Diterpenoid Total Synthesis

Part XII.[†] Racemic 4-Epipimaric and 4-Episandaracopimaric Acids

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A total synthesis of racemic 4-epipimaric and 4-episandaracopimaric acids is described.

(-)-4-Epipimaric acid [(-)-pimara-8(14), 15-dien-19-oic acid, Ia] is a diterpene recently isolated from the roots of *Aralia cordata* Thunb. (Japanese name: Udo) by Shibata and his co-workers.^{1,2)} Hanson and White also isolated the acid from spikenard root and showed that

the parent hydrocarbon, (-)-pimara-8(14), 15-diene, acts as a precursor of gibberellic acid when fed to *Gibberella fujikuroi*.^{3, cf. 4, 5)}

As a part of our efforts to synthesize diterpenes with an axial carboxyl group at C-4 such as the gibberellins⁶⁾ and kaur-16-en-19-

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oic acid,⁷⁾ we planned an approach to the racemic acid (Ia)* starting from the previously described keto ester (II).⁷⁾ Our synthetic route essentially parallels that employed for the synthesis of ($\pm$)-pimara-8(14), 15-diene by Ireland and Schiess.⁸⁾

The keto ester (II) was reduced with sodium borohydride to give an oily hydroxy ester (III). This was treated with mercuric chloride in ethanol to give crystalline aldo ester (IV) in 69% yield from II.^{9,10)} Methylation of the unsaturated aldehyde (IV) was achieved by treatment with a great excess of methyl iodide and potassium *t*-butoxide to give a mixture of β,γ -unsaturated aldehydes (V) epimeric at C-13. The mixture smoothly reacted with triphenylmethylene phosphorane in DMSO¹¹⁾ to give a mixture of methyl ($\pm$)-4-epipimarate (Ib) and methyl ($\pm$)-4-episandaracopimarate (VIb). This was chromatographed on alumina impregnated with silver nitrate¹²⁾ to effect separation of the C-13 epimers. The desired crystalline ester (Ib) with an axial vinyl group at C-13 was eluted first and then the oily epimer (VIb) with an equatorial vinyl group followed. The NMR spectra at 100 MHz of the two esters exhibited significant difference with each other, although the IR spectra as films were very similar. Thus the vinylic protons (15-H and 16-H₂) of the ester Ib absorbed at δ 5.60~5.88 (sextet) and at 4.80~5.00 (quintet) ppm representing

an ABC type splitting^{13,14)} very similar to that of methyl pimarate (Ib, antipodal framework with an α -equatorial CO₂Me at C-4). On the other hand the corresponding absorptions of the ester VIb appeared at δ 5.68~5.96 (quartet), at 4.95~5.00 (quartet) and at 4.80~4.84 (triplet) representing an ABX type splitting similar to that of methyl sandaracopimarate (VIb, antipodal framework with an α -equatorial CO₂Me at C-4).¹³⁾

The corresponding racemic crystalline acids, 4-epipimaric (Ia) and 4-episandaracopimaric (VIa) acids, were prepared from the esters (Ib and VIb) by treatment with potassium *t*-butoxide in DMSO.¹⁵⁾

The IR (in carbon tetrachloride) and NMR (in deuteriochloroform) spectra of the racemic acid (Ia) and the ester (Ib) were identical with those of the natural acid (Ia) and the ester (Ib) in every detail. The ester was also identified by GLC comparison. The NMR spectra of the natural and racemic acids (Ia) and that of the racemic acid (VIa) are shown in Figs. 1~3. The splitting patterns observed in the olefinic regions (see the enlarged spectra) are same as those observed in the cases of the corresponding esters (Ib and VIb). The acid Ia exhibited an ABC type splitting, while VIa showed an ABX type.

Although no occurrence of 4-episandaracopimaric acid (VIa) is reported hitherto, it is highly probable to be found in nature in view of the increasing examples of sets of diterpene acids with an axial or an equatorial carboxyl group at C-4 such as kaur-16-en-19-oic¹⁶⁾ and kaur-16-en-18-oic¹⁷⁾ acids, dehydro-

* Although the formulas depicted represent only one enantiomer, they are taken to mean a racemate in the cases of synthetic materials.

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FIG. 1.

FIG. 2.

FIG. 3.

NMR Spectra of the Acids.

FIG. 1. (–)-4-Epipimaric Acid (Ia).

FIG. 2. (±)-4-Epipimaric Acid (Ia).

FIG. 3. (±)-4-Episandaracopimaric Acid (VIa).

