THE SYNTHESIS OF INTERMEDEOL AND RELATED SESQUITERPENOID STUDIES

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THE SYNTHESIS OF INTERMEDEOL AND RELATED

SESQUITERPENOID STUDIES

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TO THE LORD JESUS CHRIST

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To my wife, Sharon, I owe a special debt of gratitude for her encouragement and understanding during this time. I want to thank my parents as well for their help and support in this endeavor.

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GLOSSARY OF ABBREVIATIONS

b	broad (IR)
bm	broad multiplet (NMR)
bp	boiling point
bs	broad singlet (NMR)
cm^{-1}	wave numbers (IR)
d	doublet (NMR)
Et	ethyl group (CH_3CH_2-)
g	grams
GC	gas chromatography
Hz	hertz
IR	infrared spectroscopy
J	coupling constant
ℓ	liters
m	medium (IR)
m	multiplet (NMR)
M	molar
M^+	molecular ion in mass spectrum
m/e	mass to charge ratio in mass spectrum
mg	milligrams
min	minutes
mmol	millimoles
mol	moles
NMR	nuclear magnetic resonance spectroscopy

R_t	retention time (GC)
s	strong (IR)
s	singlet (NMR)
t	triplet (NMR)
TEG	triethylene glycol
THF	tetrahydrofuran
TLC	thin-layer chromatography
vs	very strong (IR)
w	weak (IR)

SUMMARY

The synthesis of intermedeol (12) has been carried out as outlined in Figure 1. Wolff-Kishner reduction of the previously reported dienone 6 gave a mixture of the olefins 7, which was the main product, and 8 and 9, which are naturally occurring compounds. Epoxidation of 8 with m-chloroperbenzoic acid led primarily to a single product believed to be the β,β-epoxide 11. Attempts to isolate this epoxide by chromatography on silica gel led to isomerization to the ketone 14. Reduction of the epoxide with lithium aluminum hydride gave a complex mixture, composed primarily of the alcohol 13, from which was isolated a small amount of intermedeol (12). The alcohol 13 was converted into the ketone 14 by oxidation with Jones Reagent.

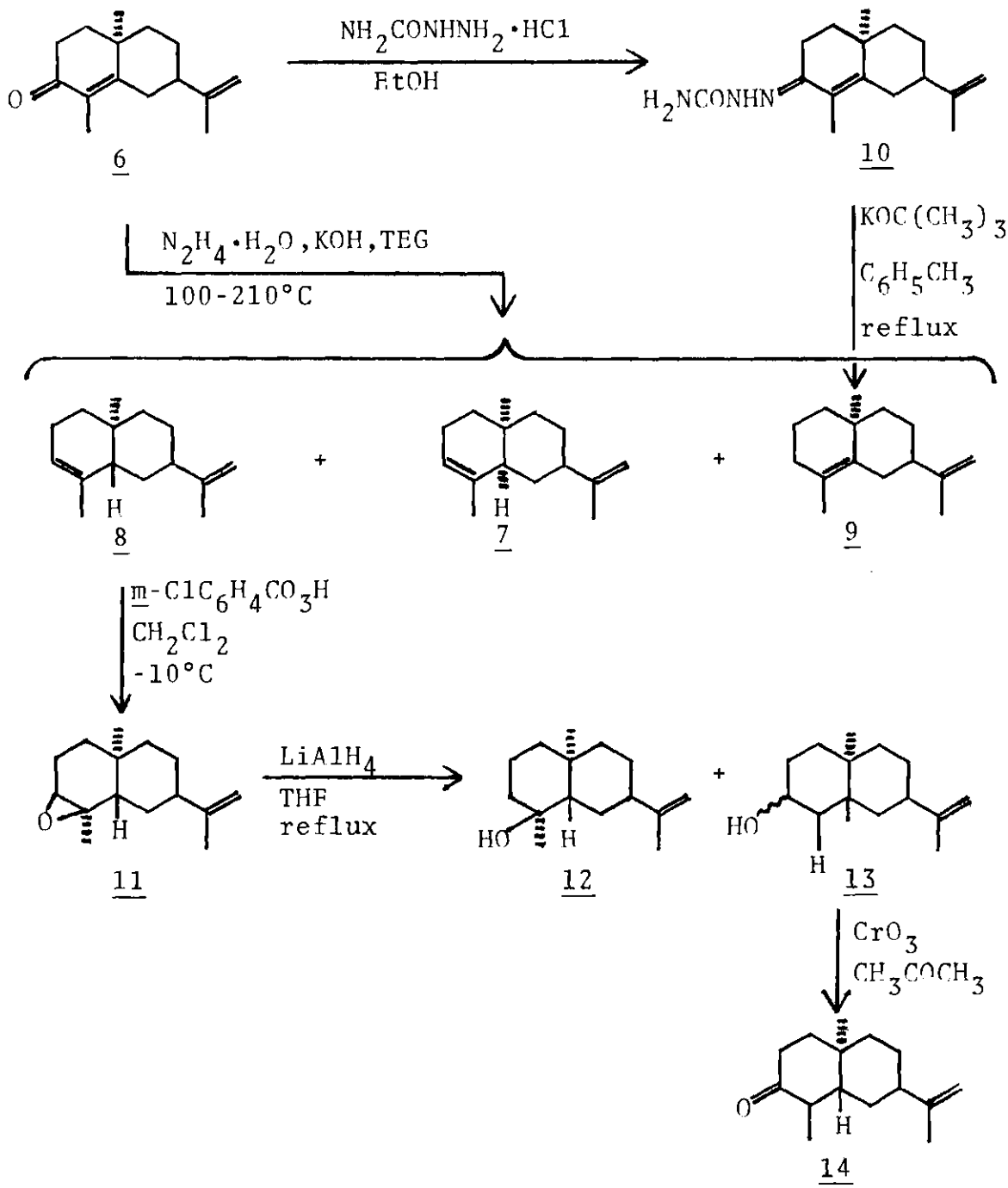


Figure 1. Synthetic Route to Intermedeol

CHAPTER I

INTRODUCTION

Intermedeol (12) is a member of a small family of sesquiterpenes which can be referred to as 10-epieudesmanes; thus they are unique in that the C-10 methyl group is trans to the C-7 isopropenyl moiety, whereas in the eudesmane skeleton these two groups are cis to one another. This structural feature is considered biogenetically important, as it would contribute to the driving force for migration of the α C-10 methyl group to the α C-5 position, thereby giving rise to the nonisoprenoid valencane skeleton, or for rearrangement to the spirovetivanes,[1] as shown in Figure 2. In addition, intermedeol, alone of the known members of this family, has a C-4 methyl group in the α position which is therefore cis to the C-10 methyl group. This is considered to be an additional favorable factor in the potential rearrangement to valencanes and spirovetivanes.[1]

Intermedeol was first isolated from the steam volatile oil of the grass Bothreochloa intermedia,[2] race numbers 5297 and 5410, which are indigenous to Lahnavala, India and Punjab, India, respectively. At that time it was assigned the structure 5β,7α,10α-selin-11-en-4β-ol,[2] but was later found not to have the same spectral properties as the

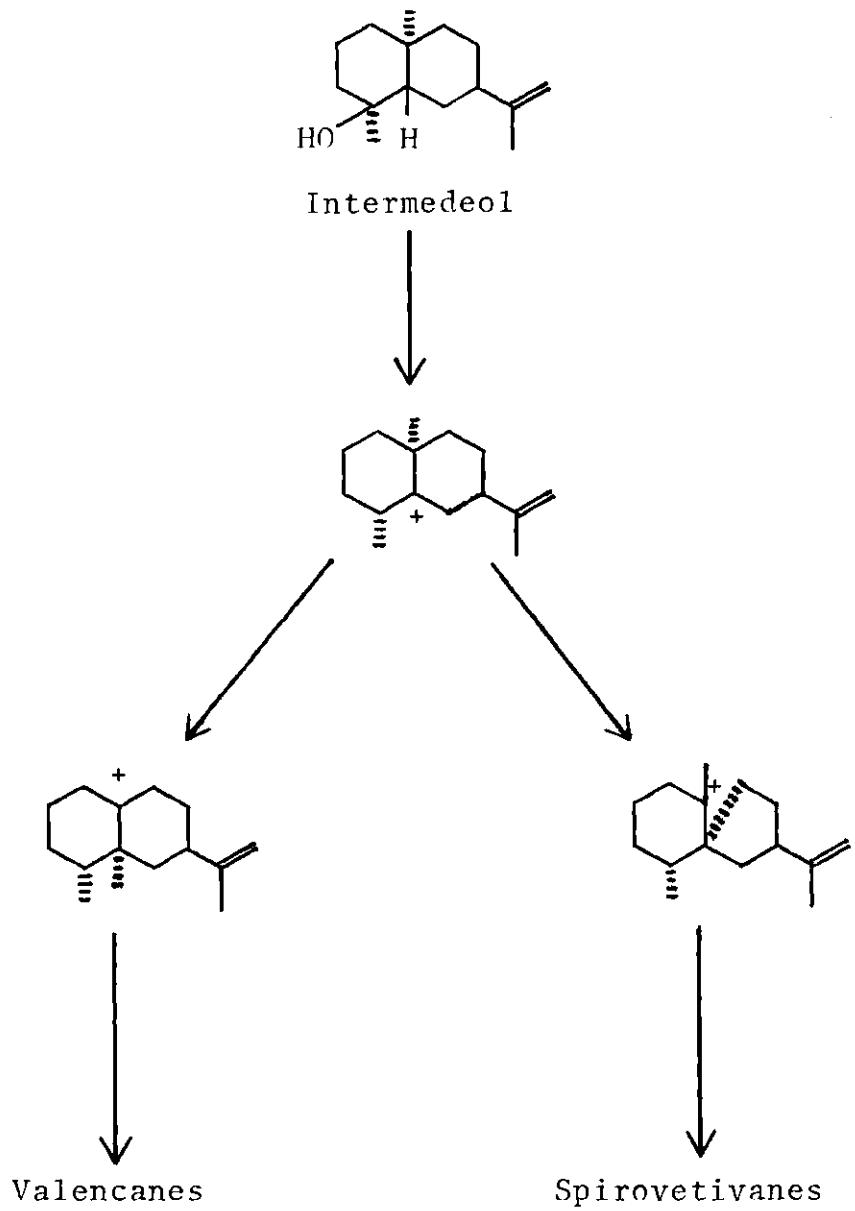
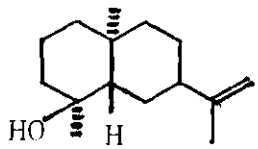


