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Studies on the Synthesis of Gymnodimine. Stereocontrolled Construction of the Tetrahydrofuran Subunit

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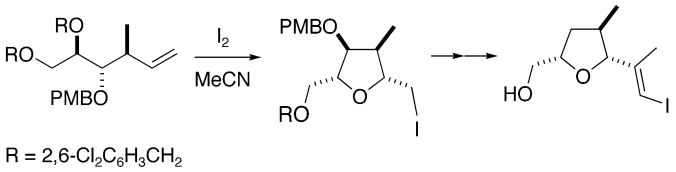
ABSTRACT



A bis-(2,6-dichlorobenzyl) ether is shown to undergo efficient and highly stereoselective intramolecular iodoetherification to yield a cis-2,5-disubstituted tetrahydrofuran, thus providing a powerful illustration of a stereodirecting effect first noted by Rychnovsky and Bartlett. The tetrahydrofuran was transformed into a subunit suitable for incorporation into the shellfish toxin gymnodimine.

Gymnodimine (**1**) first came to the public's attention in 1994 when commercial oysters grown in Southland, New Zealand, were found to contain high levels of a biotoxin that exhibited neurotoxic shellfish poisoning in a mouse bioassay.[1] The same compound, isolated from oysters (*Tiostrea chilensis*) collected at Foveaux Strait, New Zealand, was found to have a minimum lethal dose (intraperitoneal) of 700 μg/mL in the mouse bioassay.[2] The structure of gymnodimine was initially elucidated by NMR spectroscopy[1] and confirmed by X-ray crystallographic analysis, which also established its absolute configuration.[2]

The azaspiro[5.5]undecadiene core of gymnodimine places this substance in a close structural relationship with the pinnatoxins[3] and spirolides,[4] neurotoxins in which the spiroimine portion of the molecule appears to be the pharmacophore.[5] In concordance with this hypothesis, reduction of the imine moiety of **1** to give gymnodamine resulted in a significant decrease in toxicity (MLD of gymnodamine is >4040 mg/kg). Although gymnodimine is available in quantity from its natural source (5 kg of oysters yielded 8.4 mg of **1**), it is chemically unstable. The dihydro derivative gymnodamine is more tractable and is being used to form haptens in order to develop an immunoassay for a direct, quantitative detection of **1** in shellfish.[2]

The novel features associated with the structure of gymnodimine have excited the interest of several groups, notably those of Murai[6] and Romo,[7] who have disclosed their syntheses of portions of the molecule. Our own efforts toward the synthesis of **1** have focused on independent constructions of the tetrahydrofuran and spiroimine subunits with the eventual goal of connecting these segments to form the complete macrocyclic core of **1**. In this report, we describe an approach to the tetrahydrofuran moiety that employs a remarkably stereoselective cyclization of an acyclic bis-(2,6-

(1) Seki, T.; Satake, M.; Mackenzie, L.; Kaspar, H.; Yasumoto, T. *Tetrahedron Lett.* **1995**, *36*, 7093.
(2) Stewart, M.; Blunt, J. W.; Munro, M. H.G.; Robinson, W. T.; Hannah, D. J. *Tetrahedron Lett.* **1997**, *38*, 4889.
(3) Uemura, D.; Chou, T.; Haino, T.; Nagatsu, A.; Fukuzawa, S.; Zheng, S.; Chen, H. *J. Am. Chem. Soc.* **1995**, *117*, 1155.
(4) Hu, J.; Curtis, J. M.; Oshima, Y.; Quilliam, M. A.; Walter, J. A.; Waston-Wright, W. M.; Wright, J. L. C. *Chem. Commun.* **1995**, 2159.
(5) Hu, T.; Curtis, J. M.; Walter, J. A.; Wright, J. L. C. *Tetrahedron Lett.* **1996**, *37*, 7671.
(6) (a) Ishihara, J.; Miyakawa, J.; Tsujimoto, T.; Murai, A. *Synlett* **1997**, 1417. (b) Tsujimoto, T.; Ishihara, J.; Horie, M.; Murai, A. *Synlett* **2002**, 399.
(7) (a) Yang, J.; Cohn, S. T.; Romo, D. *Org. Lett.* **2000**, *2*, 763. (b) Ahn, Y.; Cardenas, G. I.; Yang, J.; Romo, D. *Org. Lett.* **2001**, *3*, 751.

