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Construction of Azaspirocyclic Ketones through α-Hydroxyiminium Ion or α-Siloxy Epoxide Semipinacol Rearrangements

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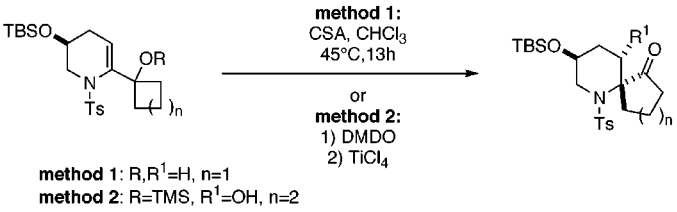
ABSTRACT



Semipinacol-type rearrangements to produce azaspirocyclic ketones are presented. The yields and stereoselectivities of these reactions range from 67–94% yield and 2.8:1 to 1:0 diastereoselectivity, respectively.

Nature continues to provide motivation for synthetic organic chemists through the discovery of new biologically active and structurally diverse natural products. For example, the alkaloids depicted in Figure 1 all share a *spiro*-connected bicyclic ring system. Unsurprisingly, these architecturally interesting alkaloids have spurred significant interest from the synthetic organic community.[1] Although a variety of methods to generate spiro compounds are available, new methods are useful to streamline synthetic approaches and improve efficiency.[2]

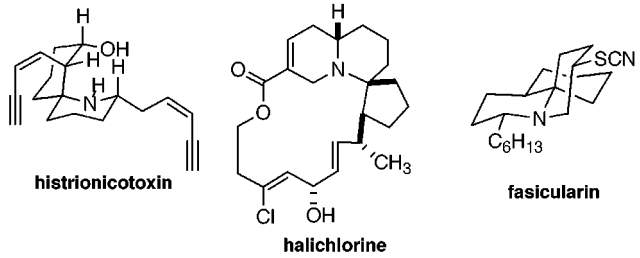


Figure 1. Natural products containing azaspirocyclic ring systems.

In examining the structures of these natural products, we were drawn to their azaspirocyclic substructures. In initiating a research program investigating the mechanistic understanding, control, and synthetic utility of group migrations to electron-deficient atoms, we thought that a semipinacol process proceeding through an α-hydroxyiminium ion intermediate would serve as an interesting entry into these types of azaspirocyclic substructures.

Paquette and co-workers have been investigating and utilizing similar α-hydroxyoxonium ion semipinacol reac-

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(1) Recent synthetic work on histrionicotoxin: (a) Williams, G. M.; Roughley, S. D.; Davies, J. D.; Holmes, A. B.; Adams, J. P. *J. Am. Chem. Soc.* **1999**, *121*, 4900. (b) Stockman, R. A. *Tetrahedron Lett.* **2000**, *41*, 9163. Halichlorine: (c) White, J. D.; Blakemore, P. R.; Korf, E. A.; Yokochi, A. F. T. *Org. Lett.* **2001**, *3*, 413. (d) Wright, D. L.; Schulte, J. P.; Page, M. A. *Org. Lett.* **2000**, *2*, 1847. (e) Trauner, D.; Schwarz, J. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3542. (f) Clive, D. L. J.; Yeh, V. S. C. *Tetrahedron Lett.* **1999**, *40*, 8503. Fasicularin: (g) Abe, H.; Aoyogi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2000**, *122*, 4583.

(2) Sannigrahi, M. *Tetrahedron* **1999**, *55*, 9007.

