Regiocontrolled cyclisation of acetylenic ketones. First example of selective desilylation of a triple bond in the presence of a silyl enol ether.

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<u>Summary</u>: The thermal cyclisation of the butynylbicyclooctanone 5a is non regiospecific, and leads to products having a propellane or a cedrane skeleton. Conditions allowing exclusive formation of either type of products are given.

2,8,9-Trifunctional [3.3.3] propellanes bearing exoproximate  $\pi$  systems have been obtained by thermal cyclisation of diynone  $\underline{1}^{i}$ . In order to perform a photoelectronic study of these compounds,



we needed the parent 2-mono- and 2,8- difunctional propellanes  $\underline{3}$  and  $\underline{4}$ . The synthesis of  $\underline{3b}$  has already been published <sup>2</sup>. After the successful synthesis of  $\underline{2}$  we felt than  $\underline{4c}$  could be obtained in



a straightforward way by heating a decalin solution of  $5a^{3}$  in a sealed pyrex tube.



In fact, after 110 min. at  $305 - 310^{\circ}$  <u>5a</u> was converted into several products which were isolated by column chromatography (Silicagel) : <u>A</u> (Y : 49.5%), <u>B</u> (12%), <u>5a</u> (5.5%) and seven other unidentified products (6.5%). The 90 MHz NMR spectra (CDCl<sub>3</sub>) showed a broad signal for only one vinylic hydrogen for <u>A</u> ( $\delta$ : 5.15 ppm) and <u>B</u> ( $\delta$ : 5.50 ppm). A doublet (1H) at  $\delta$ : 2.71 ppm was indicative of an hydrogen between C=O and C=C in <u>B</u>. The partially coupled <sup>13</sup>C NMR spectra of <u>A</u> exhibited one singlet ( $\delta$ : 139.9 ppm) and one doublet ( $\delta$ : 126.0 ppm) for tetra- and tri-substituted sp<sup>2</sup> carbon atoms, two singlets ( $\delta$ : 75.4 and 58.7 ppm) for two tetra-substituted sp<sup>3</sup> carbon atoms and a quadruplet ( $\delta$ : 13.2 ppm) for a methyl as forecast for the propellane <u>6</u>; that of <u>B</u> showed only one singlet for an sp<sup>3</sup> carbon atom ( $\delta$ : 49.2 ppm) and two doublets for sp<sup>3</sup> tri-substituted carbon atoms ( $\delta$ : 56.3 and 57.3 ppm) consistent with the carbon skeleton of enone <u>7</u>, as well as a quadruplet ( $\delta$ : 22.4 ppm), a doublet ( $\delta$ : 123.4 ppm) and a singlet ( $\delta$ : 134.5 ppm) for a methyl and two olefinic carbon atoms. The desired propellane 4c was not detected.

To our knowledge, this is the first example of simultaneous five- and six-membered ring formation during the cyclisation of an acetylenic ketone. Since entropy strongly favors the five-membered ring formation, this result reflects the high proportion of the lesser substituted enol<sup>4</sup> in the reaction medium. In his modhephene synthesis 5, Paquette did not observe such a duality in the cyclisation of <u>5b</u>, suggesting that the methyl groups exert a decisive steric hindrance on the lesser substituted enol.

However, conditions allowing the regiocontrolled cyclisation of ynone 5a towards either 4c or 8 could be found.

When <u>5a</u> was treated with  $Me_3SiI/HMDS$  in pentane <sup>6</sup>, or  $Me_2tBuSiCI/NaI$  in acetonitrile <sup>7</sup> the enol ethers <u>9(a,b)</u> were the only products isolated (Y : 93 and 73% respectively). The enol ether



<u>9b</u> was smoothly cyclised to <u>8</u> (1 eq.  $HgCl_2$ , O.2 eq. HMDS,  $CH_2Cl_2$ , 30°, 6 h ; then, 2 eq. NaI, 2 eq. 20% aqueous HCl, O°, 3 h) <sup>8</sup> which was obtained in 79% yield after column chromatography (58.4% overall yield from the bicyclooctenone l2.

