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(±)MODHEPHENE AND (±)ISOCOMENE VIA CASCADE REARRANGEMENT[1]

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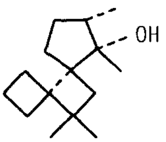
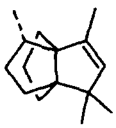
Summary: Dispiro[3.0.4.2]undecane **1** has been synthesized and rearranged to (±)modhephene **2** and triquinane **3** under kinetic control, and to (±)isocomene **4** and triquinane **5** under thermodynamic control. Molecular mechanics calculations (MM2) support the mechanism proposed.

Since their detection a decade ago, (±)modhephene **2**[2] and (±)isocomene **4**[3] have been the subject of an increasing number of total syntheses. Within the strategies used, rearrangements are rare and never comprise more than a single step. This is somewhat surprising as **2** and **4** are associated in nature[2a,b] and may formally be derived from each other by three consecutive 1,2-shifts. Despite of this fact no equilibration studies with **2** and/or **4** have become known. We now wish to report the synthesis and rearrangement of dispiro[3.0.4.2]undecane **1** and our finding that **1** may not only be rearranged to (±)modhephene **2** and triquinane **3**, but also to (±)isocomene **4** and triquinane **5**. In view of these findings an early assumption of Zalkow[2a] that **17** might be a common precursor of **2** and **4** deserves further attention.



1



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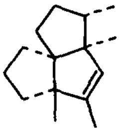

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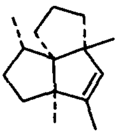

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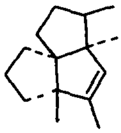
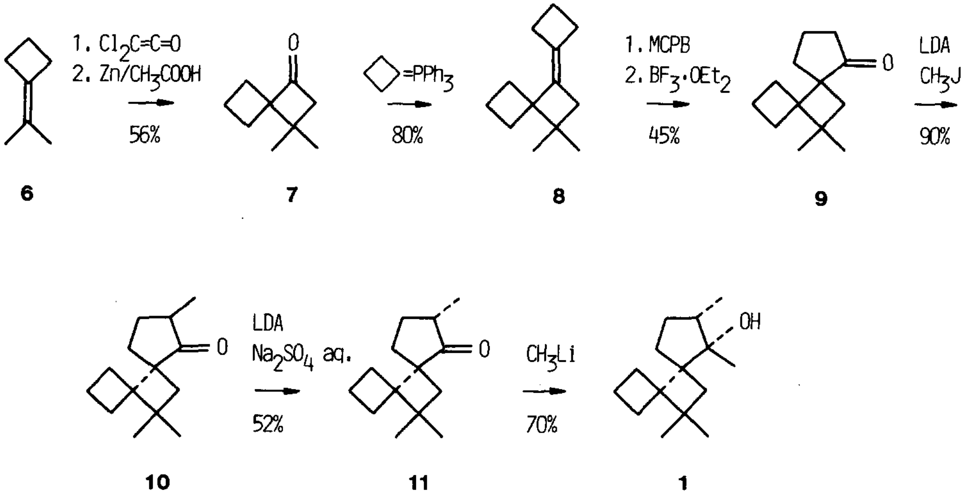


5

The synthesis of **1**, specifically devised to give access to **2**[4], was achieved as follows: regiospecific addition of dichloroketene[5] to isopropylidenecyclobutane **6** and subsequent dechlorination[6] yielded cyclobutanone **7**[7] which was cyclobutylidenated to **8**[7] and then epoxidized and rearranged to dispiroketone **9**[7]. Methylation of **9** proceeded stereospecifically, and deprotonation and stereoselective reprotonation[8] of the resulting **10**[7] then yielded **11**[7]. Stereoselective addition of methyllithium to **11** completed the synthesis of **1**[7].

When **1** was heated with an equimolar amount of a 0.040 molar solution of p-toluenesulfonic acid in benzene-d_6 and the reaction progress followed by ^{1}H-NMR spectroscopy[9], the formation and consumption of (±)modhephene **2** and triquinane **3**[7] could be observed. After 10 min at +70°C the rearrangement of **1** was complete and **2** (62%) and **3** (31%) were the principal products. After 22h at



+70°C (±)modhephene **2** had disappeared, the content of **3** had dropped to 23%, and (±)isocomene **4** (27%) and triquinane **5**[7] (24%) had formed instead. After 76h at +70°C **3** (10%) had been largely consumed, the content of (±)isocomene **4** (27%) had remained unchanged and triquinane **5** (33%) was now the main product. ^{13}C-NMR spectroscopy was used to identify (±)modhephene **2**[2a,d] and (±)isocomene **4**[3b], and the same technique revealed the absence of (±)epimodhephene **32**[2c] and (±)epiisocomene **34**[3i] throughout the whole rearrangement. The structural assignment for triquinanes **3**[7] and **5**[7] was therefore straightforward: they were the only remaining olefins which could exhibit the one proton quadruplets observed in the vinylic proton region[9]. While mixtures of **2** and **3** could readily be separated by chromatography on silica gel impregnated with silver nitrate in dichloromethane, mixtures of **3**, **4** and **5** could not. Triquinane **5**[7] was therefore identified in a difference analysis using the known ^{13}C-NMR data for **3**[7] and **4**[3b].

