A Synthesis of Methyl 2α-Acetoxy-3-deoxo-3α-hydroxyangolensate

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The title compound (**1a**) has been partially synthesised from gedunin. It is the first natural 1α,2α,3α-trihydroxy terpene molecule to have been synthesised. Attempts to introduce a 2α-hydroxy group into a preformed methyl angolensate derivative failed, and the synthesis was achieved by the prior preparation of 2α-acetoxy-7-deacetoxy-7-oxokhivorin (**2a**),[1] which was converted into the title compound. The key stage in the conversion is the Baeyer–Villiger oxidation of the 7-oxo group to a lactone, which was studied in some detail. The use of buffered peracetic acid effects the required oxidation in good yield without oxidising the furan ring; the use of pertrifluoroacetic acid oxidises the furan ring to an unsaturated lactone without attacking the carbonyl group. The implications of this are considered in an Appendix.

The limonoids of the genus *Ekebergia* (Meliaceae)[2,3] are unusual in several ways, among which is oxygenation at positions 1α,2α,3α. Since this oxidation pattern is shared with other limonoids of possible importance, such as the insecticidal trichilins[4] and the anti-cancer active aphanastatin[5] and since it has not been obtained synthetically, we decided to attempt the synthesis of the simplest member of this group, methyl 2α-acetoxy-3-deoxo-3α-hydroxyangolensate (**1a**),[1] or EP1.

Originally we hoped to succeed by oxidation of a suitable derivative of methyl angolensate (**3a**). Desulphurisation of the dithioketal of methyl angolensate with deactivated Raney nickel readily gives the required methyl Δ^2-dehydro-3-deoxoangolensate (**3b**), but this could not be oxidised. Oxidations of limonoids are frequently difficult to carry out, *e.g.* the double bond in methyl angolensate itself resists oxidation, even by ozone.

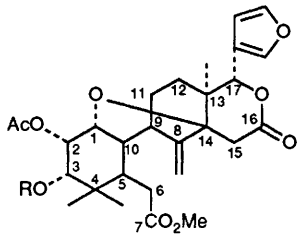
In general, a 2,3-double bond is more difficult to oxidise in a trimethyl steroid than is a 1,2-double bond, and since a ring A double bond in a methyl angolensate derivative is necessarily 2,3 we switched our attention to deoxyandirobin (**4a**). This is readily obtained from methyl angolensate by acid-catalysed ring opening and dehydration, and if the double bond could be hydroxylated, it is known that similar 1α-hydroxy compounds cyclise readily.[6]

Reduction of deoxyandirobin with aluminium isopropoxide gave a mixture of two epimeric alcohols. After separation by chromatography, the 3β epimer (**4c**) was isolated as the lactone (**5**), and the 3α epimer as an isopropyl ester, which could be reconverted into the methyl ester (**4b**) by hydrolysis and methylation. Attempts were made to oxidise the double bond in the 3α epimer, but this was again resistant to oxidation by osmium tetroxide. Although the reason for the lack of reactivity is not obvious, it is perhaps connected with the geometry adopted by the flexible deoxyandirobin molecule.

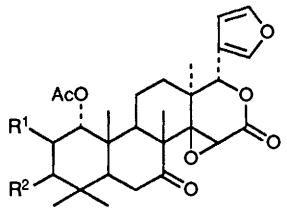
In a recent paper, Srivastava[7] has reported the isolation of a natural product which he named amoorinin, assigned the structure of 3β-hydroxy-3-deoxoandirobin, which on chromium(II) chloride reduction was said to give 3β-hydroxy-3-deoxodeoxyandirobin (**4c**). However, the recorded properties do not correspond with those of our structure (**4c**); the NMR spectrum is different, it does not form a lactone, and the spectral details are also different from those of our 3α-epimer. Unfortunately, it has not been possible to obtain a specimen of amoorinin for comparison, and we can suggest no explanation for the discrepancy.

Methyl angolensate (**3a**) has been synthesised from 7-deacetoxy-7-oxokhivorin (**2b**),[6] and it seemed that it should be possible to synthesise compound (**1a**) similarly from 2α-acetoxy-7-deacetoxy-7-oxokhivorin (**2a**). This was synthesised from gendunin, as described in the accompanying paper,[1] and we now describe the conversion.

