **76** [(*R*)-**76**] is conceptually available from the same series of reactions, beginning with (*R*)-ethyloxirane[119]. The length of the synthetic sequence was such

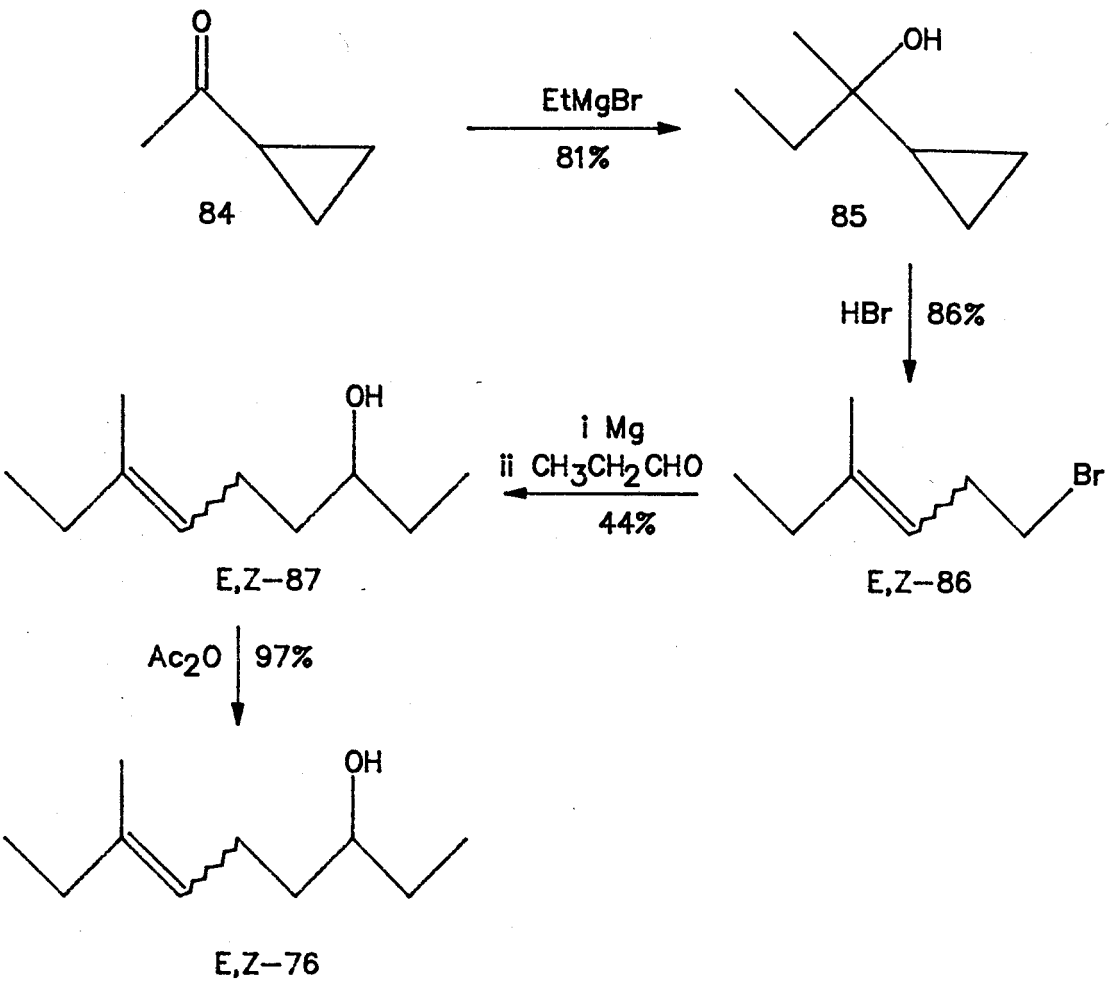
that a more attractive option appeared to be the production of the enantiomer by inversion of alcohol (*S*)-**87**. Of the several general methods for chiral secondary alcohol inversion,[120] we chose S_N2 displacement of the mesylate derivative with acetate anion. Although cesium carboxylates have been advocated as being superior to their sodium or potassium counterparts in this reaction,[120d] we found that, at least for this case, potassium acetate served the purpose satisfactorily. Thus, (*S*)-**87** was treated with methanesulphonyl chloride and triethylamine to produce the mesylate. The mesyloxy group was then displaced by reaction with excess potassium acetate in dimethylformamide at 100°C (Scheme 47). NMR and GC/MS analysis of the crude reaction mixture indicated a mixture of acetate (*R*)-**76** with the corresponding formate ester (~10:1 ratio). Purification by silica gel chromatography yielded pure (*R*)-**76** in 44% overall yield from (*S*)-**87**. The enantiomeric excess was estimated at >97% by ^{1}H NMR analysis of the (+)-MTPA ester of (*R*)-**87** (obtained by hydride reaction of (*R*)-**76**).

In summary, the structure of the beetle-produced aggregation pheromone of *Cathartus quadricollis* has been demonstrated to be (*E*)-3-methyl-7-acetoxy-3-nonene [(*E*)-**76**)] by synthesis and comparison to the natural material. Additionally, a chiral synthesis of either the *S* or the *R* enantiomer of (*E*)-**76** from readily available (*S*)-ethyloxirane in good overall yield has been developed. Details of the response of insects to the synthetic compounds are under investigation.

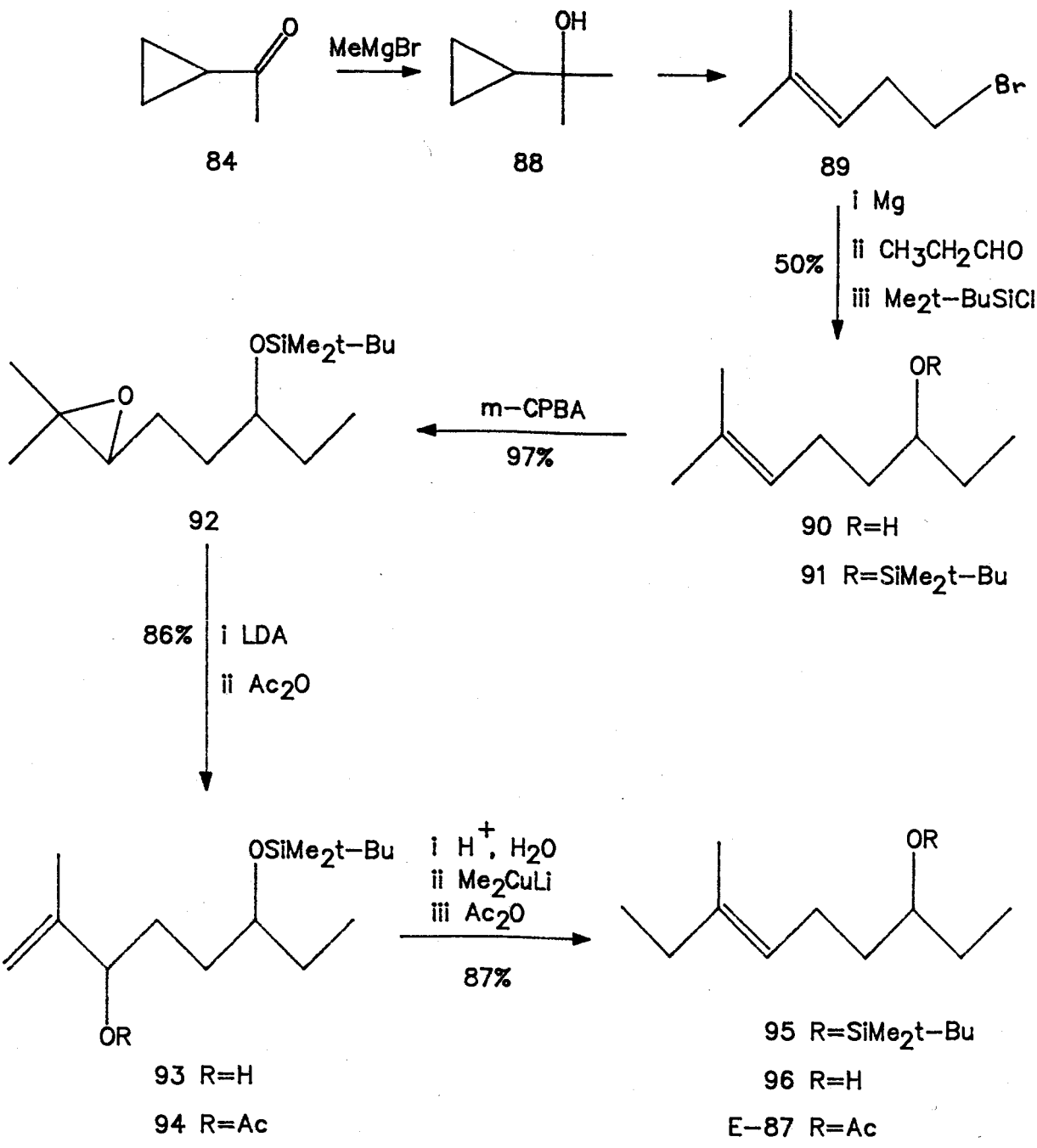
Scheme 44


H+
HO(CH2)2OH
82%
OEt
78
LiAlH4
92%
79
OH
Ø3P, Br2
80%
80
Br
i Mg
ii CH3CH2CHO
iii Ac2O
45%
R
81 R=OH
82 R=OAc
, H+
92%
83
OAc
+ −
CH3CH2CH2PØ3Br
n-BuLi
42%
OAc
E,Z-75

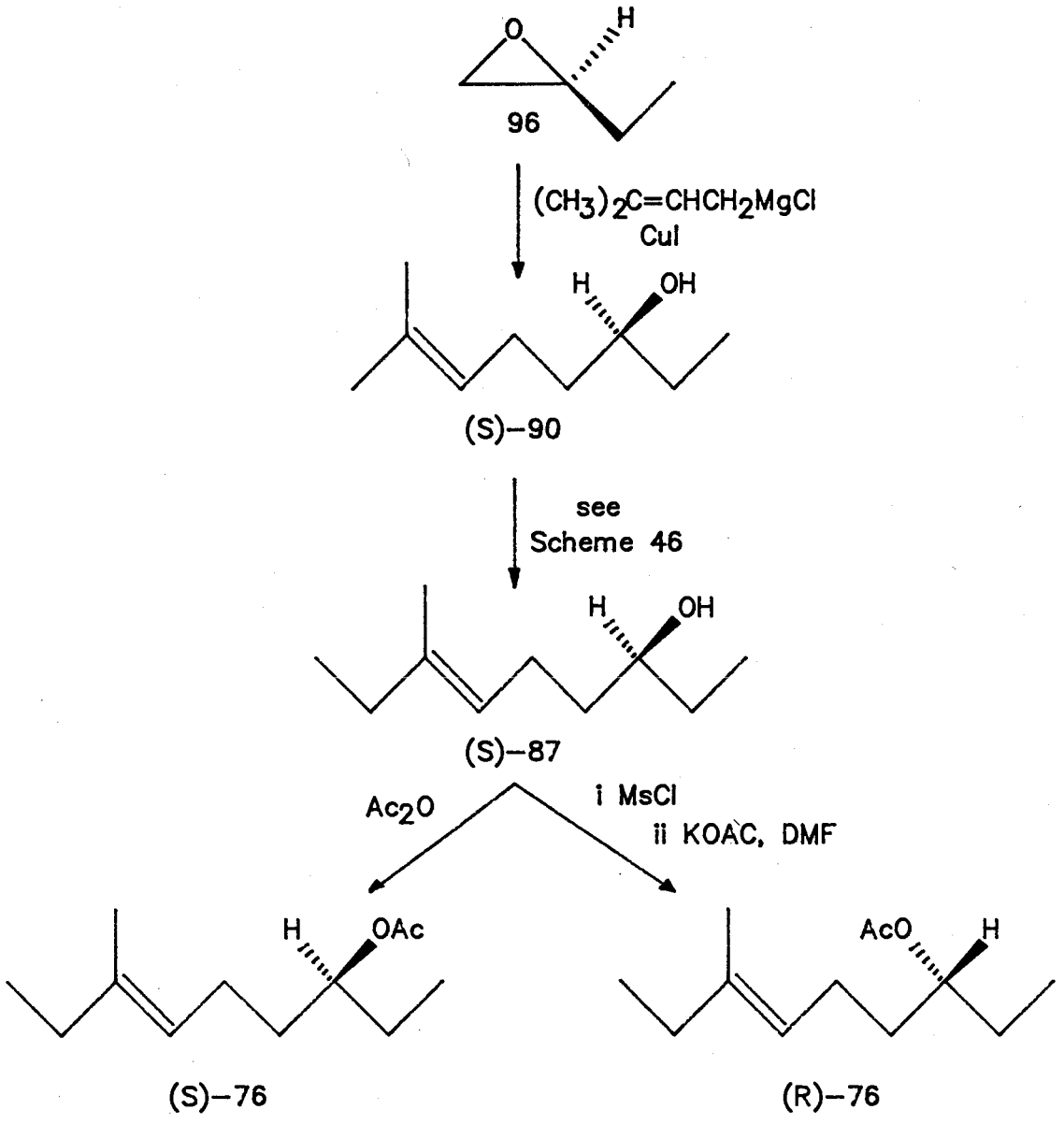
Scheme 45


O
84
EtMgBr
81%
OH
85
HBr
86%
Br
E,Z–86
i Mg
ii CH3CH2CHO
44%
OH
E,Z–87
Ac2O
97%
OH
E,Z–76

Scheme 46


O
MeMgBr
OH
Br
84
88
89
i Mg
ii CH_3CH_2CHO
iii Me_2t-BuSiCl
50%
OSiMe$_2$t-Bu
O
m-CPBA
97%
OR
92
90 R=H
91 R=SiMe$_2$t-Bu
86%
i LDA
ii Ac_2O
OSiMe$_2$t-Bu
i H^+, H_2O
ii Me_2CuLi
iii Ac_2O
87%
OR
OR
93 R=H
94 R=Ac
95 R=SiMe$_2$t-Bu
96 R=H
E-87 R=Ac

Scheme 47


O
H
96
(CH3)2C=CHCH2MgCl
CuI
H
OH
(S)–90
see
Scheme 46
H
OH
(S)–87
Ac2O
i MsCl
ii KOAC, DMF
H
OAc
AcO
H
(S)–76
(R)–76

Experimental

NMR spectra were recorded for $CDCl_3$ solutions using a Bruker WM400 spectrometer unless otherwise stated. 60 MHz ^1H NMR and 100MHz ^1H NMR spectra were recorded with Varian EM-360 and Bruker SY100 instruments. Infrared spectra were recorded using neat films between NaCl plates on a Perkin Elmer 599B spectrophotometer unless otherwise noted. Mass spectra were obtained using a Hewlett-Packard 5985B GC/MS/DS system operating at 70 eV. Gas chromatographic analysis utilized a Hewlett-Packard 5880A operated with a J+W fused silica DB-1 capillary column (15 m X 0.25 mm), a flame ionization detector and a suitable linear oven temperature program. Optical rotations were determined with a Perkin-Elmer P-22 spectropolarimeter (5 cm cell) or a Rudolph Polarimeter Model 70 (10 cm cell). Concentrations are reported in g/100 mL of solvent. Elemental analyses were performed by Mr. M. Yang of the Department of Biological Sciences, Simon Fraser University using a Perkin Elmer Model 240 elemental analyzer.

