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Synthesis of Functionalized 1-Azaspirocyclic Cyclopentanones Using Bronsted Acid or *N*-Bromosuccinimide Promoted Ring Expansions

Gregory R. Dake,* Michaël D. B. Fenster, Paul B. Hurley, and Brian O. Patrick†

Department of Chemistry, 2036 Main Mall, University of British Columbia, Vancouver, British Columbia, Canada V6T 1Z1

gdake@chem.ubc.ca

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Azaspirocyclic ring systems are present in a variety of alkaloids. Functionalized 1-azaspirocyclopentanones (**6**, **7**, **11**, **12**) can be efficiently constructed through semipinacol ring expansion reactions of 2-(1-hydroxycyclobutyl)-*p*-toluenesulfonylenamides (**4**) promoted by either a Bronsted acid ((*S*)-(+)-10-camphorsulfonic acid or HCl) or *N*-bromosuccinimide, an electrophilic bromine source. Reactions promoted by *N*-bromosuccinimide tend to proceed in higher yields (80−95%) and with greater diastereoselectivity (3:1−1:0) compared to those reactions promoted by a Bronsted acid. In addition, *N*-bromosuccinimide promoted reactions can produce a complementary stereochemical outcome compared to the reactions using Bronsted acid.

Introduction

The presence of interesting structural motifs within natural products motivates the synthetic organic chemistry community. As an example, a number of alkaloids such as lepadiformine, cephalotaxine, fasicularin, and halichlorine all share a 1-azaspirocyclic ring system as a common architectural feature (Figure 1). That these alkaloids have triggered significant attention from a number of research groups is not surprising.[1−4] Methods to construct these azaspirocyclic ring systems are continually being invented and developed.[5]

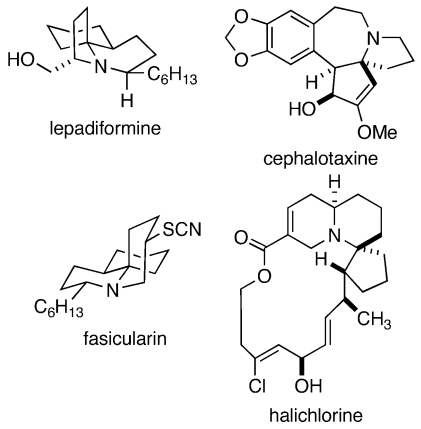

FIGURE 1. Representative alkaloids with 1-azaspirocyclic ring systems.

In developing a conceptually different approach to 1-azaspirocyclic ring systems, we became intrigued with the idea of using a semipinacol rearrangement as a key step.[6] The concept is outlined in Scheme 1. The reaction of an appropriate electrophile with a 2-(hydroxycyclobutyl)-substituted enamine derivative such as **a** should produce a transient azacarbenium ion intermediate **b**. Migration of one of the adjacent cyclobutane carbon−carbon bonds with concomitant C=O π-bond formation would generate protonated azaspirocyclic ketone **c**. Proton loss from **c** generates the desired azaspirocyclic ring system **d**.

Pinacol and semipinacol reactions have become popular methods for structural reorganization and have been utilized in the construction of both natural and unnatural products.[7] An advantage to these methods is the substantial increase in molecular complexity that can result even though the reactions are relatively "low-tech"—for

† Manager, UBC X-ray Structural Facility; to whom inquiries regarding crystal structures should be addressed.

(1) Lepidiformine. *Isolation:* (a) Biard, J. F.; Goyut, S.; Roussakis, C.; Verbist, J. F.; Vercauteren, J.; Weber, J. F.; Boukef, K. *Tetrahedron Lett.* **1994**, *35*, 2691. *Synthetic work:* (b) For a nice summary, see: Weinreb, S. M. *Acc. Chem. Res.* **2003**, *36*, 59. (c) Abe, H.; Aoyagi, S.; Kibayashi, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3017. (d) Sun, P.; Sun, C.; Weinreb, S. M. *J. Org. Chem.* **2002**, *67*, 4337. (e) Sun, P.; Sun, C.; Weinreb, S. M. *Org. Lett.* **2001**, *3*, 3507. (f) Greshock, T. J.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3511. (g) Reference 3b. (h) Abe, H.; Aoyogi, S.; Kibayashi, C. *Tetrahedron Lett.* **2000**, *41*, 1205. (i) Werner, K. M.; De los Santos, J. M.; Weinreb, S. M.; Shang, M. *J. Org. Chem.* **1999**, *64*, 4865. (j) Pearson, W. H.; Ren, Y. *J. Org. Chem.* **1999**, *64*, 688. (k) Werner, K. M.; De los Santos, J. M.; Weinreb, S. M.; Shang, M. *J. Org. Chem.* **1999**, *64*, 686. (l) Pearson, W. H.; Barta, N. S.; Kampf, J. W. *Tetrahedron Lett.* **1997**, *38*, 3369.

(2) Cephalotaxine. For recent total syntheses, see: (a) Li, W.-D. Z.; Wang, Y.-Q. *Org. Lett.* **2003**, *4*, 2931. (b) Suga, S.; Watanabe, M.; Yoshida, J. *J. Am. Chem. Soc.* **2002**, *124*, 14824. (c) Koseki, Y.; Sato, H.; Watanabe, Y.; Nagasaka, T. *Org. Lett.* **2002**, *4*, 885. (d) Tietze, L. F.; Schirok, H. *J. Am. Chem. Soc.* **1999**, *121*, 10264. (e) Planas, L.; Perard-Viret, J.; Royer, J. *J. Org. Chem.* **2004**, *69*, 3087. For a review, see: (e) Jalil Miah, M. A.; Hudlicky, T.; Reed, J. W. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1998; Vol. 51, pp 199−269.

(3) Fasicularin. *Isolation papers*: (a) Patil. A. D.; Freyer, A. J.; Reichwein, R.; Carte, B.; Killmer, L. B.; Faucette, L.; Johnson, R. K.; Faulkner, D. J. *Tetrahedron Lett.* **1997**, *38*, 363. *Synthetic work*: (b) Abe, H.; Aoyogi, S.; Kobayashi, C. *J. Am. Chem. Soc.* **2000**, *122*, 4583. (c) Maeng, J.-H.; Funk, R. L. *Org. Lett.* **2002**, *4*, 331. (d) Fenster, M. D. B.; Dake, G. R. *Org. Lett.* **2003**, *5*, 4313.

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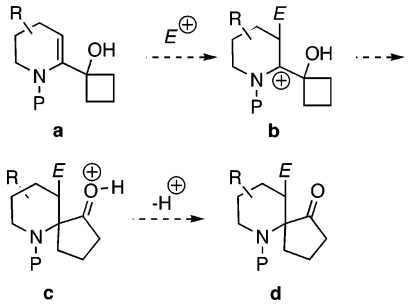
SCHEME 1. Semipinacol-Based Approach to 1-Azaspirocycles

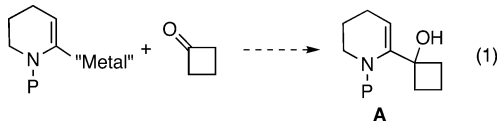


example, simple Bronsted acids can be used to promote these reactions.

