The Synthesis of a 1α,2α,3α-Triacetoxy Limonoid

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The report[1] that Meerwein–Ponndorf reduction of gedunin (**1a**) gives 3α-hydroxy-3-deoxogedunin (**2a**) is wrong; the product is the 3β-epimer (**2b**). 3α-Acetoxy-7-deacetoxy-3-deoxo-7-oxogedunin (**3c**) was prepared by a stereospecific synthesis from cedrolide (**1b**), 7-deacetoxy-7-oxogedunin; osmium tetroxide oxidation then gave the 1,2α-glycol, isolated as the acetate (**4a**). Similarly, oxidation of the 3β-alcohol (**3b**) also gave the α-oriented glycol, as anticipated from the steric hindrance of the β-face of the molecule.

Oxidation of the allylic alcohols (**2b**) or (**3b**), or of the allylic acetate (**2d**) with perbenzoic acid also takes place from the α-face of the molecule, giving the corresponding α-oxides (**5a–c**). The oxidation is pH sensitive; with a benzoate buffer the 7-oxo group in alcohol (**3b**) undergoes Baeyer–Villiger oxidation, giving the ε-lactone isolated as the acetate (**6a**). Opening of the oxide ring in the 3β,7α-diacetoxy oxide (**5c**) is complex. Identification of the products shows that the reaction involves participation by both the acetate groups. In contrast the 3β-acetoxy-7-oxo compound (**5d**) and the ε-lactone (**6a**) give the products of ring opening with assistance from the neighbouring acetate group, while the 3β-hydroxy compound (**5b**) gives the simple bromohydrin.

Some of the more biologically active limonoids, such as the trichilins[2] contain the 1α,2α,3α-triol structure, which we have also found in *Ekebergia* limonoids.[3,4] Since little is known about the preparation of such compounds, we decided to attempt the synthesis of methyl 2α-acetoxy-3α-hydroxy-3-dihydro angolensate (**7**), the simplest limonoid of this type.[4]

It seemed that this synthesis could be effected from 2α-acetoxy-7-deacetoxy-7-oxokhivorin (**4a**) in the same way that methyl angolensate was synthesised from 7-deacetoxy-7-oxokhivorin.[5] This paper describes the preparation of compound (**4a**). The obvious approach is by osmium tetroxide oxidation of either the 1α-acetoxy-Δ^2 compound (**8**), or the 3α-acetoxy-Δ^1 compound (**3c**). In both cases, the β-face of the molecule is hindered by the axial 4β,10β, methyl groups, so that oxidation was expected on the α-face. However, precedents for this are uncertain; in a recent attempt at introduction of 2α,3α-glycol grouping into a diterpene, oxidation took place on the β-face, the α-glycol only being obtained when the usual 4,4-dimethyl substituent was replaced by a cyclopropyl group.[6]

In the event, the 1α-acetoxy-Δ^2-compound was not attacked by osmium tetroxide, and work on this compound, which is in any case rather inaccessible[1] was not continued. The reason for the failure of oxidation is not obvious. Limonoid double bonds are frequently highly resistant to oxidation *e.g.* that in compound (**7**), but more readily hydrogenated, which may mean the reason is not entirely steric.

In our work on the Δ^1 compounds we initially used gedunin (**1a**) which we obtained from a log of *Cedrela odorata* harvested in Durban, and it was then convenient to carry out the earlier experiments on the 7-acetates. However, later specimens of *Cedrela odorata* yielded cedrelone (**1b**), the 7-ketone, instead of gedunin, and this raised two problems which necessitated a change in operations. Cedrolide occurs with mexicanolide (**9**), and the two are very difficult to separate.[7] After separation it is necessary to distinguish the two carbonyl groups in cedrolide. We find that the Girard reagent is effective for separation, as it only reacts with cedrolide. Differentiation of the carbonyl groups was done by reduction at a low temperature with borohydride in tetrahydrofuran (THF), which gave the 7β-alcohol (**1c**). After acetylation, this gave *epi*-gedunin (**1d**), which could be used in a similar way to gedunin.

It has long been known that the Meerwein–Ponndorf reduction of gedunin (**1a**) yields an allylic alcohol,[1] which was considered to be the 3α-epimer (**2a**), since hydrogenation of the double bond was said to give the known saturated alcohol 3α-dihydrogedol.[8]

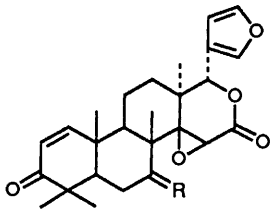
This allylic alcohol was converted by known methods[9] into the related ketone (**3b**) which was readily oxidised by osmium tetroxide. The acetate of the product unexpectedly showed J_{2-3} 9.3 Hz, an observation which was only explained when crystal structure determinations of suitable derivatives showed that the allylic alcohol was in fact the 3β-epimer, and the oxidation product acetate the 1α,2α-diacetoxy-3β-hydroxy compound (**4b**), so that something was wrong with the original identification. These crystallographic results are described in the Experimental section.

Re-examination of the reduction of gedunin confirmed that only the epimer described previously was easy to obtain. However, a small amount of the second epimer was isolated, and the NMR spectra of the two derived acetates were compared. In the 3α-epimer, the dihedral angle between 2-H and 3-H is *ca.* 90°, the angle between 3-H and the π bond being small. The observed couplings are: 3α-acetate, J_{2-3}, 4.8 Hz; J_{1-3}, not observed; 3β-acetate, J_{2-3}, 1.6 Hz; J, 1.2 Hz; which correspond well with the anticipated results.

Hydrogenation of the two epimeric alcohols now available gave the corresponding saturated alcohols, identical with authentic samples.[8] It is impossible now to say what went wrong with the original work.[1]

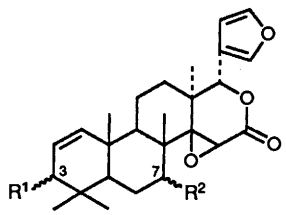
Srivastava[10] has recently reported the isolation of a compound which is claimed to be the 3β-hydroxyallylic alcohol (**10**) corresponding to anthothecol. In this compound J_{2-3} is reported to be 6 Hz, while J_{1-3} is not observed. This is more consistent with the compound being the 3α-epimer, in any case more likely in a natural limonoid.

It was now necessary to devise a preparation for the required α-epimer. Reduction of gedunin or cedrolide was carried out with many reducing agents, but the only ones found to give an



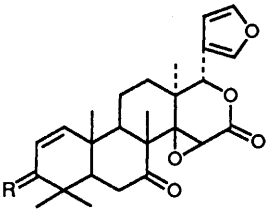
(1)

a R = H, αOAc **d** R = H, β OAc
b R = O **e** R = H, αOH
c R = H, βOH



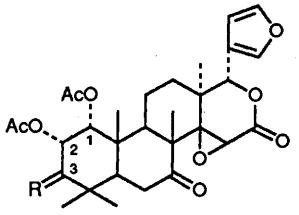
(2)

a 3-αOH, 7-αOAc **d** 3β, 7α-diOAc
b 3-βOH, 7-αOAc **e** 3β, 7α-diOAc
c 3β, 7β-diOH



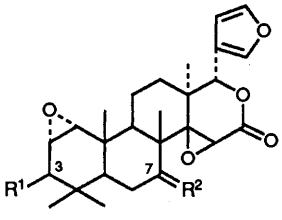
(3)

a R = H, αOH **c** R = H, αOAc
b R = H, βOH **d** R = H, βOAc



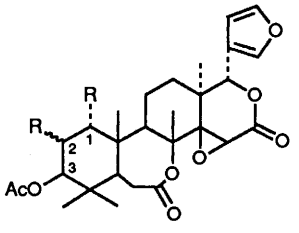
(4)

a R = H, αOAc
b R = H, βOH



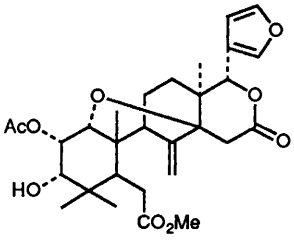
(5)

a 3β-OH, 7α-AOc **c** 3β, 7α-diOAc
b 3β-OH, 7oxo **d** 3β-OAc, 7-oxo

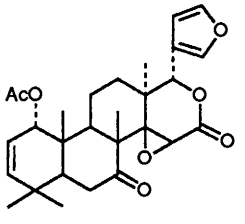


(6)

a 1, 2 α-epoxy
b 1α, 2β-diOAc



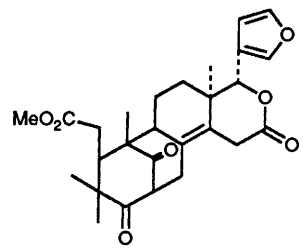
(7)



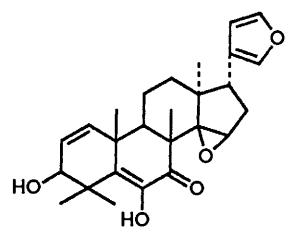
(8)

allylic alcohol were 9-BBN, which gave the 3β-epimer from gedunin and was less convenient in use than the Meerwein–Ponndorf reduction, and borohydride in the presence of a lanthanide,[11] which gave the 3β,7β-epimer from cedrelone.

