Pergamon

Tetrahedron Letters 42 (2001) 1915–1917

TETRAHEDRON
LETTERS

# Synthesis of eleven-membered carbocycles by a new five-carbon ring expansion reaction

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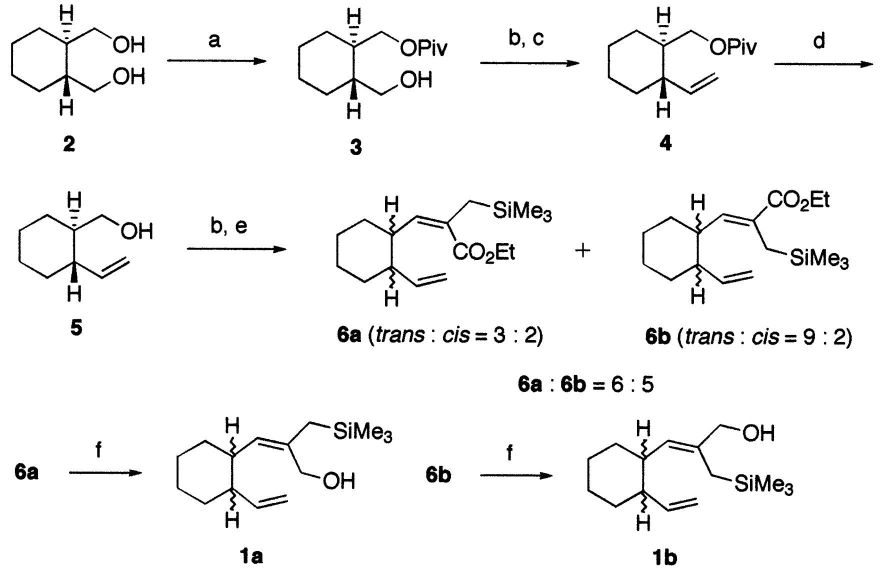
Received 18 October 2000; revised 11 December 2000; accepted 28 December 2000

**Abstract**—3-Methylenecycloundeca-1,6-diene was synthesized by a homo-Cope ring expansion reaction of 2-(trimethylsilylmethyl)-3-(2-vinylcyclohexyl)prop-2-en-1-ol. © 2001 Elsevier Science Ltd. All rights reserved.

Eleven-membered carbocycles are classified as medium-membered rings and are found in natural terpenes such as humulanes or lathylols.[1,2] To synthesize medium-membered carbocycles, ring expansion reaction is a common method,[3] in which a Cope rearrangement is widely used as the four-carbon ring expansion reaction.[4] This method is often applied to the synthesis of germacranes.[5] β-(Hydroxymethyl)allylsilanes are useful three-carbon units in organic synthesis, and thus replacement of the carbon–carbon double bond in some organic reactions with such a unit enables a one-carbon homologous reaction. Giguere et al. reported the synthesis of hydroazulene derivatives utilizing intramolecular homo-Diels–Alder reaction using β-(hydroxymethyl)-allylsilane as the dienophile.[6] During the course of our continuous study of β-functionalized allylsilanes,[7] we planned to perform a homo-Cope rearrangement by replacing one of the two C=C bonds in the Cope rearrangement with a β-(hydroxymethyl)allylsilane unit. Here we report the synthesis of 11-membered carbocycles from cyclohexane derivatives by a new homo-Cope type of five-carbon ring expansion reaction.[8,9]



**Scheme 1.** *Reagents*: (a) PivCl, pyridine, $CHCl_3$; (b) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$; (c) $Ph_3P{=}CH_2$, THF; (d) $LiAlH_4$, THF; (e) $(EtO)_2P(O)CH(CO_2Et)CH_2SiMe_3$, NaH, DME; (f) DIBAL-H, $CH_2Cl_2$.

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*Keywords*: cycloalkenes; medium-ring carbocycles; ring transformations; silicon and compounds.

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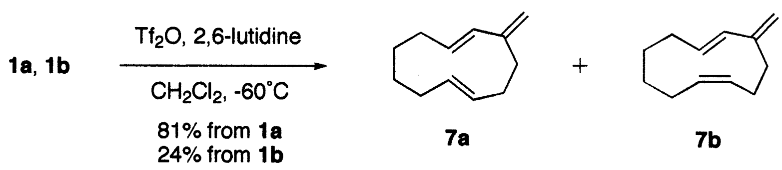
PII: S0040-4039(01)00020-X



