Enantioselective Total Synthesis of the Marine Toxin
\((-\))-Gymnodimine Employing a Barbier-Type Macrocyclization**
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In memory of John L. Hogg

Gymnodimine (1, Scheme 1) is a member of the spirocyclic-imine family of marine toxins initially isolated from oysters collected off the coast of New Zealand. The gross structure was initially reported by Yasumoto and co-workers in 1995,[1] and subsequently, Munro, Blunt and co-workers reported the relative and absolute stereochemistry, which was elucidated through X-ray crystallographic analysis of a reduced, N-acylated derivative.[2] This toxin is produced by the dinoflagellate Karenia selliformis (formerly Gymnodinium selliforme) and is active in the mouse bioassay for neurotoxic shellfish poisoning.[3] Recently, gymnodi- mine was found to sensitize neurons to the effects of okadaic acid,[4] and there is evidence that it binds to a subset of muscle nicotinic acetylcholine receptors.[5] Two additional analogues, differing only by an allylic oxidation at the C17–C18 olefin, were isolated and named gymnodimine B (2) and C (3), respectively.[6] Other members of this growing family of spirocyclic-imine toxins include the pinnatoxins,[7] spirolides,[8] pteriatoxins,[9] prorocentrolide,[10] and spiro-prorocentromine.[11]

This family of spirocyclic-imine-containing marine toxins has inspired intense synthetic efforts[12] that have culminated in total or formal syntheses of the pinnatoxins and pteriatoxins.[13] However, the total synthesis of gymnodi- mine remains elusive.[14] The seemingly simpler architecture of gymnodi- mine relative to that of other members of this family conceals subtle, challenging structural elements, in particular the known labile butenolide, which adds to the challenge of a total synthesis.[15] Herein, we describe the first total synthesis of \((-\))-gymnodimine, which provides suitable intermediates for eventual production of an enzyme-linked immunosorbent assay (ELISA) for gymnodi- mine detection and also for further mode-of-action studies.[16]

Our synthetic plan called for the convergent coupling of spirolactam 5 with a hypothetical, dual-reactivity tetrahydrofuran, 4 (Scheme 2). A Nozaki–Hiyama–Kishi (NHK) macro-

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gave greatly inferior results (17%). This was a crucial precedent for the eventual solution for the macrocyclization (see below) because numerous attempts towards an NHK macrocyclization from iodoolefins derived from 12 were unsuccessful. At this juncture, we elected to switch the order of coupling and investigate a rather unconventional strategy involving a Barbier-type macrocyclization.\[21\]

The synthesis of the required tetrahydrofuran aldehyde 14b commenced with deprotection of PMB ether 13a\[25\] and conversion of the resultant alcohol 13b into chloride 13c by treatment with PPh3/CCl4 in warm N,N-dimethylformamide (DMF; Scheme 4). After selective boronation of the terminal olefin, the intermediate alcohol 14a was oxidized with Dess–Martin periodinane to provide aldehyde 14b.\[22\]

The synthesis of the internal acetylene of 11 proved to be rather challenging. Among the protocols examined, only Pd-catalyzed hydrostannylation\[21\] gave the corresponding vinyl stannane 15 and use of a nonpolar solvent, as reported by Semmlhack and Hooley,\[24\] gave optimal conversion into stannane 15. Stannane–iodide exchange at low temperature then afforded the sensitive vinyl iodide 16 in 76% yield.

