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Tandem Syntheses of Cyclohexane Derivatives via Sequential Michael--Michael--Aldol Reaction

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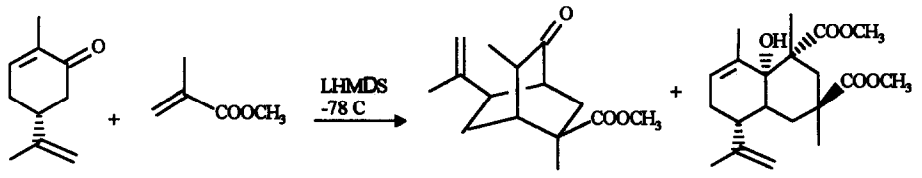
Abstract: A detailed study on the reactions of several ketones with methyl methacrylate in the presence of lithium hexamethyldisilamide has been reported.

There are many methods to form six-membered rings[1], among which Diels-Alder[2], enel[3], and annulation[4] reactions(e.g., Robinson annulation involving Michael addition followed by aldol condensation) are well known. However, it is still a challenge to look for more effective and special synthetic method. Recently, double Michael reaction received much more concerns due to its successful application in the synthesis of core structure of Taxol[5] and many other bioactive natural products[6]. During the course of our studies on the application of double Michael reaction of (-)-carvone **1** with methyl methacrylate **2** to the total synthesis of (+)-curdione[7], we occasionally obtained the Michael-Michael-Aldol reaction product **3a** in low yield besides the main product **3**. This intriguing result prompted us to explore reaction conditions to inverse products' ratio in order to obtain byproduct **3a** as a main component which was thought to be a usefull intermediate for the synthesis of natural product (Scheme 1). However, all attempts including variations in solvents, bases, as well as temperatures proved fruitless. Accordingly, we turned our attentation to the other substrates and the identification of their products. In this paper, we report our recent results in Michael-Michael-Aldol reaction, an alternative method to form six-membered ring.

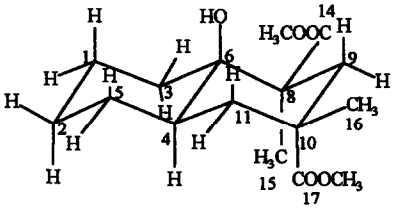
Scheme 1



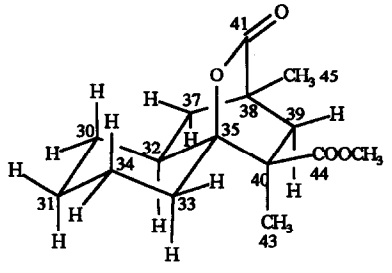
1 2 3(40%) 3a(12%)

Several aspects of this study are noteworthy. Firstly, all the reactions gave more satisfactory results when lithium hexamethyldisilazane was used as base instead of lithium diisopropylamide (LDA). Secondly, we concentrated on systematic studies on the reactions of ketones with methyl methacrylate in the presence of lithium hexamethyldisilazane. Finally, in most instances, we obtained lactone in addition to cycloalkanol, which was the sole product in Posner's practices[8].

Initially, we selected acetophenone **4** as the substrate, the reaction with two equivalent methyl methacrylate at -78 °C using lithium hexamethyldisilazane as base gave only cyclohexanol derivative **4a** in 81% yield. However, reaction of cyclohexanone **5** generated novel lactone **5b** (18.3%) and cyclalkanol **5a** (56.7%). Their stereochemistry (Figure 1) was established by 2D ^{1}HNMR and ^{13}CNMR spectroscopy which showed hydroxyl group at C-1, methyl group at C-8 and methoxycarbonyl group at C-10 in **5a** were in the same side, while hydroxyl group at C-1 and two methoxycarbonyl groups at C-8 and C-10 in **5b** were in the same side. Reaction of 4-(1',3'-dioxolane)-cyclohexan-1-one **6**[9] afforded cyclohexanol **6a** and lactone **6b** in 24.9% and 46.7% yields respectively. This result indicated that substituents at C4 position of cyclohexone have strong influences on the stereoselectivity of their reaction. When the present method was applied to some more crowded ketons such as (+)-menthone **7** and (+)-4-cholesten-3-one **8** in the same conditions, the corresponding products were obtained in relatively lower yields while starting materials were recovered mainly. For example, in the run of (+)-menthone **7**, cycloalkanol **7a** and lactone **7b** were obtained in 3.8% and 4.9% yields respectively with 90% recovery of starting material. In the test of (+)-4-cholesten-3-one **8**, lactone **8a** was obtained as a sole product in only 15.6% yield along with 68% recovery of starting material (Scheme 2).