Solvents and reagents were used as supplied from commercial sources with the following exceptions. Anhydrous CH_2Cl_2 was obtained by distillation from P_2O_5. Anhydrous solutions of *tert*-butylhydroperoxide in CH_2Cl_2 were prepared from 90% *t*-BuOOH (Aldrich) using the azeotropic distillation method described by Sharpless.[69] Chromatography solvents were distilled before use. Anhydrous ether was obtained from freshly opened cans (Fisher Scientific) or by distillation from lithium aluminum hydride.

Tetrahydrofuran (THF) was distilled from sodium or potassium benzophenone ketyl immediately prior to use. Hexamethylphosphoric triamide (HMPA) was distilled from calcium hydride and stored under argon over activated 3 angstrom molecular sieves. Acetylene was dried by passage through a trap (cooled to -78°C) and a calcium chloride drying tube. Dimethoxyethane was distilled from lithium aluminum hydride immediately prior to use. Zinc was activated by the method of Krepski and Hassner.[94] All reactions involving air or moisture sensitive reagents were performed under an argon atmosphere.

2-Methyl-2(4-pentynyl)-1,3-dioxolane (9)

A stream of dry acetylene was used to saturate 150 mL of dry THF at ice bath temperature. A 1.6 M hexane solution of *n*-BuLi (80 mL, 128 mmol) was added dropwise over 20 min while maintaining the temperature at 5-10°C. After stirring a further 0.5 h at 10°C, 16.4 g (100 mmol) of **8** and 50 mL of dry HMPA were added. The reaction was warmed to rt and stirred under an acetylene atmosphere for 24 h. The reaction was quenched by pouring it into ice water (500 mL) and extracting with ether (3 X 150 mL). The combined ether extracts were washed with water (2 X 100 mL) and brine (100 mL). The extract was dried over anhyd. $MgSO_4$, concentrated *in vacuo* and distilled (bp 86-87°C/15 mm Hg) to yield 14.5 g (94%) of **9**. Analysis by GC revealed **9** was 98% pure: mass spectrum, m/e (relative intensity) 139 (40), 99 (18), 87 (100), 43 (15). Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.43; H 9.37.

2-Methyl-2-(6-hydroxy-4-hexynyl)-1,3-dioxolane (10)

A 1.6 M hexane solution of *n*-BuLi (23 mL, 37 mmol) was added dropwise over 15 min to 5.1 g (33 mmol) of **9** in 50 mL of dry THF with ice-bath cooling. After a further 10 min, anhyd. paraformaldehyde (1.3 g, 43 mmol) was added in one portion. The cooling bath was removed and the reaction mixture was stirred under argon at 23°C for 3 h. The reaction was poured into ice-water (150 mL) and extracted with ether (3 X 75 mL). The combined ether extracts were washed with brine (100 mL), dried over anhyd. $MgSO_4$, filtered and concentrated *in vacuo* to yield after distillation 5.0 g (82%) of **10** (bp 115-117°C/0.2 mm Hg, lit.[46] bp 99-107°C/0.1 mm Hg); 97% pure by GC. ^1H NMR (60 MHz, $CDCl_3$) δ 4.1-4.3 (2H, OCH_2, m), 3.9 (4H, $O(CH_2)_2O$, s), 2.5 (1H, OH, s), 2.4-2.1 (2H, $CH_2C{\equiv}C$, m), 1.8-1.5 (4H, $2CH_2$, m), 1.35 (3H, CH_3, s). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.54; H, 8.98.

2-Methyl-2-((Z)-6-hydroxy-4-hexenyl)-1,3-dioxolane (11)

Hydrogen was bubbled through a solution of $Ni(OAc)_2{:}4H_2O$ (1.25 g, 5.0 mmol) in 50 mL of 95% ethanol while 5 mL of a solution prepared by dissolving 0.5 g $NaBH_4$ in 12 mL methanol containing 0.65 mL 2N NaOH was added. After 5 min ethylenediamine (0.8 mL) was added followed by **10** (5.6 g, 30 mmol). The reaction mixture was stirred under a H_2 atmosphere for 2 h then diluted with ether (450 mL) and filtered through Celite. The filtrate was washed with brine (100 mL), dried over anhyd. $MgSO_4$ and

concentrated *in vacuo*. Vacuum distillation yielded **11** (5.2 g, 92%). Bp 88-95°C /0.1 mm Hg; 93% pure by GC (~5% of the saturated alcohol). ^{1}H NMR (60 MHz, $CDCl_3$) δ 5.8-5.3 (2H, vinyl, m), 4.2 (2H, OCH_2, d, J=5 Hz), 3.9 (4H, $O(CH_2)_2O$, s), 2.4-2.1 (3H, $CH_2C{=}C$, OH, m), 1.8-1.6 (4H, $2CH_2$, m), 1.3 (3H, CH_3, s). Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.75. Found: C, 64.77; H, 10.13.

(*E*)-2-Octen-7-one-1-ol (13)

Three drops of conc. H_2SO_4 were added to an acetone solution (350 mL) of **11** (15.0 g, 81 mmol). After stirring for 2 h at 23°C anhyd. K_2CO_3 (~2 g) was added and the stirring continued for a further 0.5 h. The reaction was filtered and concentrated *in vacuo*. Vacuum distillation yielded **13** (10.1 g, 88%). Bp 100-102°C/0.2 mm Hg, lit.[39] bp 120-125°C/0.5 mm Hg; 98% pure by GC.

(1R,7R)-7-Hydroxymethyl-5-methyl-6,8-dioxabicyclo-[3.2.1.]octane [(+)-14]

A 0.1 M solution of titanium tetraisopropoxide (510 mL, 51 mmol) in CH_2Cl_2 at -30°C (dry ice/CCl_4 bath) was treated with 11.3 g (55 mmol) of (-)-diethyl tartrate (Aldrich). After 10 min, alkene **13** (7.1 g, 50 mmol) was added followed by 27 mL (111 mmol) of a 4.1 M anhydrous solution of tert-butylhydroperoxide in CH_2Cl_2. The reaction was kept at -25°C for 4 days under argon. An aqueous tartaric acid solution (10%, 150 mL) was added and the reaction allowed to warm slowly to 0°C. After 3 h at 0°C and 1 h at 23°C the CH_2Cl_2 phase was separated from the clear aqueous

phase that was further extracted with CH_2Cl_2 (3 X 75 mL). The combined CH_2Cl_2 extracts were dried over anhyd. K_2CO_3, filtered, and concentrated *in vacuo*, to yield a mixture of (+)-**14** and diethyl tartrate. This mixture was dissolved in ether (300 mL) and shaken for 5 min with a 1N NaOH solution (150 mL) in order to remove the diethyl tartrate by hydrolysis. The aqueous layer was extracted with ether (2 X 100 mL) and the combined ether extracts dried over anhyd. $MgSO_4$. Removal of the solvent *in vacuo* and vacuum distillation yielded (+)-**14** (6.5 g ,82%), bp 65-72°C/0.1 mm Hg. GC analysis revealed (+)-**14** was 90% pure and contaminated with <5% unreacted **13**. A sample for analysis, purified by column chromatography, (silica gel, hexane:ethylacetate, 5:1) was 95% pure by GC; $[\alpha]^{27}_D$ = + 53.7 ± 2.0° (*c*, 0.94, $CHCl_3$); ^1H NMR δ 4.26 (1H, C_1, broad s), 4.12 (1H, C_7, t J=7Hz), 3.55 (2H, CH_2O, overlapping dd, J=7 Hz), 2.12 (1H, OH, s), 2.00-1.45 (6H, $3CH_2$, m), 1.43 (3H, CH_3, s); mass spectrum m/e (relative intensity) 125 (25), 112 (20), 98 (15), 83 (22), 69 (31), 67 (39), 59 (92), 54 (100), 43 (57). Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.60; H, 8.99.

Preparation of (-)-14

Chiral isomer (-)-**14** was prepared in 73% yield using the same procedure for epoxidation of **13** with the exception that (+)-diethyl tartrate was employed: $[\alpha]^{27}_D$ = -58.0 ± 2.0° (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.71; H, 8.81.

(1*R*,7*S*)-7-Bromomethyl-5-methyl-6,8-dioxabicyclo[3.2.1.]octane [(+)-15]

To a solution of (+)-**14** (6.5 g, 41 mmol) in 30 mL of dry HMPA was added 11.0 g (42 mmol) of triphenylphosphine followed by 14.0 g (42 mmol) of carbon tetrabromide. An immediate exothermic reaction occurred that temporarily produced a homogeneous solution. The reaction cooled to rt over 0.5 h and solidified. The reaction was then reheated to 100°C for 0.5 h and after cooling, was triturated with pentane (5 X 100 mL). The combined pentane extracts were filtered, washed with water (100 mL) and brine (100 mL), then dried over anhyd. $MgSO_4$, filtered, and concentrated *in vacuo*. Vacuum distillation yielded (+)-**14** (8.0 g, 88%). Bp 82-85°C/0.1 mm Hg; $[\alpha]^{27}_D$ = + 0.9 ± 0.5 (*c*, 1.3, $CHCl_3$); 99% pure by GC; ^{1}H NMR δ 4.44 (1H, C_1, broad), 4.23 (1H, C_7, dd J=10, 5 Hz), 3.32 (1H, CHBr, dd J=10, 5 Hz), 3.22 (1H, CHBr, J=10 Hz), 1.40-2.00 (6H, $3CH_2$, m), 1.42 (3H, CH_3, s); mass spectrum, m/e (relative intensity) 180/178 (7), 141 (95), 127 (21), 113 (17), 99 (73), 81 (48), 71 (10), 43 (100). Anal. Calcd for $C_8H_{13}O_2Br$: C, 43.46; H, 5.93. Found: C, 43.70; H, 6.08.

Preparation of (-)-15

The same bromination procedure applied to (-)-**14** yielded (-)-**15** in 85% yield, 95% pure by GC, $[\alpha]^{27}_D$ = -0.6 ± 0.5° (*c*, 1.4, $CHCl_3$). Anal. Calcd for $C_8H_{13}O_2Br$: C, 43.46; H, 5.93. Found: C, 43.65; H, 5.98.

(1*R*,7*R*)-7-Ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane (1*R*,7*R*)-*exo*-Brevicomin] [(+)-1]

An ether solution of MeLi (1.6 M, 65 mL, 104 mmol) was added dropwise to a slurry of CuI (9.5 g, 50 mmol) in 200 mL dry ether under argon at 10°C. The reaction mixture was stirred for 10 min, then a solution of (+)-**15** (8.0 g, 36 mmol) in 50 mL HMPA was added. The reaction mixture was allowed to warm to room temperature, stirred for 24 h, and poured into cold saturated NH_4Cl solution (350 mL). The ether layer was separated and the aqueous phase extracted with ether (2 X 150 mL). The combined ether extracts were washed with water (100 mL) and brine (100 mL) and dried over anhyd. $MgSO_4$. Filtration and removal of the solvent by distillation at atmospheric pressure yielded crude (+)-brevicomin that was purified by distillation to yield 3.5 g (62%) of (+)-**1**, (bp 60-62°C/15 mm Hg, lit.[7] bp 72-73°C/21 mm Hg), $[\alpha]^{27}_D$ = + 59.0 ± 0.5° (*c* 2.5, $CHCl_3$). NMR and mass spectra were identical with those published.[47] GC analysis of the (+)-*exo*-brevicomin used for rotation revealed >99% chemical purity. Determination of optical purity by Prof. F.V. Schurig (University of Tubingen, West Germany) using capillary GC with a chiral stationary phase (manganese-camphor derivative) indicated 95% ee.

(1*S*,7*S*)-*exo*-Brevicomin [(-)-1]

Reaction of lithium dimethylcuprate with (-)-**15** yielded (-)-**1** in 69% yield. $[\alpha]^{27}_D$ = -60.6 ± 0.5° (*c* 2.3, $CHCl_3$).

2-Methyl-2-(4-methyl-3-pentenyl)-1,3-dioxolane (18)

This compound was prepared by the literature method using the acid catalyzed reaction of 6-methyl-5-heptene-2-one with ethylene glycol; yield 89%, bp 86-87°C/12 mm Hg; lit[76] bp 58°C/1.5 mm Hg.

(*E*)-2-Methyl-2-(4-methyl-5-hydroxy-3-pentenyl)-1,3-dioxolane (20)

To a solution of **18** (85 g, 0.50 mol) in CH_2Cl_2 (400 mL) was added *t*-butylhydroperoxide (90%, 110 mL, 0.99 mol) and SeO_2 (5.5 g, 50 mmol). The mixture was refluxed with stirring for 9 h and then poured into a 2:1 mixture of saturated aqueous $NaHCO_3$ and 10% aqueous $Na_2S_2O_3$ solutions (300 mL). The organic phase was separated and the aqueous phase extracted with ether (3 X 200 mL). The combined organics were washed with saturated brine (100 mL), dried ($MgSO_4$) and concentrated to a syrup. GC analysis of this crude material indicated ~3% starting alkene, ~78% aldehyde **19** and ~14% alcohol **20**. The mixture was taken up in methanol (150 mL) and cooled with an ice-bath while $NaBH_4$ (8 g, 0.2 mol) was added in small portions over 0.5 h. After a further 0.5 h, the ice-bath was removed and stirring continued for a further 0.5 h at ambient temperature. Water (600 mL) was then added and the reaction mixture extracted with ether (3 X 200 mL). The aqueous phase was saturated with NaCl and further extracted with ether (3 X 100 mL). The combined ether extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Distillation (bp 102-110°C/0.5 mm Hg) yielded **20** (53.6 g, 58%). Spectral data were in

accord with those reported in the literature.[77]

This procedure, utilizing catalytic amounts of SeO_2, was found to be preferable to the reported procedure involving stoichiometric amounts of SeO_2.[77]

Attempted Sharpless Asymmetric Epoxidation of 20. Preparation of 1,3-Dimethyl-3-(2-hydroxyethoxy)-7-oxabicyclo[4.2.0]octane (22)

To a solution of titanium tetraisopropoxide (28.4 g, 100 mmol) in dry methylene chloride (700 mL) was added (+)-diisopropyl tartrate (25.7 g, 110 mmol) with the temperature maintained at -30°C with a CCl_4 slush. After 10 min, allyl alcohol **20** (18.6 g, 100 mmol) was added in one portion followed in 5 min by an anhydrous 5 M solution of t-butylhydroperoxide in methylene chloride (50 mL, 0.25 mol). The mixture was kept in a freezer for 18 h (~-30°C), quenched by the addition of water (10 mL, 0.56 mol) and stirred while warming to rt over 2.5 h. The CH_2Cl_2 was removed *in vacuo* and to the residue was added ether (700 mL) and saturated aqueous NaF solution (1 L). After stirring for 20 h at rt, the mixture was filtered through Celite and the filter cake washed with ether (4 X 150 mL). The DIPT was hydrolyzed by the addition of NaOH (8 g, 0.25 mol) followed by rapid stirring at rt for 2 h. The aqueous phase was separated, saturated with NaCl and extracted with ether (4 X 150 mL). The combined ether extracts were dried ($MgSO_4$) and concentrated *in vacuo* to yield an almost colorless oil. Excess t-butyl-hydroperoxide was removed over 4 h on high vacuum (0.1 mm Hg) to

yield **22** (16.2 g, 80%), >97% pure by GC. A sample for analysis was obtained by preparative TLC (hexane:ethyl acetate, 1:5). IR 3460(s), 2940(s), 2885(s), 1645(w), 1450(m), 1390(s), 1380(s), 1358(m), 1270(m), 1245(s), 1210(s), 1130(s), 1105(s), 940(m), 843(s), 826(m) cm^{-1}; ^1H NMR δ 3.76 (1H, C_8H, d, J=7.5 Hz), 3.74 (2H, CH_2O, m), 3.72 (1H, OCH, m), 3.50 (1H, OCH, m), 3.49 (1H, C_8H, d, J=7.5 Hz), 3.13 (1H, C_6H, t, J=2.5 Hz), 2.29 (1H, OH, brs), 1.86 (2H, C_3H, m), 1.80 (1H, C_4H, m), 1.56 (1H, C_4H, m), 1.45 (3H, CH_3, s), 1.40 (3H, CH_3, s); ^{13}C NMR δ 108.2(s), 81.9(s), 76.4(d), 73.1(t), 71.0(t), 61.9(t), 31.1(t), 24.2(q), 21.5(t), 18.9(q); mass spectrum, m/e, relative intesity 202(5), 173(10), 145(56), 114(100), 99(72), 84(35), 71(48), 43(72). Anal. Calcd for $C_{10}H_{18}O_4$: C 59.35, H 8.99; Found: C 59.19, H 9.09.

