ORGANIC LETTERS

2003
Vol. 5, No. 26
4983−4986

Studies on the Synthesis of Gymnodimine. Construction of the Spiroimine Portion via Diels–Alder Cycloaddition

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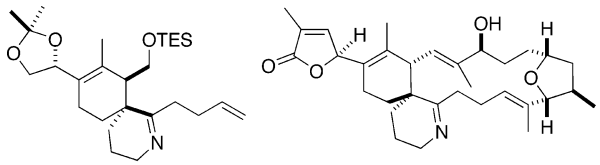
Received October 3, 2003

ABSTRACT



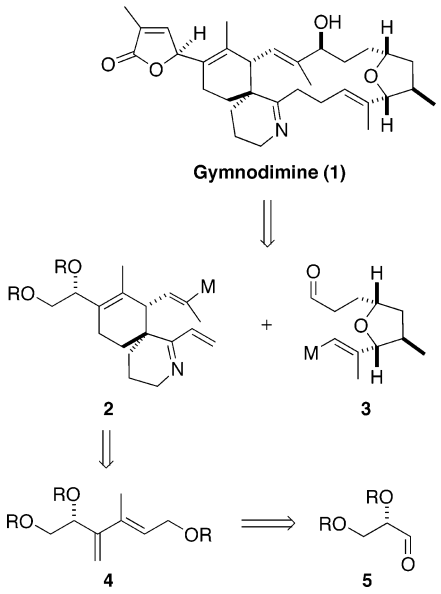
Gymnodimine (1)

An azaspiro[5.5]undecadiene corresponding to a subunit of the shellfish toxin gymnodimine was synthesized by Diels–Alder cycloaddition. One member of the pair of stereoisomeric adducts was transformed to a spiroimine, which will serve as the core around which the macrocyclic portion of the toxin will be assembled.

Gymnodimine (**1**) is a biotoxin isolated from oysters (*Tiostrea chilensis*) collected in New Zealand and has been found to exhibit neurotoxic shellfish poisoning in a mouse biossay.[1] Our strategy for the synthesis of **1** relies upon the assembly of two subunits, **2** and **3**, to create the macrocyclic core of the toxin's structure. Progress toward the tetrahydrofuran portion **3** has been reported by us[2] and others,[3−5] and we now describe a route to the azaspiro[5.5]undecadiene segment[4,5] that can serve as a progenitor of **1**. Our approach employs a Diels−Alder cycloaddition to conjugated diene **4**, which is prepared from the (*S*)-glyceraldehyde derivative **5** (Scheme 1). The latter is the enantiomer of the starting material we used to gain access to fragment **3**.

The commercially available ester **6** was saponified, and the lithium carboxylate was converted via its mixed anhydride to Weinreb amide **7**.[6] Treatment of **7** with the lithio alkene prepared from (*E*)-stannane **8**[7] gave unsaturated

Scheme 1



(1) (a) Seki, T.; Satake, M.; Mackenzie, L.; Kaspar, H.; Yasumoto, T. *Tetrahedron Lett.* **1995**, *36*, 7093. (b) Stewart, M.; Blunt, J. W.; Munro, M. H. G.; Robinson, W. T.; Hannah, D. J. *Tetrahedron Lett.* **1997**, *38*, 4889.

(2) White, J. D.; Wang, G.-Q.; Quaranta, L. *Org. Lett.* **2003**, *5*, 4109.

(3) Rainier, J. D.; Xu, Q. *Org. Lett.* **1999**, *1*, 27.

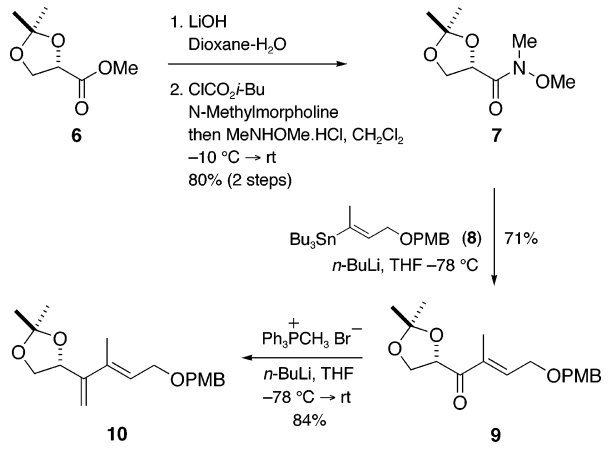
(4) (a) Ishihara, J.; Miyakawa, J.; Tsujimoto, T.; Murai, A. *Synlett* **1997**, 1417. (b) Tsujimoto, T.; Ishihara, J.; Horie, M.; Murai, A. *Synlett* **2002**, 399.

(5) (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.

