ORGANIC LETTERS

2000
Vol. 2, No. 6
763−766

Studies toward (−)-Gymnodimine: Concise Routes to the Spirocyclic and Tetrahydrofuran Moieties

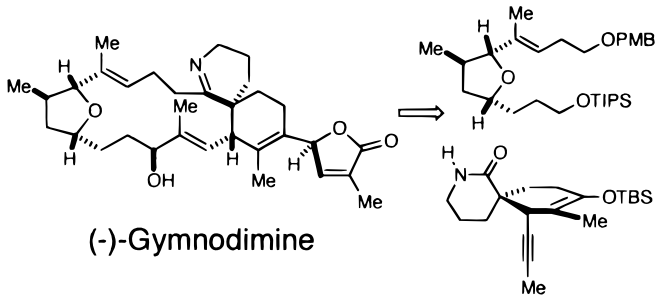
Ju Yang, Stephen T. Cohn, and Daniel Romo*

Department of Chemistry, Texas A&M University, P.O. Box 30012, College Station, Texas 77843-3012

romo@mail.chem.tamu.edu

Received January 4, 2000

ABSTRACT



(−)-Gymnodimine is a member of a unique class of potent marine toxins possessing imines within a spirocylic array. Herein we report the synthesis of the tetrahydrofuran fragment and a strategy toward the spirocyclic imine fragment of this family of toxins. Key reactions include an asymmetric anti-aldol reaction to set the stereochemistry of the tetrahydrofuran and a formal, intermolecular Diels–Alder reaction involving an α-methylene-δ-lactam and a dienyne.

Marine toxins have proven to be useful biochemical probes for the study of a variety of biological systems. Examples include the use of tetrodotoxin and brevetoxin in studies of sodium channels,[1] okadaic acid in studies of protein phosphatases,[2] and domoic acid in studies of neuronal receptors.[3] Gymnodimine (**1**) is a member of a class of recently isolated marine toxins that possess unusual spirocyclic imines within macrocycles that also contain an ether or polyether subunit.[4] Other members of this family include the spirolides[5] and pinnatoxins.[6] These natural products have attracted much synthetic interest,[7] culminating recently in an elegant synthesis of pinnatoxin A by Kishi employing an intramolecular Diels−Alder reaction.[7g] Recently, Munro and Blunt disclosed the relative and absolute stereochemistry of gymnodimine as determined by X-ray analysis of the *p*-bromobenzamide **3** of gymnodamine (**2**), the reduction product of gymnodimine.[8] A new analogue of gymnodimine, gymnodimine B, has recently been isolated.[9]

As a means to explore concise synthetic strategies to the interesting spirocyclic imines found in these toxins and to

(1) Catterall, W. A. *Physiol. Rev.* **1992**, *72*, S15−S48.
(2) (a) Bialojan, C.; Takai, A.; *Biochem. J.* **1988**, *256*, 283−290. (b) Haystead, T. A. J.; Sim, A. T. R.; Carling, D.; Honnor, R. C.; Tsukitani, Y.; Cohen, P.; Hardie, D. G. *Nature* **1989**, *337*, 78−81.
(3) Wenthold, R. J.; Hampson, D. R. *J. Biol. Chem.* **1988**, *263*, 2500−2505.
(4) Seki, T.; Masayuki, S.; Mackenzie, L.; Kaspar, H. F.; Yasumoto, T. *Tetrahedron Lett.* **1995**, *36*, 7093−7096.
(5) Hu, T.; Curtis, J. M.; Oshima, Y.; Quilliam, M. A.; Walter, J. A.; Wright, W. M.; Wright, J. L. C. *J. Chem. Soc., Chem. Commun.* **1995**, 2159−2161.
(6) Uemura, D.; Chou, T.; Haino, T.; Nagatsu, A.; Fukuzawa, S.; Zheng, S.; Chen, H. *J. Am. Chem. Soc.* **1995**, *117*, 1155−1156.
(7) For other synthetic studies toward gymnodimine, see: (a) Ishihara, J.; Miyakawa, J.; Tsujimoto, T.; Murai, A. *Synlett* **1997**, 1417−1419. (b) Rainier, J. D.; Xu, Q. *Org. Lett.* **1999**, *1*, 27−29. For synthetic studies of pinnatoxin, see: (c) Ishihara, J.; Sugimoto, T.; Murai, A. *Synlett* **1998**, 603−606. (d) Ishiwata, A.; Sakamoto, S.; Noda, T.; Hirama, M. *Synlett* **1999**, 692−694. (e) Nitta, A.; Ishiwata, A.; Noda, T.; Hirama, M. *Synlett* **1999**, 695−696. (f) Sugimoto, T.; Ishihara, J.; Murai, A. *Synlett* **1999**, 541−544. (g) McCauley, J. A.; Nagasawa, K.; Lander, P. A.; Mischke, S. G.; Semones M. A.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 7647−7648.