A rational synthesis was devised from Δ^2-3-deoxodihydrocedrolide (**11c**), which was prepared by known methods from gedunin (**1a**)[9] and later from 7-*epi*-gedunin (**1d**) in a similar way. The catalytic hydrogenation of ring *A* in either gedunin or *epi*-gedunin gave a saturated ketone which was reduced by the Meerwein–Ponndorf reagent to the 3α-alcohol,[8] followed by dehydration with phosphorus oxychloride to give the Δ^2-olefin (**11a,b**). Hydrolysis of the 7-acetate and oxidation of the alcohol then gave the desired 7-ketone. Dehydration of the more readily



(9)

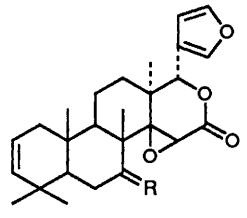


(10)

available 3β-alcohol was not successful. The olefin (**11c**) was oxidised with perbenzoic acid, the oxide (**12**) was treated with HBr, and the bromohydrin acetate (**13**) was treated with DABU,[12] to give the required 3α-allylic acetate (**3c**) in good yield.

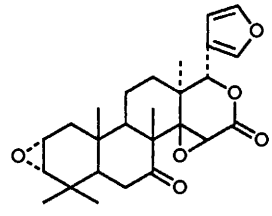
This allylic acetate was now oxidised with 4-methylmorpholine *N*-oxide catalysed by osmium tetroxide[13] to give a diol which was acetylated to the required 2α-acetoxy-7-deacetoxy-7-oxokhivorin (**4a**), thus completing the projected synthesis. The structure of the product was assumed by analogy with the 3-epimer; it is supported by the NMR spectra and proved in the sequel by the synthesis of the *Ekebergia* limonoid (**7**).

An attempt to oxidise the 3β-allylic acetate by the Woodward–Prévost[14] method was unsuccessful. A complex product was obtained which was not pursued.



(11)

a R = 7αOAc **c** R = oxo
b R = 7βOAc



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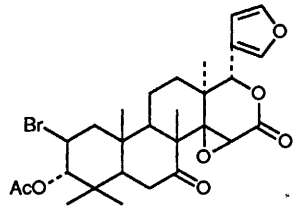
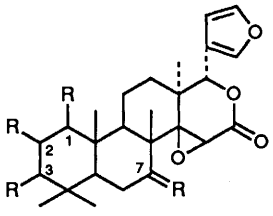


(13)

Before the discovery that the Meerwein–Ponndorf product of gedunin was the β-epimer, we had performed an investigation on the peracid oxidation of the allylic compounds. It has been shown that the oxidation of gedunin with alkaline hydrogen peroxide readily gives an oxide. This was assigned the α-configuration.[15] Reduction of the keto group with borohydride gives an alcohol, which we have now also obtained by the perbenzoic acid oxidation of the 3β-allylic alcohol (**2b**). This is therefore the 3β-hydroxy-1,2α-oxide (**5a**). In a similar way, the 7-oxo derivative (**3b**) gave the corresponding oxide (**5b**); the structure of this was confirmed by crystallographic analysis of the derived acetate (**5d**).

The orientation of peracid attack is unusual; in this case the steric hindrance of the β face of the molecule seems to be sufficient to overcome the usual *cis* directive effect of the 3β-OH

group.[16] Oxidation of the 3β-allylic acetate (**2d**) gave two products: the first of these was the expected α-oxide (**5c**), the second a compound which was eventually recognised as being produced by ring-opening of the oxide by sulphuric acid adventitiously present in the perbenzoic acid solution. In this compound, the 3-substituent must be β, as in the starting material, and the 1-substituent α from its production by opening of the α-oxide. The 2-substituent could be either α or β depending on the mechanism of the oxide ring opening. The NMR spectrum of the product shows the low-field proton geminal to the acetate as an ABX multiplet, so the acetate has shifted to C-2. The splitting is 7.1 Hz, showing that no axial–axial coupling is involved. Hence the compound is the 2β-acetoxy-1α,3β-diol (**14c**), and is the product of ring opening in a normal diaxial manner, with anchimeric assistance from the neighbouring acetate group.



(14)

a 1α, 2α-diOH-3β, 7α-diOAc **d** 1αOH-2β, 3β,7α-triOAc
b 1α, 2α-diOH-3β, 7α-diOAc **e** 1α, 2β-diOH-3βOAc-7oxo
c 1α, 3β-diOH-2β, 7α-diOAc **f** 1α, 3β-diOH-2βOAc-7oxo

This complication does not occur in the oxidation of the free allylic alcohol, due to the lack of the acetate group to provide assistance. The presence of sulphuric acid in the oxidation mixture also tends to lead to attack on the furan ring.

Control of the pH was also important in the oxidation of the related 7-ketone. To avoid furan ring oxidation, the 3β-hydroxy-7-oxo compound (**3b**) was oxidised with perbenzoic acid solution buffered with sodium benzoate. There were now two products, one the required oxide (**5b**), while the other had also undergone Baeyer–Villiger oxidation of the 7-oxo group, giving the ε-lactone, isolated as the acetate (**6a**). This was a very great surprise, because in earlier work[5] oxidation of limonoid 7-ketones has proved difficult, and has only been achieved with buffered peracetic acid. When the oxidation was repeated with perbenzoic acid lacking free sulphuric acid but not buffered, only the simple oxide was obtained.

In the earlier work,[15] the reduction product of epoxygedunin was thought to be the 3α-epimer, since it was stable to alkaline treatment, whereas the 3β-alcohol, produced as an intermediate by the reduction of epoxygedunin with the Meerwein–Ponndorf reagent, rearranged under the conditions of reaction to give the 1α-hydroxy-2,3β-epoxide. It can now be seen that both reductions of epoxygedunin give the β-isomer, which does not rearrange under mildly alkaline conditions. However, under the more vigorous conditions of the Meerwein–Ponndorf reduction, it rearranges to the isomer.

Since at the time we still thought that the epoxy acetate (**5c**) was the 3α-epimer, it seemed that the opening of the oxide ring under conditions leading to a double inversion might give the required product. It was hoped to bring this about by preparing the corresponding bromohydrin, and solvolysing it under suitable conditions for inversion at the bromine. In the event, treatment of the epoxy acetate with HBr in acetic acid gave a bromine-free product. This was found to consist of a mixture of four acetates. From the structure of the starting material and the method of preparation, it appears that the 3-substituent will remain β, the 1-substituent will be α, while the 2-substituent could be α or β, depending on the mechanism. Given this, the structure of all four compounds follows readily from the NMR data.

The first, acetate **A**, 8% was the 1α,2α-diol (**14a**), the 3-H signal showing the typical 11.2 Hz axial–axial coupling. Acetate **B**, 13%, was the epimeric 1α,2β-diol (**14b**), J_{2-3} 4.2 Hz. Acetate **C**, 19%, was recognised as the 2β-acetoxy-1α,3β-diol (**14c**), described above. Complete acetylation of acetates **B** or **C** with DMAP catalyst gave the same tetra-acetate, three acetate groups being in ring A, and the fourth at C-7. Compound **D**, 10%, has two acetate groups in ring A; the protons geminal to these show a coupling of 4.2 Hz, 1-H being represented by a doublet J 3.1 Hz at δ 3.58. Compound **D** is therefore the 2β,3β-diacetate (**14d**) related to acetates **B** and **C**, and on acetylation it gives the same tetra-acetate. Compound **B**, which contains the axial, hindered, 2β-OH group, also gives a triacetate in which the 2-OH is still free. Compound **A** also gives a triacetate, in which the 2α-OH, though equatorial, is not acetylated.

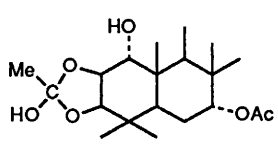
The reaction sequence was repeated on the corresponding 7-oxo compound (**5d**) with different results. Only two products were obtained, in the ratio 53:47, these were the 7-oxo analogues of the 7-acetates (**14b,c**), the products of anchimerically assisted acid-catalysed opening of the oxide, in which the neighbouring acetate group remains finally attached to either of the two possible groups. The analogues of the other two solvolysis products were not obtained. The lactone (**6a**) also gave two products, analogous to those from the 7-oxocompound.