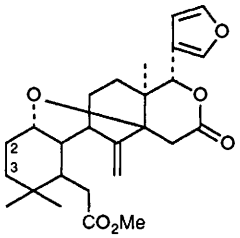
The key stage is the oxidation of the ketonic carbonyl group



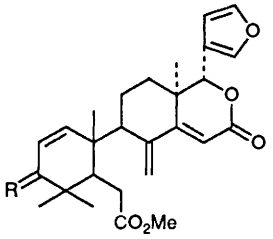
(1)
a R = H
b R = Ac



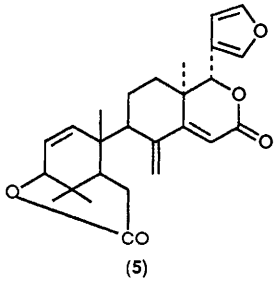
(2)
a $R^1 = R^2 = \alpha OAc$
b $R^1 = H$; $R^2 = \alpha OAc$
c $R^1 = R^2 = \beta OAc$



(3)
a 3-oxo
b Δ^2

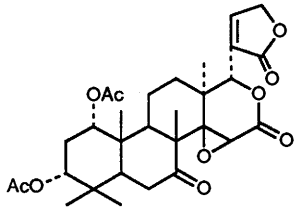


(4)
a R = O
b R = H; αOH
c R = H; βOH



(5)

to a lactone. This was carried out in the original synthesis of methyl angolensate[6] with commercial peracetic acid, and it was noted that the presence of water in the peracid was deleterious. Since we did not have access to the commercial acid, we first attempted the use of other peracids, using the more readily available 7-deacetoxy-7-oxokhivorin (**2b**) as a model. Perbenzoic and *m*-chloroperbenzoic acid were without effect on the ketone, but slowly attacked the furan ring. Trimethylsilyl peroxide[8] was without effect. Pertrifluoracetic acid, in contrast, reacted rapidly and exothermically, the product, isolated in nearly quantitative yield, was the lactone (**6**) produced by



(6)

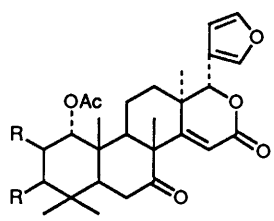
oxidation of the furan ring. It has recently been shown that compounds containing this type of lactone ring, which is isomeric to that in the cardiac aglycones, are physiologically active and have certain pharmacological advantages over the natural isomers. This method would seem to be a better route for their preparation than that used originally.[9]

In view of this lack of success, we turned back to peracetic acid, and discovered that when this was prepared by the simple method described in Houben–Weyl,[10] and used buffered with anhydrous disodium hydrogen phosphate, satisfactory yields were obtained. It was later found[1] that the required oxidation can be effected by perbenzoic acid, if this is buffered with sodium benzoate, but this discovery was made too late for use in the present work.

With the Baeyer–Villiger reaction successfully controlled, we returned to our projected synthesis. 2α-Acetoxy-7-deacetoxy-7-oxokhivorin (**2a**) was reduced with chromium(II) chloride,[11] giving the 14,15-deoxy compound (**7a**), and this was oxidised to the ε-lactone (**8a**) with peracetic acid. Mild alkaline hydrolysis of lactone (**8a**), followed by methylation and acetylation gave two products: an acetoxy methyl ester (**9a**), and a diacetoxy methyl ester (**9b**). The structures were assigned on the basis of the ^{1}H NMR spectra, neither of which showed the characteristic resonance of the vinyl proton 15-H. Dehydration of the tertiary hydroxy group in the monoacetate (**9a**) with thionyl chloride gave EP1, (**1a**), identical with the natural product. Similar treatment of the diacetate gave the 3-acetate of EP1, (**1b**). This is not obtained from EP1 by acetylation with pyridine and acetic anhydride, but is obtained rather slowly when 4-DMAP is used as the catalyst. This steric hindrance presumably accounts for the rather unusual resistance of the secondary hydroxy group to treatment with thionyl chloride.

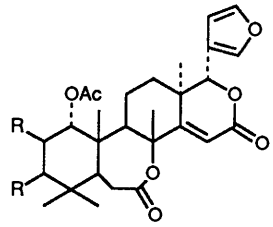
This therefore successfully completed the desired synthesis.