Examples of hydroxy−imine rearrangements are present in the chemical literature; despite their synthetic potential, the promise of these processes has yet to be fully realized.[8] A marked exception is the transformations of 3-hydroxyindolines to spiroindoxyl ring systems as in the construction of austamide and brevianamide A.[8i,9] However, we could uncover no examples of this type of process used to form spirocyclic ring systems such as those present in the natural products described in Figure 1. Relevant studies on "hydroxy−oxonium" semipinacol reactions forming oxaspirocycles had been initiated and examined by the Paquette group throughout the 1990s.[10] A key finding in their assorted examinations was that the efficiency of the semipinacol process was affected by the substituents (either inductively withdrawing or donating) on the ring bearing the oxacarbenium ion. Aware of these reports and that nitrogen is less electronegative than oxygen, we selected cyclobutanols as initial substrates. Cyclobutanols have been demonstrated to undergo facile ring expansion reactions, presumably due to both the relief of ring strain upon the formation of a five-membered ring from a four-membered ring as well as the formation of a carbon−oxygen π bond.[10a,11] This report will document the successful formation of functionalized azaspirocyclic cyclopentanones, initiated by either Bronsted acids or *N*-bromosuccinimide (NBS), an electrophilic bromine source.

Results and Discussion

Construction of Substrates. The reaction between a "2-metallo-*N*-protected-2-piperidene" and cyclobutanone appeared to be the most straightforward method of generating structures such as **A** (eq 1). The *p*-toluenesulfonyl group was selected to be the protecting group on nitrogen because of its perceived compatibility with organometallic compounds, Bronsted acids and Lewis acids. Our attempts to form the desired organometallic species using either direct lithiation or metal-halide exchange reaction were unsuccessful. Following the work of Hiemstra and Speckamp, we considered forming these nucleophilic organometallic compounds by transmetalation of an appropriate vinylstannane.[12]



The vinylstannanes were generated using a Pd(0) catalyzed coupling of a lactam-derived enol triflate and hexamethyldistannane.[12,13] The lactams[14] (**1a**−**g**) were

(4) Halichlorine. *Isolation papers*: (a) Kuramoto, M.; Tong, C.; Yamada, K.; Chiba, T.; Hayashi, Y.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3867. (b) Arimoto, H.; Hayakawa, I.; Kuramoto, M.; Uemura, D. *Tetrahedron Lett.* **1998**, *39*, 861. (c) Chou, T.; Kuramoto, M.; Otani, Y. Shikano, M.; Yazawa, K.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3871. (d) Arimoto, H.; Asano, S.; Uemura, D. *Tetrahedron Lett.* **1999**, *40*, 3583. (e) Clive, D. L. J.; Yeh, V. S. C. *Tetrahedron Lett.* **1999**, *40*, 8503. (f) Koviach, J. L.; Forsyth, C. J. *Tetrahedron Lett.* **1999**, *40*, 8529. (g) Lee, S.; Zhao, Z. *Org. Lett.* **1999**, *1*, 681. (h) Lee, S.; Zhao, Z. *Tetrahedron Lett.* **1999**, *40*, 7921. (i) Trauner, D.; Schwarz, J. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3542. (j) Trauner, D.; Danishefsky, S. J. *Tetrahedron Lett.* **1999**, *40*, 6513. (k) Trauner, D.; Churchill, D. G.; Danishefsky, S. J. *Helv. Chim. Acta* **2000**, *83*, 2344. (l) Wright, D. L.; Shulte, J. P.; Page, M. *Org. Lett.* **2000**, *2*, 1847. (m) White, J. D.; Blakemore, P. R.; Korf, E. A.; Yokochi, A. F. T. *Org. Lett.* **2001**, *3*, 313. (n) Shindo. M.; Fukuda, Y.; Shishido, K. *Tetrahedron Lett.* **2000**, *41*, 929. (o) Itoh, M.; Kuwahara, J.; Itoh, K.; Fukuda, Y.; Kohya, M.; Shindo, M.; Shishido, K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2069. (p) Carson, M. W.; Kim, G.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4453. (q) Carson, M. W.; Kim, G.; Hentemann, M. F.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4450. (r) Hayakawa, I.; Arimoto, H.; Uemura, D. *Heterocycles* **2003**, *59*, 441. (s) Takasu, K.; Ohsato, H.; Ihara, M. *Org. Lett.* **2003**, *5*, 3017. (t) Matsumura, Y.; Aoyagi, S.; Kibayashi, C. *Org. Lett.* **2003**, *5*, 3249.

(5) For some other methods to generate 1-azaspirocyclic ring systems, see: (a) Wardrop, D. J.; Burge, M. S.; Zhang, W.; Ortiz, J. A. *Tetrahedron Lett.* **2003**, *44*, 2587. (b) Planas, L.; Perard-Viret, J., Royer, J.; Selkti, M.; Thomas, A. *Synlett* **2002**, 1629. (c) Kibayashi, C.; Yamazaki, N.; Ito, T. *Synlett* **2001**, 1506. (d) Braun, N. A.; Ousmer, M.; Bray, J. D.; Bouchu, D.; Peters, K.; Peters, E.-M.; Ciufolini, M. A. *J. Org. Chem.* **2000**, *65*, 4397. (e) For a review covering spirocycle synthesis: Sannigrahi, M. *Tetrahedron* **1999**, *55*, 9007.

(6) (a) Fenster, M. D. B.; Patrick, B. O.; Dake, G. R. *Org. Lett.* **2001**, *3*, 2109. (b) Hurley, P. B.; Dake, G. R. *Synlett* **2003**, 2131.

(7) (a) Eom, K. D.; Raman, J. V.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **2003**, *125*, 5415. (b) Li, J.; Jeong, S.; Esser, L.; Harran, P. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 4765. (c) Overman, L. E.; Pennington, L. D. *J. Org. Chem.* **2003**, *68*, 7143. For reviews on the pinacol reaction, see: (d) Rickborn, B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 3, p 721. (e) Coveney, D. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 3, p 777.