It was of interest to see what would happen when anchimeric assistance was not possible, and so the 3β-hydroxy-1,2α-epoxy-7-oxo compound (**5b**) was treated with HBr in acetic acid. This gave the expected bromohydrin product of diaxial opening. An attempt was made to solvolyse the acetate of this with silver acetate in acetic acid, but no reaction occurred. However, the free bromohydrin reacted readily, giving cedrolide (**1b**). This can be rationalised as elimination of the bromine atom with a proton from C-3, giving the enol of a β-hydroxyketone, followed by ketonisation and elimination of water to give the product. However, this requires OH-3 to be β-oriented, so that the elimination can take place in the preferred diaxial manner. This was the first evidence that led us to query the accepted α-orientation of the allylic alcohol (**2b**), as a result of which we sought crystallographic structure proof.

The mechanism of the solvolysis of the epoxy acetate (**5c**) is of interest. Production of the acetates **B** (**14b**) and **C** (**14c**) is analogous to the solvolysis of *meso*-stilbene dibromide reported by Fieser, using the wet acetic acid method of Winstein and Buckles,[17] later developed by Woodward and Brutcher[14] into the now well-known Woodward–Prévost *cis* hydroxylation method. The production of the acetates **A** (**14a**) and **D** (**14d**) is not so simple. The fact that compounds of this type are only produced in the solvolysis of the 7-acetate, and not the 7-oxo compound or 7-lactone, indicates that the 7-acetate is taking part in a further neighbouring group effect, displacing the 2,3β-hemiorthoacetate (**15**) first formed at C-2, and replacing it by a 2,7α-hemiorthoacetate (**16**). Hydrolysis of this, in a similar way to that considered above, would give acetate **A** (**14a**), while acetolysis in the manner of the Winstein and Buckles 'dry acetic acid' case would give acetate **D** (**14d**). Although this mechanism involves a nine-membered ring intermediate, examination of a model shows that it is sterically possible, and other explanations of the observed results appear to be highly contrived.

Experimental

NMR spectra were determined in $CDCl_3$ on a CFT20 with Me_4Si as an internal standard, and high field spectra were determined by the CSIR in Pretoria (500 MHz) or by Dr. Brian Carter, of Glaxo Ltd. (250 MHz). Column chromatography was performed on silica gel (Merck Art 7734) using ethyl acetate–



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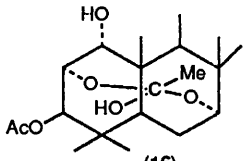

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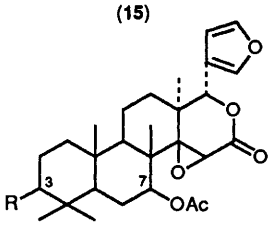
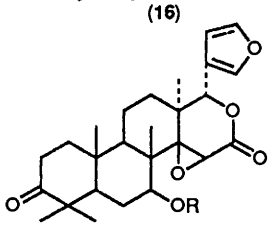


(17)

a 3β,7β-diOAc c 3βOH-7βOAc
b 3αOH-7βOAc



(18)

a R = H
b R = Ac

methylene dichloride. TLC analysis was performed on alumina backed silca sheets (Merck Art 5554) and preparative TLC on glass backed silica gel plates (Whatman PK6F). Mass spectra are by Professor Drewes, University of Natal, Pietermaritzburg, and elemental analyses by Dr. L. Strauch of the University of Basel. Acetates were prepared with pyridine–acetic anhydride, unless 4-DMAP is specified. Crystallisations are from methanol–methylene dichloride.

Cedrolide (**1b**).—Timber of *Cedrela odorata* was milled and extracted with refluxing isohexane for 36 h. The solid which separated on cooling was filtered and crystallised from methanol–methylene dichloride. The product (*ca.* 0.5%) was usually a mixture of cedrolide (**1b**) and mexicanolide (**9**), though some samples contain gedunin (**1a**) in place of cedrolide. This mixture (150 g), acetic acid (250 ml), chloroform (250 ml), and Girard reagent P (100 g), was refluxed for 0.5 h on a steam bath. The mixture was cooled, diluted with water (1 l) and ether (1 l), and the mexicanolide precipitated was removed by filtration. The aqueous layer was washed with ether (500 ml), and the ether layer with water (500 ml). Evaporation of the organic layer gave a further amount of mexicanolide. The combined aqueous layers were acidified to Congo red (conc. HCl), and heated on a steam bath for 1 h. The solid obtained was crystallised from methanol–methylene dichloride, giving cedrolide (average yield 50 g). The mother liquor sometimes contained odoratone, which is much more soluble.

Borohydride Reduction of Cedrolide.—(a) Cedrolide (**1b**) (30 g) in THF (450 ml) was treated with sodium borohydride (470 mg) in a little water, held at −20 °C for 15 min, and then acidified with dil. HCl. The solution was concentrated, diluted with water and methylene dichloride, and the product was chromatographed, to yield recovered cedrolide (6 g), 7-deacetylgedunin (**1e**) (2 g, 8%), and 7-*epi*-deacetylgedunin (**1c**) (21.6 g, 72%), m.p. 224–228 °C; $[\alpha]_D^{20}$ 48°; δ_H 7.41 (2 H, m, 21-, 23-H), 7.03 (d, *J* 10.2 Hz, 1-H), 6.32 (m, 22-H), 5.82 (d, *J* 10.1 Hz, 2-H), 5.63 (s, 17-H), 4.53 (s, 15-H), 3.8 (m, 7-H), and 1.19, 1.19, 1.16, 1.16, and 1.09 (5 × C-Me). The compound was rather insoluble in methanol, and most of the product could be isolated by crystallisation. Acetylation gave 7-*epi*-gedunin (**1d**) (not crystalline); δ_H 7.39 (2 H, m, 21-, 23-H), 7.05 (d, *J* 10.1, 1-H), 6.32 (m, 22-H), 5.85 (d, *J* 10.2 Hz, 2-H), 5.53 (s, 17-H), 5.08 (m, 7-H), 3.68 (s, 15-H), 2.11 (3 H, s, AcO), and 1.23, 1.17, 1.13, 1.13, and 1.07 (5 × C-Me).

(b) *In the presence of a lanthanide.* Cedrolide (200 mg) was dissolved in THF (5 ml) containing samarium(III) chloride hexahydrate (195 mg) and sodium borohydride (20 mg) in a little water was added. After 5 min the reaction was worked up, and the product was separated by preparative TLC to yield 3β-hydroxy-3-deoxo-7-*epi*-deacetylgedunin (**2c**) as the major product. This was identified by acetylation and hydrogenation, which gave 3β-acetoxy-3-deoxo-7-*epi*-deacetyldihydrogedunin (**17a**), m.p. 128–130 °C, identical with an authentic specimen.[9]

Osmium Tetroxide Oxidation of 3β-*Hydroxy-3-deoxocedrolide* (**3b**).—A solution was prepared from osmium tetroxide (100 mg), 4-methylmorpholine *N*-oxide (300 mg), and 3β-hydroxy-3-deoxocedrolide (**3b**) (500 mg) in t-butyl alcohol (5 ml) and acetone (2 ml). After 24 h, the solution was treated with excess aqueous sodium dithionate and dilute sulphuric acid. The organic material was extracted into methylene dichloride, and washed neutral. Chromatography gave starting material (200 mg) and products, which were acetylated. The major product, isolated by preparative TLC, was the non-crystalline 1α,2α-diacetoxy-3β-hydroxy-3-deoxodihydrocedrolide (**4b**) (255 mg, 67%); δ_H 7.39 (2, H, m, 21-, 23-H), 6.36 (m, 22-H), 5.46 (s, 17-H), 5.11, (dd, *J* 9.3 and 4.9 Hz, 2-H), 4.67 (d, *J* 5.0 Hz, 1-H), 4.22 (d, 3-H), 3.82 (s, 15-H), 1.88 (2 × AcO), and 1.30, 1.14, 1.12, 0.95, and 0.77 (5 × C-Me). Acetylation with 4 DMAP catalyst gave the triacetate, m.p. 250–256 °C; δ_H 7.39 (m, 23-H), 7.38 (m, 21-H), 6.32 (m, 2-H), 3.77 (s, 15-H), 2.06, 2.05, and 1.93 (9 H, s, 3 × OAc), and 1.30, 1.12, 1.09, 0.98, and 0.93 (5 × C-Me). (C-1,2,3,17, 5.42–5.14, were not resolved.)

