3,4-SECO-3,28-LUPANEDIOIC ACIDS SUBSTITUTED IN THE SIDE CHAIN AT $C_{(5)}$*

Irena VALTEROVÁ**, Jiří KLINOT and Alois VYSTRČIL

Department of Organic Chemistry, Charles University, 128 40 Prague 2

Received October 31st, 1979

A series of derivatives of 3,4-secolupane-3,28-dioic acid (*II*—*XIV*, *XIX*—*XXI*) containing an oxygen-containing functional group in the side chain at $C_{(5)}$ was prepared from nitrile *I* and ketone *XVII*. In the case of derivatives *III*—*XIV* both series of $C_{(4)}$-epimers, *a* and *b*, were obtained. The configuration at $C_{(4)}$ was derived on the basis of the formation of an intramolecular hydrogen bond in compounds *IX* and *XIII* and from the chiroptical properties of benzoates *VII*, and it was confirmed by a stereospecific synthesis of the 4*S*-derivative *XIIIa* from 24-nor-ketone *XV*.

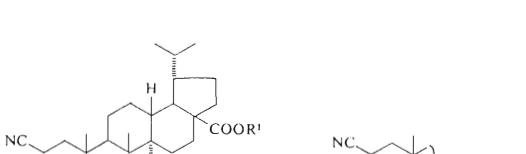
In connection with the antibacterial activity of some steroid and triterpenoid 3,4-seco-acids (see refs[1-3] and the references therein) the preparation of 3,4-secoacids of the 19β,28-epoxy-18α-oleanane series with an oxygen-containing functional group in the side chain at $C_{(5)}$ was described in our preceding paper[3]. This paper is devoted to the synthesis of analogous compounds derived from lupane skeleton, *i.e.* 3,4-secolupane--3,28-dioic acids substituted with a hydroxyl group in the side chain attached at $C_{(5)}$. Secoacids of this type fulfil the structural requirements for antibacterial activity (oxygen-containing function in the vicinity of the carboxyl group[1]). In the case of the derivatives which contain a new chirality centre at $C_{(4)}$ the configuration at this centre is derived in this paper.

As starting material both 3,4-seconitrile *I* obtained from betulinic acid in the described manner[2] and the methyl ester of 3-oxolupan-28-oic acid[4] (*XVII*) were employed. For the introduction of the hydroxyl group into the side chain and for the modifications of this chain the procedures given in the literature[3,5-9] were made use of. On reaction of nitrile *I* with 3-chloroperbenzoic acid epoxide *II* was prepared (probably a mixture of both diastereoisomers) which rearranged under the effect of formic acid[5] to a mixture of aldehydes *IIIa* and *IIIb*, epimeric at $C_{(4)}$. The reduction of this mixture with sodium borohydride led to a mixture of hydroxy nitriles *IVa* and *IVb* in which the isomer *IVa* prevailed in a 3 : 2 ratio. At this stage both

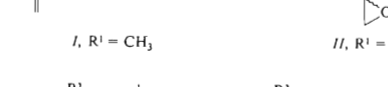
* Part LXI in the series Triterpenes; Part LX: This Journal *45*, 1366 (1980).

** Present address: Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, 166 10 Prague 6.

isomers could be separated chromatographically so that further procedure took place separately for each epimeric series, *a* and *b*. Under the effect of 10% sodium hydroxide in boiling ethylene glycol on hydroxy nitriles *IVa* and *IVb* both the nitrile and the ester groups were hydrolysed; the diacids *VIIIa* and *VIIIb* formed were converted to dimethyl esters *IXa* and *IXb*.



I, $R^1 = CH_3$ *II*, $R^1 = CH_3$



a, 4*S* *b*, 4*R*

III,	$R^1 = CH_3$,	$R^2 = CN$,	$R^3 = CHO$
IV,	$R^1 = CH_3$,	$R^2 = CN$,	$R^3 = CH_2OH$
V,	$R^1 = CH_3$,	$R^2 = CN$,	$R^3 = OCHO$
VI,	$R^1 = CH_3$,	$R^2 = CN$,	$R^3 = OH$
VII,	$R^1 = CH_3$,	$R^2 = CN$,	$R^3 = OCOC_6H_5$
VIII,	$R^1 = H$,	$R^2 = COOH$,	$R^3 = CH_2OH$
IX,	$R^1 = CH_3$,	$R^2 = COOCH_3$,	$R^3 = CH_2OH$
X,	$R^1 = CH_3$,	$R^2 = COOCH_3$,	$R^3 = CHO$
XI,	$R^1 = CH_3$,	$R^2 = COOCH_3$,	$R^3 = OCHO$
XII,	$R^1 = CH_3$,	$R^2 = COOH$,	$R^3 = OH$
XIII,	$R^1 = CH_3$,	$R^2 = COOCH_3$,	$R^3 = OH$
XIV,	$R^1 = H$,	$R^2 = COOH$,	$R^3 = OH$

