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Synthesis of spongian diterpenes: (−)-spongian-16-oxo-17-al and (−)-acetyldendrillol-1

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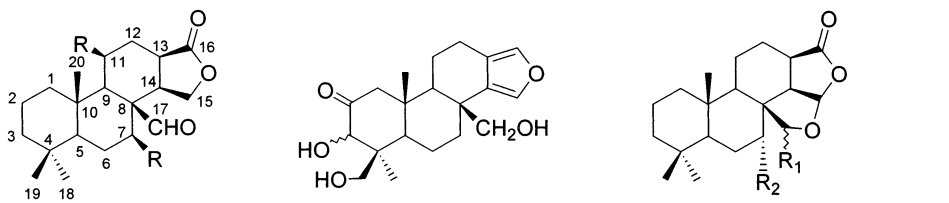
Abstract—An efficient diastereoselective synthesis of the spongian diterpenes (−)-spongian-16-oxo-17-al (**1**) and (−)-acetyldendrillol-1 (**13**) is described starting from (+)-podocarp-8(14)-13-one (**6**) via the ester-dialdehyde **11** as key intermediate. The absolute configuration at C-17 in synthetic compound **13** has conclusively been proved by NOE experiments.

Spongian diterpenes are a family of tetracyclic and pentacyclic metabolites existing in marine organisms such as sponges and nudibranches.[1,2] These compounds have attracted the attention of synthetic chemists and biologists since they were discovered in 1974,[3] because of their unique structural features and wide spectrum of biological activities.[4–6]

Some spongian diterpenes display an oxygenated function at C-17 (**1**–**5**) (Fig. 1)[6–12] having both tetracyclic and pentacyclic structures. To the best of our knowledge, a complete synthesis of tetracyclic spongians functionalized at C-17 has not yet been developed: only the preparation of an intermediate which already contains a hydroxymethyl group at C-17 has been reported.[13] In the case of the pentacyclic spongians, we have already reported the preparation of (−)-dendrillol-1 and also of three other related diterpenes oxygenated at C-7 (**4**).[14–16] Thus, in connection with our work on spongian diterpene synthesis,[17,18] we report the first diastereoselective synthesis of a 17-oxygenated tetracyclic spongian **1** isolated from the nudibranch *Ceratosoma brevicaudatum*[7] and also the preparation of **13** isolated from the dorid nudibranch *Cadlina luteomarginata*,[12] whose C-17 absolute configuration has wrongly been assigned based on a 17α-acetoxy orientation (see **5**). It is worth to note that both spongian diterpenes have been isolated in such minute amounts that no investigation of their bioactivity has been possible.

Our synthesis (Scheme 1) starts with podocarpenone **6**,[19] which is converted, in five steps, into the key intermediate **11**. Then, this intermediate is used in separate approaches to the synthesis of (−)-spongian-16-oxo-17-al **1** and (−)-acetyldendrillol-1 **13**.



1 R=H
2 R=OAc

3

4 R_1=β-OH; R_2=H,OH,OAc,OCOPr
5 R_1=α-OAc; R_2=H

Figure 1.

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Podocarpenone **6** was transformed into the ester **10** using the methodology previously developed in our laboratory for related compounds.[16] Thus, irradiation of podocarpenone **6** in dry acetone saturated with acetylene at –40°C resulted in the stereoselective formation of the photoadduct **7** in 60% yield. Treatment of cyclobutenone **7** with diethyl phosphorocyanidate [$(EtO)_2P(O)CN$] and LiCN in THF/DMF at 0°C gave a mixture of epimeric cyano phosphates at C-13 (**8**) in essentially quantitative yield. The crude cyano phosphates **8** were reduced by treatment with SmI_2 and *t*-BuOH in THF at room temperature to give a mixture of nitriles **9**.[20] Alkaline hydrolysis of both nitriles using potassium hydroxide in ethylene glycol ethyl ether at 110°C, followed by in situ treatment with dimethyl sulfate afforded a 93:7 mixture of methyl ester **10** and the corresponding epimer at C-13. Chromatographic separation of these compounds afforded the isomer **10** in 85% yield from **7**. Ozonolysis of the cyclobutene ring of ester **10** followed by decomposition of the resultant ozonide with Me_2S provided the ester–dialdehyde **11** in 90% yield. This dialdehyde **11** showed a high tendency to internal lactone–hemiacetal formation.