As a model experiment, this sequence was also carried out with the 2β,3β-epimer (**2c**), which had been obtained in an earlier attempt to make compound (**2a**).[1] In this case,



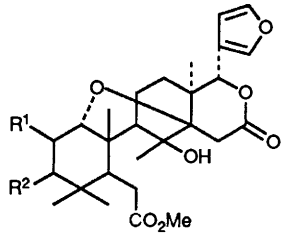
(7)

a R = H; αOAc
b R = H; βOAc



(8)

a R = H; αOAc
b R = H; βOAc



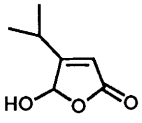
(9)

a R^1 = H, αOAc; R^2 = H, αOH
b R^1 = R^2 = H; αOAc
c R^1 = R^2 = H; βOAc

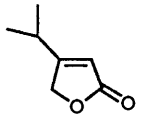
hydrolysis and acetylation gave only the diacetate (**9c**), and thionyl chloride dehydration then gave the 2β,3β-epimer of EP1 acetate.

Appendix *

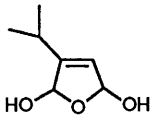
In connection with work on the synthesis of cardioactive steroids, Wiesner and his associates have shown[9] that oxidation of 3-isopropylfuran with buffered peracetic acid leads to the oxodihydrofuranol (**10**), which can be reduced with borohydride, by way of the dihydrofurandiol (**12**), to the digitoxigenin analogue (**11**). The mechanism was considered to be initial electrophilic oxidation in the less hindered 5-position, followed by nucleophilic attack in the 2-position.



(10)



(11)



(12)

When *N*-bromosuccinimide was used as the oxidising agent, the isomeric lactone (**13**) was produced; it was suggested that this arose by loss of hydrobromic acid from the intermediate (**14**).

Woodward and Eastman[12] have shown that the tetrahydrobenzofuran (**15**), on autoxidation or with hydrogen peroxide, gives the hydroxylactone (**16**), which on dehydration gives compound (**17**). Vinhaticoic† acid and vouacapenic‡ acids give similar reactions on oxidation with perphthalic acid. In these cases only one position of the furan ring is initially unsubstituted.

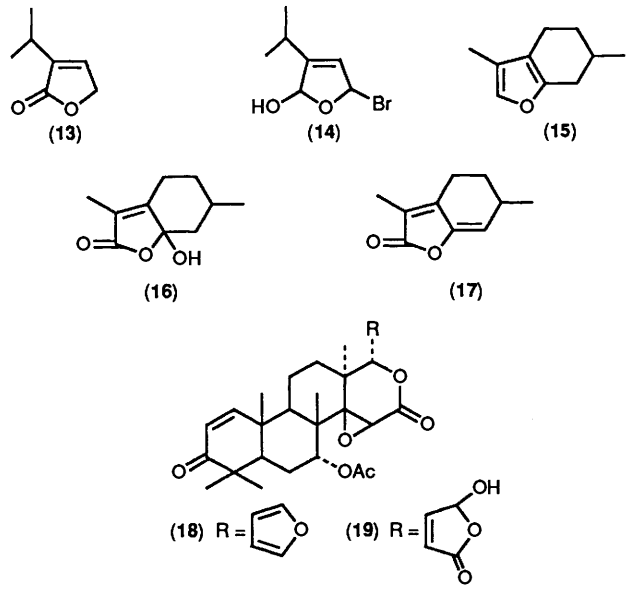
The furan ring in limonoids is not readily oxidised; some oxidised derivatives are, however, known. It has long been known that photo-oxidation of gedunin (**18**) gives the oxodihydrofuranol (**19**), while both compound (**19**) and the isomeric furanol occur as natural products.[13]

In our work described above we report that oxidation of 7-oxo-7-deacetoxykhivorin with peroxytrifluoroacetic acid leaves the ketone unattacked, but gives a quantitative yield of compound (**6**). This is the opposite direction of attack from that reported by Wiesner in the analogous case, using peracetic acid.

* Work performed with F. M. Dean, Students Visiting Lecturer's Trust Fund guest in Durban, on leave from the Dept. of Organic Chemistry, University of Liverpool, Liverpool L69 3BX, UK.

† CA recommended—1,2,3,4,4aβ,5,6,6aα,7,11,11aβ,11b-Dodecahydro-4α,7β,11bα-trimethylphenanthro[3,2-b]furan-4-carboxylic acid.

