PROGRESS IN PARTIAL SYNTHESIS OF A MARINE SECOSTEROL FROM *Gersemia fruticosa*: PREPARATION OF THE STEROIDAL CORE UNIT

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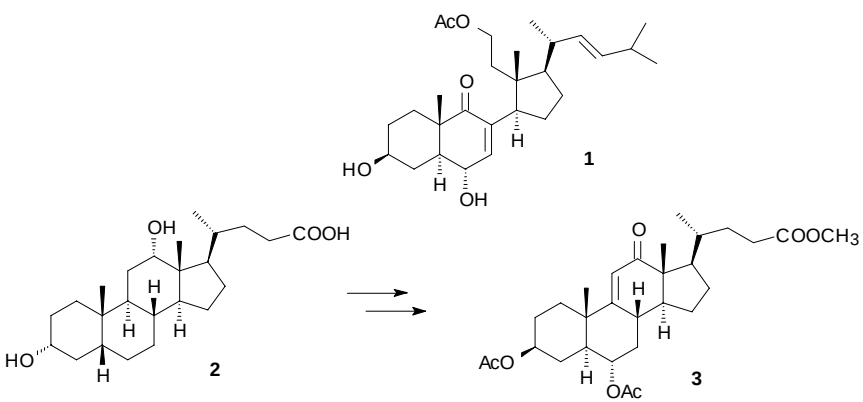
Received June 23, 1998
Accepted June 26, 1998

Dedicated to Dr Jan Fajkos on the occasion of his 75th birthday.

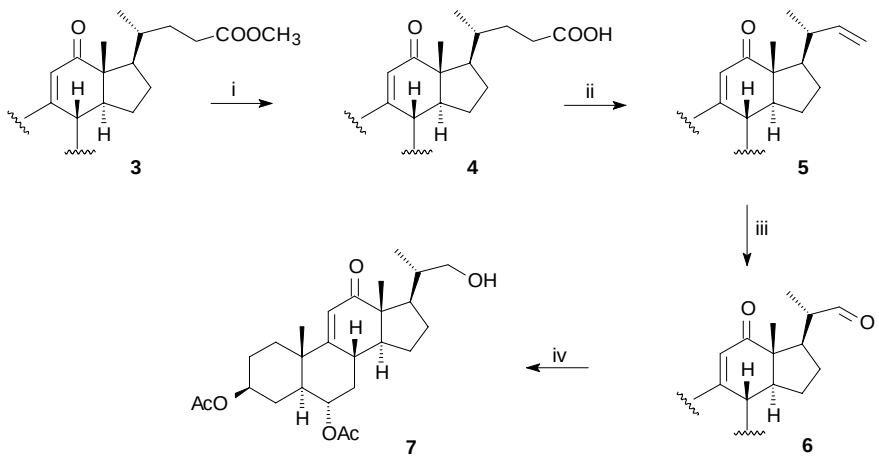
The synthesis of the requisite protected steroidal core unit **13** *en route* to secosterol **1**, a cytotoxic constituent of the soft coral *Gersemia fruticosa*, is described. The conversion of the intermediate precursor **3** into **13** succeeds through oxidative side chain degradation, deoxygenation of C-12 *via* reductive desulfurization and cleavage of the C-ring moiety by ozonolysis.
Key words: Steroids; Seco sterols; Cytotoxic effect; Soft coral.

Among the very few known examples of marine sterols containing the 9,11-*seco* moiety[1–3] some exhibit interesting biological activity[2,3], as the constituents of *Gersemia fruticosa* Sars 1860 (refs[2d,3]), which display a potent antiproliferative and cytotoxic effect[4]. Therefore secosterol **1**, the main constituent[2d] from this Arctic Ocean soft coral represents an attractive aim for synthesis[5]. In our introductory communication[6] we described the preparation of the intermediate precursor **3**, starting from cheap desoxycholic acid (**2**). Herein we wish to report on further progress to the target molecule **1** (Scheme 1).



SCHEME 1

Further pursuing our synthesis, the protected C-24 carboxyl moiety of **3** was considered a synthon for a C-22 aldehyde group, essential for later introduction of the correct side chain[7]. In order to degrade the cholanoic acid[8] at this stage the C-24 methyl ester had to be cleaved chemoselectively. This was achieved by treatment of enone **3** with lithium iodide in dry pyridine under reflux[9]. Alternatively, acid **4** (Scheme 2) was prepared *via* saponification with sodium hydroxide in THF and subsequent reacetylation. However, the latter process with 79% yield appears less satisfactory. Oxidative decarboxylation of **4** with lead tetraacetate and copper diacetate[10] leads – after alkaline extraction – to alkene **5** in quantitative yield, based on 67% conversion. In order to further accomplish the side chain degradation the Δ^{22} double bond had to be cleaved. If **5** was exposed to 1.5 equivalents of ozone in a solution of dichloromethane at –78 °C the monosubstituted double bond was readily split, rendering their $\Delta^{9(11)}$ counterpart uneffected.

