Synthesis of Kaurane Derivatives with an Oxygen Function in Ring A[†]

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A total synthesis of some kaurane derivatives with an oxygen function in ring A was accomplished. They are potential intermediates for the synthesis of highly oxygenated diterpenes such as grayanotoxins.

Our continuing efforts in the synthesis of biologically active diterpenes resulted in the total syntheses of ($\pm$)-kaur-16-en-19-oic acid,¹⁾ ($\pm$)-gibberellins A₂, A₄, A₉ and A₁₀,²⁾ ($\pm$)-steviol³⁾ and other polycyclic natural products. However, highly oxygenated diterpenes such as phorbol and grayanotoxins remain as utmost difficult synthetic objectives. We have chosen the grayanotoxins as our target in view

Grayanotoxin I

Kaur-16-en-19-oic acid

of their insecticidal activity. This paper describes in detail our preliminary endeavor along this line aiming at the synthesis of suitable kaurane derivatives with an oxygen

function in ring A. One of them served as a key intermediate in our photochemical synthesis of compounds with grayanotoxin skeleton.⁴⁾ The present synthetic route is essentially similar to that employed by us in the synthesis of ($\pm$)-kaur-16-en-19-oic acid.

The Robinson annelation of a tetralone (I)⁵⁾ with ethyl vinyl ketone or methyl vinyl ketone afforded racemic tricyclic enones IIa and IIb,⁶⁾ respectively. They were converted to phenols IIIa and IIIb with hydriodic acid. Catalytic hydrogenation⁷⁾ of IIIa gave a mixture of A/B *cis* and *trans* compounds, while the Birch reduction of IIIa and IIIb yielded only A/B *trans* alcohols, IVa and IVb, with an equatorial hydroxyl group at C-3.⁸⁾ Then the ring A hydroxyl group was protected as an acetate by acetylation of IVa and IVb with methyl acetate in the presence of *p*-toluenesulfonic acid to give Va and Vb. They were hydrogenated over Raney nickel T-1 and the resulting alcohols were oxidized with the Jones chromic acid to give ketones VIa and VIb. In the case of the oxidation of Va, a small amount of a diketone VIIa was obtained as a by-product.

In order to introduce an allyl group at C-8, the C-13 methylene group of VI was protected by *n*-butylthiomethylene group⁹⁾ in the usual manner to give VIII. During this process

[†] Diterpenoid Total Synthesis, Part XX. Part XIX, K. Mori, Y. Nakahara and M. Matsui, *Tetrahedron*, **28**, 3217 (1972). Although the formulas depicted in this paper represent only one enantiomer, they are taken to mean a racemate in the cases of synthetic compounds.

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the acetoxy group at C-3 was hydrolyzed to a hydroxyl group. Hence this was protected as a tetrahydropyranyl ether as in IX. Treatment of the ketones IXa and IXb with potassium *tert*-butoxide and allyl bromide afforded B/C *cis*-fused alkylated products, Xa and Xb.^{cf.1)} The blocking group at C-8 of X was removed by alkaline hydrolysis yielding XI. The allylated ketones XIa and XIb were treated with osmium tetroxide and sodium periodate¹⁰⁾ to give aldehydes XIIa and XIIb, respectively.

The aldol-type ring closure of these keto aldehydes by treatment with sodium methoxide afforded tetracyclic ketols, XIIIa and XIIIb. They were converted to diketones XIVa and XIVb by the Sarett oxidation with chromic anhydride-pyridine.

The 17-methyl group was introduced by the Grignard reaction of the diketone XIV with methyl magnesium iodide to give two ketols XV and XV' in the ratio of 10:1 (in the *a* series) or 7:1 (in the *b* series). The configuration at C-16 was assigned on the following

basis. The minor ketol XVb' was reduced with lithium in liquid ammonia to give an oily diol. This was treated with acetaldehyde in the presence of anhydrous zinc chloride to give two ethylidene derivatives, XVIII and XIX. The formation of the latter was obviously due to the hydrolytic removal of the tetrahydropyranyl protective group during the process. On the other hand, the major ketol XVb did not yield any ethylidene derivative when treated in the same manner as for XVb'. Inspection of a molecular model indicated that the diol derived from XVb' could afford an ethylidene derivative while that from XVb could not. The above result also suggests stereostructure XVa for the major ketol of *a* series, although no attempt was made to prepare an ethylidene derivative from XVa'.