The hydroxymethyl group in hydroxy nitriles *IVa* and *IVb* was degraded to a hydroxyl group in the following manner: Hydroxy nitriles *IVa* and *IVb* were oxidized with pyridinium chlorochromate[10] to aldehydes *IIIa* and *IIIb*. Baeyer–Villiger oxidation of these aldehydes with 3-chloroperbenzoic acid gave formates *Va* and *Vb* in which the formate group could be hydrolysed selectively (under preservation

of the nitrile and the methyl ester group) with 2% potassium hydroxide in ethanol. 24-Nor-derivatives *VIa* and *VIb* were thus obtained. The entire degradation procedure was carried out without purification or characterization of the intermediates. Thin-layer chromatography showed that during this procedure a partial weak isomerization in position 4 took place (probably at the stage of aldehyde *III*). Hydroxy nor-derivatives *VIa* and *VIb* were further converted to benzoates *VIIa* and *VIIb*. With 10% sodium hydroxide in refluxing ethylene glycol they gave diacids *XIVa* and *XIVb*, characterized as dimethyl esters *XIIIa* and *XIIIb*. In the same manner (*via* the stages of aldehydes *X* and formates *XI*) the hydroxymethyl group was also converted to a hydroxyl group in dimethyl esters *IXa* and *IXb*. After hydrolysis of formates *XIa* and *XIb* (with 2% potassium hydroxide in ethanol) and the reaction of the products with diazomethane dimethyl esters *XIIIa* and *XIIIb* were obtained, identical with the preparations obtained from benzoates *VIIa* and *VIIb*.

These reaction sequences represent a correlation of the derivatives with a full number of carbon atoms (*IV*, *VIII*, *IX*) with 24-nor-derivatives (*VI*, *VII*, *XIII*) in both series of the $C_{(4)}$-epimers *a* and *b*. The configuration at $C_{(4)}$ was determined in three ways:

a) On the basis of the formation of an intramolecular hydrogen bond between the hydroxyl group in the position 4 (or 23) and the ester group in the position 3

TABLE I

Frequences and Intensities of OH Stretching Vibrations

Measured in a $2 \cdot 10^{-3}$M solution in tetrachloromethane with a Unicam SP 700 spectrophotometer. Accuracy $\pm 2\ cm^{-1}$. $B = \pi/2 \cdot \varepsilon^{(a)} \cdot \Delta\nu^{(a)}_{1/2}$, f = free, b = bonded.

Compound	ν cm^{-1}	$\varepsilon^{(a)}$ $l\ mol^{-1}\ cm^{-1}$	$\Delta\nu^{(a)}_{1/2}$ cm^{-1}	$B \cdot 10^{-3}$ $l\ mol^{-1}\ cm^{-2}$
IXa	f 3 638	37	26	1·5
	b 3 537	24	106	4·0
IXb	f 3 638	60	22	2·1
XIIIa	f 3 621	49	15	1·2
	b 3 575	11	[a]	[a]
	b 3 522	11	[a]	[a]
XIIIb	f 3 622	34	31	1·7

[a] Owing to overlapping of the bands the values could not be determined.

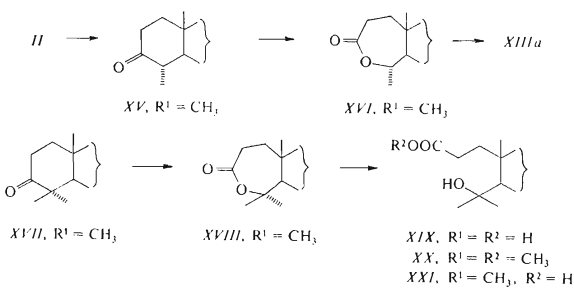
in hydroxy esters *IX* and *XIII*. In a previous paper[3] we demonstrated that the 4*S*-isomers of hydroxy esters of this type form a hydrogen bond, while the 4*R*-isomers do not. As evident from Table I hydroxy esters *IXa* and *XIIIa* have in their infrared spectra bands of a bonded hydroxyl and therefore the configuration 4*S* can be assigned to them. In the spectra of 4*R*-isomers *IXb* and *XIIIb* only a band of a free hydroxyl is present.