10.1021/ol005510c CCC: $19.00
Published on Web 02/25/2000

study their mode of action, we initiated a total synthesis of (−)-gymnodimine. In our retrosynthetic analysis, we envisioned the coupling of three fragments to provide the most convergency and the most flexibility in preparing derivatives for biomechanistic studies (Figure 1). Coupling the tetrahydrofuran fragment **4**, the spirocyclic lactam **5**, and the dihydrofuran **6** would deliver the target molecule.

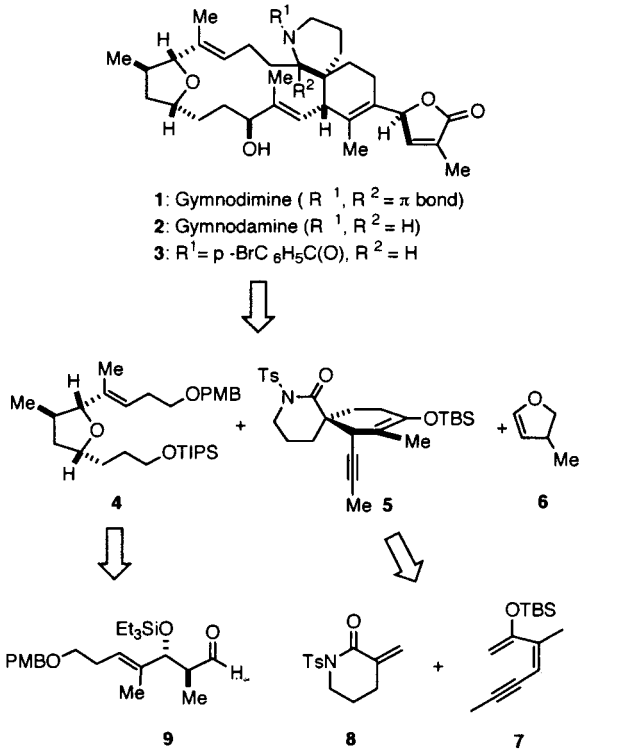
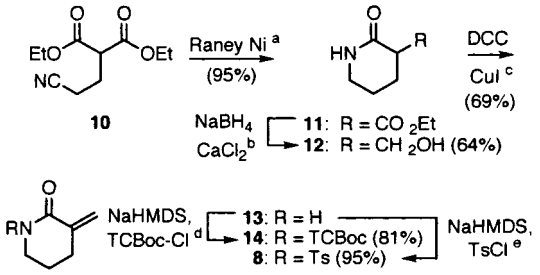


Figure 1. Retrosynthetic analysis of gymnodimine and structures of derivatives.

We envisioned the use of a Diels−Alder strategy to access the spirocyclic moiety of gymnodimine and related toxins. Initially, we recognized that application of a Diels−Alder strategy would dictate the use of either an intramolecular process to enforce exo selectivity or the use of a (*Z*)-diene as a means to access the relative stereochemistry found in gymnodimine. We chose the latter approach and thus the (*Z*)-diene **7** and α-methylene lactam **8** as our Diels−Alder substrates. The recent compilation by Roush[10] of acyclic (*Z*)-dienes that participate in Diels−Alder reactions suggested that the proposed (*Z*)-diene would participate in an intermolecular Diels−Alder reaction. A Heathcock anti-aldol[11] reaction and a stereoselective allylation would be utilized for introduction of stereochemistry in the tetrahydrofuran fragment **4**. Toward these goals, we have developed a concise formal Diels−Alder strategy to the spirocyclic moiety of gymnodimine that may also be applicable to other members of this family of toxins. In addition, we have completed an asymmetric synthesis of the tetrahydrofuran moiety.