The tetrahydropyranyl protective group of XV was removed in the usual manner to give XVI. These two diols XVIa and XVIb were oxidized with the Jones chromic acid to diketones XVIIa and XVIIb, respectively. These two diketones are potential intermediates

for the synthesis of oxygenated diterpenes. The conversion of the kaurane XVIIb to compounds with grayanotoxin skeleton will be published soon in full detail.

EXPERIMENTAL

All mp's are uncorrected.

($\pm$)-3-Oxo-4, 10-dimethyl-14-methoxy-1, 2, 3, 6, 7, 10-hexahydrophenanthrene (IIa). To a stirred solution of KOH (20 g) in MeOH (340 ml) and water (35 ml), I (48.6 g) was added at 0°C under nitrogen atmosphere. The mixture was cooled at -20~-15°C, and ethyl vinyl ketone (25.5 g) was added slowly. After 1.5 hr cooling bath was removed and stirring was continued overnight at room temperature. The resulting precipitates were filtered and washed with water, small amount of MeOH and ether to give 30 g of IIa. The mother liquor was neutralized with dil HCl aq and extracted with AcOEt. The extract was washed with water and dried (MgSO₄). Evaporation of EtOAc gave an oil. This was distilled to afford 6.0 g of IIa; bp 167°C (0.06 mmHg), (total 36 g, 55%). Recrystallization from EtOH gave prisms, mp 137.5~138.5°C. ν_{max} (Nujol) 1650, 1620, 1585, 1268, 1155 cm⁻¹. NMR (100 MHz, CDCl₃) τ 2.75~3.40 (3H), 6.22 (2H, s), 8.17 (3H, s) 8.47 (3H, s), 6.6~8.3 (8H, m). Anal. Found: C,

79.50; H, 7.77. Calcd. for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86%.

($\pm$)-3-Oxo-10-methyl-14-methoxy-1, 2, 3, 6, 7, 10-hexahydrophenanthrene (IIb). The same treatment as described above of I with methyl vinyl ketone gave IIb, in 50% yield, bp 175°C (0.1 mmHg) (lit.⁵) bp 180°C (0.1 mmHg), mp $122.5\sim 123.5^\circ\text{C}$. ν_{max} (Nujol) 1654, 1625, 1585, 1265, 1066 cm^{-1} . NMR (100 MHz, CDCl_3) τ 2.75 (3H, t, d, d), 4.12 (1H, s), 6.19 (3H, s), 8.43 (3H, s). Anal. Found: C, 79.21; H, 7.43. Calcd. for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49%.

($\pm$)-3-Oxo-10-methyl-14-hydroxy-1, 2, 3, 6, 7, 10-hexahydrophenanthrene (IIIb). III was obtained in 52.3% yield (45% recovery) by the same procedure which was described in Ref. 5).

($\pm$)-3-Oxo-4, 10-dimethyl-14-hydroxy-1, 2, 3, 6, 7, 10-hexahydrophenanthrene (IIIa). IIa was worked up as described above to give IIIa in 80% yield which was recrystallized from benzene, mp $212\sim 214^\circ\text{C}$. ν_{max} (Nujol) 3360, 1648, 1619, 1581, 1000 cm^{-1} . Anal. Found: C, 79.16; H, 7.40. Calcd. for $C_{18}H_{20}O_2$: C, 79.31; H, 7.49%.

($\pm$)-3 α ,14-Dihydroxy-10 α -methyl-1,2,3 β ,4,5 β ,6,7,10-octahydrophenanthrene (IVb). To a solution of liq NH_3 (1 liter) and Li (20 g), IIIb (57 g) in THF (1 liter) was added with stirring at $-40\sim -45^\circ\text{C}$. After 1 hr NH_4Cl (170 g) was cautiously added in small portions at $-40\sim -45^\circ\text{C}$. After the evaporation of NH_3 at room temperature, the residue was acidified with cooled HCl aq. (conc HCl- H_2O =1:1) and extracted with ether. The extract was washed with water and dried (Na_2SO_4). After treatment with activated charcoal, the ether layer was evaporated to give an oil (60 g). This oil was chromatographed on silica gel (1.1 kg) and eluted with benzene-EtOAc (9:1) to afford crystals (47.5 g) of IVb in 82% yield. ν_{max} (Nujol) 3500, 3240, 1582, 1266, 1042 cm^{-1} . This was employed for the next reaction without further purification.

($\pm$)-3 α ,14-Dihydroxy-4 β ,10 α -dimethyl-1,2,3 β ,4 α ,5 β ,6,7,10-octahydrophenanthrene (IVa). IIIa was worked up as described above to afford IVa quantitatively. ν_{max} (Nujol) 3460 (b), 1583, 1267, 1020, 1010, 996, 925, 900 cm^{-1} . This was employed for the next reaction without further purification.