10.1021/ol035939e CCC: $25.00
Published on Web 11/20/2003

ketone **9**, which underwent smooth Wittig methylenation to furnish conjugated diene **10** (Scheme 2). The selection of a

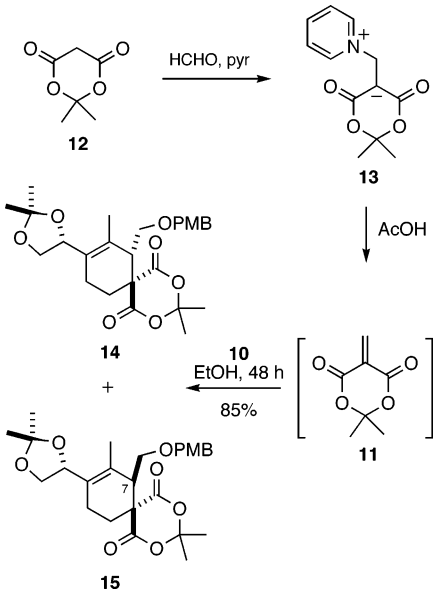
Scheme 2



suitable dienophilic partner for a Diels−Alder reaction with **10** was complicated by the fact that all of the unsymmetrical dienophiles we tested resulted in a sluggish reaction that produced mixtures of regioisomers and stereoisomers.

It was clear from these experiments that a symmetrical doubly activated dienophile would be the preferred Diels−Alder partner for **10**, and this reasoning led us to examine the methylene derivative **11**[8] of Meldrum's acid **12**. The unstable dienophile **11**, obtained by elimination of pyridine from the zwitterion **13** and used in situ, was reacted with **10** in ethanol to give **14** and **15** in a 1.2:1 ratio as the only two cycloadducts (Scheme 3). Thus, there is complete regioselectivity in the reaction of **10** with **11** but only poor asymmetric induction from the stereocenter in the dioxalane

Scheme 3



moiety. Fortunately, **14** and **15** were readily separable by chromatography and the latter was crystalline, thus allowing firm relative and absolute stereochemical assignments to be made to the pair of cycloadducts through X-ray crystallographic analysis (Figure 1).

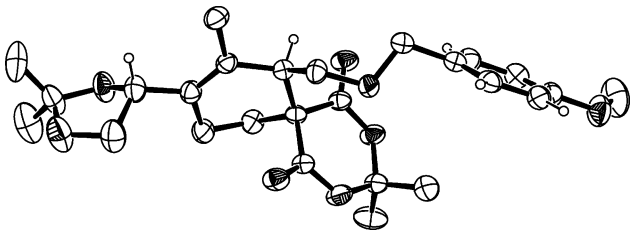
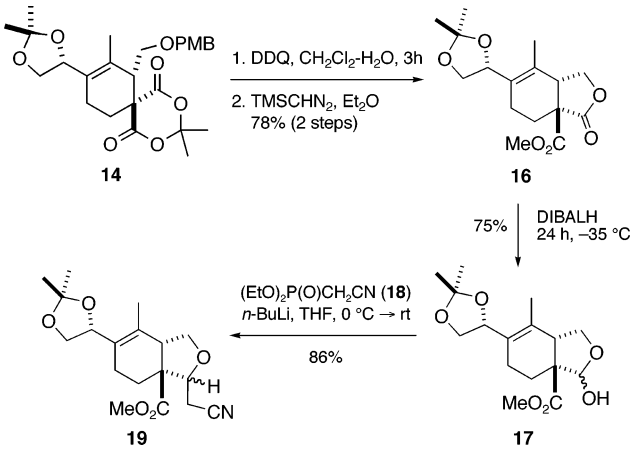


Figure 1. X-ray crystal structure of **15**.

Our initial experiments designed to lead to the spiroimine portion of gymnodimine were carried out with **14**. Cleavage of the *p*-methoxybenzyl ether from this adduct with 2,3-dichloro-5,6-dicyanobenzoquinone resulted in spontaneous formation of a γ-lactone (Scheme 4), and subsequent

Scheme 4



methylation of the carboxylic acid liberated in this process yielded the crystalline ester **16**. The structure of **16** was confirmed by X-ray crystallographic analysis (Figure 2).

The lactone moiety of **16** was selectively reduced with diisobutylaluminum hydride, and the resulting cyclic hemiacetal **17** was condensed with phosphonate **18**.[9] The transient α,β-unsaturated nitrile underwent immediate cyclization to tetrahydrofuran **19**, affording a heterocycle that was resistant to ring opening and consequently prevented further advance toward **2**.

(6) Lee, C. E.; Kick, E. K.; Ellman, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 9735.

