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RADICAL-INITIATED POLYOLEFINIC CYCLIZATIONS IN CONDENSED CYCLOPENTANOID SYNTHESIS. TOTAL SYNTHESIS OF (±)-$\Delta^{9(12)}$-CAPNELLENE

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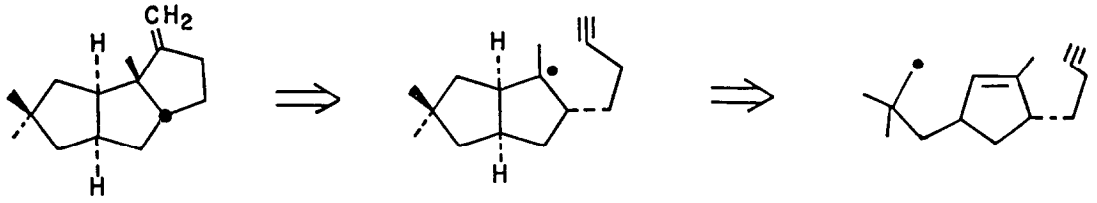
Abstract: The total synthesis of $\Delta^{9(12)}$-capnellene is reported. The key reaction involves construction of two rings in a single step via a tandem radical cyclization.

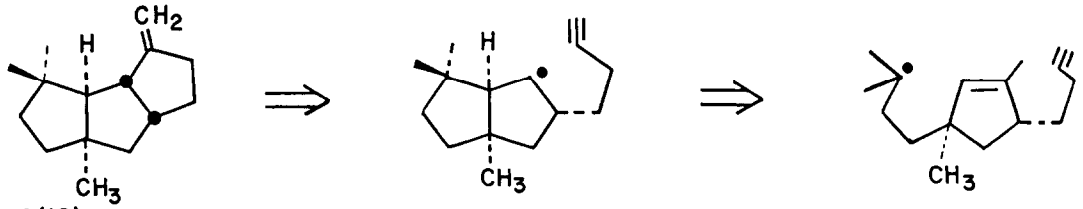
As the number of known condensed cyclopentanoid natural products continues to grow, the development of versatile synthetic entries into this class of compounds becomes increasingly important.[2] We have recently proposed that a tandem radical cyclization strategy will provide a unified entry into a wide variety of linear condensed cyclopentanoid natural products. The strategy (eq. 1) was first illustrated by a short efficient total synthesis of (±)-hirsutene (1), the parent member of the hirsutane family.[3] It was indicated that this strategy might be extended to more complex hirsutanes such as coriolin. In addition, it was proposed that the isomeric capnellane family would also be readily accessible. Along these latter lines, we now report the total synthesis of $\Delta^{9(12)}$-capnellene (2).

(Eq. 1)



Hirsutene 1

(Eq. 2)

