Lewis Acid-Catalyzed Ring-Opening Reactions of Semicyclic *N*,*O*-Acetals Possessing an Exocyclic Nitrogen Atom: Mechanistic Aspect and Application to Piperidine Alkaloid Synthesis

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Abstract: Ring-opening reactions of semicyclic *N*,*O*-acetals possessing an exocyclic nitrogen atom with silicon-based nucleophiles (silyl enol ethers, ketene silyl acetals, allylic silanes, and trimethylsilyl cyanide) were systematically studied for the first time. It was found that the reactions were effectively catalyzed by a Lewis acid, trimethylsilyl trifluoromethanesulfonate (TMSOTf), to afford 1,4- and 1,5-amino alcohols in high yields. In reactions of 3-oxygen functionalized semicyclic *N*,*O*-acetals, high 1,2-*syn*-diastereoselectivity was obtained. By ^{1}H NMR experiment, the formation of the *O*-trimethylsilylated ring-opened product was observed as the initial product. Furthermore, the epimerization between the diastereomers of a 3-benzyloxy semicyclic *N*,*O*-acetal suggested the transient formation of an acyclic iminium ion species as a reactive intermediate. It was also found that 3-acetoxy and 3-benzyloxy *N*,*O*-acetals showed a tendency for the larger nucleophile to provide higher *syn*-selectivity, while 3-*tert*-butyldiphenylsilyloxy *N*,*O*-acetals showed the opposite tendency. These stereochemical outcomes can be rationalized by assuming four transition state models for the acyclic iminium ion intermediate. The synthetic utility of the reaction has been demonstrated in the diastereoselective synthesis of piperidine alkaloids, (+)-isofebrifugine and (±)-sedacryptine.

Introduction

X,*Y*-Acetals are functional groups consisting of an sp^3-carbon atom attached to two heteroatom groups, XR^1 and YR^2, where X and Y are heteroatoms such as oxygen, nitrogen, sulfur, phosphorus, and so on, and are widely utilized as versatile intermediates in organic synthesis (Figure 1).[1] On the basis of the structural characteristics, it can be classified into three groups: *acyclic*, *cyclic*, and *semicyclic*.[2] Acyclic *X*,*Y*-acetals consist of only an acyclic skeleton, while cyclic *X*,*Y*-acetals have a cyclic structure including both X and Y heteroatoms in the same ring system. Cyclic *X*,*Y*-acetals are especially utilized as protecting groups of aldehydes or ketones such as 1,3-dioxane, 1,3-dioxolane, and 1,3-dithiane.[3] On the other hand, semicyclic *X*,*Y*-acetals possess a cyclic structure including either an X or a Y heteroatom or neither of them in the ring system. *O*-Glycoside is a naturally occurring representative of semicyclic *O*,*O*-acetals.

Under acidic conditions (with a Brϕnsted acid or a Lewis acid), an *X*,*Y*-acetal can be activated to generate an α-heteroatom substituted carbenium ion as a reactive intermediate, which reacts with a nucleophile to form a substitution product. In this process, the acid coordinates to a lone pair of one of the heteroatoms (X or Y) to cleave the heteroatom−carbon bond with the assistance of electron donation from a lone pair of the other heteroatom. It is obvious that the reaction of unsymmetrical *X*,*Y*-acetals involves a chemoselective problem, namely whether the X or Y hetereoatom is activated by the acid. The selectivity would depend on the kind of heteroatom (O, N, S, P, etc.), the type of substituents attached to the heteroatom (R^1 and R^2), and the type of acid and nucleophile used. Among three structurally distinct *X*,*Y*-acetals (Figure 1), interesting is the reaction of *semicyclic X*,*Y*-acetals possessing one of the hetereoatoms in the ring system, since these can undergo two types of reactions, i.e., *substitution* of the exocyclic heteroatom group by a nucleophile or *ring-opening addition* of a nucleophile (Scheme 1). Thus, four types of products are possible depending on the positions (exocyclic or endocyclic) of the heteroatoms X and Y.

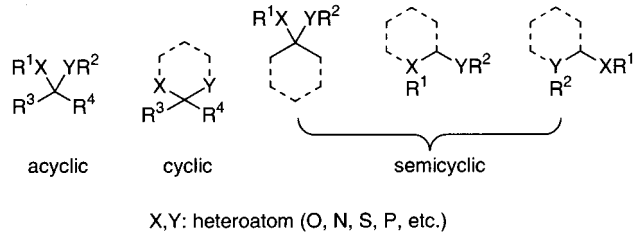

Figure 1. *X*,*Y*-Acetals.

For instance, in the presence of a Lewis acid, semicyclic *O*,*O*-acetals such as *O*-glycosides are known to react with various nucleophiles to give cyclic ether products (**2**) via cyclic oxocarbenium ion intermediates **A** (eq 1).[4,5] Similarly, reactions of semicyclic *N*,*O*-acetals (**3**) provide aza-hetereocycle compounds (**4**) via cyclic iminium ion intermediates **B** (eq 2).[6] We have also recently reported that the second type of reactions

(1) *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Kirby, G. W., Volume Ed.; Pergamon: Oxford, 1995; Vol. 4.

(2) Gabbutt, C. D.; Hepworth, J. D. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Kirby, G. W., Volume Ed.; Pergamon: Oxford, 1995; Vol. 4, pp 293−349.

(3) Greene, T. W.; Wuts, P. G. M. In *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: Now York, 1999.

(4) For a recent review on *C*-glycosides, see: Du, Y.; Linhardt, R. J.; Vlahov, I. R. *Tetrahedron* **1998**, *54*, 9913.

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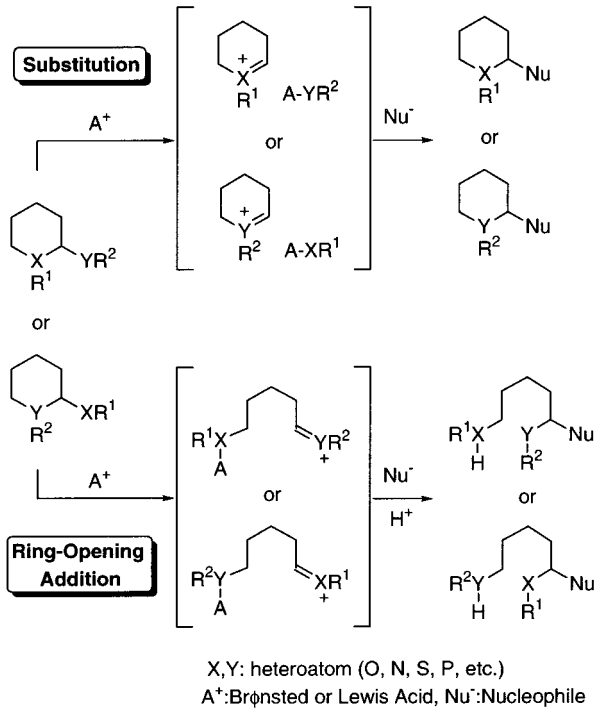
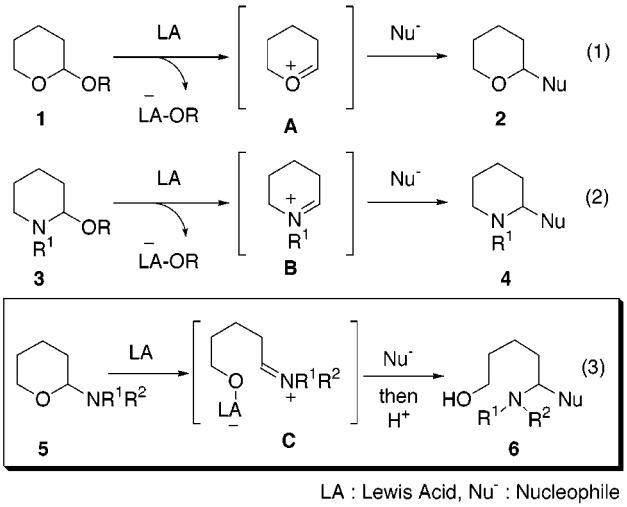
Scheme 1. Reaction Modes of Semicyclic *X,Y*-Acetals



were effectively catalyzed by scandium trifluoromethanesulfonate.[7]