b) From the changes in molecular rotation after benzoylation of the hydroxyl group in position 4 in hydroxy derivatives *VIa* and *VIb* ($\Delta M_D = M_D$(benzoate *VII*) − $- M_D$ (alcohol *VI*)). After benzoylation of derivative *VIa* a shift in molecular rotation to positive values is observed ($\Delta M_D = +97°$), while in the case of isomer *VIb* the shift is negative ($\Delta M_D = -60°$). Application of the benzoate rule[11] leads to 4*S* configuration for derivative *VIa* and to 4*R* configuration for derivative *VIb*. We also tried to use the benzoate sector rule formulated in the literature[12] for the derivation of the sense of the Cotton effect (at about 230 nm) in the benzoates of cyclic secondary alcohols. In the case of benzoates *VIIa* and *VIIb* the situation is complicated by the fact that the side chain at $C_{(5)}$ can assume various conformations from the point of view of the $C_{(4)}-C_{(5)}$ bond. Therefore, all three staggered conformers of the $C_{(4)}-C_{(5)}$ bond were considered in both benzoates *VIIa* and *VIIb*, and the effect of the α,β- and β,γ-bonds was judged for each conformer separately. According to the sector rule a positive Cotton effect may be expected for the 4*S*-isomer, while a negative one for the 4*R*-isomer. In actual fact the circular dichroism curves of both benzoates display a positive Cotton effect, but in the 4*S*-isomer *VIIa* the Δε value is higher (+4·9) than in the 4*R*-isomer *VIIb* (+1·1). The predictions from the sector rule are thus followed by the trend of these values only.

c) By synthesis of the 4*S*-hydroxy ester *XIIIa* from 24-nor-ketone *XV*. Nor-ketone *XV* was prepared using a known procedure[7] – by cyclization of epoxy nitrile *II* under the effect of boron trifluoride etherate in boiling toluene. Baeyer–Villiger oxidation of nor-ketone *XV* (with 3-chloroperbenzoic acid[8]) gave lactone *XVI* which was also obtained by oxidation of ketone *XVII* with the same peracid in the presence of sulfuric acid (the last mentioned oxidation takes place according to lit.[9] under a loss of the methyl group from the position 4). Lactone *XVI* was characterized by an infrared spectrum of crude sample only, and in both cases it was submitted to direct alkaline hydrolysis and the acid *XIIa* formed was converted to ester *XIIIa*. Since the starting nor-ketone *XV* is a 4*S*-isomer (equatorial 4α-methyl group[3,8]) the configuration 4*S* also corresponds to hydroxy ester *XIIIa*, which is in agreement with the results shown under *a*) and *b*).

A further series of 3,4-seco derivatives was prepared from ketone *XVII*. Oxidation with 3-chloroperbenzoic acid gave lactone *XVIII* and its hydrolysis with 3% potassium hydroxide at room temperature monomethyl ester *XXI*, while a hydrolysis with 10% sodium hydroxide in boiling ethylene glycol gave diacid *XIX*. On reaction

of compounds *XIX* and *XXI* with diazomethane the same dimethyl ester *XX* was formed. The antibacterial activity of the 3,4-seco derivatives formed will be discussed elsewhere.



EXPERIMENTAL

The melting points were determined on a Kofler block. Optical rotations were measured on an ETL-NPL (Bendix-Ericsson) polarimeter with a $\pm 2°$ accuracy, in chloroform solution (*c* 0·3 to 0·7), unless stated otherwise. The infrared spectra were measured on UR 10 and UR 20 (Zeiss, Jena) instruments in chloroform, unless stated otherwise. Circular dichroism was measured in cyclohexane on a Roussel-Jouan 185 dichrograph. For thin-layer chromatography silica gel G according to Stahl was used, while for column chromatography neutral alumina, act. II (Reanal) was employed. Under "conventional workup" the following procedure is understood: Washing of the extract with water, sodium or potassium hydrogen carbonate solution, and water, drying over sodium sulfate and distillation off of the solvent under reduced pressure. For the washing of the extracts dilute hydrochloric acid (1 : 4) was used. Methyl esters were prepared from the acids with the use of ethereal diazomethane solution. The identity of the samples prepared in various manners was checked by comparison of the infrared spectra, thin-layer chromatography and in the case of crystalline substances also by mixture melting point determination. Analytical samples were dried under reduced pressure over phosphorus pentoxide for 8 h; the drying temperature was 100°C for higher melting substances and 20°C for lower melting or amorphous substances.

