Tetrahedron. Vol. 30, pp. 3399 to 3405. Pergamon Press 1974. Printed in Great Britain

THE ACID CATALYSED REARRANGEMENT OF A DITERPENOID EPOXIDE[1]

R. D. H. MURRAY* and R. W. MILLS
Department of Chemistry, University of Glasgow, Glasgow, G12 8QQ.

A. J. MCALEES and R. MCCRINDLE
Chemistry Department, University of Guelph, Guelph, Ontario, Canada

(*Received in UK* 17 *April* 1974; *Accepted for publication* 1 *May* 1974)

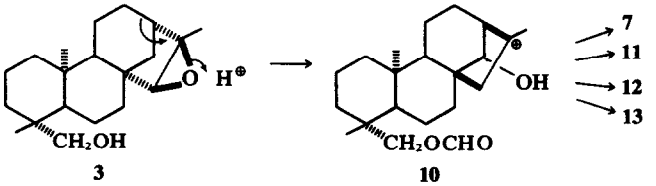
Abstract—A study has been made of the principal rearrangement products resulting from formic acid treatment of 19-hydroxy-*ent*-beyerene epoxide (**3**). In concentrated solutions **3** has been found to undergo a deep seated rearrangement to the allylic alcohol (**14**). A mechanism for the formation of **14** is proposed involving a novel 1,4-hydride shift in the bicyclo[3:2:1]octane C/D ring system following cleavage of the C_{15}–O bond. Supporting evidence has been obtained from a study of the specifically labelled epoxide (**4**), the deuterium in **14** appearing exclusively at C_{12}. Four products (**7** and **11–13**) emanating from the known beyerane → kaurane interconversion have been identified.

Erthyroxylol A, the major constituent of *Erythroxylon monogynum* Roxb. has been shown[2] to be 19-hydroxy-*ent*-beyerene having the absolute stereochemistry depicted in **1**. The observation[3,4] that **1** and especially the co-occuring[4] epoxide (**3**) underwent C–C bond cleavage on treatment with CrO_3 in acetic acid prompted the use of formic acid as solvent for the oxidation. Under these conditions at least 17 compounds were produced, but since an identical mixture was formed by simply warming a solution of **3** in formic acid, none of these products could be the result of oxidation. All but one of the new compounds contain the grouping $-CH_2OCHO$ as shown by their IR (ν_{max} 1731 and 1175 cm^{-1}) and NMR spectra (τ 5·6 and 6·1, 2H, ABq, J = 11 Hz and τ 1·95, 1H, s), and must necessarily have arisen from fission of the epoxide ring with concomitant esterification of the C_{18} OH group since exposure of *ent*-beyeran-18-ol (**5**) to warm formic acid afforded[5] only the derived formate (**6**).

The only compound not containing the grouping $-CH_2OCHO$, an unsaturated pentacyclic ether formed in 5% yield, has been tentatively formulated as **23** (*vide infra*). The genesis of **23** must involve a complex rearrangement process between initial opening of the epoxide ring and eventual generation of a carbonium ion at C_{10} to permit intramolecular capture by the C_{19} OH group. Thus it was of considerable interest to attempt to elucidate the structures of the rearrangement products, the most important of which are reported herein.†

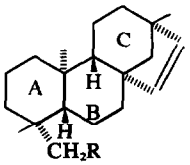
The major product (40%) formed on heating **3** with 95% formic acid (85 mg/ml) for 5 min was an enediol diformate, $C_{22}H_{32}O_4$, the NMR spectrum of which reveals two tertiary methyls (τ 9·05 and 8·87) and a vinyl methyl (τ 8·28, d, J = 1 Hz) adjacent to one vinyl proton (τ 4·98, m). This compound possesses the primary and a secondary formate group, the methine proton associated with the latter being considerably deshielded (τ 4·50, m) as a consequence of its proximity to the C_{10} Me. The mass spectrum exhibits a molecular ion at *m/e* 360 with a peak at *m/e* 314 indicating the loss of formic acid. Chemical evidence for the double bond and two ester groupings came from catalytic hydrogenation, to a mixture of dihydro epimers, and hydrolysis, to an enediol. Bearing in mind the *ent*-beyerene epoxide rearrangement,[7] the spectroscopic data are consistent with

†Part of this work has been published in a preliminary form.[6]

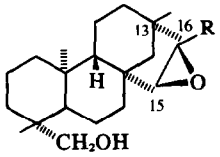


3 **10**

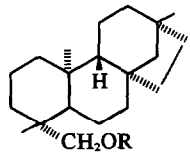
SCHEME 1



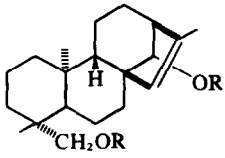
1: R = OH
2: R = H



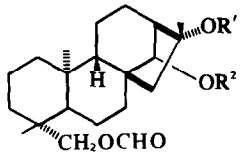
3: R = H
4: R = D



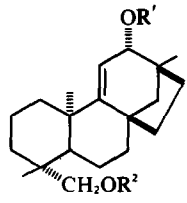
5: R = H
6: R = CHO



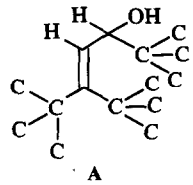
7: R = CHO
8: R = H
9: R = Ac



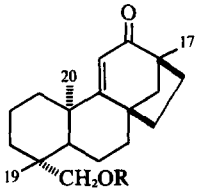
11: $R^1 = R^2 = CHO$
12: $R^1 = H$; $R^2 = CHO$
13: $R^1 = R^2 = H$



