149. A New, Stereoselective Approach to the [3.3.3]Propellane System: Synthesis of (±)-Modhephene

Preliminary Communication

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Summary

The unusual propellane skeleton of the sesquiterpene modhephene (**1**) has been synthesized starting from cyclopentenone (**2**). The key step **6**→**7** is an efficient and highly stereoselective intramolecular thermal ene-reaction. Further elaboration of the propellane **7** gave the enone **10** which had been previously converted to (±)-modhephene (**1**) in three steps.

Modhephene, isolated by *Zalkow et al.* from *Isocoma Wrightii*, is the first carbocyclic propellane to be found in nature. Its unusual structure **1** which contains three contiguous quaternary C-atoms and a tertiary center C(8) with the methyl group pointing toward the unsubstituted C_3-bridge follows from X-ray evidence [1]. We were challenged by the key problem of synthesizing the [3.3.3]propellane skeleton of **1** with unambiguous steric control over the tertiary center C(8) relative to the other two chiral bridge-head centers.

During our work two imaginative but non-stereoselective syntheses of **1** have been published both involving the same enone intermediate **10** which by three steps[1]) gave (±)-modhephene in good yield [2] [3]. An even more recent communication describes another elegant approach to (±)-**1** which solves the stereochemical problem by substituent-directed modification of the preassembled propellane framework [4]. Aiming at a direct stereoselective route to the propellane skeleton of modhephene we centered our retrosynthetic planning *(Scheme 1)* on the thermal intramolecular ene-reaction[2]) **II**→**I**.

This strategy was founded on previous observations that 1,6-dienes containing the H-donor site *cis* with regard to the enophilic chain furnish on thermal cyclization exclusively 5-membered rings with *cis*-positioned H-donor and acceptor sites [5] [11][3]).

[1]) $MeCu \cdot BF_3$; $Ph_3P{=}CH_2$; $RhCl_3$, $EtOH/H_2O$ [2].

[2]) For the classification and applications of intramolecular ene-type reactions see a recent review [5] and [6–10].

[3]) Assuming a concerted reaction the alternative stereochemistry would imply a severely strained transition state.

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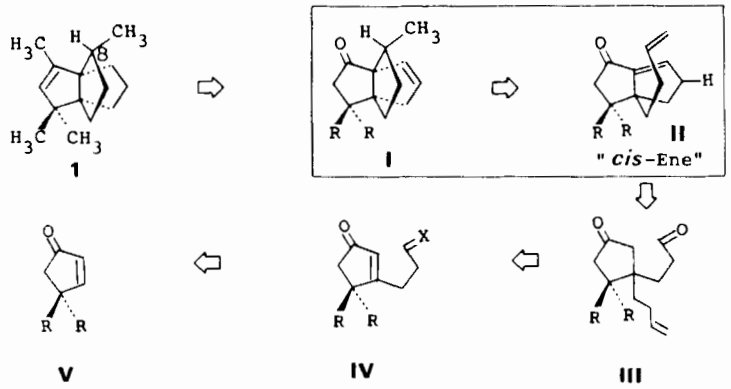
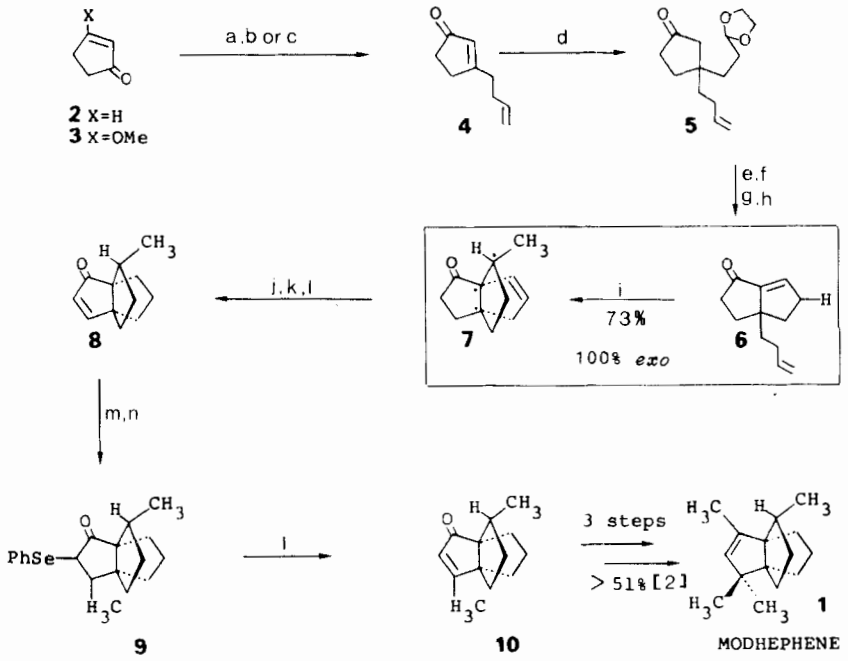
Scheme 1



Scheme 2



[a]) $CH_2{=}CH(CH_2)_2MgBr$, THF. [b]) For X=H: PCC, CH_2Cl_2, RT., 2 h [13] (22%). [c]) For X=OCH_3: 1N aq. HCl, 0° (68%). [d]) $BrMg(CH_2)_2CH$ ($-OCH_2CH_2O-$) [14], THF, CuBr · DMS, addition of **4** over 4 h at −78°, then −30°, 15 h, RT., 20 min; (50%). [e]) aq. HCOOH-solution, HCOONa, RT., 15 h [15]. [f]) 1N aq. NaOH, Et_2O, RT., 2.5 h. [g]) MsCl, Py, 0°, 15 min, RT., 30 min. [h]) DBN (1 mol-equiv.), Et_2O, RT., 4 h (45%). [i]) Toluene, 250°, 12 h, sealed pyrex tube (73%). [j]) H_2, 5% Pd/C, EtOH. [k]) LDA, THF, −78°, 45 min; PhSeBr, THF, −78°. 10 min. [l]) 15% aq. H_2O_2-solution, Py, CH_2Cl_2, RT., 2 h (43%). [m]) CH_3MgI, CuBr · DMS, Et_2O/THF, 2.5 h at −78°, 3 h at 0°. [n]) PhSeBr, THF/HMPA, 0°, 30 min.

