β-GLUCOSIDES OF STEROIDAL UNSATURATED NITRILES*

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Reaction of 3β-methoxymethoxy-5-pregnen-20-one (*Ia*) with diethyl cyanomethylphosphonate and subsequent removal of the protecting group afforded (20*E*)-3β-hydroxy-24-norchola-5,20(22)--diene-23-nitrile (*IIIa*). Besides the analogous derivative *IIIb* with another double bond in position 14, the fully saturated compounds *IIIc* and *IIId* with configuration 5α and 5β, respectively, were prepared similarly. Silver silicate-catalyzed glycosylation of *IIIa*—*IIId* with tetra-O-acetyl--α-D-glucopyranosyl bromide gave β-D-glucopyranosides *IVa*—*IVd* in 77—89% yield. A parallel series of hemisuccinates *VIa*—*VId* was prepared in 64—81% yields by reaction of *IIIa*—*IIId* with 2-(trimethylsilyl)ethyl hydrogen butanedioate followed by deblocking with tetrabutylammonium fluoride. The glucoside *IVa* was prepared also by an alternative reaction pathway starting from 3β-hydroxy-5-pregnen-20-one (*VIII*). Compound *VIII* was converted in 80% yield into the glucoside *IX* which, after protection as the tetra-O-(trimethylsilyl) derivative *XII*, was treated with diethyl cyanomethylphosphonate.

Our good experience[1] with silver silicate as an effective glycosylation catalyst[2] in the steroid series led us to study the applicability of this catalyst to further steroids. We have selected compounds differing in the number of double bonds and in annulation of the rings A and B, and consequently in reactivity of the 3β-hydroxy group. Into all these derivatives we introduced an α,β-unsaturated nitrile grouping, interesting from the standpoint of biological activity[3].

Similarly as in our previous work[4], the starting compounds were the ketones *Ia*—*Id* with the hydroxyl protected with methoxymethyl group. The crotononitrile--type side chain was synthesized using the Wittig–Horner reaction[5]. As the phosphonate component we used diethyl cyanomethylphosphonate which is considerably reactive and reacts even with hindered 20-keto derivatives[6-8]. Reaction of sodium salt of the phosphonate with the corresponding ketone in 1,2-dimethoxyethane at room temperature afforded nitriles *IIa*—*IId* in 91—94% yield. In contrast to similar reaction with aldehydes[3], we obtained a configurationally homogeneous product. Configuration of the $\Delta^{20(22)}$ double bond was determined similarly as for the analogous esters[4] using the NMR spectroscopy. The coupling constant $J(^{13}C\text{-}21,$

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^{1}H-22) in the ^{13}C NMR spectrum of nitrile *IIa* amounts to 8·0 Hz, corresponding to the 20*E*-isomer. The shifts of H-18, H-21, and H-22 signals in the ^{1}H NMR spectra of *IIa*–*IId* (Table I) are practically the same in the whole series; the slight deviations for *IIb* correspond to the presence of the Δ^{14} double bond.

Removal of the methoxymethyl protecting group led to the hydroxy derivatives *IIIa*–*IIId*. They were glycosylated using silver silicate on silica gel[2] which had given excellent results in glycosylation of Δ^5-steroid derivatives[1]. In general,hydroxyl in the position 3 of these derivatives is considerably reactive, albeit the yields can vary depending on other structural features[9,10]. In our case, the differences in the annulation and number of double bonds in the derivatives *IIIa*–*IIId* had practically no effect on the reaction course. After glycosylation with tetra-O-acetyl-α-D-glucopyranosyl bromide, deacetylation in a mixture of methanol, triethylamine, and water, and chromatography, the yields of all the four derivatives *IVa*–*IVd* were practically the same (77–89%) and no side-products were isolated. The structural proof is based on the ^{13}C NMR spectra (Table II) whose parameters agree with those of analogous derivatives[4,11,12].

In addition to glucosides, we prepared also the corresponding hemisuccinates *VIa*–*VId* from the nitriles *IIIa*–*IIId*. An indirect method[13] was used, consisting in reaction with 2-(trimethylsilyl)ethyl hydrogen butanedioate followed by deblocking the obtained succinates *Va*–*Vd* with tetrabutylammonium fluoride.

We also tried to prepare glucosides *IV* by an alternative method, consisting in addition of the nitrile moiety to the already glycosylated compound. Preliminary experiments were done with pregnenolone *VIII* which on glycosylation under the above-mentioned conditions gave the known[9,10,14] β-D-glucopyranoside *IX* in the yield of 80% (the published yields[9,10,14] are 32, 55, and 39–63%, respectively). However, we encountered problems concerning the choice of a suitable protecting group which should be alkali-stable in the Wittig–Horner reaction and less stable than a β-glycoside bond in an acid medium. We tried protection in the form of

TABLE I
Selected ^{1}H NMR spectral data (60 MHz) for nitriles *IIa*–*IId*

Compound[a]	H-18	H-19	H-21	H-22
IIa	0·58	1·00	2·08	5·13
IIb	0·79	1·02	2·10	5·23
IIc	0·55	0·80	2·07	5·12
IId	0·55	0·94	2·07	5·12

[a] For conditions of the measurements and other signals see Experimental.

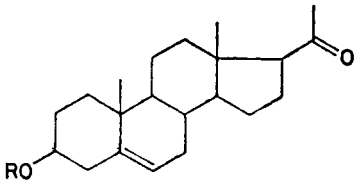
tetra-O-methoxymethyl and tetra-O-(trimethylsilyl) derivatives *X* and *XII*. The first compound *X* was prepared by treatment with chloromethyl methyl ether and diisopropylethylamine. Large excess of the reagents was necessary to achieve complete alkylation because the partially alkylated derivatives reacted very slowly and were not easily separable from compound *X*. In the next step, the protected nitrile *XI* was obtained by the Wittig–Horner reaction; the ^{13}C NMR spectrum of *XI* was well

TABLE II

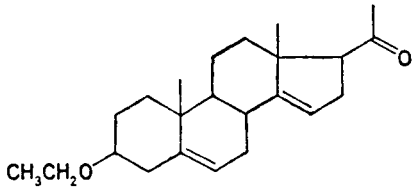
^{13}C NMR spectral data for the nitriles *IIa*, *IVa*–*IVd*, and *XI*