5a

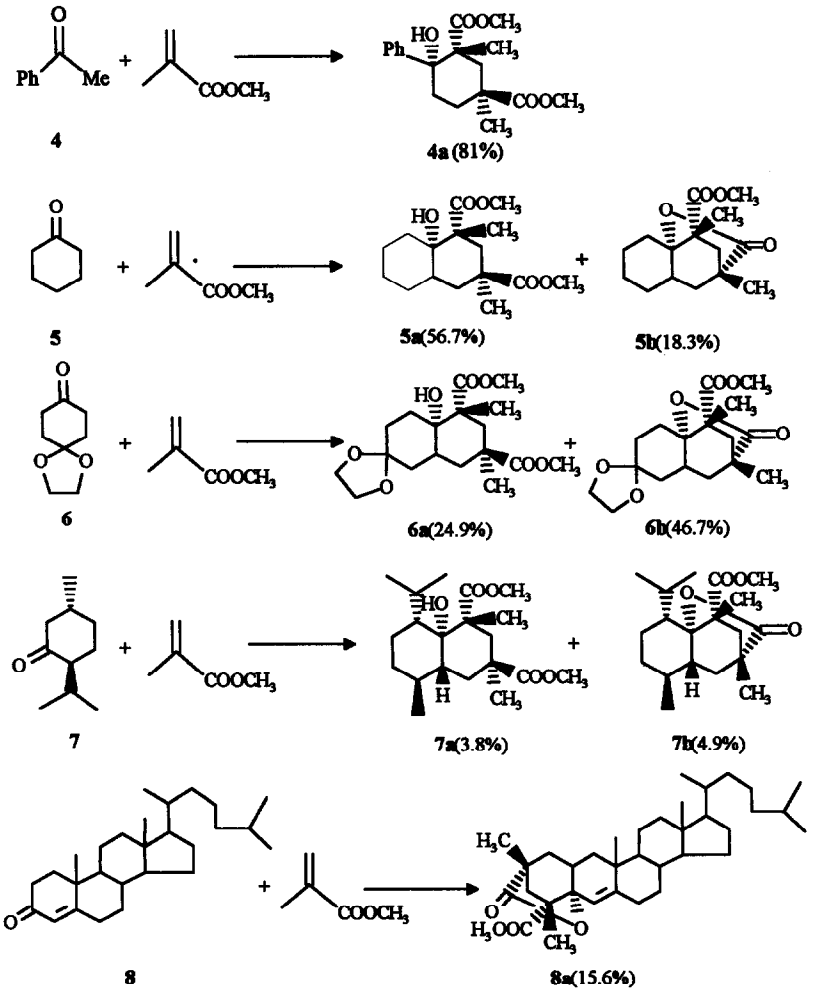


5b

Figure 1

In summary, Michael-Michael-Aldol reaction of some simply substituted ketones with methyl methacrylate proceeded smoothly, while in the case of substrates containing bulky substituted groups, the reactions gave the corresponding products only in lower yield. In the cases of cyclohexanone derivatives it is worth notice that there were four chiral centres newly formed, but only two major isomers of the eight possible isomers could be isolated. It would provide an another way for the synthesis of novel lactone with a hydroxyl group at a tertiary carbon.

Scheme 2



Experimental Section

All m.p. were uncorrected. IR spectra were measured as a film for oils or as a nujol mull for solids on a Shimadzu 440 spectrometer. ^{1}H NMR spectra were recorded with TMS as an internal standard at 300 MHz or 600 MHz Bruker spectrometer. MS spectra were obtained on a VG-Quattro GC-MS-MS spectrometer. All chromatographies were performed on silica gel H (10-40μ) with petroleum ether-ethyl acetate system as eluent.

