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SESQUITERPENOIDS—V[1]

THE SYNTHESIS AND FORMOLYSIS OF 4aβ,8β-DIMETHYL-8aα-HYDROXYDECAHYDRONAPHTH-2β-OIC ACID AND 4aβ,8β-DIMETHYL-8aα-HYDROXYDECAHYDRONAPHTH-2α-OIC ACID LACTONE

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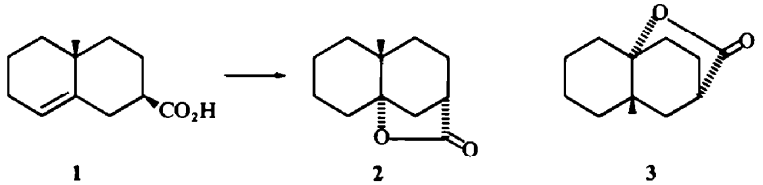
Abstract—Treatment of hydroxy-acid **4** with formic acid at room temperature leads to the unsaturated acid **9**, which forms a complex mixture of lactones on more vigorous treatment. Lactone **10** reacts with formic acid to afford equimolar amounts of lactones **14** and **15**, in a ratio of 1:2, probably *via* unsaturated acid **13**.

IN A previous paper, we outlined and discussed the merits of a "methyl-migration route" to eremophilane sesquiterpenoids.[1] The observation that unsaturated acid **1** is converted into an equilibrium ratio of lactones **2** and **3** upon treatment with refluxing formic acid prompted us to prepare the hydroxy-acid **4**. Compound **4** possesses



1 **2** **3**

two axial Me groups at the C_1 and C_3 positions of a cyclohexane chair, and we had hoped that this steric strain would lower the transition state energy for migration of the angular Me group. This design was predicated on the belief that migration would be at least partially synchronized with loss of water from the protonated alcohol.

Compound **4** was synthesized from the readily-available unsaturated acid **1**[2] by the following route. LAH reduction of **1** yields an alcohol **5**, which is converted by *m*-chloroperbenzoic acid into a mixture of eopxy-alcohols **6** and **7** in a ratio of 3:2.† Treatment of this mixture with MeMgBr in tetrahydrofuran affords a crystalline

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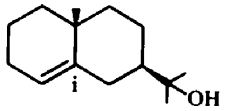
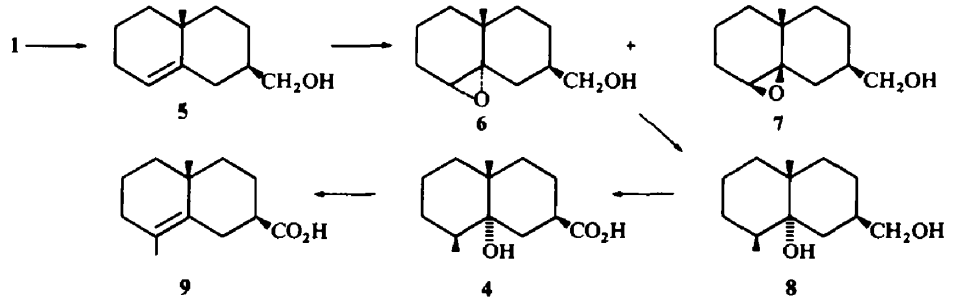
† Results from these laboratories indicate that epoxidation of compounds of type **5** invariably produce a preponderance of the epoxide with the *trans*-decalin structure.[1,2] Similar results have been obtained in the epoxidation of the unsaturated tertiary alcohol i, in which a rigorous structure proof of the product epoxides has been accomplished.[3] Marshall and Hochstetler have observed similar selectivity in the



i

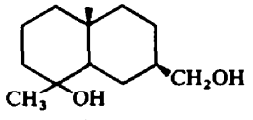
epoxidation of 10-methyl-$\Delta^{1,9}$-octalin.[4] A thorough study of the stereochemistry of electrophilic additions to 10-methyl-$\Delta^{1,9}$-decalins will be communicated separately.

