# PREPARATION AND ABSOLUTE CONFIGURATION AT $C_{(22)}$ OF 21,26,27-TRINOR-5α-CHOLESTANE-22,25-DIOL DERIVATIVES*

Vladimír POUZAR, Soňa VAŠÍČKOVÁ, Pavel DRAŠAR, Ivan ČERNÝ and Miroslav HAVEL

*Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, 166 10 Prague*

Received January 17th, 1983

Reaction of 5α-pregnan-21-al (*V*), obtained from ester of the corresponding acid *III via* the alcohol *IV*, with lithium salt of 1-methoxymethoxy-2-propyne afforded both the isomeric 25-methoxymethoxy-21,26,27-trinor-5α-cholest-23-yn-22-ols (*VI* and *VIII*) which were converted into two 21,26,27-trinor-5α-cholestane-22,25-diols (*XI*, *XV*). Absolute configuration of the alcohols *X* and *XIV* was assigned by chemical correlation with derivatives *XXVI* and *XXVII* of known absolute configuration at $C_{(20)}$. The correlation was based on reduction of thiocarbonates derived from the diols *XXII* and *XXIV* for which also Cotton effects of their complexes with nickel acetylacetonate were studied. Both diols were prepared from 5α-pregnan-20-one (*XVIII*) via 5α-pregn-20-yne (*XIX*) and the 21,26,27-trinor-5α-cholest-20-ene derivative *XXI*.

In our previous papers we described the preparation and determination of absolute configuration at $C_{(20)}$ of 20,24-disubstited 21-nor-5α-cholane derivatives[1-4] and 20,25-disubstituted 21,26,27-trinor-5α-cholestane derivatives[5]. In connection with the planned synthesis of 21,26,27-trinor-5α-cholestan-25→22-olide derivatives, preparation of 21,26,27-trinor-5α-cholestane-22,25-diol and assignment of absolute configuration at $C_{(22)}$ was desirable.

For construction of the five-carbon side chain in position 17β, the aldehyde *V*, containing a two-carbon chain with terminal carbonyl in the position 21, was condensed with a three-carbon synthone, bearing an organometallic moiety on its one end and a protected hydroxyl on the other. The aldehyde *V* was synthesized starting from the methyl ester *I* (ref.[6]). The 3β-hydroxyl in compound *I* was removed by the usual procedure[7,8] *via* the methanesulfonate *II*. The resulting methyl ester *III* was reduced with lithium aluminium hydride to give the alcohol *IV*. Its oxidation with pyridinium chlorochromate afforded the aldehyde *V* in the overall yield of 59%. As the second reaction component we have chosen lithium salt of 1-methoxymethoxy-2-propyne, prepared by treatment of the alkyne with 1-butyllithium in tetrahydro-

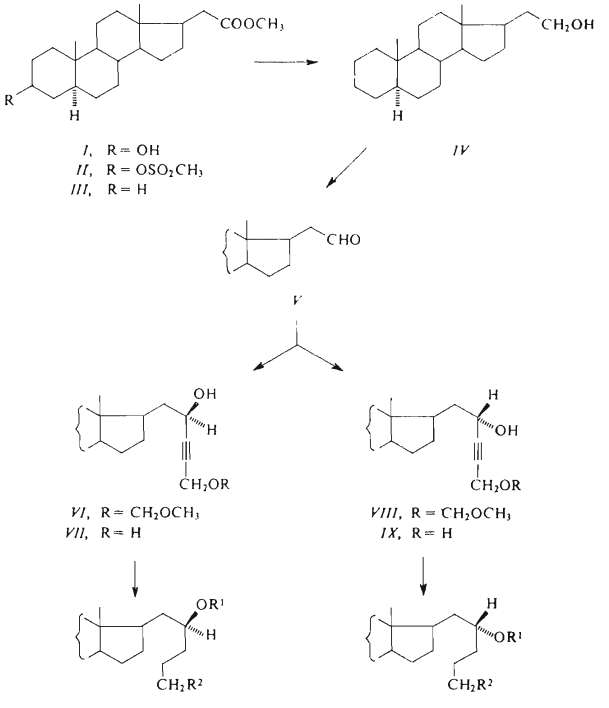
* Part CCLXXXVII in the series On Steroids; Part CCLXXXVI: This Journal *48*, 2064 (1983).

furan. 1-Methoxymethoxy-2-propyne was obtained by reaction of propargyl alcohol with chloromethyl methyl ether in the presence of N,N-dimethylaniline in dichloromethane[9]. The equimolecular mixture of hydroxy derivatives *VI* and *VIII* was separated by preparative thin-layer chromatography. Structure of these products was confirmed by $^1$H NMR spectra: shifts of the protons in positions 22 and 25 correspond to analogous structures, described previously[3,4] and the singlets at 3·37 and 4·69 show the presence of an $-OCH_2OCH_3$ grouping. Hydrogenation of the less polar hydroxy derivative *VI* afforded the saturated hydroxy derivative *X*. The absence of any 23,24-multiple bond is indicated by the chemical shifts of the 22- and 25-protons. The protecting group in position 25 was removed with hydrochloric acid in a mixture of methanol and benzene[5] to give the diol *XI*. The more polar hydroxy derivative *VIII* was analogously converted into the diol *XV via* the intermediate *XIV*. When the protecting group in position 25 of the hydroxy derivative *VI* was removed first and the resulting acetylenic diol *VII* was hydrogenated under analogous conditions, the product contained, in addition to the saturated diol *XI*, the alcohol *XII*, arising by hydrogenolysis of the terminal hydroxy group. We have observed this reaction with analogous acetylenic diols already previously[3]. The same procedure, when applied to the more polar hydroxy derivative *VIII*, afforded the acetylenic diol *IX* which on hydrogenation gave the diol *XV* and the alcohol *XVI*.