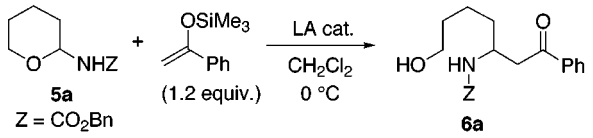


On the other hand, Lewis acid-catalyzed reactions of *other* semicyclic *N,O*-acetals (**5**) (eq 3), where the positions of nitrogen and oxygen of **3** are inverted, have been investigated less, though it has been reported that *N,N*-dialkylaminofuranosides or pyranosides reacted with excess Grignard reagents to give ring-opened alkylation products,[8] and that *N*-galactosyl-*N*-homoallylamine underwent aza-Cope rearrangement promoted by a stoichiometric amount of a Lewis acid.[9] Accordingly, we anticipated that if an oxophilic Lewis acid was employed, ring-opening reaction would proceed via formation of acyclic iminium ion intermediates **C** instead of cyclic intermediates such as **A** to afford ring-opened products (**6**) (eq 3). We have indeed found that this type of reaction was effectively catalyzed by a Lewis acid.[10] Herein, we report the first systematic study on the reactions of semicyclic *N,O*-acetals **5**, including the stereochemical aspects of this reaction as well as the synthetic utility in piperidine alkaloids synthesis.

Results and Discussion

Ring-Opening Reaction of 3-Unfunctionalized Semicyclic *N,O*-Acetals. Benzyl (tetrahydropyran-2-yl)carbamate (**5a**), which was readily prepared via an acid-catalyzed addition of benzyl carbamate to 3,4-dihydro-2*H*-pyran,[11] was first chosen as one of the simplest semicyclic *N,O*-acetals. Reactions of **5a** with the silyl enol ether derived from acetophenone were performed in the presence of a catalytic amount of a Lewis acid (0.1 or 0.2 equiv) at 0 °C in dichloromethane (Table 1). Among various Lewis acids tested (runs 1−5), trimethylsilyl trifluoromethanesulfonate (TMSOTf) was found to be the most effective (runs 1 and 2), and ring-opened alcohol (1,5-amino alcohol) **6a** was obtained in high yields. A combination of chlorotrimethylsilane or tin tetrachloride and silver perchlorate[12] was also effective (runs 6 and 7).

Table 1. Effect of Lewis Acids[a]



run	LA (equiv)	time	yield of **6a**/%
1	TMSOTf (0.2)	20 min	90
2[b]	TMSOTf (0.2)	20 min	94
3	$SnCl_4$ (0.2)	7 h	33
4	$BF_3{\cdot}OEt_2$ (0.2)	11 h	4
5	TfOH (0.1)	20 min	31
6	TMSCl−$AgClO_4$ (0.2 each)	15 imn	48
7	$SnCl_4$−$AgClO_4$ (0.2 each)	15 min	71

[a] Reactions were carried out with **5a** (0.2 mmol), the silyl enol ether (1.2 equiv), and a Lewis acid (0.1 or 0.2 equiv) in dichloromethane at 0 °C, unless otherwise noted. [b] Two equivalents of the silyl enol ether was used.

With TMSOTf as the catalyst, reactions with various nucleophiles were also investigated (Table 2). Allyltrimethylsilane, trimethylsilyl cyanide, and other silyl enol ether and ketene silyl acetal reacted smoothly to afford the desired adducts **6b**−**e** in excellent yields.

(5) Endocyclic cleavage in acid-catalyzed methanolysis and hydrolysis of a pyranoside (a semicyclic *O,O*-acetal) has been reported; (a) Liras, J. L.; Anslyn, E. V. In *Molecular Design and Bioorganic Catalysis*; Wilcox, C. S., Hamilton, A. D., Eds.; NATO SAI Ser.; Kluwer Academic Publishers: Boston, MA, 1996; Vol. 478, pp 1−15. (b) Liras, J. L.; Anslyn, E. V. *J. Am. Chem. Soc.* **1994**, *116*, 2645.

(6) For reviews on the chemistry of *N*-acyliminium ions and related intermediates, see: (a) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 1047−1082. (b) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817.

(7) (a) Okitsu, O.; Suzuki, R.; Kobayashi, S. *Synlett* **2000**, 989. (b) Okitsu, O.; Suzuki, R.; Kobayashi, S. *J. Org. Chem.* **2001**, *66*, 809.

(8) (a) Nagai, M.; Gaudino, J. J.; Wilcox, C. S. *Synthesis* **1992**, 163. (b) Lay, L.; Nicotra, F.; Paganini, A.; Pangrazio, C.; Panza, L. *Tetrahedron Lett.* **1993**, *34*, 4555. (c) Cipolla, L.; Lay, L.; Nicotra, F.; Pangrazio, C.; Panza, L. *Tetrahedron* **1995**, *51*, 4679. (d) Cipolla, L.; La Ferla, B.; Peri, F.; Nicotra, F. *Chem. Commun.* **2000**, 1289. (e) Bortolussi, M.; Cinquin, C.; Bloch, R. *Tetrahedron Lett.* **1996**, *37*, 8729. Ring-opening reactions of nucleosides by Grignard reagents or diisobutylaluminum hydride were also reported, see: (f) Kawana, M. *Chem. Lett.* **1981**, 1541. (g) Hirota, K.; Monguchi, Y.; Kitade, Y.; Sajiki, H. *Tetrahedron* **1997**, *53*, 16683.

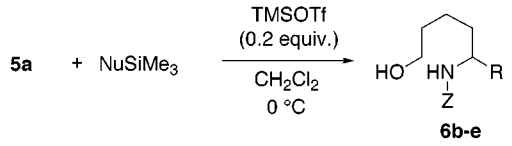
(9) Deloisy. S.; Kunz, H. *Tetrahedron Lett.* **1998**, *39*, 791.

(10) (a) Sugiura, M.; Kobayashi, S. *Org. Lett.* **2001**, *3*, 477. (b) Sugiura, M.; Hagio, H.; Hirabayashi, R.; Kobayashi, S. *Synlett* **2001**, 1225.

(11) Related reactions of benzamides have been reported: Chen, J.; Crooks, P. A.; Hussain, A. *Int. J. Pharm.* **1995**, *123*, 95.

(12) For a leading reference see: Mukaiyama, T.; Takashima, T.; Katsurada, M.; Aizawa, H. *Chem. Lett.* **1991**, 533.

