Unexpected [2+2+2] MIMIRC Annulation Between a Lithium Dienolate and Methyl Acrylate.

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Summary: We describe an unusual [2+2+2] MIMIRC reaction between a lithium dienolate 6 and methyl acrylate. The more classical double Michael addition cyclisation provides an efficient entry towards key intermediate 5 for 2-isocyanopupukeanane 1 synthesis.

We are presently investigating the palladium catalyzed cyclisation ¹ of **4** into tricyclic ketone **3** which would lead, by catalytic hydrogenation of the C=C double bond, to Corey's precursor 2^{2} of 2-isocyanopupukeanane **1**, a sesquiterpene produced by a marine sponge as a defensive substance ³. This scheme requires an efficient synthesis of key intermediate **5**. As the classical approaches using Diels-Alder cycloaddition failed ⁴, we turned our attention to the use of double Michael addition of dienolate **6** to methyl acrylate known to provide an efficient entry into the bicyclo [2.2.2] octane skeleton with the desired *endo* stereochemistry ⁵. We decribe here an unusual outcome of this well known reaction, which gives raise to a [2+2+2] MIchael-MIchael Ring Closure (MIMIRC) process ⁶ instead of the expected cyclisation into **5**, showing that an intermolecular Michael reaction is prefered to an intramolecular one when an excess of the Michael acceptor is used.



When dienolate 6⁷ is treated at - 78 °C with 1.2 equ. of methyl acrylate and quenched after one hour by trimethylchlorosilane, a mixture of 5 (30%), 7 (13%) and silyldienolether derived from starting material 6 (57%) is obtained. Compound 5 has been assigned a bicyclic structure by ¹H and ¹³C NMR spectroscopy ⁸. Nevertheless, stereochemical assignment is difficult to secure in such systems although *endo* stereochemistry is generally observed for double Michael adducts ⁵. The treatment of viscous liquid 5 by 2 equ. of isopropyllithium in THF yields crystalline ketoalcohol **8** which has an *endo* stereochemistry as clearly demonstrated by X-ray diffraction analysis ⁹.

The ¹H NMR spectrum of minor compound 7 shows the presence of one ethylenic proton (5.41 ppm), one methyl ester group (3.63 ppm) and two deshielded protons (2.95 and 2.68 ppm). Its ¹³C NMR spectrum exhibits among 15 peaks, 2 signals at 175 46 and 173.38 ppm assigned to C=O and two vinylic carbons at 131.52 and 124 41 ppm. Although, these observations suggest that the dienolate **6** has reacted with 2 molecules of methyl acrylate, it was not possible to determine this structure using NMR data ¹⁰ On the other hand, compound 7 could be obtained selectively from **6** by the rapid addition of an 2.5 equ. of methyl acrylate followed by an 18 hours reaction time at room temperature Product 7 thus obtained can be crystallized in ether; its structure determined by X-ray crystallography ¹¹ reveals that it results probably from a [2+2+2] MIMIRC reaction between dienolate **6** and two molecules of methyl acrylate.



X-ray crystal structure of 7

X-ray crystal structure of 8

The [2+2+2] MIMIRC, a well known process for enolate anions, is most likely to occur in the present case with dienolate anion 6, and is to our knowledge the first example of this type. From the chemical point of view [2+2+2] MIMIRC reactions generally are thermodynamically driven and yield decalinic derivatives such as III with the *trans* ring junction ⁶. In the present case III can further cyclise to form a sterically bridged δ lactonic derivative V. The decalinic intermediate IV with the *cis* ring junction is -at first glance- less stable but its further cyclisation gives product 7 which is much less hindered than V. As III, IV and V can interconvert via II, and as the steric hinderance is much more important in III and V as it is in IV and 7, it is the formation of the latter product which is observed.



Our results clearly show that [2+2+2] MIMIRC reactions can occur with dienolate anions. Furthermore the outcome of the reaction towards either exclusively the *endo* bicyclic product 5, or the tricyclic derivative 7 can be controlled by the stoichtometry of the acrylate and dienolate anion 6. The yield of the compound 5 can be increased to 63% without formation of 7 by a slow addition (1 h) of methyl acrylate (1.2 equ.) to 6 performed with a syringe pump. Further work is being done to complete the synthesis of 2-isocyanopupukeanane and to investigate the formation of the tricyclic compound 7 which could be a useful intermediate for eudesmane sesquiterpenes.

