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A synthetic approach towards stoloniferones: synthesis of 11-acetyl-24-desmethyl-stoloniferone C

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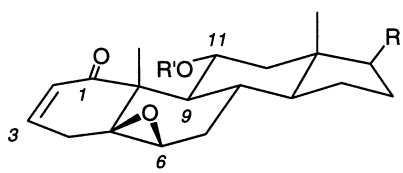
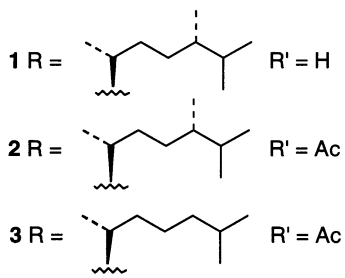
Abstract—The synthesis of 11α-acetoxy-5β,6β-epoxycholest-2-en-1-one, a compound containing the nuclear functionalities of the stoloniferones, is described starting from dihydrocholesterol. © 2001 Published by Elsevier Science Ltd.

The Okinawan soft coral *Clavularia viridis* is a marine invertebrate from which a remarkable array of bioactive secondary metabolites has been obtained. Among them the clavulones,[1] powerful antitumor prostanoids, the stoloniolides,[2] structurally unique steroids, the stoloniferones,[3] such as the cytotoxic stoloniferon C **1** and its acetylated derivative **2**,[4] can be listed. It is interesting to point out that most of the steroids isolated from *Clavularia viridis*[4,5] possess an epoxy-enone moiety, which is a current feature in some withanolides[6] and has been known as an important partial structure of cytotoxic solanoceus plant products.[7]





Described herein is the synthesis of 11α-acetoxy-5β,6β-epoxycholest-2-en-1-one **3**, that is the 11-acetyl-24-desmethylstoloniferone C **1**[3] or the 24-desmethyl analogue of the cytotoxic steroid **2**.[4]

The synthesis of compound **3** began with the stereoselective functionalization of the C ring (Scheme 1). This was easily achieved using the Breslow remote functionalization methodology.[8] Thus, commercially available dihydrocholesterol **4** was converted into the expected cholest-9(11)-en-3α-ol **6** via a three step process (77% overall yield from **4** to **6**).

Standard benzylation of **6** gave the $\Delta^{9(11)}$-steroidal ether **7**. This was subjected to a highly stereoselective hydroboration-oxidation reaction[9] (d.r.>95%, ^{1}H NMR analysis, 86% yield) to give the monobenzylated diol **8**. The equatorial nature of the alcoholic function at C-11 was confirmed through unambiguous rationalization of the ^{1}H NMR data of **8** which showed, for the C-11 methine proton, a *ddd* (J=10.5, 10.5, 5.2 Hz) at δ 3.91.

Silylation of the hindered C-11 hydroxy group with *tert*-butyldimethylsilyl trifluoromethanesulfonate and Pd-mediated debenzylation at C-3 afforded the monosilylated diol **9** (83%, two steps).

For the A and B ring functionalization we planned to follow a well established procedure[10a] including a selective quadruple dehydrogenation of **9**, transformation of the resulting trienone in the 11α-[(*tert*-butyldimethylsilyl)oxy]-cholest-5-en-1α,3β-diol following the Barton method,[10] and final elaboration of the required α,β-unsaturated ketone and β-epoxide functionalities.

Keywords: *Clavularia viridis*; stoloniferones; marine metabolites; steroids; cytotoxins.

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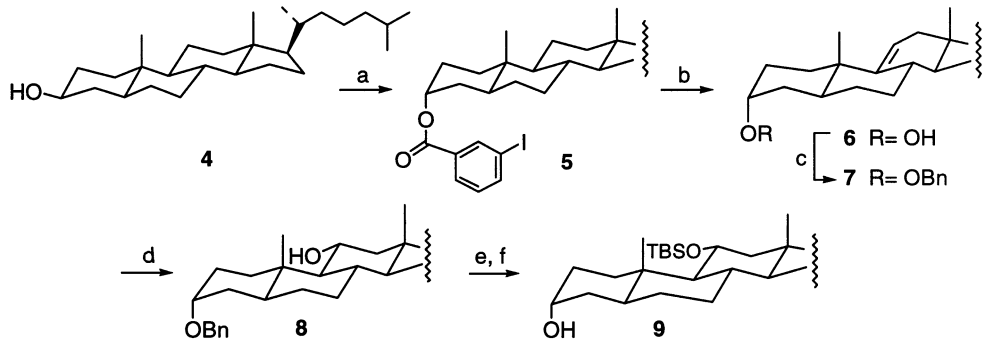


