REDUCTION AND STERIC INTERACTION OF 12-LUPANONE DERIVATIVES*

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Hydroxy ketones *XVII* and *XXXIII* were prepared by hydrolysis of 20-acetoxy-12-lupanone derivatives *XVI* and *XXXI*, and diketone *XVIII* was prepared by oxidation of hydroxy ketone *XVII*. Reduction of 12-oxo group in acetoxy ketones *XVI* and *XXXI* or in diketone *XVIII* takes place preferentially under formation of 12α-hydroxy derivatives *XIX*, *XXI* and *XXXIV*. In 12,20--disubstituted derivatives *XVII*, *XVIII*, *XIX*, *XXI*, *XXXIII* and *XXXIV* the interaction of substituents in the positions 12 and 20 was studied using IR and ^{1}H-NMR spectra and CD. They manifest themselves by the intramolecular hydrogen bond, the equilibrium of the associated and non-associated forms, and dipolar interactions in dependence on the preferred conformations of the side chain. Steric interactions in hydroxy norketone *XVII* and dinorketone *XXXIII* prevent spontaneous formation of the cyclic hemiketal system.

In the preceding communications[1-3] the syntheses of 12-oxo-lupane derivatives have been described, starting from the product of functionalization of the position 12 by means of oxygen radicals generated from 20-hydroxylupane derivatives. The reaction courses (decreased reactivity of 12(*E*)-oximinolupane derivatives) and the results of spectral measurements indicate strong steric and polar interactions between substituents in the positions 12 and 20. For a further study of these phenomena it was necessary to prepare 12-oxo- and 12-hydroxylupane derivatives with a variously modified side chain. Due to the considerable lability of the acetate protecting groups (commonly used for the protection of 3β and 28 hydroxy groups) against alkaline medium and reducing agents it was necessary to protect both hydroxy groups by methylation.

As starting material betulin dimethyl ether *IV* was used, which was prepared by methylation of betulin (*III*). Degradation of its side chain by a known[4] procedure gave norketone *V* which was reduced with sodium in 1-propanol to a mixture of epimeric noralcohols *X* and *XI*. For the determination of their absolute configuration at $C_{(20)}$ noralcohol *X* was prepared by an unambiguous synthesis from the known[4-6] 20*R* noralcohol *VI*. Noralcohol *VI* was converted to nitrate *VII* the acetoxyl groups of which were hydrolysed, under formation of diol *VIII*. Methylation of the hydroxyl

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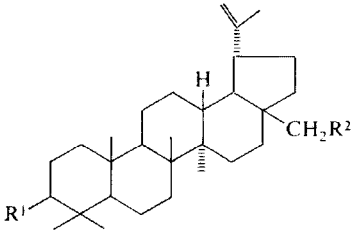
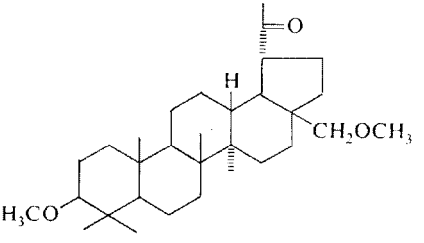
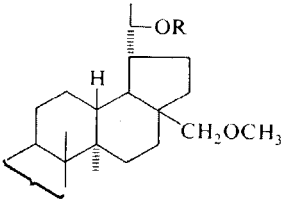
groups with diazomethane under catalysis with aluminum chloride afforded nitrate *IX* which on reaction with zinc in acetic acid gave noralcohol *X*. From noralcohol *XI* nitrite *XII* was prepared, the photolysis of which gave oxime *XIII*. Conversion of oxime *XIII* to ketone *XVI* was carried out in the earlier described manner[1,2], *via* the intermediates *XIV* and *XV*.



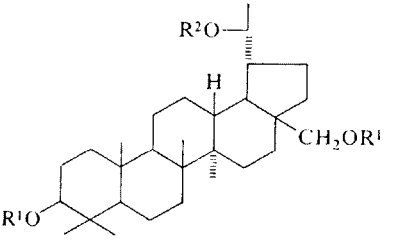
I, $R^1 = OH$, $R^2 = H$
II, $R^1 = OCH_3$, $R^2 = H$
III, $R^1 = R^2 = OH$
IV, $R^1 = R^2 = OCH_3$



V

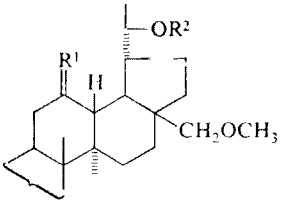


XI, R = H
XII, R = NO

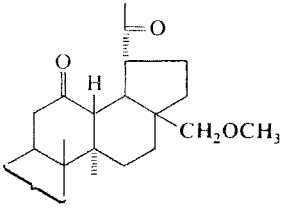


VI, $R^1 = Ac$, $R^2 = H$
VII, $R^1 = Ac$, $R^2 = NO_2$
VIII, $R^1 = H$, $R^2 = NO_2$
IX, $R^1 = CH_3$, $R^2 = NO_2$
X, $R^1 = CH_3$, $R^2 = H$

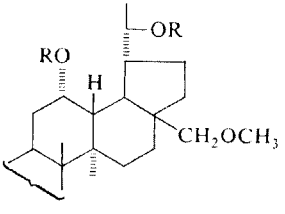
For the synthesis of 12,20-disubstituted 29,30-dinorlupane derivatives dinoracid *XXII* was selected as the starting compound. Hydrolysis of the acetoxy groups gave dihydroacid *XXIII* the reaction of which with diazomethane under catalysis with aluminum chloride gave methyl ester *XXIV*. Its reduction with lithium aluminum hydride gave dinoralcohol *XXVI* which was reacted with nitrosyl chloride to give nitrite *XXVII*. Oxime *XXVIII* was obtained by photolysis of the nitrite, and dinoraldehyde *XXV* as a by-product. An authentic sample of dinoraldehyde *XXV* was prepared according to ref.[2] by oxidation of dinoralcohol *XXVI*.