1,3-Dimethyl-3-(2-acetoxyethoxy)-7-oxabicyclo[4.2.0]octane (25)

Alcohol **22** (200 mg, 0.99 mmol) was dissolved in CH_2Cl_2 (5 mL). After addition of pyridine (350 mg, 4.4 mmol) and acetic anhydride (300 mg, 2.9 mmol), the mixture was stirred for 16 h at rt. The CH_2Cl_2 solution was washed with saturated $NaHCO_3$ solution (2 mL) and water (2 mL), dried ($MgSO_4$) and concentrated to a yellow syrup. Purification by preparative TLC (ethyl acetate: hexane, 3:1) yielded **25** (186 mg, 76%) as a colorless oil. IR 2990(m), 2945(m), 2890(m), 1744(s), 1450(m), 1392(m), 1382(m), 1256(s), 1213(m), 1113(m), 1050(m), 1033(m), 943(w), 890(w), 857(m), 830(w) cm^{-1}; ^1H NMR δ 4.22 (2H, $-CH_2O-$, m), 3.83 (1H, -OCH-, m), 3.79 (1H, C_8H, d, J=7.5 Hz), 3.61 (1H, -OCH-, m),

3.48 (1H, C_8H, d, J=7.5 Hz), 2.06 (3H, C_4,5H, m), 1.55 (1H, C_4,5H, m), 1.45 (3H, CH_3, s), 1.38 (3H, CH_3, s). Anal. Calcd for $C_{12}H_{20}O_3$: C 59.00, H 8.25; Found: C 59.16, H 8.41.

(E)-2-Methyl-2-hepten-6-one-1-ol (27)

Ethylene ketal **20** (53 g, 0.28 mol) was dissolved in acetone (150 mL) to which was added concentrated H_2SO_4 (5 drops) and the reaction stirred at rt for 2 h. Anhydrous K_2CO_3 (2 g) was then added and stirring continued for a further 0.5 h. Filtration, concentration and distillation (bp 98-102°C/0.2 mm Hg) yielded **27** (30.5 g, 75%), >94% pure by GC. IR 3400(m), 2910(m), 2860(m), 1715(s), 1410(m), 1360(m), 1165(m), 1070(m), 1015(m) cm^{-1}; ^1H NMR δ 4.32 (1H, C_3H, triplet of quartets, J=7, 1.25 Hz), 3.96 (2H, C_1H_2, s), 2.48 (2H, C_5H_2, t, J=7 Hz), 2.29 (2H, C_4H, q, J=7 Hz), 2.13 (3H, C_2 methyl, brs), 1.66 (3H, C_7H_3, s). Anal. Calcd for $C_8H_{14}O_2$: C 67.57, H 9.92; Found: C 67.38, H 10.04.

(±)-2-Hydroxy-1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octane (29)

Alkene **27** (14.2 g, 100 mmol) was dissolved in anydrous CH_2Cl_2 (200 mL). *meta*-Chloroperoxybenzoic acid (21.5 g of purity ~85%, 106 mmol) was then added in small portions over a period of 15 min with ice-bath cooling. After stirring at ambient temperature for 0.5 h, anhydrous KF (24 g, 0.5 mol) was added and stirring continued for 1 h. Filtration and removal of the solvent yielded crude epoxide **28**. ^1H NMR (100 MHz, $CDCl_3$) δ 3.72 (1H, C_1H, d, J_{AB} = 15 Hz), 3.59 (1H, C_1H', d, J_{AB} = 15 Hz), 3.05 (1H, C_3H, dd, J=8, 6 Hz), 2.68 (2H, C_5H_2, t, J=7 Hz), 2.30 (1H,

OH, brs), 2.26 (3H, C_7H_3, s), 2.1-1.6 (2H, C_4H_2, m), 1.17 (3H, C_2 methyl, s). This sample underwent slow, spontaneous rearrangement to bicyclo alcohol **29** over a period of several days.

The bulk of the crude material was dissolved in methanol (150 mL) and treated with $SOCl_2$ (5 drops). After 1 h, GC analysis showed the absence of epoxide **28** and the formation of two products in a ratio of ~60:40. Equilibration of the acidic alcohol solution for 18 h at rt gave a 15:1 ratio of the two diastereomeric bicyclo alcohols **29** with the isomer of shorter retention time predominating. Removal of the solvent *in vacuo* and distillation of the residue yielded **29** (12.8 g, 81%), bp 80-95°C/0.05 mm Hg. IR 3440(s), 2980(s), 2930(s), 2875(s), 1710(w), 1640(w), 1485(w), 1450(m), 1387(s), 1255(s), 1207(s), 1105(s), 1067(s), 1030(s), 972(m), 952(m), 938(m), 910(w), 887(w), 851(s), 811(m), 774(w), 707(m) cm^{-1}. NMR analysis of the initially formed mixture of diastereomers as well as the equilibrium mixture allowed the ^1H NMR of each isomer to be assigned as follows. Major isomer δ 3.84 (1H, C_7H, d, J=12 Hz), 3.52 (1H, C_7H, d, J=12 Hz), 3.42 (1H, C_2H, brd, J=9 Hz), 2.28 (1H, OH, d, J=9 Hz), 2.00 (1H, C_3,4H, m), 1.75 (2H, C_3,4H, m), 1.58 (1H, C_3,4H, m), 1.43 (3H, CH_3, s), 1.37 (3H, CH_3, s). Minor isomer δ 4.07 (1H, C_2H, dd, J=7, 2 Hz), 3.67 (1H, C_7H, J=12 Hz), 3.65 (1H, OH, brs), 3.51 (1H, C_7H, dd, J=12, 2 Hz), 2.08 (2H, C_3,4H, m), 1.80 (2H, C_3,4H, m), 1.51 (3H, CH_3, s), 1.02 (3H, CH_3, s); mass spectrum, m/e, relative intesity (major isomer) 158(M+,2), 129(30), 114(66), 101(100), 99(52), 98(38), 84(94), 71(58), 70(76), 69(43), 61(45), 43(44); mass spectrum, m/e, relative

intesity (minor isomer) 158(M+,1.4), 127(10), 101(100), 98(13), 95(10), 85(43), 84(44), 83(61), 71(28), 58(41), 55(15), 43(46). Anal. Calcd for $C_8H_{14}O_3$: C 60.74, H 8.92; Found: C 60.51, H 8.93.

Attempted Sharpless Epoxidation of 27

Titanium tetraisopropoxide (3.0 mL, 2.9 g, 10 mmol) was dissolved in anhydrous CH_2Cl_2 (50 mL) and the solution cooled to <-30°C with a dry ice-acetone bath while successive additions of (+)-DIPT (2.6 g, 11 mmol), alkene **27** (1.0 g, 0.7 mmol) and *t*-BuOOH (20 mL of a 1 M anhydrous CH_2Cl_2 solution) were made at 10 min intervals. The reaction was kept at -30°C for 3.5 h and then poured into a rapidly stirred mixture of ether (300 mL) and 10% aqueous tartaric acid (50 mL). After stirring for 4.5 h at rt, the organic phase was washed with saturated aqueous $NaHCO_3$ (50 mL) and saturated NaCl (50 mL). Drying ($MgSO_4$) and removal of the solvent yielded a mixture of crude **29**, excess *t*-BuOOH and (+)-DIPT. Co-evaporation with toluene (2 X 100 mL) removed most of the *t*-BuOOH and the residue was purified by column chromatography on silica gel (hexane:ethyl acetate, 1:2) to yield 0.82 g (74%) of **29** as a mixture (~9:1) of alcohols with identical spectral and GC characteristics to those observed for the racemic material.

(±)-1,5-Dimethyl-2-methanesulfonyloxy-6,8-dioxabicyclo[3.2.1]octane (30)

Alcohol **29** (1.58 g, 10 mmol) was dissolved in pyridine (10 mL). Methanesulfonyl chloride (2.0 mL, 2.9 g, 26 mmol) was added and the mixture warmed to 50°C for 1.5 h. After cooling to rt, CH_2Cl_2 (100 mL) was added and the solution washed with saturated aqueous $NaHCO_3$ (2 X 50 mL) and water (2 X 50 mL). Drying ($MgSO_4$) and removal of the solvent *in vacuo* yielded an orange syrup which crystallized upon cooling. Recrystallization (hexane:$CHCl_3$, 50:1) gave **30** as light yellow crystals (1.32 g, 56%, mp 110-112°C). IR (KBr pellet) 3010(m), 2970(m), 2935(m), 2910(m), 1393(m), 1384(m), 1360(m), 1350(s), 1343(s), 1335(s), 1260(m), 1252(s), 1208(m), 1183(s), 1116(s), 1024(m), 1012(s), 991(m), 954(s), 938(s), 917(m), 900(m), 880(s), 854(s), 774(m), 750(m) cm^{-1}; ^1H NMR δ 4.54 (1H, C_2H, dd, J=3.8, 1.9 Hz), 3.86 (1H, C_7H, d, J=7.9 Hz), 3.54 (1H, C_7H, d, J=7.9 Hz), 3.10 (3H, $-SO_2CH_3$, s), 2.17 (1H, C_3H, m), 2.06 (1H, C_3H, ddt, J=15.5, 5.7, 1.5 Hz), 1.90 (1H, C_4H, td, J=13.3, 5.7 Hz), 1.66 (1H, C_4H, ddd, J=13.3, 6.0, 1.5 Hz), 1.49 (3H, CH_3, s), 1.42 (3H, CH_3, s); ^{13}C NMR δ 108.3(s), 80.8(s), 76.6(d), 72.6(t), 38.7(q), 30.7(t), 24.5(t), 24.0(q), 19.0(q); mass spectrum, m/e, relative intesity 236(M+,0.4), 140(11), 129(30), 114(13), 99(11), 98(15), 97(19), 87(18), 83(20), 71(12), 69(12), 57(13), 55(10), 43(100). Anal. Calcd for $C_9H_{16}O_5S$: C 45.75, H 6.82; Found: C 45.75, H 7.00.

(±)-1,5-Dimethyl-6,8-dioxabicyclo[3.2.1]octan-2-one (31)

Alcohol **29** (110 mg, 0.69 mmol) was dissolved in CH_2Cl_2

(5 mL) and stirred while pyridinium chlorochromate (1.0 g, 4.6 mmol) was added in two portions at 2 h intervals. After 18 h at rt, the reaction mixture was passed through a short silica gel column using CH_2Cl_2 as the eluant. The solvent was removed and the residue subjected to bulb-to-bulb distillation to yield ketone **31** (72 mg, 67%); bp 80-100°C (bath temperature)/15 mm Hg. The purified material slowly crystallized (mp 50-52°C). A sample for analysis was prepared by recrystallization from hexane. IR 2991(w), 2940(s), 2881(s), 1729(s), 1480(w), 1449(s), 1417(m), 1388(s), 1379(s), 1261(m), 1214(s), 1184(s), 1168(m), 1135(s), 1106(s), 1079(m), 1036(s), 1011(m), 935(m), 907(m), 879(m), 855(s), 799(m) cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 3.97 (1H, C_7H, d, J=8 Hz), 3.60 (1H, C_7H, d, J=8 Hz), 2.34 (4H, $C_{3,4}H$, m), 1.58 (3H, CH_3, s), 1.40 (3H, CH_3, s); mass spectrum, m/e, relative intesity 156(M^+,2), 114(15), 99(100), 85(16), 71(22), 69(18), 58(17), 55(27), 43(58). Anal. Calcd for $C_8H_{12}O_3$: C 61.15, H 7.74; Found: C 61.10, H 7.70.

2-Methyl-2-vinyloxirane (32)

The method of Reist *et al.*[78] for the preparation of this epoxide from isoprene was modified with a resulting increase in yield. Freshly distilled isoprene (125 g, 1.8 mol) was added to water (350 mL) and vigorously stirred with ice-bath cooling. N-bromosuccinimide (200 g, 1.1 mol) was then added in small portions over a period of 1 h with the temperature of the reaction maintained at 10-15°C. The cooling bath was then removed and the reaction stirred at ambient temperature for 2 h,

after which a test for an oxidizing agent with starch iodide paper proved negative. The lower organic phase was separated and the aqueous phase extracted with ether (3 X 125 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated on a rotary evaporator to ~250 mL.

The resulting solution of isoprene bromohydrin was then added dropwise to a warm (50-55°C) aqueous 30% NaOH solution (300 mL) under aspirator vacuum (~15 mm Hg). Volatile material which distilled was collected in a dry ice/ acetone cooled trap placed in the line between the reaction flask and the water aspirator. The aqueous phase of this distillate was separated and discarded and the remainder dried over $MgSO_4$. Filtration and distillation (bp 75-82°C/750 mm Hg) yielded 54.5 g (59%) of a 10:1 mixture of the desired product **32** and its isomer, isopropenyloxirane. Distillation of the mixture using a 30 cm spinning band column allowed separation of the isomers to yield pure **32**, bp 81-82°C/760 mm Hg, lit[78] bp 78-82°C.

(*E*)-2-Methyl-2,6-heptadien-1-ol (33)

This compound was prepared by the coupling of allyl magnesium bromide with 2-methyl-2-vinyloxirane essentially by the procedure briefly outlined in reference 74. Thus, magnesium turnings (24.0 g, 1.0 mol) in dry ether (100 mL) were stirred rapidly under argon while a solution of freshly distilled allyl bromide (28.0 g, 232 mmol) in dry ether (150 mL) was added dropwise over 3 h. After cooling to rt over 0.5 h, the black solution was decanted from the excess magnesium into a dry, argon

filled dropping funnel. The excess magnesium was rinsed with an additional portion of dry ether (50 mL) which was also decanted into the dropping funnel.