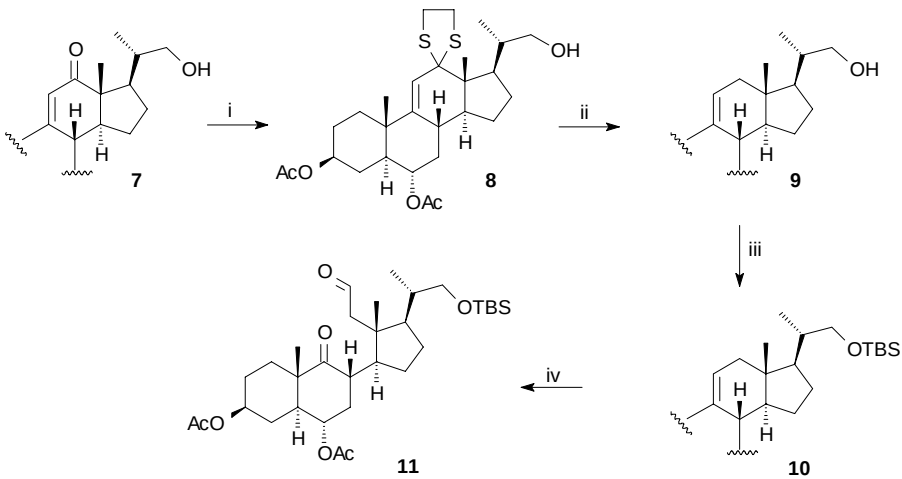


(i) LiI.3H_2O, py, Δ (100%); (ii) $Pb(OAc)_4$, $Cu(OAc)_2.H_2O$, C_6H_6, Δ (100%);
(iii) O_3, CH_2Cl_2, -78ºC, then Zn, AcOH, RT (98%); (iv) $LiAlH(OtBu)_3$, THF, 0ºC (98%)

SCHEME 2

Originally alcohol **7** has been considered a protected precursor of **6**, therefore a reductive work-up procedure employing Me_2S (ref.[11]) followed by $LiAlH(OtBu)_3$ in THF (ref.[12]) was applied. Unfortunately, the two intermediate ozonides of **5** turned out to be surprisingly stable. Under various conditions mixtures of ozonides and alcohol **7** could be isolated. Since complete decomposition of the corresponding ozonides succeeds by treatment with zinc in acetic acid[13] only, we had to isolate aldehyde **6** first. Subsequent chemoselective reduction[12] with $LiAlH(OtBu)_3$ left the C-12 carbonyl function untouched and lead to alcohol **7** in a yield of 96%, with respect to starting enone **3**.

Deoxygenation of **7** proceeded smoothly *via* Lewis acid catalyzed thioketalisation[14] and subsequent reductive desulfurization with neutrally washed Raney nickel[15]. The corresponding alkene **9** was obtained after filtration from the catalyst and then quantitatively protected as TBS ether according to a procedure by Corey[16]. Ozonolytic cleavage of the $\Delta^{9(11)}$ double bond depended tremendeously on the solvent involved, *e.g.* ozonolysis of **10** in CH_2Cl_2 and methanol[17] resulted mainly in the corresponding epoxide. However, treatment of **10** with 1.5 equivalents of ozone in a 2 : 1 mixture of CH_2Cl_2 and ethyl acetate at –78 °C gave rise – after reductive work-up with Me_2S and column chromatography – to pure **11** in 46% yield with respect to alcohol **7**. The sequence depicted in Scheme 3 may therefore be regarded as an economic alternative for the preparation of the 9,11-*seco* moiety in comparison with the known procedure[1d], which requires stoichiometrical amounts of OsO_4.

