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

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Gymnodimine (**1**, Figure 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 in 1995[i] and subsequently, Munro and Blunt reported the relative and absolute stereochemistry elucidated through X-ray crystallographic analysis of a reduced, *N*-acylated derivative.[ii] This toxin is produced by the dinoflagellate *Karenia selliforms* (formerly *Gymnodinium selliforme*) and is active in the mouse bioassay for neurotoxic shellfish poisoning.[iii] Recently, gymnodimine was found to sensitize neurons to the effects of okadaic acid[iv] and there is evidence that it binds to a subset of muscle nicotinic acetylcholine receptors.[v] Two additional analogs, differing only by an allylic oxidation at the C17–C18 olefin, were isolated and named gymnodimine B (**2**) and C (**3**), respectively.[vi] Other members of this growing family of spirocyclic imine toxins include the pinnatoxins,[vii] spirolides,[viii] pteriatoxins,[ix] prorocentrolide,[x] and spiro-prorocentrimine.[xi]

This family of spirocyclie-containing marine toxins has inspired intense synthetic efforts[xii] that have culminated in total or formal syntheses of the pinnatoxins and pteriatoxins.[xiii] However, the total synthesis of gymnodimine still remains elusive.[xiv] The seemingly simpler architecture of gymnodimine compared to other members of this family conceals subtle, challenging structural elements, in particular the known labile butenolide adding to the challenge of a total synthesis.[xv] Herein, we describe the first total synthesis of (−)-gymnodimine that provides suitable intermediates for eventual production of an enzyme-linked immunosorbent assay (ELISA) for gymnodimine detection and also further mode of action studies.[xvi]

Our synthetic plan called for a convergent coupling of the spirolactam **5** with a hypothetical, dual reactivity, tetrahydrofuran **4** (Figure 2). A Nozaki–Hiyama–Kishi (NHK) macrocyclization,[xvii] was initially envisioned for the proposed merging of C9 and C10

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(gymnodimine numbering) but ultimately led 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 even less frequently in a macrocyclization.[xviii] The fragile butenolide would be annulated at a late stage by a vinylogous Mukaiyama aldol reaction of a hypothetical furanone anion **6** to a ketone at C5 following unmasking of the silylenol ether of spirolactam **5**.

Our initial strategy for fragment coupling called for a NHK macrocyclization following joining of the iodotetrahydrofuran **10**, available in three steps from the previously described ether **7**,[xivb] and the optically active spirolactam **11** (95% ee),[xix] previously obtained via a catalytic, asymmetric Diels–Alder reaction (Scheme 1).[xivi] After some experimentation, we found optimal conditions for a Barbier-type fragment coupling involving halogen-lithium exchange in the presence of the *N*-tosyl lactam electrophile[xx] providing adduct **12** in 92% yield, while generation of the alkyl lithium and subsequent addition of the *N*-tosyl lactam gave greatly inferior results (17%). This was a crucial precedent for the eventual solution for macrocyclization (*vide infra*) since numerous attempts towards a 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.[xxi]

The synthesis of the required tetrahydrofuran aldehyde **14b** commenced with deprotection of PMB ether **13a**[xivb] and conversion to chloride **13c** by treatment with PPh_3/CCl_4 in warm DMF (Scheme 2). Following selective hydroboration of the terminal olefin, the intermediate alcohol **14a** was oxidized with Dess–Martin periodinane to provide aldehyde **14b**.[xxii]

The synthesis of the required vinyl iodide partner **16** for the projected Barbier macrocyclization began once again with optically active spirolactam **11** (Scheme 3). Functionalization of the internal acetylene in **11** proved to be rather challenging. Among all the protocols examined, only Pd-catalyzed hydrostannylation[xxiii] gave the corresponding vinyl stannane **15** and use of a non-polar solvent as reported by Semmelhack[xxiv] gave optimal conversion to 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, providing allylic alcohols **17a/b** as a diastereomeric mixture (1.3:1, β/α-epimers at C10) and the C10 epimers were readily separable (Scheme 3). The undesired α-epimer **17b** could be converted to **17a** via an oxidation-reduction sequence using the Itsuno–Corey reduction protocol (dr, 6:1) enabling greater material throughput.[xxv] Subsequent protection of the hydroxyl group and 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 (*cf.* Scheme 1) were disappointing in this instance providing a mixture of deiodinated *t*-butyl ketone derived from quenching of the alkyllithium and *t*-BuLi addition to the δ-lactam. *Surprisingly, performing the reaction in an identical manner but adding t-BuLi to the iodo N-tosyl lactam **18** at ambient temperature (23 °C) rather than −78 °C gave macrocycle **19** reproducibly on scales up to ~100 mg in 56–61% yields.* While both conformational effects

