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# TERPENOIDS—CV*

## TRANSFORMATION PRODUCTS OF ALANTOLACTONES

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**Abstract**—Three lactones have been isolated from the roots of *Inula racemosa* and identified as alantolactone (I), isoalantolactone (II) and dihydroisoalantolactone (III) respectively. III was also prepared by partial reduction of II with $NaBH_4$, while on complete catalytic reduction, it formed tetrahydroalantolactone (IV). Amine adducts and methoxy derivs were prepared from II. The lactol VII and the diol VIII obtained from IV by controlled LAH reduction, when subjected to Huang-Minlon reduction, furnished the new crystalline monol, 8$\beta$-hydroxy eudesman (IX) and the diol VIII. The selinanone X, which is a convenient compound for the synthesis of 9-ketoeudesman (XX), was obtained from IX by oxidation with Jones' reagent. On Na/n-propanol reduction, X furnished the 8$\alpha$-hydroxyeudesman (XIII) as a crystalline material. Lead tetraacetate oxidation of X yielded the rearranged keto acetate XXII. 9-Ketoeudesman (XX) was prepared from X via its furfurylidene deriv XXIII, followed by Wolff-Kishner reduction and ozonolysis. Tetrahydrocostic acid (XVIa) was obtained from the diol VIII by its oxidation to the keto-acid XV, followed by Wolff-Kishner reduction. The same sequence of reactions were carried out using III as the starting material to procure both the $\beta$- and $\alpha$-unsaturated new crystalline monols (XXVII and XXIX) and the ketone XXVIII. A new interesting crystalline alcohol, 14-hydroxytetrahydroalantolactone (XXX) was prepared by hydroboration of III, oxidation of which with Jones' reagent yielded the lactone-acid XXXI.

ALANTOLACTONE (I), isoalantolactone (II) and dihydroisoalantolactone (III) occurring in a number of natural products,[1-7] have been examined by many eminent workers.[8-10] The correct structures have been recently established[11-16] and have been further confirmed by the syntheses of alantolactone[17] and isoalantolactone.[18]

* Communication No. 978 from the National Chemical Laboratory, Poona-8, India.

[1] J. Spring, *Arch. Pharm.* **239**, 201 (1901).
[2] C. Ukita, R. Matsuda and S. Nakazawa, *J. Pharm. Soc. Japan* **72**, 796 (1952).
[3] Cecille Collin-Asselineau and Sonia Bory, *C.R. Acad. Sci., Paris* **246**, 1874 (1958).
[4] K. Tanabe, *Chem. Pharm. Bull. Tokyo* **6**, 218 (1958).
[5] Gurmit Singh, Vishwa Paul and K. L. Handa, *J. Sci. Ind. Res.* **18B**, 351 (1959).
[6] V. Benesora and V. Herout, *Coll. Czech. Chem. Commun.* **26**, 2916 (1961).
[7] I. Yashioka and Y. Yamada, *Yakugaku Zasshi* **83**, 801 (1963).
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[9] L. Ruzicka and J. A. Van Melson, *Helv. Chim. Acta* **14**, 397 (1931).
[10] L. Ruzicka, P. Pieth, T. Reichstein and L. Ehmann, *Helv. Chim. Acta* **16**, 268 (1933).
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[12] K. Tsuda, K. Tanabe, I. Iwai and K. Funakashi, *J. Am. Chem. Soc.* **79**, 5721 (1957).
[13] W. Cocker, L. O. Hopkins, T. B. H. McMurry and M. A. Nisbet, *J. Chem. Soc.* 4721 (1961); W. Cocker and M. A. Nisbet, *Ibid.* 534 (1963).
[14] Mme. C. Asselineau, Mme. S. Bory and E. Lederer, *Bull. Soc. Chim. Fr.* 1524 (1955).
[15] T. Ukita and S. Nakazawa, *J. Am. Chem. Soc.* **82**, 2224 (1960); S. Nakazawa, *Ibid.* **82**. 2229 (1960).
[16] J. A. Marshall and Noal Cohen, *J. Org. Chem.* **29**, 3727 (1964).
[17] J. A. Marshall and Noal Cohen, *J. Am. Chem. Soc.* **87**, 2773 (1965).
[18] H. Minato and I. Haribe, *Chem. Comm.* 531 (1965).

However, the correlation of the alantolides with the santanolides* has not been done and this is of importance, as one would support the stereochemistry of the other.

Interest in the alantolactones, and specially conversion into canarone (XIX) and dihydrocanarone,[19] has resulted in the present report on the chemistry of alantolactones, correlation of alantolides, santanolides and eudesmol; conversion of isoalantolactone to amine adducts[20] and methoxy derivatives[21] and also its transformation into products related to canarone.

One obvious source of alantolactones in India is the roots of *Inula racemosa*† obtainable from Kashmir. The essential oil from the roots, as well as the concrete obtained from the same by solvent extraction, has been found to contain substantial proportions of isoalantolactone and alantolactone.[5] The isolation of the concrete from the roots by a modified, low-temperature solvent extraction procedure, followed by careful chromatography on silica gel, shows that the lactonic portion of the concrete contains isoalantolactone (II), dihydroisoalantolactone (III) and alantolactone (I), in which II predominates. The lactones thus obtained, possess the physicochemical properties described in the literature[16] and show the expected IR, UV and NMR spectral characteristics.

Marshall[16] has prepared III by partial reduction of II. Since both the double bonds in II are methylenic, preferential reduction of one is beset with practical difficulties. When II was reduced with sodium borohydride[22,23] only the methylenic group conjugated with the lactone function was reduced stereospecifically to give III with all the expected properties.

When II, III or I or the total lactonic mixture obtained from the roots of *Inula racemosa* was reduced in the presence of Pt-catalyst, pure IV was obtained, more or less, as the exclusive product of hydrogenation. This is in agreement with earlier finding.[12]

An alcoholic solution of II on mixing with an adequate quantity of $NH_4OH$ and keeping at 0° for 2 days, yielded crystalline Va.[24,25] Its IR spectrum shows the absence of the exomethylene group conjugated to the lactone moiety (no IR band at 826 $cm^{-1}$), while it still exhibits the presence of the unconjugated exomethylene group (1660 and 895 $cm^{-1}$). In a similar fashion II also forms a crystalline methylamine adduct Vb.

Isoalantolactone also furnishes a crystalline 13-methoxydihydroisoalantolactone derivative (VI) on dissolving in methanol in the presence of a little base. Compound VI reveals the absence of the 826 $cm^{-1}$ band due to the conjugated methylene group

* Santanolide 'c' is represented by the structure IVa.

