Beyerane Diterpenes: Structure and Reactivity of the α-Ketol *ent*-3β-Hydroxybeyer-15-ene-2,12-dione, its Corresponding Diosphenol, and Synthesis of the Isomeric α-Ketol Acetates

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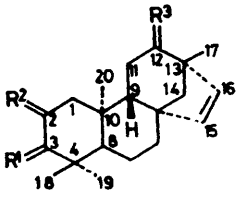
The major diterpenoid constituents of the heartwood of the Euphorbiaceae *Androstachys johnsonii* Prain are *ent*-3β-hydroxybeyer-15-ene-2,12-dione and the corresponding 2,3,12-trione. The four isomeric 2,3-α-ketol acetates were prepared by new and established methods and the chemistry of these α-ketols was investigated. A condensation reaction with ethylene glycol led to the useful ring A 2,3-ethylenedioxy blocking group. The 12-equatorial alcohol was eliminated yielding the new tetracyclic skeleton *ent*-14(13 → 12)*abeo*-beyerane. The *ent*-3β-hydroxy-2-ketone function was epimerised to the *ent*-3α-acetoxy-2-ketone function *via* the derived pyrrolidine enamine.

THE heartwood of the Euphorbiaceae *Androstachys johnsonii* Prain, known as the Lebombo Ironwood and indigenous to Southern Africa, contains oxygenated tetracyclic diterpenoids of the *ent*-beyerane class.[1,2]

The major constituents proved to be the α-ketol, *ent*-3β-hydroxybeyer-15-ene-2,12-dione (1) and the corresponding diosphenol, *ent*-2-hydroxybeyer-1,15-diene-3,12-dione (2) isolated in both the enolic and ketonic



	R^1	R^2	R^3	
(1)	α-OH	O	O	
(2b)	O	O	O	
(3)	α-OH	NOH	NOH	
(4)	α-OH	H_2	H_2	
(5)	α-OH	$-SCH_2CH_2S-$	$-SCH_2CH_2S-$	
(6)	α-OH	H_2	H_2	(15,16-Dihydro)
(7)	α-OAc	O	O	
(8)	α-OH	α-OH	α-OH	
(10)	α-OH	O	O	(15,16-Dihydro)
(11)	α-OAc	O	O	(15,16-Dihydro)
(13)	α-OBz	O	O	
(14)	α-OBz	O	β-OH	
(15)	α-OBz	O	α-OH	
(16)	α-OBz	O	α-OMS	
(19)	O	β-OAc	O	
(20)	α-OH	β-OH	α-OH	
(21)	O	α-OAc	O	(15,16-Dihydro)
(23)	α-OH	α-OH	β-OH	(15,16-Dihydro)
(24)	β-OAc	O	O	
(31)	α-OTs	O	O	
(32)	α-OBz	$-OCH_2CH_2O-$	$-OCH_2CH_2O-$	
(33)	α-ONO_2	O	O	

forms. The preponderance of the ketol or the diosphenol varied in the different batches of wood which were collected. The structure determination of the two compounds (1) and (2) was carried out with the α-ketol (1) since they could readily be interconverted.

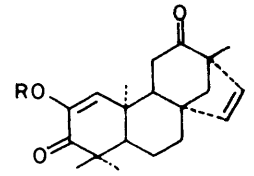
A positive colour reaction with alkaline triphenyltetrazolium chloride (TTC) indicated the presence of an easily oxidizable function, further confirmed by Bi_2O_3 oxidation [3] of (1) to the diosphenol (2α). I.r. and n.m.r. spectroscopy clearly indicated the presence of four tertiary methyl groups, carbonyl functionality, one secondary hydroxy-group whose methine proton was not coupled to any adjacent C–H protons, and an isolated 1,2-disubstituted olefinic double bond as a 2 H, AB quartet. Furthermore, the formation of a dioxime (3) from the ketol (1) confirmed the presence of two carbonyl groups whilst Huang-Minlon reduction of this ketol gave several compounds, of which the major oxygenated derivative proved to be identical to *ent*-3β-hydroxybeyer-15-ene (4),[4,†] which was also present in the heartwood extract in considerable amounts. This established the *ent*-beyerane skeleton, the position of the hydroxy-group at C-3, and the double bond between carbons 15 and 16. The hydroxy-group configuration could not be assigned with certainty by the conversion of (1) into (4) since under the extremely basic deoxygenation conditions α-ketols readily undergo isomerisation. Therefore the bis-ethylenedithio-acetal (5) was prepared and desulphurised with Raney nickel giving the known *ent*-beyerane-3β-ol (6)[4] (concomitant saturation of the double bond occurred) thereby clearly defining the *ent*-3β-hydroxy-configuration of (1).

Whereas the i.r. spectrum of (1) had a single strong carbonyl absorption at 1 705 cm^{-1}, the acetylated derivative (7) had three clearly defined peaks at 1 740, 1 720, and 1 692 cm^{-1}. The lowering of one of the carbonyl frequencies from 1 720 to 1 705 cm^{-1} in (1) was attributed to an intramolecular hydrogen bond between this carbonyl function and a neighbouring hydroxy-group, confirming their close spatial disposition. Furthermore the α-ketol (1) was reduced with $NaBH_4$ to an *ent*-2β,3β,12β-triol (8) (see later evidence) which readily yielded an acetonide (9). This evidence established the part structure for (1) as *ent*-3β-hydroxybeyer-15-en-3-one with the second isolated keto-group not yet placed. The isolated carbonyl function seemed to be influenced by the *olefinic* double bond by means of a homoconjugation effect typical of the π orbital interactions of β,γ-unsaturated ketones, since the abnormally high u.v. extinction coefficient of ε 240 at $\lambda_{max.}$ 296 nm suffered a

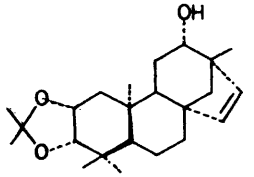
† The m.p. quoted in ref. 4 for compound (4) seems high since samples of (4) from both natural and synthetic sources were prepared in the course of this work and when pure by t.l.c. consistently melted at 159—161 °C.

considerable reduction in intensity to ε 70 at $\lambda_{max.}$ 284 nm on hydrogenation to (10). Similarly the c.d. data indicated π orbital interaction as the Δε values for (1) and (10) were −16.30 and −4.37 respectively. Comparison of the i.r. spectra of the acetate (7) and its dihydro-derivative (11) also showed an increase in carbonyl frequency from 1 692 to 1 708 cm^{-1} respectively, implying an extended carbonyl π orbital in (7).

Bromination of the dihydroketol acetate (11) gave a crystalline monobromide (12) in good yield. The n.m.r. spectrum of (12) showed the proton geminal to the halogen as a doublet at δ 4.23, consistent only with a 6-bromo-7-ketone or an 11-bromo-12-ketone. Since the above described homoconjugation evidence suggested a 12-ketone the D-homo-C-nor rearrangement characteristic



(2a) R = H
(22) R = Ac



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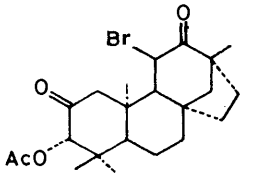

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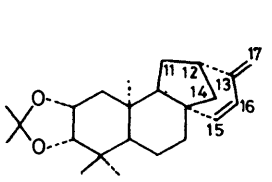

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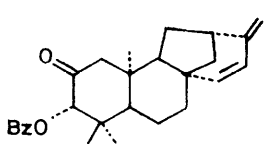

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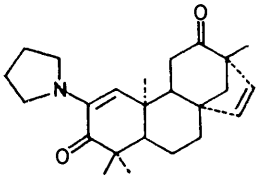

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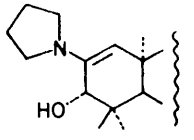

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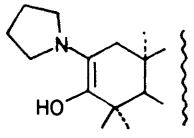


(27)

of 12-equatorial steroidal alcohols [5] was envisaged as a solution to the problem. Initially the α-ketol benzoate (13) was reduced with $NaBH_4$ in 40% conversion to give several compounds from which the *ent*-12α- and *ent*-12β-ols, (14) and (15) respectively, were separated by chromatography, the equatorial isomer (15) predominating (91% *versus* 6.7%), clearly indicating preferential hydride attack from the less hindered *ent*-α-face of ring C. This alcohol (15) was converted into the 12-mesylate (16) which on acetolysis in buffered acetic acid gave the beyerane D-homo-C-nor conjugated diene (17) as shown by u.v. and n.m.r. data. This evidence established the 12-position as the locus of the second carbonyl group.

The reaction sequence starting with the ketol (1) to produce the C/D ring rearranged 14(13 → 12)*abeo*-beyera-15(16),13(17)-diene system as in (17) was tedious and of a low overall yield because of the unselectivity of the reduction step. A superior route to this *abeo*-system involved the conversion of the triol (8) [readily available in large quantities by $NaBH_4$ reduction of the mother liquors of (1) or (2)] to its acetonide (9) and treatment of the latter with $POCl_3$ in pyridine, giving the D-homo-C-nor diene acetonide (18) in at least 65% overall yield.