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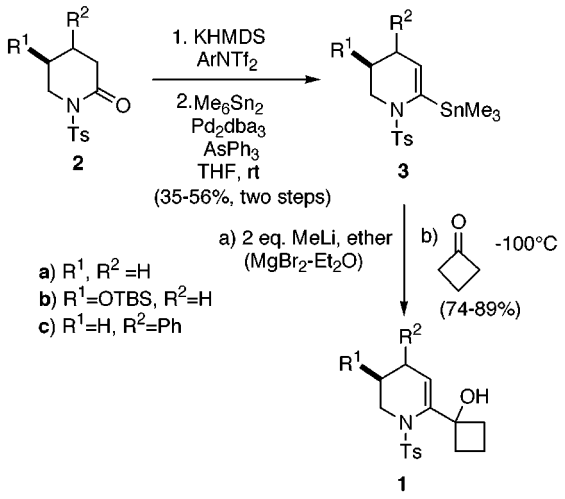
tions since the 1990s.[3] A key issue in their studies was the requirement for electron-withdrawing substituents on a six-membered oxonium ion-bearing ring, as cyclopentanols did not ring expand in their absence. Although it was expected in our case that reactions proceeding through iminium ion intermediates would be less facile compared to the oxonium species, the possible efficiency of the construction of the desired azaspirocyclic compounds outweighed this risk. Even so, our initial studies utilized cyclobutanol substrates, as relief of ring strain should promote the expansion of the cyclobutanol to the cyclopentanone.[4]

After the exploration of other (unsuccessful) options, the requisite hydroxyiminium ion intermediates were generated by the protonation of *p*-toluenesulfonyl enamides of general structure **1**. These compounds were constructed in the following manner (Scheme 1).[3,5] The *N*-*p*-toluenesulfonyl

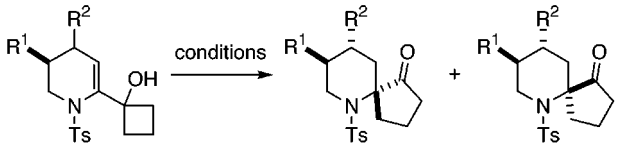
Scheme 1



lactams **2a**−**c**[6] were converted to their corresponding enol triflates under standard conditions. These were converted to vinylstannanes **3a**−**c** by palladium(0)-catalyzed cross-coupling using hexamethyldistannane.[7] The yields of the vinylstannanes were highest when the reaction was run at room temperature in THF for roughly 7 h. Shorter or longer reaction times resulted in lower isolated yields of **3a**−**c**. Tin−lithium exchange of **3a**−**c** using methyllithium was followed by quenching with cyclobutanone to give cyclobutanols **1a**−**c**. The use of a very low reaction temperature (−100 °C) and addition of magnesium bromide−etherate was sometimes necessary for improved yields (74−89%). Alternate additives such as HMPA, zinc (II) chloride, or cerium (III) chloride did not improve the reaction yields.

Subjecting cyclobutanols **1a**−**c** to the action of acid resulted in smooth expansion to cyclopentanones **4** and **5** (Table 1). Unlike Paquette's semipinacol reactions through

Table 1. Semipinacol-Type Ring Expansion of Cyclobutanols **1**



a) R^1, R^2 =H; **b**) R^1=OTBS, R^2=H; **c**) R^1=H, R^2=Ph

entry	SM[a]	acid[b]	*T* (°C)	*t* (h)	yield (%)[c]	ratio **4**:**5**[c]
1	**1a**	CSA	45	13	73	n/a
2	**1a**	HCl	25	2	67	n/a
3	**1b**	CSA	25	24	13	nd
4	**1b**	CSA	45	6	17	2:1
5	**1b**	CSA	45	13	81	2.8:1
6	**1c**	CSA	45	144	89	4.5:1
7	**1c**	HCl	25	11	93	11:1
8	**1c**	HCl	0	48	93	14:1

[a] SM = starting material. [b] CSA = camphorsulfonic acid (1.2 equiv) in dichloromethane; HCl = hydrochloric acid (1.1 equiv) in dichloromethane. [c] Ratios are determined by ^{1}H NMR integration and GC analysis of the product mixture; n/a = not applicable; nd = not determined.

