Tetrahedron Letters, Vol.22, No.44, pp 4393 - 4396, 1981
Printed in Great Britain

0040-4039/81/444393-04$02.00/0

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

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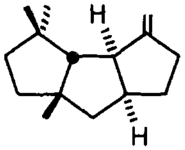
Summary: The first total synthesis of the marine triquinane sesquiterpene $\Delta^{9(12)}$-capnellene (1) is described.

We wish to report the first fully stereocontrolled synthesis of (±)-$\Delta^{9(12)}$-capnellene (1),[1] the parent of a novel triquinane[2] sesquiterpene class whose members have been isolated from the soft coral Capnella imbricata.[1,3] These substances seemingly act as chemical defense agents in the coral reef biomass to ward off algal and microbial growth[4] and to prevent larvae settlement.[5] Adding to the incentives for gaining successful entry to the capnellane ring system are its relationship to the hirsutanes, e.g., hirsutene (2), and the substantive synthetic effort which has been directed to the latter group.[6-8] Importantly, the location of the pendant functionality in 1 so differs from that in 2 that intrinsically dissimilar synthetic approaches appear to be required. The key structural problem is the proper stereochemical installation of ring C which projects an exocyclic methylene group in close steric proximity to the geminal dimethyl substituents.



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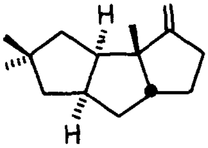

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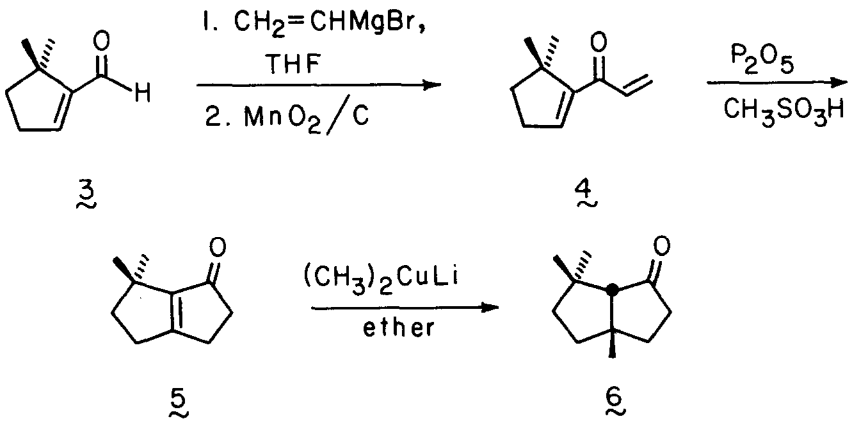
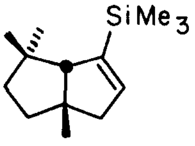
Our synthesis begins with cyclopentenyl carboxaldehyde 3 which was prepared by the method of Magnusson and Thoren[9] (and consequently was admixed with the 3,3-dimethyl isomer; ratio 4:1). Although the unwanted component could be removed by reaction with an appropriate quantity of Girard's reagent T, it proved more convenient to effect condensation of the mixture with vinylmagnesium bromide and to separate the dienols by high pressure liquid chromatography. The appropriate vinyl carbinol[10] was smoothly oxidized in 95% yield to the somewhat sensitive dienone which was subjected directly to Nazarov cyclization[11] (8% P_2O_5 in CH_3SO_3H[12]; 2 min at 20°C; 68%). Conjugate addition of lithium dimethylcuprate to ketone 5 was usually addressed immediately. In accord with previous experience,[13] the desired trimethylbicyclo[3.3.0]octanone 6 was efficiently (80%) produced. Detailed chromatographic and spectral analysis at this juncture failed to give evidence of isomeric material.