This solution, which was estimated to contain between 185 and 200 mmol of allyl magnesium bromide[79] was added dropwise over 1 h to a stirred solution of **32** (16.8 g, 200 mmol) in dry THF (250 mL) containing a catalytic amount of CuBr:$S(CH_3)_2$ (1 g, 5 mmol). The temperature during this addition was maintained at <-30°C with a dry ice/acetone bath. The yellow color of allyl copper could be observed momentarily as each drop of Grignard solution entered this reaction mixture. After a further 0.5 h at -20°C to -30°C, the reaction was quenched by the addition of saturated aqueous NH_4Cl solution (250 mL) and allowed to warm to ~10°C. The aqueous phase was separated and further extracted with ether (3 X 200 mL). The combined ethereal extracts were washed with 14% NH_4OH solution (100 mL), water (100 mL) and dried over $MgSO_4$. Concentration of the extracts by distillation of the solvents at atmospheric pressure through a 30 cm Vigreaux column followed by vacuum distillation of the residue yielded **33** (15.2 g, 73%; bp 88-92°C/12 mm Hg, lit[74] 93°C/15 torr). Analysis by GC indicated a purity of 93% with ~4% of the 2-(Z) isomer and ~3% of an unidentified more volatile impurity. The spectral data (^1H NMR,IR) were in accord with those reported.[74]

2(*S*,3*S*)-(-)-2,3-Epoxy-2-methyl-6-hepten-1-ol [(-)-34]

A dry round-bottom flask (1 L) was charged with anhydrous CH_2Cl_2 (700 mL) and stirred in a dry ice/acetone bath until the temperature reached -30°C. Titanium tetraisopropoxide (30 mL, 28.6 g, 100 mmol) was then added, followed by (+)-diisopropyl tartrate (25 g, 107 mmol). After 10 min at -20 to -30°C, dienol **33** (12.6 g, 100 mmol) was added and after a further 5 min a 4 M anhydrous CH_2Cl_2 solution of *t*-BuOOH (50 mL, 200 mmol). After 2.5 h (-30°C freezer) GC analysis showed the absence of starting material. The cold reaction mixture was then poured in a thin stream into an ice-bath cooled, rapidly stirred mixture of ether (750 mL) and 10% aqueous tartaric acid (250 mL). After stirring for 15 min in the ice bath, a clean separation into two clear layers could be achieved. The aqueous phase was further extracted with ether (2 X 100 mL) and the combined organics washed with saturated $NaHCO_3$ solution (100 mL) and saturated NaCl solution (100 mL). After drying ($MgSO_4$), the solvents were removed on a rotary evaporator and the residue subjected to two successive vacuum distillations. In the first distillation, separation of most of the excess *t*-BuOOH and (+)-DIPT was achieved and the fraction containing the epoxide (bp 50-80°C/0.5 mm Hg) was redistilled to yield (-)-**34** (12.2 g, 86%; bp 52-54°C/0.2 mm Hg); $[\alpha]^{25}_D$ -4.4° (C, 2.0, EtOH). IR 3430(s), 3080(w), 3000(m), 2970(m), 2930(s), 2875(m), 1645(m), 1450(m), 1387(m), 1040(s), 917(m), 870(m) cm^{-1}; ^1H NMR δ 5.82 (1H, C_6H, m, J_{trans}=17 Hz, J_{cis}=10.5 Hz, J_{vic}= 6 Hz), 5.06 (1H, C_7H, d of q, J=17, 2 Hz), 5.00 (1H, C_7H, d, J=10.5 Hz), 3.69 (1H, C_1H, d,

J=12 Hz), 3.56 (1H, C_1H, brdd, J=12, 6 Hz), 3.05 (1H, C_3H, t, J=6.25 Hz), 2.25 (2H, C_5H, m), 1.86 (1H, OH, brs), 1.68 (2H, C_4H, m), 1.29 (3H, C_2 methyl), s); mass spectrum, m/e, relative intesity (EI) 67(35), 58(100), 57(85), 55(30), 43(71), 41(42); (isobutane CI) 143(47) (M^++1). Anal. Calcd for $C_8H_{14}O_2$: C 67.57, H 9.92; Found: C 67.39, H 10.05.

Preparation of the (+)-α-methoxytrifluoromethylphenyl acetate ((+)-MTPA ester) of (-)-**34** and of racemic **34** by the published method[80] and analysis of the differentially shifted diastereotopic C_1 methylene hydrogens by 400 MHz ^1H NMR spectroscopy gave 95 ±1% ee for (-)-**34**.

2(*R*,3*R*)-(+)-2,3-Epoxy-2-methyl-6-hepten-1-ol [(+)-34]

This material was prepared as described for (-)-**34** with the exception that (-)-DIPT was used in the asymmetric epoxidation to yield 84%, $[\alpha]^{25}_D$ +4.3 (C 2.2, EtOH) and 96 ±1% ee by integration of the ^1H NMR spectrum of the (+)-MTPA ester as described above.

(*R*)-4-Methyl-4-(4-pentenyl)-2,2-dimethyl-1,3-dioxolane [(*R*)-36]

Lithium aluminum hydride (5.0 g, 130 mmol) was dissolved in anhydrous ether (300 mL) and the solution cooled with an ice-bath while epoxide (-)-**34** (20.6 g, 145 mmol) dissolved in anhydrous ether (100 mL) was added dropwise over 1 h. The reaction was quenched by cautious sequential addition of water (5 mL), 15% aqueous NaOH (5 mL) and, finally, water (15 mL). Filtration and thorough extraction of the aluminum salts with additional ether (3 X 200 mL) followed by removal of the solvent provided diol

(*R*)-**35** which was essentially pure by ^{1}H NMR δ 5.78 (1H, C_6H, 10 line multiplet, J_{trans}=17 Hz, J_{cis}=10 Hz, J_{vic}=7 Hz), 5.01 (1H, C_7H, dq, J_{trans}=17 Hz, $J_{gem,allylic}$=2 Hz), 4.95 (1H, C_7H, d of m, J_{cis}=10 Hz),3.46 (1H, C_1H, dd, J_{AB}=11 Hz), J_{OH}=6.5 Hz),3.40 (1H, C_1H, dd, J_{AB}=11 Hz, J_{OH}=6.5 Hz), 2.37 (1H, C_1OH, t, J=6.5 Hz), 2.13 (1H, C_2OH, s), 1.47 (4H, C_2H, C_3H, m), 2.05 (2H, C_5H, q, J=7 Hz), 1.17 (3H, C_2 methyl, s).

The above diol was dissolved in 2,2-dimethoxypropane (50 mL) and stirred while *p*-toluenesulphonic acid (100 mg) was added. After 4 h at ambient temperature, the reaction mixture was diluted with ether (300 mL) and washed with saturated $NaHCO_3$ solution (50 mL). After drying with $MgSO_4$, filtration and concentration *in vacuo*, the residue was distilled to yield (*R*)-**36** (23.9 g, 86% from **34**, bp 48-50°C/0.2 mm); $[\alpha]^{25}_D$ ~0 (*C* 5.4, EtOH). IR 3070(w), 2980(s), 2930(s), 2860(s), 1640(m), 1455(m), 1375(s), 1370(s), 1245(s), 1210(s), 1115(m), 1060(s), 990(m), 910(s), 860(m), 805(m) cm^{-1};^{1}H NMR δ 5.82 (1H, C_6H, ten line multiplet, J_{cis}=10 Hz, J_{trans}=17 Hz, J_{vic}=7 Hz), 5.02 (1H, C_7H, doublet of quartets, J_{trans}=17 Hz, $J_{gem,allylic}$=2 Hz), 4.97 (1H, C_7H, doublet of multiplets, J_{cis}=10 Hz), 3.79 (1H, C_1H, d, J_{AB}=8.1 Hz), 3.71 (1H, C_1H, d, J_{AB}=8.1 Hz), 2.07 (2H, C_5H, q, J=6.5 Hz), 1.53 (4H, C_3C_4H, m), 1.41 (3H, CH_3, s), 1.39 (3H, CH_3, s), 1.28 (3H, C_2 methyl, s); mass spectrum, m/e, relative intesity (EI) 169(100), 115(100), 109(97), 72(89), 67(54), 43(58); (isobutane CI) 185(M^++1,100). Anal. Calcd for $C_{11}H_{20}O_2$: C 71.69, H 10.94; Found: C 71.98, H 11.25.

Preparation of (*S*)-36

Reduction of epoxide (+)-**34** and protection of the diol as the acetone ketal using the procedure described for the preparation of (*R*)-**36** yielded (*S*)-**36** in 85% yield. $[\alpha]^{25}_{D}$ -0.6 (*C* 5.7, EtOH). Spectral data for (*S*)-**36** were identical with those of (*R*)-**36**.

(2*R*)-4-Methyl-4-(3,4-epoxypentyl)-2,2-dimethyl-1,3-dioxolane [(*R*)-37]

Alkene (*R*)-**36** (23.0 g, 125 mmol) was dissolved in dry CH_2Cl_2 (300 mL) and stirred at ambient temperature while *meta*-chloroperoxybenzoic acid (28.0 g, 85% pure, 138 mmol) was added in small portions over 0.5 h. After 5 h, anhydrous KF (30 g, 0.52 mol) was added[71] and stirring continued for a further 6 h. Insoluble material was removed by suction filtration and the filter cake washed with additional CH_2Cl_2 (3 X 100 mL). The combined CH_2Cl_2 solutions were concentrated to yield a 1:1 diastereomeric mixture of (*R*)-**37** as a colorless oil (24.8 g, 99%). A sample for analysis was obtained by bulb-to-bulb distillation (bath temperature 90-110°C/0.2 mm Hg); IR 3043(w), 1458(m), 1380(s), 1370(s), 1250(s), 1213(5), 1120(m), 1060(s), 985(m), 915(m), 852(m); ^{1}H NMR δ 3.79, 3.78 (1H, C_1H diastereomers, dd, J_{AB}=8.3 Hz), 3.70 (1H, C_1H, d, J_{AB}=8.3 Hz), 2.92 (1H, C_7H, brs), 2.75 (1H, C_7H, t, J=4.5 Hz), 2.47 (1H, C_6H, m), 1.56 (6H, $C_3C_4C_5H$, m), 1.39, 1.38 (6H, $2CH_3$, 2s), 1.28 (3H, C_2 methyl, s); mass spectrum, m/e, relative intesity (EI) 185(72), 125(22), 115(93), 97(25), 81(41), 79(22), 72(100),

67(31), 57(38), 55(49), 43(90); (CI isobutane) 201 (M^++1,10). Anal. Calcd for $C_{11}H_{20}O_3$: C 65.97, H, 10.07; Found: 65.73, 9.85.

Preparation of (*S*)-37

Epoxidation of (*S*)-**36**, as described above, yielded (*S*)-**37** quantitatively as a 1:1 diastereomeric mixture. Spectral data for (*S*)-**37** were identical with those of (*R*)-**37**.

(2*R*)-4-Methyl-4-(4-hydroxypentyl)-2,2-dimethyl-1,3-dioxolane [(*R*)-38]

Lithium aluminum hydride (4.5 g, 118 mmol) was added to dry ether (300 mL). With ice-bath cooling, a solution of (*R*)-**37** (23.8 g, 119 mmol) in dry Et_2O (100 mL) was added dropwise over 45 min. The cooling bath was removed and after 1 h at ambient temperature the reaction was quenched by the successive dropwise addition of water (4.5 mL), 15% NaOH (4.5 mL) and water (13.5 mL). Insoluble material was removed by suction filtration and the filter cake washed with additional ether (3 X 100 mL). Removal of the solvent *in vacuo* yielded a 50:50 diastereomeric mixture of (*R*)-**38** (24.0 g, 100%). A sample for analysis was obtained by distillation (bulb-to-bulb, bath temperature 100-120°C/ 0.2 mm Hg). IR 3420(m), 2980(s), 2935(s), 2870(m), 1457(m), 1375(s), 1245(m), 1215(s), 1125(m), 1060(s), 987(w); ^{1}H NMR δ 3.81 (1H, C_6H, m), 3.77 (1H, C_1H diastereomers, 2 doublets separated by 1.6 Hz, J=8.3 Hz), 3.69 (1H, C_1H diastereomers, 2 doublets separated by 1.6 Hz, J=8.3 Hz), 1.70 (1H, OH, s), 1.54

(2H, C_3H, m), 1.44 (4H, C_3C_4H, m), 1.36 (3H, CH_3, s),1.26 (3H, CH_3, s), 1.18 (3H, C_2 methyl, d, J=6.2 Hz); mass spectrum, m/e, relative intensity (EI) 187(53), 127(32), 115(98), 109(100), 72(99), 47(35), 43(93); (isobutane CI) 203(M^++1,8). Anal. Calcd for $C_{11}H_{22}O_3$: C 65.31, H 10.96; Found: C 65.20, H 11.20.

Preparation of (*S*)-38

Lithium aluminum hydride reduction of (*S*)-**37** yielded (*S*)-**38** as a 1:1 diastereomeric mixture in 98% yield. Spectral data for (*S*)-**38** were identical with those of (*R*)-**38**.

(1*R*,5*S*)-1,5 Dimethyl-6,8-dioxabicyclo[3.2.1]octane

(*R*)-(+)-Frontalin [(*R*)-16]

Alcohol (*R*)-**38** (23.0 g, 114 mmol) was dissolved in glacial acetic acid (100 mL). The solution was cooled in an ice-bath and 5% aqueous NaOCl solution (160 mL, ~130 mmol) was added dropwise over 0.5 h. After 18 h at ambient temperature and 5 h at 50°C, the reaction mixture was diluted with water (400 mL) and extracted with ether (4 X 100 mL). The ether was washed with 5% aqueous NaOH solution until the washings were basic (4 X 80 mL), water (100 mL) and saturated NaCl solution (100 mL). After being dried ($MgSO_4$), the extracts were concentrated to ~50 mL by distillation of the solvent through a 30 cm Vigreaux column at atmospheric pressure. The residue was fractionally distilled to yield (*R*)-**16** (12.4 g, 77%); bp 65-67°C/30 mm Hg; >98% pure by GC; $[\alpha]^{23}_D$ +50.7 (*C* 4.6, Et_2O). IR and ^1H NMR were in accord with the literature[56]. The optical purity on the basis of the

rotation compared to the highest reported value (54.4°)[57] was 93%.

As confirmation, the ^{1}H NMR spectrum of (±)-**16** and (+)-**16** were recorded in the presence of *tris*-[3-trifluoro-methylhydroxy-methylene-d-camphorato]europium(III) shift reagent as described by Mori[56]. Inspection of the low field C_7 hydrogen showed a near baseline separation of the enantiomeric signals if the higher field C_7 hydrogen was simultaneously decoupled. Integration (cut and weigh) gave an estimated 89% ee.