The structure of the alcohols *XII* and *XVI* was confirmed by their preparation from the aldehyde *V* and propylmagnesium bromide. This reaction furnished equal amounts of both the alcohols which were separated by preparative thin-layer chromatography. Benzoylation of the less polar alcohol *XII* gave the benzoate *XIII*, the more polar alcohol *XVI* afforded the benzoate *XVII*. We tried to determine the absolute configuration at $C_{(22)}$ in alcohols *XII* and *XVI* and the benzoates *XIII* and *XVII* on the basis of the parameter $\Delta M_D = \Delta M_{D(\text{benzoate})} - M_{D(\text{alcohol})}$. For the pairs *XII*, *XIII* and *XVI*, *XVII* the value of $\Delta M_D$ was $-12°$ and $-57°$, respectively. As evident, an application of the known rules[10] to this case was not possible.

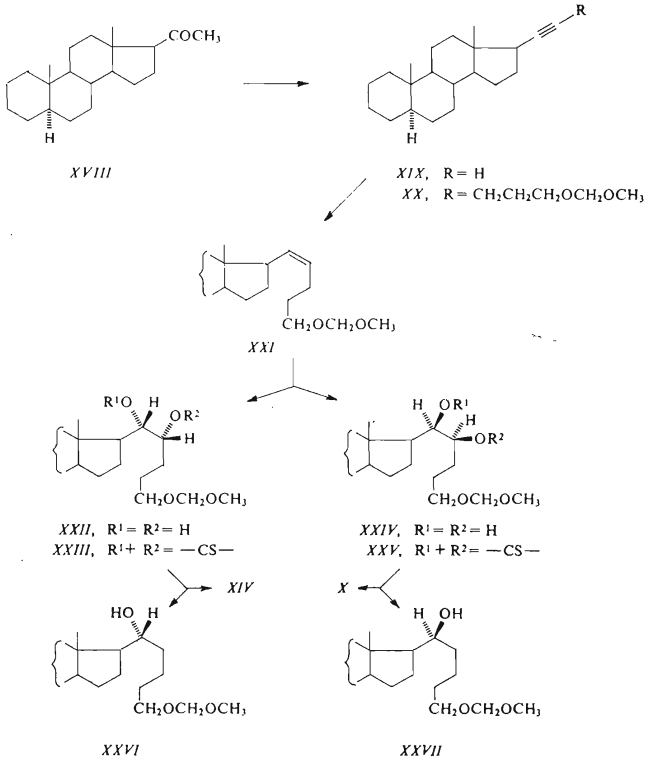
We tried therefore to correlate chemically the 22-substituted derivatives with 20-substituted derivatives of known configuration. The ketone *XVIII* was converted with lithium diisopropylamide into its enolate. Its reaction with diethyl chlorophosphate afforded the corresponding enol phosphate which with excess of lithium diisopropylamide[11] was transformed into the acetylene *XIX*. The three-carbon synthone, required for further synthesis of the side-chain, *i.e.* 3-iodo-1-methoxymethoxyl propane, was obtained by reaction of 1-hydroxy-3-iodopropane with chloromethyl methyl ether and N,N-dimethylaniline in benzene. The acetylene *XIX* was treated with 1-butyllithium in tetrahydrofuran to give the lithium salt which was added to a solution of 3-iodo-1-methoxymethoxypropane in a mixture of tetrahydrofuran and hexamethylphosphoric triamide, affording the acetylene *XX* in a low yield (20%). Molecular peak 386 in the mass spectrum of *XX* confirms that to the original molecule of the acetylene *XIX* the $CH_2CH_2CH_2OCH_2OCH_3$ moiety was attached.

Also the $^1$H NMR spectrum of compound *XX* displays signals due to the —$CH_2$. .$OCH_2OCH_3$ grouping. Hydrogenation of the acetylene *XX* over P2 nickel in the presence of diaminoethane[12] gave the olefin *XXI*. The molecular ion 388 in its mass spectrum and two olefinic proton signals in the $^1$H NMR spectrum correspond to a double bond in the molecule. The *cis*-relation of the hydrogens at the double bond follows from the known steric course of hydrogenations of acetylenes over P2 nickel[12]. Hydroxylation of the olefin *XXI* with osmium tetroxide in pyridine pro-



duced two diols which were separated by thin-layer chromatography. The less polar diol *XXII* was obtained in a 57% yield whereas its more polar isomer *XXIV* in a 40% yield. Since the reaction is a *syn*-addition, only two isomers (20*S*, 22*R* and 20*R*, 22*S*) can be formed.

On treatment with 1,1'-thiocarbonyldimidazole in boiling toluene[13], the diol *XXII* afforded the thiocarbonate *XXIII* which was reduced with tributyltin hydride[14] to give the alcohols *XIV* and *XXVI*. Since the alcohol *XXVI* is known[5] to have 20*R* configuration, configuration of the diol *XXII* is 20*S*,22*R* and the alcohol *XIV* has the



22*R* configuration. The same procedure was applied to the conversion of the diol *XXIV* into the thiocarbonate *XXV* which was reduced into the alcohols *X* and *XXVII*. From the known[5] 20*S* configuration of the alcohol *XXVII* we derived configuration 20*R*,22*S* for the diol *XXIV* and 22*S* for the alcohol *X*.

