TETRACYCLIC TRITERPENES. PART VI [1]. THE SYNTHESIS OF 4,4,14α-TRIMETHYL-19(10 → 9β) ABEO-STEROIDS. SYNTHONS FOR THE PREPARATION OF CUCURBITACINS

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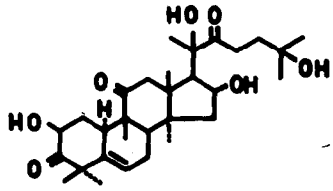
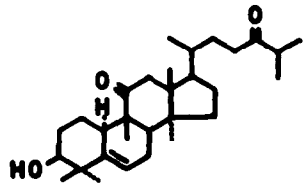
ABSTRACT

The effective synthesis of 4,4,14α-trimethyl-19(10 → 9β) abeo-steroids (IV), (V), and (VI) with two- and five-carbon side chains from lanosterol is described. Their structures were proved on the basis of spectral data. The title compounds are the first synthetic synthons for the preparation of 4,4,14α-trimethyl-steroids with an unnatural configuration.

Cucurbitacins are highly oxygenated tetracyclic triterpenes [2]. Compounds belonging to this group have characteristic functionalization of the alicyclic skeleton and variously substituted eight-carbon side chains, as exemplified in cucurbitacin D (I), and bryogenine (II). We have recently described an effective method of constructing the cucurbitane skeleton by a 1,2-shift of the 19-methyl group in lanostane derivatives by the opening of a 9,11-epoxy ring [3].



(I)



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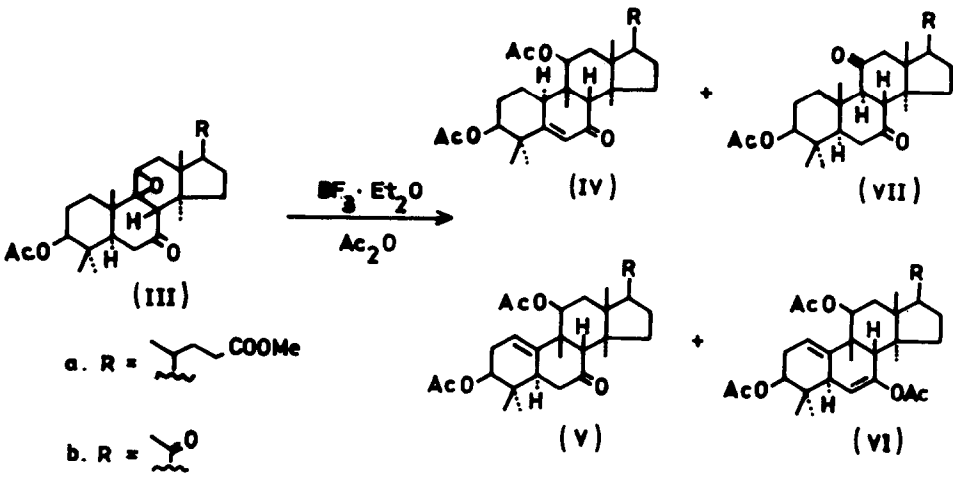
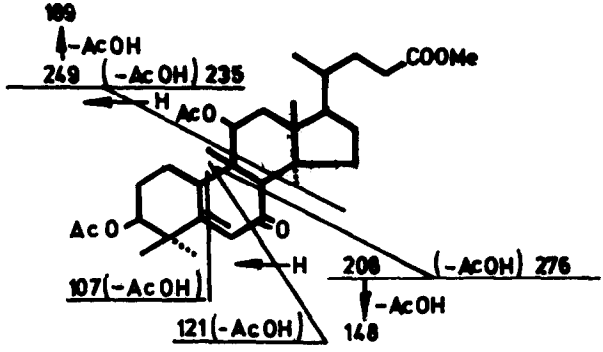


Since the side chain in natural cucurbitacins is heavily functionalized, the above approach is extended to compounds with a degraded side chain. We report here the synthesis of synthons (IVa) and (IVb), which, as we expect, might be suitable for further synthetic work, especially for the restoration of properly functionalized side chains.

The substrate compounds, 3β-acetoxy-9,11β-oxido-7-oxo-4,4,14α-trimethyl-5α-cholan-24-oic acid methyl ester (IIIa) (mp. 219-221°C) and 3β-acetoxy-9,11β-oxido-4,4,14α-trimethyl-5α-pregnane-7,20-dione (IIIb) (mp.288-290°C) were obtained from commercial "isocholesterol" by a multistep reaction sequence [1].