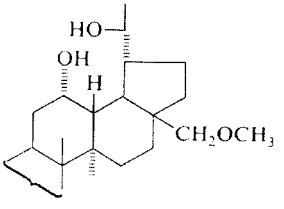
XIII, R^1 = NOH, R^2 = H
XIV, R^1 = NOAc, R^2 = Ac
XV, R^1 = NOH, R^2 = Ac
XVI, R^1 = O, R^2 = Ac
XVII, R^1 = O, R^2 = H



XVIII



XIX, R = H
XX, R = OCNHCOCCl₃



XXI

From the preceding papers[1-3,7,8] it follows that the substitution of the position 12 with polar substituents considerably changes the shifts of the signals of the methyl groups at 8β, 10β and 14α in the ^{1}H-NMR spectra. In order to make the correlation of these changes also in the 3β,28-dimethoxylupane derivatives series possible (Table I), it was necessary to carry out the assignment of all five methyl groups. For the assignment lupeol (*I*) was chosen as the basic substance the methyl signals of which have been assigned with certainty[9,10]. On the basis of the similarity[11,12] of anisotropic effects of the hydroxyl and the methoxyl group the assignment of the methyl group signals was carried out for lupeol methyl ether *II*. From the comparison of the signals of lupeol (*I*) and betulin (*III*) it is evident that the introduction of the hydroxyl group into the position 28 has no substantial effect on the signals of the methyl group bound on the lupane skeleton. On this basis the assignment was carried out for the basic substances of the whole series, *i.e. IV*, *V*, *XI* and *XXVI*. For 20-acetoxy-12-oxolupane derivatives *XVI* and *XXXI* the assignment was carried out on the basis of the known[1-3,7,8] effects of the introduction of the keto group into the position 12 on the chemical shifts of methyls.

On reaction of acetoxy ketone *XVI* with ethanolic potassium hydroxide solution hydroxy ketone *XVII* was obtained as the sole product. Its structure is confirmed

by the carbonyl band in the IR spectrum and its CD curve, which is similar to that of ketone *XVI*. In its ^{1}H-NMR spectrum the methyl signals are distributed equally as in the spectrum of ketone *XVI*; further evidence is the 13βH signal (2·88 d, $J \approx 11$ Hz) which is characteristic of 12-oxolupane derivatives. In the same manner compound *XXXIII* was prepared from *XXXI*. The structure of the former is corroborated by the IR and ^{1}H-NMR spectra. Hence, from the spectra it follows that both hydroxy ketones *XVII* and *XXXIII* exist in a non-cyclized form under the given conditions, represented by the structures *XVII* and *XXXIII* and not as cyclic hemiketals.

In both hydroxy ketones *XVII* and *XXXIII* the hydroxyl at $C_{(20)}$ forms an intramolecular hydrogen bond with the oxygen of the 12-keto group. From the measured values (Table II) it is evident that while in hydroxy ketone *XXXIII* the formation of the hydrogen bond is complete, in the spectrum of hydroxy ketone *XVII* both the

TABLE I

Methyl Group Signals in the ^{1}H-NMR Spectra of 3β,28-Dimethoxylupane Derivatives (in p.p.m.)

Compound	4α CH_3[a]	4β CH_3[a]	10β CH_3[a]	8β CH_3[a]	14α CH_3[a]
I	0·969	0·763	0·834	1·036	0·951
II	0·950	0·746	0·836	1·031	0·950
III	0·97[b]	0·761	0·827	1·025	0·97[c]
IV	0·957	0·750	0·837	1·041	0·968
V	0·953	0·746	0·830	1·021	0·992
XI	0·962	0·756	0·851	1·052	0·925
XIII	0·958	0·767	0·918	1·207	0·890
XVI	0·964	0·774	0·920	1·284	0·797
XVII	0·966	0·775	0·923	1·283	0·831
XVIII	0·973	0·775	0·902	1·235	0·862
XIX	0·974	0·768	0·893	1·065	1·212
XX	0·971	0·757	0·886	1·095	1·292
XXI	0·975	0·767	0·889	1·036	1·221
XXVI	0·959	0·753	0·849	1·048	0·920
XXXI	0·965	0·774	0·921	1·287	0·805
XXXIII	0·970	0·778	0·934	1·293	0·832
XXXIV	0·976	0·767	0·900	1·043	1·225
XXXV	0·967	0·757	0·881	1·087	1·237

[a] Accuracy of the measurement ±0·003 p.p.m.; singlets; [b] overlapping of two signals.

band of free and that of the bonded hydroxyl occur; further the spectrum contains another band at 3593 cm^{-1}. Its existence may be explained in the following manner:* from the coupling constant value $J_{19,20} = 3$ Hz, which is a result of the averageing of the values corresponding to single conformers according to their representation, it is evident that in hydroxy ketone *XVII* the conformers with the dihedral angle between 19βH and 20-H close to 90° strongly predominate. Of the two possible orientations of 20-H only the conformers with a *syn*-periplanar arrangement of 19βH and 20-CH_3 permit the formation of a hydrogen bond, in analogy to the corresponding oximes[1]. The intensive band at $\nu(OH) = 3462\ cm^{-1}$ in the IR spectrum corresponds to these conformers, while the band at 3593 probably corresponds to the

TABLE II

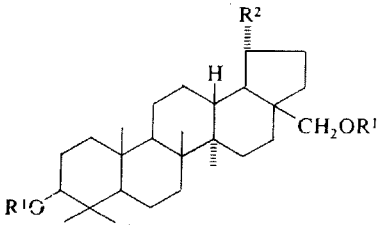
Frequencies and Intensities of OH Stretching Vibrations

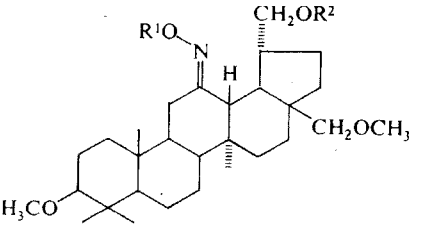
Compound[a]	Substituents[b] 12	Substituents[b] 20	ν cm^{-1}	$\varepsilon^{(a)}$ 1 mol^{-1} cm^{-1}	$\Delta\nu_{1/2}^{(a)}$ cm^{-1}	$B \cdot 10^{-3}$ 1 mol^{-1} cm^{-2}
XI	H_2	H, CH_3(20*S*)	f 3 623	53	14	1·2
XVII	=O	H, CH_3(20*S*)	f 3 624	31	24	1·2
			b 3 590	25	20	0·8
			b 3 459	24	80	3·2
XXI	α-OH	H, CH_3(20*R*)	f 3 616	65	21	2·2
			b 3 516	62	88	8·6
XXVI	H_2	H_2	f 3 637	42	28	1·9
XXXIII	=O	H_2	b 3 558	56	80	7·0
XXXIV	α-OH	H_2	f 3 627[c]	—	—	—
			f 3 609[c]	—	—	—
			b 3 509	48	76	5·7

[a] Measured on grating spectrophotometer Unicam SP 700 in tetrachloromethane (concentration $2 \cdot 10^{-3}$M); f free, b bonded; $B = \pi/2\varepsilon^{(a)} \cdot \Delta\nu_{1/2}^{(a)}$; [b] all substances measured have the hydroxyl group in the position 20; [c] the peaks cannot be separated graphically.