Acylation (TCBoc-Cl) or tosylation (TsCl) of the known *δ*-lactam **13**[12] provided the α-methylene lactams required for the Diels−Alder strategy (Scheme 1). This lactam is ultimately derived from diester **10**, readily available in >100 g quantities by Michael addition of diethylmalonate to acrylonitrile by a known procedure.[13] Although lactam **11** is commercially available, it is somewhat expensive. Therefore, it was prepared on a large scale by Raney nickel reduction of the nitrile **10**.[13] Subsequent reduction and dehydration gave the known α-methylene lactam **13**.[12] Lactam **13** is a pivotal intermediate as several nitrogen protecting groups could be appended and studied in the Diels−Alder reaction. Initially, the trichloro-*tert*-butoxy carbamate (TCBoc) protected dienophile **14** and the tosylated dienophile **8** were prepared.

Scheme 1. Synthesis of Dienophiles **8** and **14**[a]

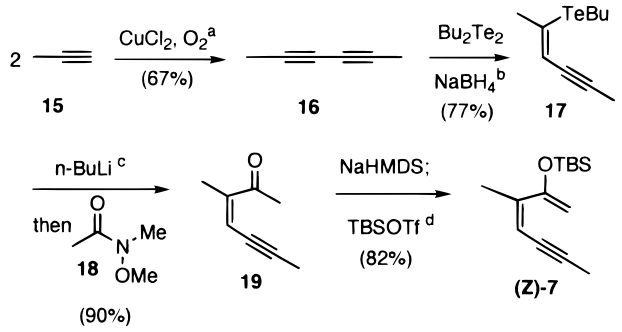


[a] (a) EtOH, 80 °C, 1000 psi H_2, 8 h; (b) MeOH, 0 → 23 °C, 12 h; (c) PhMe, reflux, 25 min; (d) THF, −78 °C, 1 h; (e) THF, −78 °C, 1 h.

The required (*Z*)-diene for the Diels−Alder strategy was prepared in a concise fashion from propyne using tellurium chemistry as outlined in Scheme 2. Highly selective hydrotelluration of hexa-2,4-diyne[14] (**16**) by the method of Comasseto[15] gave vinyl tellurium **17** (>19:1 *Z*:*E*, 300 MHz ^{1}H NMR). Metalation of vinyl tellurium **17** and addition of Weinreb amide[16] **18** gave ketone **19**. Silylation leading to enol ether **7** proceeded without isomerization under carefully

(8) Stewart, M.; Blunt, J. W.; Munro, M. H. G.; Robinson, W. T.; Hannah, D. J. *Tetrahedron Lett.* **1997**, *38*, 4889−4890.
(9) Miles, C. O.; Wilkins, A. L.; Stirling, D. J.; MacKenzie, A. L. In Proceedings of the Marine Biotoxin Science, Workshop No. 11, Wellington, New Zealand, 1999; Ministry of Agriculture and Forestry, pp 103−106.
(10) Roush, W. R.; Barda, D. A. *J. Am. Chem. Soc.* **1997**, *119*, 7402−7403.
(11) (a) Walker, M.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 5747−5750. (b) Raimundo, B. C.; Heathcock, C. H. *Synlett* **1995**, 1213−1214. (c) Hansen, M. M.; Danda, H.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 173−181.
(12) Klutchko, S.; Hoefle, M. L. *J. Med. Chem.* **1981**, *24*, 104−109.
(13) (a) Koelsch, C. F. *J. Am. Chem. Soc.* **1943**, *65*, 2458−2459. (b) Hesse, G.; Bücking, E. *Justus Liebigs Ann. Chem.* **1949**, *563*, 31−37. (c) Albertson, N. F.; Fillman, J. L. *J. Am. Chem. Soc.* **1949**, *71*, 2818−2820.
(14) Brandsma, L.; Verkruijsse, H. D.; Walda, B. *Synth. Commun.* **1991**, *21*, 137−139.
(15) (a) Dabdoub, M. J.; Dabdoub, V. B.; Comasseto, J. V. *Tetrahedron Lett.* **1992**, *33*, 2261−2264. (b) Tucci, F. C.; Chieffi, A.; Comasseto, J. V.; Marino, J. P. *J. Org. Chem.* **1996**, *61*, 4975−4989.
(16) (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815−3818. (b) Oster, T. A.; Harris, T. M. *Tetrahedron Lett.* **1983**, *24*, 1851−1854.