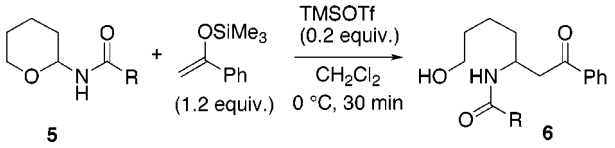
Table 2. Reactions with Various Nucleophiles[a]



$NuSiMe_3$ (equiv)	time/min	product (**6**)	yield/%
$CH_2{=}CHCH_2SiMe_3$ (2)	120	**6b**(R = $CH_2CH{=}CH_2$)	91
Me_3SiCN (2)	15	**6c**(R = CN)	99
$CH_2{=}C(t\text{-Bu})(OSiMe_3)$ (1.5)	20	**6d**(R = CH_2CO*t*-Bu)	89
$Me_2C{=}C(OMe)(OSiMe_3)$ (1.5)	20	**6e**(R = CMe_2CO_2Me)	99

[a] All reactions were carried out with **5a** (0.2 mmol), a nucleophile, and TMSOTf (0.2 equiv) in dichloromethane at 0 °C.

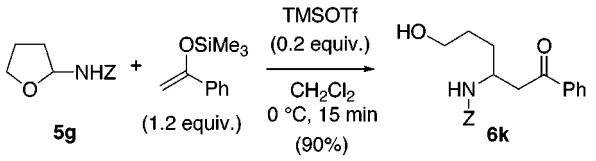
Table 3. Effect of Substituents on the Nitrogen Atom[a]



run no.	substrate (**5**)	product (**6**) (% yield)
1	**5a** (R = OCH_2Ph)	**6a** (90)
2	**5b** (R = O(9-fluorenylmethyl)	**6f** (88)
3	**5c** (R = $OCH_2CH{=}CH_2$)	**6g** (86)
4	**5d** (R = O(2-naphthyl)	**6h** (53)
5	**5e** (R = Ph)	**6i** (82)
6	**5f** (R = CH_2CH_2Ph)	**6j** (74)

[a] Reactions were carried out with **5a**−**f** (0.2 mmol), the silyl enol ether (1.2 equiv), and TMSOTf (0.2 equiv) in dichloromethane at 0 °C.

Scheme 2. The THF System

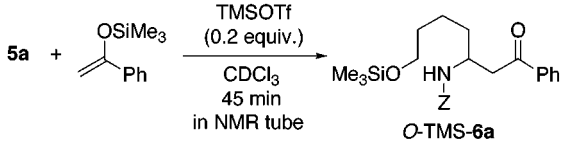


Other substituents on the nitrogen atom of the *N*,*O*-acetal were next examined (Table 3). Synthetically useful deprotectable *N*-alkoxycabonyl groups, 9-fluorenylmethoxycarbonyl (run 2) and allyloxycarbonyl (run 3), are tolerant in this reaction. Moreover, *N*-aroyl and *N*-alkanoyl *N*,*O*-acetals also reacted smoothly (runs 5 and 6). A five-membered analogue **5g** also provided the ring-opened alcohol (1,4-amino alcohol) **6k** in high yield (Scheme 2).

^{1}H NMR analysis of the TMSOTf-catalyzed reaction of **5a** in $CDCl_3$ showed that the initial product formed was *O*-trimethylsilylated ether *O*-TMS-**6a**, which was easily hydrolyzed to the alcohol **6a** by addition of water (Scheme 3).[13] This result strongly suggests a mechanism for this reaction involving coordination of TMSOTf to the ring-oxygen followed by ring-opening activation to form an acyclic iminium ion intermediate (Figure 2). After the nucleophilic addition of a trimethylsilylated nucleophile to the iminum ion intermediate, TMSOTf is regenerated by the attack of the triflate anion onto the trimethylsilyl group of the nucleophile along with the formation of

(13) Although the ^{1}H NMR spectra of *O*-TMS-**6a** and **6a** are quite similar, the chemical shifts for the methylene proton adjacent to the silyloxy group or the hydroxyl group are distinguishable; i.e., 3.55 ppm (t) for *O*-TMS-**6a** and 3.60 ppm (t) for **6a**.

Scheme 3. Obervation of the Initial Product



the initial *O*-silylated product. Note that newly formed TMSOTf after one catalytic cycle is different from the original TMSOTf. In other words, use of a catalytic amount of TMSOTf and a trimethylsilylated nucleophile must be the key to making this reaction catalytic.

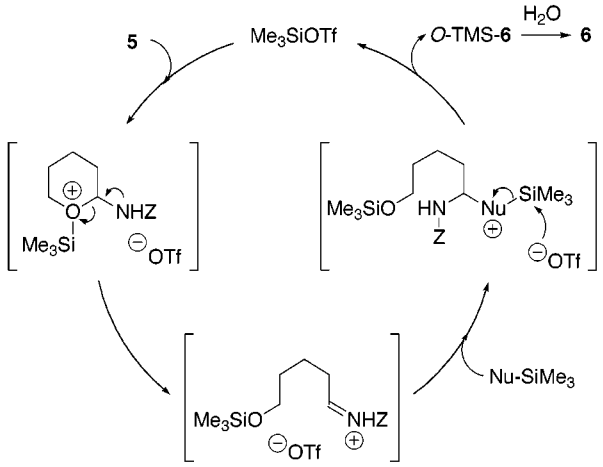


Figure 2. Assumed catalytic cycle.

Reactions of 3-Oxygen-Functionalized Semicyclic *N*,*O*-Acetals. We next focused on elucidation of the stereochemical aspects of this reaction. For this purpose, 3-acetoxy, 3-benzyloxy, and 3-*tert*-butyldiphenylsilyloxy semicyclic *N*,*O*-acetals (**5h, 5i**, and **5j**, respectively) were prepared via TMSOTf-promoted nucleophilic substitution of ester **7** and **9** or ether **8** with benzyl carbamate (Scheme 4). The substituted THP's **7**−**9** were prepared in 2 steps from 3,4-dihydro-2*H*-pyran. Since benzyl carbamate is a relatively weak nucleophile, an addition of 4 Å molecular sieves was essential to prevent the formation of hydrolyzed products. *N*,*O*-Acetals **5h**, **5i**, and **5j** were obtained as diastereomeric mixtures and used without separation. Stereochemical assignments were performed by ^{1}H NMR observation of the coupling constants between H2 and H3 protons ($J_{2,3}$ = ca. 9 Hz for *trans* and ca. 2 Hz for *cis*).