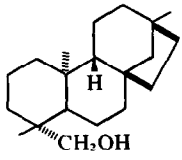
14: $R^1 = H$; $R^2 = CHO$
15: $R^1 = R^2 = H$
16: $R^1 = Ac$; $R^2 = CHO$
17: $R^1 = Me$; $R^2 = CHO$
18: $R^1 = Me$; $R^2 = H$
19: $R^1 = R^2 = CHO$



A



20: R = CHO
21: R = H



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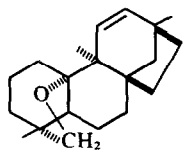
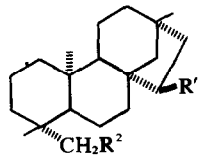
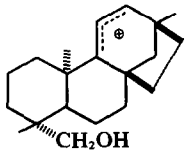


23



25: $R^1 = OCHO$; $R^2 = H$
26: $R^1 = Cl$; $R^2 = H$
27: $R^1 = R^2 = OH$
28: $R^1 = R^2 = OAc$
29: $R^1 = OH$; $R^2 = OAc$
30: $R^1 = OAc$; $R^2 = OH$



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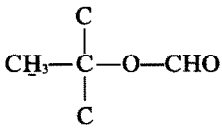
structure (7) which can arise from the carbonium ion (10) by deprotonation and esterification (Scheme 1). Three structurally related compounds, the triol triformate (11, 1%), a diformate (12, 7%) and a monoformate (13, 4%), all of which arise by solvent capture of the carbonium ion (10) from the less hindered α-face,[7] were also isolated. The NMR spectrum of the triol diformate discloses three tertiary methyls (τ 9·07, 8·90 and 8·75) and resonances for the groups $-CH_2OCHO$ and $\rangle CHOCHO$, the methine proton of the latter being deshielded by the C_{10} Me. The absence of any signals attributable to a $\underset{|}{H}-\underset{|}{C}-OH$ group requires the OH to be tertiary while the strong intramolecular H-bonding in the solution IR supports the stereochemical assignment.

The mass spectrum shows no molecular ion but there are significant peaks at *m/e* 332 and 314 corresponding to successive loss of formic acid and water. Confirmation of structure (**12**) for the triol diformate came from its clean dehydration to the enediol diformate (**7**) with phosphoryl chloride in pyridine.

The structure of the triol triformate (**11**) came from its spectra, which are very similar to those of **12**. The downfield shift of one of the three tertiary methyls (τ 9·08, 8·94 and 8·36) requires[8] that the grouping



be present. The triol monoformate, to which 12 slowly hydrolyses on standing was assigned structure (**13**) on the basis of its NMR spectrum which shows three tertiary methyls (τ 9·04, 9·01 and 8·65) with the signal at τ 5·79 (IH, bs) being the C_{14} methine resonance of a secondary alcohol, while the highest peak in the mass spectrum at *m/e* 332 indicates the facile loss of water.

At higher concentrations of the epoxide (**3**) in formic acid (750 mg/ml) the relative yields of some of the rearrangement products changed markedly, with the major compound now being an enediol monoformate, $C_{21}H_{32}O_3$ (35%) for which structure (**14**) is proposed on the basis of the following spectroscopic and chemical evidence. Since **14** was not formed when **7**, **12**, or **13** were resubjected to formic acid it appeared probable that this product arose from **3** by an alternative type of rearrangement.

From its NMR spectrum, the enediol monoformate contains a primary formate grouping (τ 5·53 and 5·85, 2H, ABq, $J = 11$ Hz; τ 1·87, 1H, s) necessarily located at C_{18}, three tertiary methyls (τ 9·03, 8·89 and 8·88) and an allylic alcohol grouping with one vinyl proton (τ 4·58, d, $J = 4$ Hz) shown by double irradiation experiments to be coupled to the methine proton (τ 6·38, d, $J = 4$ Hz) of a secondary alcohol ($\nu_{max}^{CCl_4}$ 3600 cm^{-1}). Since the vinyl resonance appears as a sharp doublet while the methine doublet is only slightly broadened, probably by 'W' coupling,[9] the partial structure (A) can be inferred. The presence of an allylic secondary alcohol moiety in **14** was verified by the ease of oxidation to a β,β-disubstituted enone (**20**), (λ_{max} 245 nm, ϵ 12,900) the lone α vinyl proton resonating in the NMR as a sharp singlet at τ 4·22. The absorption at ν_{max} 1676 cm^{-1} in the IR spectrum was consistent with the enone system being in a 6-membered ring. The NMR spectrum of the derived hydrolysis product (**21**) discloses three tertiary methyls (τ 9·05, 8·90 and 8·83), one vinyl proton singlet at τ 4·28 and a hydroxymethylene group at τ 6·20 and 6·44 (2H, ABq, $J = 11$ Hz) while the IR spectrum shows bands at 3645 (OH) and 1673 (CO) cm^{-1} but no intramolecular H-bonding.