Carbon atom[a]	*IIa*[b]	*IVa*	*IVb*	*IVc*	*IVd*	*XI*[b]
C-1	37·2	36·9	36·5	36·5	29·3	37·2
C-2	28·8	29·3	29·1	29·0	25·8	29·7
C-3	76·7	77·1	76·8	76·6	72·4	76·5
C-4	39·5	37·7	38·1	33·9	30·0	36·7
C-5	140·7	140·6	139·6	44·0	35·8	140·7
C-6	121·3	120·9	120·7	28·2	26·0	121·5
C-7	31·6	31·2	29·1	31·4	26·3	31·6
C-8	32·1	31·7	30·7	35·2	35·4	32·0
C-9	50·0	49·7	49·5	53·6	39·3	50·0
C-10	36·7	36·3	36·5	35·1	34·4	36·7
C-11	20·9	20·6	21·2	20·7	20·6	20·9
C-12	38·3	38·4	40·0	37·8	38·0	38·8
C-13	44·6	44·0	48·0	44·2	44·4	44·6
C-14	56·6	55·9	152·1	55·7	55·7	56·5
C-15	24·1	23·8	117·8	23·7	23·8	24·1
C-16	25·1	24·6	32·3	24·4	24·6	25·1
C-17	58·4	57·7	59·4	57·6	57·8	58·4
C-18	12·9	12·6	17·3	12·8	12·8	12·9
C-19	19·3	19·1	18·7	12·0	23·5	19·3
C-20	165·4	165·1	164·8	165·3	165·3	165·4
C-21	22·7	22·3	22·4	22·5	22·5	22·7
C-22	95·6	95·5	95·9	95·4	95·5	95·6
C≡N	117·5	117·8	117·6	117·6	117·6	117·5
C-1′	—	100·9	100·8	100·5	100·9	101·4
C-2′	—	73·5	73·3	73·4	73·4	78·2
C-3′	—	76·8	76·6	76·6	76·8	79·3
C-4′	—	70·3	70·0	70·0	70·0	74·4
C-5′	—	76·7	76·6	76·1	76·6	81·0
C-6′	—	61·3	61·0	61·0	61·0	66·6

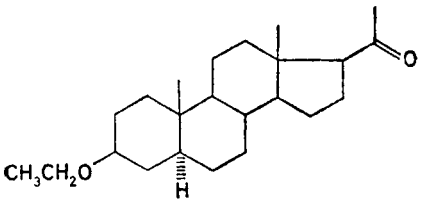
[a] For conditions of measurement see Experimental. [b] Other signals: *IIa*: 94·6 (OCH_2O), 55·1 (OCH_3), $J(^{13}C\text{-}21, {}^1H\text{-}22) = 8{\cdot}0$; *XI*: 98·5, 98·4, 97·4, 96·7 (4 × OCH_2O), 56·4, 55·2: 3 C (4 × OCH_3).



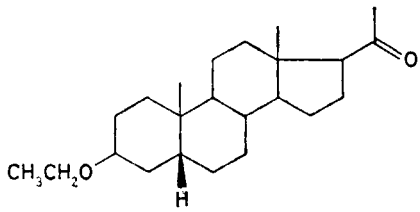
Ia, R = CH_3OCH_2
VIII, R = H



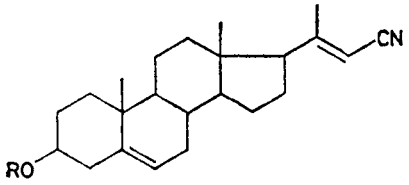
Ib



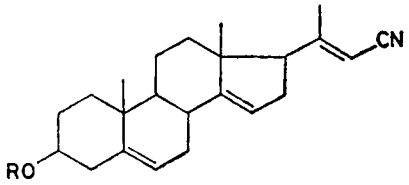
Ic



Id



a



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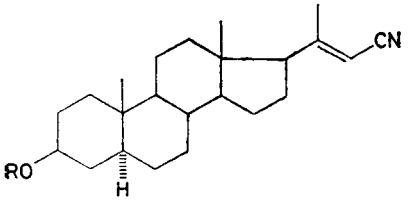

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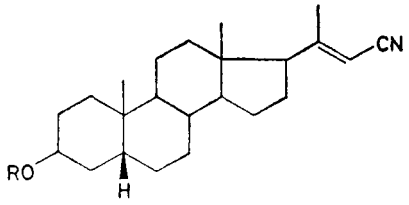
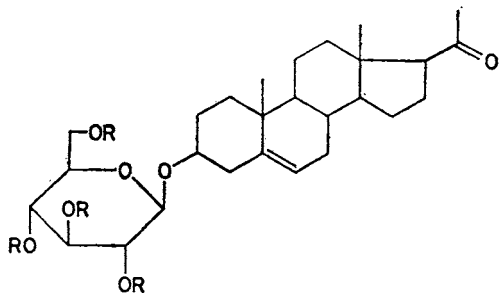


d

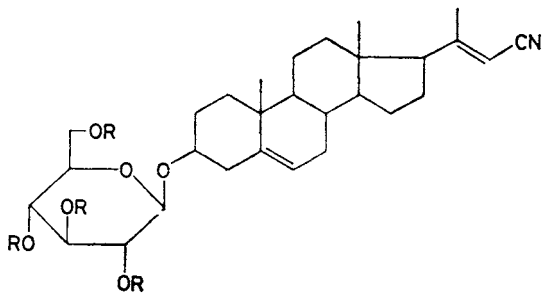
II, R = CH_3OCH_2
III, R = H
IV, R = β-D-glucopyranosyl
V, R = $OCCH_2CH_2COOCH_2CH_2Si(CH_3)_3$
VI, R = $OCCH_2CH_2COOH$

comparable to other Δ^5-derivatives (Table II). Nevertheless, its deblocking under usual conditions (benzene–methanol–hydrochloric acid) yielded an unidentified mixture of polar products instead of the desired glucoside *IVa*.

The trimethylsilyl group oproved to be more suitable for protecting. The glucoside *IX* was treated with hexamethyldisilazane in the presence of chlorotrimethylsilane as catalyst and the crude tetra-O-trimethylsilyl derivative *XII* was reacted with diethyl cyanomethylphosphonate. After the work-up, the product was deblocked in an acidic medium and purified by chromatography to give the glucoside *IVa* in 73% yield (from *IX*). However, protection with the trimethylsilyl protecting group is limited to Wittig–Horner reactions proceeding at room temperature, as shown by attempted reaction of glycoside *XII* with diethyl ethoxycarbonylmethylphosphonate at elevated temperature. The protecting groups were split off by the phosphonate salt and the only isolated product was the glucoside *IX*.



IX, R = H
X, R = CH_3OCH_2
XII, R = $(CH_3)_3Si$



XI, R = CH_3OCH_2

Silver silicate is thus suitable β-glucosylation catalyst not only for the reactive Δ^5-steroids and saturated 5α derivatives with equatorial hydroxy groups but even

for 5β-compounds with an axial hydroxy group. Utilization of glycosylated steroids for the construction of the side chain seems to be limited by the available protecting groups; for reactions with phosphonates at room temperature the trimethylsilyl group is the group of choice. The yields of both alternative ways to Δ^5-derivatives are comparable: For the reaction sequence *VIII* → *Ia* → *IIa* → *IIIa* → *IVa* the overall yield is 66% (for *VIII* → *Ia* reported[15] 80% yield) whereas the pathway *VIII* → *IX* → *XII* → *IVa*, using protected glucosides, gives the end product in total yield of 58%.