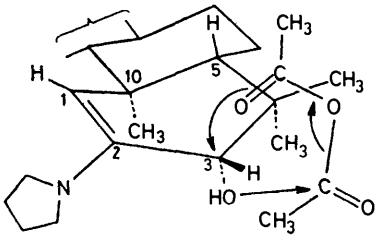
The α-ketol group is found in several natural products such as the cucurbitacins and terpenoids in general and is a readily-prepared function *via* the acyloin condensation, enolate oxidations,[6a-c] epoxidation of enol esters,[6d] α-dithian ketones,[7a-f] and from vicinal diols.[8] In the case of steroidal and diterpenoid 2,3-ketols four isomers are possible and new as well as established methods for their preparation were investigated. At the same time this study provided an additional independent proof of the assigned *ent*-3β-hydroxy-2-one configuration of (1). The strategy involved the unambiguous preparation of the isomeric *ent*-2β,3β,12β- and *ent*-2α,3β,12β-triols and the comparison of these two to the triol (8) obtained from the α-ketol (1). Heating an acetic anhydride solution of the α-ketol (1) in the presence of anhydrous aluminium trichloride gave a 7 : 3 mixture of equatorial acetates: *ent*-3β-acetoxybeyer-15-ene-2,12-dione (7) and the new *ent*-2α-acetoxybeyer-15-ene-3,12-dione (19) which were separated readily by crystallisation. The structure of (19) was ascertained from its n.m.r. spectrum since the axial methine proton at C-2 appeared as a quartet (*J* 6.0 and 13.0 Hz), consistent with published data.[8,9a-e] In the case of 4,4-dimethyl-2,3-ketols with *trans*-fused A/B steroid type ring systems the equatorial 3-hydroxy-2-ketone is favoured on thermodynamic equilibration over the equatorial 2-hydroxy-3-ketone isomer and this evidently held true in this instance. No traces of the epimeric 2-axial or 3-axial hydroxy-ketones were evident in the n.m.r. spectrum of the crude reaction mixture.

$NaBH_4$ reduction of the equatorial *ent*-2α-acetoxy-compound (19) gave the *ent*-2α,3β,12β-trihydroxybeyer-15-ene (20)* dissimilar to the triol (8) obtained from the original α-ketol (1) by similar reduction. Thus the triol (8) did not possess the *ent*-2α,3β-diol configuration and could have been an *ent*-2α,3α-, *ent*-2β,3β- or *ent*-2β,3α-diol in ring A. The *ent*-12β-alcohol configuration would be expected to remain constant in all cases. Since the configuration expected to be correct for (8) was *ent*-2β,3β,12β this triol configuration was prepared next. The axial *ent*-2β-acetoxybeyerane-3,12-dione (21) was obtained *via* catalytic hydrogenation of the diosphenol acetate (22).[10] $NaBH_4$ reduction of (21) in wet ethanol [11] and alkaline hydrolysis gave the expected *ent*-2β,3β,12β-

* In the *ent*-beyerane series, predominant hydride attack of a carbonyl at C-2 or C-3 from the less hindered *ent*-α-face is well established by analogy to similar terpenoid systems—see ref. 9*a*.

trihydroxybeyerane (23) identical in all respects to the catalytic hydrogenation product of the triol (8), and thus confirming the *ent*-3β-configuration for the 3-hydroxy-group in the ketol (1).

The fourth isomeric ketol acetate (24) [12] with an *ent*-3α-acetoxy-group was prepared *via* a novel reaction for α-ketols, although precedence does exist for alkyl substituted cyclohexanones.[13a,b] Reaction of the *ent*-3β-hydroxy-2-one (1) in boiling benzene with pyrrolidine and toluene-*p*-sulphonic acid under argon and quenching the reaction with acetic anhydride led to the isolation of the epimeric *ent*-3α-acetoxy-2-one (24) (its $NaBH_4$ reduction yielded the new triol *ent*-2β,3α,12β-trihydroxybeyer-15-ene). If air was allowed to enter the reaction system the compound isolated in a high yield was the 2-pyrrolidinyl-1-en-3-one (25) also obtainable in a high yield from the diosphenol (2) in methanol with pyrrolidine without acid catalysis. Two intermediates could be envisaged to yield the final *ent*-3α-acetoxy-2-ketone product: one would involve the allylic enamino-alcohol (26) with a 1,2-double bond, which could then suffer allylic epimerisation on attack by acetic anhydride *via* a C–O bond fission with concerted C–O bond formation from the upper face of the molecule in a 6-centred transition state.



(26)

H^+

(24)

However the driving force for this reaction is not apparent.

The alternative pathway would involve the vinyl enamino-alcohol (27). Dreiding models show that ring A of (27) is in a twist-boat conformation and this allows axial protonation to occur at C-3 from the lower, *ent*-β face thus giving the kinetic product (24) after acetylation.* However a CPK space-filling model of (27) indicates that the lower face is sterically considerably crowded and, in fact, most reagents approach the *ent*-beyerane molecule from the upper face. The latter mechanism is in line with previous work [13a] on enamines of 2-alkylcyclohexanones, which on protonation yielded a preponderance of the thermodynamically less-stable axial alkylcyclohexanones. Attempts to resolve this ambiguity by isolating the intermediate compound were unsuccessful since oxidation to (25) occurred very readily. However, by performing the reaction in an n.m.r. tube an indication that the second mechanism *via* (27) seemed more probable was obtained since the 3-methine proton signal disappeared over a period of time. Work is in progress to clarify the mechanism using suitably isotopically labelled compounds.[13b] The enaminoketone (25) was very stable to alkaline conditions: it was successfully recovered in high yield after several hours refluxing in alkaline methanol. However acid hydrolysis regenerated the 2,3-dione system as the yellow unenolised 2,3-diketone (2b) and this therefore represents a very mild alternative method to oxidize α-ketols to α-diketones. Surprisingly heterogeneous catalytic hydrogenation even under high pressure failed to saturate the enamine double bond of (25).

The influence of the 15,16-double bond on the angular methyl group at C-10 is well established in the beyerene series, and results in a marked upfield shift of the 19-H protons. For example the n.m.r. signal for this methyl group in (7) appears at δ 0.75 whereas on hydrogenation to (11) the signal appears at δ 0.96. The C-3 methine proton however does not undergo much change [from δ 4.92 to δ 4.93 for (7) and (11) respectively] since it is on the opposite side of the molecular plane to the olefinic bond. However, in the *ent*-3α-acetates [(24) and its 15,16-dihydro-derivative] the signal for the *ent*-3β-proton appears at δ 4.70 and 4.77 respectively, implying a shielding effect by the olefinic π-bond of 0.07 p.p.m. on this C-3 methine proton which is on the same side of the molecule as the double bond. Thus ring A for the ketol *ent*-3α-acetates is probably in a twist or boat form bringing the C-3 proton perpendicular to the π-bond electrons.

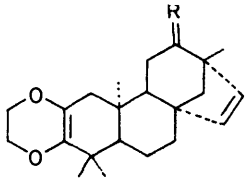
The chemistry of the α-ketol and α-diketone group in (1) and (2) respectively was investigated in some detail. Some of this work has been reported [12,14] and other aspects will be discussed here.

Reaction of (1) with ethylene glycol in refluxing toluene in the presence of a small amount of toluene-*p*-sulphonic acid gave an excellent yield of the 12-ethylenedioxy-acetal (28).[15] The 12-protecting group was readily removed by a trace of acid giving (29). Compound (28) was also prepared from (1) in dry benzene with ethylene glycol and a large excess of BF_3–Et_2O, but the former procedure was much simpler to use. The ring A ethylenedioxy-group was stable to acid even after prolonged boiling with methanolic HCl. Catalytic reduction with platinum and hydrogen at 50 atmospheres reduced the 15,16-double bond, but failed to hydrogenate the 2,3-double bond although the 12-carbonyl group was partially reduced in all attempts to a mixture of the 12-equatorial (major) and 12-axial alcohols. This resistance to undergo hydrogenation is in marked contrast to the simple analogue (30) prepared from benzoin.[16] Conditions which converted (1) into (28) were also successful when the α-ketol tosylate (31) was used. However, the *ent*-3β-benzoyloxy-2,12-dione (13) gave an excellent yield of the *ent*-3β-benzoyloxy-bis-2,12-acetal (32), whose 12-acetal was selectively hydrolysed by mild acid treatment. Analogous compounds to (28) were also

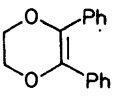
* We thank one of the referees for suggesting the inclusion of this discussion which had already been presented by one of us.[2]

prepared using 2-mercaptoethanol and ethane-1,2-dithiol.