Taking into account the molecular formula and the above spectroscopic and chemical evidence, the new enediol monoformate must be tetracyclic. Moreover, since it seems unlikely that ring A, which bears two of the tertiary methyls, is affected by the rearrangement, the allylic alcohol grouping is most probably located in ring C or ring D. Consequently the most reasonable way to incorporate the partial structure (A) is for there to be a two carbon bridge between C_9 and C_{13} giving a 5-membered ring D with the remaining tertiary Me attached to C_{13} as in **14**. Further spectroscopic support for the location of the three tertiary methyls in **14** came from the use of aromatic solvent induced chemical shifts for ketones.[10] The results of recording the NMR spectra of the enone (**21**) in $CDCl_3$-benzene solutions varying in composition from 0% to 100% benzene are given in the Table.

The Me group resonating at τ 8·83 in $CDCl_3$ experiences only a small negative shift (0·07 ppm) on changing the solvent to benzene and is therefore C_{17} Me which lies close to, but in front of, the reference plane[11] drawn through the carbon of the CO group at right angles to the C–O bond. Since Me groups behind the reference plane experience significant upfield shifts, the signal at τ 8·90 ($CDCl_3$) which exhibits the greater shielding in benzene (0·32 ppm) can be assigned to the C_{20} Me. The smaller upfield solvent shift (0·10 ppm) is associated with the C_{19} Me which is remote from the reference plane. Similar results (Table) were obtained for the enone formate (**20**), the effect of the axial formate grouping enhancing the shielding of the C_{19} and C_{20} Me groups in benzene.

In an attempt to hydrogenate the double bond of the enediol (**15**), the latter was shaken in EtOAc with hydrogen over 10% Pd-C. After 8 h, the NMR spectrum of recovered material indicated that hydrogenolysis was proceeding faster than hydrogenation. Thus a triplet at τ 4·89 ($J_{obs} = 4$ Hz) was clearly due to an isolated vinyl proton coupling to an adjacent methylene group. On resubjecting the material to hydrogenation for a further 48 hr, a saturated tetracyclic alcohol, $C_{20}H_{34}O$, was obtained. Examination of molecular models of **15** shows that irrespective of whether the two-carbon bridge between C_8 and C_{13} is α or β, the β-face of the double bond is the more accessible to hydrogenation. Thus if ring D has an α bridge, hydrogenation should have given *ent*-beyeran-18-ol (**5**). The new compound and **5** could not be separated on GLC and give rise to virtually identical mass and NMR spectra. Further, their m.ps were identical, but admixture resulted in depression, while slight differences can be detected in their IR spectra. These observations suggest that the hydrogenolysis

product is very similar to **5** differing solely in the stereochemistry of ring D.* The C_{12} position of the allylic alcohol (**14**) proved to be particularly reactive. Thus an attempted chromic acid oxidation of **15** in the presence of HOAc led to facile formation of the derived acetate (**16**). Also, treatment of **16** with MeOH and aqueous sodium bicarbonate resulted in methanolysis, a 30 min reflux producing the methoxy alcohol (**18**) together with a small amount of the corresponding formate (**17**). **18** was also obtained cleanly when a solution of the enediol monoformate (**14**) and sodium bicarbonate in aqueous MeOH was kept for 2 days.

The major product formed initially in the rearrangement of **3** at higher concentrations is believed to be the enediol diformate (**19**). However, the allylic secondary formate group hydrolyses so readily on TLC that **19** could not be isolated in the absence of **14**. Indeed, this facile hydrolysis provided a convenient method for the isolation of pure **14**. The diformate (**19**), isolated from the product mixture by preparative TLC, was invariably contaminated with rearrangement products of similar polarity, and with **14**. However, further attempts at separation (Experimental) induced extensive hydrolysis to **14** which, being considerably more polar, could be isolated readily.

The remaining less abundant rearrangement products have been briefly examined and appear to emanate from **14** since resubjection of this enediol monoformate leads initially to the diformate (**19**) followed by slow formation of products which are identical on TLC to the above. One of the least polar reaction products, the IR spectrum of which is devoid of CO and OH absorption, has been formulated as **23**. Thus its NMR spectrum discloses three tertiary methyls and a sharp singlet at τ 6·43 (2H) indicating the group $>C-CH_2OC<$ while a singlet at τ 4·64 (2H) and a band at ν_{max} 3010 cm^{-1} in the IR are indicative of two vinyl protons. Mechanistically **23** is readily derivable from **19**. A 1,2-shift of the C_{20} Me group to C_9 of the allylic cation (**24**) generated from **19** by loss of formic acid, would leave a carbonium ion at C_{10} which could be captured intramolecularly by the C_{19} OH group.

The constitution of **14** having been established, attention was directed to the mechanism of its formation from **3**. Opening of the epoxide ring of **3**, following protonation, could lead to the development of carbonium ion character at either C_{15} or C_{16}. Subsequent rearrangement of the latter intermediate results in formation of the kauranoid products (**7**, **11**, **12** and **13**), but production of **14** from the same intermediate would require an extensive series of hydride shifts and a Me group shift, formally from C_{13} to C_{16} of **3**. Since it seemed highly unlikely that such a sequence could be involved, attention was directed to the possibility that **14** might result by rearrangement of the C_{15} carbonium ion. Previous experience† had suggested that the C_{15} carbonium ion derived from *ent*-beyerene (**2**) is not subject to rearrangement,‡ solvent capture or removal of the C_{16} *exo* proton to regenerate **2** being much more favourable. In the present instance there is no *exo* proton at C_{16} and the oxygen function being released by opening of the epoxide ring protects the *exo* side of the bicyclic ring system and prevents trapping of the developing C_{15} carbonium ion by nucleophiles. However, examination of molecular models reveals that in the *ent*-beyerane skeleton the 11α hydrogen is favourably disposed to migrate to a C_{15} cation thus resulting in the transfer of carbonium ion character to C_{11} (**31**). Formation of **19** from **31** (Scheme 2) would then require conversion of **31** into the tertiary carbonium ion (**32**) (via a 1,2-hydride shift or deprotonation-reprotonation), migration of the C_{15}–C_8 bond to C_9 to give **33**, then of the C_{11}–C_9 bond to C_8 to give **34**, and finally deprotonation.