Scheme 4. Preparations of 3-Oxygen Functionalized Semicyclic *N*,*O*-Acetals

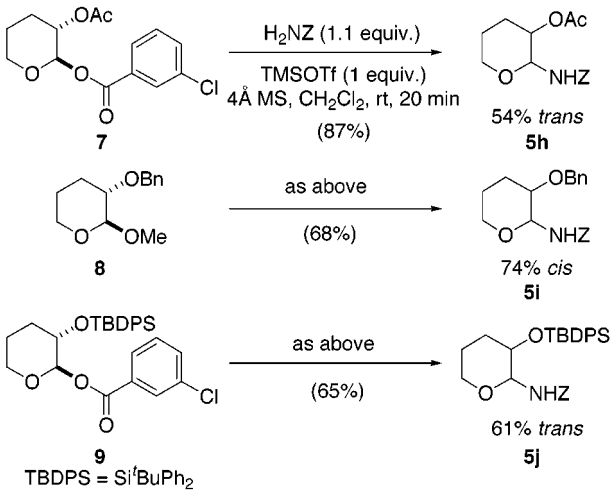
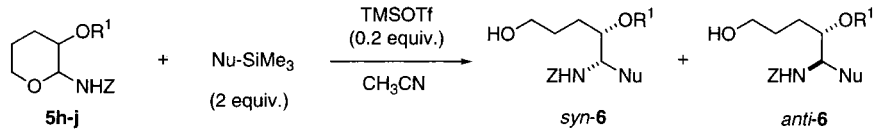
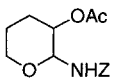
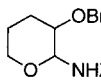
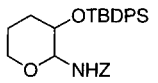
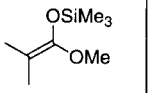
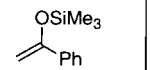
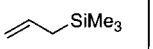


Table 4. Reactions of 3-Oxygen-Functionalized Semicyclic *N,O*-Acetals **5h**−**j** with Various Uncleophiles[a]



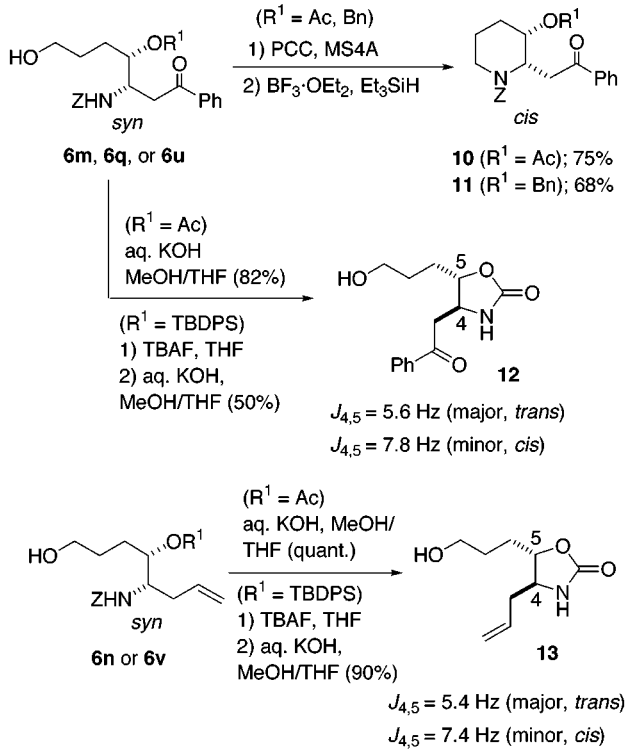
N,O-Acetals / Nu-SiMe$_3$	 **5h** (*cis* / *trans* = 46 : 54)	 **5i** (*cis* / *trans* = 74 : 26)	 **5j** (*cis* / *trans* = 39 : 61)
	**6l** 0 °C, 30 min; 87% *syn* / *anti* = **94 / 6**	**6p** (1) 0 °C, 30 min; 89% syn / anti = **92 / 8** (2) -23 °C, 40 min; 94% *syn* / *anti* = **94 / 6**	**6t** 0 °C, 30 min; 89% *syn* / *anti* = 89 / 11
	**6m** (1) 0 °C, 1 h; 89% *syn* / *anti* = **91 : 9** (2) -23 °C, 2 h; 45% *syn* / *anti* = **93 / 7**	**6q** (1) 0 °C, 1 h; 90% *syn* / *anti* = **91 / 9** (2) -23 °C, 1 h; 67% *syn* / *anti* = **94 / 6**	**6u** 0 °C, 1 h; 88% *syn* / *anti* = 86 / 14
	**6n** 0 °C, 5 h; 56% *syn* / *anti* = 71 / 29	**6r** 0 °C, 5 h; 87% *syn* / *anti* = 84 / 16	**6v** 0 °C, 5 h; 57% *syn* / *anti* = 88 / 12
Me$_3$SiCN	**6o** 0 °C, 5 h; 86% *syn* / *anti* = 62 / 38	**6s** 0 °C, 1 h; 88% *syn* / *anti* = 84 / 16	**6w** 0 °C, 5 h; 93% *syn* / *anti* = **92 / 8**

[a] Reactions were carried out with **5h**−**j** (ca. 0.2 mmol), a nucleophile (2 equiv), and TMSOTf (0.2 equiv) in acetonitrile at the indicated temperature.

We first tested the reaction of **5h** with the silyl enol ether derived from acetophenone in dichloromethane. Unlike the 3-unsubstituted *N,O*-acetals, **5h** required a stoichiometric amount of TMSOTf in dichloromethane for complete consumption to give a 58:42 diastereomeric mixture of product **6m** in 60% yield. We presumed that a polar solvent would stabilize the iminium ion intermediate to promote the reaction. Among solvents thus tested, acetonitrile and nitromethane were found to be effective, promoting the reaction *catalytically* to afford the ring-opened product in 76% and 77% yields, respectively. In terms of stereoselectivity, acetonitrile showed higher *syn*-selectivity (91% *syn*) than nitromethane (82% *syn*). With acetonitrile as the optimal solvent, we then investigated the reactions of **5h**, **5i**, and **5j** with various nucleophiles (Table 4). With a silyl enol ether, a ketene silyl acetal, allyltrimethylsilane, and trimethylsilyl cyanide, ring-opened products **6l**−**w** were obtained in good to high yields with moderate to high *syn*-diastereoselectivity. Furthermore, it was found that 3-acetoxy and 3-benzyloxy *N,O*-acetals **5h** and **5i** showed a tendency for the larger nucleophile to provide higher *syn*-selectivity, while 3-*tert*-butyldiphenylsilyloxy *N,O*-acetals **5j** showed the opposite tendency.

The relative configurations of the major diastereomers of **6m** (R^1 = Ac) and **6q** (R^1 = Bn) were determined respectively as *syn* after converting to *cis*-piperidines **10** (R^1 = Ac) or **11** (R^1 = Bn)[7] via PCC-oxidation and reductive cyclization (Scheme 5). The *syn*-configuration of **6m** (R^1 = Ac) was further confirmed after transformation to oxazolidin-2-one **12** upon base treatment. The ^{1}H NMR coupling constant between the H4 and H5 protons of this type of oxazolidin-2-one is known to be *cis* > *trans*.[14] Thus, the major diastereomer of **12** derived from **6m** was found to be *trans*, which is consistent with the formation of *cis*-**10** from **6m**. Similarly, the major diastereomer of **6u** (R^1 = TBDPS) was determined to be *syn* by formation of *trans*-**12**. Moreover, the major isomers of allylation prodducts of **6n** (R^1 = Ac) and of **6v** (R^1 = TBDPS) were also assigned to be *syn* via a similar transformation to oxazolidone **13**, while the major isomer of **6r** (R^1 = Bn) was determined to be *syn* by the synthesis of isofebrifugine (vide infra). The configuration of other products was tentatively assigned on the basis of analogy.