and relative rates of halogen-metal exchange,[xxvi] macrocyclization, *t*-BuLi addition to the *N*-tosyl lactam, and elimination of *t*-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 utilizing our recently developed protocol for this purpose (Scheme 4).[xxvii] The silyl groups of macrocycle **20** were then cleaved under acidic conditions, furnishing the crystalline hydroxy ketone **21**, which enabled confirmation of the relative stereochemistry of the macrocycle by single crystal X-ray analysis (inset, Scheme 4).

For butenolide annulation, we employed our recently described strategy via a vinylogous Mukaiyama aldol reaction.[xxviii] Brief exposure (1 min) of a mixture of the macrocyclic ketone **21** and silyloxyfuran **22**[xxix] to $TiCl_4$ at 23 °C provided butenolide **23** in good yield as a ~1:1 mixture of two diastereomers (epimeric at C4; single stereochemistry at C5, Scheme 4).[xxx] The lack of diastereoselectivity at C4 during this transformation is to a great extent offset by the conciseness of this direct vinylogous Mukaiyama aldol addition strategy for butenolide annulation. The epimeric tertiary alcohols **24a**/**b** were readily separated after alcohol protection. It was found that the undesired diastereomer **24b** could be epimerized to 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). Application of mild basic conditions for cleavage of the trifluoroacetamide **25** led to degradation of the butenolide, in agreement with the findings of Miles that the butenolide of gymnodimine is unstable under both neutral and mild alkaline conditions.[xv] Attempted acid hydrolysis also proved unsuitable for this highly functionalized substrate. Eventually, a solution was found involving *N*-Boc protection and mild trifluoroacetamide cleavage using a modified Burk protocol.[xxxi] Careful treatment of the derived Boc-amine **26** with trifluoroacetic acid led to both *t*-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 to that of the natural product.[xxxii] 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 C4.[xxxii]

In conclusion, the first total synthesis of (−)-gymnodimine was achieved in a highly convergent fashion, featuring an unusual Barbier-type macrocyclization strategy at ambient temperature. Also, a late stage appendage of the chiral butenolide *via* a vinylogous Mukaiyama aldol addition to a highly useful macrocyclic ketone **21** provides convenient avenues for synthesis of gymnodimine derivatives for further mode of action studies and hapten synthesis. The latter studies are directed towards development of a robust ELISA assay for detection of gymnodimine and congeners in the marine environment and will be reported in due course.

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xxx. The stereochemical outcome is consistent with simpler models confirmed by X-ray analysis. See ref. xxviiia for further information.

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xxxii. See Supporting Information for details.