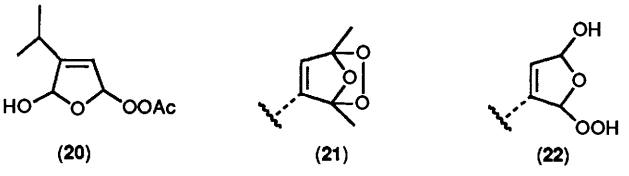
‡ CA recommended—(4*S*,4a*R*,6a*S*,7*R*,11a*S*,11b*R*)-1,2,3,4,4a,5,6,6a,7,11,11a,11b-Dodecahydro-4,7,11b-trimethylphenanthro[3,2-*b*]furan-4-carboxylic acid.



The mechanism proposed by Wiesner involves the initial attack of an electrophile on the less hindered 5-position of a 3-substituted furan. In known cases, 3-substituted furans undergo electrophilic substitution preferentially at the more hindered 2-position, which is analogous to an *ortho* position, and not in the 5-position, which is analogous to a *meta* position.[14] We therefore consider it more likely that the electrophilic oxidation of a 3-substituted furan with a peracid or with acidified peroxide is initiated by the attack of a positive hydroxy in the 2-position, the product then being stabilised by the addition of a negative ion in the 5-position.

In the buffered peracetic acid solution used by Wiesner, the most nucleophilic anion will be that of the peracid itself, giving the intermediate (**20**). Collapse of the peroxide linkage with concomitant elimination of the 5-proton will then give the product, the digitoxigenin analogue (**11**). In the *N*-bromosuccinimde oxidation, reaction will again by initiated by the attack of a positive hydroxy ion at the 2-position. The negative ion to be picked up at 5 is then the bromide ion, both ions being derived from hypobromous acid. Since bromide is a good leaving group, hydrogen bromide is readily eliminated forming the alkylfuranone (**13**).

Peroxytrifluoroacetic acid oxidation is similar; the positive ion is hydroxy, and the negative ion is trifluoroacetate, an extremely poor nucleophile. Consequently, the product is the alkylfuranone as with *N*-bromosuccinimide.



We would expect the photo-oxidation of limonoids, conducted in benzene solution, to yield a 2,5-peroxide (**21**), stable in benzene solution. Following isolation by chromatography over silica, we suggest that this peroxide is opened by acid catalysis by the silica, forming a 2-hydroperoxide with a positive ion at C-5, a similar intermediate to those discussed above. Addition of a hydroxy ion from the silica will give the intermediate (**22**) which by collapse of the peroxide linkage and elimination of water gives the furanone obtained as the product of this reaction. A similar mechanism can account for the oxidation of the tetrahydrobenzofuran (**19**).

Experimental

^{1}H NMR spectra were determined in $CDCl_3$ on a CFT 20 instrument with Me_4Si as an internal standard and highfield spectra were determined by the CSIR in Pretoria (500 MHz). Column chromatography was performed on silica gel (Merck Art 7734), using ethyl acetate–methylene dichloride. TLC analysis was on alumina backed silica sheets (Merck Art 5554) and preparative TLC was on glass backed silica gel plates (Whatman PK6F). Mass spectra are by Professor Drewes, University of Natal, Pietermaritzburg, South Africa and elemental analyses are by Professor Drewes or by Dr. L. Strauch of the University of Basel, Switzerland. Acetates were prepared with pyridine–acetic anhydride, unless 4-DMAP is specified. Crystallisations are from methanol–methylene dichloride.