The α-ketol (1) gave a good yield of the nitrate ester (33) by reaction with nitric acid in acetic acid–acetic anhydride. This compound (33) was converted into the



(28) R = —OCH_2CH_2O—
(29) R = O



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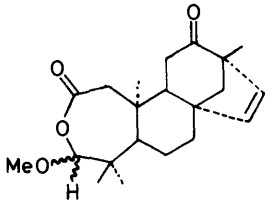

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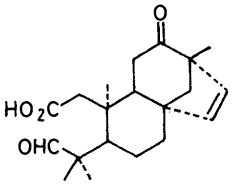

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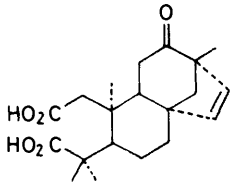
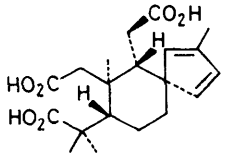


(36)
(37) 15, 16-Dihydro



(38)

vicinal diketone (2) on treatment with sodium acetate in Me_2SO.[17] Oxidation of the α-ketol function of (1) with periodic acid [18] in aqueous methanol gave the 7-membered ring lactone-acetal (34) *via* the intermediate seco-aldehydic acid (35) (which was not isolated.) Oxidation with alkaline hydrogen peroxide converted the diosphenol (2a) into the A-seco-dicarboxylic acid (36). This reaction was also brought about using periodate–permanganate [4] on (10) giving (37). When the α-ketol (1) was oxidised with H_2O_2–NaOH a new spiro-compound (38) was obtained instead, in which stereoselective Bayer–Villiger oxidation of the 12-ketone had taken place followed by dehydration as well as ring A cleavage. This spiro-compound is of interest because of its superficial similarity to the spiro[4.5]decane sesquiterpenes.[19]

EXPERIMENTAL

General.—The following generalisations apply unless otherwise stated. All melting points were determined on a Kofler micro hot-stage and are uncorrected. Optical rotations were measured on a Perkin-Elmer 141 M automatic polarimeter at 589 nm using chloroform solutions at room temperature. I.r. spectra are reported for KBr dispersions and recorded on a Perkin-Elmer 521 spectrometer. U.v. spectra were recorded on a Beckman DB grating instrument for 95% ethanol solutions: $\lambda_{max.}$ values are followed by ε values in parenthesis. Mass spectra were obtained on an AEI MS9 double-focusing mass spectrometer. N.m.r. spectra were recorded for $CDCl_3$ solutions (*ca.* 40 mg per 0.2 ml), using $SiMe_4$ as an internal standard on a Varian T60, HA100 or FT100-15 spectrometer system. G.c. analysis was performed on a Pye Unicam 104 single column instrument with a flame-ionisation detector. A glass column (2.13 m × 4 mm) packed with SE 30 (2% on Chromosorb-W-HMDS) at 225 °C was used. Silica gel for column chromatography was Merck 7734.

The TTC test (triphenyltetrazolium chloride) was performed on 2—3 mg of compound in methanol (1—2 ml) with 5—10 mg of TTC reagent in the cold. 10% Aqueous NaOH was added dropwise (2—5 drops) and a red colour developed within seconds for α-ketols and their esters and reported as +ve or −ve TTC throughout.

Isolation of the Hexane-soluble Heartwood Constituents.—The milled, air-dried heartwood was extracted three times with cold hexane, the last extract being colourless whilst the first two were yellow. Evaporation of the combined extracts deposited masses of colourless crystals and a further crop was obtained after concentrating the mother liquor. The total hexane extract was 14.7% of which 41% was pure, isolatable α-ketol, ent-3β-*hydroxybeyer*-15-*ene*-2,12-*dione* (1).

The yield of diosphenol (2) was not determined accurately, but although considerable, it was lower than that of the α-ketol.

Extraction with hot hexane did not increase the yield. The major constituent in wood (NDO 133) was the α-ketol (1) but from the wood obtained from two further trees (NDO 140 and NDO 141) it was the diosphenol ent-2-*hydroxybeyer*-1,15-*diene*-3,12-*dione* (2a). (Relevant Kruger National Park Herbarium specimens are deposited under the references Codd: 4 567 and v.s. Schyft: 978 or 2 310).

Pure (1) or (2a) was obtained by crystallisation from hexane–ethanol, ether–dichloromethane, or aqueous methanol.

The bitter tasting *α-ketol* (1) was isolated as colourless rods, (+ve TTC), m.p. 163—165.5 °C, $[\alpha]_D$ −329° (*c* 2.0); $\lambda_{max.}$ 296 (240) and 215 nm (4 110); $\Delta\varepsilon(\lambda_{max.})$ −16.30 (295) and +7.35 (203 nm); $\nu_{max.}$ 3 525 (b), 1 705 (b), and 767 cm^{-1}; δ 0.68 (3 H, s, 20-H_3), 0.72 (3 H, s, 19-H_3), 1.08 (3 H, s, 17-H_3), 1.18 (3 H, s, 18-H_3), 3.73br (1 H, s, exchanges with D_2O, 3-OH), 3.90 (1 H, s, *ent*-3α-H), and 5.62 and 6.00 (2 H, ABq, $J_{15,16}$ = 5.5 Hz, 16- and 15-H respectively) (Found: C, 75.73; H, 8.85%; M^+ 316.202 2; $C_{20}H_{28}O_3$ requires C, 75.91; H, 8.92%; M^+ 316.203 8).

The *diosphenol* (2a) was isolated as prisms (brown $FeCl_3$ test), m.p. 170—173 °C, $[\alpha]_D$ −374° (*c* 2.3); $\lambda_{max.}$ 270 (9 420) and 210 nm (3 670); $\lambda_{max.}$ NaOH 313.5 (4 920) and 215 nm (3 599); $\nu_{max.}$ 3 410, 3 055, 1 700, 1 667, 1 648, 1 570, 963, 867, and 765 cm^{-1}; δ 1.10, 1.12, 1.13, and 1.25 (4 × 3 H, 4 × s, 4 × methyl), 5.71 and 6.10 (2 H, ABq, J = 5.5 Hz, 16-H and 15-H respectively), and 6.12 (2 H, s, one H exchangeable with D_2O 1-H and enolic 2-OH) (Found: C, 74.7; H, 8.25%; M^+ 314.188 0. $C_{20}H_{26}O_3 \cdot \frac{1}{2}H_2O$ requires C, 74.27; H, 8.42%; M^+ 314.188 1).

Bismuth(III) *Oxidation* [3] *of the α-Ketol* (1) *to the Diosphenol* (2a).—A solution of (1) (3.0 g) in glacial acetic acid (40 ml) was refluxed with Bi_2O_3 (4.5 g) for 0.5 h. The cooled reaction mixture was decanted from the solids which were washed with hot acetic acid (10 ml). The dark brown residue, obtained on evaporation of the combined acetic acid solutions, was taken up in benzene (10 ml) and chromatographed on silica gel (60 g). Elution with 2% ethyl acetate

in benzene gave the diosphenol (2a), which was crystallised from aqueous methanol as large prisms (1.5 g). This diosphenol gave a brown colour with methanolic ferric chloride and was identical in all respects to the material obtained from the heartwood.

Preparation of ent-3β-*Hydroxybeyer*-15-*ene*-2,12-*dione* 2,12-*Dioxime* (3).—To a solution of the α-ketol (1) (1.0 g) in ethanol (20 ml) and pyridine (5 ml) was added a solution of hydroxylamine hydrochloride (1.5 g) in water (5 ml) and the mixture was refluxed overnight. Removal of the ethanol under reduced pressure and dilution of the residue with water gave a solid *dioxime* (3) which crystallised from a large volume of ethanol as cubes, m.p. 275—277 °C (decomp), $[\alpha]_D$ −133° (*c* 2.11); $\nu_{max.}$ 3 475, 3 400 (b), 1 660, 1 655, 1 445, 1 405, 1 380, 905, and 708 cm^{-1} (Found: C, 68.9; H, 8.85; N, 7.9%; M^+ 346.226 9. $C_{20}H_{30}N_2O_3$ requires C, 69.33; H, 8.73; N, 8.09%; M^+ 346.225 6).

ent-3β-*Hydroxybeyer*-15-*ene*-2,12-*dione* 2,12-*Dioxime* OO′-*Diacetate*.—The dioxime (3) (0.71 g, absolutely free of pyridine) was suspended in acetic anhydride (10 ml) and heated briefly (1 min) until a clear solution had been obtained which was kept in the ice chest overnight. The solid *dioxime diacetate* obtained on pouring this solution into water crystallised as needles from aqueous methanol (0.82 g), double m.p. 106—110 and 160—164 °C (decomp.); $[\alpha]_D$ +7° (*c* 2.2); $\nu_{max.}$ 3 555, 3 494, 3 290 (b), 3 060, 1 746, 1 644, 1 625, 1 605, 1 213 (b), and 763 cm^{-1}; δ 0.70, 0.78, 1.18, and 1.31 (4 × 3 H, 4 × s, 4 × methyl), 2.23 (6 H, s, 2 × acetate), 3.96 (1 H, s, *ent*-3α-H), and 5.65 and 5.92 (2 H, ABq, J = 5.5 Hz, 16-H and 15-H respectively) (Found: N, 6.05. $C_{24}H_{32}N_2O_5$ requires N, 6.40%).

Huang-Minlon Reduction of the α-Ketol (1).—A mixture of the α-ketol (1) (1.5 g), ethanol (20 ml), hydrazine hydrate (5 ml), and digol (45 ml), was refluxed for 30 min; it was then cooled before KOH (7.5 g) in H_2O (10 ml) was added to the solution, followed by a further reflux period of 3.5 h. At this point the mixture was distilled until the internal temperature had reached 210 °C, when refluxing was continued for 2.5 h. Finally the cooled reaction mixture was acidified with dilute HCl, poured into ice–water (200 ml) and thoroughly extracted with hexane. The extract was dried and concentrated before chromatography on silica gel (60 g in hexane). Elution with hexane gave a hydrocarbon fraction which by g.c. consisted of *ent*-beyer-15-ene (67%) and two other hydrocarbons (20% and 13%). Crystallisation of the hydrocarbon fraction from ethanol at 0 °C gave waxy crystals, m.p. 35—40 °C (lit.,[20] m.p. 29.5—30 °C for *ent*-beyer-15-ene); $[\alpha]_D$ +28° (*c* 0.78) (Found: M^+ 272.251 0. $C_{20}H_{32}$ requires M^+ 272.250 4. Peaks at $M^+ + 2$ and $M^+ - 2$ were also found indicating the presence of the other two by-products of the reduction).