(8) (a) Stevens, C. L.; Elliott, R. D.; Winch, B. L. *J. Am. Chem. Soc.* **1963**, *85*, 1464. (b) Stevens, C. L.; Thuillier, A.; Daniher, F. A. *J. Org. Chem.* **1965**, *30*, 2962. (c) Stevens, C. L.; Klundt, I. L.; Munk, M. E.; Pillai, M. D. *J. Org. Chem.* **1965**, *30*, 2967. (d) Morrow, D. F.; Brokke, M. E.; Moersch, G. W.; Butler, M. E.; Klein, C. F.; Neuklis, W. A.; Huang, E. C. Y. *J. Org. Chem.* **1965**, *30*, 212. (e) Stevens, C. L.; Ash, A. B.; Thuillier, A.; Amin, J. H.; Balys, A.; Dennis, W. E.; Dickerson, J. P.; Glinski, R. P.; Hanson, H. L.; Pillai, M. D.; Stoddard, J. W. *J. Org. Chem.* **1966**, *31*, 2593. (f) Stevens, C. L.; Thuillier, A.; Taylor, K. G.; Daniher, F. A.; Dickerson, J. P.; Hansom, H. T.; Nielsen, N. A.; Tikotkar, N. A.; Weier, R. M. *J. Org. Chem.* **1966**, *31*, 2601. (g) Stevens, C. L.; Hanson, H. T.; Taylor, K. G. *J. Am. Chem. Soc.* **1966**, *88*, 2769. (h) Yamada, S.-I.; Mizuno, H.; Terashima, S. *J. Chem. Soc., Chem. Commun.* **1967**, 1058. (i) Hutchison, A. J.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 6786. (j) Woolf, T.; Trevor, A.; Baillie, T.; Castagnoli, N., Jr. *J. Org. Chem.* **1984**, *49*, 3305. (k) Vatèle, J.-M.; Dumas, D.; Goré, J. *Tetrahedron Lett.* **1990**, *31*, 2277. (l) Compain, P.; Goré, J.; Vatèle, J.-M. *Tetrahedron Lett.* **1995**, *36*, 4059. (m) Compain, P.; Goré, J.; Vatèle, J.-M. *Tetrahedron Lett.* **1995**, *36*, 4063. (n) Compain, P.; Goré, J.; Vatèle, J.-M. *Tetrahedron* **1996**, *52*, 6647. (o) Devaux, J.-M.; Goré, J.; Vatèle, J.-M. *Tetrahedron: Asymmetry* **1998**, *9*, 1619. (p) Bisel, P.; Lauktein, G.; Weckert, E.; Frahm, A. W. *Tetrahedron: Asymmetry* **1998**, *9*, 4027. (q) Reference 2e.

(9) Williams, R. M.; Kwast, E.; Coffman, H.; Glinka, T. *J. Am. Chem. Soc.* **1989**, *111*, 3064.

(10) (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. (c) Paquette, L. A.; Lanter, J. C.; Wang, H.-L. *J. Org. Chem.* **1996**, *61*, 1119. (d) Paquette, L. A.; Wang, H.-L. *Tetrahedron Lett.* **1995**, *36*, 6005. (e) Lord, M. D.; Negri, J. T.; Paquette, L. A. *J. Org. Chem.* **1995**, *60*, 191. (f) Paquette, L. A.; Dullweber, U.; Cowgill, L. D. *Tetrahedron Lett.* **1993**, *34*, 8019. (g) Paquette, L. A.; Lord, M. D.; Negri, J. T. *Tetrahedron Lett.* **1993**, *34*, 5693. (h) Paquette, L. A.; Andrews, J. F.; Vanucci, C.; Lawhorn, D. E.; Negri, J. T.; Rogers, R. D. *J. Org. Chem.* **1992**, *57*, 3956. (i) Paquette, L. A.; Negri, J. T.; Rogers, R. D. *J. Org. Chem.* **1992**, *57*, 3947. (j) Paquette, L. A.; Lawhorn, D. E.; Teleha, C. A. *Heterocycles* **1990**, *30*, 765.

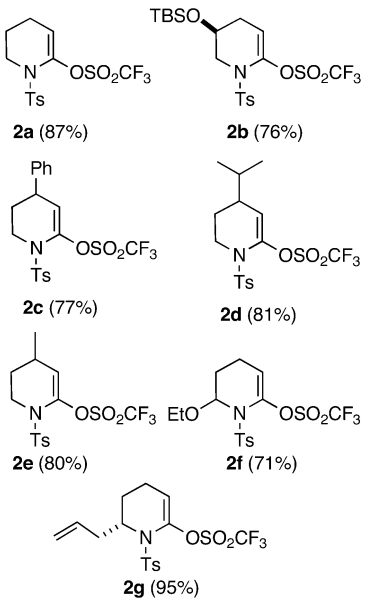
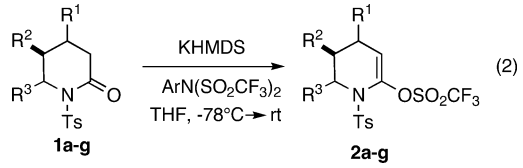


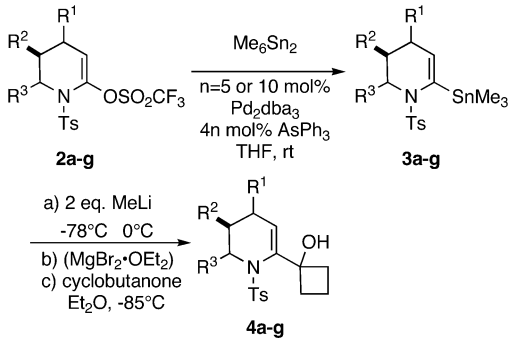
FIGURE 2. Structures of the enol triflates **2a**−**g**.

converted into their respective enol triflates (**2a**−**g**) under standard conditions (eq 2 and Figure 2).[15] In certain cases the enol triflates converted back to the starting lactams within a few hours (**2a**,**e**) and so were immediately carried onto subsequent reactions.



The conversion of the enol triflates of common structure **2** to cyclobutanols of type **4** is described in general in Scheme 2. The details for specific substrates are presented in the Supporting Information. The conversion of an enol triflate **2** to its corresponding vinylstannane **3**

SCHEME 2. Formation of Cyclobutanols 4a−g



typically was best performed using hexamethyldistannane in the presence of a catalytic amount of tris(bisdibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) with triphenylarsine in tetrahydrofuran (THF) at room temperature for 7−9 h.[13] Longer reaction times appeared to lead to the decomposition of the vinylstannane product. The use of hexabutyldistannane in place of hexamethylstannane resulted in no reaction. Yields for the conversion of **2** to **3** ranged from 42 to 71%. The transmetalation of the vinylstannane function in **3** to a vinyllithium species required at least 2 equiv of methyllithium in THF at −78 °C. The addition of anhydrous magnesium bromide etherate (or magnesium bromide)[16] prior to addition of cyclobutanone was necessary in most cases to obtain satisfactory yields of the isolated carbonyl addition product. The yields for this reaction varied from 55 to 89%.[17]

In addition to the substrates made in this manner, two further cyclobutanols were constructed (Scheme 3). After removal of the silyl ether in **4b**, the hydroxyl function was converted to its corresponding benzyl ether or *p*-nitrobenzoyl ester to produce both **4h** and **4i**, respectively.

Bronsted Acid Promoters. Initial Studies. The first attempts to initiate a semipinacol ring expansion were performed using Bronsted acids. Because of its solubility in organic solvents, (*S*)-(+)-10-camphorsulfonic acid (CSA) was selected for preliminary reactions. Treating cyclo-

(11) For examples, see: (a) Hirst, G. C.; Johnson, T. O., Jr.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 2992. (b) Trost, B. M.; Chen, D. W. C. *J. Am. Chem. Soc.* **1996**, *118*, 1254. (c) Eastieu, K.; Ollivier, J.; Salaün, J. *Tetrahedron* **1998**, *54*, 8075. For reviews of the chemistry of cyclobutane ring containing compounds: (d) Lee-Ruff, E.; Mladenova, G. *Chem. Rev.* **2003**, *103*, 1449. (e) Namyslo, J. C.; Kaufmann, D. E. *Chem. Rev.* **2003**, *103*, 1485.

