Synthesis of the AB-Ring of 9,11-Secosterols

Riina Aav[a]*, Tõnis Kanger,[b] Tõnis Pehk,[c] Margus Lopp[a]

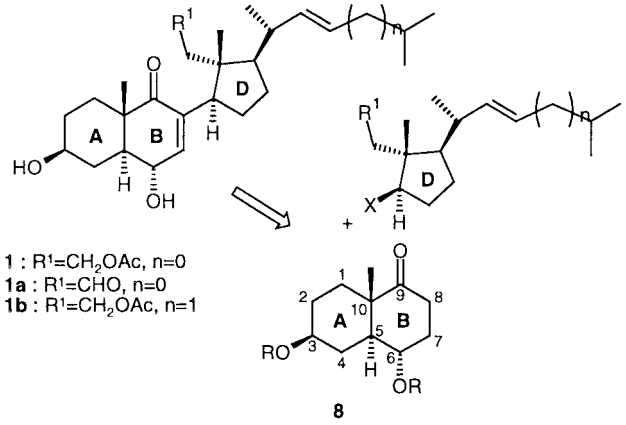
[a]Tallinn Technical University, Department of Chemistry, Ehitajate tee 5, Tallinn 19086, Estonia
[b]Tallinn Technical University, Institute of Chemistry, Akadeemia tee 15, Tallinn 12618, Estonia
[c]National Institute of Chemical Physics and Biophysics, Akadeemia tee 23, Tallinn 12618 Estonia
Fax 372 6547520; E-mail: riina@chemnet.ee
Received 26 January 2000

Abstract: The first total synthesis of AB-ring system of an antiproliferative and cytotoxic 9,11-secosterol **1** is described. Enantiomerically pure (3*S*,5*S*,6*S*,10*S*)-3,6-diacetoxy-10-methylbicyclo[4.4.0]-decan-9-one **8** (steroidal numeration) was prepared from *(S)*-Wieland-Miescher ketone.

Key words: diastereoselectivity, hydroborations, bicyclic compounds, sterols, total synthesis

9,11-Secosterols are a new class of biologically active terpenoids found in different marine organisms. The first 9,11-secosterol was isolated from gorgonia *Pseudopterogorgia americana* by E. L. Enwall et al. in 1972.[1] 9,11-Secosterol **1**, which was isolated from the White Sea soft coral *Gersemia fruticosa*,[2] exhibits strong antiproliferative and cytotoxic activity.[3] Also, its congeners **1a** and **1b** reveal cytotoxic activity.[4] These compounds are of particular importance in organic synthesis due to their high biological activity.

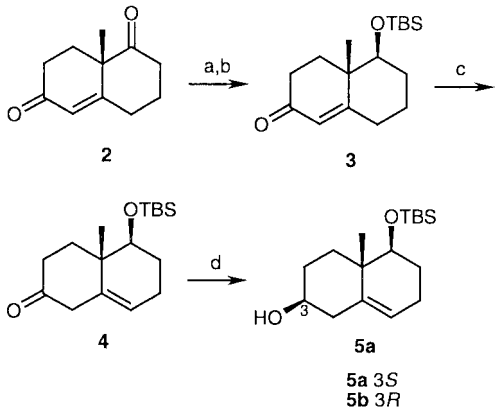
All the schemes of the synthesis of 9,11-secosterols published to date[5,6] are based on natural sterols as the starting compounds. We have envisioned the possible strategy for the total chemical synthesis of secosterol **1** and its analogues **1a**, **1b** by coupling of two main structural units (Scheme 1).



Scheme 1

In the present communication we describe a straightforward synthesis of the AB-fragment **8** of 9,11-secosterol. Readily available *(S)*-Wieland-Miescher ketone **2**[7] is an ideal precursor for building the AB-ring fragment as it possesses an appropriate carbon skeleton and has possible sites for the introduction of functional groups. Our strategy is based on the migration of the double bond to the ring B and following stereoselective hydroboration affording the appropriately substituted rings in *trans*-configuration.[8]

The synthesis started with the stereoselective reduction of ketone **2** by sodium borohydride,[9] followed by the protection of the hydroxyl group with *tert*-butyldimethylsilyl chloride, affording enone **3** in 75% (disilylated dienol ether was also isolated in *ca* 10% yield)[10] (Scheme 2).

