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DITERPENOID TOTAL SYNTHESIS—XIX[1]

(±)-STEVIOL AND ERYTHROXYDIOL A: REARRANGEMENTS IN BICYCLOOCTANE COMPOUNDS

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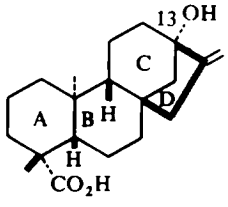
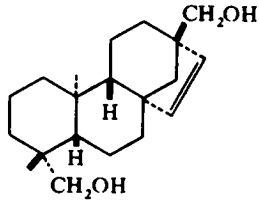
Abstract—(±)-Steviol (I) and erythroxydiol A (II), tetracyclic diterpenes with a substituent at the bridgehead C-13 position, were synthesized by using two interesting rearrangement reactions (XII→XIV and XVI→XVII, respectively).

THE interconversion of polycyclic diterpenes has attracted much attention,[2] but the conversion has been limited to compounds without a functional group at the bridgehead position as seen in the acid-catalysed rearrangement of kaurene into atisirene.[3] We describe the syntheses of (±)-steviol (I)† and erythroxydiol A (II), each with a substituent at the bridgehead C-13 position, with emphasis on the skeletal rearrangements used as the key reactions.



I



II

Reductive rearrangement of bicyclo[2.2.2]*octane-2,6-dione into bicyclo*[3.2.1]*octan-1-ol-7-one.* A bridgehead OH group at C-13 in steviol (I) makes its synthesis difficult. In the gibberellin field we recently reported a skeletal rearrangement of a β-diketone (A) into a ketol (B).[4] The prototype of this reaction is the rearrangement of bicyclo[2.2.2]octane-2,6-dione (C = III) into bicyclo[3.2.1]octan-1-ol-7-one (E = IV). As this reaction is applicable to the synthesis of steviol, we synthesized the diketone (III) and studied its reduction to the ketol (IV).

The synthesis of the bridged β-diketone (III) was achieved[5] by the intramolecular acylation of 3-oxocyclohexylacetic acid (Va) in 10% yield.[5] In our alternative synthesis, methyl 3-oxocyclohexylacetate (Vb) was ketalized to a ketal ester (VI). This was reduced with LAH to an alcohol (VII) which on oxidation with the Collins chromic

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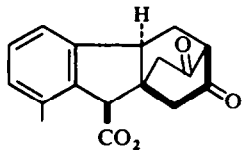
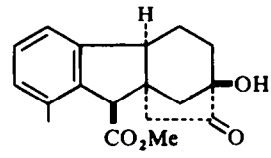
† Although the formulas depicted represent only one enantiomer, they are taken to mean a racemate in the case of totally synthetic material.

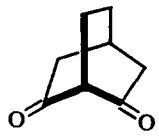
acid[6] gave an aldehyde (VIII). Cyclization of this ketal aldehyde (VIII) was effected by treatment with aqueous phosphoric acid to a bicyclic ketol (IX) in 35% yield. This reaction did not proceed smoothly if hydrochloric acid in acetone was used instead of phosphoric acid. The crystalline ketol (IX) was oxidized with the Jones chromic acid[7] to afford bicyclo[2.2.2]octane-2,6-dione (III).



