

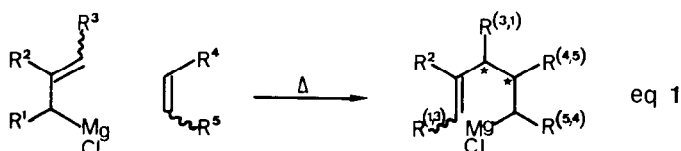
TOTAL SYNTHESIS OF (+)- $\Delta^{9(12)}$ -CAPNELLENE VIA ITERATIVE INTRAMOLECULAR
 TYPE-I-"MAGNESIUM-ENE" REACTIONS

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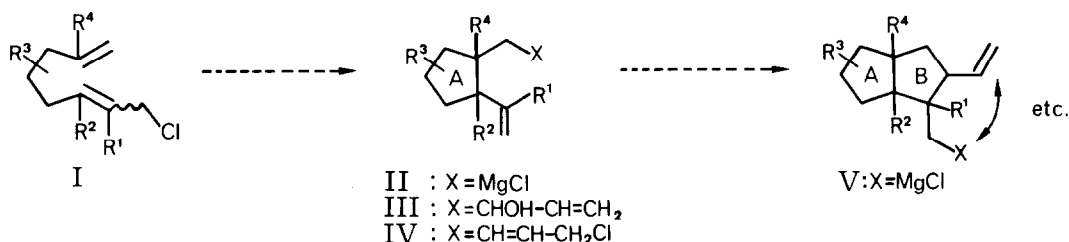
Abstract: The marine triquinane sesquiterpene $\Delta^{9(12)}$ -capnellene (1) was synthesised from 2,2,5-trimethyl-5-hexenal (2) by a sequence of 11 synthetic operations in 5% overall yield. The key steps $3 \rightarrow 4 \rightarrow 5 \rightarrow 6$ involve two intramolecular type-I-"Mg-ene" processes.

The formal ene reaction of allylic Grignard reagents to olefins (eq 1)¹ has



not yet been applied intentionally to the synthesis of complex molecules. Apart from the occasional difficulty to prepare the 2-alkenylmagnesium halides by conventional procedures² problems of efficiency and regiochemistry may limit the scope of the bimolecular process. Although the intramolecular type-I-"magnesium-ene" reaction³ of 2,7-octadienylmagnesium halide (eq 1, $R^3, R^4 = (CH_2)_3$) shows considerable promise⁴ this field remains virtually unexplored. This is surprising in view of the numerous imaginable possibilities offered by subsequent functionalisations of the δ, ϵ -unsaturated Grignard products. In conjunction with our interest in intramolecular ene reactions³ we were particularly intrigued by the idea of rendering this process iterative in order to assemble rapidly polycyclopentanoid systems (Scheme 1).⁵ It thus seemed conceivable to annelate