($\pm$)-3 α -Acetoxy-4 β ,10 α -dimethyl-14-hydroxy-1,2,3 β ,4 α ,5 β ,6,7,10-octahydrophenanthrene (Va). A solution of diol IVa (0.93 g) and *p*-TsOH (2.8 g) in MeOAc (180

ml) was heated under reflux for 4.5 hr, then cooled, and washed with dil. NaHCO_3 aq. and brine, and dried (Na_2SO_4). Evaporation of MeOAc gave crystals (0.95 g) in 87.2% yield. Recrystallization from EtOAc-EtOH (9:1) gave prisms, mp $170\sim 174^\circ\text{C}$. ν_{max} (Nujol) 3464, 1711, 1582, 1276, 976 cm^{-1} . NMR (100 MHz, CDCl_3) τ 2.80 $\sim$ 3.45 (3H, m), 5.14 (1H, m), 7.92 (3H, s), 8.86 (3H, s), 9.06 (3H, d, $J=6$ Hz). Anal. Found: C, 75.25; H, 8.10. Calcd. for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39%.

($\pm$)-3 α -Acetoxy-10 α -methyl-14-hydroxy-1,2,3 β ,4,5 β ,6,7,10-octahydrophenanthrene (Vb). IVb (25 g) was worked up as described above to give crystals (21 g) in 71% yield. Recrystallization from EtOH-EtOAc (1:9) gave prisms, mp $186\sim 187^\circ\text{C}$. ν_{max} (Nujol) 3410, 1695, 1585, 1035 cm^{-1} . NMR (100 MHz, CDCl_3) τ 2.90 $\sim$ 3.45 (3H, d, t, d), 5.23 (1H, m), 7.94 (3H, s), 8.87 (3H, s). Anal. Found: C, 74.10; H, 7.92. Calcd. for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08%.

($\pm$)-3 α -Acetoxy-4 β ,10 α -dimethyl-14-oxo-3 β ,4 α ,5 β ,8 α ,9 β -perhydrophenanthrene (VIa). The phenol Va (15 g) in 99% EtOH (120 ml) was hydrogenated over Raney nickel (T-1) (15 g) at 180°C and an initial pressure of 90 kg/cm² for 3 hr. Removal of the catalyst and the solvents gave an oily mixture which was dissolved in acetone (400 ml). To this stirred solution, Jones chromic acid reagent (35 ml) was added dropwise at $0\sim 5^\circ\text{C}$, and the mixture left to stand at room temperature for 20 min. MeOH was added to destroy the excess of the oxidant. After removal of the solvents *in vacuo*, the residue was diluted with water and extracted with EtOAc. The extract was washed with NaHCO_3 aq., dried (Na_2SO_4), and concentrated *in vacuo*. Trituration of the residue with ether-*n*-hexane gave 8.0 g of the product. The filtrate was chromatographed on alumina (140 g) to afford another VIa (2.2 g, 67% in total) and diketone VIIa (1.03 g, 6.8%) by the elution with benzene-*n*-hexane (1:1). VIa was recrystallized from ether-*n*-hexane, mp $140\sim 143^\circ\text{C}$. ν_{max} (Nujol) 1734, 1695, 1250 cm^{-1} . NMR (100 MHz, CDCl_3) τ 5.69 (1H, d, d, $J=11, 11, 5$ Hz), 7.97 (3H, s), 9.08 (3H, s), 9.17 (3H, d, $J=6$ Hz). Anal. Found: C, 74.20; H, 9.54. Calcd. for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65%. VIIa was recrystallized from ether, mp $102\sim 103^\circ\text{C}$. ν_{max} (Nujol) 1706 cm^{-1} . NMR (100 MHz, CDCl_3) τ 8.81 (3H, s), 8.98 (3H, d, $J=6$ Hz). Anal. Found: C, 77.14; H, 9.64. Calcd. for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74%.

($\pm$)-3 α -Acetoxy-10 α -methyl-14-oxo-3 β , 5 β , 8 α , 9 β -perhydrophenanthrene (VIb). The phenol Vb (60 g)

was worked up as described above to obtain 41.8 g (68.3%) of the product. This was recrystallized from ether, mp 130~131°C. ν_{max} (Nujol) 1724, 1700, 1240, 1035 cm^{-1} . NMR (100 MHz, CDCl_3) τ 5.38 (1H, m), 8.03 (3H, s), 9.14 (3H, s). *Anal.* Found: C, 73.42; H, 9.19. Calcd. for $\text{C}_{17}\text{H}_{26}\text{O}_3$: C, 73.34; H, 9.41%.