† We are very grateful to Dr. K. Ganapathi, Director, Regional Research Laboratory, Jammu, India, and Mr. K. L. Handa of the same Laboratory for generous help in procuring authentic plant material for us.

[19] V. K. Hinge, A. D. Wagh, S. K. Paknikar and S. C. Bhattacharyya, *Tetrahedron* **21**, 3197 (1965) and earlier Refs mentioned therein.

[20] G. H. Kulkarni, G. R. Kelkar and S. C. Bhattacharyya, *Tetrahedron* **20**, 1301 (1964).

[21] G. H. Kulkarni, A. Paul, A. S. Rao, G. R. Kelkar and S. C. Bhattacharyya, *Tetrahedron* **12**, 178 (1961).

[22] H. Hikino, K. Meguro, G. Kusano and T. Takemoto, *Chem. Pharm. Bull. Japan* **12**, 5, 632 (1964).

[23] S. B. Mathur, S. V. Hiremath, G. H. Kulkarni, G. R. Kelkar and S. C. Bhattacharyya, *Tetrahedron* **21**, 3575 (1965).

[24] L. Ruzicka and P. Pieth, *Helv. Chim. Acta* **14**, 1090 (1931).

[25] J. W. Steele, J. B. Stenlake and W. D. Williams, *J. Chem. Soc.* 2627 (1959).

and shows the presence of the 1660 and 895 $cm^{-1}$ bands due to the unconjugated methylene group. This is also fully supported by the NMR spectra.

Tetrahydroalantolactone (IV) on controlled reduction[25,26] with LAH, furnished a mixture of the hydroxy aldehyde VII and the diol VIII, Huang-Minlon reduction of which furnished in good yield the pure (GLC/TLC) crystalline monol, 8$\beta$-hydroxyeudesman (IX), together with the diol VIII. This diol can also be prepared independently by reduction of IV with excess of LAH.[15]

The monol IX, is crystalline and its stereochemistry at all centres follows from that of the starting material IV.

On oxidation with Jones' reagent, it yielded the pure selinanone, 8-keto-eudesman (X). Its IR and NMR spectra are identical with those of an authentic sample, previously obtained.[27] The identity of the selinanones obtained by the two routes was further confirmed by taking the mixed m.p. of the semicarbazones.

On reduction with LAH and $NaBH_4$ the ketone X regenerated the parent alcohol IX. However, on reduction with Na–n propanol[28] it gave the corresponding epimeric, pure (GLC/TLC) crystalline 8$\alpha$-hydroxyeudesman (XIII). The alcohol XIII was previously obtained[27] but its stereochemistry which could not be decided at that time, was now established by its formation by the stereospecific reduction of the ketone X and further supported by the NMR spectra of the two alcohols. These interconversions further establish the structure-stereochemical relationship of the alantolides with eudesmol and *vis-a-vis* with the santanolides.[29]

The diol VIII on heating in toluene solution in the presence of *p*-toluenesulphonic acid was converted to the oxide[30] XIV which regenerates the parent lactone IV by treatment with chromic acid.

The diol VIII on oxidation with Jones' reagent yielded the keto-carboxylic acid XV, m.p. 153–155°, $[\alpha]_D$ +0·64° which was previously obtained.[15] The acid XV on Wolff-Kishner reduction furnished a liquid acid, identical in all respects with tetrahydrocostic acid,[31] obtained by hydrogenation of crystalline costic acid.

Tetrahydrocostic acid (XVIa) was converted into dihydroeudesmol.[30] Therefore, the stereochemistry at all its centres excepting the Me and Co groups attached at C-11 have been decided. This point deserves careful examination, as an acid of identical structure was obtained by dehydration of the hydroxy acid XVIIa to XVIII, followed by hydrogenation.[30] The acid is a crystalline solid, m.p. 70–72°. Possibly the two products, the liquid product obtained by simple hydrogenation of the crystalline costic acid or Wolff-Kishner reduction product of the keto acid XV and the crystalline saturated acid obtained by hydrogenation of XVIII, are isomers.* Their relationship is now receiving our attention.

In order to prepare 9-ketoeudesman† (XX) from the selinanone (X), the latter

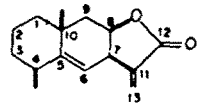
* The two compounds do not differ in stereochemistry at $C_7$.

† 9-ketoeudesman is likely to be identical with dihydrocanarone obtained by hydrogenation of canarone. Isolation of canarone from the resin *Canarium strictum*, and confirmation of its structure is being pursued in our laboratory (see Ref. 19 and other Refs mentioned therein).

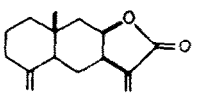
[25] A. M. Shaligram, A. S. Rao and S. C. Bhattacharyya, *Tetrahedron* **18**, 969 (1962).
[27] G. D. Joshi, S. K. Paknikar, S. N. Kulkarni and S. C. Bhattacharyya, *Tetrahedron* **22**, 1651 (1966).
[28] H. L. Herzog, M. A. Jevnik and E. B. Hershberg, *J. Am. Chem. Soc.* **75**, 269 (1953).
[29] G. D. Joshi, M. V. Kadival, S. N. Kulkarni and S. C. Bhattacharyya, *Tetrahedron* **23**, 1985 (1967).
[30] K. Tanabee, *Chem. Pharm. Bull. Tokyo* **6**, 214 (1958).
[31] A. S. Bawdekar and G. R. Kelkar, *Tetrahedron* **21**, 1521 (1965).

was subjected to lead tetraacetate oxidation,[32,33] but instead of the expected intermediate 8-keto-9-acetoxy eudesman (XXI), the product was the 8-acetoxy-9-keto eudesman (XXII), presumably via rearrangement. Such rearrangements[32-34] are quite common and have been observed in the carbohydrate field[35] and in several other cases.[36]

The attempt to reduce the 8-acetoxy-9-keto eudesman (XXII) to 9-ketoeudesman (XX) with calcium/liquid ammonia[37] failed to give satisfactory results. The synthesis



I



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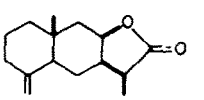

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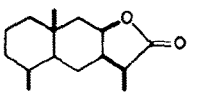

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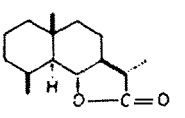
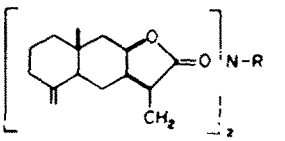
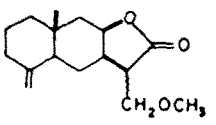