In order to get more insight into the rearrangement of **1**, we calculated[10] the heats of formation of all olefins which could be derived from the two series of epimeric tertiary carbenium ions **12-18** and **23-29**. In accordance with the experimental results, (±)isocomene **4** (ΔH_f = -26.7 kcal/mol) and triquinane **5** (ΔH_f = -28.7 kcal/mol) were found to be more stable than triquinane **3** (ΔH_f = -26.6 kcal/mol) and (±)modhephene **2** (ΔH_f = -25.5 kcal/mol), with (±)epiisocomene **34** (ΔH_f = -24.5 kcal/mol) and (±)epimodhephene **32** (ΔH_f = -23.9 kcal/mol) coming next. We deduce from the above that the rearrangement of **1** to (±)modhephene **2** and triquinane **3** is kinetically controlled, and the subsequent rearrangement of both **2** and **3** to (±)isocomene **4** and triquinane **5** is thermodynamically controlled.

It is interesting to note that the rearrangement of **1** to **5** requires no fewer than nine 1,2-shifts and an epimerization at the stage of carbenium ion **16** (**16-21-27**). However, we realize that the C7-epimer of **1** should enter the energy surface of the tricycloundecyl carbenium ions **12-18** and **23-29** specifically at **24** and therefore provide a more direct access to **5**. Moreover, as optical activity established in **1** and the C7-epimer of **1** should be preserved throughout the whole rearrangements, enantiospecific syntheses of **2**[2m], **3**, **4** and **5** should be feasible. The absolute configuration of natural isocomene **4**[3b] may thus be clarified.

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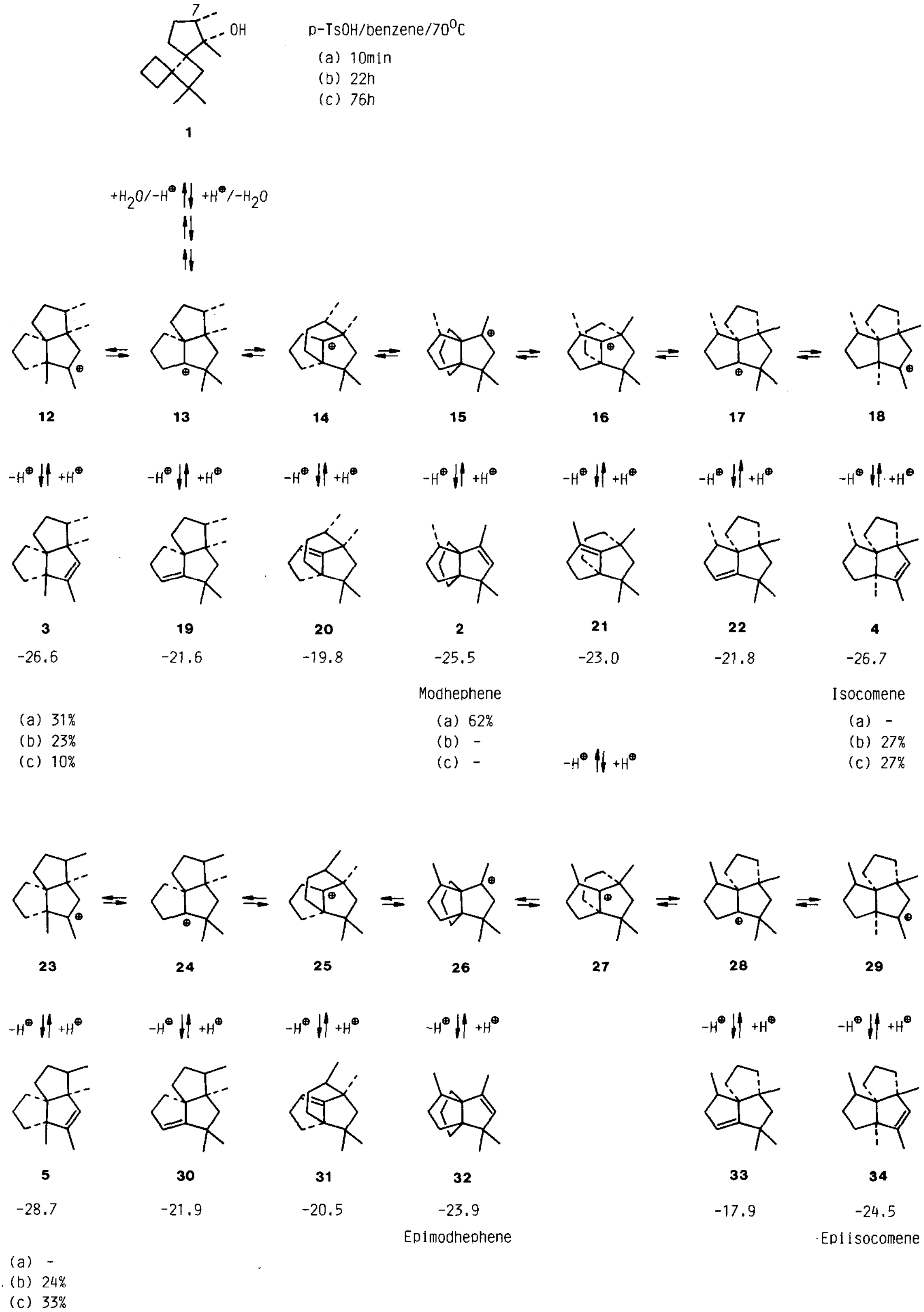
7
OH
1
p-TsOH/benzene/70^{0}C
(a) 10min
(b) 22h
(c) 76h
+H$_2$O/-H$^⊕$
+H$^⊕$/-H$_2$O
12
13
14
15
16
17
18
-H$^⊕$
+H$^⊕$
3
-26.6
(a) 31%
(b) 23%
(c) 10%
19
-21.6
20
-19.8
2
-25.5
Modhephene
(a) 62%
(b) -
(c) -
21
-23.0
22
-21.8
4
-26.7
Isocomene
(a) -
(b) 27%
(c) 27%
23
24
25
26
27
28
29
5
-28.7
(a) -
(b) 24%
(c) 33%
30
-21.9
31
-20.5
32
-23.9
Epimodhephene
33
-17.9
34
-24.5
Epiisocomene

