Natural Product Synthesis

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Enantioselective Total Synthesis of the Marine Toxin (−)-Gymnodimine Employing a Barbier-Type Macrocyclization**

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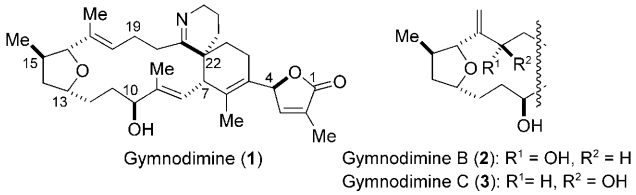
In memory of John L. Hogg

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

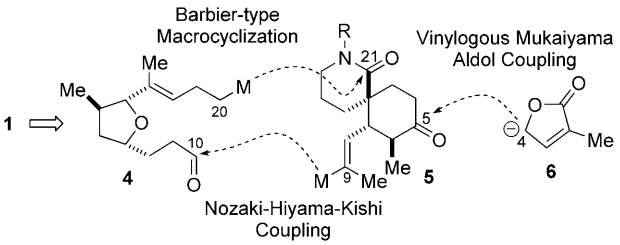


Scheme 1. Structures of known members of the gymnodimine family of spirocyclic-imine marine toxins.

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 selliforms* (formerly *Gymnodinium selliforme*) and is active in the mouse bioassay for neurotoxic shellfish poisoning.[3] Recently, gymnodimine 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-prorocentrimine.[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 gymnodimine remains elusive.[14] The seemingly simpler architecture of gymnodimine 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 gymnodimine 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-



Scheme 2. Retrosynthetic strategy toward gymnodimine (**1**) showing the principal disconnections. M: metal.

cyclization[17] was initially envisioned for the proposed merging at the C9 and C10 atoms (gymnodimine numbering), but our studies ultimately led to a Barbier-type macrocyclization. The proposed formation of the C20–C21 bond through nucleophilic opening of a δ lactam by an sp^3 carbanion is rare, especially in this complex setting, and is seen even less frequently in a macrocyclization.[18] The fragile butenolide would be coupled at a late stage by a vinylogous Mukaiyama aldol reaction of a hypothetical furanone anion **6** to a ketone at the C5 position after the unmasking of the silylenol ether of spirolactam **5**.

Our initial strategy for fragment coupling called for an NHK macrocyclization after the joining of the iodotetrahydrofuran **10**, available in three steps from the previously described ether **7**,[14b] and the optically active spirolactam **11** (95% *ee*),[19] previously obtained through a catalytic, asymmetric Diels–Alder reaction (Scheme 3).[14i] After some experimentation, we found the optimal conditions for a Barbier-type fragment coupling involving halogen–lithium exchange in the presence of the *N*-tosyl lactam electrophile[20] to provide adduct **12** in 92% yield, whereas generation of the alkyl lithium and subsequent addition of the *N*-tosyl lactam

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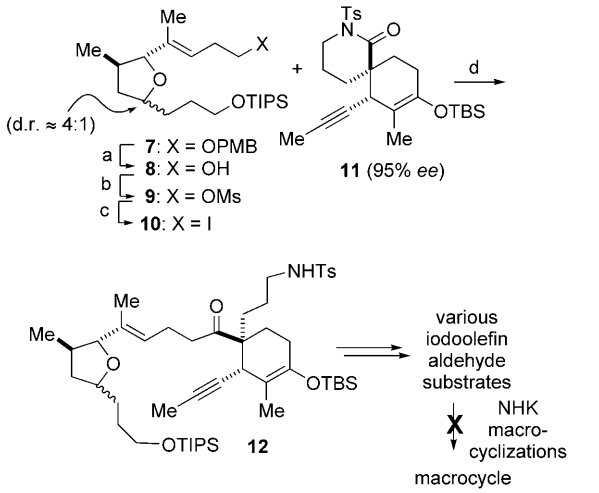
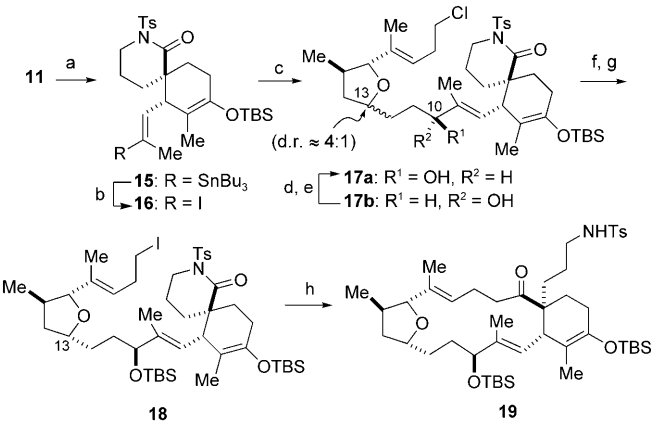