IV a



V a, R = H
b, R = $CH_3$



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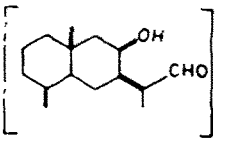
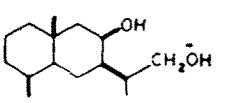
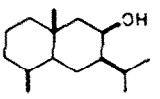


VII



VIII



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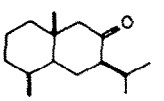
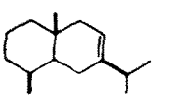
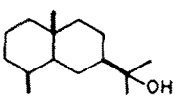


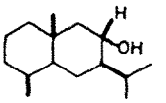
X



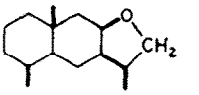
XI



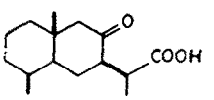
XII



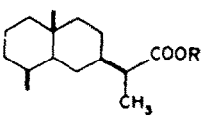
XIII



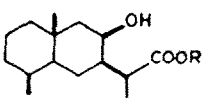
XIV



XV

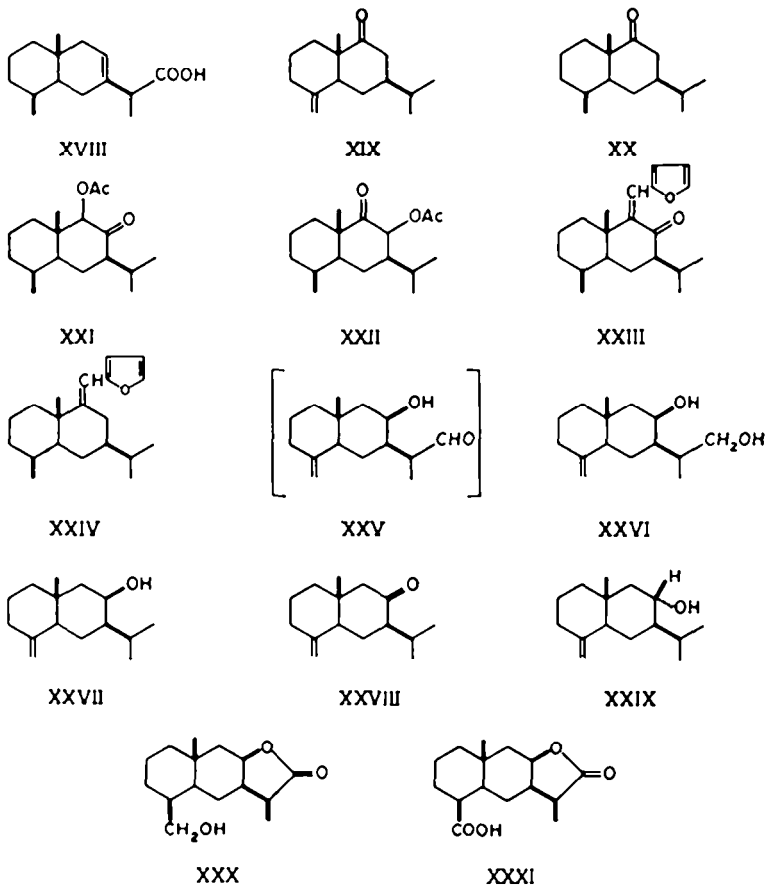


XVI a, R = H
b, R = $CH_3$



XVII a, R = H
b, R = $CH_3$

[33] H. B. Henbest, D. N. Jones and G. P. Slater, *J. Chem. Soc.* 4472 (1961).
[34] S. N. Shanbhag, C. K. Mesta, M. L. Maheshwari and S. C. Bhattacharyya, *Tetrahedron* **21**, 3591 (1965).
[35] J. H. Chapman, J. Elks and L. J. Wyman, *Chem. & Ind.* 603 (1955).
[36] H. O. Fisher, C. Taube and E. Baer, *Ber. Dtsch. Chim. bis.* **60**, 480 (1927).
[37] S. N. Shanbhag, M. L. Maheshwari and S. C. Bhattacharyya, *Tetrahedron* **23**, 1235 (1967).
[37] J. H. Chapman, J. Elks, G. H. Phillips and L. J. Wyman, *J. Chem. Soc.* 4344 (1956).




of the ketone XX was then attempted by a different route. The selinanone (X) formed a crystalline keto-furfurylidene derivative (XXIII)[38,39] which on Huang-Minlon reduction was converted to the furfurylidene derivative (XXIV), ozonization of which yielded 9-keto-eudesman (XX).

In another series of experiments, it was found that the controlled LAH reduction of dihydroisoalantolactone (III) gave a mixture of the hydroxy aldehyde XXV and the diol XXVI, Huang-Minlon reduction of which furnished a mixture of the monol 8$\beta$-hydroxy eudesm-4-(14)-ene (XXVII) and the diol XXVI which were separated by chromatography. The diol which can also be prepared independently by reduction of III with excess of LAH, is a crystalline material, m.p. 130–131°.

The unsaturated monol (XXVII) is a beautifully crystalline material, and the stereochemistry at all centres follows from that of the pure starting material III.

On oxidation with Jones' reagent, it yielded the pure 8-keto eudesm-4(14)-ene (XXVIII), $[\alpha]_D$ +22·57°, which on reduction with Na/n-propanol, furnished the corresponding epimeric, pure (GLC/TLC) crystalline alcohol, 8$\alpha$-hydroxy eudesm-4(14)-ene (XXIX), m.p. 78–80°, $[\alpha]_D$ +65·6°.

[38] W. S. Johnson, B. Bannister, R. Pappo and J. E. Pike, *J. Am. Chem. Soc.* 78, 6354 (1956).
[39] R. Hanna, C. Sandris and Guy Ourisson, *Bull. Soc. Chim. Fr.* 1454 (1959).

Dihydroisoalantolactone (III) on hydroboration[40,41] furnished a crystalline alcohol, 14-hydroxy tetrahydroalantolactone (XXX), m.p. 193–194°, $[\alpha]_D$ +15·45°, which on oxidation with Jones' reagent, yielded the pure lactone-acid (XXXI), m.p. 217–218°, $[\alpha]_D$ +42°.