Figure 2. Postulated Biosynthetic Rearrangements of Intermedeol

naturally occurring compound whose structure was enantiomeric with that assigned to intermedeol.[3] Further investigations showed that the actual structure was the 7β epimer 12 of the one originally assigned. Intermedeol has since been



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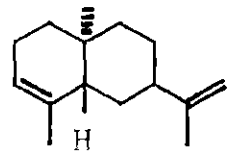

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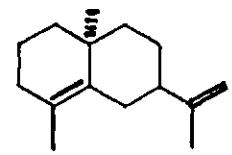

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found to be a constituent of grapefruit oil,[4] although when first isolated[5] it was assigned the 4α-OH epimeric structure and given the name paradisiol. Since the isolation of intermedeol several other members of this family have been identified,[6,7,8] including[6] 5β,7β,10α-selina-3,11-diene (8) and 7β,10α-selina-4,11-diene (9).

The purpose of this research was to perform the first total synthesis of intermedeol. The text which follows describes this synthesis, in the course of which were also synthesized the two naturally occurring dienes 8 and 9 mentioned above.

CHAPTER II

INSTRUMENTATION AND EQUIPMENT

Melting points are uncorrected and were determined on a Thomas-Hoover capillary melting point apparatus. IR spectra were obtained on a Perkin-Elmer 237B spectrophotometer using sodium chloride plates; the absorption of polystyrene film at 1601 cm^{-1} was used as the reference point. NMR spectra were obtained on either a Varian Associates Model A-60D or Model T-60 spectrometer, using tetramethylsilane as an internal standard. Mass spectra were obtained using a Varian Associates Model M-66 mass spectrometer.

GC analyses were carried out on either an F and M 400 Biomedical or a Hewlett Packard 402 Dual Column gas chromatograph, both equipped with flame ionization detectors. Unless otherwise mentioned, all analyses were carried out using a 5 ft. x 1/4 in. glass column packed with 5% Carbowax 20M on 90/100 mesh Anakrom AS. Also used were a 12 ft. x 1/4 in. column with the same packing and a 6 ft. x 1/4 in. column packed with 3% SE-30 on 100/120 mesh Gas Chrom Q.

Vacuum distillations were carried out on a Nester-Faust 36 in. stainless steel spinning band column. Removal of solvents *in vacuo* was done using a Buchler Instruments rotary evaporator at water aspirator pressure. Unless

otherwise mentioned, all drying of extracts was done with anhydrous magnesium sulfate. Low boiling (30-60°C) petroleum ether was the only petroleum ether used.

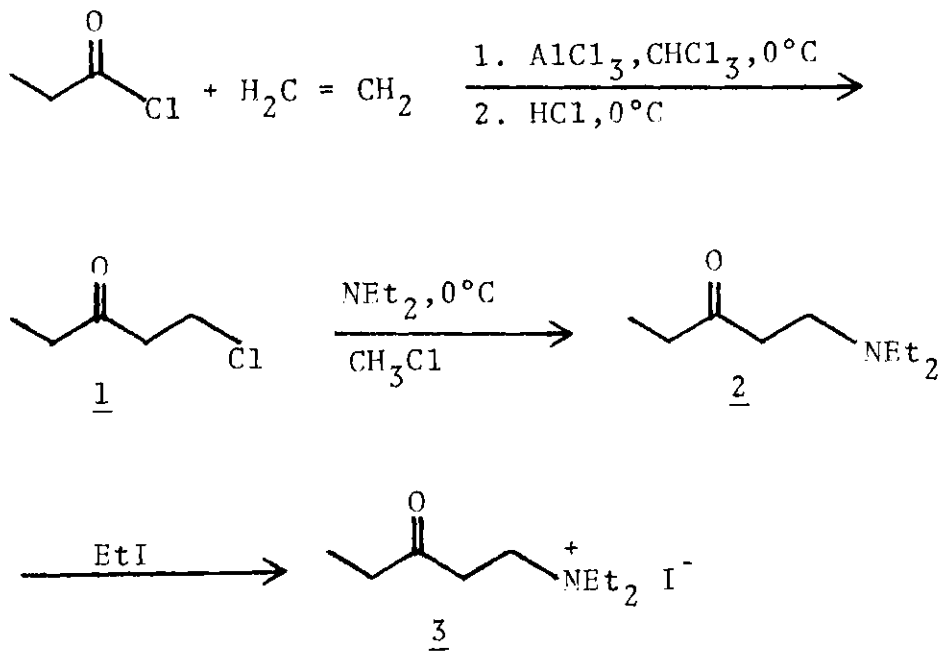
Alumina used in column chromatography was always neutral, activity I, obtained from E and M reagents, No. 70956610. Silica gel was 100-200 mesh and was obtained from Fisher Scientific Co.

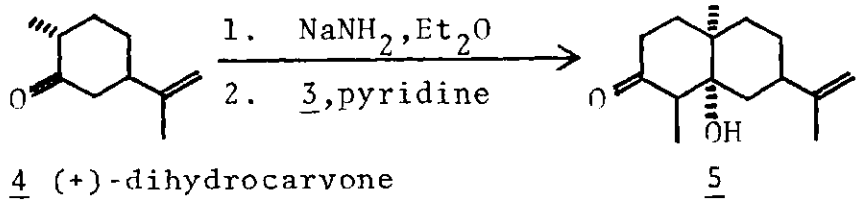
CHAPTER III

EXPERIMENTAL

N,N-Diethylaminopentan-3-one (2)[9]

Propionyl chloride (187.5 g, 2.03 mol) and aluminum chloride (288 g, 2.16 mol) were stirred in 1.25 ℓ of chloroform at 0°C, while ethylene was bubbled through the mixture until no more ethylene was being absorbed (five hours). The mixture was then poured on crushed ice containing concentrated hydrochloric acid (250 ml) in portions, to keep the temperature below 15°C. The aqueous layer was extracted with chloroform, and the combined extracts and original chloroform layer were washed with water, dried, and reduced *in vacuo* to about 900 ml. The resulting solution of 1-chloropentan-3-one (1) was then cooled to 0°C, and diethylamine (250 g, 3.42 mol) was added, dropwise with stirring, over one hour. Stirring was continued at 0°C for 24 hours, then the reaction mixture was extracted with ice-cold 1 M hydrochloric acid until the extract remained acidic (3 ℓ were required). The extracts were washed with chloroform, then made basic (pH 10) with ice-cold 2.5 M sodium hydroxide while maintaining the temperature below 10°C. The basic solution was then saturated with sodium chloride and extracted with ether. The extracts were washed with water





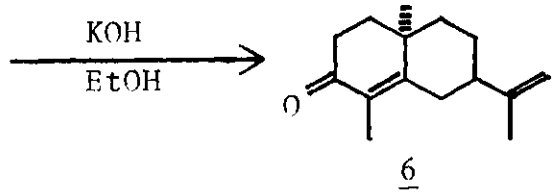


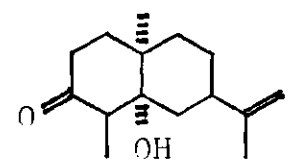
Figure 3. Synthesis of Starting Material 6

and brine and dried. The ether was removed *in vacuo* and the residue distilled through a spinning band apparatus (0.3 torr, 35°C), yielding 123 g (0.78 mol, 38% of theoretical) of N,N-diethylaminopentan-3-one (2), which was used without further purification.

IR: ν_{neat} (cm^{-1}): 3400 (w), 1712 (s).