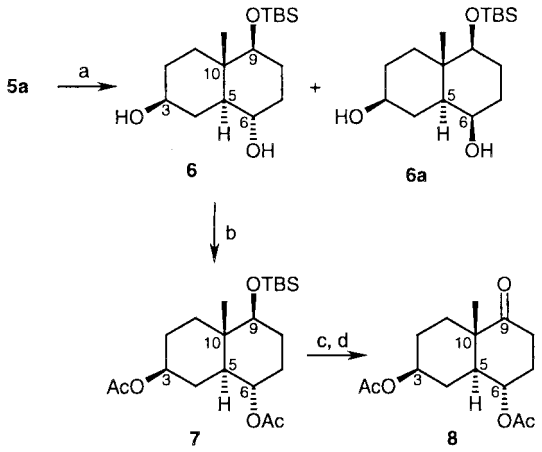


a: $NaBH_4$, CH_2Cl_2/MeOH, -78 °C, 97%; **b:** TBSCl, imidazole, DMF, 45 °C, 75%,; **c:** i) tBuOK, tBuOH, ii) 10%AcOH, 0 °C; **c:** $LiAl(OtBu)_3H$, THF, 0 °C, yield of **5a** 54% from **3**; **d:** L-Selectride, THF, -78 °C **5b**.

Scheme 2

The migration of the double bond[11] was accomplished by a generation of the thermodynamically more favoured potassium enolate, which after treatment with 10% acetic acid gave the desired ketone **4** (quite unstable). Both, the drying agent ($MgSO_4$) and silica gel were too acidic and caused the migration of the isolated double bond in compound **4** back to a conjugated position of the enone. Therefore, ketone **4** was used in the following transformation without any purification (the crude product was only dried on potassium carbonate). Reduction of **4** by L-Selectride afforded **5b** as the main product (**5a:5b** ratio 4:96). The use of a lithium tri-*tert*-butoxy aluminium hydride[12] resulted in the formation of 3*S* compound **5a**[13] in 54% overall yield (from **3**, de 97%, according to the GC).

Next, a three-step protocol was employed to convert unsaturated alcohol **5a** to the target AB-ring synthon (Scheme 3). It was found that the diastereoselectivity of the hydroboration of compound **5a** depends considerably on the reaction temperature (Table 1).



a: i) 2eq $BH_3{\cdot}(CH_3)_2S$, THF, ii) NaOH, H_2O_2, 0 °C, **6**:71%; **b:** Ac_2O, 0.1eq DMAP, Py, r.t., 82%; **c:** Bu_4NF, THF, r.t., 97%; **d:** PCC, CH_2Cl_2, r.t., 70%

Scheme 3

Table 1 Hydroboration of hydroxy alkene **5**.

No	Time	Temp.	Unreacted (%)	Isolated yield (%)	
	(h)	(°C)	**5a**[a]	**6**	**6a**
1	2.5	65	8	71	5
2	22.5	35	39	30	26

[a] Determined by GC from the crude product.

A dramatic difference in the diastereoselectivity of hydroboration was observed at selected conditions (ratio **6:6a** varied from 1.1:1 to 14:1). Also, surprisingly enough, by-product **6a**[14] has the C5-H and C6-OH in *trans*–configuration. The target intermediate **6**[15] has the expected stereochemistry at carbons C3, C5, C6, C10 and oxygen functions at C3, C6 and C9, which is consistent with the configurations of 9,11-secosterol **1**.

The synthesis of the target AB-fragment was completed by oxidation of the hydroxyl group at C9. Thus, the hydroxyl groups in diol **6** were first protected as acetates in good yield (*ca* 8% of the corresponding diastereomeric acetate of **7a**,[16] readily separable on silica gel, was also detected). Silyl ether **7** was deprotected, and the obtained C9 secondary alcohol was oxidised by PCC to afford ketone **8**[17] in 70% yield (de > 98%, determined by NMR).

As a result, we have developed a reliable method for the synthesis of the AB-fragment **8** of 9,11-secosterol **1**. Three new stereogenic centres with strictly controlled configuration were created during the synthesis. The availability of the enantiomeric starting ketone **2** and highly diastereoselective introduction of the functional groups make the described method valuable for practical use.

Further study of the presented scheme as well as the synthesis of the D-ring of 9,11-secosterol is in progress and will be published in due course.

Acknowledgement

We would like to thank Estonian Science Foundation for supporting the present work through Grant Nos. 3781, 3164 and 2293 and also A.-M. Müürisepp for the mass spectra of the compounds reported herein.