References and notes

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7) The new compounds **1,3,7,8,9,10** and **11** gave correct elemental analyses and/or high resolution mass spectroscopic data. **5** could not be separated from **3** and **4** and was characterized by 1H- and 13C-NMR spectroscopy only. The IR, 1H-NMR, 13C-NMR and mass spectroscopic data are consistent with the given structures. 13C-NMR data (CDCl3) are as follows: **1**: δ = 12.20 (Cprim), 17.69 (Csek), 21.34, 26.85 (Cprim), 27.48 (Csek), 27.62 (Cprim), 27.96, 28.25 (Csek), 33.26 (Cquart), 33.69 (Csek), 41.68 (Ctert), 44.19 (Csek), 50.47, 51.75, 83.21 (Cquart); **3**: δ = 13.00, 15.99, 17.59, 23.24 (Cprim), 24.87, 32.87, 34.97, 38.70, 39.61 (Csek), 45.55 (Ctert), 57.97, 59.49, 63.03 (Cquart), 133.96 (Ctert), 141.67 (Cquart); **5**: δ = 13.17, 14.96, 22.26, 22.44 (Cprim), 24.57, 33.36, 35.30, 37.25, 39.85 (Csek), 47.13 (Ctert), 58.03, 59.56, 62.07 (Cquart), 129.63 (Ctert), 143.67 (Cquart); **7**: δ = 15.52, 24.10, 25.84, 30.51, 56.82, 68.11, 214.69; **8**: δ = 15.74, 17.95 (Csek), 24.69 (Cprim), 28.27, 29.32, 29.68 (Csek), 35.29 (Cquart), 39.75 (Csek), 54.95, 129.41, 134.93 (Cquart); **9**: δ = 16.05, 19.86 (Csek.), 25.23 (Cprim), 25.76 (Csek), 26.76 (Cprim), 27.16 (Csek), 33.72 (Cquart), 35.28, 37.61, 39.89 (Csek), 51.45, 54.16, 220.71 (Cquart); **10**: δ = 15.15 (Cprim), 16.11 (Csek), 24.94 (Cprim), 25.94 (Csek), 26.74 (Cprim), 27.04, 27.83, 32.90 (Csek), 33.88 (Cquart), 42.33 (Csek), 43.46 (Ctert), 51.18, 53.31, 222.10 (Cquart); **11**: δ = 14.22 (Cprim), 15.51 (Csek), 25.06 (Cprim), 25.28 (Csek), 26.59 (Cprim), 27.53, 29.57, 33.36 (Csek), 33.51 (Cquart), 39.92 (Csek), 42.78 (Cprim), 51.33, 54.40, 222.14 (Cquart).

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9) The measurements were performed on a Varian VXR 500 spectrometer operated at 500 MHz and +70°C using the original rearrangement mixtures and $\delta\underline{H}$ (C6HD5) = 7.25 as reference line. Only trisubstituted olefins with the following chemical shifts for their vinylic proton absorptions were observed: δ = 4.93 (q, J = 1.3 Hz, **2**), 4.95 (q, J = 1.3 Hz, **4**), 5.03 (q, J = 1.3 Hz, **5**), 5.10 (m, unknown), 5.14 (q, J = 1.3 Hz, **3**), 5.17 (m, unknown).

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