The fact that this mechanism predicts that C_{16} of **3** becomes C_{12} of **14** while the alternative mentioned above requires C_{16} of **3** to become C_{13} of **14** means that a distinction between the two possibilities can be made if C_{16} in the substrate is labelled. To this end we have prepared the 16α-deutero derivative of **3**, as outlined in Scheme 3, and subjected it to rearrangement in formic acid. The desired product (**14**), when isolated from the resulting mixture, was shown by NMR to be deuterated exclusively at C_{12}. This finding provides support for the suggested mechanism of formation of **14** via initial cleavage of the C_{15}–O bond in **3**. In addition, the mechanism predicts the stereochemistry actually found for the C_{12} function in **14**. However, it is possible that the allylic cation (**24**), presumably involved in the formation of **23**, is an intermediate and that **14** arises, via **19**, by preferential attack of solvent at C_{12}.

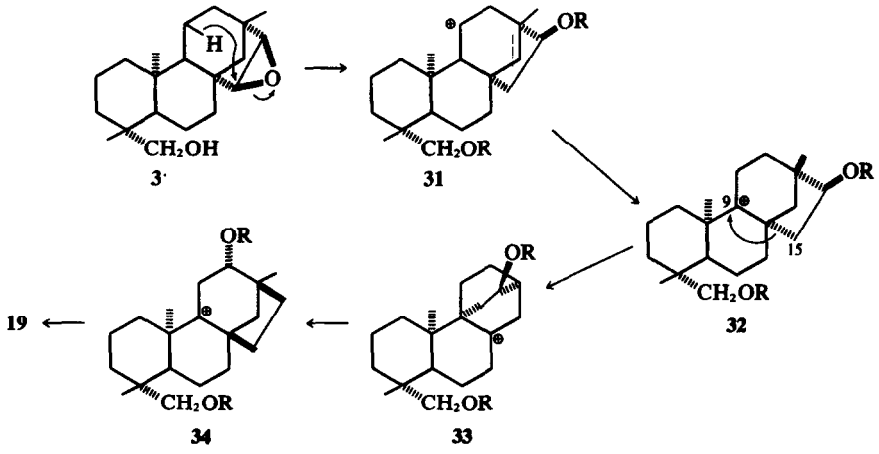
EXPERIMENTAL

M.ps were determined on a Reichert hot-stage apparatus. IR spectra of solns in CCl_4 were recorded by Mrs. F. Lawrie on Perkin-Elmer 225 and Unicam SP 100 spectrophotometers. NMR spectra of solns in $CDCl_3$ with

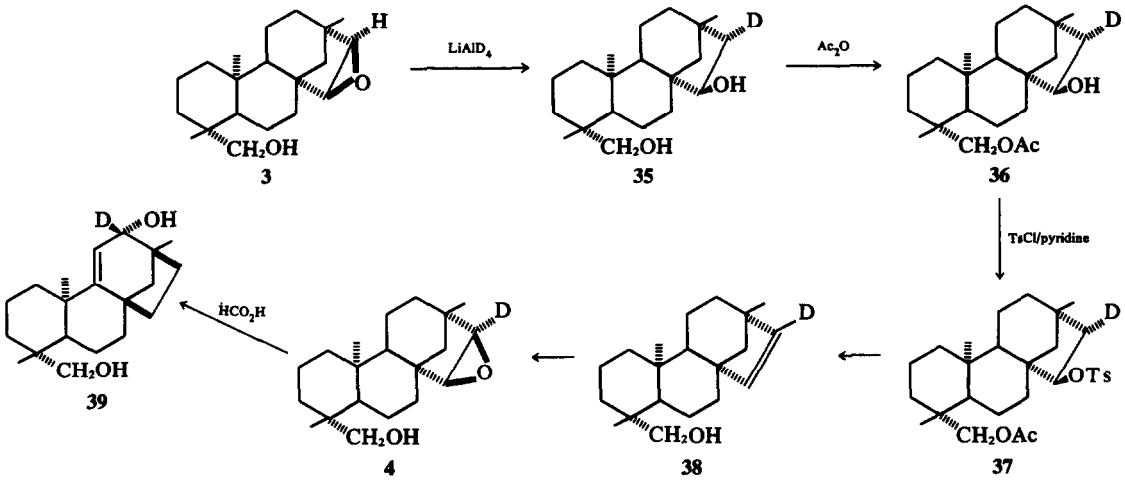
*Confirmation of the structure and stereochemistry of **14** has come from a single crystal X-ray analysis[12] which also shows the OH at C_{12} to be α. Consequently the fully saturated alcohol must have structure (**22**).

†Treatment of *ent*-beyerene (**2**) with formic acid[13] gives mainly the 15β-formate (**25**), while solvolysis of 15β-chloro-*ent*-beyerane (**26**) in sodium acetate-HOAc gives[14] almost exclusively *ent*-beyerene.

