

The Evaluation of 4-Methylcamphor as an Intermediate
in Triterpenoid Synthesis

By

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ABSTRACT

A new synthetic route to (-)-4-methylcamphor 43 is described which involved initial conversion of (+)-camphor 1 to (-)-2-methylenebornane 41. Acid-catalyzed rearrangement of 41 provided (+)-4-methylisobornyl acetate 40 which was reduced to (+)-4-methylisoborneol 42. Finally, oxidation of 42 produced (-)-4-methylcamphor 43. The optical purity of compounds 40 and 43 was determined by a chiral lanthanide shift reagent, [Eu(hfc)₃] 45 while the optical purity of 42 was determined by the Anderson-Shapiro reagent 48.

Based on a mechanistic rationale, a different approach to the synthesis of optically pure 40 was attempted which involved the synthesis of a C(5)-substituted 2-methylenebornane derivative 58 from (+)-endo-3-bromocamphor 5a.

The potential of (-)-4-methylcamphor 43 as a useful intermediate in the synthesis of triterpenoids belonging to the lanostane 49 structural sub-group was investigated. Through a series of bromination reactions followed by regioselective C-3 debromination, 43 was converted to 9,10-dibromo-4-(bromomethyl)camphor 75 which was cleaved to give 76, a possible precursor of a potentially useful intermediate 65 in triterpenoid synthesis.

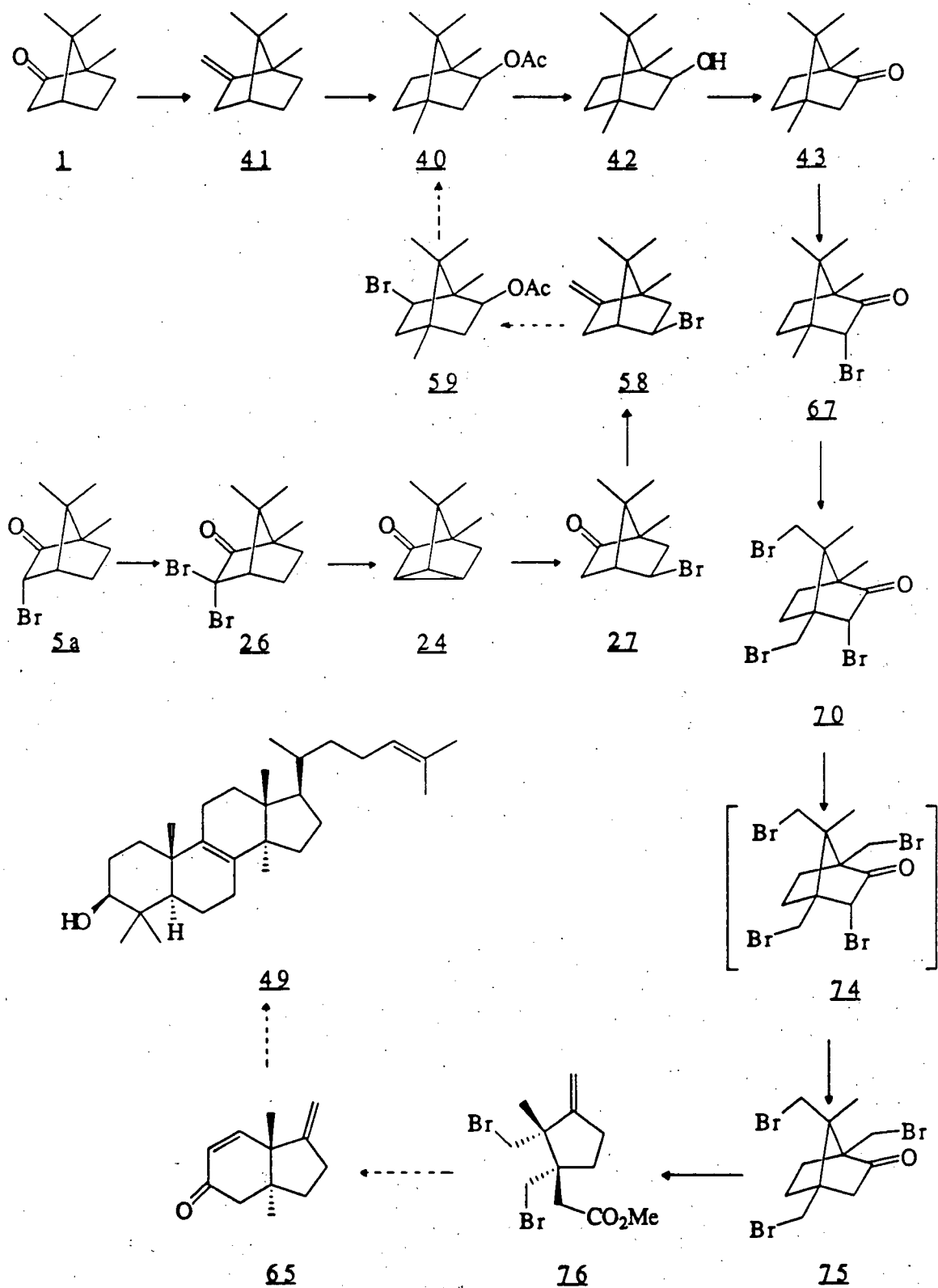


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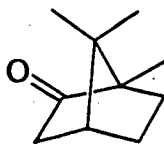
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LIST OF ABBREVIATIONS AND TERMINOLOGY

(a) Terminology

Since many of the compounds referred to in this thesis are optically active, in order to differentiate between enantiomers the term "ent" is used. "Ent" refers to the enantiomer of the compound given, eg. (+)-camphor **1** has the structure:

**1**

(-)-camphor is thus denoted as ent-1.

(b) Abbreviations

The following abbreviations are used in this thesis:

Ac	Acetyl
br	broad (^1H NMR)
But	t-Butyl
c.	concentration in g/100 mL of solvent
calcd.	calculated
d	doublet (^1H NMR)
DMAP	4-(Dimethylamino)pyridine
Et	Ethyl
[Eu(hfc) ₃]	Tris[3-(heptafluoropropylhydroxymethylene)- d-camphorato]europium(III)
GLC	Gas Liquid Chromatography
HMPA	Hexamethylphosphoramide

IR	Infrared
J	coupling constant (Hz)
LAH	Lithium Aluminum Hydride
LDA	Lithium Diisopropylamide
LSR	Lanthanide Shift Reagent
m	multiplet (^1H NMR)
Me	Methyl
m/e	mass to charge ratio
mp	melting point
NMR	Nuclear Magnetic Resonance
PCC	Pyridinium Chlorochromate
ppm	parts per million
Pri	isopropyl
q	quartet (^1H NMR)
s	singlet (^1H NMR)
t	triplet (^1H NMR)
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Tetramethylsilane
WM	Wagner-Meerwein Rearrangement
$[\alpha]_D$	Specific Rotation at 589 nm
2,3 exo Me	2,3- <u>exo</u> -Methyl shift
2,6 H	2,6-Hydride shift
δ	chemical shift in ppm from the TMS signal
ν	Wavenumbers (cm^{-1})

ACKNOWLEDGEMENTS

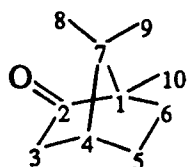
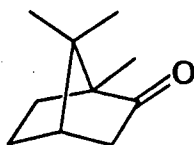
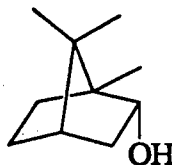
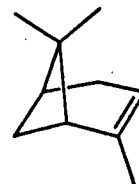
I would like to take this opportunity to thank my research supervisor Professor Thomas Money for his guidance and advice throughout the course of my graduate study. Special thanks go to my colleagues Andrew Clase, Garney Gracey and Dr. David Kuo whose help and advice during the course of this challenging project is very much appreciated.

I am grateful to Professor J. Trotter and Dr. S. Rettig for carrying out the X-ray crystallographic analysis of endo-3,9-dibromo-4-(bromomethyl)camphor. I would also like to express my appreciation to Andrew Clase for proofreading this thesis.

Finally, I am thankful to God for all that He has done for me and for my parents for their ever-present love and support throughout my life. O Lord, I am an unworthy servant possessing no merit, I have merely done what was my duty to do. May this thesis be an acceptable and pleasing sacrifice of thanksgiving in Your sight.

INTRODUCTION

Camphor, although not widespread in Nature, has been known for many centuries because of its ease of isolation.[1a] Most of the work leading to the elucidation of its structure was carried out in the nineteenth century.[1b] While the dextrorotary form of camphor occurs primarily in the wood of the camphor laurel which is indigenous to Formosa, Central China, and Japan and is cultivated elsewhere, the laevorotary form (which is a constituent of the oil of sagebrush) and racemic form are much less common in Nature.[1a] Extraction of (+)-camphor **1** is achieved by steam distillation of the chopped trunk and branches of the camphor laurel.[1a] (-)-Camphor ent-1 can be prepared cheaply in the laboratory by oxidation of commercially available (-)-borneol **2**. [2] Nowadays, camphor is used in medicine and as a plasticizer in the manufacture of explosive, celluloid and photographic film, and most of the world's requirements are supplied by the synthetic products derived from α -pinene **3**. [1b]

**1**ent-1**2****3**

Interest in the chemistry of camphor has been largely motivated by the fact that it undergoes a variety of fascinating

transformations.[3a] Much of this chemistry has had a significant impact on theoretical and mechanistic organic chemistry and various derivatives of camphor have been employed as key intermediates in organic synthesis.[3a] In fact, the use of camphor as chiral starting material in the enantiospecific synthesis of natural products is largely due to the availability of camphor in both optically pure enantiomeric forms and the availability of methods for the direct or indirect introduction of functionality at C(3), C(5), C(6), C(8), C(9), and C(10).[3a] Moreover, useful synthetic intermediates are obtained by cleavage of the C(1)-C(2), C(2)-C(3) and C(1)-C(7) bonds in camphor and its derivatives.[3a] The functionalization of camphor and its use in natural product synthesis has been extensively reviewed by Money[3a] so only a brief outline of its reactivity and use in synthesis which are relevant to the present work will be given.

A. Some Aspects of Camphor Chemistry:

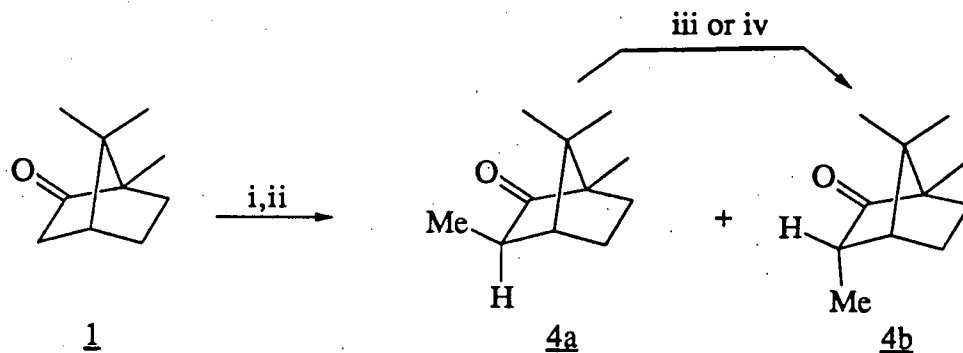
1. C(3)-Functionalization

Position 3 in camphor displays a degree of reactivity that would normally be expected for active methylene groups, and a large number of C(3)-substituted camphor derivatives have been reported.[3a]

1a. C(3) Methylation

Recent investigations have shown that sequential treatment of (+)-camphor 1 in THF with lithium diisopropylamide (1 mole

equivalent) and with methyl iodide (excess) at 0°C provides a product (~75% yield) which was shown by ^1H NMR (400 MHz) and capillary GLC to be a mixture (~4:1) of exo-3-methylcamphor 4a and endo-3-methylcamphor 4b[4] (Scheme 1). Subsequent treatment of this mixture with NaOMe in MeOH or with HCl and HOAc provides a mixture (~9:1) in which the major component is endo-3-methylcamphor 4b. Similarly, protonation of 3-methylcamphor enolate results in the formation of endo-3-methylcamphor 4b and a small amount of the exo-3-methyl epimer 4a ([endo]:[exo] = 9:1).[5]



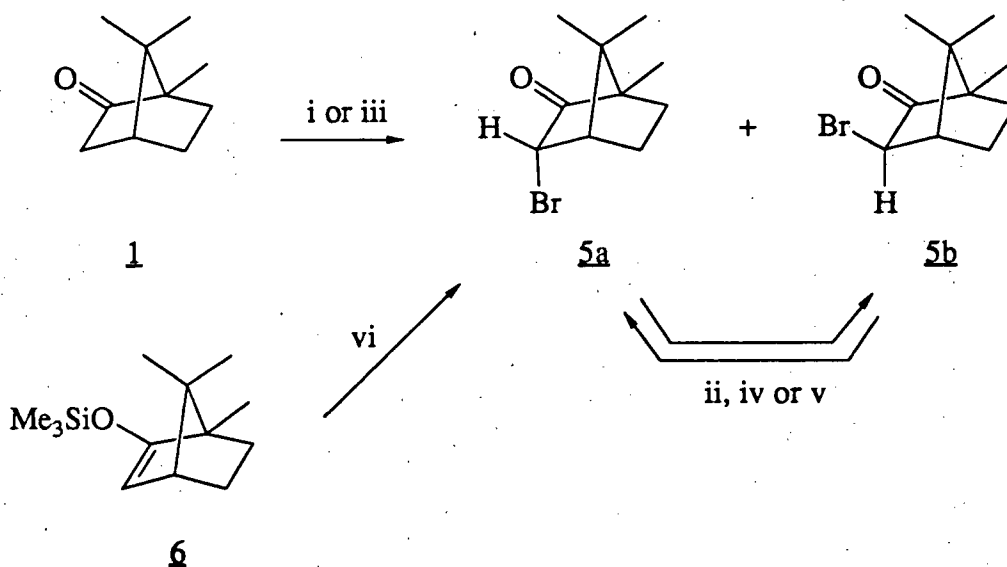
Reagents: 1, LiNPr^1_2 , THF-HMPA (20:1), at 0°C; ii, MeI, at 0°C; iii, NaOMe, MeOH, heat; iv, HCl, HOAc, heat.

Scheme 1

1b. C(3) Monobromination

Bromination of (+)-camphor 1 with bromine in acetic acid to yield (+)-endo-3-bromocamphor 5a was first accomplished by Kipping and Pope in 1893.[6] Since then, it has been established that treatment of (+)-camphor 1 with bromine in acetic acid[7], ethanol[8-10], or chloroform[8-10] provides (+)-endo-3-bromocamphor 5a as the major product (~92%). This is also the most

stable derivative since treatment with a base (NaOMe or KOBut^t) does not change the relative proportions of C(3)-epimers ([*endo*]:[*exo*] = 92:8). Bromination of (+)-camphor **1** with pyridinium bromide perbromide or of camphor enol trimethylsilyl ether **6** with bromine in dioxane-pyridine leads to approximately equal amounts of *exo*-3-bromocamphor **5b** and *endo*-3-bromocamphor **5a**. [11] Subsequent equilibration of this mixture with base (NaOMe in MeOH) provides the thermodynamic mixture ([*endo*]:[*exo*] = 92:8).



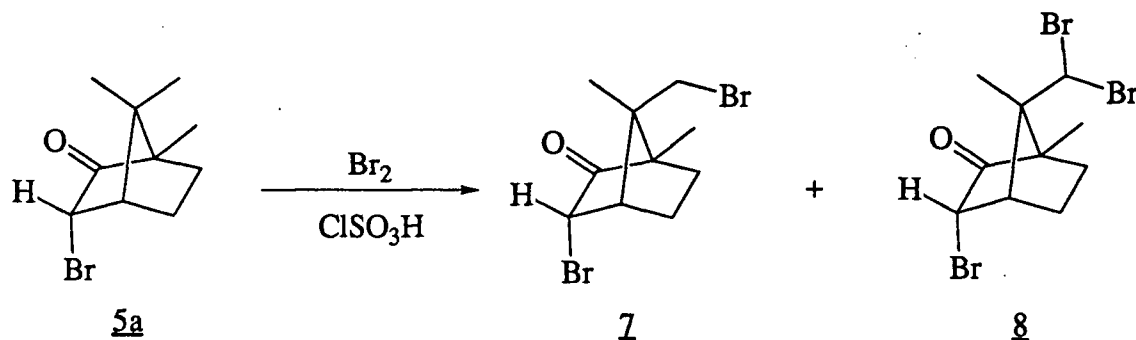
Reagents: **1**, Br₂, HOAc; **ii**, NaOMe, MeOH; **iii**, C₅H₅NHBr₃, HOAc; **iv**, KOBut^t, HOBut^t; **v**, HCl, HOAc, heat; **vi**, Br₂, dioxane-pyridine.

Scheme 2

2. C(9) and C(10)-Brominations

Treatment of (+)-*endo*-3-bromocamphor **5a** with bromine and chlorosulphonic acid provides (+)-*endo*-3,9-dibromocamphor **7**

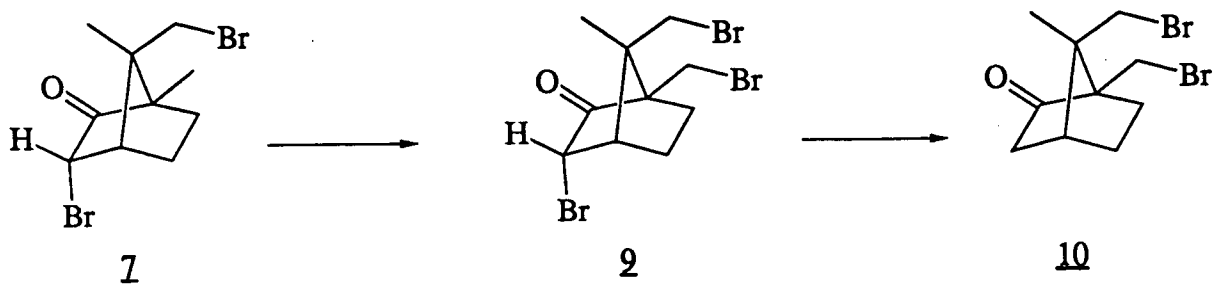
and a small amount of (+)-endo-3,9,9-tribromocamphor 8 [12,13] (Scheme 3). The mechanism of C(9)-bromination of (+)-endo-3-bromocamphor 5a is shown in scheme 4.



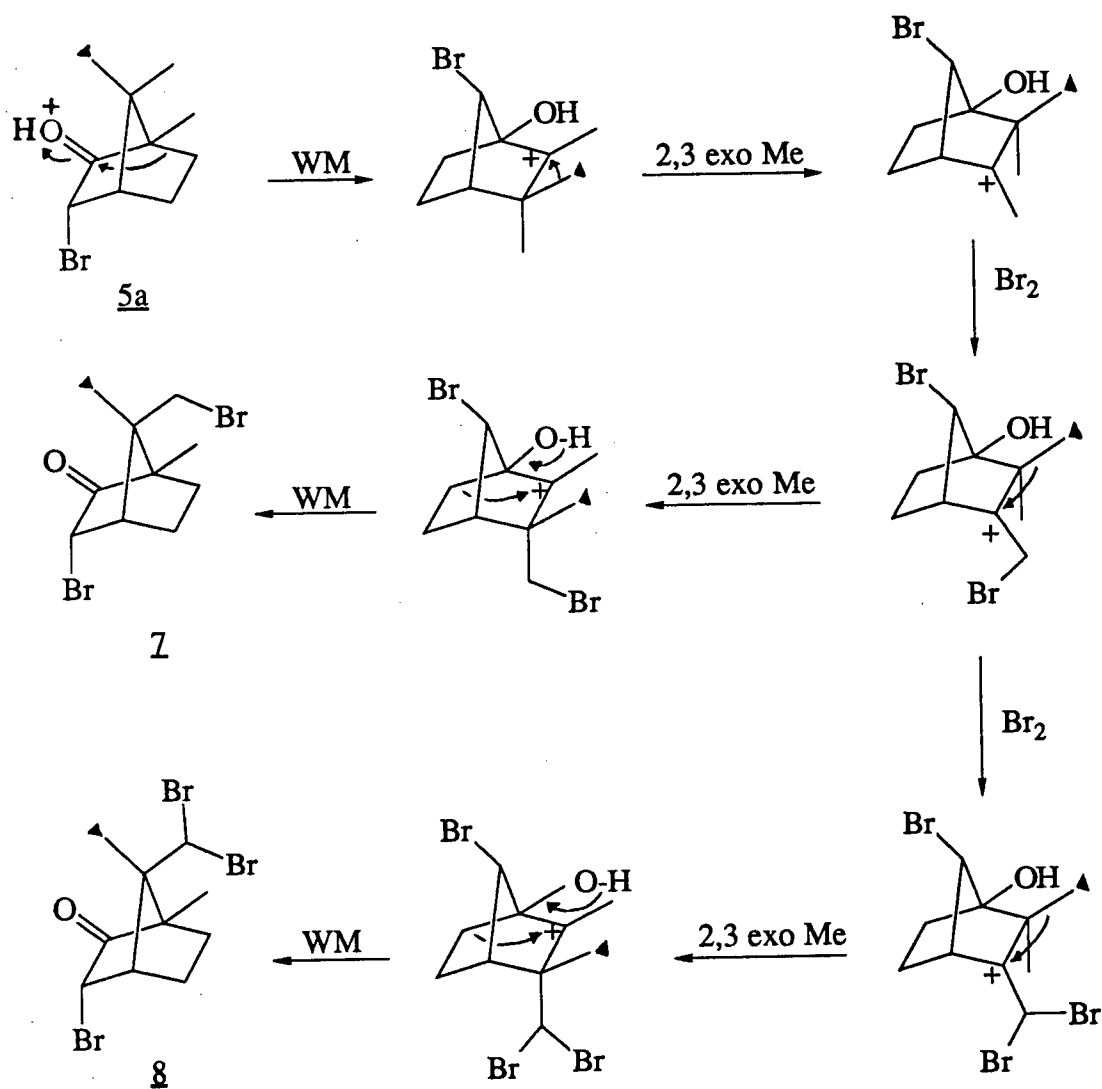
Scheme 3

Confirmation of the mechanism of bromination at C-9 that is shown in scheme 4 has been obtained by using endo-3-bromo-8-deuteriocamphor (5a, $\Delta = 2\text{H}$) in the bromination reaction. [14] The product, (+)-endo-3,9-dibromocamphor 7 has deuterium located only at C-8. Note that, according to the mechanistic proposals shown in scheme 4, the presence of an endo-bromo-substituent at C-3 in camphor ensures that C(9)-bromination provides 3,9-disubstituted derivatives with retention of configuration.

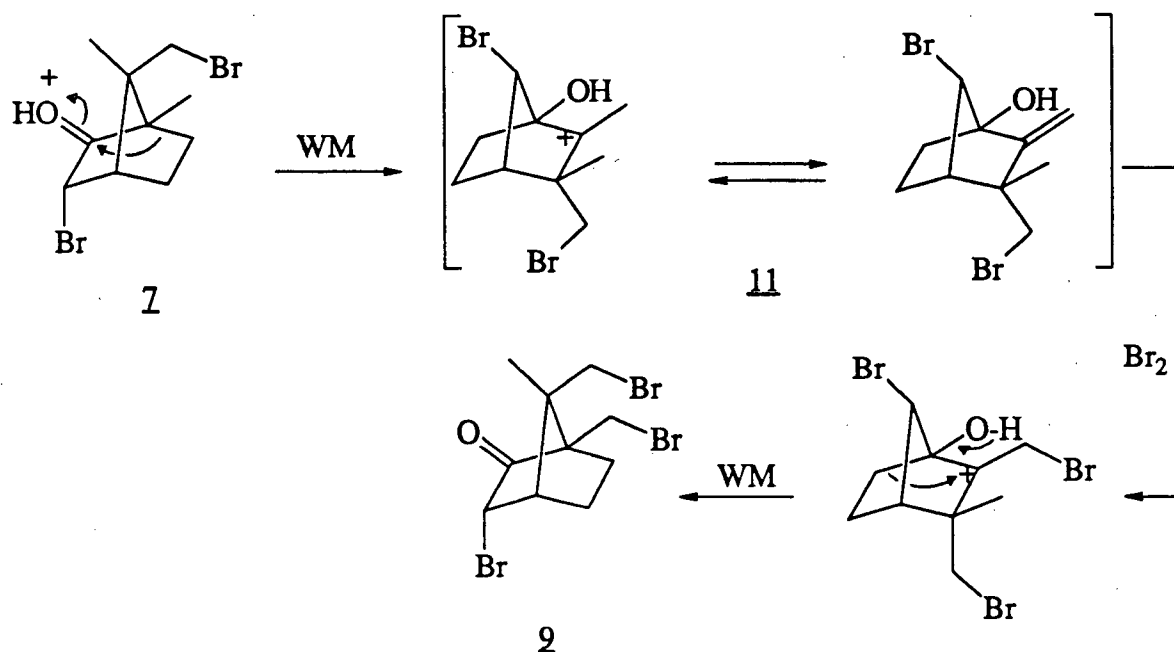
Prolonged treatment of (+)-endo-3,9-dibromocamphor 7 with bromine and chlorosulphonic acid (5 days) gives (+)-endo-3,9,10-tribromocamphor 9. [15] Selective debromination of 9 with zinc and acetic acid provides (+)-9,10-dibromocamphor 10. The mechanism [15] of the bromination of (+)-endo-3,9-dibromocamphor 7 has been postulated to involve a Wagner-Meerwein rearrangement to provide the camphene intermediate 11 (Scheme 5). Reaction



of **11** with bromine and subsequent rearrangement back to the camphor framework provides the tribromo camphor **9**.



Scheme 4



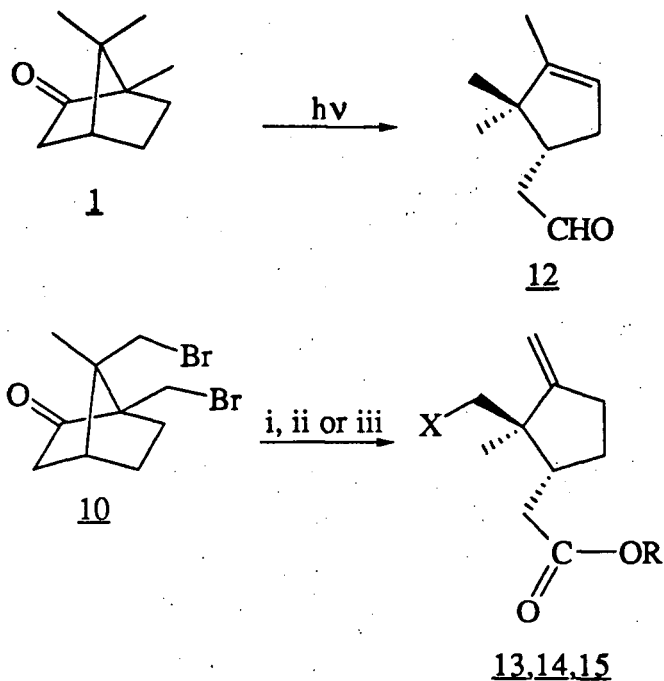
Scheme 5

3. Cleavage of C(1)-C(2) Bond in Camphor and Camphor Derivatives

Cleavage of the C(1)-C(2) bond in camphor and in various camphor derivatives results in the formation of a functionalized 5-membered ring. (+)-Camphor 1 itself undergoes cleavage upon photo-irradiation[16-20] to give the aldehyde 12 while (+)-9,10-dibromocamphor 10 can be cleaved to provide the cyclopentanoid ring systems 13, 14, and 15. [21,22]

The C(1)-C(2) ring cleavage reaction in camphor and its derivatives has been utilized in routes from camphor to the C/D ring system of steroids with control of stereochemistry at the C(13), C(17) and C(20) carbon centres of the steroidal skeleton. The utilization of the ring cleavage products of camphor derivatives as chiral synthons in terpenoid and steroid synthesis has been intensively investigated in our

laboratory.[22]



Reagents:

i, NaOMe, MeOH;

ii, KOH, THF, H₂O;

iii, KOH, DMSO, H₂O.

