Proc. Estonian Acad. Sci. Chem., 1998, **47**, 4, 196–199
https://doi.org/10.3176/chem.1998.4.05

FIRST PARTIAL SYNTHESIS OF 9,11-SECOSTEROLS WITH THE MODIFIED SIDE CHAIN

Raissa JÄÄLAID[a], Ivar JÄRVING[a], Tõnis PEHK[b], and Ülo LILLE[a]

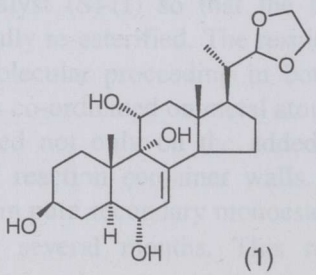
[a] Institute of Chemistry at Tallinn Technical University, Akadeemia tee 15, 12618 Tallinn, Estonia; e-mail: lille@boc.ic.ee
[b] Institute of Chemical and Biological Physics, Akadeemia tee 23, 12618 Tallinn, Estonia

Received 28 August 1998, in revised form 15 September 1998

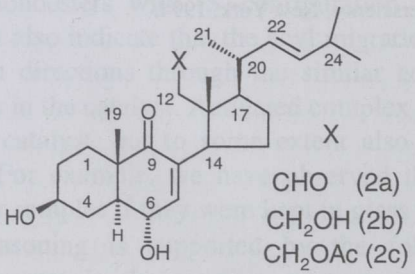
ESIMENE MODIFITSEERITUD KÜLGAHELAGA 9,11-SEKOSTEROOLIDE POOLSÜNTEES. Raissa JÄÄLAID, Ivar JÄRVING, Tõnis PEHK ja Ülo LILLE

Key words: partial synthesis of sterols, modification of sterol structure.

Modification of ergosterol resulted recently in a tetrol intermediate (1) that has proper functionalities for the synthesis of certain type of 9,11-secosterols, characterized by the enone moiety in the B-ring [1]. Another route of partial synthesis, which starts with desoxycholic acid, is targeted at this type of secosterols as well [2, 3]. In this communication we report the transformation of (1) into 9,11-secosterols (2a) and (2c), isolated among other sterols from the Arctic soft coral *Gersemia fruticosa* in our laboratory[a] [4].



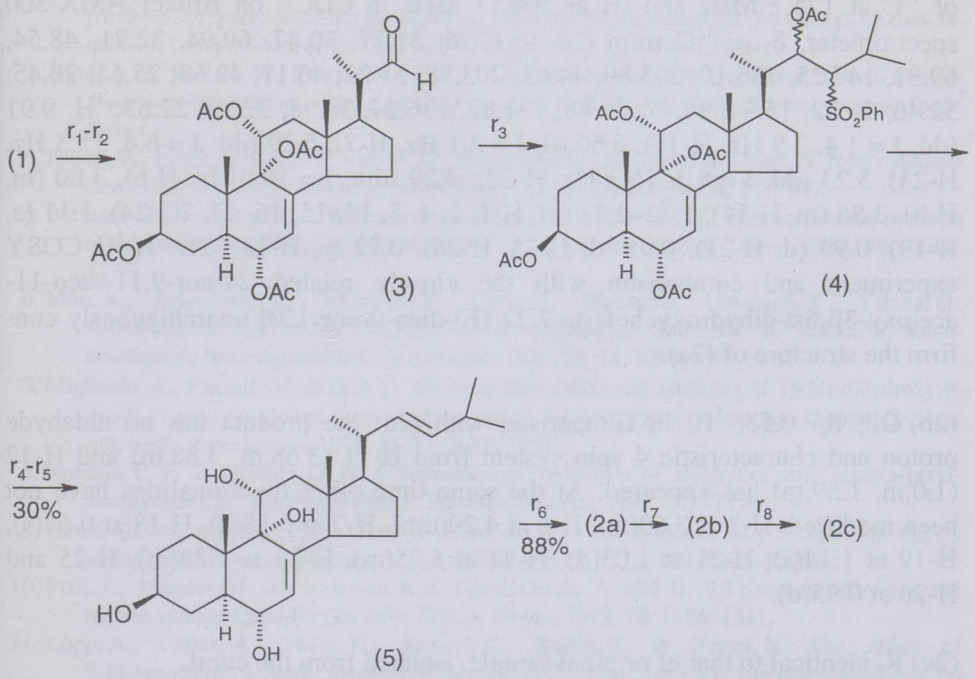
(1)



CHO (2a)
CH_2OH (2b)
CH_2OAc (2c)

