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Stereoselective Construction of Eight-Membered Carbocycles by Brook Rearrangement-Mediated [3 + 4] Annulation

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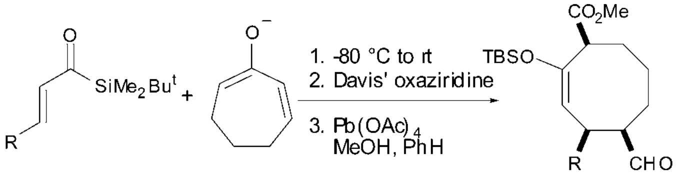
ABSTRACT



A newly developed strategy for eight-membered carbocycles via [3 + 4] annulation that involves the combination of *β*-substituted acryloylsilanes and enolates of cycloheptenone is described. A unique feature of this annulative approach is its capacity to generate, in two steps, eight-membered ring systems containing useful functionalities for further synthetic elaboration from readily available three- and four-carbon components.

Although much effort has been devoted to the construction of eight-membered carbocycles since they constitute common structural cores of a large number of biologically important molecules, general methods for the stereocontrolled synthesis of substituted cyclooctane derivatives are scarce.[1] We previously developed a Brook rearrangement-mediated [3 + 4] annulation protocol for stereospecific construction of seven-membered carbocycles, which involves the combination of acryloylsilanes as the three-carbon unit and lithium enolate of alkenyl methyl ketones as the four-carbon unit.[2] In this paper, we report our preliminary results obtained from extension of the methodology to functionalized cyclooctenone derivatives that are difficult to access by other methods.

We envisioned that the use of enolate **1** of 2-cycloheptenone instead of the enolates of alkenyl methyl ketone as the four-carbon unit in the [3 + 4] annulation would produce the bicyclo[3.3.2]decenone derivatives **3** in which, if the two-atom internal tether can be cleaved at either bond *a* or bond *b*, the *cis*-3,4,8-trisubstituted cyclooctenone enol silyl ethers **4** would be stereoselectively obtained.[3] In the reaction of acryloylsilane **5**[2d,f,4] with lithium enolate of 2-cycloheptenone[5] according to our standard annulation protocol that involves addition of the enolate to the acylsilane, significant amounts

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

[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] For a recent example of the synthesis of eight-membered carbocycles using the temporary bridge concept, see: (a) Rodriguez, J. R.; Castedo, L.; Mascareñas, J. L. *Org. Lett.* **2000**, *2*, 3209−3212. (b) Buono, F.; Tenaglia, A. *J. Org. Chem.* **2000**, *65*, 3869−3874.

[4] Nowick, J. S.; Danheiser, R. L. *J. Org. Chem.* **1989**, *54*, 2798−2802.

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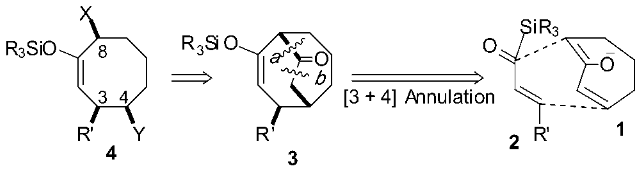
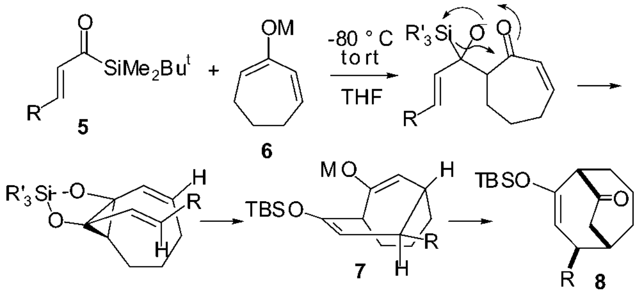
Scheme 1



of side products due to overreaction were obtained. The yields of the desired compounds were improved by an inverse addition of the acylsilane to the enolate solution. The results are shown in Table 1. The structures were assigned by spectral comparison with structurally related compounds[2d] and by ^{1}H NMR spectra showing an AB-type splitting pattern of the H-10 protons consisting of a pair of signals at δ 2.35 (1H, dd, $J = 17.9$, 5.1 Hz) and 2.82 (1H, ddd, $J = 17.9$, 3.4, 2.1 Hz) for **8e**. The low yield of **8d** (R = *i*-Pr) can be ascribed to the competitive formation of the dienolate by the abstraction of the γ-proton.

Table 1. Formation of Bicyclo[3.3.2]decenone Derivatives by [3 + 4] Annulation

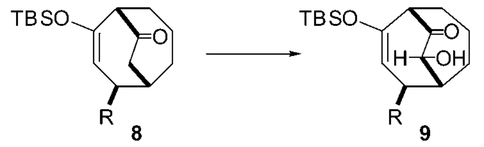


	R	**8**, yield (%)
5a	$SiMe_3$	66
5b	$SiMe_2Bu^t$	65
5c	$SiMe_2Ph$	63
5d	*i*-Pr	45
5e	*t*-Bu	84

Our initial attempts to cleave the ethano bridge by Baeyer–Villiger oxidation of **8** and its derivatives were unsuccessful. We also tried an oxidative cleavage to an oximino ester derivative via α-nitrosoketone[6] but without success. We next decided to examine the indirect cleavage of the ethano bridge that involves α-hydroxylation of the ketone in **8** followed by oxidative cleavage of the α-hydroxy ketone. When lithium enolate generated from **8** by LDA was treated with MoO_5–pyridine–HMPA complex (MoOPH),[7] α-hydroxy ketone **9** was obtained as a single diastereomer (Table 2). Similar or even better results were obtained when Davis' reagent (2-benzenesulfonyl-3-(3-nitrophenyl)oxaziridine)[8] was used for sodium enolates of **8**, generated by sodium hexamethyldisilazide (NHMDS).[9] The stereochemistry of the hydroxyl group was assigned on the basis of results of NOESY experiments.

