

Homo-Cope-Type Five-Carbon Ring-Expansion Reaction via Silyl Enol Ether

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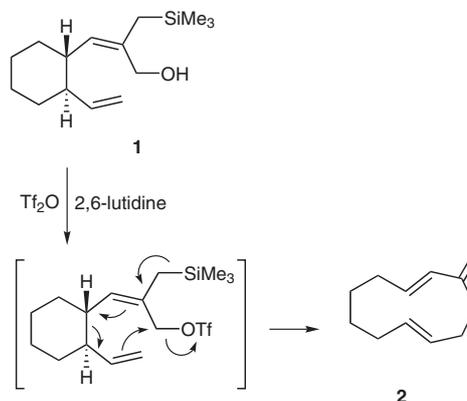
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Abstract: A five-carbon ring-expansion reaction from a cyclohexane derivative fitted with a 3-hydroxy-2-silyloxyprop-1-en-1-yl unit in lieu of one of the C=C double bonds in the Cope rearrangement was studied to synthesize cycloundecanone derivatives. It was found that (*E*)-triethylsilyl enol ether is necessary for the reaction. The *trans*-isomer with respect to the cyclohexane ring afforded (*2E,8E*)-cycloundeca-2,8-dien-1-one, while its *cis*-isomer afforded (*2E,8E*)- and (*2E,8Z*)-isomers in a 1:3 ratio.

Key words: ring expansion, carbocycles, silicon, enol ethers, Cope rearrangement

The Cope rearrangement including the oxy-Cope rearrangement is one of the fundamental reactions, which provides a useful method for a four-carbon ring expansion reaction in organic synthesis.¹ For example, the germacra- type of ten-membered carbocycle was synthesized from the easily available six-membered ring compound.² In addition, 2-(trimethylsilylmethyl)acrylate or 2-(trimethylsilylmethyl)allyl alcohol derivatives are versatile carbon 1,3-dipole equivalents, and the replacement of a C=C double bond in some organic reactions with these units enables 'homo'-type reactions. The [4+3] cycloaddition reaction ('homo-Diels–Alder' reaction),³ and related reactions are documented in review articles.⁴ We reported the synthesis of α -methylene- γ -lactones⁵ and related compounds⁶ using these moieties.⁷

During the course of our studies on the 'homo' reaction, we recently reported a new five-carbon ring expansion reaction by replacing one of the C=C double bonds in the Cope rearrangement with a 3-hydroxy-2-(trimethylsilylmethyl)prop-1-en-1-yl moiety (Scheme 1).⁸ Although the reaction is a 'homo' analogue of the Cope rearrangement, its mechanism is considered to be stepwise, which proceeds after conversion of the hydroxy group in **1** to trifluoromethanesulfonate, giving eleven-membered ring compound **2**. We supposed that the reaction is more useful in organic synthesis if the ring expansion product has an oxygen function, rather than hydrocarbon. With this in mind, we planned to use a silyl enol ether instead of the allylsilane since the product is expected to have an enone group which may be useful for further transformations.

