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INTRAMOLECULAR 1,3-DIYL TRAPPING REACTIONS: TOTAL SYNTHESIS OF THE MARINE NATURAL PRODUCT (d,l)-$\Delta^{9(12)}$-CAPNELLENE¶

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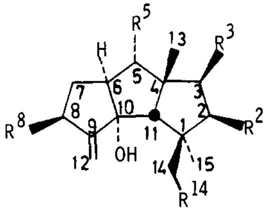
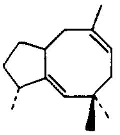
ABSTRACT: An intramolecular 1,3-diyl trapping reaction is utilized in the key step of a total synthesis of the marine natural product $\Delta^{9(12)}$-capnellene.

The capnellanes form an interesting class of sesquiterpene alcohols (1 - 5) and hydrocarbons (6, 7) which have been isolated from the soft coral Capnella imbricata collected off the coast of Serwaru, Leti Island, Indonesia and Liang Island located on the north coast of New Guinea.[1] In contrast with the hirsutanes, their terrestrial counterparts, the capnellanes possess a geminal methyl unit located at C_1 rather than at C_2, and an angular methyl group at C_4 rather than at C_{10} (capnellane numbering).[2] Another interesting structural feature which is uniquely associated with the capnellane alcohols is the presence of the A-ring bisallylic alcohol unit.



1, $R^3=R^5=R^{14}=H$; $R^2=R^8=OH$
2, $R^3=R^{14}=H$; $R^2=R^5=R^8=OH$
3, $R^2=R^5=R^{14}=H$; $R^3=R^8=OH$
4, $R^2=R^5=H$; $R^3=R^8=R^{14}=OH$
5, $R^2=R^3=R^{14}=H$; $R^5=R^8=OH$



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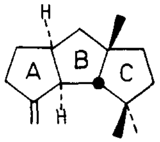

7, $\Delta^{9(12)}$-CAPNELLENE

We report herein the first total synthesis of $\Delta^{9(12)}$-capnellene (7), the presumed biosynthetic precursor of alcohols 1 - 5. The synthetic plan, illustrated in Scheme I, calls for construction of the linearly fused tricyclopentanoid skeleton through the use of an intramolecular 1,3-diyl trapping reaction (e.g., 13 → 8).[3] Inspection of Scheme I reveals that the three required methyl groups form an integral part of the diylophile chain; therefore, their regio-

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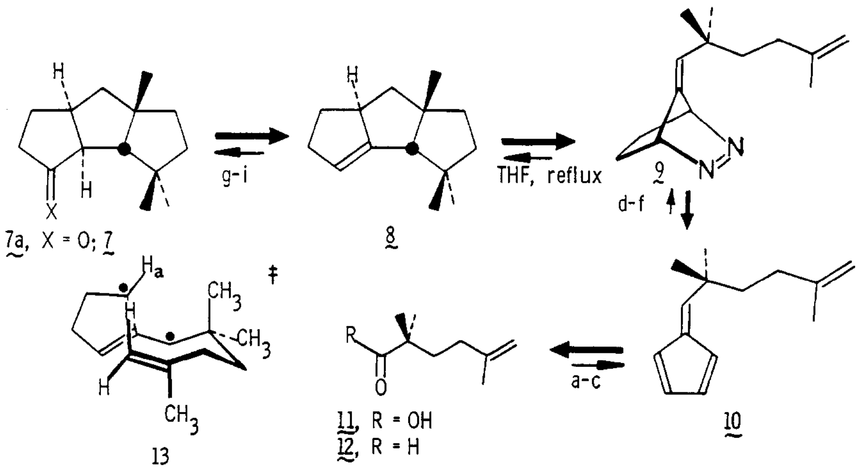
¶ The chemistry reported herein was first reported by RDL on June 4, 1981 at the 2nd European Symposium on Organic Chemistry, Stresa, Lago Maggiore, Italy.

† Fellow of the Alfred P. Sloan Foundation.

SCHEME I[a]



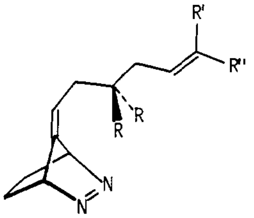
[a] Reagents: a, $LiAlH_4$, Et_2O, reflux, 0.5 h, 98%; b, 1.5 equiv $C_5H_5NHCrO_3Cl$ (PCC), equiv weight Celite, CH_2Cl_2, room temp, 2.5 h, 88 - 91%; c, 1.0 equiv cyclopentadiene, 1.0 equiv n-BuLi, THF, 0°C, 1.5 h, 67-80%; d, 5 equiv $CH_3O_2CN{=}NCO_2CH_3$, Et_2O/pentane (1:1), 0°C, 1 h; e, 5 equiv $KO_2CN{=}NCO_2K$, 10 equiv glacial AcOH, CH_2Cl_2, 0°C, 3 h, 73-91% for (d) & (e); f, 12 equiv KOH, EtOH, reflux, 1.5 h then cool to 0°C and add 3 equiv aqueous $K_3Fe(CN)_6$, 78%; g, 2 equiv BH_3·THF, 0°C, 1 h and then room temp for 44 h; HO^-, H_2O_2; h, 1.7 equiv PCC, equiv weight Celite, CH_2Cl_2, room temp, yield for trap plus (g) & (h) in text; i, $Ph_3P{=}CH_2$, THF, room temp, 50% (nonoptimized)

chemical relationship is predetermined and there is no need to add the angular methyl group at a later stage of the sequence. In practice, the sequence is short, easy to scale up, and readily modified to allow for the construction of other capnellanes.