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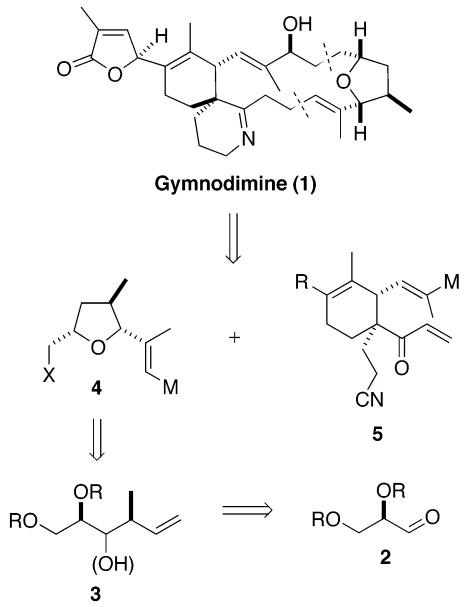
dichlorobenzyl) ether to produce the requisite cis-2,5-disubstituted heterocycle. Our plan, outlined in Scheme 1,

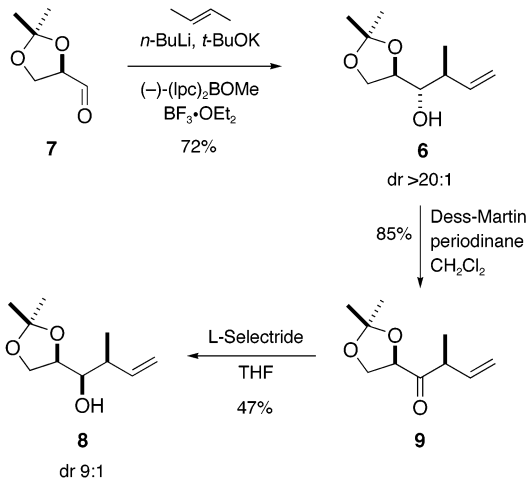
Scheme 1



envisioned a pathway from aldehyde **2** to the cyclization precursor **3**, with subsequent elaboration of the cyclization product to a tetrahydrofuran **4** suitable for linkage to a second major subunit of **1** such as **5**.[8]

Our initial approach to **3** assumed that alcohol **6**, prepared with excellent stereoselectivity by asymmetric crotylation of the glyceraldehyde derivative **7**[9] (Scheme 2), could be

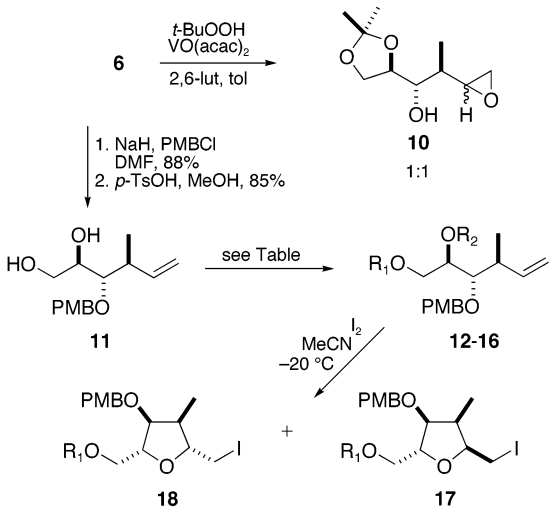
Scheme 2



deoxygenated to furnish a precursor suitable for cyclization to a tetrahydrofuran. However, neither the Barton−McCombie protocol[10] nor reductive displacement of the mesylate derived from **6** was able to accomplish removal of the superfluous hydroxyl function. On the supposition that (*R*)-alcohol **8** would be less sterically crowded and therefore a more compliant substrate for deoxygenation than its (*S*)-diastereomer **6**, the latter was oxidized to ketone **9** and then reduced with L-Selectride to give **8** with good stereoselectivity. Unfortunately, alcohol **8** proved to be equally resistant to deoxygenation, the sole product under forcing conditions being a conjugated diene resulting from elimination.

