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Construction of Polycyclic Ring Systems Fused to Cyclobutane by Sequential Three Reactions, Ring Opening of Cyclopropane-Michael-Aldol Reaction Sequence

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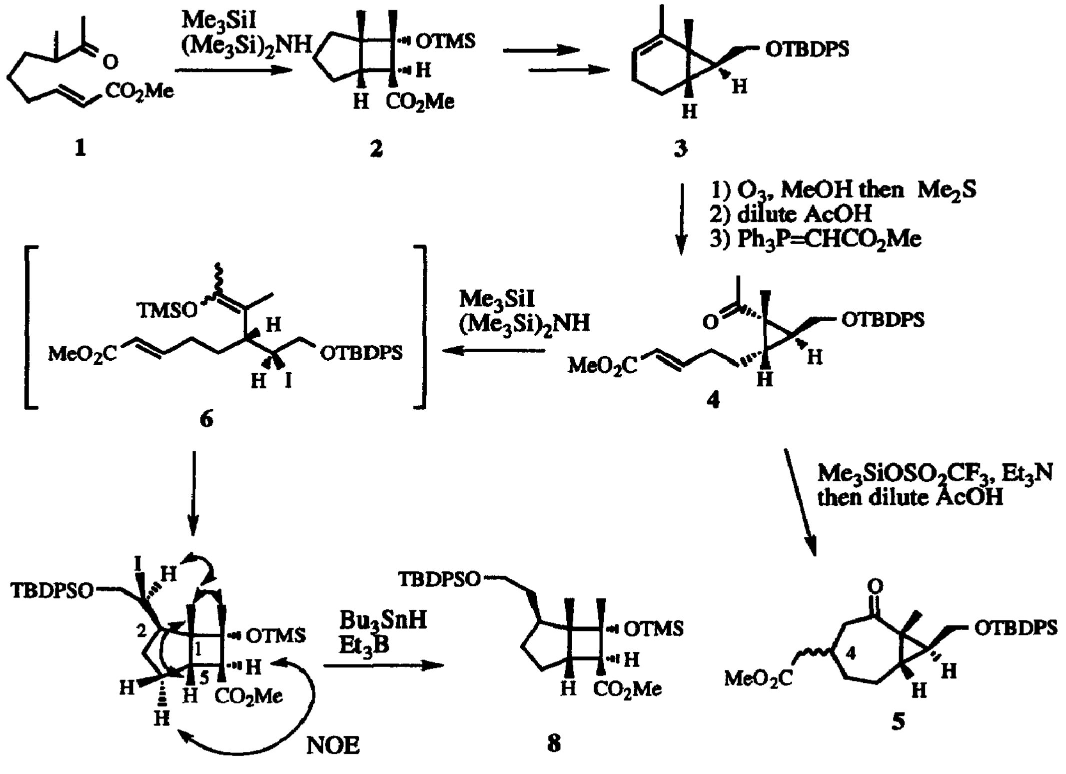
Abstract: Reaction of α,β-unsaturated esters **4** and **11** possessing a cyclopropyl ketone function, with trimethylsilyl iodide in the presence of hexamethyldisilazane caused sequential three reactions, ring opening of cyclopropane-Michael-aldol reaction sequence, to provide polycyclic cyclobutane derivatives **7** and **13**, respectively.

Recently, we developed a methodology for the construction of polycyclic ring systems fused to cyclobutane by tandem intramolecular Michael-aldol reaction, which was carried out under two different conditions, *tert*-butyldimethylsilyl trifluoromethanesulfonate in the presence of triethylamine[1] and trimethylsilyl iodide in the presence of hexamethyldisilazane.[2] When α,β-unsaturated esters having a cyclopropyl ketone function were treated under the latter conditions, sequential three reactions, ring opening of cyclopropane, Michael and aldol reaction, took place. We here report the novel sequential reaction producing polycyclic cyclobutanes.