Further elution of the silica gel column with benzene–hexane–ethanol (50 : 50 : 0.25 parts by volume respectively) gave *ent*-3β-hydroxybeyer-15-ene (4) which crystallised from aqueous ethanol as needles, m.p. 159—161 °C (lit.,[4] 164 °C), $[\alpha]_D$ +36° (*c* 1.0) (lit.,[4] +28°); $\nu_{max.}$ 3 300 (b), 3 030, 1 590, 1 045, and 750 cm^{-1}; δ 0.73 (3 H, s, 20-H), 0.77 (3 H, s, 19-H), 0.98 (6 H, s, 17- and 18-H_3), 3.18 (1 H, m, $W_{\frac{1}{2}}$ 18 Hz, *ent*-3α-H, and 5.43 and 5.67 (2 H, ABq, $J_{15,16}$ = 5.5 Hz, 16- and 15-H respectively) (Found: M^+ 288.246 1. Calc. for $C_{20}H_{32}O$: M^+ 288.245 3).

Acetylation of (4) (32 mg) gave *ent*-3β-acetoxybeyer-15-ene (32 mg from aqueous methanol) m.p. 121—123.5 °C (lit.,[4] 117.5—119.5 °C); $[\alpha]_D$ +13° (*c* 2.1) (lit.,[4] +12°), $\nu_{max.}$ 1 720, 1 240, 750, and 737 cm^{-1} (Found: M^+ 330.256 0. Calc. for $C_{22}H_{34}O_2$: M^+ 330.255 9).

ent-3β-*Hydroxybeyer*-15-*ene*-2,12-*dione* 2,2;12,12-*Bis*-(*ethylene dithioacetal*) (5). To a solution of the α-ketol (1) (1.0 g) in glacial acetic acid (12 ml) was added ethane-1,2-dithiol (1.0 ml) and BF_3–Et_2O (1.0 ml). After about 10 min the compound (5) started to crystallise from the reaction mixture to which water (5 ml) was added after 5 h. The solid obtained on filtration was washed with ethanol and crystallised reluctantly from ethanol–chloroform as 'threads' (1.0 g), (-veTTC). The *bis-dithioacetal* (5) had m.p. 293—295 °C (decomp.); $[\alpha]_D$ −28.5° (*c* 0.76); $\nu_{max.}$ 3 505 and 755 cm^{-1}; δ 0.93, 0.98, and 1.06 (3 × 3 H, 3 × s, 3 × methyl), 1.29 (3 H, s, 17-H_3), 3.0—3.4 (8 H, m, 2 × SCH_2CH_2S), and 5.73 (2 H, ABq, J = 5.0 Hz, 15- and 16-H) (Found: S, 25.46; M − 28 440.133 2. $C_{24}H_{36}OS_4$ requires, S, 27.36%; M − 28 440.133 6).

ent-3β-*Hydroxybeyerane* (6).—A solution of the bis-acetal (5) (0.800 g) in tetrahydrofuran (THF) (10 ml) was added to a slurry of freshly prepared Raney nickel (10 g) in ethanol (100 ml) and the mixture was refluxed for 7 h, cooled, and filtered. The filtrate, concentrated to 15 ml and diluted with water, yielded crystals of *ent*-3β-hydroxybeyerane (6) (0.280 g), m.p. 160.5—161.5 °C (lit.,[4] 158—159 °C); $[\alpha]_D$ −4° (*c* 1.4) (lit.,[4] −4°); $\nu_{max.}$ 3 300 (v.b.), 1 450, 1 045, and 975 cm^{-1} (Found: M^+ 290.261 4. Calc. for $C_{20}H_{34}O$: M^+ 290.261 0). Acetylation afforded the acetate, m.p. 143—146 °C from aqueous methanol (lit.,[4] 146—147 °C); $[\alpha]_D$ −15° (*c* 0.94) (lit.,[4] −12°); $\nu_{max.}$ 1 722 and 1 240 (b) cm^{-1}.

ent-3β-*Acetoxybeyer*-15-*ene*-2,12-*dione* (7).—The α-ketol (1) when acetylated in pyridine–acetic anhydride at room temperature yielded the *acetate* (7) which crystallised from aqueous methanol as large rhombs, m.p. 169—170 °C, $[\alpha]_D$ −356° (*c* 2.0); $\lambda_{max.}$ 296 (233) and 210 nm (4 010); $\nu_{max.}$ 1 740, 1 720, 1 692, 1 230, and 763 cm^{-1}; δ 0.75 (3 H, s, 20-H_3), 0.84 (3 H, s, 19-H_3), 1.10 (6 H, s, 17- and 18-H_3), 2.14 (3 H, s, acetate), 4.92 (1 H, s, *ent*-3α-H), and 5.63 and 6.02 (2 H, ABq, $J_{15,16}$ = 5.5 Hz, 16- and 15-H respectively) (Found: C, 73.45; H, 8.5; M^+ 358.215 6. $C_{22}H_{30}O_4$ requires C, 73.71; H, 8.44%; M^+ 358.214 4).

ent-2β,3β,12β-*Trihydroxybeyer*-15-*ene* (8).—A solution of the α-ketol (1) (5.00 g) in ethanol (30 ml) was stirred with $NaBH_4$ (1.0 g) overnight at ice temperature. The reaction mixture, when poured into water–ice (200 ml) and acidified with dilute HCl, yielded a solid *triol* (8) which crystallised from THF–ethanol–water or from ethyl acetate as large rhombs (3.49 g first crop), m.p. 223—226 °C (sublimes near 175 °C); $[\alpha]_D$ −38° (*c* 2.07 in THF); $\nu_{max.}$ 3 425 (v.b.), 3 035, and 765 cm^{-1}; δ (saturated solution) 1.03 (6 H, s, 2 × methyl), 1.05 (3 H, s, methyl), 1.12 (3 H, s, methyl), 3.30 (2 H, m, *ent*-3α- and *ent*-12α-H), 4.07 (1 H, m, *ent*-2α-H), and 5.55 and 5.83 (2 H, ABq, J = 6.0 Hz, 16- and 15-H respectively).

ent-2β,3β-*Isopropylidenedioxy*-12β-*hydroxybeyer*-15-*ene* (9).—(a) *From pure triol* (8). The triol (8) (0.70 g) was suspended in dry acetone (20 ml) and $HClO_4$ (3 drops, 70%) was added when a clear solution immediately formed. After 12 h the reaction was quenched with ice-cold, aqueous $NaHCO_3$ solution, and the resulting solid *acetonide* (9) crystallised from aqueous acetone as needles (0.65 g first crop), m.p. 194—196 °C, $[\alpha]_D$ −48° (*c* 2.24); $\nu_{max.}$ 3 490, 1 047, and 750 cm^{-1}; δ 0.97 (6 H, s, 2 × methyl), 1.00 (3 H, s, methyl), 1.12 (3 H, s, methyl), 1.35 and 1.50 (2 × 3 H, 2 × s, isopropylidene methyls), 3.46 (1 H, m, X part of

ABX, $J_{AX} + J_{BX}$ = 15.0 Hz, *ent*-12α-H), 3.76 (1 H, d, $J_{2,3}$ = 6.5 Hz, *ent*-3α-H), 4.35 (1 H, doublet of triplets, $J_{ent\text{-}2\alpha,ent\text{-}3\alpha}$ = $J_{ent\text{-}2\alpha,ent\text{-}1\alpha}$ = 2.0 Hz, $J_{ent\text{-}2\alpha,ent\text{-}1\beta}$ = 6.5 Hz, *ent*-2α-H), and 5.61 and 5.85 (2 H, ABq, J = 6.0 Hz, 16- and 15-H respectively) (Found: C, 76.5; H, 10.05%; M^+ 360.267 0. $C_{23}H_{36}O_3$ requires C, 76.62; H, 10.06%; M^+ 360.266 4).