Scheme 2. Synthesis of Diene (*Z*)-7[a]

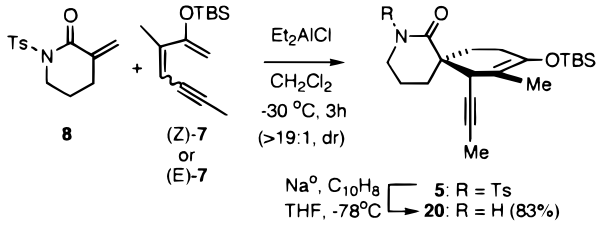


[a] (a) DBU, py, DMF, −42 → 35 °C, 3 h; (b) absolute EtOH, reflux, 3 h; (c) THF, −78 °C, 1 h then **18**, −78 °C, 0.75 h; (d) THF, −78 °C, 0.5 h.

controlled conditions; however, silica gel chromatography of this intermediate led to varying degrees of isomerization. Diene **7** could be readily prepared on a large scale (∼5 g), but due to the instability of the silyl enol ether, material was typically advanced and stored at the stage of ketone **19**.

Attempted Lewis acid-promoted Diels−Alder reactions with the TCBoc-protected lactam **14** failed under a variety of conditions. We reasoned that further activation of the dienophile was required, and tosylation of lactam dienophiles had previously been employed to increase their reactivity in Diels−Alder reactions.[17] Gratifyingly, the Diels−Alder reaction of tosylated dienophile **8** and diene **7** was found to proceed efficiently with Et_2AlCl at −30 °C to give a single diastereomer of crystalline cycloadduct **5** (67%) (Scheme 3).

Scheme 3. Synthesis of Spirocycle Moiety **5**



This spirocyclic lactam was found to possess the correct regio- and relative stereochemistry required for the synthesis of gymnodimine as determined by single-crystal X-ray analysis (Figure 2). *Interestingly, we found that the same diastereomer is obtained regardless of the geometry of the diene 7, suggestive of a stepwise, net Diels−Alder process.* Deprotection of the tosyl lactam **5** to give lactam **20** was

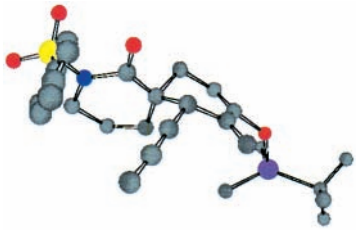


Figure 2. Chem 3D representation of the X-ray crystal structure of the formal Diels−Alder adduct **5**.

accomplished using sodium naphthalenide in 83% yield (Scheme 3).[18]

The excellent diastereoselectivity observed in this net cycloaddition deserves comment. We suggest that this reaction is, in fact, a formal Diels−Alder reaction proceeding through a stepwise process involving two sequential Michael reactions and passing through highly stabilized carbocation intermediates (i.e., **21** and **22**, Figure 3). Two of four possible

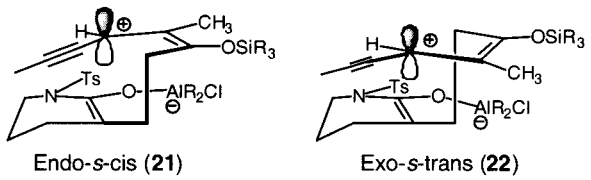


Figure 3. Two possible transition state arrangements leading to the formal Diels−Alder adduct.

transition state arrangements are shown, and these both lead to the observed cycloadduct **5**; however, transition state arrangement **22** should be preferred as it avoids nonbonded interactions present in **21**.