‡Migration of the C_9–C_8 bond to C_{15} would involve the development of substantial strain in contrast to the analogous migration of the C_{12}–C_{13} bond to C_{16} which is involved in the beyerane → kaurane transformation.



SCHEME 2



SCHEME 3

Table. Chemical shift values (τ) of tertiary methyl resonances

Solvent		Enone alcohol (21)			Enone formate (20)		
$CDCl_3$	C_6H_6	C_{17}	C_{19}	C_{20}	C_{17}	C_{19}	C_{20}
100	0	8·83	9·05	8·90	8·81	9·04	8·86
90	10	8·80	9·08	8·94	8·82	9·08	8·91
50	50	8·77	9·12	9·05	8·81	9·15	9·07
25	75	8·76	9·14	9·12	8·80	9·20	9·16
0	100	8·76	9·15	9·12	8·72	9·25	9·21

TMS as internal standard were recorded by Mr. A. Haetzman with a Varian T-60 spectrometer. Mass spectra were recorded by Mr. A. Ritchie with an AEI-GEC MS12 mass spectrometer. The UV spectrum was recorded on a Unicam SP 800 spectrometer and refers to an EtOH soln. Micro-analyses were performed by Mr. J. M. L. Cameron and his staff. Analytical GLC separations were obtained on a Pye-Argon chromatograph with a 1% OV-1 column at 175°. Kieselgel G (Merck) was used for analytical (0·25 mm) and HF 254 for preparative (1 mm) TLC. Analytical plates were sprayed with a soln of ceric ammonium sulphate (10 g) in dil H_2SO_4 (330 ml) diluted to 990 ml with water, and then warmed at 150° for 3 min. Light petroleum refers to the fraction b.p. 60–80°. Unless otherwise stated solids were crystallised from ether–light petroleum.

Reaction of 19-*hydroxy*-ent-*beyerane* (**5**) *with formic acid.* A soln of **5** (25 mg) in 95% formic acid (0·4 ml) was warmed on a steam bath for 10 min. Most of the solvent was removed by heating under reduced pressure and the residue (32 mg) distilled at 75°/0·02 mm to give 19-*formyloxy*-ent-*beyerane* (**6**) as an oil which solidified to colourless needles, m.p. 89·5–92°. (Found: C, 79·05; H, 10·7. $C_{21}H_{34}O_2$ requires C, 79·2; H, 10·75%); ν_{max} 1730, 1183 and 1160 cm^{-1}; NMR, τ 9·07 (9H, s), 6·13 and 5·67 (2H, ABq, J = 11·5 Hz, $-CH_2OCHO$) and 2·07 (1H, s, $-CHO$). Treatment of **6** (20 mg) in ether (5 ml) with LAH gave, after work up, **5** (17 mg), m.p. 130–132°, identical (mixed m.p., TLC, NMR and IR) with an authentic sample.

Acid-catalysed rearrangement of 19 - *hydroxy* - 15β,16β - *oxido* - ent - *beyerane* (3)

(i) A soln of 3 (510 mg) in 95% formic acid (6 ml) was warmed on a steam bath for 5 min. Most of the acid was removed by heating under reduced pressure and partial separation of the products effected by chromatography of the residue (700 mg) over silica (28 g). After elution with mixtures of ether and light petroleum, the eluates were combined into four arbitrary fractions based on similar TLC mobilities using EtOAc-light petroleum (1:4). R_f in solvent used for preparative TLC and colour of stain on analytical TLC are given. The material (120 mg) constituting band A (the least polar) was further purified by preparative TLC ($CHCl_3$–light petroleum, 1:3) to give an oily mixture of two compounds (82 mg, R_f 0·7, purple), b.p. 125°/0·35 mm (Found: C, 79·85; H, 9·8. $C_{21}H_{30}O_2$ requires C, 80·2; H, 9·6%); ν_{max} 1730 and 1175 cm^{-1} and the *ether* (23, 20 mg, 5%, R_f 0·5, purple), b.p. 60–63°/0·02 mm; ν_{max} 3010, 1090, 1062, 1020 and 850 cm^{-1}; *m/e* 286 (15%, M^+, $C_{20}H_{30}O$), 271 (30), 243 (100), 215 (20), 119 (30), 105 (44) and 91 (38); NMR (CCl_4), τ 9·15 (3H, s), 8·98 (6H, s), 6·43 (2H, s) and 4·64 (2H, s). Band B (52 mg) comprised three products, partial resolution of which was achieved with preparative TLC (EtOAc–light petroleum, 1:39) to give impure quantities of three brown staining compounds, 5 mg, 14 mg, and 10 mg respectively, all of R_f 0·4 to 0·5. Band C (234 mg) contained six compounds which were separated by preparative TLC (EtOAc-light petroleum, 1:9) into: an oily mixture (12 mg, R_f 0·6, grey) of **19** and another compound [NMR signals for **19** at τ 9·06, 8·94 and 8·90 (each 3H, s), 4·87 (1H, d, J = 3 Hz, H-12), 4·35 (1H, bs, H-11), 2·00 and 1·90 (each 1H, s, –OCHO)]: the *diformate* (7, 196 mg, 40% R_f 0·5, rose), m.p. 135–136° (Found: C, 73·65; H, 8·65. $C_{22}H_{32}O_4$ requires: C, 73·3; H, 8·95%); ν_{max} 1720 and 1175 cm^{-1}; *m/e* 360 (7%, M^+), 314 (50), 286 (32), 255 (27), 150 (40) and 94 (100); NMR, τ 9·05 and 8·87 (each 3H, s), 8·28 (3H, d, J = 1 Hz), 6·10 and 5·60 (2H, ABq, J = 11 Hz), 4·98 (1H, m, H-15), 4·50 (1H, bs, H-14) and 1·98 (2H, s, 2x OCHO): an oil (3 mg, R_f 0·4, yellow) and an oily mixture of two compounds (7 mg, R_f 0·3, grey).