Scheme 1. (a) 1.2 equiv. of *m*-iodobenzoic acid, 1.8 equiv. of PPh_3, 1.8 equiv. of DEAD, THF, rt, 12 h, 100%; (b) 0.3 equiv. of $(C_6H_5CO)_2O_2$, 1 equiv. SO_2Cl_2, CCl_4, reflux, 2 h, then 10% KOH in MeOH, reflux, 2 h, 77%; (c) 4 equiv. of NaH, 4 equiv. of BnBr, 0.5 equiv. of TBAI, THF, reflux, 16 h, 84%; (d) 3 equiv. catechol borane, 0.7 equiv. of $LiBH_4$, THF, 0°C, 3 h then $NaOH/H_2O_2$, 50°C, 12 h, 86%; (e) 2 equiv. of lutidine, 1.5 equiv. of TBSOTf, THF, 0°C, 1 h, 97%; (f) H_2/Pd, EtOH:AcOH (200:1), 12 h, 86%.

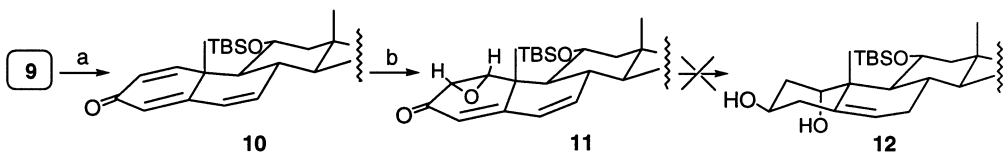
The dehydrogenation of the monosilylated diol **9** (Scheme 2) proved particularly difficult to achieve. The recent palladium-catalysed method, with allyl diethyl phosphate (ADP) and sodium carbonate,[11] gave no reaction. The use of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ),[12] furnished acceptable yields of the expected trienone **10** (40–45% yield) only when the reaction was performed with an excess of the oxidant (7 equivalents) and refluxing the reaction mixture in dioxane for 48 h.[13] Treatment of **10** with alkaline hydrogen peroxide gave stereoselectively only the expected α-epoxydienone **11** whose stereochemistry was confirmed by comparison with literature data.[14]

Birch reduction of **11**, in order to obtain the expected 1α,3β-diol **12**, which is a common practice at this stage,[10] invariably induced extensive decomposition of the starting material. We attributed this unexpected failure to the presence of the C-11 functionality. Desilylation of the secondary alcohol at C-11, to reduce the steric hindrance on C-1, did not prove useful.

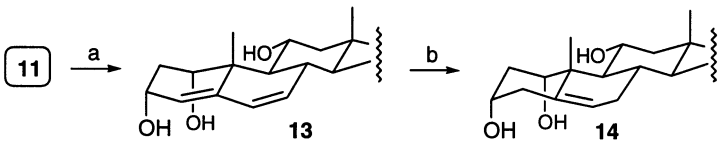
In view of these discouraging results we turned our attention to a different two step reductive method (Scheme 3). Thus, on treating the α-epoxydienone **11** with lithium aluminium hydride, cholesta-4,6-dien-1α,3α,11α-triol **13**[15] was obtained. This was shown to be epimeric at C-3 with the previously reported cholesta-4,6-dien-1α,3β-diol.[16] Finally a catalytic 1,4-addition of hydrogen yielded the key intermediate cholest-5-en-1α,3α,11α-triol **14**, which was shown to be epimeric at C-3 with the 24-methylene-cholesta-1α,3β,11α-triol, isolated by Djerassi from the soft coral *Sinularia dissecta*.[17]

Additional confirmation of the C-3 epimeric relationship in **14** and the natural sterol was obtained by acetylating **14** (pyridine/Ac_2O, overnight, 91% yield) and comparing the ^1H NMR spectral data of the 3β,11α-diacetylated natural sterol **15**, synthesized by Djerassi,[17] with the 3α,11α-diacetylated synthetic sterol **16** (3β,11α-diacetylated *natural*; *3α-H*: δ 5.00, m; 3α,11α-diacetylated *synthetic*; *3β-H*: δ 5.10, bs).

