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Total Synthesis of (−)-Sessilifoliamide C and (−)-8-*epi*-Stemoamide

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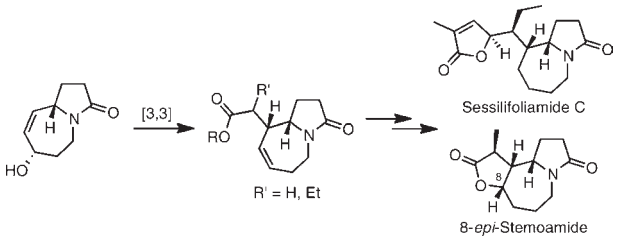
ABSTRACT



A convergent route featuring [3,3]-sigmatropic rearrangements of a linchpin azepinopyrrolidine served to install two of the four contiguous stereocenters present in the tricyclic *Stemona* alkaloids sessilifoliamide and stemoamide. In addition to the first total synthesis of (−)-sessilifoliamide C, a potential biosynthetic relationship between the sessilifoliamides and previously reported *Stemona* alkaloids is presented.

Natural products from *Stemona* and *Croomia* plants have served as an inspiration for chemical, biological, and synthetic studies since at least the 1930s, when the first derivatives were described in Western references.[1−3] Extracts from these plants have been used for centuries in Eastern cultures for the treatment of various respiratory problems, such as pertussis, bronchitis, and tuberculosis. However, with the exception of their well-documented insecticidal activities, validated evidence for other beneficial human health effects of the pure natural products is just beginning to emerge.[4]

In 2003, Takeya and co-workers isolated sessilifoliamides A−D (**1**−**4**) from the roots of the perennial herb *Stemona sessilifolia*.[5] These alkaloids possess the characteristic pyrrolo[1,2-*a*]azepine core attached to a butenolide substituent (Scheme 1). The relative configuration of **3** was confirmed by a chemical degradation to a derivative in common with sessilifoliamide A, for which an X-ray crystal structure had been obtained.[5] Interestingly, a possible biosynthetic relationship between the sessilifoliamides and the previously identified parvistemoline (**5**)[6] is apparent upon C(16)-oxidation and Michael addition. Accordingly, we decided to investigate a unified and possibly biomimetic strategy toward the sessifoliamides and prepare sessilifoliamide C first, because of its similarity to the more complex ring system present in parvistemoline.

Our retrosynthetic strategy for **3** was focused on the construction of the C(9)−C(10) adjacent stereocenters prior to butenolide formation (Scheme 2). We desired an approach that could accomplish this task in a single operation and envisioned that a [3,3]-sigmatropic Claisen rearrangement[7] with precise stereocontrol in the transition

(1) (a) Lee, H. M.; Chen, K. K. *J. Am. Pharm. Assoc.* **1940**, *29*, 391. (b) Edwards, O. E.; Feniak, G.; Handa, K. L. *Can. J. Chem.* **1962**, *40*, 455. (c) Uyeo, S.; Irie, H.; Harada, H. *Chem. Pharm. Bull* **1967**, *15*, 768. (d) Alibes, R.; Figueredo, M. *Eur. J. Org. Chem.* **2009**, 2421. (e) Pilli, R. A.; Rosso, G. B.; Ferreira De Oliveira, M. D. C. *Nat. Prod. Rep* **2010**, *27*, 1908.

(2) For recent synthetic studies reported on *Stemona* alkaloids, see, for example: (a) Chen, Z.-H.; Tu, Y.-Q.; Zhang, S.-Y.; Zhang, F.-M. *Org. Lett.* **2011**, *13*, 724. (b) Chen, Z.-H.; Zhang, Y.-Q.; Chen, Z.-M.; Tu, Y.-Q.; Zhang, F.-M. *Chem. Commun.* **2011**, *47*, 1836. (c) Frankowski, K. J.; Setola, V.; Evans, J. M.; Neuenswander, B.; Roth, B. L.; Aube, J., *Proc. Nat. Acad. Sci. U.S.A.* **2011**, early edition.

