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AN ADVANCED INTERMEDIATE FOR THE SYNTHESIS OF 9,11-SECOSTEROLS

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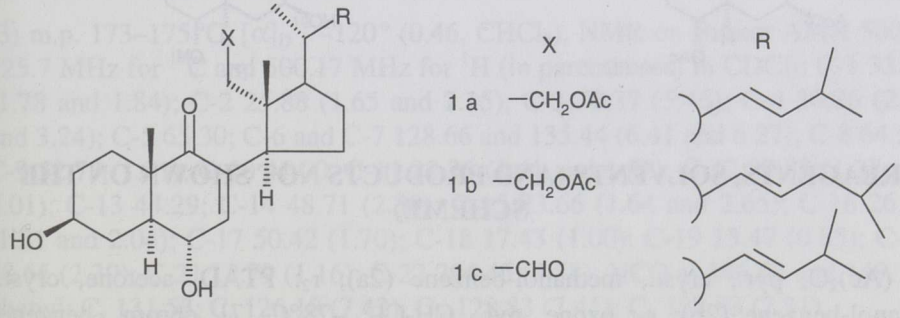
SOBIVALT FUNKTSIONALISEERITUD VAHEÜHEND 9,11-SEKOSTEROOLIDE SÜNTEESIKS. Raissa JÄÄLAID, Ivar JÄRVING, Tõnis PEHK ja Ülo LILLE

Key words: partial synthesis of sterols, modification of B- and C-rings in sterols.

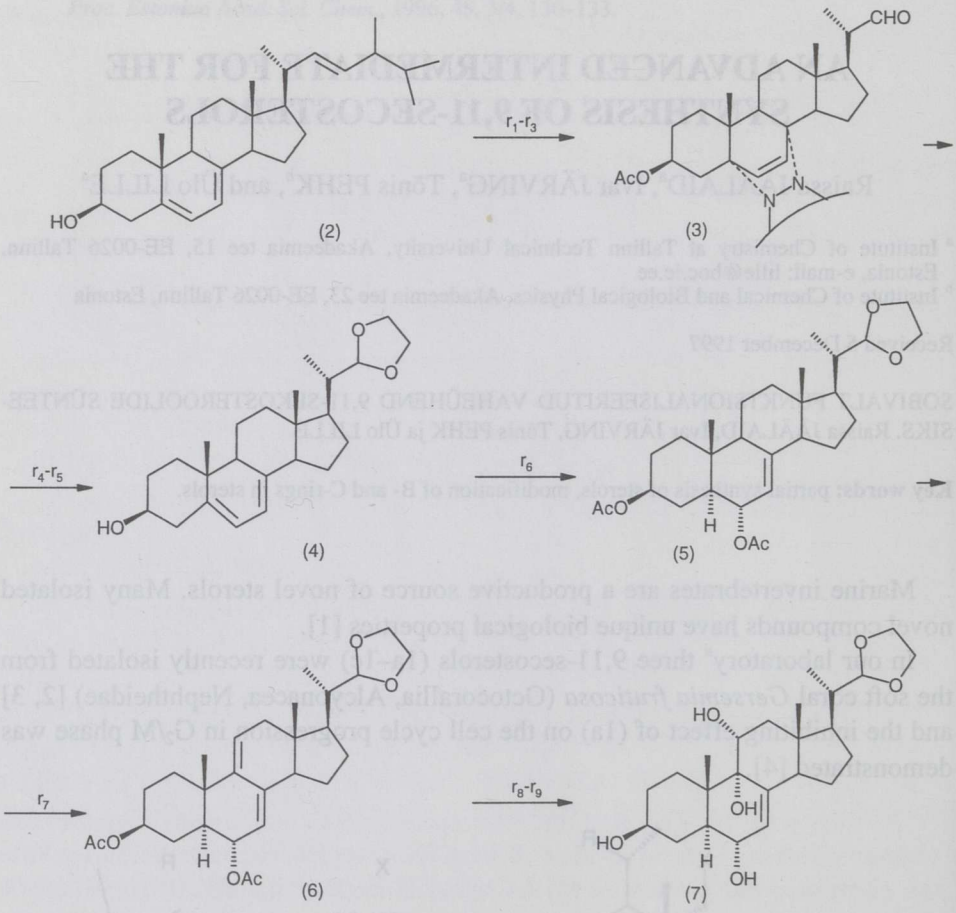
Marine invertebrates are a productive source of novel sterols. Many isolated novel compounds have unique biological properties [1].