The bicyclic azo compound 9 which serves as the direct precursor of diyl 13, was synthesized in multigram quantities starting from 2,2,5-trimethyl-5-hexenoic acid (11; note Scheme I).[4] Thus, 11 was first converted to aldehyde 12 using a simple reduction-oxidation sequence. Subsequent fulvene formation using cyclopentadienyllithium in THF, set the stage for a Diels-Alder reaction between fulvene 10 and dimethyl azodicarboxylate.[5] The resulting dicarbamate was efficiently converted into 9 by following a sequence which involved selective monohydrogenation of the C_5-C_6 pi bond with diimide, followed by saponification and subsequent oxidation of the dipotassium dicarboxylate salt so formed using aqueous potassium ferricyanide.[6]

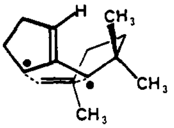
The conversion of azo compound 9 into tricyclopentanoid 8 was most efficiently accomplished through a slow, dropwise addition (66 h using a syringe pump) of a THF solution of 9 to a solution of refluxing THF. In this way, the instantaneous concentration of the azo compound was maintained at ca. 10^{-5} M and side reactions were minimized. It should be noted that while the conversion of 9 into 8 requires rather specialized conditions for optimal results, the typical procedure for a high yield intramolecular diyl trapping reaction involving an activated diylophile (one which bears an electron withdrawing group; note that 13 is unactivated) simply calls for refluxing the azo compound in acetonitrile or THF until the starting material disappears, as evidenced by TLC analysis.[3] A number of reasons for this difference in behavior could be put forth; however, we prefer to defer speculation pending the acquisition of more information.

The somewhat volatile tricyclopentanoid 8 could be isolated at this stage by chromatography after carefully removing the THF. However, a preferable procedure calls for simply subjecting the reaction mixture to a hydroboration-oxidation sequence ($BH_3 \cdot$THF; H_2O_2, HO^-, then PCC/Celite, CH_2Cl_2). In this way, an 8-9% yield (over three steps) of ketone 7a was obtained after chromatographic separation (Waters HPLC Prep 500 with two PrepPAK 500 silica columns; elution with 25% ether in hexane). In comparison with other intramolecular diyl trapping reactions which we have conducted, the amount of the desired cis,anti ring fused product formed is both suprisingly and disappointingly low. For example, the ratio of cis,anti to cis,syn ring fused products which have been obtained in yields in excess of 80% from azo compounds 14 - 16, is 9:1, 3:1, and 7:1, respectively,[3] while in the present case, the ratio is 1.6:1.[8]



14, R = CH_3; R' = H; R'' = CO_2CH_3
15, R = CH_3; R' = CO_2CH_3; R'' = H
16, R = H; R' = H; R'' = CO_2CH_3 or $CO_2C_2H_5$

Perhaps the problem stems from an unfavorable, transition state energy raising interaction between the quais-axial methyl group attached to the acyclic chain in 13 and H_a, which is located on the diyl ring (an $A^{(1,3)}$ interaction).[9] This interaction can be minimized by assuming an alternate, cis,syn ring fusion producing conformation 17. Experiments designed to test this hypothesis are currently underway.



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To complete the synthesis of $\Delta^{9(12)}$-capnellene (7), ketone 7a was treated with an excess of methylidenetriphenylphosphorane in THF at room temperature. The material formed proved to have spectral data (IR, ^1H NMR, ^{13}C NMR) which nicely matched those of authentic material (spectral data kindly supplied to us by Professor C. Djerassi).

Further, more extensive studies concerning the application of the intramolecular diyl trapping reaction to synthesis are in progress.

Acknowledgments. Financial support for this work was provided by the National Cancer Institute, DHEW, to whom we are most grateful. We wish to thank Professor Carl Djerassi for supplying us with spectral data of $\Delta^{9(12)}$-capnellene and Professor William Fenical for some authentic samples of several of the capnellane alcohols.

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(2) For an up-to-date set of references relating to the hirsutanes see Little, R.D.; Muller, G.W. J. Am. Chem. Soc. 1981, 103, 2744-2749.

(3) See, for example, Little, R.D.; Muller, G.W. J. Am. Chem. Soc. 1979, 101, 7129-7130. Little, R.D.; Muller, G.W.; J. Am. Chem. Soc. 1981, 103, 2744-2749. Little, R.D.; Muller, G.W.; Venegas, M.G.; Carroll, G.L.; Bukhari, A.; Patton, L.; Stone, K. Tetrahedron, Symposia in Print, in press.

(4) 2,2,5-Trimethyl-5-hexenoic acid was prepared from isobutyric acid, 3-methyl-3-butenyl tosylate, and LDA in THF.

(5) The method of Freisleben, which has worked so well for us in the past, proved to be unsatisfactory in this case. Freisleben, W. Angew. Chem. 1963, 75, 576.

(6) Little, R.D.; Venegas, M.G. J. Org. Chem. 1978, 43, 2921-2923. Little, R.D.; Carroll, G.L. Ibid. 1979, 44, 4720-4722.

(7) All new compounds displayed satisfactory IR, NMR, and mass spectral data. In addition, satisfactory high resolution mass spectra or combustion analyses were obtained.

(8) The cis,anti to cis,syn ratio was determined at the stage of the alcohols obtained after hydroboration in order to minimize losses of material which result upon attempted isolation of the hydrocarbons formed directly from the trapping reaction. Complete details will be reported in our full paper.

(9) Johnson, F. Chem. Rev. 1968, 68, 375 and references therein. For some recent references see Hart, D.J. J. Am. Chem. Soc. 1980, 102, 397 and Overman L.E.; Yokomatsu, T. J. Org. Chem. 1980, 45, 5229-5230.

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