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DIASTEREOSELECTIVE DOUBLE MICHAEL ADDITIONS OF VINYLOGOUS ESTERS AND THEXYLDIMETHYLSILYL TRIFLATE-INDUCED CYCLIZATIONS

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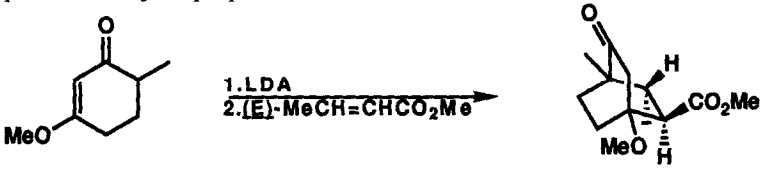
Summary: Double Michael additions of vinylogous esters of type **1** with crotyl ester generates diastereoselectively bicyclo[2.2.2]octanone **2** with four defined chiral centers via a synclinal transition state. Thexyldimethylsilyl enol ethers of type **5** and **10** undergo smooth cyclization to bicyclo[3.3.1]nonenones **7** and bicylo[3.3.0]octenones **12** by addition of Lewis acids.

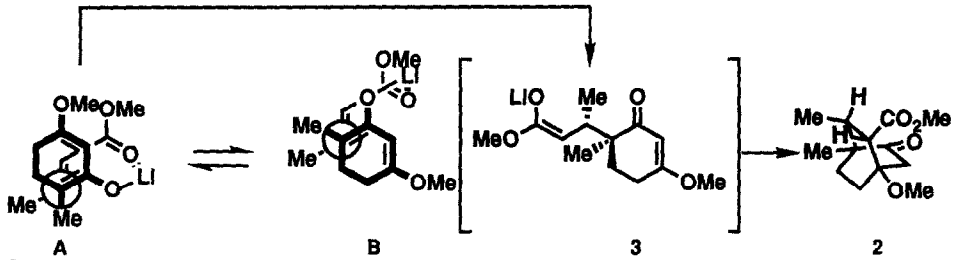
In connection with our studies on silica gel-catalyzed cyclizations and double Michael additions of vinylogous esters and -amides,[1,2] we have focused now on the addition of crotyl ester to the enolate of vinylogous ester **1**. We report here the stereospecific addition of (E)-crotyl ester to **1** which yields at -78 °C the bicyclo[2.2.2]octanone **2** in 95% yield. During this process four contiguous stereogenic centers are formed in one pot from a very simple precursor **1**.



1 **2**

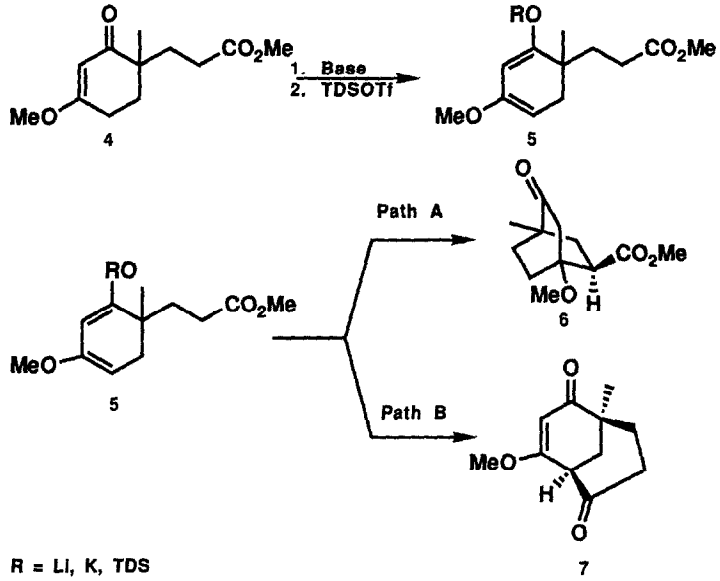
Scheme 1

The remarkable stereocontrol observed in this process can be best rationalized by a sequence of two stereoselective Michael additions[3-7] (via a chelated intermediate of type **A**; **scheme 2**) than by a Diels-Alder type mechanism.[8] The first addition generates, via a synclinal transition state, a syn addition product which smoothly cyclizes during the second Michael addition to **2**. A simple addition of acrylate could not be used, because it would give rise to identical Michael adducts (**A** and **B** would give the same product). Conformational analysis with model transition states (relative MM2 strain energies) can be used to rationalize the stereoselectivity observed.[9-11] These results are consistent with the chelated transition state **A** shown in **scheme 2** in which a lithium enolate forms a syn addition product **3** which is trapped in a one pot reaction to yield **2**.[12]
Transition state **B** would form the anti product with the opposite configuration of the methyl group in **2**.