(3) For previous studies on *Stemona* alkaloids from our laboratory, see: (a) Wipf, P.; Kim, Y. *Tetrahedron Lett.* **1992**, *33*, 5477. (b) Wipf, P.; Kim, Y.; Goldstein, D. M. *J. Am. Chem. Soc.* **1995**, *117*, 11106. (c) Goldstein, D. M.; Wipf, P. *Tetrahedron Lett.* **1996**, *37*, 739. (d) Wipf, P.; Li, W. *J. Org. Chem.* **1999**, *64*, 4576. (e) Wipf, P.; Mareska, D. A. *Tetrahedron Lett.* **2000**, *41*, 4723. (f) Wipf, P.; Spencer, S. R. *J. Am. Chem. Soc.* **2005**, *127*, 225.

(4) Greger, H. *Planta Med.* **2006**, *72*, 99.

(5) Kakua, D.; Hitotsuyanagi, Y.; Matsuura, N.; Fukaya, H.; Takeya, K. *Tetrahedron* **2003**, *59*, 7779.

(6) Lin, W.; Xu, R.; Zhong, Q. *Huaxue Xuebao* **1991**, *49*, 927.

(7) Wipf, P. Claisen Rearrangements. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon: Oxford, 1991; Vol 5, pp 827−874.

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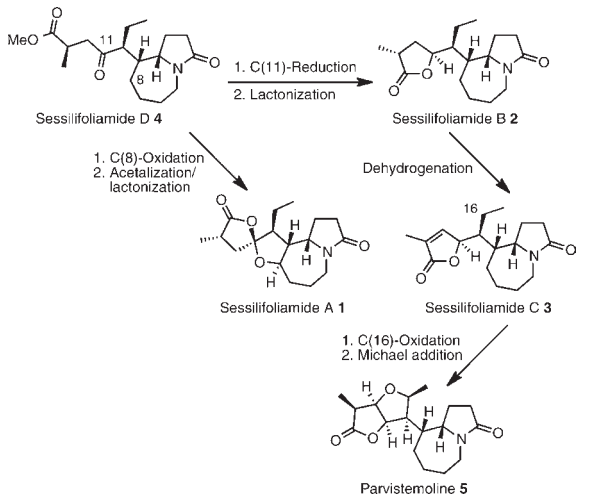
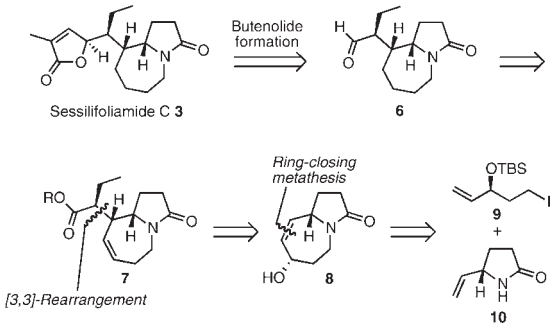
Scheme 1. Biosynthetic Hypothesis Based on the Structural Similarities between Sessilifoliamides and Parvistemoline



state could meet these requirements. The precursor to this key transformation, alcohol **8**, was accessible by ring-closing metathesis (RCM) of the diene formed from the alkylation of pyrrolidinone **10** with iodide **9**.

Scheme 2. Retrosynthetic Approach for Sessilifoliamide C

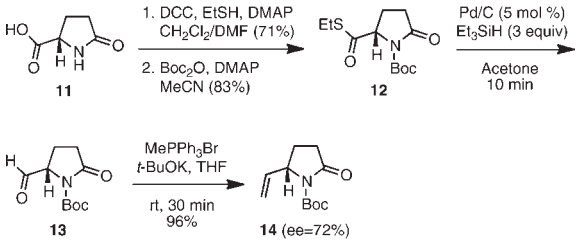


While several methods for the preparation of vinylpyrrolidinone **10** are known in the literature,[8] preliminary RCM studies established that we needed an *N*-protective group on **10**, and therefore, we pursued a new, scaleable synthesis of the Boc derivative **14** (Scheme 3). (*S*)-Pyroglutamic acid **11** was converted to the thioester with ethanethiol in the presence of carbodiimide, followed by *N*-Boc protection to afford carbamate **12**. Direct conversion of **12** to the aldehyde **13** was successful by a Fukuyama reduction.[9] Fukuyama conditions prior to *N*-Boc protection did not lead to the desired reduction product, and starting material was

(8) (a) Wei, Z.-Y.; Knaus, E. *Synlett* **1993**, 295–296. (b) Wei, Z.-Y.; Knaus, E. *Tetrahedron* **1994**, *50*, 5569. (c) Napoletano, M.; Della Bella, D.; Fraire, C.; Grancini, G.; Masotto, C.; Ricciardi, S.; Zambon, C. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 589. (d) Gheorghe, A.; Schulte, M.; Reiser, O. *J. Org. Chem.* **2006**, *71*, 2173. (e) Mo, F.; Li, F.; Qiu, D.; Wang, J. *Tetrahedron* **2010**, *66*, 1274.