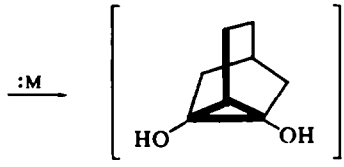
A



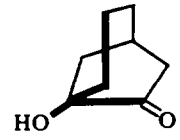
B



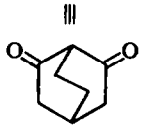
C



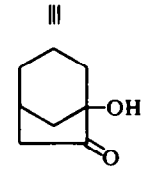
D



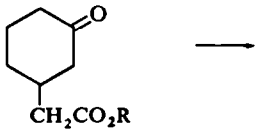
E



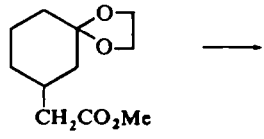
III



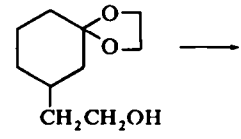
IV



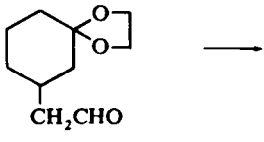
Va, R = H
b, R = Me



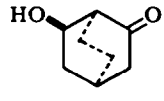
VI



VII

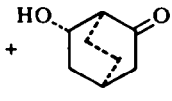


VIII



IX

III IV +



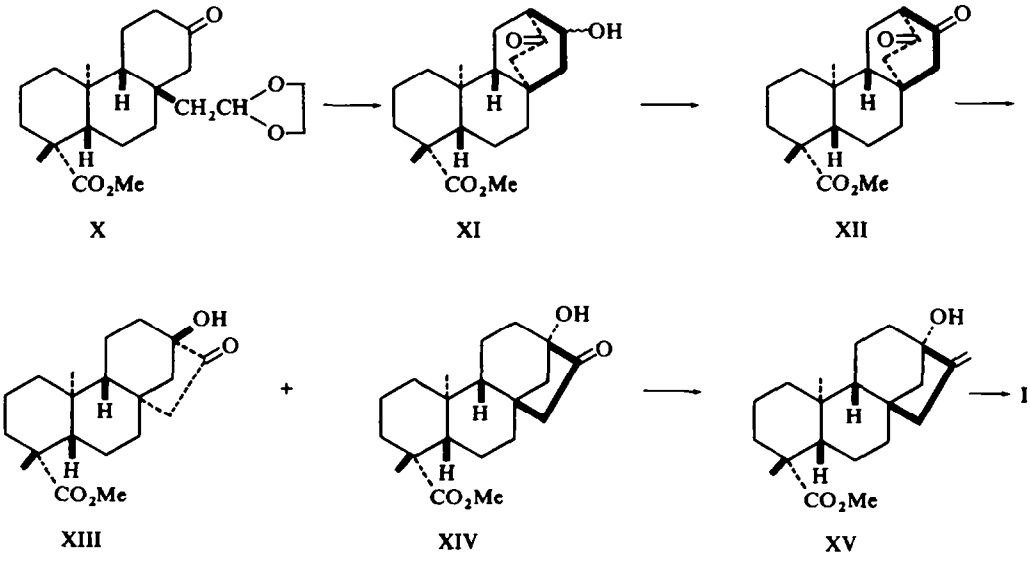
IX′

The most fruitful procedure for the rearrangement of the β-diketone was the reduction with zinc amalgam and dilute hydrochloric acid at room temperature which gave the desired bicyclo[3.2.1]octan-1-ol-7-one (IV) in a yield of 34%. When the reaction temperature was raised, no definite product could be isolated. The structure IV was supported by IR (ν_{O-H} 3400, $\nu_{C=O}$ 1745 cm^{-1}) and NMR. Especially in its NMR spectrum no CHOH proton was observed in accord with the bridgehead nature of the OH group. The reduction with zinc and acetic acid gave a complex result and three compounds were isolated by chromatographic separation over silicic acid: the starting diketone (III, 31%), the ketol (IX, 11%) and the rearranged ketol (IV, 28%). By using the Birch reduction with lithium and ammonia, another ketol (IX′, 21%) and only a trace of the desired ketol (IV, 1·3%) were isolated after chromatographic separation. The structure IX′ of the new ketol was confirmed by Jones oxidation which regenerated the starting diketone (III). The two ketols (IX and IX′) differ from each other in their m.ps, IR and NMR spectra. The CO group of IX absorbs at 1710 cm^{-1} while that of IX′ at 1720 cm^{-1}. This suggests that the configuration of the OH group of the ketol IX is *endo* while that of IX′ is *exo*. No attempt was made, however, to rigorously prove the stereochemistry of the two ketols. Our efforts to detect the possible cyclopropanediol intermediate (D) was in vain. Therefore the exact mechanism of the reaction, which is tentatively assumed as C→D→E, remains to be clarified.

Synthesis of (±)-*steviol.* Steviol (I) is the aglycon of stevioside, the remarkably sweet glucoside abundant in leaves and stems of *Stevia rebaudiana* Bertoni, a Paraguayan shrub of the composite family.[8-11] Our interest in its total synthesis was aroused in 1963 when Ruddat *et al.* demonstrated its gibberellin-like activity.[12] Our earlier efforts in this direction have been reported.[13] Application of the above described reductive rearrangement enabled us to synthesize (±)-steviol (I) in only five steps from a known intermediate (X).[14] After the publication of our preliminary communication,[14] two other syntheses of steviol (I) were announced by Cook and Knox[15] and by ourselves.[16]

The known keto acetal (X)[16] was treated with dilute hydrochloric acid in acetone to give a tetracyclic ketol (XI, 92·5%) formed by an aldol-type cyclization.[17] Jones chromic acid smoothly oxidized the ketol (XI) to afford a bicyclo[2.2.2]octane-2,6-dione with an atisane skeleton (XII, 95%). This key intermediate in toluene was heated under reflux for 1 hr with amalgamated mossy zinc and hydrochloric acid (the Clemmensen condition) to give a mixture of two ketols (XIII and XIV) with phyllocladane and kaurane skeletons, respectively. These were separated by chromatography over silicic acid. The major product, obtained in a yield of 41%, was the desired ketol (XIV) identical with a sample prepared by the more lengthy but stereospecific route[16] based on the work of Ireland *et al.*[18] The other ketol (XIII) was obtained in a yield of 19%. The IR spectra of these racemic ketols were identical with the corresponding authentic spectra of the optically active ketols.[11] This rearrangement was unsuccessful when zinc dust and acetic acid was used and resulted in a complete recovery of the starting diketone (XII). Even under the Clemmensen condition longer reaction period caused an increase in the amount of the undesired product (XIII) which was known to be more stable than the desired stereoisomer (XIV).[11] For example, when the mixture was heated for 5 hr, the ratio of the kaurane ketol to the phyllocladane ketol (XIV : XIII) decreased to 1 : 1·6. This ratio was determined by the NMR measurement of the crude reaction product, for the C-10 Me protons of XIII absorbed at δ 0·69 ppm (60 MHz, $CDCl_3$) while those of XIV absorbed at δ 0·88 ppm. The kaurane ketol XIV, therefore, seems to be the product

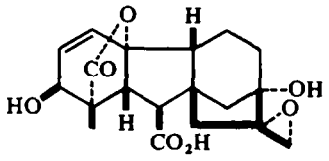
favoured by kinetic control. No attempt was made to trap the postulated cyclopropanediol intermediate. As the details of the conversion of the ketol (XIV, (±)-steviol methyl ester nor-ketone) to (±)-steviol (I) via XV have been reported,[16] this rearrangement completed the total synthesis of (±)-steviol.



