ORGANIC LETTERS

2003
Vol. 5, No. 13
2339−2342

$SiMe_3$-Based Homologation–Epoxidation–Cyclization Strategy for Ladder THP Synthesis

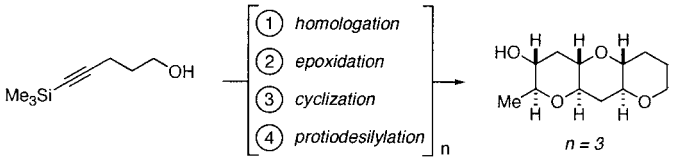
Timothy P. Heffron and Timothy F. Jamison*

Massachusetts Institute of Technology, Department of Chemistry, Cambridge, Massachusetts 02139

tfj@mit.edu

Received April 28, 2003

ABSTRACT



A trimethylsilyl ($SiMe_3$) group is the basis of a strategy that emulates the three fundamental proposed processes in ladder polyether biosynthesis: chain homologation, stereoselective epoxidation (>95% ee or >95:5 dr), and endo-selective, stereospecific (inversion) hydroxyepoxide cyclization (>95:5 endo:exo, >95% dr). A tris-THP was synthesized in 18 total operations from commercial materials using this approach.

An appealing explanation for the structural and stereochemical similarities among several families of trans-fused ("ladder") polyethers is that Nature may have devised a general solution for assembling these fascinating natural products. Nakanishi[1] proposed that three fundamental operations might comprise such a strategy: (1) polyene synthesis via iterative chain homologation, (2) asymmetric epoxidation, and (3) a series of endo-selective epoxide-opening events. While this proposal has yet to be verified experimentally, significant effort has been directed toward mimicking one or more of these steps.

The endo-selective epoxide ring-opening component has been addressed with two contrasting strategies, approaches typically described as being "iterative"[2] or involving "cascades".[3] Many of the iterative methods have been utilized in synthesis of ladder polyether natural products, but the cascade approaches have not. We report here that a trimethylsilyl ($SiMe_3$) group enables efficient and selective emulation of all three proposed biogenetic processes (homologation, epoxidation, cyclization) and is amenable to rapid, iterative synthesis of a ladder polyether subunit.

We began by evaluating suitable directing groups for these three transformations (**X**, Scheme 1). In this approach, chain homologation (1) with "R" installs all three carbon atoms of the heterocycle and therefore must contain both a "masked" nucleophile and electrophile, as it is also the site of coupling in the next iteration. Epoxidation (2) must be highly enantioselective in the first iteration and highly diastereoselective thereafter. We also required that the removal of **X** (4) be no more than one step so as not to unduly lengthen the synthesis simply to incorporate a given directing group.

(1) (a) Nakanishi, K. *Toxicon* **1985**, *23*, 473−479. (b) Lee, M. S.; Repeta, D. J.; Nakanishi, K.; Zagorski, M. G. *J. Am. Chem. Soc.* **1986**, *108*, 7855−7856. (c) Lee, M. S.; Qin, G.-w.; Nakanishi, K.; Zagorski, M. G. *J. Am. Chem. Soc.* **1989**, *111*, 6234−6241. (d) See also: Chou, H.-N.; Shimizu, Y. *J. Am. Chem. Soc.* **1987**, *109*, 2184−2185.

(2) Efforts of dozens of research groups in this area have been the subject of several recent reviews: (a) Alvarez, E.; Candenas, M.-L.; Pérez, R.; Ravelo, J. L.; Martín, J. D. *Chem. Rev.* **1995**, *95*, 1953−1980. (b) Mori, Y. *Chem. Eur. J.* **1997**, *3*, 849−852. (c) Marmsäter, F. P.; West, F. G. *Chem. Eur. J.* **2002**, *8*, 4347−4353. (d) Hirama, M., Rainier, J. D., Eds. *Tetrahedron Symposium-in-Print 90* **2002**, *58*, 1779−2040.