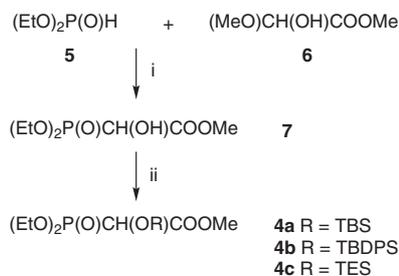


Scheme 1

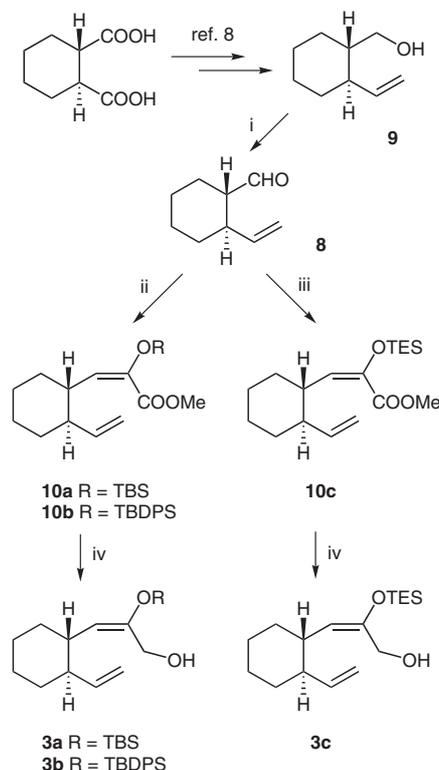
Here we report that the reaction occurs when TES enol ether was employed as the substrate.

Following the previous report, we studied the five-carbon ring expansion reaction from six- to eleven-membered carbocycles. These carbocyclic systems are found in natural terpenes, such as humulanes in sesquiterpenes^{9,10} and dollabelanes in diterpenes.^{9,11}

As the substrates of the 'homo-Cope' reaction, three silyl ethers, TBS **3a**, TBDPS **3b**, and TES **3c** were prepared via a modified Horner–Wadsworth–Emmons (HWE) reaction, which is an analogous method to the synthesis of the corresponding allylsilane.⁸ The HWE reagents **4a–c** were prepared by coupling diethyl phosphite (**5**) and methyl 2-hydroxy-2-methoxyacetate (**6**)¹² followed by silylation of the condensation product **7** (Scheme 2). The HWE reaction of **8**, obtained by the Swern oxidation of **9**,⁸ with **4a** and **4b** was carried out in accordance with Schmidt's method¹² giving the corresponding products in 95% (*E/Z*, 91:9) and 62% (*E/Z*, 77:23) yields, respectively, from which the *E*-isomers **10a** and **10b** were separated by silica gel chromatography. For the synthesis of **10c**, LDA was used instead of 1,1,3,3-tetramethylguanidine (75% yield; *E/Z*, 94:6)¹³ (Scheme 3). The *E*-isomer **10c** could not be separated from its *Z*-isomer in pure form, and therefore, the mixture was used in the following study. Compounds **3a–c** were obtained when **10a–c** were treated with DIBAL-H in hexane–Et₂O, while the reduction in CH₂Cl₂ gave only complex mixtures.

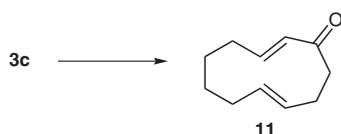


Scheme 2 Reagents: (i) see ref. 12; (ii) RCl, imidazole, DMF.



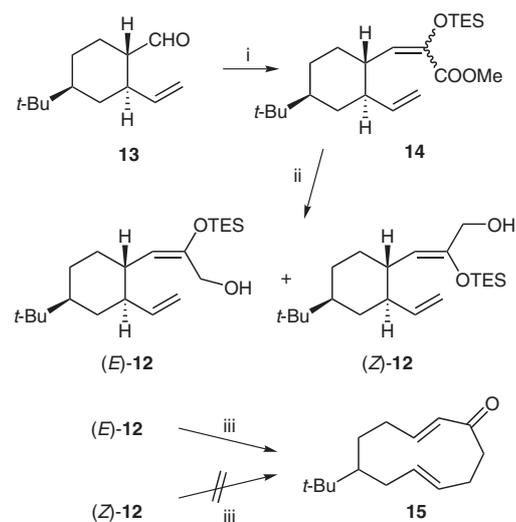
Scheme 3 Reagents: (i) DMSO, (COCl)₂, Et₃N, CH₂Cl₂; (ii) **4a** or **4b**, LiCl, 1,1,3,3-tetramethylguanidine, THF; (iii) **4c**, LDA, THF; (iv) DIBAL-H, Et₂O.

