

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

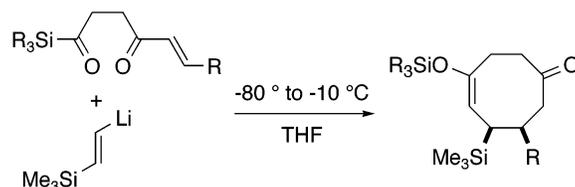
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Received July 23, 2003

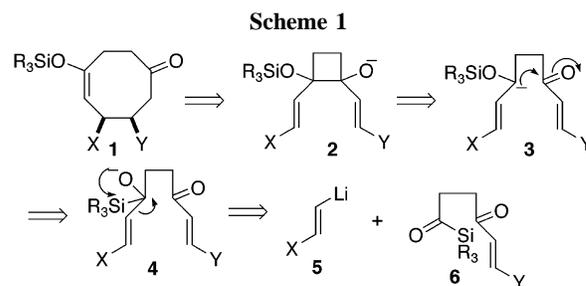
ABSTRACT



A newly developed strategy for construction of eight-membered carbocycles via [6 + 2] annulation that involves the combination of β -alkenoyl acylsilanes and a vinyl lithium 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 carbocycles³ 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 rearrangement⁴ (2 \rightarrow 1) of 1,2-divinyl cyclobutanolate, which can be generated by a tandem sequence involving an internal

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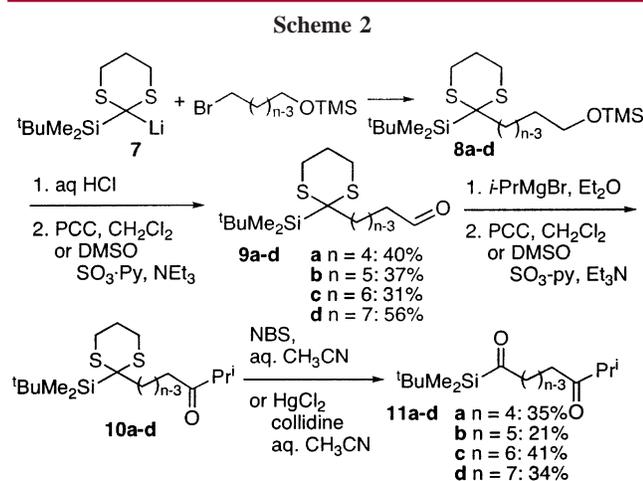
(1) (a) Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881–930. (b) Molander, G. A. *Acc. Chem. Res.* **1998**, *31*, 603–609. (c) Sieburth, S. McN.; Cunard, N. T. *Tetrahedron* **1996**, *52*, 6251–6282. (d) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757–5821.

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carbonyl attack by the siloxy carbanion (**3** → **2**) and Brook rearrangement⁵ (**4** → **3**) from β -alkenoyl acylsilane **6** and vinyl lithium 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.



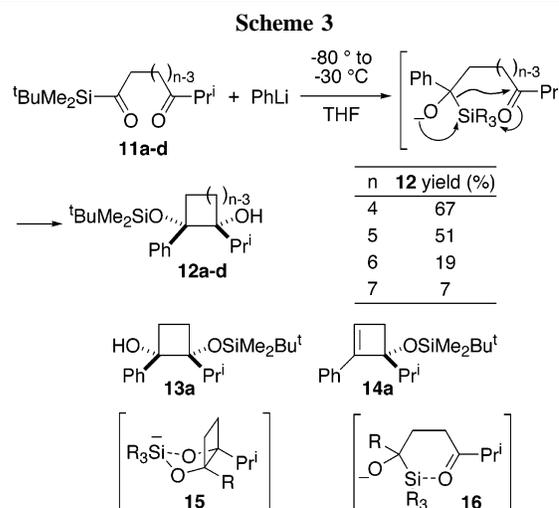
When **11a** in THF was treated with phenyllithium at -80 °C and allowed to warm to -30 °C, *cis*-1,2-cyclobutanediol derivative **12a**, Brook rearrangement/cyclization product of the adduct, was obtained in 67% yield along with silyl-rearranged products of **12a**, **13a** (10%), and its dehydration product **14a** (9%). The structural assignment of **12a** was based on the appearance and disappearance of the ¹³C 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.

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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 carbocycles. 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 acryloxy silane **18**¹¹ followed by hydrolysis of the cyanohydrin moiety into ketone.

When β -alkenoylsilanes **20** in THF were treated with β -(trimethylsilyl)vinyl lithium **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 diastereomer in acceptable yields and as the only identifiable product.¹² The

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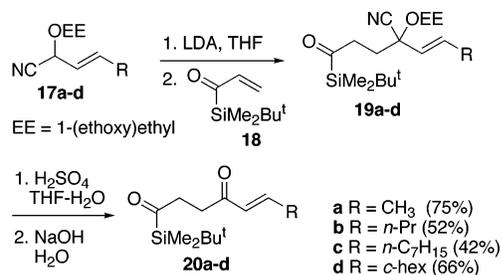
(8) In the reactions of **11b–d**, **12b–d** were the only identifiable products.

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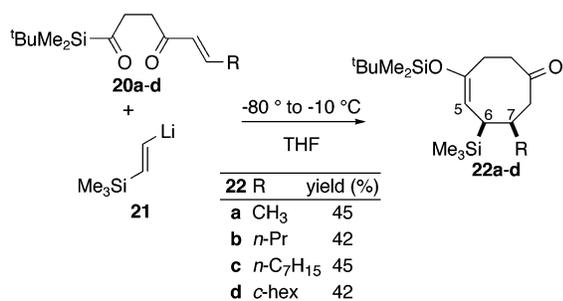
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Scheme 4



structure of **22a** was assigned on the basis of ^{13}C and ^1H 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

Scheme 5



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.

The selective addition of vinylolithium 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.

Acknowledgment. Acknowledgment is made to a grant-in-aid for Scientific Research from the Japanese Ministry of Education, Sciences, Sports and Culture, the Uehara Memorial Foundation, and the Naito Foundation for partial support of this research.

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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