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PAPER

Synthesis of the gymnodimine tetrahydrofuran core through a Ueno–Stork radical cyclization†‡

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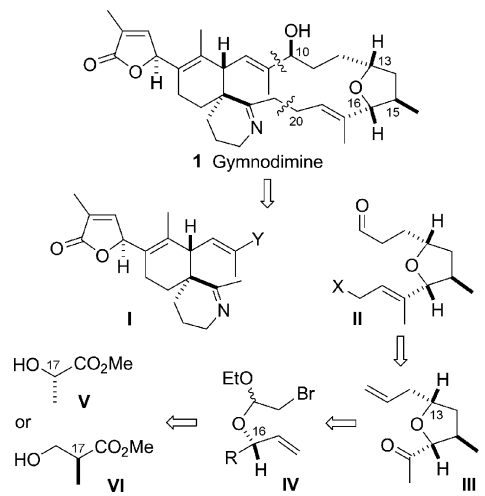
A straightforward access to the C10–C20 skeleton of gymnodimine, incorporating a tetrahydrofuran fragment, is described. The elaboration of the THF moiety is based on a stereocontrolled Ueno–Stork cyclization. A Lewis-acid mediated allylation of the resulting acetal at C13 and a Horner–Wadsworth–Emmons olefination on the ketone at C17 complete the synthesis.

Introduction

Gymnodimine **1** belongs to a family of macrocyclic imine phycotoxins produced from dinoflagellate *Karenia selliformis* and *Gymnodinium cf. mikimotoi* and isolated by Yasumoto *et al.* from oysters collected off the Foveaux Strait, South Island coast in New-Zealand.[1] Its relative and absolute configuration were elucidated later by Munro, Blunt and co-workers through X-ray crystallographic studies.[2] Closely related analogues such as gymnodimine B and C were recently isolated, possessing the same macrocyclic structure, but differing from **1** in the substitution pattern at C17–C18.[3] These marine algal toxins are concentrated into shellfish, moving up the food chain to reach crabs, fish, then human beings. While their mode of action has not yet been fully established,[4] recent studies indicate that they likely act as specific inhibitors of nicotinic acetylcholine receptors of the peripheral and central nervous system.[5] The proliferation of these neurotoxic shellfish poisoning (NSP) compounds associated with their lipophilicity and their ability to cross the blood-brain barrier thus constitutes a potent threat for public health.

The low availability of these phycotoxins along with their relevant biological activities has led several teams to investigate their synthesis. Total synthesis of **1** has recently been reported by Romo *et al.*,[6] while various approaches to the main subunits have been described since its isolation in 1995.[7,8] We report herein a straightforward approach to the tetrahydrofuran core of **1** starting from the chiral pool, which exploits the Ueno–Stork reaction as a key-step.[9] It was envisioned that the elaboration of the five-membered ring heterocycle could be carried out through the cyclization of an halogenated intermediate such as **IV** (Scheme 1). This would be followed by introduction of the C10–C12 carbon chain at C13 through allylation of the resulting acetal and the side chain would be oxidized to provide the ketone **III**. The trisubstituted olefinic appendage at C16 would be generated through a Horner–Wadsworth–Emmons reaction on the C17-ketone affording **II**. Inexpensive (*S*)-lactate **V** and (*S*)-Roche ester **VI** were designed as potent chiral starting materials.



Scheme 1 Retrosynthetic analysis of **1**.

Results and discussion

Preparation of haloacetals **3a–b** was first carried out through halo-etherification of the corresponding known alcohols **2a**[10] and **2b**[11] with vinylethyl ether. Our preliminary attempts were made following standard procedures using NIS,[9d,12] NBS,

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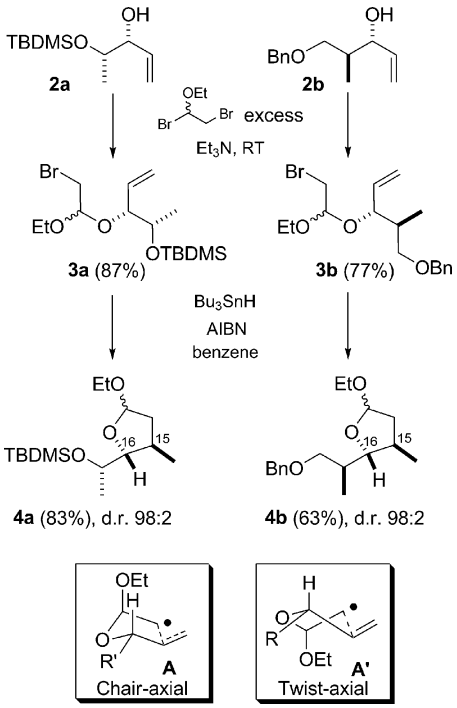
† Dedicated to the memory of Prof. A. L. J. Beckwith in recognition of his major achievements in the field of radical chemistry.

‡ Electronic supplementary information (ESI) available: Compound characterization, spectra and supplementary information are available. See DOI: 10.1039/c1ob05240c

I_2–AgOTf or $Hg(OAc)_2$.[13] Unfortunately, all our efforts resulted either in recovered starting material or low conversion into the desired halo-ethers. More satisfying results were obtained by using instead an excess of 1,2-dibromo-1-ethoxyethane freshly prepared through bromination of vinylethyl ether.[14] When an excess of this reagent was added in fractions to allylic alcohols **2a–b**, the desired bromides **3a–b** were obtained, after purification, in 87% and 77% yields respectively as an inseparable mixture of two diastereomers (**3a** d.r.~6/4, **3b** d.r.~55/45) (Scheme 2).

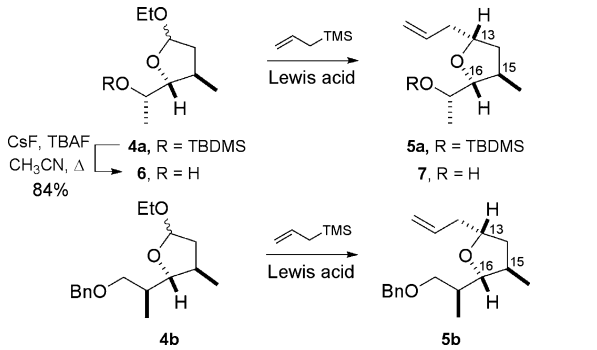


Scheme 2 Ueno–Stork cyclization of bromoethers **3a–b**.