EXPERIMENTAL

Melting points were determined on a Boetius micro melting point apparatus (G.D.R.). Optical rotations were taken on a Perkin–Elmer 141 MC polarimeter. IR spectra were taken on a Perkin–Elmer PE 580 or a UR-20 (Zeiss, Jena) spectrophotometers, wavenumbers are given in cm^{-1}. NMR spectra were measured on a Tesla BS-467 (CW; 60 MHz, for ^1H) or Varian XL-200 (FT; 200·058 MHz for ^1H and 50·309 MHz for ^{13}C nuclei) instruments in deuteriochloroform with tetramethylsilane as internal standard at room temperature unless stated otherwise. Chemical shifts are given in ppm (δ-scale), coupling constants (J) and band widths (W) in Hz. All parameters were obtained by first-order analysis except for derivatives *X* and *XI*, where AB system analyses were accomplished. Preparative chromatography was carried out on columns of silica gel (according to Pitra, 60—120 μm, Service Laboratories of this Institute) or neutral alumina (Reanal, grade II), thin-layer chromatography (TLC) was performed on silica gel G according to Stahl (Woelm). Spots were detected by spraying with sulfuric acid followed by heating. The purity of compounds *IIIa—IIId*, *IVa—IVd*, and *VIa—VId* was checked by analytical HPLC (see Table III). The solutions in organic solvents were dried over anhydrous sodium sulfate and taken down on a rotatory evaporator at bath temperature 40—50°C and pressure 2—2·5 kPa. Analytical samples were dried over phosphorus pentoxide at about 25 Pa.

Preparation of Nitriles *IIa—IId*

A 50% suspension of sodium hydride in mineral oil was washed with light petroleum (3 × 5 ml) under argon. 1,2-Dimethoxyethane (10 ml), followed by diethyl cyanomethylphosphonate was then added under stirring and cooling with ice. After stirring at room temperature for 20 min, a solution of ketone *I* in 1,2-dimethoxyethane (10 ml) was added. The mixture was stirred at room temperature for 48 h and taken down to a minimum volume. The residue was coevaporated with benzene, dissolved in benzene–ether (1 : 1) and washed with saturated sodium chloride solution. After drying and evaporation, the residue was dissolved in minimum amount of benzene (or benzene–dichloromethane) and filtered through a column of alumina (50 ml). The column was washed with benzene–dichloromethane (1 : 1), fractions containing the product *II* were combined, evaporated ans subjected to further chromatographic separation on a silica gel column (100 g).

(20*E*)-3β-*Methoxymethoxy*-24-*nor*-5,20(22)-*choladiene*-23-*nitrile* (IIa): Reaction of ketone *Ia* (ref.[15], 1·1 g; 3·1 mmol), sodium hydride (432 mg; 9 mmol), and the phosphonate (1·5 ml; 9 mmol), followed by chromatography in light petroleum–benzene–ether (100 : 100 : 2), gave *IIa* (1·1 g; 94%), m.p. 130—132°C (light petroleum–dichloromethane), $[\alpha]_D$ −56° (*c* 0·3, chloroform). IR spectrum (tetrachloromethane): 2 222, 1 618 (C=C—C≡N); 1 150, 1 110, 1 048 (C—O—C). ^1H NMR spectrum (deuteriochloroform): 5·33 bd, 1 H (H-6, J = 4·5); 5·13 bs,

1 H (H-22); 4·67 s, 2 H (OCH_2O); 3·35 s, 3 H (CH_3O); 2·08 s, 3 H (3 × H-21); 1·00 s, 3 H (3 × H-19); 0·58 s, 3 H (3 × H-18). For $C_{25}H_{37}NO_2$ (383·6) calculated: 78·28% C, 9·72% H, 3·65% N; found: 78·51% C, 9·76% H, 3·61% N.

(20*E*)-3β-*Methoxymethoxy*-24-*nor*-5,14,20(22)-*cholatriene*-23-*nitrile* (IIb): Reaction of *Ib* (ref.[4], 1·0 g; 2·8 mmol), sodium hydride (402 mg; 8·4 mmol), and the phosphonate (1·4 ml; 8·4 mmol), followed by chromatography in benzene–acetone (200 : 1), afforded 0·9 g (85%) of *IIb*, m.p. 122—124°C (ethanol), $[\alpha]_D$ −78° (*c* 0·2, chloroform). IR spectrum (tetrachloromethane): 2 222, 1 620 (C=C—C≡N); 1 670, 1 640 sh (C=C); 1 150, 1 110, 1 048, 917 (C—O—C). ^{1}H NMR spectrum (deuteriochloroform): 5·41 m, 1 H (H-6); 5·23 bs, 2 H (H-15, H-22); 4·68 s, 2 H (OCH_2O); 3·36 s, 3 H (CH_3O); 2·10 s, 3 H (3 × H-21); 1·02 s, 3 H (3 × H-18); 0·79 s, (3 × H-19). For $C_{25}H_{35}NO_2$ (381·6) calculated: 78·70% C, 9·25% H, 3·67% N; found: 78·43% C, 9·19% H, 3·55% N.

(20*E*)-3β-*Methoxymethoxy*-24-*nor*-5α-*chol*-20(22)-*ene*-23-*nitrile* (IIc): Reaction of *Ic* (ref.[4], 1·0 g, 2·8 mmol), sodium hydride (398 mg; 8·3 mmol), and the phosphonate (1·4 ml; 8·4 mmol), followed by chromatography in light petroleum–benzene–ether (100 : 100 : 2), afforded 959 mg (90%) of *IIc*, m.p. 105—107°C (ethanol), $[\alpha]_D$ +4° (*c* 0·2, chloroform). IR spectrum (tetrachloro-

TABLE III

Retention times (t_R) and capacity factors (k') of HPLC RP $C_{(18)}$[a]

Compound	Solvent system A		Solvent system B	
	t_R, min	k'	t_R, min	k'
IIIa	3·20	0·92	14·83	4·93
IIIb	3·10	0·86	13·17	4·27
IIIc	3·93	1·36	18·00	6·20
IIId	3·80	1·28	15·23	5·09
IVa	2·33	0·40	5·67	1·27
IVb	2·23	0·34	5·10	1·04
IVc	2·37	0·42	6·57	1·63
IVd	2·40	0·44	6·50	1·60
VIa	3·27	0·96	17·43	5·97
VIb	2·93	0·76	15·55	5·22
VIc	3·33	0·98	20·77	7·31
VId	2·90	0·74	14·67	4·87