**Scheme 2.**

The substrates of the present study are the compounds **1a** and **1b**, which were synthesized in accordance with Scheme 1. Namely, *trans*-1,2-cyclohexanedimethanol (**2**), prepared from *trans*-1,2-cyclohexanedicarboxylic acid, was first monoprotected with a pivaloyl group to afford **3** (93%), which was then oxidized to the aldehyde followed by a Wittig reaction to obtain **4** (83%). Reductive deprotection of **4** gave alcohol **5** (98%), which was then subjected to the introduction of a silyl group[7c] to afford an ester-conjugated allylsilane in 60% yield. It was found that the product consisted of four isomers, among which *E*-allylsilane **6a** and *Z*-allylsilane **6b** could be separated by repetition of silica gel column chromatography; however, the isomers with respect to the cyclohexane ring could not be separated. The ratio of **6a** to **6b** was 6:5, and each consisted of *trans*- and *cis*-substituted cyclohexanes in 3:2 and 9:2 ratios, respectively. The geometry of the double bond was determined from the chemical shifts of the olefinic protons[7e] (e.g. *trans*-**6a**: $\delta$ 5.41, *trans*-**6b**: $\delta$ 6.40), while the geometry on the cyclohexane ring was confirmed by the coupling pattern of the allylic protons (e.g. *cis*-**6a**: br dq, $J=10$, 5 Hz, *trans*-**6a**: ddt, $J=3.5$, 11.4, 10.1 Hz). The formation of the *cis*-isomer on the cyclohexane ring is due to isomerization during the Horner–Emmons reaction, which was confirmed by the synthesis from *cis*-1,2-cyclohexanedimethanol resulting in the same mixture of **6a**,**b**. Finally, **1a** and **1b** were obtained by DIBAL-H reduction of the ester group in **6a** and **6b**, respectively (**1a**: 95%, **1b**: 93%).

The ring expansion reaction was carried out following the report of Giguere et al.[6a] When **1a** was treated with 1.5 equiv. of $Tf_2O$ in the presence of 2.5 equiv. of 2,6-lutidine in $CH_2Cl_2$ at −60°C, 11-membered hydrocarbons **7a** and **7b**[†] were afforded as an inseparable mixture in a 81% yield (**7a**:**7b** = 3:1) (Scheme 2). The $^1H$ NMR spectrum showed that **7a** and **7b** are the isomers with respect to the non-conjugated double bond (*E* for the major isomer **7a**), as determined from their *J*-values. On the other hand, the reaction of **1b** under the same conditions resulted in the formation of the same 3:1 mixture of **7a**,**b** in a 24% yield. The isomerization from **1b** to **1a** prior to the ring expansion is a plausible pathway, since the direct cyclization of **1b** is considered to proceed through a seven-membered transition state including the highly strained *trans*-substituted double bond **8b**, while the *cis*-substituted double bond is included in **8a** (Fig. 1).

**Figure 1.**

**Table 1.**

| Entry | Isomer ratio in **1a** (*trans*: *cis*) | Ratio of **7a** and **7b** |
|---|---|---|
| 1 | 88:12 | 93:7 |
| 2 | 68:32 | 78:22 |
| 3 | 60:40[a] | 75:25 |
| 4 | 44:56 | 63:37 |

[a] Original ratio.

To explore the stereochemistry of this reaction, three mixtures of **1a** with different *cis*/*trans* ratios were prepared by repetition of column chromatography, however it was not possible to obtain pure *trans*- and *cis*-**1a**. Each mixture was exposed to the same reaction conditions, and the results are listed in Table 1. Extrapolation of these results showed that *trans*-**1a** produces **7a** selectively, whereas *cis*-**1a** produces **7a** and **7b** in a 1:2 ratio.

In conclusion, a new five-carbon ring expansion reaction from six- to eleven-membered carbocycles was established utilizing β-(hydroxymethyl)allylsilane as the three-carbon unit. The reaction proceeded under mild conditions and with easy of operation. The scope and limitations of this reaction are currently under investigation.

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[†] $^1H$ NMR ($CDCl_3$) assigned for **7a**: $\delta$ 4.81 (1H, d, $J=2.0$ Hz), 4.85 (1H, d, $J=2.0$ Hz), 5.11 (1H, dt, $J=15.5$, 7.7 Hz), 5.34 (1H, dt, $J=15.5$, 7.6 Hz), 5.40 (1H, dt, $J=15.8$, 7.3 Hz), and 5.91 (1H, br d, $J=15.8$ Hz); assigned for **7b**: $\delta$ 4.73 (2H, br s), 5.24–5.32 (1H, m), 5.49 (1H, dtt, $J=10.6$, 8.6, 1.7 Hz), 5.88 (1H, dt, $J=15.8$, 6.8 Hz), and 6.03 (1H, br d, $J=15.8$ Hz); $^{13}C$ NMR ($CDCl_3$) assigned for **7a**: $\delta$ 27.55, 29.88, 32.27, 33.98, 34.76, 34.88, 112.64, 130.82, 130.92, 134.45, 137.83, and 148.78; assigned for **7b**: $\delta$ 25.56, 26.64, 26.80, 28.64, 29.69, 32.85, 111.21, 129.52, 130.18 (2C), 135.66, and 149.65.

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