* From the measurement of the IR spectra of both hydroxy ketones, both in chloroform and in tetrachloromethane, in the 10^{-1} to 10^{-3}M range it follows that the intramolecular hydrogen bonds are not appreciably dependent either on the concentration or the change of solvent. For these reasons it is possible to compare the IR spectra measurements (10^{-3}M solution in tetrachlormethane) with the measurements of the ^{1}H-NMR spectra (10^{-1}M solution in deuteriochloroform).

second group of conformers suitable for the formation of intramolecular hydrogen bonds. These conformers are characterized by an *anti*-periplanar arrangement of 19βH and 20-H, for which high $J_{19,20}$ (about 10–15 Hz) values are characteristic. From the measured value of $J_{19,20}$ it follows that they are represented maximally up to 25%. The different behaviour of the two hydroxy ketones *XVII* and *XXXIII* is evidently caused by non-bonding interactions of the methyl group at $C_{(20)}$ in *XVII*, which decrease the energy differences between conformers with the free and the bonded hydroxy group. In hydroxy ketone *XXXIII* the intramolecular hydrogen bond is not limited by the interactions of the side chain, and therefore its energy gain leads to the disappearance of the conformers with an unassociated hydroxy group.





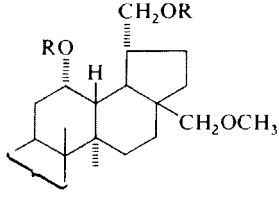
XXII, $R^1 = Ac$, $R^2 = COOH$
XXIII, $R^1 = H$, $R^2 = COOH$
XXIV, $R^1 = CH_3$, $R^2 = COOCH_3$
XXV, $R^1 = CH_3$, $R^2 = CHO$
XXVI, $R^1 = CH_3$, $R^2 = CH_2OH$
XXVII, $R^1 = CH_3$, $R^2 = CH_2ONO$

XXVIII, $R^1 = R^2 = H$
XXIX, $R^1 = R^2 = Ac$
XXX, $R^1 = H$, $R^2 = Ac$

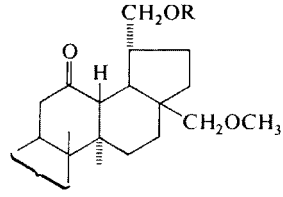
Oxidation of hydroxy ketone *XVII* gave diketone *XVIII* the structure of which follows from its ^{1}H-NMR spectrum: the signal of $COCH_3$ (2·23 s) and 13βH (2·57 d, $J_{13,18} = 11$ Hz). The complex shape of its CD curve excludes a simple superposition of the Cotton effects of both keto groups, which is a proof of their mutual polar interaction. Further its reduction with lithium aluminum hydride was studied and ketones *XVI* and *XXXI* were also reduced under the same conditions.

On reduction of ketone *XXXI* substance *XXXIV* is formed as the sole product for which the structure of 12,20-diol was deduced on the basis of its IR spectrum. The absolute configuration of the hydroxyl group in the position 12 was determined by analysis of the ^{1}H-NMR spectrum in which the 12-H signal appears as an unresolved multiplet (4·19 mt, $W = 11$ Hz), which corresponds to its equatorial conformation (a multiplet width of about 26 Hz corresponds[3] to the axial hydrogen in the position 12). Another confirmation of the axial conformation of the hydroxy group comes from its considerable downfield shift ($\Delta\delta = +0{\cdot}305$ p.p.m.) of the 14α-methyl signal in comparison with dinoralcohol *XXVI*. When diol *XXXIV* is reacted with trichloroacetyl isocyanate compound *XXXV* is formed; in its spectrum

the 12βH signal keeps its shape (W = 11 Hz) but it is shifted by 0·86 p.p.m. downfield.



XXXIV, R = H
XXXV, R = OCNHCOCCl$_3$



XXXI, R = Ac
XXXII, R = OCNHCOCCl$_3$
XXXIII, R = H

On reduction of ketone *XVI* a chromatographically pure substance is formed as the sole product, for which the structure of a 12,20-diol was proposed on the basis of its IR spectrum. An analysis of the ^{1}H-NMR spectrum shows, however, that it is a mixture of two substances, probably 12,20-diols epimeric at $C_{(12)}$. The signals pertaining to the main components (content about 70%) indicate an axial conformation of the hydroxyl group in the position 12 (4·01 mt, W = 11 Hz, 12βH), and the signal 14α CH_3 is shifted 0·287 p.p.m. downfield in comparison with *XI*. As the hydroxyl group in the position 20 must have the same absolute configuration as the acetoxyl group of the starting ketone *XVI*, the structure *XIX* has to be assigned to the main product. In the spectrum of the reaction products of the above mixture with trichloroacetyl isocyanate the signals may be found practically exclusively which belong to the derivative of the main component, *i.e.* to derivative *XX*. The signal of 12βH again appears as a multiplet (5·19, W = 11 Hz) which corroborates the axial conformation of the hydroxyl group in the position 12.

Reduction of diketone *XVIII* gave 12,20-diol *XXI* as the main product. From the practically identical distribution of the methyl signals in the ^{1}H-NMR spectra of diastereoisomeric diols *XIX* and *XXI* it follows that they have the same configuration at $C_{(12)}$; hence, diol *XXI* has the opposite absolute configuration at $C_{(20)}$ than diol *XIX*, *i.e.* 20 R. As the reduction of the 20-keto group of diketone *XVIII* takes place predominantly under formation of 20-hydroxy derivative with the 20*R* configuration, equally as in 30-nor-20-lupanol[1,13], it may be supposed that in both types of substances the side chain assumes approximately the same configuration with an antiperiplanar orientation of 19βH and 20-CH_3. The access of the hydride reagent takes place in both instances from the less hindered side, *i.e.* from the side opposite to $C_{(12)}$.

From this it can be judged that during the reduction of diketone *XVIII* the reduction of the 20-keto group takes place first predominantly under formation of hydroxy derivative with the 20*R* configuration. Acetoxy ketones *XVI* and *XXXI* react with

lithium aluminum hydride first under formation of corresponding 20-hydroxy derivatives. Then the reduction of all 20-hydroxy-12-oxo derivatives takes place in the same manner, *i.e.* by the access of the hydride reagent predominantly from the less hindered equatorial side, under formation of 12α-hydroxylupane derivatives.