We investigated also chiroptical properties of complexes of the diols *XXII* and *XXIV* with nickel acetylacetonate[15], The measured values of the CD maxima are $\Delta\varepsilon_{317}$ −1·38 and $\Delta\varepsilon_{317}$ +0·97 for *XXII* and *XXIV*, respectively. The possible arrangements of the diols *XXII* and *XXIV* in the complex are depicted in Fig. 1 and 2. Since the conformations in Fig. 1*a* and 2*a* are destabilized by non-bonded interaction of the bulky steroid moiety with the other ligands, only conformers depicted in Fig. 1*b* and 2*b* may be considered for interpretation of the observed Cotton effects. The diol *XXII* forms a complex with a negative Cotton effect and therefore the considered segment has *P* helicity, shown in Fig. 1*b*, *i.e.* compound *XXII* has 20*S*,22*R*-configuration. On the other hand, the complex of the diol *XXIV* exhibits a positive

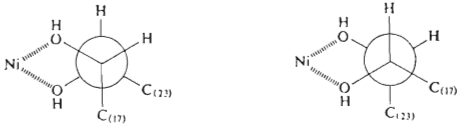



FIG. 1
Conformations of nickel(II) complex of diol *XXII*

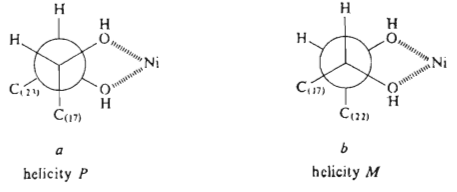



FIG. 2
Conformations of nickel(II) complex of diol *XXIV*

Cotton effect, corresponding to an *M* helicity (Fig. 2*b*), and thus to a 20*R*,22*S*--configuration. Thus, the configurations of the diols *XXII* and *XXIV*, derived from the Cotton effects of their nickel complexes, agree with those found by chemical correlations.

## EXPERIMENTAL

Melting points were determined on a Kofler block (Boetius, GDR). Optical rotations were measured in chloroform at 25°C on a Perkin–Elmer 141 MC instrument. The IR spectra were recorded on a Perkin–Elmer 580 spectrometer. CD spectra of the complexes of diols *XXII* and *XXIV* with $Ni(acac)_2$ were measured on a Dichrographe II (Roussel-Jouan) instrument under described[15] conditions. $Ni(acac)_2$ was prepared according to ref.[16]. Mass spectra were recorded on an AEI MS 901 instrument. Silica gel according to Pitra (60–120 μm) and neutral alumina

TABLE I

Characteristic $^1H$ NMR spectral parameters

| Compound[a] | $C_{(18)}$—$H_3$ | $C_{(19)}$—$H_3$ | $C_{(20)}$—H | $C_{(21)}$—H | $C_{(22)}$—H | $C_{(25)}$—$H_2$ |
|---|---|---|---|---|---|---|
| *II*[b] | 0·58 s | 0·82 s | 2·23 m[c] | — | — | — |
| *III*[d] | 0·57 s | 0·77 s | 2·23 m[c] | — | — | — |
| *IV* | 0·55 s | 0·76 s | [e] | 3·60 m[c,f] | — | — |
| *V* | 0·55 s | 0·74 s | 2·32 m[c] | 9·75 t[g] | — | — |
| *VI*[h] | 0·57 s | 0·78 s | [e] | — | 5·38 m | 4·24 bs |
| *VIII*[h] | 0·57 s | 0·77 s | [e] | — | 4·39 m | 4·24 bs |
| *X*[i] | 0·55 s | 0·77 s | [e] | — | 3·55 m[j] | 3·55 m[j] |
| *XIII*[k] | 0·58 s | 0·77 s | [e] | — | 5·15 m[l] | [e] |
| *XIV*[i] | 0·56 s | 0·78 s | [e] | — | 3·54 m[j] | 3·54 m[j] |
| *XVII*[k] | 0·56 s | 0·77 s | [e] | — | 5·13 m[m] | [e] |
| *XIX* | 0·77 s[j] | 0·77 s[j] | — | 2·06 bd[n] | — | — |
| *XX*[i] | 0·72 s | 0·77 s | — | — | — | 3·61 t[o] |
| *XXI*[i] | 0·61 s | 0·77 s | 5·32 m[j] | — | 5·32 m[j] | 3·52 t[p] |
| *XXVI*[i,r] | 0·73 s | 0·77 s | 3·50 m[j] | — | [e] | 3·50 m[j] |
| *XXVII*[i,r] | 0·65 s | 0·77 s | 3·50 m[j] | — | [e] | 3·50 m[j] |

[a] Measured in deuteriochloroform with tetramethylsilane as internal reference on a Tesla BS-467 (60 MHz) instrument. Chemical shifts are given in ppm (δ-scale). All values were obtained by first order analysis. [b] Other signals: 2·96 s ($CH_3SO_2O$), 3·63 s ($COOCH_3$), 4·59 m $W \approx 35$ Hz (3 αH). [c] Signal, corresponding to 2 H. [d] Other signal: 3·62 s ($COOCH_3$). [e] Undeterminable value. [f] $W \approx 20$ Hz. [g] $J_{20,21} = 2$ Hz. [h] Other signals: 3·37 s and 4·69 s ($OCH_2OCH_3$). [i] Other signals: 3·33–3·35 s and 4·60–4·62 s ($OCH_2OCH_3$). [j] Overlapping signals. [k] Other signals: 7·47 m and 8·05 m (benzoate). [l] $W \approx 22$ Hz. [m] $W \approx 25$ Hz. [n] $J \approx 2$ Hz. [o] $J_{24,25} = 6{\cdot}1$ Hz. [p] $J_{24,25} = 6{\cdot}5$ Hz. [r] Spectrum is identical with that of the authentic samples; see ref.[5].