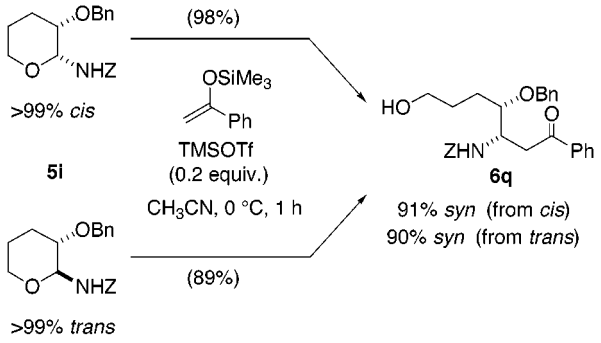
Scheme 5. Determination of Relative Configurations



Stereochemical Courses. Before discussing the origin of the stereochemical outcomes, we had to answer the question whether

(14) For example, see: (a) Dufour, M.-N.; Jouin, R.; Poncet, J.; Pantaloni, A.; Castro, B. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1895. (b) Kano, S.; Yokomatsu, T.; Iwasawa, H.; Shibuya, S. *Tetrahedron Lett.* **1987**, *28*, 6331. (c) Kiyooka, S.-I.; Nakano, M.; Shiota, F.; Fujiyama, R. *J. Org. Chem.* **1989**, *54*, 5409.

Scheme 6. Control Experiments



the diastereomeric ratios of *N*,*O*-acetals reflected those of the ring-opened products. To confirm this point, each diastereomer of the substrate **5i** was once separated by preparative TLC on silica gel and independently subjected to the reaction conditions with acetophenone−silyl enol ether and TMSOTf (Scheme 6). As a result, almost the same *syn*-stereoselectivities were obtained from both the *trans* and *cis* isomers. This result is consistent with the mechanism via formation of an acyclic iminium intermediate, where the chiral C2 carbon center of the *N*,*O*-acetal converted to a prochiral center (see Figure 2).

Furthermore, when each diasteromer of **5i** was independently treated with TMSOTf in the absence of a nucleophile at 0 °C for 10 min, epimerization to a *trans*/*cis* = 60/40 diastereomeric mixture was observed from both the *trans* and *cis* isomers. It is suggested that the epimerization between the *trans* and *cis* isomers occurs via a transient acyclic iminium ion intermediate which also can be the reactive intermediate of the ring-opening reaction (Figure 3).[15]

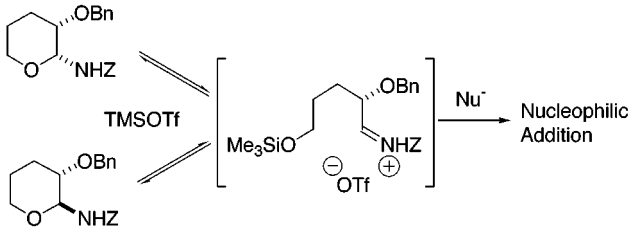


Figure 3. Epimerization of the semicyclic *N*,*O*-acetal.

Considering the above mechanistic studies, the diastereofacial selection of the acyclic iminum intermediates by a nucleophile is the key to explaining the stereochemical outcomes. We assumed four transition state models **TS$_1$**−**TS$_4$** depending on the protecting groups (Figure 4). For the 3-acyloxy and 3-alkoxy systems, a chelation model **TS$_1$** possessing a hydrogen bond between the proton bound to the iminium nitrogen and the 3-oxygen functional group is likely, and then a nucleophile could attack from the less hindered side (from the side of hydrogen) to give the *syn*-product. In **TS$_1$**, the bulkier nucleophile could cause larger steric repulsion against the alkyl side chain and, therefore, could show higher selectivity. This tendency was actually observed in the 3-acetoxy and 3-benzyloxy systems. In addition, for the 3-acyloxy system, five-membered dioxocarbenium ion intermediate **TS$_2$** might also be involved in neighboring group participation of the 3-acyloxy group. This dioxocarbenium ion would have the *trans*-configuration for steric reasons, and then an S_N2-type attack of a nucleophile would provide the *syn*-product. However, in **TS$_2$**, it is difficult to explain the relationship between the steric bulkiness of the

(15) (a) Lockhoff, O.; Stadler, P. *Carbohydr. Res.* **1998**, *314*, 13. (b) Cheng, X.; Hii, K. K. *Tetrahedron Lett.* **2001**, *57*, 5445.

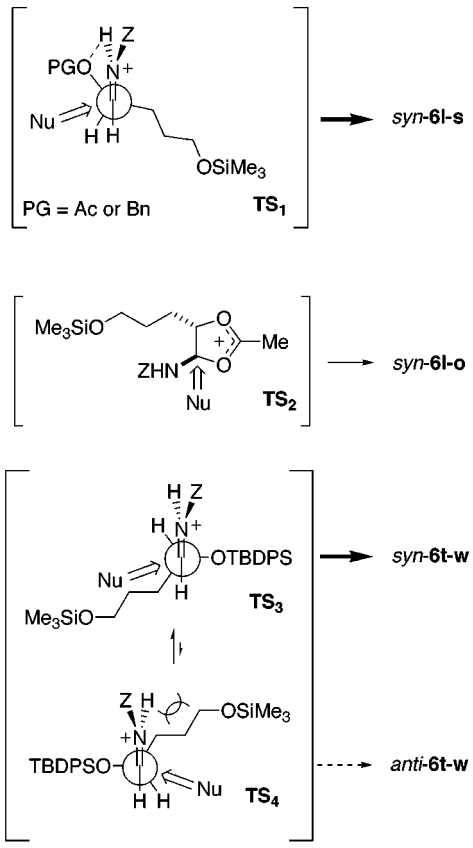


Figure 4. Assumed transition state models.

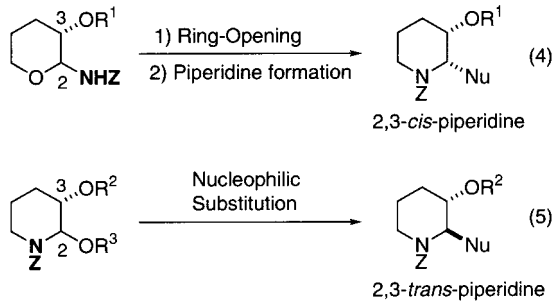
nucleophile and the stereoselectivity. On the other hand, in a bulky 3-silyloxy system, the smaller nucleophile tends to provide the higher selectivity. The steric bulkiness of the 3-silyloxy group might prevent the hydrogen bonding and, therefore, two competitive nonchelation transition states, **TS$_3$** and **TS$_4$**, where the 3-silyloxy group is perpendicular to the plane of the C=N double bond of the iminum ion intermediates for stereoelectronic reasons, could be involved in this case. Since the conformation of **TS$_4$** has a larger allylic strain between the alkyl side chain and the proton bound to the iminium nitrogen, **TS$_3$** could be favored and then the nucleophile could attack from the opposite side of the silyloxy group to give the *syn*-product selectively.[16] It is reasonable that, in **TS$_3$**, the smaller nucleophile has the advantage of overcoming the steric repulsion against the alkyl side chain to show higher selectivity.