Reaction of the epoxide (IIIa) carried out in acetic anhydride at room temperature gave a crude product representing a complex mixture which was separated by preparative layer chromatography. Four compounds were isolated in the

pure form. Their structures were inferred from spectral properties (see EXPERIMENTAL). The major product, isolated in 47% yield, was assigned structure (IVa), 3β,11β-diacetoxy-7-oxo-4,4,14α-trimethyl-19(10 → 9β)abeo-10α-chol-5-en-24-oic acid methyl ester. It showed UV and IR absorptions characteristic of a six-membered α,β-unsaturated ketone. Its PMR spectrum revealed signals attributable to protons in positions 3α, 6, and 11α. The multiplicity of the 3α-proton signal confirmed the inversion of configuration at carbon 10, and the fact that proton 8β appears as a singlet, indicates the absence of a hydrogen atom bonded to C-9. The enones (IVa) and (IVb) gave a characteristic mass spectrum. Electron impact fragmentation was clearly directed by the B-ring "enone" moiety and supported the structure of the carbon skeleton bearing a methyl substituent at position 9.



A second product was isolated in 17% yield, and also proved to have a rearranged carbon skeleton. To this product the structure of 3β,11β-diacetoxy-7-oxo-4,4,14α-trimethyl-19(10 → 9β)abeo-5α-chol-1(10)-en-24-oic acid methyl ester(Va)

was assigned. In the infrared and ultraviolet a saturated carbonyl function was apparent and in the PMR spectrum characteristic signals for the 3α- and 11α-protons, and for the ethylenic proton in position C-1 were observed. The spectrum also showed the 8β-proton as a singlet, which confirms the absence of a proton in position 9 - a consequence of the 19-methyl migration. In the mass spectrum fragments m/z 209 and 121 also supported the 19 (10 → 9β)abeo structure.

The third product, isolated in 6% yield, gave upon mild basic hydrolysis a compound identical with the abeo ketone (Va). Its spectral properties were in accordance with structure (VIa). The enol acetate moiety and the position of the enolic double bond were evident from the PMR spectrum which showed three signals of acetyl groups, a signal attributable to the "bisallylic" 5α-proton, and a singlet signal assigned to the 8β-proton.

The last product obtained in 19% yield was the known 3β-acetoxy-7,11,dioxo-4,4,14α-trimethyl-5α-cholan-24-oic acid methyl ester (VIIa), whose physical properties were in accordance with the published data [4].

In the 17β-acetyl series, rearrangement of the β-epoxide (IIIb) gave comparable results. Compounds (IVb), (Vb), (VIb), and (VIIb) were assigned their structures on the basis of spectral data (see EXPERIMENTAL), similarly to the assignments in the 5α-cholanic ester series.

The described rearrangements of β-epoxides (III) proved useful as an effective method for the migration of the 19-methyl group to position 9 in the 5α-cholanic ester and

pregnane series. The total yield of 19(10 → 9β)abeo-compounds was 70% in the ester , and 64% in the 17β-acetyl series. Compounds (IVa) and (IVb) might possibly be used as synthons for the preparation of naturally occuring and modified cucurbitacins. These aspects of the problem are under investigation.

EXPERIMENTAL [5]

Rearrangement of 3β-acetoxy-9,11β-oxido-7-oxo-4,4,14α-trimethyl-5α-cholan-24-oic acid methyl ester (IIIa)

To a solution of epoxide (IIIa) (0.265 g) in acetic anhydride (12 ml), boron trifluoride ether complex (0.265 ml) was added dropwise at room temperature. After 5 min. pyridine (12 ml) was added with cooling, followed by addition of water (25 ml). The reaction product was extracted with a 1:1 mixture of benzene-ethyl ether, the organic layer was washed with hydrochloric acid (5%), sodium hydrogen carbonate (5%), water, and dried over sodium sulphate. Evaporation of the solvent gave a crude product, which was separated on preparative t.l.c. plates with silica gel developed three times with a 10:1 mixture of benzene-ethyl acetate. The following compounds, in order of increasing polarity, were isolated:

