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A SYNTHESIS OF NOVEL NINE-MEMBERED DIENONES THROUGH A CYCLIC ACETYLENIC OXY-COPE REARRANGEMENT: THE SYNTHESIS OF dl-PHORACANTHOLIDE I

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(Dedicated to Prof. Harry H. Wasserman on the occasion of his sixty-fifth birthday)

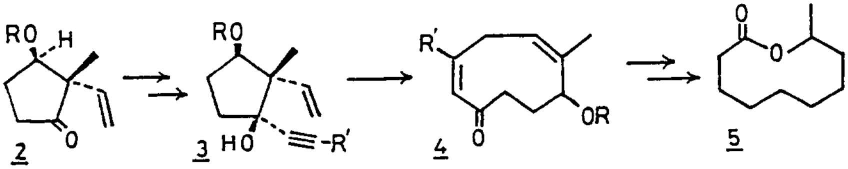
Summary: Phoracantholide I, having a ten-membered lactone, was synthesized through a new synthetic method which includes a cyclic acetylenic oxy-Cope rearrangement and ring-expansion by the Baeyer-Villiger oxidation of a nine-membered ketone.

Recently we have reported the wide utility of the remarkably reactive phenyl 2-(trimethylsilyl)ethynyl sulfone(PTES, 1) as a reagent for introduction of a vinyl group to α-carbon of carbonyl groups.[1] Among the vinylated products, the compound 2, for example, should be very useful in organic synthesis, since it could efficiently supply the compound 3 as a good substrate for an acetylenic oxy-Cope reaction.[2] We envisioned that 3 would afford the novel strained nine-membered dienone 4.

Intermediate 4 seemed to be well-suited as a common intermediate for the synthesis of medium-sized terpenoids and lactones, e.g. caryophyllenols,[3] piscicidal buddledins,[4] and fungal morphogenic pyrenolides.[5] These natural products have attracted our attention as synthetic targets, as they have not been synthesized to date.

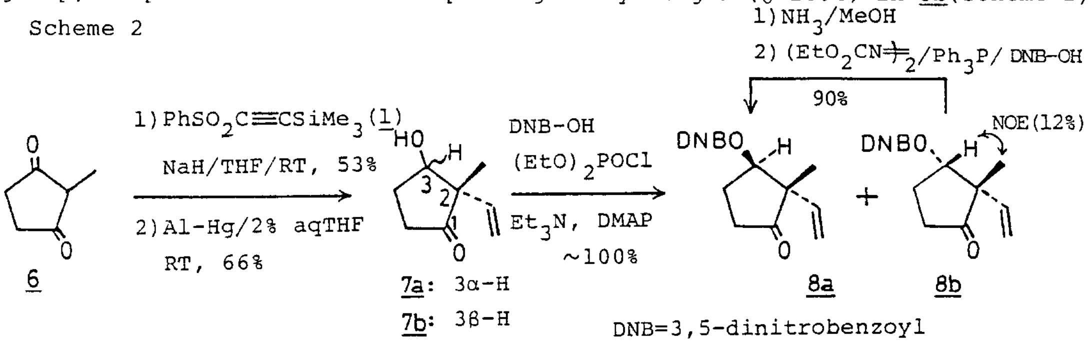
We report here the synthesis of the defensive substance of the Australian Coleoptera, dl-phoracantholide I(5),[6,7] which includes a cyclic acetylenic oxy-Cope rearrangement, followed by ring-expansion and the Baeyer-Villiger oxidation of a nine-membered ketone(Scheme 1).

Scheme 1



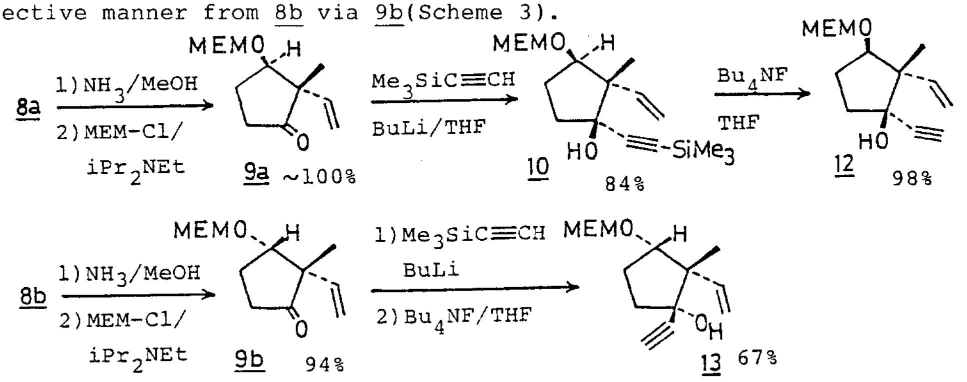
The vinyl ketals 7a and 7b as an inseparable mixture were provided by the Michael addition of the diketone 6, followed by desulfurization.[1] Fortunately, we could easily separate isomers 8a and 8b formed in a 1:1 ratio by flash chromatography after acylation of 7a,b with 3,5-dinitrobenzoic acid(DNB-OH) in the presence of diethyl phosphorochloridate.[8] The stereochemistry of each isomer was determined by the analysis of the following NMR spectra. The NOE between C_3-proton and C_2-methyl group in 8b is obserbed in 12 %, whereas the corresponding NOE in 8a was not obserbed. Furthermore, in ^{13}C NMR spectrum of 8a, the 2-methyl signal is situated upfield(δ 16.8) based on the effect of steric compression against the DNB group, compared with the corresponding methyl signal(δ 20.4) in 8b(Scheme 2).