## EXPERIMENTAL

All m.ps and b.ps are uncorrected. Rotations were determined in chf soln. The IR spectra were taken as liquid films for liquids and in nujol for solids on a Perkin-Elmer Model 137B, Infracord spectrophotometer by Miss Parkhi and Miss Shirole. The NMR spectra were taken in $CCl_4$ or $CDCl_3$ soln using TMS as internal standard on a Varian A-60 spectrometer by Mr. Mulla. GLC analyses were carried out on a Griffin George instrument (MK IIA model) on a polyester column using $H_2$ under press as the carrier gas by Mr. Bapat and Mr. Sankpal. Microanalyses were carried out by Mr. Pansare and colleagues. Anhydrous $Na_2SO_4$ was used for all drying purposes.

*Extraction of the roots of* Inula racemosa. Finely-powdered roots of *Inula racemosa* (40 kg) were stirred mechanically with pet. ether (40–60°, 65 l.) at the room temp for 2 hr in a narrow-mouthed stainless steel tank of adequate size and fitted with a false bottom, a tap for drawing off the extract and a powerful spark-proof vertical motor stirrer, as employed in the case of extraction of costus root oil.[42] The extract was allowed to settle for about ½ hr and then drawn through the tap and initially filtered through cloth. The residual plant pulp was then extracted similarly twice with 50 l. pet. ether each time. The combined extracts (140 l.) were then filtered and the filtrate concentrated in a double jacketed stainless steel distillation vessel under vacuum at a bath temp not exceeding 40 ± 2°. The concentrate was then taken out and the last traces of solvent were removed in glass vessels using higher vacuum at 40 ± 2° to yield the extract as the residue, 2·5 kg (6·26%).

*Separation of the constituents of* Inula racemosa *extract.* The oil (2·5 kg) was mixed with pet. ether (40–60°; 1·5 l.) and the soln kept at 0° in a cold room for 8 days. The crystals which separated out were filtered off (A) and washed with a little ice cold pet. ether. The combined filtrate was then kept at −18° in a deep freeze for 1 week, when a second crop of crystals (B) separated. In this communication, we have recorded some of the results of our examination of only the Fraction A. Results of examination of the other fractions will be communicated separately.

*Examination of fraction A.* The crystals (A, 144 g) were dissolved in hot MeOH (600 ml), filtered immediately and cooled at 0° for 1 day and filtered. The mother liquor was evaporated at 40 ± 2° and the same crystallization procedure was adopted several times to give the following crops.

| No. | Wt in g | m.p. |
|---|---|---|
| I | 52 | 110–11° |
| II | 20 | 101–103° |
| III | 14 | 86–92° |
| IV | 26 | 64–67° |
| V | 17 | 58–60° |

*Isolation of alantolactone* (I). Alantolactone was isolated from crop IV first by chromatography on silica gel (30 folds) and then by crystallizing several times from pet. ether to yield homogeneous material (TLC), m.p. 79–80°; $[\alpha]_D$ +165·7° (*c*, 1·77); $\lambda_{max}$ 211 mμ, (ε 9470).

IR bands at: 1754 (γ-lactone); 1645, 893, 885 and 813 (>C=CH$_2$) and 862 cm$^{-1}$ (—CH=C<). NMR signals at: 3·88 (H-13; d; J = 2 c/s); 4·41, 4·45 (H-13'; d: J = 1·8 c/s); 4·77, 4·83 (H-6; d; J = 4·2 c/s); 5·20–5·33 (H-8 m); 6·37–6·61 (H-7 m); 8·75 (C-10 Me) and 8·91 (C-4 Me, d; J = 7 c/s)τ. (Found: C, 78·12; H, 9·04. Calc. for $C_{15}H_{20}O_2$: C, 77·55; H, 8·68%.)

*Isolation of isoalantolactone* (II) *and dihydroisoalantolactone* (III). The crop I (25 g) was chromatographed on silica gel (40 folds) and eluted successively with pet. ether, pet. ether–benzene (1:1), benzene and ether. The benzene eluate consisted mainly of isoalantolactone (18 g) while the ether

[40] H. C. Brown and P. A. Tierney, *J. Am. Chem. Soc.* **80**, 1552 (1958); H. C. Brown and G. Zweifel, *Ibid.* **81**, 247 (1959).

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eluate consisted only dihydroisoalantolactone (6 g). These were further purified by crystallizing several times from MeOH to yield pure material (TLC).

*Isoalantolactone* (II), m.p. 111–112°; $[\alpha]_D$ +173·6° (*c*, 5·0); $\lambda_{max}$ 211 mμ (ε 8780). IR bands at: 1770 (γ-lactone); 1645, 890 (unconjugated >C=CH$_2$) and 826 cm$^{-1}$ (conjugated >C=CH$_2$).

NMR signals at: 3·98 (H-13, d; J = 0·8 c/s), 4·45 (H-13′; d; J = 0·6 c/s); 5·25, 5·50 (>C=CH$_2$ at C-4); 5·55 (H-8) and 9·15 (C-10 CH$_3$)τ. (Found: C, 77·43; H, 8·90. Calc. for $C_{15}H_{20}O_2$: C, 77·55; H, 8·68%.)

*Dihydroisoalantolactone* (III), m.p. 171–172°, $[\alpha]_D$ +36·4° (*c*, 5·16); $\lambda_{max}$ 211 mμ (ε 258).

IR bands at: 1770 (γ-lactone); 1650, 890 (unconjugated >C=CH$_2$) and absence of 826 cm$^{-1}$ (due to conjugated >C=CH$_2$). NMR signals at: 5·22, 5·49 (>C=CH$_2$ at C-4); 5·40–5·70 (H-8; m); 8·83 (C-11 Me, d; J = 7 c/s) and 9·18 (C-10 Me)τ. (Found: C, 76·55; H, 9·37. Calc. for $C_{15}H_{22}O_2$: C, 76·88; H, 9·46%.)

*Preparation of* III *by* $NaBH_4$*-reduction of* II. Compound II (20 g) dissolved in MeOH (500 ml) was treated with $NaBH_4$ (6 g) gradually during 1½ hr and the reaction mixture kept at the room temp for 24 hr. On removal of solvent, the crystalline ppt was washed with water containing HCl. The solid material was crystallized from MeOH to afford pure (TLC), white needles of III; m.p. 171–172°, $[\alpha]_D$ +42·0° (*c*, 5·0). (Found: C, 76·82; H, 9·41. Calc. for $C_{15}H_{22}O_2$: C, 76·88; H, 9·46%.) IR and NMR spectra are identical with those of natural III.

