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APPLICATION OF THE α-ALKYNONE CYCLIZATION : SYNTHESIS OF rac-MODHEPHENE

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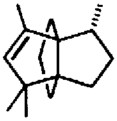
Abstract: Using the thermal α-alkynone cyclization 8 → 9 as the key step, modhephene 1, a sesquiterpene with a [3.3.3]-propellane skeleton was synthesized.

In 1978 Zalkow et al[1] described the isolation and structure elucidation of modhephene 1, the first sesquiterpene with a [3.3.3]-propellane carbon skeleton. For the synthesis of racemic 1 we envisaged as the key step the application of the α-alkynone cyclization[2] to the construction of a propellane skeleton; this reaction had previously been used successfully for the preparation of bicyclic and spiro compounds.

Modhephene



1

The synthesis[3] of the key intermediate required for this reaction, the α-alkynone 8, is shown in steps (1) to (5) of the reaction scheme. The thermolysis result (step (6)) shows that the insertion (forming cyclopentenones) of the postulated alkylidene carbene intermediate[2] into the tertiary (angular) C,H-bond is preferred over the one into the secondary (ring) C,H-bonds.

The reactions which convert 9 into rac-modhephene 1 by elaborating the cyclopentenone to a trimethylcyclopentene moiety are explained in steps (7) to (10). The properties of 1 were identical with those reported for the natural product[1]. The same sequence of reactions applied to 7 afforded the C(8)-epimer of modhephene, with a clearly different ^{1}H NMR spectrum[10].

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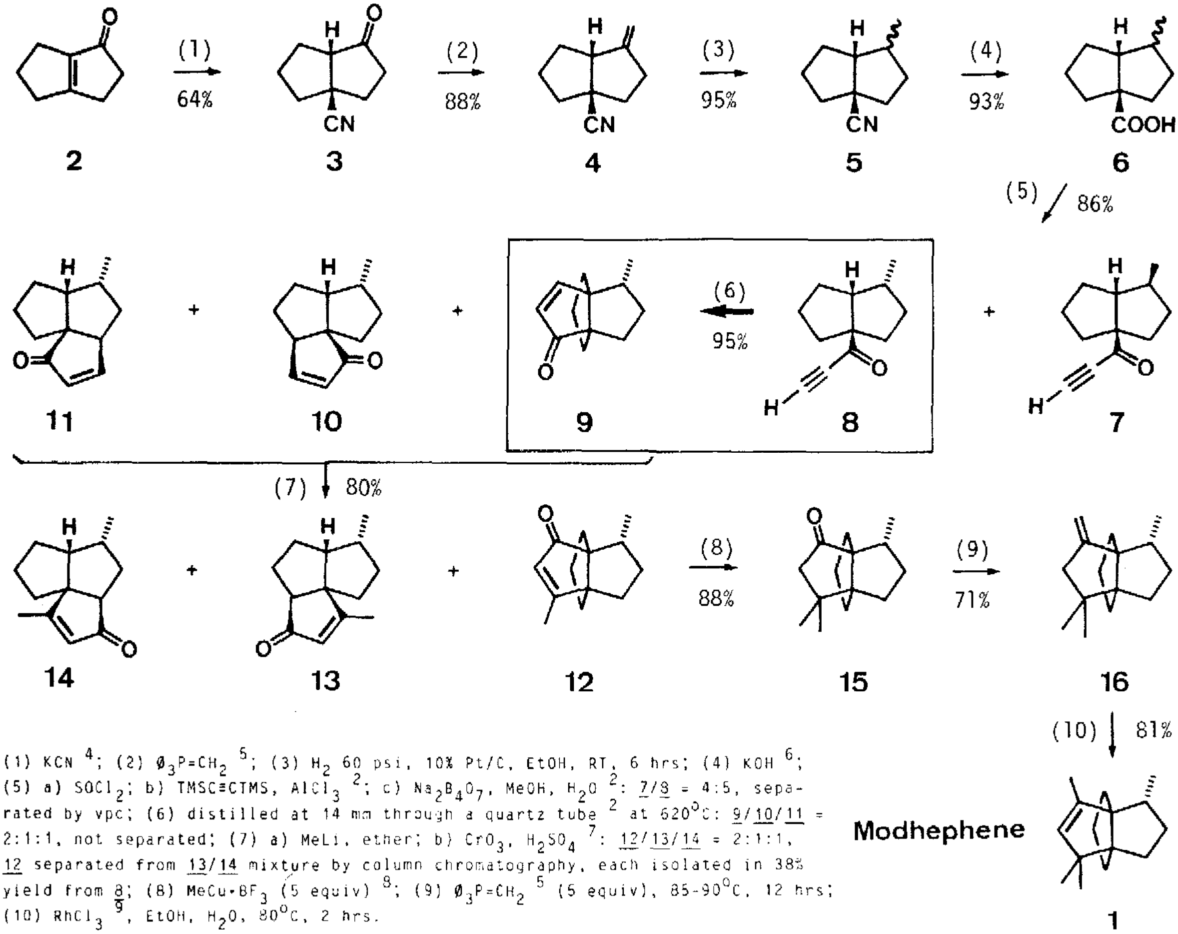

(1) KCN [4]; (2) $Ø_3P=CH_2$ [5]; (3) H_2 60 psi, 10% Pt/C, EtOH, RT, 6 hrs; (4) KOH [6]; (5) a) $SOCl_2$; b) TMSC≡CTMS, $AlCl_3$ [2]; c) $Na_2B_4O_7$, MeOH, H_2O [2]: 7/8 = 4:5, separated by vpc; (6) distilled at 14 mm through a quartz tube [2] at 620°C: 9/10/11 = 2:1:1, not separated; (7) a) MeLi, ether; b) CrO_3, H_2SO_4 [7]: 12/13/14 = 2:1:1, 12 separated from 13/14 mixture by column chromatography, each isolated in 38% yield from 8; (8) $MeCu{\cdot}BF_3$ (5 equiv) [8]; (9) $Ø_3P=CH_2$ [5] (5 equiv), 85-90°C, 12 hrs; (10) $RhCl_3$ [9], EtOH, H_2O, 80°C, 2 hrs.

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