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A New Strategy for Construction of Eight-Membered Carbocycles by Brook Rearrangement Mediated [6 + 2] Annulation

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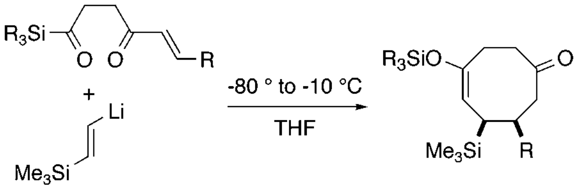
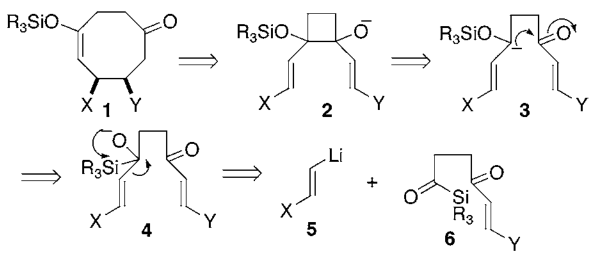
ABSTRACT



A newly developed strategy for construction of eight-membered carbocycles via [6 + 2] annulation that involves the combination of *β*-alkenoyl acylsilanes and a vinyllithium derivative is described. A unique feature of this annulative approach is that it enables in one operation and a stereoselective manner construction of eight-membered ring systems containing useful functionalities for further synthetic elaboration from readily available six- and two-carbon components.

The construction of eight-membered carbocycles remains a significant synthetic challenge because they constitute common structural cores of a large number of biologically important natural and nonnatural products.[1] Recently, we reported a novel and efficient method for constructing seven-[2] and eight-membered carbocycles[3] using Brook rearrangement mediated [3 + 4] annulation. In this letter, we describe our preliminary results for formation of eight-membered carbocycles by the unprecedented [6 + 2] annulation. Our basic strategy, shown in Scheme 1, is the formation of an eight-membered ring by oxyanion-accelerated Cope rearrangement[4] (**2** → **1**) of 1,2-divinyl cyclobutanolate, which can be generated by a tandem sequence involving an internal

Scheme 1



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(1) (a) Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881−930. (b) Molander, G. A. *Acc. Chem. Res.* **1998**, *31*, 603−609. (c) Sieburth, S. McN.; Cunard, N. T. *Tetrahedron* **1996**, *52*, 6251−6282. (d) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757−5821.

(2) (a) Takeda, K.; Takeda, M.; Nakajima, A.; Yoshii, E. *J. Am. Chem. Soc.* **1995**, *117*, 6400−6401. (b) Takeda, K.; Nakajima, A.; Yoshii, E. *Synlett* **1996**, 753−754. (c) Takeda, K.; Nakane, D.; Takeda, M. *Org. Lett.* **2000**, *2*, 1903−1905. (d) Takeda, K.; Nakajima, A.; Takeda, M.; Okamoto, Y.; Sato, T.; Yoshii, E.; Koizumi, T.; Shiro, M. *J. Am. Chem. Soc.* **1998**, *120*, 4947−4959. (e) Takeda, K.; Nakajima, A.; Takeda, M.; Yoshii, E.; Zhang, J.; Boeckman, R. K., Jr. *Org. Synth.* **1999**, *76*, 199−213. (f) Takeda, K.; Ohtani, Y. *Org. Lett.* **1999**, *1*, 677−679.

(3) Takeda, K.; Sawada, Y.; Sumi K. *Org. Lett.* **2002**, *4*, 1031−1033.

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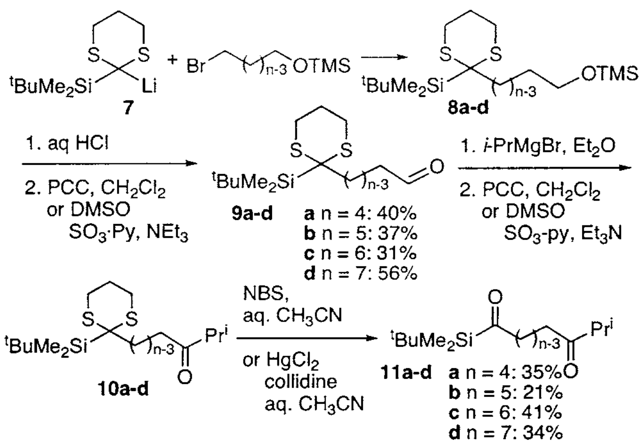
carbonyl attack by the siloxy carbanion (**3** → **2**) and Brook rearrangment[5] (**4** → **3**) from β-alkenoyl acylsilane **6** and vinyllithium derivative **5**.