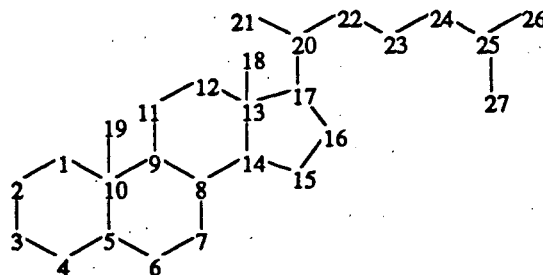
Products:

13 X=Br, R=Me

14 X=Br, R=H

15 X=OH, R=H

Scheme 6

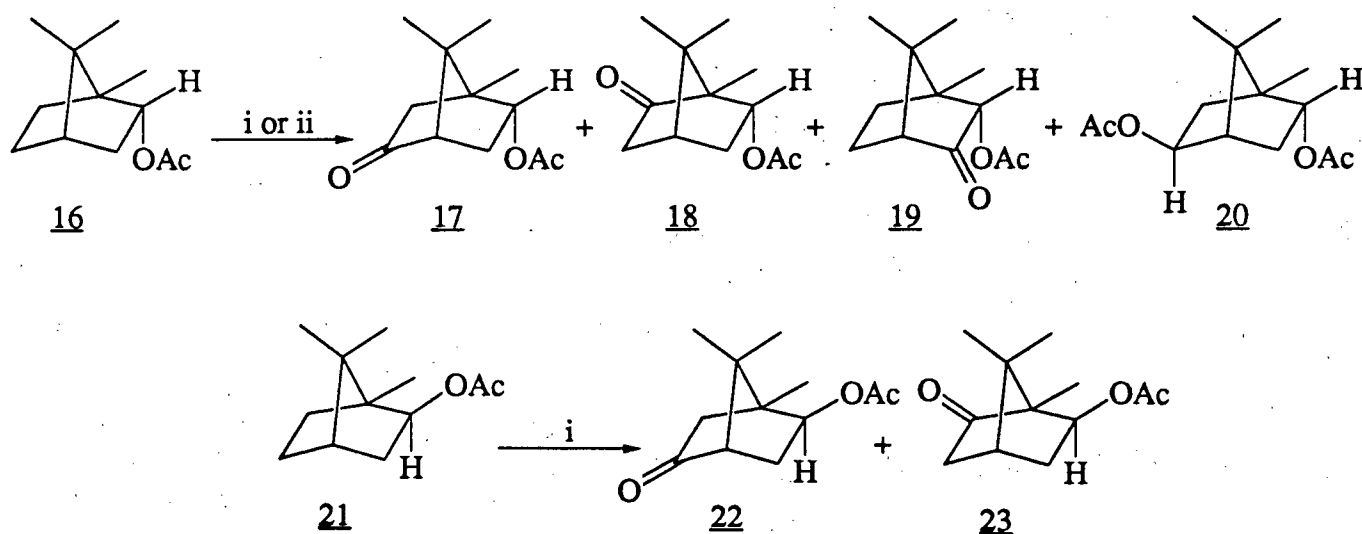


Steroidal Skeleton

4. C(5)-Functionalization

Two conventional approaches are available for the synthesis of C(5)-substituted camphor.[3a] In the first approach (Scheme

7), (-)-bornyl acetate 16 is oxidized with CrO_3 and HOAc or with CrO_3 , HOAc , and Ac_2O to provide a mixture of 5-oxobornyl acetate 17 (24-40% yield), 6-oxobornyl acetate 18 (5-15% yield), and other minor products (19 and 20).[3b] Remote oxidation of (+)-isobornyl acetate 21 with CrO_3 , HOAc , and Ac_2O provides a mixture of (4:1) 5-oxoisobornyl acetate 22 and its 6-oxo-isomer 23 in 55% yield.[3c-e] In fact, this one-step synthesis of (-)-5-oxoisobornyl acetate 22 from (+)-isobornyl acetate 21 is the most efficient way to prepare this compound and has been used in various synthetic studies.[3d-f]

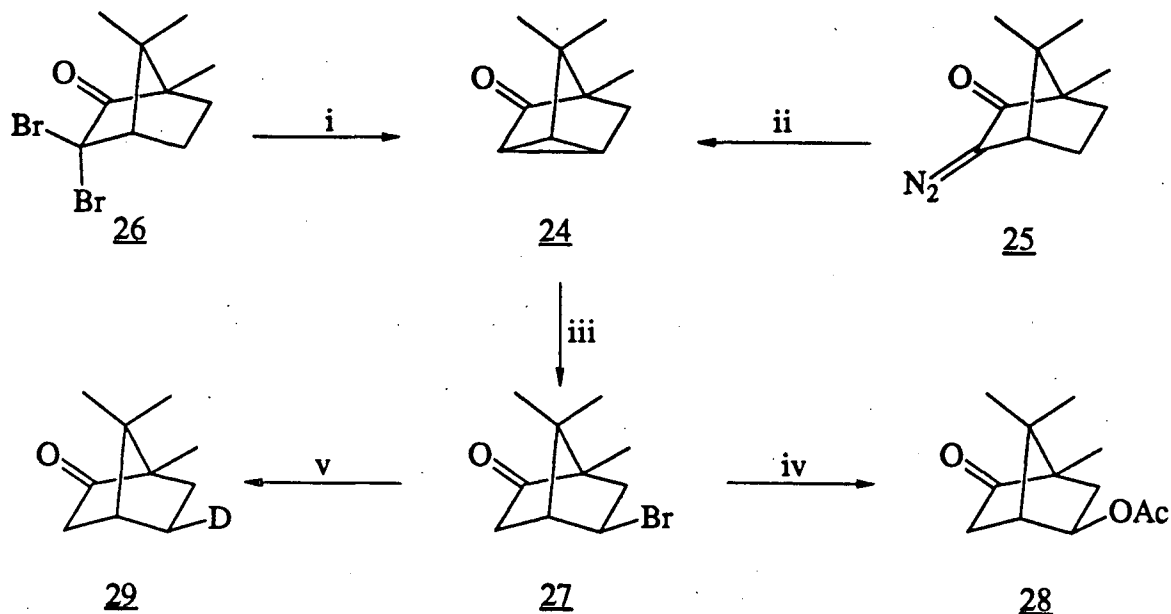


Reagents: i, CrO_3 , HOAc , Ac_2O ; ii, CrO_3 , HOAc

Scheme 7

An alternative route to C(5)-substituted camphors such as compounds 27, 28 and 29 involves ring-cleavage of pericyclocamphanone 24[23-30] which can be prepared from 3-diazocamphor 25 or 3,3-dibromocamphor 26. As shown in scheme 8, the

ring-cleavage product exo-5-bromocamphor 27 can be transformed to two other C(5) derivatives of camphor (28 and 29).



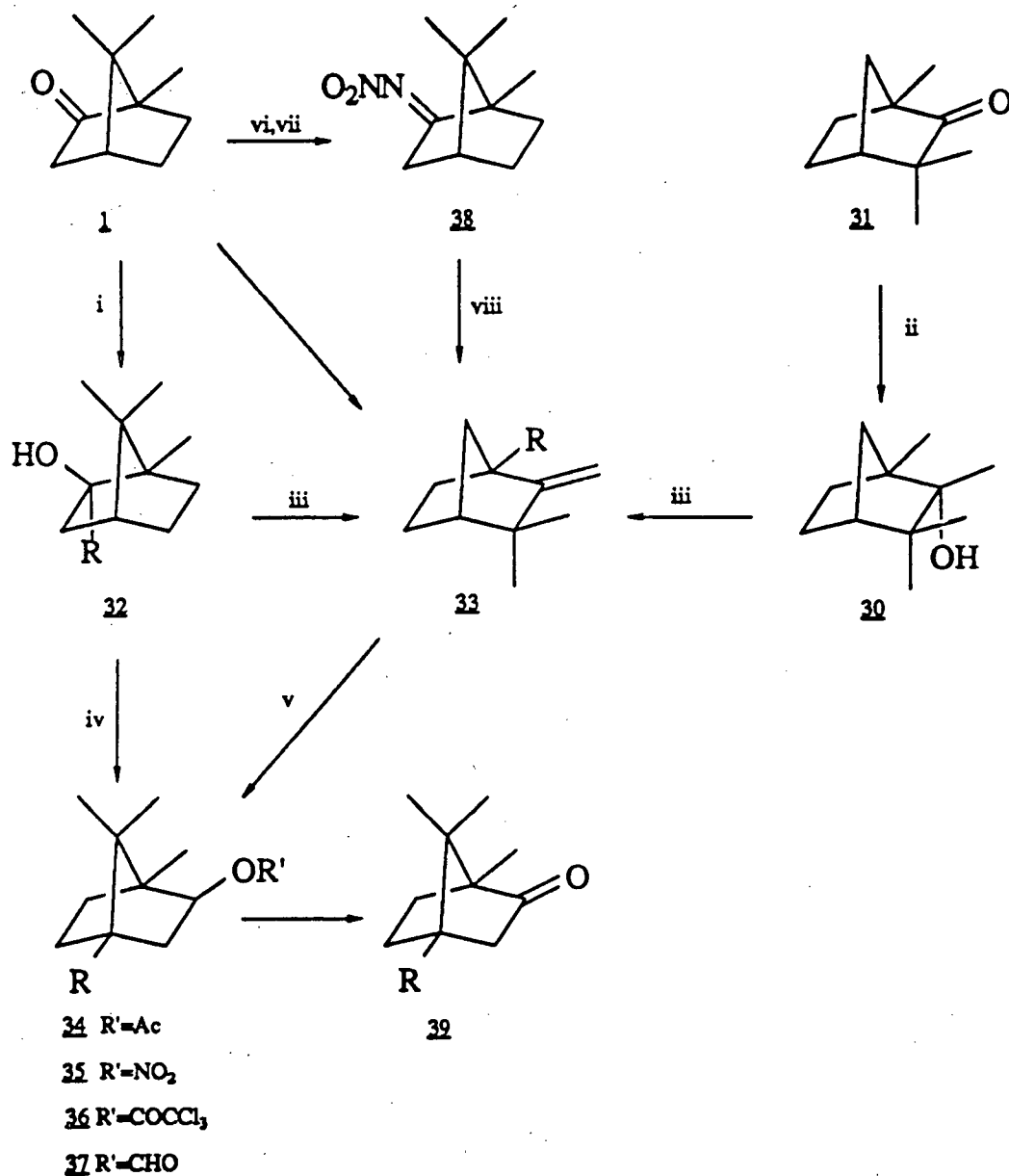
Reagents: i, Et_2Zn , benzene; ii, Ag^+ , THF or Cu, heat; iii, HBr; iv, AgOAc , HOAc ; v, aluminum amalgam, D_2O .

Scheme 8

5. C(4)-Functionalization

C(4)-substituted camphor derivatives 39 (Scheme 9) can be prepared in modest yield using (+)-camphor 1 or fenchone 31 as starting material.[8,10,23,32-34,47] In the most conventional procedure (Scheme 9), C(4)-substituted camphor 39 is prepared by first converting (+)-camphor 1 to a C(2)-isoborneol derivative 32 or a C(1)-camphene derivative 33 which rearranges to the C(4)-bornane derivatives (34-37). In one variation of this approach, camphor nitrimine 38 is converted to camphene-1-carboxylic acid (33; $\text{R}=\text{COOH}$)[33a] and

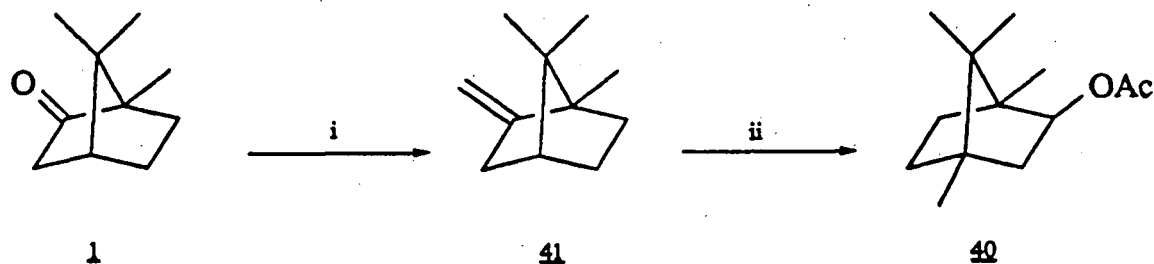
eventually to 4-carboxycamphor 39 (R=COOH). As shown in scheme 9, 1-methylcamphene (33; R=Me) can be prepared from fenchone 31.



Reagents: i, RM; ii, MeMgI; iii, KHSO₄, heat; iv, HOAc, H₂SO₄ or 65% HNO₃; v, CCl₃COOH or HCOOH or HOAc, H₂SO₄; vi, NH₂OH; vii, NaNO₂, H₂SO₄; viii, KCN, EtOH.

Scheme 9

The mechanistic rationalization of these earlier investigations prompted research in our laboratory which led to the development of a more convenient route (Scheme 10) to (+)-4-methylisobornyl acetate 40 which involves direct acid-catalyzed rearrangement of (-)-2-methylenebornane 41. This compound 41 and its enantiomer are readily prepared[12,14] in ~77% yield by Wittig reaction on (+)- and (-)-camphor, respectively. Preliminary investigations[31] in our laboratory showed that when (-)-2-methylenebornane 41 was treated with HOAc / H₂SO₄ (20:1) for 15 minutes at room temperature, (+)-4-methylisobornyl acetate 40 {[α]_D²⁵ +35.79 (c.2.28, EtOH)} was produced in ~75% yield. Subsequent conversion of 40 to (+)-4-methylisoborneol 42 {[α]_D²⁵ +20.40 (c.9.0, EtOH)} and (-)-4-methylcamphor 43 {[α]_D²⁵ -16.70 (c.1.5, EtOH)} was then accomplished in ~62% overall yield. Although the specific rotations of (+)-4-methylisobornyl acetate 40, (+)-4-methylisoborneol 42 and (-)-4-methylcamphor 43 prepared in this way were comparable to those recorded in the literature (cf. Table 1, p. 19), the optical purity of our compounds or those described in the literature had not been established.



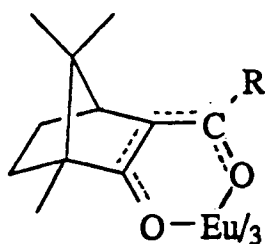
Reagents: 1, CH₃PPh₃Br, n-BuLi, THF; 11, HOAc, H₂SO₄ (20:1), 15 min., 25°C.

Scheme 10

B. Determination of Optical Purity by NMR Methods:

1. Use of Chiral Lanthanide Shift Reagents

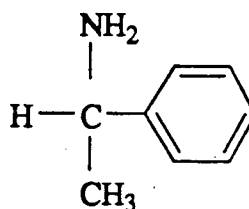
The first chiral lanthanide shift reagent (LSR), tris[3-(*t*-butylhydroxymethylene)-*d*-camphoratoleuropium(III)] **44** was reported by Whitesides and Lewis[35] who showed that it was quite effective in separating the signals of the enantiomers of α -phenylethylamine **47** and of several other amines. However, this LSR was not found useful for functional groups other than amines.



44 R=*t*-Butyl

45 R=CF₂CF₂CF₃

46 R=CF₃



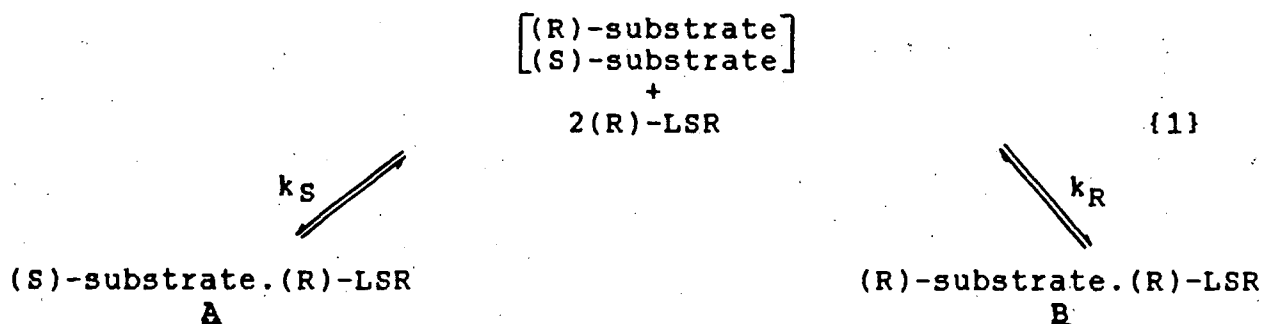
47

Soon after, Fraser[36] and Goering[37] independently introduced other chiral shift reagents, tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphoratoleuropium(III)], [Eu(hfc)₃] **45** and tris-[3-(trifluoromethylhydroxymethylene)-*d*-camphoratoleuropium(III)], [Eu(facam)₃] **46**. Both were shown to be effective for many different functional groups. Although **45** and **46** have been by far the most widely used, other chiral LSRs have also been reported.[36,38-40] An overview of the types of structures for which chiral LSRs have been successfully utilized can be found in a detailed review by Sullivan.[41] It is apparent

that virtually any chiral molecule containing a functional group capable of binding to an achiral LSR is a possible substrate for enantiomeric purity determination with a chiral LSR.

Lanthanide β -diketone shift reagents such as 44-46 function by acting as Lewis acids, forming a complex with the substrate under analysis, which acts as a nucleophile. Induced shifts are attributed to a pseudo-contact, or dipolar, interaction between the shift reagent and the nucleophile. It is believed that the magnetic field produced by summation of the magnetic moments of the six unpaired electrons of the europium ion combines with that resulting from the orbital motion of the europium electrons and generates an anisotropic magnetic field in the vicinity of the shift reagent.[38] As a result, the protons of the nucleophile coordinated to the europium atom reflect this field in their chemical shifts.

Under normal conditions, the equilibrium between the substrate and the LSR is rapid on the NMR time scale:



Thus, only a single time-averaged spectrum results from the average of complexed and uncomplexed substrate molecules.

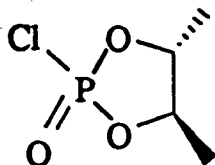
Rapidly equilibrating complexes are formed by an enantiomerically pure chiral LSR binding to each of two enantiomers. Note that the chiral LSR (arbitrary assumed in equation {1}) to have R configuration) is actually a mixture of four diastereomers in rapid equilibrium by virtue of the chirality of the octahedral europium. These diastereomeric complexes can have different averaged chemical shifts due to

- (1) the equilibrium constants (k_R , k_S) may be different for diastereomeric complexes, thus, causing larger shifts for the complex having the larger binding constant; and
- (2) the two diastereomeric complexes (A,B) formed may differ in their geometry, thus, causing a difference in the induced shift for corresponding signals in the two complexes.[38]

The use of chiral LSR offers a direct approach for determination of enantiomeric purity by NMR. Since resonances of enantiomers undergo different chemical shifts in a chiral environment, the enantiomeric relative abundances can be determined by simply choosing one or more signals that show sufficient response to the shift reagent and are adequately separated from other signals. A good discussion of practical aspects of use of these LSRs has been given by McCreary et al. [38] In general, the fastest and easiest technique for obtaining induced shifts is to add a few milligrams of shift reagent directly to the nucleophile dissolved in solvent. Then one or more signals are chosen to monitor enantiomeric shift differences or differential shifts, $\Delta\Delta\delta$. Additional amounts

of shift reagent can be added until sufficient resolution is attained.

2. Use of Anderson-Shapiro Reagent 48



48

This chiral derivatizing agent was introduced by Anderson and Shapiro in 1984[42] and is characterized by three advantages:

(1) easy to use: 48 is capable of the direct in situ determination of enantiomeric purity of both primary and secondary alcohols;

(2) analysis of enantiomeric purity is performed by ^{31}P NMR, a nucleus readily available in NMR systems having broad-band capabilities; and

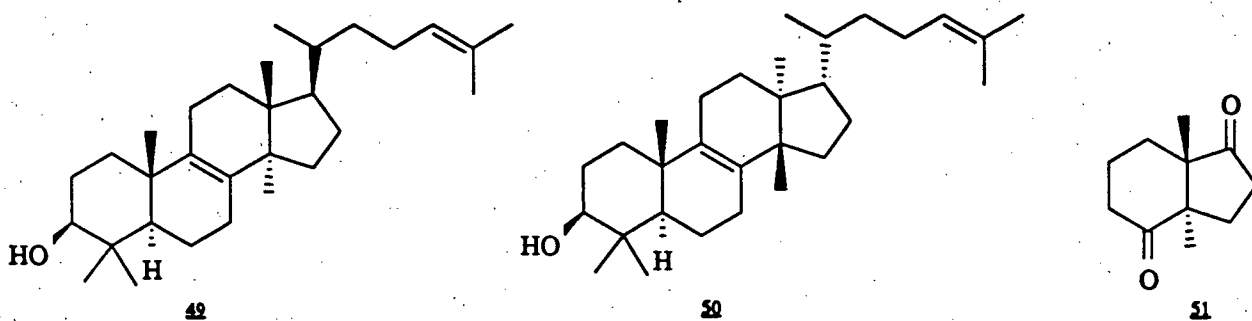
(3) due to the C_2 symmetry of the chiral glycol ligand on phosphorus, either retention or inversion at phosphorus during derivatization of an enantiomerically pure alcohol yields a single diastereomer. Thus, if the sample under examination contains enantiomers, two diastereomers having some degree of ^{31}P NMR nonequivalence ($\Delta\delta$) are expected after derivatization.

A variety of alcohols have been studied using this reagent and in general, the ^{31}P chemical shift range of all of the derivatized alcohols studied is between 12 and 15 ppm while the reagent 48 is found at 17.4 ppm.[42]

DISCUSSION

A. Potential Use of 4-Methylcamphor 43 in Triterpenoid Synthesis:

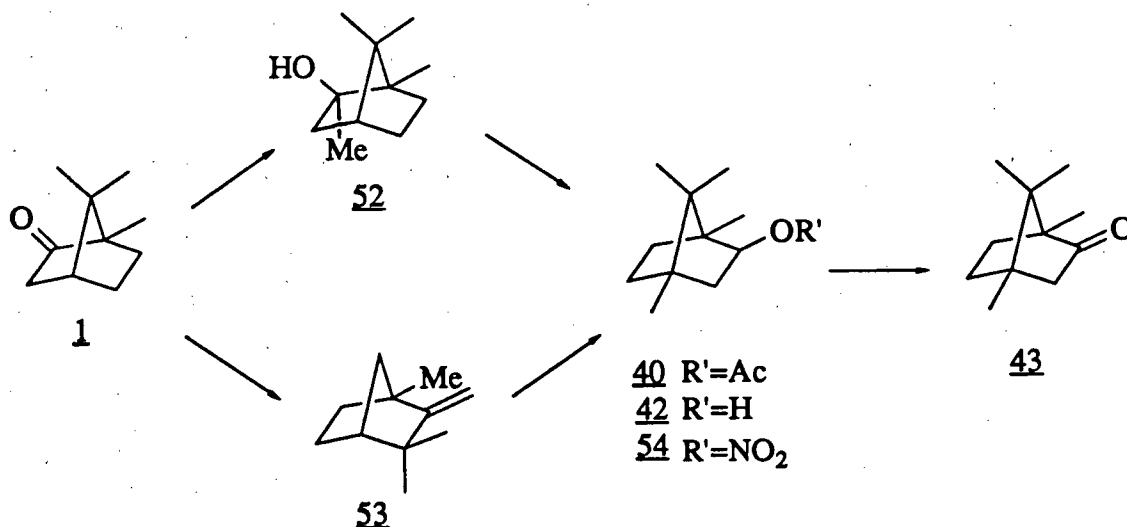
Among the C(4)-substituted camphor derivatives 34-37 mentioned earlier (cf. Scheme 9), (-)-4-methylcamphor 43 and its enantiomer (ent-43) are potentially useful intermediates in the synthesis of triterpenoids belonging to the lanostane 49 and euphane 50 structural sub-groups. The development of synthetic routes to triterpenoids belonging to these two structural sub-groups has been the objective of extensive investigations by Reusch and co-workers.[44] A key intermediate in these synthetic routes is the bicyclic diketone 51 in which the characteristic trans arrangement of the angular methyl groups in the C,D ring system of lanostane 49 triterpenoids is already in place. In addition, Reusch and co-workers[44] demonstrated that by using a photo-epimerization reaction[45], diketone 51 has potential as an intermediate in the synthesis of the C,D ring system of the euphane 50 family of triterpenoids. Diketone 51 has also been used as a key intermediate in the synthesis of 14-methyl-19-norsteroids.[46]



B. A New Synthetic Route to 4-Methylcamphor 43:

1. Literature Routes:

Literature procedures[47] for the synthesis of (-)-4-methylcamphor 43 generally involve initial conversion of (+)-camphor 1 to (-)-2-methylisoborneol 52 or 1-methylcamphene 53 followed by acid-catalyzed rearrangement to (+)-4-methylisoborneol 42[47c,g], (+)-4-methylisobornyl acetate 40[47h,i], or (+)-4-methylisobornyl nitrate 54[47d,f] (Scheme 11). In no case, however, was the optical purity of these products or the derived 4-methylcamphor 43 determined and, hence, only an estimate of relative enantiomeric purity can be gauged from literature values of specific rotations listed in table 1. Accordingly, the initial objective of the research described in this thesis was to determine the optical purity of synthetic (+)-4-methylisobornyl acetate 40 derived from (-)-2-methylenebornane 41.



Scheme 11

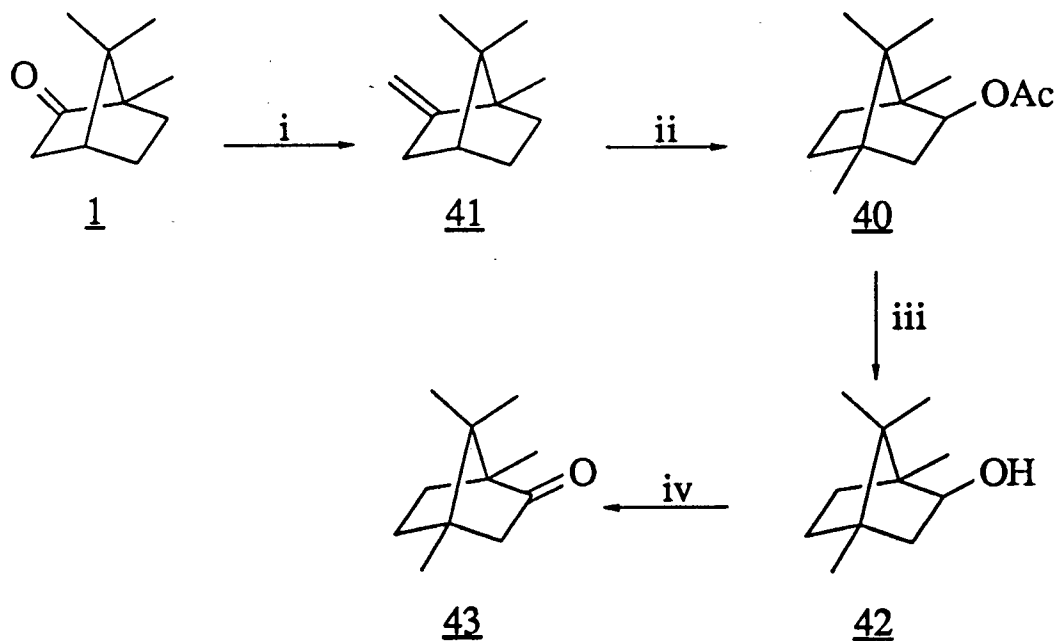
Table 1: Literature values of specific rotations

Compound	Specific Rotation $[\alpha]_D^{20}$	Reference
<u>40</u>	+18.90° +35.84°	47a 47g, i
<u>42</u>	+14.8° +22.69° (EtOH) +25.20° (c.10.0, EtOH)	47a 47g 47c, f
<u>43</u>	-14.5° (c.10.0, EtOH)	47c, f

2. Development of a New Synthetic Route to 4-Methylcamphor 43:

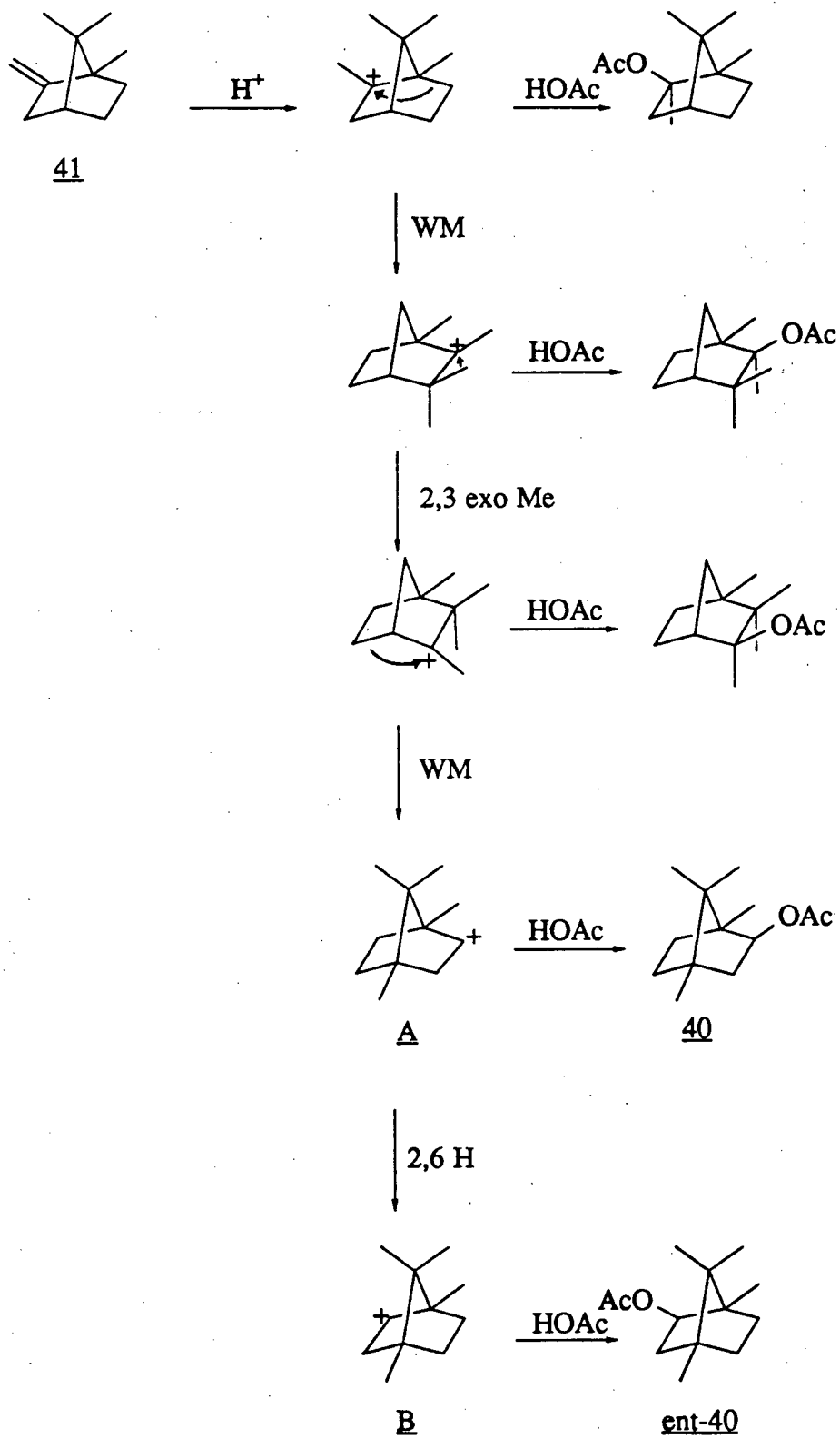
The initial work of this research project which is outlined in scheme 12 was accomplished by Linda Lo, a summer student in our laboratory. Since it is known that reactions i, iii and iv in scheme 12 occur with retention of configuration, the enantiomeric purity of (-)-4-methylcamphor 43 depends on that of (+)-4-methylisobornyl acetate 40. The formation of (+)-4-methylisobornyl acetate 40 from (-)-2-methylenebornane 41 as shown in scheme 13 probably involves a series of Wagner-Meerwein rearrangements (WM) and a 2,3-exo-methyl shift (2,3 exo Me). Preliminary investigations have shown that this reaction is extremely temperature sensitive. For example, at 70°C and for one hour, two products were produced: 4-methylisobornyl acetate and an unidentified side product (which could be any one of those shown in scheme 13). Moreover, at this temperature, the 2,6-hydride shift (cf. A → B, Scheme 13) occurred so readily that an equimolar mixture of

4-methylisobornyl acetate 40 and ent-40 was produced. A more desirable outcome was observed when this reaction was carried out at room temperature for 15 minutes as 4-methylisobornyl acetate was formed in ~75% yield. When the reaction time was increased to 30 minutes, the yield of acetate 40 was 79% but the product was racemic. When conducted at 0°C, the reaction was too slow to be practical.