(Reanal, grade II) were used for column chromatography, silica gel according to Stahl (Woelm) was employed for thin-layer chromatography (TLC). Plates with 200 × 200 × 0·7 mm silica gel layer were used for preparative thin-layer chromatography. Prior evaporation *in vacuo* (about 2 kPa), solutions in organic solvents were dried over anhydrous sodium sulfate. Reactions with hydrides or organometallic compounds were performed in an argon atmosphere. Analytical samples were dried at 50°C and 26 Pa for 12 h. The identity of compounds prepared on different routes was checked by comparison of their IR and $^1$H NMR spectra, (Table I) by TLC and mixture melting points.

Methyl 5α-Pregnan-21-oate (*III*)

Methanesulfonyl chloride (0·91 ml; 14 mmol) was added at −5°C to a solution of the hydroxy derivative *I* (ref.[6]; 1·9 g; 5·45 mmol) in pyridine (14 ml). After standing for 1 h at 0°C, the mixture was poured on ice, the separated product filtered, washed with water and dissolved in a mixture of ether (150 ml) and dichloromethane (150 ml). The solution was washed successively with dilute hydrochloric acid, water, solution of potassium hydrogen carbonate and water and taken down. The residue (2·3 g) which, according to TLC, consisted of the pure methanesulfonyl derivative *II* was dissolved in 1,2-dimethoxyethane (30 ml). After addition of water (3 ml), zinc dust (3·5 g; 53·5 mmol) and sodium iodide (3·88 g; 25·9 mmol), the stirred mixture was refluxed for 7 h, diluted with ether (300 ml) and filtered through Celite. The organic phase was washed with saturated solution of ammonium sulfate, 5% solution of sodium thiosulfate and ammonium sulfate solution and evaporated. Chromatography of the residue on a column of silica gel (80 g) in light petroleum–benzene (1 : 1) afforded 1·5 g of the crude product which on crystallization from methanol gave 1·3 g (72%) of the pure methyl ester *III*; m.p. 46–49°C; $[\alpha]_D$ +11° (*c* 0·6). IR spectrum (tetrachloromethane): 1 740 cm$^{-1}$ ($COOCH_3$). For $C_{22}H_{36}O_2$ (332·5) calculated: 79·46% C, 10·91% H; found: 79·19% C, 10·88% H.

5α-Pregnan-21-ol (*IV*)

Lithium aluminium hydride (0·4 g; 10·5 mmol) was added to a solution of the methyl ester *III* (1·25 g; 3·76 mmol) in a mixture of tetrahydrofuran (30 ml) and ether (70 ml). After refluxing for 3 h with stirring, the mixture was decomposed with water and the product was extracted with ether. The extract was washed with dilute hydrochloric acid, water, potassium hydrogen carbonate solution and water, dried and taken down. Crystallization of the residue from light petroleum afforded 1·1 g (96%) of the alcohol *IV*, m.p. 156–157°C; $[\alpha]_D$ +22° (*c* 0·4). IR spectrum (tetrachloromethane) cm$^{-1}$: 3 636 (OH). For $C_{21}H_{36}O$ (304·5) calculated: 82·83% C, 11·92% H; found: 82·53% C, 12·12% H.

1-Methoxymethoxy-2-propyne

Chloromethyl methyl ether (18·1 ml; 0·24 mol) was added at −5°C to a stirred solution of propargyl alcohol (11·2 g; 0·2 mol) and N,N-dimethylaniline (29·3 ml) in dichloromethane (60 ml) in the course of 2 h. After standing overnight at room temperature, the mixture was diluted with ether (250 ml) and the organic layer washed successively with water, dilute hydrochloric acid, water, potassium hydrogen carbonate solution and water. The solvents were distilled off under atmospheric pressure through a Vigreux column (10 cm) and the resulting 1-methoxymethoxy-2-propyne was distilled at 52°C/10·4 kPa; yield 8 g (40%). Reported[9] b.p. 54°C/10·6 kPa. $^1$H NMR spectrum: 4·70 s (2 H, $-CH_2O-$), 4·20 d (2 H, $C_{(1)}-H$, $J$ = 2·2), 3·37 s (3 H, $-OCH_3$), 2·42 t (1 H, $C_{(3)}-H$, $J$ = 2·2). For $C_5H_8O_2$ (100·1) calculated: 59·98% C, 8·05% H; found: 59·75% C, 7·82% H.

(22*R*)-25-Methoxymethoxy-21,26,27-trinor-5α-cholest-23-yn-22-ol (*VI*)

Pyridinium chlorochromate (350 mg; 1·62 mmol) was added to a solution of the alcohol *IV* (350 mg; 1·15 mmol) in dichloromethane (20 ml). After stirring for 2 h at room temperature, the mixture was diluted with ether (100 ml) and filtered through a column of alumina (30 g). Evaporation of the solvents *in vacuo* afforded 300 mg (86%) of the pure (TLC) aldehyde *V*. To a solution of 1-methoxymethoxy-2-propyne (260 mg; 2·6 mmol) in tetrahydrofuran (3 ml) a solution of 1-butyllithium in hexane (1·5 ml; *c* 1·6 mol $l^{-1}$) was added at −78°C. The mixture was stirred at −20°C for 1 h, cooled to −78°C and a solution of the aldehyde *V* (300 mg; 0·99 mmol) in tetrahydrofuran (3 ml) was added. During 1 h the mixture attained room temperature and was then stirred for 2 h. After decomposition with saturated aqueous solution of ammonium sulfate (5 ml), the product was taken up in ether, the ethereal layer washed with an ammonium sulfate solution and the solvent evaporated. The residue was chromatographed on 4 silica gel plates in ether–light petroleum (1 : 1) and zones with the less polar compound were combined. Elution with a mixture of dichloromethane–ether (1 : 1) afforded 182 mg (46%) of the oily alcohol *VI*, $[\alpha]_D$ +17° (*c* 2·1). IR spectrum (chloroform), $cm^{-1}$: 3 615, 3 445 (OH), 1 150, 1 100, 1 048 (C—O—C). For $C_{26}H_{42}O_3$ (402·6) calculated: 77·56% C, 10·51% H; found: 77·43% C, 10·73% H.