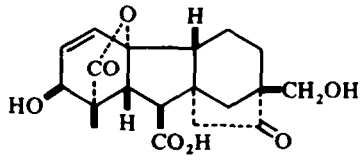
Recently Ziegler and Kloek discovered an interesting rearrangement which led to the synthesis of 1-hydroxy-7-methylene-bicyclo[3.2.1]octane as a gibbane–steviol C/D ring model.[19] Corey and Carney also published a novel synthetic route to this type of compound.[20] Therefore seven different methods are now available for the construction of the gibbane–steviol C/D ring system.[4, 15, 18-22] Three of them have been successfully employed in the syntheses of naturally occurring diterpenes.[4, 15, 18]

Synthesis of erythroxydiol A. The presence of a bridgehead hydroxymethyl group at C-13 is unique to some tetracyclic diterpenes of beyerane group. Erythroxydiol A or hydroxymonogynol (II) is a member of this group isolated from *Erythroxylon monogynum* by two groups of workers.[23-25] We have reported a conversion of (±)-kaur-16-en-19-ol (I, H instead of OH at C-13; CH_2OH instead of CO_2Me) into (±)-monogynol (II, Me instead of CH_2OH at C-13).[26] As another example of this kaurane–beyerane interconversion, erythroxydiol A was synthesized[27] employing an interesting acid-catalysed skeletal rearrangement (F→G) recently discovered in the gibberellin field by Schreiber *et al.*[28, 29] The C/D ring system of the compound G could readily be transformed into that of erythroxydiol A (II).

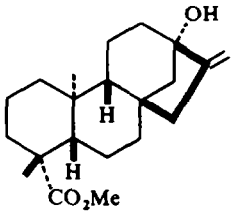
The synthesis started from (−)-steviol methyl ester (XV) whose racemate had been synthesized.[14, 16] Hence any synthesis starting from this diterpene can be regarded as a formal total synthesis. The ester (XV)[9] was oxidized with *m*-chloroperbenzoic acid to give an epoxide (XVI, 78%). This kaurane epoxide (XVI) afforded a beyerane ketol (XVII) in 86% yield upon treatment with a trace of hydrochloric acid in aqueous acetone. Jones chromic acid oxidized the ketol (XVII) to a β-keto acid (XVIII, 48%).



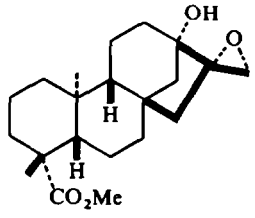
F



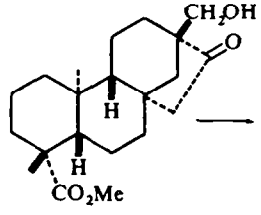
G



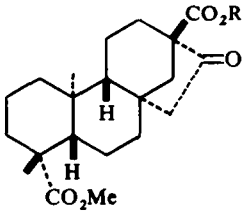
XV



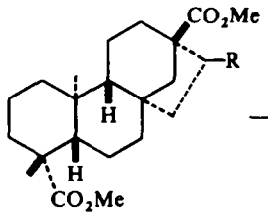
XVI



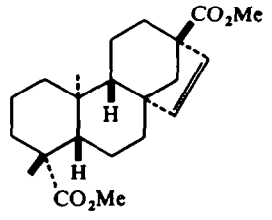
XVII



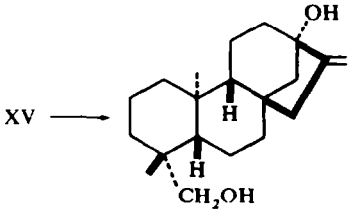
XVIII, R = H
XIX, R = Me



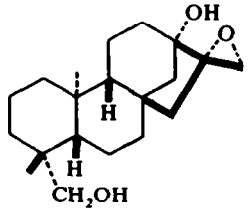
XX, R = α-OH
XXI, R = α-OMs
XXII, R = ξ-Cl



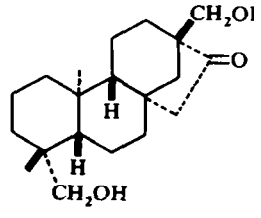
XXIII



XXIV



XXV



XXVI

The corresponding methyl ester (XIX) was obtained quantitatively by esterification with CH_2N_2. This was reduced with sodium borohydride to give a single crystalline hydroxy ester (XX, 94%). The α-configuration was tentatively assigned to the newly generated OH group in analogy with Hanson's work on the borohydride reduction of isosteviol methyl ester (XVII, Me instead of CH_2OH at C-13).[30] The hydroxy ester was treated with methanesulfonyl chloride to give an oily crude methanesulfonate (XXI). This was heated with collidine to give a crude mixture of chloro compound (XXII) and an unsaturated ester (XXIII) which were separated by chromatography. The chloro compound (XXII) was heated with lithium bromide and lithium carbonate to afford an additional amount of the ester (XXIII) as a crude crystalline substance readily soluble in light petroleum. The yield of the unsaturated ester (XXIII) was rather disappointing (*ca* 6% from XX). Reduction of the diester (XXIII) with LAH gave erythroxydiol A (II), which was indistinguishable from the natural product on the basis of m.mp., IR, NMR, MS, ORD and TLC.*