Preparation of (*S*)-(-)-Frontalin [(*S*)-16]

Alcohol (*S*)-**38** was oxidized and cyclized as described above to yield 74% of (*S*)-**16**; bp 66-67°C/30 mm Hg, $[\alpha]^{23}_D$ -52.9° (*C* 4.7, Et_2O). The optical purity of this material was estimated to be 97% ee by comparison of the observed rotation to that reported by Ohrui and Emoto[57].

2,2,4-Trimethyl-5,6-dihydro-2H-pyran (48)

Lithium aluminum hydride (52 g, 1.4 mol) was stirred with dry ether (2 L) and cooled with an ice bath while 3,5-dimethyl-(Z)-3-hexenoic acid δ-lactone[84] (265 g, 1.9 mol) was added dropwise over 1 h. The cooling bath was removed and the mixture stirred at ambient temperature for 16 h. The reaction mixture was then carefully poured (caution! - foaming) into ice-cold 2 M sulfuric acid (3 L). After stirring at rt for 1 h, the ether layer was separated and the aqueous acid extracted with additional ether (2 X 500 mL). The combined extracts were washed with saturated $NaHCO_3$ solution (300 mL) and dried over anhydrous $MgSO_4$. Removal of the solvent through a 20 cm Vigreux column at atmospheric pressure, followed by distillation of the residue, yielded **48** (197 g, 83%), bp 130-133°C/750 mm Hg. IR 2975(s), 2920(s), 2863(m), 1677(w), 1463(m), 1440(m), 1385(m), 1360(s), 1272(m), 1243(m), 1223(m), 1200(m), 1180(m), 1125(s), 1098(s), 1087(m), 939(m), 872(m), 838(m), 770(m) cm^{-1}; ^1H NMR δ 5.29 (1H, vinyl H, sextet, J=1.5 Hz), 3.78 (2H, OCH_2, t, J=5.6 Hz), 1.93 (2H, allylic CH_2, brt, J=5.4 Hz), 1.67 (3H, allylic CH_3, brs), 1.20 (6H, 2 methyls, s); mass spectrum, m/e (relative intensity) 126(3), 112(6), 111(100), 43(7). Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.31; H, 11.03.

Reaction of 48 with Dichloroketene in the Presence of Phosphorus Oxychloride.

A solution of **48** (2.70 g, 21.4 mmol) in dry ether (60 mL) was stirred at ambient temperature under Ar. Activated Zn (2.0 g, 31 mmol) was added followed by dropwise addition over 1 h of a solution of trichloracetyl chloride (4.0 g, 22 mmol) and phosphorus oxychloride (3.4 g, 22 mmol) in anhydrous ether (20 mL). The mixture was refluxed for 12 h, cooled and poured into saturated aqueous $NaHCO_3$ (200 mL). After stirring for 0.5 h, the organic phase was separated and the aqueous phase extracted with ether: pentane (1:1, 3 X 75 mL). The combined extracts were washed with saturated $NaHCO_3$ (50 mL) and saturated NaCl (50 mL), dried over anhydrous Na_2SO_4 and concentrated to give an orange syrup. After removing unreacted **48** under high vacuum (1 h, 0.2 mm) the residue was flash chromatographed on silica gel with hexane: ethyl acetate (4:1) to yield **50** (1.30 g, 26%) and **49** (350 mg, 7%). Compound **50** slowly crystallized upon cooling and was recrystallized from hexane; mp 41-43°C.

IR (KBr pellet) 3062(w), 3010(m), 2983(s), 2950(m), 2915(m), 2870(w), 1754(s), 1640(w), 1493(w), 1463(m), 1450(m), 1442(m), 1394(m), 1376(m), 1358(m), 1323(w), 1264(s), 1220(s), 1178(m), 1153(m), 1135(m), 1048(m), 1030(m), 1003(m), 988(m), 973(m), 903(m), 878(m), 861(m), 828(m), 818(m), 768(m), 740(m), 692(m), 612(m), 603(m), 534(m), 459(w), 370(m), 320(m) cm^{-1}; ^1H NMR δ 5.44, (1H, vinyl H, m), 4.7-4.2 (2H, OCH_2, brs), 3.0-2.0 (2H, allylic CH_2, very broad s), 1.82 (3H, CH_3, d, J=2 Hz), 1.49 (6H, $2CH_3$, s); mass spectrum, m/e (relative intensity) 238/236 (<0.5),

121(15), 110(12), 109(100), 93(10), 91(17), 81(30), 79(18), 77(20), 67(45), 65(12), 55(10), 53(12), 43(10), 41(12). Anal. Calcd for $C_{10}H_{14}O_2Cl_2$: C, 50.65; H, 5.95. Found: C, 50.90; H, 5.74.

7,7-Dichloro-2,2,6-trimethyl-3-oxabicyclo[4.2.0]octan-8-one (49)

Zinc-copper couple (100 g, 1.5 mol) was added to a stirred mixture of anhydrous ether (2 L) and anhydrous 1,2-dimethoxyethane (500 mL). The reaction was maintained under N_2 while ether **48** (126 g, 1 mol) was added, followed by dropwise addition of trichloroacetyl chloride (250 g, 1.4 mol) over 1 h. After 48 h at reflux, further portions of dimethoxyethane (500 mL), zinc (100 g) and trichloroacetyl chloride (250 g) were added. After an additional 48 h at reflux, the reaction was terminated by filtration and concentration *in vacuo* to a volume of ~350 mL. The dark-colored concentrate was poured in a thin stream into petroleum ether 30-60°C (3 L) with rapid stirring. Insoluble material was removed by suction filtration and the petroleum ether solution was then stirred with ice-cold saturated $NaHCO_3$ solution (1.5 L) for a period of 1 h. The organic phase was washed with an additional portion of saturated $NaHCO_3$ (1 L), water (2 X 500 mL) and saturated NaCl solution (500 mL). After drying over anhydrous $MgSO_4$, concentration *in vacuo* gave a dark brown syrup which was subjected to vacuum distillation to yield partially purified adduct **49** (141 g, 85% pure by GC), bp 70-85°C /0.1 mm Hg. A sample for analysis was obtained by flash chromatography (hexane:ethyl acetate, 10:1). IR 2970(s),

2925(m), 2870(m), 1803(s), 1478(m), 1452(m), 1436(m), 1384(m), 1368(m), 1346(m), 1321(m), 1289(m), 1272(m), 1237(m), 1210(m), 1170(m), 1130(m), 1079(m), 1020(m), 992(m), 928(m), 900(m), 872(m), 812(m), 790(m), 748(m), 714(m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.74 (1H, C_4H, ddd, J_{gem}=12, J_{cis}=5, J_{trans}=2.2 Hz), 3.68 (1H, C_4H', dt, J_{gem}= J_{trans}=12, J_{cis}=1.8 Hz), 3.24 (1H, C_1H, d, $J_{1,5}$=1.9 Hz), 1.84 (1H, C_5H, m, J_{gem}=15, J_{trans}=12, J_{cis}=5 Hz), 1.66 (1H, C_5H', dq, J_{gem}=15, J_{trans}~J_{cis}~$J_{1,5}$~2 Hz), 1.59 (3H, CH_3, d, J=0.8 Hz), 1.49 (3H, CH_3, s), 1.21 (3H, CH_3, s); mass spectrum, m/e (relative intensity) 238(0.1), 236(0.1), 152(5), 150(8), 138(7), 136(10), 83(100), 55(30). Anal. Calcd for $C_{10}H_{14}O_2Cl_2$: C, 50.65; H, 5.95. Found: C, 50.64; H, 5.79.

2,2,6-Trimethyl-3-oxabicyclo[4.2.0]octan-8-one (52)

A mixture of Zn powder (125 g, 1.9 mol) and methanol saturated with NH_4Cl (1 L) was stirred while partially purified **49** (140 g, 0.59 mol) was added dropwise at a rate sufficient to maintain a gentle reflux. After the addition was complete (~2 h), the reaction was maintained at reflux for an additional 4.5 h by external heating. After cooling to rt and filtration, the methanol was removed *in vacuo* and the semi-crystalline residue was shaken with a mixture of ether (1.5 L) and 2 M H_2SO_4 (800 mL). When the zinc salts had dissolved, the organic phase was separated and the aqueous phase extracted with additional ether (2 X 300 mL). The combined ether extracts were washed with saturated $NaHCO_3$ solution (500 mL) and water (500 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was

distilled to give **52**, bp 55-60°C/0.3 mm Hg, 58 g, 58% yield, 90% pure by GC. A sample for analysis was obtained by flash chromatography (hexane:ethyl acetate, 4:1).

IR 2975(s), 2930(s), 2875(s), 1780(s), 1464(m), 1383(m), 1365(m), 1348(m), 1323(m), 1291(m), 1273(m), 1237(m), 1208(m), 1163(m), 1083(m), 1062(m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.70 (2H, C_4H, m), 2.76 (1H, C_7H, dd, J_{gem}=16, $J_{1,7}$=1.8 Hz), 2.67 (1H, C_1H, brs), 2.60 (1H, C_7H, dd, J_{gem}=16, $J_{1,7}$=1.5 Hz), 1.80 (1H, C_5H, dm, J_{gem}=14.5 Hz), 1.63 (1H, C_5H', m), 1.49 (3H, CH_3, s), 1.44 (3H, CH_3, s), 1.22 (3H, CH_3, s); mass spectrum, m/e (relative intensity) 168(2), 154(12), 125(10), 11(100), 100(25), 83(20), 72(13), 55(14). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.60; H, 9.64.

2,2,6-Trimethyl-3-oxabicyclo[4.2.0]octan-4,8-dione (53)

A mixture of **52** (32 g, 190 mmol) in CCl_4 (400 mL) and aqueous $NaIO_4$ (120 g, 560 mmol in 1 L water) was stirred while $RuCl_3:3H_2O$ (1.5 g, 5.7 mmol) was added in one portion. After 18 h of stirring at ambient temperature, the organic phase remained yellow when the stirring was stopped and the reaction was judged to be complete by TLC. Insoluble material was removed by suction filtration and the aqueous phase was extracted with CH_2Cl_2 (3 X 250 mL). The combined extracts were treated with isopropanol (5 mL) to destroy the remaining RuO_4 and concentrated to yield a black syrup. This material was dissolved in ether (1.2 L) and washed with saturated $NaHCO_3$ solution (300 mL). The black insoluble RuO_2 remained in the aqueous layer after shaking for

~10 min. The organic layer was separated, washed with water (100 mL) and dried over anhydrous $MgSO_4$. Removal of the solvent gave a grey semi-crystalline residue which was recrystallized from hexane:ethyl acetate (4:1) to yield 21.0 g (61%) of compound **53**, mp 97-98°C. Lit.[90] mp 99-100°C.

IR (Nujol mull) 1773(s), 1725(s), 1340(m), 1290(m), 1203(m), 1145(m), 1075(m), 995(m) cm^{-1}; ^1H NMR δ 2.97 (1H, C_1H, s), 2.90 (2H, C_8H, m), 2.84 (1H, C_7H, d, J_{gem}=16.8 Hz), 2.73 (1H, C_7H', d, J_{gem}= 16.8 Hz), 1.54 (3H, CH_3, s), 1.53 (3H, CH_3, s), 1.41 (3H, CH_3, s); mass spectrum, m/e (relative intensity) 182(1), 141(10), 126(10), 125(100), 123(22), 97(32), 96(39), 83(15), 82(16), 81(17), 55(12). Anal. Calcd for $C_9H_{14}O_3$: C, 65.86; H, 7.74. Found: C, 66.19; H, 7.75.

2,2,6-Trimethyl-3,9-dioxabicyclo[4.3.0]nonan-8-one (54)

To a solution of **52** (100 mg, 0.60 mmol) in CCl_4 (20 mL) was added 5% aqueous NaOCl solution (Javex bleach, 10 mL, ~13 mmol) and $RuCl:3H_2O$ (20 mg, 0.08 mmol). After stirring at room temperature for 5 h, the CCl_4 layer was withdrawn and the aqueous layer further extracted with CCl_4 (2 X 10 mL). The combined extracts were treated with isopropanol (0.5 mL) and filtered through a short silica gel column. The column was washed with ether and the combined solution concentrated *in vacuo* to yield **54** as a crystalline solid (106 mg, 91%); mp 54-56°C. IR (KBr pellet) 3005(m), 2995(m), 2925(m), 2890(m), 1780(s), 1712(m), 1480(w), 1435(m), 1390(w), 1368(m), 1307(m), 1285(m), 1260(m), 1223(m), 1204(s), 1185(m), 1130(m), 1086(s), 1043(m), 1015(m),

1005(m), 996(m), 965(m), 873(w), 804(m), 753(w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.75 (1H, C_1H, s), 3.67 (2H, C_4H, m), 2.42 (1H, C_7H, d, J_{gem}=17 Hz), 2.32 (1H, C_7H, d, J_{gem}= 17 Hz), 1.71 (1H, C_5H, m), 1.35 (1H, C_5H, m), 1.23 (3H, CH_3, s), 1.22 (3H, CH_3, s), 1.20 (3H, CH_3, s); mass spectrum, m/e (relative intensity) 184(7), 169(10), 98(100), 83(24), 70(20), 69(32), 59(18). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.20; H, 8.76. Found: C, 64.90; H, 9.10.

7,7-Dichloro-2,2,6-trimethyl-3,9-dioxabicyclo[4.3.0]-nonan-8-one (55).

Treatment of **49** with RuO_4/NaOCl as described for the preparation of **54** from **52** yielded **55** as a crystalline solid in 85% yield, mp 82-87°C. IR (KBr pellet) 3005(m), 2995(m), 2950(m), 2890(m), 1805(s), 1465(m), 1393(m), 1370(m), 1275(m), 1215(s), 1170(m), 1113(m), 1086(m), 1040(m), 990(s), 975(s), 902(m), 842(m), 820(m), 767(m), 738(m), 690(m), 664(m), 580(m), 530(m), 503(m) cm^{-1}; ^1H NMR δ 4.10 (1H, C_1H, s), 3.83-3.67 (2H, C_4H, 14 peak multiplet), 1.90-1.50 (2H, C_5H_2, m), 1.46 (3H, CH_3, s), 1.38 (3H, CH_3, s), 1.33 (3H, CH_3, s); mass spectrum, m/e (relative intensity) 254(7), 252(10), 239(20), 237(28), 169(12), 168(18), 167(19), 166(27), 161(19), 159(52), 150(13), 139(14), 137(18), 133(36), 131(100), 123(10), 115(13), 110(11), 103(12), 101(10), 95(12), 87(10), 79(14), 77(12), 75(10), 67(15), 65(23), 59(10), 58(10), 53(11), 51(10), 43(33), 41(15); Anal. Calcd for $C_{10}H_{14}O_3Cl_2$: C, 47.45; H, 5.58. Found: C, 47.61; H, 5.57.