(22*S*)-25-Methoxymethoxy-21,26,27-trinor-5α-cholest-23-yn-22-ol (*VIII*)

Elution of combined more polar zones from the preparation of the alcohol *VI* with dichloromethane–ether (1 : 1) afforded 176 mg (44%) of the oily alcohol *VIII*, $[\alpha]_D$ +13° (*c* 2·1). For $C_{26}$·$H_{42}O_3$ (402·6) calculated: 7·56% C, 10·51% H; found: 77·44% C, 10·63% H.

(22*S*)-25-Methoxymethoxy-21,26,27-trinor-5α-cholestan-22-ol (*X*)

The alcohol *VI* (40 mg; 0·1 mmol) was hydrogenated in methanol (5 ml) over 5% palladium on charcoal (20 mg) for 30 min. After filtration of the catalyst and evaporation of solvent *in vacuo*, the residue was chromatographed on one plate of silica gel in ether–light petroleum (1 : 1; double developing), affording 35 mg (87%) of the oily alcohol *X*, $[\alpha]_D$ +11° (*c* 1·3). IR spectrum (tetrachloromethane), $cm^{-1}$: 3 627, 3 475 (OH), 1 150, 1 110, 1 045 (C—O—C). For $C_{26}H_{46}O_3$ (406·7) calculated: 76·79% C, 11·40% H; found: 76·98% C, 11·30% H.

(22*S*)-21,26,27-Trinor-5α-cholestane-22,25-diol (*XI*)

Hydrochloric acid (37%; 0·115 ml; 1·38 mmol) was added to a solution of the hydroxy derivative *X* (70 mg; 0·17 mmol) in a mixture of benzene (3·5 ml) and methanol (7 ml). The mixture was refluxed for 2 h, taken down and the dry residue dissolved in a mixture of ether–ethyl acetate (1 : 1; 75 ml). The organic layer was washed with water, potassium hydrogen carbonate solution and again water. Crystallization of the residue from ether–light petroleum afforded 35 mg (56%) of the diol *XI*, m.p. 120—122°, $[\alpha]_D$ +23° (*c* 0·2). IR spectrum (tetrachloromethane) $cm^{-1}$: 3 634 (free OH), 3 472 (bonded OH). For $C_{24}H_{42}O_2$ (362·6) calculated: 79·50% C, 11·68% H; found: 79·23% C, 11·64% H.

(22*S*)-21,26,27-Trinor-5α-cholestan-22-ol (*XII*)

A solution of the aldehyde *V* (302 mg; 1 mmol) in benzene (5 ml) was added to an ice-cooled and stirred solution of propylmagnesium bromide in ether (3 ml; *c* 1 mol $l^{-1}$) in the course of 30 min. The cooled mixture was stirred for further 30 min and decomposed with saturated aqueous solution of ammonium chloride. The product was extracted with ether, the ethereal

extract washed with ammonium chloride solution and water, dried and taken down. The residue (340 mg) was chromatographed on 4 preparative plates of silica gel in ether–light petroleum (2 : 8). Zones, containing the less polar compound, were combined and the alcohol *XII* (140 mg; 40%) eluted with ether, m.p. 95–98°C (acetone); $[\alpha]_D$ +23° (*c* 0·3). IR spectrum (tetrachloromethane), $cm^{-1}$: 3 632, 3 610 shoulder (free OH). Mass spectrum: $M^+$ 346, 258 ($M-C_5H_{12}O$). For $C_{24}H_{42}O$ (346·6) calculated: 83·17% C, 12·21% H; found: 83·45% C, 11·92% H.

Hydrogenation of the Diol *VII*

A stirred mixture of the hydroxy derivative *VI* (50 mg; 0·12 mmol), benzene (5 ml), methanol (5 ml) and *p*-toluenesulfonic acid monohydrate (50 mg) was warmed to 45°C for 10 h. After evaporation *in vacuo*, the residue was dissolved in ether and the organic phase was washed with water, potassium hydrogen carbonate solution and water. Crystallization of the residue from ether–light petroleum afforded 30 mg (67%) of the diol *VII*. IR spectrum (tetrachloromethane) $cm^{-1}$: 3 622 (free OH).

A solution of the diol *VII* (30 mg; 0·084 mmol) in ethyl acetate (5 ml) and methanol (10 ml) was hydrogenated over 10% palladium on charcoal (20 mg) for 2 h. After removal of the catalyst by filtration, the solvents were evaporated *in vacuo* and the residue chromatographed on a column of silica gel (10 g) in light petroleum–ether (95 : 5), affording 10 mg (34%) of the alcohol *XII*, m.p. 93–96°C (acetone). Elution with light petroleum–ether (2 : 3) gave 11 mg (36%) of the diol *XI*, m.p. 118–120°C (ether–light petroleum).