[a] Stainless-steel column (250 × 4 mm i.d.), column packing Separon Si $C_{(18)}$ (10 μm), solvent system A: ethanol–0·01M aqueous phosphoric acid (9 : 1), system B: methanol–0·01M aqueous phosphoric acid (8 : 2), flow rate 1·25 ml min^{-1}, pressure 11·4 MPa (1 650 p.s.i.), and 7·9 MPa (1 150 p.s.i.), respectively. Variable wavelength UV detector UVM-4; detection at 230 nm, sensitivity 0·5 a.u.f.s. Samples were applied in dichloromethane–methanol (1 : 1), *c* 10 mg ml^{-1}. In determining capacity factors the hold-up time t_0 was determined as the retention time of the first inflex point on the chromatogram which was considered to represent the front of the chromatographic zone.

methane): 2 222, 1 620 (C=C—C≡N), 1 151, 1 110, 1 047, 917 (C—O—C). ^{1}H NMR spectrum (deuteriochloroform): 5·12 m, 1 H (H-22); 4·67 s, 2 H (OCH_2O); 3·35 s, 3 H (CH_3O); 2·07 s, 3 H (3 × H-21); 0·80 s, 3 H (3 × H-18); 0·55 s, 3 H (3 × H-19). For $C_{25}H_{39}NO_2$ (385·6) calculated: 77·87% C, 10·19% H, 3·63% N; found: 77·76% C, 10·20% H, 3·66% N.

(20*E*)-3β-*Methoxymethoxy*-24-*nor*-5β-*chol*-20(22)-*ene*-23-*nitrile* (IId): Reaction of *Id* (ref.[4], 1·43 g; 3·9 mmol), sodium hydride (569 mg; 11·9 mmol), and the phosphonate (1·9 ml; 11·8 mmol), followed by chromatography in benzene–acetone (200 : 1), yielded 1·23 g (81%) of *IId*, m.p. 76—78°C (ethanol), $[\alpha]_D$ +24° (*c* 0·2, chloroform). IR spectrum (tetrachloromethane): 2 222, 1 620 (C=C—C≡N); 1 147, 1 102, 1 048, 908 (C—O—C). ^{1}H NMR spectrum (deuteriochloroform): 5·12 bs, 1 H (H-22); 4·63 bs, 2 H (OCH_2O); 3·87 m, 1 H (H-3); 3·35 s, 3 H (CH_3O); 2·07 s, 3 H (3 × H-21); 0·94 s, 3 H (3 × H-19); 0·55 s, 3 H (3 × H-18). For $C_{25}H_{39}NO_2$ (385·6) calculated: 77·87% C, 10·19% H, 3·63% N; found: 77·43% C, 10·15% H, 3·54% N.

Preparation of Hydroxy Derivatives *IIIa—IIId*

Concentrated hydrochloric acid (0·2 ml) was added to a solution of methoxymethyl derivative *II* in a mixture of benzene (25 ml) and methanol (25 ml). After warming to 40°C for 6 h, the mixture was taken down *in vacuo*. The residue was coevaporated with benzene and ethanol, dissolved in chloroform, and the solution was filtered through a column of alumina (50 g) which was then washed with chloroform. Evaporation of the solvent *in vacuo*, followed by chromatography on a silica gel column (80 g) or crystallization, afforded *III*.

(20*E*)-3β-*Hydroxy*-24-*nor*-5,20(22)-*choladiene*-23-*nitrile* (IIIa): Reaction of *IIa* (1·0 g; 2·6 mmol), followed by chromatography in chloroform and crystallization from chloroform–light petroleum, afforded 760 mg (86%) of *IIIa*, m.p. 189—191°C, $[\alpha]_D$ −56° (*c* 0·3, chloroform). Reported[8] m.p. 186—187°C, $[\alpha]_D$ −54° (chloroform). IR spectrum (chloroform): 3 610, 3 480 (OH); 2 220, 1 616 (C=C—C≡N). ^{1}H NMR spectrum (deuteriochloroform): 5·34 bd, 1 H (H-6, J = 4); 5·14 bs, 1 H (H-22); 3·46 m, 1 H (H-3, W = 36); 2·08 s, 3 H (3 × H-21); 1·01 s, 3 H (3 × H-19); 0·59 s, 3 H (3 × H-18).

(20*E*)-3β-*Hydroxy*-24-*nor*-5,14,20(22)-*cholatriene*-23-*nitrile* (IIIb): Reaction of *IIb* (900 mg; 2·4 mmol), followed by chromatography in benzene–acetone (100 : 1), yielded *IIIb* (544 mg, 68%), m.p. 187—189°C (hexane), $[\alpha]_D$ −93° (*c* 0·3, chloroform). IR spectrum (chloroform): 3 610, 3 460 (OH), 2 217, 1 618 (C=C—C≡N); 1 672, 1 645 (C=C). ^{1}H NMR spectrum (deuteriochloroform): 5·40 m, 1 H (H-6); 5·20 bs, 2 H (H-15, H-22); 3·48 m, 1 H (H-3, W = 30); 2·11 s, 3 H (3 × H-21); 1·02 s, 3 H (3 × H-19); 0·80 s, 3 H (3 × H-18). For $C_{23}H_{31}NO$ (337·5) calculated: 81·85% C, 9·26% H, 4·15% N; found: 81·51% C, 9·14% H, 3·93% N.

(20*E*)-3β-*Hydroxy*-24-*nor*-5α-*chol*-20(22)-*ene*-23-*nitrile* (IIIc): Reaction of *IIc* (720 mg; 1·9 mmol), followed by crystallization from ethanol, gave 550 mg (86%) of *IIIc*, m.p. 211—212°C (sublimation at 200°C), $[\alpha]_D$ +15° (*c* 0·3, chloroform). IR spectrum (chloroform): 3 610, 3 460 (OH); 2 217, 1 618 (C=C—C≡N). ^{1}H NMR spectrum (deuteriochloroform): 5·11 bs, 1 H (H-22); 3·57 m, 1 H (H-3, W = 40); 2·07 s, 3 H (3 × H-21); 0·80 s, 3 H (3 × H-19); 0·56 s, 3 H (3 × H-18). For $C_{23}H_{35}NO$ (341·5) calculated: 80·89% C, 10·33% H, 4·10% N; found: 80·90% C, 10·36% H, 3·92% N.