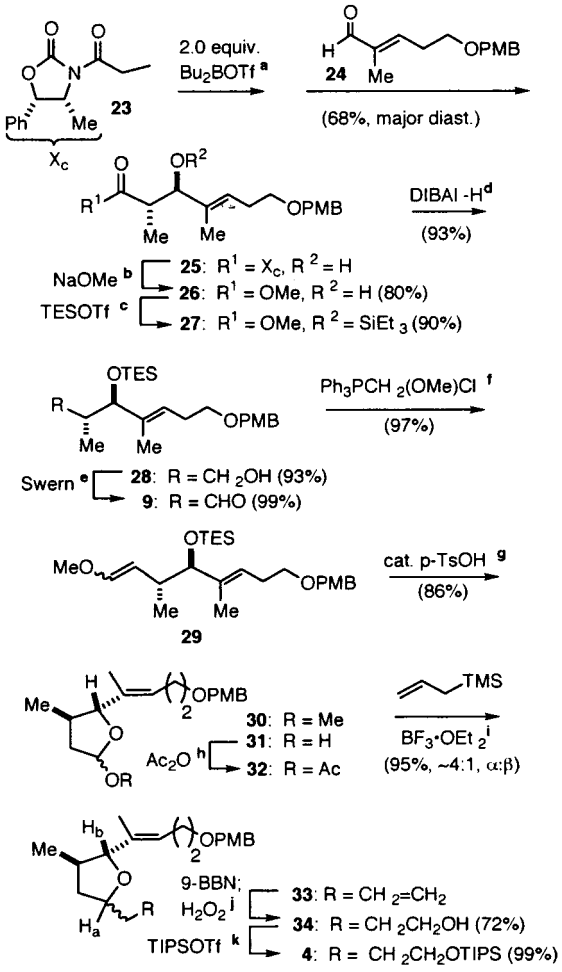
The synthesis of the tetrahydrofuran fragment commenced with a Heathcock anti-aldol reaction[11] employing the ephedrine-derived auxiliary **23**[19] and the known aldehyde **24** (Scheme 4).[20] This provided a mixture of three diastereomers (dr, 5:1:0.5) from which the major diastereomer **25** could be isolated in 68% yield. The stereochemistry of the major diastereomer was determined to be anti by $^1H-^1H$ coupling constant analysis which showed the coupling constant $J_{H\alpha,H\beta}$ = 8.7−9.3 Hz (typical values: syn, J = 3.2−6.4 Hz; anti, J = 7.2−9.6 Hz).[11] This aldol reaction set the stereochemistry corresponding to the C15 and C16 stereocenters of gymnodimine, and what was now required was homologation to the furanose. After extensive experimentation, it was determined that removal of the chiral auxiliary could best be achieved by methanolysis which gave the ester **26** in 80%

(17) (a) Torisawa, Y.; Hosaka, T.; Tanabe, K.; Suzuki, N.; Motohashi, Y.; Hino, T.; Nakagawa, M. *Tetrahedron* **1996**, *52*, 10597−10608. (b) Casamitjana, N.; Jorge, A.; Perez, C. G.; Bosch, J.; Espinosa, E.; Molins, E. *Tetrahedron Lett.* **1997**, *38*, 2295−2298. (c) Torisawa, Y.; Nakagawa, M.; Takami, H.; Nagata, T.; Ali, M. A.; Hino, T. *Heterocycles* **1994**, *39*, 277−292. (d) Oppolzer, W.; Chapuis, C.; Bernardinelli, G. *Helv. Chim. Acta* **1984**, *67*, 1397−1401.

(18) (a) Ji, S.; Gortler, L. B.; Waring, A.; Battisti, A.; Bank, S.; Closson, W. D.; Wriede, P. *J. Am. Chem. Soc.* **1967**, *89*, 5311−5312. (b) Alonso, D. A.; Andersson, P. G. *J. Org. Chem.* **1998**, *63*, 9455−9461.

(19) Evans, D. A.; Mathre, D. J.; Scott, W. L. *J. Org. Chem.* **1985**, *50*, 1830−1835.