Scheme 2



Considering the need for overlap of π-orbital for the facile oxy-Cope rearrangement of five-membered ring system,[9] the desired stereochemistry should be of the cis-configuration such as 10 or 12, in regard to the vinyl and ethynyl groups. These compounds would be derived from 8a via 9a rather than 9b, since the stereoselective approach of the reagent to the opposite α-side of the bulky β-MEM group might be expected. The isomer 8b of disfavored stereochemistry could be readily converted into 8a by hydrolysis with ammonia in MeOH, followed by the Mitsunobu reaction.[10] Thus, the vinylated compound 8a led to the ethynyl derivative 9a, through hydrolysis and methoxyethoxymethylation(MEM), which was converted to 10 by fully stereoselective ethynylation, and then to 12 by desilylation in high yields. On the other hand, the trans isomer 13 was also prepared in an entirely stereoselective manner from 8b via 9b(Scheme 3).

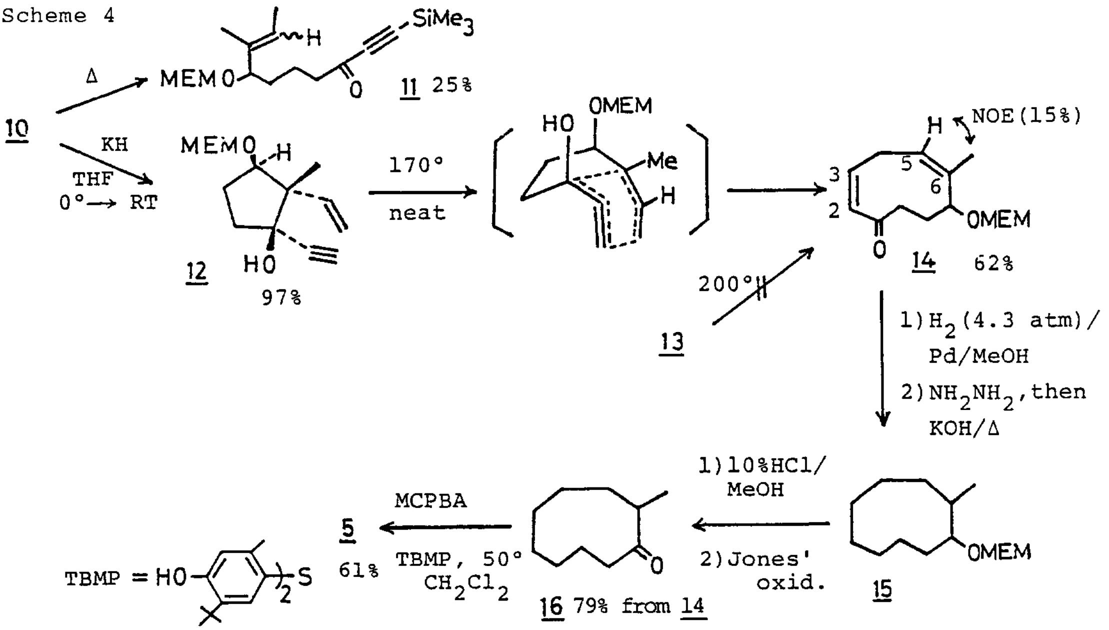
Scheme 3



Initial attempts at achieving the oxy-Cope rearrangement using silylethynyl derivative 10 upon heating or basic condition resulted in failure. On heating of 10 at 220°C, only the ring-opened product 11 was detectable. Subsequently, on treatment of 10 with potassium hydride in an attempt to effect the anionic oxy-Cope reaction, the desilylated product 12 was obtained in high yield.

However , when the rearrangement of 12 was conducted at 170°C for 20 min (neat), the desired nine-membered dienone 14 was obtained in 62% yield. The stereochemistry of the two double bonds was proved to be of the Z,Z-form by the coupling constant (J = 11.7 Hz) between C_2- and C_3-protons in the ^{1}H NMR spectrum, and by observing the NOE(15%) between C_5-H and C_6-methyl group. This type of cyclic acetylenic oxy-Cope reaction affording the nine-membered dienone is an unprecedented example.[11] On the other hand, the trans isomer 13 did not give 14, even upon heating at 200°C. In order to synthesize phoracantholide I(5) together with a firm determination of the nine-membered skeleton 14, it was necessary to proceed through the saturated ketone 16[12] via 15, which was achieved in a high overall yield. Finally oxidation of 16 with MCPBA gave 5 as a volatile oil, whose spectral data were completely identical with those of the authentic sample.[7a] Work is in progress on approaches to the other medium-sized terpenoid synthesis.

Scheme 4



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