(20*E*)-3β-*Hydroxy*-24-*nor*-5β-*chol*-20(22)-*ene*-23-*nitrile* (IIId): Reaction of *IId* (1·0 g; 2·6 mmol), followed by chromatography in benzene–acetone (25 : 1), afforded 775 mg (88%) of *IIId*, m.p. 185—186°C (ethanol), $[\alpha]_D$ +22° (*c* 0·2, chloroform). IR spectrum (chloroform): 3 615, 3 470 (OH); 2 217, 1 618 (C=C—C≡N). ^{1}H NMR spectrum (deuteriochloroform): 5·13 bs, 1 H (H-22); 4·12 m, 1 H (H-3); 2·08 s, 3 H (3 × H-21); 0·97 s, 3 H (3 × H-19); 0·57 s, 3 H (3 × H-18).

For $C_{23}H_{35}NO$ (341·5) calculated: 80·89% C, 10·33% H, 4·10% N; found: 81·11% C, 10·34% H, 3·90% N.

Preparation of β-Glucosides *IVa–IVd*

A dry mixture of *III*, silver silicate[2] (1·2 g), and ground molecular sieve 4A (1·4 g) in a dark flask were stirred *in vacuo* (10 Pa) for 1 h. The flask was then filled with argon under slight overpressure (about 5–10 kPa) and 1,2-dichloroethane (8 ml) was injected through a septum. The mixture was stirred for 30 min and then cooled in an ice bath. A solution of 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide in 1,2-dichloroethane (2 ml) was added (septum). After stirring at room temperature for 24 h, the catalyst was removed by filtration through a column of silica gel (layered with Celite). The column was washed with chloroform, the solution filtered and the solvent evaporated. The residue was coevaporated several times with ethanol and allowed to stand with triethylamine–methanol–water (10 : 10 : 1; 30 ml) for 72 h. The solvents were evaporated, the residue codistilled with ethanol, dissolved in chloroform–methanol (10 : 1) and filtered through a column of silica gel. The thus-obtained glucoside *IV* was further purified by chromatography on a silica gel column (100 g) and by crystallization.

(20*E*)-22-*Cyano*-23,24-*dinor*-5,20(22)-*choladien*-3β-*yl* β-D-*glucopyranoside* (IVa): Reaction of *IIIa* (280 mg; 0·82 mmol) with glucosyl bromide (600 mg; 1·5 mmol), followed by chromatography in chloroform–methanol (20 : 1), afforded 370 mg (89%) of *IVa*, m.p. 264–268°C (methanol); $[\alpha]_D$ −51° (*c* 0·2, methanol). IR spectrum (KBr pellet): 3 440 (OH); 2 218, 1 620 (C═C—C≡N). ^{1}H NMR spectrum (hexadeuteriodimethyl sulfoxide, 200 MHz, 50°C): 5·40 bs, 1 H (H-22); 5·32 bd, 1 H (H-6, J = 4·9); 4·70 d, 1 H (OH, J = 4·2); 4·69 d, 1 H (OH, J = 4·9); 4·68 d, 1 H (OH, J = 4·6); 4·26 t, 1 H (OH, J = 5·8); 4·23 d, 1 H (H-1′, J(1′, 2′) = 7·8); 2·02 d, 3 H (3 × H-21, J = 0·7); 0·97 s, 3 H (3 × H-19); 0·56 s, 3 H (3 × H-18). ^{1}H NMR spectrum (pentadeuteriopyridine, 200 MHz): 5·30 bd, 1 H (H-6, J = 4·0); 5·26 bs, 1 H (H-22); 4·99 d, 1 H (H-1′, J(1′, 2′) = 7·7); 4·52 dd, 1 H (H-6a′, J(6a′, 6b′) = 11·9; J(5′, 6a′) = 2·4); 4·35 dd, 1 H (H-6b′, J(6a′, 6b′) = 11·9; J(5′, 6b′) = 5·2); 4·25 system of higher order, 2 H (H-3′, H-4′, W = 30); 1·99 s, 3 H (3 × H-21); 0·88 s, 3 H (3 × H-19); 0·45 s, 3 H (3 × H-18). ^{13}C NMR spectrum: see Table II. For $C_{29}H_{43}NO_6$ (501·7) calculated: 69·43% C, 8·64% H, 2·79% N; found: 69·15% C, 8·54% H, 2·63% N.

(20*E*)-22-*Cyano*-23,24-*dinor*-5,14,20(22)-*cholatrien*-3β-*yl* β-D-*glucopyranoside* (IVb): Reaction of *IIIb* (280 mg; 0·83 mmol) with glucosyl bromide (600 mg; 1·5 mmol) and subsequent chromatography in chloroform–methanol (25 : 1) gave 320 mg (77%) of *IVb*, m.p. 282–285°C (methanol), $[\alpha]_D$ −62° (*c* 0·3, methanol). IR spectrum (KBr pellet): 3 440, 3 250 sh (OH); 2 220, 1 625 (C═C—C≡N), 1 650 sh (C═C). ^{1}H NMR spectrum (hexadeuteriodimethyl sulfoxide, 200 MHz): 5·53 bs, 1 H (H-22); 5·39 bs, 1 H (H-6); 5·23 bs, 1 H (H-15); 4·90 d, 1 H (OH, J = 4·3); 4·89 d, 1 H (OH, J = 4·3); 4·87 d, 1 H (OH, J = 4·6); 4·44 t, 1 H (OH, J = 5·8); 4·23 d, 1 H (H-1′, J(1′, 2′) = 7·5), 2·00 s, 3 H (3 × H-21); 0·98 s, 3 H (3 × H-19); 0·75 s, 3 H (3 × H-18). ^{13}C NMR spectrum: see Table II. For $C_{29}H_{41}NO_6$ (499·7) calculated: 69·71% C, 8·27% H, 2·80% N; found: 69·50% C, 8·14% H, 2·69% N.

(20*E*)-22-*Cyano*-23,24-*dinor*-5α-*chol*-20(22)-*en*-3β-*yl* β-D-*glucopyranoside* (IVc): Reaction of *IIIc* (268 mg; 0·78 mmol) with glucosyl bromide (560 mg; 1·4 mmol), followed by chromatography in chloroform–methanol (10 : 1), yielded 350 mg (89%) of IVc, m.p. 262–265°C (methanol). IR spectrum (KBr pellet): 3 560, 3 420 (OH); 2 218, 1 620 (C═C—C≡N). ^{1}H NMR spectrum (hexadeuteriodimethyl sulfoxide, 200 MHz, 50°C): 5·39 s, 1 H (H-22); 4·69 d, 2 H (2 × OH, J = 4·3); 4·64 d, 1 H (OH, J = 4·6); 4·25 t, 1 H (OH, J = 5·8); 4·22 d, 1 H (H-1′, J(1′, 2′) = = 7·7); 2·00 s, 3 H (2 × H-21); 0·77 s, 3 H (3 × H-19); 0·53 s, 3 H (3 × H-18). ^{13}C NMR

spectrum: see Table II. For $C_{29}H_{45}NO_6$ (503·7) calculated: 69·15% C, 9·01% H, 2·78% N; found: 69·01% C, 9·05% H, 2·63% N.