Measured in CDCl_3 by a JNM-4H-100 spectrometer at 100 MHz. The chemical shift, δ -scale, is based on TMS as an internal standard. The enlarged spectra of the olefinic

abietic¹⁸⁾ and 4-epidehydroabietic acids¹⁹⁻²¹⁾ and the present case, pimaric²²⁾ and 4-epipimaric acids.*

EXPERIMENTAL

All mps were uncorrected. IR spectra refer to Nujol mulls for solid samples and films for oils. NMR spectra were recorded at 100 MHz in CDCl₃ with TMS as an internal standard.

Methyl (±)-13-n-butylthiomethylene-14ξ-hydroxy-5β, 8α, 9β, 10α-podocarpin-19-oate (III). A suspension of NaBH₄ (1.0 g) in 95% EtOH (50 ml) was added portionwise to a stirred and ice-cooled solution of II (4.1 g) in THF (30 ml). After the addition, the mixture was stirred for 2 hr at 5~10°C, concentrated *in vacuo*, diluted with water and extracted with ether. The ethereal extract was washed with sat NaCl aq, dried (MgSO₄) and concentrated to give an oil. This was employed for the next step without characterization.

Methyl (±)-13-formyl-5β, 8α, 9β, 10α-podocarp-13(14)-en-19-oate (IV). A solution of III (from 4.1 g of II) in 95% EtOH (60 ml) was mixed with a suspension of CdCO₃ (2.0 g) in a solution of HgCl₂ (2.9 g) in 95%

EtOH (20 ml). The mixture was stirred and heated under reflux for 5 min, concentrated *in vacuo*, diluted with benzene and water and filtered. The benzene layer was separated and the aqueous layer was extracted with benzene. The combined benzene solution was washed with water and sat NaCl aq, dried (MgSO₄) and concentrated *in vacuo* to give 2.2 g (69% from II) of crystalline IV. Recrystallization from EtOAc-pet. ether gave prisms, mp 127~128°C; $\nu_{\max}$ 2720, 1700, 1662, 1630, 1250, 1210, 1190 cm⁻¹; δ 0.68 (3H, s), 1.20 (3H, s), 3.64 (3H, s), 6.54 (1H, broad, s), 9.43 (1H, s) ppm. *Anal.* Found: C, 74.92; H, 9.28. Calcd. for C₁₉H₂₈O₃: C, 74.96; H, 9.27%.

Methyl (±)-13-methyl-13-formyl-5β, 9β, 10α-podocarp-8(14)-en-19-oate (V). A solution of IV (2.1 g) in dry 1,2-dimethoxyethane (30 ml) was added to a solution of *t*-BuOK (from 12 g of K) in *t*-BuOH (250 ml) under N₂. The solution was stirred and heated under reflux for 30 min. Subsequently MeI (40 ml) was added in one portion to the ice-cooled solution with stirring. The stirring was continued for 8 hr under N₂ at room temperature. The mixture was diluted with water to dissolve KI, concentrated *in vacuo* and extracted with ether. The ethereal extract was washed with water and sat NaCl aq, dried (MgSO₄) and concentrated *in vacuo* to give an oily epimeric mixture at C-13 of V (2.1 g), $\nu_{\max}$ 2720, 1715, 1235, 1170 cm⁻¹. The NMR spectrum clearly indicates that this is a mixture of two epimers: α -(ax)-formyl isomer, δ 0.50 (C-4 Me), 1.05 (C-13 Me), 1.18 (C-10 Me), 3.56 (CO₂Me), 5.18 (C-14 H), 9.37 (CHO); β -(eq)-formyl isomer, δ 0.60 (C-4 Me), 1.03 (C-13 Me), 3.56 (CO₂Me), 5.26 (C-14 H), 9.27 (CHO) ppm.

Methyl (±)-4-epipimarate (Ib) and methyl (±)-4-episan-daracopimarate (VIb). Triphenyl-methylphosphonium bromide (7.8 g) was added to a solution of sodium methylsulfinyl methylide (from 1.0 g of 50% NaH) in DMSO (20 ml) under N₂ with ice-cooling. The mixture was stirred for 10 min to yield an orange-red solution of the Wittig reagent. A solution of V (2.1 g) in DMSO (20 ml) was added dropwise to the reagent and the mixture was stirred for 3 hr at room temperature. Subsequently it was poured into ice-water and extracted with *n*-hexane. The *n*-hexane layer was washed with water and sat NaCl aq, dried (MgSO₄) and concentrated *in vacuo* to give 2.5 g of oil including 0.5 g of mineral oil. This was chromatographed over Al₂O₃-AgNO₃. A column (40×3.6 cm) was prepared by mixing Al₂O₃ (300 mesh,

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* Very recently the isolation of sandaracopimar-8(14), 15-dien-19-ol (VII) from *Dacrydium colensoi* has been reported.²³⁾ A racemic alcohol (VII), sharply melting at 103~104°C, was obtained by the reduction of VIb with lithium aluminum hydride. Its NMR spectrum was quite similar to that of the natural alcohol, especially in quaternary methyl, hydroxy-methylene and olefinic regions but not identical with that of the natural material, especially in methylene region (δ 1.20~2.50). The GLC retention time of our synthetic alcohol (VII) differed from that of the natural alcohol with the assigned structure VII. Since the natural material was available in a very minute amount, no detailed comparisons were possible and no definite conclusion could be stated at present.