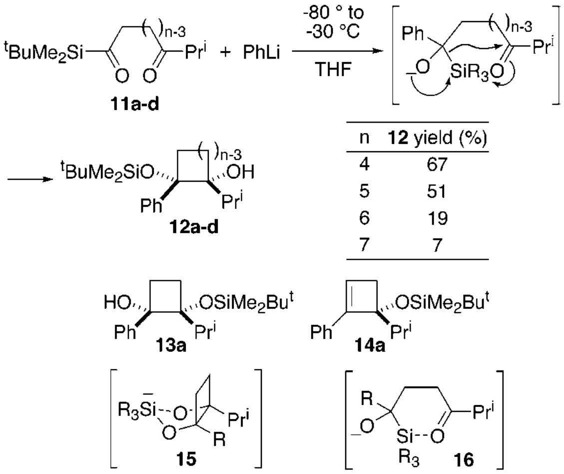
Since the formation of eight-membered carbocycles using the oxyanion-accelerated Cope rearrangement of 1,2-divinylcyclobutanes has been well-documented,[4] it seemed to us that the formation of a four-membered ring by the internal carbonyl attack by the siloxy carbanion (**3** → **2**) seemed to be the key element for realization of the above process. First, we decided to carry out a model experiment on the reaction of γ-keto acylsilane **11a**, which was prepared by a route starting from 1,3-dithiane derivative **7**[6] as shown in Scheme 2, with phenyllithium to test the feasibility of this approach.

Scheme 2



When **11a** in THF was treated with phenyllithium at −80 °C and allowed to warm to −30 °C, *cis*-1,2-cyclobutanediol derivative **12a**, Brook rearrangement/cyclization product of the adduct, was obtained in 67% yield along with silyl-rearranged products of **12a**, **13a** (10%), and its dehydration product **14a** (9%). The structural assignment of **12a** was based on the appearance and disappearance of the ^{13}C NMR signals at δ 82.7 and 83.0 for the quaternary carbons and at δ 213.4 and 245.0 for the carbonyl carbons, respectively. The 1,2-cis stereochemistry, indicated by the presence of cross-peaks between a proton on the phenyl group and a methyne proton of the isopropyl group in NOESY experiments, is interpreted as the result of the internally O−Si coordinated structure **15**.[7] The generality of this tandem process has been demonstrated by the formation of five- to seven-membered carbocycles, although the yield decreased with increase in ring sizes.[8] This trend regarding yield and ring sizes is in sharp contrast to the corresponding tandem Brook rearrangement/intramolecular Michael reaction,[9] in which similar yields were obtained with four- to six-membered carbocylces. The fact that the best yield (86% total yield) was obtained with a four-membered ring can be explained by invoking an attractive interaction between the silyl group and carbonyl oxygen in the six-membered transition state **16** and/or by assuming a reactantlike structure for an early transition state originating from the unstable siloxy carbanion. Encouraged by the above results, we proceeded to investigate the possibility of formation of eight-membered carbocycles by [6 + 2] annulation. The requisite six-carbon unit **20** was prepared by the route shown in Scheme 4, which involves addition of cyanohydrins **17**[10] to acryloylsilane **18**[11] followed by hydrolysis of the cyanohydrin moiety into ketone.

Scheme 3



n	**12** yield (%)
4	67
5	51
6	19
7	7

When β-alkenoylsilanes **20** in THF were treated with β-(trimethylsilyl)vinyllithium **21**, generated from β-(trimethylsilyl)vinyl bromide with *tert*-butyllithium, and then allowed to warm to −10 °C, the desired eight-membered carbocycles **22** were obtained as a single diasteromer in acceptable yields and as the only identifiable product.[12] The

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(4) (a) Paquette, L. A. *Tetrahedron* **1997**, *53*, 13971−14020. (b) Wilson, S. R. *Org. React.* **1993**, *43*, 93−250. (c) Bronson, J. J.; Danheiser, R. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 999−1036. (d) Hill, R. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 785−826. (e) Paquette, L. A. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 609−626. Also, see: (f) Gadwood, R. C.; Lett, R. M. *J. Org. Chem.* **1982**, *47*, 2268−2275.