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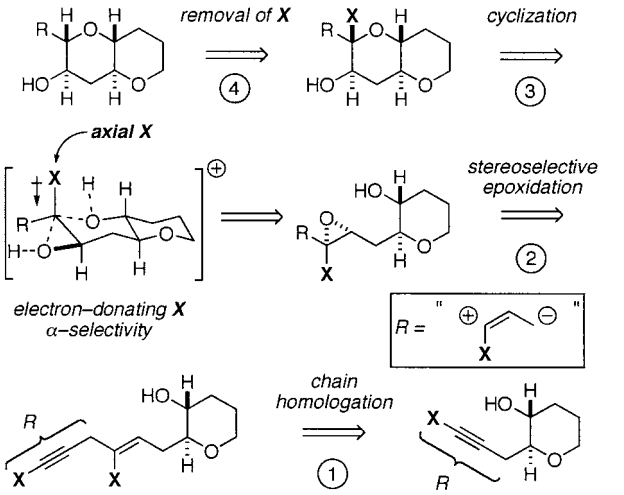
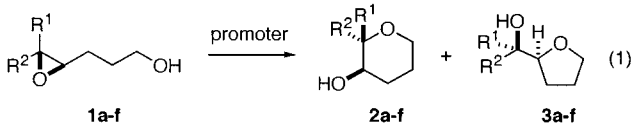
10.1021/ol0347040 CCC: $25.00
Published on Web 05/23/2003

Scheme 1



The nature of **X** merits further discussion in the context of the stereospecific hydroxyepoxide cyclization (3). A single experiment reported by Coxon in 1973 raised perhaps the most puzzling question of ladder polyether biosynthesis.[4] Treatment of epoxide **1a** with boron trifluoride etherate ($Et_2O{\cdot}BF_3$) affords an 86:14 mixture of "5-exo" tetrahydrofuran (THF, **3a**) and "6-endo" tetrahydropyran (THP, **2a**) products (Table 1, entry 1).

Table 1. Directing Group Effects in Hydroxyepoxide Cyclizations (Eq 1)



1a-f **2a-f** **3a-f**

entry	epoxide	R^1	R^2	promoter	**2:3**
1[a]	**1a**	H	Me	$Et_2O{\cdot}BF_3$	14:86
2[a]	**1b**	Me	H	$Et_2O{\cdot}BF_3$	≤3:97
3[b]	**1c**	H	$CH{=}CH_2$	(+)-CSA	>98:2
4[b]	**1d**	$CH{=}CH_2$	H	(+)-CSA	44:56
5[c]	**1e**	$SiMe_3$	Me	$Et_2O{\cdot}BF_3$	>95:5
6[c,d]	**1f**	Me	$SiMe_3$	$Et_2O{\cdot}BF_3$	see text

[a] See Coxon, ref 4. [b] See Nicolaou, refs 10a,b. [c] See Supporting Information. [d] Major product: $HO(CH_2)_4C(O)CH_3$.

Also noteworthy is that the analogous cyclization with the diastereomeric epoxide (**1b**) yields exclusively the exo cyclization product (**3b**), demonstrating the sensitivity of such cyclizations to epoxide substitution pattern (entry 2).

As a central tenet of Nakanishi's proposal involves a series of endo-selective epoxide-opening steps, how Nature overcomes the apparently disfavored mode of cyclization remains unknown. To be sure, these results do not necessarily invalidate the Nakanishi hypothesis. If hydroxyepoxide cyclizations are involved in the biosynthesis, Coxon's experiment simply illustrates the challenge of emulating this step in the laboratory. Accordingly, significant effort has been directed toward this problem.

Many strategies are based on the observations that acid-catalyzed epoxide ring-opening reactions proceed with inversion of configuration[5] and that rate[6] and regioselectivity[7] are very sensitive to the electronic nature of the epoxide substituents.[8,9]

In this vein, Nicolaou used an alkenyl group to provide π-stabilization of positive charge at the adjacent epoxide carbon[10] in pioneering studies that formed the basis of landmark total syntheses of the brevetoxins[11,12] and observed a trend with alkenyl groups (Table 1, entries 3 and 4) that was reminiscent of Coxon's experiments. These four results can be explained by a chair-like transition state (cf. Scheme 1), whereby the steric demand of a larger group in an axial position disfavors endo cyclization. Similarly, Mori found that an axial substituent other than H at the equivalent position prevented analogous epoxysulfone cyclizations.[2b,13]

