Tetrahedron Vol. 38, No. 9, pp. 1217 to 1219, 1982
Printed in Great Britain.

0040-4020/82/091217-03$03.00/0

SYNTHESIS OF LABDA-8(17),13(14)-DIENE-15,16-OLIDE AND 15,16-EPOXY-LABDA-8(17),13(16)-14-TRIENE AND THEIR REARRANGEMENT TO CLERODANE DERIVATIVES

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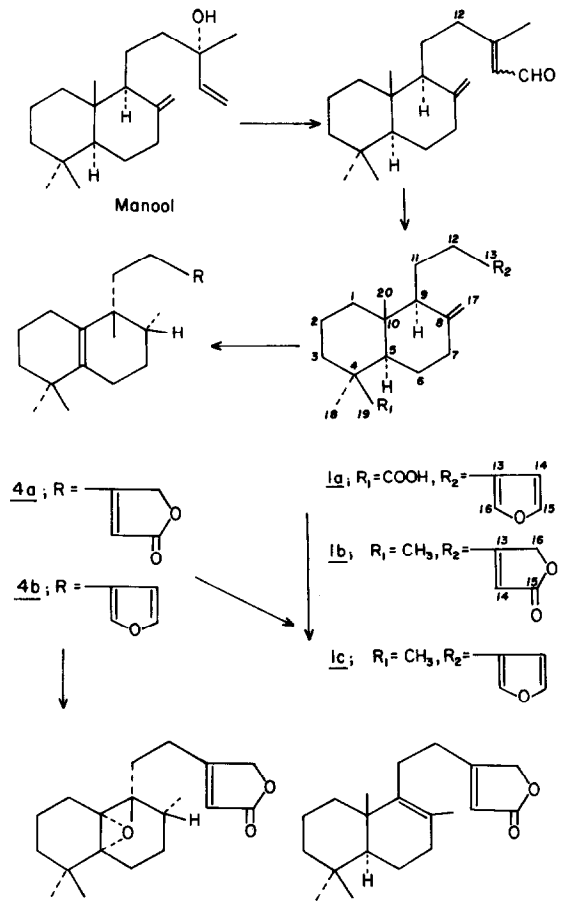
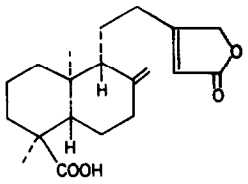
(*Received in U.S.A. 24 August* 1981)

Abstract—The title compounds **1b** and **1c** were synthesized from manool. On treatment with either trifluoroacetic acid or formic acid **1b** provided in nearly 100% yield **4a** with a rearranged labdane skeleton. With sulfuric acid, however, **1b** gave solely $\Delta^{8,9}$-isomer **5**. Reduction of **4a** with lithium diisobutylaluminum hydride afforded **4b**. On treatment with sulfuric acid **4a** reverted to **5**. Rearrangement of the epoxide **6** with boron trifluoride–etherate led to a complex product mixture from which no pure substance was obtained.

Diterpenes of the labdane or clerodane type have recently been found in nature in increasing numbers.[1,2] They also exhibit interesting physiological properties.[3] During the last few years several papers on the synthetic approach towards these compounds have appeared.[2] Although lambertianic acid[4] **1a**, compound **2**,[5] and compound **3**[6] of a rearranged labdane skeleton are known to occur in nature, related compounds, such as **1b**, and **1c**,[7] and **4a** and **4b**, have not been discovered so far. In view of the possibility of their future occurrence, we were interested in exploring a new convenient route to the synthesis of these compounds and then studying their rearrangement to clerodane derivatives.

Manool,[8] commercially available, was chosen as the starting material for this synthesis. Oxidation of manool with pyridium chlorochromate in anhydrous methylene chloride[9] afforded in 40% yield a mixture of two isomeric α,β-unsaturated aldehydes, which without separation was submitted to oxidative lactonization.[10] **1b** was obtained as the sole α,β-unsaturated butenolide.[11] It had IR absorption (KBr) bands at 1775 and 1740 (α,β-unsaturated butenolide), and 1640 and 1630 cm^{-1} (terminal and conjugate C=C). The ^1H NMR spectrum showed three tertiary Me groups at δ 0.69, 0.79 and 0.86 (s) and a terminal methylene group at δ 4.46 (broad *s*, 1 H) and 4.87 (broad s, 1H). The C–16 hydrogen absorbed as a doublet (2H) at δ





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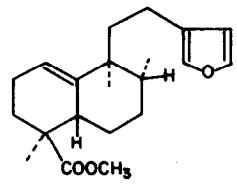

3

6

5

4.71 (J 1.6 Hz) and the C-14 proton resonated as a triplet (1H) at δ 5.83 (J 1.6 Hz).