oxonium ion intermediates, these reactions were sluggish using 1.2 equiv of camphorsulfonic acid as a promoter at room temperature (entry 3), and therefore heating to 45 °C for 13 h was required for good conversions (compare entries 1, 4, and 5). By following the reaction using ^{1}H NMR spectroscopy, we have since found that hydrochloric acid can promote this reaction at lower temperatures (entries 2, 7, and 8). The diastereoselectivity of the ring expansion reactions were moderately low (2:1 to 4.5:1) when the reaction was performed at 45 °C (entries 4−6) but improved significantly at lower temperatures (entries 7 and 8). The structures of **4b** and **5b** have been assigned by construction through an alternate path.[8] The structures of **4c** and **5c**, which are inseparable by column chromatography, are assigned by mechanistic analogy to **4b** and **5b**.

Although the examination of more substrates is necessary to determine the generality of this process, these results are consistent with the mechanistic rationale proposed by Paquette (Scheme 2).[3a] The stereoselectivities of these reactions (shown here for **1b**) are thought to derive through transition states in which the substituents are pseudoequatorial. The diastereomeric transition states differ depending

(3) (a) Paquette, L. A.; Lanter, J. C.; Johnston, J. N. *J. Org. Chem.* **1997**, *62*, 1702. (b) Paquette, L. A.; Kinney, M. A.; Dullweber, U. *J. Org. Chem.* **1997**, *62*, 1713 and references within.

(4) (a) Hirst, G. C.; Johnson, Jr, T. O.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 2992. (b) Trost, B. M.; Chen, D. W. C. *J. Am. Chem. Soc.* **1996**, *118*, 12541.

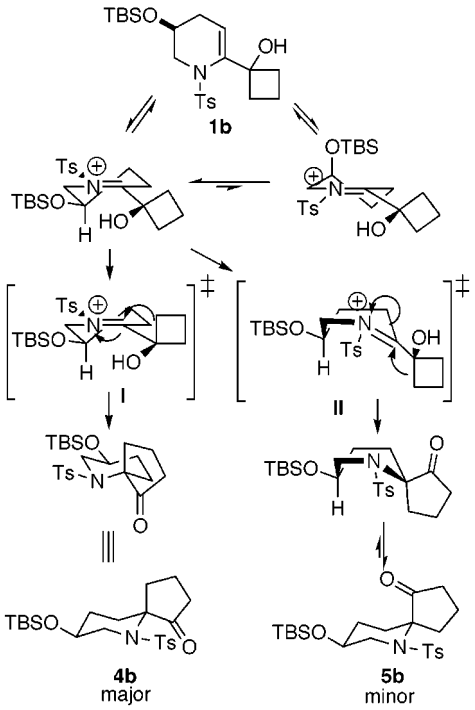
(5) All previously unreported compounds have been fully characterized spectroscopically (^{1}H and ^{13}C NMR, IR, HRMS).

(6) **2a** and **2b** were made by treating the parent lactams with BuLi and TsCl. **2b**: Herdeis, C. *Synthesis* **1986** 232. **2c** was made by the copper-catalyzed conjugate addition of PhMgBr to $\Delta^{3,4}$-*N*-*p*-toluenesulfonyl-2-oxopiperidene: Nagashima, H.; Ozaki, N.; Washiyama, M.; Itoh, K. *Tetrahedron Lett.* **1985**, *26*, 657. The details of the construction of **1a**−**c** will be published elsewhere.

(7) Luker, T.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 8131.

(8) The details of this chemical correlation will be published elsewhere.