7β,10α-Selin-11-en-5α-ol-3-one (5)[9,10]

The sodioderivative of (+)-dihydrocarvone (4) was prepared by adding sodium amide (42 g, 1.1 mol) to (+)-dihydrocarvone (150 g, 0.985 mol, from Glidden) in 940 ml of anhydrous ether, under nitrogen at 0°C, with stirring for one hour. Triethyl-3-oxopentylammonium iodide (3) was prepared separately by the addition of ethyl iodide (122 g, 0.78 mol) to 2 (123 g, 0.78 mol) in small quantities with shaking. This salt 3 was then dissolved in 295 ml of dry pyridine and added rapidly to the ether solution containing the (+)-dihydrocarvone derivative. Stirring was continued at 0°C overnight, then the mixture was refluxed for five hours. After cooling, 1.6 ℓ of water was added and the reaction mixture was extracted with ether, which was in turn washed with water and reduced *in vacuo*. Spinning band distillation of the residue yielded, in addition to pyridine and dihydrocarvone, a fraction (102-130°C,



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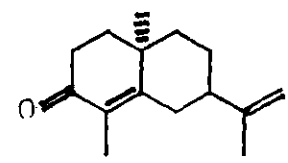
0.5-3.0 torr) which partially crystallized on standing, yielding 18.5 g (0.078 mole, 10%) of crystalline 7β,10α-selin-11-en-5α-ol-3-one (5), mp 105°C (lit.[10] 106°C).

IR: ν_{nujol} (cm^{-1}): 3323 (br,w), 1679 (s), 1636 (w).

The uncrystallized portion of this fraction (~40 g) appeared to be composed of about 80% of the ketol by GC analysis, so it was also used in subsequent reactions as described below.

7β,10α-Selina-4,11-dien-3-one (6)[9,10]

To the crystalline hydroxyketone 5 (18.5 g, 78 mmol) was added 2.5 M potassium hydroxide in ethanol (50 ml, 125 mmol of base), and the solution was refluxed for eight hours. The ethanol was removed *in vacuo* and the residue added to water followed by ether extraction. The ether extracts were washed with ice-cold dilute hydrochloric acid, aqueous sodium bicarbonate, and brine, then dried. Removal of the solvent *in vacuo* and distillation (110°C, 0.13 torr) gave a pale yellow liquid, 7β,10α-selina-4,11-dien-3-one (6), 95% pure by GC. The NMR spectrum was identical to that obtained previously from a sample prepared by the same procedure.[9]



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IR[9]: ν_{neat} (cm^{-1}): 1665 (s), 1603 (m), 893 (s).

NMR (δ,$CDCl_3$): 1.25 (s,3H), 1.75 (s,3H), 1.82 (d,3H, J = 1.5 Hz), 4.67 (bs,1H), 4.83 (m,1H).

The uncrystallized portion from the distillation of the crude hydroxyketone was dehydrated in an analogous fashion, yielding after work-up about 40 g of the dienone 6, 80% pure by GC.

7β,10α-Selina-4,11-dien-3-one Semicarbazone (10)[11]

To the dienone 6 (1.0 g, 80% pure, 3.7 mmole of ketone), in 1.0 ml of ethanol and enough water to make the solution almost saturated, were added semicarbazide hydrochloride (1.0 g, 9.0 mmol) and sodium acetate (1.5 g, 18.3 mmol). This solution was placed in a water bath at 100°C for 30 seconds, then allowed to cool to room temperature before being placed in an ice bath. The product was recrystallized from ethanol-water to give crystalline 7β,10α-selina-4,11-dien-3-one semicarbazone (10, Figure 1) (0.74 g, 2.7 mmol, 73% based on the purity of the starting ketone 6), mp 173-183°C (lit.[10] 177°C).

IR: ν_{nujol} (cm^{-1}): 3454, 1676, 1559, 890.

7β,10α-Selina-4,11-diene (9)

The semicarbazone 10 (1.0 g, 3.6 mmol) was added to potassium t-butoxide (0.80 g, 7.1 mmol) in 15 ml of sodium-dried toluene and the mixture refluxed[12] for 90 hours. Monitoring of the nitrogen being evolved indicated the reaction was complete after 68 hours; the volume of nitrogen evolved was 89% of theoretical. The cooled mixture was added to dilute hydrochloric acid; the organic phase was

washed with water, then the combined aqueous washings and acid layer were extracted with ether. The combined ether-toluene layers were dried and reduced at atmospheric pressure. Analysis of the crude product by GC and NMR indicated that 7β,10α-selina-4,11-diene (9) was the only olefin formed. The crude product was distilled *in vacuo* (85°C, 0.1 torr), then chromatographed on silica gel impregnated with silver nitrate (10%). Elution with olefin-free petroleum ether gave, after removal of the solvent and two distillations *in vacuo* (80°, 0.5 torr), an analytically pure sample of the diene 9 (exact mass 204.1878, calc. 204.1889).

NMR (δ, $CDCl_3$): 1.07 (s,3H), 1.63 (s,3H), 1.75 (t,3H), 4.77 (s,2H).

Attempted Reduction of the Crude Hydrazone of 7β,10α-Selina-4,11-dien-3-one

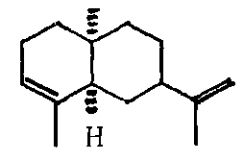
To the dienone 6 (1.0 g, 4.6 mmol) in 35 ml of ethanol was added hydrazine hydrate (Eastman's 64% hydrazine in water, 1.75 g, 35 mmol), following the procedure of Grundon, *et al*.[12] This mixture was refluxed for 66 hours, after which the ethanol was removed *in vacuo* and the residual aqueous layer extracted with ether. The ether extracts were dried and reduced *in vacuo*, followed by heating on a steam bath, and the crude hydrazone was used without further purification.

To the crude hydrazone thus obtained in 20 ml of

toluene was added potassium t-butoxide (1.0 g, 8.9 mmol, sublimed at 170°C, 0.3 torr). The mixture was refluxed under nitrogen for four hours, then allowed to cool overnight. The reaction mixture was washed with water, then the washings were extracted with ether and the ether extracts combined with the original toluene layer and reduced on a steam bath leaving a tarry mass, which GC analysis showed to be a complex mixture. A sample of this material was chromatographed on silica gel: elution with petroleum ether gave a small amount of material which had the same GC retention time as the starting ketone 6. No hydrocarbons were detected in the product.

Reduction of the Hydrazone of 7β,10α-Selina 4,11-dien-3-one 6 Formed in situ[13]: 5α,7β,10α- and 5β,7β,10α-Selina-3,11-dienes (7 and 8), and 7β,10α-Selina-4,11-diene (9)

To the dienone 6 (4.8 g, 22 mmol, made from the crystalline ketol 5) and hydrazine hydrate (8.2 g of Eastman's hydrazine hydrate (64% hydrazine in water), 165 mmol of hydrazine), in 350 ml of freshly distilled triethylene glycol, was added potassium hydroxide (7.6 g, 135 mmol) partially dissolved in 100 ml of



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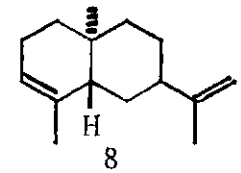

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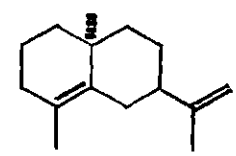

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triethylene glycol. The combined solution was heated at 100°C for 30 minutes, then the temperature was gradually raised to 210°C over 30 minutes and held at this temperature for one hour, during which time excess hydrazine and water distilled out of the reaction mixture. After cooling, the mixture was extracted with petroleum ether; the extracts were then washed with water, dried, and reduced *in vacuo*, yielding 4.2 g of a mobile yellow liquid. After filtration through alumina in petroleum ether, which removed color and smell from the product, GC analysis of the product showed that the volatile components included, in order of elution, 35% of 5α,7β,10α-selina-3,11-diene (7) (R_t = 7.6 min), 36% of 7β,10α-selina-4,11-diene (9) (R_t = 8.9 min), and 17% of 5β,7β,10α-selina-3,11-diene (8) (R_t = 12.0 min). A 250 mg sample of the mixture was chromatographed on 20 g of 10% silver nitrate-silica gel, using gradient elution, as follows: the column head reservoir (~500 ml), and the mixing flask (500 ml), which was equipped with a magnetic stirrer and fed into the column head reservoir via a glass siphon tube, were filled with petroleum ether; a second reservoir (500 ml) which fed into the mixing flask through another glass siphon tube, was filled with 10% benzene in petroleum ether. Fractions were collected automatically on a timed basis, the average volume being about 20 ml. Fractions 38 through 48 yielded, after removal of the solvent *in vacuo*, 39 mg of pure 5β,7β,10α-selina-3,11-diene

(8), identified by comparison with a authentic sample[14]; fractions 56 through 88 likewise yielded 125 mg of pure material which on the basis of its spectra had the same skeletal structure as 8, and was concluded to be 5α,7β,10α-selina-3,11-diene (7), the 5β- epimer of 8. A second chromatography of 1.0 g of the crude mixture of olefins obtained from the reaction was run on 100 g of 10% silver nitrate-silica gel, eluting first with petroleum ether (500 ml) then with petroleum ether containing, in succession, 10% benzene (1000 ml), 15% benzene (1000 ml), and 20% benzene (1000 ml); the fraction volume was again about 20 ml. In addition to about 400 mg of residues containing impurities and mixtures of the olefins, 280 mg of the material assigned structure 7 was obtained from fractions 41 through 90 (the eluting solvent entering the column, based on the total volume to this point, was 10-15% benzene in petroleum ether, changing from 10 to 15% approximately at fraction 75), and 171 mg of pure 7β,10α-selina-4,11-diene (9), identified by comparison with an authentic sample,[14] was obtained from fractions 96-165 (the eluting solvent entering the column was 15-20% benzene in petroleum ether, changing approximately at fraction 125). The samples of 8 and 9 thus obtained from the two chromatographies were identical with authentic samples[14] of the dienes by GC, alone and by mixed injection, and by superposition of their respective NMR and IR spectra.