Reduction of **1b** with lithium diisobutylaluminum hydride[12] in tetrahydrofuran gave a furanoid **1c**. The formation of a furan ring was clearly indicated by the ^{1}H NMR spectrum at δ 7.33 (t, J 1.8 Hz, 1H) and 7.18 (m, 1H, H–15 and H–16) and 6.25 (m, 1H, H–14) and also by the fragment ions at *m/e* 81 ($C_5H_5O^+$) and 95 ($C_6H_7O^+$) in the mass spectrum.

Halsall *et al.*[13] studied earlier the rearrangement of the epoxides of the labdane derivatives in order to obtain the clerodane diterpene skeletons. In this case, however, a variety of rearranged carbon skeletons was formed but not that of clerodane. We have now attempted to achieve the acid-catalyzed labdane-clerodane type rearrangement using **1b**. On treatment either with trifluoroacetic acid at room temperature for 24 hr or with formic acid at refluxing temperature for 4 hr, **1b** provided in nearly 100% yield **4a** as a single rearranged product. That the α,β-unsaturated γ-lactone ring was intact was indicated by the ^{1}H and ^{13}C NMR as well as IR spectra. The migration of the C-20 Me group to the C-9 position was supported by the ^{1}H NMR spectrum. It showed, besides three tertiary Me groups [δ 0.88 (s, 3H) and 1.00 (s, 6H)], a secondary Me group at δ 0.87 (d, J 6.5 Hz)], a secondary Me group at δ 0.87 (d, J 6.5 Hz), but no terminal double bond. The presence of a double bond between C–5 and C–10 was confirmed by two quaternary carbon signals at 138.8 and 131.4 in the ^{13}C NMR spectrum. The assignment of the higher field one to C-10 was based upon the γ-shielding effects of C-12 and the Me bonded to C-8. The stereochemistry at C-8 and C-9 was supported by the chemical shifts of the groups bonded to them. Comparison of the ^{13}C NMR data (Table) with those reported for ajugarin[14] which possesses an 8α-Me, 9α-Me, 9β-side chain arrangement revealed a shielding of *ca* 5 ppm for the C-11 methylene and a deshielding of *ca* 4 ppm for the C-9 Me. This suggested that in compound **4a** the secondary Me at C-8 must be on the same side as the side chain at C-9, and therefore, is α-oriented since the migrating C-20 Me group assumes the β-configuration.

In the mass spectrum of compound **4a**, the fragment ion, [$C_{14}H_{23}^+$] at *m/e* 191 occurs as the base peak, indicating the facile cleavage of the allylic C-9–C-11 bond.

It is interesting to note that on treatment with sulfuric acid compound **1b** rearranged to compound **5**. Its ^{1}H NMR spectrum showed no terminal methylene protons, but a Me group at δ 1.23 (s, 3H) attached to $\Delta^{8,9}$-double bond. When compound **4a** was treated with sulfuric acid, it was reverted to compound **5**.

On reduction with lithium diisobutylaluminum hydride in tetrahydrofuran compound **4a** yielded a furan **4b**.

We then attempted the rearrangement of the epoxide of compound **4a** by boron trifluoride-etherate in the hope that a further migration of one of the C-4 Me groups might occur. On epoxidation with *m*-chloroperbenzoic acid in chloroform compound **4a** afforded the epoxide **6**. Treatment of the epoxide **6** with boron trifluoride-etherate in benzene, however, gave rise to a complex product mixture from which no pure substance was isolated.

EXPERIMENTAL

M.ps were measured on a Kofler hot-stage apparatus and are uncorrected. Unless otherwise specified, IR spectra were recorded in liquid films with a Perkin–Elmer 337 spectrometer. ^{1}H and ^{13}C NMR spectra were obtained for solutions in $CDCl_3$ on a Varian EM 3940 and a Bruker WP-80 spectrometer, respectively. Chemical shifts are reported in ppm downfield from internal TMS. Abbreviations s = singlet, d = doublet, t = triplet, and m = multiplet. Mass spectra were determined on a Du Pont 21-492B (Data System 21-094B) at 70 eV using a direct inlet system. Rotations were measured in $CHCl_3$ solns at 23° with a Zeiss polarimeter (0.01°). For column chromatography silica gel 60 (Merck, 70–230 mesh) was used. TLC was prepared on silica gel G or silica gel GF_{254}60 (Merck) and the spots were observed by exposure to I_2 vapor or UV light. All organic extracts were dried over $MgSO_4$ and evaporated under reduced pressure below 60°. Microanalyses were carried out by A. Bernhardt microanalytical laboratory, 5251 Elbach über Engelskirchen, West Germany.