(9) Tokuyama, H.; Yokoshima, S.; Lin, S.-C.; Li, L.; Fukuyama, T. *Synthesis* **2002**, 1121.

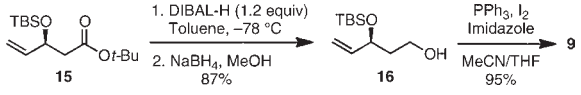
Scheme 3. Preparation of Vinylpyrrolidinone **14**



recovered cleanly despite modifications in the reaction time, catalyst loading, and solvent. Pyrrolidinone protection facilitated the desired transformation. Immediate exposure of the aldehyde **13** to Wittig olefination delivered a 96% yield of alkene **14**. Boc-protected **14** was found to be stable to bench-top storage, whereas amide **10** decomposed within hours. However, because of partial racemization prior to and/or during olefination, **14** was obtained in 72% ee, as determined by chiral HPLC analysis on a Chiralcel OD-H column.

The second segment, iodide **9**, was prepared by an enzymatic resolution strategy which provided the *t*-butyl ester **15** on a large scale (Scheme 4).[10] A two-step reduction procedure was used to generate alcohol **16** in 87% yield; in the presence of 2 equiv of DIBAL-H, **16** was isolated in lower yield (ca. 70%). Finally, a straightforward iodination of **16** afforded **9**.

Scheme 4. Preparation of Iodide **9**

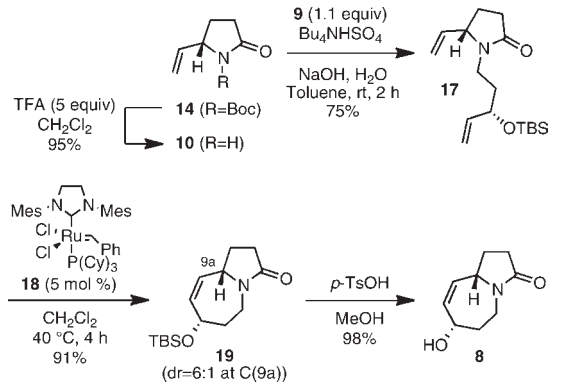


In preparation for the segment condensation, the *N*-Boc group in **14** was cleaved with TFA (Scheme 5). After some optimization, we discovered that alkylation of amide **10** under phase-transfer conditions was more reproducible and manageable on scale than NaH/DMF conditions, providing us with a reliable access to diene **17**. Ring closure to the pyrrolo-[1,2-*a*]azepine core characteristic of *Stemona* alkaloids by RCM of **17** afforded **19** in 91% yield as an inseparable 6:1 mixture of C(9a) diastereomers resulting from partially racemized **14**. Removal of the TBS group under acidic conditions led to the allylic alcohol **8** as a hygroscopic solid.

Prior difficulties with [3,3]-rearrangements on bicycles motivated us to probe whether this reaction could occur on the sterically congested concave face of pyrrolo-[1,2-*a*]azepine **8**. We selected an Eschenmoser–Claisen reaction[7] to address this question, in analogy to our stenine[3f] and tuberostemonine[3b] syntheses (Scheme 6). The desired rearrangement occurred readily, and amide **21** was obtained in 92% yield under optimized conditions.

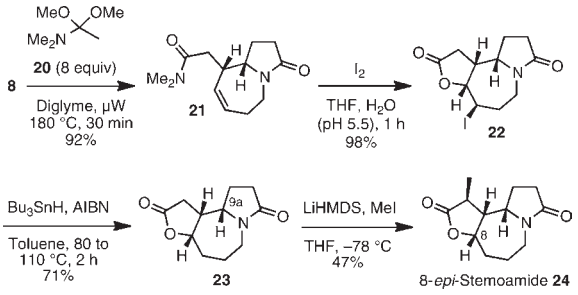
(10) (a) Ghosh, A. K.; Kulkarni, S. *Org. Lett.* **2008**, *10*, 3907. (b) Ghosh, A. K.; Yuan, H. *Tetrahedron Lett.* **2009**, *50*, 1416. (c) Vrielynck, S.; Vandewalle, M. *Tetrahedron Lett.* **1995**, *36*, 9023.