Methyl Δ^2*-Deoxoangolensate* (**3b**).—Aged Raney nickel (*ca.* 6 months; 5 g) was heated under reflux for 1 h in ethyl acetate (300 ml). The solvent was then decanted, replaced by fresh ethyl acetate (300 ml) and methyl angolensate dithioketal (1 g) was added. After 1 h under reflux the nickel was filtered off, and the solvent evaporated. The residue was chromatographed on a fast column to yield methyl Δ^2 3-deoxoangolensate (**3b**) (210 mg), which did not crystallise, as the main product; δ_H(500 MHz) 7.41 (m, 21-H), 7.34 (m, 23-H), 6.37 (m, 22-H), 5.71 (s, 17-H), 5.57 (d, *J* 2 Hz, 3-H), 5.44 (dd, *J* 2.0 and 1.0 Hz, 2-H), 5.10 and 4.87 (2 H, 2 × s, 30-H_2), 3.69 (3 H, s, CO_2Me), 3.26 (d, *J* 1 Hz, 1-H), 2.91 and 2.62 (2 H, *J* 4 Hz, 15-H_2), 1.02, 0.96, 0.86, and 0.76 (4 × C-Me); δ_C 175.8 (s), 170.8 (s), 146.3 (s), 142.5 (d), 142.3 (d), 140.6 (d), 121.0 (s), 120.1 (d), 110.0 (t), 109.8 (d), 79.8 (d), 79.3 (s), 71.8 (d), 51.7 (q), 49.2 (d), 43.3 (s), 41.4 (s), 39.9 (t), 35.4 (s), 33.8 (t), 32.4 (t), 32.2 (d), 29.3 (t), 23.7 (q), 23.1 (q), 21.4 (q), and 13.4 (q). Further elution gave the known methyl 3-deoxoangolensate, and unchanged thioketal.

After standing for 4 weeks with *m*-chloroperbenzoic acid, only the furan ring appeared to have been attacked. Osmium tetroxide gave no reaction.

Meerwein–Ponndorf Reduction of Deoxyandirobin.—To a solution derived from aluminium foil (2 g) and propan-2-ol (150 ml) was added deoxyandirobin (**4a**) (5 g), and the solution was boiled under partial reflux for 2 h. The solution was concentrated under reduced pressure, diluted with aqueous H_2SO_4 and methylene dichloride, and the organic layer was separated. Chromatography gave the 3β-*hydroxylactone* (**5**) (1.7 g, 35%), m.p. 222–224 °C; $[\alpha]_D^{20}$ 452° (Found: C, 73.4; H, 7.1. $C_{26}H_{30}O_5$ requires C, 73.9; H, 7.2%); δ_H 7.74 (m, 21-H), 7.37 (m, 23-H), 6.41 (m, 22-H), 6.09–5.70 (not resolved at 80 MHz, 15-H, 2-H, 1-H), 5.43, 5.12, (2 H, s, 30-H_2), 5.18 (s, 17-H), 4.17 (dd, *J* 2.3, 1.7, 3-H), 1.26, 1.16, 0.97, 0.89 (4 × C-Me); δ_C 171.2 (s), 166.7 (s), 164.8 (s), 144.3 (s), 142.8 (d), 141.0 (d), 136.0 (d), 124.6 (d), 120.3 (t), 119.8 (s), 112.6 (d), 109.8 (d), 80.2 (d), 78.1 (d), 46.4 (d), 42.8 (s), 42.0 (d), 39.6 (s), 33.3 (s), 31.3 (t), 30.1 (t), 27.4 (q), 27.2 (q), 26.4 (q), 21.8 (t), and 18.3 (q).

Further elution gave the 3α-epimer, isolated as the non-crystalline isopropyl ester, δ_H 7.41 (m, 21-H), 7.36, (m, 23-H), 6.36 (m, 22-H), 5.92 (s, 15-H), 5.4–4.95 (unresolved at 80 MHz, 30-H_2, 17-H, 2-H, 1-H), 3.94 (bs, 3-H), and 1.19 (6 H, 2 × d, *J* 6 Hz, Pr^i), 0.94, 0.92, 0.86, and 0.80 (4 × C-Me). Acetylation (DMAP catalyst) gave the crystalline *acetate* (1.1 g, 22%), m.p. 189–191 °C; $[\alpha]_D^{20}$ 350°, (Found: C, 70.9; H, 7.6. $C_{31}H_{40}O_7$ requires C, 71.0; H, 7.7%); δ_H 7.49, (m, 21-H), 7.39 (m, 23-H), 6.43 (m, 22-H), 5.96 (s, 15-H), 5.43–4.91 (unresolved at 80 MHz, 30-H_2, 17-H, 3-H, 2-H, 1-H), 2.08 (3 H, s, AcO), 1.24 and 1.23 (6 H, 2 × d, *J* 6 Hz, Pr^i), and 1.01, 0.93, 0.91, and 0.87 (4 × C-Me); δ_C 173.6 (s), 170.9 (s), 167.8 (s), 165.3 (s), 143.9 (s),

142.9 (d), 141.3 (d), 136.4 (d), 126.3 (d), 120.6 (t), 120.1 (s), 112.4 (d), 110.0 (d), 80.7 (d), 77.6 (d), 68.1 (d), 49.6 (d), 42.3 (s), 41.8 (d), 39.8 (s), 38.5 (s), 31.5 (t), 29.4 (t), 25.3 (q), 22.3 (q), 22.0 (q), 21.7 (t), 21.6 (q), 21.1 (q), 18.3 (q), and 16.8 (q).