(20*E*)-22-*Cyano*-23,24-*dinor*-5β-*chol*-20(22)-*en*-3β-*yl* β-D-*glucopyranoside* (IVd): Reaction of *IIId* (438 mg; 1·3 mmol) with glucosyl bromide (790 mg; 1·9 mmol) and subsequent chromatography on silica gel in chloroform–methanol (25 : 1) afforded 567 mg (88%) of *IVd*, m.p. 262 to 264°C (methanol), $[\alpha]_D$ 0° (*c* 0·3, methanol). IR spectrum (KBr pellet): 3 590, 3 430, 3 345 (OH); 2 215, 1 618 (C═C—C≡N). ^{1}H NMR spectrum (hexadeuteriodimethyl sulfoxide, 200 MHz): 5·43 s, 1 H (H-22); 4·86 d, 2 H (2 × OH, J = 4·3); 4·80 d, 1 H (OH, J = 4·8); 4·39 t, 1 H (OH, J = 5·6); 4·14 d, 1 H (H-1′, J(1′, 2′) = 7·9); 3·93 m, 1 H (H-3); 3·70 dd, 1 H (H-6a′, J(6a′, 6b′) = = 11·4, J(6a′, 5) = 4·8); 2·01 s, 3 H (3 × H-21); 0·90 s, 3 H (3 × H-19), 0·51 s, 3 H (3 × H-18). ^{13}C NMR spectrum: see Table II. For $C_{29}H_{45}NO_6$ (503·7) calculated: 69·15% C, 9·01% H, 2·78% N; found: 68·94% C, 8·96% H, 2·63% N.

Preparation of 2-(Trimethylsilyl)ethyl Butanedioates *Va—Vd*

2-(Trimethylsilyl)ethyl hydrogen butanedioate[13] (188 mg; 0·86 mmol), 4-dimethylaminopyridine (3 mg), and a solution of N,N′-dicyclohexylcarbodiimide (103 mg; 0·50 mmol) in benzene (1 ml) were added to a solution of *III* in benzene (7 ml). After stirring for 5 h at room temperature, the mixture was diluted with light petroleum (10 ml), the separated N,N′-dicyclohexylurea was filtered off and the solution was taken down *in vacuo*. The residue was chromatographed on a column of silica gel (18 g). Non-polar impurities were washed out with light petroleum–benzene–ether (50 : 49 : 1), the product *V* was eluted with light petroleum–benzene–ether (50 : 47 : 3).

(20*E*)-22-*Cyano*-23,24-*dinor*-5,20(22)-*choladien*-3β-*yl* 2-(*trimethylsilyl*)*ethyl butanedioate* (Va): Reaction of *IIIa* (154 mg; 0·45 mmol) afforded 235 mg (96%) of *Va*, m.p. 96—98°C, $[\alpha]_D$ −31° (*c* 1·4, chloroform). IR spectrum (tetrachloromethane): 2 220, 1 620 (C═C—C≡N); 1 738 (COOR); 1 252, 860, 840 (Si$(CH_3)_3$). ^{1}H NMR spectrum (deuteriochloroform, external lock): 5·34 bd, 1 H (H-6, J = 4); 5·11 bs, 1 H (H-22); 4·58 m, 1 H (H-3, W = 36); 4·14 m, 2 H (COO. .CH_2CH_2Si, W = 17); 2·56 s, 4 H (OOCCH_2CH_2COO); 2·06 s, 3 H (3 × H-21); 0·98 s, 3 H (3 × H-19); 0·56 s, 3 H (3 × H-18); 0·02 s, 9 H (Si$(CH_3)_3$). For $C_{32}H_{49}NO_4Si$ (539·8) calculated: 71·20% C, 9·15% H, 2·59% N; found: 71·28% C, 9·13% H, 2·41% N.

(20*E*)-22-*Cyano*-23,24-*dinor*-5,14,20(22)-*cholatrien*-3β-*yl* 2-(*trimethylsilyl*)*ethyl butanedioate* (Vb): Reaction of *IIIb* (152 mg; 0·45 mmol) afforded 229 mg (95%) of *Vb*, m.p. 85—86°C, $[\alpha]_D$ −52° (*c* 1·4, chloroform). IR spectrum (tetrachloromethane): 2 220, 1 621 (C═C—C≡N); 1 739 (COOR); 1 251, 860, 841 (Si$(CH_3)_3$). ^{1}H NMR spectrum (deuteriochloroform, external lock): 5·42 m, 1 H (H-6); 5·22 bs, 2 H (H-15, H-22); 4·62 m, 1 H (H-3); 4·19 m, 2 H (COOCH_2CH_2Si, W = 17); 2·61 s, 4 H (OOCCH_2CH_2COO); 2·13 s, 3 H (3 × H-21); 1·05 s, 3 H (3 × H-19); 0·81 s, 3 H (3 × H-18); 0·07 s, 9 H (Si$(CH_3)_3$). For $C_{32}H_{47}NO_4Si$ (537·8) calculated: 71·47% C, 8·81% H, 2·60% N; found: 71·62% C, 9·03% H, 2·45% N.

(20*E*)-22-*Cyano*-23,24-*dinor*-5α-*chol*-20(22)-*en*-3β-*yl* 2-(*trimethylsilyl*)*ethyl butanedioate* (Vc): Reaction of *IIIc* (154 mg; 0·45 mmol) yielded 236 mg (97%) of *Vc*, m.p. 54—57°C, $[\alpha]_D$ +4° (*c* 1·4, chloroform). IR spectrum (tetrachloromethane): 2 217, 1 618 (C═C—C≡N); 1 733, 1 163 (COOR); 1 259, 859, 838 (Si$(CH_3)_3$). ^{1}H NMR spectrum (deuteriochloroform, external lock): 5·14 bs, 1 H (H-22); 4·71 m, 1 H (H-3); 4·19 m, 2 H (COOCH_2CH_2Si, W = 17); 2·61 s, 4 H (OOCCH_2CH_2COO); 2·10 s, 3 H (3 × H-21); 0·86 s, 3 H (3 × H-19); 0·60 s, 3 H (3 × H-18); 0·09 s, 9 H (Si$(CH_3)_3$). For $C_{32}H_{51}NO_4Si$ (541·9) calculated: 70·93% C, 9·49% H, 2·58% N; found: 70·67% C, 9·63% H, 2·61% N.

