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Investigations of α-Siloxy−Epoxide Ring Expansions Forming 1-Azaspirocyclic Ketones

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The construction of 1-azaspirocyclic cycloalkanones using a siloxy−epoxide semipinacol ring expansion process was examined. Functionalized 1-azaspiro[5.5]undecan-7-ones (1-azaspirocyclic cyclohexanones) proceeded in high chemical yields with complete diastereoselectivity using titanium tetrachloride as the Lewis acid promoter. The formation of functionalized 6-azaspiro[5.4]-decan-1-ones (1-azaspirocyclic cyclopentanones) proceeded in high chemical yield with little diastereoselectivity. Modification of reaction parameters such as the Lewis acid promoter or the nature of the silyl ether allowed for the preferential formation of either ("anti" or "syn" 1,2 alkyl shift) diastereomeric product. An explanation for the different reactivity profiles between the cyclobutanol silyl ethers and cyclopentanol silyl ethers is provided.

Introduction

The stereocontrolled formation of carbon atoms with four different substituents (quaternary carbons) continues to be a significant problem in synthetic organic chemistry.[1] Stereoselective 1,2-rearrangement reactions of epoxides and their derivatives have proven to be a useful solution for this difficult challenge. Several research groups have contributed to the understanding of these processes so that a number of procedures for these rearrangements, including the Tsuchihashi−Suzuki,[2] the Yamamoto,[3] or the Jung[4] variants, are available to the synthetic organic chemist.[5−7] A useful representative example of the power of this method is shown in eq 1. Treatment of epoxide **1** with 1.1 equiv. of titanium tetrachloride leads to the smooth formation of substituted cyclohexanone **2** in 89% yield.[2a] A noteworthy feature of this process is the facile formation of the spiro-ring junction with complete diastereocontrol, which is pre-

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(7) α-Hydroxy *N*-*p*-toluenesulfonylaziridine rearrangement reactions have also been performed: (a) Wang, B. M.; Song, Z. L.; Fan, C. A.; Tu, Y. Q.; Shi, Y. *Org. Lett.* **2002**, *4*, 363. (b) Song, Z. L.; Wang, B. M.; Tu, Y. Q.; Fan, C. A.; Zhang, S. Y. *Org. Lett.* **2003**, *5*, 2319.

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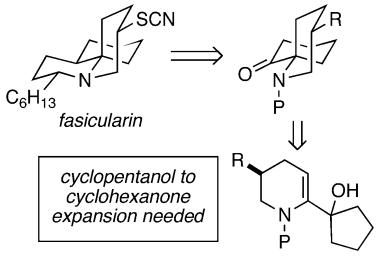
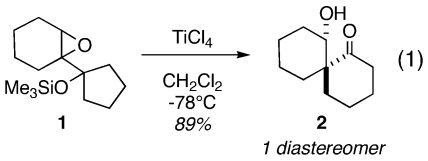
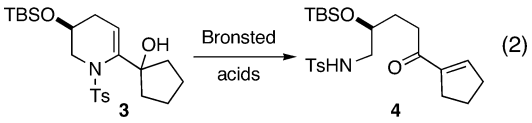
SCHEME 1. Analysis of Fasicularin



sumably dictated by the stereochemistry of the epoxide.[8] As the facility to construct epoxides of one stereochemical identity has increased substantially over the past twenty-five years, the potential power of this protocol is significant.[9] The incorporation of semipinacol reactions in total synthesis ventures is a testament to their growing significance in the field.[10]

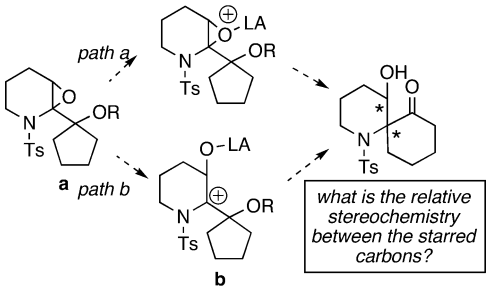


Our interest in siloxy−epoxide rearrangement processes stemmed from our investigations of semipinacol reaction-based approaches to 1-azaspirocycle ring systems present in alkaloids.[11] Specifically, a proposed route to fasicularin required a ring expansion of a cyclopentanol to a cyclohexanone (Scheme 1).[12] Unfortunately, the reaction of cyclopentanol **3** with Bronsted acids did not provide the desired ring expansion product but rather enone **4** (eq 2).[13] Through NMR studies, it was established that **4** is produced via initial acid promoted dehydration of the tertiary alcohol followed by hydrolytic ring opening of the enesulfonamide moiety.