EXPERIMENTAL

The melting points were determined on a Kofler block. Optical rotations were measured in chloroform with a 1—2° accuracy. The infrared spectra were measured in chloroform on a UR-10 (Zeiss, Jena GDR) spectrophotometer, unless stated otherwise. The ^{1}H-NMR spectra were measured on a Varian HA-100 (100 MHz) instrument in deuteriochloroform, with tetramethylsilane as internal reference; the chemical shifts are given in p.p.m., δ-scale. The methyl group signals and their assignments are given in Table I. The CD curves were recorded on a Roussel-Jouan Dichrographe 185 in dioxane. For column chromatography neutral alumina (Reanal, activity II) was used, and silica gel according to Pitra (60—120 μ). For thin-layer chromatography silica gel G (Merck) was employed. The working up of ethereal solution in the usual manner means washing with water, saturated sodium hydrogen carbonate solution and water. The solutions were dried over sodium sulfate. Samples for analysis were dried over phosphorus pentoxide at 80°C and 0·1—1 Torr for 8—12 hours. The identity of the samples prepared by various procedures was checked by mixture melting point determination, thin-layer chromatography and infrared spectra.

3β-Methoxylup-20(29)-ene (*II*)

A solution of lupeol (*I*, 700 mg) and methyl iodide (2 ml) in tetrahydrofuran (20 ml) was added under argon over 30 minutes to a stirred suspension of sodium hydride (560 mg) in tetrahydrofuran (20 ml), heated at 45—47°C. After 4 hours' stirring and heating at 45—47°C the excess sodium hydride was decomposed with ethanol and water, and the mixture was poured into dilute hydrochloric acid (1 : 4). The product was extracted with ether, the extract was worked up in the conventional manner. The residue (710 mg) was chromatographed on alumina (70 g). Light petroleum–ether mixture (95 : 5) eluted 506 mg of ether *II*, m.p. 249—251°C (hexane–ether), $[\alpha]_D$ +33° (0·67). Literature[14] gives m.p. 250—251°C, $[\alpha]_D$ +35·6°, ^{1}H-NMR spectrum: 0·790 s (17β-CH_3); 1·68 s (20-CH_3); 2·63 mt, W = 16 Hz (3α-H); 3·33 s (OCH_3); 4·58 and 4·68, two narrow mt (29-H_2).

3β,28-Dimethoxylup-20(29)-ene (*IV*)

A solution of 6 g of betulin (*III*) and methyl iodide (12 ml) in tetrahydrofuran (90 ml) was added under argon at 45—47°C to a stirred suspension of sodium hydride (1·9 g) in tetrahydrofuran (40 ml). The addition lasted 40 minutes and the stirring at 45—47°C continued for another 4 hours. Excess sodium hydride was decomposed with ethanol and water and the mixture was poured into dilute hydrochloric acid (1 : 4). The product was extracted with ether, the extract worked up in the conventional manner. The residue, when crystallized from ether, gave 5 g of ether *IV*, m.p. 185—187°C, $[\alpha]_D$ +22·6° (*c* 1·06). IR spectrum: 1101 (OCH_3), 3087, 1645, 885 (C=CH_2). ^{1}H-NMR spectrum: 1·683 s (20-CH_3); 2·62 mt, W = 16 Hz (3αH); 3·04 and 3·48 d $J_{gem} \approx -9$ Hz (28-H_2); 3·344 s (2 × OCH_3); 4·58 and 4·68 two narrow mt (29-H_2). For $C_{32}H_{54}O_2$ (470·8) calculated: 81·64% C, 11·56% H; found: 81·96% C, 11·66% H.

3β,28-Dimethoxy-30-norlupan-20-one (*V*)

a) Formic acid (20 ml) and 10 ml of hydrogen peroxide (30%) were added into a solution of olefin *IV* (4·2 g) in chloroform (20 ml) and the mixture was stirred for 5 hours. It was then poured into water and the product extracted with chloroform. Chloroform was evaporated and the residue dissolved in 30 ml of benzene, and 4 g of potassium hydroxide in 80 ml of methanol were added to this solution. After 5 hours' refluxing the mixture was concentrated *in vacuo* to 1/3 of the original volume and then poured into water. The product was extracted with ether and the extract worked up in the conventional manner. The residue was dissolved in 90 ml acetone and oxidized with Jones's reagent (5 ml). The excess oxidant was decomposed with oxalic acid. The mixture was poured into water and the product extracted with ether. The ethereal extracts were filtered through an alumina column (30 g) and evaporated in a vacuum. The residue was dissolved in 50 ml of ether and cooled to −78°C. After 3 hours cooling the separated product was filtered off under suction. Yield 3 g of norketone *V*, m.p. 170−173°C, $[\alpha]_D$ −9·2° (*c* 3·16). IR spectrum: 2830, 1100 (OCH_3), 1707, 1360 (CH_3CO) cm^{-1}. CD: $\Delta\varepsilon$ +1·01 (286) nm). ^{1}H-NMR spectrum: 2·15 s ($COCH_3$); 2·99 d and 3·44 d, J_{gem} = 9·5 Hz (28-H_2); 3·336 s, 3·345 s (2 × × OCH_3). For $C_{31}H_{52}O_3$ (472·8) calculated: 78·76% C, 11·09% H; found: 78·53% C, 11·21% H.

b) Jones's reagent (0·5 ml) was added to a solution of 32 mg of *X* in 4 ml of acetone and the mixture stirred for 5 minutes when the excess reagent was decomposed by the addition of 0·2 ml of methanol, and the mixture poured into water. The product was extracted with ether and the extract worked up in the conventional manner. Crystallization of the residue from ether gave 25 mg of ketone *V*, m.p. 171−173°C, $[\alpha]_D$ −9·5° (*c* 0·94).

c) Oxidation of noralcohol *XI* (32 mg) was carried out in the same manner as the oxidation of alcohol *X*. Crystallization of the residue from ether gave 22 mg of ketone *V*, m.p. 168−171°C, $[\alpha]_D$ −9·3° (*c* 0·97).

(20*R*)-3β,28-Diacetoxy-30-norlupan-20-ol 20-Nitrate (*VII*)

Noralcohol *VI* (200 mg) was added into a mixture of acetic anhydride (10 ml) and 99% of nitric acid (1 ml) under stirring and cooling at −15°C, over 3 minutes. After 20 minutes' stirring and cooling at −15°C the reaction mixture was poured onto ice. The separated product was filtered off under suction, washed with water and dissolved in ether. The ethereal solution was dried over sodium sulfate. Crystallization of the residue from light petroleum gave 195 mg of nitrate *VII*, m.p. 185−188°C (decomp.), $[\alpha]_D$ −28 2° (*c* 0·67). IR spectrum: 1723, 1257, 1030 (CH_3COO), 1623, 1278 (ONO_2) cm^{-1}. For $C_{33}H_{53}NO_7$ (575.8) calculated: 68·84% C, 9·28% H, 2·43% N; found: 69·02% C, 9·34% H, 2·55% N.