In our laboratory[a] three 9,11-secosterols (1a–1c) were recently isolated from the soft coral *Gersemia fruticosa* (Octocorallia, Alcyonacea, Nephtheidae) [2, 3] and the inhibiting effect of (1a) on the cell cycle progression in G_2/M phase was demonstrated [4].



In this communication we propose an advanced intermediate for partial synthesis of 9,11-secosterols. For some earlier examples of partial synthesis of sterols see in [5, 6].

We started with cheap and stereochemically proper ergosterol (2) and the transformations shown on the following scheme were carried out.



REAGENTS, SOLVENTS (AND PRODUCTS NOT SHOWN ON THE SCHEME)

r_1: $(Ac)_2O$, pyr., cryst., methanol-benzene (2a); r_2: PTAD, acetone, cryst., ethanol-benzene (2b); r_3: ozone, pyr., CH_2Cl_2, –78 °C [7], chrom., benzene-acetone /20 : 1/; r_4: CH_2OHCH_2OH, pTSA, CH_2Cl_2, chrom., petrol ether-acetone /8 : 1–6 : 1/ (3a); r_5: $LiAlH_4$, THF, Δ, chrom., chloroform-acetone /50 : 1–40 : 1/, r_1: (4a); r_6: a. BH_3, THF, b. H_2O_2, NaOH, c. r_1, chrom., petrol ether-acetone-

dichloromethane /15:1:1/; r_7: $Hg(OCOCH_3)_2$, $CHCl_3$, CH_3COOH, chrom., petrol ether-diethylether /5:1/ (6a–6b); r_8: OsO_4, dioxane, chrom., chloroform-ethanol /9:1/ (6c); r_9: $LiAlH_4$, diethylether, chrom., chloroform-ethanol /9:1/ (r_6–r_8 as in [5]). (2) from "Sigma", min. 90% purity.

All reaction products were purified over silica (if not stated otherwise) using flash chromatography under slight pressure and were obtained as crystallinic substances. The yields were not optimized.

The aldehyde (3) was obtained as pure 20S epimer, $[\alpha]_D^{19}$ –120° (0.46, $CHCl_3$). After customary protection/deprotection procedures, resulting in (4), ethylene acetal (5) was prepared smoothly with the necessary α-orientated (equatorial) hydroxyl group at C-6 (9.8 Hz coupling between H-6 and H-5). In the dehydrogenation step three chromatographic fractions were obtained. The expected diene-acetal (6) was found in the second fraction together with the starting acetal (5). In the first and third fractions the corresponding 3-acetyl- and 3,6,12-triacetyldiene acetals were identified/designated respectively as (6a) and (6b) [8]. The intermediate osmate ester (6c) was cleaved immediately to the tetrolacetal (7) obtained from ergosterol with ca 10% yield.

The 3β,6α,9α,11α-tetrahydroxy-5α-pregn-7-ene-20(S)-carbaldehyde ethylene acetal (7) was prepared using quite a short sequence of transformations, whose preliminary outlines were given above. It is an advanced intermediate in the synthesis towards target compounds. This molecule has necessary functionalities for introduction of the side chain and for selective cleavage of the bond between carbon atoms C-9 and C-11 resulting in keto functions at these atoms. With the aim of improving the limiting dehydrogenation step, other methods, among them microbiological 11-hydroxylation of ethylene acetal (5), are being studied.

CHARACTERIZATION OF COMPOUNDS

(2a) m.p. 177–179, (2b) 173–174°C.

(3) m.p. 173–175°C, $[\alpha]_D^{19}$ –120° (0.46, $CHCl_3$), NMR on Bruker AMX 500 at 125.7 MHz for ^{13}C and 500.17 MHz for ^1H (in parentheses) in $CDCl_3$: C-1 33.62 (1.78 and 1.84); C-2 25.88 (1.65 and 2.15); C-3 70.37 (5.46); C-4 30.86 (2.21 and 3.24); C-5 65.30; C-6 and C-7 128.66 and 135.44 (6.41 and 6.27); C-8 64.58; C-9 52.73 (1.81); C-10 41.00; C-11 22.26 (1.41 and 1.51); C-12 37.83 (1.37 and 2.01); C-13 44.29; C-14 48.71 (2.39); C-15 23.66 (1.64 and 2.65); C-16 26.00 (1.51 and 2.04); C-17 50.42 (1.70); C-18 17.43 (1.00); C-19 13.47 (0.85); C-20 48.66 (2.39); C-21 13.79 (1.16); C-22 204.45 (9.58); NCO at 146.68 and 149.12; phenyl: C_s 131.53; C_o 126.18 (7.42); C_m 128.83 (7.41); C_p 127.83 (7.31).
(3a) m.p. 204–206°C.