(5) For reviews on the Brook rearrangement, see: (a) Brook, M. A. *Silicon in Organic, Organometallic, and Polymer Chemistry*; John Wiley & Sons: New York, 2000. (b) Brook, A. G.; Bassindale, A. R. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980; pp 149−221. (c) Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77−84. For the use of the Brook rearrangement in tandem bond formation strategies, see: (d) Moser, W. H. *Tetrahedron* **2001**, *57*, 2065−2084. Also, see: (e) Ricci, A.; Degl'Innocenti, A. *Synthesis* **1989**, 647−660. (f) Bulman Page, P. C.; Klair, S. S.; Rosenthal, S. *Chem. Soc. Rev.* **1990**, *19*, 147−195. (g) Qi, H.; Curran, D. P. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Moody, C. J., Eds.; Pergamon: Oxford, 1995; pp 409−431. (h) Cirillo, P. F.; Panek, J. S. *Org. Prep. Proc. Int.* **1992**, *24*, 553−582. (i) Patrocinio, A. F.; Moran, P. J. S. *J. Braz. Chem. Soc.* **2001**, *12*, 7−31.

(6) Scheller, M. E.; Frei, B. *Helv. Chim. Acta* **1984**, *67*, 1734−1747.

(7) For intramolecular chelation involving pentacoordinate silicon species: (a) see ref 2d. (b) Takeda, K.; Yamawaki, K.; Hatakeyama, N. *J. Org. Chem.* **2002**, *67*, 1786−1794. (c) Takeda, K.; Nakatani, J.; Nakamura, H.; Sako, K.; Yoshii, E.; Yamaguchi, K. *Synlett* **1993**, 841−843.

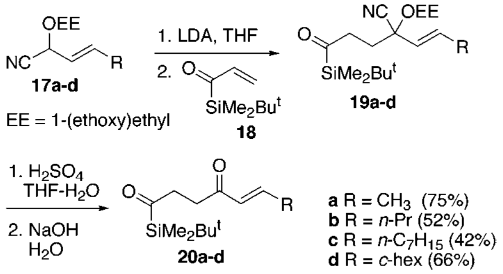
(8) In the reactions of **11b**−**d**, **12b**−**d** were the only identifiable products.

(9) Takeda, K.; Tanaka, T. *Synlett* **1999**, 705−708.

(10) Jacobson, R. M.; Lahm, G. P.; Clader, J. W. *J. Org. Chem.* **1980**, *45*, 395−405.

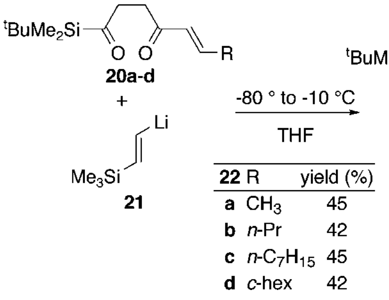
(11) Reich, H. J.; Kelly, M. J.; Olson, R. E.; Holtan, R. C. *Tetrahedron* **1983**, *39*, 949−960.

Scheme 4

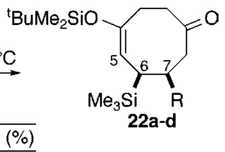


structure of **22a** was assigned on the basis of ^{13}C and ^{1}H NMR spectra, which show the carbonyl signal at δ 214.7 and a proton signal at δ 4.64 (d, J = 11.5 Hz, H-5) and carbon signals at δ 102.7 and 153.4 corresponding to the enol silyl ether moiety, and of comparison of their spectral data with those of the corresponding seven-membered carbocycles.[2] The relative stereochemistry was assigned on the basis of $J_{6,7}$ (3.6 Hz) and of the presence of cross-peaks between H-6 and H-7 protons in NOESY experiments.

Scheme 5



22	R	yield (%)
a	CH$_3$	45
b	*n*-Pr	42
c	*n*-C$_7$H$_{15}$	45
d	*c*-hex	42



The selective addition of vinyllithium to the acylsilane moiety in the presence of ketones observed in both reactions with **11** and **20** can be attributed to the less encumbered nature of acylsilanes arising from the abnormally long Si−CO bond relative to the analogous bond length in C−CO.[13]

In conclusion, we have developed a novel strategy for the construction of functionalized eight-membered carbocycles in a stereodefined manner featuring a Brook rearrangement mediated tandem process. Further expansion and applications of this methodology are in progress and will be reported in a forthcoming paper.

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Supporting Information Available: Full experimental details and characterization data for all new compounds described. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) For conversion of the γ-silyl enol silyl ethers into enones, see ref 2d.

(13) Chich, P. C.; Trotter, J. *J. Chem. Soc. A* **1969**, 1778−1783.