*Tetrahydroalantolactone* (IV). A mixture of the lactones I, II and III (50 g) in EtOH (1 l.) was hydrogenated with pt-catalyst (0·6 g) at the room temp. After filtration the solvent was removed under suction and the crude solid on recrystallization from MeOH yielded the pure (TLC) IV, m.p. 143–144°, $[\alpha]_D$ +10·78° (*c*, 4·78). IR bands at: 1770 (γ-lactone); 1465, 1385, 1370, 1345, 1300, 1200, 1180, 1130, 1095, 1028, 970 and 935 cm$^{-1}$.

NMR signals at: 5·52–5·76 (H-8, m); 8·98 (C-10 Me); 8·91 (C-11Me); 9·12 (C-4 Me)τ. (Found: C, 76·12; H, 10·33. Calc. for $C_{15}H_{24}O_2$: C, 76·20; H, 10·24%.)

*Ammonia adduct of isoalantolactone* (II). The lactone (0·32 g) dissolved in EtOH (20 ml) was mixed with $NH_4OH$ (10 ml) and kept at 0° for 2 days. Dilution with water and working up, yielded a solid (0·3 g) which crystallized from MeOH–Chf to furnish Va as a pure (TLC), white, crystalline flaky material, m.p. 248–249°; $[\alpha]_D$ +81·12° (*c*, 4·0).

IR bands at: 1770 (γ-lactone); 1660, 895 (unconjugated >C=CH$_2$); 1470, 1375, 1340, 1000, 980, 975, 780 and 730 cm$^{-1}$.

NMR signals at: 5·20, 5·49 (>C=CH$_2$ at C-4), 5·45–5·65 (H-8, m); 7·02 (—CH$_3$ at C-13) and 9·18 (C-10 Me)τ. (Found: C, 74·57; H, 8·53; N, 3·06. Calc. for $C_{30}H_{43}O_4N$: C, 74·81; H, 9·00; N, 2·91%.)

*Methylamine adduct of* II. Isoalantolactone (0·61 g), dissolved in EtOH (25 ml) was treated with a freshly prepared soln of $MeNH_2$ and the reactants were kept at 0° for 2 days. Dilution with water and working up, yielded a solid (0·6 g), which was crystallized from MeOH–Chf to furnish the pure (TLC) white crystalline adduct Vb, m.p. 220–221°, $[\alpha]_D$ +73·2° (*c*, 3·2).

IR bands at: 1770 (γ-lactone); 1660, 892 (unconjugated >C=CH$_2$); 1470, 1375, 1340, 1310, 1280, 1175, 1050, 1035, 1005, 990, 970, 955, 912 and 730 cm$^{-1}$.

NMR signals at: 5·18, 5·50 (>C=CH$_2$ at C-4); 5·40–5·62 (H-8, m); 7·15 (—CH$_3$ at C-13); 7·65 (—N Me) and 9·18 (C-10 Me)τ. (Found: C, 74·71; H, 8·84; N, 2·75. $C_{31}H_{45}O_4N$ requires: C, 75·11; H, 9·15; N, 2·83%.)

*Preparation of* 13*-methoxydihydroisoalantolactone* (VI). Isoalantolactone (0·54 g) dissolved in MeOH (10 ml) was treated with half a pellet of KOH and was kept at 0° for 4 days. The mixture was acidified with HCl (1:1), diluted with water and extracted with ether. The ether layer was washed with water till neutral, dried and the solvent removed to yield 13-methoxydihydroisoalantolactone (0·55 g), which was crystallized from pet. ether, m.p. 90–91°; $[\alpha]_D$ +78·0° (*c*, 4·0).

IR bands at: 1770 (γ-lactone); 1660, 895 (unconjugated >C=CH$_2$); 1470, 1380, 1315, 1225, 1180, 1140, 1110, 1010, 990, 975, 960, 905 and 730 cm$^{-1}$. NMR signals at: 5·22, 5·52 (>C=CH$_2$ at C-4); 5·35–5·68 (H-8, m); 6·29–6·48 (—CH$_2$ of —CH$_2$OMe); 6·65 (—OMe) and 9·15 (C-10 Me)τ. (Found: C, 73·02; H, 9·18. $C_{16}H_{24}O_3$ requires: C, 72·69; H, 9·15%.)

*LAH reduction of tetrahydroalantolactone* (IV). A soln of the lactone (14·4 g) in dry ether (250 ml) was added gradually to a soln of LAH (7·21 g) in dry ether (150 ml) at the room temp under stirring during 1½ hr. After additional stirring for 6 hr at the same temp the reaction mixture was worked up to yield VIII (13·5 g), which was crystallized from pet. ether, m.p. 110–111°, $[\alpha]_D$ −3·84° (*c*, 4·85).

IR bands at: 3180, 2900, 1470, 1385, 1335, 1220, 1165, 1090, 1080, 1050, 902 and 875 $cm^{-1}$. NMR signals at: 4·82 (2H; H of —O*H* and H of —$CH_2O$*H*); 5·98–6·18 (H-8, m); 6·42–6·76 (2H of —$CH_2$OH); 8·88, 9·02, 9·12 (C-4 Me; C-10 Me and C-11 Me)$\tau$. (Found: C, 75·01; H, 11·68. Calc. for $C_{15}H_{26}O_3$: C, 74·95; H, 11·74%.)

*Controlled LAH reduction of* IV *and preparation of 8β-hydroxyeudesman* (IX). The lactone IV (10 g) dissolved in dry ether (300 ml) was reduced by gradual addition of an ethereal soln of LAH (0·4 mole, 1 g of 60%) under cooling (−10°) during 1½ hr. The reaction mixture was stirred for 3 hr at −10° and for another 3 hr at the room temp. It was then worked up to give a solid (9 g). Its TLC showed it to be a mixture of the unreacted IV, the lactol VII and the diol VIII. It was dissolved in freshly distilled diethylene glycol (90 ml); hydrazine hydrate (22·5 ml) and KOH pellets (9 g) were introduced. The contents were heated at 140–150° for 6 hr. After cooling, the product was diluted with water and extracted with ether to yield a material (7 g) which was chromatographed over alumina (grade III; 150 g). The pet. ether eluate consisted of the pure (GLC/TLC) IX (3 g) and the ether eluate yielded the pure (TLC), diol VIII (3 g). The unreacted lactone IV was recovered from the alkaline extract of the reaction product. The monol IX was crystallized from pet. ether, m.p. 66–67°; $[\alpha]_D$ ±0°.