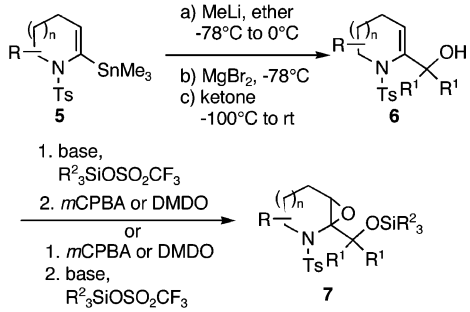


Given this setback, we considered a siloxy−epoxide variant of this proposed semipinacol reaction. It had been demonstrated that an oxacarbenium ion derived from a

SCHEME 2



SCHEME 3. General Synthesis of Substrates



dihydropyran with several inductively withdrawing substituents was sufficiently reactive to induce expansion of a cyclopentanol to a cyclohexanone.[14] In addition, as exemplified in eq 1, six-membered (and larger) rings are easily produced using siloxy−epoxide rearrangement reactions. Thus, it was anticipated that the epoxide functionality could enable the desired reaction in two respects. The inductive withdrawing oxygen substituent resulting from the epoxide was anticipated to render the intermediate more electrophilic, and thus more reactive to 1,2-migration reactions. It was also hoped that the hydroxyl (or siloxyl) functionality in the starting material would be less prone to acid promoted dehydration, as it would no longer be tertiary and allylic as in **3**.

We were also aware of some points of concern (Scheme 2). The first was whether compounds such as **a** could be made and isolated. A second equally important matter was the predictability of the stereochemical outcome of the reaction. Within carbocyclic systems at least, it appeared that the stereochemistry of the epoxide function effectively controlled this process (anti migration of the alkyl group to the epoxide). In the proposed heterocyclic system, the result was less obvious. Would a Lewis acid induce a synchronous epoxide opening−1,2-alkyl migration reaction (path a) or would an azacarbenium ion **b** be a significant intermediate (path b). In short, what would be the relative stereochemistry between the alcohol function and the spiro ring junction in the products? This report presents our investigations into this matter.

Results and Discussion

Synthesis of Substrates. A general outline of the synthetic route used to build the α-epoxy silyl ethers used in this study is shown in Scheme 3. Functionalized vinylstannanes of general structure **5** were reacted with ketones to produce allylic alcohols of type **6**.[13,15] The

(8) A review on the formation of spirocyclic ring systems: Sannigrahi, M. *Tetrahedron* **1999**, *55*, 9007.

(9) (a) Katsuki, T.; Martin, V. S. *Org. React. (N. Y.)* **1996**, *48*, 1. (b) Pfenninger, A. *Synthesis* **1986**, 89. (c) Larrow, J. F., Jacobsen, E. N. *Org. Synth.* **1998**, *75*, 1. (d) Schaus, S. E,; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307. (e) Frohn, M.; Shi, Y. *Synthesis* **2000** 1979.

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(12) (a) Fenster, M. D. B.; Dake, G. R. *Org. Lett.* **2003**, *5*, 4314. For other syntheses of fasicularin, see: (b) Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2000**, *122*, 4583. (c) Maeng, J.-H.; Funk, R. L. *Org. Lett.* **2002**, *4*, 331.

(13) Dake, G. R.; Fenster, M. D. B.; Hurley, P. B.; Patrick, B. O. *J. Org. Chem.*, preceding paper in this issue.

(14) Paquette, L. A.; Kinney, M. A.; Dullweber, U. *J. Org. Chem.* **1997**, *62*, 1713.

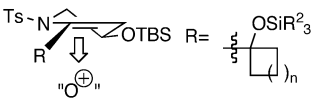
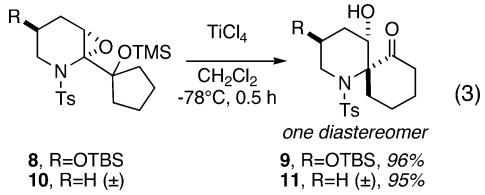


FIGURE 1.

optimal ordering and method of subsequent transformations—the silylation of the tertiary alcohol and the epoxidation[16] of the enesulfonamide—to produce α-epoxy silyl ethers of general structure 7 were best defined through experimentation for each particular compound. The synthetic details for each of the substrates described in the article are given in the Supporting Information.

Expansions of Cyclopentanol Silyl Ethers. The first α-siloxy epoxide that we examined was derived from **3**, in part because of our keen interest in a synthetic route toward fasicularin. Interestingly, the reaction of **3** (or its corresponding trimethylsilyl ether) with dimethyldioxirane (DMDO) produced a single epoxide. The diastereoselectivity of this process can be rationalized by the "axial" addition of the electrophilic oxygen on the most stable half-chair conformer of **3** (Figure 1).

We were delighted to find that treatment of α-siloxy epoxide **8** with 1.1 equiv of titanium tetrachloride in dichloromethane at −78 °C for 30 min furnished a new compound **9** in 96% isolated yield (eq 3). The trimethylsilyl ether in **8** was required for good efficiency as the ring expansion reaction of the analogous 3° alcohol produced **9** in only 30% yield.[17] Signals in the IR and ^{13}C NMR spectra ($\nu = 1718$ cm^{-1}; ^{13}C NMR: δ 209.9 ppm) of **9** clearly established the presence of a cyclohexanone function. The structural connectivity and relative stereochemistry of **9** was ultimately established using X-ray analysis.