(20*R*)-3β,28-Dimethoxy-30-norlupan-20-ol 20-Nitrate (*IX*)

A solution of nitrate *VII* (480 mg) and potassium hydroxide (900 mg) in a mixture of benzene (3 ml) and ethanol (30 ml) was refluxed for 4 hours. After evaporation to one third of its original volume under reduced pressure the reaction mixture was poured into water and the product was extracted with ether. The extract was worked up in the conventional manner. After evaporation under reduced pressure 400 mg of a chromatographically pure gel-like nitrate *VIII* were obtained. IR spectrum: 3626, 1024 (OH), 1623, 1279 (ONO_2) cm^{-1}. A solution of 450 mg of diazomethane in 23 ml of ether was added to a solution of 390 mg of nitrate *VIII* in 8 ml of dichloromethane. Anhydrous aluminum chloride (40 mg) was then added to the reaction mixture over one hour and the reaction mixture poured into water and the product extracted with ether: the extract was worked up in the usual manner. Crystallization of the residue from

ether gave 300 mg of nitrate *IX*, m.p. 184–187°C, $[\alpha]_D$ −29·9° (*c* 0·54). IR spectrum: 1100 (OCH_3), 1631, 1282 (ONO_2) cm^{-1}. For $C_{31}H_{53}NO_5$ (519.8) calculated: 71·64% C, 10·28% H, 2·69% N; found: 71·77% C, 10·09% H, 2·55% N.

(20*R*)-3β,28-Dimethoxy-30-norlupan-20-ol (*X*)

a) Zinc dust (1·8 g) was added into a solution of 200 mg of nitrate *IX* in 30 ml of acetic acid over one hour under stirring. After 30 minutes' stirring the mixture was poured into a solution of sodium carbonate, the solution was neutralized with potassium hydrogen carbonate and the product extracted with ether. The extract was washed with water, the residue chromatographed on 2 preparative silica gel plates (20 × 20 cm) in light petroleum-ether (1 : 1). The corresponding zones were combined and eluted with dichloromethane. Yield, 160 mg of noralcohol *X*, m.p. 183–185°C (hexane). $[\alpha]_D$ −8·4° (*c* 1·42). IR spectrum: 2830, 1100 (OCH_3), 3625 (OH) cm^{-1}. For $C_{31}H_{54}O_3$ (474·8) calculated: 78·43% C, 11·46% H; found: 78·59% C, 11·67% H.

b) Sodium (10·5 g) was added into a refluxing solution of 1·9 g of ketone *V* in 150 ml 1-propanol under stirring over one hour. The mixture was stirred and refluxed for 30 minutes, then cooled and poured into water, acidified with hydrochloric acid and extracted with ether. The extract was worked up in the conventional manner. The residue was chromatographed on a column of alumina (200 g), using a light petroleum–ether (3 : 2) mixture for elution of 800 mg of noralcohol *X*, m.p. 180–183°C (hexane), $[\alpha]_D$ −8·5° (*c* 0·66).

(20*S*)-3β,28-Dimethoxy-30-norlupan-20-ol (*XI*)

Further elution with light petroleum–ether (1 : 1) (after isolation of *X*, procedure *b*)) gave 700 mg of *XI*, m.p. 145–155°C, under decomposition (hexane), $[\alpha]_D$ −9° (*c* 0·87). IR spectrum: 2819, 1101 (OCH_3), 3620 (OH) cm^{-1}. ^{1}H-NMR spectrum: 1·092 d, $J_{20,29}$ = 6·4 Hz (20-CH_3); 2·64 mt, W = 16 Hz (3αH); 3·03 d and 3·46 d, $J_{gem} \approx -9{\cdot}5$ Hz (29-H_2); 3·333 s, 3·351 s (2 × × OCH_3); 4·07 dq, $J_{20,29}$ = 6·4 Hz, $J_{19,20}$ = 4·1 Hz (20-H). For $C_{31}H_{54}O_3$ (474·8) calculated: 78·43% C, 11·46% H; found: 78·28% C, 11·62% H.

(20*S*)-3β,28-Dimethoxy-20-nitrosyloxy-20-norlupane (*XII*)

An excess of nitrosyl chloride was distilled into a solution of 200 mg of noralcohol *XI* in 5 ml of pyridine under stirring at −20°C, until the reaction mixture remained orange. After 10 minutes' stirring at −20°C and 5 minutes' stirring at room temperature the mixture was poured into water, the product extracted with ether, the extract washed with water (5 times), dried, and the solvent evaporated in a vacuum. Yield 190 mg of nitrite *XII*, m.p. 178–180°C under decomposition (from ether–hexane), $[\alpha]_D$ +28·1° (*c* 0·64). IR spectrum: 2820, 1097 (OCH_3), 1632 (ONO) cm^{-1}.

Photolysis of Nitrite *XII*

A solution of 450 mg of nitrite *XII* in 60 ml of benzene was irradiated in a Sial glass flask for 6 hours, using a UV lamp (Tesla RKV 125 W). The photolysis was carried out under nitrogen at 14–15°C. After evaporation of benzene in a vacuum the residue was chromatographed on 5 preparative silica gel plates in light petroleum–ether (2 : 3). The zones containing the less polar component were combined and eluted with dichloromethane. Yield 50 mg of *XI*, m.p. 145 to 155°C (hexane), under decomposition, $[\alpha]_D$ −8° (*c* 0·76). From the combined zones containing the more polar component 250 mg of amorphous oxime *XIII* were obtained on elution with

dichloromethane. IR spectrum: 1099 (OCH_3), 3590, 1665 (C=NOH), 3220, 3118 (OH) cm^{-1}. ^{1}H-NMR spectrum: 1·157 d, $J_{20,29} = 6·9$ Hz (20-CH_3); 2·50–2·72 mt (overlapped 3αH and 13βH); 3·05 d and 3·46 d, $J_{gem} \approx -9$ Hz (28-H_2); 3·33 s (2 × OCH_3); 3·75 bq, $J_{20,29} = 6·9$ Hz, $J_{19,20} < 2$ Hz (20-H).