The ring expansion reaction was then studied. When **3c** was treated with Tf₂O and 2,6-lutidine in CH₂Cl₂ at room temperature,^{8,14} the expected product **11**¹⁵ was obtained in 69% yield (Scheme 4) without the accompanying normal Cope rearrangement product. However, compounds **3a** and **3b** afforded only complex mixtures under the same reaction conditions. The reaction of **3a** was studied under various conditions but was unsuccessful. The geometry of the two double bonds in **11** was determined to be *2E,8E* based on coupling constants (15.5 Hz, 16.2 Hz) in the ¹H NMR spectrum.



Scheme 4 Reagents: Tf₂O, 2,6-lutidine, CH₂Cl₂.

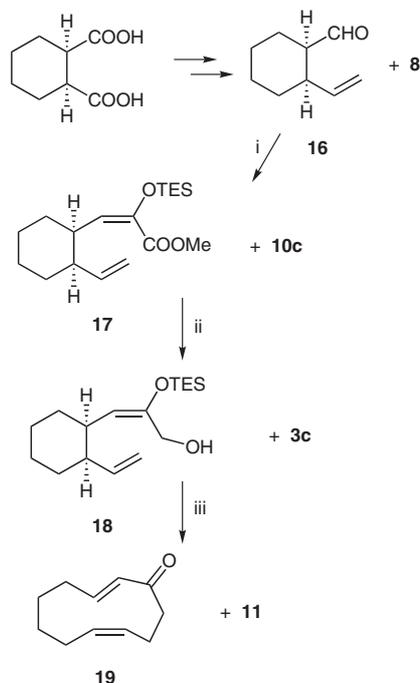
The reaction from a substrate having a *tert*-butyl substituent on the cyclohexane ring was also studied (Scheme 5). The TES enol ether **12** (*E/Z*, 87:13) was prepared analogously from **13**⁸ via DIBAL-H reduction of **14**. Since (*E*)-**12** and (*Z*)-**12** could be separated from each other, the ring-expansion reaction of both isomers was examined. The reaction proceeded smoothly from (*E*)-**12** to afford **15**¹⁶ in 71% yield, while (*Z*)-**12** afforded a complex mixture. This indicated that (*E*)-silyl enol ether is necessary for the ring-expansion reaction. These results are in contrast to the case of the corresponding allylsilane, in which the *Z*-isomer also afforded the eleven-membered carbocycle via a *Z* to *E* isomerization, although its yield was low.⁸ Those results indicate that *Z* to *E* isomerization of silyl enol ether did not occur.



Scheme 5 Reagents: (i) **4c**, LDA, THF; (ii) DIBAL-H, Et₂O; (iii) Tf₂O, 2,6-lutidine, CH₂Cl₂.

In order to determine the stereochemistry with respect to the cyclohexane ring, the *cis*-substituted diastereomer was prepared from *cis*-1,2-cyclohexanedicarboxylic acid (Scheme 6). However, since isomerization occurred during the preparation, only a mixture of **18** and **3c** (68:32) could be obtained. When this mixture was treated with Tf₂O and 2,6-lutidine as above, a mixture of **11** and its 8*Z*-isomer **19**¹⁷ was obtained in a 46:54 ratio. The geometry of the double bonds in **19** was determined to be *2E,8Z* based on the coupling constants in the ¹H NMR spectrum. Since **3c** afforded only **11**, it can be deduced that **18** gives **11** and **19** in approximately a 1:3 ratio. This result is roughly consistent with our previous observation for the corresponding allylsilane.⁸

In conclusion, a new enol homo-Cope-type five-carbon ring-expansion reaction was established, which provides a new entry to cycloundecane derivatives. This method is considered to be more useful than the previously reported reaction of the corresponding allylsilane, since the product has an enone group, and therefore, further reactions such as alkylation can be performed easily.



Scheme 6 Reagents: (i) **4c**, LDA, THF; (ii) DIBAL-H, Et₂O; (iii) Tf₂O, 2,6-lutidine, CH₂Cl₂.

