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SYNTHETIC STUDIES ON THE CAPNELLANE ALCOHOLS: AN EFFICIENT METHOD FOR THE CONSTRUCTION OF THE C-RING BISALLYLIC ALCOHOL UNIT

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An efficient method for the construction of the bisallylic alcohol unit, which is uniquely associated with the capnellane alcohols, is reported.

Capnellane is the generic name applied to the group of tricyclic sesquiterpene alcohols(1~6) and the hydrocarbons, isolated from the soft coral *Capnella imbricata*.[1,2] It seems likely that these substances act as chemical defense agents in the coral reef biomass to ward off algal and microbial growth and to prevent larval settlement.[3] A fascinating structural feature which is uniquely associated with the capnellane alcohols(1~6) is the presence of the C-ring bisallylic alcohol unit. As a part of our synthetic program of the capnellane alcohols(1~6), we have developed an efficient method for the construction of this functional unit, which should be applicable to the synthesis of the alcohols(1~6). The recent report by Pattenden and Teague describing a synthesis of $\Delta^{9(12)}$-capnellene-8α,10α-diol(7), the 8-epimer of natural $\Delta^{9(12)}$-capnellene-8β,10α-diol(1),[4] prompted us to communicate our own result concerning a general method for the synthesis of the bisallylic alcohol functionality having the natural configuration.

The bisallylic alcohol(21) was selected as the target molecule for the present purpose. It occurred to us that the target molecule(21) could be synthesized from the tricyclic keto-ester(14) in the route involving the sigmatropic rearrangement of the appropriate intermediate as a key step. The tricyclic keto-ester(14) was efficiently synthesized starting from the bicyclic ketone(8)[5] as illustrated in the Scheme. Methoxycarbonylation of 8 (dimethyl carbonate, sodium hydride, a catalytic amount of ethanol) afforded the β-keto-ester(9)[6] in nearly quantitative yield, which was subsequently treated with potassium *t*-butoxide and ethyl 4-iodo-3-methoxycrotonate in THF[7] to give the alkylated product(10)[6] as an isomeric mixture (80%). Demethoxycarbonylation of 10 was successfully carried out (lithium iodide, γ-collidine) to produce 11[6] in 75% yield[8] as an

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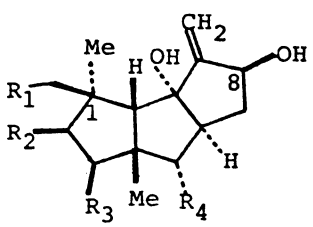
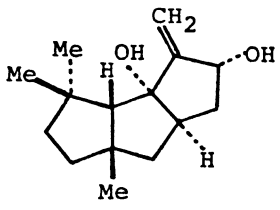


1: R_1-R_2-R_3-R_4=H
2: R_1-R_3-R_4=H, R_2=OH
3: R_1-R_2-R_4=H, R_3=OH
4: R_2-R_4=H, R_1-R_3=OH
5: R_1-R_2-R_3=H, R_4=OH
6: R_1-R_3=H, R_2-R_4=OH