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

(13) Wulff, W. D.; Peterson, G. A.; Bauta, W. E.; Chan, K.-S.; Faron, K. L.; Gilbertson, S. R.; Kaesler, R. W.; Yang, D. C.; Murray, C. K. *J. Org. Chem.* **1986**, *51*, 279.

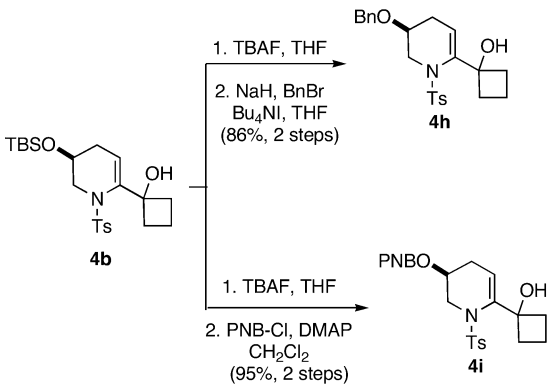
(14) The *N*-*p*-toluenesulfonylated lactams were typically made by treating the "parent" lactams with *n*-BuLi and TsCl. (a) Lactam **1b**: Herdeis, C. *Synthesis* **1986**, 232. (b) Lactams **1c**−**1e** were made using a copper-catalyzed conjugate addition reaction of an appropriate Grignard reagent to $\Delta^{3,4}$-*N*-*p*-toluenesulfonyl-2-oxopiperidene: Nagashima, H.; Ozaki, N.; Washiyama, M.; Itoh, K. *Tetrahedron Lett.* **1985**, *26*, 657. (c) Lactam **1f**: Luker, T.; Heimstra, H.; Speckamp, W. N. *Tetrahedron Lett.* **1996**, *37*, 8257. Luker, T.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 3592. (d) Lactam **1g** was made by reacting *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide with (5*R*)-5-hydroxyoct-7-enoate (Ramachandran, P. V.; Krzeminski, M. P.; Reddy, M. V. R.; Brown, H. C. *Tetrahedron: Asymmetry* **1999**, *10*, 11) under Mitsunobu conditions as described by Weinreb (Henry, J. R.; Marcin, L. R.; McIntosh, M. C.; Scola, P. M.; Harris, G. D.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 5709) followed by thermal deprotection of the Boc group and trimethylaluminum promoted lactamization. Please refer to the Supporting Information for details.

(15) Use of lactam-derived enol triflates in metal catalyzed or promoted reactions: (a) Foti, C. J.; Comins, D. L. *J. Org Chem.* **1995**, *60*, 2656. (b) Okita, T.; Isobe, M. *Synlett* **1994**, 589. (c) Okita, T.; Isobe, M. *Tetrahedron* **1995**, *51*, 3737. (d) Reference 12. (e) Reference 14c. (f) Ha, J. D.; Cha, J. K. *J. Org. Chem.* **1997**, *62*, 4550. (g) Ha, J. D.; Lee, D.; Cha, J. K. *J. Am. Chem. Soc.* **1999**, *121*, 10012. (h) Toyooka, N.; Okumura, M.; Takahata, H.; Nemoto, H. *Tetrahedron* **1999**, *55*, 10673. (i) Toyooka, N.; Okumura, M.; Takahata., H. *J. Org. Chem.* **1999**, *64*, 2182. (j) Coe, J. W. *Org. Lett.* **2000**, *2*, 4205. (k) Lindström, S.; Ripa, L.; Hallberg, A. *Org. Lett.* **2000**, *2*, 2291. (l) Li, X.; Xu, Z.; DiMauro, E. F.; Kozlowski, M. C. *Tetrahedon Lett.* **2000**, *43*, 3747. (m) Occhiato, E. G.; Trabocchi, A.; Guarna, A. *Org. Lett.* **2000**, *2*, 1241. (n) Occhiato, E. G.; Trabocchi, A.; Guarna, A. *J. Org. Chem.* **2001**, *66*, 2459. (o) Occhiato, E. G.; Prandi, C.; Ferrali, A.; Guarna, A.; Deagostino, A.; Venturello, P. *J. Org. Chem.* **2002**, *67*, 7144. (p) Toyooka, N.; Fukutome, A.; Nemoto, H.; Daly, J. W.; Spande, T. F.; Garraffo, Kaneko, T. *Org. Lett.* **2002**, *4*, 1715. (q) Easton, L. P.; Dake, G. R. *Can. J. Chem.* **2004**, *82*, 139. For a review, see: (r) Occhiato, E. G. *Mini-Rev. Org. Chem.* **2004**, *1*, 149.

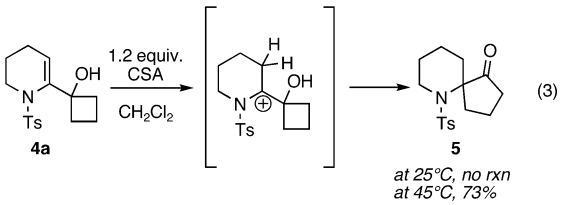
(16) Initial experiments were conducted with magnesium bromide etherate purchased from Aldrich. Later experiments gave varying results, perhaps because of the inconsistent quality of this reagent. The use of anhydrous magnesium bromide purchased from Strem alleviated this problem.

(17) The significant byproduct from this reaction seemed to result from enolization of the cyclobutanone rather than carbonyl addition. For a study of the enolization of cyclobutanone, see: Cantlin, R. J.; Drake, J.; Nagorski, R. W. *Org. Lett.* **2002**, *4*, 2433.

SCHEME 3. Formation of 4h and 4i



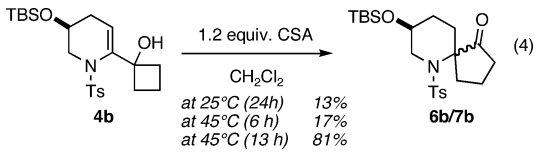
butanol **4a** with 1.2 equiv of CSA in dichloromethane at room temperature gave largely no reaction after 24 h (eq 3). Fortunately, it was discovered that the desired ring expansion occurred quite smoothly when the reaction mixture was warmed to 45 °C for 13 h. The spirocyclic cyclopentanone **5** was isolated as a white solid (mp 103−104 °C) in 73% yield after purification.



(3)

That a reaction involving the alkene had taken place was clearly indicated by the absence of a signal corresponding to the vinyl proton in **4a** (δ 5.66 ppm, t, $J = 4$ Hz) in the ^{1}H NMR spectrum. A ketone functional group was clearly present in **5** (IR: $\nu = 1746$ cm^{-1}; ^{13}C NMR: δ 216.4 ppm). An APT spectrum was used to establish the presence of the spirocyclic carbon atom adjacent to nitrogen (^{13}C NMR: δ 66.7 ppm) that had zero attached protons.

