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

Manuel Arnó,* Miguel A. González, M. Luisa Marín and Ramón J. Zaragozá*

Departament de Química Orgànica, Universitat de Valencia, Dr. Moliner 50, E-46100 Burjassot, Valencia, Spain

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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. © 2001 Elsevier Science Ltd. All rights reserved.

Spongian diterpenes are a family of tetracyclic and pentacyclic metabolites existing in marine organisms such as sponges and nudibranche{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 brevicaudatum7 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.

Figure 1.
Podocarpenone 6 was transformed into the ester 10 using the methodology previously developed in our laboratory for related compounds. 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 SmI2 and t-BuOH in THF at room temperature to give a mixture of nitriles 9 in 85% yield from 7. Ozonolysis of the cyclobutene ring of ester 10 followed by decomposition of the resultant ozonide with Me2S 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 NaBH4: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 had spectroscopic data identical to those recorded for the natural product.

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 had spectroscopic data identical to those recorded for the natural product. 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.

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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References

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–CH2Cl2); [α]D20 = −59 (c 1.64, CHCl3); IR (KBr): νmax/cm−1 2943, 2738, 1769, 1708; δH (300 MHz; CDCl3) 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-β), 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); δC (75 MHz; CDCl3) 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 C22H30O3 (M+): 318.2195, found 318.2193.

22. Compound 13: white solid, mp 218–219°C (from MeOH); [α]D20 = −75 (c 1.90, CHCl3); IR (KBr): νmax/cm−1 2930, 2985, 1754, 1575, 1519, 1462; δH (400 MHz; CDCl3) 6.39 (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, OCOMe), 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); δC (75 MHz; CDCl3) 176.6, 169.1, 104.2, 100.6, 56.8, 55.3, 49.2, 46.2, 42.1, 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 C22H22O4 (M+): 376.2250, found 376.2240.

23. Once we noted that the stereochemistry at C-17 for compounds 13 and (−)-dendrillol-1 (4 R1 = β-OH, R2 = 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.