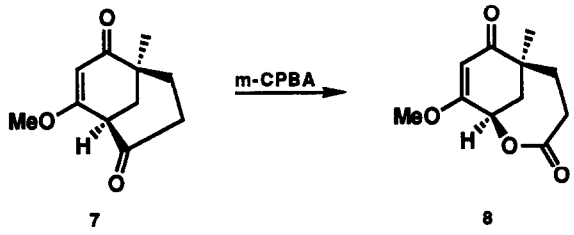
Scheme 2

In order to gain in further details of this reaction we have alkylated **1** with methyl iodopropionate to obtain the alkylated compound **4** in 45% yield. It has been known that compounds of type **4** can be regioselectively deprotonated with LHMDS (lithium hexamethyldisilazide) or KHMDS (potassium hexamethyldisilazide) in THF to generate the dienolate **5**. However, compound **5** (with counter ion Li^+) cyclized via transprotonation (**path A** in **scheme 3**) to yield **6**. Trapping of the dienolate **5** (with counter ion K^+) with TDS triflate (thexyldimethylsilyl triflate) gave the expected TDS dienolate **5** (R= TDS). The trapped enolate **5** surprisingly underwent smooth cyclization to **7** by addition of a second equivalent of TDS triflate or $TiCl_4$ at low temperature in 62% and 50% yield, respectively (**path B** in **scheme 3**).[12] This reaction represents a novel 1,3-annulation sequence via a kinetically controlled Dieckmann condensation involving a simple enolate trapping as a silyl dienol ether.



Scheme 3

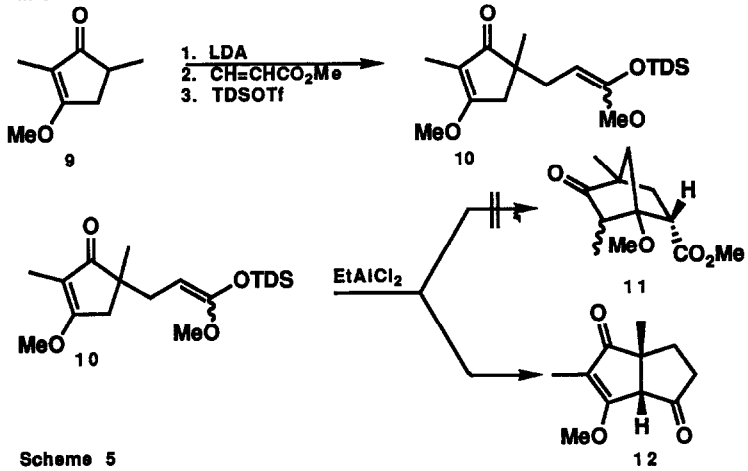
Compound **7** can be stereoselectively converted to the lactone **8** (95% yield) via a Baeyer-Villiger oxidation with m-CPBA. Compound **8** represents a very useful precursor along the total synthesis of pinguisone.[12,13]



7 8

Scheme 4

The use of the five-membered vinylogous ester **9** afforded only the bicyclooctene **12** as the cyclization product.[1] Deprotonation with LDA followed by a Michael addition with acrylate and in situ trapping with TDS triflate yielded exclusively compound **10**. However, addition of $EtAlCl_2$ at low temperature did not generate compound **11** by a second Michael addition, but instead produced the bicyclooctene **12** in 57% yield, probably by some Lewis acid-induced silyl-oxygen rearrangement. We could not detect compound **11** via a direct cyclization mode.