3β,7,11β-triacetoxy-4,4,14α-trimethyl-19(10 → 9β)abeo-5α-chola-1(10),6-dien-24-oic acid methyl ester (VIa) (0.021 g): oil; PMR δ 5.52-6.00 (m, 1-,6-, and 11α-H), 4.82 (dd, J 9Hz, J 8Hz, 3α-H), 3.63 (s, 24-CO_2CH_3), 2.88 (m, 5α-H), 2.50 (s, 8β-H), 2.07 and 2.02 (two s, 3β-, 7-, and 11β-OAc), 1.02, 0.94, 0.90, 0.85, and 0.72 (methyl groups); mass spectrum m/z (%) 544(M^+-42) (3), 484(10), 424(47), 409(53), 377(27), 209(23), 189(78), 173(20), 121(30), 95(69), and 43(100) (Found: C, 69.43; H, 8.87. $C_{34}H_{50}O_8$ requires C, 69.60; H, 8.59)

3β-acetoxy-7,11-dioxo-4,4,14α-trimethyl-5α-cholan-24-oic acid methyl ester (VIIa) (0.050 g): mp. 210-213°C (MeOH); $[\alpha]_D^{23}$ +54° (c, 0.7, $CHCl_3$); PMR δ 4.52 (dd, J 9Hz, J 7Hz, 3α-H), 3.67 (s, 24-CO_2CH_3), 2.96, 2.79, 2.56, 2.43, and 2.28 (α-protons to carbonyls), 1.30, 1.22, 0.90, 0.84, and 0.70 (methyl groups); ν_{max} 1730, 1705, and 1255 cm^{-1}; mass spectrum m/z 502(M^+) (lit. [4] mp. 203-205°C, $[\alpha]_D$ +59°) (Found: C, 71.82; H, 9.40. $C_{30}H_{46}O_6$ requires C, 71.68; H, 9.22);

3β,11β-diacetoxy-7-oxo-4,4,14α-trimethyl-19(10 → 9β)abeo-5α-chol-1(10)-en-24-oic acid methyl ester (Va) (0.048 g): mp. 152-154°C (aq. MeOH); PMR δ 5.93 (m, $w_{1/2}$ 9Hz, 1-H), 5.75 (br t, J 3Hz, 11α-H), 4.83 (dd, J 10Hz, J 7Hz, 3α-H), 3.65 (s, 24-CO_2CH_3), 2.61 (s, 8β-H), 2.06 and 2.04 (two s, 3β- and 11β-OAc), 1.03, 0.97, 0.89, and 0.82 (methyl groups); ν_{max} 1730, 1700, and 1255 cm^{-1}; $\Delta\varepsilon$ = -2.53(304 nm); mass spectrum m/z (%) 502(M^+-42)(6), 484(5), 424(34), 409(42), 377(24), 249(8), 209(18), 189(74), 185(23), 173(18), 161 (11), 121(27), 95(65), and 43(100) (Found: C, 70.72; H, 9.05. $C_{32}H_{48}O_7$ requires C, 70.86; H, 8.88);

and 3β,11β-diacetoxy-7-oxo-4,4,14α-trimethyl-19(10 → 9β) abeo-10α-chol-5-en-24-oic acid methyl ester (IVa) (0.137 g): mp. 170-173°C (aq. MeOH); PMR δ 6.06(br d, J 2Hz, 6-H), 5.26 (m, $w_{1/2}$ 7Hz, 11-H), 4.83(br s, $w_{1/2}$ 4Hz, 3α-H), 3.62(s, 24-CO_2CH_3), 2.63(s, 8β-H), 2.04 and 1.99(two s, 3β- and 11β-OAc), 1.19, 1.00, 0.96, and 0.90(methyl groups); ν_{max} 1725, 1650, 1620, and 1250 cm^{-1}; λ_{max} 246 nm (ε 12 000); $\Delta\varepsilon$ = +17.1(240 nm), -0.82(339 nm); mass spectrum m/z (%) 544(M^+)(31), 502(18), 484(44), 424(8), 276(80), 241(31), 208(29), 189(63), 148(69), 132(49), 121(59), 95(40), and 44(100) (Found: C, 70.34; H, 8.90. $C_{32}H_{48}O_7$ requires C, 70.56; H, 8.88).