(20*S*)-3β,28-Dimethoxy-20-acetoxy-30-norlupan-12-one (*XVI*)

Acetic anhydride (5 ml) was added into a solution of 208 mg of oxime *XIII* in 7·5 ml of pyridine and the mixture was heated at 40°C for 18 hours. It was then poured onto ice and the product extracted with ether. The extract was worked up, and the residue chromatographed on two preparative silica gel thin-layer plates (20 × 20 cm) in hexane–ether (1 : 1). Yield 177 mg of amorphous diacetate *XIV*. IR spectrum: 2821, 1100 (OCH_3), 1710, 1261, 1049 (CH_3COO), 1755, 1648 (C=NOOCCH_3) cm^{-1}. A solution of 167 mg of acetate *XIV* in 8 ml of benzene was put into a column of alumina (25 g) and allowed to stand at room temperature overnight. Elution with dichloromethane gave 155 mg of amorphous oxime *XV*. IR spectrum: 2810, 1097 (OCH_3), 1714, 1266, 1051 (CH_3COO), 3581, 3415, 1657 (C=NOH) cm^{-1}. A saturated aqueous solution of sodium nitrite (7 ml) was then added to a solution of 145 mg of oxime *XV* in acetic acid (16 ml) and dichloromethane (4 ml) over one hour and the mixture was stirred at room temperature for one hour. Then another 3·5 ml of saturated sodium nitrite solution were added over one hour and the mixture stirred for another hour. It was then poured into water and the product extracted with dichloromethane. The extract was worked up and the residue dissolved in 20 ml of dioxane. After addition of 8 ml of water the mixture was refluxed for 8 hours. The mixture was poured into water and the product extracted with dichloromethane. The residue was chromatographed on a column of alumina (17 g). Light petroleum–ether (3 : 2) mixture eluted 98 mg of ketone *XVI*, m.p. 196–198°C (hexane), $[\alpha]_D$ −5·5° (*c* 1·46). IR spectrum: 2815, 1100 (OCH_3), 1710, 1264, 1049 (CH_3COO). CD: $\Delta\varepsilon$ −1·70 (294 nm). ^{1}H-NMR spectrum: 1·307 d, $J_{20,29} = 6·2$ Hz (20-CH_3); 1·947 s (CH_3COO); 2·28, AB part of an ABX system, $J_{gem} = -12·6$ Hz, $J_{9\alpha,11\beta} = 13·7$ Hz, $J_{9\alpha,11\alpha} = 2·3$ Hz (11-H_2); 2·62 mt, $W = 16$ Hz (3αH); 2·82 d, $J_{13,18} = 11·2$ Hz (13βH); 2·99 d and 3·39 d, $J_{gem} = -9$ Hz (28-H_2); 3·326 s, 3·345 s (2 × OCH_3); 5·22 bp, $J_{19,20} = 4·6$ Hz, $J_{20,29} = 6·2$ Hz (20-H). For $C_{33}H_{54}O_5$ (530·8) calculated: 74·67% C, 10·25% H; found: 74·78% C, 10·41% H.

(20*S*)-3β,28-Dimethoxy-20-hydroxy-30-norlupan-12-one (*XVII*)

Potassium hydroxide (100 mg) dissolved in 2 ml of ethanol was added to a solution of 85 mg of acetate *XVI* in 2 ml of benzene and the mixture allowed to stand for 24 hours at room temperature. The reaction mixture was then poured into water and the product was extracted with ether. The extract was washed with water (six times) and evaporated under reduced pressure. The residue (80 mg) was alcohol *XVII*, chromatographically pure and amorphous, $[\alpha]_D$ −4° (*c* 0·99). IR spectrum: 2829, 1101 (OCH_3), 1710, 1699 shoulder (CO), 3625, 3440 (OH) cm^{-1}. CD: $\Delta\varepsilon$ −1·32 (292 nm). ^{1}H-NMR spectrum: 1·161 d, $J_{20,29} = 6·3$ Hz (20-CH_3); 2·63 mt $W = 16$ Hz (3αH); 2·88 d, $J_{13,18} \approx 11$ Hz (13βH); 3·04 and 3·40 d, $J_{gem} = -9$ Hz (28-H_2); 3·33 s, 3·36 s (2 × OCH_3); 3·96 mt, $J_{19,20} = 3·0$ Hz, $J_{20,29} = 6·3$ Hz (20-H). For $C_{31}H_{52}O_4$ (488·8) calculated: 76·18% C, 10·72% H; found: 76·35% C, 10·65% H.

3β,28-Dimethoxy-30-norlupan-12,20-dione (*XVIII*)

Jones's reagent (1 ml) was added into a solution of 62 mg of alcohol *XVII* in 5 ml of acetone, and after 3 minutes' reaction time excess reagent was decomposed with oxalic acid and the reaction

mixture was poured into water. The product was extracted with ether, the extract worked up in the usual manner and the residue crystallized from hexane to yield 53 mg of ketone *XVIII*, m.p. 135–150°C (decomp.), $[\alpha]_D$ +10·3° (*c* 1·55). IR spectrum: 2827, 1100 (OCH_3), 1709 (CO), 1709, 1365 (CH_3CO) cm^{-1}. CD: $\Delta\varepsilon$ 0 (330 nm), +0·14 (313 nm), 0 (299 nm), −0·05 (296 nm), −0·02 (292 nm), −0·03 (289 nm), 0 (285 nm), +0·07 (271 nm), 0 (256 nm), −0·05 (242 nm), 0 (227 nm), ^{1}H-NMR spectrum: 2·23 s ($COCH_3$); 2·57 d, $J_{13,18}$ = 11 Hz (13βH); 2·63 mt W = 16 Hz (3αH); 2·95 d, J_{gem} = −9 Hz (28-H); 3·325 s, 3·341 s (2 × OCH_3). For $C_{31}H_{50}O_4$ (486·7) calculated: 76·50% C, 10·35% H; found: 76·39% C, 10·20% H.

(20*S*)-3β,28-Dimethoxy-30-norlupan-12α,20-diol (*XIX*)

Lithium aluminum hydride (100 mg) was added into a solution of ketone *XVI* (80 mg) in tetrahydrofuran (10 ml) and the mixture was refluxed under argon for 90 minutes, cooled, decomposed with water, and poured into dilute hydrochloric acid. The product was extracted with ether and the extract worked up. Yield 70 mg of an amorphous, chromatographically inseparable mixture containing approximately 70% of diol *XIX* (determined from the ^{1}H-NMR spectrum). IR spectrum (tetrachloromethane); 2822, 1104 (OCH_3), 3619, 3558 shoulder, 3271 broad, 1030 (OH) cm^{-1}. ^{1}H-NMR spectrum: 1·225 d, $J_{20,29}$ = 6·2 Hz (20-CH_3); 2·67 mt, W = 16 Hz (3αH); 2·89 s (2 × OH); 3·02 d, J_{gem} = −9 Hz (28-H); 3·32 s, 3·36 s (2 ≈ OCH_3); 4·01 mt, W = 11 Hz (12βH); after addition of trichloroacetyl isocyanate: 1·234 d, $J_{20,29}$ = 6·5 Hz (20-CH_3); 2·66 mt, W = 16 Hz (3αH); 3·01 d, J_{gem} = −9 Hz (28-H); 3·31 s, 3·33 s (2 × OCH_3); 4·91 mt, $J_{20,29}$ = 6·5 Hz, $J_{19,20}$ = 4 Hz (20-H); 5·19 mt, W = 11 Hz (12βH); 8·34 s, 8·48 s (2 × $OOCNHCOCCl_3$).