The cyclopropyl ketone **4**[3] was prepared from the bicyclo[4.1.0]heptane **3**, which was synthesized through the tandem reaction[2] of **1** and the rearrangement[4] of the derivative of **2**, as depicted in the Scheme 1. Reaction of **4** with trimethylsilyl trifluoromethanesulfonate in the presence of triethylamine in hot dichloroethane caused the intramolecular Michael reaction.[5] Acidic treatment of the product provided the bicyclo[5.1.0]octane derivative **5** in 63% yield from **4**. The product **5**[6] was obtained as a 1 : 1.1 mixture of two separable diastereoisomers at the 4 position.

When **4** was treated with 1.2 equivalent mol of trimethylsilyl iodide in the presence of 1.5 equivalent mol of hexamethyldisilazane in dichloroethane at room temperature, the bicyclo[3.2.0]heptane derivative **7**[6] was produced in 67% yield as a single stereoisomer.[7] The relative configurations at the 1, 2, 5, 6 and 7 positions were determined by nuclear Overhauser effect (NOE) as indicated. The stereochemistry of the iodine atom was assigned on the basis of the consideration of reaction mechanism. The reaction would be initiated by the ring opening of cyclopropane with trimethylsilyl iodide.[8] The formation of the silyl enol ether **6** was detected on TLC. The selective attack of the iodide anion on the carbon atom carrying the hydrogen atom oriented *syn* to the acetyl group is noteworthy. It was proved by the preceding work that the formation of cyclobutanes using trimethylsilyl iodide in the presence of hexamethyldisilazane is not a concerted reaction but a stepwise Michael-aldol reaction.[2] It is interesting that the treatments of **4** under two different conditions, with trimethylsilyl trifluoromethanesulfonate-triethylamine and with trimethylsilyl iodide-hexamethyldisilazane, produce the bicyclo[5.1.0]octane **5** and the bicyclo-[3.2.0]heptane **7**, respectively.

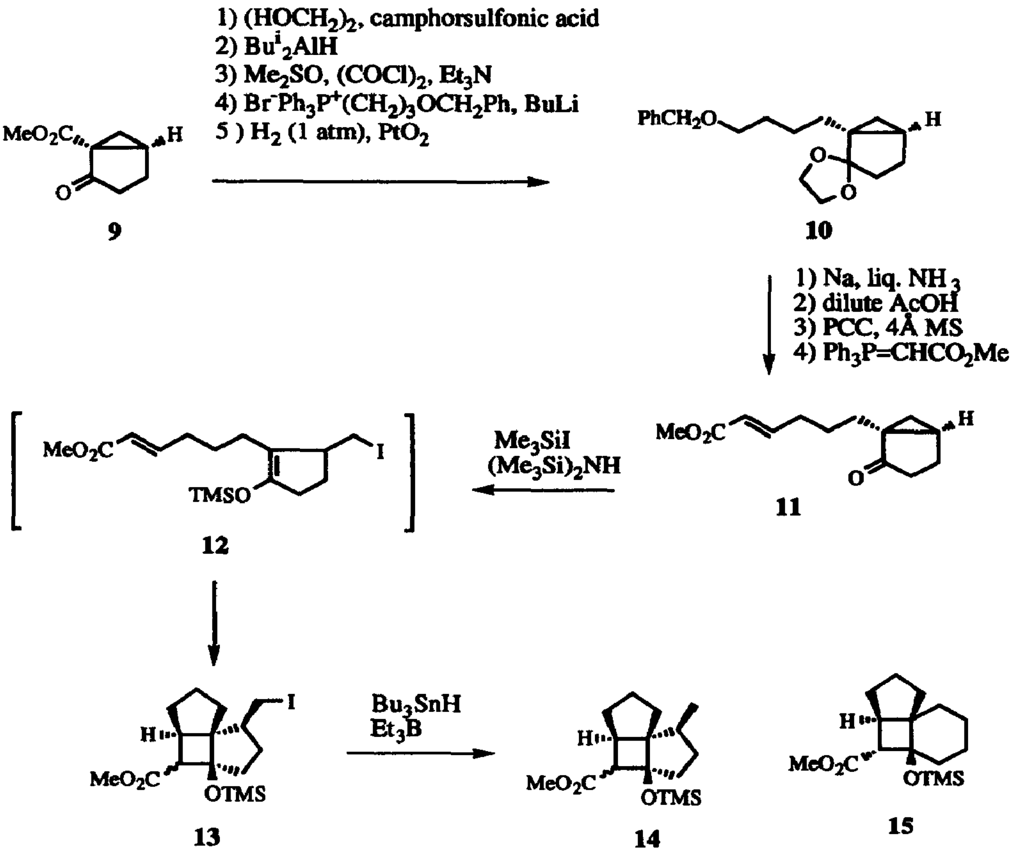
Removal of the iodine atom with tributyltin hydride in the presence of triethylborane[9] provided **8**[6] in 92% yield. The overall process implies the introduction of a carbon side chain at the 2 position of the original bicyclo[3.2.0]heptane derivative **2**.