These acetals were then submitted to the Ueno–Stork reaction conditions using Bu_3SnH and AIBN in benzene, either under reflux or under UV irradiation at room temperature (see experimental part). Initiation using Et_3B and oxygen at room temperature led in contrast to poor conversion.[9d] The corresponding cyclic acetals **4a–b** were isolated as a 1 : 1 mixture of two diastereomers at the C13 position, indicating that the cyclization had occurred with complete diastereocontrol, likely through transition state models **A** and **A′** proposed originally by Beckwith[15] and later refined by Renaud and Schiesser.[16] The C10–C12 chain was then installed through a Lewis acid-mediated allylation at C13 on acetals **4a–b**.[7a–b,17]

Our preliminary attempts using acetal **4a**, treated with allyltrimethylsilane and BF_3–OEt_2, led to the desired tetrahydrofuran **5a** in 73% yield but with no stereocontrol (Table 1, entry 1). The use of other Lewis acids such as TMSOTf or $SnBr_4$ provided no beneficial effects (entries 2–3). In contrast, when **4b** was treated under the same conditions (entry 4), tetrahydrofuran **5b** was obtained in good yield and with slightly better diastereocontrol. In order to improve the required C13–C16 stereoselectivity, we also tried to deliver intramolecularly (in a *syn* fashion) the allyl moiety by treating **6**[18] with allyldimethylchlorosilane and TMSOTf (entry 5).[19] The reaction proceeded cleanly to afford **7** in reasonable yield but again with poor diastereocontrol. As rationalized by Woerpel

Table 1 Lewis-acid mediated allylation of acetals **4a–b** and **6**



Entry	Acetal	Product	Conditions	*cis*/*trans* Ratio[a]	Yield
1	**4a**	**5a**	BF_3–OEt_2 (1.5 equiv.), –80 °C, 30 h	1 : 1	73%
2	**4a**	**5a**	TMSOTf (1 equiv.), –80 °C, 2.5 h	1 : 1	75%
3	**4a**	**5a**	$SnBr_4$ (1.6 equiv.), –80 °C, 24 h	1.25 : 1	83%
4	**4b**	**5b**	TMSOTf (1 equiv.), –80 °C, 2 h	2.7 : 1	70%
5	**6**	**7**	$SnCl_4$ (1.5 equiv.), 0 °C, 4 h[b]	2.5 : 1	67%
6	**6**	**7**	TMSOTf (1.2 equiv.), –80 °C, 2 h	4 : 1	71%
7	**4a**	**7**	TMSOTf (5 equiv.), –80 °C, 24 h	2 : 1	61%
8	**4a**	**7**	TMSOTf (5 equiv.), BF_3–OEt_2 (2.5 equiv.), –80 °C, 2 h	2.3 : 1	77%
9	**4a**	**7**	TMSOTf (5 equiv.), CsF (5 equiv.), –80 °C, 20 h	1.5 : 1	63%

[a] Estimated from the ^1H NMR of the crude reaction mixture. [b] The allylation reaction was carried out with allyldimethylchlorosilane.

et al.[20] for related Lewis acid-mediated allylation, the approach of the allylmetal reagent onto the oxonium intermediate should occur "inside" an envelope conformation, with a C3 methyl substituent in a pseudo-equatorial position (Model **B**, Fig. 1), to give the 1,3-*trans* product with high diastereocontrol. Decreasing the steric hindrance at C4 should in turn favor the desired stereochemistry. This is effectively the case, as shown by the slightly improved diastereocontrol observed with **4b**.

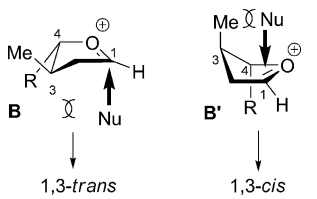


Fig. 1 Transition-state models for the allylation of acetals **4a–b**, and **6**.

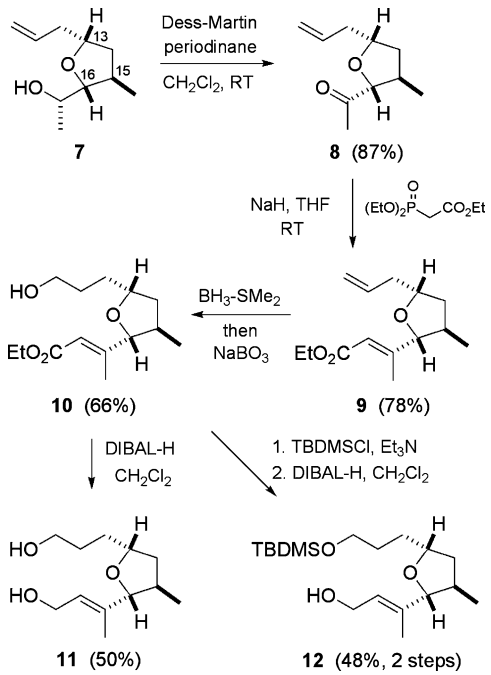
In such a model, a bulky substituent at C4 (such as OTBDMS in **4a**), should however induce strong interactions with the incoming allylsilane. In this case, the diequatorial oxocarbenium conformer **B** would be disfavored and the attack of the nucleophile might instead occur "inside" another envelope conformation **B′**, in which the methyl substituent at C3 would occupy a pseudo-axial position, leading to the 1,3-*cis* product.