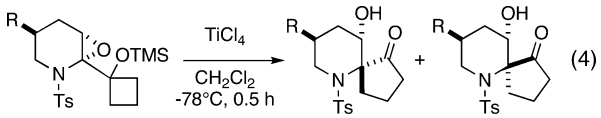


8, R=OTBS
10, R=H (±)

9, R=OTBS, *96%*
11, R=H (±), *95%*

That **9** was formed as a single diastereomer suggested that the titanium(IV) induced epoxide opening and 1,2-alkyl migration occurred as a synchronous step. The stereochemistry of the spiro center appeared to be dictated by the epoxide. To test if the *tert*-butyldimethylsiloxy function in **9** conformationally anchored this substrate as it reacted through an azacarbenium ion intermediate, this reaction sequence was repeated on **10**. This compound lacks the *tert*-butyldimethylsiloxy function and so might be expected to form the spiro compound with lower diastereoselectivity if an azacarbenium ion was an important intermediate. Epoxide **10**, when subjected to the identical reaction conditions as those used for **8**, similarly generated azaspirocyclic cyclohexanone **11** in 95% yield as one detectable diastereomer. The connectivity and relative stereochemistry of **11** was established using the X-ray crystallography of its *p*-nitrobenzoate derivative.

Expansions of Cyclobutanol Silyl Ethers. In attempting to define the scope of the method, ring expansions of **12** and **13** were attempted. Cyclobutane rings are known to undergo ring expansions,[18] and thus compounds **12** and **13** appeared to be minor modifications of **8** and **10**. Although **12** and **13** each undergo facile ring expansions to cyclopentanones, it was somewhat surprising to discover that these reactions occurred *with low stereoselectivity* (eq 4). Epoxide **12** produced ketones **14** and **15** in 95% yield as a 1.1:1 mixture of diastereomers.[19] Cyclopentanone **14** is the apparent product of an antiperiplanar 1,2-alkyl migration toward the epoxide, while **15** seemingly results via a synperiplanar 1,2-alkyl migration process. Similar results were obtained with **13**, as cyclopentanones **16** and **17** were produced as a 2.6:1 mixture in 96% yield. As **17** could have derived from **16** through a retro-aldol−aldol sequence, each of **16** and **17** were individually resubjected to titanium tetrachloride in dichloromethane. Even at higher reaction temperatures or prolonged reaction times, compounds **16** and **17** did not interconvert, suggesting that this ratio represented a "kinetic" mixture of the products of ring expansion. X-ray analysis of crystals of **16** as well as a derivative of **17** established each of their structures.



12, R=OTBS
13, R=H (±)

14, R=OTBS, *50%* **15**, R=OTBS, *45%*
16, R=H (±), *69%* **17**, R=H (±), *27%*

Superficially it appears that the cyclobutane-derived substrates **12** and **13** reacted through an azacarbenium ion intermediate while the cyclopentane-derived compounds **8** and **10** underwent a synchronous epoxide opening−ring expansion process. These counterintuitive results prompted further investigation. Three mechanistic options were formulated in an attempt to interpret this phenomenon (Scheme 4).[20] It was hoped that further experiments could be used to distinguish between these options.

In the case of the cyclobutane-containing substrates, the first explanation invokes the formation of an azacarbenium ion intermediate before an unselective ring expansion (option 1). This explanation requires that **8** and **12** (or **10** and **13**) undergo ring expansions through different mechanistic paths. Put another way, why is the reaction of **8** (or **10**) selective while the reaction of **12** (or

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

(16) 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.

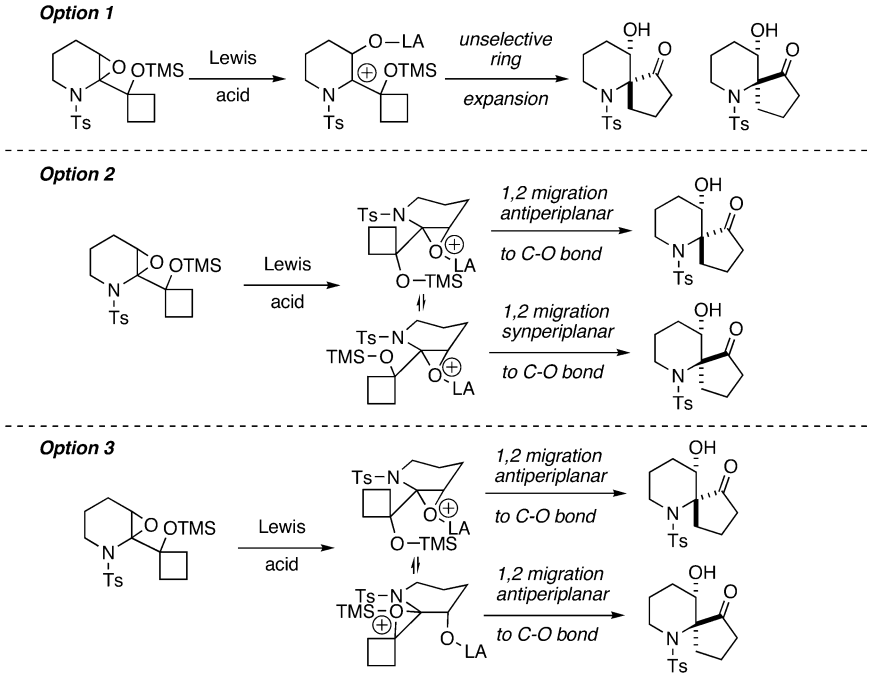
(17) At least three other uncharacterizable byproducts were also obtained.