9 10 10 11 12

Scheme 5

In conclusion, we have shown that double Michael additions proceed via a synclinal transition state. Both, computational and experimental results favor geometry **A** over **B**. The regioselective deprotonation of **4** can be used to generate either **6** or **7** depending on the trapping conditions. On the other hand, the TDS enol ether **10** could not be used to synthesize **11**, but instead formed **12** by Lewis acid treatment.

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10. W.C. Stills program **MacroModel** (version 3.0) was used. Transition states of type **A** always showed lower energies than the alternative **B**.
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12. All new compounds are full characterized by standard methods. Compound **2**: IR ($CDCl_3$): 3014; 2955; 1724; 1460; 1438; 1370; 1285; 1230; 1201; 1170; 1119; 1021. ^{1}H-NMR ($CDCl_3$): 3.72 (s, 3H); 3.25 (s, 3H); 3.04 (dd, J= 3 Hz, J= 18 Hz, 1H); 2.61 (dd, J= 3 Hz, J= 8 Hz, 1H); 2.35 (dd, J= 2 Hz, J= 18 Hz, 1H); 2.14 - 1.61 (m, 4 H); 1.51 - 1.31 (m, 1H); 1.05 (d, J= 7 Hz, 3H); 0.92 (s, 3H). ^{13}C-NMR ($CDCl_3$): 211.92; 174.12; 75.84; 54.71; 51.89; 49.85; 45.44; 43.12; 36.60; 29.32; 23.97; 16.30; 15.27. High resolution mass spectrum calcd for $C_{13}H_{20}O_4$: 240.1361; found 240.1361.
Compound **7**: IR ($CDCl_3$): 3016; 2937; 1719; 1656; 1610; 1461; 1366; 1253; 1190; 1176; 1093; 979; 846. ^{1}H-NMR ($CDCl_3$): 5.55 (s, 1H); 3.74 (s, 3H); 3.23 - 3.16 (m, 1H); 2.825 (ddd, J= 8 Hz, J= 14 Hz, J= 16 Hz, 1 H); 2.46 (dtr, J= 3 Hz, J= 13 Hz, 1 H); 2.38 - 2.19 (m, 1H); 2.19 - 1.97 (m, 2H); 1.,805 (dtr, J= 6 Hz, J= 13 Hz, 1H); 1.22 (s, 3H). ^{13}C-NMR ($CDCl_3$): 206.02; 201.62; 175.96; 103.59; 56.55; 53.59; 41.33; 40.92; 36.76; 34.73; 23.51. MS: m/z (%): 194 (84); 167 (13); 166 (98); 151 (22); 140 (16); 139 (51); 138 (20); 125 (100); 124 (15); 123 (12); 111 (41); 107 (11); 101 (24); 96 22); 91 (12); 79 (14); 77 (12); 69 (24); 68 (21); 59 (13); 55 (19); 53 (12); 41 (19); 39 (14).
Compound **8**: IR ($CDCl_3$): 3030; 3016; 2937; 1733; 1664; 1622; 1435; 1383; 1289; 1258; 1230; 1201; 1177; 1159; 1133; 1102; 1047. ^{1}H-NMR ($CDCl_3$): 5.715 (s, 1H); 4.82 (dd, J= 2 Hz, J= 6 Hz, 1H); 3.81 (s, 3H); 2.77 - 2.62 (m, 2H); 2.40 (ddd, J= 2 Hz, J= 4.5 Hz, J= 15 Hz, 1 H); 2.155 (dd, J= 2Hz, J= 18 Hz, 1H); 1.80 (dtrd J= 2 Hz, J= 4 Hz, J= 14 Hz, 1H); 1.65 (ddd, J= 7 Hz, J= 8 Hz, J= 8.5 Hz, 1H); 1.22 (s, 3H). ^{13}C-NMR ($CDCl_3$): 201.16; 173.31; 169.48; 107.32; 70.77; 56.58; 42.73; 39.74; 34.53; 33.33; 24.77. MS: m/z (%): 210 (3); 169 (9); 158 (27); 156 (100); 141 (25); 139 (80); 114 (17); 113 (24); 111 (37); 97 (18); 77 (9); 75 (24); 69 (11); 51 (9); 50 (12).
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