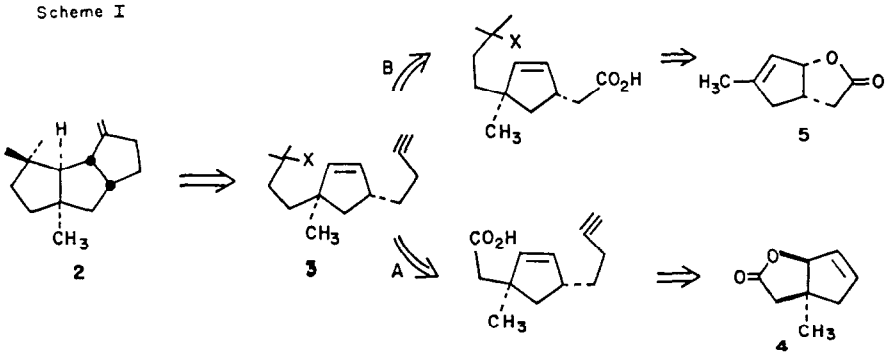


$\Delta^{9(12)}$-Capnellene 2

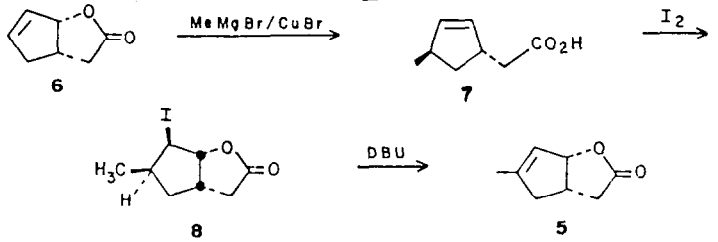
$\Delta^{9(12)}$-Capnellene (2)[4a], an isomer of hirsutene, is the parent member of a relatively small class of marine natural products isolated from soft coral. While a variety of polyhydroxylated relatives of capnellene have been isolated[4b-d], it has recently been proposed that these are artifacts, the actual natural products being peracetylated derivatives.[4e] It has been suggested that the role of these capnellanes may be one of protection against fish predation. Indeed, several of the polyols and acetates exhibit fish deterrent activities.[4e] In common with hirsutene, $\Delta^{9(12)}$-capnellene has been a popular target for illustration of new methods for construction of fused five-membered rings.[5]

The planned tandem-radical cyclization for capnellene is outlined in eq. 2.[3] Generation of an initial radical by tin hydride reduction of an appropriate halide sets off a sequential hexenyl-hexynyl radical cyclization. In a subsequent step, the resulting tricyclic vinyl radical then abstracts a hydrogen atom from tri-n-butyltin hydride. This produces $\Delta^{9(12)}$-capnellene in a single step from a simple trans-disubstituted cyclopentene precursor. The key step in synthesis of the cyclization precursor 3 (Scheme I) is an S_n2'-anti opening of a vinyl lactone with an appropriate side chain equivalent. It is readily ascertained that two strategies are then available, depending on which side chain is chosen as nucleophile for the vinyl lactone opening. In fact, the options seem equally straightforward and both lactones 4 and 5 have been prepared.[6] Further steps along both routes have been simultaneously pursued and the sequence outlined in route B has presently led to synthesis of $\Delta^{9(12)}$-capnellene.

Scheme I



Vinyl lactone 5 is readily available as detailed in equation 3. Opening of well known unsubstituted vinyl lactone 6[7] with MeMgBr/CuBr•Me_2S (THF, -20°C) provided acid 7 as a single (S_n2'-anti) isomer in nearly quantitative yield.[8] Standard iodolactonization to 8, followed by base promoted elimination (DBU, THF, RT), provided ready access to 5[11] as a single regioisomer in 66% overall yield from 6.



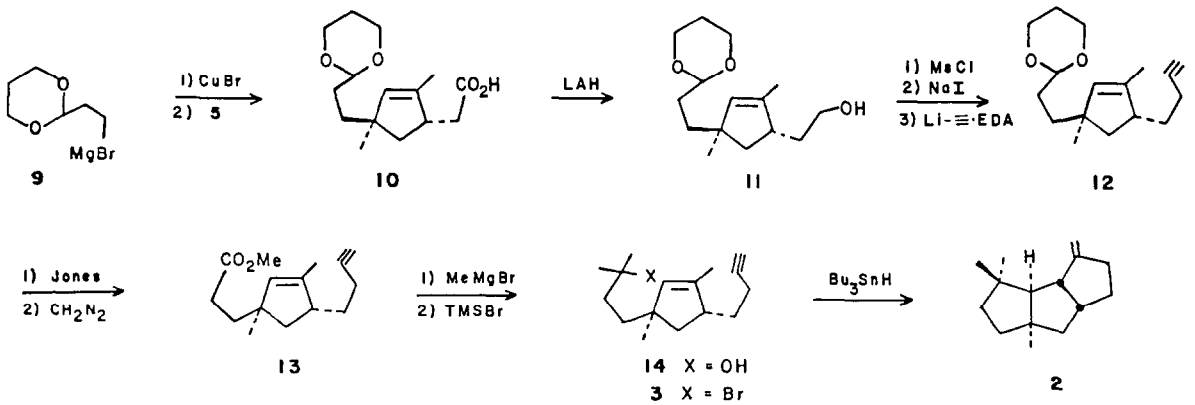
(Eq. 3)

