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STUDIES ON REARRANGEMENTS IN DERIVATIVES OF GRANDIFLORENIC ACID, PART 2. SYNTHESIS OF METHYL (−)-20-NORKAUR-9α-METHYL-5(10),16-DIEN-19-OATE, A NEW TETRACYCLIC ROSANE-TYPE DITERPENE

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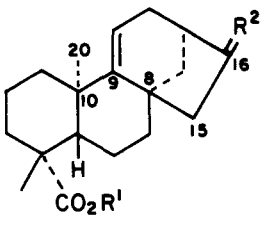
ABSTRACT.—The synthesis of the title compound (**4e**), a new tetracyclic rosane-type diterpene, from grandiflorenic acid (**1c**), is described.

In Part 1 of this series (1), we have reported on the rearrangement of the epoxides of dihydrograndiflorenic acid (**1a**) [(−)-kaur-9(11)-en-19-oic acid] and its methyl ester (**1b**). In this case, the epoxidation of compounds **1a** and **1b** yielded the α-epoxide. Hence, upon cleavage of these epoxides with boron trifluoride-Et_2O complex, the C(8)-C(15) bond rather than the C(20)-methyl group migrated to C(9), resulting in the formation of compounds **2a** and **2b**, respectively. Because transformation of grandiflorenic acid (**1c**) to the analogues of zoapatlin (**3a**) (2), eupatalbin (**3b**), or eupatoral-



1

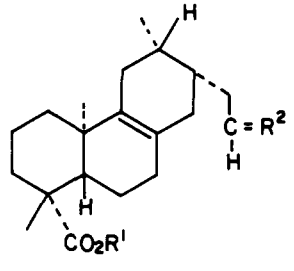
a $R^1 = H$, $R^2 = \lessdot^{Me}_{H}$

b $R^1 = Me$, $R^2 = \lessdot^{Me}_{H}$

c $R^1 = H$, $R^2 = CH_2$

d $R^1 = H$, $R^2 = O$

e $R^1 = Me$, $R^2 = O$



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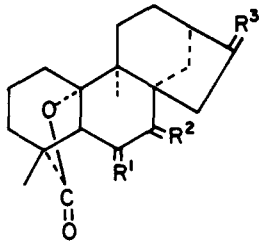
a $R^1 = H$, $R^2 = O$

b $R^1 = Me$, $R^2 = O$



3

a $R^1 = R^2 = H_2$, $R^3 = CH_2$

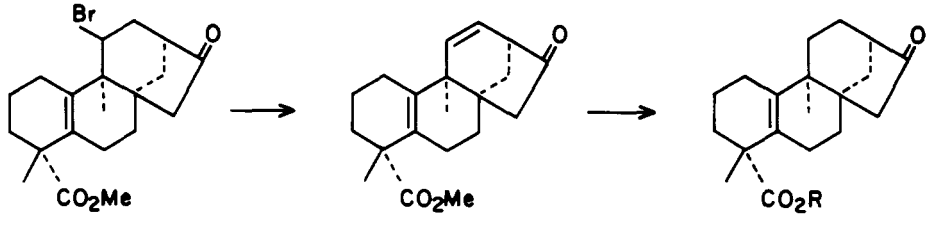
b $R^1 = H_2$, $R^2 = \lessdot^{H}_{OH}$, $R^3 = \lessdot^{Me}_{OH}$

c $R^1 = \lessdot^{H}_{OH}$, $R^2 = H_2$, $R^3 = \lessdot^{Me}_{OH}$

bin (**3c**) (3) was our continued interest, we sought to synthesize one of the derivatives of this new skeletal type.