Table 1. ^{13}C NMR spectral data of compound **4a**

	δ (ppm)[a]
C-1	25.9 (t)[b]
C-2	20.0 (t)
C-3	40.0 (t)
C-4	34.7 (s)
C-5	138.8 (s)
C-6	25.3 (t)[b]
C-7	23.8 (t)[b]
C-8	33.9 (d)
C-9	40.8 (s)
C-10	131.4 (s)
C-11	27.7 (t)
C-12	33.6 (t)
C-13	174.2 (s)
C-14	115.1 (d)
C-15	171.6 (s)
C-16	73.2 (t)
8α-CH_3	16.2 (q)
C-18	27.2 (q)[c]
C-19	29.3 (q)[c]
9β-CH_3	21.0 (q)

[a] In ppm downfield from internal TMS; multiplicities given in parentheses are those in the SFORD spectra.

[b,c] Assignments may have to be interchanged.

Labda-8(17),13(14)-*diene*-15,16-*olide* **1b**

A mixture of the two isomeric α,β-unsaturated aldehydes (5 g), obtained by oxidation of manool with pyridium chlorochromate,[9] was dissolved in CH_2Cl_2 (40 ml) and treated with trimethylsilylcyanide (4.4 ml) at 0° in the presence of KCN/18-crown-6-complex (20 mg). The mixture was allowed to stand at 0° with stirring for 4 hr. The solvent and the excess reagent were removed at room temp under reduced pressure. The residue in dimethylformamide (40 ml) was treated with pyridium dichromate (18 g) and the mixture was allowed to stand at room temp with stirring for 18 hr. The product, isolated after usual work up, was chromatographed over silica gel. Elution with 15% ether in hexane yielded the α,β-unsaturated butenolide **1b** (0.9 g; 16% yield), which after recrystallization from hexane–ether showed m.p. 76–78°, $[\alpha]_D$ +41° (*c*, 1.2); MS: *m/e* 302 (M^+). (Found: C, 79.21; H, 9.69. Calc. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00%).

15,16-*Epoxy-labda*-8(17),13(16),14-*triene* **1c**

A 40% lithium diisobutylaluminum hydride soln (0.4 ml) in toluene was added in two portions during 30 min at −15° to a stirred soln of **1b** (100 mg) in dry tetrahydrofuran (25 ml) in an atmosphere of N_2. The soln was then allowed to stand at room temp for an additional 2 hr. 10% aq H_2SO_4 was added, the product was extracted with ether and then chromatographed over silica gel. Elution with 5% ether in hexane yielded **1c** as an oil (30 mg) (21% yield), $[\alpha]_D$ −4° (*c*, 1.6); IR: 3050, 1635, 1495, 885, 870 cm^{-1}; MS: *m/e* 286 (M^+); NMR: δ 0.66 (s, 3H, CH_3), 0.78 (s, 3H, CH_3), 0.84 (s, 3H, CH_3), 4.53 (broad s, 1H, H-17), 4.84 (broad s, 1H, H-17), 6.25 (m, 1H, H-14), 7.18 (m, 1H) and 7.33 (t, J 1.8 Hz, 1H, H-15 and H-16). (Found: C, 83.56; H, 10.41. Calc. for $C_{20}H_{30}O$: C, 83.86; H, 10.56%).

Further elution with 10% ether in hexane gave the unreacted material.

Rearrangement of labda-8(17),13(14)-*diene*-15,16-*olide* **1b**

(a) With trifluoroacetic acid. **1b** (200 mg) in CH_2Cl_2 (24 ml) was treated with CF_3COOH (16 ml) and the mixture was allowed to stand at room temp with stirring for 24 hr. H_2O was added and the product was extracted with CH_2Cl_2. **4a**, obtained as an oil (200 mg), was pure and required no further purification; $[\alpha]_D$ −35°(*c*, 5.9); MS: *m/e* 302 (M^+); IR: 1780 and 1730 (α,β-unsaturated butenolide), 1640 cm^{-1} (conjugate C=C); NMR: δ 0.87 (d, J 6.5 Hz, 3H, CH_3–CH), 0.88 (s, 3H, CH_3), 1.00 (s, 6H, $2CH_3$), 4.75 (d, J 1.6 Hz, 2H, H-16), 5.83 (m, 1H, H-14). (Found: C, 79.12; H, 9.75. Calc. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00%).