diol, isolated in 71% yield (based on stereoisomer **6**). This diol was assigned structure **8** on the basis of its NMR spectrum, which showed a Me doublet at δ 1·03. The stereo-



chemistry assigned to compound **8** is based on mechanistic probability and on analogy to the reaction of *trans*-10-methyl-1,9-oxidodecalin with MeMgI.[4]

When the mixture of epoxides **6** and **7** is treated with MeMgI in ether, compound **8** may be isolated in only 13% yield. These conditions lead to the additional formation of another crystalline diol, which was also obtained, albeit in lesser amounts, from the reaction of **6** and **7** with MeMgBr. This second diol, isolated by fractional crystallization of the crude reaction product, showed two unsplit methyl resonances, at δ 1·05 and δ 1·20, and was assigned structure ii (stereochemistry unknown). The for-

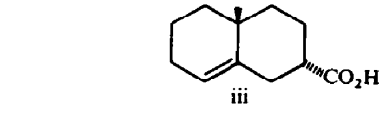


ii

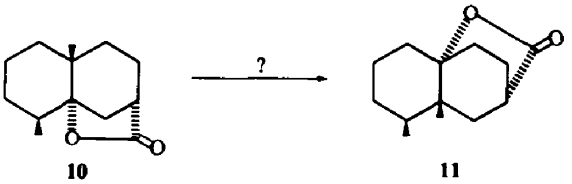
mation of such a product upon treatment of an epoxide with a Grignard reagent has ample precedent.[5]

Oxidation of diol **8** with chromic acid in acetone yields the desired hydroxy acid **4**. Our hopes for a clean Me migration in the formolysis of **4** were not realized. It was found that simple dissolution of the material in cold formic acid leads to a rapid dehydration, with the formation of unsaturated acid **9**. Apparently, Me migration is not synchronized with ionization of the protonated OH group. A free carbonium ion must be produced, and the steric interference inherent in the 1:3 diaxial Me:Me interaction is relieved by simple deprotonation. Upon heating, the formic acid solution of **9** leads to a complex lactone mixture consisting of at least seven components.

One possible means of circumventing this difficulty suggested itself to us. If lactone **2**