($\pm$)-3 α -Hydroxy-10 α -methyl-13-*n*-butylthiomethylene-14-oxo-3 β ,5 β ,8 α ,9 β -perhydrophenanthrene(VIIIb). The ketone VIb (1.6 g) in dry THF (40 ml) was added to a stirred suspension of powdered NaOMe (1.5 g) in dry benzene (25 ml). To the ice-cooled mixture, redistilled ethyl formate (4 ml) was added with stirring. The mixture was left to stand overnight at room temperature. It was poured into ice-water (25 ml) and aqueous layer was separated. The organic layer was diluted with ether and extracted with 5% NaOH aq. (15 ml $\times$ 3). The combined aqueous solution was acidified with dil. HCl at 0~5°C and rapidly extracted with EtOAc. The extract was washed with water, dried (MgSO_4) and concentrated to give 1.7 g of the oily product. This formylated ketone (1.7 g) dissolved in dry benzene (50 ml) was mixed with *n*-butyl mercaptan (0.8 ml) and *p*-TsOH (20 mg). The mixture was heated under reflux for 4 hr and poured into water. The benzene layer was separated and aqueous layer was extracted with ether. The combined extract was washed with water and brine, dried (MgSO_4) and concentrated *in vacuo* to give an oily product. This oil was chromatographed on alumina (30 g). The elution with benzene gave 1.62 g (83.5%) of VIIIb, mp 114~115°C. ν_{max} (Nujol) 3560, 1642, 1530, 1305, 1078, 1063, 832, 784 cm^{-1} . NMR (100 MHz, CDCl_3) τ 2.52 (1H, s), 6.40 (1H, m), 7.17 (2H, t, $J=7$ Hz), 7.75 (1H, s, D_2O exchanged), 9.08 (3H, t, $J=7$ Hz), 9.19 (3H, s). *Anal.* Found: C, 71.81; H, 9.17; S, 9.37. Calcd. for $\text{C}_{20}\text{H}_{32}\text{O}_2\text{S}$: C, 71.39; H, 9.59; S, 9.51%.

($\pm$)-3 α -Hydroxyl-4 β , 10 α -dimethyl-13-*n*-butylthiomethylene-14-oxo-3 β , 4 α , 5 β , 8 α , 9 β -perhydrophenanthrene (VIIIa). The ketone VIa (1.6 g) was worked up as described above to afford 1.15 g of crystals, mp 54~57°C. ν_{max} (Nujol) 3360, 1640, 1550, 1325, 1195, 1073, 790 cm^{-1} . NMR (100 MHz, CDCl_3) τ 2.25 (1H, bs), 6.93 (1H, d, t), 7.22 (2H, t, $J=6$ Hz). *Anal.* Found: C, 72.24; H, 9.57; S, 8.89. Calcd. for $\text{C}_{21}\text{H}_{34}\text{O}_2\text{S}$: C, 71.96; H, 9.78; S, 9.13%.

($\pm$)-3 α -Tetrahydropyranyloxy-10 α -methyl-13-*n*-butylthiomethylene-14-oxo-3 β , 5 β , 8 α , 9 β -perhydrophenanthrene (IXb). A solution of VIIIb (32 g) in dry ben-

zene (750 ml) was mixed with dihydropyran (100 ml) and *p*-toluenesulfonic acid (750 mg) and stirred for 6 hr at room temperature. Then the solution was washed with NaHCO_3 aq., dried (Na_2SO_4) and concentrated *in vacuo*. Chromatography on alumina (600 g) of the residue eluted with benzene gave 36 g (90%) of crystals. ν_{max} (Nujol) 1655, 1550, 1060, 1030, 972 cm^{-1} . This was employed for the next step without further purification.

($\pm$)-3 α -Tetrahydropyranyloxy-4 β , 10 α -dimethyl-13-*n*-butylthiomethylene-14-oxo-3 β , 4 α , 5 β , 8 α , 9 β -perhydrophenanthrene (IXa). The alcohol VIIIa was worked up as described above. The crystalline IXa was obtained in 90% yield and recrystallized from ether, mp 128~130°C. ν_{max} (Nujol) 1658, 1556, 1040, 993 cm^{-1} . NMR (100 MHz, CDCl_3) τ 5.0~6.6 (4H), 2.53 (1H, bs), 7.21 (2H, t, $J=7$ Hz). *Anal.* Found: C, 71.85; H, 9.74; S, 7.37. Calcd. for $\text{C}_{26}\text{H}_{42}\text{O}_3\text{S}$: C, 71.85; H, 9.73; S, 7.31%.

