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

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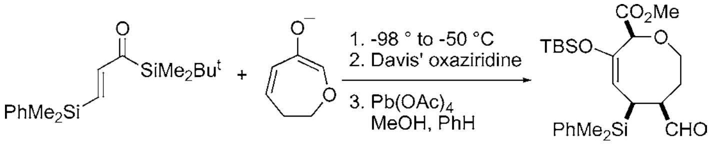
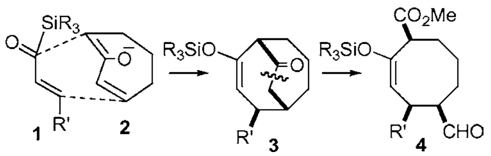
ABSTRACT



A newly developed strategy for eight-membered oxygen heterocycle construction via [3 + 4] annulation is described. The method involves the combination of *β*-substituted acryloylsilanes and enolates of 6-oxacyclohept-2-en-1-one. A unique feature of this annulative approach is its capacity to generate eight-membered ring systems containing useful functionalities for further synthetic elaboration from readily available three- and four-carbon components.

We recently developed a new [3 + 4] annulation method for eight-membered carbocycles that uses a combination of β-substituted acryloylsilanes **1** and enolates **2** of cycloheptenone.[1,2] A unique feature of the methodology is that highly functionalized eight-membered carbocycles can be formed rapidly and in a predictable fashion via an oxidative cleavage of the two-atom internal tether of the bicyclo[3.3.2]decenone derivatives **3**, which are constructed by the [3 + 4] annulation (Scheme 1). We have since found that our method can now be extended to the synthesis of eight-membered oxygen heterocycles, for which ring-construction technology remains sparse,[3] despite the fact that such ring systems are found in many structurally interesting and biologically active natural products.[4]

Scheme 1



An application of our protocol for the cycloheptenone enolate to 6-oxacyclohept-2-en-1-one **5**[5] initially resulted in significantly lower yields of the bicyclic derivative **8** than expected, presumably due to instability of the enolate at −80 °C.[6] A change in the solvent from THF to cyclopentyl methyl

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[1] Takeda, K.; Sawada, Y.; Sumi, K. *Org. Lett.* **2002**, *4*, 1031−1033.

[2] For the original Brook rearrangement mediated [3 + 4] annulation protocol for seven-membered carbocylcles, see: (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] (a) Moody, C. J.; Davies, M. J. In *Studies in Natural Products Chemistry*; Attaur-Rahman, A., Ed.; Elsevier Science Publishers: New York 1992; Vol. 10. Also, see: (b) Boeckman, Jr. R. K.; Zhang, J. Reeder, M. R. *Org. Lett.* **2002**, *4*, 3891−3894 and references therein.

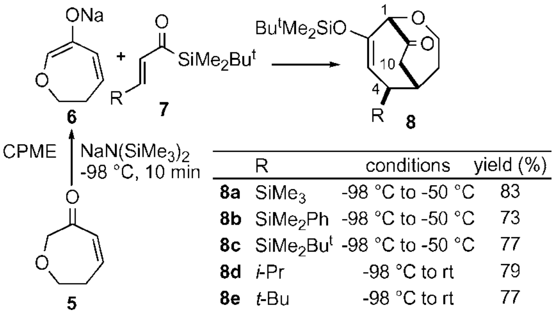
[4] Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653−5660 and references therein.

[5] Cossy, J.; Taillier, C.; Bellosta, V. *Tetrahedron Lett.* **2002**, *43*, 7263−7266.

10.1021/ol0492243 CCC: $27.50

ether (CPME)[7,8] and lowering of the reaction temperature to −98 °C did, however, improve the yield of **8** (Scheme 2). The structures were assigned by spectral comparison with **3** and in the case of **8a** by a ^{1}H NMR spectrum that showed a doublet at δ 4.46 (J = 1.8 Hz) for H-1 and an AB-type splitting pattern for the H-10 protons, which consisted of a pair of signals at δ 2.59 (1H, ddd, J = 18.5, 5.5, 1.6 Hz) and δ 2.84 (1H, br d, J = 18.5 Hz).

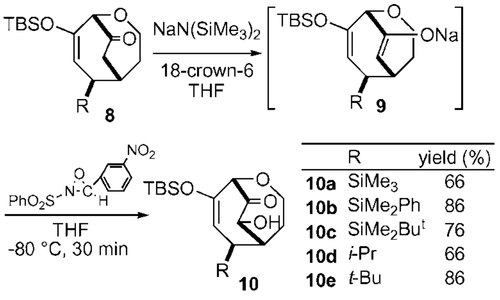
Scheme 2. Formation of 2-Oxabicyclo[3.3.2]decenone Derivatives by [3 + 4] Annulation



	R	conditions	yield (%)
8a	SiMe$_3$	-98 °C to -50 °C	83
8b	SiMe$_2$Ph	-98 °C to -50 °C	73
8c	SiMe$_2$Bu^t	-98 °C to -50 °C	77
8d	*i*-Pr	-98 °C to rt	79
8e	*t*-Bu	-98 °C to rt	77

α-Hydroxylation of the ketone, to allow cleavage of the ethano bridge, did not proceed satisfactorily under the same conditions as those used previously for the carbon analogue.[9] After considerable experimentation, addition of a crown ether was found to be effective. Thus, treatment of the sodium enolate **9** generated from **8** with NaN(SiMe$_3$)$_2$ (NaHMDS) in the presence of 18-crown-6 with Davis' reagent (2-benzenesulfonyl-3-(3-nitrophenyl)oxaziridine)[10] gave the α-hydroxy ketone **10** in satisfactory yields (Scheme 3). The stereochemistry of the hydroxyl group was assigned on the basis of NOESY experiments that showed a cross-peak correlating the H-10 and the C-4 substituent.