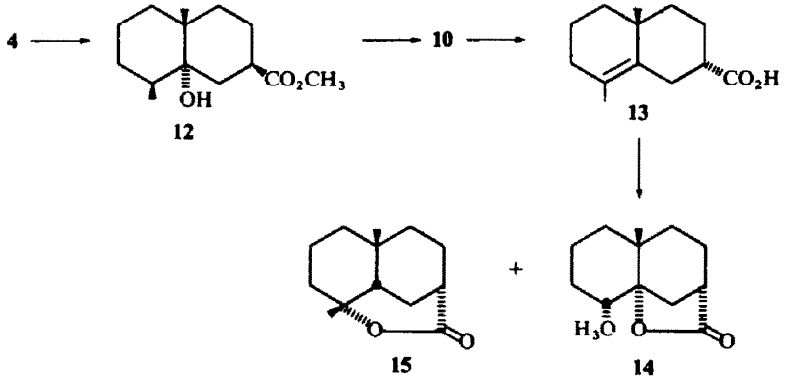
iii



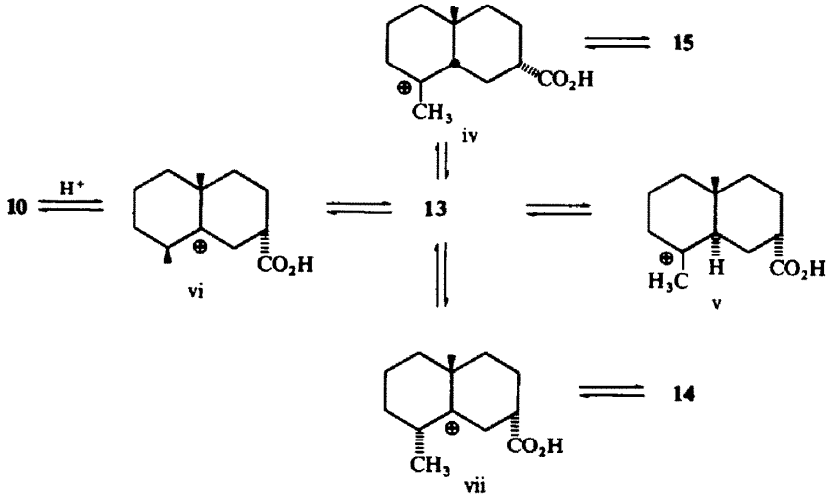
10 11

is converted into lactone **3** by some synchronous mechanism, and does not proceed by reversal to unsaturated acid iii, then perhaps lactone **10** would rearrange cleanly to the desired lactone **11**. Relief of steric hindrance is still possible and therefore **11** might be the first-formed transformation product of **10**. Since **11** should be much more stable relative to **10** than **3** is relative to **2**, the desired rearrangement might be realized in this case.

In the event, formolysis of lactone **10** (obtained by treatment of hydroxy ester **12** with methanolic sodium methoxide) for 8·5 min at 85° gave an equimolar mixture of a γ-lactone (**14**, ν_{max} 1780 cm^{-1}) and a δ-lactone (**15**, ν_{max} 1735 cm^{-1}).



Compound **15** shows two unsplit Me resonances, at δ 1·05 and δ 1·33. Compound **14** shows a Me singlet at δ 1·08 and a Me doublet at δ 0·92. The formation of **14** and **15** can be understood in terms of the initial formation of unsaturated acid **13**, which undergoes protonation at either end of the double bond to give a tertiary carbonium ion (iv–vii). Ion iv can immediately lactonize to afford **15**. Ion v cannot lactonize for



geometrical reasons, and must undergo deprotonation back to **13**. Ion vi is simply the intermediate in opening of **10**; lactonization gives back starting material. Ion vii can lactonize to form **14**. In both **14** and **15**, the 1:3 diaxial Me:Me interaction

has been relieved, but without the desired Me migration. In support of the above scheme, it was observed that subjection of pure lactone **15** to the identical conditions gave a similar mixture of **14** and **15**, in a ratio of 36:64.

EXPERIMENTAL

IR spectra were determined on a Perkin–Elmer 237 Infrared Spectrometer. NMR spectra were determined on a Varian A-60 instrument. Chemical shifts are given in ppm downfield from internal TMS. Microanalyses were performed by the University of California Microanalytical Laboratory, Berkeley, California.

4aβ-Methyl-2β-hydroxymethyl-1,2,3,4,4a,5,6,7-octahydronaphthalene (**5**). A soln of 5·0 g of **1**[1] in 55 ml dry THF was added through a dropping funnel over a 5 min period to a soln of 2 g LAH (2·8 molar excess) in 50 ml of THF. After refluxing for 20 hr, the reaction was quenched by the dropwise addition of 8 ml of 10% NaOH aq. The resulting mixture was stirred for 30 min, then filtered. The ethereal filtrate was dried and evaporated to yield 4·20 g (88%) of **5**. Analytically pure material was obtained by preparative VPC. (Found: C, 79·87; H, 10·93. Calc. for $C_{12}H_{20}O$: C, 79·94; H, 11·18%); NMR in CCl_4: δ 1·02 (Me), δ 3·35 ($C\underline{H}_2OH$), and δ 5·27 (C_7-H).

4aβ-Methyl-8,8aα-oxido-2β-(hydroxymethyl) decahydronaphthalene (**6**) *and 4aβ-methyl-8,8aβ-oxido-2β-(hydroxymethyl) decahydronaphthalene* (**7**). To 10·4 g of **5**, in 130 ml reagent grade $CHCl_3$, was added over a 30 min period a soln of 22·5 g 85% *m*-chloroperbenzoic acid in 200 ml CCl_4. After 4 hr at room temp, 10 g Na_2SO_3, in water, was cautiously added and the resulting mixture stirred for 15 min. The organic layer was separated, washed with 10% NaOH aq, sat NaCl aq, and dried. Removal of the solvent afforded 9·2 g of cloudy white oil. Spectra examination of this oil revelaed it to be a mixture of **6** and **7**. NMR in CCl_4: δ 1·01 and δ 1·02 (Me groups in **36** and **37**, respectively, in a ratio of 3:2), δ 2·87 (C_7-H), and δ 3·37 ($C\underline{H}_2OH$); IR in CCl_4: ν_{max} 3300 (OH), 1230, 920 and 835 cm^{-1}.