(4) m.p. 163–165°C.

(4a) m.p. 144–147 °C NMR (in $CDCl_3$): C-1 37.87 (1.36 and 1.89); C-2 28.08 (1.58 and 1.91); C-3 72.75 (4.69); C-4 36.63 (2.38 and 2.47); C-5 141.16; C-6 and C-7 120.14 and 116.47 (6.22 and 6.45); C-8 138.68; C-9 46.01 (2.00); C-10 37.07; C-11 23.17 (1.44 and 1.73); C-12 38.93 (1.31 and 2.08); C-13 43.26; C-14 53.82 (1.91); C-15 20.99 (2.04); C-16 27.25 (1.45 and 2.00); C-17 52.05 (1.51); C-18 11.63 (0.63); C-19 16.14 (0.95); C-20 39.60 (1.81); C-21 11.71 (0.95); C-22 106.01 (4.87); —O—CH_2—CH_2—O— 65.04 and 65.21 (3.86, 3.87, 3.93, 3.95); OAc 21.36 (2.04) and 170.45.

(5) m.p. 205–207 °C, $[\alpha]_D^{23}$ +76° (0.26, $CHCl_3$), (5) NMR (in $CDCl_3$): C-1 36.63 (1.24 and 1.81); C-2 27.11 (1.49 and 1.83); C-3 72.62 (4.68); C-4 29.63 (1.34 and 1.93); C-5 44.80 (1.58); C-6 73.06 (5.06); C-7 118.03 (5.05); C-8 142.68; C-9 48.76 (1.78); C-10 35.30; C-11 22.83 (1.43 and 1.61); C-12 38.93 (1.31 and 2.04); C-13 43.89; C-14 54.13 (1.87); C-15 21.22 (1.47 and 1.63); C-16 26.97 (1.45 and 1.96); C-17 52.20 (1.51); C-18 11.75 (0.55); C-19 13.83 (0.92); C-20 39.47 (1.78); C-21 11.66 (0.94); C-22 105.88 (4.85); —O—CH_2—CH_2—O— 65.02 (3.85 and 3.97) and 65.18 (3.85 and 3.93); OAc 21.31 (2.05) and 21.36 (2.03); 170.54 and 171.26.

(6) MS: 472 (M^+), 412 (M^+ –60), 352 (M^+ –120), UV, λ_{max}: 251.5, 242.0, 235.0 nm.
(6a) MS: 414 (M^+), 354 (M^+ –60), UV, λ_{max}: 250.5 nm.
(6b) MS: 531 (M^+ +1), 471 (M^+ –59), 410 (M^+ –120), 350 (M^+ –180), UV, λ_{max}: 249.5, 242.5, 236.0 nm.

(7) m.p. 212–213 °C, $[\alpha]_D^{18}$ +10 (0.70, $CHCl_3$), NMR (in pyridine d5): C-1 33.05 (2.46a, 2.82e); C-2 32.70 (2.02a, 2.32e); C-3 70.24 (4.11a); C-4 36.00 (3.31e, 1.97a); C-5 43.51 (2.66); C-6 69.56 (4.32); C-7 129.56 (5.99); C-8 139.57; C-9 75.18; C-10 41.25; C-11 69.53 (4.60); C-12 47.41 (2.56e, 2.14a); C-13 43.64; C-14 50.63 (2.91); C-15 23.46 (1.61); C-16 27.43 (1.56 and 2.06); C-17 52.60 (1.90); C-18 12.47 (0.80); C-19 16.21 (1.44); C-20 39.96 (2.01); C-21 12.29 (1.24); C-22 106.10 (5.02); —O—CH_2—CH_2—O— 65.58 and 65.66 (3.86, 3.89, 3.98 and 4.00).

NMR data were assigned by 2D ^1H - ^1H and ^1H - ^{13}C COSY correlation diagrams. MS measurements: EI – 70 eV, CI – isobutane, gas-chromatographic separation: 200–300 °C, RLS –150, 10 m.

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