(18) For examples, see: (a) Creary, X.; Inocencio, P. A.; Underiner, T. L.; Kostromin, R. *J. Org. Chem.* **1985**, *50*, 1932. (b) Hirst, G. C.; Johnson, T. O., Jr.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 2992. (c) Trost, B. M.; Chen, D. W. C. *J. Am. Chem. Soc.* **1996**, *118*, 12541. (d) Larock, R. C.; Reddy, C. K. *J. Org. Chem.* **2002**, *67*, 2027. For reviews of the chemistry of cyclobutane ring containing compounds: (e) Lee-Ruff, E.; Mladenova, G. *Chem. Rev.* **2003**, *103*, 1449. (f) Namyslo, J. C.; Kaufmann, D. E. *Chem. Rev.* **2003**, *103*, 1485.

(19) Interestingly, ring expansions promoted by *N*-bromosuccinimide apparently produce only the "anti" 1,2-migration product. See ref 13.

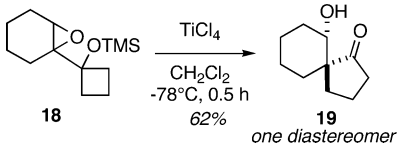
(20) It is important to note that these options represent mechanistic extremes. Both subtle variations from these extremes and the consideration that the reactions could occur simultaneously through more than one option complicate matters significantly.

SCHEME 4



13) is nonselective? A (simplistic) consideration of ring strain arguments would suggest that a cyclobutane ring would expand more readily (or more likely through a synchronous manner) than a cyclopentane ring. An assumption for option 2 in Scheme 4 is that the migrating σ bond of the cycloalkane undergoing expansion is aligned with the breaking C−O bond (the σ^*) of the epoxide. Generally, antiperiplanar orientations are preferred for 1,2-migration reactions.[21] Because the cyclopentane ring is less reactive, the lowest energy transition state reflects this preference for an antiperiplanar orientation between the migrating and rupturing bonds. The complexation of **12** or **13** with titanium(IV) would generate an electron-deficient site adjacent to the cyclobutane. The more reactive cyclobutane ring could undergo expansion through either the antiperiplanar or the synperiplanar orientations. A third option is, under Lewis acid promotion, in addition to the aforementioned antiperiplanar 1,2-migration reaction, the oxygen atom of the silyl ether could participate by opening the epoxide ring (an anti process). If 1,2-alkyl migration of the cyclobutane ring took place in an anti fashion through this intermediate, the net result would be an overall syn 1,2-alkyl migration reaction. Our efforts to sort through these options began.

Carbocyclic Version. The first scenario suggested the intermediacy of an azacarbenium ion. Did the adjacent cyclobutane ring stabilize this intermediate such that it became a factor in the reaction expansion reaction?[22] Because we could not find carbocyclic versions of a α-epoxy silyl ether ring expansion involving a cyclobutane ring, the expansion of epoxide **18** was attempted (eq 5).[2a] Interestingly, unlike **12** or **13**, the ring expansion of **18** (1.1 equiv of $TiCl_4$, −78 °C, 30 min) produced a single diastereomeric cyclopentanone **19** in 62% yield. The lowered yield of this reaction probably reflects the difficulty in recovering the volatile product and not the efficiency of the semipinacol reaction (see below). The relative stereochemistry of **19** was established using X-ray crystallography. This reaction was repeated at progressively higher temperatures (0 °C, 25 °C) in order to examine if alternative diastereomers could be observed. Other diastereomeric products were not observed (TLC, HPLC, NMR) during these experiments. In the carbocyclic system, the cyclobutane ring was not sufficient to induce the formation of a carbenium ion intermediate. Clearly, the sterics and electronic properties of the *p*-toluenesulfonylamido function in **12** or **13** affects the reactivity profile of the expansion process considerably, and consequently option 1 in Scheme 4 cannot be ruled out.



(5)

Effect of Different Lewis Acids. At this point the effect of the Lewis acid on the outcome of the reaction of **13** was examined (eq 6 and Table 1). In general, 1.1−1.4 equiv of a Lewis acid was used to promote a given reaction. The temperatures presented in the table represent the minimum at which a reaction was observed to take place. Warming of the reaction temperature was occasionally required in order to force reactions to completion. Reactions with triethylaluminum or titanium tetraisopropoxide were quite sluggish even at room temperature (entries 1 and 2). The lowered isolated yields

(21) (a) Deslongchamps, P. In *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983; pp 182−190. (b) Goodman, R. M.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 9392. (c) Crudden, C. M.; Chen, A. C.; Calhoun, L. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 2851. (d) Sahasrabudhe, K.; Gracias, V.; Furness, K.; Smith, B. T.; Katz, C. E.; Reddy, D. S.; Aubé, J. *J. Am. Chem. Soc.* **2003**, *125*, 7914.

(22) (a) Wilcox, C. F., Jr.; Mesirov, M. *J. Am. Chem. Soc.* **1962**, *84*, 2757. (b) Hahn, R. C.; Corbin, T. F.; Shecter, H. *J. Am. Chem. Soc.* **1968**, *90*, 3404.