Reagents: i, $\text{CH}_3\text{PPh}_3\text{Br}$, $n\text{-BuLi}$, THF
 ii, HOAc , H_2SO_4 (20:1), 15 min., 25°C
 iii, LAH, THF
 iv, PCC, CH_2Cl_2

Scheme 12



Scheme 13

At that point, the enantiomeric purity of the (-)-4-methylcamphor 43 derived from (+)-4-methylisobornyl acetate 40 (cf. Scheme 12) was evaluated by comparing its specific rotation with literature values (cf. Table 1). Thus, the first objective of the present work was directed toward the synthesis of enantiomerically pure (+)-4-methylisobornyl acetate 40 in a reasonably good yield and to investigate convenient methods to determine the enantiomeric purity of (+)-4-methylisobornyl acetate 40, (+)-4-methylisoborneol 42 and (-)-4-methylcamphor 43.

3. Determination of Optical Purity of Synthetic 4-Methylisobornyl Acetate 40, 4-Methylisoborneol 42 and 4-Methylcamphor 43:

During the course of this study, two convenient methods were employed to determine the enantiomeric purity of the samples of interest. A chiral lanthanide shift reagent, namely tris-[(3-(heptafluoropropylhydroxymethylene)-d-camphoratoleuropium(III), [Eu(hfc)₃] 45 was used to determine the enantiomeric purity of the (+)-4-methylisobornyl acetate 40 samples produced under different experimental conditions. In addition, a specific acetate sample 40a was reduced to (+)-4-methylisoborneol 42, the enantiomeric purity of which was then determined by the Anderson-Shapiro reagent 48 and was correlated to the enantiomeric purity of the acetate precursor 40a determined by the lanthanide shift reagent. Finally, this specific

(+)-4-methylisoborneol sample was oxidized and the enantiomeric purity of the product (-)-4-methylcamphor 43 was evaluated by the lanthanide shift reagent.

3a. Determination of Enantiomeric Purity Using Chiral Lanthanide Shift Reagent, [Eu(hfc)₃] 45:

The theory of the use of chiral lanthanide shift reagents for the determination of enantiomeric purity is briefly covered in the introduction of this thesis and therefore, the discussion in this section will be focused specifically on the results. The chiral lanthanide shift reagent [Eu(hfc)₃] 45 was used to determine the enantiomeric purity of the samples of the following four compounds: (1) racemic isobornyl acetate (±)-21, (2) (-)-isobornyl acetate ent-21, (3) synthetic (+)-4-methylisobornyl acetate 40 and (4) (-)-4-methylcamphor 43 derived from 40a.

First, (±)-isobornyl acetate (±)-21 and (-)-isobornyl acetate ent-21 were used in a model study to test the effectiveness and reliability of [Eu(hfc)₃]. The procedure is described in the experimental section on page 76. Table 2 summarizes the results and the 400 MHz ¹H NMR spectra recorded are included below in figures 1 and 2.

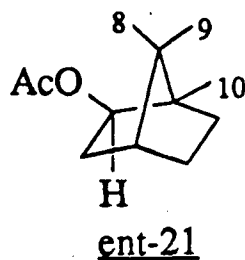
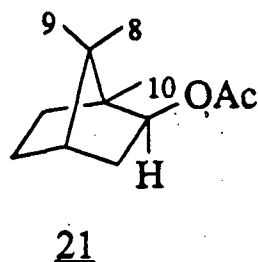


Table 2: A summary of the results of the $[\text{Eu}(\text{hfc})_3]$ study using (+)-isobornyl acetate (+)-21 (Sample A) and (-)-isobornyl acetate ent-21 (Sample B)

Sample	Equiv. of $[\text{Eu}(\text{hfc})_3]$	Markers (multiplicities & chemical shifts)*			$\Delta\Delta\delta$ (Hz)		
		C-9Me	C-8Me	C-10Me	C-9Me	C-8Me	C-10Me
A	0	C-9 & C-8: s, 0.85		s, 0.98	0	0	0
	0.10	s, 0.97	1.21 1.22	1.26 1.27	0	4	4
	0.25	s, 1.11	1.59 1.61	1.64 1.67	0	8	10
	0.50	1.32 1.33	2.08 2.12	2.30 2.35	2	16	20
B	0	C-9 & C-8: s, 0.85		s, 0.98	0	0	0
	0.10	s, 0.96	s, 1.19	s, 1.25	0	0	0
	0.25	s, 1.11	s, 1.60	s, 1.63	0	0	0
	0.50	s, 1.32	s, 2.10	s, 2.37	0	0	0

* s = singlet, δ in ppm

The spectra of (+)-isobornyl acetate (+)-21 from this model study showed that:

(1) as the concentration of $[\text{Eu}(\text{hfc})_3]$ increased, the resonances of the substrate shifted (in most cases, downfield) and separated into two signals due to the presence of enantiomers in the racemic sample. The line width increased with increased chemical shift and with increasing concentration of the shift reagent;

(2) particularly useful markers are the C-8 and C-10 methyls where 0.5 mole equivalence of the shift reagent allowed accurate determination of enantiomeric purity from signal integrations which was found to be 1:1;

(3) the values of $\Delta\Delta\delta$ (enantiomeric shift differences) increased as the concentration of the shift reagent increased. The useful markers exhibited $\Delta\Delta\delta$ up to 20 Hz with 0.5 mole equivalence of the shift reagent.

When a sample of (-)-isobornyl acetate ent-21 was studied under the same experimental conditions, the resonances of the substrate shifted (in most cases, downfield) but did not separate. However, it was interesting to note that in the presence of $[\text{Eu}(\text{hfc})_3]$, the singlet of C-8 and C-9 methyls separated, suggesting that the C-8 methyl was influenced differently by the presence of the lanthanide shift reagent than the C-9 methyl. As mentioned in the introduction, lanthanide β -diketone shift reagents function by acting as Lewis acids, forming a complex with the substance under study, which acts as a nucleophile. Induced shifts are attributed to a pseudo-contact, or dipolar, interaction between the shift reagent and the nucleophile and the "shifted spectrum" represents the averaged environments of the nuclei in the complexed and uncomplexed nucleophiles. Although the nature of the interaction between $[\text{Eu}(\text{hfc})_3]$ and isobornyl acetate was not investigated in the present work, it appeared to be reasonable to speculate that the acetyl functionality in isobornyl acetate interacted

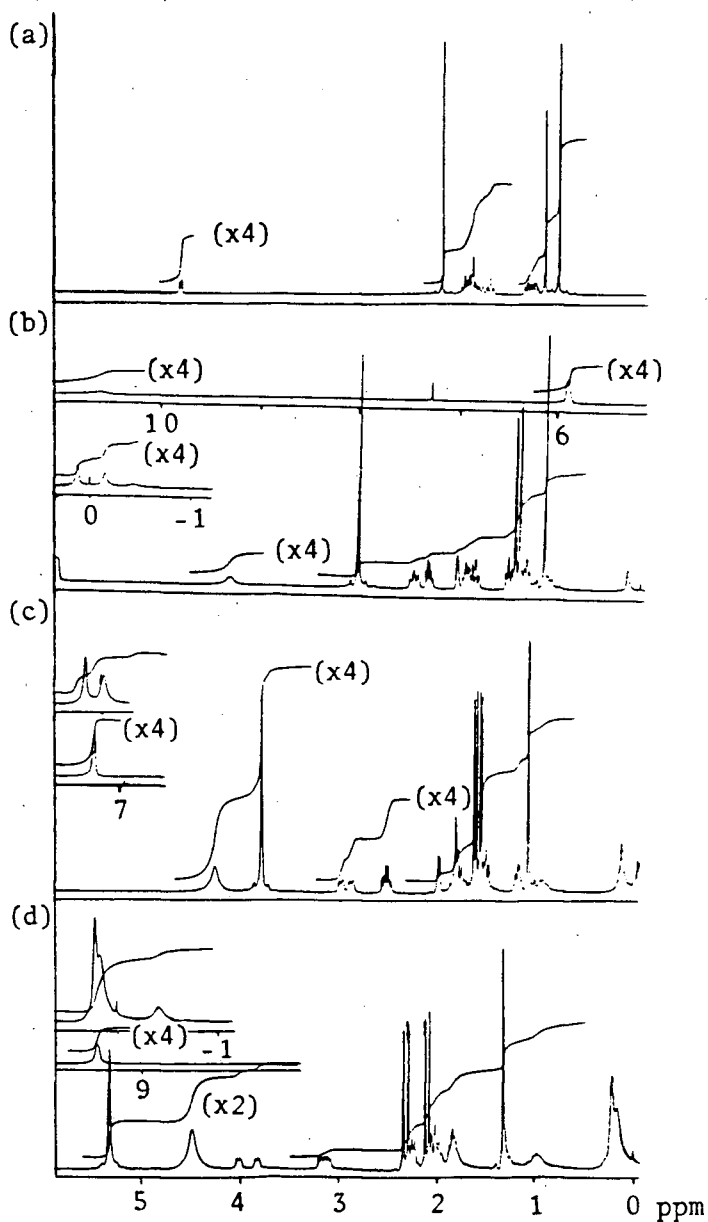


Figure 1: Results of the $[\text{Eu}(\text{hfc})_3]$ study using (\pm) -isobornyl acetate (\pm) -21

a. The 400 MHz ^1H NMR spectrum of a 0.1M sample concentration of (\pm) -isobornyl acetate

b. The spectrum of the same sample after the addition of 0.10 mole equivalence of $[\text{Eu}(\text{hfc})_3]$

c. The spectrum recorded after the amount of $[\text{Eu}(\text{hfc})_3]$ was increased to 0.25 mole equivalence

d. The spectrum recorded after the amount of $[\text{Eu}(\text{hfc})_3]$ was increased to 0.50 mole equivalence

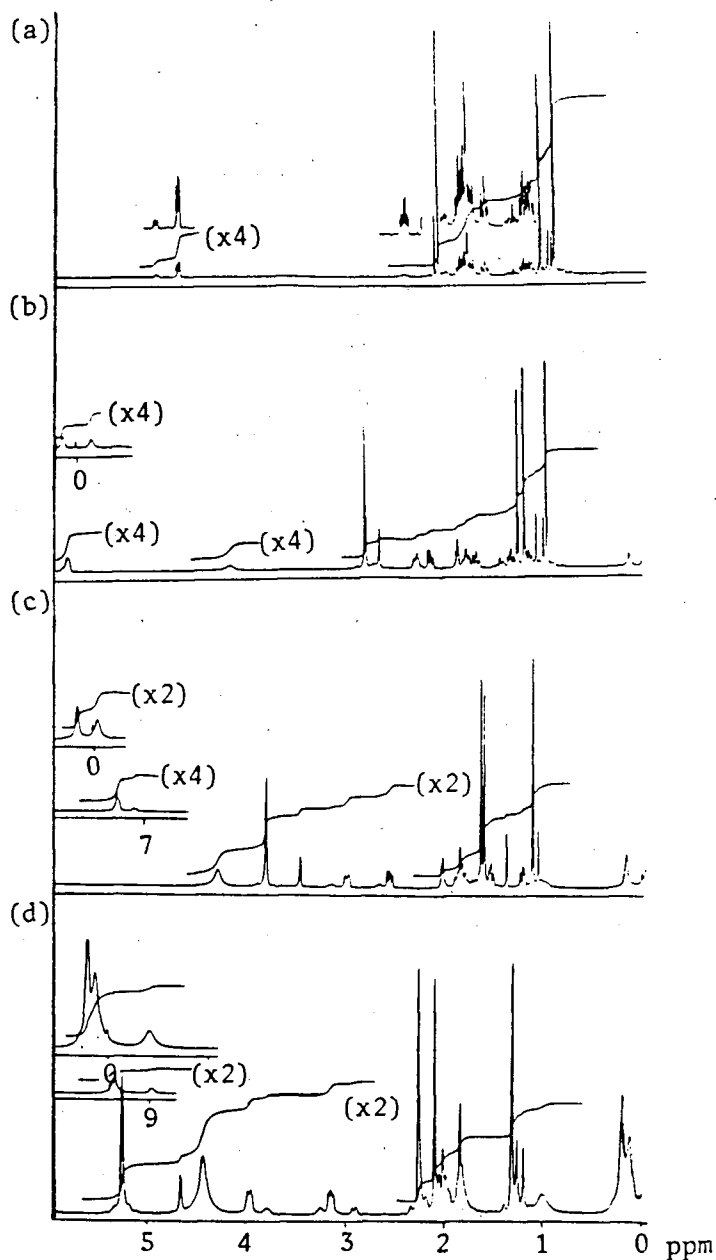


Figure 2: Results of the $[\text{Eu}(\text{hfc})_3]$ study using $(-)$ -isobornyl acetate ent-21

a. The 400 MHz ^1H NMR spectrum of a 0.1M sample concentration of $(-)$ -isobornyl acetate

b. The spectrum of the same sample after the addition of 0.10 mole equivalence of $[\text{Eu}(\text{hfc})_3]$

c. The spectrum recorded after the amount of $[\text{Eu}(\text{hfc})_3]$ was increased to 0.25 mole equivalence

d. The spectrum recorded after the amount of $[\text{Eu}(\text{hfc})_3]$ was increased to 0.50 mole equivalence

with the shift reagent in such a way that the C-8 and C-10 methyls were brought close to the shift reagent.

At this point, from the results of this model study, it can be concluded that $[\text{Eu}(\text{hfc})_3]$ was useful in determining the enantiomeric purity of isobornyl acetate and that it may be used to determine the enantiomeric purity of the samples of two other related compounds: (+)-4-methylisobornyl acetate 40 and (-)-4-methylcamphor 43.

The procedure used for the determination of enantiomeric purity of three different samples of (+)-4-methylisobornyl acetate 40 is described on page 76 in the experimental. Table 3 summarizes the results and the 400 MHz ^1H NMR spectra recorded are included in figures 3, 4, and 5. The spectra from the enantiomeric purity study of the three different samples of (+)-4-methylisobornyl acetate 40 showed that:

- (1) as the concentration of $[\text{Eu}(\text{hfc})_3]$ increased, the resonances of the substrate shifted (in most cases, downfield) and separated into two signals due to the presence of enantiomers in the sample. The line width increased with increased chemical shift and with increasing concentration of the shift reagent;
- (2) particularly useful markers are the C-8, C-10 and C-4 methyls where 0.5 mole equivalence of $[\text{Eu}(\text{hfc})_3]$ allowed accurate determination of the enantiomeric purity;
- (3) the values of $\Delta\Delta\delta$ increased as the concentration of the shift reagent increased. The useful markers exhibited $\Delta\Delta\delta$ up to 18 Hz with 0.5 mole equivalence of the shift reagent.

Table 3: A summary of the results of the [Eu(hfc)₃] study using different samples of (+)-4-methylisobornyl acetate 40^a

S	Equiv. of [Eu(hfc) ₃]	Markers (multiplicities & chemical shifts) ^b				$\Delta\Delta\delta$ (Hz)			
		C-9Me	C-8Me	C-10Me	C-4Me	C-9Me	C-8Me	C-10Me	C-4Me
A	0	s, 0.70	s, 0.85	s, 0.88	s, 0.91	0	0	0	0
	0.10	s, 0.79	s, 0.95	s, 1.04	s, 1.14	0	0	0	0
	0.25	s, 0.92	1.02 1.03	1.36 1.37	1.54 1.56	0	4	6	8
	0.50	s, 1.14	1.16 1.17	1.91 1.94	^c 2.24 2.28	0	4	12	18
B	0	s, 0.70	s, 0.85	s, 0.88	s, 0.91	0	0	0	0
	0.50	s, 1.12	1.12 1.14	1.82 1.85	^d 2.12 2.16	0	8	12	17
C	0	s, 0.70	s, 0.85	s, 0.88	s, 0.91	0	0	0	0
	0.50	s, 1.12	1.12 1.14	1.82 1.85	^e 2.12 2.16	0	8	12	17

- a. Sample A: 40a produced under the conditions of 25°C, 15 minutes;
 Sample B: 40b produced under the conditions of 25°C, 10 minutes;
 Sample C: 40c produced under the conditions of 0°C, 30 minutes.

- b. s = singlet, δ in ppm
 c. integration ratio 4.5:1
 d. integration ratio 3.7:1
 e. integration ratio 5.0:1

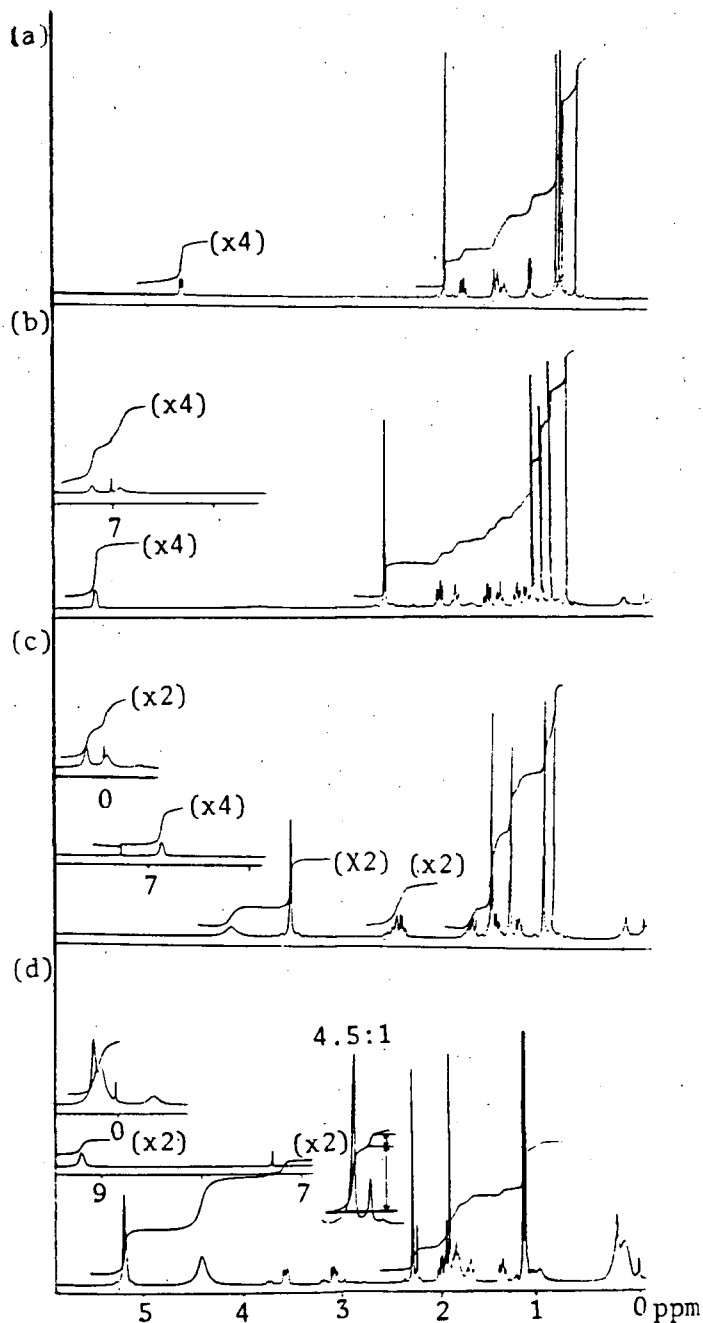


Figure 3: Results of the $[\text{Eu}(\text{hfc})_3]$ study using (+)-4-methylisobornyl acetate **40a** produced under the conditions of 25°C , 15 minutes.

a. The 400 MHz ^1H NMR spectrum of a 0.1M sample concentration of (+)-4-methylisobornyl acetate

b. The spectrum of the same sample after the addition of 0.10 mole equivalence of $[\text{Eu}(\text{hfc})_3]$

c. The spectrum recorded after the amount of $[\text{Eu}(\text{hfc})_3]$ was increased to 0.25 mole equivalence

d. The spectrum recorded after the amount of $[\text{Eu}(\text{hfc})_3]$ was increased to 0.50 mole equivalence

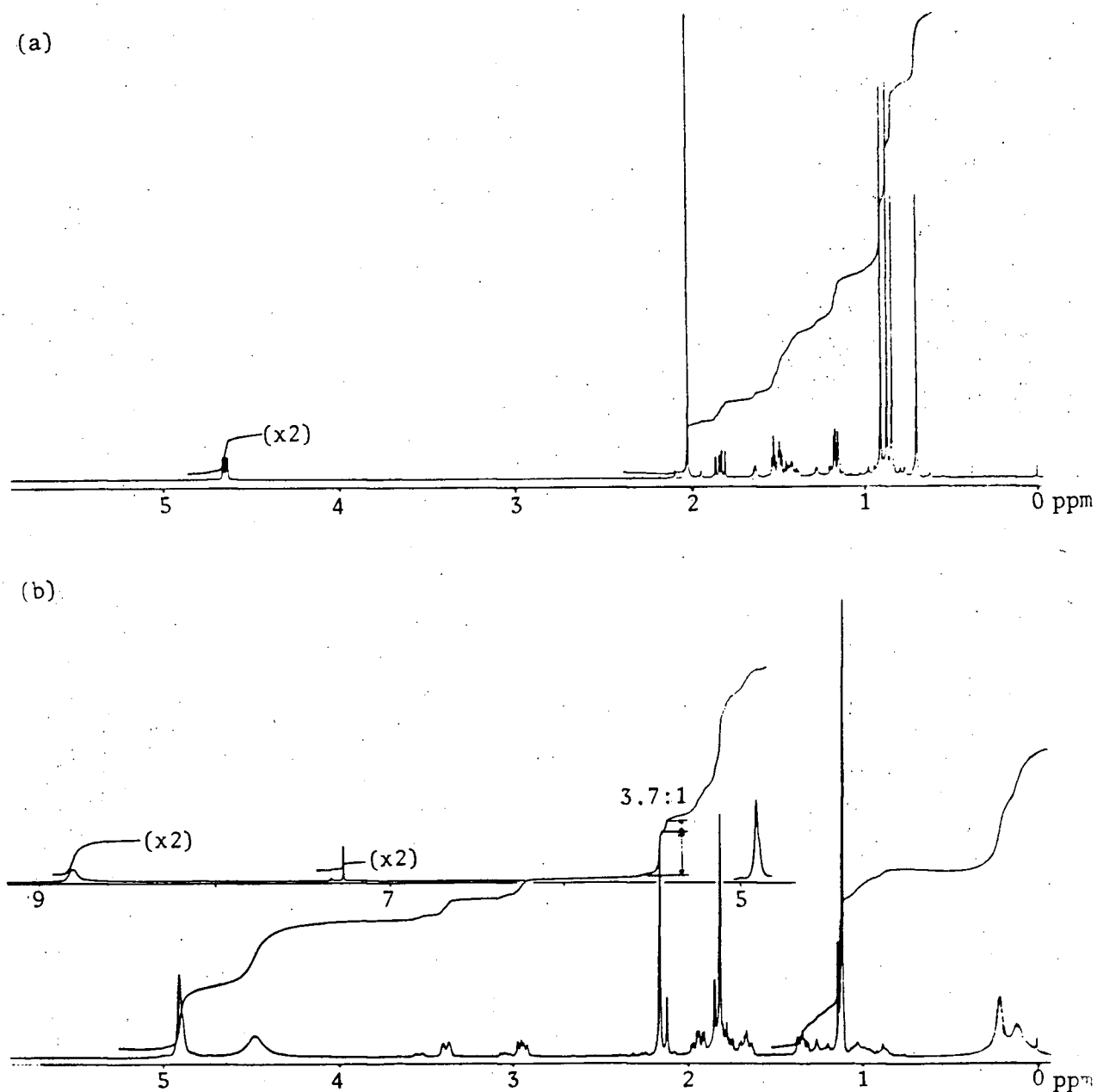


Figure 4: Results of the $[\text{Eu}(\text{hfc})_3]$ study using (+)-4-methylisobornyl acetate 40b produced under the conditions of 25°C , 10 minutes.

- a. The 400 MHz ^1H NMR spectrum of 0.1M sample concentration of (+)-4-methylisobornyl acetate
- b. The spectrum of the same sample after the addition of 0.5 mole equivalence of $[\text{Eu}(\text{hfc})_3]$

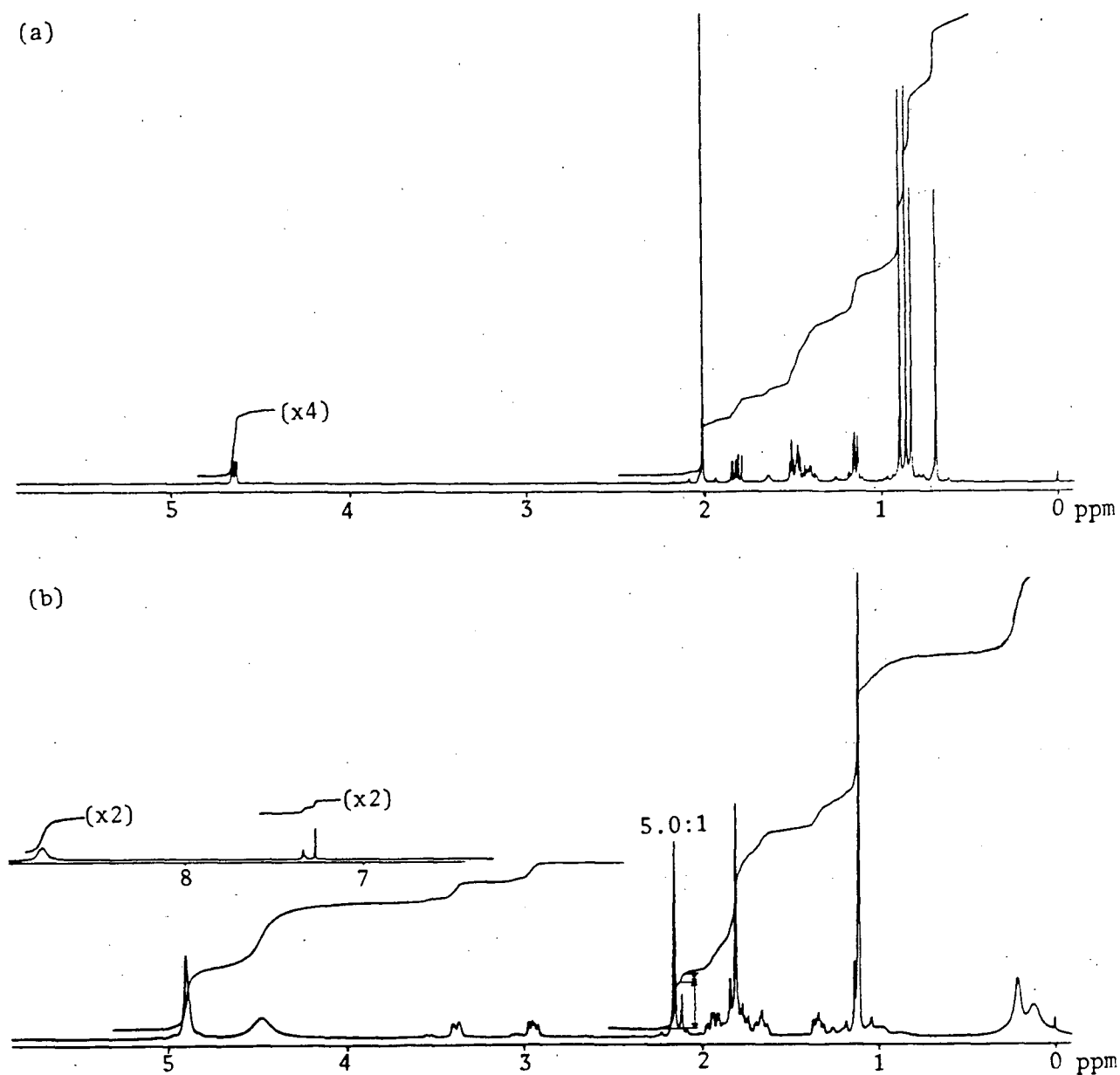


Figure 5: Results of the [Eu(hfc)₃] study using (+)-4-methylisobornyl acetate 40c produced under the conditions of 0°C, 30 minutes.

a. The 400 MHz ¹H NMR spectrum of 0.1M sample concentration of (+)-4-methylisobornyl acetate

b. The spectrum of the same sample after the addition of 0.5 mole equivalence of [Eu(hfc)₃]

The above result indicated that $[\text{Eu}(\text{hfc})_3]$ was effective in the determination of the enantiomeric purity of (+)-4-methylisobornyl acetate 40. The enantiomeric purity of 40 synthesized under different reaction conditions is summarized in table 4. One can see that among these three sets of reaction conditions, the conditions of 30 minutes at 0°C produced acetate 40c with the best optical purity.

Table 4: The enantiomeric purity of (+)-4-methylisobornyl acetate 40 synthesized under different conditions^a

Compound	Experimental Conditions		Yield %	$[\alpha]_D$ of the Acetate Product	Optical Purity ^b
	Time(min.)	Temperature			
<u>40a</u>	15	25°C	80	+35.79 (c.2.28, 95% ethanol)	64%
<u>40b</u>	10	25°C	62	+32.12 (c.3.12, 95% ethanol)	57%
<u>40c</u>	30	0 °C	73	+39.23 (c.2.20, 95% ethanol)	67%

a. Reagents: acetic acid / sulphuric acid (20:1)

b. from $[\text{Eu}(\text{hfc})_3]$ study: based on the integration ratio obtained when 0.5 mole equivalence of $[\text{Eu}(\text{hfc})_3]$ was used (cf. table 3).

Again, although the nature of the interaction between $[\text{Eu}(\text{hfc})_3]$ and (+)-4-methylisobornyl acetate 40 was not investigated in the present work, it appeared to be reasonable to speculate that the acetyl functionality in this substrate interacted with the shift reagent in such a way that the C-8, C-10 and C-4 methyls were brought close to the shift reagent. Among these three "markers", C-4 methyl appeared to be influenced most extensively and therefore most useful in the determination of the enantiomeric purity of (+)-4-methylisobornyl acetate 40.

The use of $[\text{Eu}(\text{hfc})_3]$ was extended to determine the enantiomeric purity of (-)-4-methylcamphor 43. A specific sample of (-)-4-methylcamphor 43 was obtained by reducing a (+)-4-methylisobornyl acetate 40a sample (cf. table 4), then oxidizing alcohol 42 to (-)-4-methylcamphor 43. The procedure used for the determination of the enantiomeric purity of this sample is described on page 77 in the experimental. Table 5 summarizes the results and the 400 MHz ^1H NMR spectra recorded are included in figure 6.