Since the diene **II** meets this steric disposition the methyl group was expected to be formed *cis* to the olefinic bridge in the product **I**. The stereochemistry thus secured, subsequent olefin-hydrogenation and carbonyl-functionalization should lead to modhephene. Planning further backwards we envisioned that the butenyl-[3.3.0]enone-system **II** could be derived from aldolisation of a 1,6-ketoaldehyde **III** potentially accessible *via* cuprate addition to a cyclopentenone **IV.** Following this plan 4,4-dimethylcyclopentenone [12] was converted in 82% overall yield into the 3,4,4-trisubstituted cyclopentenone **IV** (R = Me, X = $(-O-CH_2-CH_2-O-)$)[4])[5]).

Now a serious problem emerged due to the steric crowding at C(3) in **IV** (R = Me, X = $(-O-CH_2-CH_2-O-)$) obstructing all our attempts to effect conjugate addition. To avoid this complication we preferred to incorporate the geminal methyl groups at a later stage in the synthesis and to start with commercially available cyclopentenone (**2**) *(Scheme 2).*

The butenylcyclopentenone **4**[5]) easily accessible from **2** or **3** underwent smooth conjugate addition at the relatively uncongested C(β)-atom to give the acetal **5**[5]) in 50% yield. Successive liberation of the aldehyde group, base promoted aldol-cyclization and β-elimination of the mesylated aldol furnished the bicyclic enone **6**[5]) in 45% overall yield.

Having accomplished a simple route to the 1,6-diene precursor **6** we proceeded to the crucial ene-reaction which occurred readily on heating a solution of **6** in toluene at 250° for 12 h using a sealed tube[6]). It was gratifying to see that only the desired propellane **7**[5])[7]) was obtained in 73% yield. Not even a trace of the undesired C(8)-epimeric product could be detected[8]).

There remained the final task to exploit the carbonyl group of **7** in order to introduce the missing methyl groups. Catalytic hydrogenation of the olefinic bond followed by selenation of the enolate and selenoxide elimination [16] furnished the enone **8**[5]). β-Methylation by cuprate addition, enolate trapping with phenylselenyl bromide and further selenoxide elimination gave the key intermediate **10** which was identified by careful comparison (GC.[9]), IR., ^{1}H-NMR. (360 MHz), ^{13}C-NMR. (90.561 MHz) and MS.) with an authentic sample. Since the conversion

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[4]) i) Addition of 4,4-dimethylcyclopentenone in ether over 4 h to $BrMg(CH_2)_2CH(-OCH_2-CH_2-O-)$, CuBr · DMS, THF, −78°; then −78°, 30 min, −30°, 15 h; ii) PhSeBr, THF, HMPA, 0°, 45 min; iii) 15% aq. H_2O_2-solution, Py, CH_2Cl_2, RT., 30 min.

[5]) All new compounds were characterized by IR., ^{1}H-NMR. (360 MHz) and mass spectroscopy. Their purity was confirmed by GC.-analysis. The following compounds showed the indicated UV. spectra (hexane, λ_{max} in nm, ($\log\varepsilon$)): **IV** (R = Me, X = $(-O-CH_2-CH_2-O-)$): 217 (4.1); **4**: 215 (4.1); **6**: 239 (4.2); **8**: 215 (3.8).

[6]) The pyrex tube was treated with a 2% solution of N,O-bis(trimethylsilyl)acetamide in Et_2O for 30 min, washed with Et_2O and dried prior to use.

[7]) ^{1}H-NMR. (360 MHz): 1.01 (*d*, *J* = 7, 3 H); 1.1-2.7 (11 H); 5.49 (*d* × *t*, *J* = 5 and 2.5, 1 H); 5.74 (*d* × *t*, *J* = 5 and 2.5, 1 H). – ^{13}C-NMR. (90.56 MHz): 219.4 (*s*), 133.2 (*d*), 127.8 (*d*), 76.0 (*s*), 58.0 (*s*), 49.2 (*t*), 42.1 (*d*), 39.0 (*t*), 37.2 (*t*), 35.5 (*t*), 33.4 (*t*), 15.8 (*qa*). (NMR. spectra in $CDCl_3$, standard TMS δ(ppm) = 0; abbreviations: *s* = singlet, *d* = doublet, *t* = triplet, *qa* = quadruplet, *J* = spin-spin coupling constant (Hz)).

[8]) This stereochemical assignment was proven by conversion of the ene-reaction product to the enone **10** as described below, which was then compared with authentic **10** and its corresponding C(8)-epimer.

[9]) Capillary column-WCOT, 25 m, stationary phase: OV-101, 140°.

10→(±)-**1** has already been achieved [2] [3] this work constitutes a formal total synthesis of (±)-modhephene.

The 100% stereoselective approach to the [3.3.3]propellane system, reported here, may be of general value in propellane synthesis [17] since it seems to be governed by stereoelectronic rather than by substituent effects.

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