(7) Stannane **8** was prepared from methyl butynoate by modification of a method reported by Piers (Piers, E.; Wong, T.; Ellis, K. A. *Can. J. Chem.* **1992**, *70*, 2058).

(8) Zia-Ebrahimi, M.; Huffman, G. W. *Synthesis* **1996**, 215.

(9) Deschamps, B.; Lefebvre, G.; Seyden-Penne, J. *Tetrahedron* **1972**, *28*, 4209.

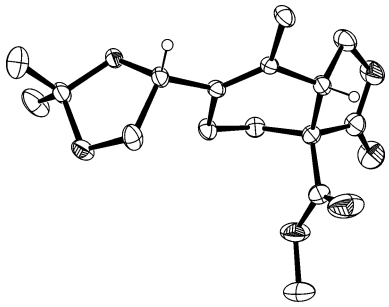
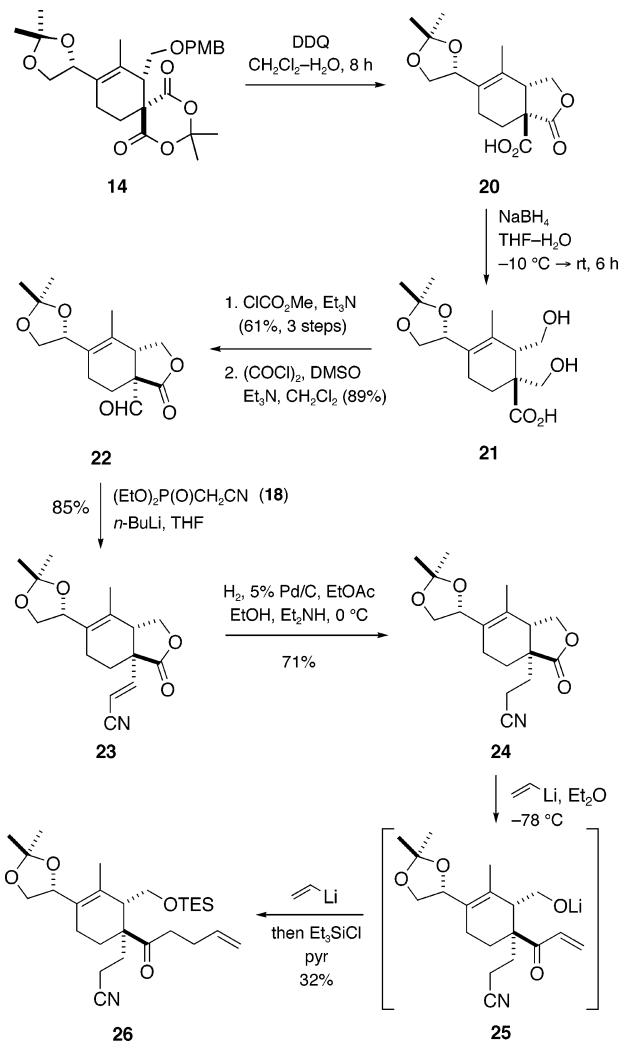


Figure 2. X-ray crystal structure of **16**.

An alternative route to an amine that could serve as a precursor to **2** appeared to lie through the dihydroxy carboxylic acid **21**. The latter was prepared by reduction of the cis-fused lactone acid **20** (Scheme 5), a substance obtained previously by cleavage of the *p*-methoxybenzyl ether from **14** (Scheme 4). Activation of carboxylic acid **21** via its mixed anhydride led to a trans-fused γ-lactone, and

Scheme 5



Swern oxidation of the angular primary alcohol furnished the crystalline aldehyde **22** whose structure was established by X-ray crystallographic analysis (Figure 3).