Scheme 3. α-Hydroxylation of 2-Oxabicyclo[3.3.2]decenones **8**

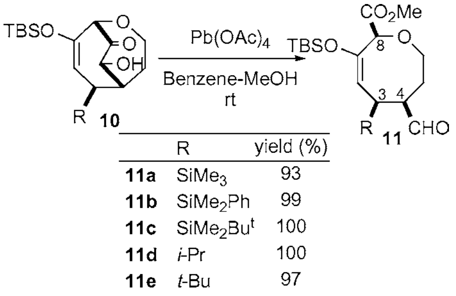


	R	yield (%)
10a	SiMe$_3$	66
10b	SiMe$_2$Ph	86
10c	SiMe$_2$Bu^t	76
10d	*i*-Pr	66
10e	*t*-Bu	86

Carrying out the [3 + 4] annulation and α-hydroxylation on the resultant ketone enolate in a one-pot operation proved less rewarding in terms of yields in contrast to the case of **3**. One reason for this arises from the low yield of the α-hydroxylation step in a solvent system containing CPME, which is a better solvent for the [3 + 4] annulation step.

Oxidative cleavage of the α-hydroxy ketone proceeded smoothly when **10** was treated with Pb(OAc)$_4$ in MeOH−benzene. The eight-membered oxygen heterocycle **11** was formed in excellent yield (Scheme 4).

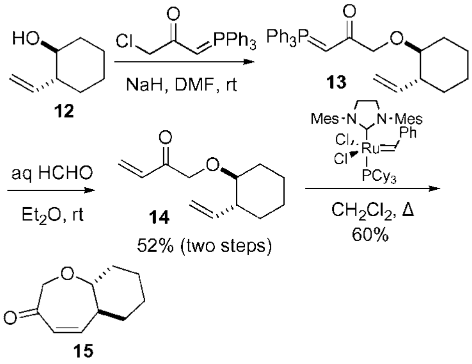
Scheme 4. Oxidative Cleavage of the Internal Tether of **10**



	R	yield (%)
11a	SiMe$_3$	93
11b	SiMe$_2$Ph	99
11c	SiMe$_2$Bu^t	100
11d	*i*-Pr	100
11e	*t*-Bu	97

The same strategy could be applied to the synthesis of cyclohexane-fused oxacyclooctene derivatives using cycloheptenone derivative **15**, which was prepared (Scheme 5) according to the procedure for **5** starting from 2-ethenylcyclohexanol **12**.[11]

Scheme 5. Preparation of **15**



[3 + 4] annulation of **7** with the sodium enolate of **15** proceeded smoothly, with **16** typically being obtained as a single diastereomer and in good yield (Scheme 6). For **16a** the relative stereochemistry was assigned on the basis of a peak at δ 3.08 ppm (1H, ddd, J = 10.3, 10.3, 3.9 Hz) for H-7, indicating a 2,7-trans configuration. The presence of

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(6) Significant decomposition was observed upon quenching of the enolate generated in THF with AcOH at −80 °C.

(7) Watanabe, K.; Goto, K. *J. Synth. Org. Chem. Jpn.* **2003**, *61*, 806−808.

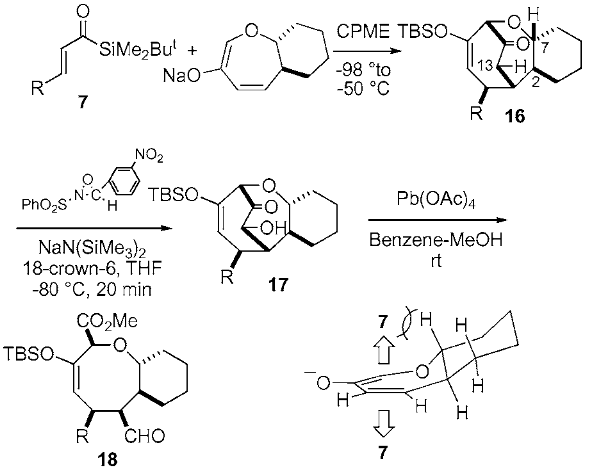
(8) We thank Ube Industries, Ltd., for providing CPME.

(9) When sodium enolates of **8**, generated by sodium hexamethyldisilazide in THF, was treated with Davis' reagent, conditions used for the carbon analogue, lower yields of **10** with recovery of the starting materials were obtained.

(10) (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.

(11) Henin, F.; Muzart, J. *Synth. Commun.* **1984**, *14*, 1355−1358.

Scheme 6. Synthesis of 18 via [3 + 4] Annulation of **15**



		yield (%)		
	R	**16**	**17**	**18**
a	$SiMe_3$	89	52	93
b	$SiMe_2Ph$	85	59	100
c	$SiMe_2Bu^t$	82	49	83
d	*i*-Pr	79	39	80
e	*t*-Bu	83	66	99

cross-peaks between H-7 and H-13 protons in NOESY experiments confirmed our structural assignment. The stereoselectivity can be explained by the preferential approach of the acryloylsilane **7** from the less crowded side.

In conclusion, we have developed a new approach to construction of eight-membered oxygen heterocycles possessing functionality that can easily be manipulated to other substrates.[12]

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Supporting Information Available: Full experimental details and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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[12] We have already reported that the γ-silyl enol silyl ether moiety in **11** and **18** can be transformed 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.