1β-4aβ-Dimethyl-7β-(hydroxymethyl) decahydronaphth-8aα-ol (**8**). A soln of 9·4 g of the mixture of **6** and **7** (*vide supra*), in 75 ml dry THF was added to 0·26 moles MeMgBr in 20 ml THF (prepared from 5 g Mg and excess MeBr) and the mixture was refluxed 18 hr. The mixture was then cooled and cautiously acidified with sat NH_4Cl aq. The product was isolated by extracting the resulting mixture several times with ether. Removal of the ether, after drying, gave 10·2 g of yellow oil. Repeated trituration of this oil with 4:1 pet. ether–ethyl ether gave 4·7 g of **8** as white needles (48% based on the mixture, 71% based on epoxide **6**). The analytical sample, m.p. 116–117·5°, was obtained by several recrystallizations from benzene; NMR in $CHCl_3$: δ 1·03 (Me groups, broad singlet), δ 3·50 ($C\underline{H}_2OH$, doublet, J = 6 c/s); IR in Nujol: ν_{max} 3500 cm^{-1}. (Found: C, 73·49; H, 11·19. Calc. for $C_{13}H_{24}O_2$: C, 73·54; H, 11·39%).

The mother liquors from the above crystalline yielded 0·34 g of an isomeric diol, m.p. 137–138° after recrystallization from 9:1 benzene–MeOH. (Found: C, 73·30; H, 11·46. Calc. for $C_{13}H_{24}O_2$: C, 73·54; H, 11·39%). Structure ii was assigned to this diol on the basis of its NMR spectrum (in MeOH): δ 1·05 and δ 1·19 (Me singlets).

1β,4aβ-Dimethyl-8aα-hydroxydecahydronaphth-7β-oic acid (**4**). To a soln of 0·956 g of **8**, in 30 ml 9:1 acetone–water, Jones oxidant[6] was added until the orange color of Cr(VI) persisted for 5 min. The opaque mixture was made basic with $NaHCO_3$ aq and twice extracted with 50 ml portions of ether. The aqueous layer, after acidification with dil H_2SO_4 aq, was extracted with four 75 ml portions of ether. The combined ether extracts were washed with sat NaCl aq. and dried, then evaporated to yield 0·670 g (70%) of white, crystalline solid, m.p. 148–151°. The analytically pure material, m.p. 149–150°, was obtained after four recrystallizations from benzene; NMR in pyridine: δ 1·12 (Me) and δ 0·99 (Me, doublet, J = 8 c/s); IR in $CHCl_3$: ν_{max} 3100, 1700 cm^{-1}. (Found: C, 68·72; H, 9·98. Calc. for $C_{13}H_{22}O_3$: C, 68·99; H, 9·80%).

Ester **12** was obtained by treating 400 mg of **4** with ethereal diazomethane until the yellow color persisted for 5 min. The product so obtained was chromatographed on alumina to yield 402 mg (90%) of **12** as a pale yellow oil; NMR in CCl_4: δ 1·10 (Me), δ 1·03 (Me, doublet, J = 7 c/s), δ 3·56 (OMe).

1β,4aβ-Dimethyl-8aα-hydroxydecahydronaphth-7α-oic acid, lactone (**10**). A soln of 1·26 g of **12** and 0·74 g NaOMe in 55 ml abs MeOH was refluxed under N_2 for 19 hr. The resulting soln was acidified with AcOH, diluted with water, and the mixture extracted with ether. The ether extracts were dried and evaporated to yield 1·08 g of oily **10**. Chromatography on silica gel yielded 0·757 g (73%) crystalline **10**, m.p. 49–52°. The analytical sample was obtained after several recrystallizations from light pet. ether, m.p. 53·5–54°. (Found: C, 75·30; H, 9·60. Calc. for $C_{13}H_{20}O_2$: C, 74·96; H, 9·68%); NMR in CCl_4: δ 1·15 (Me), δ 1·03 (Me, doublet, J = 8 c/s); IR in CCl_4: ν_{max} 1170 cm^{-1}.