In transition state **B′**, one may however predict strong destabilizing 1,3-diaxial interactions between the incoming nucleophile and the methyl substituent at C3. Therefore, with bulky substituents at C4, low stereocontrol should be predicted, as verified by experiments in entries 1–2 (Table 1). Based on these premises, we repeated the reaction with precursor **6** having a smaller free hydroxyl group. Using TMSOTf as a Lewis acid, **6**, (which may however react as its OTMS form) effectively led to tetrahydrofuran **7** in good yield and a 4 : 1 ratio (entry 6). This is in good agreement with the selectivity observed by Romo *et al.*[7a] during their synthesis of the THF core of **1**, through allylation of a related intermediate. Other Lewis acids, including $Bi(OTf)_3$, APTS or $SnCl_4$ led to recovered starting material along with the hemiacetal derived from **6**, which could not be isolated pure. We finally tried to carry out both the deprotection of **4a** into **6** and the subsequent allylation in one pot (entries 7–9). An excess of TMSOTf was first added fractionally to provide **7** in good yield, albeit with low diastereocontrol (entry 7). Deprotection of the TBDMS protective group using TMSOTf probably generates, under our conditions, the corresponding trimethylsilyl ether, leading as in **4a** to low diastereocontrol. Additives such as CsF and BF_3–OEt_2 were thus introduced in order to remove the putative TMS protective group. Unfortunately, none of them were able to afford **7** with much higher selectivity (entries 8–9). The remaining part of the synthesis was thus performed with THF **7**, having the desired C13–C16-*cis*-configuration, which was obtained pure, on a gram scale, after simple chromatography. Tetrahydrofuran **7** was then subjected to the Dess–Martin periodinane oxidation,[21] affording the volatile ketone **8** in 87% yield (Scheme 3). Horner–Wadsworth–Emmons olefination on **8** was carried out using NaH in THF, eventually affording the desired unsaturated ester **9** in 78% yield as 9 : 1 mixture of *E*- and *Z*-stereoisomers that could be separated through column chromatography.[22] Subsequent hydroboration–oxidation sequence of the allylic chain at C13 using BH_3–Me_2S then H_2O_2–NaOH led to the desired alcohol **10**, but in a non reproducible manner. In contrast, when the reaction was carried out adding BH_3–Me_2S at room temperature, then gently heating the mixture at 35 °C, followed by the oxidation of the borane using $NaBO_3$ and H_2O,[23] the alcohol **10** was obtained in reasonable yield. Protection of the primary alcohol with TBDMSCl (71% yield) followed by the ester reduction with DIBAL-H gave the corresponding allylic alcohol **12** (68% yield). In Parallel, **10** could be directly reduced into diol **11** using again DIBAL-H in a moderate 50% yield.

Conclusions

In summary, we reported along these lines a straightforward access to the tetrahydrofuran core of gymnodimine **1** in only 9 steps starting from alcohol **2a**. Both **11** and **12** possess the functionalities for further coupling to the spiroimine skeleton of **1**. Efforts at synthesizing the spiroimine skeleton and connecting the fragments together are underway and will be reported in due course.

The ability of **11** and allylic alcohol **12** to inhibit the binding of biotinylated α-bungarotoxin to nicotinic acetylcholine receptors (*n*AChRs) was finally assessed by a non-radioactive ligand binding assay (see the ESI‡).[24] Neither **11** nor **12** could inhibit biotinylated α-bungarotoxin binding to *Torpedo*-nAChR even at millimolar concentrations, while gymnodimine-A inhibited α-bungarotoxin binding to the nAChRs in a concentration dependent manner



Scheme 3 Synthesis of the tetrahydrofuran core of gymnodimine **1**.

with an IC_{50} of 7.65×10^{-8} M (6.94×10^{-8} to 8.42×10^{-8} M, 95% confidence limits).

Experimental part

(3*R*,4*S*)-5-(Benzyloxy)-4-methylpent-1-en-3-ol 2b: 3 step-sequence synthesis

Roche ester (447 mg, 3.793 mmol) was dissolved in dry dichloroethane, then MgO (303 mg, 7.586 mmol, 2 equiv.) and Dudley reagent[25] (2.647 g, 7.586 mmol, 2 equiv.) were added. The reaction was refluxed during 15 h. The reaction media was filtered on a celite pad then washed with 15 mL of a mixture petroleum ether (PE)/EtOAc (80/20). Purification on silica gel (PE 100% then PE/EtOAc: 96/4) provided the benzylated intermediate ester as a clear oil (665 mg, 84% yield). The protected ester (665 mg, 3.193 mmol) was dissolved in dry Et_2O (32 mL) under an inert atmosphere at −110 °C and then DIBAL-H (1.2 M in toluene) was added (5.31 mL, 6.38 mmol, 2 equiv.). After 18 min, TLC indicated that reaction went to completion. 10 mL of a Rochelle's salt solution were added at −110 °C and the reaction medium was allowed to warm to room temperature. 100 mL water were added and then extraction was performed with Et_2O (3×20 mL). The organic layers were dried over $MgSO_4$ and solvents were removed under vacuum. The intermediate aldehyde (550 mg, 3.0859 mmol, 97%) was obtained clean enough to be used in the next step without any further purification. The crude aldehyde was dissolved in dry Et_2O (10 mL) under an inert atmosphere and the solution was cooled at −80 °C, then vinylmagnesium bromide (1 M in THF) (6.17 mL, 6.17 mmol, 2 equiv.) was added slowly. The mixture was stirred at −80 °C overnight. At reaction completion, the reaction was quenched with a saturated aqueous solution of NH_4Cl (10 mL). The mixture was warmed to room temperature and water was added. Extraction was performed with Et_2O (3×15 mL), organic layers were dried over Na_2SO_4 and

solvents were removed under vacuum. Purification of the crude by automatically performed flash chromatography (gradient from PE 100% to PE/EtOAc 92/8) provided the *anti* desired isomer **2b** as a colourless oil (240 mg, 67%). **FTIR** (film, NaCl): ν = 3422, 2967, 2901, 1454, 1364, 1075, 924, 737, 698 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ (ppm) = 7.49–7.19 (m, 5H), 5.85 (ddd, J ~ 6.6, 10.4, 17 Hz, 1H), 5.24 (d, J ~ 24.6 Hz, 1 H), 5.18 (d, J ~ 17.6 Hz, 1 H), 4.52 (s, 2H), 4.03 (t, J ~ 6.8 Hz, 1 H), 3.61 (dd, J ~ 3.2, 4.4 Hz, 1 H), 3.48 (dd, J ~ 7, 9 Hz, 1 H), 3.38 (br s, 1H), 2.05–1.80 (m, 1H), 0.92 (d, J ~ 7 Hz, 3 H). **^{13}C NMR** ($CDCl_3$, 52.5 MHz): δ (ppm) = 139.6, 137.9, 128.5, 127.8, 127.7, 115.9, 77.5, 74.6, 73.5, 38.6, 13.8. **HRMS** (ESI): $[M+Na]^+$ $C_{13}H_{18}O_2Na$: calcd 229.12045; found 229.1205.

(5*S*,6*R*)-8-(Bromomethyl)-2,2,3,3,5-pentamethyl-6-vinyl-4,7,9-trioxa-3-silaundecane 3a. Preparation of 1,2-dibromo-1-ethoxyethane solution (sol. A): To a solution of vinyl ethyl ether (16.7 mL, 186.2 mmol, 7 eq.) in CH_2Cl_2 (53 mL, ~2 mL $mmol^{-1}$ of alcohol) at −78 °C, was added dropwise Br_2 (8.2 mL, 159.6 mmol, 6 eq.). The mixture turned slightly yellow and was stirred 1 h at −78 °C prior its use.