Meerwein–Ponndorf Reductions.—(a) *Gedunin* (**1a**). Aluminium foil (20 g) was dissolved in refluxing dry propan-2-ol (1.8 l), containing a trace of mercury(II) chloride. Gedunin (10 g) was added, and the solution was boiled under partial reflux until a test sample showed no gedunin to be present (*ca.* 2 h). The solvent was removed under reduced pressure, and the residue was treated with dilute H_2SO_4 and methylene dichloride. The organic layer was washed neutral and evaporated and the gum remaining was chromatographed on silica. Elution with 5% EtOAc–CH_2Cl_2 gave: (*i*) 3β-hydroxy-3-deoxogedunin (**2b**) (4 g, 40%), m.p. 220–221 °C; $[\alpha]_D^{20}$ 48°; δ_H 7.3 (2 H, m, 21-, 23-H), 6.33 (m, 22-H), 5.85 (dd, *J* 10.1 and 1.2 Hz, 1-H), 5.58 (s, 17-H), 5.35 (dd, *J* 10.0 and 1.3 Hz, 2-H), 3.94 (m, 3-H), 4.52 (m, 7-H), 3.52 (s, 15-H), 2.09 (AcO), and 1.20, 1.08, 1.06, 0.87, and 0.79 (5 × C-Me); acetate (**2d**) m.p. 158 °C; $[\alpha]_D^{20}$ 4°; δ_H 7.39 (2 H, m, 21-, 23-H), 6.32 (m, 22-H), 5.88 (dd, *J* 9.3 and 1.2 Hz, 1-H), 5.58 (s, 17-H), 5.22 (dd, *J* 9.7 and 1.6 Hz, 2-H), 5.16 (3-H), 4.52 (m, 7-H), 3.48 (s, 15-H), 2.11, 2.09 (2 × AcO), and 1.21, 1.14, 1.08, 0.89, and 0.81 (15 H, s, 5 × C-Me), and then: (*ii*) 3α-hydroxy-3-deoxogedunin (**2a**) (900 mg, 9%), which did not crystallise; δ_H 7.38 (2 H, m, 21-, 23-H), 6.33 (m, 22-H), 6.03 (d, *J* 10.3 Hz, 1-H), 5.60 (dd, *J* 10.2 and 4.8 Hz, 2-H), 5.59 (s, 17-H), 4.49 (m, 7-H), 3.56 (d, *J* 4.9 Hz, 3-H), 3.50 (s, 15-H), 2.10 (AcO), and 1.23, 1.10, 1.09, 0.89, and 0.82 (5 × C-Me); acetate (**2d**), m.p. 160–163 °C; δ_H 7.40 (2 H, m, 21-, 23-H), 6.33 (m, 22-H), 6.09 (d, *J* 10.4 Hz, 1-H), 5.60 (s, 17-H), 5.53 (dd, *J* 10.3 and 4.7 Hz, 2-H), 4.89 (d, *J* 4.9 Hz, 3-H), 4.52 (m, 7-H), 3.52 (s, 15-H), 2.10 and 2.04 (2 × AcO), and 1.24, 1.10, 1.09, 0.90, and 0.80 (5 × C-Me).

(b) *Cedrolide* (**1b**). Cedrolide (50 g) in a similar way gave recovered starting material (10 g), a trace of 3β-hydroxy-3-deoxocedrolide (**3b**), 7-deacetylgedunin (**1e**) (6 g, 15%), and 3β-hydroxy-7-deacetyl-3-deoxogedunin (**2e**) (20 g, 50%), m.p. 160–164 °C; $[\alpha]_D^{20}$ 40°; δ_H 7.39 (2 H, m, 21-, 23-H), 6.33 (m, 22-H), 5.79 (dd, *J* 10.5 and 2.3 Hz, 1-H), 5.57 (s, 1-H), 5.28 (dd, *J* 10.4 and 1.7 Hz, 2-H), 3.91 (m, 3-H), 3.84 (s, 15-H), 3.47 (m, 7-H) and 1.20, 1.09, 1.02, 0.97, and 0.83 (5 × C-Me). Acetylation of this gave 3β-acetoxy-3-deoxogedunin (**2d**), identical with the sample from the reduction of gedunin.

Hydrogenation of the Allylic Alcohols.—Hydrogenation of the allylic alcohols in ethyl acetate over Adams' catalyst (Johnson Matthey), gave the corresponding saturated alcohols, identical with authentic samples[9] with respect to m.p., optical rotation, and NMR spectra. Use of palladium or Adams' catalyst in methanol hydrogenated the furan ring, whereas palladium catalyst in ethyl acetate brought about no hydrogenation.

Hydrogenation of 7-epi-*Gedunin and* 7-*Deacetyl*-7-epi-*gedunin.*—Hydrogenation over Adams' catalyst in ethyl acetate yielded the dihydro derivatives. 7-Deacetyl-7-*epi*-dihydrogedunin (**18a**), m.p. 229–233 °C; $[\alpha]_D^{20}$ −34°; δ_H 7.38 (2 H, m, 21-, 23-H), 6.3 (m, 22-H), 5.6 (s, 17-H), 4.53 (s, 15-H), 3.8 (m, 7-H), and 1.18, 1.1, 1.08, 1.02, and 1.02 (5 × C-Me). The acetate, 7-*epi*-dihydrogedunin (**18b**), had m.p. 233–236 °C; $[\alpha]_D^{20}$ 12°; δ_H 7.35 (2 H, m, 21-, 23-H), 6.29 (m, 22-H), 5.48 (s, 17-H), 4.98 (m, 7-H), 3.64 (s, 15-H), 2.09 (AcO), and 1.22, 1.05, 1.02, 0.99, and 0.96 (5 × C-Me).

Meerwein–Ponndorf Reduction of 7-epi-*Dihydrogedunin* (**18b**).—7-*epi*-Dihydrogedunin (**18b**) (26 g) was refluxed with aluminium isopropoxide (from aluminium, 20 g) in propan-2-ol (1.5 l) for 0.5 h. After work-up as usual, the product was chromatographed to give 3a-hydroxy-3-deoxo-7-*epi*-dihydrogedunin (**17b**) (14.6 g, 56%), m.p. 126–128 °C $[\alpha]_D^{20}$ 21°; δ_H 7.38 (2 H, m, 21-, 23-H), 6.31 (m, 22-H), 5.51 (s, 17-H), 4.95 (m, 7-H), 3.66 (s, 15-H), 3.43 (m, 3-H), 2.10 (AcO), and 1.25, 1.05, 0.93, 0.93, and 0.83 (5 × C-Me), and the 3b-epimer (**17c**) (900 mg, 3%), acetate m.p. 128–130 °C; identical with the previous sample.

Δ^2-3-*Deoxodihydrocedrolide* (**11c**).—The 3α-alcohol (**17b**) (10.4 g) was dissolved in pyridine and treated with phosphorus oxychloride (15 ml) at room temperature. After 2 h the solution was poured onto ice and HCl, and extracted with methylene dichloride. The non-crystalline product, Δ^2-3-deoxo-7-epidihydrogedunin (**11b**); δ_H 7.38 (m, 23-H), 7.36 (m, 21-H), 6.32 (m, 22-H), 5.5 (s, 17-H), 5.38 (2-, 3-H), 5.08 (m, 7-H), 3.67 (s, 15-H), 2.11 (AcO), and 1.24, 1.03, 0.95, 0.95, and 0.87 (C-Me); was refluxed with a solution from sodium (1 g) in methanol (110 ml) for 2 h. The mixture was acidified, concentrated, diluted with methylene dichloride and water, and the organic residue was oxidised with Jones' reagent, to give Δ^2-3-deoxodihydrocedrolide (**11c**), (6.5 g, 71%), m.p. 215 °C; $[\alpha]_D^{20}$ − 72°; δ_H 7.40 (m, 23-H), 7.38 (m, 21-H), 6.36 (m, 22-H), 5.48 (2-, 3-, 17-H), 3.76 (s, 15-H), and 1.17, 1.13, 1.13, 0.97, and 0.96 (5 × C-Me).

2,3α-*Epoxy*-3-*deoxodihydrocedrolide* (**12**).—The olefin (**11c**) (1.35 g) was dissolved in chloroform (10 ml) and perbenzoic acid (8 ml; 0.56M solution in $CHCl_3$) was added. After being kept overnight at room temperature, the solution was washed with sodium hydrogen carbonate solution and evaporated. Chromatography gave unchanged starting material (0.25 g) and the *epoxide* (**12**) (0.6 g, 58%), m.p. 248–249 °C; $[\alpha]_D^{20}$ −106° (Found: C, 70.8; H, 7.4. $C_{26}H_{32}O_6$ requires C, 70.9; H, 7.32%); δ_H 7.39 (m, 23-H), 7.37 (m, 21-H), 6.34 (m, 22-H), 5.40 (s, 17-H), 3.69 (s, 15-H), 2.72 and 2.35 (m, 2-, 3-H), and 1.10, 1.09, 1.09, 1.07, and 1.07 (5 × C-Me).