5β,7β,10α-Selina-3,11-diene (8):

IR: ν_{neat} (cm^{-1}): 3080 (w), 2920 (s), 1636 (w), 1447 (s), 1372 (m), 884 (s).

NMR (δ, $CDCl_3$): 0.85 (s,3H); 1.23, 1.28, 1.35, 1.42; 1.62 (m,3H); 1.75 (m,3H); 4.93 (m,2H), 5.37 (m,1H).

7β,10α-Selina-4,11-diene (9):

IR: ν_{neat} (cm^{-1}): 3070 (w), 2930 (s), 1640 (w), 1450 (s), 1368 (m), 888 (s).

NMR (δ, $CDCl_3$): 1.07 (s,3H), 1.62 (s,3H), 1.71 (m,3H), 4.80 (m,2H).

Diene 7 as further characterized by its mass spectrum, including an exact mass determination, which proved the molecular formula to be $C_{15}H_{24}$.

5α,7β,10α-Selina-3,11-diene (7):

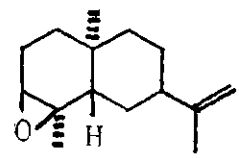
IR: ν_{neat} (cm^{-1}): 3070 (w), 2930 (s), 1640 (m), 1438 (s), 1373 (m), 885 (s), 804 (w).

NMR (δ, $CDCl_3$): 0.88 (s,3H), 1.50, 1.67-1.75 (m,6H), 4.72 (m,2H), 5.30 (bm,1H).

Mass spectrum: M^+_{found} exact mass m/e = 204.1878 (60%); calculated for $C_{15}H_{24}$ = 204.1889; base peak 107; other major peaks: m/e 189 (87%), 161 (40%), 133 (35%), 109 (33%), 108 (37%), 105 (73%).

Epoxidation of 5β,7β,10α-Selina-3,11-diene (8)

To the diene 8 (0.994 g, 89% pure by GC, 4.33 mmol of 8) in 25 ml of methylene chloride at -10°C, was added m-chloroperbenzoic acid (0.944 g, Aldrich technical grade (85%), 4.65 mmol of peracid) in 25 ml of methylene chloride, dropwise over five minutes. The reaction was monitored by GC, which indicated that it was essentially complete after 15 minutes total. The remaining peracid was decomposed after 20 minutes total by adding a saturated aqueous solution of sodium sulfite. The reaction mixture was washed three times with 10 ml of saturated aqueous sodium bicarbonate and twice with brine, then dried, and reduced in vacuo, yielding 0.997 g of a clear, viscous oil. Analysis of the product by GC showed it to be a mixture which consisted of 71% of a single product (R_t = 2.5 min), 5% of a product with a similar retention time (R_t = 2.2 min), less than 5% of starting material, and a number of other components, none of which composed more than 5% of the mixture mixture.[15] The IR spectrum of the crude product showed the isopropenyl double bond was still present, and in the NMR spectrum the absorption at 5.37 δ due to the C-3 vinyl proton was no longer present, being replaced by an absorption at 2.92 δ (t,1H), all of which is compatible with the structure of the desired (3β,4β-epoxy-5β,7β,10α-selin-11-ene (11).



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IR: ν_{neat} (cm^{-1}): 3435 (br,m), 3080 (w), 2930 (vs), 1707 (br,w), 1636 (w), 1445 (s), 1376 (m), 882 (s).

NMR (δ, $CDCl_3$): 0.85 (s,3H), 1.22 (s,3H), 1.75 (m,6H), 2.92 (t,1H), 4.90 (m,2H).

(δ, CCl_4): 0.82 (s,3H), 1.13 (s,3H), 1.75 (m,6H), 2.75 (t,1H), 4.88 (m,2H).

In another run of the epoxidation reaction, the diene 8 (2.00 g, 89% pure, 8.72 mmol) was dissolved in 40 ml of methylene chloride and chilled to -10°C as above, but the chilled solution of m-chloroperbenzoic acid (2.00 g, 85%, 9.86 mmol) in 40 ml of the same solvent was added rapidly, with stirring. After 30 min, a 10% solution of aqueous sodium sulfite was added, then the mixture was worked up as above. NMR and IR spectra of the crude product were identical to those of the epoxide obtained in the reaction described above, but GC analysis showed it to be a mixture consisting of only 60% of a single compound (R_t = 3.4 min) and 18% of the compound with a similar retention time (R_t = 3.0 min) which composed only 5% of the mixture in the other case. Since the spectra did not change, this suggests that the two main products might be the 3,4-epimers of each other. In another run, a solution of the peracid (3.38 g, 16.6 mmol) in 100 ml of methylene chloride was added dropwise over five hours to the diene 8 (4.00 g, 16.7 mmol) at room temperature; the product in this case consisted of 58% of the main product

(R_t = 3.5 min) and 19% of the second most abundant product (R_t = 3.1 min).

When an excess of peracid was used and the peracid was not destroyed before allowing the reaction mixture to warm up, a third major product was formed, with a retention time 2.0 to 2.4 times that of the major product. Thus, the diene 8 (500 mg, 2.18 mmol) in 10 ml of methylene chloride, cooled in ice, was added rapidly to the peracid (500 mg, 2.46 mmol); after two hours at -5 to 0°C, a test with starch-iodide paper showed peracid still present; after another hour the peracid was gone and the temperature had risen to 16°C. The product was comprised of 43% of the main component (R_t = 7.1 min), about 9% of a material which appeared as a shoulder on the main peak ($R_t \cong$ 6.6 min), 8% of the material with a similar retention time (R_t = 6.2 min), and 23% of the material with a relatively long retention time (R_t = 17.2 min), suspected to be a diepoxide. In a similar run, the solution of peracid (750 mg, 3.70 mmol) in 25 ml of methylene chloride was chilled to -10°C and added rapidly to an equally cold solution of the diene 8 (750 mg, 3.27 mmol) in 10 ml of solvent. The mixture was kept at -10°C for one hour, then allowed to warm up to room temperature; no sodium sulfite was added to destroy the peracid. The product consisted of 50% of the usual main product (R_t = 9.6), 1% of the product with a similar retention time (R_t = 8.2 min), and 39% of material with a long retention

time (R_t = 19.8 min).

Attempted Isolation of 3β,4β-Epoxy-5β,7β,10α-selin-11-ene (11)

Numerous attempts were made to isolate the pure epoxide 11 by column chromatography, without success. Several different absorbents were tried: alumina (neutral, activity I), silica gel, 10% and 20% silver nitrate silica gel, and florosil. Regardless of the abosrbent used, the main product could not be isolated in pure form, and the recovery of the material from the column was generally poor, suggesting that the epoxide was rearranging on the column. In one instance, the epoxide obtained from 4.0 g of the diene (58% of a single product, 19% of the suspected 3,4-epimer) was chromatographed on 350 g of silica gel: after elution with 1.0 ℓ of hexanes and 2.4 ℓ of 25% benzene in hexanes, elution with another 4.3 ℓ of 25% benzene followed by 1.5 ℓ of 50% benzene yielded, after removal of the solvent in vacuo, 1.0 g of a dark yellow-orange oil, which gave a single peak on GC with the same retention time as the suspected 3,4-epimer, but appeared to be a ketone, presumably 4β,5β,7β,10α-selin-11-en-3-one (14). This compound had the following spectral properties:

IR: ν_{neat} (cm^{-1}): 2925 (s), 1721 (vs), 1636 (m), 1449 (s), 1375 (m), 892 (s).

NMR (δ, C_6H_6): 0.92 (d,3H,J = 4.5 Hz), 1.38 (s,3H?), 1.62 (s,3H?), 4.87 (bs,2H).

After successive elution with 6.9 ℓ more of 50% benzene, 6.7 ℓ of pure benzene, 0.75 ℓ of 10% diethyl ether in benzene, and 0.4 ℓ of 50% ether in benzene, all of which yielded 1.0 g after removal of the solvent, the column was flushed with 1.0 ℓ of a mixture of 20% ethanol, 30% ether, and 50% benzene. This yielded, after removal of the solvent, 2.6 g of material which contained none of the major products by GC, and whose IR spectrum did not exhibit the absorption due to the isopropenyl double bond at around 890 cm^{-1}.