4 equiv. of sol. A (4 × 12 mL) were added at RT by portion every hour to a solution of **2a** (5.767 g, 26.6 mmol) in Et_3N (53 mL, ~ 2 mL $mmol^{-1}$ of alcohol). At reaction completion (TLC), the mixture was quenched with water and extracted with DCM (3 × 20 mL). The organic layer was dried over $MgSO_4$, filtrated and solvents were removed under vacuum. Purification on silica gel (PE/EtOAc: 99/1 to 96/4) provided **3a** as a clear oil (8.50 g, 87% yield). **FTIR** (film, NaCl): ν/cm^{-1} = 3084, 2931, 2866, 1256, 1111. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ (ppm) = 5.85–5.67 (m, 1 H), 5.35–5.19 (m, 2 H), 4.75 (dd, J~ 6.5, 4.0 Hz, 0.4 H), 4.71 (appearing t, J~ 5.2 Hz, J~ 5.6 Hz, 0.6 H), 3.89–3.77 (m, 2 H), 3.74–3.56 (m, 1.8 H), 3.52–3.41 (m, 1 H), 3.40–3.28 (m, 1.6 H), 1.22 (t, J~ 6.1 Hz, 1.8 H), 1.19 (t, J~ 7.0 Hz, 1.2 H), 1.13 (d, J~ 6.4 Hz, 1.8 H), 1.12 (d, J~ 6.4 Hz, 1.2 H), 0.88 (s, 3.6 H), 0.87 (s, 5.4 H), 0.05 (s, 2.4 H), 0.04 (s, 3.6 H).**^{13}C NMR** ($CDCl_3$, 100 MHz): δ (ppm) = 136.3, 135.3, 119.9, 117.9, 102.0, 99.0, 84.6, 82.7, 71.3, 70.7, 62.6, 61.7, 32.6, 32.3, 26.0, 20.2, 19.0, 18.3, 18.2, 15.4, 15.1, −4.4, −4.5, −4.6. **HRMS** (ESI): $[M+Na]^+$ $C_{15}H_{31}BrO_3SiNa$: calcd. 389.11235 found 389.1123.

(((2*S*,3*R*)-3-(2-Bromo-1-ethoxyethoxy)-2-methylpent-4-enyloxy)methyl)benzene 3b. Following the same procedure as for **3a**, **3b** was obtained from (3*R*,4*S*)-5-(benzyloxy)-4-methylpent-1-en-3-ol (350 mg, 1.699 mmol) in dry DCM in Et_3N (3.4 mL, ~2 mL $mmol^{-1}$ of alcohol) and 12 eq. sol. A (2.2 mL) at 25 °C. After 30 min, sol. A was added by portion of 2 eq. successively (6 × 2eq, 6 × 2.2 mL). Purification on silica gel (PE/EA: 98/2 then 97/3) provided **3b** as a clear oil (458 mg, 77% yield). **FTIR** (film, NaCl): ν = 3030, 2976, 2877, 1642, 1454, 1422, 1374, 1202, 1105, 1023, 929, 735, 697 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ = 7.47–7.14 (m, 5H, d_1+d_2), 5.89–5.54 (m, 1H, d_1+d_2), 5.36–5.09 (m, 2 H, d_1+d_2), 4.77–4.56 (m, 1H, d_1+d_2), 4.50 (s, 2H, d_1+d_2), 4.09 (t, J ~ 7.8 Hz, 0.5 H, d_1 or d_2), 3.93 (t, J ~ 7.8 Hz, 0.5 H, d_1 or d_2), 3.82–3.22 (m, 7 H, d_1+d_2), 2.16–1.89 (m, 1H, d_1+d_2), 1.33–1.06 (m, 4H, d_1+d_2), 0.99–0.77 (m, 4H, d_1+d_2). **^{13}C NMR** ($CDCl_3$, 52.5 MHz): δ = 138.8, 138.6, 136.8, 136.1, 128.4, 127.8, 127.6, 119.4, 118.3, 100.7, 99.1, 80.7, 79.8, 73.2, 73.1, 71.7, 63.0, 61.7, 38.2, 38.0, 32.6, 32.4, 15.4, 15.1, 13.1. **HRMS** (ESI): $[M+Na]^+$ $C_{17}H_{25}BrO_3Na$: calcd 379.08848; found 379.0888.

(*S*)-1-((2*R*,3*R*)-5-Ethoxy-3-methyl-tetrahydrofuran-2-yl)ethanol 4a. To a solution of ((2*S*,3*R*)-3-(2-bromo-1-ethoxyethoxy)pent-4-en-2-yloxy)(*tert*-butyl)dimethylsilane (7.852 g, 21.39 mmol) in degassed benzene (200 mL), was added fresh Bu_3SnH (6.90 mL, 26.674 mmol, 1.2 eq) and AIBN (350 mg, 2.14 mmol, 0.1 eq.). The solution was then refluxed until reaction completion (~3 h TLC control). Benzene was removed under vacuum and the crude was purified on silica gel (PE/EA – 98/2). Filtration with SiO_2 and KF (PE/EA – 8/2) was performed to remove tin derivatives providing pure product **4a** as a clear oil (5.145 g, 83%, d.r.~6/4). Diastereoisomers could be separated and fully characterized but they were used as a mixture in further steps. **FTIR** (film, NaCl): ν/cm^{-1} = 2970, 2930, 2853, 1257, 1092. **^{1}H NMR** ($CDCl_3$, 300 MHz). Fraction 1: δ (ppm) 5.09–5.02 (m, 1 H), 3.86–3.64 (m, 2 H), 3.51–3.33 (m, 2 H), 2.26–2.07 (m, 2 H), 1.58–1.44 (m, 1H), 1.22–1.08 (m, 10 H), 0.87 (s, 9 H), 0.05 (s, 3 H), 0.03 (s, 3 H). Fraction 2: δ (ppm) 5.0 (d, J~ 4.8 Hz, 1 H), 3.77–3.58 (m, 2 H), 3.45–3.29 (m, 2 H), 2.36–2.21 (m, 1 H), 2.04 (dd, J~ 12.6, 7.3 Hz, 1 H), 1.65–1.52 (m, 1 H), 1.22 (d, J~ 6.0 Hz, 3 H), 1.16 (t, J~ 7.2 Hz, 3 H), 1.10 (d, J~ 6.6 Hz, 3 H), 0.89 (s, 9 H), 0.07 (s, 6 H). **^{13}C NMR** ($CDCl_3$, 75.5 MHz): Fraction 1: δ (ppm) 104.1, 89.4, 70.4, 62.7, 41.2, 32.9, 26.0, 20.8, 20.6, 18.2, 15.5, −4.4, −4.5. Fraction 2: δ (ppm) 103.5, 90.9, 72.8, 62.4, 42.1, 35.4, 26.0, 21.4, 19.5, 18.2, 15.3, −4.1, −4.5. **HRMS** (ESI): $[M+Na]^+$ $C_{15}H_{32}O_3SiNa$: calcd. 311.20184, found 311.2018