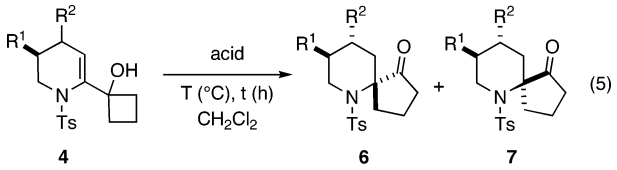
Similar results were observed using **4b** (eq 4). Experimental conditions that involved either ambient temperature or short reaction times resulted in poor conversions to product. The protocol adopted for **4a** (45 °C, 13 h) led to the formation of a mixture of diastereomeric ketones **6b** and **7b** (vide infra) in 81% isolated yield.



(4)

Because the starting materials (**4a** or **4b**) coeluted with their respective products (**5** or **6b**/**7b**) using a variety of solvent systems for thin-layer chromatography, no extensive efforts to optimize the Bronsted acid promoter were undertaken. By following these reactions using ^{1}H NMR spectroscopy, it was discovered that a much stronger acid such as hydrochloric acid could also be used at lower reaction temperatures for shorter reaction times. Under unoptimized conditions, cyclobutanol **4a**, when treated with 1.1 equiv of hydrochloric acid at 25 °C for 2 h, gave **5** in 67% yield. The silyl ether in **4b** was partially cleaved under these reaction conditions, resulting in an intractable mixture of compounds.

Diastereoselectivity. What would be the intrinsic effect of a substituent on the ring containing the *N*-*p*-toluenesulfonylazacarbenium ion on the stereoselectivity of the cyclobutanone ring expansion? The ring expansion reactions of **4b**−**4d**, **4h**, and **4i** were attempted to probe this question (eq 5 and Table 1). Only modest diastereoselectivities were observed in reactions using CSA at 45 °C. As examples, **4b** generates a 2.7:1 mixture of diastereomeric cyclopentanones **6b** and **7b** in 81% yield (entry 1), while the 4-phenyl derivative **4c** produces a 4.5:1 ratio of inseparable ring expansion products **6c** and **7c** in 89% yield (entry 2).[18] Interestingly, while **4b** only required 13 h for reaction, **4c** was stirred for 144 h to ensure complete conversion. In the limited number of cases attempted, substrates with inductively electron-withdrawing groups on the ring bearing the azacarbenium ion appeared to be more reactive. To examine the effect of the *tert*-butyldimethylsiloxy group on the chemistry of **4b**, substrates with alternative protecting groups were examined. Cyclobutanol **4h**, which bears a benzyl ether substituent, decomposed when it was subjected to acid (entry 3). Compound **4i** sluggishly underwent a ring expansion reaction, producing cyclopentanones **6i** and **7i** in 51% combined yield after 13 h in refluxing dichloromethane. Unreacted **4i** was also recovered in 31% yield (entry 4). Although the diastereoselectivity is still quite poor (1.8:1), this reaction predominantly produces the alternative diastereomer compared to the reaction of **4b**.[19]



(5)

Because **4c** did not contain any extraneous acid-sensitive functional groups, attempts to promote ring expansion were made using hydrochloric acid to try to improve the overall diastereoselectivity (entries 5 and 6). The reaction temperature could be lowered substantially when a stronger acid was used to catalyze the reaction. Consequently, much better stereoselectivities in this process were observed at the expense of reaction time. The most selective conditions were 1.1 equiv of hydrochloric acid at 0 °C, which resulted in the formation of **6c** and **7c** in 93% yield as a 14:1 mixture of diastereomers. Unfortunately, the reactions of **4d** or **4e** proved to be very sluggish using these conditions (entries 7 and 8).[20] Several days were required for these reactions, and in the case of **4d** warming the reaction to room temper-

(18) The relative stereochemistry of **6b** and **7b** was established through chemical correlation with products derived from α-siloxy epoxide rearrangement reactions. The relative stereochemistry of **7c** was confirmed by converting **11c**, a product of the NBS promoted reaction, to **7c** ((1) Super-Hydride; (2) Bu_3SnH, AIBN; (3) TPAP, NMO). Please see the Supporting Information for details.

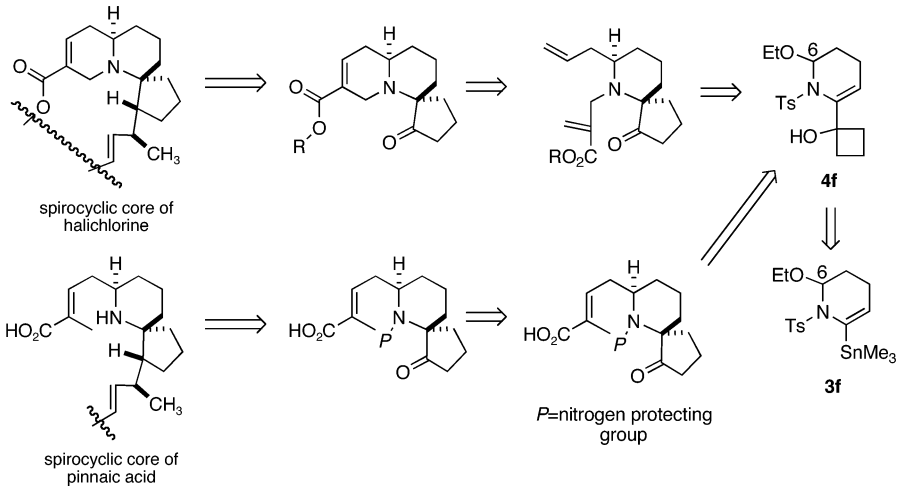
(19) This result was confirmed as **6b** could be converted to **6i**. For a study on the electrostatic stabilization of pseudoaxial conformers on oxacarbenium ions by heteroatom substituents and its resulting stereochemical consequences, see: Ayala, L.; Lucero, C. G.; Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 15521.

TABLE 1. Acid Promoted Reactions of Substrates of Structure 4

entry	substrate	R^1	R^2	acid[a]	T (°C)	t (h)	pdts	% yield[b]	ratio[e]
1	**4b**	OTBS	H	CSA	45	13	**6b**:**7b**	81	2.7:1
2	**4c**	H	Ph	CSA	45	144	**6c**:**7c**	89	4.5:1
3	**4h**	OBn	H	CSA	45	13	see text		
4	**4i**	OPNB	H	CSA	45	13	**6i**:**7i**	51[c]	1:1.8
5	**4c**	H	Ph	HCl	25	11	**6c**:**7c**	93	11:1
6	**4c**	H	Ph	HCl	0	48	**6c**:**7c**	93	14:1
7	**4d**	H	*i*Pr	HCl	25	50	**6d**:**7d**	71[d]	4.7:1
8	**4e**	H	CH_3	HCl	0	67	**6e**:**7e**	68	3.7:1

[a] CSA = (+)-camphorsulfonic acid (1.2 equiv) in dichloromethane; HCl = hydrochloric acid (1.1 equiv) in dichloromethane. [b] Isolated yield. [c] Unreacted **4i** was recovered in 31% yield. [d] A more polar byproduct was isolated in 23% yield. [e] Ratios are determined by ^{1}H NMR integration and/or GC analysis of the product mixture.