Table 5: A summary of the results of the $[\text{Eu}(\text{hfc})_3]$ study using a specific sample of (-)-4-methylcamphor 43^a

Equiv. of $[\text{Eu}(\text{hfc})_3]$	Markers (multiplicities & chemical shifts) ^b				$\Delta\Delta\delta$ (Hz)			
	C-9Me	C-8Me	C-10Me	C-4Me	C-9Me	C-8Me	C-10Me	C-4Me
0	s, 0.72	s, 0.84	s, 0.93	s, 1.05	0	0	0	0
0.10	s, 1.04	1.06 1.08	s, 1.18	s, 1.46	0	7	0	0
0.30	s, 1.41	1.42 1.43	1.66 1.71	s, 2.39	0	2	18	0
0.60	s, 1.89	1.73 1.75	c 2.45 2.53	s, 3.60	0	7	32	0

a. obtained by reducing a (+)-4-methylisobornyl acetate 40a (cf. table 4), then oxidizing the alcohol 42.

b. s = singlet, δ in ppm

c. integration ratio 4.3:1

The spectra in figure 6 showed that:

- (1) as the concentration of $[\text{Eu}(\text{hfc})_3]$ increased, the resonances of the substrate shifted (in most cases, downfield) and separated into two signals due to the presence of enantiomers in the sample. The line width increased with increased chemical shift and with increasing concentration of the shift reagent;
- (2) particularly useful markers are the C-8 and C-10 methyls where 0.6 mole equivalence of the shift reagent allowed accurate determination of the enantiomeric purity which is ~62% for this sample;
- (3) the values of $\Delta\Delta\delta$ increased as the concentration of the shift reagent increased. The useful markers exhibited $\Delta\Delta\delta$ up to 32 Hz with 0.6 mole equivalence of $[\text{Eu}(\text{hfc})_3]$.

The major reason for the extension of the $[\text{Eu}(\text{hfc})_3]$ study from (+)-4-methylisobornyl acetate 40 to (-)-4-methylcamphor 43 was to confirm the reliability of this shift reagent in determining the enantiomeric purity of two related compounds where one is the precursor of the other in a chemical synthesis. As mentioned earlier, since reactions iii and iv in scheme 12 (p. 20) occur with retention of configuration and the enantiomeric purity of (-)-4-methylcamphor 43 depends on that of (+)-4-methylisobornyl acetate 40, the individual $[\text{Eu}(\text{hfc})_3]$ studies of these two compounds were expected to provide comparable values of their optical purity. In fact, it was found that the optical purity of the precursor (+)-4-methylisobornyl acetate 40a (cf. table 4) was ~64% which

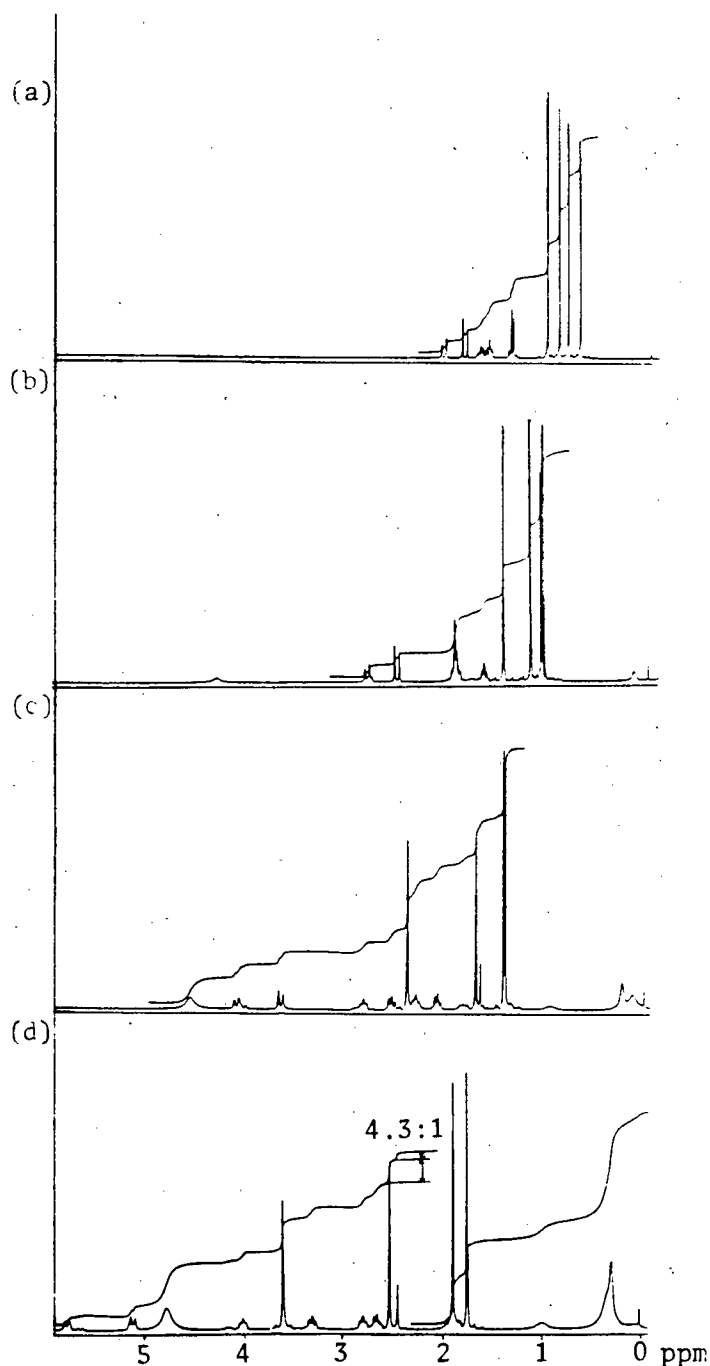


Figure 6: Results of the $[\text{Eu}(\text{hfc})_3]$ study using a specific sample of (-)-4-methylcamphor 43

a. The 400 MHz ^1H NMR spectrum of a 0.1M sample concentration of (-)-4-methylcamphor

b. The spectrum of the same sample after the addition of 0.10 mole equivalence of $[\text{Eu}(\text{hfc})_3]$

c. The spectrum recorded after the amount of $[\text{Eu}(\text{hfc})_3]$ was increased to 0.30 mole equivalence

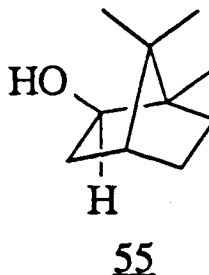
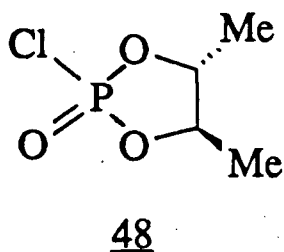
d. The spectrum recorded after the amount of $[\text{Eu}(\text{hfc})_3]$ was increased to 0.60 mole equivalence

was comparable to that of (-)-4-methylcamphor 43 which was ~62%. In addition, it was found that although the C-4 methyl was a good "marker" in acetate 40, it was not useful in (-)-4-methylcamphor 43. This suggested that the two compounds interact differently, from a spatial perspective, with $[\text{Eu}(\text{hfc})_3]$.

In conclusion, the optical purity of our synthetic (+)-4-methylisobornyl acetate 40a $\{[\alpha]_D^{21.5} +35.79 (\text{c.2.28}, \text{EtOH})\}$ was established to be ~64% using this technique of enantiomeric purity determination. In a similar fashion, the optical purity of (-)-4-methylcamphor 43 $\{[\alpha]_D^{25} -16.70 (\text{c.1.5}, \text{EtOH})\}$ derived from 40a was determined to be ~62%. A comparison of the specific rotations quoted in the literature (cf. Table 1) and those recorded in our laboratory leads to the conclusion that all of the current methods of preparing 4-methylisobornyl acetate 40 provide product which is not enantiomerically pure. From the mechanism proposed for the conversion of (-)-2-methylenebornane 41 to (+)-4-methylisobornyl acetate 40 (Scheme 13, page 21), it is obvious that optically pure 4-methylisobornyl acetate 40 can only be obtained if the 2,6-hydride shift which converts **A** to **B** is inhibited. As a result, two approaches to the synthesis of enantiomerically pure 4-methylisobornyl acetate 40 were attempted and will be described later (page 43).

3b. Determination of Enantiomeric Purity of 4-methylisoborneol 42 Using Anderson-Shapiro Reagent 48:

The theory of the use of the Anderson-Shapiro reagent, 2-chloro-4(R),5(R)-dimethyl-2-oxo-1,3,2-dioxapholane 48, in the study of enantiomeric purity by NMR is briefly covered in the introduction and therefore, the discussion here will focus on the results. This chiral derivatizing agent 48 was used to determine the enantiomeric purity of the samples of the following three compounds: (1) racemic isoborneol (\pm)-55, (2) (-)-isoborneol 55 and (3) (+)-4-methylisoborneol 42.



First, (\pm)-isoborneol (\pm)-55 and (-)-isoborneol 55 were used in a model study to test the effectiveness and reliability of the Anderson-Shapiro reagent. The procedure is described in the experimental on page 71. Table 6 summarizes the results and the 121.4 MHz ^{31}P NMR spectra recorded are shown in figure 7.

Table 6: Results of the study of enantiomeric purity of the three alcohols {(±)-55, 55 and 42} using the Anderson-Shapiro reagent.

Spectrum	Sample	Markers ^a (δ in ppm)	$\Delta\delta$ (Hz)	I.R. ^b
Fig.7(a)	(±)-isoborneol	δ 13.341, 13.404	7.89	1:1
Fig.7(b)	(-)-isoborneol	δ 13.478	--	---
Fig. 8	(+)-4-methyl-isoborneol ^c	δ 13.628, 13.667	4.85	2.1:1 ^d

a. The ^{31}P chemical shifts of the derivatized alcohols. The Anderson-Shapiro reagent was observed at δ 17.480 and 17.375 in spectra Fig. 7(a) and Fig. 7(b) respectively.

b. I.R. = Integration Ratio

c. This particular sample of (+)-4-methylisoborneol 42 was obtained by reducing a specific sample of (+)-4-methylisobornyl acetate 40a (cf. table 4).

d. The signal separation was too small to provide more than an approximate estimation of relative signal areas.

As mentioned earlier, the Anderson-Shapiro reagent reacted with the enantiomers in the racemic alcohol sample, that is, (±)-isoborneol (±)-55 to yield diastereomers 56 and 57 which exhibited:

(1) a significant degree of ^{31}P NMR nonequivalence ($\Delta\delta$ 7.89 Hz); and

(2) an integration ratio of 1:1 which was the same as the ratio of enantiomers in the racemic sample.

With the enantiomerically pure (-)-isoborneol 55, a single diastereomer was observed (δ 13.478 ppm) as expected after derivatization with the reagent. In both spectra, the excess reagent was observed at $\sim \delta$ 17 ppm which agreed with the literature.[42]

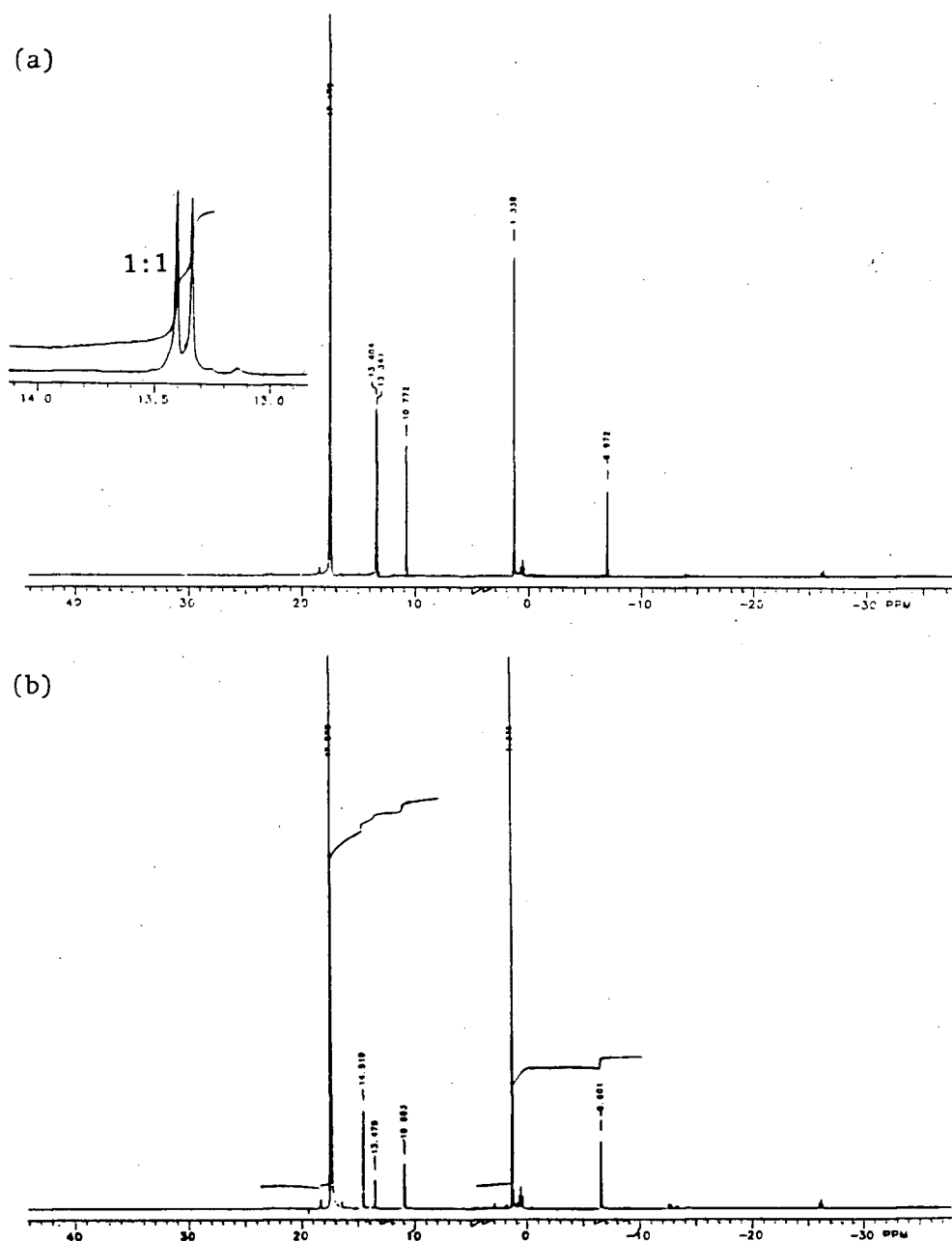
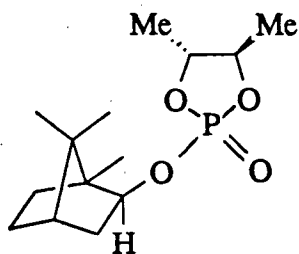
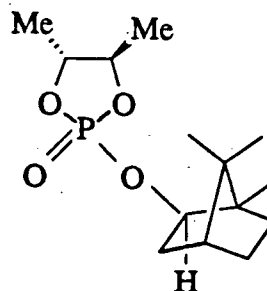


Figure 7: Results of the model study using (+)-isoborneol 55 and (-)-isoborneol 55

a. The 121.4 MHz ^{31}P NMR spectrum of the derivatized (+)-isoborneol.

b. The 121.4 MHz ^{31}P NMR spectrum of the derivatized (-)-isoborneol.

Based on the success of the above model study, the Anderson-Shapiro reagent was used to determine the enantiomeric purity of a specific sample of (+)-4-methylisoborneol 42 $\{[\alpha]_D^{25} +20.40$ (c. 9.0, EtOH) $\}$. The procedure is described in the experimental on page 72. The results is shown in table 6 while the 121.4 MHz ^{31}P NMR spectrum recorded is shown in figure 8. In this spectrum, the two signals observed at δ 13.628 and δ 13.667 were believed to come from the diastereomers 58 and 59 produced. As shown in table 6, the ^{31}P NMR nonequivalence ($\Delta\delta$ 4.85 Hz) between the two diastereomeric phosphate esters was too small to provide a reliable estimate of optical purity.

5657

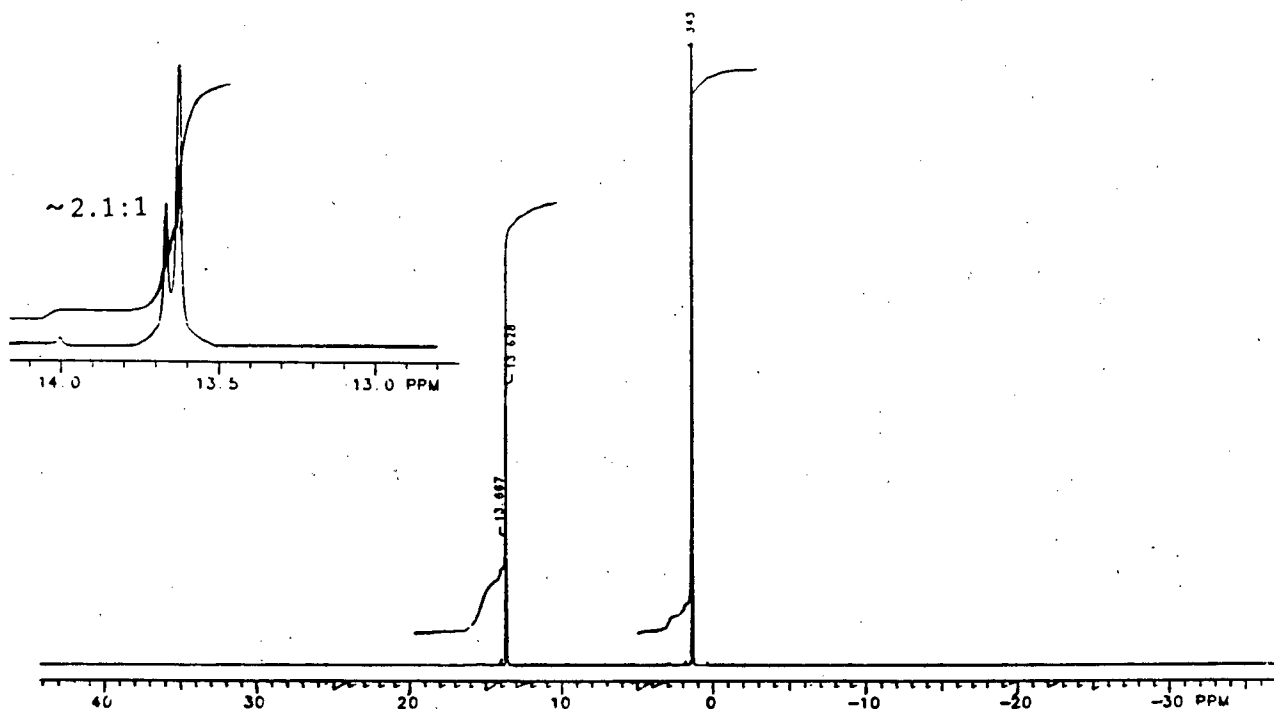
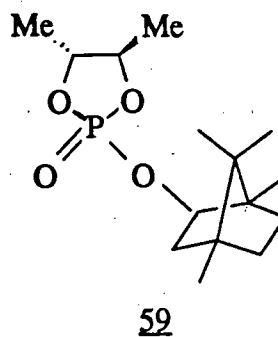
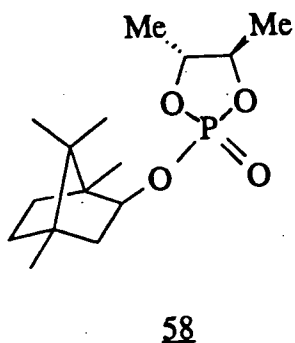


Figure 8: The 121.4 MHz ^{31}P NMR spectrum of the derivatized sample of (+)-4-methylisoborneol **42** (obtained by reducing **40a**, cf. table 4).

C. Alternative Synthetic Routes to Enantiomerically Pure (-)-4-Methylcamphor 43:

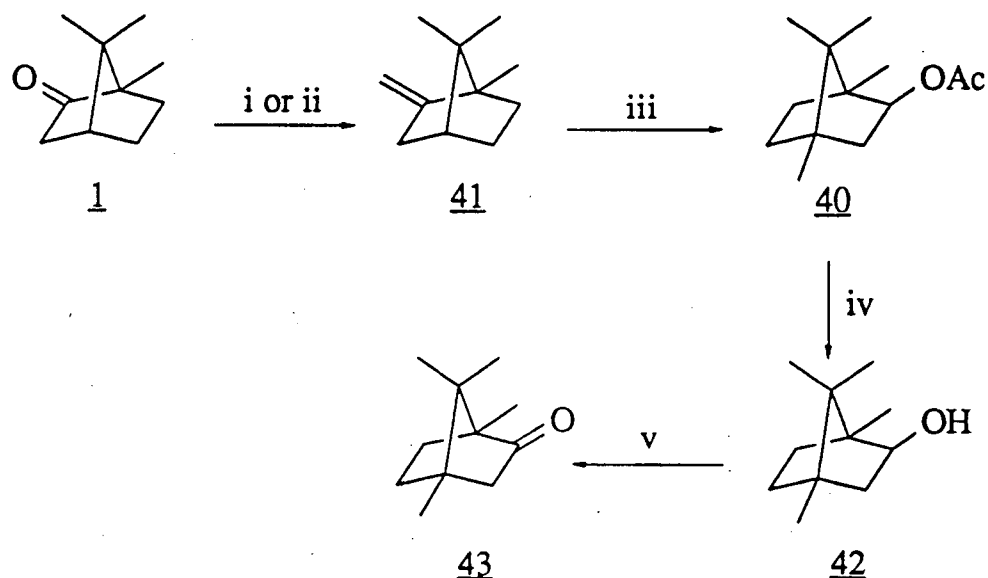
1. Route A:

The first alternative approach to the synthesis of enantiomerically pure 4-methylisobornyl acetate 40 was an extension of the initial work described earlier, that is, (-)-2-methylenebornane 41 was reacted with acetic acid / sulphuric acid (20:1) and it was found that the experimental conditions of 30 minutes at 0°C appeared to give the most desirable results. At a lower temperature, -10°C and for 85 minutes, many side reactions occurred, producing 4-methylisobornyl acetate 40 in less than 15% yield.

Scheme 14 shows the improved synthesis of (-)-4-methylcamphor 43 from (+)-camphor 1. As shown in scheme 14, a modification of the method used by Oshima *et al.* [48] (CH₂Br₂, Zn, TiCl₄) was found superior to a modification of the method used by Gream *et al.* [49] (CH₃PPh₃Br, BuLi, THF). Methylenation with a system consisting of CH₂Br₂-Zn-TiCl₄ was first introduced by Oshima *et al.* (1978) [50] and has since shown to be a useful alternative (characterized by high yields and mild conditions) for the Wittig carbonyl methylenation. [48,50] However, little is known about the chemistry of this method of methylenation.

Although the synthesis of (-)-4-methylcamphor 43 from (+)-camphor 1 was achieved with good yields, the attempt to maximize the optical purity of acetate 40 by varying the reaction time and temperature appeared to be unsatisfactory for the system

using acetic acid / sulphuric acid (20:1). Therefore, a different approach was attempted and is described below.



Reagents: 1, $\text{CH}_3\text{PPh}_3\text{Br}$, BuLi , THF (87%)
 ii, CH_2Br_2 , Zn, TiCl_4 (99%)
 iii, $\text{HOAc} / \text{H}_2\text{SO}_4$, 20:1; 30 min., 0°C (73%)
 iv, LiAlH_4 , THF (99%)
 v, PCC, CH_2Cl_2 (99%)

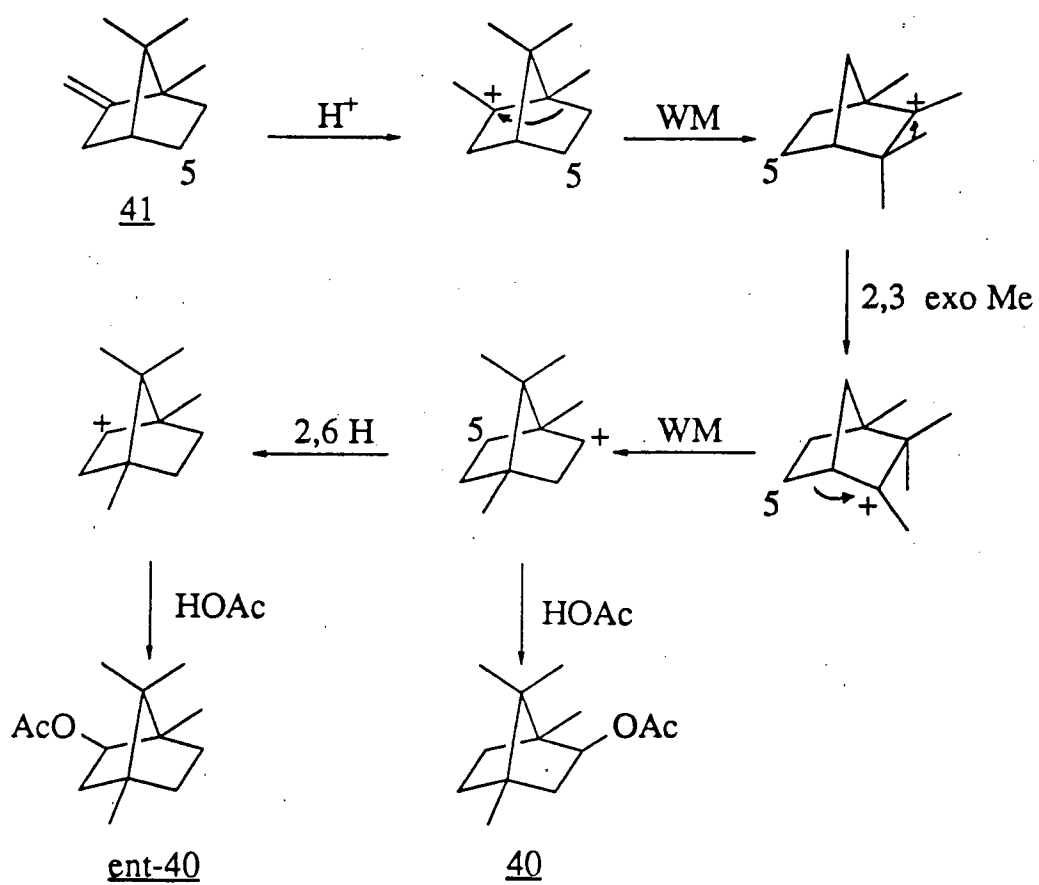
Scheme 14

2. Route B:

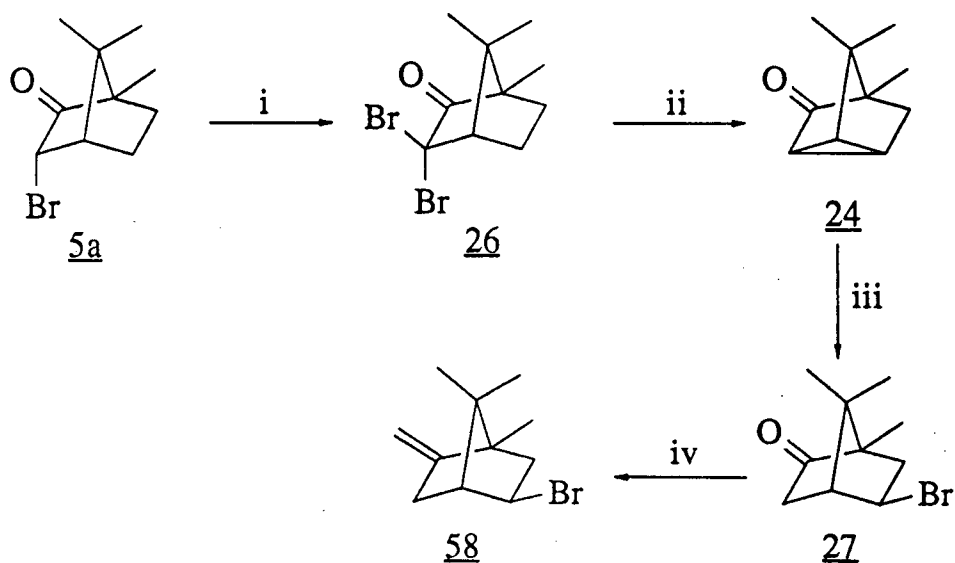
The second approach was based on the assumption that the formation of (-)-4-methylisobornyl acetate ent-40 (shown in scheme 15) was the result of a 2,6-hydride shift (cf. Scheme 15). Thus, either inhibiting this crucial 2,6-hydride shift to suppress the formation of ent-40 or enhancing the same step to favor the formation of ent-40 should produce enantiomerically

pure product. We considered the possibility that the presence of an electronegative substituent replacing a hydrogen on C(5) in 41 (Scheme 15) would inhibit the 2,6-hydride shift which leads to ent-40. Therefore, exo-5-bromo-2-methylenebornane 58 was synthesized in 69% overall yield by the reaction sequence outlined in scheme 16. This involved treatment of commercially available (+)-endo-3-bromocamphor 5a with bromine and acetic acid to provide (+)-3,3-dibromocamphor 26 which was subsequently reacted with diethylzinc in benzene[28] to yield pericyclocamphanone 24. It has been suggested[28] that this reaction involves intermediate formation of ketocarbene 61 followed by insertion into the C(5)-H bond (Scheme 17).

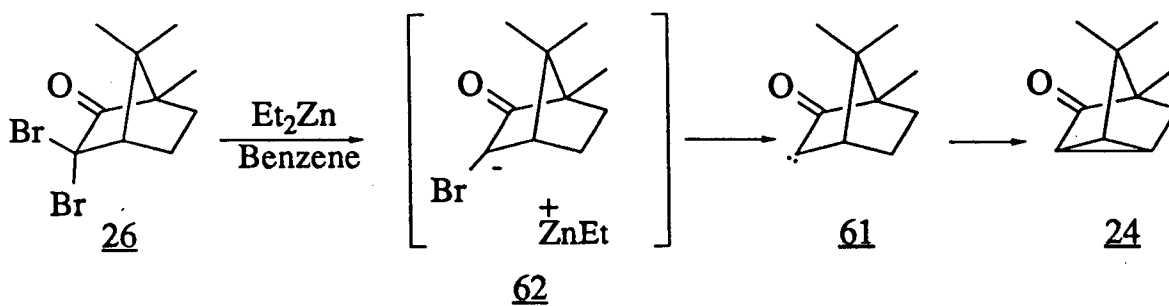
Exo-5-bromocamphor 27 was obtained subsequently by treating pericyclocamphanone 24 with hydrobromic acid (48%) and acetic anhydride for 3 hours at 65°C. Exo-5-bromocamphor 27 has been prepared previously[24] in 82% yield by treating pericyclocamphanone 24 with dry hydrogen bromide and acetic acid for 24 hours at room temperature. Scheme 18 shows a possible mechanism for this transformation of 24 into 27.