Aldehyde 14b and vinyl iodide 16 were coupled under standard NHK conditions to provide allylic alcohols 17a/b as a diastereomeric mixture (1:3.1/β/α epimers at C10); the C10 epimers were readily separable (Scheme 5). The undesired α epimer 17b could be converted into 17a through an oxidation/reduction sequence by using the Isuono–Corey reduction protocol (d.r. 6:1) to enable greater material throughput.\[21\] Subsequent protection of the hydroxy group and a Finkelstein reaction furnished alkyl iodide 18, the required intermediate for the crucial macrocyclization, which could be separated from the undesired C13 epimer at this stage. The low-temperature conditions (−78 °C) developed for the intermolecular Barbier-type coupling (compare with Scheme 3) were disappointing in this instance and provided mainly a deiodinated tert-butyl ketone derived from quenching of the alkyl lithium and tBuLi addition to the δ lactam. Surprisingly, performing the reaction in an identical manner but with addition of the tBuLi to N-tosyl lactam 18 at ambient temperature (23 °C) rather than at −78 °C gave macrocycle 19 reproducibly on scales up to approximately 100 mg in 56–61% yields. Although both conformational effects and the relative rates of the halogen–metal exchange,\[26\] macrocyclization, tBuLi addition to the N-tosyl lactam, and elimination of tert-butyl iodide must all play a role in this process, further understanding of this intriguing process must await additional studies.

At this stage, it was necessary to switch the robust N-tosyl group to a more labile trifluoroacetamide by utilizing our recently developed protocol for this purpose (Scheme 6).\[27\] The silyl groups of macrocycle 20 were then cleaved under acidic conditions to furnish the crystalline hydroxy ketone 21, which enabled confirmation of the relative stereochemistry of the macrocycle by single-crystal X-ray analysis (inset, Scheme 6).
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gymnodimine is unstable under both neutral and mildly basic conditions for cleavage of the trifluoroacetamide butenolide of 25 a solution was found that involved tert-butyloxycarbonyl, DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene, DMAP: 4-(N,N-diisopropyl)amine (NEt3), TFA: trifluoroacetic acid. SOCl2 tert-tertiary alcohols could be epimerized into a 2:1 mixture of the diastereomeric butenolides upon treatment with DBU at ambient temperature. Also, the late-stage appendage of the chiral butenolide through a vinylogous Mukaiyama aldol addition to the highly useful macrocyclic ketone 21 provides convenient avenues for the synthesis of gymnodimine derivatives for further mode-of-action studies and hapten synthesis. The latter studies are directed towards the development of a robust ELISA assay for the detection of gymnodimine and congeners in the marine environment; these studies will be reported in due course.

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For butenolide coupling, we employed our recently described strategy involving a vinylogous Mukaiyama aldol reaction. Brief exposure (1 min) of a mixture of the macrocyclic ketone 21 and silyloxyfuran to TiCl4 at 23°C provided butenolide 23 in good yield as an approximately 1:1 mixture of two diastereomers (epimeric at the C4 position, single stereochemistry at the C5 position; Scheme 6). The lack of diastereoselectivity at the C4 position during this transformation is, to a great extent, offset by the conciseness of this direct vinylogous Mukaiyama aldol addition strategy for butenolide coupling. The epimeric tertiary alcohols 24a/b were readily separated after alcohol protection. It was found that the undesired diastereomer 24b could be epimerized into a 1:2 mixture of the diastereomeric butenolides 24a/b upon treatment with DBU at ambient temperature. Dehydration of the tertiary alcohol 24a (Et3N, SOCl2) afforded the desired tetrasubstituted olefin 25 as the predominant regioisomer (Δ21/Δ24, 3:1). The application of mild basic conditions for cleavage of the trifluoroacetamide led to degradation of the butenolide, in agreement with the findings of Miles and co-workers that the butenolide of gymnodimine is unstable under both neutral and mildly alkaline conditions. Attempted acid hydrolysis also proved unsuitable for this highly functionalized substrate. Eventually, a solution was found that involved N-Boc protection and mild trifluoroacetamide cleavage by using a modified Burk proto-col.
The absolute configuration of this spirolactam was previously determined by X-ray analysis (anomalous dispersion) of a derivative; see reference [14i].


The stereochemical outcome is consistent with simpler models confirmed by X-ray analysis. See reference [28a] for further information.