28-Methyl Ester, 3-Nitrile of 4ξ,23-Epoxy-3,4-secolupane-3,28-dioic Acid (*II*)

A solution of 3-chloroperbenzoic acid (320 mg) in chloroform (10 ml) was added to nitrile *I* (500 mg; see[2]) in chloroform (10 ml) cooled at 0°C and the mixture was allowed to stand at 0°C for 67 h, then diluted with chloroform and worked up in the conventional manner. Epoxide *II* (500 mg) was obtained in the form of a mixture of diastereoisomers, m.p. 88—98°C (light petroleum), $[\alpha]_D$ −8°. IR spectrum: 2248 (CN), 1720, 1434, 1160 cm^{-1} ($COOCH_3$). For $C_{31}H_{49}NO_3$ (483·7) calculated: 76·97% C, 10·21% H; found: 77·19% C, 10·41% H.

28-Methyl Ester, 3-Nitrile of (4*S* and 4*R*)-23-Hydroxy-3,4-secolupane-3,28-dioic Acid (*IVa* and *IVb*)

Formic acid (5 ml) was added to a solution of epoxide *II* (500 mg) in chloroform (20 ml) and the mixture was allowed to stand at room temperature under nitrogen for 5·5 h. Solid sodium hydrogen carbonate was added, the mixture was diluted with chloroform and submitted to the conventional workup. Yield, 480 mg of a mixture of aldehydes *IIIa* and *IIIb*. IR spectrum: 2828, 2725, 1719 (CHO), 2247 (CN), 1719, 1435, 1162 cm^{-1} ($COOCH_3$). The mixture of aldehydes *IIIa* and *IIIb* was dissolved in a mixture of chloroform (10 ml) and methanol (5 ml), sodium borohydride (200 mg) was added and the mixture allowed to stand at room temperature for 5 h. After dilution with water and acidification with hydrochloric acid the mixture was extracted with chloroform. The extract was worked up in the conventional manner and the residue (410 mg) chromatographed on alumina (60 g). Elution with light petroleum–acetone (85 : 15) gave 110 mg of amorphous 4*S*-isomer *IVa*: $[\alpha]_D$ −32°. IR spectrum: 3632 (OH), 2245 (CN), 1718, 1434, 1161 ($COOCH_3$), 1029 cm^{-1} (C—O). For $C_{31}H_{51}NO_3$ (485·7) calculated: 76·65% C, 10·58% H; found: 76·61% C, 10·61% H. Elution with a mixture of light petroleum and acetone (4 : 1) gave 80 mg of the 4*R*-isomer *IVb*, m.p. 163–165°C (ether–light petroleum), $[\alpha]_D$ −27°. IR spectrum: 3632 (OH), 2246 (CN), 1717, 1433, 1160 ($COOCH_3$), 1015 cm^{-1} (C—O). For $C_{31}H_{51}NO_3$ (485·7) calculated: 76·65% C, 10·58% H; found: 76·75% C, 10·31% H.

28-Methyl Ester, 3-Nitrile of (4*S*)-4-Hydroxy-24-nor-3,4-secolupane-3,28-dioic Acid (*VIa*)