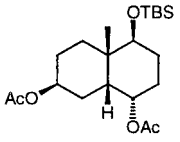
References and Notes

(1) Enwall, E. L.; Van der Helm, D.; Hsu, I. N.; Pattabhiraman, T.; Schmitz, F. J.; Spraggins, R. L.; Weinheimer, A. J. *J. Chem. Soc. Chem. Comm.* **1972**, 215.
(2) Koljak, R.; Pehk, T.; Järving, I.; Liiv, M.; Lopp, A.; Varvas, K.; Vahemets, A.; Lille, Ü.; Samel, N. *Tetrahedron Lett.* **1993**, *34*, 1985.
(3) Lopp, A.; Pihlak, A.; Paves, H.; Samuel, K.; Koljak, R.; Samel, N. *Steroids* **1994**, *59*, 274.
(4) Koljak, R.; Lopp, A.; Pehk, T.; Varvas, K.; Müürisepp A.-M.; Järving, I.; Samel, N. *Tetrahedron* **1998**, *54*, 179.
(5) Migliuolo, A.; Piccialli, V.; Sica, D. *Tetrahedron* **1991**, *47*, 7937. Migliuolo, A.; Piccialli, V.; Sica, D. *Steroids* **1992**, *57*, 344.
(6) For the synthesis of secosterol **1**: Kuhl, A.; Kreiser, W. *Tetrahedron Lett.* **1998**, *39*, 1145. Kuhl, A.; Kreiser, W. *Collect. Czech. Chem. Commun.* **1998**, *63*, 1007. Jäälaid, R.; Järving, I.; Pehk, T.; Lille, Ü. *Proc. Estonian Acad. Sci. Chem.* **1998**, *47*, 39. *Chem. Abstr.* **1998,** *129*, 4776n. Jäälaid, R.; Järving, I.; Pehk, T.; Lille, Ü. *Proc. Estonian Acad. Sci. Chem.* **1998**, *47*, 196. *Chem. Abstr.* **1999**, *130*, 282221z.
(7) Buchschacher, P.; Fürst, A.; Gutzwiller, J. *Org. Synth.* **1990**, Col. Vol. *7*, 368.
(8) An elegant method for the synthesis of similar *cis*-AB-fragment was recently reported. Kurosu, M.; Marcin, L. R.; Grinsteiner, T. J.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 6627.
(9) Ward, D. E.; Rhee, C. K.; Zoghalb, W. M. *Tetrahedron Lett.* **1988**, *29*, 517.
(10) The structures of all products were confirmed by ^1H, ^{13}C NMR and 2D FT COSY spectra.
(11) Sondheimer, F.; Elad, D. *J. Am. Chem. Soc.* **1957**, *79*, 5542. Cheung, W. S.; Wong, H. N. C. *Tetrahedron* **1999**, *55*, 11001. Rychnovsky, S. D.; Mickus, D. E. *J. Org. Chem.* **1992**, *57*, 2732.
(12) Minnaard, A. J.; Stork, G. A.; Wijnberg, J. B.; Groot, A. *J. Org. Chem.* **1997**, *62*, 2344.
(13) Compound **5a** (*3S*): ^1H NMR (500 MHz, $CDCl_3$), δ: 1.08 (dt, H-1α, *J* = 4.0, 13.4 Hz), 1.94 (td, H-1β, *J* = 3.4, 13.4 Hz), 1.52 (m, H-2β), 1.87 (m, H-2α), 3.52 (tt, H-3α, *J* = 4.6, 11.3 Hz), 2.18 (m, H-4β), 2.34 (ddd, H-4α, *J* = 2.3, 4.8, 13.1 Hz), 5.28 (m, H-6), 2.04 (m, H-7αβ), 1.56 (m, H-8α), 1.72 (dq, H-8β, *J* = 6.8, 12.5 Hz), 3.43 (dd, H-9α, *J* = 3.4, 11.8 Hz), 1.04 (s, C-10-CH_3), 0.90 (s, *t*-Bu), 0.04 and 0.06 (s, Si- CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$), δ: from C-1 to C-10, C-10-CH_3 and Si-block: 36.57, 31.47, 71.75, 41.67, 140.06, 120.94, 24.79, 27.56, 78.41, 39.49, 17.55, -3.98, -4.88, 25.85, 18.05.