IR bands at: 3440, 2900, 1480, 1395, 1245, 1220, 1175, 1165, 1125, 1045, 1032, 1005, 988, 975, 948, 938, 902, 865, 845 and 725 $cm^{-1}$.

NMR signals at: 5·88–6·02 (H-8, m), 8·95 (C-10 $CH_3$), 9·02, 9·12 (C-4 Me and —HC(Me)(Me))$\tau$.

(Found: C, 80·95; H, 12·61. $C_{15}H_{26}O$ requires: C, 80·29; H, 12·58%.)

*Diol* VIII was crystallized from pet. ether, m.p. 110–111°, $[\alpha]_D$ −8·48° (*c*, 3·5). (Found: C, 75·08; H, 11·83. Calc. for $C_{15}H_{28}O_3$: C, 74·95; H, 11·74%.) IR and NMR spectra are identical with those of an authentic sample.

*Preparation of the selinanone 8-ketoeudesman* (X). The monol IX (2 g) was dissolved in acetone (20 ml) and Jones' reagent was added gradually till a permanent brown colour persisted. The mixture was kept at the room temp for 2 hr and worked up to give a liquid (1·9 g), purified by passing through gr. II alumina. The pure (GLC/TLC) X, had b.p. 160° (bath)/0·8 mm, $[\alpha]_D$ −21·33° (*c*, 3·5).

IR bands at: 1704 (>C=O); 1418 (—CO·$CH_2$); 1460, 1379, 1361, 1295, 1279, 1212, 1163, 1064, 990, 980, 952, 926 and 855 $cm^{-1}$.

NMR signals at: 8·98, 8·95, 9·00 and 9·12 (C-4, Me; C-10 Me and —HC(Me)(Me))$\tau$. (Found: C, 82·08; H, 12·06. Calc. for $C_{15}H_{24}O$: C, 81·62; H, 11·71%.)

It formed a semicarbazone, crystallized from EtOH, m.p. 207–208°. (Found: C, 68·90; H, 10·40; N, 15·50. Calc. for $C_{16}H_{29}ON_3$: C, 68·77; H, 10·46; N, 15·04%.)

*LAH reduction of* X. The ketone (0·57 g) in dry ether (25 ml) was added dropwise to a soln of LAH (0·2 g) in dry ether (50 ml) with stirring at 0° during 1 hr. The reaction mixture was then brought to the room temp and then refluxed for 7 hr. On working up, it yielded the pure (GLC/TLC) monol IX, m.p. 66–67°, undepressed with an authentic sample.

$NaBH_4$ *reduction of* X. The ketone (0·5 g) dissolved in MeOH (15 ml), was treated with $NaBH_4$ (0·1 g) at the room temp and was stirred for 3 hr at the same temp. Dilution with water and working up gave the pure (GLC/TLC) white crystalline monol IX(0·49 g), m.p. 66–67°, undepressed with an authentic sample.

*Preparation of 8α-hydroxyeudesman* (XIII). To a soln of X (0·16 g) in n-propanol (20 ml), freshly cut Na pieces (0·2 g) were added rapidly so as to keep a vigorous reaction which was maintained afterwards by heating till all the Na disappeared (~3 hr). The reaction mixture was cooled, diluted with water (150 ml) and extracted with ether. The ether extract was washed neutral with brine, dried and the solvent evaporated to afford a pure (GLC/TLC) white solid, XIII, crystalilzed from pet. ether and sublimed, m.p. 105–106°, $[\alpha]_D$ +42·08° (*c*, 2·4). IR bands at: 3200, 2900, 1475, 1395, 1050, 930 and 730 $cm^{-1}$.

NMR signals at: 6·32–6·65 (H-8 m); 9·02 (C-10 Me), 9·10, 9·20 (C-4 Me and —HC(Me)(Me))$\tau$.

(Found: C, 80·85; H, 12·73. $C_{15}H_{28}O$ requires: C, 80·29; H, 12·58%.)

*Preparation of the oxide* (XIV). The diol VIII (0·44 g) in dry toluene (25 ml) and *p*-toluenesulphonic acid (55 mg) was refluxed at 140–145° for 2 hr. The product was cooled, washed with water till neutral and solvent removed under vacuum to give a liquid (0·4 g) which was chromatographed

on alumina (gr. III; 10 g). The pet. ether eluate consisted of the pure (GLC/TLC) oxide XIV (0·33 g), b.p. 140°/4 mm, $[\alpha]_D$ −16·82° (*c*, 1·6).

IR bands at: 2900, 1460, 1390 and 1040 $cm^{-1}$. (Found: C, 81·00; H, 11·94. Calc. for $C_{15}H_{26}O$: C, 81·02; H, 11·79%.)

*Chromic acid oxidation of the oxide* XIV. The oxide (0·15 g) in AcOH (15 ml) was treated with $CrO_3$ (0·2 g) at 15° and kept at the room temp for 36 hr. It was diluted with water and extracted with ether. The ether layer was washed with water, $Na_2CO_3$aq and finally with water till neutral. Removal of solvent furnished a material (0·1 g) which was chromatographed on alumina (gr. III; 3 g) and the crude lactone (24 mg), m.p. 134–137°, crystallized from pet. ether to give the pure (TLC) IV, m.p. 141–143°, undepressed with an authentic sample; $[\alpha]_D$ +10·65° (*c*, 1·3). (Found: C, 76·02; H, 10·38. Calc. for $C_{15}H_{24}O_3$: C, 76·20; H, 10·24%.) IR and NMR spectra are identical with those of an authentic sample.

*Oxidation of the diol* VIII *with Jones' reagent*. The diol (5·28 g), dissolved in acetone (50 ml) was treated with Jones' reagent till a permanent brown colour persisted. It was kept at the room temp for 1 hr and on working up gave a mixture (4·2 g) of IV and the unreacted VIII in the neutral portion and XV (0·87 g) in the acidic part. The XV was crystallized from aqueous MeOH, m.p. 153–155°, $[\alpha]_D$ +0·64° (*c*, 2·5). IR bands at: 3200 (broad), 2900, 1715, 1460, 1390, 1230, 1120, 1035 and 970 $cm^{-1}$.

*Wolf-Kishner reduction of the keto acid* (XV). The keto acid (0·71 g) dissolved in freshly distilled diethylene glycol (8 ml), hydrazine hydrate (2 ml) and KOH pellets (0·7 g) were refluxed at 140–150° for 3 hr and then at 190–200° for 3 hr under $N_2$. It was cooled, diluted with water and extracted with ether. The aqueous layer on acidification and extraction with ether, furnished the acid (0·12 g) which was converted into its Me ester by diazomethane and purified by passing through alumina (gr. II). The pure (GLC/TLC) XVIb had b.p. 140° (bath)/0·8 mm, $[\alpha]_D$ + 19·86° (*c*, 2·78).