After necessary protection/deprotection procedures the side chain was introduced by Julia olefination with moderate yield. The carbanion for alkylsulphonation was generated from *i*-$BuSO_2Ph$, prepared smoothly from

i-butyl iodide and thiophenol followed by oxidation with *m*-chloroperbenzoic acid. Selective diol cleavage yielded smoothly the first target secosterol (2a) with high yield.



r_1: Ac_2O, Py, chrom., chloroform–acetone /40 : 1/; r_2: H_2O, AcOH, 75 °C, 20 min [5], chrom., petrol ether–ether /4 : 1/; r_3: *n*-BuLi, *i*-$BuSO_2Ph$, THF, –70 °C; r_4: Na/Hg, MeOH, –40–20 °C [6]; r_5: 2N KOH, EtOH (95%), chrom., chloroform–ethanol /10 : 1–8 : 1/; r_6: $Pb(OAc)_4$, AcOH [7], chrom., chloroform–ethanol /20 : 1/; r_7: Bu_4NBH_4, AcOH, benzene, reflux [8], chrom., chloroform–ethanol /5 : 1/; r_8: 1,2 eq. Ac_2O, Py, $CHCl_3$, –7 °C [9]. Reaction products were purified over silica using flash chromatography (except (2b), which was purified on precoated glass plate, Baker, Si 500F).

Selective hydrogenation of aldehyde functionality (C-11) with tetrabutyl ammonium borohydride resulted in a poor yield of triol (2b). The formed primary hydroxyl group was selectively acetylated with customary acetic anhydride at lowered temperature to obtain the second target secosterol (2c). None of the mentioned yields were optimized. Further synthetic work is being carried out on preparative level.

Using synthetic schemes outlined in [1] and in this paper other related secosterols can be obtained by building a proper side chain and, if necessary, by further modification of B-ring. It will enable further insights into antiproliferative and cytotoxic properties [10–13] of these interesting natural compounds.

CHARACTERIZATION OF COMPOUNDS

(2a) Oil, R_f 0.52 (chloroform–ethanol /5:1/, Merck, silica gel 60 F_{254} and so below as well if not stated otherwise), $[\alpha]_D^{19}$ +26° (0.27 g/ml, methanol), NMR of ^{13}C at 125.7 MHz and ^1H at 500.17 MHz in $CDCl_3$ on Bruker AMX-500 spectrometer, δ_{TMS}; ^{13}C from C-1 to C-26: 31.77, 30.47, 69.94, 32.71, 48.54, 69.31, 147.25, 136.19, 203.89, 44.63, 203.78, 51.22, 46.11, 43.68, 25.64, 26.45, 52.46, 16.82, 15.94, 38.47, 21.68, 131.82, 136.24, 30.98, 22.53, 22.63; ^1H: 9.91 (dd, J = 1.4, 3.9 Hz, H-11), 6.60 (d, J = 2.1 Hz, H-7), 5.29 (dd, J = 6.4, 15.3 Hz, H-23), 5.23 (dd, J = 8.2, 15.3 Hz, H-22), 4.29 (dm, J = 10.0 Hz, H-6), 3.60 (m, H-3), 3.56 (m, H-14), 1.22–2.32 (m, H-1, 2, 4, 5, 12, 15, 16, 17, 20, 24), 1.11 (s, H-19), 0.99 (d, H-21), 0.95 (d, H-25, H-26), 0.72 (s, H-18). 2D ^1H-^1H COSY experiment and comparison with the closely related 24-nor-9,11-seco-11-acetoxy-3β,6α-dihydroxycholesta-7,22 (E)-dien-9-one [10] unambiguously confirm the structure of (2a).

(2b) Oil, R_f 0.58, ^1H: in comparison with (2a) the product has no aldehyde proton and characteristic 4 spin system from H-11 (3.68,m, 3.88,m) and H-12 (1.0,m, 1.59,m) has appeared. At the same time other functionalities have not been modified: H-3 at 3.60(m), H-6 at 4.29(dm), H-7 at 6.58(d), H-18 at 0.64(s), H-19 at 1.14(s), H-21 at 1.03(d), H-22 at 5.25(m), H-23 at 5.28(m), H-25 and H-26 at 0.95(d).

(2c) R_f identical to that of original sample, isolated from the coral.

(3) m.p. 178–180°C, R_f 0.32 (hexane–acetone /2:1/), IR (KBr), ν_{max}:2720 (—CHO), 1730, 1715 (—CHO, —$COCH_3$), 1670 (—C═C—), 1390 (—$OCOCH_3$), 1235, 1015 (—C—O—), 970, 920, 900 (—CH═CH—) cm^{-1}.