A solution of compound *IVa* (850 mg) in dichloromethane (20 ml) was poured into a stirred suspension of pyridinium chlorochromate (1 g) in dichloromethane (10 ml) and the mixture was stirred for 80 min. After dilution with ether and filtration through a column of alumina (15 g) the solvents were evaporated under reduced pressure to give 660 mg of aldehyde *IIIa* which was characterized by its IR spectrum: 2830, 2724, 1710 sh (CHO), 2246 (CN), 1718, 1434, 1162 cm^{-1} ($COOCH_3$). Crude aldehyde *IIIa* (660 mg) was dissolved in dichloromethane (40 ml), 3-chloroperbenzoic acid (700 mg) was added and the mixture allowed to stand at room temperature in the dark for 21 h. After dilution with chloroform and working up the residue (formate *Va*) was dissolved in benzene (10 ml). 2% potassium hydroxide (50 ml) in ethanol was added and the mixture allowed to stand at room temperature for 15 h, then diluted with water and extracted with ether. The extract was washed with dilute hydrochloric acid and water, dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue (500 mg) was chromatographed on alumina (50 g) with light petroleum–acetone (4 : 1) to give 310 mg of amorphous *VIa*, $[\alpha]_D$ −18°. IR spectrum: 3617 (OH), 2247 (CN), 1716, 1432, 1162 cm^{-1} ($COOCH_3$). For $C_{30}H_{49}NO_3$ (471·7) calculated: 76·38% C, 10·47% H; found: 76·55% C, 10·55% H.

28-Methyl Ester, 3-Nitrile of (4*R*)-4-Hydroxy-24-nor-3,4-secolupane-3,28-dioic Acid (*VIb*)

Compound *VIb* was prepared from compound *IVb* (600 mg) in the same manner as compound *VIa*, with the difference that the hydrolysis of formate *Vb* was carried out by 1 h refluxing. Aldehyde *IIIb* was characterized by its IR spectrum: 2840, 2740, 1718 (CHO), 2247 (CN), 1718, 1433, 1161 cm^{-1} ($COOCH_3$). Product *VIb* (360 mg) was purified chromatographically on alumina (60 g; elution with light petroleum–acetone, 85 : 15) and by crystallization from light petroleum. Yield, 250 mg of compound *VIb*, m.p. 214–216°C, $[\alpha]_D$ −24°. IR spectrum: 3619 (OH), 2246 (CN), 1717, 1434, 1161 cm^{-1} ($COOCH_3$). For $C_{30}H_{49}NO_3$ (471·7) calculated: 76·38% C, 10·47% H; found: 76·55% C, 10·63% H.

28-Methyl Ester, 3-Nitrile of (4*S*)-4-Benzoyloxy-24-nor-3,4-secolupane-3,28-dioic Acid (*VIIa*)

Benzoyl chloride (0·5 ml) was added to a solution of compound *VIa* (250 mg) in pyridine (11 ml) and the mixture left at room temperature for 4 days. After dilution with water and 30 min standing it was extracted with ether and the extract washed with dilute hydrochloric acid and water and worked up in the conventional manner. The residue was chromatographed on alumina (20 g) with light petroleum–ether mixture (4 : 1) to give 230 mg of benzoate *VIIa*, m.p. 154–157°C (ether–light petroleum), $[\alpha]_D$ +2°. IR spectrum: 3067, 1710, 1600, 1584, 1279 ($OCOC_6H_5$), 2246 (CN), 1710, 1433, 1162 cm^{-1} ($COOCH_3$). Circular dichroism: λ_{max} 228 nm ($\Delta\varepsilon$ +4·9). For $C_{37}H_{53}NO_4$ (575·8) calculated: 77·17% C, 9·28% H; found: 77·35% C, 9·30% H.

28-Methyl Ester, 3-Nitrile of (4*R*)-4-Benzoyloxy-24-nor-3,4-secolupane-3,28-dioic Acid (*VIIb*)

Benzoate *VIIb* was prepared from compound *VIb* (90 mg) using the same procedure as in the case of the preparation of benzoate *VIIa*. Yield, 60 mg of benzoate *VIIb*, m.p. 106–109°C (ether–methanol), $[\alpha]_D$ −30°. IR spectrum: 3067, 1710, 1601, 1583, 1280 ($OCOC_6H_5$), 2246 (CN), 1710, 1434, 1162 cm^{-1} ($COOCH_3$). Circular dichroism: λ_{max} 229 nm ($\Delta\varepsilon$ +1·1). For $C_{37}H_{53}NO_4$ (575·8) calculated: 77·17% C, 9·28% H; found: 77·35% C, 9·24% H.