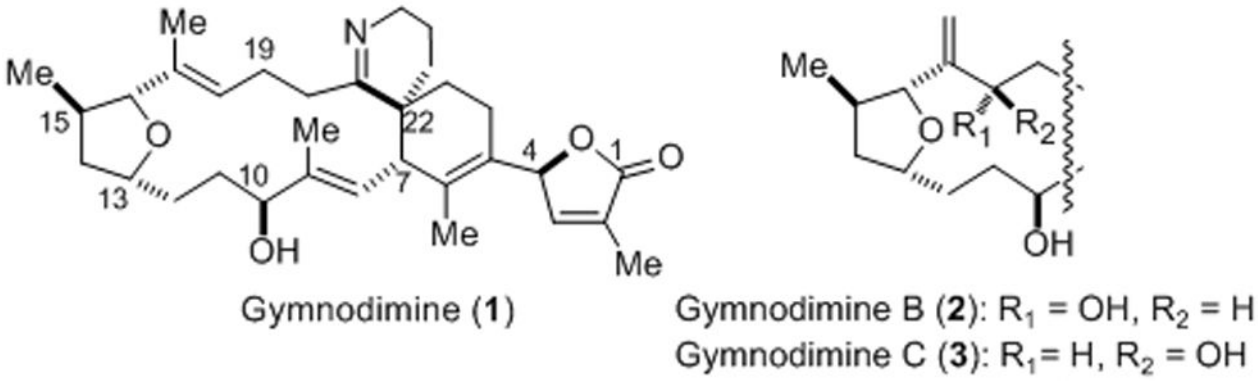


Figure 1.
Structures of known members of the gymnodimine family of spirocyclic imine marine toxins.

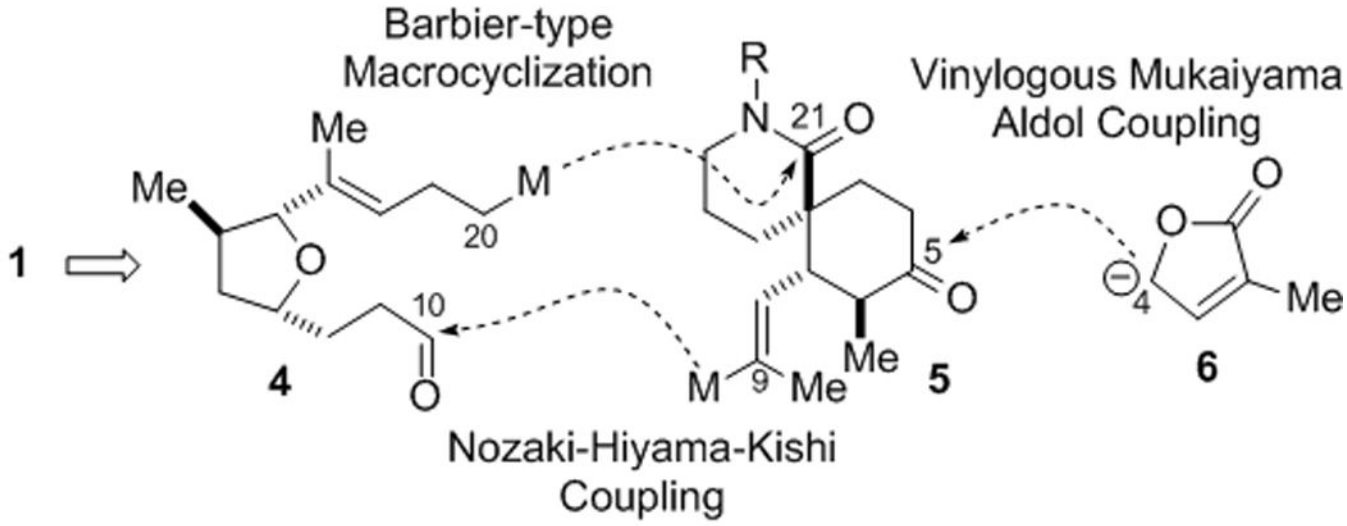
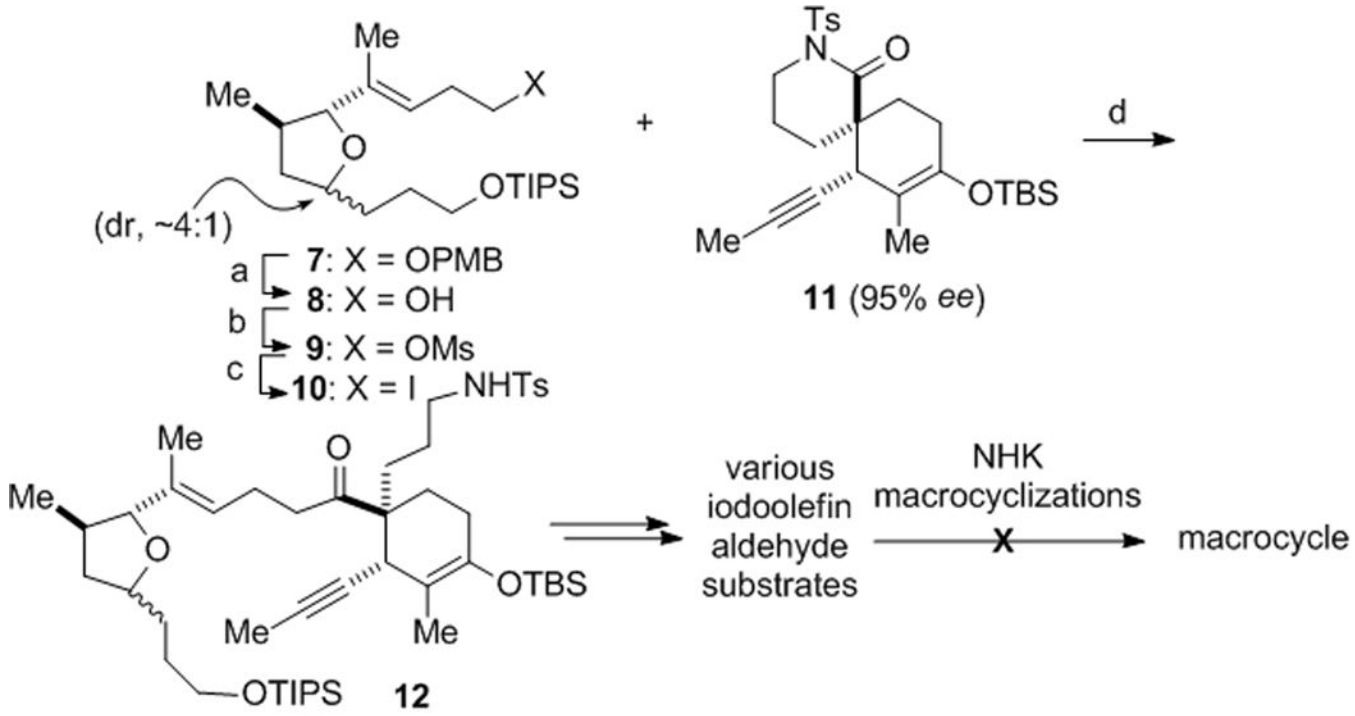