1,4aβ-*Dimethyl*-2,3,4,4a,5,6,7,8-*octahydronaphth*-7β-*oic acid* (**9**). A freshly-prepared soln of 70 mg of **4** in 1·5 ml formic acid was placed in an NMR tube and the NMR spectrum determined immediately. The conversion of **4** into **9** was followed by the disappearance of the Me doublet at δ 1·0 (C_1-Me of **41**) with the simultaneous appearance of a broad singlet at δ 1·48 (C_1-Me of **9**). After 35 min at room temp, the conversion was essentially quantitative. Evaporation of the formic acid gave crystalline **9**. Recrystallization from light pet. ether afforded the pure acid, m.p. 133·5–135°. (Found: C, 74·92; H, 9·77. Calc. for $C_{13}H_{20}O_2$: C, 74·96; H, 9·68%); NMR in benzene: δ 0·95 (Me), δ 1·48 (broadened singlet of C_1-Me); IR in $CHCl_3$: ν_{max} 2400–3000 (OH) and 1700 cm^{-1} (C=O).

When a soln of **9** in formic acid was heated at reflux for 12 hr, and the formic acid evaporated, there was obtained a crude product which showed IR absorptions at 1700 cm^{-1} (acid C=O), 1750 cm^{-1} (γ-lactone) and 1780 cm^{-1} (δ-lactone). The brown oil was filtered through alumina to remove acids. The eluted material had IR bands at 1750 cm^{-1} and 1780 cm^{-1} The NMR spectrum had 10–12 peaks due to Me groups between δ 0·70 and δ 1·3. When analyzed by VPC, the mixture showed at least 5 components in major amounts. The two major fractions were collected and shown to be mixtures, since each showed IR bands at 1750 cm^{-1} and 1780 cm^{-1}.

Formolysis of 4aβ,8β-*dimethyl*-8aα-*hydroxydecahydronaphth*-2α-*oic acid, lactone* (**10**). A soln of 237 mg of **10** in 2 ml formic acid was heated at 85° and 8·5 min. The soln was cooled to 0° and the formic acid evaporated at reduced press. Analysis by VPC (150 ft × 0·01 in SF-96-50 capillary) showed 10% unchanged **10**, 30% lactone **14**, and 60% lactone **15**. A portion of the material (100 mg) was purified by preparative TLC (30, 40, and 30 mg on three 8 in by 8 in plates, coated with 15 g silica gel containing 13% $CaSO_4$). Compound **15** was obtained as a waxy white solid, m.p. 47–51° (36 mg). A second chromatograph gave analytically pure lactone, m.p. 87–88°. (Found: C, 74·68; H, 9·54. Calc. for $C_{13}H_{20}O_2$: C, 74·96; H, 9·68%); NMR in CCl_4: δ 1·04 (C_{4a}-Me, singlet), δ 1·32 (C_8-Me, singlet); IR in CCl_4: ν_{max} 1725 cm^{-1} (δ-lactone C=O).

Compound **14** was obtained as a pale yellow oil (29 mg). The analytical sample was obtained by a second preparative TLC. (Found: C, 74·83; H, 9·87. Calc. for $C_{13}H_{20}O_2$: C, 74·96; H, 9·68%); NMR in CCl_4: δ 1·08 (angular Me) and δ 0·92 (C_8-Me, doublet, J = 6·5 c/s); IR in CCl_4: ν_{max} 1780 cm^{-1} (γ-lactone C=O).

When a soln of 4 mg of VPC purified lactone **15** in 20 μl of formic acid was heated at 85° for 10 min, and the reaction worked up as above, there was obtained a mixture of **14** and **15** in a ratio of 36:64.

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