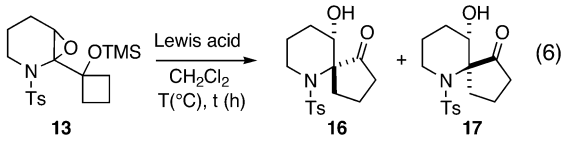
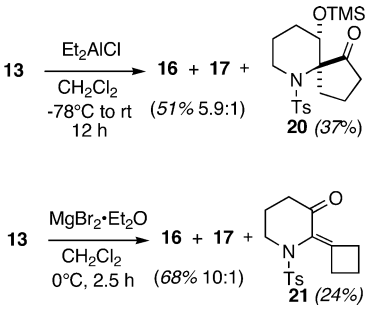


TABLE 1. Lewis Acid Screen for Reactions of Epoxide 13

entry	Lewis acid[a]	*T* (°C)	*t* (h)	yield[b] (%)	ratio **16**:**17**[c]
1	$Al(Me)_3$	−78−rt		sluggish reacn	
2	$Ti(OiPr)_4$	−78−rt		sluggish reacn	
3	$TiCl_4$	−78	0.5	96	2.6:1
4	ZnI_2	−78−0	3.5	89	2.5:1
5	$ZnCl_2$	0−rt	17	93	4.2:1
6	$EtAlCl_2$	−78	0.5	95	4.6:1
7	Et_2AlCl	−78−rt	12	51	5.9:1
8	TMSOTf	−78	0.5	89	6.0:1
9	$ZrCl_4$	−78	1	89	6.1:1
10	BF_3Et_2O	−78	0.5	89	6.8:1
11	$Y(OTf)_3$	−15−0	7	54	6.9:1
12	$MgBr_2Et_2O$	0	2.5	68	10:1
13	$Yb(OTf)_3$	−45−0	7	99	7.4:1

[a] 1.1−1.4 equiv of Lewis acid was used. [b] Isolated yields (after purification using column chromatography). [c] Ratios were determined by HPLC analysis of the product mixture.

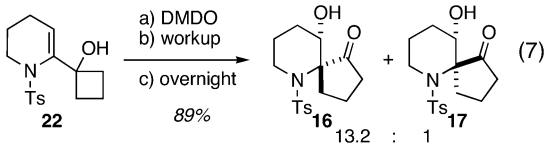
SCHEME 5



of **16** and **17** in entries 7 and 11 were the result of byproduct formation that was not observed using other Lewis acid promoters (see below). Although a rationalization of the stereochemical result for each entry is not possible, "milder" Lewis acids such as magnesium bromide etherate or ytterbium(III) trifluorosulfonate gave greater selectivity compared to titanium(IV) tetrachloride.[23,24] The most selective, synthetically useful result is that in entry 13. The use of ytterbium(III) trifluorosulfonate smoothly promoted the ring expansion of **13** to produce **16** and **17** in 99% isolated yield as a 7.4:1 ratio of diastereomers.[25]

Certain Lewis acids promoted the formation of byproducts as well as the desired ring expansion reaction (Scheme 5). When diethylaluminum chloride was used, a substantial amount (37%) of **20** was also isolated. Compound **20** was the formal result of "syn" 1,2-alkyl migration in which the trimethylsilyl group has also been transferred to the newly formed 2° alcohol.[26] Although magnesium bromide−diethyl etherate appeared to result in the formation of **16** in a highly selective manner (10:1) relative to **17**, α,β-unsaturated ketone **21** also was obtained in 24% yield. These byproducts were not observed, even in trace amounts, using other Lewis acids.

The observation that "mild" Lewis acid promotion results in a greater amount of "anti"-1,2-migration suggests that an antiperiplanar arrangement is energetically preferred. In fact, the most selective ring expansion that was uncovered to form an azaspirocyclic cyclopentanone was one that did not involve a Lewis acid promoter (eq 7). While the optimal ordering of epoxidation and trialkylsilylation steps for substrate construction was being defined, the allyl alcohol **22** was epoxidized using DMDO. After workup the α-hydroxy epoxide was placed under vacuum for 10 h. Examination of the synthetic material at that point clearly demonstrated it to be a 13.2:1 mixture of **16** and **17**.



Effect of Silicon Protecting Group. The steric bulk of the trialkylsilyl protecting group in these substrates was then modified to examine its effect on the reaction. If the silyl ether actively participates as a "neighboring group" as delineated in the third mechanistic suggestion (Scheme 4, option 3), then modifying this group should have a substantial impact on the diastereoselectivity of the reaction. Specifically, because bulkier groups should inhibit the "bridging" ability of the silyl ether, it was anticipated that an increase in steric bulk of the trialkylsilyl unit would lead to a corresponding increase of anti 1,2-alkyl migration product.

In fact, the opposite effect was observed (eq 8 and Table 2). As the steric bulk of the trialkylsilyl ether increases from trimethylsilyl (**13**) to triethylsilyl (**23**) to *tert*-butyldimethylsilyl (**24**), **17** is formed in increasingly larger proportions. The most dramatic example is in entry 4. Surprisingly, treatment of the triisopropylsilyl ether **25** with titanium tetrachloride led to the formation of **17** as the *exclusive* diastereomer.[27]