Preparative TLC of band D (91 mg) in EtOAc–light petroleum (1:1) afforded the *triol triformate* (**11**, 4 mg, R_f 0·8, rose), m.p. 124–125° (Found: C, 67·85; H, 8·35. $C_{23}H_{34}O_6$ requires: C, 67·95; H, 8·45%); ν_{max} 1728 and 1178 cm^{-1}; *m/e* 360 (16%, M- HCO_2H), 314 (52), 255 (50), 121 (54), 105 (64), 91 (92) and 41 (100); NMR, τ 9·08, 8·94 and 8·36 (each 3H, s), 6·11 and 5·66 (2H, ABq, J = 11 Hz), 4·54 (1H, bs), 2·06 (1H, s) and 1·89 (2H, s): the *enediol monoformate* (**14**, 18 mg, R_f 0·7, grey) and m.p. 105–106° (Found: C, 75·9; H, 9·85. $C_{21}H_{32}O_3$ requires: C, 75·85; H, 9·7%); ν_{max} 3600, 1728 and 1165 cm^{-1}; *m/e* 314 (52%, M–H_2O), 286 (95), 271 (50), 225 (58), 157 (48), 131 (64) and 118 (100): an oil (3 mg, R_f 0·6, yellow): the *triol diformate* (**12**, 32 mg, R_f 0·5, rose), m.p. 126–128° (Found: C, 70·05; H, 9·2. $C_{22}H_{34}O_5$ requires: C, 69·8; H, 9·05%); ν_{max} 3600, 3500 and 1728 cm^{-1}; *m/e* 332 (36%, M–HCO_2H), 273 (100), 255 (20), 229 (38) and 91 (94); NMR, τ 9·07, 8·90 and 8·75 (each 3H, s), 6·20 and 5·60 (2H, ABq, J = 11 Hz), 4·41 (1H, bs) and 2·04 and 1·93 (each 1H, s): and the *triol monoformate* (**13**, 17 mg, R_f 0·4, rose), m.p. 161–164° (Found: C, 71·65; H, 9·7. $C_{21}H_{34}O_4$ requires: C, 71·95; H, 9·8%); ν_{max} 3628, 3603, 3510 and 1728 cm^{-1}; *m/e* 332 (18% M^+), 273 (100, 255 (18), 229 (15), 135 (56), and 81 (75); NMR, τ 9·04, 9·01 and 8·65 (each 3H, s), 6·06 and 5·64 (2H, ABq, J = 11 Hz), 5·79 (1H, bs, H-14) and 1·95 (1H, s).

(ii) A soln of 3 (1·13 g) in 95% formic acid (1·5 ml) was warmed for 5 min. After work-up, TLC showed the formation of the same range of compounds as above, but occurring in different relative proportions. Preparative TLC of the residue in EtOAc–light petroleum (1:9) yielded **14** (80 mg) and a mixture of **7** and **19**. The latter mixture was warmed in EtOAc for 10 min when further preparative TLC afforded **14** (178 mg).

Reactions of the enediol diformate (7)

(i) *Reduction.* A soln of 7 (60 mg) in ether (5 ml) was stirred overnight with LAH (19 mg). Work up gave the *enediol* (**8**, 49 mg 97%), m.p. 195–196° (Found: C, 78·65; H, 10·55. $C_{20}H_{32}O_2$ requires: C, 78·9; H, 10·6%); ν_{max} 3610 and 3400 cm^{-1}; *m/e* 304 (25%, M^+), 286 (28), 255 (40), 210 (50), and 94 (100); NMR, τ 9·03 and 8·97 (each 3H, s), 8·26 (3H, d, J = 1 Hz), 6·58 and 6·25 (2H, ABq, J = 11 Hz), 5·87 (1H, bs) and 5·0 (1H, bs). Acetylation of **8** (38 mg) with Ac_2O and pyridine at 0° gave, after work up, the *enediol diacetate* (**9**, 37 mg, 75%), b.p. 140°/0·004 mm (Found: C, 74·4; H, 9·3. $C_{24}H_{36}O_4$ requires: C, 74·2; H, 9·35%), ν_{max} 1735 and 1245 cm^{-1}; *m/e* 388 (15%, M^+), 328 (50), 94 (60) and 43 (100); NMR, τ 9·06 and 8·86 (each 3H, s), 8·26 (3H, d, J = 1 Hz), 7·96 (6H, s, $OCOCH_3$) 6·15 and 5·79 (2H, ABq, J = 11 Hz), 5·0 and 4·6 (each 1H, bs).

(ii) *Catalytic hydrogenation.* A soln of 7 (84 mg) in EtOAc (15 ml) was shaken with 10% Pd-C (12 mg) under hydrogen for 20 h. After removal of catalyst and solvent, the residue was purified by preparative TLC (EtOAc–light petroleum, 3:17) to give a 3:2 mixture (GLC) of *dihydro epimers* (54 mg), m.p. 154–158° (Found: C, 72·65; H, 9·15. $C_{22}H_{34}O_4$ requires: C, 72·9; H, 9·45%).