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300 g) and AgNO_3 aq (60 g in 80 ml) and drying it in an oven at 130°C for 1 hr. All fractions were 300 ml. The eluants were as follows: fractions No. 1~3, pet. ether; No. 4~6, pet. ether-ether (9:1); No. 7~21, pet. ether-ether (85:15). Fractions No. 1~11 gave hydrocarbons. Fractions No. 12 and 13 gave an unidentified oil with a carbonyl absorption in IR spectrum (185 mg). Fraction No. 14 gave almost pure methyl ($\pm$)-4-epipimarate (Ib, 95 mg). Fractions No. 15~20 gave a mixture of Ib and VIb (1.112 g).

The ester Ib gradually crystallized. Recrystallization from pet. ether gave rhombs, mp $68\sim69^\circ\text{C}$; ν_{max} 1715, 1630 (w), 1345 (w), 1325 (w), 1240, 1225, 1200, 1150, 1000, 920, 865, 850 cm^{-1} ; ν_{max} (CCl_4), 2945, 1735 (s), 1635 (w), 1445 (m), 1210 (m), 1180 (m), 1165 (m), 1145 (s), 1135 (sh.), 1118 (sh), 1085 (w), 1022 (w), ~ 975 (w), 915 (m), 855 (w), 845 (w) cm^{-1} ; δ 0.55 (3H, s), 1.00 (3H, s), 1.20 (3H, s), 3.62 (3H, s), 4.80~5.00 (2H, quintet), 5.10 (1H, broad s), 5.60~5.88 (1H, sextet) ppm; GLC: Column, 3% SE-30 on Celite 545, $2\text{ m}\times 3\text{ mm}$ i.d. at 210°C , Carrier gas, N_2 , 0.8 kg/cm^2 , R_t 11.0 min. The IR (CCl_4), NMR and GLC data are indistinguishable from those of the natural product kindly provided by Dr. Mihashi of Tokyo College of Pharmacy. *Anal.* Found: C, 80.00; H, 10.32. Calcd. for $\text{C}_{21}\text{H}_{32}\text{O}_2$: C, 79.70; H, 10.19%.

A pure sample of the ester VIb was obtained by treating the pure VIa (see below) with CH_2N_2 but it could not be crystallized. ν_{max} 1715, 1630 (w), 1345 (w), 1325 (w), 1240, 1225, 1200, 1150, 1000, 920, 850 cm^{-1} . This spectrum is very similar to that of the almost pure Ib measured as a film except that an absorption at 865 cm^{-1} is very weak in the spectrum of VIb. δ 0.65 (3H, s), 1.06 (3H, s), 1.22 (3H, s), 3.64 (3H, s), 4.80~5.00 (2H, septet), 5.26 (1H, broad s), 5.68~5.96 (1H, q) [or 4.90 (1H, q, H_A), 4.92 (1H, q, H_B), 5.82 (1H, q, H_X), $J_{AB}=2$, $J_{AX}=17$, $J_{BX}=10\text{ Hz}$] ppm.

($\pm$)-4-Epipimaric acid (Ia). Solid *t*-BuOK obtained by evaporation *in vacuo* of the solvent from a solution of K (0.2 g) in *t*-BuOH (10 ml) was dissolved in dry DMSO (5 ml) by gentle heating. This was added to a solution of crystalline Ib (40 mg) in DMSO (1 ml). The mixture was stirred and heated at 100°C for 1.5 hr under N_2 . After cooling it was diluted with water and the acid fraction was taken in ether in the usual manner. As the Na salt of Ia is soluble in ether, care should be taken during the separation not to discard the necessary material. The ethereal extract

was washed with water and sat NaCl aq, dried (MgSO_4) and concentrated *in vacuo*. The residue was triturated with ether to give 23 mg of crystalline Ib. Recrystallization from EtOAc-pet. ether afforded prisms, mp $180\sim182^\circ\text{C}$ (dec., sinter at 173°C); ν_{max} $\sim 3200\sim 2600$, 1680, 1630 (w), 1270, 1000, ~ 960 , 920, 865 (w), 850 cm^{-1} ; ν_{max} (CCl_4) ~ 3100 , 2950, ~ 2650 , 1695 (s), 1635 (w), 1465 (s), 1445 (s), 1430 (m), 1400 (m), 1355 (w), 1325 (w), 1310 (w), 1255 (s), 1180 (m), 1175 (m), 1145 (w), 1085 (w), 1023 (m), 990 (m), ~ 960 (m), 915 (s), 860 (w), 845 (m) cm^{-1} ; δ 0.69 (3H, s), 1.04 (3H, s), 1.29 (3H, s), 4.82~5.02 (2H, quintet), 5.18 (1H, broad, s), 5.62~5.90 (1H, sextet) ppm. The IR and NMR spectra were in good accord with those of the natural product. *Anal.* Found: C, 79.12; H, 9.45. Calcd. for $\text{C}_{20}\text{H}_{30}\text{O}_2$: C, 79.42; H, 10.00%.