Scheme 5. Segment Condensation, RCM, and Synthesis of Linchpin Intermediate **8**



Because of the structural similarity of **21** and stemoamide,[11] we decided to complete the remaining three steps to the tricyclic core of this natural product. Iodolactonization of **21** and reduction of the resulting iodide proceeded in 98% and 97% yield, respectively, to give **23** as a 6:1 mixture of C(9a) diastereomers. Chromatographic removal of the remaining C(9a) isomer provided the major isomer of **23** in 71% yield for this step. Finally, lactone α-methylation led to 8-*epi*-stemoamide (**24**). While many syntheses of stemoamide and its stereoisomers have been reported,[12] our effort represents the first synthesis of the C(8) epimer.

Scheme 6. Conversion of **8** to (−)-8-*epi*-Stemoamide



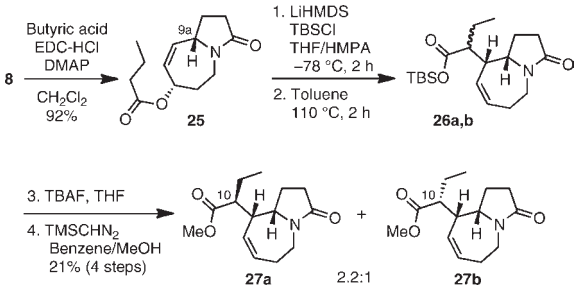
Additionally, among the plethora of synthetic approaches to stemoamide, this is the first example of a [3,3]-rearrangement to install the C(9) stereocenter in this ring system.

(11) Lin, W.; Ye, Y.; Xu, R. *J. Nat. Prod.* **1992**, *55*, 571.

(12) (a) Williams, D. R.; Reddy, J. P.; Amato, G. S. *Tetrahedron Lett.* **1994**, *35*, 6417. (b) Khim, S.-K.; Schultz, A. G. *J. Org. Chem.* **2004**, *69*, 7734. (c) Bogliotti, N.; Dalko, P. I.; Cossy, J. *J. Org. Chem.* **2006**, *71*, 9528. (d) Kohno, Y.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2063. (e) Bates, R. W.; Sridhar, S. *Synlett* **2009**, *12*, 1979. (f) Jacobi, P. A.; Lee, K. *J. Am. Chem. Soc.* **1997**, *119*, 3409. (g) Jacobi, P. A.; Lee, K. *J. Am. Chem. Soc.* **2000**, *122*, 4295. (h) Kinoshita, A.; Mori, M. *J. Org. Chem.* **1996**, *61*, 8356. (i) Kinoshita, A.; Mori, M. *Heterocycles* **1997**, *46*, 287. (j) Sibi, M. P.; Subramanian, T. *Synlett* **2004**, 1211. (k) Olivo, H. F.; Tovar-Miranda, R.; Barragán, E. *J. Org. Chem.* **2006**, *71*, 3287. (l) Torssell, S.; Wanngren, E.; Somfai, P. *J. Org. Chem.* **2007**, *72*, 4246. (m) Gao, P.; Tong, Z.; Hu, H.; Xu, P.-F.; Liu, W.; Sun, C.; Zhai, H. *Synlett* **2009**, 2188. (n) Wang, Y.; Zhu, L.; Zhang, Y.; Hong, R. *Angew. Chem., Int. Ed.* **2011**, *50*, 2787. (o) Honda, T.; Matsukawa, T.; Takahashi, K. *Org. Biomol. Chem.* **2011**, *9*, 673.

