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Partial Synthesis of a Marine Secosterol from *Gersemia fruticosa*: Preparation of the Intermediate Precursor 3β,6α-Diacetoxy-24-methyl-12-oxo-5α-chol-9,11-en-24-oate

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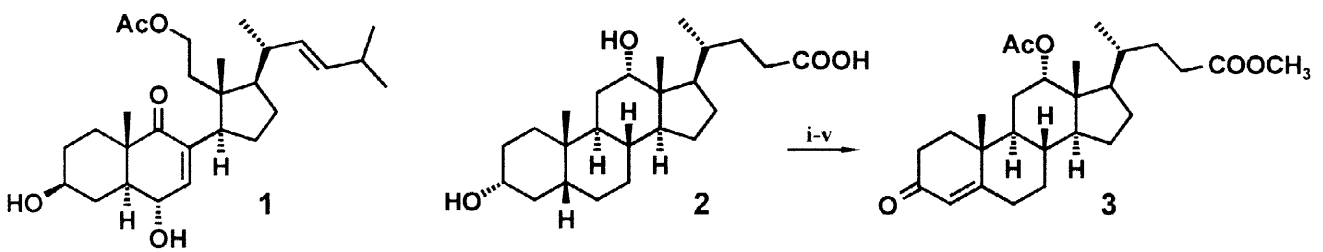
Abstract: The conversion of desoxycholic acid (**2**) into the title compound **14** by 13 respectively 17 steps is described herein, including stereoselective construction of C-3 and C-6 hydroxy moieties and introduction of a $\Delta^{9,11}$ double bond by dehydrogenation. **14** is believed to serve as a putative precursor for the synthesis of secosterol **1**, isolated from the soft coral *Gersemia fruticosa*.

Target molecule **1**, a highly oxygenated 9,11-secosteroid, first isolated from North Pacific soft coral *Gersemia fruticosa*[1], represents one for many known examples of sterols by marine origin[2,3]. The natural product exhibits a strong antiproliferative and cytotoxic effect, which is attributed to its interaction in m-phase of mitosis[4]. Because of its attractive biological activity secosterol **1** is believed to be a rewarding aim for synthesis. In this communication we wish to describe the first part[5] of our envisaged synthesis of secosterol **1**.



Scheme 1: **i) Ac_2O, AcOH, Δ (ii) MeOH, HCl, Δ (iii) Jones ox. (iv) Br_2, AcOH (v) LiCl, DMF, 85 °C (70% overall)**

Desoxycholic acid **2** was chosen as a starting material, since it carries at C-3, C-12 and C-24 suitable functions for modification[6]. This in mind, enone **3** was formed (scheme 1) by an optimized five step sequence according to Reichstein[7] in an 150 mmol scale. The following reductive rearrangement of the enone moiety in **3** facilitates later B-ring manipulations (scheme 2). Therefore, dienolacetate **4** was prepared quantitatively[8] by treatment of **3** with isopropenyl acetate[9] and a catalytic amount of concentrated H_2SO_4. Its reduction[10] with $NaBH(OCH)_3$ leads diastereoselectively to the 3β-configurated homoallylalcohol **5** in 61 % yield, apart from 21 % of diol **6** (scheme 4), which was easily separated by chromatography. The requisite assignment of confi-