IR bands at: 2900, 1730, 1453, 1379, 1353, 1258, 1212, 1159, 1107 and 1017 $cm^{-1}$. (Found: C, 76·17; H, 10·85. $C_{16}H_{28}O_3$ requires: C, 76·14; H, 11·18%.)

*Lead tetraacetate oxidation of the selinanone* (X). A soln of X (0·5 g) and lead tetraacetate (0·5) in AcOH (20 ml) was refluxed for 4 hr under $N_2$ with stirring. It was diluted with an excess of water and extracted with ether. The ether extract was washed thoroughly with water, $NaHCO_3$aq and finally with water, dried and solvent removed to furnish a viscous liquid (0·5 g). It was purified by chromatography on silica gel (20 g) and eluted successively with pet. ether, pet. ether–AcOEt (5, 7, 10 and 20%) mixture and ether. The pet. ether (7%) AcOEt eluate consisted of pure (TLC) XXII (0·15 g), b.p. 145° (bath)/0·05 mm.

IR bands at: 1740, 1253 (acetate); 1480, 1470, 1370, 1290, 1198, 1058, 1029 and 1015 $cm^{-1}$.

NMR signals at: 7·95 (acetate); 8·95 (C-10 Me); 9·0–9·18 (C-4 Me and —HC(Me)(Me)) τ. (Found: C, 72·31; H, 9·92. $C_{17}H_{28}O_3$ requires: C, 72·82; H, 10·06%.)

*Furfurylidene derivative of 8-ketoeudesman* (X). A sample of the ketone (3·5 g) was dissolved in MeOH (300 ml), 33% NaOHaq (60 ml) was added to the cooled soln, followed by freshly distilled furfural (10 ml). After 24 hr at the room temp under $N_2$, the crystalline ppt was separated and washed with aqueous MeOH (15%), AcOH (5%) and finally with water until the filtrate was neutral to litmus. It was crystallized from MeOH, m.p. 102–104°, $\lambda_{max}$ 325 mμ (ε 14,660).

IR bands at: 1680 (conjugated >C=O); 1660, 1592, 1538, 1449, 1370, 1253, 1190, 1163, 1066, 1015, 970, 926, 885, 810 and 735 $cm^{-1}$. (Found: C, 80·34; H, 9·78. $C_{20}H_{28}O_3$ requires: C, 79·95; H, 9·39%.)

*Wolff-Kishner reduction of* XXIII. The keto-furfurylidene deriv (2 g) dissolved in freshly distilled diethylene glycol (20 ml), hydrazine hydrate (5 ml) and KOH pellets (2 g) were heated at 140–150° for 3 hr under $N_2$ and then at 180–190° for another 3 hr. It was cooled, diluted with water and extracted with ether. The ether layer was washed free of alkali, dried and ether removed to furnish XXIV, as a solid (1·6 g), crystallized from MeOH, m.p. 88–90° $\lambda_{max}$ 325 mμ (ε 1460). (Found: C, 83·64; H, 10·40. $C_{20}H_{30}O$ requires: C, 83·86; H, 10·56%.)

*Ozonolysis of* XXIV. A soln of XXIV (1·2 g) in chf (25 ml) was ozonized at 0° for 2 hr. Chf was removed under vacuum and the residual ozonide was heated with water (20 ml) for 2 hr and extracted with ether. The ether extract was separated into acidic and neutral portions by treatment with $Na_2CO_3$.

The neutral part was purified by chromatography on grade II alumina. The pure (GLC/TLC) XX had b.p. 140° (bath)/0·08 mm, $[\alpha]_D$ +15·73° (*c*, 1·78).

IR bands at: 1704 (>C═O), 1420 (—CO·$CH_3$); 1379, and 1370 $cm^{-1}$. NMR signals at 7·35, 7·50 (2H of C-8); 8·73 (C-10; Me), 9·00 (C-4 Me) and 9·02, 9·15 (d due to —HC(Me)(Me)) $\tau$. (Found: C, 81·47; H, 12·03. Calc. for $C_{15}H_{26}O$: C, 81·02; H, 11·79%.)

*LAH reduction of dihydroisoalantolactone* (III). A soln of the lactone (1·34 g) in dry ether (50 ml) was added dropwise to a soln of LAH (0·85 g) in dry ether (50 ml) at the room temp under stirring during 45 min. After additional stirring for 4 hr at the same temp, the reaction mixture was treated to yield the pure (TLC) XXVI (1·2 g), crystallized from pet. ether, m.p. 130–131°, $[\alpha]_D$ +29·4° (*c*, 3·33).

IR bands at: 3125, 1088, 1055 and 1030 (—OH); 1660, 890 and 880 (>C═$CH_2$) $cm^{-1}$.

NMR signals at: 4·65 (2H, d; H of —O*H* and H of —$CH_2$O*H*; after $D_2O$ exchange this doublet disappears), 5·33, 5·55 (>C═$CH_2$); 6·05 (H-8, m centred at); 6·5, 6·65 (2H, d of —$CH_2$OH); 9·0 and 9·10 (C-10 Me and C-11 Me)$\tau$. (Found: C, 75·58; H, 11·18. Calc. for $C_{15}H_{26}O_2$: C, 75·5; H, 11·00%.)

*Controlled LAH reduction of* III *and the preparation of* 8β*-hydroxyeudesm-*4(14)*-ene.* The lactone III (12 g) dissolved in dry ether (400 ml) was reduced by gradual addition of an ethereal soln of LAH (0·4 mole, 1·54 g of 50%) under cooling (−10°) during 1½ hr. The reaction mixture was stirred for 2½ hr at −10° and for another hr at the room temp. It was then worked up to give a solid (11 g). Its TLC showed it to be a mixture of unreacted III, lactol XXV and the diol XXVI. This mixture dissolved in freshly distilled diethylene glycol (110 ml), hydrazine hydrate (27·5 ml) and KOH pellets (11 g) was heated at 140–150° under $N_2$ for 4 hr. After cooling, it was diluted with water and extracted with ether to yield a material (8 g), which was chromatographed on alumina (gr. III; 200 g). The pet. ether eluate consisted of the pure (GLC/TLC) XXVII and the ether eluate yielded the pure (TLC) diol XXVI. The unreacted lactone III was recovered from the alkaline extract of the reaction product. The monol XXVII was crystallized from pet. ether and further purified by sublimation, m.p. 50–51°; $[\alpha]_D$ +40·92° (*c*, 4·13). IR bands at: 3820, 1060, 1045 and 1025 (—OH), 1665, 896, 868 and 846 (>C═$CH_2$); 1398 and 1382 (—HC(Me)(Me)) $cm^{-1}$.