(2*R*,3*R*)-2-((*S*)-1-(Benzyloxy)propan-2-yl)-5-ethoxy-3-methyltetrahydrofuran 4b. To a solution of (((2*S*,3*R*)-3-(2-bromo-1-ethoxyethoxy)-2-methylpent-4-enyloxy)methyl)benzene (450 mg, 1.264 mmol) in degassed benzene (12 mL), was added Bu_3SnH (distillated or freshly opened) (400 µL, 1.516 mmol, 1.2 eq) and AIBN (20.67 mg, 0.1264 mmol, 0.1 eq.). The solution was then refluxed until reaction completion (~3 h TLC control). Benzene was removed under vacuum and the crude was purified on silica gel (PE/EA – 97/3). To remove tin derivative, purification was performed using SiO_2 (20 g) and KF (1% weight), providing the expected product as a colorless oil (220 mg, 63%, d.r.~55/45). Diastereoisomers were used as a mixture in further steps. **FTIR** (film, NaCl): ν = 2972, 2902, 1454, 1372, 1201, 1084, 1042, 995, 934, 734, 696 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ (ppm) 7.47–7.18 (m, 5H, d_1+d_2), 5.06 (dd, J ~ 1.8 Hz, 5 Hz, 0.45H), 4.99 (d, J ~ 4.8 Hz, 0.55H), 4.60–4.46 (m, 2 H, d_1+d_2), 3.83–3.24 (m, 5H, d_1+d_2), 2.45–1.85 (m, 3H, d_1+d_2), 1.72–1.44 (m, 1H, d_1+d_2), 1.41–0.82 (m, 9 H, d_1+d_2). **^{13}C NMR** ($CDCl_3$, 52.5 MHz): δ (ppm) 138.9, 138.8, 128.3, 127.5, 127.41, 127.37, 103.3, 103.0, 88.3, 86.0, 73.1, 73.0, 73.0, 72.8, 62.5, 62.2, 42.3, 41.4, 39.5, 37.5, 34.8, 34.7, 19.7, 18.9, 15.4, 15.2, 14.6, 14.1. **HRMS** (ESI): $[M+Na]^+$ $C_{17}H_{26}O_3Na$: calcd 301.17796; found 301.1779.

***tert*-Butyl((*S*)-1-((2*R*,3*R*)-5-ethoxy-3-methyl-tetrahydrofuran-2-yl)ethoxy)dimethylsilane 5a.** To a solution of (*S*)-1-((2*R*,3*R*)-5-ethoxy-3-methyl-tetrahydrofuran-2-yl)ethanol (60 mg, 0.208 mmol) in DCM (4 mL) at −78 °C was added $BF_3{\cdot}Et_2O$ (26 µL, 0.208 mmol, 1 eq.) and then allyltrimethylsilane (100 µL, 0.624 mmol, 3 eq.). The reaction was stirred overnight at −40 °C, then quenched with a saturated aqueous solution of $NaHCO_3$ at −78 °C and warmed quickly to RT. The crude was extracted with DCM (3 × 20 mL), organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification on silica gel (PE/EA – 99/1) afforded a clean mixture of the

two diastereoisomers as a clear oil (43 mg, yield 73%). Clear NOESY connectivities established unambiguously the 2,5-*cis* configuration of THF core of the major compound. **FTIR** (film, NaCl): ν/cm^{-1} = 3079, 2964, 2861, 1644, 1254, 1102. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ (ppm) = 5.88–5.71 (m, 1 H), 5.11–4.98 (m, 2 H), 4.00–3.87 (m, 1 H), 3.82 (m, 0.5 H), 3.72 (m, 0.5 H), 3.35 (dd, *J*~ 7.2, 4.8 Hz, 0.5 H), 3.24 (t, *J*~ 5.4 Hz, 0.5 H), 2.42–2.05 (m, 4 H), 1.74–1.48 (m, 1 H), 1.17–1.02 (m, 6 H), 0.88 (s, 9 H), 0.06 (s, 6 H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ (ppm) = 135.4, 135.3, 116.7, 116.6, 90.9, 89.6, 78.6, 77.7, 71.2, 70.7, 42.0, 40.4, 40.3, 39.8, 35.5, 34.2, 26.0, 20.9, 20.8, 20.4, 19.9, 18.2, –4.2, –4.3, –4.4, –4.5. **HRMS** (ESI): $[M+Na]^+$ $C_{16}H_{32}O_2SiNa$: calcd. 307.20693, found 307.2070