***Typical procedure-Reaction of acetophenone with methyl methacrylate*:** To a well-stirred solution of hexamethyldisilazane (968 mg, 6 mmol) in 20 mL hexane at -78°C was added n-BuLi (6 mmol, 2.5 M in hexane). After stirring for 30 min, a mixture of acetophenone **4** (601 mg, 5 mmol) and methyl methacrylate (1.10 g, 11 mmol) in 3 mL ether was dropped at -78°C. The reaction mixture was stirred at this temperature for another 1 hr, warmed to 0°C over 2 hr and then stirred at room temperature for additional 2 hr. The reaction mixture was filtered through a silical gel column to afford crude product which was purified further by flash chromatography to yield cyclohexanol **4a** (1.22 g, 81%). **4a**: colorless oil, IR(film) 3410, 2945, 1730, 1600 cm $^{-1}$; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.43 (2H, d, J=7.8 Hz), 7.34 (2H, t, J=7.4 Hz), 7.24 (1H, t, J=7.0 Hz), 3.68 (3H, s), 3.65 (3H, s), 1.70 (1H, dd, J=13.2, 2 Hz), 1.69~1.50 (2H, m), 1.47 (1H, dt, J=13.2, 1.7 Hz), 1.45~1.18 (2H, m), 1.16 (3H, s), 1.09 (3H, s); MS (EI, m/z): 300 (M^+), 282, 267, 239; Anal. Calcd.for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55; Found: C, 67.21; H, 7.63.

***Reaction of cyclohexone with methyl methacrylate*:** Following the typical procedure, reaction of cyclohexone **5** (300 mg, 3.06 mmol) with methacrylate methyl methacrylate (673 mg, 6.72 mmol) at -78°C in the presence of lithium hexamethyldisilazane afforded cyclohexanol **5a** (516 mg, 56.7%) and lactone **5b** (149 mg, 18.5%). **5a**: mp 131°C, IR ($CHCl_3$) 3500, 2950, 2845, 1742, 1720, 1450, 965 cm $^{-1}$; ^{1}H NMR ($CDCl_3$, 600 MHz) 3.70 (3H, s), 3.68 (3H, s), 2.16 (1H, dd, J=13.6, and 1Hz, H-3β), 2.13 (1H, d, J=13.6 Hz, H-3α), 1.81 (1H, br.d, J=13.3 Hz, H-5α), 1.72 (1H, m, H-6), 1.71 (1H, m, H-9β), 1.66 (1H, br.d, J=13.4 Hz, H-8β), 1.54 (1H, br.d, J=13.4 Hz, H-10β), 1.48 (1H, dt, J=13.4, 2 Hz, H-9α), 1.40 (2H, m, H-7), 1.37 (1H, t, J=13.2 Hz, H-5β), 1.33 (1H, td, J=13.3, 1.2 Hz, H-10α), 1.2 (1H, 8-α), 1.15 (3H, s, 13-CH_3), 1.11 (3H, s, 11-CH_3); ^{13}C NMR ($CDCl_3$, 600 MHz), 178.5 (C-14), 178.4 (C-12), 73.6 (C-1), 52.1 (OCH_3), 51.63 (OCH_3), 50.6 (C-2), 41.08 (C-3), 40.96 (C-4), 37.46 (C-5), 35.88 (C-6), 33.04 (C-10), 29.73 (C-13), 28.75 (C-7), 25.91 (C-8), 21.61 (C-9), 18.27 (C-11). MS (EI, m/z): 298 (M^+), 280; Anal. Calcd.for $C_{16}H_{26}O_5$: C, 64.41; H, 8.78; Found: C, 64.29; H, 8.75. **5b**: mp 112°C, IR($CHCl_3$) 2981, 2870, 1762, 1732, 1465, 1458, 1380, 1160, 1060 cm $^{-1}$; ^{1}H NMR ($CDCl_3$, 600 MHz) 3.71 (3H, s), 2.65 (1H, dd, J=13.2, H-3β), 2.42 (1H, d, J=13.7 Hz, H-10 β), 1.95 (1H, d, J=13.2 Hz, H-3α), 1.95 (1H, t, J=13.2 Hz, H-6), 1.83 (1H, m, H-9α), 1.82 (1H, m, H-7β), 1.81 (1H, m, H-8β), 1.70 (1H, tt, J=13.7 Hz, and 3 Hz, H-9β), 1.62 (1H, m, H-7α), 1.61 (1H, m, H-10α), 1.57 (3H, s), 1.43 (1H, d, J=13.2 Hz, H-5α), 1.42 (1H, d, J=13.2 Hz, H-3α), 1.41 (1H, m, H-8α), 1.22 (3H, s, 11-CH_3); ^{13}C NMR ($CDCl_3$, 600 MHz), 177.23 (C-12), 174.86 (C-14), 73.6 (C-1), 83.70 (C-1), 52.52 (OCH_3), 50.83 (C-2), 45.78 (C-5), 43.51 (C-6), 38.85 (C-4), 38.14 (C-5), 32.93 (C-10), 29.48 (C-7), 25.39 (CH_3), 25.17 (C-8), 23.11 (C-9), 20.90 (CH_3); MS (EI, m/z): 267 $(M+H)^+$, 239, 221, 207, 164, 139, 95; Anal. Calcd.for $C_{15}H_{22}O_4$: C, 67.65; H, 8.32; Found: C, 67.34; H, 8.27.