($\pm$)-3 α -Tetrahydropyranyloxy-8 β -allyl-10 α -methyl-13-*n*-butylthiomethylene-14-oxo-3 β , 5 β , 9 β -perhydrophenanthrene (Xb). To a stirred and ice-cooled solution of *t*-BuOK (from 23 g K) in *t*-BuOH (700 ml), IXb (45 g) dissolved in dry benzene (600 ml) was added under N_2 atmosphere. After 10 min stirring, allyl bromide (110 ml) was rapidly added with stirring. Ice-cooling was continued for 10 min after the addition. Then the mixture was heated under reflux for 2 hr. During this period an additional amount of allyl bromide (50 ml) was added. After cooling, the mixture was poured into dil. NaHCO_3 aq. and extracted with ether. The extract was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to give an oil (49 g). ν_{max} (film), 3100 (w), 1660, 1550, 1032, 920 cm^{-1} . This was employed for the next reaction without further purification.

($\pm$)-3 α -Tetrahydropyranyloxy-4 β , 10 α -dimethyl-8 β -allyl-13-*n*-butylthiomethylene-14-oxo-3 β , 4 α , 5 β , 9 β -perhydrophenanthrene (Xa). The pyranil ether IXa was worked up as described above. The oily product Xa was obtained in 92% yield. ν_{max} (film) 3060 (w), 1663, 1545, 1078, 1025, 970, 916 cm^{-1} . This was employed for the next reaction without further purification.

($\pm$)-3 α -Tetrahydropyranyloxy-8 β -allyl-10 α -methyl-14-oxo-3 β , 5 β , 9 β -perhydrophenanthrene (XIb). The oily Xb (49 g) dissolved in 95% EtOH (600 ml) was mixed with KOH (50 g) in water (250 ml). The mixture was heated under reflux for 32 hr under N_2 at-

mosphere. EtOH was removed *in vacuo* and the residue was extracted with ether. The extract was washed with water followed by brine, dried (MgSO₄) and concentrated to give 35 g (two steps overall yield 90.5%) of crystalline XIb which was recrystallized from *n*-hexane as needles, mp 92~94°C. ν_{max} (Nujol) 3100 (w), 1698, 1639 (w), 1030, 990, 914 cm⁻¹. NMR (100 MHz, CDCl₃) τ 4.50 (1H, m), 4.90~5.35 (2H+1H, m), 6.16 (1H, m), 6.52 (2H, m), 9.19 (3H, s). *Anal.* Found: C, 76.98; H, 9.65. Calcd. for C₂₃H₃₆O₃: C, 76.62; H, 10.07%.

($\pm$)-3 α -Tetrahydropyranyloxy-4 β , 10 α -dimethyl-8 β -allyl-14-oxo-3 β , 4 α , 5 β , 9 β -perhydrophenanthrene (XIa). Xa was worked up as described above to give an oil (XIa) in 98% yield. ν_{max} (film), 3090 (w), 1698, 1635 (w), 1080, 1035, 970, 915 cm⁻¹. NMR (100 MHz, CDCl₃) τ 4.50 (1H, m), 4.95~5.48 (2H+1H, m), 6.10~6.60 (3H, m), 9.21 (3H, s). This was employed for the next reaction without further purification.

($\pm$)-3 α -Tetrahydropyranyloxy-8 β -formylmethyl-10 α -methyl-14-oxo-3 β , 5 β , 9 β -perhydrophenanthrene (XIb). OsO₄ (630 mg) was added to a stirred solution of XIb (35 g) in THF (630 ml) and water (200 ml) under N₂ atmosphere. After stirring 10 min, powdered sodium metaperiodate (63 g) was added under cooling by water, and stirring was continued for 15 hr at room temperature. The mixture was diluted with ether. The ether solution was washed with water and brine, dried (Na₂SO₄) and evaporated to give 34 g of an oil (XIb). ν_{max} (film), 2800 (w), 1720, 1705, 1130, 1040, 990, 920 cm⁻¹. This was employed for the next reaction without further purification.

($\pm$)-3 α -Tetrahydropyranyloxy-4 β , 10 α -dimethyl-8 β -formylmethyl-14-oxo-3 β , 4 α , 5 β , 9 β -perhydrophenanthrene (XIIa). The ketone XIa worked up as described above to give an oil (95%) of XIIa, ν_{max} (film), 2790 (w), 1710, 1692, 1075, 1025, 970 cm⁻¹. This was employed for the next reaction without further purification.