(2*R*,3*R*,5*R*)-5-Allyl-2-((*S*)-1-(benzyloxy)propan-2-yl)-3-methyltetrahydrofuran 5b. To a solution of (2*R*,3*R*)-2-((*S*)-1-(benzyloxy)propan-2-yl)-5-ethoxy-3-methyltetrahydrofuran (210 mg, 0.754 mmol) in DCM (3 mL) at −84 °C was added TMSOTf (163 µL, 0.905 mmol, 1.2 eq.) and then allyltrimethylsilane (481 µL, 3.016 mmol, 4 eq.). After 2 h the mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (4 mL) at −84 °C and warmed quickly to RT. 30 mL H_2O were added and then the crude was extracted with DCM (3 × 20 mL), organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Crude ^{1}H-NMR in C_6D_6 (600 MHz) allowed to measure a 2.7 : 1 d.r. in favour of *cis* isomer. Purification on silica gel afforded the mixture of both diastereoisomers as clear oil (145 mg, yield 70%). **FTIR** (film, NaCl): ν = 3030, 2958, 1642, 1248, 1089, 1028, 995, 913, 838, 733, 696 cm^{-1}. **^{1}H NMR** (C_6D_6, 600 MHz): δ = 7.27 (d, *J* ~ 7.8 Hz, 2H), 7.18–7.10 (m, 2H), 7.06 (t, *J* ~ 7.2 Hz, 1H), 5.86–5.77 (m, 1H), 5.06–4.97 (m, 2H), 4.37–4.30 (m, 2H), 3.82–3.75 (m, 1H), 3.64 (dd, *J* ~ 4.8 Hz, 6.6 Hz, 0.25H), 3.62 (dd, *J* ~ 4.8 Hz, 9 Hz, 0.70H), 3.40 (t, *J* ~ 6.6 Hz, 0.25H), 3.39–3.34 (m, 1H), 3.29 (t, *J* ~ 6.6 Hz, 0.7H), 2.38–2.26 (m, 1H), 2.18–2.08 (m, 1H), 1.99–1.84 (m, 2H), 1.80–1.75 (m, 0.25H), 1.51–1.44 (m, 0.75H), 1.25 (ddd, *J* ~ 4.8 Hz, 6 Hz, 12 Hz, 1H), 1.03 (d, *J* ~ 6.6 Hz, 3H), 0.85 (d, *J* ~ 6.6 Hz, 0.86H), 0.81 (d, *J* ~ 6.6 Hz, 2.14 H). **^{13}C NMR** (C_6D_6, 151 MHz): δ = 140.2, 136.31, 136.30, 129.1, 128.3, 128.1, 117.1, 88.9, 87.7, 78.3, 77.6, 73.8, 73.8, 73.7, 42.5, 41.4, 41.3, 40.7, 39.3, 39.2, 38.2, 36.3, 20.2, 19.4, 15.3, 15.3. **HRMS** (ESI): $[M+Na]^+$ $C_{18}H_{26}O_2Na$: calcd 297.18305; found 297.1831.

(*S*)-1-((2*R*,3*R*)-5-Ethoxy-3-methyl-tetrahydrofuran-2-yl)ethanol 6. To a solution of *tert*-butyl((*S*)-1-((2*R*,3*R*)-5-ethoxy-3-methyl-tetrahydrofuran-2-yl)ethoxy)dimethylsilane **4a** (3.025 g, 10.50 mmol) in dry acetonitrile, was added CsF (7.98 g, 52.5 mmol, 5 eq.) and a 1 M solution of TBAF in THF (210 µL, 2.1 mmol, 0.2 eq.). The insoluble mixture was stirred at 80 °C for 22 h. After cooling to RT, water was added and the mixture was extracted with DCM (3 × 20 mL). Organic layers were dried over $MgSO_4$, filtered and solvents were removed under vacuum. Purification on silica gel (PE/EA – 9/1 to 8/2 +1% Et_3N) afforded the expected product as a clear oil (1.539 g, 84%, d.r. ~6/4). Major diastereoisomer was noted M and the minor one m. **FTIR** (film, NaCl): ν/cm^{-1} = 3848, 2975, 2880, 1083, 1001. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ (ppm) = 5.13–5.07 (m, 0.4 H, m), 5.02 (d, *J* ~ 5.1 Hz, 0.6 H, M), 4.02–3.87 (m, 1 H, M+m), 3.81–3.67 (m, 1 H, M+m), 3.64 (dd, *J* ~ 6.9, 2.7 Hz, 0.6 H), 3.58 (dd, *J* ~ 6.6, 3.3 Hz, 0.4 H, m), 3.51–3.37 (m, 1 H, M+m), 3.15 (broad s, 0.6 H, M), 2.61–2.44 (m, 0.6 H, M), 2.27–2.06 (m, 1.8 H), 1.69–1.50 (m, 1 H), 1.22–1.05 (m, 9 H). **^{13}C NMR** ($CDCl_3$, 75.5 MHz): δ (ppm) = 104.1 (M), 104.0 (m), 91.6 (M), 88.3 (m), 68.4 (M), 68.0 (m), 63.4 (M), 62.9 (m), 42.5 (M), 41.6 (m), 31.3 (m), 29.8 (M), 20.3 (m), 20.2 (M), 18.0 (M), 18.0 (m), 15.4 (m), 15.2 (M). **HRMS** (ESI): $[M+Na]^+$ $C_9H_{18}O_3Na$: calcd. 197.11536, found 197.1155

1-((2*S*,3*R*,5*R*)-5-Allyl-3-methyltetrahydrofuran-2-yl)ethanol 7. To a solution of **6** (1.365 g, 7.84 mmol) in DCM (20 mL) at −78 °C was added TMSOTf (1.70 mL, 9.41 mmol, 1.2 equiv.) and then allyltrimethylsilane (4.96 mL, 31.36 mmol, 4 eq.). After 2 h the mixture was quenched with saturated aqueous $NaHCO_3$ solution at −78 °C and warmed quickly to RT. The crude was extracted with DCM (3 × 20 mL), organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by automatic flash chromatography on silica gel (15–40 µ) (petroleum ether/ethyl acetate: 9/1 to 8/2 (1% Et_3N)) afforded a 4 : 1 mixture of the two diastereomers (951 mg, overall yield 71%). **7** eluted first and was obtained as a clear oil (760 mg). $[\alpha]^D$ = −1.1 (*c* = 0.3, $CHCl_3$). **FTIR** (film, NaCl): ν/cm^{-1} = 3438, 3078, 2964–2873, 1092, 1027. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ (ppm) = 5.91–5.72 (m, 1 H), 5.15–5.01 (m, 2 H), 4.06–86 (m, 2 H), 3.37 (dd, *J* ~ 6.3, 3.3 Hz, 1 H), 2.41–2.17 (m, 3 H), 2.11 (broad s, 1H), 1.83–1.67 (m, 1 H), 1.65–1.53 (m, 1 H), 1.16 (d, *J* ~ 6.6 Hz, 3 H), 1.05 (d, *J* ~ 6.9 Hz, 3 H).**^{13}C NMR** ($CDCl_3$, 75.5 MHz):.δ (ppm) = 134.8, 117.1, 90.1, 77.4, 68.2, 40.0, 32.3, 19.8, 18.0. **HRMS** (ESI): $[M+Na]^+$ $C_{10}H_{18}O_2Na$: calcd. 193.12045, found 193.1206.