(B) *With formic acid.* **1b** (50 mg) was heated under reflux with 98–100% HCOOH (3 ml) for 4 hr. Usual work up yielded **4a** (50 mg).

(c) *With sulfuric acid.* A soln of **1b** (100 mg) in $CHCl_3$ (2 ml) was stirred with conc H_2SO_4 (2 ml) at 0° for 1 hr. H_2O was then added and the product was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with 1% aq NaOH (4 ml), then the H_2O, dried, and evaporated. The residue (33 mg) was filtered on silica gel impregnated (20%) with $AgNO_3$. Elution with 10% ether in hexane yielded **5** as an oil (30 mg); MS: *m/e* 302 (M^+); IR: 1775 and 1740 (α,β-unsaturated butenolide), 1640 cm^{-1} (conjugate C=C); NMR: δ 0.79 (s, 3H, CH_3), 0.87 (s, 6H, $2CH_3$), 1.23 (s, 3H, CH_3-C=), 4.73 (broad s, 2H, H-16), 5.81 (broad s, 1H, H-14). (Found: C, 79.71; H, 10.31. Calc. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00%).

Reduction of **4a** *with lithium diisobutylaluminum hydride*

Compound **4a** (100 mg) in dry THF (25 ml) was treated with lithium diisobutylaluminum hydride (0.4 ml) in the same manner as **1b**. The product obtained was chromatographed over silica gel. Elution with 2% ether in hexane yielded **4b** as an oil (20 mg), (17% yield), $[\alpha]_D$ −78° (*c*, 1.5); MS: *m/e* 286 (M^+); NMR; δ 0.83 (s, 3H, CH_3), 0.84 (d, J 6 Hz, 3H, CH_3–CH), 0.97 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 6.26 (m, 1H, H-14), 7.19 (m, 1H) and 7.33 (t, J 1.8 Hz, 1H, H-15 and H-16). (Found: C, 83.66; H, 10.26. Calc. for $C_{20}H_{30}O$: C, 83.86; H, 10.56%).

Rearrangement of **4a** *with sulfuric acid*

Compound **4a** (40 mg) was dissolved in $CHCl_3$ (1 ml), followed by conc H_2SO_4 (1 ml) at 0°. The mixture was stirred at 0° for 1 hr and then treated with H_2O. The product, obtained by usual work up, was identical (IR and NMR) with **5**.

Epoxide **6** *and its rearrangement with boron trifluoride-etherate*

Compound **4a** (60 mg) in $CHCl_3$ (10 ml) was treated with *m*-chloroperbenzoic acid (80 mg) at room temp for 13 min. The mixture was filtered on silica gel and elution with 10% ether in hexane yielded **6** as an oil (50 mg); MS *m/e* 318 (M^+); IR: 1775 and 1740 (α,β-unsaturated butenolide), 1630 cm^{-1} (conjugate C=C); NMR: δ 0.76 (d, J 6Hz, 3H, CH_3–CH), 0.89 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 4.74 (d, J 1.6 Hz, 2H, H-16), 5.83 (t, J 1.6 Hz, 1H, H-14). (Found: C, 75.22; H, 9.21. Calc. for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50%).

The above epoxide (0.334 g) in benzene (5 ml) was treated with a few drops of BF_3-etherate and the soln was stirred at room temp for 45 min. H_2O was then added and the product was extracted with benzene. The benzene extract was washed with 1% $NaHCO_3$ aq, H_2O, and then dried. The crude product (0.3 g), obtained after evaporation of solvent, showed an olefinic proton as a multiplet at δ 5.42 in its NMR spectrum. Chromatography over silica gel and elution with 20% ether in hexane yielded a fraction whose IR spectrum showed an OH band. The mass spectrum gave a molecular ion at *m/e* 318 which corresponded to $C_{20}H_{30}O_3$. The ^{13}C NMR spectrum indicated a mixture of at least two related compounds. Further attempts to purify it failed.

Acknowledgements—We thank M. Gómez, A. Morales, and M. L. Tasayco, and J. Bermudez for the determination of the IR, ^1H NMR, and mass spectra. Part of this work has been supported by a research grant No.S1-1209 from the Consejo Nacional de Investigaciones Científicas y Tecnológicas, Caracas.

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