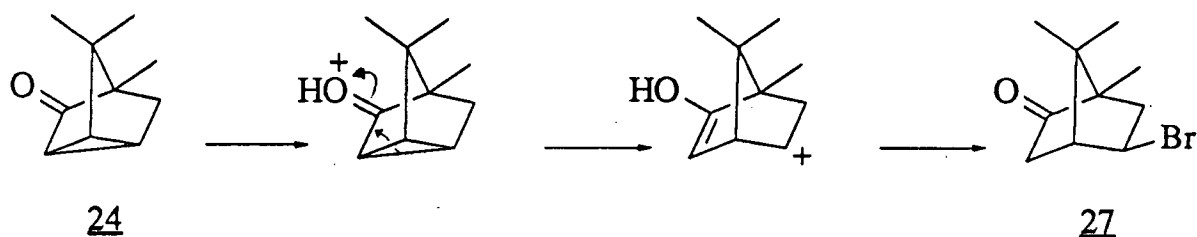
Scheme 15



Scheme 16

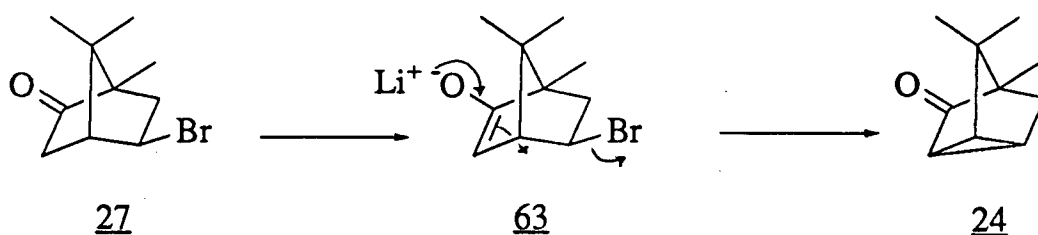


Scheme 17



Scheme 18

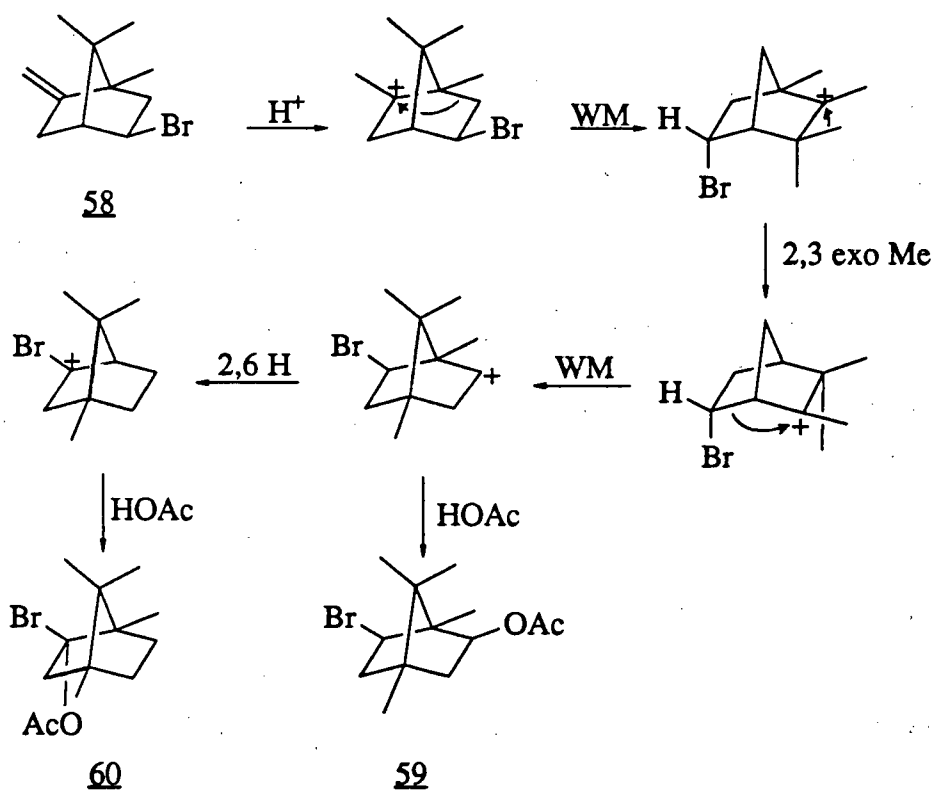
The synthesis of exo-5-bromo-2-methylenebornane 58 from exo-5-bromocamphor 27 was attempted by using a modification of the method used by Gream *et al.*[49] ($\text{CH}_3\text{PPh}_3\text{Br}$, BuLi , THF) for the conversion of (+)-camphor 1 to (-)-2-methylenebornane 41. However, it was found that under these conditions, exo-5-bromocamphor 27 reverted to pericyclocamphanone 24 in 99% yield (Scheme 19)! An alternative carbonyl methylenation reported by Oshima *et al.*[48] (CH_2Br_2 , Zn , TiCl_4) is known to work well for the methylenation of easily enolizable ketones[48,50] and the use of this methodology led to the successful conversion of exo-5-bromocamphor 27 to exo-5-bromo-2-methylenebornane 58 in 86% yield (Scheme 16).



Scheme 19

Treatment of exo-5-bromo-2-methylenebornane 58 with acetic acid / sulphuric acid (20:1) at 0°C for 35 minutes and then at room temperature for 3 hours provided starting material and heating the reaction mixture to ~80°C produced extensive decomposition. In a separate run, the reaction mixture was stirred at room temperature for 21 days. GLC and TLC analyses showed that the starting material 58 slowly underwent decomposition and that no major reaction products were observed.

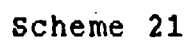
It was speculated that the failure of exo-5-bromo-2-methylenebornane 58 to undergo acid-catalyzed rearrangement was due to the fact that the electronegative bromine substituent on C(5) inhibited the second Wagner-Meerwein rearrangement in scheme 20. Since the acid-catalyzed rearrangement of 58 was found to be unsuccessful, this approach to the synthesis of enantiomerically pure 4-methylcamphor 43 was terminated.



Scheme 20

3. Future Study:

Since it is assumed that the formation of (-)-4-methylisobornyl acetate ent-40 (shown in scheme 15) was the result of a 2,6-hydride shift (cf. Scheme 15), future work will be concerned with the synthesis of a C(5)-disubstituted 2-methylenebornane derivative that lacks a C(5) proton. An immediate synthetic target will be the thioketal 79 of 5-keto-2-methylenebornane 78 if this could possibly be derived from (+)-endo-3-bromocamphor 5a by the sequence outlined in scheme 21. It is hoped that treatment of thioketal 79 with acetic acid / sulphuric acid (20:1) will provide compound 80 and then subsequent treatment of compound 80 with Raney nickel will provide enantiomerically pure (+)-4-methylisobornyl acetate 40.



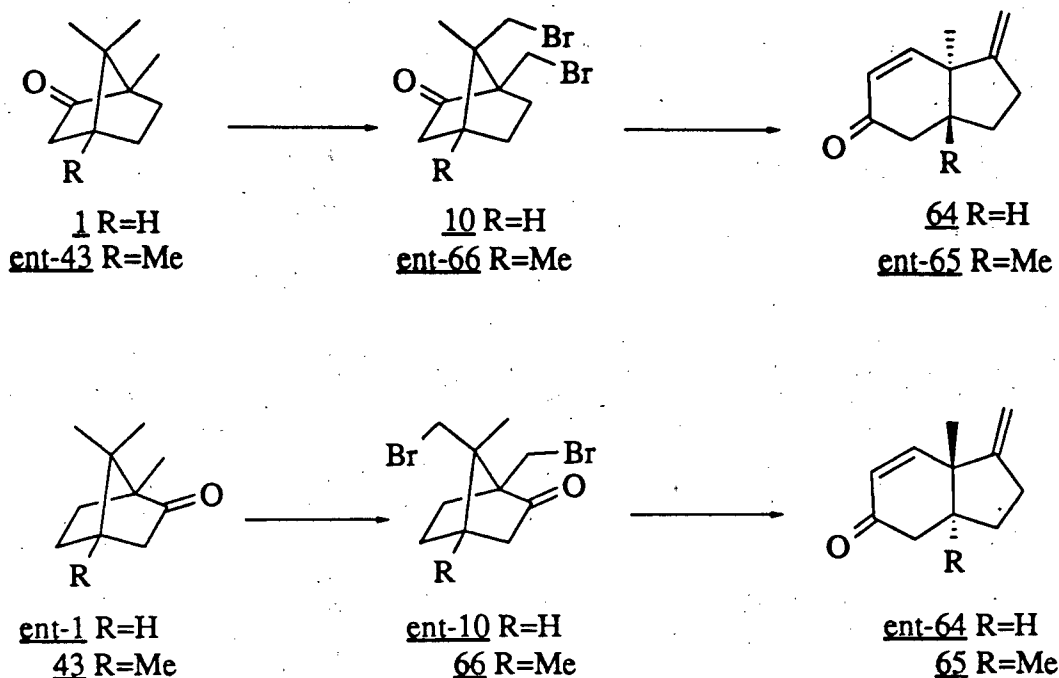
Scheme 21

D. Use of 4-Methylcamphor 43 in a New Synthetic Approach to Triterpenoids:

While efforts were spent in attempting to synthesize enantiomerically pure (+)-4-methylisobornyl acetate 40 (and hence, enantiomerically pure (-)-4-methylcamphor 43), the potential of (-)-4-methylcamphor 43 and its enantiomer ent-43 as intermediates in the synthesis of triterpenoids belonging to the lanostane 49 and euphane 50 structural sub-groups was investigated. Previous investigations in our laboratory have shown that (+)-9,10-dibromocamphor 10[15] or its enantiomer ent-10 can be converted to intermediates 64 and ent-64 in steroid synthesis.[21,43] We realized that if the same kind of chemical transformations could be accomplished with the enantiomers of 4-methylcamphor 43 and ent-43, then a simple route (Scheme 22) to potentially useful intermediates 65 and ent-65 in triterpenoid synthesis would be available. The retrosynthetic analysis shown in scheme 22 is based on two assumptions, viz:

- (1) 4-methylcamphor can be prepared readily in either enantiomeric form; and
- (2) 4-methylcamphor can be converted to 9,10-dibromo-4-methylcamphor 66 /ent-66 by the same type of rearrangement / bromination sequence as that used in the conversion of camphor to 9,10-dibromocamphor 10 /ent 10. [15]

Our present investigations were designed to test the validity of these assumptions and the results are described below.



Scheme 22

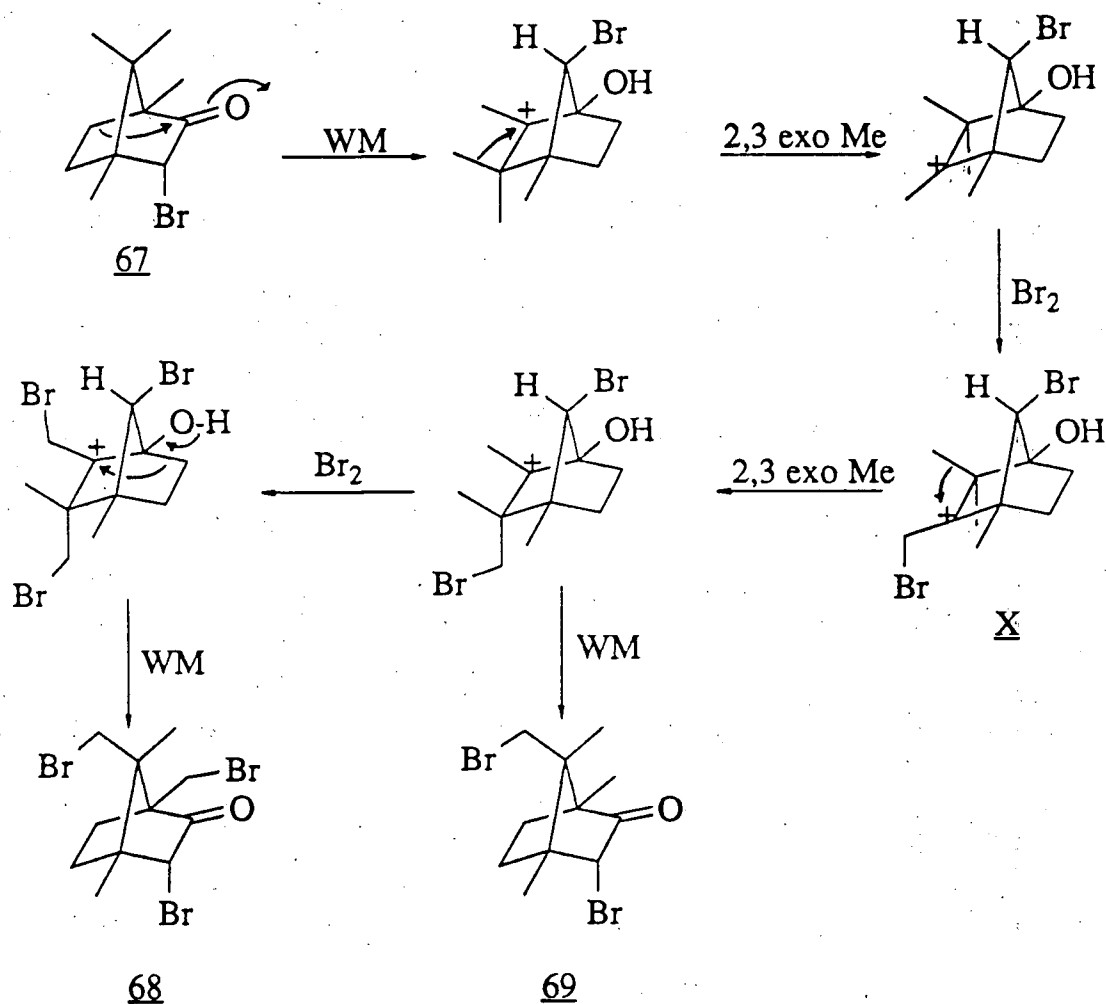
When (-)-4-methylcamphor 43 was treated with bromine and acetic acid endo-3-bromo-4-methylcamphor 67 was produced in 99% yield. Subsequent treatment of endo-3-bromo-4-methylcamphor 67 with 2.3 equivalents of bromine in chlorosulphonic acid did not provide the expected endo-3,9-dibromo-4-methylcamphor 69. Spectroscopic evidence (400 MHz ^1H NMR, IR and mass spectrometry) led us to conclude that the product was endo-3,9,10-tribromo-4-methylcamphor 68. The formation of endo-3,9,10-tribromo-4-methylcamphor 68 from endo-3-bromo-4-methylcamphor 67 was completely unexpected although it was possible to rationalize

its formation by the mechanism shown in scheme 23. Thus we speculated that after a 2,3-exo-methyl shift of intermediate X (Scheme 23), a second bromination occurred readily and this was followed by a Wagner-Meerwein rearrangement to produce the tribromo compound 68.

Regioselective debromination of proposed 68 with zinc/acetic acid yielded a dibromo compound with ^1H NMR and mass spectra consistent with our expectation that this product was 9,10-dibromo-4-methylcamphor 66. A characteristic feature of 10-bromocamphor and derivatives is the ease with which they undergo ring cleavage of the C(1)-C(2) bond when treated with base. The failure of so-called 9,10-dibromo-4-methylcamphor 66 to undergo C(1)-C(2) bond cleavage when treated with sodium methoxide led to the conclusion that this compound did not contain a bromo substituent at C(10). The only other alternative structure* consistent with the NMR evidence was the tribromo compound 70 (Scheme 24) and this was later confirmed by X-ray crystallographic analysis**. Thus, the tribromo compound was shown to be endo-3,9-dibromo-4-(bromomethyl)camphor 70 and the derived dibromo compound was therefore 9-bromo-4-(bromomethyl)camphor 71. A mechanism which explains the formation of tribromo compound 70 is shown in scheme 24. Thus, intermediate X undergoes a Wagner-Meerwein rearrangement

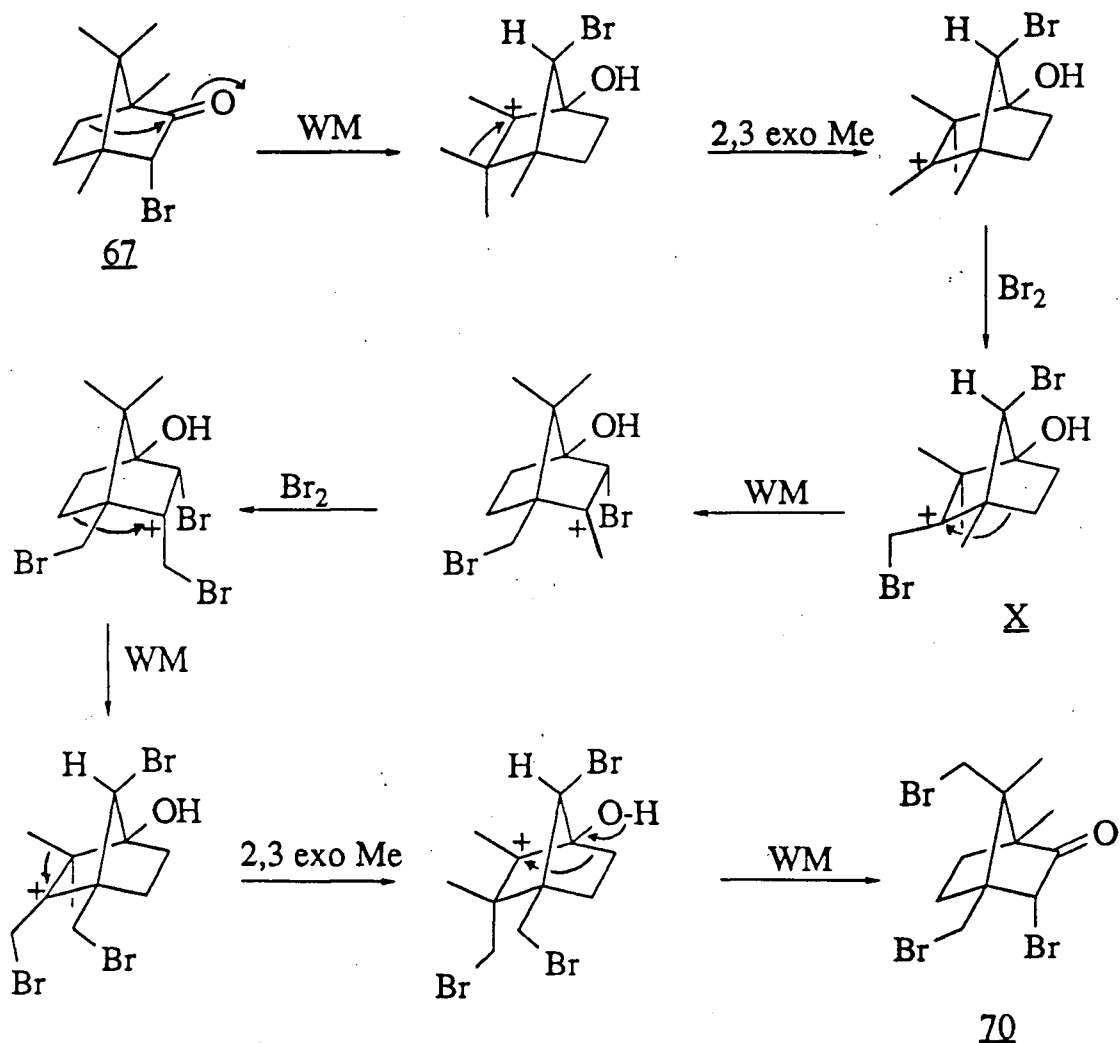
* I am grateful to Mr. Andrew Clase for this suggestion.

** I am grateful to Professor J. Trotter and Dr. S. Rettig for this analysis.



Scheme 23

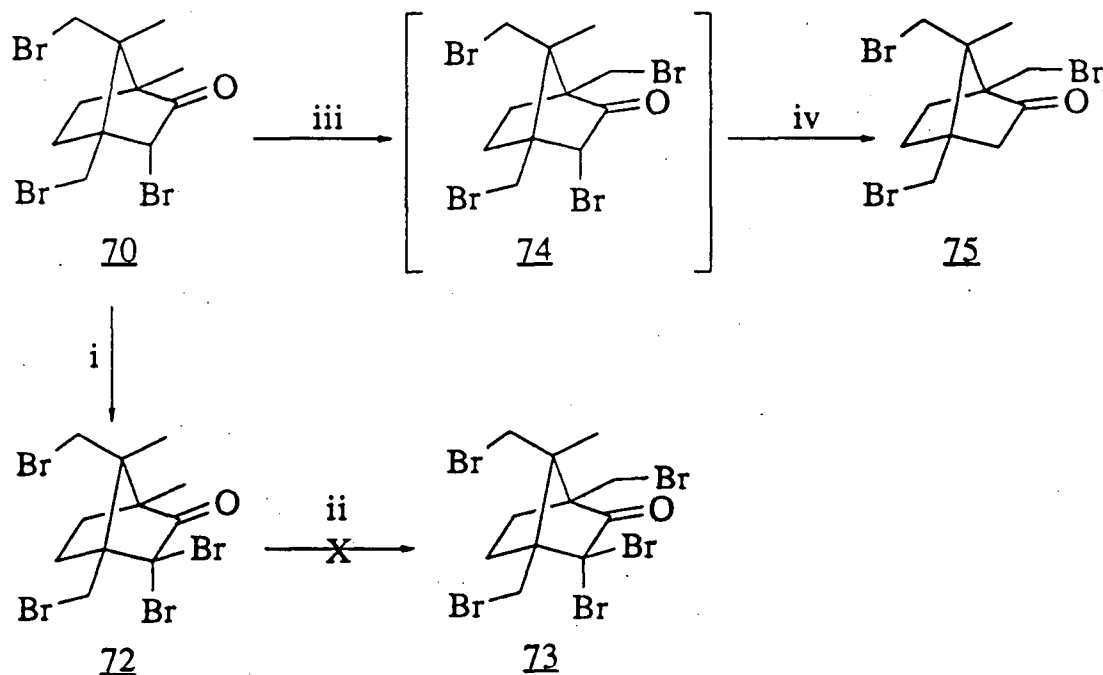
(Scheme 24) instead of undergoing a second 2,3-exo-methyl shift (cf. Scheme 23). And this is followed by bromination, Wagner-Meerwein rearrangement, 2,3-exo-methyl shift, and Wagner-Meerwein rearrangement to give product 70.



Scheme 24

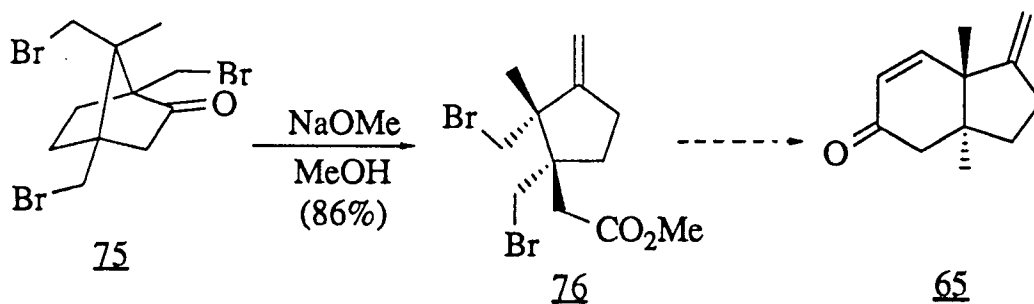
In an attempt to promote C-10 bromination, endo-3,9-dibromo-4-(bromomethyl)camphor 70 was treated with bromine and chlorosulphonic acid (Scheme 25) for 5 days at room temperature, followed by heating at 80°C for 2.5 days, but 3,3,9-tribromo-4-(bromomethyl)camphor 72 was produced. When 70 was treated with bromine and chlorosulphonic acid at room temperature for 12

days, approximately half of the starting material was converted to endo-3,9,10-tribromo-4-(bromomethyl)camphor 74. Since attempts made to isolate and purify 74 by column chromatography and recrystallization were unsatisfactory, the crude product mixture was treated with zinc and acetic acid to give 9,10-dibromo-4-(bromomethyl)camphor 75 (96% from 74). Treatment of 75 with sodium methoxide in methanol (Scheme 26), resulted in C(1)-C(2) bond cleavage as expected, to give dibromoester 76. It is hoped that this compound can be converted to bicyclic enone 65, a potentially useful intermediate in triterpenoid synthesis.



Reagents: i, ClSO_3H , Br_2 , 2.5 days at 80°C (62%)
 ii, ClSO_3H , Br_2 , 25°C , 19 days
 iii, ClSO_3H , Br_2 , 12 days at 25°C (50%)
 iv, Zn / HOAc , 0°C , 2 hours (96%)

Scheme 25



Scheme 26

Thus, the research described above has shown that (-)-4-methylcamphor 43 can be converted to an intermediate 76 which could be of value in the synthesis of triterpenoids belonging to the lanostane 49 structural sub-group. Obviously enantiomer ent-43 will undergo the same type of chemical transformation to give ent-76 as a potentially useful intermediate in the synthesis of triterpenoids belonging to the euphane 50 structural sub-group.

EXPERIMENTAL

General

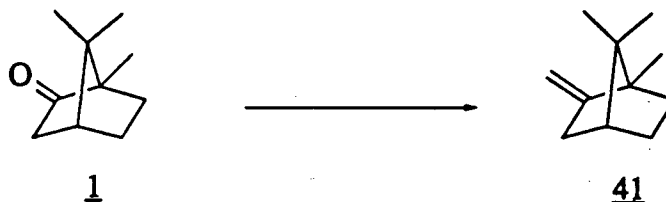
Melting points (mp) were determined on a Kofler micro heating stage and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer model 710B spectrophotometer and were calibrated using the 1601 cm^{-1} band of polystyrene. Absorption positions (ν_{max}) are given in cm^{-1} . Optical rotations ($[\alpha]_D$) were measured on a Perkin-Elmer 141 polarimeter at ambient temperature. The proton nuclear magnetic resonance (^1H NMR) were taken in deuteriochloroform and recorded at 400 MHz on a Bruker WH-400 spectrometer. Signal positions are given in parts per million (ppm) downfield from tetramethylsilane (TMS) using the δ scale. Signal multiplicity, coupling constants and assignments of selected signals are indicated in parentheses. ^{31}P NMR spectra were obtained in benzene and determined on a Varian XL-300 spectrometer at 121.421 MHz with signal positions given in parts per million downfield from H_3PO_4 (used as an external reference standard) with an internal C_6D_6 lock. Low resolution mass spectra were obtained using a Varian MAT CH-4B spectrometer and exact masses were obtained by high resolution mass spectroscopy on a Kratos MS-50 mass spectrometer. All compounds characterized by high resolution mass spectrometry exhibited one spot on a TLC (thin layer chromatography) plate. Low resolution gas liquid chromatography / mass spectra (GC/MS) were obtained on a Carlo Erba 41 60 /

Krato MS 80 RFA instrument using a 0.25 mm X 15 m column with helium as the carrier gas. Gas-liquid chromatography (GLC) was performed on either a Hewlett Packard model 5830A gas chromatograph with a 6 ft X 1/8 in. column of 3% OV-17 or a Hewlett Packard model 5880A gas chromatograph using a 50 m or 12 m X 0.2 mm column of Carbowax 10 M or a 12 m X 0.2 mm column of OV-101. The carrier gas was nitrogen for the 5830A and helium for the 5880A. In all cases a flame ionization detector was used. X-ray crystallographic analysis was carried out by Dr. S. Rettig and microanalyses were performed by Mr. P. Borda, Microanalytical Laboratory, University of British Columbia.

All reactions involving moisture sensitive reagents were performed under an atmosphere of dry argon using either oven or flame dried glassware. All reaction products were dried by allowing the solutions to stand over anhydrous magnesium sulphate. The solvents and reagents used were purified as follows: tetrahydrofuran (THF) was distilled from calcium hydride and then from lithium aluminum hydride (LAH). Diethyl ether was distilled from LAH and hexamethylphosphoramide (HMPA), benzene, methylene chloride, diisopropylamine, triethylamine, and pyridine were distilled from calcium hydride. Methanol was distilled from dry magnesium and iodine following reflux. Petroleum ether (the hydrocarbon fraction of boiling range ~30-60 °C) was distilled prior to use.

Flash Chromatography was performed using Merck silica gel 60, 230-400 mesh and TLC using Merck silica gel 60 F₂₅₄ sheets.

All chemicals were supplied by Aldrich Chemical Company unless otherwise stated.

Preparation of (-)-2-methylenebornane 41

(1) Method A *

Methyltriphenylphosphonium bromide (154.73 g, 0.43 mol) was vacuum pumped for 3 hours to remove any trace of moisture before it was dissolved in pure THF (400 mL). n-Butyllithium (0.43 mol, 270.7 mL of a 1.6 M solution) was added dropwise at room temperature and the resultant mixture was stirred at 50°C for 2 hours under argon. (+)-Camphor 1 (41.21 g, 0.27 mol) in pure THF (160 mL) was then added dropwise to the Wittig reagent and the reaction mixture was refluxed for 15 hours at 65°C under argon. Upon completion of the reaction, half of the THF was removed by rotary evaporation and the rest was diluted with water and extracted with pentane (3X). The pentane extracts were combined and washed with water (3X) and dried over anhydrous magnesium sulphate. Evaporation of the solvent yielded a viscous yellow oil which was purified by column chromatography (silica gel 230-400 mesh, elution with 100% petroleum ether) to provide (-)-2-methylenebornane 41 as a white crystalline solid (35.5 g, 87%), mp 70-71 °C (sealed tube; lit. ref. mp 68-70 °C); $[\alpha]_D^{23}$ -52.88 (c. 2.67, benzene) (lit.

* This is a modification of the method used by Gream et al. [49]

$[\alpha]_D^{26} -48.5$ (c. 2.12, benzene)[49]; ν_{\max} (CHCl_3): 1650 cm^{-1} , 885 cm^{-1} ; δ (CDCl_3 , 400 MHz): 0.76 (3H, s, C-8 methyl), 0.89 (3H, s, C-10 methyl), 0.92 (3H, s, C-9 methyl), 1.16-1.30 (2H, m, C-5 and C-6 endo protons), 1.64 (1H, ddd, $J=12\text{ Hz}$, 12 Hz and 4 Hz , C-6 exo proton), 1.73 (1H, dd, $J=8\text{ Hz}$ and 4 Hz , C-4 proton), 1.78 (1H, m, C-5 exo proton), 1.91 (1H, bd, $J=16\text{ Hz}$, C-3 endo proton), 2.38 (1H, bd, $J=16\text{ Hz}$, C-3 exo proton), 4.63 (d) and 4.69 (d) (2H, AB quartet, $J=22\text{ Hz}$, exo-methylene protons); m/e (relative intensity): 150 (M^+ , 10.2), 135 (8.6), 69 (80.6), 55 (26.9), 41 (52.4).

Exact mass calcd. for $\text{C}_{11}\text{H}_{18}$: 150.1409; found 150.1413.

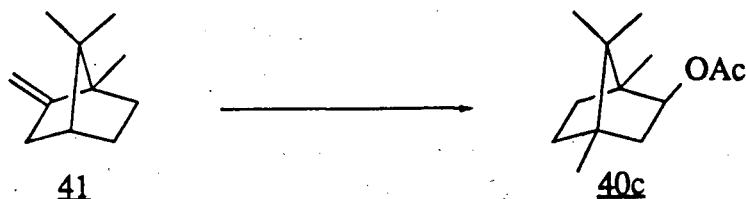
Anal. calcd. for $\text{C}_{11}\text{H}_{18}$: C 87.93, H 12.07; found: C 87.71, H 12.10 .