($\pm$)-3 α -Tetrahydropyranyloxy-14-oxo-16 ξ -hydroxy-17, 18, 19-trisnorkaurane (XIIIb). The oily aldehyde XIIb (52 g) dissolved in THF (750 ml) was added to a solution of NaOMe (from 20 g Na) in MeOH (1 liter). The mixture was refluxed for 2 hr under N₂ atmosphere. After concentration *in vacuo*, the residue was diluted with water and extracted with ether. The ether extract was washed with water and brine, dried (Na₂SO₄) and concentrated *in vacuo* to give 46 g of crude crystals. ν_{max} (Nujol) 3340, 1730, 1123, 1032, 980 cm⁻¹.

This was employed for the next reaction without further purification.

($\pm$)-3 α -Tetrahydropyranyloxy-14-oxo-16 ξ -hydroxy-17, 19-bisnorkaurane (XIIIa). XIIIa was worked up as described above to give crude crystals (65%). ν_{max} (Nujol) 3300, 1743, 1120, 1030, 980 cm⁻¹. This was employed for the next reaction without further purification.

($\pm$)-3 α -Tetrahydropyranyloxy-14, 16-dioxo-17, 18, 19-trisnorkaurane (XIVb). To a solution of chromic anhydride-pyridine complex (750 ml of pyridine and 60 g of CrO₃), the crude alcohol XIIIb (46 g) in dry pyridine (500 ml) was added with stirring at 15~20°C. The reaction mixture was stirred overnight at room temperature and poured into dil. NaHCO₃ aq. (2 liters) and extracted with ether. The extract was washed with water and brine, and dried (Na₂SO₄). The ether solution was evaporated to give crude crystals. Tritulation of these crystals with ether-pet. ether gave 23 g of the product and the residual oily mixture was chromatographed on alumina to give further amount of XIVb (5.6 g). Recrystallization from benzene-*n*-hexane gave needles, mp 146~148°C. ν_{max} (Nujol) 1770, 1730, 1026, 983 cm⁻¹. NMR (100 MHz, CDCl₃) τ 5.30 (1H, m), 6.10 (1H, m), 6.47 (2H, m), 9.12 (1H, s). *Anal.* Found: C, 73.26; H, 8.87. Calcd. for C₂₂H₃₂O₄: C, 73.30; H, 8.95%.

($\pm$)-3 α -Tetrahydropyranyloxy-14, 16-dioxo-17, 19-bisnorkaurane (XIVa). XIIIa was worked up as described above to give crystals (XIVa) in 32% overall yield from XIa. Recrystallization from ether-ethanol gave leaflets, mp 201~204°C. ν_{max} (Nujol) 1770, 1745, 1025, 977 cm⁻¹. *Anal.* Found: C, 73.76; H, 9.15. Calcd. for C₂₃H₃₄O₄: C, 73.74; H, 9.05%.

($\pm$)-3 α -Tetrahydropyranyloxy-14-oxo-16 β -hydroxy-18, 19-bisnorkaurane (XVb) and its C-16 epimer (XVb'). To a stirred solution of the Grignard reagent (15.4 g of Mg, 91 g of MeI, and 500 ml of dry ether), XIVb (23 g) in dry THF (500 ml) was added dropwise under N₂ atmosphere at 5~10°C. After 3 hr stirring at room temperature, sat NH₄Cl aq. (130 ml) was added slowly to the reaction mixture cooled by ice-salt. After 1 hr cold water was added. The reaction mixture was extracted with ether. The ether extract was washed with water and brine, dried (Na₂SO₄) and concentrated to give crude crystals. These were triturated with ether-pet. ether to give 13 g of crystals (XVb). The residual was chromatographed on alumina. Elution with benzene-AcOEt (9:1) afforded further amount of

XVb (6.0 g). ν_{max} (Nujol) 3520, 1738, 1130, 1120, 1024, 984 cm^{-1} . And the latter elution gave XVb' (2.1 g). ν_{max} (Nujol) 3390, 1728, 1115, 1046, 1025 cm^{-1} . These were employed for the next reaction without further purification.