In connection with this kaurane–beyerane transformation, another beyerane alcohol (XXVI) was also synthesized. Reduction of (−)-steviol methyl ester (XV) with LAH gave kaur-16-ene-13,19-diol (XXIV) in a quantitative yield. This was oxidized with *m*-chloroperbenzoic acid to give an epoxide (XXV, 62%).† The acid-catalysed rearrangement of this kaurane epoxide (XXV) afforded *ent*-16-oxo-beyerane-17.19-diol (XXVI) in 51% yield. Thus it was established that this skeletal rearrangement (F→G) was a very useful method for the conversion of steviol-type kauranes into hydroxymonogynol-type beyeranes.

EXPERIMENTAL

All m.ps were uncorrected. IR spectra refer to Nujol mulls for crystalline samples and films for gums unless otherwise stated.

Methyl 3-ethylenedioxycyclohexylacetate (VI). The keto ester Vb (12 g) in benzene (100 ml) was mixed with ethylene glycol (12 ml) and *p*-TsOH (10 mg). The mixture was heated under reflux for 5 hr with continuous removal of water. After cooling, the benzene soln was washed with water, dried over Na_2SO_4 and concentrated. The residue was distilled *in vacuo* to give 12·4 g (82%) of VI, b.p. 107—108°/3 mm, n_D^{25} 1·4658; ν_{max} 1720, 1170, 1095, 1075 cm^{-1}; δ (60 MHz, $CDCl_3$) 3·66 (3H, s), 3·93 (4H, s) ppm.

β-(3-*Ethylenedioxycyclohexyl*) *ethanol* (VII). A soln of VI (47 g) in dry ether (80 ml) was added dropwise to a stirred suspension of LAH (10 g) in dry ether (200 ml) kept below 10° by external cooling. After the addition the mixture was stirred for 2·5 hr at room temp and then for 30 min under reflux. At the end of this period the mixture was cooled in an ice-bath and the excess of LAH was destroyed by cautious addition of water. The ethereal soln was separated and the aqueous layer was extracted with ether. The combined ethereal soln was washed with water and sat NaCl soln, dried (Na_2SO_4) and concentrated. The residue was distilled to give 33·1 g (81%) of VII, b.p. 118–119°/2–3 mm, n_D^{25} 1·4773; ν_{max} 3400, 1150, 1070 cm^{-1}.

3-*Ethylenedioxycyclohexylacetaldehyde* (VIII). The Collins reagent (chromic anhydride–pyridine complex, 190 g) was added portionwise to a stirred soln of the alcohol VII (24 g) in dry CH_2Cl_2 (3·5 l). After the addition, the mixture was stirred for 30 min at room temp. Then it was filtered through Celite and concentrated *in vacuo*. The residue was mixed with ether and filtered through Celite. The ethereal soln was

* Dr. J. R. Hanson of University of Sussex kindly informed us of his independent transformation of steviol into erythroxydiol A in his personal communication to K.M. dated 27 October, 1970.

† The α-configuration is tentatively assigned to the epoxy rings in XVI and XXV in analogy with the previous cases in the gibberellins[28] or kaurene,[31] for attack from the less hindered face of the molecule is generally favoured.

concentrated and the residue was distilled to give 13·2 g (67% based on the amount of VII consumed) of VIII, b.p. 104–105°/3 mm, n_D^{25} 1·4765; ν_{max} 2700, 1710, 1160, 1100, 1070 cm^{-1}; δ (60 MHz, $CDCl_3$) 3·95 (4H, s), 9·73 (1H, t) ppm. As a higher boiling fraction 4 g of VII was recovered.

Bicyclo[2.2.2]*octan*-2-*ol*-6-*one* (IX). The aldehyde VIII (12 g) was added dropwise to dilute phosphoric acid (10 v/v%, 110 ml) at 100°. The mixture was heated at 100° for 2 hr, cooled and extracted with ether. The ethereal soln was washed with water and sat NaCl soln, dried (Na_2SO_4) and concentrated to give crude crystalline IX. The crude product was washed with isopropyl ether to give 3·2 g (35%) of IX. Recrystallization from benzene-n-hexane gave crystals melting at 201° with sublimation; ν_{max} (KBr) 3400, 1710, 1090 cm^{-1}; δ (60 MHz, $CDCl_3$) 2·62 (1H, s, —O<u>H</u>) 4·22 (1H, br.m, —C<u>H</u>OH) ppm. (Found: C, 68·22; H, 8·23. $C_8H_{12}O_2$ requires: C, 68·54; H, 8·63%).