Reaction of 4-(1',3'-dioxolane)-cyclohexan-1-one with methyl methacrylate: Following the typical procedure, reaction of 4-(1',3'-dioxolane)-cyclohexan-1-one **6** (600 mg, 3.85 mmol) with methacrylate (847 mg, 8.46 mmol) at -78°C in the presence of lithium hexamethyldisilazane afforded cyclohexanol **6a** (341 mg, 24.9%) and lactone **6b** (586 mg, 46.7%). **6a**: mp 116°C, IR($CHCl_3$) 3487, 2952, 2860, 1735, 1455, 1260, 1125 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) 3.93~3.92 (4H, m), 3.74 (3H, s), 3.71 (3H,s), 2.22 (1H, d, J=13.2 Hz, H-3β), 2.20 (1H, d, J=13.2 Hz, H-3α), 2.05 (1H, t, J=13.5 Hz, H-6), 2.04 (1H, td, J=13.7, and 1..2 Hz, H-9β), 1.82 (1H, dt, J=13.5, and 1.0 Hz, H-5α), 1.70 (1H, td, J=13.5, and 1.3 Hz, H-7β), 1.67 (1H, td, J=13.7, and 1.2 Hz, H-10α), 1.60 (1H, dt, J=13.5, and 1.0 Hz, H-7α), 1.58 (1H, br.d, j+13.7 Hz, H-9α), 1.55 (1H, dt, J=13.7, and 1 Hz, H-10α), 1.39 (1H, t, J=13.5 Hz, H-5β), 1.17 (3H, 3, C-13), 1.12 (3H, s, C-11); ^{13}C NMR ($CDCl_3$, 600 MHz), 178.6 (C-14), 178 (C-12),108.7 (C-8), 72.1 (C-1), 64.7 (C-1'), 64.3 (C-2'), 52.2 (OCH_3), 51.7 (OCH_3), 50.2 (C-2), 41.0 (C-3), 40.9 (C-4), 37.13 (C-10), 36.1 (C-5), 33.8 (C-6), 30.5 (C-9), 30.4 (C-7), 29.7 (13-CH_3), 18.26 (C-11). MS (EI, m/z): 357 $(M+H)^+$, 340, 326, 301, 280, 258, 198, 157, 145; Anal. Calcd.for $C_{18}H_{28}O_7$: C, 60.66; H, 7.91; Found: C, 60.79; H, 7.92. **6b**: mp 143°C, IR($CHCl_3$) 2950, 2875, 1760, 1735, 1470, 1430, 1390, 1370, 1100 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) 3.94 (4H, m), 3.72 (3H, s), 2.62 (1H, d, J=13.0 Hz, H-3β), 2.51 (1H, d, J=13.2, H-10β), 1.97 (1H, d, J=13.0 Hz, H-3α), 1.97 (1H, t, J=13.7 Hz, H-6), 1.83~1.81 (2H, m, H-9α, H-7β), 1.68 (1H, tt, J=13.7, and 3 Hz, H-9β), 1.60 (1H, m, H-5α), 1.58 (1H, m, H-10α), 1.57 (3H, s), 1.40 (1H, br.d, J=13.2, H-3α), 1.18 (3H, 3, C-13), 1.12 (3H, s, C-11); ^{13}C NMR ($CDCl_3$, 600 MHz), 178.6 (C-14), 178 (C-12),108.7 (C-8), 72.1 (C-1), 64.7 (C-1'), 64.3 (C-2'), 52.2 (OCH_3), 51.7 (OCH_3), 50.2 (C-2), 41.0 (C-3), 40.9 (C-4), 37.13 (C-10), 36.1 (C-5), 33.8 (C-6), 30.5 (C-9), 30.4 (C-7), 29.7 (13-CH_3), 18.26 (C-11). MS (EI, m/z): 325 $(M+H)^+$, 266, 200, 150, 97; Anal. Calcd.for $C_{17}H_{24}O_6$: C, 62.95; H, 7.45; Found: C, 63.23; H, 7.59.

