Graphical Abstract

Studies in Selective 6-Membered Bromoether Formation via Bromonium- and Thiiranium-induced Cyclizations

Adam M. Levinson, Phillip J. Milner, and Scott A. Snyder*

Leave this area blank for abstract info.

Studies in selective 6-membered bromoether formation via bromonium and thiiranium-induced cyclizations

Adam M. Levinson,^a Phillip J. Milner,^a and Scott A. Snyder^{a,b*}

^aDepartment of Chemistry, Columbia University, New York, NY 10027

^bDepartment of Chemistry, The Scripps Research Institute, Jupiter, FL 33458

*Corresponding author. Tel.: 561-228-2350; fax: 561-228-2351; e-mail: ssnyder@scripps.edu

ARTICLE INFO

Article history:

Received

Received in revised form

Accepted

Available online

Keywords:

Bromonium

Natural Product

Total Synthesis

Bromoetherification

6-endo/5-exo

ABSTRACT

The formation of 6-*endo* bromoether ring systems from linear alkenol precursors through bromonium-induced cyclizations has historically proven challenging, with 5-*exo* products typically predominating, even on rigid scaffolds. This communication describes our efforts to achieve such cyclizations directly using new bromonium sources such as BDSB (Et₂SBr•SbCl₅Br) as well as two alternative, stepwise approaches based on either thiiranium-induced cyclization and subsequent sulfur manipulation or bromonium-induced closure of secondary alcohols and oxidative functionalization to generate fully substituted carbon centers. In some cases, 6-*endo* bromoethers could be controllably formed without generating 5-*exo* alternatives.

2009 Elsevier Ltd. All rights reserved.

During the past several decades, chemists have isolated and characterized a variety of structurally interesting and bioactive bromoether-containing natural products with a core brominated tetrahydropyran ring that possesses a 2,2,6,6-tetrasubstitution pattern (such as **1–4**, Scheme 1).¹ Biosynthetically, these ring systems are believed (and in some cases verified) to be the product of a bromonium-induced cyclization of a precursor tertiary alkenol as orchestrated by a vanadium-based enzyme.² Efforts to replicate that chemistry in a laboratory flask using simple reagents, however, have highlighted that it is quite challenging to achieve with any measure of control. Indeed, as indicated by the representative work shown in the lower half of Scheme 1 from the Corey and Crimmins groups, 5-*exo* products tend to predominate, even when the reaction process is executed on a rigid scaffold.³ Moreover, in those cases where a 6-*endo* product is favored, control over stereochemistry can be problematic, as can be product purification in terms of separating unwanted regio- and/or diastereomers.⁴ In the absence of enzymatic control, such selectivity for the 5-*exo*-tet product can be rationalized by both Baldwin's rules for kinetic ring closure as well as the avoidance of an impending A_{1,3}-interaction between two axial groups in a 6-*endo* transition state.⁵ Although others have previously achieved a degree of selectivity in the synthesis of natural products containing these ring systems, notably using electronic effects to direct the bromocyclization or through formation of these ring systems through indirect methods, no truly general solution to this problem has been developed.⁶ Herein, we highlight several directions of study seeking to determine if access to highly substituted 6-*endo* bromoethers can be achieved in a more controlled manner. After several failures, we ultimately developed a two-step alternative that can deliver

some specific materials in relatively good yield and stereoselectivity without the formation of 5-*exo* products.

Scheme 1. Natural products containing 6-membered bromoethers (such as **1–4**) and the challenges in achieving their laboratory synthesis from linear precursors using bromonium-induced cyclizations.