Bicyclo[2.2.2]*octane*-2,6-*dione* (III). The Jones chromic acid (7 ml) was added to a soln of IX (3·2 g) in acetone (100 ml) cooled at 0–5°. After the addition, the mixture was shaken for 5 min at room temp. Then the excess oxidant was destroyed by adding a small amount of MeOH and the mixture was concentrated *in vacuo*. The residue was mixed with water. NaCl was added to salt out the product. The mixture was extracted with ether. The ethereal soln was washed with sat NaCl soln, dried (Na_2SO_4) and concentrated to give 1·8 g (56%) of crystalline III. Recrystallization from isopropyl ether gave pure III, m.p. 191° (sublimable) (lit.[5] 190–191°), ν_{max} (KBr), 1735, 1710 cm^{-1}, δ (60 MHz, $CDCl_3$) 1·9~2·2 (4H, $2CH_2$), 2·4~2·6 (4H, $2C\underline{H}_2CO$), 2·6–2·9 (1H, m, C<u>H</u>), 7·21 (1H, t, $J = 6$ Hz, COC<u>H</u>CO) ppm. (Found: C, 69·44; H, 7·22. Calc. for $C_8H_{10}O_2$: C, 69·54; H, 7·30%).

Reductive rearrangement of the diketone (III)

A. *With zinc and hydrochloric acid.* A soln of III (400 mg) in benzene (100 ml) was added to a mixture of Zn–Hg (from 13 g of mossy Zn), conc HCl (50 ml) and water (40 ml). The mixture was stirred at room temp for 1·5 hr and filtered to remove Zn. The benzene layer was separated and the aqueous layer was extracted with EtOAc. The combined extract was washed with water, dried (Na_2SO_4) and concentrated to give a semi-solid mass. Recrystallization from isopropyl ether-n-hexane gave 46 mg of *bicyclo*[3.2.1]*octan*-1-*ol*-7-*one* (IV). The mother liquor was chromatographed over silicic acid (Mallinckrodt AR, 100 mesh, 3 g). Elution with EtOAc–n-hexane (1:9) gave 89 mg of IV. Thus the total yield of IV was 135 mg (34%). Recrystallization from isopropyl ether-n-hexane gave pure IV, m.p. 191° (sublimable), ν_{max} (KBr) 3400, 1745, 1110, 1060, 1035 cm^{-1}; δ (60 MHz, $CDCl_3$) 1·5–1·8 (6H), 1·8–2·1 (2H), 2·15–2·4 (2H), 2·62 (1H, br), 2·80 (1H, s, —O<u>H</u>) ppm. (Found: C, 68·29; H, 8·57. $C_8H_{12}O_2$ requires: C, 68·54; H, 8·63%).

B. *With zinc and acetic acid.* Zn dust (30 g) was added to a soln of III (300 mg) in AcOH (100 ml) containing water (3 ml). The mixture was stirred and heated under reflux for 7 hr. The hot mixture was filtered to remove Zn and $Zn(OAc)_2$. The filtrate was concentrated *in vacuo*. The residue was dissolved in water and extracted with ether. The ethereal soln was washed with sat $NaHCO_3$ soln and water, dried (Na_2SO_4) and concentrated. The residue was chromatographed over silicic acid (Mallinckrodt AR 100 mesh, 10 g). Elution with benzene–EtOAc (9:1) gave, in the order of elution, III (95 mg, 32%), IV (85 mg, 28%) and IX (32 mg, 11%). They were identified by IR comparison.

C. *With lithium and ammonia.* Lithium (100 mg) was added to a soln of III (300 mg) in THF (10 ml) and liq NH_3 (50 ml). After stirring for 3 hr at Dry Ice–acetone temp, MeOH was added to destroy the excess of Li. After the evaporation of NH_3, the residue was dissolved in water and extracted with ether. The ethereal soln was washed with water and sat NaCl soln, dried ($NaSO_4$) and concentrated. The residual semi-solid was chromatographed over silicic acid (Mallinckrodt AR 100 mesh, 4 g). Elution with benzene–EtOAc (9:1) gave IV (4 mg, 1·3%) and IX′ (63 mg, 21%). The former was identified with an authentic sample by IR comparison. The latter was recrystallized from n-hexane–benzene to give pure IX′, m.p. 225° (dec), ν_{max} (KBr) 3350, 1720, 1090 cm^{-1}; δ (60 MHz, $CDCl_3$) 1·40, 1·70, 1·75, 2·31 (1·1–2·6, 10 H), 3·53 (1H, s, OH), 4·17 (1H, br, C<u>H</u>OH) ppm. (Found: C, 68·09; H, 9·05. $C_8H_{12}O_2$ requires: C, 68·54; H, 8·63%).

Methyl (±)-13-*oxo*-16*ξ*-*hydroxy*-17-*noratisan*-19-*oate* (XI). To a soln of X (1·2 g) in acetone (100 ml), 3N–HCl (30 ml) was added and the mixture heated under reflux for 3 hr. After cooling, water (50 ml) was added and most of acetone was removed *in vacuo*. The residual aqueous soln was extracted with ether. The ethereal soln was washed with sat $NaHCO_3$ soln, water and sat NaCl soln and dried ($MgSO_4$). Removal of the solvent gave a crystalline epimeric mixture of XI (980 mg, 92·5%) which was sufficiently pure for further reaction. Recrystallization from n-hexane–EtOAc gave needles, m.p. 178–179°, ν_{max} (KBr) 3410, 3350, 1720, 1705 cm^{-1}; δ (ppm from TMS at 60 MHz, $CDCl_3$) 0·58 (3H, s), 1·15 (3H, s), 3·59 (3H, s), 4·20 (1H, m). (Found: C, 71·89; H, 9·21. $C_{20}H_{30}O_4$ requires: C, 71·82; H, 9·04%).