(b) *Preparation from heartwood mother liquors.* The mother liquor (100 g), remaining after the α-ketol (1) had crystallised from the heartwood extract, was reduced in ethanol (300 ml) with $NaBH_4$ (5 g) at 0—5 °C for 48 h. The solid, obtained when the reaction mixture was poured into ice–HCl (2 l) was filtered and dried (100 g). T.l.c. indicated a mixture of mono-, di-, and tri-ols. The pulverized material was thoroughly extracted with boiling hexane (2 × 600 ml) to remove the bulk of the mono-alcohols; it was then similarly extracted with boiling benzene (2 × 600 ml) to remove a further portion of mono-alcohol together with the bulk of the diols as well as a little triol. The residue (45 g), suspended in a mixture of dry acetone (300 ml), and 2,2-dimethoxy-propane (10 ml), went into solution on addition of $HClO_4$ (6 ml, 70%). After a prolonged period in the dark this solution deposited the product which was filtered off and crystallised from acetone to give 20 g of the pure acetonide (9). A further crop was obtainable from the original dark acetone filtrate by diluting it with water containing some $NaHCO_3$. The combined hexane and benzene extracts containing mono- and di-ols on column chromatography over SiO_2 gave large amounts of *ent*-3β-hydroxybeyer-15-ene (4) as well as some of the epimeric *ent*-3α-hydroxybeyer-15-ene, m.p. 95—99 °C (lit.,[9a] 88—90 °C); $\nu_{max.}$ 3 380 (b) and 760 cm^{-1}; δ 0.76, 0.84, 0.94, and 0.98 (4 × 3 H, 4 × s, 20-, 19-, 18-, and 17-H_3 respectively), 3.38 (1 H, m, $W_{\frac{1}{2}}$ 7.0 Hz, *ent*-3β-H), and 5.43 and 5.68 (2 H, ABq, J = 5.5 Hz, H-16 and H-15 respectively), which by t.l.c. comparison was shown to be present in the original heartwood extract.

ent-3β-*Hydroxybeyerane*-2,12-*dione* (10).—A solution of the α-ketol (1) in ethanol was hydrogenated over Pd–C until the hydrogen uptake ceased. The filtered hydrogenation mixture was concentrated and a little water was added when the *dihydro-ketol* (10) crystallised as needles (+veTTC), m.p. 107—108 °C, $[\alpha]_D$ −34° (*c* 2.05); $\lambda_{max.}$ 284 (71) and 210 nm (2 150); $\Delta\varepsilon(\lambda_{max.})$ −4.37 (293) and +6.86 (198 nm); $\nu_{max.}$ 3 483, 3 400 (b), 1 705 (b), and 1 115 cm^{-1}; δ 0.72, 0.95, 1.10, and 1.21 (4 × 3 H, 4 × s, 19-, 20-, 18- and 17-H_3 respectively), 3.82br (1 H, s, exchanges with D_2O, 3-OH), and 3.91 (1 H, d, $J_{3,1}$ = 1.0 Hz, *ent*-3α-H) (Found: M^+ 318.219 3. $C_{20}H_{30}O_3$ requires 318.219 4).

ent-3β-*Acetoxybeyerane*-2,12-*dione* (11).—Compound (11) was prepared either by acetylation of (10) or by hydrogenating the α-ketol acetate (7) in ethanol over a Pd–C catalyst, as described above, and was obtained as colourless spars from aqueous methanol, m.p. 215—216 °C (sublimes above 175 °C); $[\alpha]_D$ −112° (*c* 2.07); $\lambda_{max.}$ 288 (59) and 210 nm (564); $\nu_{max.}$ 1 742, 1 724, 1 708, 1 235, 680, and 667 cm^{-1}; δ 0.86 (3 H, s, 19-H_3), 0.96 (3 H, s, 20-H_3), 1.08 and 1.11 (2 × 3 H, 2 × s, 17- and 18-H_3), 2.15 (3 H, s, acetate), and 4.93 (1 H, s, *ent*-3α-H) (Found: C, 73.41; H, 9.09%; M^+ 360.231 0. $C_{22}H_{32}O_4$ requires C, 73.3; H, 8.95%; M^+ 360.230 0).

ent-3β-*Acetoxy*-11α-*bromobeyerane*-2,12-*dione* (12).—Either the dihydro-ketol (10) or its acetate (11) could be used for the bromination. Thus to a solution of (11) (0.937 g) in glacial acetic acid (5 ml) and acetic anhydride (5 ml) was added an excess of bromine (0.5 ml) and the mixture left overnight. The solid *bromide* (12) obtained on pouring the reaction mixture into water containing $NaHSO_3$ and filtering was crystallised from aqueous ethanol or aqueous acetone as leaflets (0.940 g), m.p. 238.5—239.5 °C (decomp), $[\alpha]_D$ −85° (*c* 2.01), $\lambda_{max.}$ 294 (86), 237.5 (sh) (448), and 210 nm (2 008); $\nu_{max.}$ 1 740, 1 725, 1 715, 1 235, 1 090, 905, and 735 cm^{-1}; δ 0.85 (3 H, s, 19-H_3), 0.96 (3 H, s, 20-H_3), 1.13 (3 H, s, 18-H_3), 1.27 (3 H, s, 17-H_3), 2.16 (3 H, s, acetate), 2.43 (1 H, d, $J_{9,11}$ = 6.5 Hz, *ent*-9α-H), 2.67 (2 H, t, J_{gem} = 12 Hz, *ent*-1α- and *ent*-1β-H), 4.23 (1 H, d, $J_{11,9}$ = 6.5 Hz, *ent*-11β-H), and 4.97 (1 H, s, *ent*-3α-H) (Found: C, 60.4; H, 7.25%; M^+ 438.141 2. $C_{22}H_{31}BrO_4$ requires C, 60.14; H, 7.11%; M^+ $C_{22}H_{31}{}^{79}BrO_4$ 438.140 6).

ent-3β-*Benzoyloxybeyer*-15-*ene*-2,12-*dione* (13).—The α-ketol (1) (5.0 g) was benzoylated in pyridine (30 ml) with benzoyl chloride (5.0 ml) at 0 °C for two days. The reaction mixture, when poured into water, yielded a sticky gum which eventually crystallised. The solid *benzoate* (13) was filtered off and recrystallised from aqueous acetone as spars (6.6 g), m.p. 224—226 °C; $[\alpha]_D$ −292° (*c* 2.01); $\nu_{max.}$ 1 735, 1 717, 1 705, 1 602, 1 585, 1 283, 1 120, 767, and 710 cm^{-1}; δ 0.80 (3 H, s, 20-H_3), 1.02 (3 H, s, 19-H_3), 1.10 (3 H, s, 17-H_3), 1.18 (3 H, s, 18-H_3), 5.17 (1 H, s, *ent*-3α-H), 5.63 and 6.02 (2 H, ABq, J = 5.5 Hz, 16- and 15-H respectively), and 7.50 and 8.08 (3 × H and 2 × H, m, aromatic ring) (Found: C, 76.8; H, 7.7. $C_{27}H_{32}O_4$ requires C, 77.11; H, 7.67%).

$NaBH_4$ *Reduction of the* 12-*Ketone Function of the Ketol Benzoate* (13) *to* (14) *and* (15) *and Formation of the* ent-12β-*Mesylate* (16).—To a solution of the α-ketol benzoate (13) (1.5 g) in THF (10 ml) and ethanol (20 ml) was added an ethanolic boric acid solution (300 mg in 5 ml) and the mixture cooled in ice before $NaBH_4$ (33 mg) was added. This reaction mixture was stirred at 5 °C for 15 h when it was acidified before removal of most of the ethanol under reduced pressure. The concentrate when poured onto ice yielded a solid (1.5 g) which was chromatographed on silica gel (Merck 7729) in benzene. Unchanged (13) (900 mg) was removed on elution with benzene and subsequent elution with 2% ethyl acetate in benzene furnished first *ent*-3β-benzoyloxy-12α-hydroxybeyer-15-en-2-one (14) (40 mg, 6.7%) (+veTTC) which was characterised by its spectral properties only, $\nu_{max.}$ 3 470, 3 065, 1 708, 1 680, 1 578, 1 273, 767, 752, 713, and 707 cm^{-1}; δ 3.67br (1 H, s, $W_{\frac{1}{2}}$ = 7.0 Hz, *ent*-12β-H); followed by the required *ent*-12β-epimer (15), *ent*-3β-benzoyloxy-12β-hydroxybeyer-15-ene-2-one (547 mg, 91%), (+veTTC) which was not characterised but converted directly into the *ent*-12β-mesylate (16) using pyridine (10 ml) and mesyl chloride (1 ml). The mesylate (16) crystallised from aqueous THF as leaflets, (+veTTC), m.p. 157—158 °C (decomp.). T.l.c. indicated that (16) was impure as it had already partially decomposed to the required diene (17), therefore it was not characterised further.