Hydrolysis of the isopropyl ester followed by re-esterification with diazomethane gave the corresponding methyl ester, and, after acetylation, its acetate, but neither was obtained crystalline. Neither epimer was significantly attacked by osmium tetroxide after 8 days.

Pertrifluoracetic Acid Oxidation of 7-Deacetoxy-7-oxokhivorin.—7-Deacetoxy-7-oxokhivorin (1.5 g) was added to a cooled mixture of hydrogen peroxide (0.25 ml; 30%) and trifluoroacetic anhydride (1.5 ml) in methylene dichloride (20 ml). The mixture became warm and after being kept overnight, was washed with aq. sodium hydrogen carbonate before being evaporated. The *lactone* (**6**) crystallised from methanol–methylene dichloride in prisms (1.35 g, 90%), m.p. 295–297 °C (Found: *m/z*, 558.2424. $C_{30}H_{38}O_{10}$ requires 558.2464); δ_H(500 MHz), 7.60 (m, *J* 1.00, 1.60, and 1.76 Hz, 22-H), 5.40 (m, *J* 1.00, 1.01, and 1.80 (17-H), 4.91 (m *J* 18.76, 1.60, and 1.01 Hz (23a-H), and 4.86 (m, *J* 18.76, 1.76, and 1.80 Hz). The remainder of the spectrum was almost identical with that of 7-deacetoxy-7-oxokhivorin.

Chromium(II) *Chloride Reduction.*—An excess of aqueous chromium(II) chloride was added to a solution of 2α-acetoxy-7-deacetoxy-7-oxokhivorin (**2a**) (300 mg) in acetone, and the mixture was allowed to stand for 3 days before being concentrated. The product was extracted with methylene dichloride, to yield 2α-acetoxy-7-deacetoxy-7-oxo-14,15-deoxykhivorin (**7a**) as a gum (300 mg); δ_H 7.43 (m, 21-H), 7.39 (m, 23-H), 6.37 (m, 22-H), 6.51 (s, 15-H), 5.40 (s, 17-H), 5.44 (m, 2-H), 5.0 (2 H, m, 1-H, 3-H), 2.05, 1.99, and 1.92 (3 × AcO), and 1.50, 1.31, 1.11, 1.07 and 0.91 (5 × C-Me).

In a similar way the 2β,3β-epimer (**2c**) (1.5 g) gave the *deoxy derivative* (**7b**) (1.4 g, 96%); m.p. 259 °C; $[\alpha]_D^{20}$ −13° (Found: C, 65.7; H, 6.95. $C_{32}H_{40}O_{10}$ requires C, 65.7; H, 6.9%); δ_H 7.45 (m, 21-H), 7.39 (m, 23-H), 6.39 (m, 22-H), 6.63 (s, 15-H), 5.23 (m, 2-H), 4.8 (2 H, m, 1-H, 3-H), 4.8 (s, 17-H), 2.09, 2.06, and 1.99 (3 × AcO), and 1.54, 1.45, 1.13, 1.10, and 0.93 (5 × C-Me).

Baeyer–Villiger Oxidation.—The 2α-acetoxy deoxy compound (**7a**) (300 mg) was oxidised overnight with peracetic acid (0.3 ml; 3M) in methylene dichloride (15 ml) containing anhydrous disodium hydrogen phosphate (400 mg). Chromatography of the product gave the required ε-lactone (**8a**) as a gum (160 mg, 52%); δ_H 7.41 (m, 21-H), 7.39 (m, 23-H), 6.46 (s, 15-H), 6.36 (m, 22-H), 5.28 (m, 2-H), 5.1 (2 H, H-1, H-3), 4.97 (s, 17-H), 2.05, 2.02, and 1.90 (3 × AcO), and 1.74, 1.32, 1.20, 1.11, and 1.03 (5 × C-Me).