($\pm$)-4-*Episandaracopimaric acid* (VIa). Solid *t*-BuOK obtained by evaporation *in vacuo* of the solvent from a solution of K (2.0 g) in *t*-BuOH (100 ml) was dissolved in dry DMSO (50 ml) by gentle heating. A solution of Ib and VIb (1.1 g, fractions No. 15~20 of the chromatographic purification, predominantly VIb) in DMSO (10 ml) was added to this solution. The mixture was stirred and heated at 100°C for 8 hr under N_2 , poured into ice-water, acidified with AcOH and extracted with ether. The ethereal extract was washed with water and sat NaCl aq, dried (MgSO_4) and concentrated *in vacuo*. The residue was triturated with EtOAc-pet. ether to give 530 mg of crude crystalline VIa contaminated with some Ia. Three recrystallizations from EtOAc-pet. ether gave pure VIa as prisms, mp $184\sim185^\circ\text{C}$ (sinter at *ca.* 170°C), ν_{max} $\sim 3100\sim 2600$, 1695, 1635, 1255, 1183, 992, ~ 930 , 906, 857 (sh.), 850 cm^{-1} ; ν_{max} (CCl_4) ~ 3100 , 2950, ~ 2650 , 1695 (s), 1635 (w), 1460 (s), 1440 (s), 1430 (m), 1400 (m), 1365 (w), 1355 (w), 1325 (w), 1310 (w), 1255 (s), 1182 (m), 1172 (s), 1147 (w), 1130 (w), 1085 (w), 1023 (m), 990 (m), ~ 945 (m), 910 (s), 857 (sh.), 840 cm^{-1} ; δ 0.75 (3H, s), 1.05 (3H, s), 1.28 (3H, s), 4.80~5.00 (2H, septet), 5.26 (1H, broad s), 5.68~5.96 (1H, q) [or 4.90 (1H, q, H_A), 4.98 (1H, q, H_B), 5.82 (1H, q, H_X), $J_{AB}=2$, $J_{AX}=17$, $J_{BX}=10\text{ Hz}$] ppm. *Anal.* Found: C, 79.08; H, 9.94. Calcd. for $\text{C}_{20}\text{H}_{30}\text{O}_2$: C, 79.42; H, 10.00%.

($\pm$)-*Sandaracopimaradien-19-ol* (VII). A solution of VIb (218 mg) in THF (20 ml) was added to a suspension of LAH (300 mg) in ether (40 ml). The mixture was stirred and heated under reflux for 2 hr. After cooling the excess of LAH was destroyed by adding

ice-water and the mixture was filtered through Celite. The Celite layer was washed with ether. The filtrate and washings were combined and the ethereal layer was separated. The ethereal solution was washed with sat NaCl aq, dried (MgSO₄) and concentrated *in vacuo* to give crude crystalline VII. Recrystallization from pet. ether gave 85 mg (43%) of pure VII as needles, mp 103~104°C, $\nu_{\max}$ 3350, 1665 (w), 1630 (w), 1040, 1030, 995, 975, 955, 935, 920, 865 (sh), 855 cm⁻¹; $\nu_{\max}$ (CHCl₃) ~3700, ~3100, 1660, 1630, 1015, 910, 860, 850 cm⁻¹; δ 0.80 (3H, s), 1.04 (3H, s), 1.08 (3H, s), 3.42, 3.84 (2H, AB, J_{AB} =11 Hz), 4.85~5.01 (2H, septet), 5.24 (1H, broad s), 5.68~5.96 (1H, q) [or 4.90 (1H, q, H_A), 4.93 (1H, q, H_B), 5.82 (1H, q, H_X), J_{AB} =1.5, J_{AX} =17, J_{BX} =10 Hz] ppm. The NMR spectrum was slightly different from that of the natural alcohol kindly provided by Professor P. K. Grant. *Anal.* Found: C,

83.19; H, 11.16. Calcd. for C₂₀H₃₂O: C, 83.27; H, 11.18%. GLC: Column, 3% SE-30 on Celite 545, 2 m×3 mm *i.d.* at 210°C, Carrier gas, N₂, 1.0 kg/cm², R_t 8.6 min. *cf.* Prof. Grant's alcohol: R_t 8.0 min.

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