Methyl (±)-13,16-*dioxo*-17-*noratisan*-19-*oate* (XII). 8N-Jones chromic acid (1·5 ml) was added to a

soln of XI (670 mg) in acetone (50 ml) at 0–5°. The mixture was shaken for 1 min. The excess oxidant was destroyed by the addition of MeOH and the mixture was concentrated *in vacuo*. The residue was diluted with water and extracted with ether–$CHCl_3$ (4:1). The extract was washed with water and sat NaCl soln and dried ($MgSO_4$). Removal of the solvent gave crystalline XII (630 mg, 95%). An analytical sample was recrystallized from EtOAc, m.p. 230·5°, ν_{max} (KBr) 1745, 1715 cm^{-1}; δ (60 MHz, $CDCl_3$) 0·69 (3H, s), 1·19 (3H, s), 3·62 (3H, s) ppm. (Found: C, 72·47; H, 8·25. $C_{20}H_{28}O_4$ requires: C, 72·26; H, 8·49%).

Reductive rearrangement of XII

Methyl (±)-13-*hydroxy*-17-*norphyllocladan*-16-*on*-19-*oate* (XIII) *and methyl* (±)-13-*hydroxy*-17-*norkauran*-16-*on*-19-*oate* (XIV). A mixture of XII (810 mg), Zn–Hg prepared from mossy Zn (12 g) and $HgCl_2$ (1·2 g), toluene (180 ml), conc HCl (100 ml) and water (80 ml) was stirred and heated under reflux for 1 hr. After cooling, the toluene layer was separated and the aqueous soln was extracted with two 50-ml portions of benzene. The combined organic layer was washed with sat $NaHCO_3$ soln, water and sat NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo*. The obtained solid was washed with n-hexane. Chromatography of the residual crystals on silicic acid (Mallinckrodt AR 100 mesh, 150 g) afforded XIII (154 mg, 19%) and XIV (331 mg, 41%) by elution with benzene–EtOAc (9:1). The nor-ketone XIII was recrystallized from n-hexane–EtOAc, m.p. 196°; ν_{max} (KBr) 3450, 1735, 1720 ($CHCl_3$) 3550, 1745, 1720 cm^{-1}. The IR spectrum in $CHCl_3$ was identical with the authentic spectrum kindly sent to us by Dr. J. A. Waters. δ (60 MHz, $CDCl_3$) 0·69 (3H, s), 1·18 (3H, s), 3·61 (3H, s) ppm. (Found: C, 71·98; H, 8·88. $C_{20}H_{30}O_4$ requires: C, 71·82; H, 9·04%). The nor-ketone XIV was twice recrystallized from n-hexane–EtOAc to give plates, m.p. 217°, ν_{max} (KBr) 3450, 1740, 1720 ($CHCl_3$) 3540, 1745, 1720 cm^{-1}; δ (60 MHz, $CDCl_3$) 0·88 (3H, s), 1·18 (3H, s), 3·61 (3H, s) ppm. This was identical (IR, NMR and mixed m.p.) with an authentic racemic XIV synthesized in an entirely different manner.[16] (Found: C, 71·79; H, 8·93. Calc. for $C_{20}H_{30}O_4$: C, 71·82; H, 9·04%).

Steviol methyl ester 16,17α-*epoxide* (XVI). A soln of *m*-chloroperbenzoic acid (Aldrich Chemical Co., 85% purity, 0·5 g) in benzene (15 ml) was added to a soln of XV (1·0 g) in dioxane (35 ml). The mixture was left to stand at 5° for 5 days and then diluted with EtOAc. The organic soln was washed with $FeSO_4$ soln, water, sat $NaHCO_3$ soln and sat NaCl soln, dried (K_2CO_3) and concentrated *in vacuo*. The residue was twice recrystallized from EtOAc–light petroleum to give 818 mg (78%) of XVI as prisms, m.p. 144–145°, ν_{max} (Nujol) 3580, ~3440, 1720 cm^{-1}; δ (100 MHz, $CDCl_3$) 0·85 (3H, s), 1·18 (3H, s), 2·78; 2·92 (2H, ABq, J = 5 Hz), 3·63 (3H, s) ppm. (Found: C, 72·49; H, 9·19. $C_{21}H_{32}O_4$ requires: C, 72·38; H, 9·26%).

Methyl ent-16-*oxo*-17-*hydroxybeyeran*-19-*oate* (XVII). A soln of the epoxide XVI (755 mg) in acetone (20 ml) was mixed with dil HCl (0·1 ml of conc HCl in 20 ml of water). The mixture was stirred and heated at 50–60° for 20 min and left to stand overnight at room temp. Acetone was removed *in vacuo* and the residue was extracted with EtOAc. The extract was washed with sat $NaHCO_3$ soln and sat NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was recrystallized from EtOAc–light petroleum to give 649 mg (86%) of XVII, m.p. 171–172°. ν_{max} (Nujol) ~3500, 1735 (sh), 1705 (br) cm^{-1}; δ (100 MHz, $CDCl_3$) 0·70 (3H, s), 1·19 (3H, s), 3·46; 3·63 (2H, ABq, J = 12 Hz), 3·62 (3H, s) ppm. (Found: C, 72·12; H, 9·18. $C_{21}H_{32}O_4$ requires: C, 72·38; H, 9·26%).