The stage was now set for the crucial S_n2'-anti opening of 5. This reaction sets the proper regio- and stereochemical relationships for capnellene. Note that, in contrast to the hirsutene synthesis,[3] the location of the methyl group on vinyl lactone 5 actually

biases against S_n2'-anti substitution (S_n2=2°; S_n2'=3°). We were pleased to find that conditions developed for exclusive S_n2' substitution in unbiased systems were most successful.[8] Thus, reaction of 5 with the species generated by addition of Grignard reagent 9[9] to one full equivalent of copper bromide/dimethyl sulfide complex (THF, -20°C) produced acid 10 in high yield. In addition, a small amount of the S_n2 regioisomer was produced (10/1). To facilitate isolation the crude mixture was directly reduced ($LiAlH_4$) and purified by chromatography. In this manner alcohol 11[11] was isolated in 80% yield from 5. Standard chain extension was effected by mesylation of the alcohol, exchange with iodide, and displacement with lithium acetylide/ethylene diamine complex (DMSO, RT). Compound 12 was then obtained in 43% overall yield. Dioxane cleavage and oxidation of 12 was accomplished in a single step by treatment with Jones reagent. After exposure of the resulting acid to diazomethane, ester 13 was isolated in 70% yield. Finally, addition of excess methyl magnesium bromide produced tertiary alcohol 14[11] in high yield. Treatment of 14 with trimethylsilylbromide[10] produced slightly impure cyclization precursor 3 in 90% yield. Since attempted purification of this 3° bromide by chromatography was not found to be practical, crude 3 was cyclized directly after formation.

Indeed, treatment of 3 under standard conditions (1.2eq Bu_3SnH, ϕH, 80°C, AIBN, 0.02M) produced $\Delta^{9(12)}$-capnellene. After careful medium pressure liquid chromatography (100% pentanes) 2 was isolated in 61% yield as a clear oil. The overall (unoptimized) yield from 6 was 8%. Synthetic capnellene so produced exhibited spectra (^1H-NMR, ^{13}C-NMR, IR, MS) identical with authentic $\Delta^{9(12)}$-capnellene kindly provided by Professor R. D. Little and also co-eluted with this sample on analytical TLC and capillary GC.

SCHEME 2



While the syntheses of hirsutene served to demonstrate the viability of the radical-initiated polyolefinic cyclization route to condensed cyclopentanoids, the synthesis of capnellene begins to show its versatility. By selecting appropriate starting materials and/or subsequent functional group modification steps, a wide variety of linear condensed cyclopentanoids should be readily avilable via this single strategy. In closing, we note that cyclization of the tertiary iodide analogous to 3 followed a different course and proved most interesting. The results of these experiments will be described shortly.[12]

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11. All new compounds showed spectra consistent with the assigned structures and exhibited satisfactory high resolution MS and/or elemental analysis. 5: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.51 (1H, s), 5.46 (1H, d, J=7.6Hz), 3.14 (1H, m), 2.81 (1H, dd, J=11Hz, 18 Hz), 2.67 (1H, dd, J=8.5Hz, 17Hz), 2.34 (1H, dd, J=5Hz, 18Hz), 2.19, (1H, d, J=17Hz), 1.80 (3H, s); IR($CHCl_3$) 1760 cm^{-1}; 11 ^{1}H-NMR ($CDCl_3$) 5.50 (2H, m), 4.46 (1H, t), 4.09 (2H, m), 3.74 (2H, m); 3.66 (2H, m), 2.78 (1H, m) 2.1-1.2 (10H, m), 1.16 (1H, dd), 1.07 (3H,s); ^{13}C-NMR($CDCl_3$) δ 139.3(d), 132.8(d), 102.8(d), 66.7(t) 61.5(t), 48.0(s), 43.6(t), 42.1(d), 39.7(t), 35.4(t), 31.0(t), 28.2(q), 25.7(dd). 14 ^{1}H-NMR($CDCl_3$) δ 5.52 (2H, m), 2.84 (1H, m), 2.21 (2H, m) 2.0-1.1 (10H, m), 1.19 (6H, s), 1.08 (3H, s).
12. M.-H. Chen, unpublished observations. In addition to capnellene, an isomerized tricyclic vinyl iodide is also produced.

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