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TOTAL SYNTHESIS OF (±)-$\Delta^{9(12)}$-CAPNELLENE

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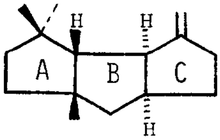
Abstract: Starting from 2-cyclopentenone, the title compound has been synthesized via a combination of [2+2] and [4+2] cycloaddition reactions.

$\Delta^{9(12)}$-Capnellene (**1**) and its oxygenated congeners[1] such as tetraol **2**, isolated from soft coral Capnella imbricata, are part of the chemical defence system of the animal to inhibit the growth of microorganisms and the settlement of larvae.[2] Due to their interesting biological properties and structural novelty, capnellanoids have been the subject of extensive synthetic efforts which have culminated in several total syntheses of the natural hydrocarbon **1** in recent years.[3,4] Most of the reported approaches, however, do not permit facile incorporation of hydroxyl functionalities present in all the other natural capnellanoids. We wish to describe a highly regioselective and stereoselective total synthesis of racemic $\Delta^{9(12)}$-capnellene (**1**) by an approach which is sufficiently flexible to be extended to the synthesis of more complex capnellenoids.



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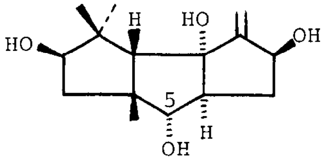

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Our synthetic plan called for the use of 2-cyclopentenone as a ring C equivalent and two cycloaddition reactions as key operations to facilitate the incorporation of the remaining A and B rings; the latter by a [2+2] photocycloaddition and the former by a [4+2] Diels-Alder reaction. To construct the B/C ring system, the starting 2-cyclopentenone was irradiated (Hanovia 450 W medium pressure mercury vapor lamp and Pyrex filter) with a ten-fold excess of 1,1-diethoxyethene[5] in benzene at ~10°C for 24 hr giving keto ketal **3** as the only adduct possessing the expected head-to-tail regiochemistry.[6] The ketone carbonyl, which would eventually be used for introducing the exocyclic methylene group required for the target molecule, was reduced with a bulky reducing agent lithium tri-t-butoxyaluminum hydride to enhance the stereoselectivity and the resulting alcohol was protected in the form of a benzyl ether by treatment with sodium hydride and benzyl bromide. Subsequent deketalization using aqueous oxalic acid afforded cyclobutanone **4** as a single stereoisomer in greater than 75% yield over four steps. To effect the required ring expansion of its cyclobutanone ring, compound **4** was treated with ethyl diazoacetate in ether in the presence of boron trifluoride etherate at 0°C overnight.[7] The desired keto ester **5** was formed preferentially along with a small amount of its regioisomer **6** as an inseparable mixture in a total yield of 80%. The observed regioselectivity, which has ample precedent,[7] permits the introduction, to a suitable position, of an ester group which can, in principle, be converted to the angular methyl present in capnellanoids. At the same time, the ketone carbonyl is retained at a location strategically important for the construction of those oxygenated capnellanoids containing a C-5 hydroxyl.

The mixture of the isomeric keto esters **5** and **6** was treated with sodium hydride and phenylselenenyl chloride.[8] The resulting selenides, without purification, were subjected to oxidative elimination using 30% hydrogen peroxide to afford a 60% yield of enone ester **7** possessing a highly dienophilic double bond[9] suitable for a [4+2] cycloaddition to induce ring A formation.

Under stannic chloride catalysis, the Diels-Alder addition of isoprene to enone ester 7 proceeded readily at -78°C with complete regioselectivity (in accordance with the para-rule) and stereoselectivity (cis-addition from the sterically less hindered side)[10] to give a single adduct **8**, m.p. 68-69°C, in 60% yield. For the present work, both the ketone and the ester groups are required to be reduced to the hydrocarbon level. This was effected as follows. Reduction of **8** with sodium bis(2-methoxyethoxy)aluminum hydride in tetrahydrofuran at room temperature gave a single diol **9**[11] (m.p. 136-137°C) in quantitative yield. Its primary hydroxyl group reacted preferentially with phenoxythiocarbonyl chloride in acetonitrile at room temperature in the presence of 4-(N,N-dimethylamino)pyridine.[12] Reduction of the resulting monothionocarbonate with tri-n-butyltin hydride and a small amount of azobisisobutyronitrile in refluxing toluene[12] gave alcohol **10** (60% yield from **9**). Further deoxygenation was effected via the corresponding mesylate which furnished olefin **11** (40% yield) upon heating with zinc dust and lithium iodide[13] in dimethylformamide at 145°C.