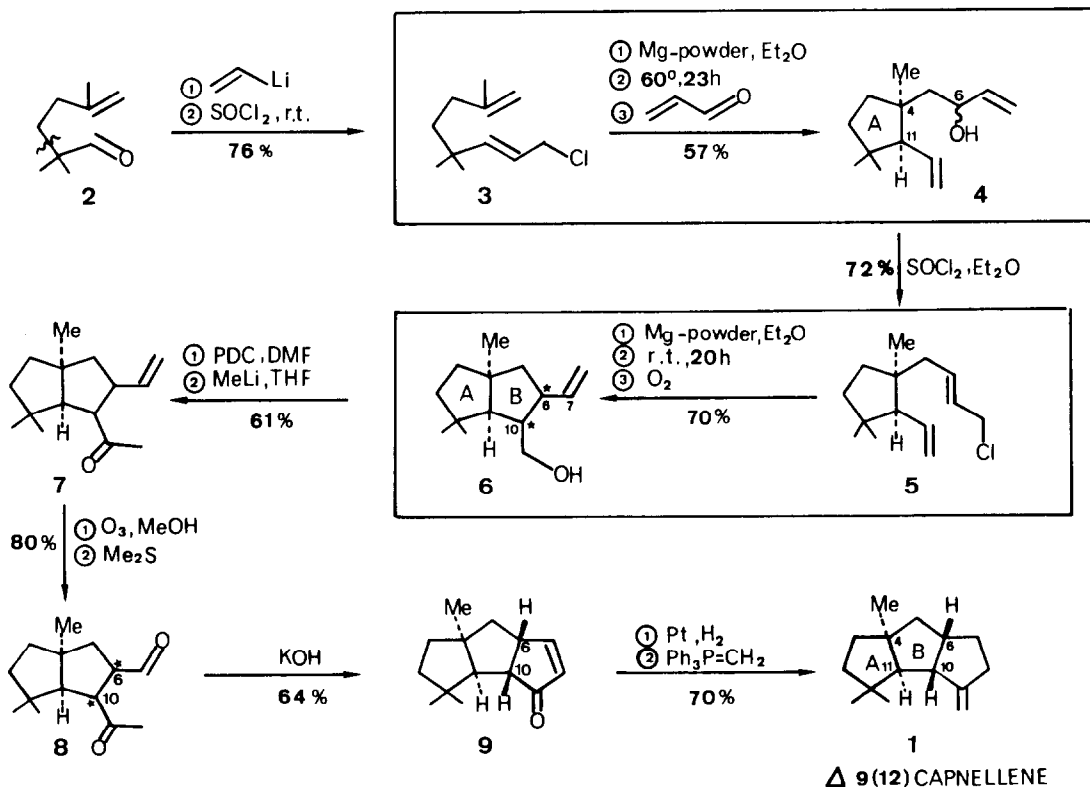
Scheme 1



three carbons in a repetitive manner by two successive synthetic operations e.g. 1) $\text{I} \rightarrow (\text{II}) \rightarrow \text{III}$ and 2) $\text{III} \rightarrow \text{IV}$.

We report here the first strategic application of this approach to a new synthesis of $\Delta^{9(12)}$ -capnellene (**1**) isolated from the soft coral *Capnella imbricata*⁶. Two elegant syntheses of its racemate have been recently achieved in the laboratories of *R.D. Little*⁷ and *L.A. Paquette*⁸. Our results are summarised in Scheme 2.

Scheme 2



Starting from the known aldehyde 2⁷ addition of vinylolithium (1.5 equiv, THF, -70° → r.t. 1h, 91%) followed by treatment of the resulting alcohol⁹ with a 0.7 N solution of SOCl₂ (2 equiv, ether, r.t. 2h, 83%) furnished the allylic chloride 3⁹. Slow addition of 3 (over 4h) to a stirred suspension of commercially available magnesium powder (Merck, 1.5 equiv) in ether at r.t., heating of the thus obtained 0.1 N 2-alkenylmagnesium chloride solution at 60° for 23 h and subsequent addition of acrolein (2 equiv -10° → r.t.) furnished the cyclopentane 4⁹ (1:1-mixture of C(6)¹⁰-epimers) in 57% overall yield. It is worth noting that this key step 3 → 4 involves the first known successful "magnesium-ene" addition to a non-activated 1,1-disubstituted olefin thereby closing the congested bond C(4),C(11)¹⁰ with high stereochemical control. Consequently, the allylic chloride 5⁹ was obtained as a single stereoisomer on reaction of 4 with SOCl₂ (2 equiv, Et₂O, r.t., 2 h, 72%). The prerequisites are now secured for the second key step. In fact, the Grignard reagent prepared from 5 (Mg-powder, ether, r.t.) cyclised smoothly at r.t. (20h) to give after trapping with O₂¹¹ a 3:2-mixture of C(6)/C(10)¹⁰-*cis/trans*-stereoisomeric alcohols 6^{9,12} in 70% overall yield from 5. The kinetic nature of this surprisingly poor stereoselection follows from metalation of 5 (using precondensed Mg² -5°) and cyclisation in ether at 0° (18 h) which after quenching with O₂ gave the same 3:2-ratio of isomers 6 together with 75% of non-cyclised alcohol. It is nevertheless remarkable that this ring closure occurs at such low reaction temperature obviously owing to entropic reasons. Having assembled rings A and B of 1 by a sequence of two "magnesium-ene" reactions we aimed at the remaining closure of ring C with concomitant thermodynamic control over the configurations at C(6) and C(10)¹⁰. Oxidation of the primary alcohols 6 with PDC¹⁴ (5 equiv, DMF, r.t., 17h, 81%) to the corresponding carboxylic acids⁹ followed by addition of methylolithium (2.2 equiv, THF, r.t., 18h, 75%) afforded the methylketones 7⁹ identified by comparison (¹H-NMR, IR) with an authentic, sterically pure sample of 7⁸. The final transformations 7 → 1 rely on the protocol previously employed by *Paquette et al.*⁸ Ozonisation of 7 (MeOH, -78°) and subsequent reduction with dimethylsulfide (-78°→r.t.) gave the ketoaldehydes 8⁹ (80%). For the critical aldolisation 8→9 conditions were chosen (5% aq. KOH, EtOH, 1:1, 50°, 1.5 h) which channeled both isomers 8 into the same *cis-anti-cis*-tri-cyclo[6.3.0.0^{2,6}]-undecenone 9⁹ (64%) *via* base-induced epimerisation at C(6) and/or at C(10). Hydrogenation of 9 (H₂/Pt, EtOAc) followed by methylenation of the saturated ketone⁹ using a salt-free solution of Ph₃P=CH₂¹⁵ (excess, THF, 90°, 3h) gave (±)Δ⁹⁽¹²⁾-capnellene (1) (70% from 9). The enone 9 as well as (±)-1 display spectra (¹H-NMR, ¹³C-NMR, IR) identical to those of authentic (±)-9⁸ and of naturally occurring (-)-Δ⁹⁽¹²⁾-capnellene⁶, respectively. In summary, this work together with the recently accomplished syntheses of (±)-sinularene^{16a} and

(±)-khusimone^{16b} exemplifies the utility of intramolecular "magnesium-ene" reactions. Work is in progress to employ this and related iterative cyclopentane annelations to the syntheses of further triquinane sesquiterpenoids.

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