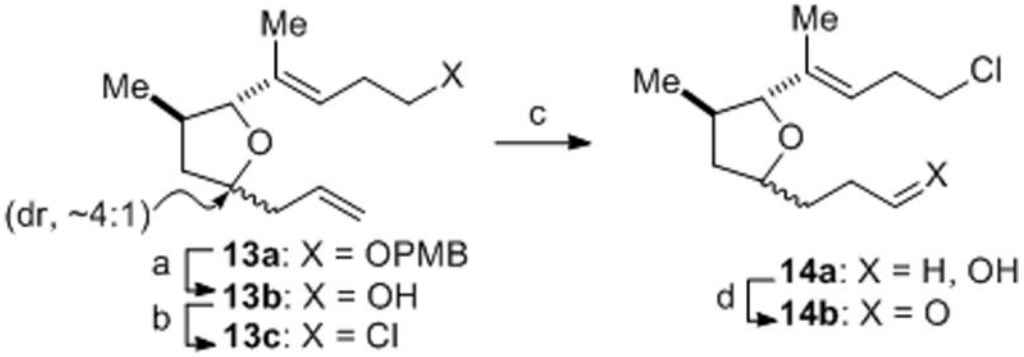
Figure 2.

Retrosynthetic strategy toward gymnodimine (**1**) showing principal disconnections. M = metal.