SCHEME 4. Retrosynthesis of the Spirocyclic Cores of Halichlorine and Pinnaic Acid

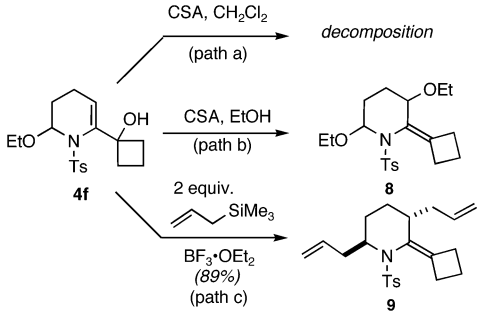


ature was necessary for good conversion of the starting material. The diastereoselectivity for each reaction was modest.

Chemoselectivity Problems: Use of a *N*-Bromosuccinimide Promoted Reaction. With these early results in hand, a synthetic route toward the spirocyclic cores of halichlorine and pinnaic acid was planned (Scheme 4). In essence, an azaspirocyclic ketone with a functional group at the 6-position of the piperidine ring was required. The vinylstannane **3f** was known in the literature as we began our studies.[12] It was believed that the 6-ethoxy aminal, despite its possible sensitivity toward acid, could serve as a chemical handle for the installation of appropriate side chains at the 6-position of the heterocycle. In principle, these transformations of the heterocycle could be executed prior to the proposed semipinacol rearrangement reaction or after the formation of the azaspirocycle.

In the event, attempts to promote the ring expansion of **4f** (CSA, CH_2Cl_2) led to decomposition (Scheme 5, path a). The formation of a *N*-toluenesulfonylazacarbenium ion at the 6-position of **4f** was believed to be the major complication. It was postulated that if this reaction was performed in ethanol, a simple "exchange" reaction would take place in the event that an azacarbenium ion was formed at the 6-position of **4f**. After switching to ethanol

SCHEME 5. Reactions of 6-Ethoxy Aminal 4f



as solvent, we were surprised to observe the formation of a new product that apparently did not undergo ring expansion (Scheme 5, path b). The structure is consistent with compound **8**, although the relative stereochemistry was not established.

We then opted to try to chemoselectively functionalize the 6-position.[21] When **4f** was treated with 2 equiv of allyltrimethylsilane in the presence of magnesium bromide etherate for 15 min, the *bis*-allylated product **9** was isolated in 89% yield as a single diastereomer (tentatively assigned as shown). When only 1 equiv of allyltrimethylsilane was used, **9** and unreacted **4f** was recovered.

Clearly, **4f** was unstable to Bronsted or Lewis acids. We then opted to attempt to functionalize the 6-position of the heterocycle after a projected semipinacol rear-

(20) The relative stereochemistries of **6e** and **7e** were established by chemical correlation with the products resulting from the NBS promoted ring expansions. The minor constituent of the NBS promoted reaction, **12e**, was converted to **6e** ((1) Super-Hydride; (2) Bu_3SnH, AIBN; (3) TPAP, NMO). Similarly, **11e** was converted to **7e**.

(21) Åhman, J.; Somfai, P. *Tetrahedron* **1992**, *48*, 9537. For a review of *N*-acyl(sulfonyl)iminium ion chemistry, see: Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817.

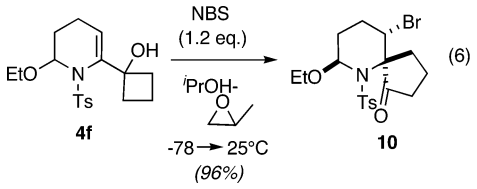
TABLE 2. Ring Expansions Promoted by NBS[a]

entry	substrate	R^1	R^2	R^3	pdts	% yield[b]	ratio[c]
1	**4a**	H	H	H	**11a**	85	single isomer
2	**4b**	H	OTBS	H	**11b**:**12b**	95	3.5:1
3	**4c**	Ph	H	H	**11c**	80	single isomer
4	**4d**	*i*Pr	H	H	**11d**:**12d**	85	3.5:1
5	**4e**	CH_3	H	H	**11e**:**12e**	79	1.9:1
6	**4g**[d]	H	H	allyl	**11g**[d]	98	single isomer
7	**4h**	H	OBn	H	**11h**:**12h**	90	5:1

[a] Standard conditions: NBS (1.2 equiv) in a 1:1 mixture of 2-propanol and propylene oxide at −78 °C. [b] Isolated yields. [c] Ratio was determined by integration of the ^{1}H NMR spectrum of the crude reaction mixture and typically confirmed by isolation of each of the diastereomeric products. [d] For consistency throughout eq 7 and Table 2, the *enantiomer* of **4g** and **11g** is shown.

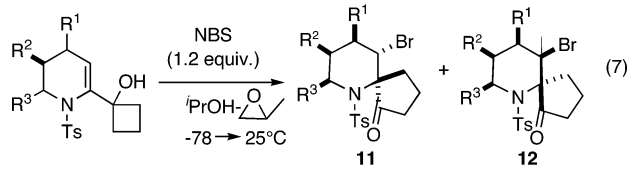
rangement. A nonacidic method for triggering the ring expansion was required. We believed that activation of the alkene through the formation of a bromonium ion could conceivably coerce the cyclobutanol to ring expand.[22]

Thus, we were quite pleased when the reaction between **4f** and 1.2 equiv of NBS in a 1:1 mixture of 2-propanol and propylene oxide (as an acid scavenger) at −78 °C produced the cyclopentanone **10** in 96% yield as a single diastereomer (eq 6).[23] The structure of **10** was tentatively determined using NMR spectroscopy and was ultimately assigned using X-ray analysis.



(6)

NBS Promoted Reactions: Diastereoselectivity. As the NBS protocol seemed to be both higher yielding and more stereoselective than the use of a Bronsted acid for the ring expansion, a number of substrates were subjected to these reaction conditions (eq 7 and Table 2). The yields of isolated and purified cyclopentanone products were uniformly high (80−98%). The diastereoselectivities of the ring expansions ranged from little selectivity (entries 4 and 5) to complete selectivity (entries 3 and entry 6). Similar to the reaction of **4f**, the reaction of **4c** and **4g** each resulted in the formation of a single diastereomeric product, **11c** and **11g**, respectively (entries 3 and 6). Modifying the substituent at the 4-position from phenyl to isopropyl to methyl lowered the stereoselectivity of the process considerably, although the major diastereomer (where the bromine is trans to the substituent at the 4-position) was the same in each case (entries 3−5). Substrates having oxygen substituents at the 5-position reacted much less selectively overall, the 5-*tert*-butyldimethylsiloxy substituted compound **4b** producing products **11b** and **12b** in a 3.5:1 ratio, while the 5-benzyloxy derivative **4h** produced a 5:1 mixture of diastereomers. In each case, the ether substituent in the major diastereomeric product was trans to the bromine substituent.[24]



(7)

Stereochemical Assignments. Because the assignment of the configuration of the products was quite challenging using NMR spectroscopy, X-ray analysis of single crystals of the products was used whenever feasible. The structures of **10**, **11c,** and **11g** were verified in this way.[25] In each case the methylene group of the cyclopentanone was trans to the bromine substituent.