(4*S*)-23-Hydroxy-3,4-secolupane-3,28-dioic Acid (*VIIIa*)

A mixture of compound *IVa* (700 mg), ethylene glycol (35 ml) and sodium hydroxide (3·5 g) was refluxed for 7 h, diluted with water, acidified with dilute hydrochloric acid and extracted with ether. The extract was washed with water and repeatedly extracted with 5% sodium carbonate solution. The aqueous extracts were combined, acidified with dilute hydrochloric acid and extracted with ether. The ethereal phase was washed with water, dried over sodium sulfate and ether evaporated. The residue was dissolved in a small amount of ether and the solution filtered through a layer of charcoal. Yield, 570 mg of diacid *VIIIa*, m.p. 263–264°C (ether–light petroleum), $[\alpha]_D$ −27° (acetone). IR spectrum (in KBr pellet): 2200–3700, 1700 (COOH, OH), 1032 cm^{-1} (C—O). For $C_{30}H_{50}O_5$ (490·7) calculated: 73·43% C, 10·27% H; found: 73·17% C, 10·29% H.

Dimethyl ester *IXa* was purified chromatographically on alumina using benzene–ether mixtures 9 : 1 and 7 : 3 for elution. After crystallization from light petroleum, m.p. 160–163°C, $[\alpha]_D$ −29°. IR spectrum: 3630 (OH), 1718, 1438, 1162 ($COOCH_3$), 1031 cm^{-1} (C—O). For $C_{32}H_{54}O_5$ (518·7) calculated: 74·09% C, 10·49% H; found: 74·16% C, 10·54% H.

(4*R*)-23-Hydroxy-3,4-secolupane-3,28-dioic Acid (*VIIIb*)

Compound *IVb* (550 mg) was hydrolysed in the same manner as the isomeric compound *IVa* (see the preparation of the diacid *VIIIa*). Yield 320 mg of diacid *VIIIb*, m.p. 248·5–250°C (ether–light petroleum), $[\alpha]_D$ −26° (acetone). IR spectrum (in KBr pellet): 2300–3700, 1700, 1688 (COOH, OH), 1016 cm^{-1} (C—O). For $C_{30}H_{50}O_5$ (490·7) calculated: 73·43% C, 10·27% H; found: 73·63% C, 10·36% H.

Dimethyl ester *IXb* was crystallized from light petroleum, m.p. 153·5–155°C (change of modification at 88–92°C), $[\alpha]_D$ −25°. IR spectrum: 3634 (OH), 1720, 1438, 1164 ($COOCH_3$), 1015 cm^{-1} (C—O). For $C_{32}H_{54}O_5$ (518·7) calculated: 74·09% C, 10·49% H; found: 73·84% C, 10·62% H.

Dimethyl (4*S*)-4-hydroxy-24-nor-3,4-secolupane-3,28-dioate (*XIIIa*)

A) *From norketone* XV: A solution of norketone *XV* (110 mg) and 3-chloroperbenzoic acid (560 mg) in chloroform (7 ml) was allowed to stand in the dark and at room temperature for 24 h. After dilution with chloroform the solution was washed with a 5% potassium iodide solution, then a 5% potassium disulfite solution, and worked up as usual. Amorphous lactone *XVI* (100 mg) was obtained which was characterized by its IR spectrum: 1718, inflexion at 1438, 1172, 1162 ($COOCH_3$), 1718, 1130 cm^{-1} (lactone). A 1M solution of potassium hydroxide in methanol (5 ml) was added to lactone *XVI* (80 mg) in benzene (10 ml) and the mixture was refluxed for 90 min. After dilution with ether it was washed with dilute hydrochloric acid and water and dried over sodium sulfate. After evaporation of ether 70 mg of compound *XIIa* were obtained, IR spectrum: 3613 (OH), 2400–3350, 1708 (COOH), 1708, 1434, 1162 cm^{-1} ($COOCH_3$). Compound *XIIa* was converted to ester *XIIIa* with diazomethane and purified by preparative thin-layer chromatography on silica gel (20 × 20 cm plate), using light petroleum–acetone mixture 9 : 1 for development. Yield, 60 mg of amorphous ester *XIIIa*. $[\alpha]_D$ −17°. IR spectrum: 3617 (OH), 1721, 1438, 1163 cm^{-1} ($COOCH_3$). For $C_{31}H_{52}O_5$ (504·7) calculated: 73·76% C, 10·38% H; found: 74·07% C, 10·64% H.