($\pm$)-3 α -Tetrahydropyranyloxy-14-oxo-16 β -hydroxy-19-norkaurane (XVa) and its C-16 epimer (XVa'). The Grignard reaction of XIVa as described above gave a mixture of XVa and XVa'. These were separated by chromatography on alumina. The fractions eluted with benzene gave crystals of XVa (81% yield) which were recrystallized from ether-pet. ether, mp 180~182°C. ν_{max} (Nujol) 3460, 1740, 1130, 1077, 1020, 978 cm^{-1} . *Anal.* Found: C, 73.68; H, 9.68. Calcd. for $\text{C}_{24}\text{H}_{38}\text{O}_4$: C, 73.80; H, 9.81. The fractions eluted with benzene-AcOEt (19:1) gave its C-16 epimer (12% yield). ν_{max} (Nujol) 3550, 1737, 1040, 1010, 960 cm^{-1} .

Ethylidene formation of XVb'. To a solution of liquid NH_3 (50 ml) and Li (200 mg), XVb' (1.0 g) in dry THF (50 ml) was added with stirring at -60~-40°C. One hour later, NH_4Cl (6 g) was added to the reaction mixture at -60~-40°C. The reaction mixture turned from deep-blue to white. After the evaporation of NH_3 at room temperature, it was diluted with sat NH_4Cl aq. (40 ml) and extracted with ether. The organic layer was washed with brine and dried (MgSO_4). Evaporation of ether gave an oily mixture (1.0 g), to which 99% acetaldehyde (15 ml) and ZnCl_2 (1.0 g) was added. After 20 hr stirring at room temperature, the reaction mixture was diluted with dil. NaHCO_3 aq. and extracted with ether. The organic layer was washed with water and brine, dried (Na_2SO_4). Evaporation of ether *in vacuo* gave an oily mixture of XVIII, XIX and XX, which was chromatographed on alumina (20 g). The fraction (No. 1~3) eluted with *n*-hexane-benzene (1:1) (100 ml $\times$ 3) gave crystals (150 mg) of XVIII, mp 162~165°C (from acetone). ν_{max} (Nujol) 1113, 1020, 963 cm^{-1} . NMR (100 MHz, CDCl_3) τ 4.81 (1H, q, $J=5$ Hz), 5.30 (1H), 5.70 (C-14 H, s), 6.14 (1H, m), 6.48 (2H, m), 8.70 (3H, s), 8.73 (3H, d, $J=5$ Hz), 9.12 (3H, s). *Anal.* Found: C, 74.14; H, 10.13. Calcd. for $\text{C}_{25}\text{H}_{40}\text{O}_4$: C, 74.21; H, 9.97%. The fraction (No. 4) eluted with benzene (100 ml) gave an oil (70 mg). The fractions (No. 5~9) eluted with benzene (100 ml $\times$ 5) gave crystals (210 mg) of XIX, mp 157~159°C. ν_{max} (Nujol) 3300, 1150, 1000, 1052, 1029, 946 cm^{-1} . NMR (100 MHz, CDCl_3) τ 4.82 (1H, q, $J=5$ Hz), 5.71 (C-14 H, s), 4.45 (1H, m), 8.73 (3H, s), 8.74 (3H, d, $J=5$ Hz), (There is NOE of $20\pm 2\%$ between C-10 methyl

and C-14 hydrogen.). *Anal.* Found: C, 74.69; H, 10.39. Calcd. for $\text{C}_{20}\text{H}_{32}\text{O}_3$: C, 74.96; H, 10.06%. The fraction (No. 10) eluted with benzene-MeOH (9:1) (100 ml) gave crystals (30 mg) of XX, mp 224.5~225.5°C (from EtOAc-ether). ν_{max} (Nujol) 3400~3300, 1125, 1055, 1032, 966 cm^{-1} . NMR (100 MHz, $\text{C}_6\text{D}_5\text{N}$) τ 3.79 (C-14 OH, d, $J=6$ Hz, coupling with C-14 H), 4.09 (C-16 OH, s), 4.18 (C-3 OH, d, $J=2$ Hz coupling with C-3 H), 5.57 (C-14 H, d, $J=6$ Hz, $16\pm 2\%$ NOE with C-10 methyl), 6.16 (C-3 H, m), 8.47 (C-16 CH_3 , s), 9.09 (C-10 CH_3 , s). *Anal.* Found: C, 73.09; H, 10.32. Calcd. for $\text{C}_{18}\text{H}_{30}\text{O}_3$: C, 73.43; H, 10.27%. The fractions (No. 11~14) eluted with benzene-MeOH (9:1) gave an oil (280 mg).