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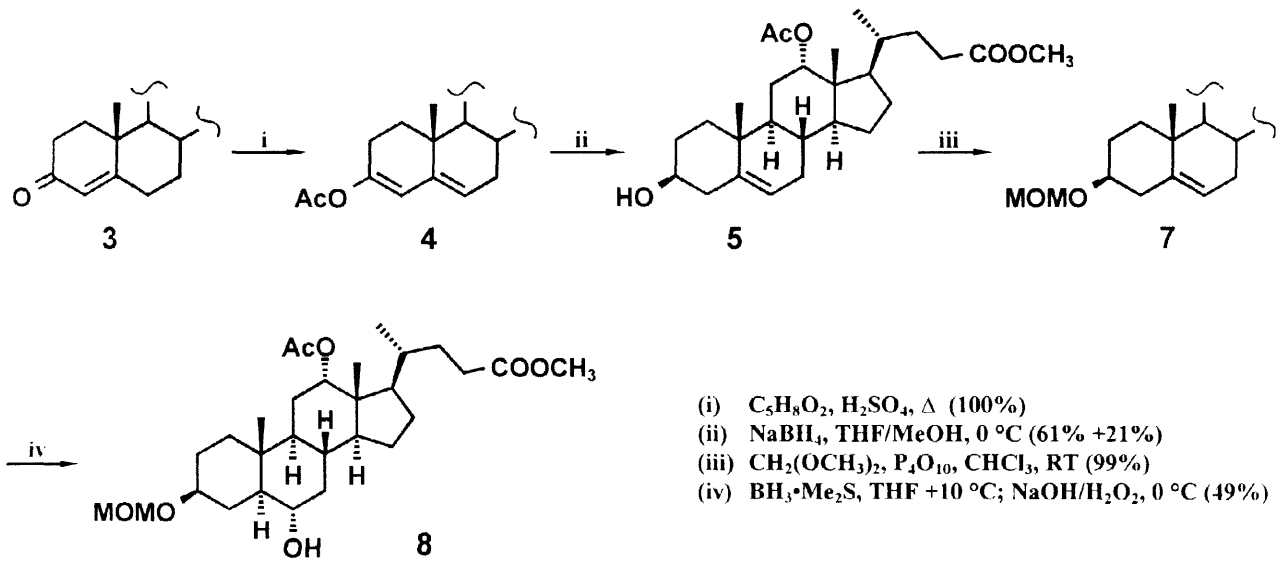
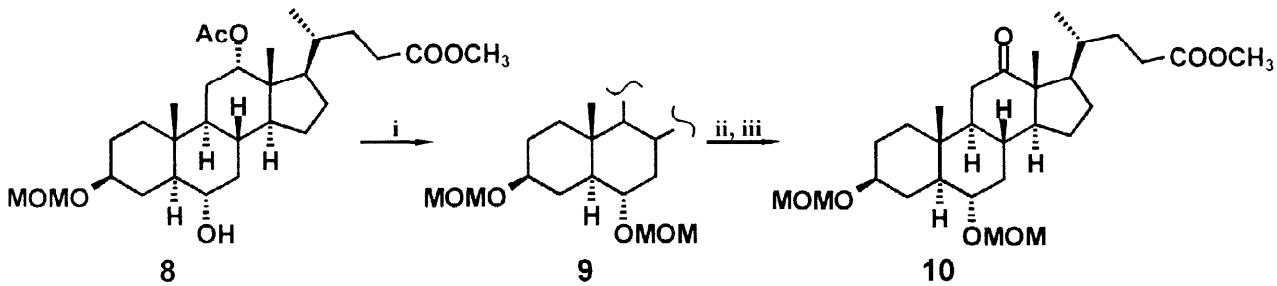
guration at C-3 was done through ^{1}H NMR spectroscopy. Significantly, the α-H (C-3) in **5** and **6** displays a broad multiplet between 3.46 and 3.54 ppm[11]. Since direct hydroboration of homoallylalcohol **5** was accompanied by loss of both chemo- and stereoselectivity, **5** was protected as methoxymethyl ether using the procedure by Fujita and coworkers[12]. Subsequent hydroboration[13] with BH_3•Me_2S provides after oxidative work up the 6α-hydroxy compound **8** in 49 % yield. These optimized results have been obtained by utilizing 1.1 equivalent of borane reagent at +10 °C for 27 h. The moderate yield of this step is partly due to losses of the protective groups at C-3 and C-12, respectively, apart from formation (5-10 %) of the undesired 5β,6β-diastereomer of **8** .