Having demonstrated that the [3,3]-sigmatropic rearrangement and chain extension from C(7) to C(9) on **8** was indeed feasible, we studied the Ireland−Claisen rearrangement[7,13] for the stereoselective installation of the tertiary methine C(11) in the sessilifoliamides. Acylation of alcohol **8** (still as a 6:1 mixture of C(9a) diastereomers derived from **19**) with butyric acid under carbodiimide coupling conditions provided ester **25** in 92% yield (Scheme 7). Enolization with LiHMDS in a THF/HMPA mixture[14] followed by trapping with TBSCl provided the (*Z*)-silyl ketene acetal as the sole stereoisomer according to ^{1}H NMR analysis of the crude reaction product. The subsequent thermal rearrangement in toluene led to an approximately 2:1 ratio of silyl esters **26a** and **26b**, which were treated with TBAF followed by TMS-diazomethane to give the corresponding methyl esters. Unfortunately, both the yield of the four-step sequence and the ratio of diastereomeric products **27a** and **27b** remained low (21% yield, 2.2:1 dr) despite attempts to optimize the reaction time, temperature, and solvent polarity.

Scheme 7. TBS-Mediated Ireland−Claisen Rearrangement of **8**

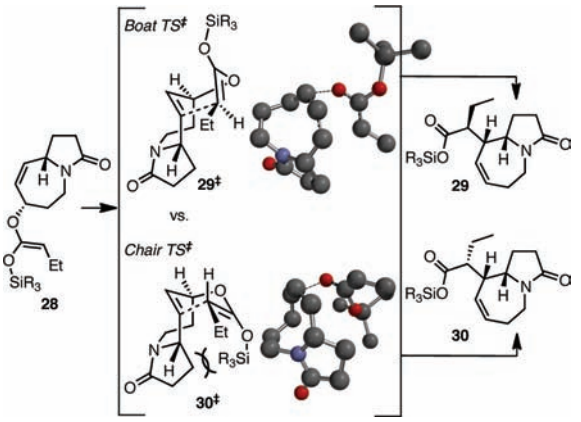


A significant improvement in this key transformation could be achieved after an analysis of the competing transition states of the Ireland−Claisen rearrangement (Scheme 8). Specifically, we noticed that the orientation of the trialkylsilyl group was remarkably different in **29**‡ and **30**‡ and therefore offered an opportunity to influence the course of the reaction. We hypothesized that a significant increase in the size of the alkyl groups on silicon would likely selectively destabilize chair transition state **30**‡, where the silyl group is positioned underneath the 7-membered ring during the C−C bond formation, and be more readily tolerated in boat transition state **29**‡, in which the silyl group is kept distant from the 5,7-ring system. This hypothesis could be readily put to test (Scheme 9). Ireland−Claisen rearrangement of the TIPS-silyl ketene acetal, formed by enolization of **25** in the presence of TIPSCl, required heating at reflux in degassed[15] xylenes for 3 h to go to completion. The resulting **31a** and **31b** were again converted to the methyl esters to simplify analysis.

(13) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.

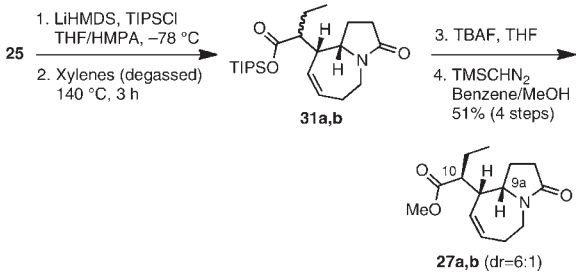
(14) (a) Ireland, R. E.; Wipf, P.; Armstrong, J. D. *J. Org. Chem.* **1991**, *56*, 650. (b) Ireland, R. E.; Wipf, P.; Xiang, J. N. *J. Org. Chem.* **1991**, *56*, 3572.

Scheme 8. Transition-State Analysis of the Ireland–Claisen Rearrangement



Gratifyingly, esters **27a** and **27b** were isolated in 51% yield from **25** in an improved 6:1 ratio of C(10) diastereomers, in support of our transition-state analysis.[16] Chromatography on SiO_2 was used to remove the diastereomers at C(9a) from the 6:1 mixture of **27a** and **27b**. Confirmation of the assignment of the major isomer **27a** was gained upon completion of the natural product and comparison of the spectroscopic data.

Scheme 9. TIPS-Mediated Ireland–Claisen Rearrangement of **8**



Surprisingly, methyl esters **27a** and **27b** proved to be resistant to nucleophilic addition of Grignard reagents and metalated dimethylhydroxylamine, even at elevated temperatures. We speculated that increased conformational flexibility and a lower oxidation state at carbonyl C(11) could promote reactivity.