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- 4. Capillary gas chromatography of Diels-Alder adduct of silyldienolether derived from 6 and methyl acrylate showed the presence of the four possible isomers among which compound 5 was less than 30%. The regio- and stereoselectivity are completely unsatisfactory because of the contrary donor effects of the two methyl groups and of the trimethylsilyloxy group. Fleming I. in *Frontier Orbitals and Organic Chemical Reactions*, John Wiley and Sons, 1976, pp. 132. Jung M. E.; Mc Combs C. A.; Takeda Y.; Pan Y-G. J. Am. Chem. Soc. 1981, 103, 6677. Mirrington R. N.; Schmalzl K. J. J. Org. Chem. 1969, 34, 2358.
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- 7 Dienolate 6 was obtained by reaction of 2,6-dimethyl 2-cyclohexenone 12 with 1 equ. of LDA in THF.
- NMR data of compound 5 : ¹H NMR (400 MHz, CDCl₃) δ in ppm . 0.16 (s; 9H); 1.05 (s, 3H); 1.25 (ddd, J 11 3, 7.5, 3.1 Hz; 1H); 1 34-1.26 (m, 1H); 1.36 (ddd, J 11.3, 8.3, 3 2 Hz; 1H); 1.58-1.47 (m; 2H); 1.61 (s; 3H); 1 71 (ddd, J = 13 1, 5.1, 3.2 Hz; 1H); 2.57 (ddd, J 10 1, 5 1, 2 4 Hz; 1H); 2 74 (dd, J 5 5, 2 5 Hz; 1H); 3 60 (s; 3H) ¹³C NMR (50 MHz, CDCl₃), δ in ppm : 0 00 (Me₃S₁-); 14.35 (CH₃); 20.81 (CH₃); 25.61 (CH₂); 33.47 (CH₂); 35.99 (C); 37 70 (CH₂); 39 07 (CH); 42.89 (CH); 50.63 (CH₃O-); 112.22 (C); 149.01 (C); 174.77 (C=O)
- 9. Crystal data of compound **8** · crystal size 0.4 x 0.4 x 0.5 in mm; orthorombic; space group Pbca; a = 11 829 (4) Å, b = 17.726 (4) Å, c = 15.028 (4) Å, $\alpha = \beta = \gamma = 90.00$ (2) °; V = 3151.1 (7) Å³; Z = 8; ρ (calcd.) = 1 123 g/cm³, μ (MoK) = 0 663 cm⁻¹; out of 2462 unique reflections, 1632 were with I > 3 σ (I); R = 0.059 and R_w = 0.057. All hydrogen atoms were localized on difference Fourier.
- NMR data of compound 7 : ¹H NMR (200 MHz, CDCl₃) δ in ppm · 0.91 (s; 3H); 1.34 (d, J 13.1 Hz; 1H);
 1.65 (s; 3H); 2.00-2.60 (m; 4H), 2 10 (bs, W_{1/2} = 16 Hz; 2H); 2.22 (ddt, J 13 1, 5 7, 2.8 Hz; 1H); 2.68 (bs, W_{1/2} = 9 Hz; 1H); 2 94 (dd, J 10.3, 6.1 Hz, 1H); 3.63 (s; 3H, CH₃O-); 5.41 (bs, 1H) ¹³C NMR (50 MHz, CDCl₃), δ in ppm : 18 04 (CH₃), 22 54 (CH₂); 22 65 (CH₃)29.43 (CH₂); 32.88 (CH₂), 35.47 (CH); 37 55 (C); 39 71 (CH₂); 44 75 (CH); 52.41 (CH₃O-); 85.99 (C); 124.41 (CH)); 131 52 (C); 173.38 (C=O); 175 46 (C=O).
- 11. Crystal data of compound **7** : crystal size 0 4 x 0 4 x 0.5 in mm; orthorombic; space group P2₁2₁2₁; a = 11.500 (3) Å, b = 14 877 (2) Å, c = 8.102 (1) Å, $\alpha = \beta = \gamma = 90\ 00\ (2)\ ^{\circ}$; V = 1386.2 (5) Å³; Z = 4; ρ (calcd) = 1 007 g/cm³, μ (MoK) = 0 666 cm⁻¹, out of 1425 unique reflections, 1300 were with I > 3 σ (I); R = 0.064 and R_w = 0 064. Hydrogen atoms were not refined.
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