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TOTAL SYNTHESIS OF (±)-SANADAOL

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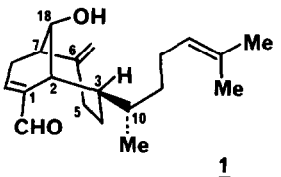
Abstract: The first total synthesis of (±)-sanadaol, a structurally unique marine diterpene, was achieved in a fully stereocontrolled manner.

Sanadaol[1] (β-crenulal)[2] (1) found in the brown algae Pachydictyon coriaceum and Dictyota crenulata is known to be a diterpene having a unique bicyclo[4.3.-1]decane ring system with five continuous asymmetric carbon centers. The relative stereochemistry for these asymmetric centers was determined by detailed NMR analysis of 1 and its derivatives.[1,2] However, the structural assignment has not yet received confirmation by X-ray analysis or total synthesis. In this paper, we report the first total synthesis of (±)-1 by a highly stereocontrolled route. The synthesis involves stereoselective construction of tricyclic key intermediate 14 from 1,3-cyclohexanedione, base-induced fragmentation reaction of 14 affording bicyclic intermediate 15, and adjustment of functionality (Scheme 1).



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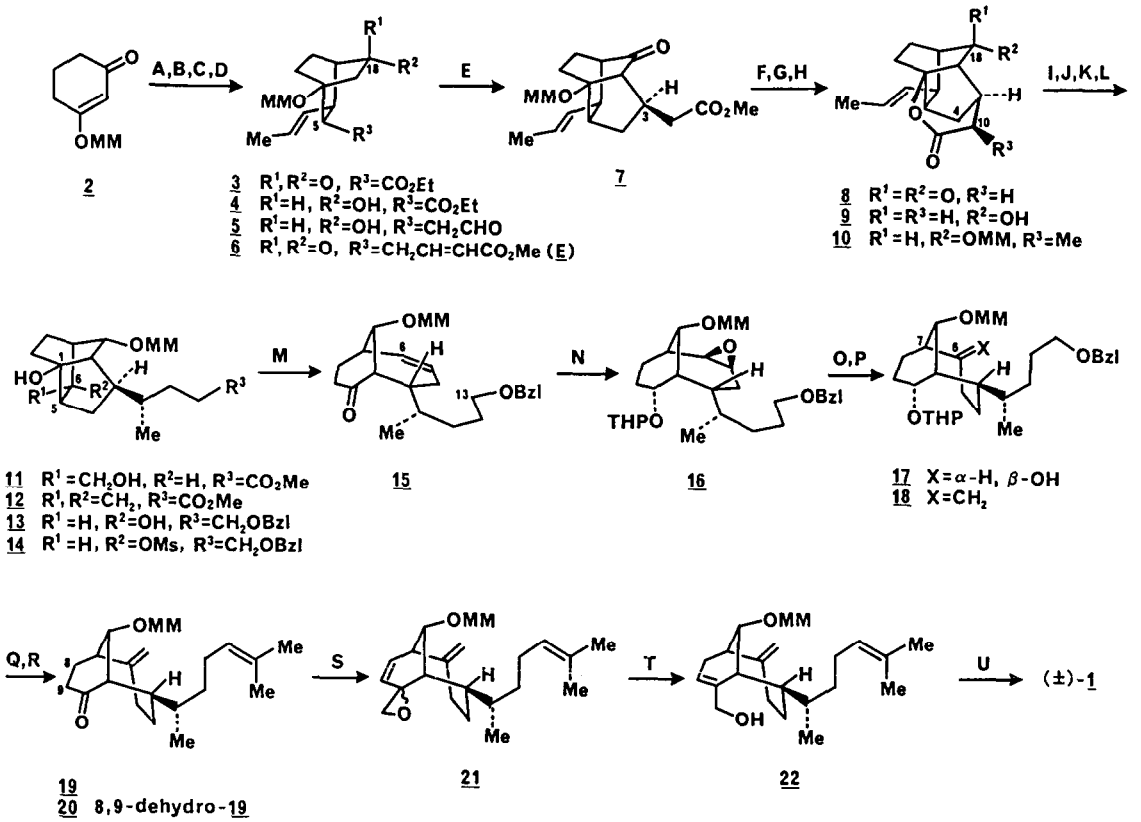
Sequential Michael reaction of the kinetic enolate of 2[3] with ethyl sorbate gave bicyclo[2.2.2]octane derivative 3[4,5] in 82 % yield. Ester 3 was transformed into (E)-α,β-unsaturated ester 6 via 4[7,8] and 5 in 36 % yield over eight steps. The (Z)-isomer of 6 was not detected in the reaction product of 5 with the phosphonate reagent. Intramolecular Michael reaction of 6 with 0.2 equiv of potassium tert-butoxide in THF at -78 °C gave tricyclic ketone 7 with requisite configuration at C(3) as a single product in 97 % yield.[10] Stepwise acid treatment of 7 afforded lactone 8, the formation of which confirmed the configuration at C(3) in 7. It also made it possible to introduce a methyl group stereoselectively to the α-position of the ester carbonyl group in 7. Reduction of the ketone in 8 with L-selectride at low temperature produced alcohol 9 exclusively in quantitative yield.[11,12] After protection of the hydroxyl group in 9 as its methoxymethyl ether, the compound was treated first with 1 equiv of LDA in THF at -78 °C and then with 1.8 equiv of methyl iodide in THF at -78 °C to 25 °C to give methylated lactone 10[7] having desired configuration: the reagent attacked the less screened face of the enolate.[13] Compound 10 was subjected to (1) ozonolysis, (2) reduction with DIBAH, (3) Wittig reaction with methyl (triphenylphosphoranylidene)acetate and (4) catalytic hydrogenation to give 11. From 11, the key intermediate 14 was synthesized as follows: (1) dehydration of 11 giving exo-olefin 12, (2) i) reduction of the ester group with