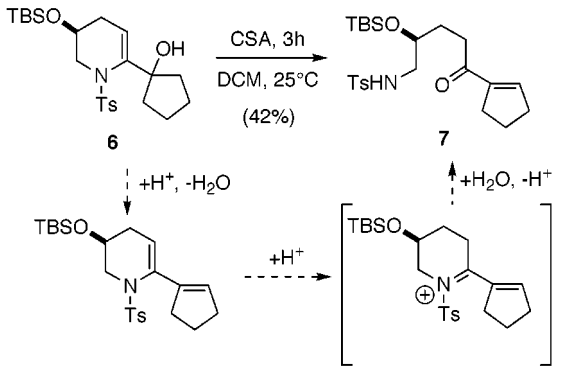
Scheme 2



on whether the cyclic iminium ion is reacted through a "chair" (**I**) or a "twist-boat" (**II**) conformation, with the chair orientation providing the major diastereomer **4b** in preference to **5b**. Of course, these substrates differ significantly from Paquette's compounds because of the *N*-*p*-toluenesulfonyl substituent. The role and effect of the substituent on nitrogen is currently under investigation.

Unfortunately, the analogous semipinacol-type ring expansion of cyclopentanols to cyclohexanones was not successful. For example, subjecting the cyclopentanol **6** (from **3b** and cyclopentanone) to the action of camphorsulfonic acid in dichloromethane at 25 °C for 3 h led to the formation of a new compound (Scheme 3). Complete spectral analysis (^{1}H NMR, ^{13}C NMR, IR, MS, and HMQC) revealed it to be enone **7**, which is derived from **6** by acid-catalyzed elimination of water and hydrolysis of the intermediate iminium ion.

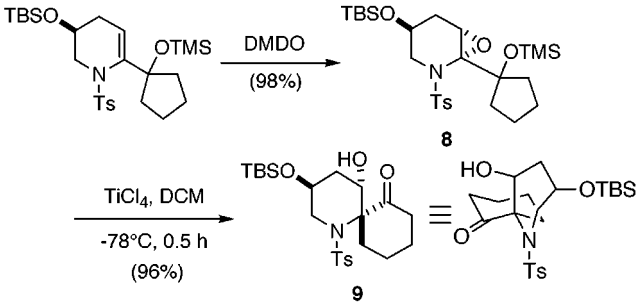
Scheme 3



This result is a serious setback in our attempts to construct certain azaspirocyclic substructures (for example, fasicularin) using this methodology.

The following alternative was then considered (Scheme 4). The use of an epoxide as the precursor to the iminium

Scheme 4



ion intermediate would be beneficial in two respects.[9] The additional electron-withdrawing oxygen substituent on the ring should increase the electrophilicity of the intermediate iminium ion. The hydroxy (or siloxy) group that initiates semipinacol rearrangement would also not be allylic, and thus much less prone to elimination reactions. Yamamoto has reported an all-carbon version of this semipinacol process.[10] Epoxidation of the trimethylsilyl ether of **6** using dimethyldioxirane in the presence of potassium carbonate gave epoxide **8** in 98% yield with complete selectivity.[11] The source of this high selectivity is under investigation. Exposure of **8** to titanium tetrachloride in methylene chloride at −78 °C for 0.5 h stereoselectively produced cyclohexanone **9** in 96% yield. The relative stereochemistry of **9** was confirmed by X-ray analysis (Figure 2). The structure of **9** is appropriately functionalized for a construction of fasicularin.

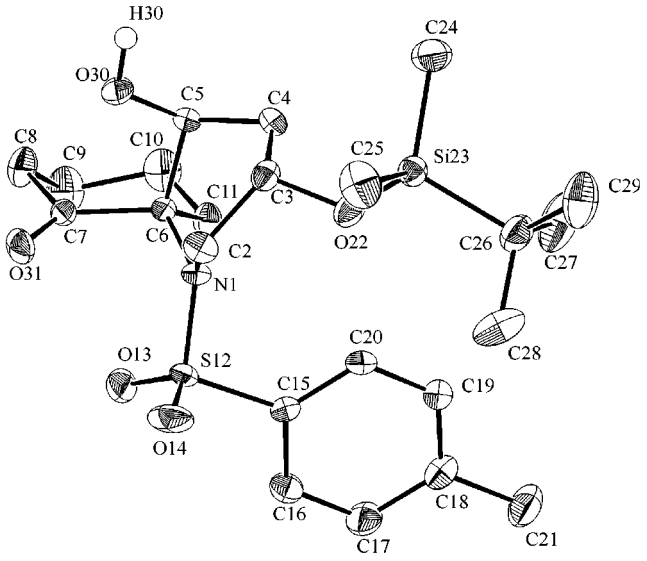
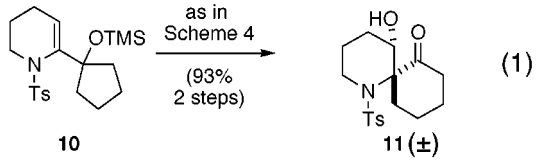