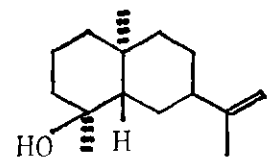
Attempted Reduction of 3β,4β-Epoxy-5β, 7β,10α-Selin-11-ene (11)

The crude epoxide 11 (from 1.75 g of the diene 8, 60% of a single product by GC (R_t = 3.4 min), 18% of a component with a similar retention time (R_t = 3.0 min), thus about 4.77 mmol of 11) was dissolved in 25 ml of tetrahydrofuran (freshly distilled from lithium aluminum hydride) and added to a slurry of lithium aluminum hydride (1.0 g, 26 mmol) in 75 ml of tetrahydrofuran in a 250 ml three-necked round bottom flask equipped with a reflux condenser, gas inlet tube, and a pressure-equalizing dropping funnel containing 75 ml more tetrahydrofuran. The mixture was heated under potassium hydroxide-dried nitrogen in an oil bath at 65°C for two days, then after one more day the solvent was found to have evaporated, so the oil bath was removed. After cooling, ether and a 10% aqueous solution of

sodium potassium tartrate were added; the layers were then separated and the aqueous layer extracted with ether. The combined ether layers were dried and reduced in vacuo, yielding 1.4 g of the recovered epoxide, which was taken up in benzene and dried, then taken up in hexanes and dried again. The NMR and IR spectra of the recovered epoxide were identical to that of the starting material, with the exception that the broad, weak absorption at 1710 cm^{-1} in the IR spectrum was no longer present. GC analysis showed the mixture to consist of 60% of the same major product, but only 5% of the material with a similar retention time which formerly composed 18% of the mixture; no peak was present in the trace at the retention time of the desired product, intermedeol.

Intermedeol (12)

The recovered epoxide 11 (1.4 g, 60% pure, 3.8 mmol) was dissolved in 125 ml of tetrahydrofuran (freshly distilled from lithium aluminum hydride) in a 500 ml two-necked flask equipped with a dropping funnel and reflux condenser, and heated to 50°C. The dropping funnel was charged with a slurry of lithium aluminum hydride (1.5 g,



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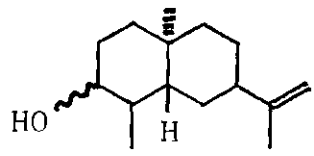


13

39.5 mmol) in 150 ml of tetrahydrofuran. This slurry was allowed to drip in over three hours, leaving a mud of the hydride in the dropping funnel. After one hour (before all the hydride had been added), GC analysis showed no discernible reaction; after 20 hours, less than 10% of the starting material remained, so the reaction mixture was allowed to cool, and 10% aqueous sodium potassium tartrate was added. The resulting aqueous layer and tetrahydrofuran layer were each extracted with chloroform, then the combined extracts were washed with brine, dried, and reduced *in vacuo*, yielding 1.3 g of a crude product, GC analysis of which showed it to be a mixture of at least eight different compounds, with the retention times and percentages listed in Table 1.

Table 1. GC Analysis of the Product of a 20-Hour Reduction of Epoxide *11*

R_t (min)	%	Possible Identity
1.3	1.4	
1.5	17	solvent impurity
2.3	4.9	unreacted epoxide, or ketone *14*
2.5	4.2	
3.1	2.6	intermedeol (*12*)
3.7	58	4β,5β,7β,10α-selin-11-en-3-ol (*13*)
4.2	4.2	
6.4	6.5	
8.1	2.0	

Isolation of Intermedeol (12)

Because intermedeol was present in such a small percentage, isolation was tedious: the crude reduced product was chromatographed four times in succession on neutral, activity I aluminum oxide, then intermedeol was isolated by preparative gas chromatography. In the first chromatography on alumina (100 g), after 2.4 ℓ of hexanes had been eluted from the column, the intermedeol containing fractions were eluted with 1 ℓ of hexanes followed by 2.1 ℓ of 1% benzene in hexanes. The residue (1.0 g, about 75% benzene) contained some of each of the products of the reaction, but intermedeol now composed 18% of the products. Subsequent elution with 5% benzene in hexanes yielded a 95% pure sample of the main product of the reduction, 4β,5β,7β,10α-selin-11-en-3-ol (13) (220 mg, 0.99 mmol), isolated as an oil, which had the following absorptions in the NMR spectrum (δ, CCl_4): 0.83 (s,3H), 0.95 (d,3H,J = 6 Hz), 1.68 (m), 3.67 (m,1H), and 4.83 (m,2H). Further proof of its structure was obtained by oxidation to the ketone 14, described later. In the second chromatography (60 g of alumina), after 11 ℓ of hexanes, 350 ml of 5% benzene in hexanes, and 0.5 ℓ of 25% benzene in hexanes, elution with 2.1 ℓ more of 25% benzene gave, upon reduction *in vacuo*, 48 mg of a residue which contained 57% of the material with R_t = 2.5 min, which composed 4.2% of the original product mixture. (Later, chromatography of this material, which was thought possibly

to be the 4α-OM epimer of intermedeol, paradisiol, on alumina gave a sample which was 85% pure by GC and had the following NMR spectrum (δ, CCl_4): 0.55 (s), 1.00, 1.05, 1.08, 1.70 (m), 3.73 (m,1H), 4.50 (m,1H), 4.77 (m,2H)). After further elution with 0.6 ℓ of 25% benzene, the following 1.75 ℓ of 25% benzene gave, upon reduction in vacuo, 123 mg of a residue which contained intermedeol as the major component (39% of the products by GC). A third chromatography on 44 g of alumina, after 3 ℓ of 1% benzene in hexane, 6.3 ℓ of a 2-3% gradient of benzene in hexanes, and 18 ℓ of 5% benzene, yielded, on elution with another 7.7 ℓ of 5% benzene, a fraction of which intermedeol composed 59% of the products by GC. A final, fourth chromatography on 2.5 g of alumina yielded, on elution with hexanes only, 60 mg of material which contained about the same percentage of intermedeol, but was free of benzene. Synthetic intermedeol was finally obtained in pure form by preparative gas chromatography on a 12 ft. x 1/4 in. 5% Carbowax 20M on 90/100 mesh Anakrom AS column, at an oven temperature of 148°C; 3.2 mg of crystalline intermedeol were obtained from this sample.

In another preparation of intermedeol, the epoxide 11 (made from 750 mg of the diene 8 and consisting of 50% of the main product (R_t = 9.6 min), 1% of the material with a similar retention time (R_t = 8.2 min), and 39% of the suspected diepoxide (R_t = 19.8 min) thus 1.52 mmol of 11), was dissolved

in 15 ml of freshly distilled tetrahydrofuran and heated to 50°C. Lithium aluminum hydride (750 mg, 19.8 mmol) in 25 ml of tetrahydrofuran was added dropwise to the stirred mixture over 12 hours. A mud of the hydride was left behind in the dropping funnel, as before, so 15 ml more of the solvent was added to the dropping funnel and allowed to drip in after one day and again after three days. The reaction was monitored by GC, and after 96 hours appeared to be changing no more, so 10% aqueous sodium potassium tartrate was added and the mixture extracted with ether. The extracts were washed with brine, dried, and evaporated, yielding a complex mixture with the GC retention times and percentages listed in Table 2.

Table 2. GC Analysis of the Products of a Three-Day Reduction of Epoxide 11

R_t (min)	%	Possible Identity
2.4	3.3	
3.1	2.3	
5.7	6.0	unreacted epoxide, or ketone 14
7.3	5.0	
8.9	8.6	intermedeol (12)
10.2	0.8	
11.5	44	4β,5β,7β,10α-selin-11-en-3-ol (13)
13.8	8.9	diepoxide
48.0	21	reduced diepoxide

Attempts were made to isolate intermedeol from the product by TLC on silica gel and alumina, but without

success. Likewise, chromatography on 100 g of silica gel, while eliminating the unreacted epoxides and the material with a very long retention time (R_t = 48.0 min), failed to significantly improve the percentage of intermedeol: after passing 1 ℓ of hexanes through the column, followed by 3.1 ℓ of 5% ether in hexanes, elution with another 1.7 ℓ of 5% ether yielded 360 mg of a material containing some solvent. Preparative gas chromatography of this sample yielded 10 mg of 95% pure intermedeol, which was reinjected on the column, giving 3.2 mg of pure intermedeol. The two pure samples of synthetic intermedeol were combined, and the NMR and IR spectra of the combined samples were identical to those of authentic natural intermedeol. A portion of this mixture was repurified by GC, and gave a mp of 30-33°C (lit.[2] 45°C).

IR: ν_{CCl_4} (cm^{-1}): 3610 (w), 3482 (b,w), 3090 (w), 2931 (vs), 1640 (m), 1450 (s), 1383 (s), 908 (s), 894 (s).

NMR (δ, CCl_4): 0.90 (s,3H), 1.00 (s,3H), 1.72 (s,3H), 4.83 (bs,2H).

In another reduction, the epoxide 11 (98 mg, recovered from the attempted reduction with sodium borohydride, described below; the original epoxide contained 43% of the main product (R_t = 7.1 min), 9% of a material which appeared as a shoulder on the main product's GC peak ($R_t \cong$ 6.6 min), 8% of the compound with a similar retention time (R_t = 6.2 min), and 23% of the suspected diepoxide (R_t = 17.2 min),

thus there were about 0.19 mmol of 11) was dissolved in 10 ml of tetrahydrofuran and heated to 58°C in an apparatus identical to that described for the first reduction, then a slurry of lithium aluminum hydride (103 mg, 27.1 mmol) in 10 ml of tetrahydrofuran was allowed to drip in over 30 minutes. After 16 hours, no epoxide remained, and the reaction was worked up in the usual way. GC analysis of the product showed peaks with the retention times and percentages given in Table 3.