Scheme I



(A) LDA, THF, -78°C / ethyl sorbate, -78°C to 25°C over 10 h, 82%; (B) L-selectride, THF, -78°C, 87%; (C) i) 3,4-dihydro-2H-pyran, dl-CSA, 94%, ii) $LiAlH_4$, 97%, iii) PDC, 91%, iv) $Ph_3P^+CH_2OMeCl^-$, n-BuLi, THF, 0°C, 82%, v) 4:1 AcOH - H_2O, 23°C, 67%; (D) i) $(i\text{-PrO})_2P(O)CH_2CO_2Me$,[9] t-BuOK, THF, -42°C, 96%, ii) PCC, 94%; (E) t-BuOK, THF, -78°C, 97%; (F) i) 1:10 conc. HCl - MeOH, 25°C, ii) dl-CSA, C_6H_6, 50°C, 89% two steps; (G) L-selectride, THF, -78°C, 98%; (H) i) $MeOCH_2Cl$, i-Pr_2NEt, CH_2ClCH_2Cl, 60°C, 93%, ii) LDA / MeI, 96%; (I) i) O_3 / Me_2S, 91%, ii) DIBAH, THF, -78°C, 98%, iii) $Ph_3P{=}CHCO_2Me$, CH_2ClCH_2Cl, 40°C, 88%, iv) H_2, 10% Pd-C, 84%; (J) i) PhSSPh,[14] n-Bu_3P, Py, 100°C, 96%, ii) MCPBA, iii) i-Pr_2NH, 1,2-dichlorobenzene, 180°C, 90% two steps; (K) i) $LiAlH_4$, 99%, ii) $PhCH_2Br$, KH, 78%, iii) O_3 / Me_2S, 85%, iv) $NaBH_4$, 98%; (L) MsCl, Py, CH_2Cl_2, 24°C, 96%; (M) NaH, 15-crown-5, $PhCH_3$, 100°C, 5 min, 72%; (N) i) $NaBH_4$, 97%, ii) 3,4-dihydro-2H-pyran, dl-CSA, 93%, iii) MCPBA, Na_2HPO_4, CH_2Cl_2, 25°C, 94%; (O) DIBAH, $PhCH_3$, -78°C to 0°C, 92%; (P) i) PDC, 86%, ii) $Ph_3P^+CH_3I^-$, n-BuLi, THF, 0°C, 51% (94% based on the recovered ketone); (Q) i) Li, liq. NH_3 - THF, -34°C, 93%, ii) PDC, 82%, iii) $Ph_3P^+CHMe_2Br^-$, n-BuLi, THF, 0°C, 80%, iv) 4:1 AcOH - H_2O, 40°C, 91%, v) PDC, 88%; (R) i) LDA / $PhSSO_2Ph$,[19] -78°C, 71%, ii) MCPBA, iii) i-Pr_2NEt, 1,2-dichlorobenzene, 160°C, 95% two steps; (S) $Me_3S^+I^-$, n-BuLi, THF, 0°C; (T) Ca, liq. NH_3 - THF, -78°C, 56%; (U) i) PDC, ii) 4:1 AcOH - H_2O, 100°C, 73% two steps.