Synthetic Application. From the synthetic point of view, the present reaction provides a powerful tool for the preparation of a wide variety of 1,4- and 1,5-amino alcohols. In addition, the reaction is applied to the stereoselective synthesis of the 2,3-*cis*-substituted aza-hetereocycles such as piperidines[17] (eq 4). This outcome is complementary to the Lewis acid-catalyzed reactions of 2,3-diacyloxy or 2-alkoxy-3-acyloxy piperidine derivatives with nucleophiles which provide preferably 2,3-*trans*-substituted piperidines (eq 5).[7] To exploit this stereocontrol, our methodology has successfully been applied to diastereoselective syntheses of piperidine alkaloids, i.e., an antimalarial agent, (+)-isofebrifugine and (±)-sedacryptine.

(+)-Isofebrifugine. (+)-Febrifugine and (+)-isofebrifugine, isolated first from the Chinese plant *Dichroafebrifuga*[18] and later

(16) Nagai et al. suggested a similar transition state model for the α-alkoxy-*N*,*N*-dibenzyliminium ion system (see ref 8a).

(17) For a recent review on stereoselective synthesis of piperidines, see: Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781.



from the common hydrangea,[19] have attracted considerable attention due to their potentially powerful antimalarial activity.[20] Among several synthetic efforts,[21] we have achieved the catalytic asymmetric synthesis of these compounds and revised their absolute configurations as shown in Figure 5.[21b,c] In our continuous interest in developing synthetic methodologies of nitrogen-containing compounds such as febrifugine analogues, we first undertook the synthesis of isofebrifugine utilizing the methodology developed herein (Scheme 7). The optically pure 3-benzyloxy *N,O*-acetal (3*S*)-**5i** was prepared from D-arabinose in seven steps.[22] The reaction of (3*S*)-**5i** with the quinazolinone-containing silyl enol ether[21a] was carried out in the presence of 2.5 equiv of TMSOTf. The slight excess amount of the Lewis acid was required due to the basicity of the quinazolinone moiety. Without epimerization, the desired *syn*-adduct **6x** was obtained in good yield with satisfactory diastereoselectivity. The ring formation of **6x** via an oxidation/reductive cyclization sequense provided piperidine **15**. Finally, deprotection of the *N*-benzyloxy carbonyl and benzyl ether groups in one pot under refluxing 6 N aqueous HCl furnished (+)-isofebrifugine in good yield (11 steps from D-arabinose).

The stereoselective synthesis of (+)-isofebrifugine was also accomplished via ring-opening allylation (Scheme 8). The TMSOTf-catalyzed reaction of (3*S*)-**5i** with allyltrimethylsilane at −20 °C afforded the optically active ring-opened product (*S*)-**6r** in good yield. Epoxidation of (*S*)-**6r** followed by an introduction of 4-hydroxyquinazoline gave diol **16** as a diastereomeric mixture. Oxidation of both hydroxyl groups of **16** with Dess−Martin periodinane and a sequential piperidine ring formation by triethylsilane reduction gave *cis*-piperidine **15** (vide supra). Compared with the former synthesis, the key ring-opening allylation of this route requires only a catalytic amount of the Lewis acid. Moreover, the later introduction of the quinazolinone part may provide a variation of this step in the synthesis of febrifugine analogues.

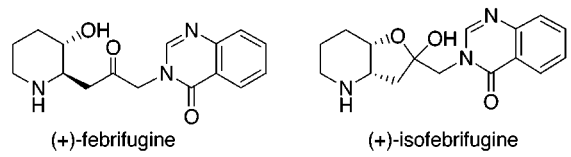
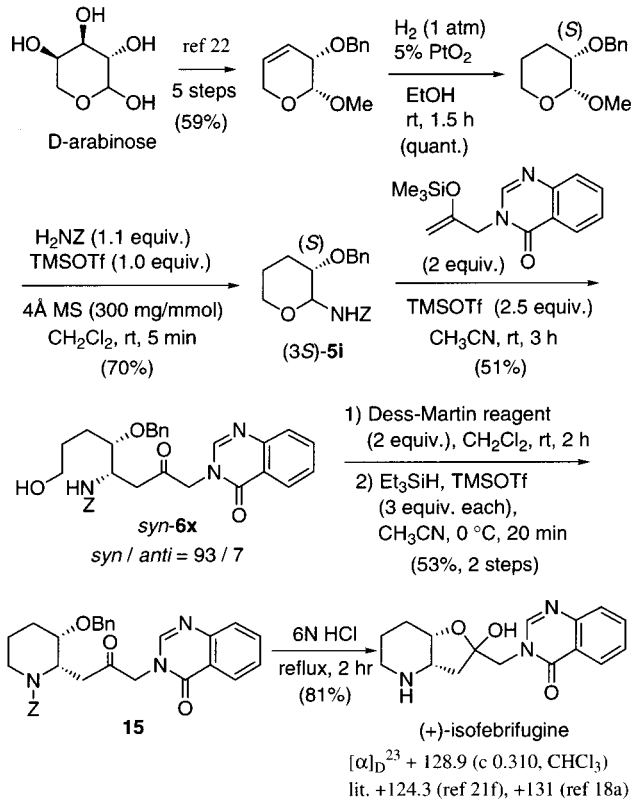
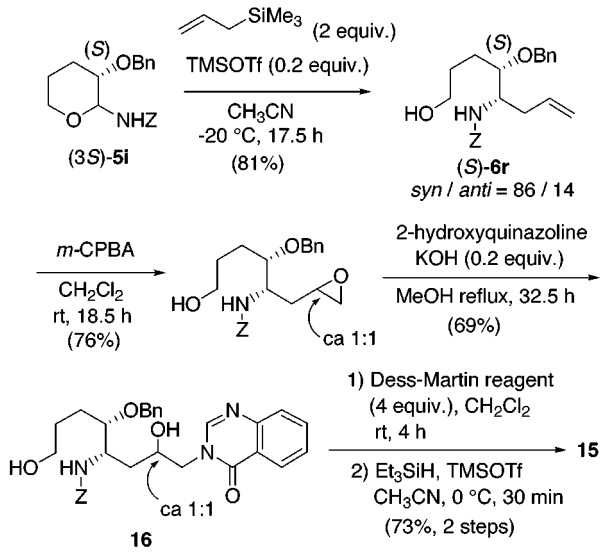


Figure 5. (+)-Febrifugine and (+)-isofebrifugine.

Scheme 7. Synthesis of (+)-Isofebrifugine (1)



Scheme 8. Synthesis of (+)-Isofebrifugine (2)



(±)-Sedacryptine. Sedacryptine was isolated from *Sedum acre* as a minor alkaloid along with sedinine.[23] Although three total syntheses including two diastereoselective asymmetric syntheses have been reported so far,[24] these syntheses need an

(18) (a) Koepfly, J. B.; Mead, J. F.; Brockman, J. A., Jr. *J. Am. Chem. Soc.* **1947**, *69*, 1048. (b) Koepfly, J. B.; Mead, J. F.; Brockman, J. A., Jr. *J. Am. Chem. Soc.* **1947**, *69*, 1837. (c) Koepfly, J. B.; Mead, J. F.; Brockman, J. A., Jr. *J. Am. Chem. Soc.* **1948**, *70*, 1048.