Scheme 4. Synthesis of Tetrahydrofuran Moiety **4**[a]



[a] (a) *i*-Pr_2NEt, Et_2O, 0 °C, 45 min, −78 °C, then **24**, Et_2O, −78 °C, 6 h; (b) MeOH, −78 → −10 °C, 2 h; (c) 2,6-lutidine, CH_2Cl_2, −78 °C, 10 min; (d) CH_2Cl_2, −78 °C, 30 min; (e) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, 10 min, then **28**, Et_3N, −78 °C, 1 h; (f) K-O-*t*-Bu, THF, 0 → 22 °C, 2 h; (g) MeOH, 25 °C (for **30**), or THF, H_2O, 25 °C (for **31**); (h) Et_3N, CH_2Cl_2, catalytic DMAP, 22 °C, 2 h; (i) Et_2O, 0 °C (for **30**) or Et_2O, −78 °C (for **32**); (j) THF, 0 °C, 24 h; NaOH; (k) 2,6-lutidine, CH_2Cl_2, −78 °C, 40 min.

yield.[21] Silylation followed by a reduction−oxidation sequence provided aldehyde **9** in good overall yield. Wittig olefination proceeded smoothly to give methoxy olefins **29** as a 3:1 mixture (300 MHz ^{1}H NMR) of geometrical isomers in 97% yield.[22] Acid-promoted desilylation and cylization in MeOH provided epimeric furanoses **30**.

Allylation of furanose **30** was employed for setting the remaining stereocenter at C13. Allylation with BF_3•OEt_2 and allylsilane did not proceed at −78 °C but required warming to 0 °C and delivered a 4:1 mixture of diastereomers.[23] The stereochemistry of the major diastereomer was determined to be α on the basis of a ROESY experiment that showed a cross-peak for H_a and H_b for the major diastereomer of tetrahydrofuran **33**. The moderate diastereoselectivity is surprising in light of an allylation by Murai on a related substrate that differs only by the nature of the substituent at C4 (ribose numbering).[7a,24] With the hope of performing the allylation at lower temperature, acetoxyfuranoses **32** were prepared. While allylation of these substrates did proceed at −78 °C, the ratio of epimers did not improve. The diastereomeric tetrahydrofurans **33** were inseparable at this stage, so they were converted to silyl ethers **4** by a hydroboration/oxidation sequence followed by silylation.

This overall sequence provides a concise entry into the spirocyclic array of gymnodimine that is functionalized appropriately for elaboration to the complete spirocyclic fragment. Asymmetric versions of this process are being explored. Importantly, this approach would also appear to be applicable to the synthesis of the related spirolides. We have also developed an asymmetric route to the tetrahydrofuran fragment of gymnodimine. However, the allylation step suffers from moderate selectivity and current studies are focused on alternative methods for introduction of the final three carbons on this fragment with the goal of improving stereoselectivity while also increasing convergency.

Acknowledgment. We thank the NIH (GM 52964−01) and Zeneca Pharmaceuticals for support of these investigations. D.R. is an Alfred P. Sloan Fellow and a Camille-Henry Dreyfus Teacher−Scholar. We thank Profs. Murray M. H. G. Munro and John W. Blunt (University of Canterbury, NZ) for informative discussions regarding the relative and absolute stereochemistry of gymnodimine. We thank Aaron Reuland for expert technical assistance. We thank Dr. Joe Reibenspies for obtaining the X-ray structure of **5** using instruments obtained with funds from the NSF (CHE-9807975) and Dr. Lloyd Sumner of the Texas A&M Center for characterization for mass spectral analyses obtained on instruments acquired by generous funding from the NSF (CHE-8705697) and the TAMU Board of Regents Research Program.

Supporting Information Available: Experimental procedures and full characterization data (including IR and ^{1}H and ^{13}C NMR spectra) for compounds **4**, **5**, **7**, **8**, **25**, **28**, **30**, and **33**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL005510C

(20) Hirama, M.; Noda, T.; Takeishi, S.; Itô, S. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2645−2646.

(21) For a related deprotection/cyclization, see: Walba, D. M.; Thurmes, W. N.; Haltiwanger, R. C. *J. Org. Chem.* **1988**, *53*, 1046−1056.

(22) For a detailed procedure of this Wittig reaction, see: Pyne, S. G.; Hensel, M. J.; Fuchs, P. L. *J. Am. Chem. Soc.* **1982**, *104*, 5719−5728.

(23) Kozikowski, A. P.; Sorgi, K. L.; Wang, B. C.; Xu, Z. *Tetrahedron Lett.* **1983**, *24*, 1563−1566.

(24) Due to space limitations, a possible rationalization for the moderate selectivity will be described in a full account of this work. For a recently proposed stereoelectronic model rationalizing nucleophilic additions to five-membered-ring oxocarbeniums and applicable to the present system, see: Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12208−12209.