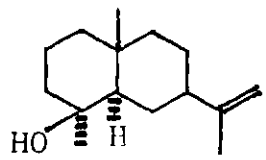
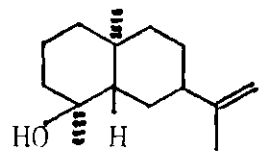
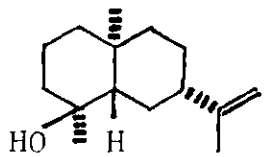
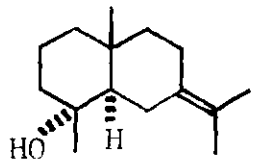
Table 3. GC Analysis of the Product of a 16-Hour Reduction of the Epoxide 11

R_t Min	%	Possible Identity
2.6	0.5	
3.2	9.8	unreacted diene 8
4.8	2.8	
8.8(mixture)	13.2	
10.8	14.1	intermedeol (12)
13.2	3.5	
14.1	36.1	4β,5β,7β,10α-selin-11-en-3-ol (13)
16.8	20.0	diepoxide

The presence of intermedeol (14.1%) was confirmed by a mixed injection of the crude product and authentic natural intermedeol, which showed enhancement of the peak at R_t = 10.8 min without broadening. This was supported by determining the ability of the column to separate some compounds

of similar structure, as shown in Table 4.

Table 4. Retention Times of Compounds Similar to Intermedeol on a Carbowax 20M Column

Compound		R_t (min, mixed injection)
		5.0
	(Intermedeol)	6.2
		7.1
		8.1

Attempted Reduction of Epoxide 11 with Sodium Borohydride

The crude epoxide 11 (98 mg, 50% of the main product, 0.45 mmol) was added directly to a stirred solution of sodium borohydride (250 mg, 6.61 mmol) in 20 ml of 2-propanol. The

mixture was then refluxed for 70 hours, after which GC analysis (SE-30) indicated no reaction had occurred, so the mixture was allowed to cool, and 10% aqueous sodium potassium tartrate was added. Later, water and ether were added to the reaction mixture; after the layers were separated, the reaction mixture was saturated with salt and extracted with ether again. The combined extracts were washed with brine, dried, and reduced *in vacuo*, yielding 132 mg of an oil which by GC appeared to be unreacted starting material. The NMR spectrum was partially obscured by 2-propanol, but supported this conclusion.

Attempted Reduction of Epoxide 11 with Lithium Aluminum Hydride in Dioxane

The epoxide 11 (20 mg, 60% of a single product, 0.054 mmol) in 1 ml of purified dioxane was added to a stirred slurry of lithium aluminum hydride in 9 ml of dioxane. The mixture was refluxed at 110°C for a total of 17 hours, after which GC analysis indicated no reaction had occurred. Addition of a solid mixture of lithium aluminum hydride (25 mg, 0.66 mmol) and aluminum chloride (50 mg, 0.38 mmol) resulted in ignition of the mixture; GC analysis showed the epoxide was completely gone, and the main component had the same retention time as the usual main product 13 from reduction in tetrahydrofuran. This mixture was not examined further.

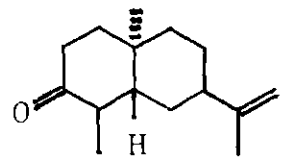
Attempted Reduction of Epoxide 11 with Lithium in Ammonia

The epoxide 11 (112 mg, 60% of the main component, recovered from an unsuccessful attempt to reduce the epoxide with lithium aluminum hydride in tetrahydrofuran, thus 0.305 mmol) was dissolved in 3 ml of anhydrous ether in a flask equipped with a condenser, a pressure-equalizing dropping funnel, and a gas inlet tube connected to a cooled flask containing a solution of sodium in liquid ammonia. The sodium-ammonium solution was allowed to evaporate into the reaction flask for a minute or two to purge the system, then dry ice-cooled acetone was allowed to flow into the condenser and ammonia was condensed in until about 5 ml was in the flask. Lithium ribbon (0.74 cm, 66 mg, 9.5 mmol) was dissolved in more ammonia and added to the reaction flask. The blue color of the solution disappeared after only approximately one minute, so more lithium was added, in portions as necessary to maintain a blue color, until a total of approximately 100 mg (14.4 mmol) of lithium had been added to the reaction, then solid ammonium chloride was added to quench the reaction. The ammonia was allowed to evaporate overnight, then the residue was partitioned between ether and water. The water layer was extracted with ether, then the combined ether layers were washed with brine, dried, and reduced *in vacuo*. Analysis of the residue by GC and NMR indicated that no reaction had occurred, and the

product was not further characterized.

Oxidation of 4β,5β,7β,10α-Selin-11-en-3-ol (13) with Jones Reagent: 4β,5β,7β,10α-Selin-11-en-3-one (14)

To the alcohol 13 (220 mg, 0.99 mmol) in 3 ml of acetone, cooled in an ice bath, was added Jones reagent (0.3 ml of a solution made by adding 7.7 ml of water to 2.67 g of chromium trioxide in 2.3 ml of 12 M sulfuric acid), dropwise with stirring. The brown color of the reagent disappeared after the addition of each drop until 0.2 ml had been added, after which it persisted. The excess acid was then neutralized with aqueous sodium bisulfite, and the resulting bilayer was separated. The aqueous layer was extracted with hexane, and the extracts were added to the original organic layer, forming another bilayer, which was separated as before; the lower layer from this separation was combined with the original aqueous layer, and these were again extracted with hexanes. The two hexane extracts were now combined, washed with brine, dried, and reduced *in vacuo*, yielding a residue whose NMR spectrum was identical to that of an authentic sample[16] of 4β,5β,7β,10α-selin-11-en-3-one prepared as described previously.[16] A portion of this sample was purified by preparative gas chromatography



14

on a 6' x 1/4" 3% SE-30 on 100/120 mesh Gas Chrom Q column at 130°C, yielding an oil which crystallized on standing, mp 43-45°C (lit.[6] 49.5-50°C), whose IR was identical to that of the authentic sample.

IR: ν_{CCl_4} (cm^{-1}): 3033 (w), 2932 (s), 1707 (s), 1634 (w), 1451 (m), 1376 (m), 891 (m).

NMR (δ, CCl_4): 0.95 (d,3H,J = 6 Hz), 1.12 (s,3H), 1.72 (m,3H), 4.83 (d,2H,J = 8 Hz).

CHAPTER IV

DISCUSSION OF RESULTS

As stated in the introduction, the purpose of this research was the first total synthesis of intermedeol (12). This synthesis was achieved by the sequence of reactions outlined in Figure 4. In addition, two other naturally occurring compounds, 8 and 9, were synthesized, with 8 being an intermediate in the synthesis of intermedeol. The yield of intermedeol from this sequence of reactions is, however, quite low, and separation from the other products difficult.

As shown in Figure 4, the synthesis of intermedeol began with the preparation of the previously reported dienone 6, according to the procedure of McQuillen.[9,10] In the annelation reaction, ethyl iodide was used instead of methyl iodide. This may be partly responsible for the low yield (10%) of crystalline ketol 5. The absolute stereochemistry of the bicyclic compounds was determined at this point by using (+)-dihydrocarvone (4), rather than its (-)-enantiomer, which was used by McQuillen.[10] Thus the absolute stereochemistry is 7β,10α, which is the same as that of naturally occurring intermedeol and the selinadienes 8 and 9. The ketol 5 was then smoothly dehydrated in