(22*S*)-21,26,27-Trinor-5α-cholestan-22-ol 22-Benzoate (*XIII*)

Benzoyl chloride (0·3 ml; 2·6 mmol) was added to a solution of the alcohol *XII* (80 mg; 0·23 mmol) in pyridine (4 ml). After standing at room temperature for 48 h, the mixture was poured on ice and the product taken up in ether. The ethereal layer was washed with dilute hydrochloric acid, water, potassium hydrogen carbonate solution and water. Evaporation of the solvents *in vacuo* afforded 103 mg (99%) of the chromatographically pure oily benzoate *XIII*, $[\alpha]_D$ +15° (*c* 2·1). IR spectrum (tetrachloromethane), $cm^{-1}$: 1 719, 1 274, 1 112 (benzoate). For $C_{31}H_{46}O_2$ (450·7) calculated: 82·61% C, 10·29% H; found: 82·88% C, 10·19% H.

(22*R*)-25-Methoxymethoxy-21,26,27-trinor-5α-cholestan-22-ol (*XIV*)

The title compound was prepared from the alcohol *VIII* (40 mg; 0·1 mmol) as described for the preparation of the alcohol *X* from compound *VI*. Yield 30 mg (74%) of the oily alcohol *XIV*, $[\alpha]_D$ +13° (*c* 1·1). IR spectrum (tetrachloromethane), $cm^{-1}$: 3 627, 3 480 (OH), 1 150, 1 110, 1 044 (C—O—C). For $C_{26}H_{46}O_3$ (406·7) calculated: 76·79% C, 11·40% H; found: 76·59% C, 11·50% H.

(22*R*)-21,26,27-Trinor-5α-cholestane-22,25-diol (*XV*)

The diol *XV* was prepared from the hydroxy derivative *XIV* (70 mg; 0·17 mmol) as described for *XI* from the hydroxy derivative *X*. Crystallization from ether–light petroleum afforded 42 mg (67%) of the diol *XV*, m.p. 147–148°C, $[\alpha]_D$ +24° (*c* 0·5). IR spectrum (tetrachloromethane), $cm^{-1}$: 3 633 (free OH), 3 472 (bonded OH). For $C_{24}H_{42}O_2$ (362·6) calculated: 79·50% C, 11·68% H; found: 79·48% C, 11·79% H.

(22*R*)-21,26,27-Trinor-5α-cholestan-22-ol (*XVI*)

The more polar chromatographic zones in the preparation of the alcohol *XII* were combined and eluted with ether, affording 147 mg (42%) of the alcohol *XVI*, m.p. 70–72°C (acetone),

$[\alpha]_D$ +23° (*c* 0·3). IR spectrum (tetrachloromethane), $cm^{-1}$: 3 631, 3 610 shoulder (free OH). Mass spectrum: $M^+$ 346, 258 ($M-C_5H_{12}O$). For $C_{24}H_{42}O$ (346·6) calculated: 83·17% C, 12·21% H; found: 83·39% C, 12·06% H.

Hydrogenation of Diol *IX*

The diol *IX* was prepared from the hydroxy derivative *VIII* (50 mg; 0·12 mmol) as described for *VII* from *VI*; yield 32 mg (72%) of *IX*. The diol *IX* (30 mg; 0·084 mmol) was hydrogenated under the same conditions as the diol *VII*. The residue was chromatographed on a column of silica gel (11 g) in light petroleum–ether (95 : 5), yielding 11 mg (38%) of the alcohol *XVI*, m.p. 70–73°C (acetone). Ether eluted 12 mg (40%) of the diol *XV*, m.p. 144–147°C (hexane–ether).

(22*R*)-21,26,27-Trinor-5α-cholestan-22-ol 22-Benzoate (*XVII*)

The title compound was prepared from the alcohol *XVI* (80 mg; 0·23 mmol) as described for *XIII* from *XII*. Evaporation of solvents *in vacuo* gave 90 mg (87%) of the chromatographically pure oily benzoate *XVII*, $[\alpha]_D$ +5° (*c* 2·7). IR spectrum (tetrachloromethane), $cm^{-1}$: 1 719, 1 276, 1 115 (benzoate). For $C_{31}H_{46}O_2$ (450·7) calculated: 82·61% C, 10·29% H; found: 82·70% C, 10·61% H.

5α-Pregn-20-yne (*XIX*)

1-Butyllithium in hexane (1·9 ml; *c* 1·6 mol $l^{-1}$) was added at −78°C to a solution of diisopropylamine (304 mg; 3 mmol) in tetrahydrofuran (5 ml). After stirring at −78°C for 30 min, a solution of the ketone *XVIII* (ref.[2]; 605 mg; 2 mmol) in tetrahydrofuran (5 ml) was added and the mixture was stirred at the same temperature for 1 h. Diethyl chlorophosphate (ref.[17]; 543 mg; 3·15 mmol) was added and the stirred mixture was allowed to warm to room temperature during 1 h. The resulting solution of the enol phosphate was added at −78°C *via* cannula during 5 min into a stirred solution of lithium diisopropylamide, prepared from diisopropylamine (653 mg; 6·45 mmol), 1-butyllithium in hexane (4 ml, *c* 1·6 mol $l^{-1}$) and tetrahydrofuran (10 ml) as described above. The mixture was left for 3 h to warm to room temperature, decomposed with water and the product was extracted with a 1 : 1 mixture of ether and light petroleum. The organic phase was washed with dilute hydrochloric acid, water, potassium hydrogen carbonate solution and water. After evaporation, the residue was chromatographed on a column of silica gel (100 g). Elution with light petroleum afforded 430 mg (76%) of the acetylene *XIX*, m.p. 76–78°C (light petroleum); $[\alpha]_D$ +64° (*c* 1·8). Mass spectrum: $M^+$ 284. IR spectrum (tetrachloromethane), $cm^{-1}$: 3 310, 2 110 (C≡C–H). For $C_{21}H_{32}$ (284·5) calculated: 88·66% C, 11·34% H; found: 88·42% C, 11·23% H.