(4) Oil, IR (neat), ν_{max}:3060 (Ph), 1740 (—$COCH_3$), 1660 (—C═C—), 1600 (Ph), 1400 (—$OCOCH_3$), 1310 (—SO_2), 1240 (—C—O—), 1140 (—SO_2), 1020 (—C—O—), 970, 920 (—CH═CH—), 760, 720, 680 (Ph) cm^{-1}.

(5) m.p. 192–194°C, R_f 0.39 (chloroform–ethanol /5:1/), $[\alpha]_D^{19}$ +10° (0.2 g/ml, methanol), IR (KBr), ν_{max}:3400 (—OH), 1660 (—C═C—), 1415 (—OH), 1010, 970, 830, 805 (—CH═CH—) cm^{-1}.

ACKNOWLEDGEMENT

Financial support of the Estonian Science Foundation (grant No. 3501) is gratefully acknowledged.

REFERENCES

1. Jäälaid, R., Järving, I., Pehk, T. & Lille, Ü. An advanced intermediate for the synthesis of 9,11-secosterols. *Proc. Estonian Acad. Sci. Chem.*, 1998, **47**, 1, 39–43.
2. Kuhl, A. & Kreiser, W. Progress in partial synthesis of a marine secosterol from *Gersemia fruticosa*: Preparation of the intermediate precursor 3β,6α-diacetoxy-24-methyl-12-oxo-5a-chol-9,11-ene-24-oate (14). *Tetrahedron Lett.*, 1998, **39**, 1145–1148.
3. Kuhl, A. & Kreiser, W. Progress in partial synthesis of a marine secosterol from *Gersemia fruticosa*: Preparation of the steroidal core unit. *Coll. Szech. Chem. Comm.*, in press (pers. comm.).
4. Koljak, R., Lopp, A., Pehk, T., Varvas, K., Müürisepp, M., Järving, I. & Samel, N. New cytotoxic sterols from the soft coral *Gersemia fruticosa*. *Tetrahedron*, 1998, **54**, 179–186.
5. Bernstein, R., Lenhard, R. & Williams, J. H. Steroidal cyclic ketals. V. Transformations products of adrenosterone. The synthesis of related $C_{19}O_3$ steroids. *J. Org. Chem.*, 1953, **18**, 1166–1175.
6. Mori, K., Sakakibara, M., Ichikawa, Y., Ueda, H., Okada, K., Umemura, T., Yabuta, G., Kuwahara, S., Kondo, M., Minobe, M. & Sogabe, A. Synthesis of (22S,23S)-homobrassinolide from stigmasterol. *Tetrahedron*, 1982, **38**, 14, 2099–2109.
7. Migliuolo, A., Piccialli, V. & Sica, D. Structure elucidation and synthesis of 3β,6α-dihydroxy-9-oxo-9,11-seco-5α-cholest-7-en-11-al, a novel 9,11-secosterol from the sponge *Spongia officinalis*. *Tetrahedron*, 1991, **47**, 37, 7937–7950.
8. Nutaitis, C. F. & Gribble, G. W. Chemoselective reduction of aldehydes with tetra-*n*-butylammonium triacetoxyborohydride. *Tetrahedron Lett.*, 1983, **24**, 4287–4290.
9. Stork, G., Takahashi, T., Kawamoto, I. & Suzuki, T. Total synthesis of prostaglandin $F_{2\alpha}$ by chirality transfer from D-glycose. *J. Am. Chem. Soc.*, 1978, **100**, 8272–8273.
10. Pika, J., Tischler, M. & Andersen, R. J. Glaciasterols A and B, 9,11-secosterols from the marine sponge *Aplysilla glacialis*. *Can. J. Chem.*, 1992, **70**, 1506–1511.
11. Lopp, A., Pihlak, A., Paves, H., Samuel, K., Koljak, R. & Samel, N. The effect of 9,11-secosterol, a newly discovered compound from the soft coral *Gersemia fruticosa*, on the growth and cell cycle progression of various tumour cells in culture. *Steroids*, 1994, **59**, 274–281.
12. Lu, Q. & Faulkner, D. J. Two new sesterterpenoids and new 9,11-secosterol from *Spongia matamata*. *J. Nat. Prod.*, 1997, **60**, 195–198.
13. Koljak, R., Pehk, T., Järving, I., Liiv, M., Lopp, A., Varvas, K., Vahemets, A., Lille, Ü. & Samel, N. New antiproliferative 9,11-secosterol from the soft coral *Gersemia fruticosa*. *Tetrahedron Lett.*, 1993, **34**, 12, 1985–1986.