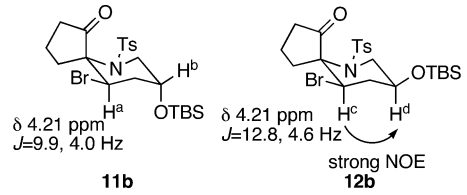


FIGURE 3. NMR data used to establish the structures of **11b** and **12b**.

The spirocyclic carbon centers in the other products were assigned (methylene group trans to the bromine substituent) by analogy. The relative stereochemistry of **11b** and **12b** was established by examining coupling constants of specific protons in conjunction with NOE studies (Figure 3). For each of the compounds **11b** and **12b**, the protons on the carbon bearing the bromine substituent (H^a and H^c) were assigned to be pseudoaxial on the basis of a large coupling constant for each (H^a: δ 4.21 ppm, dd, J = 9.9, 4.0 Hz; H^c: δ 4.21 ppm, dd, J = 12.8, 4.6 Hz). The proton on the carbon bearing the siloxy group in either **11b** or **12b** (H^b or H^d) could not be as trivially assigned as axial or equatorial. A significant NOE enhancement was present between H^c and H^d in **12b**, while no NOE enhancement could be observed between

(22) Examples of the use of NBS and other electrophilic bromine sources to promote migration reactions: (a) Trost, B. M.; Mao, M. K.-T.; Balkovec, J. M.; Buhlmayer, P. *J. Am. Chem. Soc.* **1986**, *108*, 4965. (b) Trost, B. M.; Mao, M. K.-T. *J. Am. Chem. Soc.* **1983**, *105*, 6753. (c) Wasserman, H. H.; Hearn, M. J. *J. Org. Chem.* **1980**, *45*, 2874. (d) 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. (e) Maroto, B. L.; Cerero, S. de la M.; Martinez, A. G.; Fraile, A. G.; Vilar, E. T. *Tetrahedron: Asymmetry* **2000**, *11*, 3059. (f) Martinez, A. G.; Vilar, E. T.; Fraile, A. G.; Cerero, S. de la M.; Maroto, B. L. *Tetrahedron Lett.* **2001**, *42*, 6539.

(23) The reaction of **4f** with PhSeCl generated a complex mixture of products. Studies using other potential electrophilic promoters are ongoing at the present time.

(24) For some examples of electrophilic addition to an alkene in which nonbonding interactions play a crucial stereochemical role: (a) Crimmins, M. T.; Lever, J. G. *Tetrahedron Lett.* **1986**, *27*, 291. (b) Tanner, D.; Somfai, P. *Tetrahedron* **1986**, *42*, 5657. (c) Tanner, D.; Sellén, M.; Bäckvall, J. E. *J. Org. Chem.* **1989**, *54*, 3374. (d) Murray, R. W.; Singh, M.; Williams, B. L.; Moncrieff, H. M. *J. Org. Chem.* **1996**, *61*, 1830.

(25) Please refer to the Supporting Information for details.

	R	δH^a (ppm)	m	J (Hz)
11c	Ph	4.52	d	11.6
11d	*i*-Pr	4.16	d	11.6
11e	Me	3.99	d	11.0

	R	δH^a (ppm)	m	J (Hz)
12d	*i*-Pr	4.15	d	1.8
12e	Me	4.01	bs	n/a

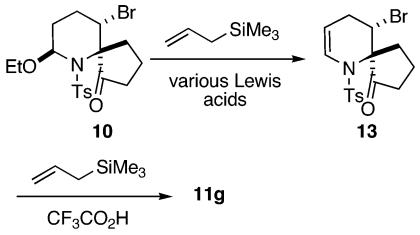
FIGURE 4. NMR data used to establish the structures of **11c**−**e** and **12d**−**e**.

H^a and H^b in **11b**. The major diastereomer in this reaction, **11b**, was converted to benzyl ether **11h** ((1) HCl, EtOH; (2) $PhCH_2N_2$) in order to assign the stereochemical configurations of **11h** and **12h**.

Interestingly, the 3-phenyl-substituted compound **4c** reacted to form **11c** as a single diastereomer. The 4-phenyl and 3-bromo substituents were assigned to be trans to each other due to the coupling constant ($J = 11.6$ Hz) between the protons attached at C-3 and C-4 (Figure 4). Cyclopentanones **11d** (isopropyl substituent) and **11e** (methyl substituent), which were the major diastereomers formed in their respective reactions, also had similar coupling constants between the attached protons at C-3 and C-4 ($J = 10.6$ Hz for **11d**; $J = 11.0$ Hz for **11e**). The coupling constants between the corresponding protons in the minor diastereomers were much smaller ($J = 1.8$ Hz for **12d**; no coupling observed in **12e**).

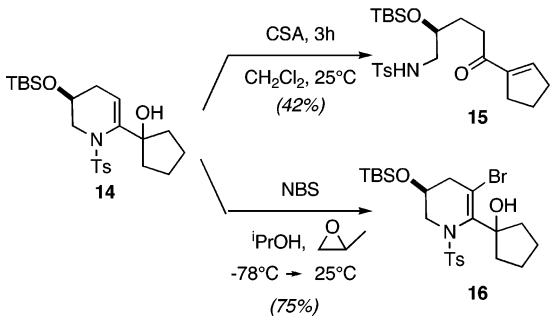
Synthetic Elaboration of 10. As described in Scheme 3, the initial interest in a compound such as **10** was derived from its potential as a synthetic intermediate in the synthesis of azaspirocyclic alkaloids such as halichlorine and pinnaic acid. To test the feasibility of **10** as an intermediate, further functionalization of the ethyl aminal function in **10** was attempted (Scheme 6). Attempts to substitute the ethyl aminal function in **10** with an allyl group using trimethylallylsilane and Lewis acid generated alkene **13**. This reaction took place within minutes at −78 °C. Interestingly, an allyl group could be installed at the 6-position of the heterocycle via **13**. Reacting **13** with allyltrimethylsilane and trifluoroacetic acid generated **11g** as a single diastereomer.[26]

SCHEME 6. Elaboration of 10



Attempts To Expand Cyclopentanols. Attempts to promote the expansion reactions of cyclopentanols to cyclohexanones using either Bronsted acid or NBS initiation have not met with success (Scheme 7). For example, the reaction of **14** with CSA produced enone **15** in 42% yield. Following this reaction by ^{1}H NMR, this compound results from elimination of the tertiary allylic alcohol with concomitant hydrolytic ring opening of the enesulfonamide. Mixing **14** with NBS produces the vinyl bromide **16** in 75% yield. Elimination to form a vinyl bromide is apparently faster than the ring expansion process.