1-((2*R*,3*R*,5*R*)-5-Allyl-3-methyl-tetrahydrofuran-2-yl)ethanone 8. To a solution of (*S*)-1-((2*R*,3*R*)-5-allyl-3-methyl-tetrahydrofuran-2-yl)ethanol (450 mg, 2.65 mmol) in DCM (13 mL), was added Dess–Martin periodinane at RT (1.68 g, 3.975 mmol, 1.5 eq.). The mixture was then stirred at RT for 5 h. Saturated aqueous $NaHCO_3$ was added to quench the reaction. After extraction with DCM (3 × 20 mL), the organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. The crude was purified on silica gel (pent/Et_2O: 9/1) to give **8** as a clear white oil (582 mg, 87%). **FTIR** (film, NaCl): ν/cm^{-1} = 3078, 2964, 2931, 2873, 1715, 1107. **^{1}H NMR** ($CDCl_3$, 200 MHz): δ (ppm) = 5.95–5.71 (m, 1 H), 5.17–5.01 (m, 2 H), 4.14 (quint, *J* ~ 6.5 Hz, 1 H), 3.75 (d, *J* ~ 7.4 Hz, 1 H), 2.50–2.11 (m, 3 H), 2.19 (s, 3H), 1.90–1.57 (m, 2 H), 1.12 (d, *J* ~ 6.8 Hz, 3 H). **^{13}C NMR** ($CDCl_3$, 50.3 MHz): δ (ppm) = 210.0, 134.4, 117.1, 90.4, 78.8, 40.3, 38.7, 36.8, 25.6, 17.9. **HRMS** (ESI): $[M+Na]^+$ $C_{10}H_{16}O_2Na$: calcd. 191.10480, found 191.1049

(*E*)-Methyl 3-((2*R*,3*R*,5*R*)-5-allyl-3-methyl-tetrahydrofuran-2-yl)but-2-enoate 9. To a solution of fresh dry NaH (85 mg, 3.56 mmol, 2 eq.) in THF (3.7 mL) was added methyl diethylphosphonoacetate (691 µL, 3.74 mmol, 2.1 eq.) dropwise at 0 °C. After stirring 10 min at 0 °C, this solution was added dropwise to a solution of 1-((2*R*,3*R*,5*R*)-5-allyl-3-methyl-tetrahydrofuran-2-yl)ethanone **8** (300 mg, 1.78 mmol, 1 eq.) in THF (3.7 mL) at 0 °C. The temperature was allowed to slowly reach RT. After completion (5 h) the reaction was quenched with saturated aqueous NH_4Cl and extracted with DCM (3 × 10 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. Purification on silica gel (PE/EA: 98/2 to 95/5) afforded **9** as a colorless oil (312 mg, 78%). $[\alpha]^D$ = −19.4 (*c* = 0.24, $CHCl_3$). **FTIR** (film, NaCl): ν/cm^{-1} = 2961, 2873, 1721, 1654, 1232, 1139. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ (ppm) = 5.91–5.72 (m, 2 H), 5.14–4.99 (m, 2 H), 4.07 (quint, *J* ~ 6.5 Hz, 1 H), 3.77 (d, *J* ~ 7.0 Hz,

1 H), 3.67 (s, 3 H), 2.45–2.18 (m, 2 H), 2.10 (s, 3 H), 2.15–1.95 (m, 1 H), 1.90–1.71 (m, 1 H), 1.69–1.55 (m, 1 H), 1.04 (d, J ~ 6.8 Hz, 3 H). **^{13}C NMR** ($CDCl_3$, 75.5 MHz): δ (ppm) = 167.2, 158.4, 134.8, 117.2, 115.0, 90.5, 78.1, 51.0, 40.5, 39.0, 38.1, 18.2, 14.7. **HRMS** (ESI): $[M+Na]^+$ $C_{13}H_{20}O_3Na$: calcd. 247.13101, found 247.1310.

(*E*)-Methyl 3-((2*R*,3*R*,5*R*)-5-(3-hydroxypropyl)-3-methyl-tetrahydrofuran-2-yl)but-2-enoate 10. To a solution of (*E*)-methyl 3-((2*R*,3*R*,5*R*)-5-allyl-3-methyl-tetrahydrofuran-2-yl)but-2-enoate **9** (102 mg, 0.455 mmol) in THF (4.5 mL) at 0 °C, was added a 2 M solution of BH_3–Me_2S in THF (228 µL, 0.91 mmol, 1 eq.). The mixture was allowed to reach RT and stirred for 1.5 h Then The mixture was cooled to −40 °C and $NaBO_3 \cdot H_2O$ (136 mg, 1.365 mmol, 3 eq.) then water (4.5 mL) were added. The mixture was stirred 5 h. Water was then added and the mixture was extracted with DCM (3 × 15 mL). The organic layers were dried over $MgSO_4$, filtrated and concentrated under vacuum. Purification on silica gel (DCM/acetone: 98/2 to 95/5) provided **10** as a colorless oil (73 mg, 66%). $[\alpha]^D = -10.5$ ($c = 0.36$, $CHCl_3$). **FTIR** (film, NaCl): ν/cm^{-1} = 3362, 2958, 2875, 1720, 1652, 1159. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ (ppm) = 5.89 (br s, 1 H), 4.11–3.98 (m, 1 H), 3.81 (d, J ~ 6.9 Hz, 1 H), 3.73–3.61 (m, 2 H), 3.69 (s, 3H), 2.19 (t, J ~ 5.7 Hz, 1 H), 2.15–2.00 (m, 1 H), 2.11 (s, 3 H), 1.82–1.59 (m, 6 H), 1.06 (d, J ~ 6.9 Hz, 3 H). **^{13}C NMR** ($CDCl_3$, 75.5 MHz): δ (ppm) = 167.2, 158.3, 115.0, 90.6, 78.9, 62.9, 51.1, 39.8, 38.2, 32.9, 29.9, 18.5, 14.8. **HRMS** (ESI): $[M+Na]^+$ $C_{13}H_{22}O_4Na$: calcd. 265.14158, found 265.1418.