RESULTS AND DISCUSSION

MacMillan, *et al.* (4) reported, in an unsuccessful attempt to rearrange compound **1c** to rings C/D analogues of antheridiogen (A_{An}), that on treatment with acetyl hypobromite or bromine, the 17-nor-ketones **1d** and **1e** underwent 10α⟶9α-methyl migration to yield 11β-bromo-derivatives **4a** and **4b**, respectively.[1] This indicated that in the case of the 17-nor-ketones **1d** and **1e**, bromination apparently occurred from the β-side. These results were in contrast with our previous observation that the epoxidation of compounds **1a** and **1b** led to the α-side attack of the molecules. The difference for the stereoselectivity in these cases deserves comment. The steric environment about the olefinic double bond in molecules **1a**, **1b**, **1d**, and **1e** seems rather different. The C(16)-endo methyl group in structures **1a** and **1b** would provide an effective shield over the β-face of the olefinic double bond, an observation in accord with the observed direction of epoxidation. The lack of this sterically shielding methyl group in olefins **1d** and **1e** would allow a bromine molecule (or a bromonium ion) to attack from the β-side in essentially the spot where the C(16)-methyl group is located. The β-stereochemistry of the intermediate bromonium ion would greatly facilitate subsequent proferential migration of the α-oriented C(20)-methyl group to C(9) (formation of **4a** or **4b**). Indeed, on being treated with *N*-bromosuccinimide in Me_2CO-H_2O (8:1), compound **1e** afforded a bromo-derivative with the rearranged skeleton whose structure was confirmed as **4b** after conversion via compound **5** to compound **4c** (Scheme 1). The ^{13}C-nmr spectrum of compound **4c** clearly showed the signals of a fully substituted olefin at δ 137.1 and 128.2 ppm. Furthermore, the other spectroscopic properties of compounds **4b** and **4c** agreed with those reported in the literature (4). We noted that compound **4c** possesses a basic skeleton of a new tetracyclic rosane-type diterpene and considered it significant to transform it to a C_{20}-derivative (**4e** in view of the possibility of its future occurrence in nature. On methylation with CH_2N_2, compound **4c** yielded the methyl ester **4d**, which, on treatment with excess of methylenetriphenylphosphorane, led to compound **4e** in 51% yield.



4b **5** **4** **c** R=H **d** R=Me

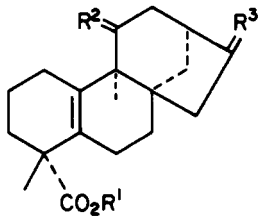
SCHEME 1

We also tried to lactonize[2] compound **4c** under a variety of conditions reported recently. For this purpose, compound **4c** was converted to the ethylene acetal (**4f**), and the latter was treated with phenylselenyl chloride (5), thallium(I) carboxylate and iodine (6), lead tetraacetate, and thallium(III) triacetate (7). However, all these at-

[1]When dihydrograndiflorenic acid (**1a**) was allowed to react with *N*-bromosuccinimide in Me_2CO-H_2O (8:1), no corresponding bromo-compound was obtained, yielding an intractable mixture of products.

[2]MacMillan, *et al.* (4) reported that compound **4c** did not lactonize with acidic reagents nor iodolactonize.

tempts failed. We also converted compound **4f** to the epoxide with *m*-chloroperbenzoic acid and treated the latter with boron trifluoride-Et_2O complex. However, no lactone formation was observed. It is interesting to note that Overton, *et al.* (8) reported that the tricyclic rosadienoic acid (**6**) lactonized directly with acids as the catalyst, and it was also convertible via the mono-epoxide into the hydroxy-lactone (**7**) with boron trifluoride-Et_2O complex. The reason this tetracyclic analogue (**4f**) resisted lactonization is not clear, but we presume that it may be due to long-range effects that have their origin in a distortion of the ring system caused by the introduction of an additional ring D.