TMS = $-SiMe_3$
TBDPS = $-SiPh_2Bu^t$

Scheme 1

In order to establish the generality of the above transformation, the reaction was applied to a bicyclo[3.1.0]hexan-2-one derivative **11**. The substrate **11** was synthesized *via* the ketal **10** in nine steps starting from **9**[10] as shown in the Scheme 2. Treatment of **11** under the same reaction conditions gave the tricyclo[5.3.0.0^{3,7}]-decane derivative **13**[6] in 66% yield. The product **13** was composed of two diastereoisomers in a 1 : 2.4 ratio. The iodine atom of **13** was replaced with hydrogen atom to afford **14**[6] in a quantitative yield. No formation of the tricyclo-[5.4.0.$0^{3,7}$]undecane **15**[2] was observed. The selective attack of iodide anion on the less hindered carbon atom on the cyclopropane ring of **11** would form the silyl enol ether **12** as the intermediate.



Scheme 2

Thus, the new methodology providing polycyclic cyclobutanes by three sequential reactions with single operation, ring opening of cyclopropane-Michael-aldol reaction, has been elaborated.

References and Notes

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3. All new compounds gave spectral data (IR, NMR and MS) in accord with the assigned structure and satisfactory combustion analysis or accurate mass measurement.
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5. Ihara, M.; Suzuki, S.; Taniguchi, N.; Fukumoto, K. *J. Chem. Soc., Chem. Commun.* **1993**, 755-756.
6. Selected spectral data of **5** (less polar): IR vmax: cm^{-1} (neat) 1725 (C=O) and 1665 (C=O); NMR: δ_H (500 MHz, CDCl$_3$) 3.78 (1 H, dd, *J* 11.0 and 6.1 Hz), 3.69 (1 H, dd, *J* 11.0 and 7.3 Hz), 3.66 (3 H, s), 1.22 (3 H, s), 1.04 (9 H, s), 1.03 (1 H, m) and 0.97 (1 H, m); δ_C (125 MHz, CDCl$_3$) 209.5, 172.8, 135.72, 135.69, 133.9, 133.8, 129.8, 127.8, 63.4, 51.7, 44.2, 38.4, 38.1, 33.2, 31.5, 31.3, 30.8, 30.4, 26.9, 25.4, 19.3 and 15.5; MS: *m/z* 421 (M$^+$ - Bu^t).