In view of these difficulties, it was decided to postpone removal of the hydroxyl group from **6** and to examine the cyclization of precursors with this alcohol present in protected form. Initially, we believed that an epoxide prepared from **6** would be a suitable candidate for this purpose, but epoxidation of this homoallylic alcohol proceeded without stereoselectivity and gave **10** as an inseparable mixture (Scheme 3). Alcohol **6** was therefore converted

Scheme 3



to its *p*-methoxybenzyl ether, and the acetonide was cleaved to furnish diol **11**, which now became the focal point for our intramolecular iodoetherification studies.

The diol **11** proved to be a poor substrate for cyclization, but the monopivalate **12** gave a single tetrahydrofuran in high yield (Table 1), which was found to be the undesired trans-2,5-disubstituted iodomethyltetrahydrofuran as determined by NOE experiments. Some improvement toward the cis-2,5-disubstituted stereoisomer **18** was noted in the intramolecular iodoetherification of silyl ether **13**, the bis-(benzyl) ether **14**, and the pivalate **15**, but a dramatic increase in the proportion of the desired cis-disubstituted product **18** occurred when the bis-(2,5-dichlorobenzyl) ether **16** of diol **11** was treated with iodine in acetonitrile at low temperature (Table 1, entry 5).

(8) For a different approach to the tetrahydrofuran subunit of gymnodimine, see: Rainier, J. D.; Xu, Q. *Org. Lett.* **1999**, *1*, 27.

(9) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293.

(10) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

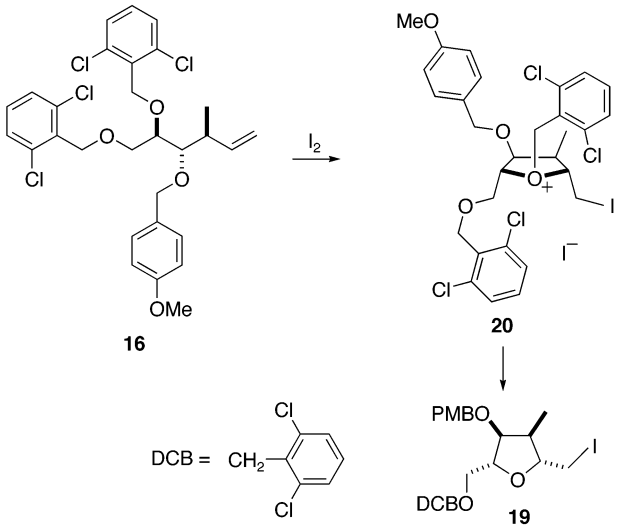
Table 1. Effect of Substituents upon Tetrahydrofuran Formation via Intramolecular Iodoetherification

entry	compd	R_1	R_2	yield (%)	ratio[a] **18**:**17**
1	**12**	Piv	H	80[b]	>1:20
2	**13**	Piv	TBS	85	1:3
3	**14**	Bn	Bn	72	1:1
4	**15**	Piv	Bn	66	3:1
5	**16**	DCB[c]	DCB[c]	87	>20:1

[a] Determined by ^{1}H and ^{13}C NMR. [b] *p*-Methoxybenzyl group was cleaved in this case. [c] DCB = 2,6-Dichlorobenzyl.

Confirmation of the structure of this tetrahydrofuran as **19** (Scheme 4) was obtained by both NOE experiments and

Scheme 4



by X-ray crystallographic analysis (Figure 1). The formation of **19** as the sole detectable isomer from **16** is in concert