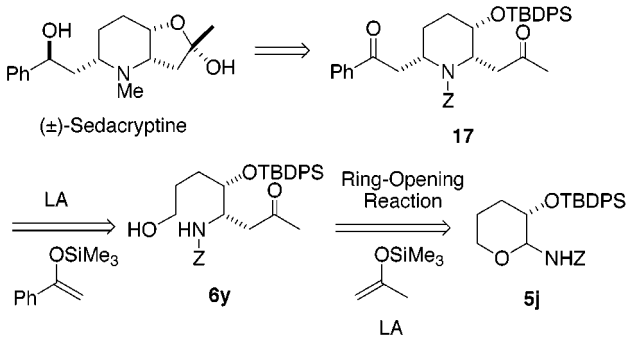
(19) (a) Ablondi, F.; Gordon, S.; Morton, J., Jr., II; Williams, J. H. *J. Org. Chem.* **1952**, *17*, 14. (b) Kato, M.; Inada, M.; Itahana, H.; Ohara, E.; Nakamura, K.; Uesato, S.; Inouye, H.; Fujita, T. *Shoyakugaku Zasshi* **1990**, *44*, 288.

(20) (a) Jang, C. S.; Fu, F. Y.; Wang, C. Y.; Huang, K. C.; Lu, G.; Thou, T. C. *Science* **1946**, *103*, 59. (b) Chou, T.-Q.; Fu, F. Y.; Kao, Y. S. *J. Am. Chem. Soc.* **1948**, *70*, 1765. (c) Frederick, A. K., Jr.; Spencer, C. F.; Folkers, K. *J. Am. Chem. Soc.* **1948**, *70*, 2091.

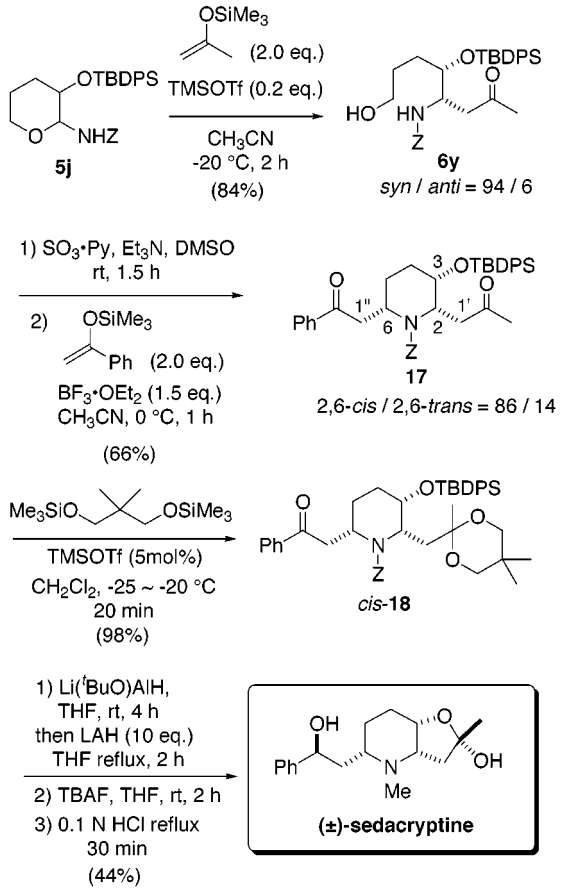
(21) For recent syntheses of isofebrifugine and/or febrifugine, see: (a) Burgess, L. E.; Gross, E. K. M.; Jurka, J. *Tetrahedron Lett.* **1996**, *37*, 3255. (b) Kobayashi, S.; Ueno, M.; Suzuki, R.; Ishitani, H. *Tetrahedron Lett.* **1999**, *40*, 2175. (c) Kobayashi, S.; Ueno, M.; Suzuki, R.; Ishitani, H.; Kim, H.-S.; Wataya, Y. *J. Org. Chem.* **1999**, *64*, 6833. (d) Takeuchi, Y.; Abe, H.; Harayama, T. *Chem. Pharm. Bull.* **1999**, *47*, 905. (e) Takeuchi, Y.; Hattori, M.; Abe, H.; Harayama, T. *Synthesis* **1999**, 1814. (f) Takeuchi, Y.; Azuma, K.; Takakura, K.; Abe, H.; Harayama, T. *Chem. Commun.* **2000**, 1643. (g) Taniguchi, T.; Ogasawara, K. *Org. Lett.* **2000**, *2*, 3193. (h) Ooi, H.; Urushibara, A.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Org. Lett.* **2001**, *3*, 953.

(22) (a) Tanaka, D.; Yoshino, T.; Kouno, I.; Miyashita, M.; Irie, H. *Tetrahedron* **1993**, 49, 10253. (b) Charette, A. B.; Mellon, C.; Motamedi, M. *Tetrahedron Lett.* **1995**, *36*, 8561.

Scheme 9. Retrosynthetic Analysis of Sedacryptine



Scheme 10. Diastereoselective Synthesis of (±)-Sedacryptine



inversion of the stereogenic center or include key steps with low diastereoselectivity. As shown in our retrosynthetic analysis (Scheme 9), we anticipated that the ring-opening reaction of **5j** with the silyl enol ether derived from acetone followed by oxidation/Lewis acid-catalyzed nucleophilic substitution of the ring-opened product **6y** would construct the sedacryptine skeleton **17** stereoselectively.

The synthesis of sedacryptine is summarized in Scheme 10. The ring-opening reaction of **5j** with acetone−silyl enol ether provided adduct **6y** in high yield with high *syn*-diastereoselectivity as expected. Subsequent SO_3•Py-DMSO oxidation of **6y** and BF_3•OEt_2 promoted nucleophilic substitution with acetophenone−silyl enol ether to give piperidine **17** with good 2,6-*cis*-

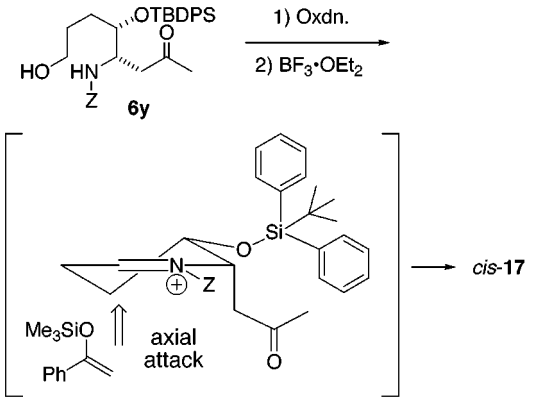


Figure 6. Assumed transition state for the formation of 2,6-*cis*-piperidine **17**.