(15) Degassing was necessary to suppress the formation of oxidative byproducts.

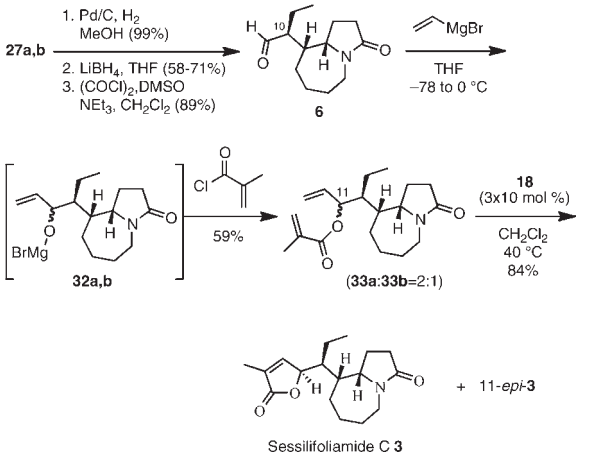
(16) (a) Transition states were identified using a PM3 transition state search in Spartan 10 (Wavefunction, Inc., Irvine, CA). A substituent-simplified (R = Me, Me in place of Et) boat analogue of **29**‡ was found to be approximately equal in energy to the corresponding analog of chair **30**‡ (Scheme 8). (b) For another observation of the effect of the steric bulk of the silyloxy group on the diastereoselectivity of the Ireland–Claisen rearrangement, see: Chen, C.-L.; Namba, K.; Kishi, Y. *Org. Lett.* **2009**, *11*, 409.

(17) The synthetic product was spectroscopically identical to the natural product,[5] with the exception of the magnitude of the specific rotation (natural: $[\alpha]^{26}_D$ −140 (*c* 0.17, $CHCl_3$), synthetic: $[\alpha]^{23}_D$ −84.6 (*c* 2.5, $CHCl_3$).

(18) (a) Castro, A. M. M. *Chem. Rev.* **2004**, *104*, 2939. (b) Gül, S.; Schoenebeck, F.; Aviyente, V.; Houk, K. N. *J. Org. Chem.* **2010**, *75*, 2115.

Therefore, the 6:1 mixture of **27a**,**b** was hydrogenated and converted to the corresponding aldehyde by sequential treatment with $Pd/C/H_2$, $LiBH_4$, and Swern reagent (Scheme 10). The minor C(10)-stereoisomer could be removed chromatographically from either alcohol or aldehyde intermediate after the latter two steps to afford pure **6**. Exposure of **6** to vinylmagnesium bromide afforded the allylic alkoxides **32a** and **32b**, which were acylated in situ with methacryloyl chloride to afford a 2:1 mixture of the labile **33a** and **33b**. A final RCM successfully assembled the butenolide ring in 84% yield, and MPLC separation revealed the major isomer to be (−)-sessilifoliamide C (**3**) by comparison of the spectroscopic data with the reported literature values of the natural product.[17]

Scheme 10. Conversion of **27** to (−)-Sessilifoliamide C



In summary, we have completed the first synthesis of the *Stemona* alkaloid (−)-sessilifoliamide C, which also represents the first member of the sessilifoliamide family to succumb to total synthesis. Noteworthy aspects of our approach include a convergent strategy featuring a [3,3]-rearrangement to install two contiguous stereocenters at C(9)–C(10) and the ability to access the stemoamide ring system in a unified strategy from linchpin intermediate **8**. The synthetic efficiency of the key Ireland–Claisen rearrangement benefited from increasing the steric bulk of the ketene acetal silyl substituent to proceed through a preferred boat-like transition state while providing a level of diastereoselection that is notable in a bicyclic system.[18]

Acknowledgment. This work was supported by the NIH/NIGMS CMLD program (GM067082). We thank Dr. John Williams (University of Pittsburgh) for high resolution mass spectrometry and Mr. Mike Delk (University of Pittsburgh) for NMR spectrometer maintenance. A.T.H. thanks the Goldblatt family for a University of Pittsburgh graduate fellowship.

Supporting Information Available. Experimental procedures and spectral data for all new compounds, including copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.