Scheme 2:

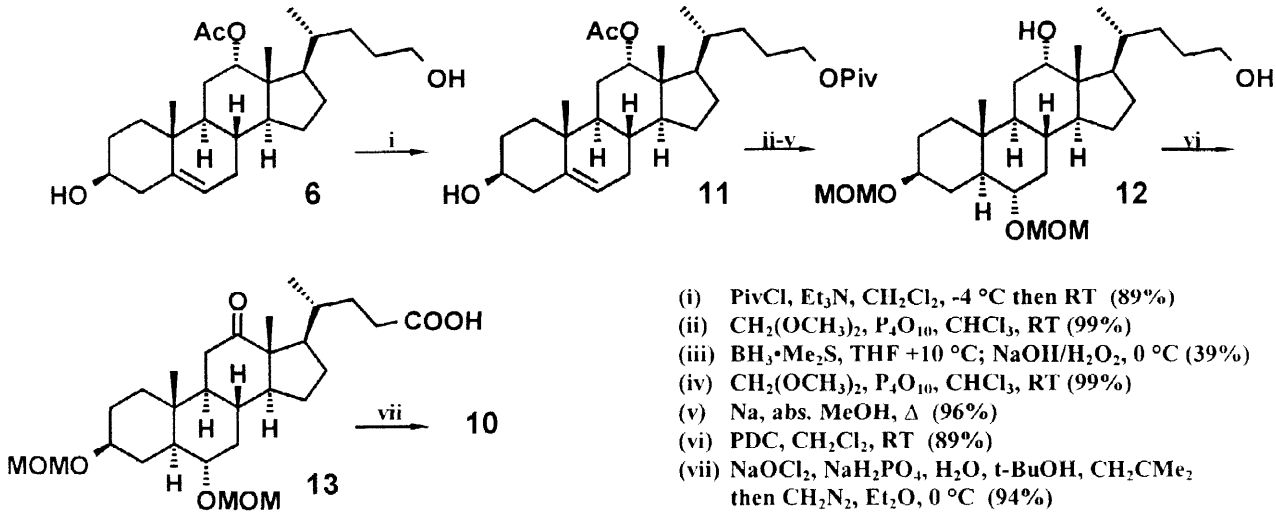
Normal transacetalization[7] in this case (scheme 3) leads to the dimethoxymethyl ether **9**, in quantitative yield, too. Selective deprotection of the 12α-acetate of **9** succeeds through methanolysis. The yield of the latter process was advantageously increased by the use of sodium metal in abs. methanol. Oxidation with PDC[14] in dichloromethane provides ketone **10** in a yield of 44 % with respect to homoallylalcohol **5**.



Scheme 3: i) $CH_2(OCH_3)_2$, P_4O_{10}, $CHCl_3$, RT (ii) Na, abs. MeOH, Δ (iii) PDC, CH_2Cl_2, RT (90% overall)

In order to increase the total yield of the sequence, the side product **6** from reduction was transformed into the desired ketone **10**, as well: The C-24 hydroxy group had to be protectected first. This was selectively accomplished by pivaloylation. By virtue of higher selectivity and yield the use of dichloromethane and triethylamine

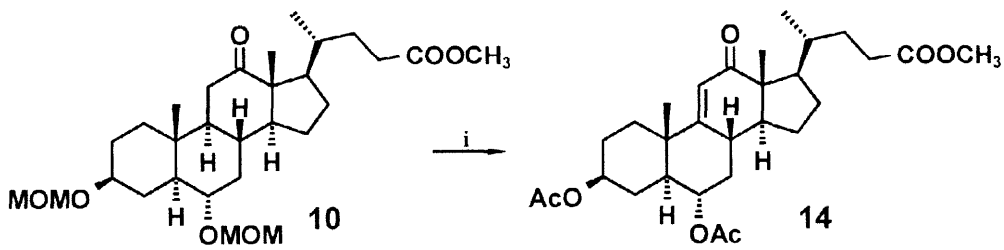
is superior to the application of pyridine[15]. The latter base also leads to the formation of the corresponding dipivaloate in 50 % yield. By the above described sequence (schemes 2 and 3) **11** could be transformed into diprotected tetrol **12**, which was subsequently oxidized[14,16] by PDC and $NaOCl_2$ to give ketoacid **13**. The desired methylester is formed simply by treatment of **13** with an etheral solution of diazomethane in a 27 % yield with respect to starting diol **6**.