Our initial efforts sought to see if our recently developed bromonium source, BDSB (**14**, $\text{Et}_2\text{SBr}\cdot\text{SbCl}_5\text{Br}$)^{7abdef} a representative of a class of reagents with members recently rated as the most electrophilic halonium ions in existence,^{7g} could provide a different outcome in the direct cyclization of tertiary alkenols than previously available bromonium sources had achieved. Unfortunately, as defined in Scheme 2 with a few representative cases, we found that its use in a variety of solvents and reaction temperatures could never afford better than a 1:1 ratio of the 6-*endo* product and 5-*exo* alternative; in most cases explored with substrates of type **11** and **15**, the 5-*exo* product predominated. A key finding, however, was that if we used higher reaction temperatures (such as 25 °C), prolonged stirring at lower temperatures, or subsequently re-exposed the 6-*endo* products (i.e. **13** and **16**) to BDSB or MeSO_3H , the 6-*endo* product could be converted fully into the 5-*exo* alternative. These results suggest that these products may be both thermodynamically, as well as kinetically preferred, and is, to the best of our knowledge, the first time that such a conversion under acidic conditions has been described for these systems. A series of MM2 calculations on energy minimized structures confirm this thermodynamic product stability assertion (see Supporting Information) not only for these compounds, but some later materials as well. Only with highly biased systems, such as phenol **18**, were 6-*endo* products obtained cleanly, but their patterning does not match that found in the large variety of natural products highlighted earlier.

Scheme 2. Initial efforts to form 6-membered bromoethers using BDSB with key results being the ready formation of 5-*exo* bromoethers and the conversion of 6-*endo* products into 5-*exo* ethers under the reaction conditions.

Given these findings, we next wondered whether a different electrophile might be able to afford the desired outcome. Namely, if bromohydrins such as **20** were exposed to an appropriate thiiranium source, could the 6-*endo* product (**22**) be favored in general, and if not, based on the known reversibility of thiiranium addition to alkenes, could a 5-*exo* product (**21**) ultimately funnel to the 6-*endo* alternative in a manner opposite to that observed above?⁸ As an added benefit of this design, the sulfur electrophile could either be removed by treatment with Raney Nickel to give systems as needed for **2** or **4** or replaced by an alcohol through Pummerer chemistry to reach the core ring of **1** and related C-5 oxygenated THP natural products.⁹ In practice, however, the outcome of such reactions paralleled our previous results, with 5-*exo* products predominating. As shown in Scheme 3, the ratio of materials formed from substrate **23** using

electrophile source **24** was the best result obtained in terms of amount of 6-*endo* products formed.¹⁰ Prolonged reaction times led to enhanced production of 5-*exo* materials at the expense of 6-*endo* products in similar combined yields, highlighting again a possible thermodynamic preference for such compounds. Even the use of a known diene-containing substrate (**29**) bearing an additional olefin to help stabilize the carbocation needed for 6-*endo* closure saw 5-*exo* products predominate.^{11,12}

Scheme 3. Explorations into thiiranium-induced cyclizations, again highlighting preferential 5-*exo* cyclizations.

We next turned to the cyclization of secondary alkenols such as **31**, species shown in some contexts to be more controlled in leading to 6-*endo* products in electrophile-induced closures.¹³ That outcome likely has to do with the removal of $A_{1,3}$ -strain within the product and transition state. Here, assuming cyclization to **32**, our goal was then to develop ways to functionalize the tetrahydropyran product so as to reach fully-substituted carbons as in **33**. Pleasingly, this strategy bore fruit.

Following the synthesis of compounds of type **34** possessing several different R groups, we were pleased to find that subsequent exposure to 1.3 equivalents of BDSB in MeNO_2 at –25 °C afforded the desired 6-*endo* product as the only major observable product by ^1H NMR analysis of the crude reaction mixture and as essentially a single stereoisomer (with the structure of **35a** assigned by X-ray). Subsequent efforts to functionalize the C–H bond next the tetrahydropyran oxygen where R = alkyl failed to deliver any useful products. However, benzylic stabilization enabled functionalization in two distinct modes. In the first, oxidation of **36** with DDQ in methanolic solution yielded hemiacetal **37** as a single diastereoisomer, noting that this material and derivatives thereof were found to be unstable to even mildly protic or Lewis acidic conditions, with facile ring-opening undermining our efforts to install an additional carbon substituent. In the second, we found that C–H insertion of dichlorocarbene could take place cleanly under phase-transfer conditions, yielding dichloromethyl tetrahydropyran **39** in 28% yield as a single diastereomer from the differentially protected **38**, with recovered starting material accounting for the remaining material balance.¹⁴ The structure of **39** was confirmed by X-ray crystallographic analysis. Finally, to