(20*E*)-22-*Cyano*-23,24-*dinor*-5β-*chol*-20(22)-*en*-3β-*yl* 2-(*trimethylsilyl*)*ethyl butanedioate* (Vd): Reaction of *IIId* (154 mg; 0·45 mmol) gave 235 mg (96%) of oily *Vd*, $[\alpha]_D$ +19° (*c* 1·7, chloroform). IR spectrum (tetrachloromethane): 2 220, 1 620 (C═C—C≡N); 1 737 (COOR); 1 251, 860, 841 ($Si(CH_3)_3$). ^{1}H NMR spectrum (deuteriochloroform, external lock): 5·14 m, 2 H (H-3, H-22); 4·19 m, 2 H ($COOCH_2CH_2Si$, W = 17); 2·56 s, 4 H ($OOCCH_2CH_2COO$); 2·17 s, 3 H (3 × H-21); 0·99 s, 3 H (3 × H-19); 0·58 s, 3 H (3 × H-18); 0·06 s, 9 H ($Si(CH_3)_3$). For $C_{32}H_{51}NO_4Si$ (541·9) calculated: 70·93% C, 9·49% H, 2·58% N; found: 71·15% C, 9·65% H, 2·35% N.

Preparation of Hydrogen Butanedioates *VIa*—*VId*

A solution of tetrabutylammonium fluoride in tetrahydrofuran (0·7 ml; *c* 1 mol l^{-1}) was added to a solution of the butanedioate *V* in tetrahydrofuran (5 ml). After stirring at room temperature for 5 h, the mixture was diluted with benzene (100 ml), washed with 10% sulfuric acid (2×), water (2×), dried over anhydrous sodium sulfate and taken down. The product *VI* was obtained by crystallization of the residue from dichloromethane–light petroleum.

(20*E*)-22-*Cyano*-23,24-*dinor*-5,20(22)-*choladien*-3β-*yl hydrogen butanedioate* (VIa): Reaction of *Va* (189 mg; 0·35 mmol) afforded 129 mg (84%) of *VIa*, m.p. 179—182°C, $[\alpha]_D$ −45° (*c* 1·1, chloroform). IR spectrum (chloroform): 3 500—2 500, 1 724 (COOH); 2 220, 1 618 (C═C—C≡N); 1 724 (COOR). ^{1}H NMR spectrum (deuteriochloroform): 5·38 m, 1 H (H-6); 5·13 bs, 1 H (H-22); 4·60 m, 1 H (H-3, W = 36); 2·62 bs, 4 H ($OOCCH_2CH_2COO$); 2·08 s, 3 H (3 × H-21); 1·03 s, 3 H (3 × H-19); 0·60 s, 3 H (3 × H-18). For $C_{27}H_{37}NO_4$ (439·6) calculated: 73·77% C, 8·48% H, 3·19% N; found: 73·56% C, 8·49% H, 3·08% N.

(20*E*)-22-*Cyano*-23,24-*dinor*-5,14,20(22)-*cholatrien*-3β-*yl hydrogen butanedioate* (VIb): Reaction of *Vb* (188 mg; 0·35 mmol) gave 103 mg (67%) of *VIb*, m.p. 176—179°C, $[\alpha]_D$ −68° (*c* 1·7, chloroform). IR spectrum (chloroform): 3 500—2 500, 1 726 (COOH); 2 220, 1 618 (C═C—C≡N); 1 726 (COOR). ^{1}H NMR spectrum (deuteriochloroform): 5·43 m, 1 H (H-6); 5·22 bs, 2 H (H-15, H-22); 4·62 m, 1 H (H-3, W = 36); 2·64 bs, 4 H ($OOCCH_2CH_2COO$); 2·12 s, 3 H (3 × H-21); 1·04 s, 3 H (3 × H-19); 0·80 s, 3 H (3 × H-18). For $C_{27}H_{35}NO_4$ (437·6) calculated: 74·11% C, 8·06% H, 3·20% N; found: 74·38% C, 7·98% H, 3·09% N.

(20*E*)-22-*Cyano*-23,24-*dinor*-5α-*chol*-20(22)-*en*-3β-*yl hydrogen butanedioate* (VIc): Reaction of *Vc* (190 mg; 0·35 mmol) yielded 118 mg (76%) of *VIc*, m.p. 160—163°C, $[\alpha]_D$ +8° (*c* 1·5, chloroform). IR spectrum (chloroform): 3 500—2 500, 1 718 (COOH); 2 220, 1 618 (C═C—C≡N); 1 718 (COOR). ^{1}H NMR spectrum (deuteriochloroform): 5·13 bs, 1 H (H-22); 4·71 m, 1 H (H-3); 2·62 bs, 4 H ($OOCCH_2CH_2COO$); 2·08 s, 3 H (3 × H-21); 0·82 s, 3 H (3 × H-19); 0·56 s, 3 H (3 × H-18). For $C_{27}H_{39}NO_4$ (441·6) calculated: 73·44% C, 8·90% H, 3·17% N; found: 73·35% C, 8·67% H, 3·25% N.

(20*E*)-22-*Cyano*-23,24-*dinor*-5β-*chol*-20(22)-*en*-3β-*yl hydrogen butanedioate* (VId): Reaction of *Vd* (190 mg; 0·35 mmol) afforded 120 mg (78%) of *VId*, m.p. 95—100°C, $[\alpha]_D$ +15° (*c* 1·4, chloroform). IR spectrum (chloroform): 3 500—2 500, 1 723 (COOH); 2 220, 1 618 (C═C—C≡N); 1 723 (COOR). ^{1}H NMR spectrum (deuteriochloroform): 5·13 m, 2 H (H-3, H-22); 2·65 s, 4 H ($OOCCH_2CH_2COO$); 2·08 s, 3 H (3 × H-21); 0·98 s, 3 H (3 × H-19); 0·57 s, 3 H (3 × H-18). For $C_{27}H_{39}NO_4$ (441·6) calculated: 73·44% C, 8·90% H, 3·17% N; found: 73·76% C, 8·64% H, 2·90% N.