(14) Compound **6a**: ^{1}H NMR (500 MHz, $CDCl_3$), δ: 0.85 (mt, H-1α, *J* = 13Hz), 1.68 (m, H-1β), 1.36 and 1.72 (m, H-2αβ), 3.50 (tt, H-3α, *J* = 5, 10 Hz), 1.56 (m, H-4αβ), 1.01 (td, H-5α, *J* = 3, 12.5 Hz, pointing to β-orientation of 6-OH), 3.60 (m, H-6α, missing of *J* values more than 10 Hz points to equatorial (α) orientation of this carbinol proton), 1.50 and 1.71 (m, H-7αβ), 1.39 (m, H-8α), 1.80 (mq, H-8β, *J* = 12 Hz, low field chemical shift of this axial proton is caused from the proximity of 6β-OH group), 3.12 (dd, H-9α, *J* = 4.2, 11.4 Hz), 0.97 (s, C-10-CH_3, low field chemical shift as compared with **6** is caused from the proximity with 6β-OH group), 0.81 (s, *t*-Bu), -0.03 and -0.05 (s, Si- CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$), δ: from C-1 to C-10, C-10-CH_3 and Si-block: 37.60, 30.76, 71.17, 33.99, 45.12, 70.43, 31.78, 26.14, 79.82, 38.67, 13.01, -4.19, -5.07, 25.64, 17.89, comparison of these chemical shifts with the values of **6** confirms the configuration of **6a**. EIMS m/z 314(M^+), 299, 257, 221, 147, 75.

(15) Compound **6**: ^{1}H NMR (500 MHz, $CDCl_3$), δ: 0.81 (mt, H-1α, *J* = 13 Hz), 1.63 (m, H-1β), 1.23 (dq, H-2β, *J* = 4.0, ~13 Hz), 1.61 (m, H-2α), 3.33 (tt, H-3α, *J* = 4.5, 11.2 Hz), 0.98 (q, H-4β, *J* = 12 Hz), 1.89 (md, H-4α, *J* = 12 Hz), 0.80 (m, H-5α), 3.18 (dt, H-6β, *J* = 4.7, 11 Hz), 1.09 (m, H-7α), 1.77 (qd, H-7β, *J* = 4, 12.7 Hz),1.43 (m, H-8αβ), 3.03 (dd, H-9α, *J* = 6.5, 9.4 Hz), 0.66 (s, C-10-CH_3), 0.70 (s, *t*-Bu), -0.14 and -0.15 (s, Si- CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$), δ: from C-1 to C-10, C-10-CH_3 and Si-block: 36.38, 29.92, 70.44, 31.37, 48.21, 68.29, 33.14, 29.12, 78.69, 38.77, 10.73, -4.51, -5.34, 25.38, 17.63.

(16) The formation of **7a** is probably caused by the presence of strong base DMAP.



7a

Compound **7a** gave at room temperature exchange broadened spectra, pointing to the presence of *cis* ring junction. In ^{13}C NMR spectrum there are 3 secondary carbinol carbons at 69.88 (sharp), 71.74 (broad) and 73.5 (very broad); 5 methylene carbons at 25.49, 26.6 (broad), 27.35, 27.4 (broad), 29.44; 10-CH_3 at 23.06, C-5 at 40.96, C-10 at 38.93, 2 acetyl groups at 170.63, 170.28, 21.33, 21.21, OTBS at -4.29, -4.89, 18.15, 25.90. In exchange broadened ^{1}H NMR spectrum sharp signals are obtained from two acetyl groups at 2.01 and 2.08 ppm, from 10-CH_3 at 1.08 and from OTBS at 0,91 and 0.05 ppm. Three exchange broadened carbinol protons are observed at 3.41 (H-9) and 4.90-4.92 (H-3, H-6). Relatively narrow signal from H-5 at 1.92 ppm (confirmed by ^{1}H-^{13}C 2D FT COSY) shows two 3 Hz and one 10 Hz coupling, thus pointing to the prevailing conformation in which H-5 is equatorial to B ring in this compound.

(17) Analytical data for compound **8**:
White crystals with m.p. 111-114 °C; $[\alpha]^{22}_{546}$ -89° (c 1, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$), δ: 1.55 (dt, H-1α, *J* = 2.8, 14 Hz), 1.78 (m, H-1β), 1.92 (m, H-2α), 1.49 (m, H-2β), 4.62 (tt, H-3α, *J* = 4.6, 11.2 Hz), 1.40 (q, H-4β, *J* = 12 Hz), 1.97 (m, H-4α),1.75 (m, H-5α), 5.06 (dt, H-6β, *J* = 4.5, 10.8 Hz), 1.65 (m, H-7α), 2.33 (m, H-7β),2.33 (m, H-8α), 2.76 (m, H-8β), 1.20 (s, C-10-CH_3), 2.03 and 2.06 (s, Ac); ^{13}C NMR (125.7 MHz, $CDCl_3$), δ: from C-1 to C-10, C-10-CH_3 and Ac: 30.93, 26.32, 71.93, 28.29, 45.95, 70.01, 30.86, 35.00, 212.45, 46.39, 16.67, 170.38, 170.70, 21.09, 21.28. CIMS (isopropane) m/z 283 (MH^+), 223, 163.

Article Identifier:
1437-2096,E;2000,0,04,0529,0531,ftx,en;G02100ST.pdf