access the desired methyl group, a ring-opening/ring-closing sequence was found to be possible. As shown in Scheme 4, treatment of **38** with DDQ under aqueous conditions led to smooth ring opening to generate bromohydrin **40** as a single stereoisomer. Subsequent Tebbe olefination set the stage for an acid-catalyzed reclosure of the tetrahydropyran ring in a 6-*exo* fashion to afford **41** in 53% overall yield with 3:1 diastereoselection.¹⁵ We tentatively assign the major isomer of this cyclization to have an axial methyl group in line with the spectra obtained for **36** and **39**. Globally, although longer than a direct bromonium-induced ring closure of a tertiary alkenol, this multi-step approach could afford materials of the type desired with some measure of control without the formation of 5-*exo* products.

Scheme 4. A two-step solution for 6-bromoether formation using bromonium electrophiles and subsequent oxidative functionalization.

In conclusion, we have explored several different methods for the selective synthesis of brominated 2,2,6,6-tetrasubstituted tetrahydropyran rings. Importantly, BDSB-induced cyclization of secondary alcohols, rather than their tertiary counterparts, yielded the desired 6-*endo* regioisomer in moderate to good yields with a high level of diastereoselectivity. Although subsequent direct methylation of these cyclization products has not yet been achieved, we have shown that benzylic stabilization does help facilitate a number of transformations, leading to diverse substitution at this position. Work to address these, and other shortcomings of this challenging group of

bromoetherifications is ongoing and will be reported in due course.

Acknowledgments

We wish thank Dr. Daniel S. Treitler for helpful discussions and experimental guidance. We also thank Dr. John Decatur and Dr. Yasuhiro Itagaki of Columbia University for NMR spectroscopic and mass spectrometric assistance, respectively, and the NSF (CHE-0619638) for an X-ray diffractometer and Prof. Gerard Parkin, Dr. Joshua Palmer, and Mr. Serge Ruccolo for performing crystallographic analyses. Financial support for this work was provided by the NSF (CAREER Award CHE-0844593 and REU funding for P.J.M. through CHE-0754919), the ACS Petroleum Research Fund (47481-G), Bristol-Myers Squibb, Eli Lilly, and Amgen.