5-Pregnen-20-on-3β-yl β-D-Glucopyranoside (*IX*)

A dry mixture of pregnenolone *VIII* (2·96 g; 9·32 mmol), silver silicate (6 g) and ground molecular

sieve 4A (6 g) was stirred *in vacuo* (10 Pa) for 2 h. 1,2-Dichloroethane (60 ml) was added under argon through a septum and the mixture was stirred for 1 h. After cooling to 0°C, a solution of 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (6·5 g; 15·8 mmol) in 1,2-dichloroethane (8 ml) was added and the mixture was stirred at room temperature for 24 h. The solid material was removed by filtration through Celite and washed with dichloromethane, the filtrate was washed with saturated solution of potassium hydrogen carbonate, dried over sodium sulfate and taken down. The residue was coevaporated with toleune, dried *in vacuo* and dissolved in benzene (20 ml). The solution was diluted with methanol (200 ml) and a solution of sodium methoxide (*c* 1 mol l^{-1}; 0·5 ml) was added with stirring. After standing at room temperature for 48 h, the mixture was concentrated to a small volume, filtered through a column of silica gel (layered with Celite) which was then washed with chloroform–methanol (10 : 1). Further purification by chromatography on a silica gel column (120 g) in chloroform–methanol (20 : 1) yielded 3·57 g (80%) of *IX*, m.p. 270—275°C, whose properties as well as properties of its tetraacetate (m.p. 221—223°C) agreed with the literature data: for *IX* reported[9] m.p. 270—278°C, for its tetraacetate m.p. 190—192°C (ref.[9]) and 216—218°C (ref.[10]).

5-Pregnen-20-on-3β-yl 2,3,4,6-Tetra-O-methoxymethyl-β-D-glucopyranoside (*X*)

A mixture of glucoside *IX* (1·0 g; 2·1 mmol), dichloromethane (15 ml), diisopropylamine (3·7 ml; 21 mmol) and chloromethyl methyl ether (1·5 ml; 20 mmol) was stirred to homogeneity and then set aside for 5 days. The reaction was followed by TLC in chloroform–ethanol (50 : 1). The solution was diluted with dichloromethane, washed with water, 5% hydrochloric acid, saturated solution of potassium hydrogen carbonate and dried over sodium sulfate. After evaporation of the solvent, the residue was dissolved in dichloromethane, filtered through an alumina column, washed out with dichloromethane and crystallized from ethanol; yield 800 mg (38%) of *X*, m.p. 98—99°C, $[\alpha]_D$ +20° (*c* 0·2, chloroform). IR spectrum (chloroform): 1 698 (C=O); 1 152, 1 102, 1 032, 920 (CH_3OCH_2). ^{1}H NMR spectrum (deuteriochloroform, 200 MHz): 5·34 bd, 1 H (H-6, J = 5·3); 4·92 and 4·83, AB system, 2 H (CH_3OCH_2, J(A, B) = 6·2); 4·92 and 4·77, AB system, 2 H (CH_3OCH_2, J(A, B) = 6·2); 4·87 and 4·73, AB system, 2 H (CH_3OCH_2, J(A, B) = 6·4); 4·67 s, 2 H (CH_3OCH_2); 4·41 d, 1 H (H-1′, J(1′, 2′) = 7·7); 3·87 dd, 1 H (H-6a′, J(6a′, 6b′) = 11·4; J(6a′, 5′) = 1·9); 3·68 dd, 1 H (H-6b′, J(6a′, 6b′) = 11·4; J(6b′, 5′) = 5·0); 3·45, 3·44, 3·42, and 3·37, 4 × s, 4 × 3 H (4 × CH_3OCH_2); 2·12 s, 3 H (3 × H-21); 0·99 s, 3 H (3 × H-19); 0·63 s, 3 H (3 × H-18). For $C_{35}H_{58}O_{11}$ (654·8) calculated: 64·20% C, 8·93% H; found: 64·01% C, 8·90% H.

(20*E*)-22-Cyano-23,24-dinor-5,20(22)-choladien-3β-yl
2,3,4,6-Tetra-O-methoxymethyl-β-D-glucopyranoside (*XI*)

A mixture of *X* (660 mg; 1·0 mmol), sodium hydride (145 mg; 3·0 mmol), diethyl cyanomethylphosphonate (0·55 ml; 3·1 mmol) reacted as described for the preparation of compounds *II*. Chromatography on silica gel in chloroform–methanol (25 : 1) gave 610 mg (90%) of the oily *XI*; $[\alpha]_D$ −10° (*c* 0·2, chloroform). IR spectrum (chloroform): 2 215, 1 618 (C=C—C≡N); 1 152, 1 102, 1 032, 920 (CH_3OCH_2). ^{1}H NMR spectrum (deuteriochloroform, 200 MHz): 5·34 bd, 1 H (H-6, J = 4·9); 5·14 p, 1 H (H-22, J = 1·1); 4·92 and 4·76, AB system, 2 H (CH_3OCH_2, J(A, B) = 6·2), 4·91 and 4·83, AB system, 2 H (CH_3OCH_2, J(A, B) = 6·4); 4·87 and 4·73, AB system, 2 H (CH_3OCH_2, J(A, B) = 6·4); 4·66 s, 2 H (CH_3OCH_2); 4·41 d, 1 H (H-1′, J(1′, 2′) = = 7·6); 3·87 dd, 1 H (H-6a′, J(6a′, 6b′) = 11·1, J(6a′, 5′) = 1·7); 3·68 dd, 1 H (H-6b′, J(6a′, 6b′)= = 11·2, J(6b′, 5′) = 5·0); 3·45, 3·44, 3·42, 3·36 × s, 4 × 3 H (4 × CH_3OCH_2); 2·19 d, 3 H (3 × H-21, J = 1·1); 0·99 s, 3 H (3 × H-19); 0·59 s, 3 H (3 × H-18). ^{13}C NMR spectrum see

Table II. For $C_{37}H_{59}NO_{10}$ (677·9) calculated: 65·56% C, 8·77% H, 2·07% N; found: 65·45% C, 8·70% H, 2·01% N.

Preparation of Glucoside *IVa via* Trimethylsilyl Derivative *XII*

Glucoside *IX* (262 mg; 0·55 mmol) in pyridine (5 ml) was silylated with hexamethyldisilazane (1·5 ml; 7·1 mmol) and chlorotrimethylsilane (1 drop) at room temperature overnight. The mixture was concentrated, coevaporated with benzene and the residue was dissolved in benzene and filtered through a column of Celite, pre-washed with benzene. After elution with benzene, the solvent was evaporated and the product *XII* was treated with the phosphonate salt (prepared from sodium hydride (144 mg; 3 mmol) and diethyl cyanomethylphosphonate (0·5 ml; 3 mmol)) in the same manner as described for the preparation of nitriles *II*. After the end of reaction, the mixture was taken down, the residue was coevaporated with benzene, dissolved in chloroform (10 ml), and tetrahydrofuran (10 ml) and acetic acid (1 ml) were added. The mixture was taken down and the residue was coevaporated several times with ethanol and dried *in vacuo* over sodium hydroxide. Chromatography on a column of silica gel in chloroform–methanol (25 : 1) afforded 201 mg (73%) of *IVa*, m.p. 262—268°C (methanol); IR spectrum identical with that of *IVa* prepared above.

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