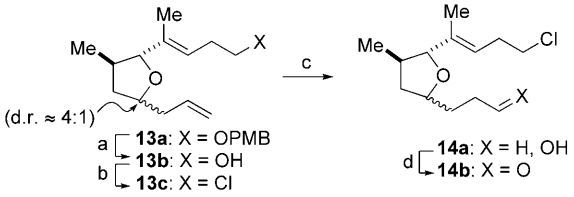
Scheme 3. Reagents and conditions: a) Na^0, NH_3(liq.), THF, −78 °C, 92%; b) MsCl, Et_3N, CH_2Cl_2, 92%; c) nBu_4NI, THF, 66 °C, 91%; d) *t*BuLi, Et_2O, −78 °C, then **11**, 17%; or **10** and **11**, *t*BuLi, Et_2O, −78 °C, 92%. Ms: methanesulfonyl, PMB: *para*-methoxybenzyl, TBS: *tert*-butyldimethylsilyl, THF: tetrahydrofuran, TIPS: triisopropylsilyl, Ts: toluene-4-sulfonyl.



Scheme 5. Reagents and conditions: a) $[PdCl_2(PPh_3)_2]$, nBu_3SnH, THF/hexanes (1:7), 85%; b) I_2, CH_2Cl_2, −78 °C, 76%; c) **14b**, $CrCl_2$/0.5 mol% $NiCl_2$, DMF/THF (1:1), 97%, **17a**/**17b** 1.3:1; d) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 88%; e) (*R*)-Me-CBS, catecholborane, CH_2Cl_2, 0 °C, 80%, d.r. = 6:1; f) Et_3N, TBSOTf, CH_2Cl_2, −78 °C, 86%; g) NaI, acetone, 65 °C, 99%; h) *t*BuLi, Et_2O, 23 °C, 56–61%. (*R*)-Me-CBS: (*R*)-methyl-oxazaborolidine, Tf: trifluoromethanesulfonyl.

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**[14b] and conversion of the resultant alcohol **13b** into chloride **13c** by treatment with PPh_3/CCl_4 in warm *N*,*N*-dimethylformamide (DMF; Scheme 4). After selective hydroboration of the terminal olefin, the intermediate alcohol **14a** was oxidized with Dess–Martin periodinane to provide aldehyde **14b**.[22]