With the 1,4-dialdehyde **11** in hand, our next objective was to accomplish the preparation of the aforementioned spongians **1** and **13**. Toward the preparation of **1**, regioselective reduction of the carbonyl group at C-15 of dialdehyde **11** was carried out using $NaBH_4$/MeOH at 0°C to afford a 2:1 mixture of ester–hemiacetals **12**. Subsequent lactonization of the crude hemiacetals **12** using *p*-toluenesulfonic acid (PTSA) in refluxing benzene for 18 h furnished (–)-spongian-16-oxo-17-al (**1**) in 65% overall yield from **11**. The synthetic tetracyclic spongian **1**[21] had spectroscopic data identical to those recorded for the natural product.[7]

After completion of the synthesis of tetracyclic spongian **1** we studied the utility of the key intermediate **11** for the synthesis of the pentacyclic spongian **13**. A variety of methods were explored for the lactone–hemiacetal formation and in situ acetylation of **11**. In the end this conversion was successfully accomplished by using a catalytic amount of sulfuric acid (1%) in a 9:1 mixture of acetic acid and acetic anhydride at 65°C for 17 h. Thus, **13** was obtained in 85% yield directly from **11**. The synthetic pentacyclic spongian **13**[22] had spectroscopic data identical to those recorded for the natural product.[12] Furthermore, a detailed analysis of the NMR spectra of the synthetic **13** permitted us to unequivocally assign the configuration at C-17 of natural product as 17β-acetoxy instead of the 17α reported by Andersen and co-workers (see **5**). In particular, the NOE enhancement of the signals due to protons H20, H6β and H7β when proton H17 was irradiated conclusively proved this assignment.[23]

Application of our synthetic route to the preparation of other spongians as well as studies of the antiviral and antitumor activities of compounds **1** and **13** are currently under study.

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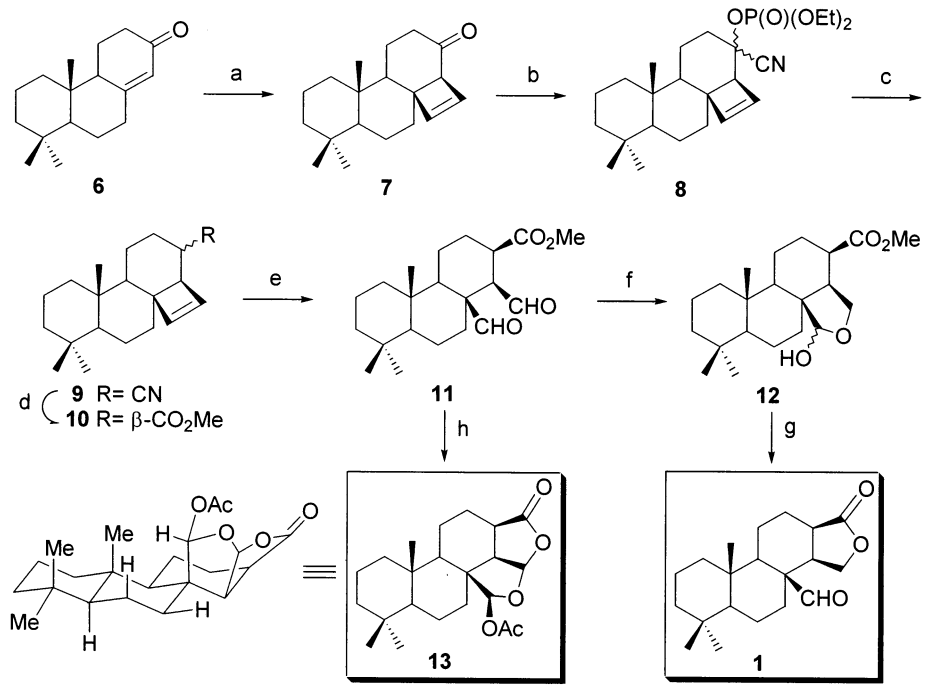