3,3,7-Trimethyl-2,9-dioxatricyclo[3.3.1.0^{4,7}]nonane

(±)-Lineatin (40)

Bicyclic keto-lactone **53** (38 g, 0.21 mol) was added to dry ether (500 mL) and cooled in an ice bath. To the stirred heterogeneous mixture was added dropwise a 1 M hexane solution of DIBAL (500 mL, 0.50 mol) over 1.5 h with the temperature maintained at 5-7°C. After a further 0.5 h at 5°C, the reaction mixture was poured into ice-cold 10% aqueous tartaric acid (800 mL) and stirred until a clean separation into two layers occurred (~45 min). The organic phase was separated and the aqueous phase extracted with ether (2 X 100 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (100 mL), water (100 mL) and saturated NaCl (100 mL), dried over anhydrous $MgSO_4$ and concentrated by distillation through a 30 cm Vigreux column. The residue was vacuum distilled to yield **40** (24.6 g, 70%), bp 61°C/2.5 mm Hg, Lit.[85] bp 70°C/12 mm Hg. This material was >98% pure by GC and had spectral data in complete accord with earlier reports[81-83].

Synthesis of Allyl Ethers and Allyl Sulfides

Allyl phenyl ether (**65**) and allyl methyl sulfide (**70**) were commercial products (Aldrich). Cinnamyl methyl ether (**74**) and 2-methyl-2-propenyl methyl ether (**71**) were prepared by methylation of the corresponding alcohols with dimethyl sulphate[98]. Allyl phenyl sulfide (**67**) was prepared from allyl bromide and thiophenol[99].

3-Methyl-2-butenyl Phenyl Ether (56)

Phenol (10.0 g, 106 mmol) was added to a stirred mixture of acetone (50 mL) and K_2CO_3 (17.0 g, 123 mmol) at rt. After 10 min, 1-bromo-3-methyl-2-butene (14.9 g, 100 mmol) was added and the mixture stirred at rt for 16 h. After filtration and solvent removal *in vacuo*, the residue was dissolved in hexane (100 mL) and washed with water (2 X 50 mL). Drying ($MgSO_4$), solvent removal and distillation yielded **56** (10.2 g, 63%). bp 60-63°C/0.1 mm Hg; ^{1}H NMR δ 7.28 (2H, phenyl, m), 6 93 (3H, phenyl, m), 5.51 (1H, C=CH, tm, J_{vic}=7 Hz), 4.51 (1H, OCH_2, d, J_{vic}=7 Hz), 1.80 (3H, CH_3, s), 1.74 (3H, CH_3, s).

3-Methyl-2-butenyl Methyl Ether (59)

1-Bromo-3-methyl-2-butene (7.45 g, 50.0 mmol) was added dropwise to a solution of $NaOCH_3$ (61 mmol) in anydrous methanol with stirring over 10 min. After a further 0.5 h the reaction mixture was poured into pentane (75 mL) and water (100 mL). The pentane layer was separated and dried over $MgSO_4$. Careful removal of the pentane at atmospheric pressure through a Vigreux column followed by distillation of the residue yielded **59** (2.3 g, 46%). bp 104-105°C. A forerun (1.2 g, bp 80-104°C) was contaminated with ~20% of the tertiary ether resulting from S_N2' reaction. ^{1}H NMR δ 4.95 (1H, C=CH, s), 4.89 (1H, C=CH, s), 3.82 (2H, OCH_2, s), 3.32 (3H, OCH_3, s), 1.73 (3H, CH_3, s).

3-Methyl-2-butenyl Phenyl Sulfide (62)

This compound was prepared in 50% yield by the ZnI_2

catalyzed reaction of 2-methyl-3-buten-2-ol with thiophenol.[100] bp 75-78°C/0.2 mm Hg; ^{1}H NMR (100 MHz, $CDCl_3$) δ 7.6-7.1 (5H, aromatic, m), 5.41 (1H, vinyl H, t, J=8 Hz), 3.63 (2H, SCH_2, d, J=8 Hz), 1.83 (3H, CH_3, s), 1.70 (3H, CH_3, s).

General Procedure for the Cycloaddition of Dichloroketene With Allyl Ethers or Allyl Sulfides

A solution of the allyl ether or sulfide (20 mmol) in anhydrous ether (75 mL) and dimethoxyethane (10 mL) containing activated zinc (4.0 g, 62 mmol) and trichloroacetyl chloride (6.0 mL, 54 mmol) was refluxed under an argon atmosphere for 40-60 h. The reaction mixture was filtered and the excess Zn rinsed with anhydrous ether (3 X 25 mL). The ether was removed *in vacuo* and the residue dissolved in hexane (100 mL). Insoluble material was removed by filtration and the filtrate washed with saturated $NaHCO_3$ solution (2 X 100 mL) and with brine (50 mL). After drying ($MgSO_4$) the solvent was removed *in vacuo* and the crude product purified by distillation or chromatography on silica gel.

General procedure for Reductive Dechlorination of the Dichlorocyclobutanone Adducts

A solution of the dichloro-cycloadduct (5 mmol) in methanol (20 mL) saturated with NH_4Cl was stirred with Zn powder (2 g) at rt for 1 - 3 h. Filtration and solvent removal *in vacuo* yielded a mixture of the product with Zn salts. The residue was partitioned between ether (75 mL) and water (25 mL). After further washing with water (2 X 25 mL), the ether solution was

dried ($MgSO_4$) and concentrated to yield the product. Final purification consisted of bulb-to-bulb distillation at reduced pressure.

2,2-Dichloro-3,3-dimethyl-4-(phenoxymethyl)cyclobutanone (57)

Reaction of dichloroketene with **56** yielded **57** (65%) after purification by distillation (bp 110-115°C /0.1 mm Hg). The distillate slowly crystallized and an analytical sample was obtained by recrystallization from pentane. Mp 46-47°C; ^1H NMR δ 7.3-6.8 (5H, phenyl, m), 4.28 (1H, OCH, dd, J_{gem}=10 Hz, J_{vic}=5 Hz), 4.11 (1H, OCH', t, J=10 Hz), 3.97 (1H, C_4H, dd, $J_{OCH'}$=10Hz, J_{OCH}=5 Hz), 1.61 (3H, CH_3, s), 1.32 (3H,CH_3, s); mass spectrum, m/e, relative intesity (EI) 274,272(2,M^+), 148(32), 107(14), 94(16), 79(7), 77(15), 55(100). Anal. Calcd for $C_{13}H_{14}O_2Cl_2$: C 57.16, H 5.17; Found: C 57.35, H 5.06.

3,3-Dimethyl-2-(phenoxymethyl)cyclobutanone (58)

Dechlorination of **57** yielded **58** in 89% yield after bulb-to-bulb distillation (bp 90-100°C/0.2 mm Hg). ^1H NMR δ 7.3-6.8 (5H, phenyl, m), 4.19 (1H, OCH, dd, J_{gem}=10 Hz, J_{vic}=4 Hz), 4.07 (1H, OCH', t, J=10 Hz), 3.45 (1H, C_2H, m), 2.92 (1H, C_4H, dd, J_{gem}=17 Hz, J_{C2H}=3 Hz), 2.69 (1H, C_4H, dd, J_{gem}=17 Hz, J_{C2H}=2 Hz), 1.50 (3H, CH_3, s), 1.26 (3H, CH_3, s); mass spectrum, m/e, relative intensity (EI) 204(7,M^+), 111(37), 95(12), 94(100), 78(10), 69(80), 55(48), 41(15). Anal. Calcd for $C_{16}H_{16}O_2$: C 76.44, H 7.90; Found: C 76.80, H 7.82.

2,2-Dichloro-3,3-dimethyl-4-(methoxymethyl)cyclobutanone (60)

Reaction of **59** with dichloroketene yielded **60** (76%) after vacuum distillation. Bp 65-67°C/0.1 mm Hg; IR 2970(m), 2930(m), 2880(m), 2825(m), 1805(s), 1466(m), 1390(m), 1245(m), 1202(m), 1178(m), 1130(s), 1103(s), 932(m), 860(m), 808(s) cm^{-1}; ^1H NMR δ 3.72 (1H, OCH, dd, J_{gem}=9 Hz, J_{vic}=5 Hz), 3.62 (1H, C_4H, dd, J=10 Hz,5 Hz), 3.56 (1H, OCH', dd, J_{gem}=9 Hz, J_{vic}=10 Hz), 3.32 (3H, OCH_3, s), 1.53 (3H, CH_3, s), 1.27 (3H, CH_3, s); mass spectrum, m/e, relative intensity (EI) 139/141(23), 125(15), 119/121(100),45(12); (CI, isobutane) 213/211(100, M^++1).

3,3-Dimethyl-2-(methoxymethyl)cyclobutanone (61)

Dechlorination of **60** yielded **61** (73%) after bulb-to-bulb distillation. Bp 65-75°C/15 mm Hg; IR 2960(m), 2920(m), 2865(m), 1775(s), 1460(m), 1380(m), 1370(m), 1248(m), 1190(m), 1123(m), 1085(m), 1040(m); ^1H NMR δ 3.52 (2H, OCH_2, m), 3.31 (3H, OCH_3, s), 3.19 (1H, C_2H, m), 2.83 (1H, C_4H, dd, J_{gem}=17 Hz, J_{c2H}=3 Hz), 2.62 (1H, C_4H', dd, J_{gem}=17 Hz, J_{c2H}=2 Hz), 1.42 (3H, CH_3, s), 1.22 (3H, CH_3, s); mass spectrum, m/e, relative intensity (EI) 110(15), 85(100),83(13), 82(30), 69(23), 67(12), 45(15), 41(20); (CI, isobutane) 143(10, M^++1) 111(100).

2,2-Dichloro-3,3-dimethyl-4-(phenylthiomethyl)cyclobutanone (63)

Reaction of **62** with dichloroketene yielded **63** (66%) after distillation. Bp 135-140°C/0.3 mm Hg; ^1H NMR δ 7.5-7.3 (5H, phenyl, m), 3.69 (1H, C_4H, dd, $J_{BCH'}$=10Hz, J_{BCH}=6 Hz), 3.49 (1H SCH, dd, J_{gem}=14 Hz, J_{vic}=6 Hz), 3.00 (1H, SCH', dd, J_{gem}=14 Hz,

J_{vic}=10 Hz), 1.65 (3H, CH_3, s), 1.38 (3H, CH_3, s). Anal. Calcd for $C_{13}H_{14}Cl_2OS$: C 53.99, H 4.88; Found: C 54.15, H 5.10.

3,3-Dimethyl-2-(phenylthiomethyl)cyclobutanone (64)

Dechlorination of **63** yielded **64** (69%) after bulb-to-bulb distillation. Bp 105-110°C/0.2 mm Hg; ^{1}H NMR δ 7.3-6.8 (5H, phenyl, m), 3.25 (1H, SCH, dd, J_{gem}=13 Hz, J_{vic}=8 Hz), 2.85 (1H, C_2H, dm, $J_{SCH'}$=11 Hz), 2.70 (1H, SCH', dd, J_{gem}=13 Hz, J_{vic}=11 Hz), 2.31 (1H, C_4H, dd, J_{gem}=16.5 Hz, J_{C2H}=2.2 Hz), 2.15 (1H, C_4H, dd, J_{gem}=16.5 Hz, J_{C2H}=1.8 Hz), 1.09 (3H, CH_3, s), 0.88 (3H, CH_3, s); mass spectrum, m/e, relative intensity (EI) 220(100, M^++), 178(10), 111(42), 110(35), 69(39), 45(20). Anal. Calcd for $C_{13}H_{16}OS$: C 70.87, H 7.32; Found: C 71.03, H 7.42.

2,2-Dichloro-3-(phenoxymethyl)cyclobutanone (66)

Reaction of **65** with dichloroketene yielded **66** (86%) after vacuum distillation. Bp 103-110°C/0.1 mm Hg; ^{1}H NMR δ 7.3-6.8 (5H, phenyl, m), 4.38 (1H, OCH, dd, J_{gem}=10 Hz, J_{vic}=6 Hz), 4.23 (1H, OCH', dd, J_{gem}=10 Hz, J_{vic}=6 Hz), 3.58 (1H, C_4H, dd, J_{gem}=17 Hz, J_{vic}=9 Hz), 3.40 (1H, C_3H, m), 3.28 (1H, C_4H',dd, J_{gem}=17 Hz, J_{vic}=9 Hz). This compound proved to be unstable in air and decomposed over a period of several days.

2,2-Dichloro-3-(phenylthiomethyl)cyclobutanone (68)

Reaction of **67** with dichloroketene yielded **68** (33%) after purification by silica gel chromatography (hexane/ethyl acetate, 4:1). The chromatography caused extensive decomposition and the

yield of crude product was much greater. IR 3060((m), 2930(m), 1810(s), 1584(m), 1483(m), 1440(m), 1390(m), 1258(m), 1215(m), 1180(m), 1088(m), 1060(m), 1027(m), 983(m), 746(m), 695(m) cm^{-1}; ^1H NMR δ 7.2-7.5 (5H, phenyl, m), 3.43 (2H, C_2H, C_3H, m), 3.08 (3H, C_2H', SCH_2, m). This adduct was further characterized after dehalogenation because of its unstable nature.

3-(Phenylthiomethyl)cyclobutanone (69)

Dechlorination of **68** yielded **69** (73%) after bulb-to-bulb distillation. Bp 80-90°C/0.2 mm Hg; IR 3050(m), 2960(m), 2910(m), 1780(s), 1578(m), 1476(m), 1433(m), 1378(m), 1255(m), 1229(m), 1085(m), 1020(m), 737(s), 688(m) cm^{-1}; ^1H NMR (C_6D_6) δ 7.3-6.9 (5H, phenyl, m), 2.65-2.55 (2H, C_2H, C_4H, 19 line multiplet), 2.46 (2H, SCH_2, d, J=7.5 Hz), 2.37-2.27 (2H, C_2H', C_4H', 14 line multiplet), 2.05-1.92 (1H, C_3H, 28 line multiplet); mass spectrum, m/e, relative intensity (EI) 192(100), 150(75), 149(33), 148(46), 135(95), 130(27), 123(48), 117(60), 110(20), 109(26), 83(23), 69(20), 65(15), 55(19), 45(15), 41(18). Anal. Calcd for $C_{11}H_{12}OS$: C 68.71, H 6.29; Found: C 68.88, H 6.40.

2,2-Dichloro-3-methyl-3-(methoxymethyl)cylobutanone (72)

Reaction of **71** with dichloroketene yielded **72** (28%) after distillation. The yield of crude product was better but extensive decomposition occurred during the distillation. Bp 70-80°C/0.1 mm Hg; IR 2985(m), 2930(m), 2890(m), 2825(m), 1815(s), 1460(m), 1400(m), 1202(m), 1118(s), 985(m), 756(m); ^1H NMR δ 3.60 (1H, OCH, d, J_{gem}=9.5 Hz), 3.50 (1H, OCH', d, J_{gem}=9.5 Hz), 3.37

(3H, OCH_3, s), 3.23 (1H, C_4H, d, J_{gem}=17 Hz), 3.01 (1H, C_4H, d, J_{gem}=17 Hz), 1.44 (3H, CH_3, s); mass spectrum, m/e, relative intensity (CI, isobutane) 197/199(80, M^++1).