   5 (polar): IR vmax: cm^{-1} (neat) 1725 (C=O) and 1665 (C=O); NMR: δ_H (500 MHz, CDCl$_3$) 3.83 (1 H, dd, *J* 11.0 and 5.5 Hz), 3.69 (1 H, dd, *J* 11.0 and 7.3 Hz), 3.67 (3 H, s) 1.26 (1 H, m), 1.21 (3 H, s), 1.05 (1 H, m) and 1.04 (9 H, s,); δ_C (125 MHz, CDCl3) 208.5, 170.9, 134.1, 132.4, 132.2, 128.2, 126.2, 62.0 50.1, 44.4, 39.9, 36.2, 30.9, 30.5, 30.2, 29.8, 28.8, 25.3, 23.9, 17.7 and 13.8; MS: *m/z* 421 (M$^+$ - Bu^t).

   7: IR vmax: cm^{-1} (neat) 1730 (C=O); NMR: δ_H (500 MHz, C$_6$D$_6$) 4.27 (1 H, dt, *J* 10.5 and 2.5 Hz), 4.14 (1 H, dd, *J* 12.5 and 10.3 Hz), 3.91 (1 H, dd, *J* 12.5 and 2.6 Hz), 3.33 (3 H, s), 2.72 (1 H, d, *J*. 8.4 Hz), 1.35 (9 H, s), 1.10 (3 H, s), 0.56 (3 H, s) and 0.02 (9 H, s); δ_C (125 MHz, C$_6$D$_6$) 172.1, 136.1, 134.2, 133.7, 130.0, 75.5, 71.2, 58.6, 54.9, 50.6, 48.7, 43.8, 43.4, 39.0, 30.4, 30.1, 29.1, 27.5, 27.1, 21.7, 19.5, 14.9 and 1.9; MS: *m/z* 551 (M$^+$ - I).

   8: IR vmax: cm^{-1} (neat) 1725 (C=O); NMR: δ_H (300 MHz, CDCl$_3$) 3.72-3.57 (2 H, m), 3.66 (3 H, s), 2.76 (1 H, d, *J* 8.1 Hz), 1.16 (3 H, s), 1.05 (9 H, s), 0.78 (3 H, s) and 0.04 (9 H, s); MS: *m/z* 552 (M$^+$).

   13: IR vmax: cm^{-1} (neat) 1725 (C=O); δ_H (500 MHz, CDCl$_3$) 3.71 (2.1 H, s), 3.67 (0.9 H, s), 3.28 (0.7 H, dd, *J* 12.8 and 4.1 Hz), 3.21 (0.3 H, dd, *J* 12.8 and 4.1 Hz), 2.95 (0.3 H, dd, *J* 12.8 and 10.3 Hz), 2.88 (0.7 H, dd, *J* 12.8 and 10.3 Hz), 2.63 (0.3 H, dd, *J* 10.7 and 2.1 Hz), 2.62 (0.7 H, d, *J* 5.1 Hz), 0.13 (2.6 H, s), and 0.12 (6.4 H, s); MS: *m/z* 422 (M$^+$).

   14: IR vmax: cm^{-1} (neat) 1725 (C=O); δ_H (500 MHz, CDCl$_3$) 3.69 (3 H, s), 2.63 (0.3 H, dd, *J* 8.3 and 1.0 Hz), 2.61 (0.7 H, d, *J* 6.2 Hz), 0.82 (0.9 H, d, *J* 6.2 Hz), 0.81 (2.1 H, d, *J* 7.0 Hz), 0.121 (2.6 H, s) and 0.117 (6.4 H, s); MS: *m/z* 296 (M$^+$).
7. The typical procedure for the tandem reaction: To a stirred solution of **4** (40 mg, 0.08 mmol) and (TMS)$_2$NH (0.03 mL, 0.13 mmol) in dry dichloroethane (0.8 mL) was added at 0 °C TMSI (0.01 mL, 0.10 mmol), and the mixture was stirred for 10 min at 0 °C and for 7 h at room temperature. After dilution with Et$_2$O, the mixture was washed with H$_2$O and brine, dried over MgSO$_4$, and evaporated. Chromatography of the residue on silica gel with Et$_2$O-hexane (1 : 15 v/v) as eluent gave **7** (38 mg, 67%).
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