C-19 *Monomethyl ester of* ent-16-*oxobeyerane*-17,19-*dioic acid* (XVIII). The Jones chromic acid (1·2 ml) was added to an ice-cooled soln of XVII (641 mg) in acetone (60 ml). The mixture was left to stand at room temp for 2 hr and then concentrated *in vacuo*. The residue was diluted with water and extracted with EtOAc. The extract was washed with water and sat NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was triturated with ether to give 321 mg (48%) of XVIII. Recrystallization from EtOAc–light petroleum gave prisms, m.p. 205–206°, ν_{max} (Nujol) ~3400, ~2600, 1745, 1715, 1690, ~970 cm^{-1}; δ (100 MHz, $CDCl_3$) 0·68 (3H, s), 1·19 (3H, s), 3·61 (3H, s) ppm. (Found: C, 69·14; H, 8·28. $C_{21}H_{30}O_5$ requires: C, 69·58; H, 8·34%).

Methyl ent-16-*oxobeyerane*-17,19-*dioate* (XIX). Ethereal CH_2N_2 was added to a soln of the acid XVIII (300 mg) in EtOAc. After 10 min at room temp the soln was concentrated *in vacuo*. The residue was recrystallized from MeOH to give XIX as rods (300 mg), m.p. 168–169°, ν_{max} (Nujol) 1748, 1715, 1220, 1150 cm^{-1}; δ (100 MHz, $CDCl_3$) 0·69 (3H, s), 1·19 (3H, s), 3·62 (3H, s), 3·69 (3H, s) ppm. (Found: C, 70·06; H, 8·47. $C_{22}H_{32}O_5$ requires: C, 70·18; H, 8·57%).

Methyl ent-16α-*hydroxybeyerane*-17,19-*dioate* (XX). $NaBH_4$ (150 mg) was added to a soln of XIX (262 mg) in 95% EtOH (15 ml) and the soln was left to stand at room temp for 3 hr. After the removal of EtOH *in vacuo* the mixture was acidified with ice and dil HCl, and extracted with EtOAc. The extract was washed with water and sat NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo* to give 246 mg (94%) of

XX. Recrystallization from MeOH–H_2O gave prisms, m.p. 143–144°, ν_{max} (Nujol) 3520, 1715, 1695, 1235, 1160, 1060, 980 cm^{-1}; δ (100 MHz, $CDCl_3$) 0·74 (3H, s), 1·16 (3H, s), 3·61 (3H, s), 3·65 (3H, s), 4·45 (1H, m) ppm. (Found: C, 70·03; H, 9·09. $C_{22}H_{34}O_5$ requires: C, 69·81; H, 9·05%).

Methyl ent-16α-*mesyloxybeyerane*-17,19-*dioate* (XXI). To a soln of XX (250 mg) in pyridine (4 ml), MsCl (200 mg) was added at 0–5° and the soln was left to stand at room temp for 2 days. Then the mixture was poured into ice and dil HCl, and extracted with ether. The ethereal soln was washed with dil HCl, water, sat $NaHCO_3$ soln and sat NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo* to give 250 mg of a gummy XXI, ν_{max} (film) 1715, 1380, 1250, 1190, 980, 760 cm^{-1}; δ (100 MHz, $CDCl_3$) 0·78 (3H, s), 1·20 (3H, s), 3·03 (3H, s), 3·62 (3H, s), 3·68 (3H, s), 5·30 (1H, m) ppm.

Treatment of XXI *with collidine*

Methyl ent-*beyer*-15-*ene*-17,19-*dioate* (XXIII) *and methyl* ent-16ξ-*chlorobeyerane*-17,19-*dioate* (XXII). A soln of XXI (250 mg) in collidine (5 ml) was heated under reflux for 4 hr, cooled, diluted with ether and washed with dil HCl. The extract was washed with dil HCl, water, sat $NaHCO_3$ soln and sat NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over alumina (Wako Pure Chemicals, 8·5 × 1·5 cm) in light petroleum. Elution with light petroleum–ether (3 : 1 ~ 1 : 1) gave XXIII (5 mg) and XXII (51 mg). The latter was recrystallized from EtOAc–light petroleum to give prisms, m.p. 165–169° (sinter at 150°), ν_{max} (Nujol) 1720, 1700, 1240, 1120 cm^{-1}; δ (100 MHz, $CDCl_3$) 0·74 (3H, s), 1·20 (3H, s), 3·62 (3H, s), 3·69 (3H, m), 4·15 (1H, m) ppm; Beilstein test positive; M^+ 395. This chloro compound XXII (39 mg) was dissolved in DMF (5 ml) and heated under reflux for 5 hr with LiBr (100 mg) and Li_2CO_2 (20 mg). After the removal of the solvent, the residue was diluted with water and extracted with ether. The ethereal soln was washed with water and sat NaCl soln, dried ($MgSO_4$) and concentrated to give a gum. This was chromatographed over alumina (Wako Pure Chemicals, 6 × 1·5 cm) in light petroleum. Elution with light petroleum–ether (3 : 1) gave 10 mg of XXIII as needles readily soluble in light petroleum, ν_{max} (Nujol) 1720, 1710 (sh), 1300, 1280, 1260, 1240, 1190, 1160, 1090, 750 cm^{-1}; δ (100 MHz, $CDCl_3$) 0·63 (3H, s), 1·22 (3H, s), 3·63 (3H, s), 3·67 (3H, s), 5·75; 5·87 (2H, ABq, J = 6 Hz) ppm.

