244. A Short and Efficient Synthesis of (±)-Modhephene by a Stereoelectronically-Controlled Ene-Reaction

Preliminary Communication[1])

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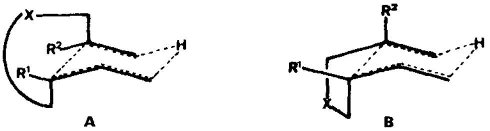
Summary

(±)-Modhephene (**6**) has been synthesized from the easily available trimethylpentalenone **1** in 6 steps in 26% overall yield *(Scheme 2)*. The remarkably smooth 1,4-addition/enolate trapping **1**→**2** and subsequent selenoxide elimination after oxidation furnished the key intermediate **3** which underwent an expedient and highly stereoselctive intramolecular *ene*-reaction to give the propellane **4**, readily convertible to (±)-**6**.

In conjunction with a general program exploring the scope and limits of intramolecular ene-reactions [1] we have observed previously that 1,6-dienes with the H-donor site *cis* relative to the enophile cyclize thermally to give exclusively 5-membered rings containing *cis*-related H-donor and acceptor sites [2]. These results could be rationalized by inspection of the alternative transition states **A** and **B**; whereas **A** shows a severe angle strain, **B** is perfectly attainable *(Scheme 1)*.

Scheme 1



As published in a recent short communication we have exploited these findings for a stereoselective synthesis of the naturally occurring propellane modhephene (**6**) [3]. Modhephene, isolated by *Zalkow et al.* from rayless goldenrod *(Isocoma wrightii)* [4] and by *Bohlmann et al.* from South African *Berkheya* species [5] has attracted considerable attention as a target for synthesis. However all synthetic

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[1]) Presented by one of us *(W.O.)* at the First International Conference on Chemistry and Biotechnology of Biologically Active Natural Products, Varna, Bulgaria, September 1981.

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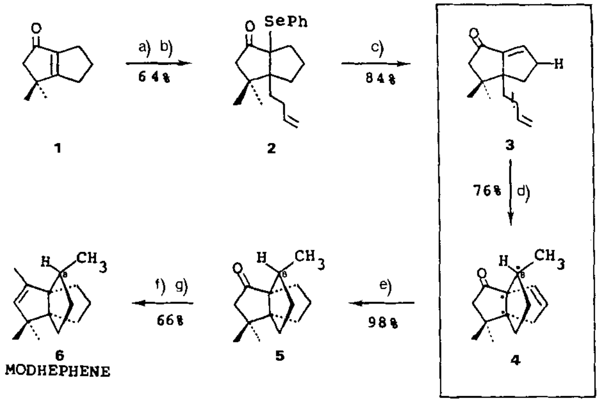
approaches to **6** so far are either non-stereoselective (requiring GC.-separation of intermediates) [6] [7] or lengthy [3] [8][2]).

In contrast, we report here a direct and highly stereocontrolled synthesis of (±)-modhephene (**6**) *(Scheme 2)*.

Scheme 2



[a] $CH_2{=}CH(CH_2)_2MgBr$ (30 mmol), THF (43 ml), CuBr·DMS (7.5 mmol), DMS (20 ml), −78°; addition of **1** (15 mmol) in THF (15 ml) over 8 h at −78°, then → RT. over 16 h. [b] PhSeBr (20 mmol), THF/HMPA 3:1 (10 ml), 0°, 10 min, RT., 30 min. [c] 5% aq. H_2O_2-solution (10 mol-equiv.), Py (3 mol-equiv.), CH_2Cl_2, RT., 1.5 h. [d] 1% solution of **3** in toluene at 250°, 16 h, sealed pyrex tube. [e] H_2 (3 atm.), 10% Pd/C, EtOH, RT., 12 h. [f] $H_2C{=}P(Ph)_3$ (6 mol-equiv.) THF, 90°, 6 h. [g] TsOH, CH_2Cl_2, 25°, 6 h.

The pentalenone **1**, readily available from cyclopentene (60% yield)[3]) underwent a surprisingly smooth conjugate addition of butenylmagnesium bromide in the presence of freshly crystallized $CuBr/Me_2S$-complex[4]).

Subsequent enolate-trapping with freshly prepared phenylselenyl bromide [11] furnished the crystalline selenide **2**[5]) (m.p. 64–70°) in 64% yield. Oxidation of **2** with H_2O_2-solution/pyridine led to a selenoxide elimination giving the key precursor **3**[5]) in 84% yield.

The stage was now set for the decisive *ene*-reaction. Heating a solution of **3** in toluene at 250° for 16 h using a sealed, pre-dried *Pyrex* tube gave the desired [3.3.3]-

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[2]) Thus, our previous synthesis of (±)-**6** suffers from the need to introduce the *gem*-dimethyl group at an advanced stage [3].

[3]) The *Friedel-Crafts* acylation of cyclopentene with 3,3-dimethylacryloyl chloride [9] (1 mol-equiv. of $AlCl_3$, CH_2Cl_2) was greatly improved when carried out at −78°. Heating the crude reaction mixture with NEt_3 furnished 1-(1-cyclopentenyl)-3-methyl-2-buten-1-one (79% yield) which on *Nazarov* cyclization ($SnCl_4$) [10] furnished the pentalenone **1**.

[4]) Cuprate addition to the hindered C(*β*) of **1** previously required promotion by borontrifluoride etherate [8]. Furthermore, numerous attempts have failed to achieve the conjugate addition of butenylcuprates to 4,4-dimethyl-3-[2-(1,3-dioxolan-2-yl)ethyl]-2-cyclopentenone [3].

[5]) All new compounds were characterized by IR., ^1H-NMR. (360 MHz) and mass spectroscopy. Their purity was confirmed by GC. analysis.

propellane **4**[5]) in 76% yield. According to our prediction the relative configuration of C(8) with the methyl group pointing towards the cyclopentene bridge has been nicely controlled in the cyclization step[6]).

Catalytic hydrogenation of **4** furnished the ketone **5**[5]) (98% yield), identified by comparison (IR., ^{1}H-NMR. and MS.) with a sample of **5** prepared previously by *Karpf & Dreiding* [6]. Modifying the published procedure [6] ketone **5** was successively treated with methylidene triphenylphosphorane and *p*-toluenesulfonic acid in CH_2Cl_2 at 25° to give (±)-modhephene (**6**) showing IR., ^{1}H-NMR. and mass spectra identical to those of the natural sesquiterpene.

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[6]) The configuration of **4** was established by its conversion to **5** and **6**. Two not yet fully characterized minor compounds (10% and 8% yield, respectively) were separated from **4** by simple chromatography (SiO_2, hexane/ether 40:1).