Dehydration of the triol diformate (**12**). A soln of **12** (80 mg) and phosphoryl chloride (0·2 ml) in pyridine (0·5 ml) was kept overnight then poured into water (10 ml). An ether extraction work up gave 7 (72 mg, 94%), identical (mixed m.p., NMR and IR) with an authentic sample.

Reactions of the enediol monoformate (**14**)

(i) *Reduction.* A soln of **14** (53 mg) in ether (4 ml) was stirred with LAH (10 mg) for 30 min. Work up gave the *enediol* (**15**, 47 mg, 97%), m.p. 150–152° (Found: C, 78·75; H, 10·45. $C_{20}H_{32}O_2$ requires: C, 78·9; H, 10·6%), ν_{max} 3620 and 3550 cm^{-1}; *m/e* 304 (12%, M^+), 286 (32), 273 (48) and 243 (100); NMR, τ 9·07, 8·96 and 8·90 (each 3H, s), 6·42 (1H, d, J = 4 Hz, H-12), 6·42 and 6·16 (2H, ABq, J = 11 Hz) and 4·64 (1H, d, J = 4 Hz, H-11).

(ii) *Oxidation.* A soln of **14** (20 mg) in benzene (4 ml) at 5° was treated with a cold soln of sodium dichromate and sulphuric acid containing a little HOAc until an orange colour persisted in the reaction medium.[15] The soln was poured into ice-water (10 ml) and the product extracted into benzene. Work up gave the *enone* (**20**, 19 mg, 95%), m.p. 130–131· (Found: C, 76·45; H, 8·85. $C_{21}H_{30}O_3$ requires: C, 76·3; H, 9·15%); ν_{max} 1731 and 1676 cm^{-1}; λ_{max} 245 nm (ε 12,900); *m/e* 330 (52%, M^+) and 271 (100); NMR, τ 9·00, 8·82 and 8·76 (each 3H, s), 5·82 and 5·57 (2H, ABq, J = 11 Hz), 4·22 (1H, sharp s, H-11) and 1·88 (1H, s). The enone formate (39 mg) was stirred overnight in aqueous MeOH (1:1, 3 ml) containing $NaHCO_3$ (20 mg). Removal of the MeOH under reduced pressure, followed by extraction with ether and conventional work up, yielded the *enone alcohol* (**21**, 30 mg, 85%), m.p. 133–134° (Found: C, 79·4; H, 9·8. $C_{20}H_{30}O_2$ requires: C, 79·4; H, 10·0%), ν_{max} 3640 and 1673 cm^{-1}; *m/e* 302 (25%, M^+) and 271 (100); NMR τ 9·05, 8·90 and 8·83 (each 3H, s), 6·44 and 6·20 (2H, ABq, J = 11 Hz) and 4·28 (1H, s).

(iii) *Acetylation.* A soln of **14** (98 mg) in benzene (10 ml) was treated at 5° with a cold soln made by saturating 50%

H_2SO_4 (30 ml) with sodium dichromate and adding HOAc (5 ml). When the orange colour persisted, the benzene soln was poured into ice-water (20 ml) and the product extracted with benzene. Work up afforded the *acetate* (**16**, 93 mg, 85%), m.p. 134–136° (Found: C, 73·65; H, 9·0. $C_{23}H_{34}O_4$ requires: C, 73·8; H, 9·15%); ν_{max} 1730, 1240 and 1170 cm^{-1}; *m/e* 374 (8%, M^+), 314 (44) and 286 (100); NMR, τ 9·11, 9·02 and 8·96 (all 3H, s), 8·05 (3H, s, $OCOCH_3$), 5·95 and 5·65 (2H, ABq, J = 11 Hz), 5·17 (1H, d, J = 4 Hz), 4·78 (1H, d, J = 4 Hz) and 1·96 (1H, s). A soln of **16** (40 mg) in aqueous MeOH (1:1, 10 ml) containing $NaHCO_3$ was refluxed for 30 min. After removal of MeOH under reduced pressure the product was extracted into ether and separated by preparative TLC (EtOAc–light petroleum, 1:4) into the *methoxy alcohol* (**18**, 23 mg, 65%), m.p. 158–160° (Found: C, 79·0; H, 10·6. $C_{21}H_{34}O_2$ requires: C, 79·2; H, 10·8%); ν_{max} 3620 cm^{-1}; *m/e* 318 (10%, M^+) and 243 (100); NMR, τ 9·05, 8·90 and 8·87 (each 3H, s), 6·88 (1H, d, J = 4 Hz); 6.59 (3H, s, OCH_3), 6·38 and 6·09 (2H, ABq, J = 11 Hz) and 4.52 (1H, d, J = 4 Hz); and the methoxy formate (**17**, 3 mg, 8%), ν_{max} 1725 cm^{-1}; NMR, τ 9·04, 9·01 and 8·90 (each 3H, s), 6·90 (1H, d, J = 4 Hz), 6·64 (3H, s), 5·90 and 5·58 (2H, ABq, J = 11 Hz), 4.55 (1 H, d, J = 4 Hz) and 1·90 (1H, s).