References and notes

1. a) Faulkner, D. J. *Nat. Prod. Rep.* **1999**, *16*, 155–198. b) Gribble, G. W. *Naturally Occurring Organohalogen Compounds: A Comprehensive Update*. Wien: Springer-Verlag, 2010.
2. For a review on the role of bromoperoxidase enzymes, see: Butler, A.; Carter-Franklin, J. N. *Nat. Prod. Rep.* **2004**, *21*, 180–188.
3. a) Corey, E. J.; Ha, D.-C. *Tetrahedron Lett.* **1988**, *29*, 3171–3174. b) Crimmins, M. T.; Hughes, C. O. *Org. Lett.* **2012**, *14*, 2168–2171.
4. a) Hashimoto, M.; Kan, T.; Nozaki, K.; Yanagiya, M.; Shirahama, H.; Matsumoto, T. *J. Org. Chem.* **1990**, *55*, 5088–5107. b) González, I. C.; Forsyth, C. J. *J. Am. Chem. Soc.* **2000**, *122*, 9099–9108. c) Hartung, J.; Greb, M. *Tetrahedron Lett.* **2003**, 6091–6093. d) Brücher, O.; Bergsträßer, U.; Kelm, H.; Hartung, J.; Greb, M.; Svoboda, I.; Fuess, H. *Tetrahedron* **2012**, *68*, 6968–6980. e) Jung, M. E.; D'Amico, D. C.; Lew, W. *Tetrahedron Lett.* **1993**, *34*, 923–926.
5. Baldwin, J. E. *J. Chem. Soc., Chem. Comm.* **1976**, 734–736.
6. See Ref. 4b and a) McDonald, F. E.; Wei, X. *Org. Lett.* **2002**, *4*, 593–595. b) Nishiguchi, G. A.; Little, R. D. *J. Org. Chem.* **2005**, *70*, 5249–5256. c) Jung, M. E.; Lew, W. *J. Org. Chem.* **1991**, *56*, 1347–1349.
7. a) Snyder, S. A.; Treitler, D. S. *Angew. Chem. Int. Ed.* **2009**, *48*, 8039–8043. b) Snyder, S. A.; Treitler, D. S.; Brucks, A. P. *J. Am. Chem. Soc.* **2010**, *132*, 14303–14314. c) Snyder, S. A.; Treitler, D. S. *Org. Syn.* **2011**, *88*, 54–69. d) Snyder, S. A.; Gollner, A.; Chiriac, M. I. *Nature* **2011**, *474*, 461–466. e) Snyder, S. A.; Treitler, D. S.; Brucks, A. P.; Sattler, W. *J. Am. Chem. Soc.* **2011**, *133*, 15898–15901. f) Snyder, S. A.; Brucks, A. P.; Treitler, D. S.; Moga, I. *J. Am. Chem. Soc.* **2012**, *134*, 17714–17721. g) Ashtekar, K. D.; Marzijarani, N. S.; Jagannathan, A.; Holmes, D.; Jackson, J. E.; Borhan, B. *J. Am. Chem. Soc.* **2014**, *136*, 13355–13362.
8. a) Wang, H.; Huang, D.; Cheng, D.; Li, L.; Shi, Y. *Org. Lett.* **2011**, *13*, 1650–1653. b) Eames, J.; Kuhnert, N.; Sansbury, F. H.; Warren, S. *Synlett.* **1999**, 1211–1214.
9. a) de Carvalho, L. R.; Fujii, M. T.; Roque, N. F.; Kato, M. J.; Lago, J. H. G. *Tetrahedron Lett.* **2003**, *44*, 2637–2640. b) de Carvalho, L. R.; Fujii, M. T.; Roque, N. F.; Lago, J. H. G. *Phytochem.* **2006**, *67*, 1331–1335. c) Gonzalez, A. G.; Darias, J.; Martin, J. D. *Tetrahedron Lett.* **1973**, *26*, 2381–2384. d) Chang, M.; Vazquez, J. T.; Nakanishi, K.; Cataldo, F.; Estrada, D. M.; Fernandez, J.; Gallardo, A.; Martin, J. D.; Norte, M.; Perez, R.; Rodriguez, M. L. *Phytochem.* **1989**, *28*, 1417–1424.
10. a) Denmark, S. E.; Kornfilt, D. J. P.; Vogler, T. *J. Am. Chem. Soc.* **2011**, *133*, 15308–15311. b) Forbes, D. C.; Bettinger, S. V.; Al-Azzeh, N. N.; Finnigan, B. P.; Kundukulam, J. A. *Tetrahedron Lett.* **2009**, *50*, 1855–1857.
11. Andersson, P. G.; Bäckvall, J. E. *J. Org. Chem.* **1991**, *56*, 5349–5353.
12. For an example of the use of allylic stabilization to guide 6-*endo*-tet cyclizations, see: Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C. K. *J. Am. Chem. Soc.* **1989**, *111*, 5330–5334.
13. For representative examples of secondary alkenols favoring a 6-*endo* cyclization mode with various electrophiles: a) Ting, P. C.; Bartlett, P. A. *J. Am. Chem. Soc.* **1984**, *106*, 2668–2671. b) Bartlett, P. A.; Ting, P. C. *J. Org. Chem.* **1986**, *51*, 2230–2240. c) Mori, K.; Puapoomchareon, P. *Liebig. Ann. Chem.* **1988**, 175–177.

- d) Broka, C. A.; Hu, L.; Lee, W. J.; Shen, T. *Tetrahedron Lett.* **1987**, 28, 4993–4996. d) Coulombel, L.; Favier, I.; Duñach, E. *Chem. Commun.* **2005**, 2286–2288.
14. a) Masaki, Y.; Arasaki, H.; Shiro, M., *Chem. Lett.* **2000**, 1180–1181. b) Arasaki, H.; Iwata, M.; Makida, M.; Masaki, Y. *Chem. Pharm. Bull.* **2004**, 52, 848–852.
15. Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, 100, 3611–3613.