(*E*)-3-((2*R*,3*R*,5*R*)-5-(3-Hydroxypropyl)-3-methyltetrahydrofuran-2-yl)but-2-en-1-ol 11. To a solution of (*E*)-methyl 3-((2*R*,3*R*,5*R*)-5-(3-hydroxypropyl)-3-methyl-tetrahydrofuran-2-yl)but-2-enoate (73 mg, 0.301 mmol) in DCM (6 mL) at −50 °C was added DIBAL-H (1 M solution in heptane) (1.2 mL, 1.20 mmol, 4 eq.) dropwise over a period of 20 min. The mixture was stirred for 1 h at −50 °C. The reaction was quenched by addition of a saturated aqueous $NaHCO_3$ solution at −50 °C, warmed to RT and extracted with DCM (3 × 10 mL). The organic phase was dried over $MgSO_4$, filtered and solvents were removed under reduced pressure. Purification on silica gel (DCM/acetone: 7/3) afforded (*E*)-3-((2*R*,3*R*,5*R*)-5-(3-hydroxypropyl)-3-methyltetrahydrofuran-2-yl)but-2-en-1-ol **11** as a colorless oil (32 mg, 50%). $[\alpha]^D = -15.9$ ($c = 0.3$, $CHCl_3$). **FTIR** (film, NaCl): ν/cm^{-1} = 3332, 2929, 2869, 1668, 1001. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ (ppm) = 5.63 (t, J~ 6.3 Hz, 1 H), 4.27–4.07 (m, 2 H), 4.06–3.93 (m, 1 H), 3.71 (d, J~ 7.8 Hz, 1 H), 3.66–3.52 (m, 2 H), 2.03 (q, J~ 7.2 Hz, 1 H), 1.89–1.49 (m, 8 H), 0.98 (d, J~ 6.6 Hz, 3 H). **^{13}C NMR** ($CDCl_3$, 75.5 MHz): δ (ppm) = 137.0, 126.6, 91.7, 78.2, 62.8, 59.0, 40.0, 36.6, 33.4, 29.8, 17.6, 11.9. **HRMS** (ESI): $[M+Na]^+$ $C_{12}H_{23}O_3Na$: calcd. 237.14666, found 237.1470.

(*E*)-3-((2*R*,3*R*,5*R*)-5-(3-(*tert*-Butyldimethylsilyloxy)propyl)-3-methyl-tetrahydrofuran-2-yl)but-2-en-1-ol 12. To a solution of (*E*)-methyl 3-((2*R*,3*R*,5*R*)-5-(3-(*tert*-butyldimethylsilyloxy)-propyl)-3-methyl-tetrahydrofuran-2-yl)but-2-enoate (85 mg, 0.238 mmol) in DCM (2.4 mL, C ~ 0.1) stirred at −50 °C was added dropwise DIBAL-H (1 M in heptane) (952 µL, 0.952 mmol, 4 eq.) over 20 min. After, completion (50 min), the reaction was quenched by addition of a saturated aqueous $NaHCO_3$ solution and a 0.5 M solution of Rochelle salt at −50 °C. When the mixture was at RT, it was extracted with DCM (3 × 15 mL). The organic layers were dried over $MgSO_4$, filtrated and concentrated under vacuum. Purification on silica gel (DCM/acetone: 95/5) afforded **12** as a clear oil (53 mg, 68%). $[\alpha]^D = -14.2$ ($c = 0.196$, $CHCl_3$). **FTIR** (film, NaCl): ν/cm^{-1} = 2388, 2956, 2858, 1097. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ (ppm) = 5.64 (t, J ~ 6.3 Hz, 1 H), 4.28–4.10 (m, 2 H), 4.05–3.91 (m, 1 H), 3.73–3.54 (m, 3 H), 2.0 (q, J ~ 7 Hz, 1 H), 1.85–1.39 (m, 10 H), 0.97 (d, J ~ 6.6 Hz, 3 H), 0.88 (s, 9 H), 0.03 (s, 6 H). **^{13}C NMR** ($CDCl_3$, 75.5 MHz): δ (ppm) = 137.7, 126.5, 91.6, 78.0, 63.2, 59.3, 39.9, 36.5, 32.8, 29.5, 26.1, 18.5, 17.5, 11.7, −5.2. **HRMS** (ESI): $[M+Na]^+$ $C_{18}H_{36}O_3Si$ Na: calcd. 351.23314, found 351.2330

Non-radioactive ligand-binding assay. Biotinylated α-bungarotoxin and streptavidin coupled to horseradish peroxidase were purchased from Molecular Probes (Invitrogen). Non-radioactive ligand-binding assays to assess the biological activity of the tetrahydrofuran core of gymnodimine A **11** and **12** were performed at room temperature (25 °C) as reported elsewhere with some modifications.[23] Briefly, *Torpedo* electrocyte membranes rich in nAChR purified as described previously[24,25] were diluted in TBS (150 mM NaCl, 50 mM Tris-HCl, pH 7.4) containing 0.1% bovine serum albumin (BSA) and 0.1% Tween 20, to a final protein concentration of 0.14 mg mL^{-1}. *Torpedo* membranes (100 µL) were incubated for 4 h with **11**, **12** and gymnodimine A in the concentration range of 10^{-3} to 10^{-10} M. Thereafter, a volume of 2 µL of 2×10^{-6} M biotinylated α-bungarotoxin in TBS, 0.1% BSA, pH 7.4 was added to each reaction mixture. Following 15 min incubation, *Torpedo* electrocyte membranes were immobilized by filtration on a Whatman GF/C glass microfiber membrane presoaked with TBS, 0.1% BSA using a Hoefer 48-well slot-blot. The wells were washed with 3 mL ice-cold TBT (TBS, 0.1% Tween 20, pH 7.4). To detect biotinylated α-bungarotoxin bound to nAChRs, *Torpedo* membranes were incubated for 15 min with streptavidin coupled to horseradish peroxidase (100 µL, 200 ng mL^{-1} protein). The solution was removed by filtration and the membrane was washed with 3 mL ice-cold TBT followed by 250 µL sterile water. The membrane was then incubated for 5 min with ECL-Plus™ detection reagent (50 µL). Peroxidase activity was recorded directly on the GF/C filter membrane using a GeneGnome chemiluminescence imager. In the absence of a competitive nAChR-ligand, peroxidase activity is maximal giving higher chemiluminescence signals. In contrast, the presence of a competitive antagonist such as gymnodimine A prevents the binding of biotinylated α-bungarotoxin to *Torpedo* nAChR which results in lower chemiluminescence signals. The percentage of inhibition was calculated as reported.[23] Independent experiments were performed at least twice in duplicate.

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