NMR signals at: 5·29, 5·48 (2H, d; >C═$CH_2$); 5·82–5·98 (H-8 m), 8·98, 9·07 (C-10 Me, —HC(Me)(Me)) $\tau$. (Found: C, 80·34; H, 11·53. $C_{15}H_{26}O$ requires: C, 81·02; H, 11·79%.) The diol XXVI was crystallized from pet. ether, m.p. 130–131°, undepressed with that of an authentic sample, $[\alpha]_D$ +28·5° (*c*, 4·12). IR and NMR spectra are identical.

*Preparation of* 8*-ketoeudesm-*4(14)*-ene* (XXVIII). The monol XXVII (0·21 g) dissolved in acetone (5 ml) and Jones' reagent was added gradually till a permanent brown colour persisted. The reaction product was kept at the room temp for ½ hr and worked up to give a liquid (0·2 g), purified by passing through alumina (gr. II). The pure (GLC/TLC) XXVIII, had b.p. 115° (bath)/0·04 mm, $[\alpha]_D$ +22·57° *c*, 2·66). IR bands at: 1704 (>C═O); 1660, 895 (>C═$CH_2$); 1418 (—CO·$CH_3$); 1470, 1450, 1393, 1379, 1222, 1202, 1070, 885 and 870 $cm^{-1}$.

NMR signals at: 5·18, 5·45 (>C═$CH_2$); 7·85 (3H; H-7 and 2H of C-9); 8·97, 9·00 (d), 9·08, 9·15 (d) (—HC(Me)(Me)); 9·30 (C-10 Me) $\tau$. (Found: C, 81·34; H, 10·72. $C_{15}H_{24}O$ requires: C, 81·76; H, 10·98%.)

It formed a semicarbazone deriv, crystallized from MeOH, m.p. 219–220°. (Found: C, 68·69; H, 9·99; N, 15·01. $C_{16}H_{27}ON_3$ requires: C, 69·27; H, 9·81; N, 15·15%.)

*Preparation of* 8α*-hydroxyeudesm-*4(14)*-ene* (XXIX). To a soln of XXVIII (0·25 g) in n-propanol (25 ml), freshly cut Na pieces (0·3 g) were added rapidly so as to keep a vigorous reaction which was maintained afterwards by heating till all the Na disappeared (~3 hr). The reaction mixture was worked up as before to afford pure (GLC/TLC) XXIX as a white solid, crystallized from pet. ether and sublimed, m.p. 78–80°; $[\alpha]_D$ +65·6° (*c*, 2·5).

IR bands at: 3350, 1060, 1045, 1020 (—OH); 1660, 890, 870 (>C═$CH_2$); 1480, 1460, 1390, 1265, 1220 and 995 $cm^{-1}$.

NMR signals at: 5·28, 5·52 (2H, d; >C=$CH_2$); 5·82–5·98 (H-8, m); 9·09 (C-10 Me); 8·98, 9·18, 9·27 (6H, —HC(Me)(Me)) $\tau$. (Found: C, 80·67; H, 11·82. $C_{16}H_{26}O$ requires: C, 81·02; H, 11·79%.)

*Hydroboration of dihydroisoalantolactone* (III). Through a soln of the lactone (5 g) dissolved in dry THF (175 ml) diborane gas ($B_2H_6$) was passed at 0° for 1½ hr and then for further 1 hr at the room temp. The diborane gas was prepared separately by adding slowly a soln of $NaBH_4$ (7 g) in pure freshly distilled diglyme (75 ml) to a mixture of freshly distilled $BF_3$. ethereate (50 ml). N was used as the carrier gas. Excess of diborane in the reaction flask was decomposed by adding small pieces of ice. The reaction mixture was kept in a deep freeze for 24 hr. It was then cooled in the ice bath, 5% KOH (50 ml) was added followed by slow addition of $H_2O_2$ (60 ml; 30%). The reaction product was then kept overnight at the room temp. Since in the presence of alkali, the lactone ring was hydrolysed, it was acidified with HCl (1:1) to regenerate the lactone, diluted with water and extracted with sufficient amount of ether. The ether extract was washed till neutral and dried. Removal of the solvent gave XXX (4 g), crystallized from MeOH, m.p. 193–194°, $[\alpha]_D$ +15·45° (*c*, 3·65). IR bands at: 3500, 1087, 1036, 1013 (—OH); 1770 ($\gamma$-lactone), 1471, 1379, 1282, 1266, 1205, 1176, 1160, 1087, 965, 952, 930, 892, 870, 800, 738 and 719 $cm^{-1}$.

NMR signals at: 5·42–5·63 (H-8, m); 6·29, 6·40 (2H, d of —$CH_2$OH); 7·08–7·30 (H-7 m); 8·10 (1H of —$CH_2$O*H* which vanishes after $D_2O$ exchange); 8·75, 8·88 (d, C-11 Me, J ≈ 7 c/s); 9·12 (C-10 Me) $\tau$. (Found: C, 71·76; H, 9·73. $C_{15}H_{24}O_3$ requires: C, 71·39; H, 9·59%.)

*Oxidation of the hydroxy-lactone* XXX *with Jones' reagent.* To the hydroxy-lactone (0·54 g) dissolved in acetone (20 ml) was added dropwise a soln of Jones' reagent (3 ml) during 10 min at the room temp, kept for further 1 hr at the same temp. The product was diluted with water and extracted with ether. The ether layer was separated into acidic and neutral parts by washing with $Na_2CO_3$aq. The alkaline extract was acidified with HCl (1:1) and extracted with ether to yield XXXI as a white crystalline material, crystallized from MeOH, m.p. 217–218°, $[\alpha]_D$ +42° (*c*, 3·5). IR bands at: 3280, 1690 (—COOH); 1770 ($\gamma$-lactone); 1449, 1408, 1374, 1282, 1250, 1166, 1121, 1081, 1012, 965, 950, 875, 865, 810, 796 and 753 $cm^{-1}$. (Found: C, 67·92; H, 8·38. $C_{15}H_{22}O_4$ requires: C, 67·64; H, 8·33%.)