3-Iodo-1-methoxymethoxypropane

Chloromethyl methyl ether (8·38 ml; 110·3 mmol) was added at +5°C in the course of 10 min to a stirred solution of 1-hydroxy-3-iodopropane (ref.[18]; 17·15 g; 92·2 mmol) and N,N-dimethylaniline (13·6 ml) in benzene (34 ml). After standing overnight at room temperature, the mixture was poured into water and the product extracted with ether. The extract was washed with dilute hydrochloric acid, water, dilute aqueous ammonia and water. Magnesium oxide (50 mg) was added and the solvents were distilled off through a 10 cm Vigreux column. 3-Iodo-1-methoxymethoxypropane (9·2 g; 43%) distilled at 82–85°C/1·87 kPa; $d = 1{\cdot}54$ g $cm^{-3}$. $^1H$ NMR spectrum: 4·60 s (2 H, $-OCH_2O-$), 3·58 t (2 H, $C_{(1)}-H$, $J = 6$), 3·35 s (2 H, $OCH_3$), 3·28 t

(2 H, $C_{(3)}$—H, $J$ = 6), 2·08 p (2 H, $C_{(2)}$—H), $J$ = 6). For $C_5H_{11}IO_2$ (230·1) calculated: 26·11% C, 4·82% H, 55·17% I; found: 26·40% C, 4·77% H, 55·13% I.

25-Methoxymethoxy-21,26,27-trinor-5α-cholest-20-yne (*XX*)

1-Butyllithium in hexane (6·25 ml; *c* 1·6 mol $l^{-1}$) was added at 0°C during 10 min to a stirred solution of the acetylene *XIX* (900 mg; 3·16 mmol) in tetrahydrofuran (5 ml). After stirring for 30 min at 0°C, the resulting solution was added during 20 min *via* a cannula to a cooled (−20°C) and stirred mixture of 3-iodo-1-methoxymethoxypropane (2·3 g; 10 mmol), tetrahydrofuran (2 ml) and hexamethylphosphoric triamide (1 ml). The mixture was stirred at room temperature for 12 h, poured into water and the product was taken up in ether. The ethereal extract was washed with dilute hydrochloric acid, water, potassium hydrogen carbonate solution and again water. The solvents were evaporated and the residue chromatographed on a silica gel column (100 g). Elution with light petroleum afforded 600 mg (67%) of the unreacted acetylene *XIX*, a 96 : 4 mixture of light petroleum–ether eluted 600 mg of the crude product which was chromatographed on 6 plates of silica gel in light petroleum–ether (94 : 6). The thus-obtained oily acetylene *XX* (240 mg; 20%) crystallized on standing at −20°C; m.p. 40–42°C; $[\alpha]_D$ +60° (*c* 1·6). IR spectrum (tetrachloromethane), $cm^{-1}$: 1 1481 1 110, 1 040 (C—O—C). Mass spectrum: 386 $M^+$. For $C_{26}H_{42}O_2$ (386·6) calculated: 80·77% C, 10·95% H; found: 80·95% C, 11·22% H

(20*Z*)-25-Methoxymethoxy-21,26,27-trinor-5α-cholest-20-ene (*XXI*)

A solution of sodium borohydride in ethanol (0·25 ml; *c* 1·0 mol $l^{-1}$; prepared according to ref.[19]) was added to a solution of nickel(II) acetate tetrahydrate (62·5 mg) in ethanol (7 ml) and the mixture was stirred under hydrogen for 30 s. Solutions of 1,2-diaminoethane (0·033 ml) in ethanol (1 ml) and the acetylene *XX* (220 mg; 0·57 mmol) in ethanol (30 ml) were added and the mixture was stirred in a hydrogen atmosphere until the theoretical amount (13·7 ml) of hydrogen was consumed. The mixture was filtered through a column of silica gel (10 g) which was then washed with ethanol. The combined ethanolic solutions were evaporated to dryness *in vacuo*, the residue was dissolved in benzene, the solutions dried over anhydrous sodium sulfate, filtered and taken down *in vacuo*, leaving 220 mg (99%) of the oily olefin *XXI*, pure according to thin-layer chromatography; $[\alpha]_D$ −32° (*c* 1·5). IR spectrum (tetrachloromethane), $cm^{-1}$: 1 650 (C=C), 1 149, 1 111, 1 040 (C—O—C). Mass spectrum: 388 $M^+$. For $C_{26}H_{44}O_2$ (388·6) calculated: 80·35% C, 11·41% H; found: 80·68% C, 11·34% H.

(20*S*,22*R*)-25-Methoxymethoxy-21,26,27-trinor-5α-cholestane-20,22-diol (*XXII*)

Osmium tetroxide (200 mg; 0·79 mmol) was added to a solution of the olefin *XXI* (208 mg; 0·54 mmol) in pyridine (2 ml) and the mixture was set aside for 21 h at room temperature. The unreacted osmium tetroxide was decomposed with a solution of potassium disulfite (400 mg) in aqueous pyridine (1 : 1; 10 ml). After standing for 15 min at room temperature, the mixture was poured into water and the product was extracted with ether. The extract was washed with dilute hydrochloric acid, water, potassium hydrogen carbonate and water. After evaporation of the solvent, the residue was chromatographed on 4 plates of silica gel in benzene–acetone (8 : 2). Zones, containing the less polar compound, were combined and eluted with dichloromethane–acetone (1 : 1), affording 130 mg (57%) of the diol *XXII*, m.p. 128–131°C (light petroleum); $[\alpha]_D$ +14° (*c* 1·2). IR spectrum (tetrachloromethane), $cm^{-1}$: 3 635 shoulder (free OH), 3 583, 3 445 (bonded OH), 1 149, 1 110, 1 044 (C—O—C). For $C_{26}H_{46}O_4$ (422·7) calculated: 73·89% C, 10·97% H; found: 73·64% C, 11·02% H.