Rearrangement of 3β-acetoxy-9,11β-oxido-4,4,14α-trimethyl-5α-pregnane-7,20-dione (IIIb)

The reaction of (IIIb) (0.310 g) was carried out as above. The crude product was separated on preparative t.l.c. plates with silica gel developed six times with a 5:1 mixture of benzene-ethyl acetate. The following compounds were isolated in order of increasing polarity:

3β,7,11β-triacetoxy-4,4,14α-trimethyl-19(10 → 9β)abeo-5α-pregna-1(10),6-dien-20-one (VIb) (0.014 g): oil; PMR δ 5.88 (m, 1- and 11α-H), 5.67(br d, J 2Hz, 6-H), 4.86(dd, J 10Hz, J 8Hz, 3α-H), 2.94(m, 5α-H), 2.47(s, 8β-H), 2.14, 2.10, 2.07, and 2.05(four s, 3β-, 7-, 11β-OAc, and 17-Ac), 1.10, 1.00, 0.87, and 0.79(methyl groups); ν_{max} 1730, 1705, and 1250 cm^{-1}; mass spectrum m/z (%) 514(M^+)(4), 472(19), 412(25), 337(16), 203(21), 189(27), 187(54), 173(22), 163(18), 146(29), 137(33), 121(35), and 95(100) (Found: M^+, 514.2995. $C_{30}H_{42}O_7$ requires M, 514.2928);

3β-acetoxy-4,4,14α-trimethyl-5α-pregnane-7,11,20-trione (VIIb) (0.042 g): mp. 245-247°C (MeOH); PMR δ 4.50(dd, J 9Hz, J 7Hz, 3α-H), 2.27-2.93(m, protons α to carbonyls), 2.08(s, 21-CH_3), 2.03(s, 3β-OAc), 1.28, 0.90, 0.83, and 0.65(methyl groups): ν_{max} 1725, 1705, and 1255 cm^{-1}; mass spectrum m/z 430(M^+) (Found: C, 72.44; H, 8.78. $C_{26}H_{38}O_5$ requires C, 72.53; H, 8.90);

3β,11β-diacetoxy-4,4,14α-trimethyl-19(10 → 9β)abeo-5α-pregn-1(10)-ene-7,20-dione (Vb) (0.072 g): mp. 213-215°C (MeOH); PMR δ 5.98(br s, $w_{1/2}$ 9Hz, 1-H), 5.85(br t, J 3Hz, 11α-H), 4.88(dd, J 10Hz, J 7Hz, 3α-H), 2.63(s, 8β-H), 2.10 and 2.07(two s, 3β-, 11β-OAc and 17β-Ac), 1.06, 0.97, 0.94, and 0.86(methyl groups): ν_{max} 1730, 1705, and 1250 cm^{-1}; $\Delta\varepsilon$ = +1.52(281 nm), -1.69(316 nm); mass spectrum m/z (%) 412(M^+-60)(4), 352(13), 337(31), 249(12), 189(60), 95(25), and 43(100) (Found: C, 70.82; H, 8.41. $C_{28}H_{40}O_6$ requires C, 71.16; H, 8.53);

and 3β,11β-diacetoxy-4,4,14α-trimethyl-19(10 → 9β)abeo-10α-pregn-5-ene-7,20-dione (IVb) (0.132 g): mp. 230-232°C (MeOH);

PMR δ 6.10(br d, J 2Hz, 6-H), 5.35(m, $w_{1/2}$ 8Hz, 11α-H), 4.84(br s, $w_{1/2}$ 5Hz, 3α-H), 2.62(s, 8β-H), 2.11(s, 21-CH_3), 2.04 and 2.01(two s, 3β- and 11β-OAc), 1.21, 1.19, 0.96, and 0.92(methyl groups); ν_{max} 1725, 1710, 1655, and 1250 cm^{-1}; λ_{max} 246 nm (ε 11 100); $\Delta\varepsilon$ = +17.2(240 nm), +3.5(285 nm), and -0.83(339 nm); mass spectrum m/z (%) 472(M^+)(8), 430(25), 412(27), 352(12), 337(11), 249(11), 208(35), 204(32), 189(41), 161(19), 148(59), 133(45), 121(28), 107(19), and 43(100) (Found: C, 70.92; H, 8.38. $C_{28}H_{40}O_6$ requires C, 71.16; H, 8.53).

Hydrolysis of compounds [VI]

Compound (VI) (20 mg) was dissolved in methanol (1 ml) and a saturated solution of potassium carbonate in methanol (0.05 ml) was added. After 2 h reaction at room temperature the product was isolated in the usual manner. Compounds (VIa) and (VIb) gave materials identical (mp., PMR, mass spectrum) with compounds (Va) and (Vb), respectively.

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5. For general experimental directions see ref. 3. The PMR, IR, UV, and CD spectra were measured in $CDCl_3$ (TMS), $CHCl_3$, EtOH, and CH_3CN, respectively.