3α-*Acetoxy*-2β-*bromo*-3-*deoxodihydrocedrolide.* (**13**).—The epoxide (**12**) was dissolved in acetic acid (40 ml) and HBr (1.25 ml; 48%) was added. After 4 h at room temperature the reaction mixture was diluted with water, and the product was isolated with methylene dichloride. Acetylation gave the *bromohydrin acetate* (**13**) (2.65 g, 83%), m.p. 213 °C; $[\alpha]_D^{20}$ −63° (Found: C, 59.5; H, 6.4. $C_{28}H_{35}O_7Br$ requires C, 59.7; H, 6.26%); δ_H 7.38 (m, 23-H), 7.36 (m, 21-H), 6.33 (m, 22-H), 5.43 (m, 3-H), 5.42 (s, 17-H), 4.22 (m, 2-H), 3.72 (s, 15-H), 2.10 (AcO), and 1.40, 1.11, 1.11, 1.01, and 0.93 (5 × C-Me).

3α-*Acetoxy*-3-*deoxocedrolide* (**3c**).—The above bromohydrin acetate (**13**) (5.2 g) and DABU (1 ml) were warmed on a steam bath for 1 h. The product was reacetylated, giving the *allylic acetate* (**3c**) (3.9 g, 88%), m.p. 217–220 °C; $[\alpha]_D^{20}$ −164° (Found: C, 69.5; H, 7.3; $C_{28}H_{34}O_7$ requires C, 69.7; H, 7.10%); δ_H 7.38 (2 H, m, 21-, 23-H), 6.33 (m, 22-H), 6.09 (d, *J* 10.1 Hz, 1-H), 5.59 (dd, *J* 10.1 and 4.8 Hz, 2-H), 5.48 (s, 17-H), 4.89 (d, *J* 4.7 Hz, 3-H), 4.06 (s, 15-H), 2.02 (AcO), and 1.21, 1.18, 1.14, 0.94, and 0.89 (5 × C-Me).

2α-*Acetoxy*-7-*deacetoxy*-7-*oxokhivorin* (**4a**).—The above allylic acetate (**3c**) (1 g) was dissolved in THF (16 ml) and t-butyl alcohol (10 ml), and 4-methylmorpholine *N*-oxide (2 g) and osmium tetroxide (150 mg) were added. After 24 h the solution was diluted with methylene dichloride and washed with acidified sodium hydrogen sulphite solution. Removal of the solvent and acetylation (4 DMAP catalyst) yielded 2α-*acetoxy*-7-*deacetoxy*-7-*oxokhivorin* (**4a**) (850 mg, 68%), m.p. 265–268 °C; $[\alpha]_D^{20}$ −115°; (Found: C, 63.7; H, 6.9. $C_{32}H_{40}O_{11}$ requires C, 64.0; H, 6.71%); δ_H 7.37 (2 H, m, 21-, 23-H), 6.31 (m, 22-H), 5.50 (m, $W_{\frac{1}{2}}$ 6.8 Hz, 2-H), 5.42 (s, 17-H), 5.14 (d, *J* 3.1 Hz, 1-H), 5.01 (d, *J* 3.7 Hz, 3-H), 3.75 (s, 15-H), 2.05, 1.98, and 1.92 (3 × AcO), and 1.26, 1.12, 1.12, 1.07, and 0.89 (5 × C-Me).

Perbenzoic Acid Oxidation of the Allylic Compounds—(a) 3β-*Hydroxy*-3-*deoxogedunin* (**2b**). The alcohol (120 mg) was dissolved in chloroform (5 ml) and perbenzoic acid solution (titrated amount, 1.5 ml; contained traces of sulphuric acid from the preparation), was added. After 24 h the solution was washed neutral and evaporated to give 1,2α-epoxy-3β-hydroxy-3-deoxodihydrogedunin (**5a**) as a gum, δ_H 7.38 (2 H, m, 21-, 23-H), 6.33 (m, 22-H), 5.58 (s, 17-H), 4.50 (m, 7-H), 3.54 (m, 3-H), 3.50 (s, 15-H), 3.02 (m, 2-H), 2.13 (AcO) and 1.31, 1.16, 1.12, 0.87, and 0.82 (5 × C-Me). Acetylation gave the acetate (**5c**) (104 mg, 78%), m.p. 168–171 °C; $[\alpha]_D^{20}$ −14° (Found: C, 66.3; H, 7.2. $C_{30}H_{38}O_9$ requires C, 66.4; H, 7.06%); δ_H 7.38 (2 H, m, 21-, 23-H), 6.33 (m, 22-H), 5.58 (s, 17-H), 4.85 (m, 3-H), 4.50 (m, 7-H), 3.50 (s, 15-H), 2.11 (2 × AcO), and 1.29, 1.17, 1.10, 0.85, and 0.78 (5 × C-Me).

(b) 3β-*Acetoxy*-3-*deoxogedunin* (**2d**). Oxidation of the acetate (200 mg) as above gave a mixture which was separated by preparative TLC, to give 3β-acetoxy-1,2α-epoxy-3-deoxodihydrogedunin (**5c**) (58 mg, 28%), identical with the above sample, and 2β-acetoxy-1α,3β-dihydroxy-3-deoxodihydrogedunin (**14c**), (100 mg, 47%), m.p. 231–236 °C; $[\alpha]_D^{20}$ −21°; δ_H, 7.38 (2 H, m, 21-, 23-H), 6.32 (m, 22-H), 5.58 (s, 17-H), 4.98 (dd, *J* 4.2 and 2.9 Hz, 2-H), 4.41 (m, 7-H) 3.67 (2 H, m, 1-, 3-H), 3.48 (s, 15-H), 2.11, and 2.09 (2 × AcO), and 1.24, 1.24, 1.08, 0.92, and 0.92 (5 × C-Me).

(c) 3β-*Hydroxy*-3-*deoxocedrolide* (**3b**). (*i*) With acidic perbenzoic acid. Oxidation of the alcohol (**3b**) (4.3 g) as above gave 1,2α-epoxy-3β-hydroxy-3-deoxodihydrocedrolide (**5b**) (3.6 g, 74%), m.p. 212–215 °C; $[\alpha]_D^{20}$ −49°; δ_H 7.38, (2 H, m, 21-, 23-H), 6.33 (m, 22-H), 5.45 (s, 17-H), 3.98 (s, 15-H), 3.53 (m, 3-H), and 1.26, 1.15, 1.14, 0.89, and 0.83 (5 × C-Me). The acetate (**5d**) had m.p. 256–260 °C; $[\alpha]_D^{20}$, −39°; δ_H, 7.39 (2 H, m, 21-, 23-H), 6.34 (m, 22-H), 5.47 (s, 17-H), 4.74 (bs, 3-H), 4.02 (s, 15-H), 3.04 (m, 2-H), 2.13 (AcO), and 1.33, 1.33, 1.25, 0.94, and 0.83 (5 × C-Me).

(*ii*) With buffered perbenzoic acid. The alcohol (**3b**) (5 g) was treated with peracid solution, buffered with excess solid sodium benzoate. The product was acetylated and the acetates chromatographed to give (**5d**), (1.9 g, 35%), and the ε-lactone (**6a**), (2 g, 37%), m.p. 254–257 °C; δ_H 7.41 (2 H, m, 21-, 23-H),

6.37 (m, 22-H), 5.39 (s, 17-H), 4.64 (s, 3-H), 3.76 (s, 15-H), 3.18 (d *J* 1.3 Hz, 2-H), 3.04 (d, *J* 1.3 Hz, 1-H), 2.13 (AcO), and 1.33, 1.33, 1.25, 0.94, and 0.83 (5 × C-Me).

Reaction of the Epoxides with HBr *in Acetic Acid.*—(a) 3β-*Acetoxy*-1α,2α-*epoxy*-3-*deoxodihydrogedunin.* A solution of the acetate (**5c**) (750 mg) and HBr (0.5 ml; 48% in acetic acid), in acetic acid (20 ml) was kept for 1 h at room temperature, and then diluted with water and methylene dichloride. The organic layer was washed neutral and evaporated. Chromatography gave the following compounds.

(i) 3β-Acetoxy-1α,2α-dihydroxy-3-deoxodihydrogedunin (**14a**) (64 mg, 8%), m.p. 224–226 °C; $[\alpha]_D^{20}$ −6°; δ_H 7.39 (2 H, m, 21-, 23-H), 6.33 (m, 22-H), 5.73 (s, 17-H), 5.59 (d, *J* 12 Hz, 3-H), 4.63 (m, 7-H), 4.2 (m, 2-H), 4.1, (m, 1-H 3.63, (m, 15-H), 2.26 (2 × AcO), and 1.32, 1.21, 1.11, 0.95, and 0.91 (5 × C-Me). Acetylation gave the 1α,3β,7α-triacetate, δ_H 7.38 (2 H, m, 21-, 23-H) 6.27 (m, 22-H), 5.54 (s, 17-H), 5.44 (d, *J* 11.2 Hz, 3-H), 5.28 (d, *J* 3.5 Hz, 1-H), 4.47 (m, 7-H), 3.93 (dd, *J* 11.2 and 3.5 Hz, 2-H), 3.47 (s, 15-H), 2.10, 2.08, and 2.06 (3 × AcO), and 1.15, 1.18, 1.03, 0.92, and 0.87 (5 × C-Me).