ent-*Beyer*-15-*ene*-17,19-*diol* (= *Erythroxydiol A, hydroxymonogynol*, II). LAH (60 mg) was added to a soln of XXIII (13 mg) in dry ether (5 ml). The mixture was stirred and heated under reflux for 2·5 hr. A small amount of water was added to destroy the excess of LAH and the ethereal soln was dried ($MgSO_4$) and concentrated *in vacuo* to give 8 mg of crystalline II. Recrystallization from EtOAc–light petroleum gave prisms, m.p. 180–181° (lit.[25] 179–181°) ν_{max} (Nujol) ~3250 (br.s), 1290 (w), 1230 (w), 1220 (w), 1160 (w), 1130 (w), 1095 (w), 1080 (m), 1060 (sh), 1035 (s), 1025 (s), 1005 (m), 980 (w), 930 (w), 760 (w), 745 (s), 730 (m) cm^{-1}; δ (100 MHz, $CDCl_3$) 0·75 (3H, s), 0·99 (3H, s), 3·48 (2H, br.s), 3·44; 3·77 (2H, ABq, J = 12 Hz), 5·56; 5·78 (2H, ABq, J = 6 Hz) ppm; M^+ 304; TLC, R_f 0·38 (Kieselgel G, EtOAc–benzene 1 : 1). This was identified with an authentic sample by mixed m.p. and comparisons of IR, NMR, MS, TLC and ORD (plain positive curve). (Found: C, 78·73; H, 10·40. $C_{20}H_{32}O_2$ requires: C, 78·89; H, 10·59%).

ent-*Kaur*-16-*ene*-13,19-*diol* (XXIV). A soln of XV (950 mg) in dry ether (40 ml) was added at 0–5° to a stirred suspension of LAH (0·4 g) in dry ether (40 ml). After addition, the mixture was stirred and heated under reflux for 1 hr and then left to stand overnight at room temp. The mixture was treated with a small amount of water to destroy the excess of LAH, filtered through Celite and extracted with EtOAc. The extract was washed with water and sat NaCl aq, dried ($MgSO_4$) and concentrated to give 869 mg (quantitative) of XXIV. Recrystallization from MeOH–EtOAc gave needles of pure XXIV, m.p. 243–244°, ν_{max} (Nujol) ~3300, 1660, 1015, 875 cm^{-1}; δ (100 MHz, DMSO-d_6) 0·89 (3H, s), 0·98 (3H, s), ~3·65 (4H, br, $C\underline{H}_2OH$), ~4·85 (2H, br, $=CH_2$) ppm. (Found: C, 78·53; H, 10·37. $C_{20}H_{32}O_2$ requires: C, 78·89; H, 10·59%).

15, 16α-*Oxido*-ent-*kaurane*-13,19-*diol* (XXV). A soln of *m*-chloroperbenzoic acid (Aldrich Chemical Co., 85% purity, 0·5 g) in benzene (50 ml) was added to a soln of XXIV (700 mg) in dioxane (120 ml). The mixture was left to stand at 5° for 5 days and then diluted with EtOAc. The organic soln was washed with $FeSO_4$ soln, water, sat $NaHCO_3$ soln and sat NaCl soln, dried (K_2CO_3) and concentrated in *vacuo*. The residue was recrystallized from EtOAc–light petroleum to give 460 mg (62%) of XXV as prisms, m.p. 189–190°, ν_{max} (Nujol) ~3400, 1040, 1020, 790, 770 cm^{-1}; δ (100 MHz, $CDCl_3$) 1·10 (3H, s), 1·15 (3H, s), 2·78; 2·93 (2H, ABq, J = 5 Hz) 3·43; 3·75 (2H, ABq, J = 10 Hz) ppm. (Found: C, 74·22; H, 9·73. $C_{20}H_{32}O_3$ requires: C, 74·96; H, 10·06%).

ent-16-*Oxobeyerane*-17,19-*diol* (XXVI). A soln of XXV (428 mg) in acetone (20 ml) was mixed with dil

HCl (0·1 ml of conc HCl in 25 ml of water). The mixture was stirred and heated at 50° for 10 min and left to stand overnight at room temp. Acetone was removed *in vacuo* and the residue was extracted with EtOAc. The extract was washed with sat $NaHCO_3$ soln and sat NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was triturated with ether to give 220 mg (51%) of XXVI. Recrystallization from EtOAc–light petroleum gave fine prisms, m.p. 181–182°, ν_{max} (Nujol) ~3400 (br), 1735, 1030 cm^{-1}; δ (100 MHz, $CDCl_3$) 0·90 (3H, s), 1·03 (3H, s), 3·55–3·80 (4H, m, $C\underline{H}_2OH$) ppm. (Found: C, 74·15; H, 9·88. $C_{20}H_{32}O_3$ requires: C, 74·96; H, 10·06%).

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