(20*R*,22*S*)-25-Methoxymethoxy-21,26,27-trinor-5α-cholestane-20,22-diol (*XXIV*)

The more polar zones from the thin-layer chromatography in the preparation of the diol *XXII* were combined and eluted with dichloromethane–acetone (1 : 1), affording 90 mg (40%) of the diol *XXIV*, m.p. 91–92°C (light petroleum), $[\alpha]_D + 5°$ (*c* 1·1). IR spectrum (tetrachloromethane), $cm^{-1}$: 3 639 (free OH), 3 587, 3 450 (bonded OH), 1 149, 1 110, 1 044 (C–O–C). For $C_{26}H_{46}O_4$ (422·7) calculated: 73·89% C, 10·97% H; found: 74·10% C, 11·21% H.

Reduction of Thiocarbonate *XXIII*

1,1′-Thiocarbonyldiimidazole (ref.[20,21]; 100 mg; 0·56 mmol) was added to a solution of the diol *XXII* (110 mg; 0·26 mmol) in toluene (3 ml). After reflux under stirring for 1 h, the mixture was applied on a column of silica gel (15 g). Elution with benzene–acetone (98 : 2) gave 60 mg of the chromatographically homogeneous thiocarbonate *XXIII* which was dissolved in toluene (3 ml). A solution of tributyltin hydride (100 mg) in benzene (0·33 ml), followed by 2,2′-azobis (2-methylpropionitrile) (2 mg), was added and the resulting solution was added dropwise during 45 min into refluxing toluene (2 ml). The stirred mixture was refluxed for 2 h, treated with tributyltin hydride (100 mg) in benzene (0·33 ml) and 2,2′-azobis(2-methylpropionitrile) (2 mg) and refluxed again for 2 h. The addition was then repeated. After total 6 h of reflux, all the starting thiocarbonate reacted (according to thin-layer chromatography). The mixture was cooled, treated with 10% aqueous sodium hydroxide (3 ml), stirred at 40°C for 12 h and poured into water. The product was extracted with ether and the extract washed with water. The residue was chromatographed on one plate of silica gel in ether–light petroleum (1 : 1). Elution of the corresponding zones with ether gave 7 mg of the alcohol *XXVI* and 9 mg of the alcohol *XIV*. Compounds *X* and *XXVII* were not detected.

Reduction of Thiocarbonate *XXV*

The thiocarbonate *XXV* was prepared from the diol *XXIV* (70 mg) in the same manner as the thiocarbonate *XXIII* from the diol *XXII*. The procedure afforded 60 mg of the chromatographically homogeneous thiocarbonate *XXV* which was reduced as described for the thiocarbonate *XXIII*. Chromatography of the residue on a preparative silica gel plate in chloroform–methanol (9 : 1) yielded 11 mg of the alcohol *X* and 8 mg of the alcohol *XXVII*. Compounds *XIV* and *XXVI* were not detected.

*Our thanks are due to Dr L. Kalvoda for a valuable advice. The analyses were carried out in the Analytical Laboratory of this Institute (Dr J. Horáček, Head).* $^1$H NMR *spectra were recorded by Mrs J. Jelinková, Dr M. Masojídková and Mrs M. Snopková, mass spectra were measured and interpreted by Dr A. Trka.*

REFERENCES

1. Pouzar V., Havel M.: This Journal *45*, 2443 (1980).
2. Pouzar V., Havel M.: This Journal *46*, 107 (1981).
3. Pouzar V., Havel M.: This Journal *46*, 917 (1981).
4. Pouzar V., Drašar P., Kočovský P., Havel M.: This Journal *47*, 96 (1982).
5. Pouzar V., Havel M.: This Journal *46*, 2758 (1981).
6. Drašar P., Pouzar V., Černý I., Havel M., Ananchenko S. N., Torgov I. V.: This Journal *47*, 1240 (1982).
7. Fujimoto Y., Tatsuno T.: Tetrahedron Lett. *1976*, 3325.

8. Kočovský P., Černý V.: This Journal *44*, 246 (1979).
9. Atavin A. S., Trofimov B. A., Lavrov V. I.: Zh. Org. Khim. *8*, 1569 (1972).
10. Miyamoto M., Morita K., Kawamatsu Y., Kuwashima K., Nakanishi K.: Tetrahedron *23*, 411 (1967).
11. Negishi E., King A. O., Klima W. L.: J. Org. Chem. *45*, 2526 (1980).
12. Brown C. A., Ahuja V. K.: Chem. Commun. *1973*, 553.
13. Vedejs E., Wu E. S. C.: J. Org. Chem. *39*, 3641 (1974).
14. Barton D. H. R., Subramanian R.: J. Chem. Soc., Perkin Trans 1, *1977*, 1718.
15. Dillon J., Nakanishi K.: J. Amer. Chem. Soc. *97*, 5409 (1975).
16. Charles R. G., Pawlikowski M. A.: J. Phys. Chem. *62*, 440 (1958).
17. Mukaiyama T., Fujisawa T.: Bull. Chem. Soc. Jap. *34*, 812 (1961).
18. Hodgson G. L., MacSweeney D. F., Money T.: J. Chem. Soc., Perkin Trans. 1, *1973*, 2113.
19. Brown C. A., Ahuja V. K.: J. Org. Chem. *38*, 2226 (1973).
20. Staab H. A., Walther G.: Justus Liebigs Ann. Chem. *657*, 98 (1962).
21. Sharma S.: Synthesis *1978*, 803.

Translated by M. Tichý.