(11) Method B **

Titanium tetrachloride (0.48 mL, 4.37 mmol) was added dropwise to a stirred suspension of zinc dust (1.18 g, 18.0 mmol) and dibromomethane (1.04 g, 0.42 mL, 6.0 mmol) in THF (20 mL) at -40°C . The reaction mixture was allowed to warm to 5°C and kept in the refrigerator for 3 days to give a thick brown slurry. The ice-cold slurry was added portionwise to a stirred solution of (+)-camphor **1** (0.30 g, 2.0 mmol) in dichloromethane (2.0 mL) and the resultant mixture was stirred at room temperature for 18 hours under argon. The reaction

** This is a modification of the method used by Oshima et al.[48]

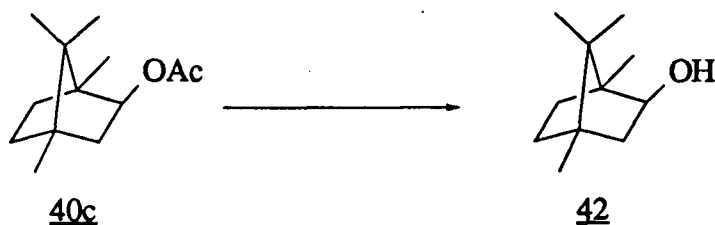
mixture was then quenched with saturated sodium bicarbonate solution, extracted with ether (3X) and the combined ether extracts washed with water (3X), and dried over anhydrous magnesium sulphate. Evaporation of the solvent yielded pure (-)-2-methylenebornane 41 as a white crystalline solid (0.30 g, 99%) exhibiting spectral data comparable to those above.

Preparation of (+)-4-methylisobornyl acetate 40c

Concentrated sulphuric acid (1.31 mL, 0.016 mol) was added dropwise to (-)-2-methylenebornane 41 (12.64 g, 0.084 mol) in glacial acetic acid (54.4 mL). The reaction mixture was stirred at 0°C for 30 minutes, quenched in water and extracted with ether (3X). The ether extracts were combined, washed with saturated sodium bicarbonate solution (3X), water (2X), and dried over anhydrous magnesium sulphate. Evaporation yielded a light yellow oil (12.58 g) which was purified by column chromatography (silica gel 230-400 mesh). Elution with petroleum ether / ether 98:2 provided pure (+)-4-methylisobornyl acetate 40c as a clear colorless oil (9.54 g, 73%), $[\alpha]_D^{19.5} +39.23$ (c. 2.20, 95% ethanol) (lit. $[\alpha]_D +35.84$) [47g,1]; ν_{\max} (film): 1740 cm^{-1} , 1250 cm^{-1} , 1040 cm^{-1} ; δ (CDCl_3 , 400 MHz): 0.69 (3H, s, C-9 methyl), 0.83 (3H, s, C-8 methyl), 0.86 (3H, s, C-10 methyl), 0.90 (3H, s, C-4 methyl), 1.10-1.19 (2H, m, C-5 and C-6 endo protons), 1.36-1.54 (3H, m, C-6 exo, C-3 endo, and C-5 exo protons), 1.82 (1H, dd, $J=14$ Hz and 8 Hz, C-3 exo proton), 2.01 (3H, s, acetyl), 4.65 (1H, dd, $J=9$ Hz and 3.5 Hz, C-2 proton); m/e (relative intensity): 210 (M^+ , 2.0), 150 (50.9), 135 (48.3), 109 (82.3). 43 (100.0).

Exact mass calcd. for $\text{C}_{13}\text{H}_{22}\text{O}_2$: 210.1620; found 210.1622.

Anal. calcd. for $C_{13}H_{22}O_2$: C 74.24, H 10.54; found: C 74.82,
H 10.70 .

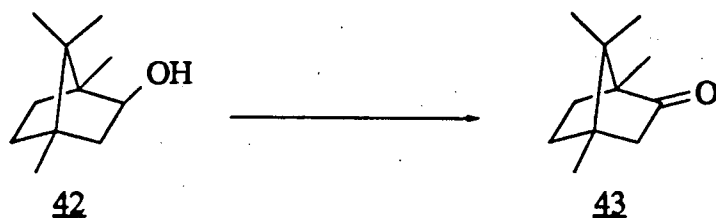
Preparation of (+)-4-methylisoborneol 42

Lithium aluminum hydride (3.1 g, 0.082 mol) was added to a solution of dry (+)-4-methylisobornyl acetate 40c (9.54 g, 0.045 mol) in pure THF (160 mL) and the reaction mixture was stirred at 0°C for 4 hours. The reaction mixture was then quenched in water, extracted with ether (3X), and the ether extracts washed with 1M HCl solution (3X), brine (2X), and water (2X), and dried over anhydrous magnesium sulphate. Evaporation of the ether yielded (+)-4-methylisoborneol 42 as white needles (7.56 g, 99%), mp 193-194 °C (sealed tube; lit. ref. mp 195-196.5 °C); $[\alpha]_D^{30.5} +19.47$ (c.10.0, 95% ethanol) {lit. $[\alpha]_D +25.2$ (c. 10.0, EtOH)} [47c,f]; ν_{\max} (CHCl₃): 3600 cm⁻¹, 1210 cm⁻¹; δ (CDCl₃, 400 MHz): 0.67 (3H, s, C-9 methyl), 0.87 (3H, s, C-8 methyl), 0.90 (3H, s, C-10 methyl), 0.93 (3H, s, C-4 methyl), 0.94-1.11 (2H, m, C-5 and C-6 endo protons), 1.34-1.46 (2H, m, C-6 exo and C-3 endo protons), 1.51 (1H, ddd, J=8 Hz, 8 Hz and 4 Hz, C-5 exo proton), 1.74 (1H, dd J=14 Hz and 8 Hz, C-3 exo proton), 3.52 (1H, dd, J=8 Hz and 4 Hz, C-2 proton); m/e (relative intensity): 168 (M⁺, 2.1), 150 (14.4), 109 (100.0), 41 (70.6).

Exact mass calcd. for C₁₁H₂₀O: 168.1514; found 168.1514.

Anal. calcd. for C₁₁H₂₀O: C 78.51, H 11.98; found: C 78.57,

H 11.99 .

Preparation of (-)-4-methylcamphor **43**

(+)-4-Methylisoborneol **42** (7.50 g, 0.045 mol) was dissolved in pure methylene chloride (150 mL) and the solution added dropwise to PCC (14.4 g, 0.067 mol) in methylene chloride (150 mL) and then stirred at room temperature for 3.5 hours. The reaction mixture was filtered through a layer of silica gel and anhydrous magnesium sulphate and washed with ether. Evaporation of the solvent provided (-)-4-methylcamphor **43** as a white crystalline solid (7.45 g, 99%), mp 150-151 °C (sealed tube; lit. ref. mp 167-168 °C); $[\alpha]_D^{21}$ -16.05 (c. 2.04, 95% ethanol) {lit. $[\alpha]_D$ -14.50 (c. 10.0, EtOH)} [47f]; ν_{\max} (CHCl₃): 1730 cm⁻¹; δ (CDCl₃, 400 MHz): 0.71 (3H, s, C-9 methyl), 0.83 (3H, s, C-8 methyl), 0.92 (3H, s, C-10 methyl), 1.04 (3H, s, C-4 methyl), 1.35-1.43 (2H, m, C-5 and C-6 endo protons), 1.57-1.75 (2H, m, C-5 and C-6 exo protons), 1.87 (1H, d, J=18 Hz, C-3 endo proton), 2.08 (1H, dd, J=18 Hz and 3 Hz, C-3 exo proton); m/e (relative intensity): 166 (M⁺, 39.8), 138 (13.9), 109 (94.8), 83 (92.6), 82 (100.0).

Exact mass calcd. for C₁₁H₁₈O: 166.1358; found 166.1360.

Anal. calcd. for C₁₁H₁₈O: C 79.47, H 10.91; found: C 79.67, H 11.03 .

Determination of Optical Purity Using the Anderson-Shapiro Reagent 48

(1) Model study using (+)-isoborneol (+)-55 and (-)-isoborneol 55:

The alcohol (+)-55 or 55 (308.5 mg, 2.0 mmol) was dissolved in dry benzene (2.0 mL) and dry triethylamine (0.42 mL, 303.6 mg, 3.0 mmol) and 4-(dimethylamino)pyridine (24.4 mg, 0.20 mmol) were added. The Anderson-Shapiro reagent 48 (358.1 mg, 2.10 mmol) was then added and the vial was shaken for 30 seconds. After allowing the reaction mixture to stand for 15 minutes, a small amount of C₆D₆ was added for NMR locking purposes, and the mixture was filtered through a cotton plug into a 5-mm NMR tube and a 121.4 MHz ³¹P NMR spectrum was recorded using H₃PO₄ as the external reference standard:

(a) Using (+)-isoborneol (+)-55 as substrate,

δ : 13.404, 13.341 (two diastereomeric Anderson-Shapiro derivatives, relative intensity ~ 1:1, Δδ 7.89 Hz), 17.480 (Anderson-Shapiro reagent).

(b) Using (-)-isoborneol 55 as substrate,

δ : 13.478 (Anderson-Shapiro derivative), 17.375 (Anderson-Shapiro reagent).

(ii) Examination of (+)-4-methylisoborneol 42 prepared by the LAH reduction of 40a*:

(+)-4-Methylisoborneol 42 $[\alpha]_D^{30.5} +19.47$ (c. 10.0, 95% ethanol), 334.5 mg, 2.0 mmol} was treated in the manner described above and a 121.4 MHz ^{31}P NMR spectrum of the Anderson-Shapiro derivatives was recorded:

δ : 13.667, 13.628 (two diastereomeric derivatives, relative intensity ~2.1:1, $\Delta\delta$ 4.86 Hz.). The signal separation was too small to provide more than an approximate estimation of relative signal areas.

* 40a was prepared by a similar procedure as described on page 66 with the temperature and time of reaction changed to room temperature and 15 minutes.

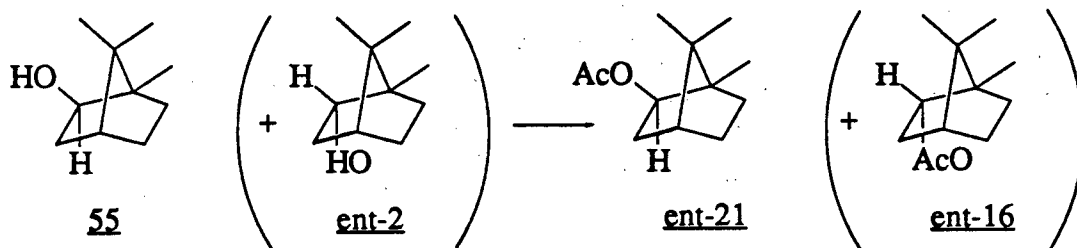
Preparation of (±)-isobornyl acetate (±)-21



4-(Dimethylamino)pyridine (3.7 g, 30.0 mmol) and dry acetic anhydride (2.84 mL, 30.0 mmol) were added to a solution of (±)-isoborneol (±)-55 (1.54 g, 10.0 mmol) in dry pyridine (50 mL) under argon at room temperature. The reaction mixture was then stirred at room temperature overnight, quenched with water and extracted with ether (3X). The ether extracts were combined, washed with 1M HCl solution (3X), saturated sodium bicarbonate solution (3X), water (2X), and dried over anhydrous magnesium sulphate. Evaporation of the solvent yielded an orange oil (2.1 g) which was purified by column chromatography (silica gel 230-400 mesh, elution with petroleum ether / ether 95:5) to provide (±)-isobornyl acetate (±)-21 as a clear colorless oil (1.63 g, 83%), $[\alpha]_D^{19.5}$ 0.00 (c. 12.1, 95% ethanol); ν_{max} (film): 1735 cm^{-1} , 1250 cm^{-1} , 1035 cm^{-1} ; δ (CDCl_3 , 400 MHz): 0.85 (6H, s, C-8 and C-9 methyls), 0.98 (3H, s, C-10 methyl), 1.04-1.19 (2H, m, C-5 and C-6 endo protons), 1.51-1.83 (5H, m, C-6 exo, C-3 endo, C-5 exo, C-4 and C-3 exo protons), 2.03 (3H, s, acetyl), 4.67 (1H, dd, $J=8$ Hz and 4 Hz, C-2 proton); m/e (relative intensity): 196 (M^+ , 0.6), 136 (66.2), 121 (63.0), 95 (98.4), 43 (94.3).

Exact mass calcd. for $\text{C}_{12}\text{H}_{20}\text{O}_2$: 196.1463; found 196.1454.

Anal. calcd. for $C_{12}H_{20}O_2$: C 73.43, H 10.27; found: C 73.63,
H 10.29 .

Preparation of (-)-isobornyl acetate ent-21

A mixture of (-)-isoborneol 55 and (+)-borneol ent-2 (1.54 g, 10.0 mmol; 9:1 by capillary GLC [OV-101, 100°C]) was acetylated with acetic anhydride / pyridine using the procedure described above (page 73) for (±)-isoborneol (±)-55. A mixture of (-)-isobornyl acetate ent-21 and (+)-bornyl acetate ent-16 (85.7% ent-21, 14.3% ent-16 by capillary GLC [OV-101, 100°C]) was obtained as a clear colorless oil (1.57 g, 80% yield based on recovered starting materials), ν_{max} (film): 1738 cm^{-1} , 1240 cm^{-1} , 1050 cm^{-1} ; δ (CDCl_3 , 400 MHz): 2.06 (s, CH_3CO_2 -), 4.89 (dd, $J=10$ Hz and 4 Hz, C-2 exo-hydrogen) were observed; m/e (relative intensity): 196 (M^+ , 1.6), 136 (50.1), 121 (41.0), 95 (94.1), 43 (100.0).

Exact mass calcd. for $\text{C}_{12}\text{H}_{20}\text{O}_2$: 196.1463; found 196.1456.

Anal. calcd. for $\text{C}_{12}\text{H}_{20}\text{O}_2$: C 73.43, H 10.27; found: C 72.61, H 10.08.

Determination of Optical Purity using Tris[3-(heptafluoropropyl-hydroxymethylene)-d-camphoratoleuropium (III)] 45

(i) Model study using (+)-isobornyl acetate (+)-21 and (-)-isobornyl acetate ent-21:

The acetate (+)-21 or ent-21 (19.63 mg, 0.10 mmol) was weighed in a pipette and transferred to a 5-mm NMR tube. The volume of the sample in the tube was made up to 1 mL with CDCl₃. A 400 MHz ¹H NMR spectrum (with TMS as the internal reference standard) was recorded at room temperature before the addition of [Eu(hfc)₃]. [Eu(hfc)₃] (11.94 mg, 0.010 mmol) was then added directly to the NMR tube and a second spectrum was recorded. Additional spectra were obtained after the concentration of [Eu(hfc)₃] was increased to 0.025 mmol/mL (addition of 17.9 mg) and 0.050 mmol/mL (addition of 29.85 mg) respectively.

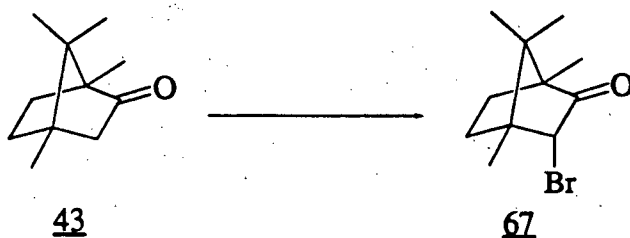
(ii) Synthetic (+)-4-Methylisobornyl acetate 40 (cf. p.66):

Sample	Experimental Conditions	[α] _D
<u>40a</u>	25°C, 15 min.	+35.79 (c. 2.28, 95% ethanol)
<u>40b</u>	25°C, 10 min.	+32.12 (c. 3.12, 95% ethanol)
<u>40c</u>	0°C, 30 min.	+39.23 (c. 2.20, 95% ethanol)

(+)-4-Methylisobornyl acetate 40 (21.03 mg, 0.10 mmol) was treated in the same manner and a series of four 400 MHz ¹H NMR spectra were recorded as described above.

(iii) Synthetic (-)-4-Methylcamphor 43 derived from 40a:

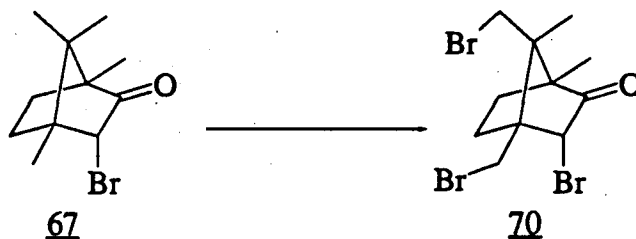
(-)-4-Methylcamphor 43 (16.63 mg, 0.10 mmol) was dissolved in CDCl_3 (1 mL) and a 400 MHz ^1H NMR spectrum (with TMS as the internal reference standard) was recorded at room temperature before addition of $[\text{Eu}(\text{hfc})_3]$. Three additional spectra were recorded after sequential addition of 11.94 mg (0.01 mmol), 23.87 mg (0.02 mmol) and 35.81 mg (0.03 mmol) of $[\text{Eu}(\text{hfc})_3]$.

Preparation of endo-3-bromo-4-methylcamphor 67

A solution of (-)-4-methylcamphor 43 (6.37 g, 0.038 mol) in glacial acetic acid (28 mL) was warmed to 80°C and bromine (2.29 mL, 6.87 g, 76.6 mmol) in glacial acetic acid (2.29 mL) was added dropwise. The mixture was stirred at 80°C for 31 hours, then cooled, poured into ice-water. The resulting solid was filtered off, washed with water to yield endo-3-bromo-4-methylcamphor 67 as a white crystalline solid (9.30 g, 99%), mp 119.5-120.5 °C (sealed tube); ν_{max} (CHCl₃): 1750 cm⁻¹; δ (CDCl₃, 400 MHz): 0.81 (3H, s, C-9 methyl), 0.98 (3H, s, C-8 methyl), 1.00 (3H, s, C-10 methyl), 1.06 (3H, s, C-4 methyl), 1.40 (1H, m, C-6 endo proton), 1.55-1.67 (2H, m, C-5 endo and C-6 exo protons), 2.07 (1H, m, C-5 exo proton), 4.31 (1H, d, J=1.5 Hz, C-3 proton); m/e (relative intensity): 246/244 (M⁺, 5.0/4.9), 165 (48.1), 137 (52.1), 123 (45.0), 109 (75.7), 83 (100.0).

Exact mass calcd. for C₁₁H₁₇OBr: 246.0442/244.0462; found 246.0439/244.0467.

Anal. calcd. for C₁₁H₁₇OBr: C 53.89, H 6.99, Br 32.59; found: C 53.81, H 6.86, Br 32.80.

Preparation of endo-3,9-dibromo-4-(bromomethyl)camphor 70

Endo-3-bromo-4-methylcamphor 67 (7.36 g, 0.030 mol) and bromine (3.47 mL, 0.069 mol) were added to a single-neck flask. Chlorosulphonic acid (5.48 mL, 0.082 mol) was added slowly to the reaction mixture. After being stirred at room temperature for 19 hours, the reaction mixture was added to ice-cold bisulphite solution and extracted with ether (3X). The ether extracts were combined, washed with saturated sodium bicarbonate solution (2X) and water (2X), and dried over anhydrous magnesium sulphate. Evaporation of the solvent yielded a yellow solid which was washed with ice-cold ether to provide endo-3,9-dibromo-4-(bromomethyl)camphor 70 as a white crystalline solid (6.20 g, 51%), mp 142.5-143.5 °C (sealed tube); ν_{\max} (CHCl₃): 1750 cm⁻¹; δ (CDCl₃, 400 MHz): 1.07 (3H, s, C-8 methyl), 1.27 (3H, s, C-10 methyl), 1.53 (1H, ddd, J=14 Hz, 9 Hz and 4 Hz, C-6 endo proton), 1.72 (1H, ddd, J=14 Hz, 14 Hz and 4 Hz, C-5 endo proton), 1.85 (1H, dddd, J=14 Hz, 14 Hz, 4 Hz and 2.5 Hz, C-5 exo proton), 2.22 (1H, ddd, J=14 Hz, 9 Hz and 4 Hz, C-6 exo proton), 3.45 (d, J=11 Hz), 3.74 (d, J=11 Hz) (2H, AB quartet, C-9 methylene), 3.52 (d, J=11.5 Hz), 4.05 (d, J=11.5 Hz) (2H, AB quartet, C-4 methylene), 4.92 (1H, d, J=2.5 Hz, C-3 proton); m/e (relative intensity): 406/404/402/400 (M⁺, 0.4/1.8/2.0/0.7),

325/323/321 (17.1/41.7/18.8), 245/243 (14.0/18.8), 201/199
(28.7/22.2), 163 (16.9), 121 (36.3), 107 (50.8), 105 (37.8),
93 (66.7), 91 (69.2).

Exact mass calcd. for $C_{11}H_{15}OBr_3$:

405.8612/403.8632/401.8652/399.8672; found

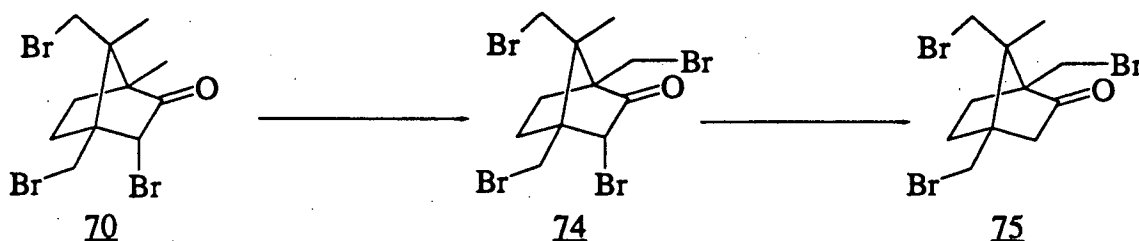
405.8605/403.8637/401.8667/399.8675.

Anal. calcd. for $C_{11}H_{15}OBr_3$: C 32.79, H 3.75, Br 59.49; found:
C 33.05, H 3.78, Br 59.22.

The structure and absolute configuration of this compound was
confirmed by X-ray analysis.*

* I am grateful to Professor J. Trotter and Dr. S. Rettig
for carrying out this analysis.

Preparation of 9,10-dibromo-4-(bromomethyl)camphor 75



Endo-3,9-dibromo-4-(bromomethyl)camphor 70 (0.80 g, 0.0020 mol) and bromine (0.17 mL, 0.0034 mol) were added to a single-neck flask. Chlorosulphonic acid (0.70 mL, 0.010 mol) was added slowly to the reaction mixture which was then stirred at room temperature under nitrogen and followed by capillary GLC (OV-101, 190°C). After 6 days, more bromine (0.17 mL, 0.0034 mol) and chlorosulphonic acid (0.35 mL, 0.0052 mol) were added. After another 6 days, capillary GLC analysis indicated that approximately half of the starting material 70 was brominated and that bromination failed to proceed further. Thus, the reaction mixture was added to cold sodium bisulphite solution and extracted with ether (3X). The ether extracts were combined, washed with saturated sodium bicarbonate (3X) and water (3X), and dried over anhydrous magnesium sulphate. Evaporation of the solvent yielded a yellow solid (0.84 g). Capillary GLC analysis (OV-101, 190°C) of the crude product indicated the ratio of the starting material 70 to the product 74 to be 1:1. The crude product was subsequently treated with zinc / acetic acid in a procedure described below.

Zinc dust (235.8 mg, 3.61 mmol) was carefully added to a solution of the crude tetrabromo product (0.84 g) in acetic

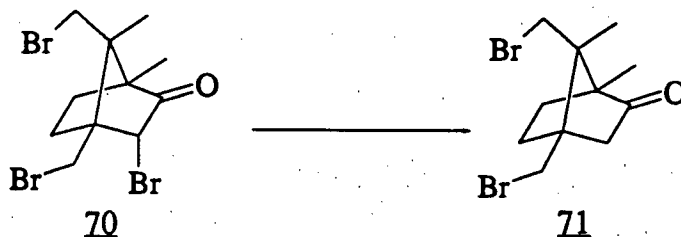
acid (3.37 mL, 58.87 mmol) at 0°C. The reaction mixture was stirred for 2 hours at 0°C, added to water, and extracted with ether (3X). The ether extracts were combined, washed with saturated sodium bicarbonate solution (2X), brine (2X), and water (2X), and dried over anhydrous magnesium sulphate. Evaporation of the solvent yielded a yellow oil (0.83 g). Column chromatography (silica gel 230-400 mesh, elution with petroleum ether / ether 98:2) yielded 9-bromo-4-(bromomethyl)camphor 71 as a clear oil (0.30 g, 47% yield from 70) (cf. p.84) followed by 9,10-dibromo-4-(bromomethyl)camphor 75 as a white crystalline solid (0.39 g, 48% yield from 70), mp 158-159 °C (sealed tube); ν_{max} (CHCl₃): 1745 cm⁻¹; δ (CDCl₃, 400 MHz): 1.15 (3H, s, C-8 methyl), 1.62 (1H, ddd, J=14.5 Hz, 9.5 Hz and 5.5 Hz, C-6 endo proton), 1.92-2.08 (2H, m, C-6 exo and C-5 endo protons), 2.25 (1H, ddd, J=14.5 Hz, 11 Hz and 5 Hz, C-5 exo proton), 2.35-2.45 (2H, m, C-3 endo and exo protons), 3.47 (d, J=12 Hz), 3.71 (d, J=12 Hz) (2H, AB quartet, C-9 methylene), 3.67 (d, J=11.5 Hz), 3.72 (d, J=11.5 Hz) (2H, AB quartet, C-10 methylene), 3.59 (d, J=10.5 Hz), 4.02 (d, J=10.5 Hz) (AB quartet, C-4 methylene); m/e (relative intensity): 406/404/402/400 (M⁺, 0.1/0.3/0.3/0.1), 325/323/321 (21.9/45.8/23.2), 243/241 (27.3/21.3), 215/213 (33.4/30.5), 201/199 (95.0/100.0), 163 (18.7), 121 (26.7), 107 (25.7), 105 (35.8), 93 (49.6), 91 (49.8).

Exact mass calcd. for C₁₁H₁₅Br₃:

405.8612/403.8632/401.8652/399.8672; found

405.8568/403.8621/401.8679/399.8667.

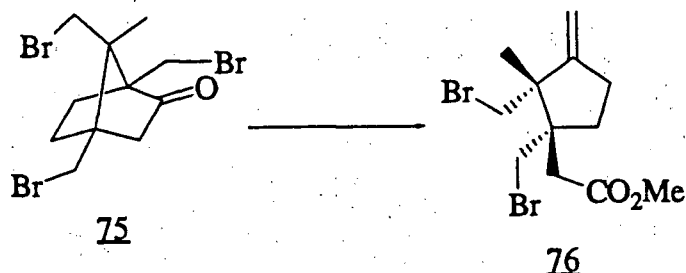
Anal. calcd. for $C_{11}H_{15}OBr_3$: C 32.79, H 3.75, Br 59.49; found:
C 32.64, H 3.71, Br 59.32.

Preparation of 9-bromo-4-(bromomethyl)camphor **71**

Zinc dust (30.59 mg, 0.47 mmol) was carefully added to a solution of endo-3,9-dibromo-4-(bromomethyl)camphor **70** (100 mg, 0.25 mmol) in acetic acid (0.44 mL, 7.63 mmol). The reaction mixture was stirred for 90 minutes at 0°C, added to water, and extracted with ether (3X). The ether extracts were combined, washed with saturated sodium bicarbonate solution (2X), brine (2X), and water (2X), and dried over anhydrous magnesium sulphate. Evaporation of the solvent yielded a viscous yellow oil (88.1 mg). Column chromatography (silica gel 230-400 mesh, elution with petroleum ether / ether 95:5) yielded **71** as a clear oil (60.5 mg, 75%), ν_{max} (CHCl₃): 1740 cm⁻¹; δ (CDCl₃, 400 MHz): 1.00 (3H, s, C-8 methyl), 1.04 (3H, s, C-10 methyl), 1.54 (1H, m, C-6 endo proton), 1.75 (1H, ddd, J=14.5 Hz, 11 Hz and 5 Hz, C-5 endo proton), 1.87-2.02 (2H, m, C-5 and C-6 exo protons), 2.28-2.39 (2H, m, C-3 exo and endo protons), 3.35 (d, J=11 Hz), 3.65 (d, J=11 Hz) (2H, AB quartet, C-9 methylene), 3.61 (d, J=10.5 Hz), 4.00 (d, J=10.5 Hz) (2H, AB quartet, C-4 methylene); m/e (relative intensity): 326/324/322 (M⁺, 11.4/23.9/12.7), 245/243 (56.2/56.2), 217/215 (35.5/35.2), 201/199 (83.9/76.6), 163 (50.3), 135 (85.8), 121 (77.8), 107 (69.6), 93 (90.0), 81 (97.4), 41 (100.0).

Exact mass calcd. for $C_{11}H_{16}OBr_2$:

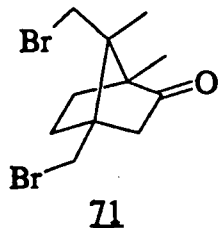
325.9527/323.9547/321.9567; found 325.9532/323.9543/321.9585.

Preparation of the Dibromoester 76

9,10-Dibromo-4-(bromomethyl)camphor 75 (74.5 mg, 0.18 mmol) in dry methanol (1.0 mL) was added to a solution of sodium methoxide in methanol {prepared from sodium (6.4 mg, 0.28 mmol) and methanol (0.8 mL)} under argon at 0°C. After 4 hours at room temperature, the reaction mixture was acidified with 1M HCl solution and extracted with ether (3X). The combined ether extracts were washed with brine (3X) and water (2X), dried (anhydrous magnesium sulphate), and the solvent removed to yield the crude product as a light yellow oil (0.143 g). Column chromatography (silica gel 230-400 mesh, elution with petroleum ether / ether 99:1) yielded 76 as a clear colorless oil (56.3 mg, 86%); ν_{max} (CHCl₃): 1720 cm⁻¹, 1640 cm⁻¹; δ (CDCl₃, 400 MHz): 1.28 (3H, s), 1.80-1.96 (2H, m), 2.38-2.50 (3H, m), 2.82 (1H, dd, J=15.5 Hz and 1 Hz), 3.47 (d, J=10 Hz), 3.59 (d, J=10 Hz) (2H, AB quartet, CH₂Br), 3.68 (3H, s, CO₂CH₃), 3.76 (d, J=11 Hz), 3.90 (d, J=11 Hz) (2H, AB quartet, CH₂Br), 4.94 (1H, t, J=2 Hz), 5.05 (1H, t, J=2 Hz); m/e (relative intensity): 356/354/352 (M⁺, 0.1/0.2/0.1), 275/273 (3.1/3.7), 201/199 (28.2/30.9), 154 (0.5), 133 (41.8), 119 (100.0), 105 (52.5), 91 (48.3).