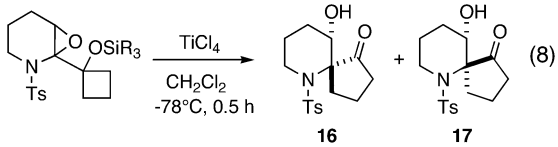


TABLE 2. Effect of Bulk of Trialkylsilyl Protecting Group

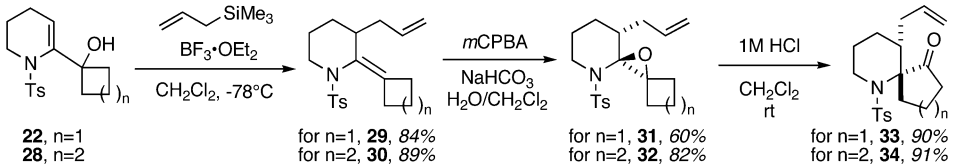
entry	compd	SiR_3	% yield[a]	ratio **16**:**17**[b]
1	**13**	$SiMe_3$	96	2.6:1
2	**23**	$SiEt_3$	99	2.5:1
3	**24**	$Si(^tBu)Me_2$	89	1.3:1
4	**25**	$Si(^iPr)_3$	88	0:1

[a] Isolated yields (after purification using column chromatography). [b] Ratios were determined by HPLC analysis of the product mixture.

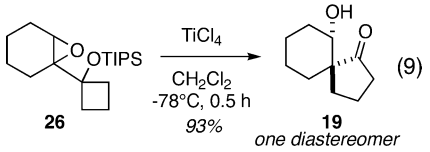
(23) The organization (and even the definition) of "strong" and "mild" Lewis acids is still unclear at the present time. (a) Childs, R. F.; Mulholland, D. L.; Nixon, A. *Can. J. Chem.* **1982**, *60*, 801. (b) Laszlo, P.; Teston, M. *J. Am. Chem. Soc.* **1990**, *112*, 8750. (c) Kobayashi, S.; Busujima, T.; Nagayama, S. *Chem. Eur. J.* **2000**, *6*, 3491, and references therein. For a recent review discussing Lewis acids, see: (d) Corma, A.; Garcia, H. *Chem. Rev.* **2003**, *103*, 4307. For earlier, useful reviews, see: (e) Jensen, W. B. *Chem. Rev.* **1978**, *78*, 1. and (f) Satchell, D. P. N.; Satchell, R. S. *Chem. Rev.* **1969**, *69*, 251.

(24) For a review of rare earth salts as catalysts in synthetic organic chemistry, see: Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W. L. *Chem. Rev.* **2002**, *102*, 2227.

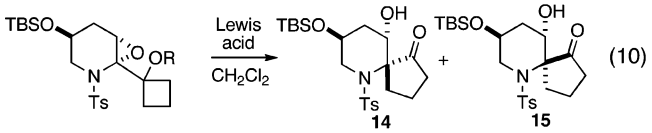
SCHEME 6



To examine whether this "TIPS" effect was more general, the triisopropyl silyl ether **26** was treated with titanium tetrachloride (eq 9). This initiated a smooth ring expansion process from which only **19** (anti migration) was obtained in 93% yield. Unfortunately, attempts to form the triisopropylsilyl ether analogues of either **8** or **10** have to this point been unsuccessful.



Because it appeared possible that one could manipulate the diastereoselective outcome of the cyclobutanol silyl ether to cyclopentanone semipinacol reaction by adjusting the nature of the Lewis acid and the trialkylsilyl protecting group, we examined this effect on **12** (eq 10). As observed previously, the reaction of **12** with titanium tetrachloride produces **14** and **15** in a 1.1:1 ratio, albeit in 95% yield. Using ytterbium(III) triflate to promote the semipinacol process led to a much higher ratio of **14** versus **15** (4.4:1) in 87% yield. This enables the isolation of **14** in 71% yield. Conversely, reaction of **27** with titanium tetrachloride generates **14** and **15** in 94% as a 1:6.2 ratio of diastereomers. Cyclopentanone **15** can be isolated in 81% yield from this reaction. This may provide a useful method to generate either diastereomeric cyclopentanone in the context of total synthesis ventures.



12, R=TMS	$TiCl_4$, -78°C	*95%*	1.1	:	1
12, R=TMS	$Yb(OTf)_3$, 0°C	*87%*	4.4	:	1
27, R=TIPS	$TiCl_4$, -78°C	*94%*	1	:	6.2

3-Substituted Heterocyclic Substrates. An epoxide resembling the "bridging" siloxy intermediate in option 3 allowed us to consider the reactivity and selectivity of this putative intermediate. Quite by accident, it was discovered that the allyl alcohol functionality in **22** or **28** could be reacted smoothly with allyltrimethylsilane in the presence of boron trifluoride−diethyl etherate to produce the allylated compounds **29** and **30** in 84 and 89% yields, respectively (Scheme 6).[13] This result was significant in our laboratories, as substitution at the 3-position was not tolerated in the established synthetic sequence (cf. Scheme 3) used to build precursors for semipinacol reactions. It was surmised that if the ene-sulfonamide moiety could react chemoselectively with an epoxidizing agent, the possibility of an alternative aza-spirocycle-building epoxide-based rearrangement reaction existed.

In the event, the reaction of **29** or **30** with purified *m*-CPBA took place uneventfully to produce **31** and **32** in 60 and 82% yields, respectively. In each case a single diastereomeric product was observed (GC and NMR analysis). Fortunately, X-ray quality crystals of **32** were obtained and established the relative stereochemistry of the epoxide as depicted. The stereochemistry of **31** is assigned by analogy. This stereochemical result is expected as the allyl group in **29** or **30** would be expected to be pseudoaxial in order to minimize $A^{1,3}$ strain with the cycloalkylidene function on the heterocyclic ring, causing the epoxidizing agent to approach the opposite alkene face.[28] Because of the structural similarity between **31** or **32** and the "bridging siloxy" intermediate in option 3 shown in Scheme 4, we envisioned that the reactions of this substrate would be a good test of this mechanistic premise.