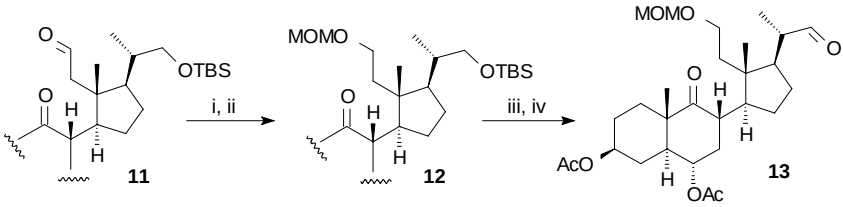


(i) $HSCH_2CH_2SH$, $BF_3.Et_2O$, RT (95%); (ii) Raney-Ni, EtOH, Δ (96%);
(iii) TBSCl, DMF, Im, RT (100%); (iv) O_3, CH_2Cl_2, AcOEt, -78ºC, then Me_2S, RT (50%)

SCHEME 3

The remaining steps leading straightforward to relay material **13** are summarized in Scheme 4. Reduction of **11** with $LiAlH(OtBu)_3$ proceeded predominantly at the sterically less hindered formyl group, as anticipated[18] with the minor formation of the corresponding 9β-diol. This mixture of alcohols was carried through the following reactions without separation, since the protection of the primary C-11 hydroxy group as MOM ether proceeds chemoselectively with MOMCl and diisopropylethylamine[19]. Cleavage of the C-22-silyl ether with the HF·pyridine complex under buffered anhydrous conditions left the acetale moiety in **12** untouched. Finally, Swern oxidation[20] quantitatively

converted the C-22 alcohol and its still accompanying 9β-diol, as well into aldehyde **13**, which was obtained after purification by chromatography as a colourless oil[21] with 41% yield in 13 steps, based on the starting precursor **3**.



(i) LiAlH(O*t*Bu)$_3$, THF, -50°C; (ii) MOMCl, *i*Pr$_2$NEt, CH_2Cl_2, 0°C; (iii) HF.py, py/CH_3CN, 0°C; (iv) Swern (93% overall)

SCHEME 4

With aldehyde **13** an appropriately protected core unit for the introduction of the *nor*-cholestene side chain of **1** is available. The completion of our synthesis directed towards the natural target **1** hopefully will form the last part of our communications in due course.

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21. Spectroscopic data of **13**: $[\alpha]_D^{20}$ +4° (*c* = 0.95, $CHCl_3$); IR (KBr), 2 704 cm^{-1} (C–H, CHO), 1 734 cm^{-1} (C=O, aldehyde and acetates), 1 717 cm^{-1} (C=O, ketone); ^1H NMR (400.13 MHz, $CDCl_3$) δ 0.70 (3 H, s, Me-18), 0.90 (3 H, d, *J* = 7.0 Hz, Me-21), 1.19 (3 H, s, Me-19), 1.98 (3 H, s, OCOC**H**$_3$), 2.02 (3 H, s, OCOC**H**$_3$), 2.17–2.23 (1 H, m, H-4), 2.34–2.38 (1 H, m, H-20), 2.50–2.54 (1 H, m, H-14), 2.91–2.96 (1 H, m, H-8), 3.27 (3 H, s, OCH_3), 3.44–3.49 (2 H, m, H_2-11), 4.44–4.49 (2 H, q, *J* = 6.5 Hz, OCH_2O), 4.54–4.60 (1 H, m, H-3), 5.05–5.11 (1 H, m, H-6), 9.58 (1 H, d, *J* = 3.5 Hz, H-22); ^{13}C NMR ($CDCl_3$) δ 14.2 (q, C-18), 16.8 (q, C-21), 17.9 (q, C-19), 21.1 (q, OCO**C**H$_3$), 21.3 (q, OCO**C**H$_3$), 22.8 (t, C-15), 24.9 (t, C-16) 26.4 (t, C-2), 28.2 (t, C-7), 31.2 (t, C-1), 36.4 (t, C-4), 37.2 (t, C-12), 40.4 (d, C-14), 41.0 (d, C-8), 45.4 (s, C-13), 46.4 (d, C-17), 46.5 (s, C-10), 47.5 (d, C-5), 47.7 (d, C-20), 55.1 (q, OCH_3), 63.5 (t, C-11), 70.4 (d, C-6), 71.9 (d, C-3), 96.3 (t, OCH_2O), 170.4 (s, O**C**OCH$_3$), 170.7 (s, O**C**OCH$_3$), 205.0 (d, C-22), 212.5 (s, C-9); MS *m/z* (%): 508 ($M^{+\bullet}$, 1), 463 ($M^{+\bullet}$ – MOM, 26), 448 ($M^{+\bullet}$ – AcOH, 12), 447 ($M^{+\bullet}$ – MOMO, 12), 416 ($M^{+\bullet}$ – MOMO – AcOH, 10), 388 ($M^{+\bullet}$ – 2 AcOH, 14).