(20*R*)-3β,28-Dimethoxy-30-norlupan-12α,20-diol (*XXI*)

Lithium aluminum hydride (100 mg) was added into a solution of diketone *XVIII* (80 mg) in tetrahydrofuran (5 ml) and the mixture was refluxed under argon for 90 minutes. After cooling it was decomposed with water and poured into dilute hydrochloric acid (1 : 4). The product was extracted with ether and the extract worked up. The residue (70 mg) was chromatographed on a preparative silica gel thin-layer plate (20 × 20 cm) in hexane–ether (3 : 2). Elution of the zone containing a less polar component gave 50 mg of diol *XXI*, m.p. 186–188°C (light petroleum–acetone), $[\alpha]_D$ −4·3° (*c* 1·11). IR spectrum: 1097 (OCH_3), 3614, 3478 broad (OH) cm^{-1}. ^{1}H-NMR spectrum: 1·162 d, $J_{20,29}$ = 6·5 Hz (20-CH_3); 2·38 s (2 × OH); 2·66 mt, W = 16 Hz (3αH); 3·00 d and 3·39 d, J_{gem} = −9 Hz (28-H_2); 3·31 s, 3·35 s (2×OCH_3); 4·16 mt (overlapped 12βH and 20-H). For $C_{31}H_{54}O_4$ (490·8) calculated: 75·87% C, 11·09% H; found: 75·61% C, 11·28% H. On elution of the zone containing the more polar component 14 mg of product were obtained, which according to thin-layer chromatography and its IR spectrum was identical with the product of the reduction of ketone *XVI*.

Methyl 3β,28-Dimethoxy-29,30-dinorlupan-20-oate (*XXIV*)

A solution of 2 g of potassium hydroxide in 50 ml of ethanol was added to a solution of dinoracid[2] *XXII* (1 g) in 50 ml of benzene and the mixture was refluxed for 3·5 hours, then cooled to room temperature and poured into dilute hydrochloric acid (200 ml). The product was extracted with ethyl acetate, the extract washed with water (five times) and evaporated. The residue (800 mg) was dissolved in 30 ml of an ethereal diazomethane solution and 0·25 ml of methanol were added. The mixture was allowed to stand at room temperature overnight and evaporated. The residue was dissolved in 50 ml of dichloromethane, 30 ml of an ethereal diazomethane solu-

tion were added, followed by 100 mg of anhydrous aluminum chloride which was added in four portions over one hour. Excess diazomethane was decomposed with acetic acid (3 ml) and the mixture poured into water. The product was extracted with ether and the extract worked up in the usual manner. The residue was chromatographed on an alumina column (100 g). A light petroleum–ether (4 : 1) mixture eluted 450 mg of ester *XXIV*, m.p. 185–187°C (light petroleum), $[\alpha]_D$ −14·7° (*c* 1·22). IR spectrum: 2814, 1100 (OCH_3), 1726, 1439 ($COOCH_3$) cm^{-1}. For $C_{31}H_{52}O_4$ (488·8) calculated: 76·18% C, 10·72% H; found: 76·33% C, 10·90% H.

3β,28-Dimethoxy-29,30-dinorlupan-20-al (*XXV*)

Trifluoroacetic acid (0·008 ml) and pyridine (0·016 ml) were added into a solution of 74 mg of alcohol *XXVI* and 88 mg of N,N′-dicyclohexylcarbodiimide in 2 ml of benzene and 2 ml of dimethyl sulfoxide and the mixture was allowed to stand for 20 hours at room temperature. A solution of anhydrous oxalic acid (37 mg) in 0·5 ml of methanol was then added. After 15 minutes' standing the mixture was diluted with ether and the separated N,N′-dicyclohexylurea was filtered off and the filtrate washed with water. Crystallization of the residue from hexane gave 50 mg of aldehyde *XXV*, m.p. 175–180°C (decomp.), $[\alpha]_D$ +5·6° (*c* 2·87). IR spectrum: 1100 (OCH_3), 2722, 1723 (CHO), cm^{-1}. For $C_{30}H_{50}O_3$ (458·7) calculated: 78·55% C, 10·99% H; found: 78·49% C, 11·11% H.

3β,28-Dimethoxy-29,30-dinorlupan-20-ol (*XXVI*)

Lithium aluminum hydride (1·5 g) was added to a solution of ester *XXIV* (850 mg) in tetrahydrofuran (100 ml) and the mixture was refluxed under argon for 6 hours. It was then decomposed with ethyl acetate and dilute hydrochloric acid (1 : 4); after dilution with ether (500 ml) the organic phase was worked up. The residue was chromatographed on an alumina column (80 g). Light petroleum–ether (2 : 3) mixture eluted 700 mg of alcohol *XXVI*, m.p. 147–149°C, $[\alpha]_D$ −15·5° (*c* 2·83). IR spectrum: 2827, 1099 (OCH_3), 3628, 1020 (OH) cm^{-1}. ^{1}H-NMR spectrum: 2·64 mt, W = 16 Hz (3α H); 3·01 d and 3·46 d, J_{gem} = −9·6 Hz (28-H_2); 3·34 s, 3·36 s (2 × × OCH_3); 3·78 dd, J_{gem} = −10·2 Hz, $J_{19,20}$ = 2 Hz (20-H). For $C_{30}H_{52}O_3$ (460·7) calculated: 78·21% C, 11·38% H; found: 78·35% C, 11·54% H.

Photolysis of Nitrite *XXVII*

An excess of nitrosyl chloride was distilled under stirring at −20°C into a solution of 450 mg of alcohol *XXVI* in 10 ml of pyridine (orange coloration of the mixture). After ten minutes' stirring and cooling and five minutes' stirring at room temperature the mixture was poured into water, the product was extracted with ether, the extract washed with water, then dried and evaporated. Yield, 436 mg of oily *XXVII*: IR spectrum: 2826, 1100 (OCH_3), 1632 (ONO) cm^{-1}.