lithium aluminum hydride, ii) protection of the primary hydroxyl group, iii) ozonolysis of the exo-double bond and iv) stereoselective reduction of the ketone with sodium borohydride to give 13[7,11,15] and (3) selective mesylation of the secondary hydroxyl group.

The cleavage of C(1) - C(5) bond in 14 was successfully carried out by treatment of 14 with 2.8 equiv of sodium hydride in the presence of 0.2 equiv of 15-crown-5 in toluene at 100 °C for 5 min to afford 15 which has the same ring system as that of the natural product.[16,5c] After reduction of the keto in 15 to alcohol and the protection of the resulting hydroxyl group as its tetrahydropyranyl ether, it was converted to epoxide 16,[17] which was then reduced regioselectively using DIBAH in toluene to give alcohol 17.[18] This alcohol was oxidized with PDC and the resulting ketone was treated with Wittig reagent to give 18. Conversion of 18 to isopropylidene ketone 19 was carried out by the following sequence: (1) removal of the benzyl group, (2) oxidation with PDC, (3) Wittig reaction, (4) removal of the tetrahydropyranyl group, and (5) oxidation of the hydroxyl group (49 % overall yield from 18). Sulfenylation of the α-position of the ketone group in 19 using Trost's procedure[19] followed by oxidation and pyrolysis at 160 °C in the presence of N,N-diisopropylethylamine gave enone 20. Reaction of 20 with the sulfur ylide gave epoxide 21 (diastereomeric mixture, unstable) which was immediately treated with calcium in liquid ammonia to cleave the epoxide ring to afford alcohol 22. Finally, allylic oxidation of 22 and subsequent deprotection gave (±)-sanadaol. ^{1}H NMR, IR, UV and mass spectra, and HPLC behavior were identical with those of the natural specimen in every respect.[20]

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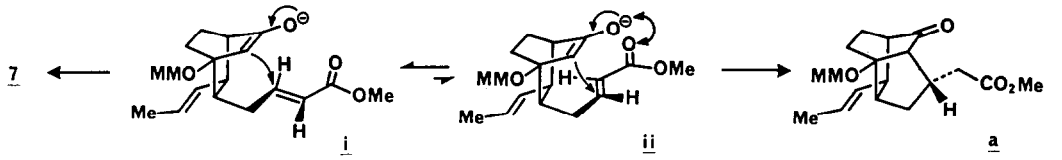
References and Notes