In order to obtain the propellane 4c, the mercury induced cyclisation had to be run from 10: since these enol ethers cannot be prepared by kinetic nor equilibrating methods from the ketone 5a, we trapped the enolate resulting from the l,4-addition of the acetylenic chain on enone 12 by  $Me_3SiCl$  (3.6 eq., THF/HMPT (3:1), 25°C, overnight) : <u>11a</u> was thus obtained in 87% yield. However such a substituted acetylenic enol ether reacted sluggishly in mercury-induced cyclisation ; therefore we intended to remove selectively the acetylenic protecting group. To the best of our knowledge, this reaction has not yet been described <sup>9</sup>, and the usual nucleophilic reagents (F<sup>-</sup>, OH<sup>-</sup>) are obviously inappropriate. Acetylenic carbon silicon bonds have been cleaved by Schmidt and Arens <sup>10</sup> using Ag<sup>+</sup>, the resulting acetylide beeing protonated by  $CN^-/H_2O$ . Using this method and adding one equivalent of HMDS to trap the acidity generated in the first step, an extensive protolysis of the enol ether was observed. Although the use of I<sup>-</sup> instead of CN<sup>-</sup> sped up the protolysis of the acetylide, the

ketone  $\underline{5a}$  was still the major product <sup>11</sup>. Since the Me<sub>2</sub>tBuSi group is more resistant to hydrolysis than the Me<sub>3</sub>Si group, we trapped the enolate (see above) with Me<sub>2</sub>tBuSiCl (THF/HMPT, 30°, 30h). The yield fell to 75% and the enol ether <u>9c</u> was also formed (<u>11b:9c</u> = 63:37), despite the apparent absence of unreacted enone before the trapping. This mixture was used to test the selective deprotection of the triple bond (Ag<sup>+</sup> : 1.5 eq. as a 0.667 M hydroalcoholic solution, HMDS : 1.5 eq., 20°, 3h ; then Et<sub>2</sub>O, NaI : 2 eq. <sup>12</sup> as a 8 M aqueous solution, O°, 10 min. and 20°, 5 min.). A mixture of <u>10b</u> and <u>9b</u> ( $\alpha$  63:37) was obtained in 77% yield, along with some ketone <u>5a</u> ( $\alpha$  7%). Mercury (II) chloride induced the cyclisation of the mixture and compounds <u>4c</u> and <u>8</u> were obtained in nearly the same ratio in 73% yield (same conditions as for <u>9b</u>).

Since we needed about 10 g of 4c a more efficient synthesis was required, and we turned to the thermal generation of the enol 13 under conditions allowing its immediate cyclisation to 4c. To this end, the enolate resulting from the 1,4-addition (see above) was trapped



with formaldehyde following House conditions  $1^3$ , leading to <u>14</u> in 87% yield. <u>14</u> was deprotected (Ag<sup>+</sup> (1.33 eq. ; 0°C, 5 min. and 20°, 5 min.) and I<sup>-</sup> (2 eq. ; 0°, 5 min. and 20°, 10 min.)) and roughly recrystallised. Flash-thermolysis of <u>15</u> in the range 650-750° ( $\sim 4.10^{-2}$  torr ; 1 - 1.5 g/h) led clearly to the desired propellane  $1^4$  as the unique product of the reaction (formol polymerized on warming up). Thus 10.7 g of <u>4c</u> were conveniently obtained in three steps from 13.1 g of the bicyclooctenone <u>12</u> in an overall yield of 56.7%.

The regiospecific synthesis either of  $\underline{4c}$  using the flash-thermolysis regiodirected enolisation of  $\underline{5a}$  via  $\underline{15}$ , or of  $\underline{8}$  using the mercury (II) induced cyclisation of enol ethers  $\underline{9}$  high-light the potency and complementarity of the most elaborated 8,15 methods of cyclisation of acetylenic ketones. Moreover, the cyclisation of  $\underline{9}$  opens a new entry in the field of natural products having a cedrane-type skeleton.

## References and footnotes

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- 11) We are presently able to accomplish the selective deprotection of trimethylsilylacetylenic groups in the presence of primary, secondary, tertiary and allylic trimethyl silyl ethers, using variations of the  $Ag^+/I^-$  method. These results will be published elsewhere.
- 12) Relative to Ag<sup>+</sup>.
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- 14) All new compounds gave satisfactory  ${}^{1}$ H,  ${}^{13}$ C NMR, IR and mass spectra.