(ii) 3β-Acetoxy-1α,2β-dihydroxy-3-deoxodihydrogedunin (**14b**) (102 mg, 13%), m.p. 262–265 °C; $[\alpha]_D^{20}$ −6°; δ_H 7.39 (2 H, m, 21-, 23-H), 6.33 (m, 22-H), 5.60, (s, 17-H), 4.90 (d, *J* 4.2 Hz, 3-H), 3.8 (m, 2-H), 3.7 (m, 1-H), 3.49 (s, 15-H), 2.15 and 2.12 (2 × AcO), and 1.26, 1.26, 1.10, 1.04, 0.79 (15 H, s, 5 × C-Me). Acetylation gave the 1α,3β,7α-triacetate δ_H 7.38 (2 H, m, 21-, 23-H), 6.33 (m, 22-H), 5.58 (s, 17-H), 4.8 (d, *J* 2.6 Hz, 1-H), 4.7 (d, *J* 4.2 Hz, 3-H), 4.47 (m, 7-H), 4.0 (m, 2-H), 3.48 (s, 15-H), 2.10, 2.10, and 2.04 (3 × AcO), and 1.28, 1.16, 1.07, 1.04, and 0.78 (5 × C-Me), and the 1α,2β,3β,7α-tetra-acetate, δ_H 7.38 (2 H, m, 21-, 23-H), 6.30 (m, 22-H), 5.56 (s, 17-H), 5.10 (m, 2-H), 4.7 (2 H, m, 1-, 3-H), 4.49 (m, 7-H), 3.48 (s, 15-H), 2.10, 2.07, 2.04, and 1.96 (4 × AcO), and 1.24, 1.16, 1.07, 0.98, and 0.78 (5 × C-Me).

(iii) 2β-Acetoxy-1α,3β-dihydroxy-3-deoxodihydrogedunin (**14c**) (147 mg, 19%), identical with the previous sample. Acetylation gave the above 1α,2β,3β-triacetate.

(iv) 2β,3β-Diacetoxy-1α-hydroxy-3-deoxodihydrogedunin (**14d**) (83 mg, 10%), not obtained crystalline, δ_H 7.38 (2 H, m, 21-, 23-H), 6.33 (m, 22-H), 5.58 (s, 17-H), 5.17 (m, *J* 3.1 and 4.2 Hz, 2-H), 4.92 (d, *J* 4.2 Hz, 3-H), 3.58 (d, *J* 3.1 Hz, 1-H), 4.47 (m, 7-H), 3.47 (s, 15-H), 2.10, 2.04, and 1.98 (3 × AcO), and 1.24, 1.14, 1.08, 0.98, and 0.78 (5 × C-Me). Acetylation gave the same tetra-acetate as above.

(b) 3β-*Acetoxy*-1,2α-*epoxy*-3-*deoxodihydrocedrolide* (**5d**). A solution of the acetate (**5d**) (7.5 g) and HBr (4 ml; 48% in acetic acid) in acetic acid (150 ml) was stored for 2 h, and then diluted with methylene dichloride and water. The product was chromatographed to give the following compounds.

(i) 3β-Acetoxy-1α,2β-dihydroxy-3-deoxodihydrocedrolide (**14e**), m.p. 257 °C; $[\alpha]_D^{20}$ −68°; δ_H 7.37 (2 H, m, 21-, 23-H), 6.33 (m, 22-H), 5.44 (s, 17-H), 4.87 (d, *J* 3.8 Hz, 3-H), 3.94, (2-H), 3.91 (1-H), 3.82 (s, 15-H), 2.14 (AcO), and 1.38, 1.14, 1.09, 1.09, and 0.85 (5 × C-Me). Acetylation gave the 1α,3β-diacetate, not obtained crystalline, δ_H 7.37 (2 H, m, 21-, 23-H), 6.32, (m, 22-H), 5.42 (s, 17-H), 5.0 (d, *J* 2.8 Hz, 3-H), 4.6 (d, *J* 4.4 Hz, 1-H), 4.1 (m, 2-H), 3.78 (s, 15-H), and 2.15, 2.04, (2 × AcO), and 1.48, 1.17, 1.15, 1.12, and 0.89 (5 × C-Me), and the 1α,2β,3β-triacetate m.p. 237–239 °C; $[\alpha]_D^{20}$ −86°; (Found: C, 63.75; H, 6.8; *m/z* 600. $C_{32}H_{40}O_{11}$ requires C, 64.0; H, 6.7; *m/z* 600); δ_H 7.37 (2 H, m, 21-, 23-H), 6.32 (m, 22-H), 5.44, (s, 17-H), 5.13 (dd, *J* 4.2 and 3.0 Hz, 2-H), 4.9 (d, *J* 3.0 Hz, 3-H), 4.74 (d, *J* 4.3 Hz, 1-H), 3.84 (s, 15-H), 2.15, 2.10, and 2.05 (AcO), and 1.48, 1.22, 1.17, 1.15, and 0.98 (5 × C-Me).

(ii) 2β-Acetoxy-1α,3β-dihydroxy-3-deoxodihydrocedrolide (**14f**) not obtained crystalline; δ_H 7.37 (2 H, m, 21-, 23-H), 6.34 (m, 22-H), 5.45, (s, 17-H), 5.11, (m, 2-H), 3.88 (s, 15-H), 3.8 (m, 1-H), 3.8 (m, 3-H), 2.16 (AcO), and 1.28, 1.20, 1.17, 1.07, and 1.05 (5 × C-Me), which gave the above triacetate (total yield 5.3 g, 59%), the product ratio (**15e**)/(**15f**) determined by

Table 1. Crystal data, experimental details of the data collection and final refinement of $C_{28}H_{34}O_8 \cdot 0.25CH_3OH$ (**5d**).

Crystal data	
Molecular formula	$C_{28}H_{34}O_8 \cdot 0.25CH_3OH$
Molar mass/g mol^{-1}	506.58
Space group	$P2_12_12_1$
a/Å	9.789(9)
b/Å	13.309(3)
c/Å	19.824(5)
V/Å^3	2 583(3)
D_c (for $Z = 4$) Mg m^{-3}	1.30
μ(Mo-K_α) cm^{-1}	0.57
F(000)	1 082
Data collection	
Crystal dimensions/mm	0.03 × 0.48 × 0.50
Scan mode	ω − 2θ
Scan width (in ω°)	(0.79 + 0.35 tan θ)
Aperture width/mm	(1.35 + 1.05 tan θ)
Stability of standard reflections (%)	1.1
θ range/°	1–25
No. of reflections collected	2 208
No. of reflections observed, *N* (with $F > \sigma F$)	2 012
Refinement	
Number of variables, N_P	356
$R = \Sigma\|\Delta\|/\Sigma\|F_o\|$	0.069
$R_w = \Sigma w^{\frac{1}{2}}\|\Delta\|/\Sigma w^{\frac{1}{2}}\|F_o\|$	0.059
w	$(\sigma^2 F)^{-1}$
$S = (\Sigma w\|\Delta\|^2/N - N_P)$	1.92

Table 2. Crystal data, experimental details of the data collection and final refinement of $C_{32}H_{40}O_{12}$ (**6b**).

Crystal data	
Molecular formula	$C_{32}H_{40}O_{12}$
Molar mass/g mol^{-1}	616.66
Space group	$P2_12_12_1$
a/Å	10.442(5)
b/Å	13.030(3)
c/Å	23.721(3)
V/Å^3	3 227(2)
D_c (for $Z = 4$) Mg m^{-3}	1.27
μ(Mo-K_α) cm^{-1}	0.907
F(000)	1 312
Data collection	
Crystal dimensions/mm	0.13 × 0.41 × 0.50
Scan mode	ω − 2θ
Scan width (in ω°)	(1.05 + 0.35 tan θ)
Aperture width/mm	(1.78 + 1.05 tan θ)
Stability of standard reflections (%)	1.7
θ range/°	1–25
No. of reflections collected	2 573
No. of reflections observed, *N* (with $F > \sigma F$)	2 299
Refinement	
Number of variables, N_P	423
$R = \Sigma\|\Delta\|/\Sigma\|F_o\|$	0.064
$R_w = \Sigma w^{\frac{1}{2}}\|\Delta\|/\Sigma w^{\frac{1}{2}}\|F_o\|$	0.048
w	$(\sigma^2 F)^{-1}$
$S = (\Sigma w\|\Delta\|^2/N - N_P)$	1.395