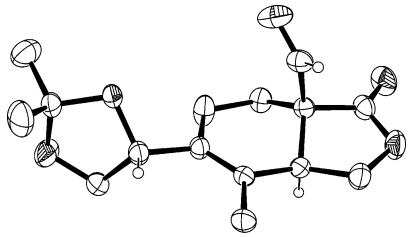
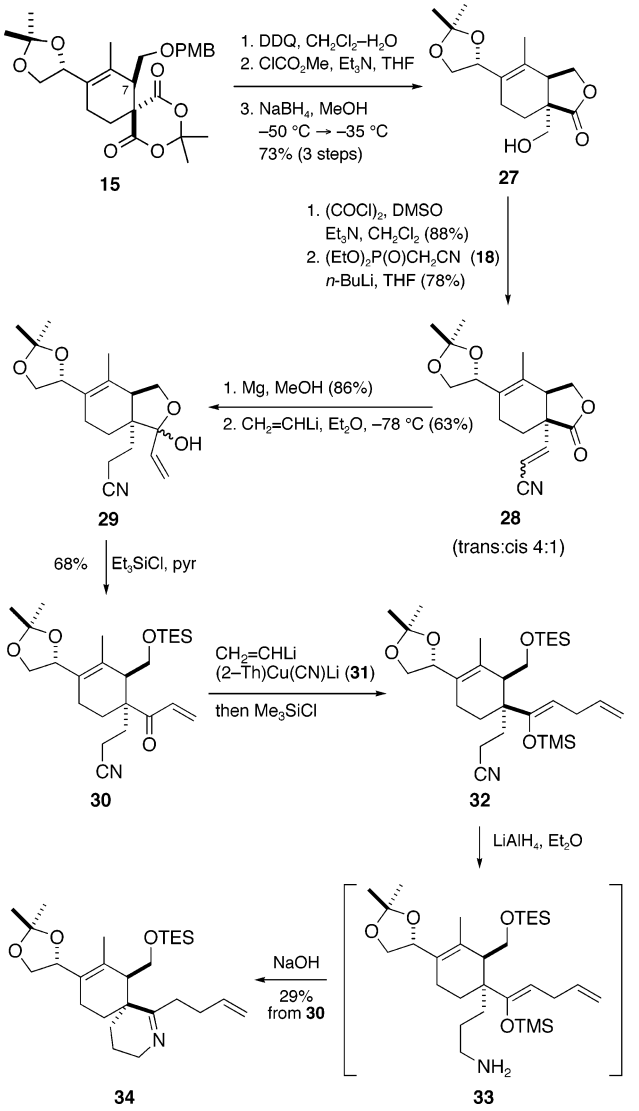


Figure 3. X-ray crystal structure of **22**.

The aldehyde of **22** was now positioned for elaboration to the requisite nitrile **24**, and this was accomplished by Horner−Wadsworth−Emmons condensation with phospho-

Scheme 6



nate **18**, followed by selective hydrogenation of the resulting α,β-unsaturated nitrile **23**. When **24** was reacted with vinyllithium, reaction took place selectively at the lactone carbonyl as expected, but this was followed by a second rapid addition of vinyllithium to the intermediate vinyl ketone **25** to give **26** after silylation of the alkoxide. Apparently, the trans ring fusion of **24** imparts strain sufficient to trigger opening of the lactol after the first equivalent of vinyllithium has been added. While the double vinylation of **24** is a potentially solvable problem, difficulties in reducing the nitrile of **26** in the presence of the ketone function prompted us to examine a parallel sequence with Diels−Alder cycloadduct **15**. Although the center at C7 of **15** is inverted from that required for gymnodimine, a later correction of this stereogenic center can be envisioned to attain the (presumably) more stable configuration of **1**.

Removal of the *p*-methoxybenzyl group from **15** again led to spontaneous lactonization, in this case yielding a cis-fused γ-lactone stereoisomeric with **20** (Scheme 6). The angular carboxyl function was reduced to primary alcohol **27**, and Swern oxidation followed by condensation with phosphonate **18** produced α,β-unsaturated nitrile **28**. This substance did not respond well to catalytic hydrogenation, but reduction of the conjugated double bond was accomplished efficiently with magnesium in methanol.[10] Treatment of the resulting lactone with vinyllithium allowed isolation of **29** without the complication of double vinylation seen with **24**, confirming that strain associated with the trans ring fusion in the latter is responsible for its opening to **25**. Exposure of **29** to triethylsilyl chloride resulted in silylation of the primary alcohol formed upon opening of the lactol and led to vinyl ketone **30**. This substance underwent conjugate addition with the reagent prepared from vinyllithium and thienylcuprate **31**,[11] and the resulting enolate was trapped with trimethylsilyl chloride to afford **32**. Reduction of the nitrile followed by treatment of the intermediate primary amine **33** with sodium hydroxide resulted in spontaneous intramolecular condensation to furnish the cyclic imine **34**.

The sequence leading to **34** provides a template upon which a viable approach to the spiroimine nucleus of gymnodimine can now be framed. Further studies that will assemble the full macrocyclic core of **1** from a substance similar to **30** and a tetrahydrofuran subunit already in hand will be reported in due course.

Acknowledgment. We thank Professor Alexandre F. T. Yokochi of this department for the X-ray crystal structures of **15**, **16**, and **22**. L.Q. is grateful to the Swiss National Science Foundation for a Postdoctoral Fellowship. Financial support for this work was provided by the National Institute of General Medical Sciences through Grant GM58889.

Supporting Information Available: Experimental procedures and characterization data for new compounds and crystallographic data for **15**, **16**, and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Profitt, J. A.; Watt, D. S.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 127.

(11) Lipshutz, B. H.; Koerner, M.; Parker, D. A. *Tetrahedron Lett.* **1987**, *28*, 945.