3-Methyl-3-methoxymethylcyclobutanone (73)

Dechlorination of **72** yielded **73** (87%) after bulb-to-bulb distillation. Bp 80-90°C/15 mm Hg; IR 2960(m), 2920(m), 2870(m), 1780(s), 1460(m), 1383(m), 1275(m), 1185(m), 1105(m), 962(m) cm^{-1}; ^1H NMR δ 3.40 (3H, OCH_3, s), 3.39 (2H, OCH_2, s), 3.02 (2H, C_2H,C_4H, dm, J_{gem}= 20 Hz), 2.67 (2H, C_2H',C_4H', dm, J_{gem}=20 Hz), 1.33 (3H, CH_3, s); mass spectrum, m/e, relative intensity (CI, isobutane) 129(90, M^++1), 97(100). Anal. Calcd for $C_7H_{12}O_2$: C 65.60, H 9.44; Found: C 65.55, H 9.37.

Reaction of Dichloroketene with 70 and 74

Reaction of dichloroketene with allyl methyl sulphide (**70**), using the standard protocol, rapidly produced a complex mixture of products which promptly decomposed. Reaction with cinnamyl methyl ether (**74**), on the other hand, went extremely slowly with over 70% enreacted allyl ether left after 48 h. ^1H NMR analysis of the crude reaction mixture indicated that the major product was the result of Claisen rearrangement rather than [2+2] cycloaddition. Neither of these reactions was investigated further.

Ethyl Acetoacetate Ethylene Ketal (78)

Acid-catalyzed reaction of ethyl acetoacetate **77** with ethylene glycol, according to the procedure of Paulsen *et al.*[110], yielded **78** (82%): bp 70-71°C/0.1 mm Hg; lit.[110] bp 135-138°C/50 mm Hg.

4-Hydroxy-2-butanone Ethylene Ketal (79)

Reduction of **78** with lithium aluminum hydride in diethyl ether, as described by Bigalke *et al.*.[111], yielded **79** (92%): bp 85-86°C/10 mm Hg; lit.[111] bp 88-91°C/12 mm Hg.

4-Bromo-2-butanone Ethylene Ketal (80)

Triphenylphosphine (27.5 g, 105 mmol) was dissolved in anhydrous CH_2Cl_2 (150 mL) and stirred with ice-bath cooling while bromine was added dropwise until a definite yellow color persisted. The color was discharged by addition of a small amount of triphenylphosphine. Pyridine (12 mL, 150 mmol) was added in one portion, followed after 5 min by dropwise addition of a CH_2Cl_2 solution of **79** (13.2 g, 100 mmol in 25 mL) over 0.5 h. The cooling bath was removed and the mixture stirred at ambient temperature for 1 h. Filtration and removal of solvent *in vacuo* yielded a semi-crystalline residue which was triturated with pentane (200 mL). The pentane solution was filtered, washed with water (2 X 50 mL), dried ($MgSO_4$), and concentrated at atmospheric pressure. Distillation of the residue yielded **80** (15.7 g, 80%): bp 72-74°C/10 mm Hg; lit.[111] bp 75-81°C/12 mm Hg.

5-Hydroxy-2-heptanone Ethylene Ketal (81)

Magnesium turnings (1.45 g, 62.8 mmol) were stirred with dry THF (50 mL). A small portion of bromide **80** (~0.4 g) and a single crystal of I_2 were added. After decolorization, the mixture was cooled with a dry-ice acetone bath while the remainder of bromide **80** (6.00 g, 30.8 mmol in total) in THF (20 mL) was added dropwise over 0.5 h. The cooling bath was replaced with an ice bath and stirring continued for 0.5 h, at which time analysis of a hydrolyzed sample by GC showed almost entire consumption of **80**. Propionaldehyde (2.00 g, 34.4 mmol) in dry THF (20 mL) was added dropwise over 10 min. After 0.5 h at ice bath temperature, the reaction was warmed to rt over 0.5 h and poured into 10% NH_4Cl solution (100 mL). The aqueous phase was extracted with ether (3 X 100 mL), the combined extracts were washed with water (100 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (hexane:ethyl acetate, 2:1) to yield **81** (2.59 g, 49%). Bp 70-80°C/0.3 mm Hg; IR 3445(s), 2975(s), 2943(s), 2890(s), 1453(m), 1383(m), 1258(m), 1235(s), 1156(m), 1068(s), 1046(s), 985(m), 953(m), 935(m), 879(m), 856(m) cm^{-1}; ^1H NMR δ 3.95 (4H, OCH_2, m), 3.50 (1H, CHO, m), 2.13 (1H, OH, brs), 1.4-1.9 (6H, 3-CH_2, m), 1.32 (3H, CH_3, s), 0.93 (3H, CH_3, t, J=7.4 Hz); mass spectrum, m/e (relative intensity) 87(100), 83(13), 43(28), CI (isobutane) 175(2,M^++1), 173(4), 157(7), 129(3), 113(100). Anal. Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 61.91; H, 10.58.

5-Acetoxy-2-heptanone Ethylene Ketal (82)

A solution of **81** (1.90 g, 10.9 mmol) in dry pyridine (12 mL) was treated with acetic anhydride (2.0 mL, 21 mmol) for 12 h at ambient temperature. The reaction mixture was partitioned between ice water (100 mL) and ether (100 mL). The aqueous phase was extracted with ether (50 mL), the combined extracts dried ($MgSO_4$), and the solvent removed *in vacuo* to yield **82** (2.18 g, 92%). A sample for analysis was obtained by bulb-to-bulb distillation: bp 60-70°C/0.1 mm Hg; IR 2985(s), 2950(m), 2900(m), 1740(s), 1460(m), 1385(s), 1250(s), 1050(s), 958(m), 892(m) cm^{-1}; ^1H NMR δ 4.81 (1H, CHOAc, m), 3.93 (4H, OCH_2, m), 2.04 (3H, acetate CH_3, s), 1.7-1.5 (6H, 3-CH_2, m), 1.30 (3H, CH_3, s), 0.88 (3H, CH_3, t, J=7.4 Hz); mass spectrum, m/e (relative intensity) 201(12,M^+-CH_3), 141(21), 99(14), 87(100), 55(9), 43(61), CI (isobutane), 217(18,M^++1), 157(100). Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 60.79; H, 9.37.

5-Acetoxy-2-heptanone (83)

A mixture of **82** (2.00 g, 9.26 mmol), acetone (50 mL) and *p*-toluene sulphonic acid (100 mg) was stirred at ambient temperature for 12 h. The volume was reduced on a rotary evaporator at <35°C to ~10 mL. Dilution with ether (150 mL), washing with saturated $NaHCO_3$ solution (2 X 30 mL) and water (2 X 30 mL), drying ($MgSO_4$), and concentration on a rotary evaporator yielded crude **83**. Vacuum distillation, bulb-to-bulb at 60-75°C bath temperature /0.5 mm Hg, gave pure **83** (1.47 g, 92%): IR 2975(m), 2945(m), 2890(m), 1730(s), 1460(m), 1430(m), 1373(s), 1245(s), 1170(m), 1093(m), 1022(m), 963(m) cm^{-1}; ^1H NMR δ 4.79

(1H, OCH, m), 2.45 (2H, $CH_2C=O$, t, J=7.5 Hz), 2.13 (3H, $CH_3C=O$, s), 2.04 (3H, acetate CH_3, s), 1.9-1.7 (4H, 2-CH_2, m), 1.56 (2H, CH_2, pentet, J=7.3 Hz), 0.86 (3H, CH_3, t, J=7.3 Hz); mass spectrum, m/e (relative intensity) 129(35), 115(15), 112(16), 101(38), 97(16), 83(24), 73(14), 72(11), 69(12), 55(13), 43(100), CI (isobutane) 173(8,M^++1), 113(100). Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.57; H, 9.57.

(E,Z)-4-Methyl-7-acetoxy-3-nonene (75)

Propyltriphenylphosphonium bromide (2.00 g, 5.19 mmol) was suspended in dry THF (20 mL). n-Butyl lithium (2.0 mL of 2.1 M solution in hexane, 4.2 mmol) was added dropwise over 5 min with ice bath cooling. After 10 min of stirring the phosphonium salt had dissolved to yield an orange homogeneous solution. The cooling bath was switched to a dry-ice acetone bath and a solution of ketone **83** (0.86 g, 5.8 mmol) in dry THF (5 mL) was added dropwise over 5 min. After 0.5 h, the cooling bath was removed and the reaction warmed to rt over 0.5 h. After a further 1 h the almost colorless reaction mixture was poured into ice-cold saturated NH_4Cl solution (50 mL) with stirring. Ether (120 mL) was added and the aqueous phase discarded. The ether solution was washed with water (50 mL) and saturated NaCl solution (50 mL), dried ($MgSO_4$), and concentrated to yield a crude mixture of starting ketone **83**, two main products, and triphenylphosphine oxide. Purification by chromatography on silica gel (hexane:ethyl acetate, 10:1) yielded a colorless oil which was distilled bulb-to-bulb, at bath temperature 60-70°C /1.0 mm Hg,

to yield (*E,Z*)-**75** (0.34 g, 42%). Capillary GC analysis indicated a 5:4 mixture of geometric isomers, neither of which corresponded to the natural pheromone by mixed injection. Separation of the geometric isomers was not achieved by chromatography; therefore, the spectral data which follow refer to the mixture: IR 2980(s), 2945(m), 2890(m), 1740(s), 1460(m), 1374(m), 1245(m), 1020(m), 950(m) cm^{-1}; ^1H NMR δ 5.11 (1H, vinyl H, m), 4.78 (1H, OCH, quintet, J=6.0 Hz), 2.05, 2.04 (3H, acetate CH_3, 2s), 2.04-1.90 (4H, allylic CH_2, m), 1.66 (3H, allylic CH_3, s), 1.6-1.5 (4H, 2-CH_2, m), 0.95-0.85 (6H, 2-CH_3, overlapping triplets); mass spectrum, m/e (relative intensity) 138(29), 109(66), 95(100), 96(16), 82(71), 81(67), 69(15), 68(13), 67(73), 55(30), 43(62), 41(25), CI (isobutane) 199(3,M^++1), 139(100). Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.89; H, 11.30.

2-Cyclopropyl-2-butanol (85)

A solution of EtMgBr in ether (150 mL, 2.5 M, 0.34 mol) was stirred and cooled with an ice bath while methyl cyclopropyl ketone (27.0 g, 0.32 mol) in dry THF (75 mL) was added dropwise over 45 min. The cooling bath was removed and the mixture stirred for 45 min at ambient temperature. The reaction mixture was partitioned between cold aqueous 10% NH_4Cl solution (300 mL) and ether (100 mL). The aqueous phase was extracted with ether (3 X 100 mL) and the combined extracts washed with water (50 mL). After drying ($MgSO_4$) and concentration to remove solvents, the residue was distilled to yield **85** (29.8 g, 81%): bp 70-72°C /20 mm Hg; lit.[112] bp 130-140°C.

(E,Z)-1-Bromo-4-methyl-3-hexene (86)

A mixture of 48% aqueous HBr (50 mL) and alcohol **85** (29.0 g, 254 mmol) was stirred with ice bath cooling for 45 min. The mixture was diluted to 250 mL with water and the lower bromide layer separated. The aqueous layer was extracted with CH_2Cl_2 (2 X 50 mL) and the combined extracts dried over $CaCl_2$. The CH_2Cl_2 was carefully removed *in vacuo* and the residue distilled to yield **86** (38.6 g, 86%): bp 74-78°C/12 mm Hg; lit.[112] bp 114-116°C/120 mm Hg. Capillary GC analysis indicated a 3:1 (E:Z) ratio of isomers.

(E,Z)-7-Methyl-6-nonen-3-ol [(E,Z)-87)]

Bromide **86** (38.0 g, 215 mmol) dissolved in anhydrous ether (100 mL) was added dropwise to magnesium turnings (12.0 g, 500 mmol) in ether (150 mL) with ice bath cooling over a period of 45 min. The cooling bath was removed and the Grignard solution stirred at ambient temperature for 1.5 h. The solution was again cooled in an ice bath and propionaldehyde (15.0 g, 258 mmol) in anhydrous ether (50 mL) was added dropwise over 0.5 h. The cooling bath was removed and the reaction stirred at ambient temperature for a further 2 h. Decantation from the excess magnesium into cold 10% aqueous NH_4Cl (300 mL) and extraction of the aqueous phase with ether (2 X 100 mL) produced an ether solution which was washed with saturated $NaHCO_3$ solution (50 mL), water (50 mL), and saturated NaCl solution (50 mL). Drying ($MgSO_4$) and solvent removal *in vacuo* gave a yellow syrup

which was chromatographed in two portions on silica gel (hexane:ethyl acetate, 10:1) to yield (E,Z)-**87** (14.8 g, 44%). The major impurity isolated in a yield of ~20% was a 3:1 (*E:Z*) mixture of 7-methyl-6-nonen-2-one. This identification was confirmed by reduction of the ketone with $LiAlH_4$ in ether to yield (*E,Z*)-**87**, identical in all respects to the material isolated above. Separation of the geometric isomers by flash chromatography was not achieved. Spectral and analytical data for **87** refer to the mixture of isomers: bp 55-60°C/0.5 mm Hg; IR 3360(m), 2975(s), 2940(s), 2885(s), 1460(m), 1380(m), 1120(m), 970(m), 850(m) cm^{-1}; ^1H NMR δ 5.14 (1H, vinyl H, m), 3.55 (1H, OCH, m), 2.2-1.9 (4H, allylic CH_2, m), 1.69 and 1.62 (3H, allylic CH_3, 2s), 1.4-1.6 (4H, 2-CH_2, m), 1.1-0.8 (6H, 2-CH_3, overlapping triplets); mass spectrum, m/e (relative intensity) 138(10,M^+-H_2O) 127(33), 109(100), 95(17), 85(31), 83(22), 82(34), 81(43), 72(12), 69(20), 68(18), 67(71), 59(18), 57(27), 55(61), 43(20), 41(27), CI(isobutane) 157(100,M^++1) 155(20), 139(46), 137(21), 127(20), 109(12). Anal. Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.86. Found: 76.54; H, 13.14.

(*E,Z*)-3-Methyl-7-acetoxy-3-nonene [(E,Z)-76]

To a solution of alcohol **87** (8.50 g, 54.5 mmol) in dry pyridine (50 mL) was added acetic anhydride (10 mL, 106 mmol). The mixture was stirred at rt for 14 h, poured into ice water (300 mL), and extracted with ether (3 X 125 mL). The combined extracts were washed with water (50 mL), saturated NaCl solution (50 mL), and dried ($MgSO_4$). Solvent removal and distillation

yielded **88** (10.5 g, 97%): bp 55-58°C/0.5 mm Hg, GC ratio of (E:Z) isomers was 3:1; IR 2975(s), 2940(m), 2885(m), 1735(s), 1455(m), 1375(m), 1250(s), 1020(m), 955(m) cm^{-1}; ^1H NMR δ 5.08 (1H, vinyl H, m), 4.81 (1H, CHOAc, pentet, J=5.5 Hz), 2.04 (3H, $COCH_3$, s), 2.1=1.9 (4H, allylic CH_2, m), 1.67 and 1.57 (1H, E,Z allylic CH_3, 2 singlets), 1.6-1.5 (4H, 2-CH_2, m), 0.97 and 0.87 (6H, 2-CH_3, overlapping triplets); mass spectrum, m/e (relative intensity) 138(12,M^+-HOAc) 127(31), 109(100), 95(15), 85(32), 83(23), 82(35), 81(43), 67(72), 55(60), 43(20), 41(28), CI (isobutane) 199(M^++1,5) 139(100). Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.82; H, 11.40.