A trimethylsilyl ($SiMe_3$) group emerged as an attractive candidate in other parts of the strategy and because of the regioselectivity of intermolecular epoxysilane ring-opening reactions with oxygen-centered nucleophiles.[14]

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(12) Total or formal synthesis of hemibrevetoxin: (a) Nicolaou, K. C.; Reddy, K. R.; Skokotas, G.; Sato, F.; Xiao, X.-Y. *J. Am. Chem. Soc.* **1992**, *114*, 7935−7936. (b) Nicolaou, K. C.; Reddy, K. R.; Skokotas, G.; Sato, F.; Xiao, X.-Y.; Hwang, C.-K. *J. Am. Chem. Soc.* **1993**, *115*, 3558−3575. (c) Kadota, I.; Park, J.-Y.; Koumura, N.; Pollaud, G.; Matsukawa, Y.; Yamamoto, Y. *Tetrahedron Lett.* **1995**, *36*, 5777−5780. (d) Morimoto, M.; Matsukura, H.; Nakata, T. *Tetrahedron Lett.* **1996**, *37*, 6365−6368. (e) Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Am. Chem. Soc.* **1997**, *119*, 4557−4558. (f) Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Org. Chem.* **1998**, *63*, 6200−6209. (g) Kadota, I.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 6597−6606. (h) Rainier, J. D.; Allwein, S. P.; Cox, J. M. *J. Org. Chem.* **2001**, *66*, 1380−1386. (i) Holland, J. M.; Lewis, M.; Nelson, A. *J. Org. Chem.* **2003**, *68*, 747−753.

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Nevertheless, its effect on the cyclization was still a significant concern since no such cyclization of a trisubstituted epoxysilane or one in which a $SiMe_3$ group would occupy an axial position in the proposed transition state had been reported. Schaumann had investigated cyclizations with $SiMe_3$ in an equivalent *equatorial* position, but formation of endo products in these cases could be ascribed to a significant conformational predisposition such as avoidance of forming a highly strained trans-5,5 system or the presence of one or more equatorial "anchoring" groups.[15] These results, along with the trends observed by Coxon, Nicolaou, and Mori, did not augur well for our plan of placing a large $SiMe_3$ group in the axial position.

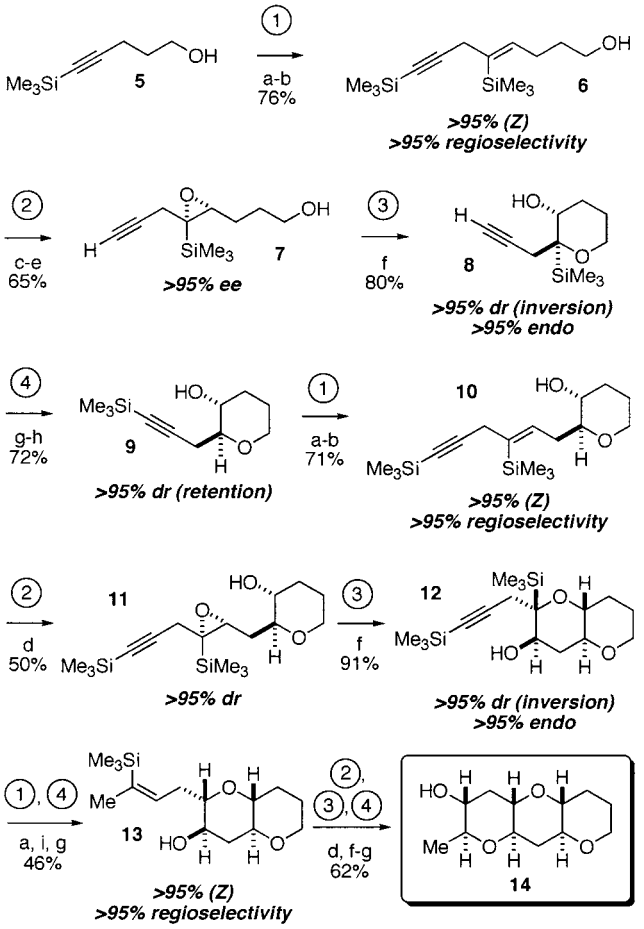
The trends we observed with respect to epoxysilane substitution pattern were therefore quite unexpected (Table 1, entries 5 and 6), as they are exactly *opposite* those predicted by the Nicolaou, Mori, and Schaumann studies. Epoxide **1e** ($SiMe_3$ axial) underwent cyclization at 0 °C with inversion of configuration (>95% dr) and >95% regioselectivity (^{1}H NMR), affording *exclusively* the "6-endo" THP (**2e**, entry 5). More surprising was that isomeric epoxide **1f** ($SiMe_3$ equatorial, entry 6) afforded primarily 1-hydroxy-5-hexanone[14b] along with a complex mixture of cyclization products. Thus, even though it is *larger* than methyl, an axial $SiMe_3$ appears to be accommodated more easily in the transition state.