Similar treatment of the 2β,3β-epimer (**7b**) (0.3 g) gave unchanged starting material (80 mg, 27%), and the ε-*lactone* (**8b**) (130 mg, 57%), m.p. 279 °C; $[\alpha]_D^{20}$ 35° (Found: C, 63.7; H, 6.8. $C_{32}H_{40}O_{11}$ requires C, 64.0; H, 6.7%); δ_H 7.42 (m, 21-H), 7.40 (m, 23-H), 6.49 (s, 15-H), 6.37 (m, 22-H), 5.21 (m, H-2), 4.9 (2 H, 1-H, 3-H), 4.96 (s, 17-H), 2.09, 2.05, and 1.98 (3 × AcO), and 1.76, 1.45, 1.13, 1.08, and 1.01 (5 × C-Me).

Hydrolysis of the ε-Lactone.—The ε-lactone (**8a**) (160 mg) in methanol (10 ml) was hydrolysed overnight with potassium carbonate (160 mg) dissolved in a little water. The solution was acidified with dilute HCl, and the product isolated with methylene dichloride. Esterification with diazomethane followed by acetylation gave a mixture separated by preparative TLC to give the *monoacetate* (**9a**); δ_H 7.40 (m, 21-H), 7.37 (m, 23-H), 6.38 (m, 22-H), 5.76 (s, 17-H), 5.05 (m, 2-H), 4.47 (d, *J* 5.0 Hz, 1-H), 3.69 (s, OMe), 3.6 (d, 3-H), 2.07 (s, AcO), and 1.19, 1.09, 1.01, and 1.01 (4 × C-Me); and the diacetate (**9b**); δ_H 7.44, (m, 21-H), 7.38 (m, 23-H), 6.39 (m, 23-H), 6.02 (s, 17-H), 5.08 (2 H, m, 2-H, 3-H), 4.35 (d, *J* 4.6 Hz 1-H), 3.70 (s, OMe), 2.00 and 1.99 (6 H, s, 2 × AcO), and 1.25, 1.12, 1.12, and 1.11 (4 × C-Me). Similar treatment of the 2β,3β-epimer (**8b**) (190 mg) gave only the diacetate (**9c**); δ_H 7.44 (m, 21-H), 7.35 (23-H), 6.38 (m, 22-H), 5.70 (s, 17-H), 5.36 (dd, *J* 7.8 and 2.3 Hz, 2-H), 4.94 (d, *J* 2.3 Hz, 3-H), 4.07 (d, *J* 7.8 Hz, 1-H), 3.68 (s, OMe), 2.06 and 1.99 (2 × AcO), and 1.29, 1.21, 1.05, and 1.02 (4 × C-Me).

Methyl 2α-Acetoxy-3α-hydroxy-3-deoxoangolensate (**1a**).—The monoacetate (**9a**) (40 mg) was dissolved in pyridine (3 ml) and treated with thionyl chloride (5 drops). After 0.5 h the solution was poured onto ice, and the organic material was isolated with methylene dichloride. Removal of the solvent yielded methyl 2α-acetoxy-3α-hydroxy-3-deoxoangolensate (**1a**), m.p. 245–248 °C; $[\alpha]_D^{20}$ −70°, identical with the natural material (TLC and NMR).

Similar treatment of the diacetate (**9b**) gave the non-crystalline acetate (**1b**), identical with a sample obtained from EP1 by acetylation with DMAP catalyst; δ_H 7.40 (m, 21-H), 7.38 (m, 23-H), 6.38 (m, 22-H), 5.79 (s, 17-H), 5.0 (2 H, m, 2-H, 3-H), 3.68 (s, OMe), 3.63 (d, 1-H), 2.12 and 1.98 (2 × AcO), and 1.10, 0.90, 0.84, and 0.84 (4 × C-Me).

In a similar way, the epimeric ether (**9c**) gave the epimer of the natural product, which did not crystallise; δ_H 7.45 (m, 21-H), 7.36 (m, 23-H), 6.39 (22-H), 5.71 (s, 17-H), 5.21 (m, 2-H), 5.12 and 4.90 (2 H, s, 30-H_2), 4.92 (m, 3-H), 3.68 (s, OMe), 3.25 (d, *J* 2.7 Hz, 1-H), 2.02 and 2.02 (6 H, s, 2 × AcO), and 1.11, 0.99, 0.85, and 0.85 (4 × C-Me).

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