B) *From ketone* XVII. A 10% solution (3 ml) of sulfuric acid in acetic acid was added to a solution of ketone *XVII* (500 mg; see[4]) and 3-chloroperbenzoic acid (1 g) in dichloromethane (20 ml) and the mixture allowed to stand for 2 days at room temperature and in the dark. The mixture was worked up as under *A*). Yield, 460 mg of lactone *XVI*, which was further converted to compound *XIIa* and ester *XIIIa* using the procedure described under *A*). Ester *XIIIa* was purified by chromatography on alumina (50 g, elution with a mixture of light petroleum and acetone 9 : 1). Yield, 290 mg of amorphous ester *XIIIa*, $[\alpha]_D$ −17°. Compounds *XVI*, *XIIa* and *XIIIa* were identical with the preparations described under *A*).

C) *From hydroxy ester* IXa: Oxidation of hydroxy ester *IXa* (240 mg) with pyridinium chlorochromate gave 230 mg of amorphous aldehyde *Xa* which was characterized by IR spectrum: 2825, 2718, 1720 (CHO), 1720, 1438, 1162 cm^{-1} ($COOCH_3$). The crude aldehyde *Xa* was oxidized with 3-chloroperbenzoic acid under formation of formate *XIa*, which was hydrolysed to compound *XIIa*. This reaction sequence was carried out in the same manner as in the preparation of compound *VIa*. Compound *XIIa* was converted to ester *XIIIa* using the procedure described under *A*). It was identical with the preparation obtained by the same procedure *A*), $[\alpha]_D$ −15·5°.

D) *From benzoate* VIIa: A mixture of benzoate *VIIa* (160 mg), sodium hydroxide (800 mg) and ethylene glycol (8 ml) was refluxed for 5·5 h and worked up in the same manner as in the preparation of diacid *VIIIa*. The acid *XIVa* formed was converted directly to ester *XIIIa* which was purified as under *A*). Yield, 100 mg of ester *XIIIa*, identical with the preparation described under *A*), $[\alpha]_D$ −15°.

Dimethyl (4*R*)-4-hydroxy-24-nor-3,4-secolupane-3,28-dioate (*XIIIb*)

A) *From hydroxy derivative* IVb: Ester *XIIIb* was prepared from hydroxy derivative *IVb* (250 mg) using the following reaction sequence: *IVb* → *Xb* → *XIb* → *XIIb* → *XIIIb*, carried out equally as in the case of the 4*S*-isomer *IVa* (see the preparation of compound *XIIIa* under *C*). Among the intermediates only aldehyde *Xb* was characterized by IR spectrum: inflexion 2850, 2730, 1728 (CHO), 1728, 1440, 1163 cm^{-1} ($COOCH_3$). Ester *XIIIb* was purified by chromatography on three silica gel plates (20 × 20 cm) in light petroleum–acetone (9 : 1) and crystallization from hexane. Yield 60 mg, m.p. 154–156°C, $[\alpha]_D$ −21·5°. IR spectrum: 3630 (OH), 1728,

1442, 1168 cm^{-1} ($COOCH_3$). For $C_{31}H_{52}O_5$ (504·2) calculated: 73·76% C, 10·38% H; found: 73·82% C, 10·62% H.

B) *From benzoate* VIIb: Benzoate *VIIb* (60 mg) was converted to diacid *XIVb* and dimethyl ester *XIIIb* in the same manner as in the case of benzoate *VIIa* (see the preparation of the dimethyl ester *XIIIa* under *D*)). Yield, 40 mg of ester *XIIIb*, identical with the preparation obtained under *A*). M.p. 158–159°C, $[\alpha]_D$ −22°.

Methyl 3-oxo-24-norlupan-28-oate (*XV*)

A solution of epoxynitrile *II* (500 mg) and boron trifluoride etherate (0·75 ml) in toluene (25 ml) was refluxed for 6 h, diluted with ether and worked up. The residue was chromatographed on a column of alumina (50 g). A mixture of light petroleum–ether (4 : 1) eluted compound *XV* (160 mg), m.p. 199–200°C (chloroform–methanol), $[\alpha]$ +2°. IR spectrum: 1713, 1435, 1171 ($COOCH_3$), 1704 cm^{-1} (CO). For $C_{30}H_{48}O_3$ (456·7) calculated: 78·89% C, 10·59% H; found: 78·82% C, 10·51% H.