4

a $R^1 = H$, $R^2 =$  , $R^3 = O$

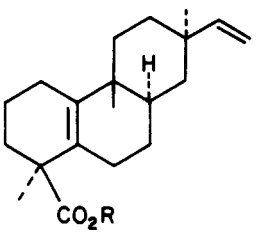
b $R^1 = Me$, $R^2 =$  , $R^3 = O$

c $R^1 = H$, $R^2 = H_2$, $R^3 = O$

d $R^1 = Me$, $R^2 = H_2$, $R^3 = O$

e $R^1 = Me$, $R^2 = H_2$, $R^3 = CH_2$

f $R^1 = H$, $R^2 = H_2$, $R^3 =$ 



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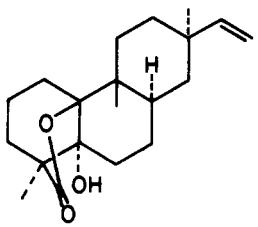

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EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Unless otherwise specified, ir spectra were recorded for KBr discs with a Perkin-Elmer 337 spectrometer. ^1H- and ^{13}C-nmr spectra were determined in $CDCl_3$ with TMS as internal standard on a Varian EM 3940 spectrometer and a Bruker WP 60 spectrometer, respectively. Mass spectra were recorded with a DuPont 21-492B mass spectrometer at 70 eV using a direct inlet system. For column chromatography, Merck silica gel 60 (35-70 mesh ASTM) was used. Thin layer chromatograms were prepared on Merck silica gel GF_{254}, and the spots were observed either by exposure to iodine vapor or by uv light. All organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure below 60°. Microanalyses were carried out by A. Bernhardt microanalytical laboratory, 5251 Elbach über Engelskirchen, West Germany.

REACTION OF METHYL GRANDIFLORENATE NORKETONE (**1e**) WITH *N*-BROMOSUCCINIMIDE IN Me_2CO-H_2O.—A solution of compound **1e** (1.8 g) in Me_2CO-H_2O (8:1; 27 ml) was stirred with *N*-bromosuccinimide (1.5 g) at room temperature until no starting material was observed on tlc. After 2.5 h,

H_2O was added, and the product was extracted with Et_2O. The Et_2O extract was evaporated, yielding crude methyl (−)-17,20-dinorkaur-11β-bromo-9α-methyl-16-oxo-5(10)-en-19-oate (**4b**). The ^{1}H-nmr spectrum clearly showed a triplet (J=3 Hz) at δ 4.39 ppm, corresponding to 11-H. This compound, without further purification, was treated with 4% methanolic KOH (50 ml) at room temperature for 2 h, and then at 60° for 2 h. The solution was diluted with H_2O, acidified with concentrated HCl, and extracted with EtOAc. The crude product (1.5 g) thus obtained was chromatographed over silica gel and elution with 10% Et_2O in hexane afforded methyl (−)-17,20-dinorkaur-9α-methyl-16-oxo-5(10), 11-dien-19-oate (**5**) (0.9 g), mp 84-86°; ^{1}H nmr δ 1.23 (6H, s, 2Me), 3.63 (3H, COOMe), 5.62 (1H, ddd, J=9, 7, and 2 Hz, 12-H), and 5.90 ppm (1H, d, J=9 Hz, 11-H); ms *m/z* 314 (M^+). *Anal.* calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.11; H, 8.62.

CATALYTIC HYDROGENATION OF METHYL (−)-17,20-DINORKAUR-9α-MEHTYL-16-OXO-5(10),11-DIEN-19-OATE (**5**).—Compound **5** (0.8 g) in EtOH-Et_2O (3:5, 8 ml) was hydrogenated with 10% palladium on carbon (80 mg) at room temperature. After 2 h, one equivalent of hydrogen was absorbed. Usual workup yielded a dihydro-derivative (**4d**) (0.8 g), mp 98-100°; ir 1745 (COOMe) and 1725 cm^{-1} (C=O); ^{1}H nmr 1.19 (3H, s, Me), 1.23 (3H, s, Me), and 3.66 ppm (3H, s, COOMe); ms *m/z* 316 (M^+). *Anal.* calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.62; H, 8.69.