(iv) *Methanolysis.* A soln of **14** (50 mg) in aqueous MeOH (1:1, 10 ml) containing $NaHCO_3$ was kept for 2 days. Work up gave **18** (48 mg, 92%) identical, mixed m.p. and TLC, with an authentic sample.

Hydrogenolysis of the enediol (**15**). A soln of **15** (47 mg) in EtOAc (15 ml) was shaken under H_2 with 10% Pd-C (13 mg). After 8 h, the NMR of recovered material disclosed a signal at τ 4·89 (2H, t, J = 4 Hz). On resubjection of the product to the reaction conditions for 48 h, work up, followed by preparative TLC (EtOAc–light petroleum, 3:7) afforded the saturated *alcohol* (**22**, 20 mg, 45%), m.p. 130–131° (from light petroleum) (Found: C, 82·5, H, 11·5. $C_{20}H_{34}O$ requires: C, 82·7; H, 11·8%); ν_{max} 3640 and 3480 cm^{-1}; *m/e* 290 (4%, M^+) and 259 (100); NMR, τ 9·04 (9H, s), 6·58 and 6·22 (2H, ABq, J = 11 Hz).

Preparation of 16α - *deutero* - 19 - *hydroxy* - 15β,16β - *oxido* - ent - *beyerane* (**4**)

(i) 16α - *Deutero* - 15β,19 - *dihydroxy* - ent - *beyerane* (**35**). The epoxide (**3**, 2·6 g) was reduced[3] with $LiAlD_4$ (2 g initially, 1 g after 2 days, 1 g after a further day) in refluxing 1,2-dimethoxyethane (150 ml) over a period of 4 days. Reduction was still incomplete after this time. The product (**35**, 1·6 g), m.p. 211–213°, was recovered by preparative TLC (EtOAc–light petroleum, 1:9 run thrice). NMR signal (pyridine) at τ 5·50 (broad s, 15-αH). The following transformation was carried out initially on the protium analogue, for which experimental details and analytical figures are given. Reaction of the deuterated species was carried out similarly.

(ii) *Acetylation of* 15β,19 - *dihydroxy* - ent - *beyerane* (**27**). A mixture of the diol (**27**, 0·21 g) and Ac_2O (0·084 g) in pyridine (5 ml) was allowed to react overnight at 5°. TLC (EtOAc–light petroleum, 1:3) showed the presence of four components which were separated by preparative TLC (EtOAc–light petroleum, 1:9, run thrice) into: the *diacetate* (28, 55 mg), m.p. 136–137° (from light petroleum) (Found: C, 74·0; H, 9·7. $C_{24}H_{38}O_4$ requires: C, 73·8; H, 9·7%); NMR, τ 9·07, 9·02 and 8·98 (each 3H, s), 7·97 (6H, s, $COCH_3$), 6·12 and 5·75 (2H, ABq, J = 11 Hz) and 4·67 (1H, broad d, J = 7 Hz, H-15); in the deuterio analogue, a broad singlet appears at τ 4·67 in place of the doublet reported above: the 19-*monoacetate* (**29**), m.p. 158–159° (from light petroleum) (Found: C, 76·0; H, 10·7. $C_{22}H_{36}O_3$ requires: C, 75·8; H, 10·4%); NMR, τ 9·03 (3H, s), 9·01 (6H, s), 7·98 (3H, s), 6·12 and 5·70 (2H, ABq, J = 11 Hz) and 5·72 (1H, m, H-15, partly obscured): the 15-monoacetate (**30**, very minor and not fully characterised): and starting material (**27**).

(iii) 16 - *Deutero* - 19 - *hydroxy* - ent - *beyer* - 15 - *ene* (**38**). The 6α-deuterodiol-19-monoacetate (**36**, 1·4 g) was converted into the corresponding **37** with toluene-*p*-sulphonyl chloride in pyridine at 20° overnight. The resulting crude product was heated with NaOH in refluxing aqueous MeOH (1:1) for 18 h. TLC (EtOAc–light petroleum, 1:3) showed the presence of the corresponding diol and two minor products in addition to the required alcohol (**38**). The last (0·70 g) was purified by preparative TLC (EtOAc–light petroleum, 1:9, run thrice) and crystallisation from light petroleum. **38** had m.p. 119–120° and in the NMR spectrum, the pair of doublets due to H-15 and H-16 of **1**[2] are replaced by a singlet at τ 4·40 (H-15) in this deutero analogue.

(iv) 16α - *Deutero* - 19 - *hydroxy* - 15β,16β - *oxido* - ent - *beyerane* (**4**). This compound was prepared by oxidation of **38** with *m*-chloroperbenzoic acid in $CHCl_3$[3] and purified by preparative TLC (EtOAc–light petroleum, 1:9, run thrice) and crystallisation from MeOH. **4** had m.p. 115–117°; NMR, τ 6·61 (1H, s, H-15); *m/e* 305 (M^+).

Formic acid treatment of 16α - *deutero* - 19 - *hydroxy* - 15β,16β - *oxido* - ent - *beyerane*. The deutero-epoxide (**4**, 0·62 g) was warmed on a steam bath with formic acid (0·75 ml) for 5 min and worked up as described above. Preparative TLC gave **39**, m.p. 105–108° (from light petroleum); NMR, τ 4·70 (1H, s, H-11).

Acknowledgments—One of us (R. McC) is grateful to the National Research Council of Canada for the award of an operating grant. We also thank the S. R. C. for a studentship (to R. W. M.).

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