These results led us to perform the annulation and subsequent oxidation in a one-pot operation by treatment of enolate **7** with the oxidizing reagents, enabling the direct transformation from **5** and **6** into **9**. When MoOPH was added to a THF solution of lithium enolate **7e** at −80 °C and then allowed to warm to room temperature, only a trace amount of **9e** was obtained along with **8e**. The use of Davis' reagent also gave almost the same result, which was not surprising considering that Davis reported the reactions with lithium enolates are sluggish. Treatment with Davis' reagent after addition of NHMDS (1.2 equiv) to the lithium enolate solution, however, resulted in improvement of the yield

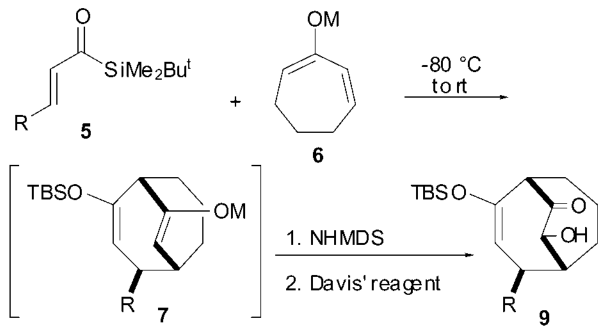
Table 2. α-Hydroxylation of Bicyclo[3.3.2]decenones **8**



	9, yield (%)	method[a]
8a	52	A
8a	76	B
8e	66	A
8e	71	B

[a] A: (1) LDA, (2) MoOPH. B: (1) NHMDS, (2) 2-benzenesulfonyl-3-(3-nitrophenyl)oxiziridine.

Table 3. Tandem [3 + 4] Annulation/α-Hydroxylation



	M	yield (%)
5a	Na	48
5b	Na	72
5c	Na	58
5d	Li	50
5e	Li	62

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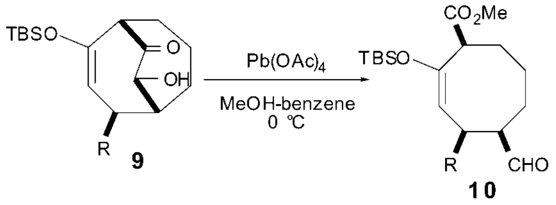
(5) This compound was prepared by House's method for cyclooctenone. House, H. O.; Sieloff, R. F.; Lee, T. V.; DeTar, M. B. *J. Org. Chem.* **1980**, *45*, 1800–1806.

(6) Moorhoff, C. M.; Paquette, L. A. *J. Org. Chem.* **1991**, *56*, 703–710.

(7) Vedejs, E.; Larsen, S.; Hill, G.; Sharpless, K. B. *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. VII, pp 277–282.

Table 4. Oxidative Cleavage of the Internal Tether of **9**



	yield (%)
10a	95
10b	96
10c	95
10d	97
10e	93

(Table 3). In the cases of **5a**−**c**, a better yield was obtained using sodium enolate **6** generated by NHMDS and addition of an extra amount (1.2 equiv) of NHMDS before treatment with Davis' reagent.

Oxidative cleavage of the α-hydroxy ketone moiety by $Pb(OAc)_4$ in MeOH−benzene[10] afforded 4-formylcyclooctenecarboxylate derivative **10** in excellent yields (Table 4). The cis stereochemistries of the substituents were assigned on the basis of results of NOESY experiments.

In summary, we have developed an efficient method for the stereodefined synthesis of eight-membered carbocycles bearing functional groups that are useful for further synthetic transformation.[11]

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

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(8) (a) Vishwakarma, L. C.; Stringer, O. D.; Davis, F. A.; Pribish, J.; Vedejs, E. *Org. Synth.* **1987**, *66*, 203−210. (b) Davis, F. A.; Vishwakarma, L. C.; Billmers, J. M.; Finn, J. *J. Org. Chem.* **1984**, *49*, 3241−3243. The 3-nitrophenyl derivative was used to obtain better chromatographic separation after the reaction. The reaction using the parent phenyl derivative resulted in the formation of inseparable mixtures.

(9) The use of KHMDS, the more common base for Davis' hydroxylation, was less efficient. The addition of HMPA also resulted in lower yields.

(10) Di Grandi, M. J.; Coburn, C. A.; Isaacs, R. C. A.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 7728−7731.

(11) For transformation of the γ-silyl enol silyl ether moiety in **10a**,**b** into the corresponding α,β-enone by NBS/TBAF, see: ref 2d. Also, it is well-known that a dimethylphenylsilyl group can act as a hydroxyl surrogate in combination with Fleming's oxidative desilylation protocol; see: Fleming, I.; Henning, R.; Parker, D. C.; Plaut, H. E.; Sanderson, P. E. J. *J. Chem. Soc., Perkin Trans. 1*, **1995**, 317−337.