selectivity. The 2,6-*cis*-isomer could be separated by silica gel chromatography. The 2,6-*cis*-configuration was confirmed by the ^{1}H NMR measurement of NOE enhancement between one of the methylene protons at C1′ and one of the methylene protons at C1″ (in DMSO-d_6 at 80 °C, 5.5% enhancement of the H1′ proton on the irradiation at H1″ and 4.0% enhancement of the H1″ proton on the irradiation at H1′ were observed). On the other hand, no NOE enhancement between H2 and H6 protons was observed, implying the piperidine has a rather rigid conformation with the diaxial substituents at C2 and C6 and the equatorial substituent at C3. A nucleophilc attack to a cyclic iminium ion intermediate from the axial direction has been proposed to be favored due to the stereoelectronic effect.[25] Moreover, the C2 or C6 substituent in *N*-acyl piperidine is known to locate in a pseudoaxial position because of steric repulsion between the C2 or C6 substituent and the planar *N*-acyl group.[25] In our case, the cyclic iminium ion intermediate would have a pseudoaxial 2-oxopropane group at C2 and a pseudoequatorial *tert*-butyldiphenylsilyloxy group at C3 as depicted in Figure 6 and, therefore, the nucleolphile would attack from the axial direction to give 2,6-*cis*-piperidine **17** selectively. With the 2,3,6-all-*cis*-isomer **17** in hand, further transformations to sedacryptine were performed. First, a chemoselective acetal protection of the methyl ketone moiety[26] afforded mono-acetal **18**. Use of the neopentyl glycol derivative was a key to decreasing polarity of the acetal product, since the separation of the corresponding ethylene glycol derived acetal from the unreacted starting ketone **17** was difficult. The stereoselective reduction of the phenyl ketone part of **18** with Li(*tert*-BuO)$_3$AlH[27] followed by LAH reduction of the *N*-benzyloxycarbonyl group to the *N*-methyl group, deprotection of the *tert*-butyldiphenylsilyl group by TBAF, and acid hydrolysis of the acetal protection furnished almost pure (±)-sedacriptine, which was further purified by alumina TLC. All NMR spectroscopic data for the synthetic sedacryptine were completely consistent with those of the litereature.[28] While we have shown efficient racemic synthesis of sedacryptine, enantioselective synthesis of

(23) Hootelé, C.; Colau, B.; Halin, F. *Tetrahedron Lett.* **1980**, *21*, 5061.

(24) (a) Natsume, M.; Ogawa, M. *Heterocycles* **1983**, *20*, 601 (racemate). (b) Akiyama, E.; Hirama, M. *Synthesis* **1996**, 100 (optically active). (c) Plehiers, M.; Hootelé, C. *Can. J. Chem.* **1996**, *74*, 2444 (optically active).

(25) For example, see: (a) Palasz, P. D.; Utley, J. H. P. *J. Chem. Soc., Perkin Trans. 2* **1984**, 807. (b) Irie, K.; Tanaka, T.; Saito, S. *J. Chem. Soc., Chem. Commun.* **1985**, 633. (c) Comins, D. L.; Foley, M. A. *Tetrahedron Lett.* **1988**, *29*, 6711. (d) Driessens, F.; Hootelé, C. *Can. J. Chem.* **1991**, *69*, 211. (e) Herdeis, C.; Held, W. A.; Kirfel, A. *Libigs. Ann. Chem.* **1994**, 1117.

(26) (a) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357. (b) Hwu, J. R.; Wetzel, J. M. *J. Org. Chem.* **1985**, *50*, 3946.

(27) The stereoselective reduction of a phenyl ketone moiety by this reagent in a similar system has been reported: Herdeis, C.; Held, W. A.; Kirfel, A.; Schwabenländer, F. *Liebigs. Ann.* **1995**, 1295.

(28) (a) See ref 24c for ^{1}H NMR. (b) For ^{13}C NMR: Colau, B.; Hootelé, C.; Tourwe, D. *Tetrahedron* **1984**, *40*, 2171 .

(+)- or (−)-sedacryptine would be readily performed starting from L- or D-arabinose according to the transformation shown in Schemes 7 and 10.

Conclusion

In summary, we have revealed that ring-opening reactions of various types of semicyclic *N*,*O*-acetals **5** with silicon-based nucleophiles such as silyl enol ethers, ketene silyl acetals, allylic silanes, and trimethylsilyl cyanide were effectively catalyzed by a Lewis acid (TMSOTf) to afford acyclic 1,4- and 1,5-amino alcohols **6** with high diastereoselectivities. The stereochemical outcomes were mechanistically rationalized. This is the first systematic study of the reactions of the semicyclic *N*,*O*-acetals **5** under Lewis acidic conditions, showing quite different reaction modes and stereoselectivity from those in the reactions of other semicyclic acetals **1** and **3**. Furthermore, the synthetic utility of this methodology has been demonstrated in the stereoselective syntheses of (+)-isofebrifugine and (±)-sedacryptine.

Experimental Section

General Procedure for the Preparation of 3-Unsubstituted Semicyclic *N,O*-Acetals (5a−f). To a solution of a carbamate or an amide (1−3 mmol) and 3,4-dihydro-2*H*-pyran (1−1.2 equiv) in dichloromethane (1.0 M) was added *p*-toluenesulfonic acid monohydrate (1 mol %) at room temperature. The reaction mixture was stirred for 1−3 h. The mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by recrystallization and/or silica gel chromatography to give a 3-unsubstituted semicyclic *N*,*O*-acetal **5a**−**f**. (Benzyl carbamate was purchased from Tokyo Chemical Industry Co., Ltd. and was used without purification. 9*H*-Fluoren-9-ylmethyl carbamate, allyl carbamate, and naphthalen-2-yl carbamate were prepared according to the literature procedure.[29])

General Procedure for the Preparation of 3-Oxygen-Functionalized Semicyclic *N,O*-Acetals (5h−j). To a suspension of **7**, **8**, or **9** (1 equiv), benzyl carbamate (1.1 equiv), and 4 Å molecular sieves powder (activated by using a domestic microwave oven, 300 mg/1 mmol of **7**, **8**, or **9**) in dichloromethane (0.2 M) was added dropwise TMSOTf (1 equiv) at room temperature. After being stirred for 10−30 min, the mixture was quenched with saturated aqueous $NaHCO_3$, diluted with ethyl acetate, and filtered through a Celite pad. After separation of the organic layer, the aqueous layer was extracted with ethyl acetate (2×) and washed with brine. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel chromatography to give a 3-oxygen-fuctionalized semicyclic *N*,*O*-acetal **5h**−**j**.

General Procedure for TMSOTf-Catalyzed Ring-Opening Reactions of Semicyclic *N,O*-Acetals. To a solution of semicyclic *N*,*O*-acetal **5** (1 equiv.) and a nucleophile (a silyl enol ether, a ketene silyl acetal, an allylic silane, or trimethylsilyl cyanide, 1.2−2 equiv) in dichloromethane or acetonitrile (0.1 M) was added dropwise trimethylsilyl trifluoromethanesulfonate (TMSOTf, 0.2 equiv) at 0 °C or room temperature. After being stirred at that temperature for the indicated time, the mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate (2×). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by preparative TLC to give a ring-opened product **6**.

NMR Experiment: **TMSOTf-Catalyzed Reaction of 5a with 1-Phenyl-1-(trimethylsilyloxy)ethylene in $CDCl_3$.** In a dry NMR tube with a septum, **5a** (14.3 mg, 0.06 mmol) was dissolved in $CDCl_3$ (dried over 4 Å molecular sieves pellet, 0.6 mL). 1-Phenyl-1-(trimethylsilyloxy)ethylene (12 mg, 1.0 equiv) and TMSOTf (2.2 μL, 0.2 equiv) were successively introduced to the solution. Then the reaction had been monitored by a NMR spectrometer. The gradual consumption of **5a** and the formation of ***O*-TMS-6a** were observed and the reaction was almost completed after 45 min. Addition of water (5 μL) to this mixture showed an immediate formation of alcohol **6a**.

Acknowledgment. This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Full experimental procedure and compound characterizations (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA0170448

(29) Loev, B.; Kormendy, M. F.; Goodman, M. M. *Org. Synth. Coll. Vol. 5* **1973**, 162.