These epoxides were unstable to acid and promptly underwent ring expansion reactions when treated with 1 M HCl. In particular, epoxide **31** reacted within 10 min of stirring with hydrochloric acid to form azaspirocyclic cyclopentanone **33** in 90% yield. An important feature of the reaction is that the 1,2-migration reaction generates a single diastereomeric product (established by X-ray crystallography) in which the migrated C−C bond is on the *same face* as the epoxide C−O bond. When treated with acid, epoxide **32** formed an azaspirocyclic cyclohexanone. As in the case with **31**, a single diastereomeric product was obtained. Unfortunately, **34** exists as a low-melting solid, and X-ray quality crystals could not be obtained. At this time, based on similar spectroscopic data, the stereochemical identity of **34** is assigned in analogy to that of **33**.

The results of the epoxide rearrangement of **31** tend to disfavor the third option in Scheme 4. It appears that the stereocontrolling element in the rearrangement of **31** is not the epoxide, but rather the adjacent allyl substituent. The alkyl group undergoes migration on the face *opposite* the allyl group, perhaps to minimize steric interactions during the transition state. To the extent that these results and option 3 in Scheme 4 can be compared (e.g. an allyl group is not the same as an

(25) The nature of the displaced anion after Lewis acid complexation is an additional consideration that could affect the diastereoselectivity of the expansion, although a clear trend is still not observed. We thank a reviewer for this suggestion.

(26) The stereochemistry was initially assigned by comparison of the ^{13}C chemical shifts of the *spiro* carbon and the methylene carbon adjacent to the nitrogen atom to that of **16** and **17**. This assignment was confirmed by conversion of **20** to **17** (TBAF, THF, 82%).

(27) For a review of the chemistry of the triisopropylsilyl group: Rücker, C. *Chem. Rev.* **1995**, *95*, 1009.

(28) The allyl group is pseudoaxial in the solid-state structure of **29**. For reviews on 1,3-allylic strain and its impact on acyclic conformational space: (a) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841. (b) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1124. (c) Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2000**, *39*, 2054.

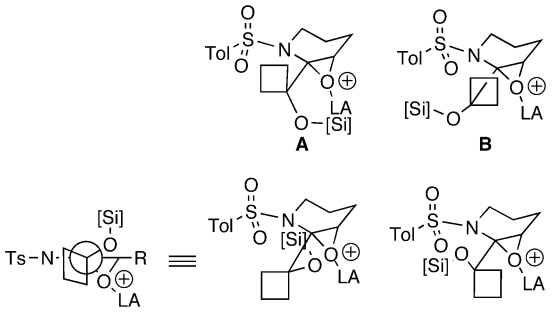


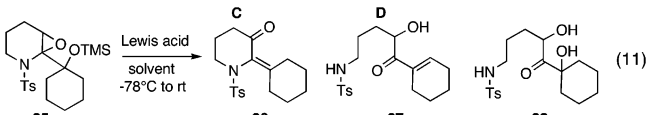
FIGURE 2.

oxygen atom−Lewis acid complex, or that an epoxide is not identical to a "bridging" siloxy group) it could be extrapolated that the putative "bridged" siloxy intermediate in Scheme 4 may react through similar pathways. Thus, the putative "bridged" siloxy intermediate in Scheme 4 would not dictate the stereochemical outcome of the ring expansion process. That diastereoselectivity, assuming that the reaction proceeded in a fashion similar to that of **31**, would in part be dictated by the adjacent C−O−Lewis acid complex, forming the "anti" migration product.

Taken together, these experimental results appear to be most consistent with the second proposal in Scheme 4. The expansion in the absence of Lewis acid favors the stereoelectronically preferred *antiperiplanar* orientation of the migrating C−C σ bond and the epoxide C−O bond. However, as progressively "stronger" Lewis acids are used to promote the ring expansion reaction, the amount of "syn" migration increases. This observation seems to corroborate well with the notion that the cyclobutane C−C bond will migrate readily as an electron-deficient atom is formed at an adjacent position. The unusual selectivity in the reactions of the triisopropylsilyl protected substrates are also consistent with this interpretation (Figure 2). Conformations that have a coplanar relationship between a cyclobutane C−C bond that could migrate and the C−O bond of the epoxide are shown. Two of these conformations (**A** and **B**) would migrate in an *antiperiplanar* fashion, while in conformations **C** and **D** these two bonds are in a syn orientation. The 20 lowest energy conformations of **13** (no Lewis acid is templated; using the MM2* force field) resemble **C** or **D**.[29] No conformations resembling **A** or **B** were found. These conformations are believed to be destabilized through steric interactions between either the cyclobutane ring (in **A**) or the trialkylsilyl ether (in **B**) and the aromatic ring of the *p*-toluenesulfonyl group. The results of this ring expansion reflect the conformational constraints of the starting materials (in a non-Curtin−Hammett scenario). A similar explanation was used to explain the "syn" migration of alkyl groups in a Jung non-aldol−aldol process.[4h] In the case examined by Jung and Houk, the syn 1,2-migration was believed to derive through specific conformations via a carbenium ion intermediate. This situation could be occurring in these systems as well (C−O breaking prior to C−C migration), but under those circumstances the selectivity differences in the expansions of the cyclobutane and cyclopentane rings still are difficult to rationalize.