Preparation of ent-3β-*Benzoyloxy*-14(13 ⟶ 12)abeo-*beyera*-15(16),13(17)-*dien*-2-*one* (17).—A solution of the crude mesylate (16) (329 mg) in acetic acid (20 ml) buffered with freshly fused sodium acetate (1.0 g) was refluxed for 2.5 h before it was cooled and poured onto ice. The resulting solid *diene* (17) crystallised from ethanol–acetone–water as leaflets (190 mg), (+veTTC), m.p. 180—185 °C, $[\alpha]_D$ +128° (*c* 2.04); $\lambda_{max.}$ 300(sh) (53), 280.5 (873), 272.7 (1 091), and 230 nm (31 530) ($\lambda_{max.}$ calculated 229 nm); $\nu_{max.}$ 1 735, 1 726, 1 708, 1 634, 1 601, 1 587, 1 448, 1 297,

1 115, 873, and 710 cm^{-1}; δ 0.77 (3 H, s, 20-H_3), 1.03 (3 H, s, 19-H_3), 1.18 (3 H, s, 18-H_3), 2.27 (2 H, s, 1-H_2), 2.87br (1 H, m, 12-H), 4.48 and 4.62 (2 H, ABq, J_{gem} = 2.0 Hz, 17-H_3), 5.16 (1 H, s, *ent*-3α-H), 5.72 and 5.92 (2 H, ABq, $J_{15,16}$ = 9.5 Hz, 15- and 16-H), and 7.4—8.2 (5 H, m, aromatic) (Found: M^+ 404.235 1. $C_{27}H_{32}O_3$ requires M^+ 404.235 1).

ent-2β,3β-*Isopropylidenedioxy*-14(13 ⟶ 12)abeo-*beyera*-15(16),13(17)-*diene* (18).—A solution of the triol acetonide (9) (2.0 g) and $POCl_3$ (2.0 ml) in dry pyridine (40 ml) at 0 °C was set aside at room temperature for 48 h. The reaction mixture was then warmed to 60 °C for 30 min before it was poured into an ice-cold sodium acetate solution (200 ml). The crystalline solid *diene* (18) which separated crystallised from acetone–THF as laths (1.48 g, 78%), m.p. 180—185 °C, $[\alpha]_D$ +139° (*c* 2.5); $\lambda_{max.}$ 238.5 (17 600) and 210 nm (5 372); $\nu_{max.}$ 1 250, 1 055, 1 030, 883, 875(vs), 838, and 793 cm^{-1}; δ 0.94 (6 H, s, 2 × methyl), 1.00 (3 H, s, methyl), 1.33 and 1.50 (2 × 3 H, s, isopropylidene methyls), 2.82br (1 H, m, $W_{\frac{1}{2}}$ = 14 Hz, 12-H), 3.71 (1 H, d, $J_{3,2}$ = 6.0 Hz, *ent*-3α-H), 4.30 (1 H, d of t, $J_{ent\text{-}2\alpha,ent\text{-}3\alpha} = J_{en\text{-}2\alpha,ent\text{-}1\alpha}$ = 2.0 Hz, $J_{ent\text{-}2\sigma,ent\text{-}1\beta}$ = 6.0 Hz, *ent*-2α-H), 4.46 and 4.58 (2 H, ABq, J_{gem} = 2.0 Hz, 17-H_2), and 5.80 (2 H, t, J = 10.0 Hz, 15- and 16-H) (Found: C, 80.75; H, 10.3. $C_{23}H_{34}O_2$ requires C, 80.65; H, 10.01%). The yield for the sequence starting from the triol (8) and producing the diene (18) was not maximised.

ent-2α-*Acetoxybeyer*-15-*ene*-3,12-*dione* (19).—To an ice-cold solution of the α-ketol (1) (3.0 g) in acetic anhydride (25 ml), was added anhydrous $AlCl_3$ (4.0 g). The reaction mixture was heated at 80 °C for 30 min (evolution of HCl gas and CH_3COCl), and then allowed to cool and stand at room temperature for 5 h before being poured onto ice (300 g). The resulting sticky gum was collected and crystallised from ethanol (similarly methanol can be used) giving 0.81 g (24%) of the *isoketol acetate* (19), (+veTTC), m.p. 228—231 °C (range: 227—235 °C varies with heating rate), $[\alpha]_D$ −322° (*c* 2.0); $\lambda_{max.}$ 296 (225) and 210 nm (3 440); $\nu_{max.}$ 1 745, 1 725, 1 695, 1 235, and 763 cm^{-1}; δ 1.11 (3 H, s, methyl), 1.17 (9 H, s, 3 methyls), 2.14 (3 H, s, acetate), 5.58 (1 H, q, J = 6.0 and 13.0 Hz, *ent*-2β-H), and 5.68 and 6.11 (2 H, ABq, J = 5.5 Hz, 16- and 15-H respectively) (Found: C, 74.0; H, 8.55%; M^+ 358.215 6. $C_{22}H_{30}O_4$ requires C, 73.71; H, 8.44%; M^+ 358.214 4). The n.m.r. spectrum of the *crude* reaction mixture showed ketol acetates (7) and (19) in a ratio of 7 : 3 respectively by comparing the n.m.r. integrals for the respective acetoxymethine protons and also of the 19- and 20-methyl group integrals of (7) which are upfield to the corresponding signals in the n.m.r. spectrum of (19).

Hydrogenation with Pd–C as for (10) in ethanol–THF gave the dihydro-derivative ent-2α-*acetoxybeyerane*-3,12-*dione* as needles, m.p. 221—223 °C (sublimes), $[\alpha]_D$ −54° (*c* 1.13); $\lambda_{max.}$ 288 (62) and 210 nm (423); $\nu_{max.}$ 1 745, 1 725, 1 700, 1 235, 1 025, 975, and 870 cm^{-1}; δ 1.07 (3 H, s, methyl), 1.13 (6 H, s, 2 methyls), 1.35 (3 H, s, 20-H_3), 2.13 (3 H, s, acetate), and 5.58 (1 H, q, J = 6.0 and 13.0 Hz, *ent*-2β-H) (Found: C, 73.1; H, 8.85%; M^+ 360.230 7. $C_{22}H_{32}O_4$ requires C, 73.30; H, 8.95%; M^+ 360.230 0).

ent-2α,3β,12β-*Trihydroxybeyer*-15-*ene* (20).—A solution of the isoketol acetate (19) (0.75 g) in ethanol–THF (20 ml; 1 : 1) was reduced with $NaBH_4$ (1.0 g) with concomitant addition of 10% NaOH (1 ml) to the stirred reaction mixture. After 15 h the reaction mixture was acidified with HCl and concentrated to a small volume before it was poured onto ice. The granular precipitate crystallised from aqueous ethanol as needles (0.27 g first crop). The *triol* (20) had m.p. 218—221.5 °C; $[\alpha]_D$ −11° (*c* 1.86), $\nu_{max.}$ 3 615, 3 600—3 100 (vb), 3 045, 1 055, and 755 cm^{-1} (Found: M^+ 320.235 1. $C_{20}H_{32}O_3$ requires M^+ 320.235 1).

ent-2β-*Acetoxybeyerane*-3,12-*dione* (21).—A THF solution of the diosphenol acetate (22) (1.0 g) was hydrogenated over a Pd–C catalyst until 2 mol equiv. of hydrogen had been consumed. The *reduction product* (21) crystallised from aqueous methanol as needles (0.97 g) which gave a positive TTC test, and had m.p. 156—158 °C; $[\alpha]_D$ −157° (*c* 2.16), $\lambda_{max.}$ 286 (87) and 210 nm (300); $\nu_{max.}$ 1 745, 1 730, 1 710, and 1 293 cm^{-1}; δ 0.90 (3 H, s, methyl), 1.08 (6 H, s, 2 × methyl), 1.20 (3 H, s, methyl), 2.12 (3 H, s, acetate), and 5.58 (1 H, q, J = 8.3 and 11.2 Hz, *ent*-2α-H) (Found: C, 73.0; H, 9.0%; M^+ 360.231 0. $C_{22}H_{32}O_4$ requires C, 73.30; H, 8.95%; M^+ 360.230 0).

Hydrogenation of (22) in ethanol resulted (after *ca.* 1 mol equiv. of hydrogen uptake) in the solution setting to a solid mass of needles, m.p. 173—188 °C after crystallisation from ethanol, consisting of a 1 : 1 molecular complex of (21) and the 15,16-dihydro-diosphenol acetate, ent-2-*acetoxybeyer*-1-*ene*-3,12-*dione*, as was apparent from the n.m.r. spectrum of this complex. This dihydrodiosphenol acetate had been made by Bi_2O_3 oxidation of the dihydro-ketol (10) as described above, followed by acetylation and it had m.p. 204—207 °C (from methanol); $[\alpha]_D$ −88° (*c* 2.0), $\lambda_{max.}$ 329 (88) and 238 nm (9 872); $\nu_{max.}$ 1 757, 1 705, 1 678, 1 213, 1 200, 1 185, and 1 034 cm^{-1}; δ 1.10, 1.13, 1.20, and 1.26 (4 × 3 H, 4 × s, 4 × methyl), 2.17 (3 H, s, acetate), and 6.53 (1 H, s, olefinic 1-H) (Found: C, 73.6; H, 8.4%; M^+ 358.214 8. $C_{22}H_{30}O_4$ requires C, 73.71; H, 8.44%; M^+ 358.214 4).

ent-2-*Acetoxybeyer*-1,15-*diene*-3,12-*dione* (22).—This compound was prepared either by acetylating (acetic anhydride–pyridine) the Bi_2O_3 oxidation product of (1) [see compound (2)] in 66% overall yield from (1) or by acetylating the material (2) obtained naturally. The *diosphenol acetate* (22) had m.p. 135—137 °C (rhombs from methanol); $[\alpha]_D$ −334° (*c* 2.43), $\lambda_{max.}$ 296 (386) and 234 nm (12 204); $\nu_{max.}$ 1 763, 1 695, 1 650, 910, and 763 cm^{-1}; δ 1.11 (6 H, s, 2 × methyl), 1.13 (3 H, s, methyl), 1.18 (3 H, s, methyl), 2.18 (3 H, s, acetate), 5.71 and 6.07 (2 H, ABq, J = 5.5 Hz, 16- and 15-H respectively), and 6.44 (1 H, s, olefinic 1-H) (Found: C, 74.4; H, 7.9. $C_{22}H_{28}O_4$ requires C, 74.13; H, 7.92%).