SYNTHESIS OF METHYL (−)-20-NORKAUR-9α-METHYL-5(10),16-DIEN-19-OATE (**4e**).—A suspension of methyltriphenylphosphonium bromide (1.35 g) in dry THF (20 ml) was treated with a 1.42 M solution of butyllithium (2.7 ml) in hexane, and the mixture was stirred in an atmosphere of N_2 for 2 h. A solution of compound **4d** (100 mg) in dry THF (5 ml) was then added, and stirring was continued for a further 2 h. Then H_2O was added, and the product was extracted with Et_2O. After evaporation of the ether extract, the residue (0.1 g) was chromatographed over silica gel, and elution with 5% Et_2O in hexane afforded compound **4e** as a gum (50 mg); ir (neat) 1706 (COOH) and 1656 cm^{-1} (C=C); ^{1}H nmr δ 1.11 (3H, s, Me), 1.23 (3H, s, Me), 3.62 (3H, s, COOMe), 4.64 (1H, broad s, 17-H), and 4.71 ppm (1H, broad s, 17-H); ms *m/z* 314.2249 (M^+; calcd. for $C_{21}H_{30}O_2$, 314.2245).

HYDROLYSIS OF METHYL (−)-20-NORKAUR-9α-METHYL-16-OXO-5(10)-EN-19-OATE (**4d**).—Compound **4d** (0.6 g) was heated under reflux with 10% methanolic NaOH (40 ml) for 48 h. After dilution with H_2O and acidification with concentrated HCl, the product was extracted with $CHCl_3$. Removal of $CHCl_3$ yielded (−)-20-norkaur-9α-methyl-16-oxo-5(10)-en-19-oic acid (**4c**) (0.4 g), mp 195-197° (from $CHCl_3$-Et_2O-hexane); ir 1735 (C=O) and 1695 cm^{-1} (COOH); ^{1}H nmr δ 1.19 (3H, s, Me) and 1.26 ppm (3H, s, Me); ms *m/z* 302 (M^+). *Anal.* calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: 75.17; H, 8.47.

ACETALIZATION OF (−)-20-NORKAUR-9α-METHYL-16-OXO-5(10)-EN-19-OIC ACID (**4c**).—Compound **4c** (0.1 g) in C_6H_6 (10 ml) was heated under reflux with ethylene glycol (1 ml) in the presence of a catalytic amount of *p*-toluenesulfonic acid until no more H_2O was separated out. After 20 h, the C_6H_6 solution was washed with H_2O, dried, and evaporated. The product was crystallized from Et_2O to afford the ethylene acetal (**4f**) (0.1 g), mp 275-278°; ir 1710 cm^{-1} (COOH); ^{1}H nmr δ 1.06 (3H, s, Me), 1.21 (3H, s, Me), and 3.87 ppm (4H, m, OCH_2CH_2O); ms *m/z* 346 (M^+). *Anal.* calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.52; H, 8.46.

EPOXIDATION OF THE ETHYLENE ACETAL (**4f**) WITH *m*-CHLOROPERBENZOIC ACID, FOLLOWED BY BORON TRIFLUORIDE-Et_2O COMPLEX.—Compound **4f** (200 mg) in $CHCl_3$ (8 ml) was stirred with *m*-chloroperbenzoic acid (150 mg) at room temperature for 24 h. Then, solid Na_2SO_4 was added, and the solution was stirred for an additional 1 h, washed with H_2O, dried, and evaporated. The epoxide was obtained as an oil which was induced to crystallize from Et_2O-hexane, mp 104-106° (170 mg), *m/z* 362 (M^+). This epoxide (150 mg) was dissolved in dry C_6H_6 (5 ml), followed by 4 drops of boron trifluoride-Et_2O complex. The mixture was stirred at room temperature for 2 h. After addition of H_2O, the product was extracted with Et_2O. Evaporation of the Et_2O extract yielded an oil (90 mg) that was chromatographed over silica gel. The product was eluted with hexane-$CHCl_3$, but none contained any lactone according to the ir spectra.

ACKNOWLEDGMENTS

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