To our delight, the $SiMe_3$ group also satisfied all other requirements, enabling efficient emulation of all three proposed processes in ladder polyether biogenesis (Scheme 2).

After highly selective hydroalumination−iodination,[16] direct propargylation ($Me_3Si-C\equiv C-Me$ (**4**), *n*-BuLi, TMEDA; CuI) proceeds in high yield and good propargyl/allenyl selectivity.[17] Use of a molar excess of the copper reagent obviates hydroxyl group protection, and neither π-bond isomerization nor erosion of geometric purity is observed in "skipped enynes" **6** and **10**. The commercially available **4** thus embodies the "masked" electrophile/nucleophile in this strategy (Scheme 1).

The method of Shi proved to be superior for the enantioselective epoxidation of trisubstituted alkene **6** (>95% ee),[18] and Lewis acid-promoted hydroxyepoxide cyclization as discussed above completed construction of the first THP ring. Straightforward protiodesilylation (TBAF) cleanly removes the multipurpose $SiMe_3$ group and proceeds with retention of configuration. Despite the cis relationship of the Me_3Si and OH groups and the basic character of TBAF solutions, byproducts corresponding to formal elimination of Me_3SiOH are not observed.[19] The very high degree of reagent control in subsequent epoxidations was a key factor in the assembly of THP triad **14** by reiteration of these same four procedures.

Scheme 2[a]



[a] Reaction conditions: (a) DIBAL; I_2. (b) $Me_3Si-C\equiv C-Me$ (**4**), *n*-BuLi, TMEDA; CuI, DMAP. (c) Ac_2O, DMAP, Et_3N. (d) See ref 17. (e) LiOH, H_2O, THF, MeOH. (f) $Et_2O\cdot BF_3$, CH_2Cl_2. (g) TBAF, THF. (h) *n*-BuLi, Me_3SiCl. (i) $Me_2CuCNLi_2$.

The Nicolaou, Mori, and $SiMe_3$-based approaches to iterative ladder polyether synthesis each mirror all three proposed biogenetic operations. Nicolaou's strategy uses an alkenyl group for π-stabilization of positive charge at the adjacent (α) epoxide carbon in the hydroxyepoxide cyclization and is part of the carbon framework, whereas Mori uses the inductive effect of an electron-withdrawing $PhSO_2$ group to favor epoxide opening at the β carbon. In contrast, a $SiMe_3$ group appears to direct α opening in a different stereoelectronic manner and can occupy an axial position in the course of the stereospecific and endo-selective cyclization. These features, in conjunction with the *complete* stereo- and regiocontrol in each step, make possible the assembly of THP triad **14** in 18 *total* operations, whereas the Nicolaou and

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Mori approaches average 10−13 operations per THP, including preparation of necessary building blocks. Our current studies include synthesis of ladder polyether natural products based on this strategy.

Acknowledgment. We thank the James H. Ferry Fund (MIT) for partial support of this work and Johnson & Johnson for a research assistantship to T.P.H. We also thank the National Institute of General Medical Sciences (GM-063755), the NSF (CAREER CHE-0134704), the donors of the Petroleum Research Fund, administered by the American Chemical Society, Amgen, Boehringer-Ingelheim, Bristol-Myers Squibb, Merck, Pfizer, and 3M for financial support. The NSF (CHE-9809061 and DBI-9729592) and NIH (1S10RR13886-01) provide partial support for the MIT Department of Chemistry Instrumentation Facility.

Supporting Information Available: Experimental procedures and data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0347040