ent-2β,3β,12β-*Trihydroxybeyerane* (23).—The *dihydro-triol* (23) was prepared either by hydrogenation of (8) with Pd–C in THF or by $NaBH_4$ reduction in THF–wet ethanol of (21); the crystals obtained from aqueous ethanol had m.p. 226—227 °C (sublimes); $[\alpha]_D$ −31° (*c* 2.05, THF); $\nu_{max.}$ 3 558, 3 550—3 050 (v.b.), 1 450, 1 390, 1 045, 1 020, and 973 cm^{-1} (Found: C, 74.0; H, 10.4%; M^+ 322.250 3. $C_{20}H_{34}O_3$ requires C, 74.49; H, 10.63%; M^+ 322.250 8).

ent-3α-*Acetoxybeyer*-15-*ene*-2,12-*dione* (24).—A solution of the α-ketol (1) (3.2 g) in dry benzene (50 ml) was degassed by refluxing it under dry, oxygen-free argon for 30 min. Tosic acid (50 mg) and dry pyrrolidine (3 ml) were then added and the reaction mixture refluxed for 15 h under argon. The cooled reaction mixture was treated with acetic anhydride (10 ml) and left for 12 h at room temperature before the benzene was removed under reduced pressure. The reddish concentrate was poured onto ice–sodium acetate solution (250 ml; 10 g sodium acetate) when the cloudy water layer slowly deposited crystals and

a semi-crystalline red oil and crystals which were filtered off. A methanol solution of the crystals obtained on filtration was charcoaled after which it deposited long white needles (2.0 g, 55%). A further crystal crop was obtained on similarly charcoaling a methanol solution of the red oil. The *epi-ketol acetate* (14) had m.p. 183—184°; $[\alpha]_D$ −310° (*c* 2.2), $\lambda_{max.}$ 298 (254) and 212 nm (8 390); $\nu_{max.}$ 1 747, 1 725, 1 700, 1 230, and 763 cm^{-1}; δ 0.89, 0.94, 1.03, and 1.10 (4 × 3 H, 4 × s, 4 × methyl), 2.13 (3 H, s, acetate), 4.70 (1 H, s, *ent*-3β-H), and 5.65 and 6.04 (2 H, ABq, J = 5.5 Hz, 16- and 15-H respectively) (Found: C, 73.9; H, 8.6%; M^+ 358.214 8. $C_{22}H_{30}O_4$ requires C, 73.71; H, 8.44%; M^+ 358.214 4).

ent-3α-*Acetoxybeyerane*-2,12-*dione*.—Hydrogenation of a THF solution of (24) over Pd–C gave the title compound, ent-3α-*acetoxybeyerane*-2,12-*dione*, as leaflets from aqueous ethanol, m.p. 200—201 °C; $[\alpha]_D$ −58° (*c* 2.84); $\lambda_{max.}$ 292 (88), and 210 nm (877); $\nu_{max.}$ 1 743, 1 735, 1 702, 1 225, and 1 040 cm^{-1}; δ 0.93, 1.00, 1.07, and 1.08 (4 × 3 H, 4 × s, 4 × methyl), 2.12 (3 H, s, acetate), and 4.77 (1 H, s, *ent*-3β-H) (Found: C, 73.15; H, 9.05%; M^+ 360.229 9. $C_{22}H_{32}O_4$ requires C, 73.30; H, 8.95%; M^+ 360.230 0).

ent-2β,3α,12β-*Trihydroxybeyer*-15-*ene*.—The epi-ketol acetate (24) was reduced in ethanol solution with $NaBH_4$ as described before. The *triol* crystallised from aqueous methanol, m.p. 200—207 °C, $[\alpha]_D$ −50° (*c* 2.1 in THF); $\nu_{max.}$ 3 600—3 050 (v.b.) and 763 cm^{-1} (Found: C, 71.0; H, 10.45%; M^+ 320.234 7. $C_{20}H_{32}O_3 \cdot H_2O$ requires C, 70.97; H, 10.12%; M^+ 320.235 1).

ent-2-*Pyrrolidinobeyera*-1,15-*diene*-3,12-*dione* (25).—(a) A solution of the α-ketol (1) (1.0 g) and *p*-tosic acid (100 mg) in pyrrolidine (2 ml) and benzene (60 ml) was refluxed for 20 h with access to air before the cooled reaction mixture was washed with water, dried, and the solvents evaporated. The yellow residue crystallised from methanol as spars (0.95 g). The *enamine* (25) had m.p. 190—193 °C (decomp.); $[\alpha]_D$ −319° (*c* 2.4); $\lambda_{max.}$ 319 (3 319) and 215 nm (11 127); $\nu_{max.}$ 1 705, 1 670, 1 600, and 765 cm^{-1}; δ 0.92 (3 H, s, methyl), 1.11 (6 H, s, 2 × methyl), 1.17 (3 H, s, methyl). 5.34 (1 H, s, 1-H), and 5.70 and 6.10 (2 H, ABq, J = 5.5 Hz, 16- and 15-H respectively) (Found: C, 78.6; H, 9.08; N, 3.65%; M^+ (100%) 367.250 7. $C_{24}H_{33}NO_2$ requires C, 78.43; H, 9.05; N, 3.81%; M^+ 367.251 1).

(b) A solution of the diosphenol in pyrrolidine and methanol with or without tosic acid was refluxed for 12 h. The product that crystallized out in a quantitative yield on cooling of the reaction mixture was identical in all respects with the enamine (25) described above.

Hydrolysis of the Enamino-ketone (25) *to the* 2,3,12-*Trione* (2).—A solution of the enamine (25) (1.0 g) in glacial acetic acid (30 ml) was treated with concentrated H_2SO_4 (0.5 ml) and left for 3 h. The reaction mixture was then poured into water and the resulting yellow solid filtered and crystallised from methanol to give yellow crystals of the *triketone* (2) (0.9 g) which in methanol were immediately converted into the enolised form (2) by treatment with a trace of alkali.

ent-2,3-*Ethylenedioxy*-12-*oxobeyera*-2,15-*diene* *Ethylene Acetal* (28). A solution of the α-ketol (1) (3.0 g), and *p*-tosic acid (300 mg) in toluene (50 ml) was refluxed with ethanediol (10 ml) with separation of water for 2 h until homogeneous. The cooled reaction mixture was poured into $NaHCO_3$ solution and extracted with ethyl acetate. The residue obtained from the dried and evaporated ethyl acetate extract crystallised from methanol containing a few drops of pyridine to give 2.34 g of the *acetal* (28), m.p. 177—182 °C; $[\alpha]_D$ −30° (*c* 2.48); $\nu_{max.}$ 1 705 (O–C=C–O) and 755 cm^{-1}; δ 0.81, 0.95, 0.98, and 1.07 (4 × 3 H, 4 × s, 4 × methyl), 3.93 (4 H, m, 12-ethylenedioxy acetal); 4.00 (4 H, s, ethylenedioxy), and 5.68 and 5.83 (2 H, ABq, J = 5.5 Hz, 16- and 15-H). (Found: C, 74.9; H, 8.95%; M^+ 386.246 4. $C_{24}H_{34}O_4$ requires C, 74.58; H, 8.87%; M^+ 386.245 7).

ent-2,3-*Ethylenedioxy*-12-*Oxobeyera*-2,15-*diene* (29).—(*a*) The procedure for (28) above was followed with the α-ketol (1) (3.0 g) but the hydrogen carbonate was omitted from the aqueous wash and a drop of conc. HCl was added to the methanol used for crystallisation to yield compound (29) (3.0 g, 93%); m.p. 195—197.5 °C (sublimes 180—190 °C); $[\alpha]_D$ −319° (*c* 2.25); $\lambda_{max.}$ 296 (204) and 210 nm (5 878); $\nu_{max.}$ 1 702 (O–C=O–C, C=O), 1 590, 766, and 757 cm^{-1}; δ 0.87, 0.97 (2 × 3 H, 2 × s, 20- and 19-H respectively), 1.10 (6 H, s, 18- and 17-H), 2.20—2.80 (2 H, m, *ent*-11β- and *ent*-11α-H, removed by deuteriation), 4.00 (4 H, s, ethylenedioxy protons), and 5.63 and 6.08 (2 H, ABq, J = 5.5 Hz, 16- and 15-H respectively) (Found: C, 76.95; H, 8.9%; M^+ 342.220 2. $C_{22}H_{30}O_3$ requires C, 77.16; H, 8.83%; M^+ 342.219 5).