The conversion of 6 to dihydro-16 can be perceived to require, in overall terms, a regiospecific [3+2] cyclopentannulation in which the new carbonyl group is bonded to the site of the old. Although several protocols have been described which effect such a trans-



formation,[14] most lack the intrinsic regiochemical control required to deliver exclusively the proper linearly fused tricyclopentanoid framework. The one exception, that based upon vinylsilane acylation-cyclization,[15] proceeds in the desired sense because production of the vinylsilane is achieved via a nonrandomization mechanism involving proton abstraction from the less substituted α carbon.[16]

We therefore next gave attention to the preparation of 7 via the triisopropylbenzenesulfonyl hydrazone[17] of 6. Surprisingly, all attempts to acylate 7 with 3-chloropropionyl chloride according to previously developed procedures[15] led only to its destruction. In contrast, subjection of 7 to the action of dichloromethyl methyl ether and $AlCl_3$[18] gave 8 (50%) which served nicely as a precursor to 9 (100%). However, this dienone failed to undergo Nazarov cyclization as induced by a wide range of Bronsted and Lewis acids. Our inability to arrive at 10 may be the result of steric impedance by the geminal methyl groups to attainment of planarity within the pentadienyl cation intermediate (11) which must experience the requisite conrotatory electrocyclization (cf Newman's Rule of Six[19]).



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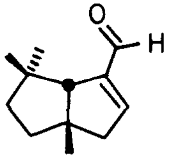

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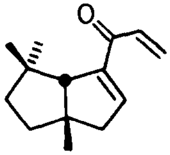

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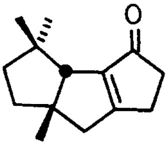

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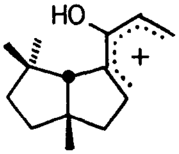

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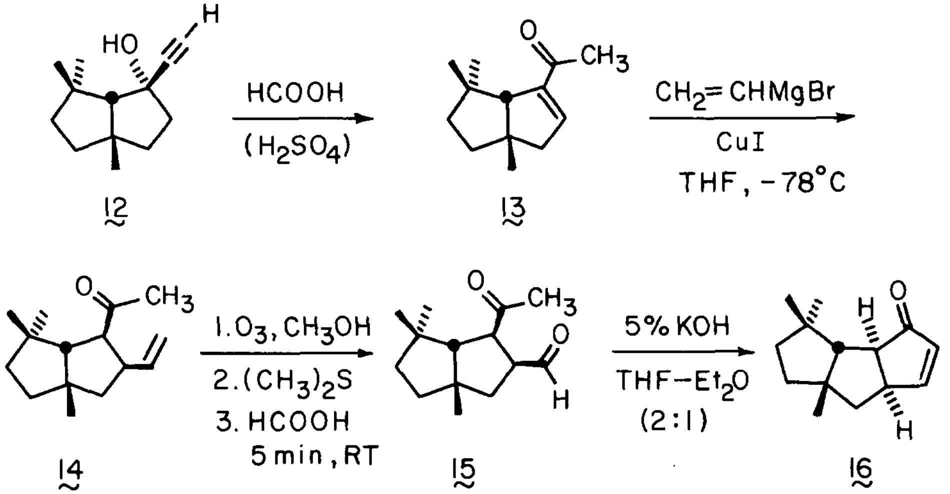
A different regiospecific cyclopentenone annulation was clearly mandated. Viewed with special desirability was early introduction of the new carbonyl group. To this end, 6 was condensed with lithium acetylide[20] to arrive at propargylic alcohol 12 (91%), Rupe rearrangement[21] of which (HCOOH, trace H_2SO_4, 90°C, 15 min) gave rise to 13 (89%). The high predilection for formation of the lesser substituted enone under these conditions is noteworthy. Reaction of 13 with vinylmagnesium bromide and cuprous iodide in THF at -78°C[22] led to a single epimer of 14 (55%). The assignment of stereochemistry to the vicinal acetyl and vinyl substituents was not rigorously ascertained at this point. The ozonolysis of 14 proceeded uneventfully. The resulting keto aldehyde was cyclized with 5% KOH in THF-ether (2:1)[23] containing a catalytic amount of tetra-n-butylammonium hydroxide to give 16 (79%), whose stereochemical assignment rests on its ultimate conversion to 1 via catalytic hydrogenation (H_2, Pt, EtOAc) and Wittig olefination ($Ph_3P=CH_2$, benzene, reflux, 60% overall). The



racemic hydrocarbon so produced was identical with the natural product by spectroscopic comparison (^1H NMR spectrum supplied by Professor Djerassi).

Further work aimed at extending the approach described herein to the synthesis of polyhydroxylated capnellanes is planned.[24]

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(24) The authors acknowledge with pleasure the financial support of this investigation by the National Institutes of Health through Grant GM-28468 and the early synthetic work of Dr. David Dime.

(Received in USA 27 July 1981)