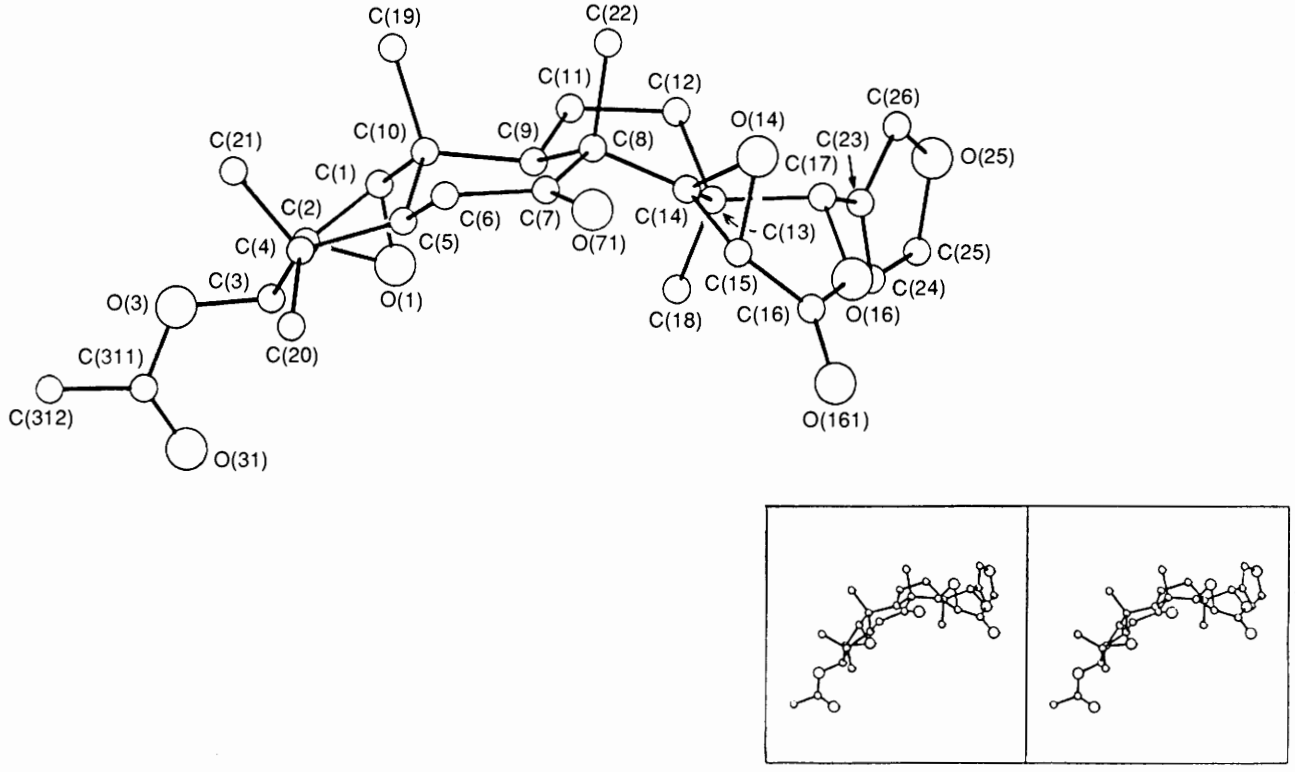


Figure 1. Structure of the oxide (**5d**).

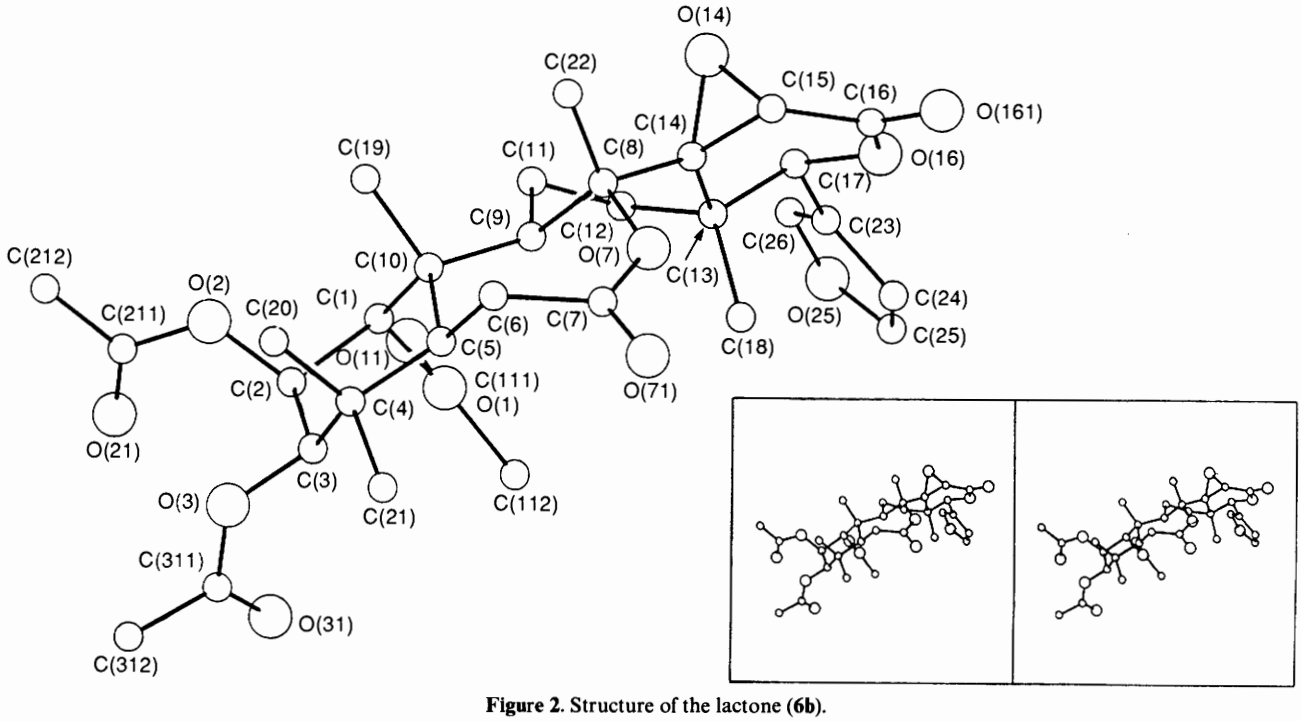


Figure 2. Structure of the lactone (**6b**).

HPLC on a reversed-phase column with acetonitrile–water, was 53:47.

(c) *The* ε-*lactone* (**6a**). A solution of the ε-lactone (300 mg) and HBr (0.2 ml; 48%) in glacial acetic acid (10 ml) was kept at room temperature for 1 h. After isolation, the product was chromatographed, to give the following products.

(i) The 3β-acetoxy-1α,2β-dihydroxy-ε-lactone (120 mg, 39%), m.p. 291–292 °C; δ_H 7.38 (2 H, m, 21-, 23-H), 6.36 (m, 22-H), 5.39 (s, 17-H), 4.94 (d, *J* 3.2 Hz, 3-H), 4.12 (2 H, m, 1-, 2-H), 3.74 (s, 15-H), 2.19 (AcO), and 1.42, 1.39, 1.35, 1.10, and 1.05 (5 × C-Me). Acetylation (4-DMAP) gave the 1α,2β,3β-triacetate (**6b**), m.p. 284–286 °C; $[\alpha]_D^{20}$ −36°; (Found: *m/z* 616. $C_{32}H_{40}O_{12}$ requires 616); δ_H 7.40 (2 H, m, 21-, 23-H), 6.34 (m, 22-H), 5.57 (s, 17-H), 5.07 (d, *J* 3.2 Hz, 1-H), 5.13 (m, 2-H), 4.86 (d, *J* 4.1 Hz, 3-H), 3.73 (s, 15-H), 2.09, 2.09, and 2.00 (3 × AcO), and 1.39, 1.36, 1.31, 1.04, and 1.02 (5 × C-Me), of which the structure was confirmed by X-ray crystallography.