Olefin **11** underwent facile ring contraction when subjected to ozonolysis in dichloromethane at -78°C followed by reductive work-up with dimethyl sulfide, during which time the cyclization of the expected keto aldehyde was also effected. Enone **12** thus obtained in 60% yield was converted to the corresponding oxime using hydroxyamine hydrochloride and sodium acetate in methanol. Beckmann rearrangement of the oxime with phosphorus oxychloride[14] in pyridine-triethylamine followed by addition of hydrochloric acid gave ketone **13** (70% yield from **12**). This ketone was subjected to Wittig reaction with methylenetriphenylphosphorane and the resulting methylidene compound was treated with an excess of diethylzinc and methylene iodide in benzene at 50°C in the presence of air[15] to effect cyclopropanation. The benzyl ether and the cyclopropyl ring of compound **14** produced in 65% yield over two steps, were sequentially hydrogenolyzed (glacial acetic acid, two atmospheres of hydrogen) using 5% palladium on carbon and platinum as a catalyst respectively. Subsequent oxidation with pyridinium chlorochromate gave ketone **15** (80% yield over three steps) which was transformed to $\Delta^{9(12)}$-capnellene (**1**) in 75% yield using methylenetriphenylphosphorane. Both ketone **15** and the synthetic hydrocarbon **1** exhibited spectral properties in agreement with those reported.[1d,3a]

The extension of the synthetic approach to the highly oxygenated capnellanoid **2** is currently under investigation.[16]

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11. The stereochemistry of this compound was assigned on the basis of the following findings. Reduction of **8** sequentially with potassium tri-*s*-butylborohydride (to the monoalcohol) and sodium bis(2-methoxyethoxy)-aluminum hydride gave the epimeric diol (m.p. 110-111°C) which readily formed the cyclic phosphoramidate with *N*,*N*-dimethylamidophosphoro-

dichloridate, and the cyclic thionocarbonate with phenoxythiocarbonyl chloride strongly indicating a cis relationship of the hydroxyl and the hydroxymethyl groups.

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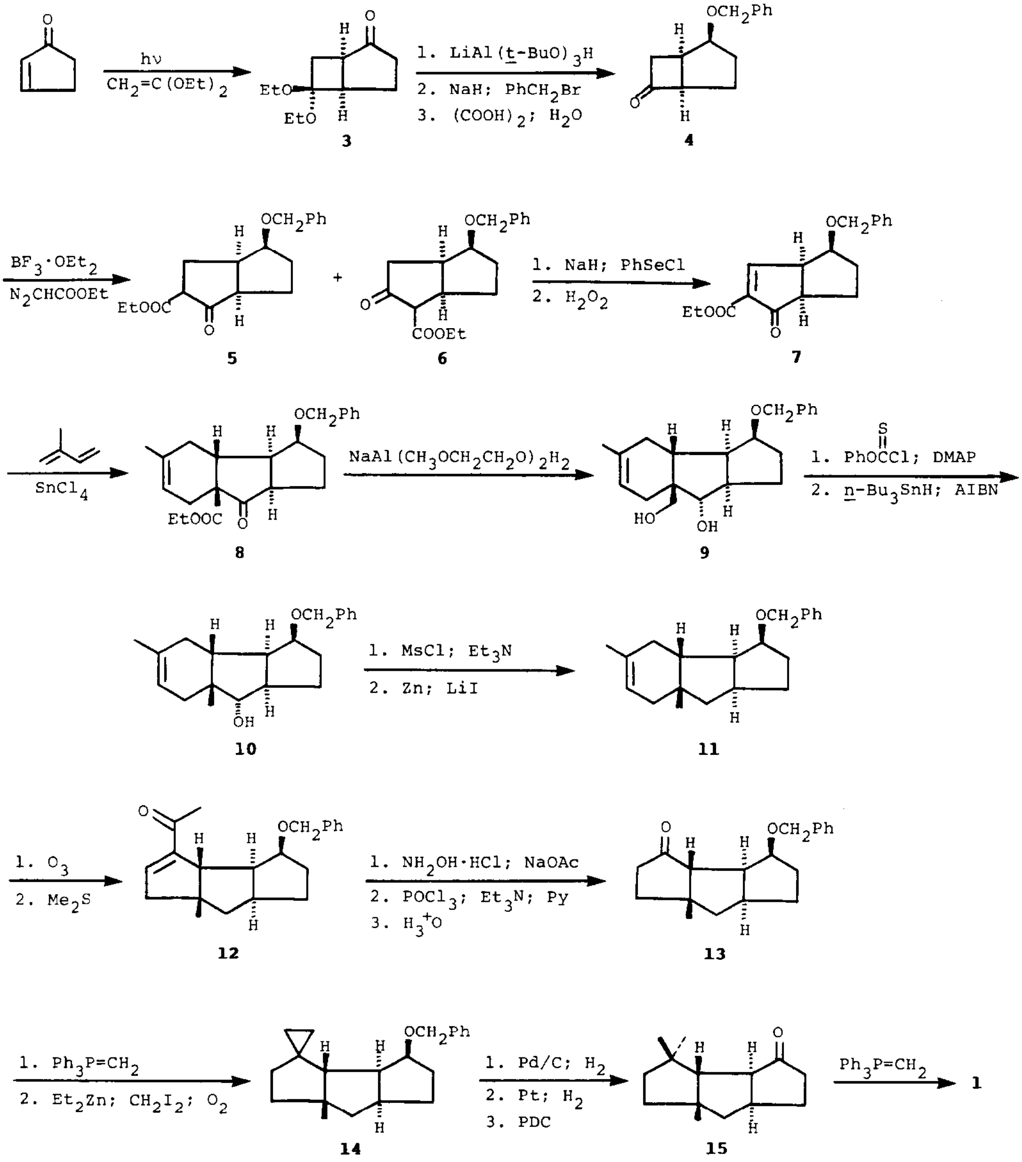
16. We are grateful to the Natural Sciences and Engineering Research Council of Canada and the University of Alberta for financial support.



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