(b) Compound (29) was also prepared by the procedure (a) above substituting the α-ketol tosylate (31) for the α-ketol (1).

ent-3β-*Tosyloxybeyer*-15-*ene*-2,12-*dione* (31).—A solution of the α-ketol (1) (1.0 g) in dry pyridine (10 ml) was treated with *p*-tosyl chloride (1.0 g) for 15 h at room temperature before it was poured into water. The *tosylate* (31) crystallized from aqueous acetone as long spars (1.1 g), m.p. 202—203 °C (decomp.); $[\alpha]_D$ −214° (*c* 2.83); $\nu_{max.}$ 1 727, 1 700, 1 598, 1 340, 1 175, 980, 862, and 686 cm^{-1}; δ 0.72, 0.78, 1.09 and 1.13 (4 × 3 H, 4 × s, 20-, 19-, 17-, and 18-H_3 respectively), 2.42 (3 H, s, aromatic methyl), 4.84 (1 H, s, *ent*-3α-H), 5.62 and 5.97 (2 H, ABq, J = 6.0 Hz, 16- and 15-H respectively), and 7.28 and 7.82 (4 H, 1,4-disubstituted benzene ring) (Found: C, 69.05; H, 7.4. $C_{27}H_{34}SO_5$ requires C, 68.91; H, 7.28%).

ent-3β-*Benzoyloxy*-2,2;12,12-*bis*(*ethylenedioxy*)-*beyer*-15-*ene* (32).—A solution of the α-ketol benzoate (13) (5.0 g), ethanediol (15 ml), and *p*-tosic acid (100 mg) in toluene (200 ml) was refluxed with separation of water for 4 h. The cooled reaction solution was washed with aqueous $NaHCO_3$ before the toluene was removed to leave a crude crystalline mass of the *bis-acetal* (32); this crystallised from aqueous acetone containing a few drops of pyridine, to give 4.0 g of needles (first crop), m.p. 234—239 °C, $[\alpha]_D$ 0° (*c* 2.15); $\nu_{max.}$ 1 727, 1 720, 1 715, 1 450, 1 270, 760, and 708 cm^{-1}; δ 0.91 (3 H, s, methyl), 0.97 (6 H, s, 2 × methyl), 1.13 (3 H, s, methyl), 3.4—4.2 (8 H, m, 2 × OCH_2CH_2O), 5.06 (1 H, s, *ent*-3α-H), 5.67 and 5.84 (2 H, ABq, J = 5.0 Hz, 15- and 16-H respectively), and 7.4—8.2 (5 H, m, aromatic protons) (Found: C, 73.25; H, 8.1. $C_{31}H_{52}O_6$ requires C, 73.20; H, 7.93%).

ent-3β-*Hydroxybeyer*-15-*ene*-2,12-*dione* 3-*Nitrate* (33).—To an ice cold solution of the α-ketol (1) (1.0 g) in a mixture of acetic acid (3 ml) and acetic anhydride (5—10 ml) was slowly added concentrated nitric acid (2—3 ml). The reaction mixture, allowed to warm to 45—50 °C (but no higher), was quenched in ice–water after 5 min. The precipitated solid *nitrate* (33) obtained on filtration crystallised from aqueous acetone as leaflets (0.76 g, first crop, giving an intense blue colour with the diphenylamine–conc. H_2SO_4 reagent), m.p. 193—194 °C (vigorous decomposition); $[\alpha]_D$ −407° (*c* 1.84); $\lambda_{max.}$ 295 (215) and 210 nm (5 370);

$\nu_{max.}$ 1 728, 1 715, 1 700, 1 649, 1 635, 1 300, 1 293, 1 285, 1 087, 990, 850, and 760 cm^{-1}; δ 0.80 (3 H, s, 20-H_3), 0.88 (3 H, s, 19-H_3), 1.12 (3 H, s, 17-H_3), 1.25 (3 H, s, 18-H_3), 2.27br (4 H, s), 5.03 (1 H, s, *ent*-3α-H), 5.67 and 6.03 (2 H, ABq, J = 5.5 Hz, 16- and 15-H respectively) (Found: C, 66.5; H, 7.75; N, 3.3%; M^+ 361.188 4. $C_{20}H_{27}NO_5$ requires C, 66.46; H, 7.53; N, 3.88%; M^+ 361.188 9).

ent-3ξ-*Methoxy*-2,12-*dioxo*-2,3-*secobeyer*-15-*eno*-2,3-*lactone* (34).—A solution of the α-ketol (1) (1.0 g) in methanol (15 ml) and water (5 ml) was treated with periodic acid (1.0 g) and *p*-tosic acid (20 mg) for 24 h at room temperature. The needles of the *lactone* (34) that had separated during this period were filtered off and recrystallised from aqueous methanol to yield 0.45 g of product m.p. 207—210 °C; $[\alpha]_D$ −272° (*c* 0.79); $\lambda_{max.}$ 296 (213) and 213 nm (2 958); $\nu_{max.}$ 1 720, 1 706, 1 594, 985, and 765 cm^{-1}; δ 0.93, 1.01, 1.06, and 1.10 (4 × s, 4 × methyl), 3.18 (3 H, s, *O*-methyl), 4.60 (1 H, s, OCHO), and 5.68 and 6.10 (2 H, ABq, J = 5.5 Hz, 16- and 15-H respectively) (Found: C, 72.65; H, 8.6%; M^+ 346.213 8. $C_{21}H_{30}O_4$ requires C, 72.80; H, 8.73%; M^+ 346.214 4).

ent-12-*Oxo*-2,3-*secobeyer*-15-*ene*-2,3-*dioic Acid* (36).—To an ice-cold solution of the diosphenol (2a) (2.0 g) and KOH (3 g) in ethanol (70 ml), was added H_2O_2 (10 ml, 30%). The reaction mixture was left in an ice-box for 48 h, before most of the solvent was removed below 30 °C and poured into a slurry of ice–dilute HCl. The precipitated crude *acid* (38) crystallized from aqueous methanol (0.95 g first crop) as soft, silky needles, m.p. 174—177 °C; $[\alpha]_D$ −381° (*c* 2.3); $\lambda_{max.}$ 297 (212) and 210 nm (3 559); $\nu_{max.}$ 3 700—2 400 (v.b.), 1 720, 1 690 (b), and 765 cm^{-1}; δ[$(CD_3)_2SO$–$CDCl_3$] 0.87, 1.10, 1.18, and 1.27 (4 × 3 H, 4 × s, 4 × methyl), 5.59 and 6.05 (2 H, ABq, J = 5.5 Hz, 16- and 15-H respectively), and 10.73br (2 H, bs, exchanged with D_2O, 2 × CO_2H) (Found: C, 68.67; H, 8.2%; M^+ 348.194 5. $C_{20}H_{28}O_5$ requires C, 68.94; H, 8.10%; M^+ 348.193 7).

ent-12-*Oxo*-2,3-*secobeyerane*-2,3-*dioic Acid* (37).—To a solution of the dihydro-ketol (10) (0.9 g) in t-butyl alcohol (100 ml) was added a solution of K_2CO_3 (1.8 g), sodium metaperiodate (7.5 g), and $KMnO_4$ (0.2 g) in H_2O (150 ml). After vigorously stirring for 36 h the reaction mixture was evaporated under reduced pressure to half its volume and the concentrate was decolourised with SO_2 gas. On removing the remaining butanol from the distinctly acid, straw-yellow concentrate, the crude *seco-acid* (37) crystallised out. This acid crystallised from aqueous methanol as square plates (0.4 g), m.p. 250 °C (decomp.); $[\alpha]_D$ −90° (*c* 1.43); $\lambda_{max.}$ 283 (47) and 210 nm (263); $\nu_{max.}$ 3 250 (b), 1 740, 1 718, 1 690 (b), 837 (b), and 795 cm^{-1} (Found: C, 68.15; H, 8.5%; M^+ − 18, 332.197 2, M^+ − 59, 291.1 956 and M^+ − 87, 263.164 5; $C_{20}H_{30}O_5$ requires C, 68.55; H, 8.63%; M^+ − 18, 332.198 7; M^+ − 59, 291.196 0, and M^+ − 87, 263.164 7).

The derived *dimethyl ester* was prepared with diazomethane and crystallised from aqueous methanol as needles, m.p. 154—156 °C, $\lambda_{max.}$ 210 (298), 216 (sh) (268), and 276 nm (68); $\nu_{max.}$ 1 739, 1 727, 1 700, and 1 140 (b) cm^{-1}.

ent-2,3;12,13-*Bis*-*secobeyer*-13,15-*diene*-2,3,12-*trioic Acid* (38).—To an ice-cold solution of the α-ketol (1) (3.0 g) in ethanol (100 ml) was added KOH (5.0 g) in ethanol (20 ml) and H_2O_2 (30 ml, 30%). The reaction mixture was left overnight in an ice-box and worked up as for (28) above. The pure *acid* (38) obtained (3.5 g) crystallised from aqueous methanol as needles. m.p. 251—252 °C (decomp.); $[\alpha]_D$ −50.5° (*c* 2.0 EtOH); $\lambda_{max.}$ 254 (1 392) and 210 nm (1 374); $\nu_{max.}$ 3 500—2 400 (v.b.), 1 700 (b), 799, and 792 cm^{-1}; δ[$(CD_3)_2SO$–$CDCl_3$]$_3$) 0.96 (3 H, s, 20-H_3), 1.23 (6 H, s, 19- and 18-H_3), 1.82 (3 H, s with the shoulder, collapses to a sharp singlet on irradiation at 5.70, 17-H_3), 5.70 (1 H, m, $W_{\frac{1}{2}}$ = 5 Hz, collapses to a narrow multiplet, $W_{\frac{1}{2}}$ = 3.0 Hz, on irradiation at 1.82, olefinic 14-H), 6.16 (1 H, dd, J = 5.5 and 1.5 Hz, olefinic H), 6.43 (1 H, dd, J = 5.5 and 2.0 Hz, olefinic H), and 5.0—7.7 (3 H, v.b., exchanged with D_2O, 3 × CO_2H) (Found: C, 65.0; H, 7.7%; M^+ 364.188 2. $C_{20}H_{28}O_6$ requires C, 65.91; H, 7.74%; M^+ 364.188 6).

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