Methyl 3-Oxo-4-oxa-A-homolupan-28-oate (*XVIII*)

3-Chloroperbenzoic acid (400 mg) was added to a solution of ketone *XVII* (250 mg) in dichloromethane (5 ml) and the mixture allowed to stand at room temperature and in the dark for 3·5 h. After dilution with chloroform the solution was washed with 5% potassium iodide solution, 5% potassium disulfite solution, a potassium hydrogen carbonate solution and water. The organic layer was dried over sodium sulfate, filtered through a layer of alumina (5 g) and the solvent was distilled off. The residue was crystallized from ether–light petroleum. Yield, 210 mg of compound *XVIII*, m.p. 195–210°C (decomp.), $[\alpha]_D$ +30°. IR spectrum: 1715, 1435, 1162 ($COOCH_3$), 1715, 1115 cm^{-1} (lactone). For $C_{31}H_{50}O_4$ (486·7) calculated: 76·50% C, 10·36% H; found: 76·63% C, 10·17% H.

4-Hydroxy-3,4-secolupane-3,28-dioic Acid (*XIX*)

A mixture of compound *XVIII* (200 mg), sodium hydroxide (1 g) and ethylene glycol (10 ml) was refluxed for 5 h. After a workup similar to that as in the preparation of diacid *VIIIa* and triple crystallization of the residue from ether–light petroleum pure diacid *XIX* (120 mg) was obtained, m.p. 255–256°C (decomp.), $[\alpha]_D$ −17° (acetone). For $C_{30}H_{50}O_5$ (490·7) calculated: 73·43% C, 10·27% H; found: 73·67% C, 10·52% H.

Dimethyl ester *XX* was purified by filtration of ethereal solution through a layer of alumina and crystallization from hexane, m.p. 140–142°C, $[\alpha]_D$ −13°. IR spectrum: 3624 (OH), 1726, 1444, 1170 cm^{-1} ($COOCH_3$). For $C_{32}H_{54}O_5$ (518·7) calculated: 74·09% C, 10·49% H; found: 74·03% C, 10·62% H. The same dimethyl ester was also obtained from the monoester *XXI* with diazomethane.

28-Methyl Ester of 4-Hydroxy-3,4-secolupane-3,28-dioic Acid (*XXI*)

A 5% solution of potassium hydroxide in ethanol (14 ml) was added to a solution of compound *XVIII* (210 mg) in benzene (14 ml). After 19 h standing at room temperature the mixture was diluted with water, acidified with dilute hydrochloric acid and extracted with ether. The extract was washed with water until neutral and dried over sodium sulfate. After elimination of ether by distillation 190 mg of ester *XXI* were obtained. Attempts at crystallization led to a gel which

when dried melted at 138–141°, $[\alpha]_D$ −9°. IR spectrum: 3622 (OH), 2400–3400, 1711 (COOH), inflexion 1718, 1436, 1163 cm^{-1} ($COOCH_3$). For $C_{31}H_{52}O_5$ (504·7) calculated: 73·76% C, 10·38% H; found: 73·47% C, 10·48% H.

For measurement of the circular dichroism the authors thank Dr I. Frič, Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, Prague.

REFERENCES

1. Fried J., Krakower G. W., Rosenthal D., Basch H.: J. Med. Chem. *8*, 279 (1965).
2. Klinot J., Šumanová V., Vystrčil A.: This Journal *37*, 603 (1972).
3. Klinot J., Úlehlová E., Straka R., Vystrčil A.: This Journal *38*, 2648 (1973).
4. Ruzicka L., Brenner M., Rey E.: Helv. Chim. Acta *24*, 515 (1941).
5. Klinot J., Hovorková N., Vystrčil A.: This Journal *35*, 1105 (1970).
6. Vystrčil A., Pouzar V., Křeček V.: This Journal *38*, 3902 (1973).
7. Cohen K. F., Kazlauskas R., Pinhey J. T.: J. Chem. Soc., Perkin Trans. 1, *1973*, 2076.
8. Rosenthal D., Niedermeyer A. O., Fried J.: J. Org. Chem. *30*, 510 (1965).
9. Holker J. S. E., Jones W. R., Ramm P. J.: J. Chem. Soc. C *1969*, 357.
10. Corey E. J., Suggs J. W.: Tetrahedron Lett. *1975*, 2647.
11. Miyamoto M., Morita K., Kawamatsu Y., Kawashima K., Nakanishi K.: Tetrahedron *23*, 411 (1967).
12. Harada N., Ohashi M., Nakanishi K.: J. Amer. Chem. Soc. *90*, 7349 (1968).

Translated by Ž. Procházka.