(i) PivCl, Et_3N, CH_2Cl_2, -4 °C then RT (89%)
(ii) $CH_2(OCH_3)_2$, P_4O_{10}, $CHCl_3$, RT (99%)
(iii) $BH_3{\cdot}Me_2S$, THF +10 °C; NaOH/H_2O_2, 0 °C (39%)
(iv) $CH_2(OCH_3)_2$, P_4O_{10}, $CHCl_3$, RT (99%)
(v) Na, abs. MeOH, Δ (96%)
(vi) PDC, CH_2Cl_2, RT (89%)
(vii) $NaOCl_2$, NaH_2PO_4, H_2O, t-BuOH, CH_2CMe_2 then CH_2N_2, Et_2O, 0 °C (94%)

Scheme 4:

The C-12 carbonyl moiety in **10** allows now the convenient introduction of the required $\Delta^{9,11}$-double bond[17]. For that purpose **10** was treated with SeO_2 in glacial acetic acid under reflux (scheme 5). For successful dehydrogenation a catalytic amount of 1 M HCl solution proved to be essential. After separation from grey selenium the raw material was solved in acetic anhydride for complete acetylation. Simple aqueous work up yields pure C-ring enone[18] **14** in 88 %, which means 44 % overall yield starting from **2**. Attempts to accomplish this reaction in other solvents than acetic acid, like pyridine, dioxane or ethanol failed.



Scheme 5: (i) SeO_2, AcOH 1M HCl, Δ then AcOH, Ac_2O, Δ (88%)

In our point of view enone **14** may serve as an appropriate intermediate for the synthesis of **1**, since convenient methods for side chain modification[19,20] are known in literature. Moreover, the $\Delta^{9,11}$ double bond allows further C-ring manipulation.

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18. Spectroscopic data of **14**: mp: 73-76 °C; $[\alpha]_D^{20}$: +76° (c=1.00, $CHCl_3$); IR (KBr) 1611 cm^{-1} (C=C), 1681 cm^{-1}(C=O), 1736 cm^{-1} (C=O, ac.); ^1H NMR (400.13 MHz, $CDCl_3$) δ 0.89 (3H, s, Me-18), 0.96 (3H, d, J= 6.0 Hz, Me-21), 1.12 (3H, s, Me-19), 2.00 (3H, s, $OCOC\underline{H}_3$), 2.01 (3H, s, $OCOC\underline{H}_3$), 3.62 (3H, s, COOMe), 4.56 - 4.65 (1H, m, H-3), 4.82 - 4.91 (1H, m, H-6), 5.63 (1H, s, H-11); ^{13}C NMR ($CDCl_3$) δ 10.7 (q, C-18), 19.1 (q, C-21), 19.2 (q, C-19), 21,1 (q, $OCO\underline{C}H_3$) 21.3 (q, $OCO\underline{C}H_3$), 24.0 (t, C-15), 26.8 (t,C-2), 27.4 (t,C-16), 28.4 (t, C-7), 30.5 (t, C-22), 31.3 (t, C-23), 34.5 (t, C-1), 35.3 (d, C-20), 26.5 (d, C-8), 37.4 (t, C-4), 39.2 (s, C-10), 45.8 (d, C-14), 46.9 (d, C-17), 51.4 (q, OMe), 53.1 (s, C-13), 53.4 (d, C-5), 70.7 (d, C-6), 72.1 (d, C-3), 120.9 (d, C-11), 165.3 (s, C-9), 170.4 (s, $O\underline{C}OCH_3$), 170.8 (s, $O\underline{C}OCH_3$), 174.6 (s, C-24), 205.2 (s, C-12); MS *e/z* (%): 502 (M^+, 5), 501 (13), 441 (79), 382 (32), 287 (33), 227 (100).
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