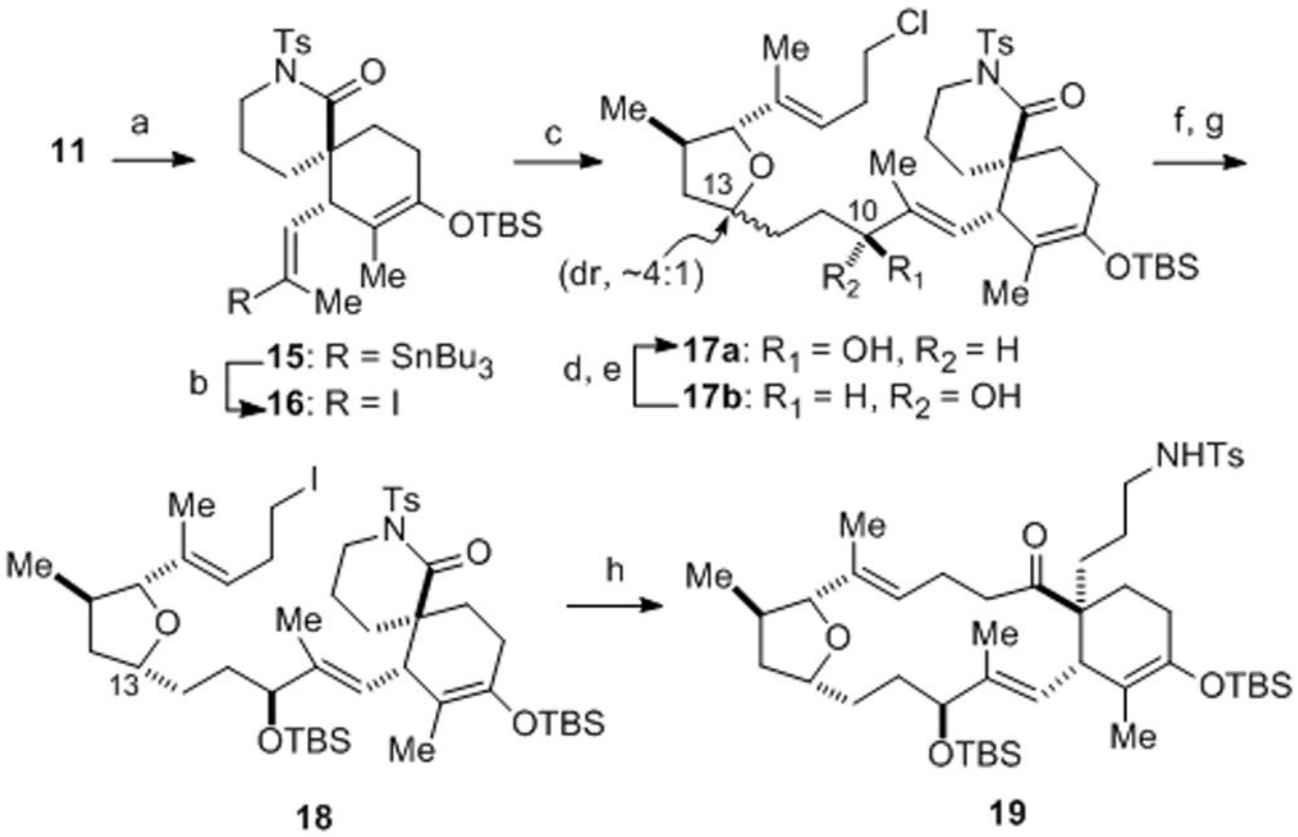
Scheme 1.

Reagents and conditions. a) Na°, NH_3(l), THF, −78 °C, 92%; b) MsCl, Et_3N, CH_2Cl_2, 92%; c) *n*-Bu_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%. PMB = *para*-methoxybenzyl, THF = tetrahydrofuran, Ms = methanesulfonyl, TIPS = triisopropylsilyl.