5-Bromo-2-methyl-2-pentene (89)

A 3.2 M solution of methyl magnesium bromide in ether (130 mL, 420 mmol) was reacted with ketone **84** (27.5 g, 327 mmol) by a procedure analogous to that described for the preparation of the ethyl derivative **85**. The crude cyclopropyl alcohol **88** was reacted with aqueous HBr as described in the preparation of **86**. Distillation yielded **89** (29.0 g, 54%): bp 65-70°C/12 mm Hg. This compound has recently become commercially available from Aldrich Chemical Co.

7-Methyl-6-octen-3-ol (90)

Magnesium (4.86 g, 200 mmol) was stirred with dry ether (100 mL). After initiation with a small amount of ethylene dibromide, a solution of **89** (15.0 g, 92.0 mmol) in dry ether (300 mL) was added dropwise with ice bath cooling over 1 h. The

Grignard solution was stirred a further 1.5 h at ambient temperature and propionaldehyde (6.00 g, 103 mmol) was added dropwise over 0.5 h. After a further 0.5 h, the reaction mixture was poured into cold saturated NH_4Cl solution (200 mL) and extracted with ether (3 X 100 mL). The ether extracts were washed with water (50 mL) and saturated NaCl solution (50 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by column chromatography (hexane:ethyl acetate, 4:1) to yield pure **90** (9.40 g, 76%): bp 45-46°C/0.5 mm Hg; IR (neat film) 3360(s), 2985(s), 2930(s), 2885(s), 1450(m), 1380(m), 1113(m), 972(m), 937(m), 835(m) cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 5.14 (1H, vinyl H, m), 3.54 (1H, OCH, pentet, J=7.0 Hz), 2.09 (2H, allylic CH_2, m), 1.63 (6H, allylic CH_3, s), 1.6-1.1 (4H, 2-CH_2, m), 0.94 (3H, CH_3, t, J=6.5 Hz); mass spectrum, m/e (relative intensity) 142(3,M^+), 95(33), 82(10), 69(42), 67(32), 59(13), 57(22), 55(18), 53(13), 43(58), 41(100), CI (isobutane) 143(100,M^++1), 125(60). Anal. Calcd for $C_9H_{18}O$: C, 76.00; H, 12.76. Found: C, 75.94; H, 13.03.

2-Methyl-6-(tert-butyldimethylsilyloxy)-2-octene (91)

A solution of alcohol **90** (2.60 g, 18.3 mmol) in dry DMF (30 mL) was treated with imidazole (4.0 g, 59 mmol) and *tert*-butyldimethylsilyl chloride (3.50 g, 23.3 mmol) for 1 h at ambient temperature. The reaction was poured into ice water and extracted with methylene chloride (3 X 50 mL). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to yield **91** (3.22 g, 69%): bp 64-65°C

/0.05 mm Hg; IR 2970(s), 29409s), 2870(s), 1468(m), 1381(m), 1368(m), 1260(s), 1082(m), 1056(s), 1012(m), 843(s), 780(s) cm^{-1}; ^1H NMR δ 5.11 (1H, vinyl H, t, J=5 Hz), 3.58 (1H, OCH, pentet, J=6 Hz), 2.1-1.8 (2H, allylic CH_2, m), 1.68 (3H, allylic CH_3, s), 1.60 (3H, allylic CH_3, s), 1.5-1.4 (4H, 2-CH_2, m), 0.89 (9H, $SiC(CH_3)_3$, s), 0.86 (3H, CH_3, t, J=7.5 Hz), 0.04 (3H, $SiCH_3$, s); mass spectrum, m/e (relative intensity) 199(22), 129(11), 117(62), 95(12), 75(100), 73(24), 69(17), 41(13), CI (isobutane) 257(10,M^++1), 199(11), 125(100). Anal. Calcd for $C_{15}H_{32}OSi$: C, 70.24; H, 12.58. Found: C, 70.69; H, 12.88.

2,3-Epoxy-2-methyl-6-(tert-butyldimethylsilyloxy)-octane (92)

A solution of alkene **91** (3.20 g, 12.5 mmol) in dry CH_2Cl_2 (50 mL) was stirred with ice bath cooling while 85% *meta*-chloroperoxybenzoic acid (3.5 g, ~17 mmol) was added in portions over 0.5 h. The reaction was stirred 0.5 h at ambient temperature, poured into saturated $NaHCO_3$ solution (100 mL), and extracted with CH_2Cl_2 (3 X 50 mL). Drying ($MgSO_4$), removal of solvent *in vacuo*, and purification by chromatography on silica gel (hexane:ethyl acetate, 10:1) yielded **92** (3.29 g, 97%). This material appeared to be homogeneous by GC and TLC but was a mixture of diastereomers (^1H NMR). The relative stereochemistry was not determined: IR 2970(s), 2940(s), 2895(m), 2870(m), 1469(m), 1384(m), 1260(m), 1125(m), 1060(m), 1013(m), 843(s), 781(m) cm^{-1}; ^1H NMR δ 3.60 (1H, CHOSi, m), 2.71 (1H, CHO, m), 1.7-1.4 (6H, 3-CH_2, m), 1.30 (3H, CH_3, s), 1.26 (3H, CH_3, s), 0.88 (9H, $SiC(CH_3)_3$, s), 0.86 (3H, CH_3, m), 0.04 (6H, $Si(CH_3)_2$,

s); mass spectrum, m/e (relative intensity) 215(17), 173(19), 159(66), 81(28), 75(100), 73(47), 69(12), 59(12), 41(12), CI (isobutane) 273(3,M^++1), 215(7), 141(100). Anal. Calcd for $C_{15}H_{32}O_2Si$: C, 66.11; H, 11.84. Found: C, 66.33; H, 11.99.

2-Methyl-3-acetoxy-6-(tert-butyldimethylsilyloxy)-1-octene (94)

Diisopropylamine (2.50 g, 247 mmol) in dry THF (30 mL) was cooled with an ice bath while a 2.1 M solution of n-butyl lithium in hexane (10 mL, 21 mmol) was added dropwise over 5 min. After a further 10 min, epoxide **92** (3.20 g, 11.8 mmol) in THF (15 mL) was added dropwise over 10 min. The reaction mixture was stirred 16 h at ambient temperature, poured into ice water (100 mL), and extracted with ether (3 X 50 mL). The combined extracts were washed with water (50 mL) and saturated NaCl solution (50 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude alcohol **93** was dissolved in pyridine (30 mL). Acetic anhydride (10 mL, ~100 mmol) was then added and the mixture kept at 50-60°C for 4 h. The reaction mixture was poured into ice water (150 mL) and extracted with ether (3 X 75 mL). The combined extracts were washed with water (2 X 50 mL) and saturated NaCl solution (50 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (hexane:ethyl acetate, 20:1) to yield **94** (3.31 g, 90% from **92**); IR 2970(s), 2940(s), 2900(m), 2870(m), 1748(s), 1657(m), 1466(m), 1373(m), 1245(s), 1060(m), 1025(m), 908(m), 845(s), 783(m) cm^{-1}; ^1H NMR δ 5.14 (1H, CHOAc, m), 4.93 (1H, vinyl H, brs), 4.88 (1H, vinyl H, brs), 3.58 (1H, CHOSi, 6-line multiplet), 2.05 (3H,

$COCH_3$, s), 1.71 (3H, allylic CH_3, brs), 1.7-1.3 (6H, 3 X CH_2, m), 0.88 (9H, $SiC(CH_3)_3$, s), 0.85 (3H, CH_3, m), 0.03 (6H, $Si(CH_3)_2$, s); mass spectrum, m/e (relative intensity) 123(44), 117(70), 81(100), 75(54), 73(36), 67(13), 57(10), 43(21), CI (isobutane) 315(12,M^++1), 255(15), 173(10), 123(100). Anal. Calcd for $C_{17}H_{34}O_3Si$: C, 64.92; H, 10.90. Found: C, 65.22; H, 11.11.

(E)-3-Methyl-7-(tert-butyldimethylsilyloxy)-3-nonene (95)

A suspension of CuI (2.75 g, 14.4 mmol) in dry ether (50 mL) was cooled to -20°C. A solution of MeLi in ether (18.0 mL, 28.8 mmol) was added dropwise over 5 min. After 15 min, acetate **94** (2.72 g, 8.66 mmol) in ether (10 mL) was added dropwise over 10 min. The mixture was stirred for 45 min at -20°C to -30°C and poured into sat. NH_4Cl solution (100 mL). The insoluble copper salts were removed by filtration and the aqueous phase further extracted with ether (2 X 50 mL). The combined ether extracts were washed with saturated NaCl solution (2 X 20 mL), dried ($MgSO_4$), and concentrated to a syrup. Purification by silica gel chromatography (hexane:ethyl acetate, 10:1) yielded **95** (2.21 g, 94%). Capillary GC analysis indicated an (E:Z) ratio of (40:1). IR 2975(s), 2945(s), 2890(m), 2870(m), 1470(m), 1385(m), 1368(m), 1263(m), 1090(m), 1062(m), 1014(m), 847(s), 783(m) cm^{-1}; ^1H NMR δ 5.11 (1H, vinyl H, m), 3.58 (1H, CHOSi, pentet, J=6 Hz), 1.97 (4H, allylic CH_2, m), 1.59 (3H, allylic CH_3, brs), 1.45 (4H, 2 X CH_2, m), 0.98 (3H, CH_3, t, J=7.5 Hz), 0.89 (9H, $SiC(CH_3)_3$, s), 0.86 (3H, CH_3, t, J=7.5 Hz), 0.04 (6H, $Si(CH_3)_2$, s); mass spectrum, m/e (relative intensity) 213(26), 138(18), 129(11),

117(82), 109(19), 83(13), 75(100), 73(24), 55(11), CI (isobutane) 271(12,M^++1), 213(18), 139(100). Anal. Calcd for $C_{16}H_{34}OSi$: C, 71.04; H, 12.67. Found: C, 70.98; H, 12.68.

(E)-7-Methyl-6-nonen-3-ol (E-87)

A mixture of **95** (2.00 g, 7.41 mmol), MeOH (50 mL) and *para*-toluenesulphonic acid (100 mg) was stirred at rt for 1 h. The solvent was removed on a rotary evaporator at <35°C. The residue was partitioned between ether (100 mL) and saturated $NaHCO_3$ solution (30 mL). The aqueous phase was extracted with ether (50 mL) and the combined extracts dried ($MgSO_4$) and concentrated to a syrup. Bulb-to-bulb distillation yielded (E)-**87** (1.12 g, 97%): bp 60-70°C bath temperature /0.5 mm Hg. Capillary GC analysis indicated an (E:Z) ratio of (40:1). IR and mass spectral data were virtually identical with the (E,Z) mixture **87**. ^{1}H NMR δ 5.14 (1H, vinyl H, m), 3.53 (1H, CHO, m), 2.15-2.00 (2H, allylic CH_2, m), 1.98 (2H, allylic CH_2, q, J=7.5 Hz), 1.62 (3H, allylic CH_3, brs), 1.6-1.4 (4H, 2 X CH_2, m), 0.98 (3H, CH_3, t, J=7.5 Hz), 0.94 (3H, CH_3, t, J=7.5 Hz).

(E)-3-Methyl 7 acetoxy 3 nonene [(E)-76]

Conversion of the alcohol (*E*)-**87** to the acetate (*E*-**76** using the method described for the (E,Z) mixture **87** yielded E-**76** in 96% yield. Capillary GC indicated a (40:1) (E:Z) mixture. IR and mass spectral data were identical with the (E,Z)-**75** mixture. ^{1}H NMR δ 5.08 (1H, vinyl H, m), 4.81 (1H, CHO, pentet, J=7 Hz), 2.04 (3H, $COCH_3$, s), 2.0-1.9 (4H, allylic CH_2, m), 1.6-1.5 (4H, 2 X

CH_2, m), 0.97 (3H, CH_3, t, J=7.5 Hz), 0.88 (3H, CH_3, t, J=7.5 Hz).

(*S*)-7-Methyl-6-octene-3-ol [(*S*)-90]

A Grignard solution was prepared from 1-chloro-3-methyl-2-butene (2.08 g, 20 mmol) and magnesium (0.72 g, 30 mmol) as described previously[118]. Addition of CuI (0.38 g, 20 mmol) and (*S*)-(+)-ethyloxirane (0.68 g, 12 mmol) followed by aqueous extractive processing yielded crude (*S*)-**90**. Purification by chromatography on silica gel gave pure (*S*)-**90** (1.32 g, 77%). Spectral data were identical with (*R,S*)-**90**. Preparation of the (+)-MTPA esters of (*S*)-**90** and (*R,S*)-**90** by the standard method[80] and analysis by ^1H NMR spectroscopy (400 MHz) indicated >99% ee (δ for C_1 protons = 0.11 ppm).

(*S*)-(E)-3-Methyl-7-acetoxy-3-nonene [(*S*)-76]

Conversion of (*S*)-**90** to (*S*)-**76** by the sequence of reactions described for the racemic material yielded (*S*)-**76** in an overall yield of 33% for seven steps. Preparation of the (+)-MTPA esters[80] of (*S*)-**87** and (*R,S*)-**87** and analysis by 400 MHz NMR spectroscopy indicated an ee of >99%, proving that no racemization had occurred.

(*R*)-(E)-3-Methyl-7-acetoxy-3-nonene [(*R*)-76]

Alcohol (*S*)-**87** (0.312 g, 2.00 mmol) was dissolved in dry CH_2Cl_2 (10 mL) and cooled in an ice bath. Triethylamine (0.7 mL, 5 mmol) and methanesulphonyl chloride (0.3 mL, 4 mmol) were added

and the reaction mixture was stirred for 0.5 h. Ice water (5 mL) was added and the organic phase washed with water (3 X 5 mL), dried ($MgSO_4$) and concentrated to a light yellow syrup. This crude mesylate was dissolved in dry DMF (10 mL), KOAc (1.0 g, 10 mmol) was added and the reaction stirred at 100°C for 2 h. After cooling, dilution with water (60 mL), extraction with hexane (3 X 20 mL), washing with saturated NaCl solution (10 mL), drying ($MgSO_4$), and removal of solvent, the crude product was shown by capillary GC to be a (10:1) mixture of two compounds. Silica gel chromatography (hexane:ethylacetate, 20:1) resulted in partial separation of the two components. A 97% pure fraction of (*R*)-**76** (178 mg, 44%), having an (E:Z) ratio of (35:1), was isolated. In addition, a less pure fraction (126 mg) consisting of a mixture of the two components ~75% (*R*)-**76**] was obtained. Analysis of this mixture by GC/MS and ^1H NMR spectroscopy (δ 8.13) indicated the minor component to be the formate ester of alcohol **87**. A small sample of (*R*)-**76** was reduced with lithium aluminum hydride in ether to yield (*R*)-**87**, which was analyzed by ^1H NMR spectroscopy of the (+)-MTPA ester[80] to be >97% ee.

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