A solution of 420 mg of nitrite *XXVII* in 50 ml of benzene was irradiated in a sial glass flask with a UV lamp (Tesla RVK 125W) for 6 hours. This was done under nitrogen at 14–16°C. After evaporation of benzene in a vacuum the residue was chromatographed on four preparative silica gel plates in hexane–ether (1 : 1). From the combined zones, containing the least polar substances, 58 mg of dinoraldehyde *XXV* were obtained by elution with dichloromethane. M.p. 176–181°C (from hexane, decomp.), $[\alpha]_D$ +5° (*c* 2·30). From the zones containing the substance of medium polarity 20 mg of alcohol *XXVI* were obtained, m.p. 146–148°C (hexane), $[\alpha]_D$ −14° (*c* 2·24). Elution of the zones containing the most polar substance gave 150 mg of amorphous oxime *XXVIII*; IR spectrum: 2823, 1095 (OCH_3), 3237, 3125 (OH), 3589, 1665 (C=NOH) cm^{-1}.

3β,28-Dimethoxy-20-acetoxy-29,30-dinorlupan-12-one (*XXXI*)

A solution of oxime *XXVIII* (140 mg) in 5 ml of pyridine and 3 ml of acetic anhydride was heated at 40°C for 24 hours. The mixture was poured onto ice and the product was extracted with ether. The extract was worked up and the residue chromatographed on 2 preparative silica gel plates with light petroleum–ether mixture (4 : 1). The zones containing *XXIX* were combined and eluted with dichloromethane; the residue was dissolved in 8 ml of benzene and applied onto a column of alumina (20 g). On elution with chloroform after 20 hours' standing at room temperature chromatographically pure oxime *XXX* (110 mg) was obtained. This was dissolved in 3 ml of dichloromethane and 11 ml of acetic acid, and an aqueous solution of sodium nitrite (5 ml) was added to it under stirring over one hour. The mixture was stirred for one hour at room temperature, then another 2·5 ml of sodium nitrite solution were added over one hour, and the mixture was poured into water and the product extracted with dichloromethane. The extract was worked up and the residue dissolved in dioxan (12 ml). After addition of 5 ml of water the mixture was refluxed for 10 hours, then poured into water and the product extracted with dichloromethane. The residue was chromatographed on a column of alumina (20 g) with light petroleum–ether (4 : 1). An amorphous ketone (60 mg) was eluted, *XXXI*, with $[\alpha]_D$ −7·4° (*c* 1·13). IR spectrum: 2827, 1096 (OCH_3), 1727, 1251, 1026 ($OCOCH_3$), 1710 (CO) cm^{-1}. ^{1}H-NMR spectrum: 2·00 s (CH_3COO); 2·26, AB part of an ABX system, $J_{gem} = -11{\cdot}9$ Hz, $(J_{9\alpha,11\alpha} + J_{9\alpha,11\beta}) = 16$ Hz (11-H_2); 2·64 mt, $W = 16$ Hz (3αH); 2·85 d, $J_{13,18} = 11{\cdot}2$ Hz (13βH); 3·01 d and 3·39 d, $J_{gem} = -9{\cdot}2$ Hz (28-H_2); 3·32 s, 3·34 s (2 × OCH_3); 3·39 dd and 4·40 dd, $J_{gem} = -11$ Hz, $J_{vic_1} = 7{\cdot}6$ Hz, $J_{vic_2} = 3{\cdot}4$ Hz (20-H_2). For $C_{32}H_{52}O_5$ (516·8) calculated: 74·38% C, 10·14% H; found: 74·44% C, 10·36% H.

3β,28-Dimethoxy-20-hydroxy-29,30-dinorlupan-12-one (*XXXIII*)

Potassium hydroxide (70 mg) in 2 ml of ethanol was added into a solution of 30 mg of acetate *XXXI* in 2 ml of benzene and the mixture was allowed to stand at room temperature for 24 hours. The mixture was poured into water and the product was extracted with ether. The extract was washed with water and the solvents evaporated under reduced pressure. Yield 23 mg of chromatographically pure *XXXIII*, m.p. 212–214°C (light petroleum), $[\alpha]_D$ −3° (*c* 1·20). IR spectrum (tetrachloromethane): 2822, 1103 (OCH_3); 1714 (CO), 3548 (OH) cm^{-1}. ^{1}H-NMR spectrum: 2·0–3·3 unresolved multiplet (11-H_2, 13βH, 3αH, 20-H_2, 28-H_2); 3·32 s, 3·34 s (2 × OCH_3); after addition of trichloroacetyl isocyanate: 2·25 mt (11-H_2); 2·63 mt, $W = 16$ Hz (3αH); 2·87 d, $J_{13,18} \approx 11{\cdot}5$ (13βH); 3·00 d and 3·40 d, $J_{gem} \approx -9{\cdot}5$ Hz (28-H_2); 4·15 dd and 4·65 dd, $J_{gem} \approx -11$ Hz, $J_{vic_1} \approx 6{\cdot}5$ Hz, $J_{vic_2} \approx 4$ Hz (20-H_2). For $C_{30}H_{50}O_4$ (474·7) calculated: 75·90% C, 10·62% H; found 76·15% C, 10·85% H.

3β,28-Dimethoxy-29,30-dinorlupan-12α,20-diol (*XXXIV*)

Lithium aluminum hydride (100 mg) was added into a solution of ketone *XXXI* (80 mg) in tetrahydrofuran (10 ml), and the mixture was refluxed under argon for 90 minutes. After cooling the mixture was decomposed with water and poured into dilute hydrochloric acid. The product was extracted with ether and the extract worked up. The residue was chromatographed on a preparative silica gel plate (20 × 20 cm) in light petroleum–ether (1 : 1). Yield, 59 mg of amorphous *XXXIV*, $[\alpha]_D$ +8° (*c* 0·39). IR spectrum: 1103 (OCH_3); 3350 broad, 3620 (OH) cm^{-1}. ^{1}H-NMR spectrum: 2·67 mt, $W = 16$ Hz (3αH); 2·69s (2 OH); 3·01 d and 3·41 d, $J_{gem} = -9$ Hz (28-H_2); 3·32 s, 3·36 s (2× OCH_3); 3·73 mt (20-H_2); 4·11 mt, $W = 11$ Hz (12βH); after addition of trichloroacetyl isocyanate: 2·65 mt, $W = 16$ Hz (3αH); 3·02 d and 3·40 d, $J_{gem} = -9$ Hz (28-H_2);

4·11 mt (20-H_2); 4·97 mt, $W = 11$ Hz (12β H); 8·42 s, 8·73 s (2 × $OOCNHCOCCl_3$). For $C_{30}H_{52}O_4$ (476·7) calculated: 75·58% C, 10·99% H; found: 75·79% C, 11·11% H.

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