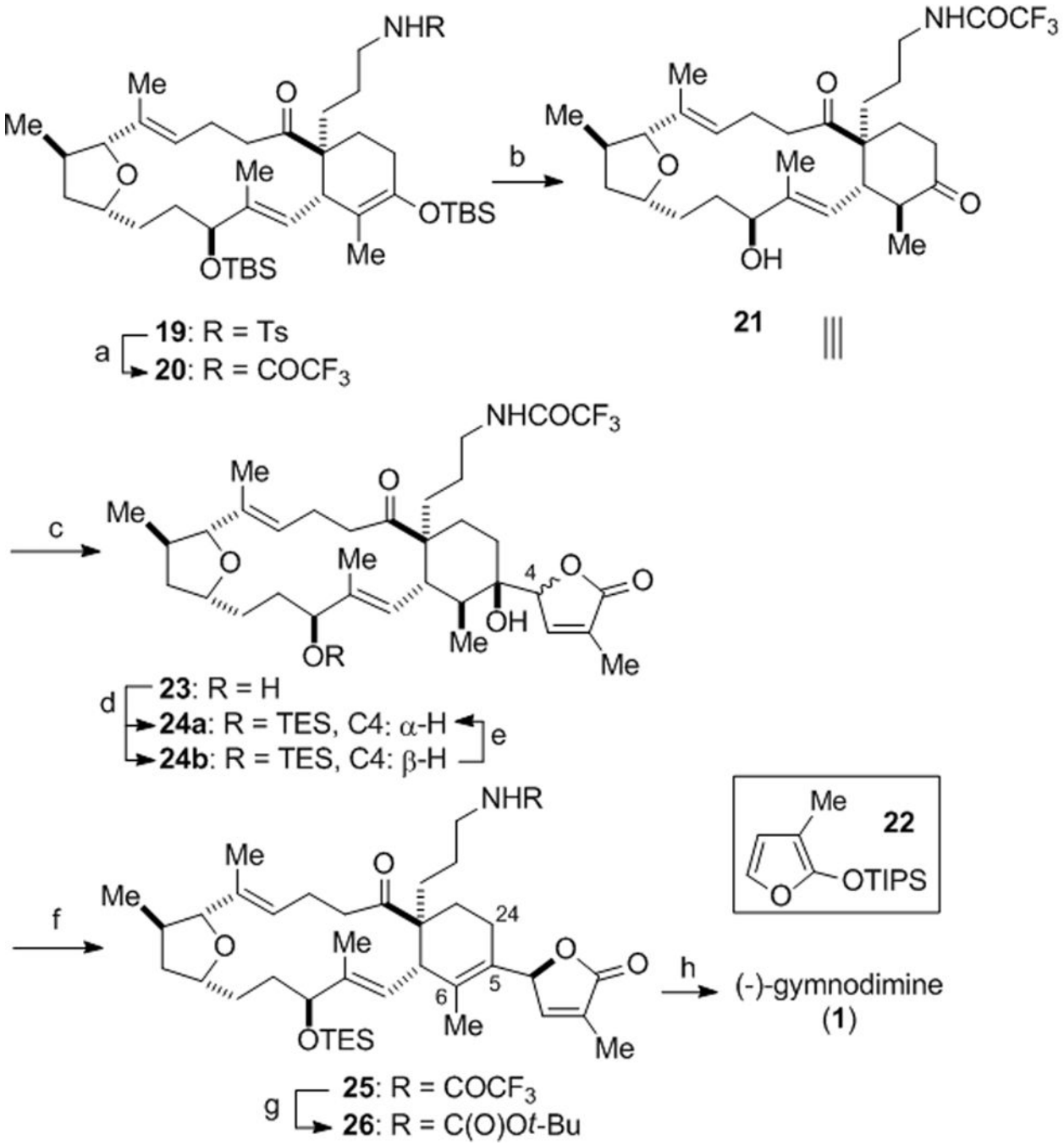
Scheme 2.

Reagents and conditions: a) Na^0, NH_3(l), 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%. DMF = *N*,*N*-dimethylforamide, 9-BBN = 9-borabicyclo[3.3.1]nonane.



Scheme 3.

Reagents and conditions: a) $PdCl_2(PPh_3)_2$, *n*-Bu_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%, dr = 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.



Scheme 4.

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% (dr, 1:1); d) TESCl, imidazole, DMAP, CH_2Cl_2, 23 °C, 76% (dr, 1:1, **24a**/**b**); e) DBU, CH_2Cl_2, 60% (dr,2:1, **24a**/**b**); 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 X-ray structure of ketone **21**). *p*-TSA = *para*-toluenesulfonic acid, TES = triethylsilyl, DMAP = 4-

dimethylaminopyridine, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, Boc = *tert*-butoxycarbonyl, TFA = trifluoroacetic acid