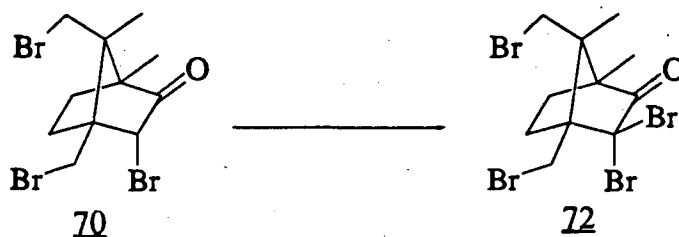
Anal. calcd. for C₁₂H₁₈O₂Br₂: C 40.71, H 5.12, Br 45.13; found:

C 40.64, H 5.03, Br 45.06.

Attempted cleavage of 9-bromo-4-(bromomethyl)camphor 71

9-Bromo-4-(bromomethyl)camphor 71 (60.0 mg, 0.19 mmol) in dry methanol (1.0 mL) was added to a solution of sodium methoxide in methanol {prepared from sodium (6.4 mg, 0.28 mmol) and methanol (0.8 mL)} under argon at 0°C. The starting material remained unchanged after 10 hours at 50°C.

Preparation of 3,3,9-tribromo-4-(bromomethyl)camphor **72**



Chlorosulphonic acid (2.10 mL, 0.031 mol) was added slowly to a mixture of endo-3,9-dibromo-4-(bromomethyl)camphor **70** (2.4 g, 0.0060 mol) and bromine (0.51 mL, 0.010 mol). After stirring at room temperature for 5 days, the reaction mixture was heated to 80°C and terminated after 2.5 days. The reaction mixture was cooled and quenched with water, and sodium bisulphite was added to destroy excess bromine. Extraction with ether (3X), followed by washing with saturated sodium bicarbonate (3X) and water (3X), drying over anhydrous magnesium sulphate, and evaporation of the solvent yielded a yellow solid which on trituration with ice-cold ether provided tetrabromo compound **72** as a white crystalline solid (1.80 g, 62%), mp 182-183 °C (sealed tube); ν_{max} (CHCl₃): 1755 cm⁻¹; δ (CDCl₃, 400 MHz): 1.12 (3H, s, C-8 methyl), 1.30 (3H, s, C-10 methyl), 1.70-1.85 (2H, m, C-5 and C-6 endo protons), 2.27 (1H, ddd, J=14.5 Hz, 11.5 Hz and 6.5 Hz, C-5 exo proton), 2.89 (1H, ddd, J=14.5 Hz, 9 Hz and 3.5 Hz, C-6 exo proton), 3.38 (d, J=11 Hz), 3.71 (d, J=11 Hz) (2H, AB quartet, C-9 methylene), 3.91 (d, J=11 Hz), 4.28 (d, J=11 Hz) (2H, AB quartet, C-4 methylene); m/e (relative intensity): 486/484/482/480/478 (M⁺, 0.6/5.2/7.5/4.8/1.4), 405/403/401/399 (1.8/4.9/4.3/1.5), 325/323/321 (26.1/54.3/29.1),

243/241 (16.5/18.5), 161 (30.5).

Exact mass calcd. for $C_{11}H_{14}OBr_4$:

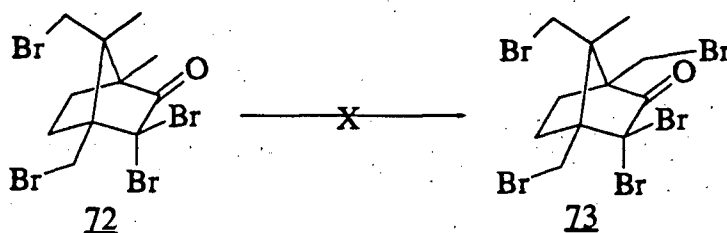
485.7697/483.7717/481.7737/479.7757/477.7777; found

485.7747/483.7729/481.7727/479.7774/477.7820.

Anal. calcd. for $C_{11}H_{14}OBr_4$: C 27.42, H 2.93, Br 66.33; found:

C 27.23, H 2.87, Br 66.58.

Attempted C-10 bromination of 3,3,9-tribromo-4-(bromomethyl)-camphor 72



Chlorosulphonic acid (1.31 mL, 0.019 mol) was added slowly to a mixture of 3,3,9-tribromo-4-(bromomethyl)camphor 72 (1.80 g, 0.0037 mol) and bromine (0.32 mL, 0.0063 mol) and the reaction mixture stirred at room temperature for 19 days. Workup as described above (page 89) provided starting material.

Preparation of (+)-3,3-dibromocamphor **26**

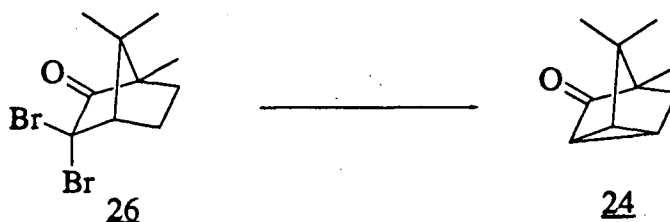
Bromine (40.0 g, 12.5 mL, 0.25 mol) was added dropwise to a solution of (+)-endo-3-bromocamphor **5a** (46.2 g, 0.20 mol) in glacial acetic acid (200 mL) and the reaction mixture was heated at 55°C for an hour followed by three more additions of bromine (10 mL, 0.20 mol each) at one-hourly intervals. After the last addition of bromine, the reaction mixture was further heated for an hour before it was cooled, poured into ice-water, neutralized with solid sodium bicarbonate and excess bromine destroyed by solid sodium bisulphite. The mixture was then extracted with ether (3X), washed with brine (3X) and water (3X), and dried over anhydrous magnesium sulphate. Removal of the solvent yielded a yellow solid which was crystalized from ether in the refrigerator to provide (+)-3,3-dibromocamphor **26** as a white crystalline solid (57.0 g, 92%), mp 60-61 °C (sealed tube; lit. ref. mp 64°C); ν_{max} (CHCl₃): 1755 cm⁻¹; δ (CDCl₃, 400 MHz): 1.02 (3H, s, C-8 methyl), 1.11 (3H, s, C-10 methyl), 1.25 (3H, s, C-9 methyl), 1.60-1.67 (2H, m, C-5 and C-6 endo protons), 2.08 (1H, m, C-6 exo proton), 2.33 (1H, m, C-5 exo proton), 2.82 (1H, d, J=4 Hz, C-4 proton); m/e (relative intensity): 312/310/308 (M⁺, 1.4/2.5/1.2), 284/282/280 (3.3/6.0/2.7), 232/230 (3.1/3.0), 203/201 (18.9/19.8), 123

(22.0), 83 (100.0).

Exact mass calcd. for $C_{10}H_{14}OBr_2$:

311.9371/309.9391/307.9411; found 311.9363/309.9386/307.9413.

Anal. calcd. for $C_{10}H_{14}OBr_2$: C 38.74, H 4.55, Br 51.55; found
C 38.46, H 4.62, Br 51.33.

Preparation of Pericyclocamphanone 24

Diethyl zinc (50.0 mL of a 15% wt. solution in toluene; 0.05 mol) was added to a solution of dry (+)-3,3-dibromocamphor 26 (15.5 g, 0.05 mol) in dry benzene (500 mL). The reaction mixture was refluxed for 24 hours, quenched with ice-water (the white emulsion produced was destroyed by the addition of 1M HCl solution), and extracted with ether (3X). The ether extracts were combined and washed with water (3X), dried over anhydrous magnesium sulphate. Removal of the solvent yielded a yellowish crystalline solid (8.3 g). The crude product which on column chromatography (silica gel 230-400 mesh, elution with petroleum ether / ether 95:5) provided pericyclocamphanone 24 (7.1 g, 94 %) as a white crystalline solid, mp 168-170 °C (sealed tube; lit. ref. mp 168-170 °C); ν_{\max} (CHCl₃): 1720 cm⁻¹; δ (CDCl₃, 400 MHz): 0.81 (3H, s, C-8 methyl), 0.90 (3H, s, C-10 methyl), 0.97 (3H, s, C-9 methyl), 1.44 (1H, t, J=5.5 Hz, C-3 proton), 1.72 (1H, d, J=11 Hz, C-6 endo proton), 1.94 (1H, dd, J=11 Hz and 1.5 Hz, C-6 exo proton), 1.97 (1H, t, J=5.5 Hz, C-4 proton), 2.01 (1H, bt, J=5.5 Hz, C-5 proton); m/e (relative intensity): 151 (M⁺+1, 21.6), 150 (M⁺, 24.1), 123 (60.0), 107 (100.0).

Exact mass calcd. for C₁₀H₁₄O: 150.1045; found 150.1054.

Anal. calcd. for C₁₀H₁₄O: C 79.96, H 9.39; found C 78.50, H

9.26.

Preparation of exo-5-bromocamphor **27**

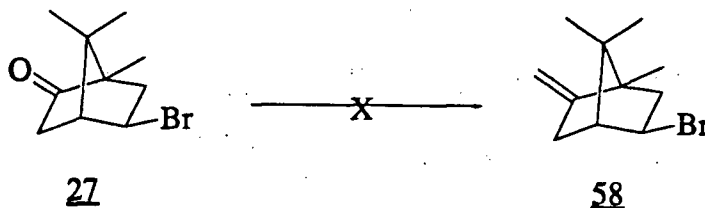
Hydrobromic acid (48%, 100 mL) was added carefully to a solution of pericyclocamphanone **24** (5.00 g, 0.033 mol) in acetic anhydride (15 mL). The reaction mixture was stirred at 65°C for 3 hours, cooled and poured into ice-water. The resulting solid was filtered off, dissolved in ether, washed with saturated sodium bicarbonate solution, then with water (2X), and the ether solution dried over anhydrous magnesium sulphate. Evaporation of the solvent yielded a light yellow solid which was purified by column chromatography (silica gel 230-400 mesh, elution with petroleum ether / ether 98:2) to afford exo-5-bromocamphor **27** as a white crystalline compound (7.15 g, 93%), mp 110.5-111.5 °C (sealed tube; lit. ref. mp 111-111.5 °C); ν_{\max} (CHCl₃): 1735 cm⁻¹; δ (CDCl₃, 400 MHz): 0.90 (3H, s, C-8 methyl), 0.96 (3H, s, C-10 methyl), 1.38 (3H, s, C-9 methyl), 1.84 (1H, d, J=18.5 Hz, C-3 endo proton), 2.15 (1H, dd, J=15.5 Hz and 8.5 Hz, C-6 endo proton), 2.28 (1H, dd, J=15.5 Hz and 5 Hz, C-6 exo proton), 2.47 (1H, dd, J=18.5 Hz and 5 Hz, C-3 exo proton), 2.53 (1H, d, J=5.5 Hz, C-4 proton), 4.70 (1H, dd, J=8.5 Hz and 5 Hz, C-5 proton); m/e (relative intensity): 232/230 (M⁺, 4.5/4.5), 151 (18.8), 123 (38.4), 109 (100.0).

Exact mass calcd. for C₁₀H₁₅OBr: 232.0286/230.0306; found

232.0292/230.0309.

Anal. calcd. for $C_{10}H_{15}OBr$: C 51.97, H 6.54, Br 34.57; found:
C 51.67, H 6.64, Br 34.40.

Attempted preparation of exo-5-bromo-2-methylenebornane 58



Methyltriphenylphosphonium bromide (1.73 g, 0.0048 mol) was vacuum pumped for 1.5 hours to remove any trace of moisture before it was dissolved in pure THF (4.5 mL) and flushed with argon. n-Butyllithium (3.88 mL of the 1.25M solution, 0.0048 mol) was added dropwise and the resultant mixture was stirred at 50°C for 2 hours under argon. A solution of exo-5-bromo-camphor 27 (0.70 g, 0.0030 mol) in distilled THF (1.8 mL) was added dropwise to the Wittig reagent and the reaction mixture was refluxed at 65°C under argon. After 1 hour, capillary GLC and TLC analyses indicated that a single product had been formed. The reaction mixture was cooled, diluted with water, extracted with pentane (3X) and the pentane extracts were combined and washed with water (3X) and dried over anhydrous magnesium sulphate. Evaporation of the solvent yielded a white crystalline compound (0.45g, 99%). Capillary GLC (OV-101, 120°C) and TLC analyses, the low resolution mass spectrum and the ¹H NMR spectrum (CDCl₃, 400 MHz) of this compound confirmed that the product was pericyclocamphanone 24!

Preparation of exo-5-bromo-2-methylenebornane 58

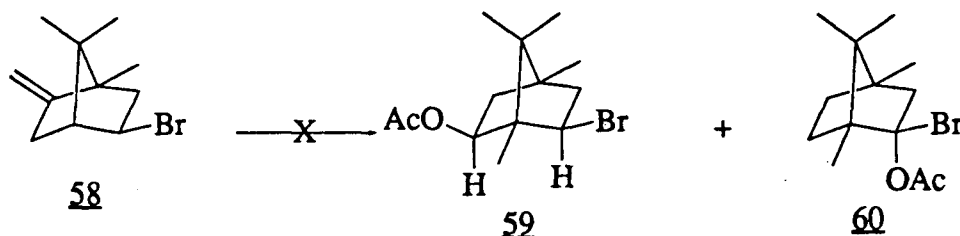
Titanium tetrachloride (4.8 mL, 43.7 mmol) was added dropwise to a stirred suspension of zinc dust (11.8 g, 180 mmol) and dibromomethane (10.4 g, 4.2 mL, 60.0 mmol) in THF (200 mL) at -40°C . The reaction mixture was allowed to warm to 5°C and kept in the refrigerator for 3 days to give a thick brown slurry. The ice-cold slurry was added portionwise to a stirred solution of exo-5-bromocamphor 27 (2.3 g, 10.0 mmol) in dichloromethane (20 mL) and the resultant mixture was stirred at room temperature for 1 day under argon. The reaction mixture was then quenched with saturated sodium bicarbonate solution, extracted with ether (3X) and the ether extracts were combined and washed with water (3X), and dried over anhydrous magnesium sulphate. Evaporation of the solvent yielded pure exo-5-bromo-2-methylenebornane 58 as a white crystalline solid (1.98 g, 86%), mp $88-89.5^{\circ}\text{C}$ (sealed tube); ν_{max} (CHCl_3): 1645 cm^{-1} , 880 cm^{-1} ; δ (CDCl_3 , 400 MHz): 0.80 (3H, s, C-8 methyl), 0.97 (3H, s, C-10 methyl), 1.28 (3H, s, C-9 methyl), 1.91 (1H, d, $J=18\text{ Hz}$, C-3 endo proton), 2.02 (1H, dd, $J=14\text{ Hz}$ and 8.5 Hz , C-6 endo proton), 2.18 (1H, d, $J=6\text{ Hz}$, C-4 proton), 2.27 (1H, dd, $J=14\text{ Hz}$ and 4.5 Hz , C-6 exo proton), 2.50 (1H, bd, $J=18\text{ Hz}$, C-3 exo proton), 4.01 (1H, dd, $J=8.5\text{ Hz}$ and 4.5 Hz , C-5 endo

proton), 4.74 (d) and 4.79 (d) (2H, AB quartet, exo-methylene protons); m/e (relative intensity): 230/228 (M^+ , 1.2/1.1), 215/213 (1.5/1.6), 149 (86.2), 107 (72.3), 80 (100.0).

Exact mass calcd. for $C_{11}H_{17}Br$: 230.0493/228.0513; found 230.0497/228.0512.

Anal. calcd. for $C_{11}H_{17}Br$: C 57.65, H 7.48, Br 34.87; found: C 57.75, H 7.56, Br 34.79.

Attempted acid-catalyzed rearrangement of exo-5-bromo-2-methylenebornane 58



Concentrated sulphuric acid (0.013 mL, 0.17 mmol) was added to a solution of exo-5-bromo-2-methylenebornane 58 (0.20 g, 0.86 mmol) in glacial acetic acid (0.55 mL) at 0°C and the reaction mixture stirred at 0°C for 35 minutes. GLC (OV-101, 120°C) and TLC analyses indicated that no reaction had taken place and further stirring at room temperature for 3 hours made no difference. Finally, the reaction mixture was heated to about 80°C which caused the starting material 58 to decompose.

In a separate run, concentrated sulphuric acid (0.12 mL, 1.54 mmol) was added to exo-5-bromo-2-methylenebornane 58 (1.83 g, 7.91 mmol) in glacial acetic acid (5.0 mL) at 0°C. The reaction mixture was stirred at room temperature and followed by GLC and TLC for 21 days, GLC and TLC analyses showed that the starting material 58 slowly underwent decomposition and that no major products were observed.

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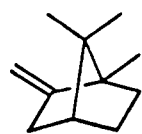
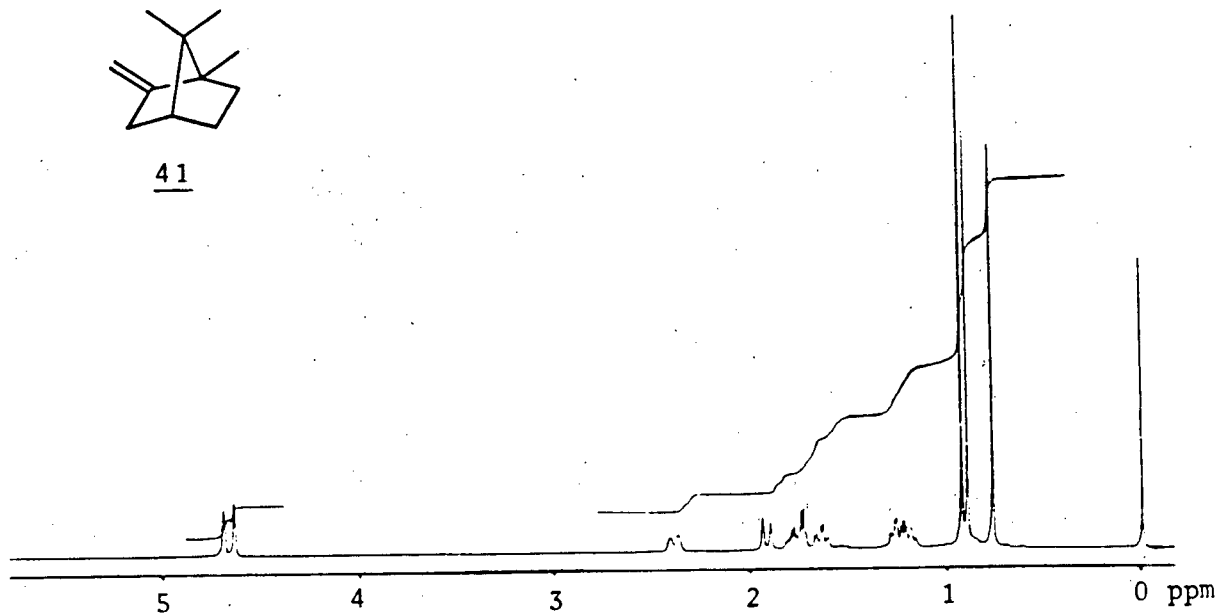
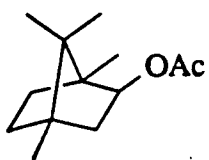
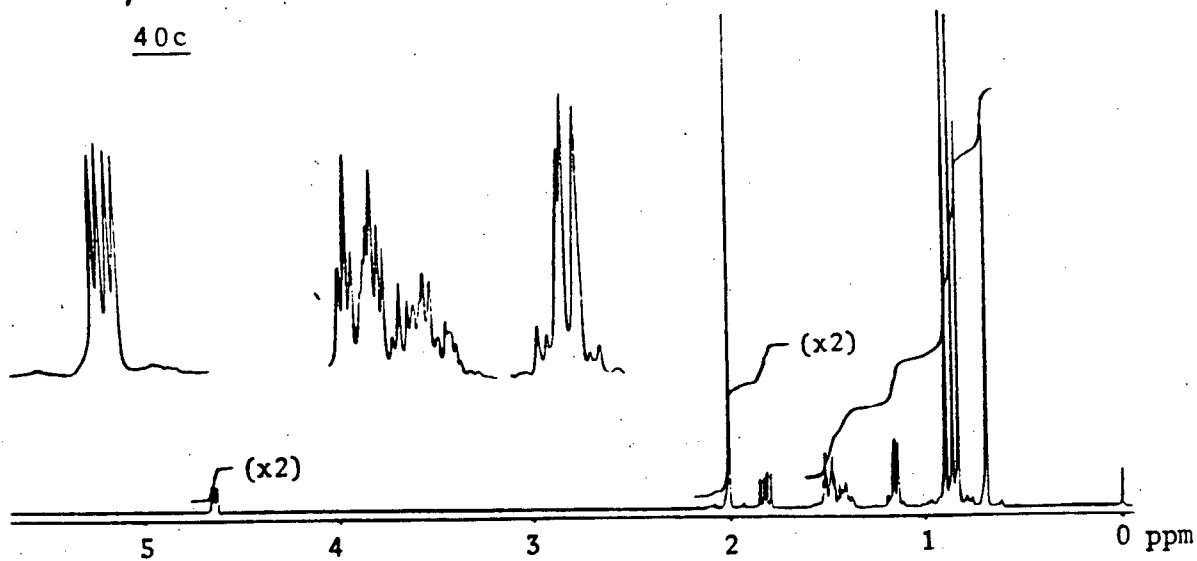
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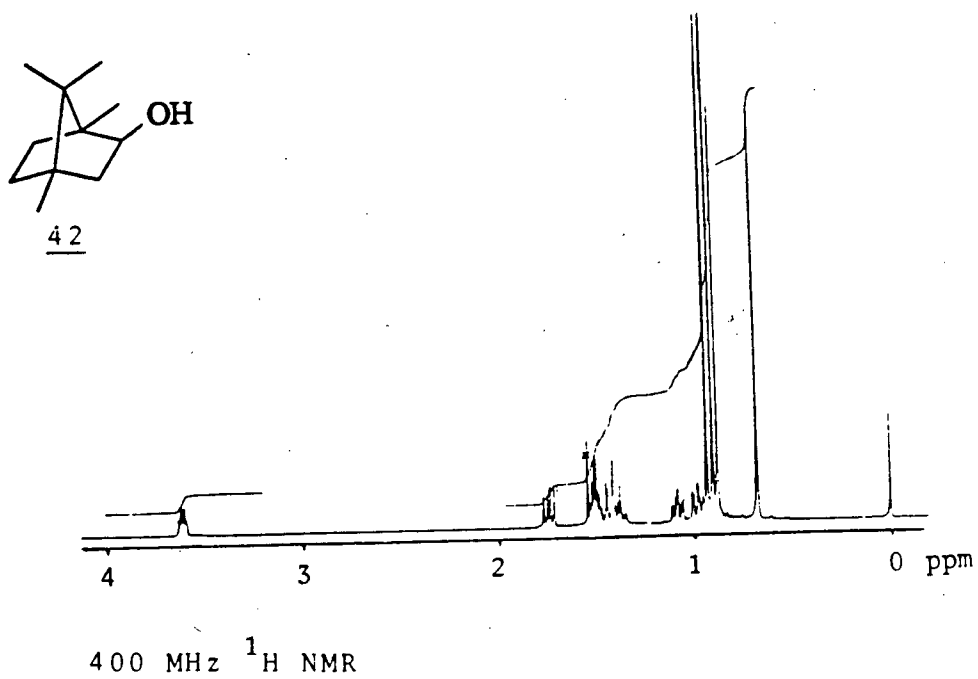
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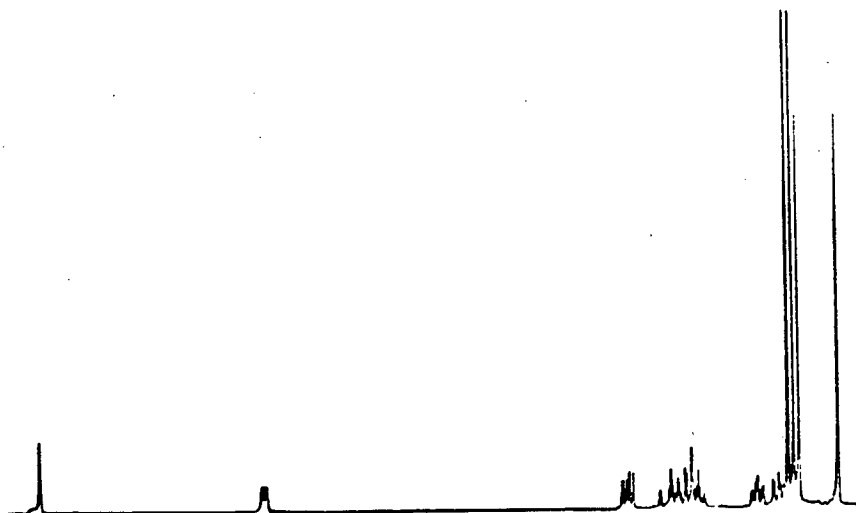
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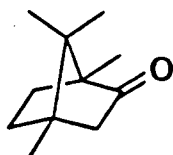
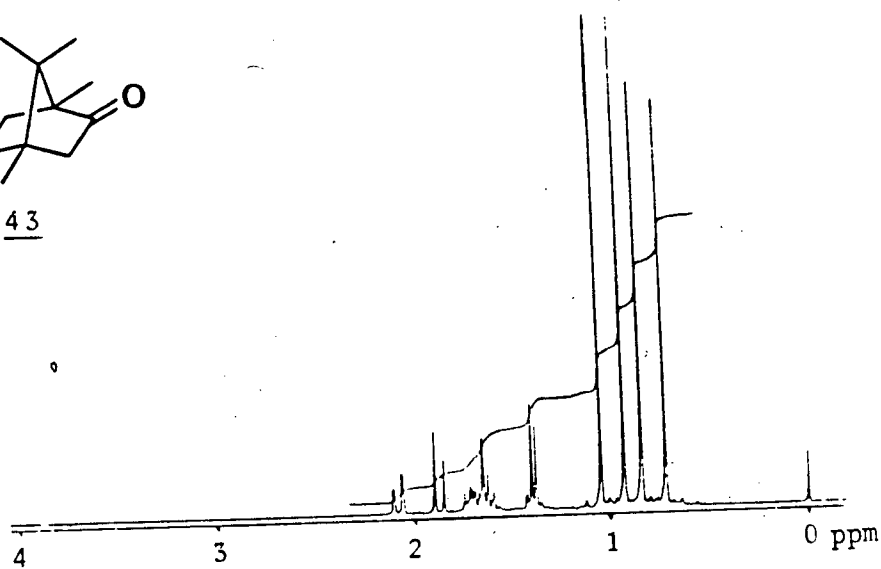
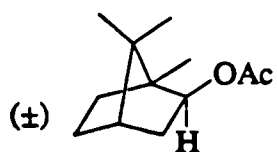
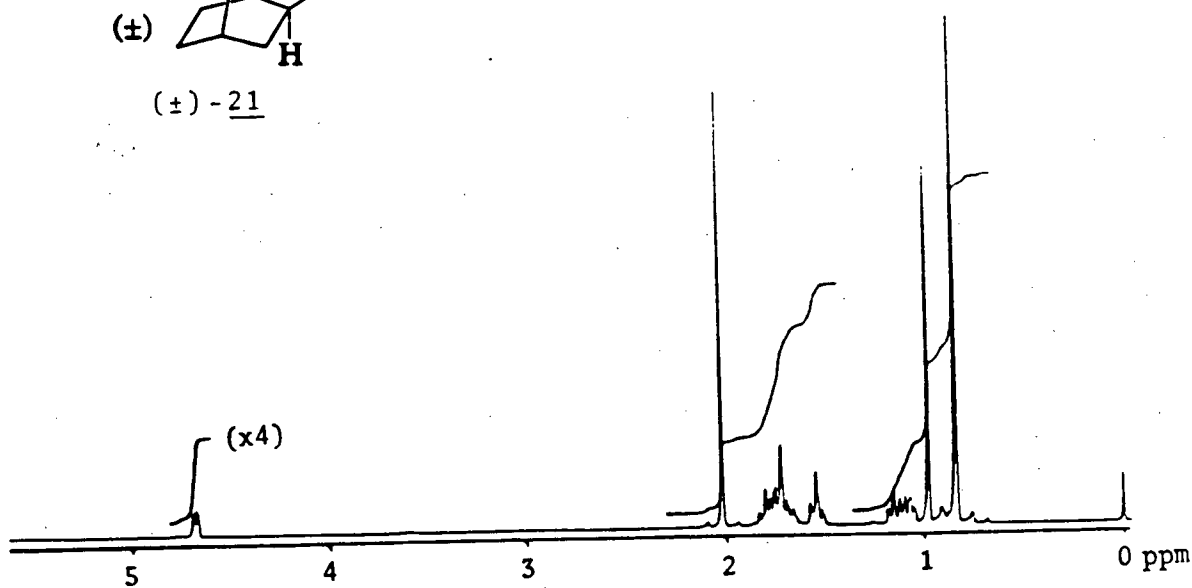
APPENDIX 1: 400 MHz ^1H NMR Spectra of Selected Compounds