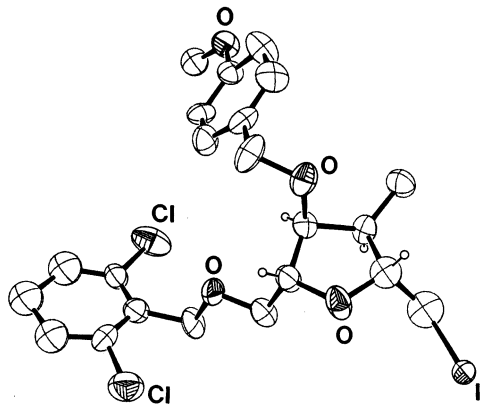
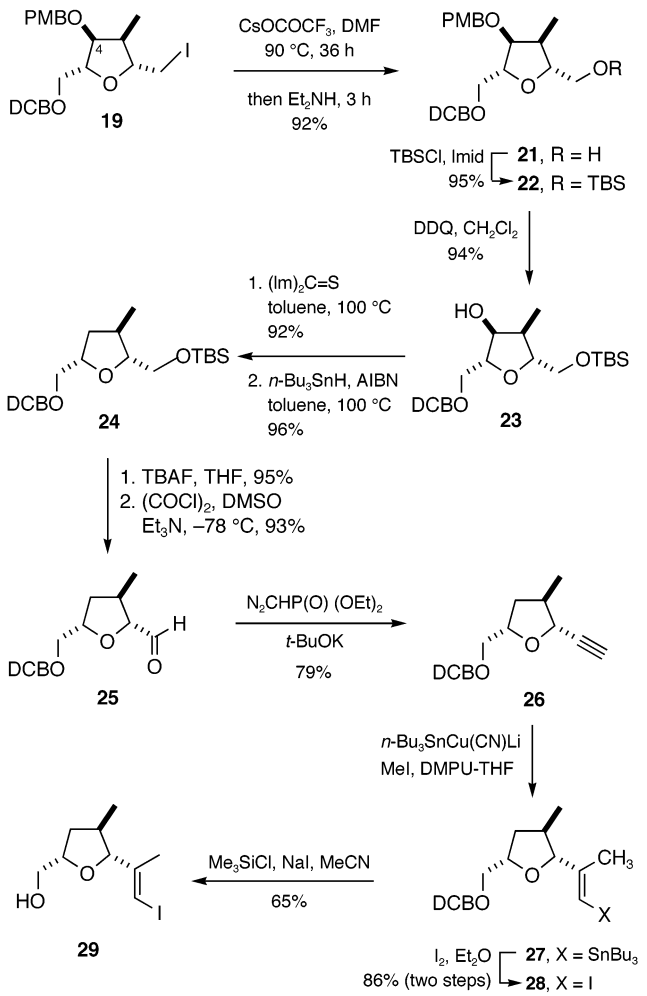


Figure 1. X-ray crystal structure of **19** (ellipsoids are drawn at the 50% probability level).

with earlier observations by Rychnovsky and Bartlett,[11] who showed that the 2,6-dichlorobenzyl substituent represents the optimal combination of steric and electronic properties for promoting a transition state for cyclization that avoids 1,2-steric interactions, accommodates 1,3-interactions, and permits facile cleavage of the intermediate oxonium ion **20** (Scheme 4).

With **19** in hand, it was then obligatory to remove the oxygen function from C4 of the tetrahydrofuran; however, before this could be done, it was necessary to replace the iodo substituent with a group that would withstand the deoxygenation process. This was achieved by displacement of iodide from **19** with cesium trifluoroacetate followed by cleavage of the trifluoroacetate ester with diethylamine to give alcohol **21** (Scheme 5). The latter was then protected as its silyl ether **22**.

Scheme 5



After removal of the *p*-methoxybenzyl protection from **22**, alcohol **23** was subjected to reductive deoxygenation by reaction with thiocarbonyldimidazole, followed by tributyl-

(11) Rychnovsky, S. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 3963.

stannane,[10] to produce tetrahydrofuran **24** in excellent yield. Swern oxidation of the primary alcohol from cleavage of silyl ether **24** afforded aldehyde **25**, which reacted with diethyl diazomethylphosphonate in the presence of base to give alkyne **26**. Stannylcupration−methylation[12] of this alkyne gave (*E*)-alkenylstannane **27**, which underwent metal−halogen exchange to yield (*E*)-iodoalkene **28**. Finally, removal of the dichlorobenzyl group from **28** was accomplished with trimethylsilyl iodide, generated in situ from the chloride, and furnished alcohol **29** cleanly. This substance now stands ready for connection to the second principal subunit of **1**, e.g., **5**, whose synthesis will be described in due course.

(12) Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H. *Tetrahedron Lett*. **1989**, *30*, 2065.

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Supporting Information Available: Experimental procedures and characterization data for new compounds and crystallographic data for **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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