Table 3. Fractional atomic co-ordinates (× 10^4) with esds in parentheses for compound $C_{28}H_{34}O_8 \cdot 0.25CH_3OH$ (**5d**)

Atom	x/a	y/b	z/c
C(1)	5 402(7)	6 687(5)	3 046(3)
C(2)	5 569(8)	6 944(5)	3 748(3)
C(3)	4 792(8)	6 406(5)	4 307(4)
C(4)	4 237(7)	5 353(5)	4 125(3)
C(5)	3 579(6)	5 471(5)	3 409(3)
C(6)	2 725(8)	4 556(6)	3 187(3)
C(7)	1 810(9)	4 781(6)	2 598(4)
C(8)	2 401(7)	5 420(5)	2 024(3)
C(9)	3 520(7)	6 177(5)	2 266(3)
C(10)	4 530(7)	5 795(5)	2 829(3)
C(11)	4 208(7)	6 714(5)	1 669(3)
C(12)	3 167(7)	6 992(5)	1 100(3)
C(13)	1 740(7)	7 098(5)	1 370(3)
C(14)	1 294(7)	6 053(5)	1 658(3)
C(15)	−201(7)	5 965(6)	1 754(3)
C(16)	−1 063(8)	6 818(6)	1 538(4)
C(17)	728(7)	7 325(5)	789(3)
C(18)	1 619(8)	7 946(5)	1 896(3)
C(19)	5 579(8)	4 996(6)	2 562(4)
C(20)	3 159(9)	5 076(7)	4 635(4)
C(21)	5 406(9)	4 569(6)	4 162(4)
C(22)	3 007(9)	4 624(6)	1 523(4)
C(23)	975(7)	8 295(5)	411(3)
C(24)	657(8)	9 284(6)	589(4)
C(25)	1 074(9)	9 874(6)	64(5)
C(26)	1 589(10)	8 337(7)	−211(4)
O(1)	4 726(5)	7 531(3)	3 321(2)
O(71)	752(7)	4 384(5)	2 549(3)
O(14)	477(5)	5 471(3)	1 206(2)
O(16)	−641(5)	7 418(4)	1 037(2)
O(161)	−2 192(6)	6 978(5)	1 783(3)
O(25)	1 633(7)	9 319(5)	−419(3)
O(3)	5 659(6)	6 287(4)	4 891(2)
C(311)	5 491(19)	6 916(8)	5 401(5)
O(31)	4 833(16)	7 616(7)	5 358(4)
C(312)	6 433(14)	6 635(9)	5 983(5)
O(111)	5 187(22)	8 673(15)	6 545(10)
C(111)	4 074(31)	8 474(21)	6 635(14)

(ii) The 2β-acetoxy-1α,3β-dihydroxy derivative (97 mg, 32%), m.p. 284–288 °C; δ_H 7.41 (2 H, m, 21-, 23-H), 6.38 (m, 22-H), 5.39 (s, 17-H), 5.11 (m, 2-H), 3.98 (m, 3-H), 3.77 (m, 1-H), 3.74 (s, 15-H), 2.13 (OAc), and 1.38, 1.34, 1.22, 1.19, and 0.94 (5 × C-Me).

(d) 1,2α-*Epoxy*-3β-*hydroxy*-3-*deoxodihydrocedrolide*. (**5b**). A solution of the alcohol (**5b**) (100 mg) in acetic acid (5 ml) and HBr (0.1 ml; 48% in acetic acid) was kept for 1 h, and then diluted with methylene dichloride and water. The bromohydrin (94 mg) did not crystallise. δ_H 7.37 (2 H, m, 21-, 23-H), 6.33 (m, 22-H), 5.42 (s, 17-H), 4.4 (m, 2-H), 4.2 (m, 3-H), 3.76 (s, 15-H), 3.6 (m, 1-H), and 1.61, 1.25, 1.21, 1.14, and 1.11 (5 × C-Me). The acetate was also non-crystalline; δ_H 7.37 (2 H, m, 21-, 23-H), 6.3 (m, 22-H), 5.42 (s, 17-H), 5.32 (d, *J* 2.5 Hz, 3-H) 4.67, (d, *J* 5.5 Hz, 1-H), 4.42 (dd, *J* 5.3 and 2.6 Hz, 2-H), 3.79 (s, 15-H), 2.12 and 2.02 (2 × AcO), and 1.65, 1.24, 1.15, 1.1, and 0.95 (5 × C-Me).

Reaction of the Bromohydrin with Silver Acetate.—The bromohydrin (50 mg) was heated for 2 h on a steam bath with silver acetate (30 mg) in acetic acid. Work-up gave cedrolide (**1b**) (23 mg, 59%). The bromohydrin acetate was unchanged.

Crystal Structure Determinations.—Crystal structure determinations were performed on 3β-acetoxy-1,2α-epoxy-3-deoxocedrolide (**5d**), and on the 1α,2α,3β-triacetoxy-ε-lactone (**6b**).

Suitable single crystals were selected, and irradiated with Mo-K_α (λ = 0.7107 Å) radiation, using an Enraf-Nonius CAD4 diffractometer. Cell parameters were obtained by least-squares analysis of the setting angles of 24 reflections in the range $16 \leqslant \theta \leqslant 17°$. During the data collection, intensities of three standard reference reflections were monitored every hour and centering was checked every hundred measured reflections. Intensities were corrected for Lorentz polarisation effects and an empirical absorption correction applied.[18]

Table 4. Fractional atomic co-ordinates (× 10^4) of non-hydrogen atoms for $C_{32}H_{40}O_{12}$ (**6b**).

Atom	x/a	y/b	z/c
C(1)	7 315(5)	4 769(4)	1 180(2)
C(2)	7 738(5)	3 939(4)	759(2)
C(3)	8 558(5)	4 382(4)	303(2)
C(4)	9 744(5)	4 994(4)	487(2)
C(5)	9 228(5)	5 843(4)	895(2)
C(6)	10 313(5)	6 595(4)	1 080(2)
C(7)	9 867(5)	7 714(4)	1 095(2)
C(8)	8 468(5)	7 361(4)	1 921(2)
C(9)	7 698(4)	6 461(3)	1 654(2)
C(10)	8 387(5)	5 490(4)	1 400(2)
C(11)	6 623(4)	6 218(4)	2 074(2)
C(12)	5 561(4)	7 010(3)	2 026(2)
C(13)	6 104(4)	8 129(3)	1 944(2)
C(14)	7 462(5)	8 122(4)	2 174(2)
C(15)	7 911(5)	9 055(4)	2 438(2)
C(16)	7 075(6)	9 995(4)	2 433(3)
C(17)	5 265(5)	8 834(4)	2 325(2)
C(18)	6 097(5)	8 512(4)	1 334(2)
C(19)	9 117(5)	4 878(4)	1 862(2)
C(20)	10 818(6)	4 319(5)	742(3)
C(21)	10 281(7)	5 513(5)	−58(3)
C(22)	9 455(5)	7 102(4)	2 376(2)
C(23)	3 936(5)	8 959(4)	2 101(2)
C(24)	3 487(6)	9 670(5)	1 696(2)
C(25)	2 265(6)	9 435(6)	1 603(3)
C(26)	2 943(5)	8 360(5)	2 225(3)
C(111)	5 149(6)	5 167(5)	926(3)
C(112)	4 375(6)	5 803(6)	524(3)
C(211)	8 108(7)	2 131(5)	903(3)
C(212)	9 037(7)	1 410(5)	1 172(3)
C(311)	8 177(8)	3 357(5)	−500(3)
C(312)	8 748(9)	2 524(6)	−855(3)
O(7)	9 044(3)	8 022(3)	1 488(1)
O(71)	10 228(4)	8 322(3)	753(2)
O(14)	7 505(4)	8 221(3)	2 786(2)
O(16)	5 814(3)	9 873(2)	2 350(2)
O(161)	7 507(4)	10 847(3)	2 480(2)
O(25)	1 890(4)	8 618(4)	1 920(2)
O(1)	6 413(3)	5 367(3)	854(1)
O(11)	4 738(4)	4 604(4)	1 268(2)
O(2)	8 405(4)	3 121(3)	1 052(2)
O(21)	7 267(6)	1 922(4)	584(3)
O(3)	8 971(4)	3 574(3)	−74(2)
O(31)	7 198(5)	3 768(4)	−588(2)

The structures were solved by direct methods, using SHELXS-86,[19] and refined using SHELX-76.[20] In the final refinements all carbon and oxygen atoms were treated anisotropically, and hydrogen atoms isotropically; methyl groups were treated as rigid groups with a single temperature factor, and the methine, methylene and furan hydrogen atoms were placed in calculated positions, again with a single temperature factor. At this stage in the refinement of the structure (**5d**) two additional peaks corresponding to *ca.* 1 e $Å^{-3}$ each were observed in the difference map. Their assignment to the C and O atoms in the methanol of crystallisation was confirmed from the ^1H NMR spectrum, which allowed the determination of the methanol ratio as 1:4. The best model of the structure was achieved with the fixing of the site occupancy of the methanol C and O atoms at 0.25. The protons of the methanol were not modelled.

In the difference map computed after the final cycles of refinement, electron density max./min. was 0.4/−0.3 e Å^{-3}. No attempt was made to determine the absolute configuration of the molecules on the basis of the *X*-ray data. Further details of the data collection, structure solutions and refinement are given in Tables 1 and 2.

The program PARST[21] was used to obtain molecular parameters, and PLUTO[22] to obtain drawings of the structures.

Fractional atomic co-ordinates are reported in Tables 3 and 4, and the structures are illustrated in Figures 1 and 2. Bond lengths and angles, torsion angles, hydrogen atom co-ordinates, and anisotropic temperature factors have been deposited at the Cambridge Crystallographic Data Centre.* Any further details may be obtained from M. N.

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* For details, see 'Instructions for Authors', (1990), *J. Chem. Soc., Perkin Trans. 1*, in the January issue.

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