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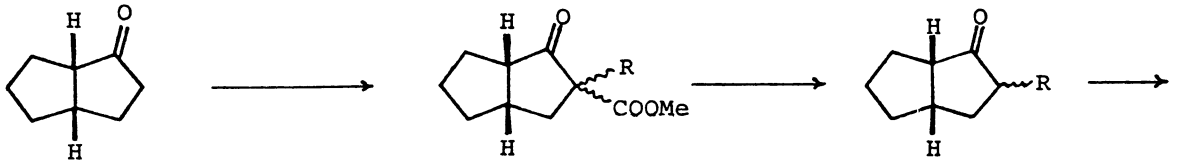
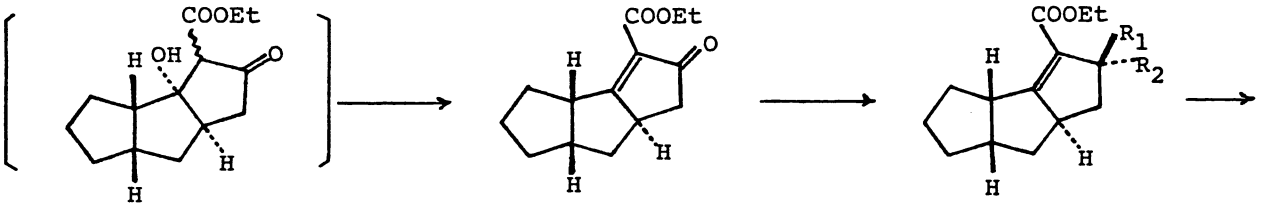
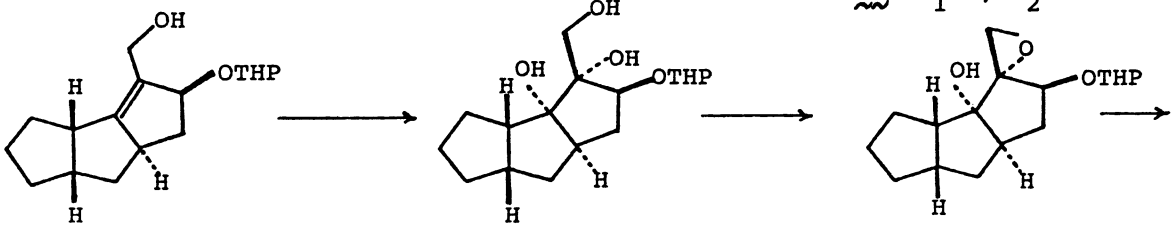


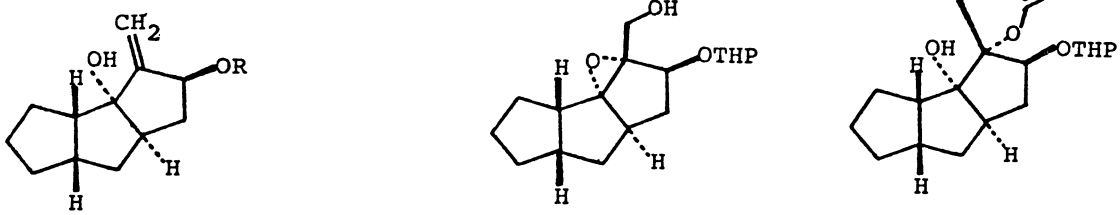
8 9: R=H 10: R=CH_2(MeO)C=CHCOOEt 11: R=CH_2(MeO)C=CHCOOEt 12: R=CH_2COCH_2COOEt



13 14 15: R_1=OH, R_2=H 16: R_1=H, R_2=OH



17 18 19



20: R=THP 21: R=H 22 23

isomeric mixture. Reaction of 11 with 30% aqueous perchloric acid in ether afforded the β-keto-ester(12), which was directly cyclized to the key intermediate(14)[6] *via* 13 in 80% yield by treatment with sodium ethoxide in ethanol. Judging from the fact that the *endo*-chain in 12 should epimerize to the *exo*-chain under the cyclization conditions, it was anticipated that the above cyclization would provide only the thermodynamically more stable isomer(14).[9] As was expected, the CMR spectrum of the cyclized product(14) indicated its stereochemical homogeneity.

Reduction of 14 with sodium borohydride in methanol containing cerium(III) chloride heptahydrate[10] provided cleanly the *endo*-alcohol(15)[6] in 71% yield together with its stereoisomer(16)[6] (*ca.* 9%).[11,12] The undesired isomer(16) could be recycled to the ketone(14) in nearly quantitative yield by treatment with PCC in CH_2Cl_2. Protection of the *endo*-alcohol as THP ether, followed by reduction with DIBAL-H in toluene, afforded the alcohol(17)[6] in nearly quantitative yield. Transformation of 17 to the target molecule(21) employing sigmatropic rearrangements was found to be unsuccessful. Furthermore, conversion of 17 to 21 *via* the epoxide(22)[6] turned out to be also unfruitful. Accordingly an alternative route was investigated. Thus, treatment of 17 with a catalytic amount of osmium tetroxide and 1.8 equiv. of *N*-methylmorpholine-*N*-oxide monohydrate in H_2O-acetone-*t*-butanol produced the triol(18)[6] in 76% yield. Transformation of the triol(18) to 20 *via* the thionocarbonate(23)[6] was first attempted, but resulted in the formation of a complex mixture.[13] Then, 18 was converted to the epoxide(19)[6] in 80% yield by treatment with methanesulfonyl chloride and triethylamine in benzene followed by the addition of DBU. The *exo*-methylene compound(20)[6] was cleanly formed from the epoxide(19) in 77% yield by reaction with trimethylsilyllithium in HMPA at room temperature. The target molecule(21)[14] was finally obtained as a colorless solid in nearly quantitative yield by treatment of 20 with PPTS in aqueous ethanol.