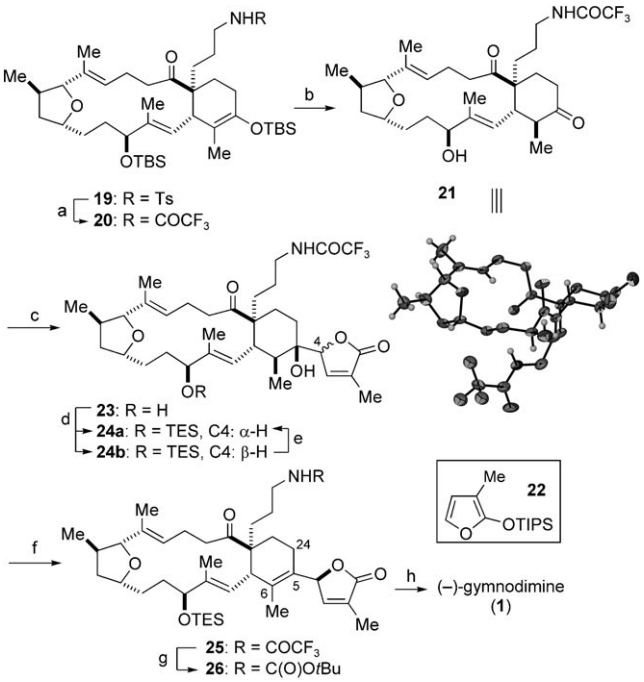


Scheme 4. Reagents and conditions: a) Na^0, NH_3(liq.), THF, −78 °C, 92%; b) PPh_3, CCl_4, DMF, 65 °C, 85%; c) 9-BBN, THF; NaOH, H_2O_2, 98%; d) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 71%. 9-BBN: 9-borabicyclo[3.3.1]nonane, DMF: *N*,*N*-dimethylformamide.

The synthesis of vinyl iodide partner **16**, required for the projected Barbier macrocyclization, began once again with optically active spirolactam **11** (Scheme 5). Functionalization of the internal acetylene in **11** proved to be rather challenging. Among the protocols examined, only Pd-catalyzed hydrostannylation[23] gave the corresponding vinyl stannane **15** and use of a nonpolar solvent, as reported by Semmelhack 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 Itsuno–Corey reduction protocol (d.r. 6:1) to enable greater material throughput.[25] 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 *t*BuLi addition to the δ lactam. Surprisingly, performing the reaction in an identical manner but with addition of the *t*BuLi 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, *t*BuLi 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).



Scheme 6. Reagents and conditions: a) Et_3N, $(CF_3CO)_2O$, CH_2Cl_2, 0 °C, then SmI_2, 23 °C, 73 %; b) *p*-TSA, CH_2Cl_2/THF/MeOH, 84 %; c) $TiCl_4$, **22**, CH_2Cl_2, 61 %, d.r. = 1:1; d) TESCl, imidazole, DMAP, CH_2Cl_2, 23 °C, 76 %, **24a**/**b** d.r. = 1:1; e) DBU, CH_2Cl_2, 60 %, **24a**/**b** d.r. = 2:1; f) Et_3N, $SOCl_2$, CH_2Cl_2, −78 °C, 82 %, $\Delta^{5,6}/\Delta^{5,24} = 3:1$; g) $(Boc)_2O$, Et_3N, DMAP, CH_2Cl_2, then H_2NNH_2, 99 %; h) TFA, CH_2Cl_2, 68 %. Inset: ORTEP representation of the X-ray crystal structure of ketone **21**. Boc: *tert*-butoxycarbonyl, DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene, DMAP: 4-dimethylaminopyridine, *p*-TSA: *para*-toluenesulfonic acid, TES: triethylsilyl, TFA: trifluoroacetic acid.

For butenolide coupling, we employed our recently described strategy involving a vinylogous Mukaiyama aldol reaction.[28] Brief exposure (1 min) of a mixture of the macrocyclic ketone **21** and silyloxyfuran **22**[29] to $TiCl_4$ 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).[30] 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 2:1 mixture of the diastereomeric butenolides **24a**/**b** upon treatment with DBU at ambient temperature. Dehydration of the tertiary alcohol **24a** (Et_3N, $SOCl_2$) afforded the desired tetrasubstituted olefin **25** as the predominant regioisomer ($\Delta^{5,6}/\Delta^{5,24}$, 3:1). The application of mildly basic conditions for cleavage of the trifluoroacetamide **25** 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.[15] 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 protocol.[31] Careful treatment of the derived Boc-amine **26** with trifluoroacetic acid led to both *tert*-butylcarbamate and silylether cleavage. Finally, cyclization to the cyclic imine under vacuum led to (−)-gymnodimine (**1**), as evidenced by correlation of spectral data of the synthetic material with that of the natural product.[32] By using an identical synthetic sequence, C4-*epi*-gymnodimine (C4-*epi*-**1**) was also synthesized from the diastereomeric butenolide alcohol **24b** (not shown) for comparison and provided further evidence that alcohol **24a** possessed the natural configuration at the C4 position.[32]

In conclusion, the first total synthesis of (−)-gymnodimine was achieved in a highly convergent fashion and featured an unusual Barbier-type macrocyclization strategy with *t*BuLi 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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[32] See the Supporting Information for details.