Reaction of (+)-menthone with methyl methacrylate: Following the typical procedure, reaction of (+)-menthone **7** (300 mg, 1.95 mmol) with methyl methacrylate (429 mg, 4.28 mmol) at -78°C in the presence of lithium hexamethyldisilazane afforded cyclohexanol **7a** (26 mg, 3.8%) and lactone **7b** (31 mg, 4.9%) with 90% recovery of starting materials. **7a**: mp 130°C, IR ($CHCl_3$) 3450, 2950, 2860, 1735, 1700, 1460, 1260, 1120 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 2.16 (1H, d, J=12.3 Hz), 2.10 (1H, dd, J=13.2, and 2 Hz), 1.72 (1H, br.d, J=13.0, and 3.42 Hz), 1.64 (1H, qd, J=13.0, and 3.1 Hz), 1.50 (1H, br), 1.37 (3H, m), 1.28 (3H, m), 1.15 (3H, s), 1.07 (3H, s), 0.93 (3H, d, J=6.5 Hz), 0.92 (1H, m), 0.84 (3H, d, J=6.0 Hz), 0.75 (3H, d, J=6.6 Hz); MS (EI, m/z): 354 M^+, 323, 294, 268, 253, 177; Anal. Calcd.for $C_{20}H_{34}O_5$: C, 67.77; H, 9.66; Found: C, 67.69; H, 9.67. **7b** : mp 167°C, IR ($CHCl_3$) 2980, 1750, 1735, 1260 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 2.55 (1H, dd, J=13.3, 1.7 Hz), 2.37 (1H, dd, J=13.3, and 9 Hz), 2.16 (1H, m), 2.07 (1H, m), 1.95 (1H, m), 1.75~1.46 (6H, m), 1.43 (1H, m), 1.39 (1H, m), 1.34 (3H, s), 1.23 (3H, s), 1.22 (3H, d, J=6.6 Hz), 1.03 (3H, d, J=7 Hz), 0.94 (3H, d, J=6 Hz); MS (EI, m/z): 324 (M^+), 309, 292, 277, 264, 223, 195, 152; Anal. Calcd.for $C_{20}H_{34}O_5$: C, 70.78; H, 9.37; Found: C, 70.55; H, 9.41.

Reaction of (+)-4-cholesten-3-one with methyl methacrylate: Following the typical procedure, reaction of (+)-4-cholesten-3-one **8** (600mg, 1.56 mmol) with methyl methacrylate (343 mg, 3.43 mmol) at -78°C in the presence of lithium hexamethyldisilazane afforded corresponding lactone **8a** (135 mg, 15.6%). **8a:** mp 81°C, IR ($CHCl_3$) 2915, 2890, 1760, 1735, 1467, 1380 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 5.52 (1H, s), 3.72 (3H, s), 2.48~2.01 (5H, m), 1.98~1.61 (7h, m), 1.60~1.33(18H, m), 1.30 (3H, m), 1.28~1.07 (7H, m), 1.13 (3H, s),

1.06 (3H, d, J=7 Hz), 0.91 (6H, d, J=6 Hz);MS (EI, m/z): 553 $(M+H)^+$, 521, 451, 424, 384, 261, 229; Anal. Calcd.for $C_{36}H_{56}O_4$: C, 78.22; H, 10.2; Found: C, 78.25; H, 10.24.

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