 $\underline{IR}$  : (sol.) (CDCl<sub>3</sub>) :

 $\frac{4c}{(vw)}; 1735 (vs); 1650 (m). \frac{6}{2}: 3040 (vw); 1730 (vs); 1650 (w); 1380 (m). \frac{7}{2}: 3040 (vw); 1730 (vs); 1650 (w); 1380 (m). \frac{8}{2}: 3080 (w); 1735 (vs); 1645 (w). \frac{9b}{2}: 3300 (vs); 3060 (w); 2110 (w); 1650 (vs); 1250 (vs); 1220 (vs); 835 (vs). <u>11a</u>: 2180 (s); 1695 (s); 1250 (vs); 840 (vs). <u>14</u>: 3600 (m); 2160 (s); 1720 (vs); 1250 (vs); 840 (vs).$ 

<sup>1</sup><u>H\_NMR</u> : (CDCl<sub>3</sub>) ; δ (ppm) :

<u>4c</u> 1.50 - 1.95 (m) (10H) ; 2.25 - 2.60 (m) (4H) ; 4.95 (two overlapping triplets) (2H). <u>6</u> : 1.20 - 2.05 (m) (11H) ; 2.10 - 2.45 (m) (4H) ; 5.15 (s, broad) (1H). <u>7</u> : 1.05 - 2.50 (m) (14H) ; 2.71 (d) (J = 4 Hz) (1H) ; 5.50 (s, broad) (1H). <u>8</u> : 1.40 - 2.10 (m) (10H) ; 2.20 - 2.60 (m) (3H) ; 3.12 (d, J = 5 Hz) (1H) ; 4.72 (s, broad) (2H). <u>9b</u> : 0.30 (s) (6H) ; 1.10 (s) (9H) ; 1.55 - 2.75 (m) (14H) ; 4.50 (s) (broad). <u>11a</u> : 0.20 (s) (9H) ; 0.25 (s) (9H) ; 0.80 - 2.90 (m) (14H). <u>14</u> : 0.10 (s) (9H) ; 1.30 - 2.00 (m) (10H) ; 2.05 - 2.60 (m) (5H) ; 3.66 (d) (J = 8 Hz) (2H).

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<sup>13</sup><u>C NMR</u> (CDCl<sub>3</sub>); δ (ppm) :
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 $\frac{4c}{1}: 27.11 (t) ; 31.14 (t) ; 37.20 (t) ; 37.96 (t) ; 38 (86) (t) ; 40.29 (t) ; 59.94 (s) ; 69.73 (s); 106.60 (t) ; 154.27 (s) ; 219.56 (s). <u>6</u> : 13.20 (q) ; 26.85 (t) ; 33.04 (t) ; 33.71 (t) ; 38.32 (t) ; 41.42 (t) ; 46.70 (t) ; 58.65 (s) ; 75.40 (s) ; 126.01 (d) ; 139.90 (s) ; 219.64 (s). <u>7</u> : 22.36 (q) ; 24.91 (t) ; 27.64 (t) ; 35.29 (t) ; 37.05 (t) ; 39.78 (t) ; 49.18 (s) ; 56.34 (d) ; 57.19 (d) ; 123.4 (d) ; 134.50 (s) ; 215.30 (s). <u>8</u> : 25.07 (t) ; 27.78 (t) ; 30.23 (t) ; 36.54 (t) ; 37.21 (t) ; 40.49 (t) ; 50.99 (s) ; 55.91 (d) ; 60.71 (d) ; 109.46 (t) ; 145.76 (s) ; 221.00 (s).$ 

## Masse :

 $\frac{4c}{110} : 176 (M^{+}) ; 148 ; 133 ; 121 ; <u>120</u> ; 119 ; 105 ; 92 ; 91 ; 79 ; 77. <u>6</u> : 176 (M^{+}) ; 121 ; <u>120</u> ; 119 ; 105 ; 92 ; 91 ; 79 ; 77. <u>7</u> : 176 (M^{+}) ; 120 ; <u>119</u> ; 105 ; 79 ; 53. <u>8</u> : 177 ; 176 (M^{+}) ; 147 ; 120 ; <u>119</u> ; 105 ; 79 ; 53 ; 41 ; 39.$ 

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