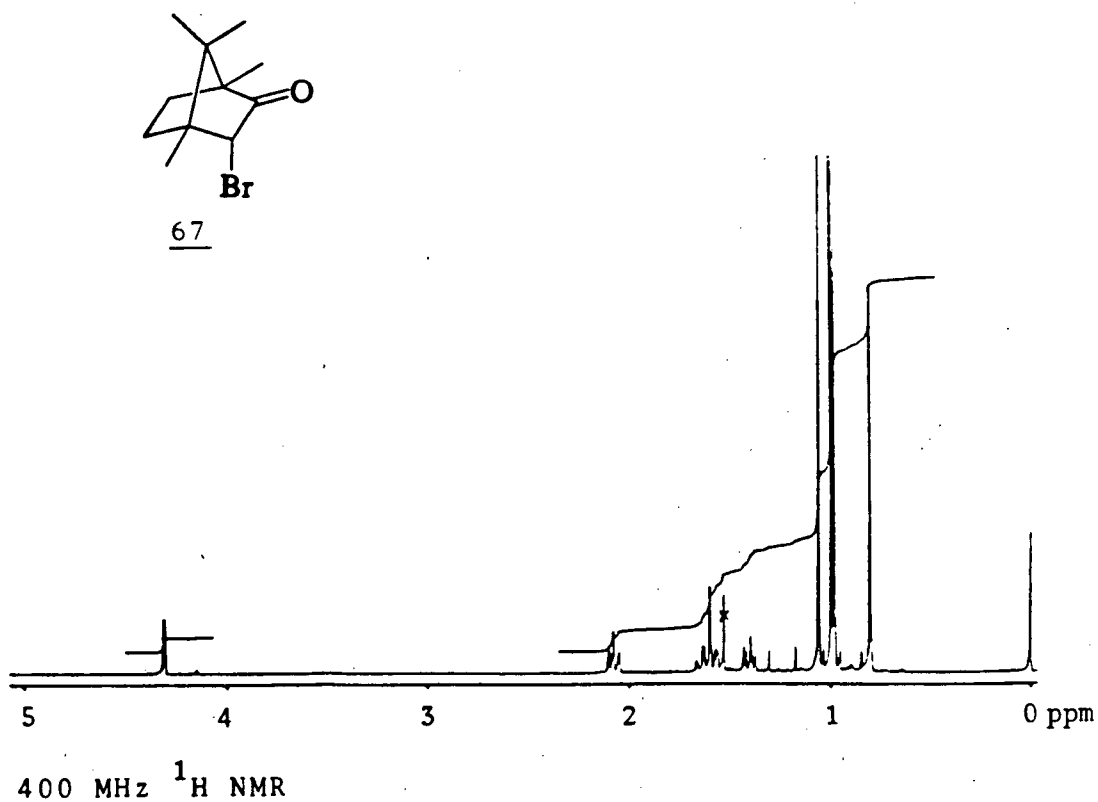
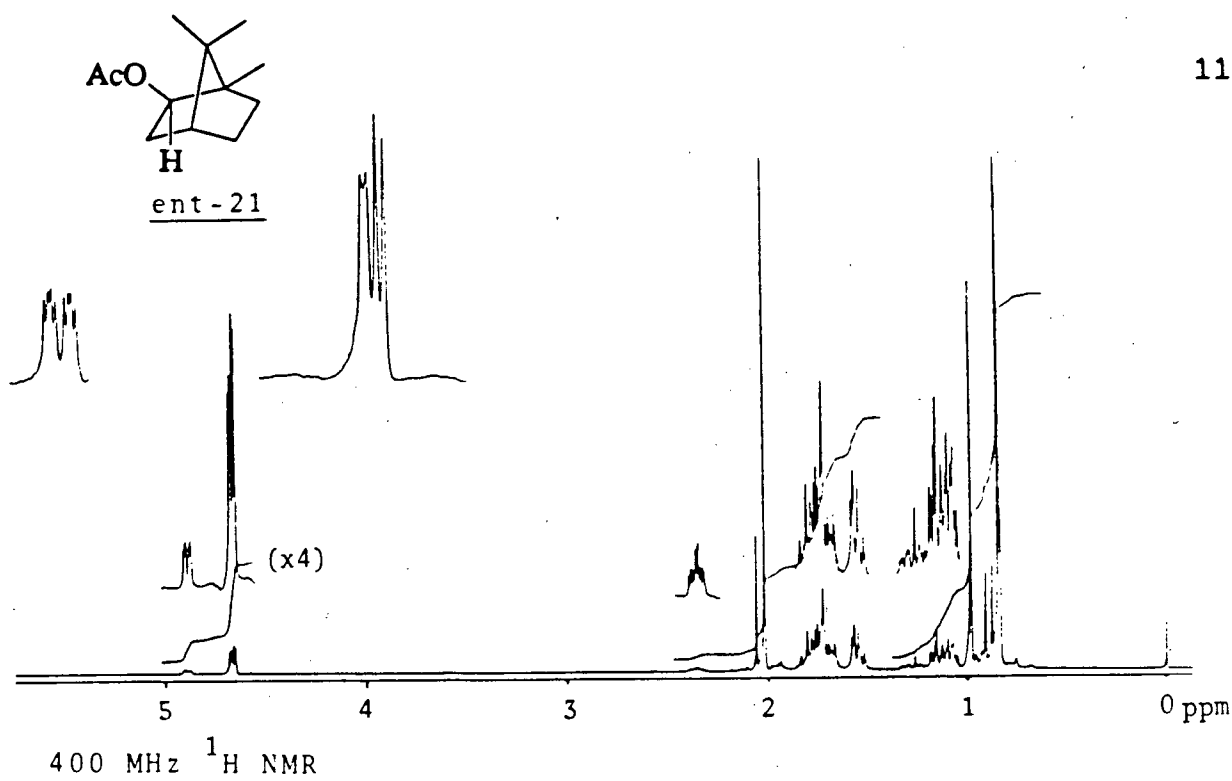
41400 MHz ^1H NMR40c400 MHz ^1H NMR

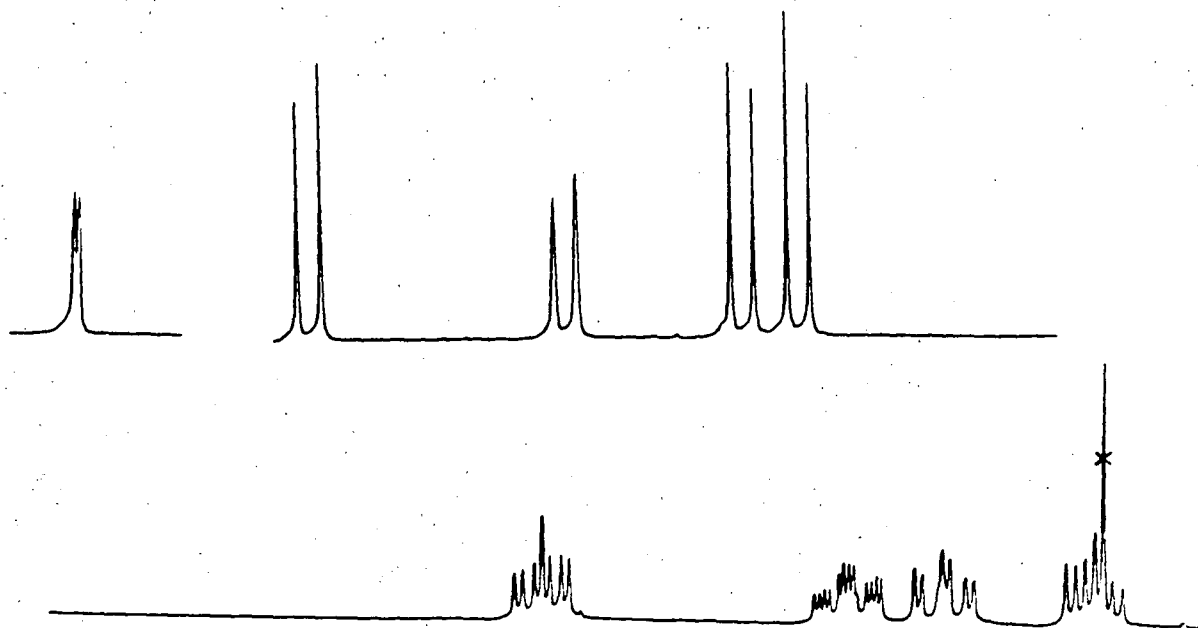
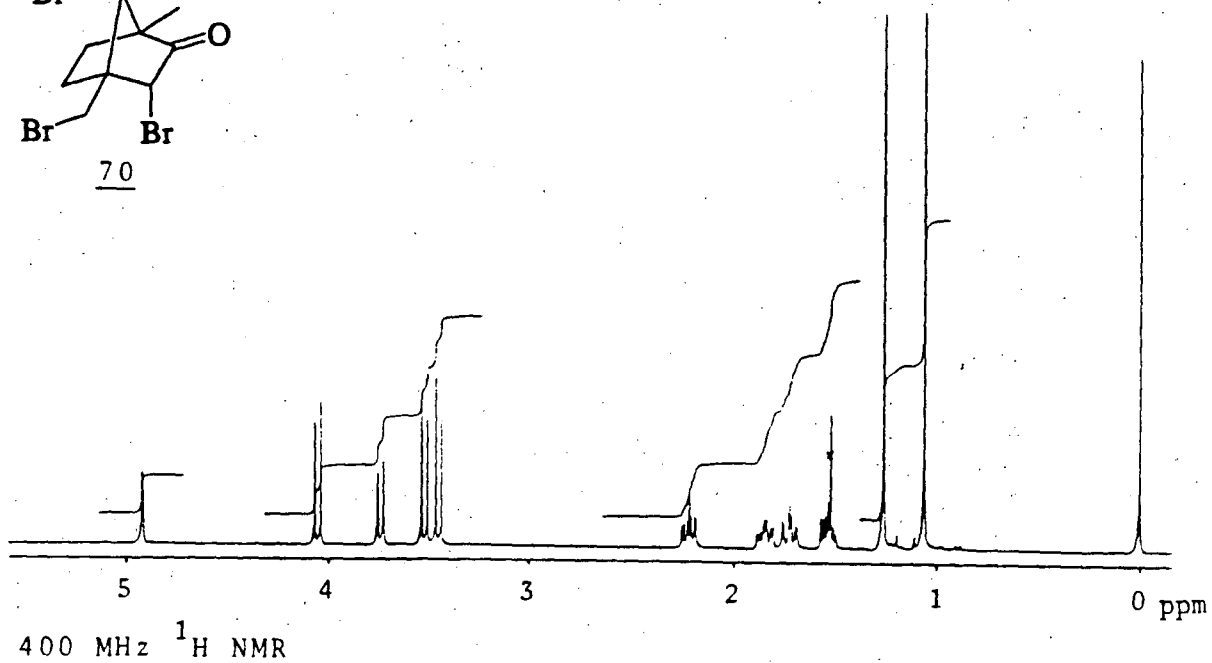
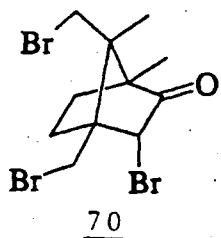


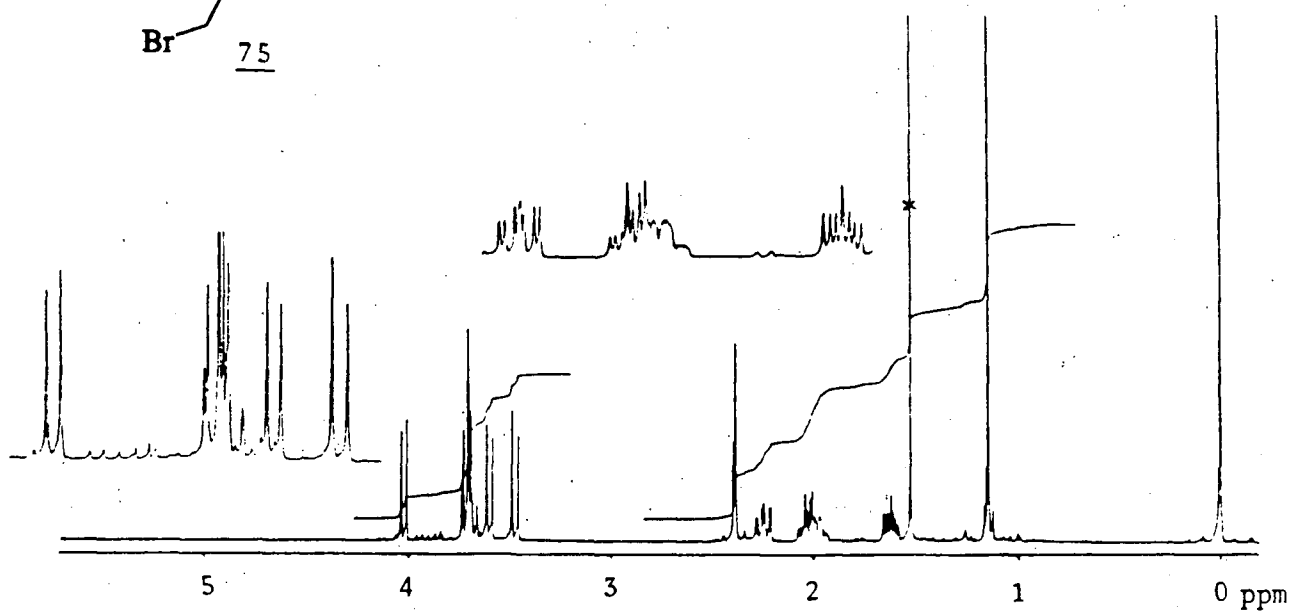
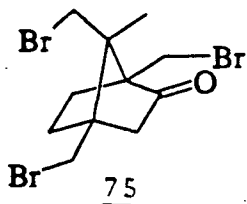
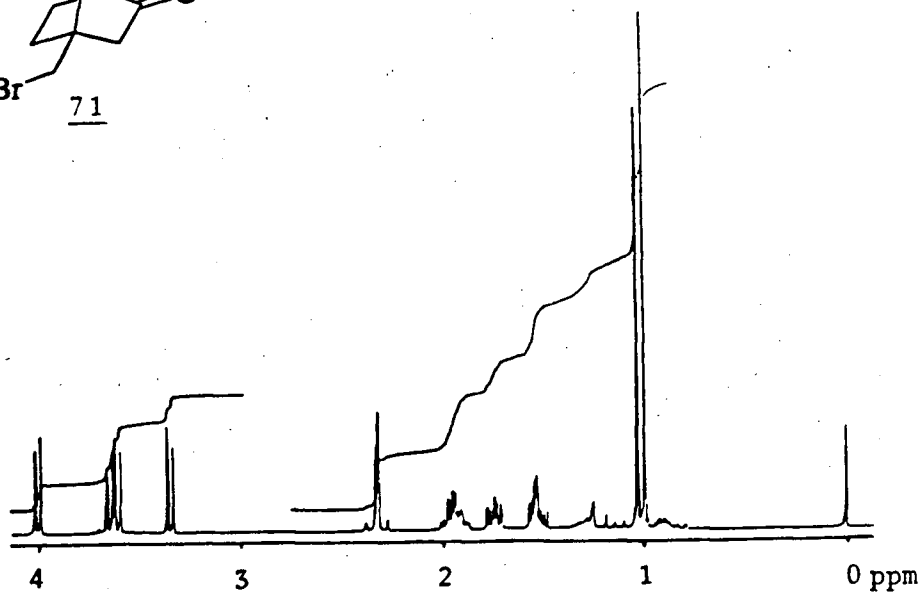
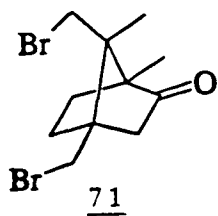
D₂O added

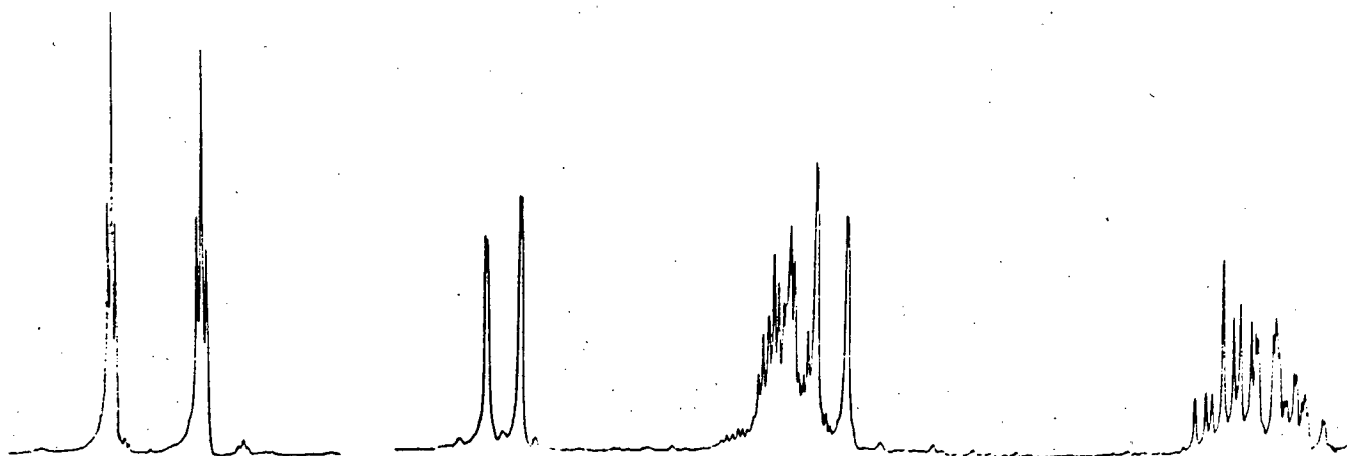
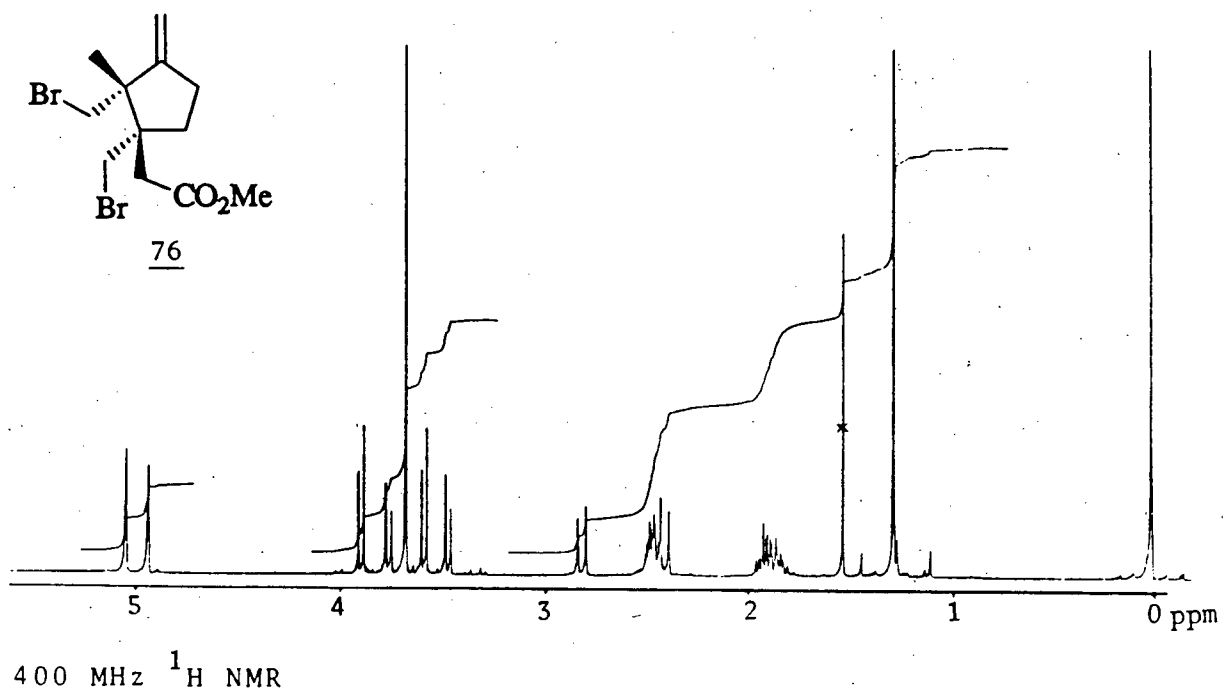


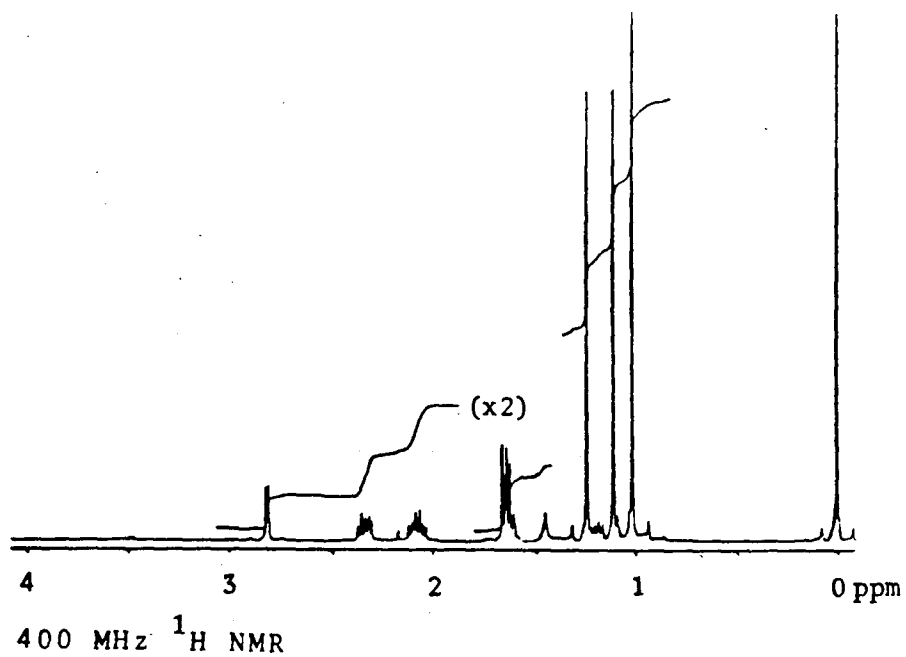
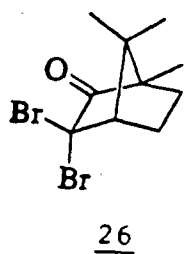
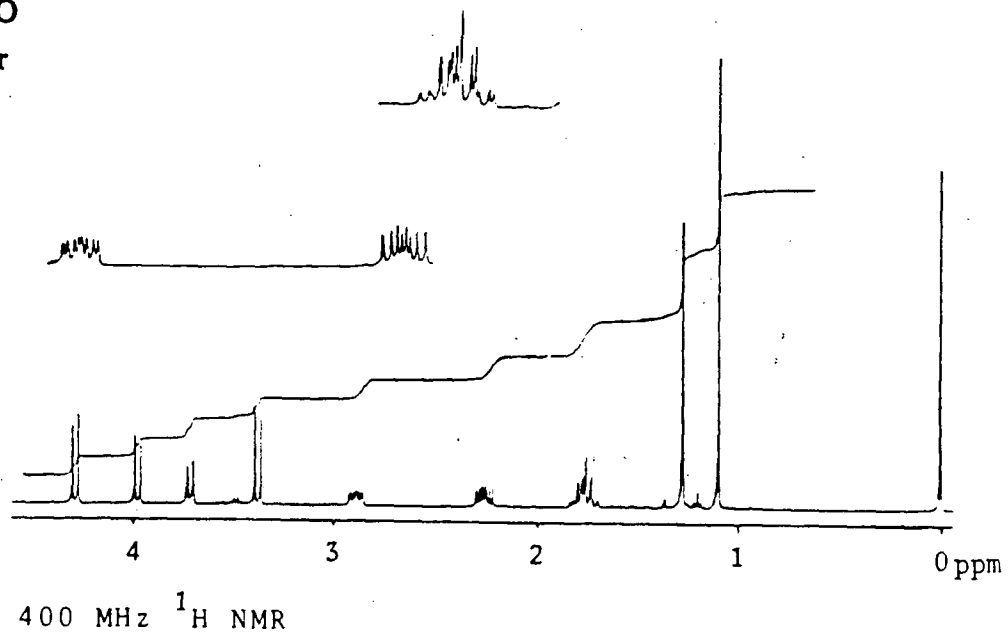
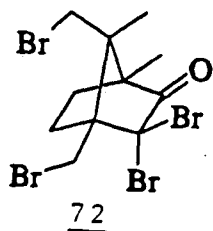
43400 MHz ^1H NMR(±)-21400 MHz ^1H NMR

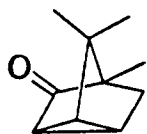
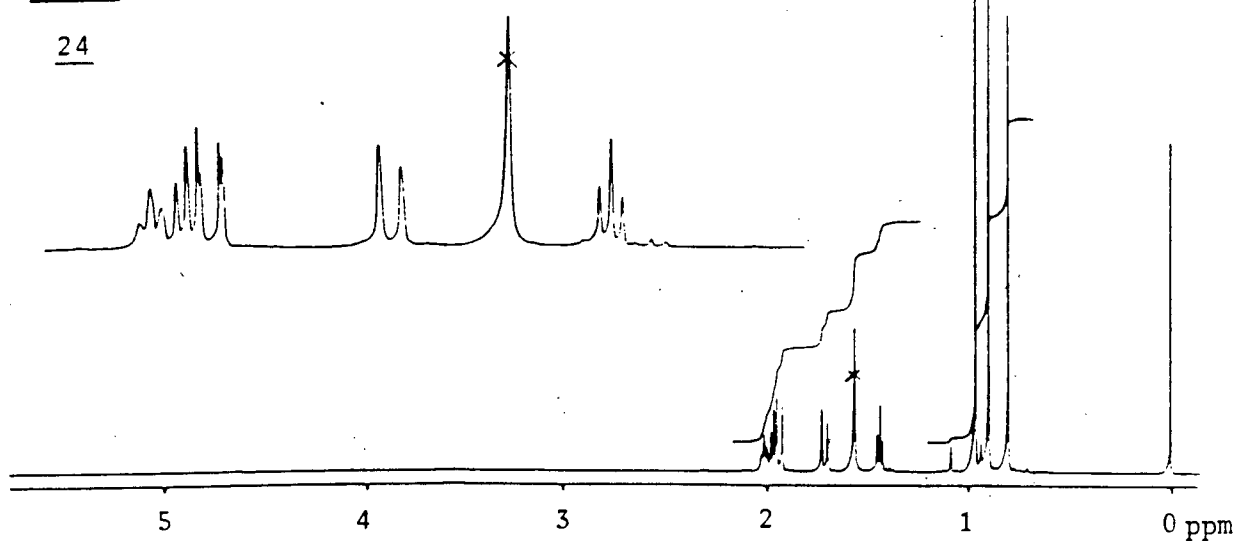
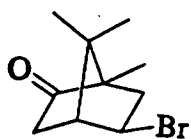
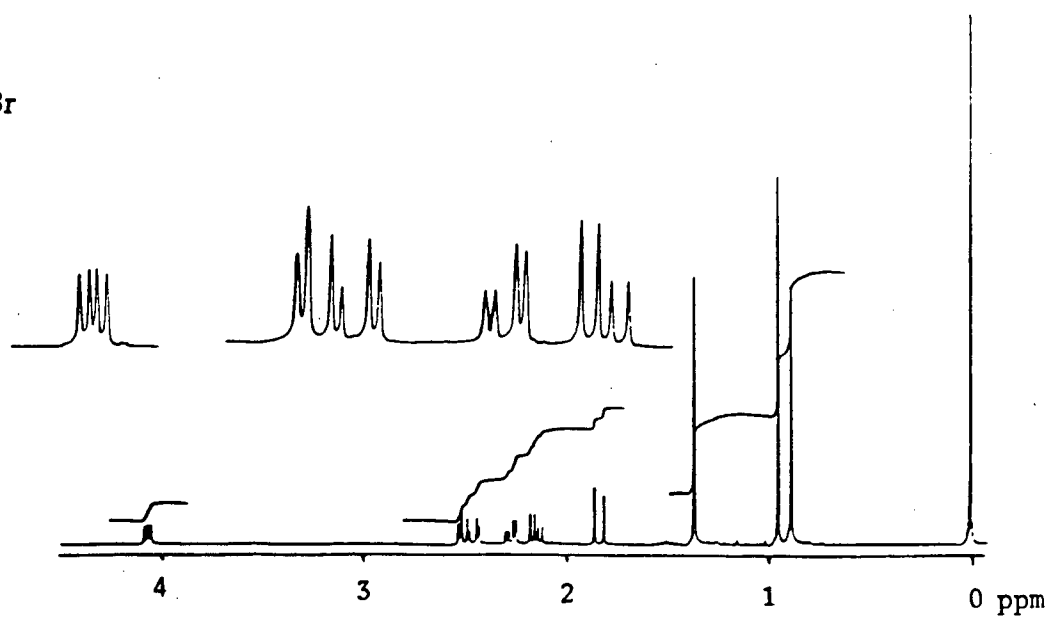


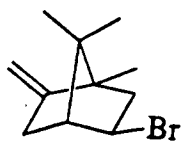
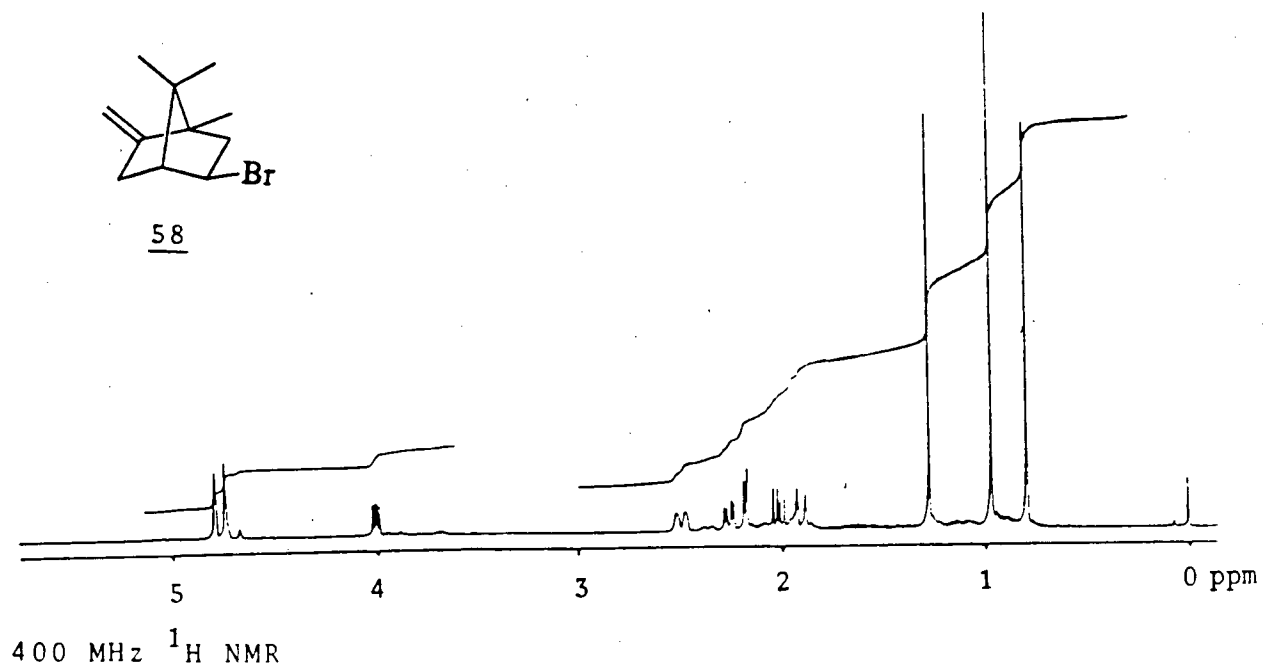


400 MHz ^1H NMR400 MHz ^1H NMR





24400 MHz ^1H NMR27400 MHz ^1H NMR

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APPENDIX 2

Stereoview of endo-3,9-dibromo-4-(bromomethyl)camphor 70