Scheme 1. *Reagents and conditions*: (a) C_2H_2, acetone, *hv*, –40°C, 60%; (b) $(EtO)_2P(O)CN$, LiCN, THF/DMF, 0°C; (c) SmI_2, *t*-BuOH, THF; (d) KOH, $HOCH_2CH_2OEt$, 110°C; then $(CH_3)_2SO_4$, DMF, 85% from **7**; (e) O_3, CH_2Cl_2, –78°C; then $(CH_3)_2S$, –78 to 5°C, 90%; (f) $NaBH_4$, MeOH, 0°C; (g) PTSA, benzene, reflux, 65% from **11**; (h) H_2SO_4 (1%), $AcOH/Ac_2O$ (9:1), 65°C, 85%.

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20. The conversion of ketone **7** to nitriles **9** could also be achieved using tosylmethyl isocyanide (TosMIC), but the yield is lower (see Ref. 15).
21. Compound **1**: white solid, mp 176–178°C (from hexane–CH_2Cl_2); $[\alpha]_D^{24}$ −59 (*c* 1.64, $CHCl_3$); IR (KBr): ν_{max}/cm^{-1} 2943, 2738, 1769, 1708; δ_H (300 MHz; $CDCl_3$) 9.96 (1H, d, *J* 1.5, H-17), 4.09 (1H, dd, *J* 10, 4.5, H-15), 4.04 (1H, br d, *J* 10, H-15), 2.67 (1H, m, H-13), 2.54 (1H, dt, *J* 13, 3, H-7β), 2.50 (1H, m, H-12β), 2.28 (1H, dd, *J* 7.5, 4.5, H-14), 0.85 (3H, s, H-19), 0.75 (3H, s, H-18), 0.69 (3H, s, H-20); δ_C (75 MHz; $CDCl_3$) 203.8, 177.7, 66.9, 56.6, 55.9, 50.8, 49.0, 41.8, 39.0, 38.5, 37.8, 35.7, 33.4, 33.3, 23.1, 21.4, 18.8, 18.6, 16.3, 14.9; HRMS (EI): *m/z* calcd for $C_{20}H_{30}O_3$ (M^+) 318.2195, found 318.2193.
22. Compound **13**: white solid, mp 218–219°C (from MeOH); $[\alpha]_D^{25}$ −75 (*c* 1.90, $CHCl_3$); IR (KBr): ν_{max}/cm^{-1} 2930, 1785, 1754, 1223; δ_H (400 MHz; $CDCl_3$) 6.29 (1H, s, H-17), 6.11 (1H, d, *J* 6, H-15), 2.76 (1H, dd, *J* 11, 7, H-13), 2.65 (1H, dd, *J* 11, 6, H-14), 2.45 (1H, br d, *J* 11.5, H-12β), 2.04 (3H, s, OCO*Me*), 1.94 (1H, dt, *J* 13.5, 3, H-7β), 0.86 (3H, s, H-18), 0.81 (3H, s, H-19), 0.72 (3H, s, H-20); δ_C (75 MHz; $CDCl_3$) 176.6, 169.1, 104.2, 100.6, 56.8, 55.3, 49.2, 46.2, 41.8, 41.7, 39.0, 38.1, 37.5, 33.3, 33.3, 23.7, 21.5, 21.3, 19.9, 18.7, 16.6, 15.6; HRMS (EI): *m/z* calcd for $C_{22}H_{32}O_5$ (M^+) 376.2250, found 376.2240.
23. Once we noted that the stereochemistry at C-17 for compounds **13** and (−)-dendrillol-1 (**4** R_1 = β-OH, R_2 = H) was the same, we envisaged that (−)-dendrillol-1 could be transformed into **13** under acetylation conditions. However, when (−)-dendrillol-1 was submitted to the usual acetylation conditions only products resulting from acetylation after opening of the hemiacetal system were obtained. Eventually, (−)-dendrillol-1 could be converted into **13** under the conditions described for the conversion of **11** into **13**.