($\pm$)-3 α , 16 β -Dihydroxyl-14-oxo-18, 19-bisnorkaurane (XVIb). To a solution of XVb (13.0 g) in THF (240 ml), AcOH-H₂O (2:1) (720 ml) was added. The mixture was stirred for 20 hr at room temperature and then for 3 hr at 40°C. The reaction mixture was concentrated *in vacuo* and extracted with ether. The ether extract was washed with sat NaHCO_3 aq. and brine, and dried (MgSO_4). Evaporation of ether gave crystals (10.0 g), which were recrystallized from EtOAc, mp 215~216°C. ν_{max} (Nujol) 3400, 1730, 1125, 1026, 943 cm^{-1} . *Anal.* Found: C, 73.88; H, 9.57. Calcd. for $\text{C}_{18}\text{H}_{28}\text{O}_3$: C, 73.93; H, 9.65%.

($\pm$)-3 α -16 α -Dihydroxy-14-oxo-18, 19-bisnorkaurane (XVIb'). XVb' was worked up as described above to give crystals. Recrystallization from EtOAc gave needles, mp 207~211°C. ν_{max} (Nujol) 3430, 3380, 1732, 1045, 1026, 970, 875 cm^{-1} . NMR (60 MHz, $\text{C}_6\text{D}_5\text{N}$) τ 8.43 (3H, s), 9.09 (3H, s). *Anal.* Found: C, 73.68; H, 9.43. Calcd. for $\text{C}_{18}\text{H}_{28}\text{O}_3$: C, 73.93; H, 9.65%.

($\pm$)-3 α , 16 β -Dihydroxy-14-oxo-19-norkaurane (XVIa). XVa was worked up as described above to give crystalline diol XVIa (83%), which was recrystallized from ether-MeOH, mp 222~223.5°C. ν_{max} (Nujol) 3400, 1743, 1130, 1028, 955 cm^{-1} . NMR (100 MHz, CDCl_3) τ 8.91 (OH $\times$ 2), 7.72 (3H, s), 9.00 (3H, d, $J=6$ Hz), 9.12 (3H, s). *Anal.* Found: C, 74.14; H, 9.72. Calcd. for $\text{C}_{19}\text{H}_{30}\text{O}_3$: C, 74.47; H, 9.87%.

($\pm$)-3, 14-Dioxo-16 β -hydroxy-18, 19-bisnorkaurane (XVIIb). Jones chromic acid reagent (15 ml) was added to ice-cooled solution of XVIb (10.0 g) in acetone (870 ml) and the mixture left to stand at room temperature for 10 min. MeOH was added to destroy the excess of the oxidant. After the removal of the solvents *in vacuo*, the residue was diluted with water and ex-

tracted with ether. The ether extract was washed with NaHCO_3 aq. and brine. Concentration of the solution after drying (MgSO_4) gave 9.0 g of the diketone. Recrystallization from acetone gave needles, mp $189 \sim 190^\circ\text{C}$. ν_{max} (Nujol) 3430, 1740, 1700, 1126, 953 cm^{-1} . NMR (100 MHz, CDCl_3) δ 8.13 (OH), 8.75 (3H, s), 9.00 (3H, s). *Anal.* Found: C, 74.26; H, 8.94. Calcd. for $\text{C}_{18}\text{H}_{26}\text{O}_3$: C, 74.44; H, 9.03%.

($\pm$)-3, 14-Dioxo-16 α -hydroxy-18,19-bisnorkaurane (XVIIb'). XVIIb' was worked up as described above to give crystals which were recrystallized from AcOEt-benzene, mp $200 \sim 203^\circ\text{C}$. ν_{max} (Nujol) 3470, 1746, 1705, 1138, 1045, 957, 870 cm^{-1} . NMR (60 MHz, CDCl_3) δ 8.14 (OH), 8.53 (3H, s), 9.00 (3H, s). *Anal.* Found: C, 74.42; H, 8.96. Calcd. for $\text{C}_{18}\text{H}_{26}\text{O}_3$: C, 74.44; H, 9.03%.

($\pm$)-3, 14-Dioxo-16 β -hydroxy-19-norkaurane (XVIIa). XVIIa was worked up as described above to give the diketone in 98% yield. Recrystallization from MeOH-benzene-*n*-hexane gave prisms, mp $231 \sim 233^\circ\text{C}$. ν_{max} (Nujol) 3520, 1735, 1693, 1168, 1124, 945 cm^{-1} . NMR (100 MHz, CDCl_3) δ 8.20 (OH), 8.72 (3H, s), 8.91 (3H, s), 8.97 (3H, d, $J=6.5\text{ Hz}$). *Anal.* Found: C, 74.95; H, 9.13. Calcd. for $\text{C}_{19}\text{H}_{28}\text{O}_3$: C, 74.96; H, 9.27%.

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