1) M.Ishitsuka, T.Kusumi, and H.Kakisawa, Tetrahedron Lett., 23, 1379 (1982).
2) M.P.Kirkup and R.E.Moore, Phytochemistry, 22, 2527 (1983).
3) The enone 2 was prepared from 1,3-cyclohexanedione by reaction with $ClCH_2OMe$ (1.1 equiv) and i-Pr_2NEt (1.1 equiv) in CH_2Cl_2 at 25 °C in 81 % yield.
4) All new compounds have been fully characterized by IR, ^{1}H NMR (400 MHz), and high resolution mass spectroscopy and/or combustion analysis.
5) The stereochemistry at C(5)[6] was confirmed by the synthesis of 7 from 3. Similar tandem conjugate addition reactions have been reported. See: a) M.R.Roberts and R.H.Schlessinger, J. Am. Chem. Soc., 103, 724 (1981). b) E.G.Gibbons, ibid., 104, 1767 (1982). c) H.Nagaoka, K.Ohsawa, T.takata, and Y.Yamada, Tetrahedron Lett., 25, 5289 (1985).
6) Numbering of compounds used here was accorded with that for sanadaol.
7) This compound was obtained as a single isomer.

8) The configuration at C(18) in 4 was estimated on the basis of hydride attack at the less screened face of the ketone.

9) B.M.Trost, J.Lynch, P.Renaut, and D.H.Steinman, J. Am. Chem. Soc., 108, 284 (1986).

10) The stereoselectivity was found to be influenced by the reaction temperture: at -20 °C, 6 gave a 6:1 mixture of 7 and its epimer a; at 25 °C, 6 gave a 4:1 mixture. From analysis of the results, i and ii were considered to be reaction intermediates, through which tricyclic keto esters 7 and a were produced, respectively. The conformer i is a lower energy substrate as it lacks steric interaction encountered in ii.



11) This compound was produced by hydride attack at less hindered face of the ketone group.

12) Reduction with $NaBH_4$ gave a 7:1 mixture of 9 and its isomer. Configurations at C(18) in both compounds were determined from their ^1H NMR spectra. The carbinyl proton at C(18) in 9 shows a signal at 4.28 ppm (J = 2.8 and 9.7 Hz), while the corresponding proton in its isomer shows a diffuse signal at 3.69 ppm (half height width of 6.6 Hz).

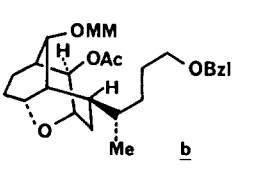
13) Treatment of the lithium enolate, prepared from 10 and LDA, with NH_4Cl in THF at -78 °C to 0 °C over 20 min afforded a 1:10 mixture of 10 and its epimer at C(10). The proton at C(10) in the epimer shows a signal split by W-coupling (between C(10) proton and one of C(4) proton, J = 1.8 Hz) in addition to usual vicinal coupling.

14) I.Nakagawa and T.Hata, Tetrahedron Lett., 1409 (1975).

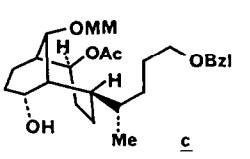
15) The coupling constant (J = 9.0 Hz) of the carbinyl proton at C(6) with the vic proton at C(5) in 13 indicates cis arrangement of these protons.

16) H.Seto, S.Hirokawa, Y.Fujimoto, and T.Tatsuno, Chem. Lett., 989 (1983).

17) The configuration of the asymmetric centers newly formed in 16 was determined by mild acid treatment (4:1 AcOH - H_2O) followed by acetylation (Ac_2O, pyridine, 25 °C) to form acetoxy ether b.



18) The position of the hydroxyl group in 17 was indicated by ^1H NMR analysis of the hydroxy acetate c prepared from 17 by acetylation and deprotection of the pyranyl group. Vicinal coupling was observed (J = 1.5 Hz) between protons at C(6) and C(7) in this compound.



19) B.M.Trost and G.S.Massiot, J. Am. Chem. Soc., 99, 4405 (1977).

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