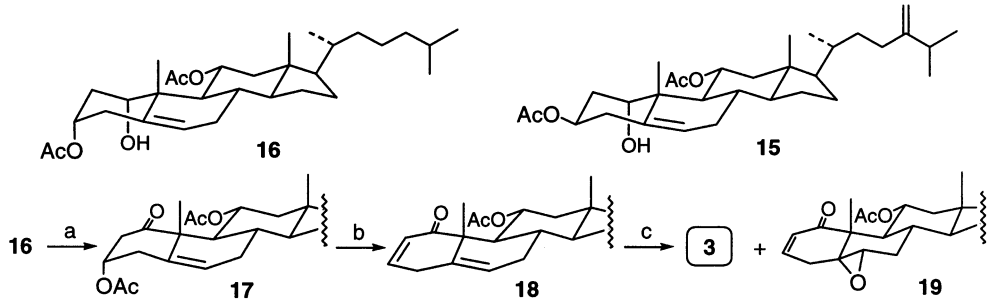
The diacetate **16** was subjected to a pyridinium dichromate oxidation to provide the ketone **17** in 75% yield (Scheme 4). The latter was easily transformed into the 2,5-dien-1-one **18**, using Al_2O_3 in refluxing benzene.[18] Epoxidation of **18** with *m*-CPBA[18] gave a 1:1.6 mixture of two isomeric[19] 5,6-epoxides, which were separated by flash chromatography. The minor and less polar product was the desired 5β,6β target epoxide **3**.[20]



Scheme 2. (a) 7 equiv. DDQ, dioxane, reflux, 48 h, 40–45%; (b) H_2O_2/NaOH, MeOH, 36 h, 60%.



Scheme 3. (a) 6 equiv. $LiAlH_4$, THF, reflux; (b) H_2/Pt, EtOH, rt, 6 h, 30%, two steps.



Scheme 4. (a) 2 equiv. of PDC, 3 Å molecular sieves, CH_2Cl_2, rt, 6 h, 75%; (b) Al_2O_3, benzene, reflux, 80%; (c) 2 equiv. MCPBA, 0.1 equiv. $NaHCO_3$, CH_2Cl_2, 0°C, 5 h, **3** (28%); **19** (45%).

In summary the synthesis of A/B/C rings of stoloniferones has been reported for the first time. In vitro biomimetic studies on the formation of stoloniolides[2] are currently underway.

Acknowledgements

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12. This method works relatively well when Δ^4- or Δ^5-3-alcohols or ketones are used as starting materials; see: *Organic Reactions in Steroid Chemistry*; Fried, J.; Edwards, J. A., Eds.; Van Nostrand Reinhold Company: New York, 1972; Vol. 1, pp. 308–316.
13. When different reaction conditions were used extensive decomposition or the presence of the 11α-[(*tert*-butyldimethylsilyl)oxy]-cholesta-1,4-diene-3-one were invariably observed.
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15. Triol **13**: $[\alpha]=+67$ ($c=1.0$, $CHCl_3$); EIMS, m/z: 562 $[M]^+$; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.98 (1H, dd, $J=9.8$, 2.2 Hz, H-6), 5.68 (1H, d, $J=4.9$ Hz, H-4), 5.60 (1H, bd, $J=9.8$ Hz, H-7), 4.21 (1H, bs, H-1), 4.09 (1H, bs, H-3), 4.02 (1H, ddd, $J=10.5$, 10.5, 4.9 Hz, H-11), 0.97 (3H, s, H-19), 0.92 (3H, d, $J=6.4$ Hz, Me-21), 0.85 (6H, d, $J=6.6$ Hz, Me-26 and Me-27), 0.74 (3H, s, H-18); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 140.9, 130.4, 129.4, 125.0, 71.9, 67.6, 63.3, 55.8, 53.3, 51.1, 49.9, 43.4, 40.9, 39.4, 35.9, 35.6, 35.2, 32.5, 28.2, 27.9, 23.8, 23.7, 22.8, 22.5, 18.5, 17.8, 12.9.
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20. Epoxide **3**: $[\alpha]=-54$ ($c=0.05$, $CHCl_3$); HREIMS, m/z: 456.3221 (calcd for $C_{29}H_{44}O_4$, 456.3240); ^1H NMR ($CDCl_3$, 400 MHz): δ 6.67 (1H, ddd, $J=10.1$ 6.0, 2.3 Hz, H-3), 6.11 (1H, dd, $J=10.1$, 2.9 Hz, H-2), 4.97 (1H, ddd, $J=10.5$, 10.5, 5.2 Hz, H-11), 3.09 (1H, bs, H-6), 2.85 (1H, bd, $J=18.3$ Hz, H-4), 1.94 (3H, s, CH_3CO), 1.28 (3H, s, H-19), 0.86 (9H, d, Me-21, Me-26 and Me-27 overlapping), 0.71 (3H, s, H-18); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 201.8, 170.1, 140.3, 130.1, 70.4, 62.4 (×2), 56.0, 55.0, 50.0, 46.7, 45.4, 42.6, 39.4, 35.9, 35.5, 33.2, 31.6, 28.5, 28.2, 28.0, 24.0, 23.8, 22.8, 22.5, 21.4, 18.6, 13.5, 12.3.