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- (14) Five-Carbon Ring Expansion: In a 100-mL round-bottomed flask, a solution of **3c** (114.4 mg, 0.386 mmol) in anhyd CH₂Cl₂ (40 mL) was prepared at –60 °C under Ar. To this was added 2,6-lutidine (0.13 mL) and Tf₂O (0.1 mL) successively with stirring; stirring was continued for 1 h at the same temperature. A sat. aq solution of NH₄Cl was added and the mixture was extracted with CH₂Cl₂. The organic layer was dried and the solvent was evaporated to afford an oily residue, which was chromatographed on silica gel (3 g; hexane–EtOAc, 95:5) to give **11** (43.7 mg, 69%).
- (15) Compound **11**: Oil. IR (neat): 1657 cm⁻¹. ¹H NMR (CDCl₃): δ = 1.47–1.80 (4 H, m), 2.01–2.10 (2 H, m), 2.21–2.30 (4 H, m), 2.61–2.67 (2 H, m), 5.03 (1 H, dt, *J* = 15.5, 7.6 Hz, CH=CH), 5.31 (1 H, dt, *J* = 15.5, 7.7 Hz, CH=CH), 5.90 (1 H, d, *J* = 16.2 Hz, CH=CHCO), 6.31 (1 H, dt, *J* = 16.2, 7.5 Hz, CH=CHCO). ¹³C NMR (CDCl₃): δ = 27.28, 28.53, 30.07, 34.21, 34.45, 38.59, 128.81, 132.01, 137.38, 156.96, 202.88. HRMS: *m/z* calcd for C₁₁H₁₆O (M⁺): 164.1201; found: 164.1235.
- (16) Compound **15**: Oil. IR (neat): 1658 cm⁻¹. ¹H NMR (CDCl₃): δ = 0.87–0.96 (1 H, m), 0.89 (9 H, s, *t*-Bu), 1.15 (1 H, dddd, *J* = 2.3, 3.5, 12.5, 14.6 Hz), 1.54 (1 H, dt, *J* = 12.5, 10.0 Hz), 1.93 (1 H, ddt, *J* = 1.4, 9.5, 12.5 Hz), 2.07 (1 H, ddt, *J* = 5.6, 14.6, 2.5 Hz), 2.17–2.37 (3 H, m), 2.44–2.54 (2 H, m), 2.81 (1 H, dt, *J* = 2.5, 11.3 Hz), 5.08–5.20 (1 H, m, CH=CH), 5.30 (1 H, br dt, *J* = 15.7, 7.5 Hz, CH=CH), 5.90 (1 H, br d, *J* = 16.1 Hz, CH=CHCO), 6.45 (1 H, ddd, *J* = 6.0, 9.4, 16.1 Hz, CH=CHCO). ¹³C NMR (CDCl₃): δ = 27.14 (3 C), 30.07, 31.07, 34.20, 34.42, 35.03 (br), 38.86, 49.56, 129.12 (br), 132.31, 136.33, 156.27, 202.97. HRMS: *m/z* calcd for C₁₅H₂₄O (M⁺): 220.1827; found: 220.1812.
- (17) Compound **19**: Oil. IR (neat): 1672 cm⁻¹. ¹H NMR (CDCl₃): δ = 1.64–1.74 (4 H, m), 2.17–2.31 (6 H, m), 2.53–2.57 (2 H, m), 5.36–5.43 (1 H, m, CH=CH), 5.52 (1 H, ddt, *J* = 10.5, 8.2, 1.7 Hz, CH=CH), 6.19 (1 H, dt, *J* = 16.2, 1.5 Hz, CH=CHCO), 6.80 (1 H, dt, *J* = 16.2, 6.7 Hz, CH=CHCO). ¹³C NMR (CDCl₃): δ = 22.92, 25.10, 25.15, 28.50, 32.10, 39.81, 128.81, 129.73, 131.57, 151.11, 203.56. HRMS: *m/z* calcd for C₁₁H₁₆O (M⁺): 164.1201; found: 164.1221.