In this way we have developed a stereocontrolled route to the bisallylic alcohol(21) starting from the simple carbonyl compound(8) (*ca.* 18% overall yield). Application of this methodology to total synthesis of the capnellane alcohols(1~6) is now under investigation.

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References

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2) For the total synthesis of $\Delta^{9(12)}$-capnellene, see a) R.D.Little and G.L.Carroll, Tetrahedron

Lett., 22, 4389(1981), R.D.Little, G.L.Carroll, and J.L.Petersen, J. Am. Chem. Soc., 105, 928 (1983); b) K.E.Stevens and L.A.Paquette, Tetrahedron Lett., 22, 4393(1981); c) W.Oppolzer and K.Bättig, *ibid.*, 23, 4669(1982); d) T.Fujita, T.Ohtsuka, H.Shirahama, and T.Matsumoto, *ibid.*, 23, 4091(1982).

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4) G.Pattenden and S.J.Teague, Tetrahedron Lett., 23, 5471(1982).

5) J.K.Crandall and L.-H.Chang, J. Org. Chem., 32, 532(1967).

6) Satifactory spectroscopic data (mass spectrum, PMR, IR, etc.) were obtained for this substance.

7) S.Danishefsky, K.Vaugham, R.Gadwood, and K.Tsuzuki, J. Am. Chem. Soc., 103, 4136(1981).

8) Direct alkylation of 8 afforded 11 in unsatisfactory yield.

9) The stereocontrolled synthesis of the tricyclic skeleton possessing the *cis-anti-cis* ring fusion *via* base-induced epimerization was recently reported in the synthesis of $\Delta^{9(12)}$-capnellene, see Ref. 2c. Stereochemistry of 14 was further supported at the later stage by comparing the spectral data of the bisallylic alcohol(21) with those of natural $\Delta^{9(12)}$-capnellene-8β,10α-diol(1).

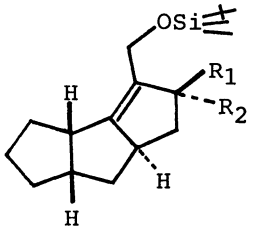
10) A.L.Gemal and J.-L.Luche, J. Am. Chem. Soc., 103, 5454(1981).

11) Chemoselective reduction of 14 with DIBAL-H proceeded, affording the desired alcohol(15) in less satisfactory yield. Reduction of 14 with sodium borohydride in the absence of cerium(III) chloride gave the saturated alcohols exclusively.

12) Stereochemistry of both 15 and 16 was chemically determined as follows. The alcohols(15 and 16) were converted to the silyl ether(i and ii) respectively. Epoxidation of ii using the Sharpless method produced the epoxide(iii) more readily than in the case of i.

13) E.J.Corey and P.B.Hopkins, Tetrahedron Lett., 23, 1979(1982).

14) $\nu_{max}(CHCl_3)$ 3400, 1640 cm^{-1}; δ(ppm) 5.27(1H, d, J=2 Hz), 5.23(1H, d, J=2 Hz), 4.72(1H, m); MS(m/e) 194(M^+), 176(M^+-H_2O), 158(M^+-2H_2O).
Oxidation of 21 with PDC in DMF, followed by reduction with sodium borohydride in the presence of cerium(III) chloride, affording the epimer(iv) exclusively.



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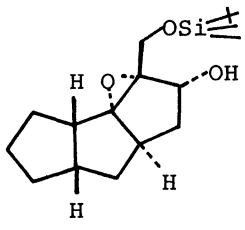
ii: R_1=H, R_2=OH



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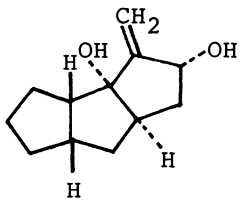

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