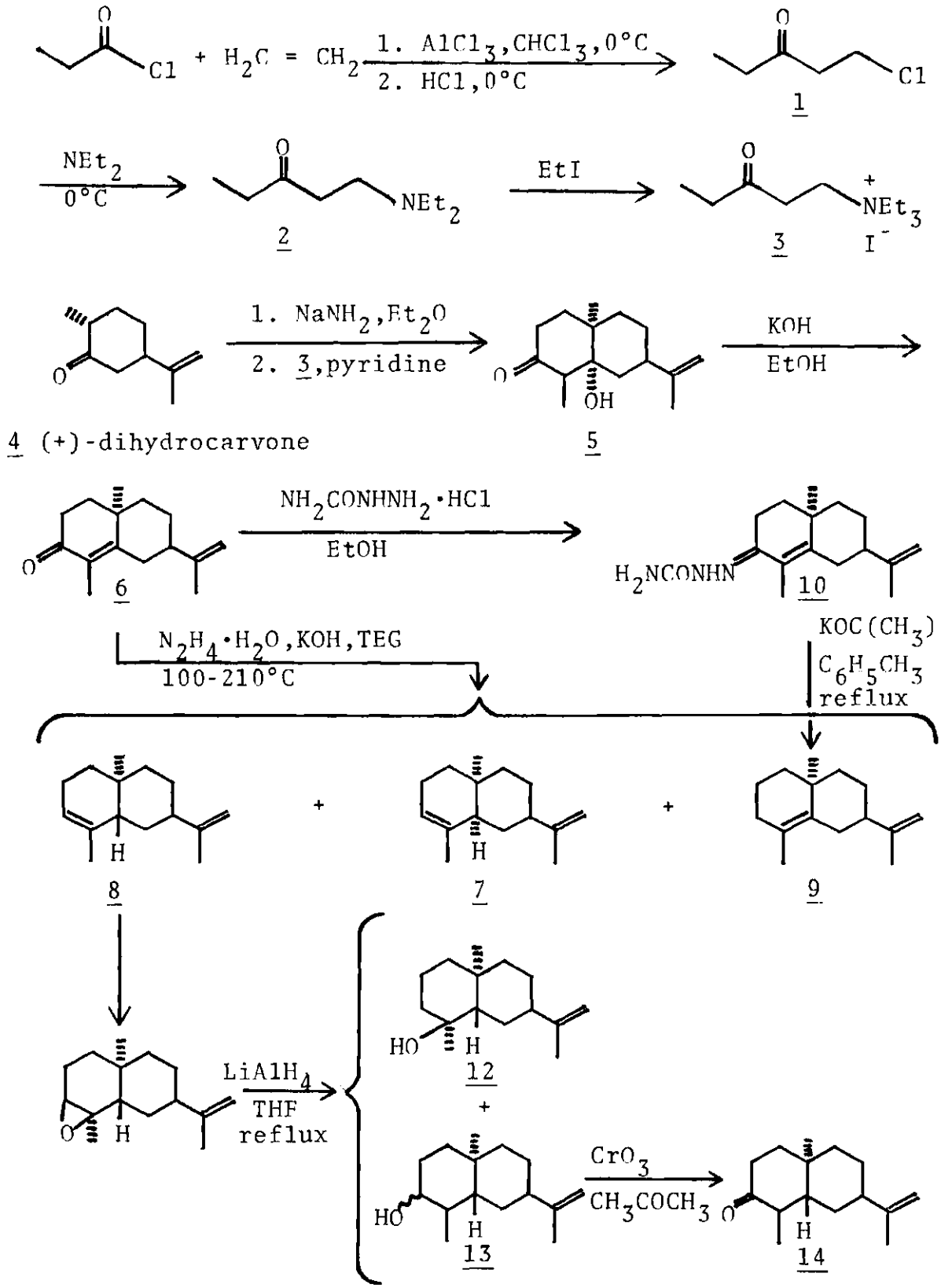


Figure 4. Summary of Results

alcoholic KOH to give 7β,10α-selina-4,11-dien-3-one (6), isolated as an oil which was 95% pure by GC. The NMR spectrum of this compound in deuterochloroform exhibited singlet absorbances at 1.25 δ (C-15 methyl) and 1.75 δ (C-14 methyl), while the C-13 vinyl methyl protons' absorbance appeared as a doublet at 1.82 δ due to splitting by the trans vinyl proton (J = 1.5 Hz). The two vinyl portons exhibited different chemical shifts, absorbing at 4.67 and 4.83 δ.

The dienone 6 was then reduced by a modified Wolff-Kishner procedure;[13] the conditions were chosen to obtain the maximum amount of double bond migration. The dienone and hydrazine hydrate were dissolved in freshly distilled triethylene glycol, then potassium hydroxide was added and the solution heated at 100°C for 30 minutes. The temperature was then raised to 210°C over 30 minutes, during which time water and excess hydrazine hydrate distilled out of the mixture. After one hour at this temperature, the reaction was worked up and the product filtered through alumina in petroleum ether. Analysis of the mixture by GC on a Carbowax 20M on Anakrom AS column showed the product to consist of three main components, comprising, in order of elution, 35% (R_t = 7.6 min), 36% (R_t = 8.9 min) and 17% (R_t = 12.0 min) of the products.

Samples of the three compounds were isolated by chromatography on silica gel impregnated with 10% by weight of silver nitrate. The order of elution from the column was

not the same as the order of elution on GC: the compound with R_t = 12.0 min came off first, followed by the compound with R_t = 7.6 min, and finally the compound with R_t = 8.9 min.

The first compound to be eluted from the column (R_t = 12.0 min) was identified as 5β,7β,10α-selina-3,11-diene (8), the desired product, by direct comparison with an authentic sample.[14] The two samples gave identical NMR and IR spectra, and were identical by GC analysis, both alone and by mixed injection.

The second compound to be eluted from the column (R_t = 7.6 min) was assigned the structure 7 on the basis of its spectral properties, as follows: The presence of the isopropenyl double bond was shown by absorptions at 1640 and 884 cm^{-1} in the IR spectrum. The NMR spectrum contained an absorption whose integration corresponded to two protons at 4.72 δ, which confirmed the presence of an isopropenyl double bond, and an absorption at 5.30 δ whose integration corresponded to one proton, thus suggesting the same skeletal structure as the known product 8. The spectra of this compound was in all other ways very similar to those of 8, and an exact mass analysis showed that for M^+ = 204.1878 (calc. 204.1889), $C_{15}H_{24}$ was the only possible formula for the compound. Thus the conclusion was reached that this compound is the 5α-epimer of 8, which is 5α,7β,10α-selina-3,11-diene (7).

Finally, the last compound to be eluted from the

column (R_t = 8.9 min) was identified as 7β,10α-selina-4,11-diene (9) by direct comparison with an authentic sample[14] by IR, NMR, and GC. The order of elution of the compounds from the silver nitrate-impregnated column can be explained in terms of the relative ability of the three isomers to involve both of the double bonds in coordinating with a single silver cation: the 4,11-diene 9 has the shortest distance between its double bonds and the fewest intervening atoms, thus is held more tightly; in the case of the cis-diene 7, since the stereochemistry is 5α,7β,10α, the isopropenyl group is closer to the Δ^3 double bond, the whole molecule being bent so that the two groups could more easily coordinate with a single cation than could the more planar 5β,7β,10α trans-diene 8.

The preference for protonation of the intermediate anion of the hydrazone of 6 in such a way as to give the cis-fused diene 7 can be explained as follows:[17] If it is assumed that the orbital at C-5 in the anion is sp^3, as is presumed in the case of metal ammonia reductions of α,β-unsaturated ketones,[18] then continuous overlap with the C-4 sp^2 orbital can be maintained by an α-oriented C-5 orbital, which would thus be cis to the C-10 methyl group. This orientation would be expected to be preferred over the β orientation (leading to 8), since the former intermediate, after protonation at C-5, would lead to an all-chair arrangement with an equatorial C-7 isopropenyl group, whereas the

latter case would lead to the less favorable B-ring twist-boat conformation.

Grundon, Henbest, and Scott[12] showed that by using a modification of the Wolff-Kishner reduction procedure involving potassium t-butoxide in toluene double bond migration in α,β-unsaturated ketones could be minimized; in particular, by using the preformed semicarbazone of cholest-4-en-3-one, essentially pure cholest-4-ene was obtained in high yield. The semicarbazone of 6 was prepared by adding semicarbazide hydrochloride to a near-saturated solution of the dienone and sodium acetate in ethanol-water and heating at 100°C for 30 seconds. The recrystallized product was then refluxed with potassium t-butoxide in sodium-dried toluene for 90 hours, monitoring of the nitrogen evolved indicated the reaction was complete after 68 hours. Analysis of the crude product by GC and NMR indicated that the unrearranged diene 9 was the only product. An attempt was made to prepare the hydrazone of 6 and isolate it, then reduce it by the above procedure. Thus, the dienone 6 and hydrazine hydrate were refluxed in ethanol for 66 hours; the crude product was then refluxed with potassium t-butoxide in toluene for 4 hours. The resulting product after work-up was a tarry mass in which no olefins could be detected.

The epoxide 11 was prepared from the trans-fused diene 8 by reaction with m-chloroperbenzoic acid in methylene chloride. A solution of the diene (89% pure by GC) was cooled

to -10°C, and a solution of the peracid (1.1 moles/mole diene) was added dropwise over five minutes. Monitoring of the reaction by GC showed it to be complete after 15 minutes. After 20 minutes total, a solution of sodium sulfite was added to the still cold reaction mixture to decompose the remaining peracid. Analysis of the product by GC showed it to be a mixture which consisted of 71% of a single product, presumed to be the β,β-epoxide 11, less than 5% of the starting material, and a number of other products, none of which composed more than 5% of the mixture; one of these products, however, composing 5% of the mixture, had an R_t which was 0.9 times that of the main product and was suspected to be the isomeric α,α-epoxide. Examination of Dreiding models shows that approach by the peracid should be much more facile from the β face than the α face because of the C-10 methyl group, thus the main product is expected to be the β,β-isomer 11.[17]

The IR spectrum of the crude product exhibited absorptions at 882 and 1636 cm^{-1}, indicating the presence of the isopropenyl double bond. The NMR spectrum contained absorptions at 4.90 δ (m,2H) for the isopropenyl double bond, and at 2.92 δ (t,3H) for the hydrogen at C-3 of the epoxide. The IR spectrum also exhibited a broad absorption in the O-H stretching region at 3435 cm^{-1} which was not removed by further drying over magnesium sulfate.