SCHEME 7. Attempted Reactions of Analogous Cyclopentanol 14



Rationalization of Diastereoselectivity. Bronsted Acid. The results using Bronsted acid appear to be consistent with previous work on ring expansions of cyclobutanols to oxacarbenium ions.[10a] The major diastereomer results from an alkyl migration toward the azacarbenium ion that takes place through "chairlike" transition state **I** with pseudoequatorial substituents (Scheme 8). The minor diastereomer could be formed from either (a) a "chairlike" transition state with pseudoaxial substituents or (b) a "twist-boat-like" transition state **II** with pseudoequatorial substituents. The latter possibility is probably lower in energy relative to the former.

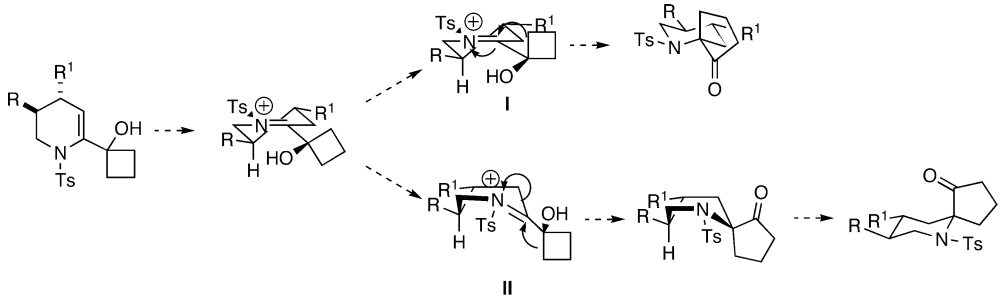
NBS Promoted Expansions. (a) Substitution at the 6-Position. The diastereoselectivity of the NBS promoted ring expansion was complete on substrates with substitution at the 6-position (**4f** and **4g**). The substituent at the 6-position probably resides in a pseudoaxial orientation to reduce A^{1,3} interactions with the *p*-toluenesulfonyl group on nitrogen.[27] This inference is supported by the small coupling constants for the ^{1}H NMR signal corresponding to the pseudoequatorial methine proton at the 6-position (5.2 and 3.7 Hz) of **4f**. The results are consistent with axial attack of the electrophilic brominating reagent on the less sterically hindered face of the more stable half-chair conformer of **4f** or **4g** (Scheme 9). Formation of a "bromonium ion" or bromine alkene π-complex triggers an alkyl shift that forms the cyclopentanone products. The relative stereochemistry of the spiro carbon and the bromine-bearing carbon appear to be the results of *antiperiplanar* alkyl migration, where the migrating methylene group ends up on the face opposite the bromine atom (a S_N2-like process).

(b) Substituent at the 5-Position. Because the electrophilic bromine atom can reasonably react on either face of the alkene in substrates such as **4b** or **4h**, only modest diastereoselectivities are obtained. A slight stereoelectronic bias could be present for "(pseudo)-axial" approach of the NBS to these substrates.

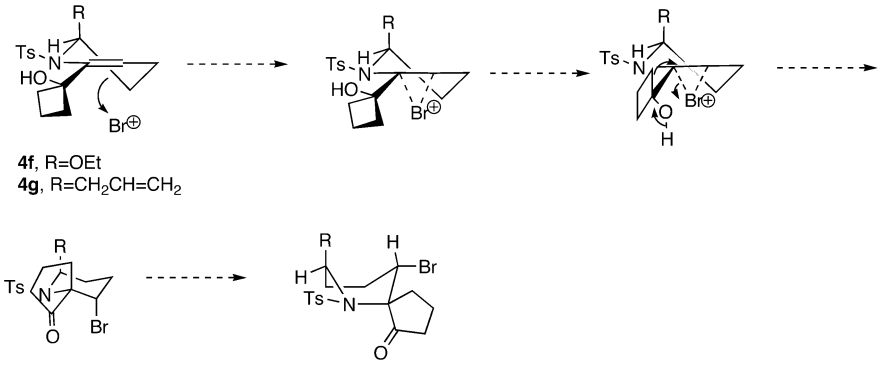
(26) Greshock, T. J.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3511.

(27) A similar effect has been noted in conjugate addition reactions of 2- or 6-substituted 2*H*-pyridinones: (a) Harris, J. M.; Padwa, A. *J. Org. Chem.* **2003**, *68*, 4371. For reviews on the effect of the A^{1,3} strain on conformational analysis and its applications to stereoselective reactions: (b) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841. (c) Hoffmann, R. W. *Angew. Chem., Int. Ed. Eng.* **1992**, *31*, 1124. (d) Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2000**, *39*, 2054.

SCHEME 8. Rationalization for Diastereoselectivity in Acid Promoted Reaction

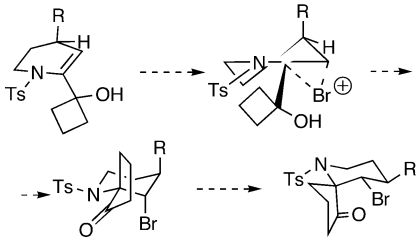


SCHEME 9. Diastereoselective Reactions of 4f and 4g



4f, R=OEt
4g, R=$CH_2CH{=}CH_2$

SCHEME 10. Reactions of 4-Substituted Substrates



(c) Substituent at the 4-Position. In this case, the electrophilic bromine may approach from the less hindered face of the alkene (Scheme 10).[28] Axial attack of the bromine results in the R group residing in a pseudoaxial orientation during the reaction as well. Ring expansion once again occurs wherein the migrating alkyl group is oriented trans to the bromine atom on the piperidine ring.

Conclusion

We have demonstrated that substrates of general structure **4** can be induced to undergo ring expansion reactions to form highly functionalized 1-azaspirocyclopentanones. Our experience suggests that, given an option, the reaction protocol using NBS is faster, higher yielding, and exhibits typically greater diastereoselectivity than reactions involving Bronsted acid promotion. Interestingly, the expansions of 4-substituted substrates using acid or NBS produce complementary diastereomers with respect to the newly formed spirocyclic carbon and the substituent at the 4-position. Separating and establishing the relative stereochemistry of brominated azaspirocyclopentanones is also somewhat easier than in the products lacking the 3-bromo substituents. In accord with Paquette's work, electron-donating substituents on the ring bearing the azacarbenium ion typically retard the reaction rate. As yet, we have been unable to induce cyclopentanols to ring-expand using either of these methods. By careful design of the substrates, however, these reactions are capable of generating structurally intricate molecules in excellent yields and diastereoselectivities. We are currently exploring versions of these processes using more structurally complex substrates to produce azaspirocyclic cyclopentanones that will be useful intermediates in the total synthesis of alkaloids.

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. and P.B.H. each individually thank the Gladys Estella Laird Foundation for Laird Fellowships.

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://pubs.acs.org.

JO0493572

(28) Similar trends are observed during the epoxidation of 3-substituted cyclohexenes: Inglis, D. B. *Chem. Ind.* **1971**, 1268. See also: Shimizu, M.; Morita, O.; Itoh, S.; Fujisawa, T. *Tetrahedron Lett.* **1992**, *33*, 7003.