Figure 2. ORTEP structure of **9**.

To determine whether the source of the stereocontrol in the reaction of **8** to **9** was due to the epoxide stereochemistry ("S_N2" like) or to conformational constraints of the iminium ion in the transition state ("S_N1"-like), an analogous substrate without a pendant siloxy group was subjected to these reaction conditions (eq 1). Treatment of cyclopentanol silyl



10 **11 (±)** (1)

ether **10** with DMDO and titanium tetrachloride under the conditions identical to those used previously led to the generation of one diastereomeric cyclohexanone, **11**, in 93% yield (two steps). The relative stereochemistry of **11** was determined by X-ray crystallography of its *p*-nitrobenzoate derivative. This result strongly suggests that the reaction proceeds through a synchronous epoxide ring opening−ring enlargement process.

In summary, semipinacol-type reactions to construct azaspirocyclic ketones have been presented. The reaction works well for the acid-promoted ring expansion of cyclobutanols, but cyclopentanol-derived substrates require an epoxide precursor to successfully undergo ring expansion. The generation of complex nitrogen-containing spirocyclic structures initiated by the action of a Bronsted or Lewis acid makes this process synthetically efficient and it has good atom economy. The mechanistic details and further exploration of the synthetic utility of this process in the construction of azaspirocyclic alkaloids are the subject of continuing investigations of our laboratory.

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Supporting Information Available: Representative experimental procedures for ring expansion processes (**4a**/**5a**, **7**, **8**, **9 11)** and characterization data for **4a**−**c**, **5a**−**c**, **7**, **8**, **9**, and **11**. An X-ray crystallographic file (CIF) for **9** and the *p*-nitrobenzoate derivative of **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0160708

(9) During the preparation of this manuscript, the Paquette group reported the use of *N*-bromosuccimide to promote related semipinacol reactions (cyclobutanol to cyclopentanone): Paquette, L. A.; Owen, D. R.; Bibart, R. T.; Seekamp, C. K.; Kahane, A. L.; Lanter, J. C.; Corral, M. A. *J. Org. Chem.* **2001**, *66*, 2828. We had independently attempted using *N*-iodosuccimide for the expansion of **6**, with no success.

(10) (a) Maruoka, K.; Hasegawa, M.; Yamamoto, H.; Suzuki, K.; Shimazaki, M.; Tsuchihashi, G. *J. Am. Chem. Soc.* **1986**, *108*, 3827. See also: (b) Marson, C. M.; Walker, A. J.; Pickering, J.; Hobson, A. D.; Wrigglesworth, R.; Edge, S. *J. Org. Chem.* **1993**, *58*, 5944. (c) Baldwin, S. W.; Chen, P.; Nikolic, N.; Weinseimer, D. C. *Org. Lett.* **2000**, *2*, 1193. (d) Jung, M. E.; Marquez, R. *Org. Lett.* **2000**, *2*, 1669. (e) Jung, M. E.; Lee, W. S.; Sun, D. *Org. Lett.* **1999**, *1*, 307.

(11) For related epoxidations using DMDO: (a) Burgess, L. E.; Gross, E. K. M.; Jurka, J. *Tetrahedron Lett.* **1996**, *37*, 3255. (b) Sugisaki, C. H.; Carroll, P. J.; Correia, C. R. D. *Tetrahedron Lett.* **1998**, *39*, 3413.