This reaction was run several times, in slightly

different ways, and it was found that temperature, method of addition, and work-up all had a significant effect on the proportions of various products obtained. When a chilled (-10°C) solution of the peracid (1.1:1 mole ratio, as above) was added rapidly to a chilled solution of the diene and the reaction worked up as above after 30 minutes, GC analysis showed the product to be a mixture of 60% of the same main product and 18% of the suspected α,α-epimer. The NMR and IR spectra were, however, identical to those of the crude product from the above reaction. When a solution of the peracid (1:1 mole ratio) was added to the diene dropwise over 5 hours at room temperature, virtually the same proportions were obtained (58% and 19%) as in the second reaction described.

In another run, an ice-cold solution of the diene was added rapidly to an ice-cold solution of the peracid (1.13 mol/mol diene), but the reaction mixture was allowed to warm up until all of the peracid had reacted, at which point the temperature had reached 16°C. Analysis by GC showed, in addition to the main product (43%) and the suspected α,α-epimer (8%), a third product (23%), which had an R_t approximately 2.4 times that of the main product; this compound, although never characterized, is presumed to be a diepoxide. In a similar case, a solution of the peracid (1.13 mole ratio) at -10°C was added rapidly to a solution of the diene at the same temperature and the mixture was

kept at -10°C for one hr, then allowed to warm up to room temperature without decomposing the remaining peracid. The products in this case consisted of 50% of the main product, 1% of the suspected epimer, and 39% of the presumed diepoxide. Since this method is the same as the second method reported above, which produced 60% of the main product and 18% of the epimer, except for the destruction of the excess peracid, it would appear that the α,α-epoxide is epoxidized at the remaining double bond more rapidly than its epimer.

Attempts were made to isolate the main products by column chromatography on alumina, silica gel, 10% and 20% silver nitrate on silica gel, and florosil, but all were unsuccessful. The epoxide never came off the column in pure form, and the amount of material recovered was always low, suggesting that rearrangement of the epoxide, presumably to a ketone, was taking place. In one instance, chromatography of 4 g of crude epoxide containing 58% of the main product produced 1 g of a yellow-orange oil which gave a single peak on GC analysis. The spectral properties of this material suggested it was a ketone (absorption at 1721 cm^{-1} in the IR spectrum) and that it still contained the isopropenyl double bond (absorption for 2H at 4.87 δ in the NMR spectrum, run in benzene); in addition, the NMR spectrum showed an absorption at 0.92 δ which was a doublet, representing a methyl group on a tertiary carbon atom, all of which is compatible with the structure of the ketone 14. Further

characterization was not attempted.

Intermedeol (12) was prepared and isolated from two different samples of the crude epoxide 11 as follows. An attempt was made to reduce the crude epoxide containing 60% of the main product and 18% of the suspected epimer with lithium aluminum hydride in tetrahydrofuran, but GC analysis of the product after three days of refluxing showed no intermedeol and no significant amount of any other products had been formed. The recovered starting material, however, was different in that while the main component of the epoxide was still 60% of the mixture, the suspected epimer composed only 5%, and in that a broad, weak absorption at 1710 cm^{-1} in the IR spectrum was no longer present; otherwise, the NMR and IR spectra were the same as before. Apparently, then, enough water was present in the reaction mixture to destroy the hydride.

The recovered epoxide was then dissolved again in tetrahydrofuran and heated to 50°C, then a slurry of lithium aluminum hydride (10:1 mole ratio) in tetrahydrofuran was allowed to drip in over three hours, leaving a mud of the hydride in the dropping funnel. Analysis by GC showed less than 10% of starting material remaining after 20 hrs, so the reaction was worked up after cooling by adding a saturated solution of sodium potassium tartrate and extracting with chloroform. Analysis by GC showed the crude product to contain 2.6% of intermedeol, 58% of another product, 4.9% of

starting material, and small percentages of six other compounds, believed to be primarily solvent impurities and impurities in the starting material.

Isolation of the intermedeol required four successive chromatographies on alumina followed by preparative gas chromatography on a 12 ft. x 1/4 in. 5% Carbowax 20M on 90/100 mesh Anakrom AS column, at an oven temperature of 148°C. Only 3.2 mg of intermedeol were obtained from this sample, so it was stored until more could be made and isolated.

In the other reduction of the epoxide which led to isolation of intermedeol, the crude epoxide, containing 50% of the main product, only 1% of the suspected epimer, and 39% of the presumed diepoxide, was treated with the hydride (10:1 mole ratio) in tetrahydrofuran at 50° as in the other case, except that the hydride slurry was added over 12 hours, and additional solvent was added to the dropping funnel containing the mud of the hydride after one day, and again after three days, and allowed to drip into the reaction mixture. Monitoring by GC showed the reaction to be essentially complete after 96 hours, at which point it was worked up by adding a 10% solution of sodium potassium tartrate and extracting with ether. Analysis of the product by GC showed it to consist of 8.6% intermedeol, 44% of the main product, 6.0% of starting material or ketone 14, 9% of the unreacted by-product of the epoxidation, thought to

be a diepoxide, 21% of a material with a very long retention time, presumed to be the reduction product of the diepoxide, and four other compounds, none of which composed more than 5% of the mixture.

Attempts were made to isolate intermedeol by TLC on silica gel and alumina, but without success. Column chromatography on silica gel eliminated the epoxides and reduced diepoxide, then 10 mg of intermedeol was obtained in 95% purity by preparative GC. A second purification by GC yielded 3.2 mg of pure intermedeol, which was combined with the other sample to obtain spectra. The NMR and IR spectra of the combined material were identical by direct comparison to those obtained from authentic natural intermedeol.[3] A portion of this mixture was repurified by GC after spectra were obtained, and gave a mp of 30-33°C (lit.[2] 45°C).

In the process of obtaining a pure sample of intermedeol, samples of two other products were also obtained. The main product of the reduction was identified as 13 by its NMR spectrum, which showed a high field methyl doublet (0.95 δ, J = 6 Hz) and a broad single hydrogen absorption (3.67 δ), and by its conversion into the known ketone 14, identified by direct comparison of its NMR spectrum with that obtained earlier from an authentic sample of 14,[16] by oxidation with chromic acid in toluene. The other reaction product, which composed 4.2% of the crude product, was not obtained in sufficient quantity or purity to be characterized.

Its R_t was 0.8 times that of intermedeol, and it was thought that it might be paradisiol, the 4α-OH epimer of intermedeol.

Both the amount of intermedeol obtained in the second reaction described, and the lack of any intermedeol or the main product 13 being produced when the suspected α,α-epimer reacted in the first attempt to reduce the epoxide, support the conclusion that the main product of the epoxidation is the expected β,β isomer. However, this epoxide has no low-energy pathway available for reduction to intermedeol, as is indicated by the long time required for the reaction.[17] The formation of intermedeol from the epoxide 11 requires attack from the α side of the molecule at the C-3 position. Although lithium aluminum hydride normally reacts with an epoxide in such a way as to yield the more highly substituted alcohol, which would in this case give intermedeol, it has been found that in molecules with a relatively rigid conformation that attack preferentially occurs in such a way as to give diaxial opening of the epoxide, and that this factor is predominant over the other in determining the products.[19] Diaxial ring opening to give intermedeol requires that the A ring be in a boat conformation, whereas in the chair conformation diaxial opening would lead to the 3β isomer of alcohol 13; this, however requires attack at C-4 from the highly hindered β face of the molecule. An alternative pathway to the alcohol 13 would be prior rearrangement of the epoxide to the ketone 14, catalyzed by a Lewis acid

impurity, before reduction to the alcohol. This pathway should lead almost exclusively to the equatorial 3α alcohol because of the preference for axial attack of the hydride and the hindrance of the C-10 methyl group. Evidence for this pathway was found in the experiment described below, wherein addition of a mixture of lithium aluminum hydride and aluminum chloride to the epoxide in dioxane led to immediate loss of the epoxide and formation of a material with the same R_t as the alcohol 13 usually obtained as the main product.

In another reduction of the epoxide performed in a manner analogous to the reactions described above, GC analysis indicated a higher percentage (14%) of intermedeol present in the product, but it was not isolated from this sample. Attempts to reduce the epoxide with sodium borohydride in 2-propanol, with lithium aluminum hydride in dioxane, and with lithium in ammonia were unsuccessful. In the first case, the product appeared to be mainly starting material. With the hydride in dioxane, no reaction had occurred after 17 hours at 110°C, but when aluminum chloride and more of the hydride were added, the mixture ignited, and GC analysis showed no starting material remained; instead, the product had the same R_t as the usual main product of the reduction, 13. With lithium in ammonia, the blue color of the dissolved lithium disappeared rapidly, but the product after work-up appeared to be only starting material, even

though a 50:1 mole ratio of lithium to the epoxide had been added.

CHAPTER V

CONCLUSIONS AND RECOMMENDATIONS

Intermedeol has been synthesized by the sequence of reactions outlined in Figure 4. In addition, the natural products 8 and 9 and the diene 7 have been prepared. The overall yield of intermedeol is, however, too low, and the resulting separation too difficult to make this a practical method for obtaining intermedeol in quantity. The yield of intermedeol might improve if Lewis acid impurities could be scrupulously eliminated from the reduction reaction, or if a more hindered hydride were used. The reaction could also be done again with the idea of trying to isolate the third product of the reduction reaction to see if it is indeed the previously unreported paradisiol.

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