Chelation? Another conceivable explanation for the anomalous selectivity profiles between the TMS ether **13** and the TIPS ether **25** is a chelation effect. Specifically, if chelation of a Lewis acid between the silyl ether and epoxide oxygen atoms takes place, the conformation of the reactive intermediate would most resemble that of **A** (Figure 2). Provided that a large amount of structural reorganization does not occur prior to rearrangement, semipinacol rearrangements proceeding through **A** should provide anti 1,2-migration products.[30] It is possible that the trimethylsilyl ether could significantly chelate, but the triisopropylsilyl ether, being substantially more hindered, does not chelate.[31] If chelation of the Lewis acid between the epoxide and silyl ether oxygen plays a significant role in these reactions, the selectivity difference in the expansions of the cyclobutanol silyl ethers and the cyclopentanol silyl ethers is still not clear. It is not obvious how a chelation effect could be invoked for one set of substrates and not its homologues. Although it cannot be stringently ruled out, an explanation of the "TIPS effect" invoking chelation is disfavored.

Larger Rings. Unfortunately, our efforts to extend this system beyond the formation of cyclopentanones and cyclohexanones have as yet been unsuccessful. Typical results are shown in eq 11. Treatment of the silyl ether **35** with a Lewis acid promoter generates a mixture of **36**−**38**. "Optimized" conditions for the formation of each byproduct are given in eq 11. Other Lewis acids such as titanium tetrachloride give only these three products; no products of ring expansion are observed. As larger rings have a reduced tendency to ring-expand, reactions that involve the intermediacy of an azacarbenium ion (such as in option 1; Scheme 4) become favored.



	36	**37**	**38**
$MgBr_2$, CH_2Cl_2	*73%*	*trace*	*trace*
TMSOTf, CH_2Cl_2	–	*77%*	*trace*
BF_3·OEt_2, MeOH	*14%*	–	*85%*

(11)

Conclusions

The predictability and stereochemical outcome of α-siloxy−epoxide rearrangements within carbocyclic frameworks do not appear to be significantly affected by structural variations (size of "expanding" ring; nature (cyclic or acyclic) of epoxide).[2−5] In contrast, the reactions that form 1-azaspirocyclic ketones through a α-siloxy−epoxide rearrangement reaction in this present work can be dramatically affected by structural changes. Although

(29) Calculations were performed as a Monte Carlo conformational search over the MM2* surface (see: (a) Burkert, U.; Allinger, N. L. *Molecular Mechanics*; ACS Monograph 177; American Chemical Society: Washington, DC, 1982) using MacroModel v. 4.5 (see: Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440) on a Silicon Graphics R5000 Indy workstation.

(30) A reviewer points out that the use of the "nonchelating" Lewis acid, BF_3·OEt_2, provides the "anti" migration product as the major product.

(31) Lewis acid promoted nucleophilic additions to α- or *β*-siloxy aldehydes are not believed to proceed in a chelate-controlled manner. (a) Keck, G. E.; Castellino, S. *Tetrahedron Lett.* **1987**, *28*, 281. (b) Chen, X.; Hortelano, E. R.; Eliel, E. L. Frye, S. V. *J. Am. Chem. Soc.* **1992**, *114*, 1778. An exception: (c) Evans, D. A.; Allison, B. D.; Yang, M. G.; Masse, C. E. *J. Am. Chem. Soc.* **2001**, *123*, 10840.

cyclopentanol silyl ethers expand to form cyclohexanones in a 1,2-anti fashion, cyclobutanol silyl ethers expand via either a 1,2-anti or 1,2-syn manner, depending on conditions and substituents. Although the mechanistic underpinnings of this selectivity difference are still not fully understood, the lower selectivity in the process may be prescribed to the greater propensity of the cyclobutane ring to expand compared to the cyclopentane ring. With appropriate conditions, diastereomeric 1-azaspiro[5.4]-decanones can be constructed in a complementary fashion. A new method to form 1-azaspiro[5.4]decanones substituted at the 3-position of the heterocycle was also uncovered.

Although not as general as the standard "carbocyclic" versions of the α-siloxy−epoxide process, this method can generate complex spiro-fused heterocyclic ring systems containing two contiguous stereogenic carbon centers in a single operation. Because of the relative difficulties in accessing the necessary substrates, an important factor in these systems that has not been addressed to date is the nature of the substituent on the nitrogen atom. In addition, enabling larger rings to undergo ring expansion would be a useful advance as well. Efforts to resolve these issues as well as to apply these reactions in the total synthesis of alkaloids are ongoing.

Acknowledgment. The authors thank the University of British Columbia and the Natural Sciences and Engineering Research Council (NSERC) of Canada for the financial support of our programs. M.D.B.F. thanks the Gladys Estella Laird Foundation for a Laird Fellowship.

Supporting Information Available: Experimental procedures, characterization data, copies of spectra, and CIF files for previously unreported compounds. This material is available free of charge via the Internet at http://www.pubs.acs.org.

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