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Synthesis of the NO ring model of gymnocin-B

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Abstract—A synthetic route to the NO ring model of gymnocin-B, a cytotoxic marine polycyclic ether with the largest contiguous rings, has been achieved. The synthesis features construction of the seven-membered O ring with 1,3-dimethyl substituents flanking the ether oxygen by ring-closing metathesis.

Gymnocins represent a series of cytotoxic marine polycyclic ethers, isolated from the notorious red tide dinoflagellate, *Karenia mikimotoi*, by Satake et al.[1,2] These toxin molecules are rare polycyclic ethers that exhibit potent in vitro cytotoxic activity against P388 murine leukemia cells. Recently, gymnocin-B (**1**) has been isolated from *K. mikimotoi* and its structure has been established on the basis of extensive 2D-NMR analysis and collision-induced MS/MS experiments.[2] Structurally, gymnocin-B is characterized by 15 contiguous ether rings, the number of which is the largest among the polycyclic ether compounds hitherto known (Fig. 1).[3]

Given the structural complexity and intriguing biological property of gymnocins, we undertook their total synthesis and structure–activity relationship studies, culminating in the first total synthesis of gymnocin-A (**2**) based on our developed Suzuki–Miyaura coupling-based strategy.[4] In this letter, we describe the synthesis of the NO ring model **3** of gymnocin-B.

A formidable challenge in synthesizing the NO ring model **3** was the construction of the seven-membered O ring containing 1,3-dimethyl groups. To the best of our knowledge, there has been no report on the

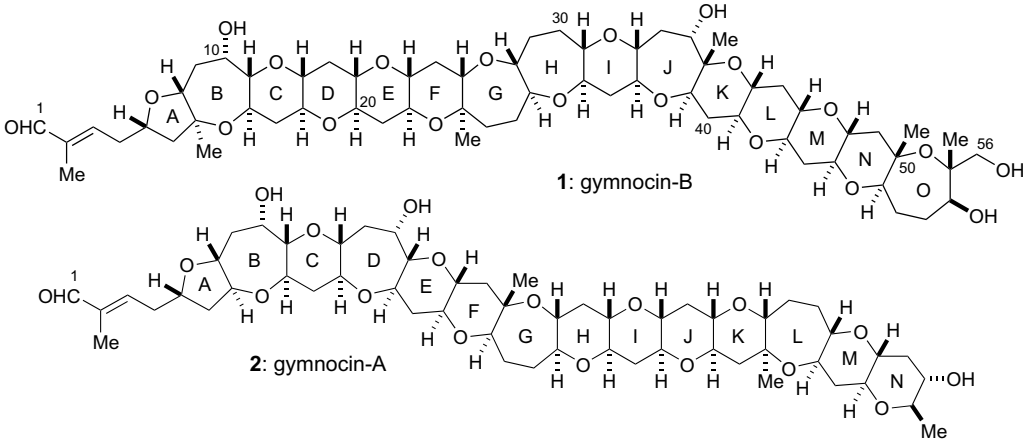

Figure 1. Structures of gymnocin-B (**1**) and gymnocin-A (**2**).

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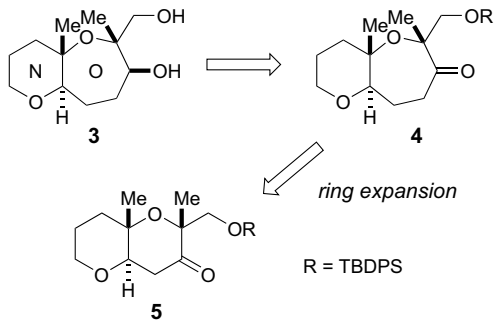
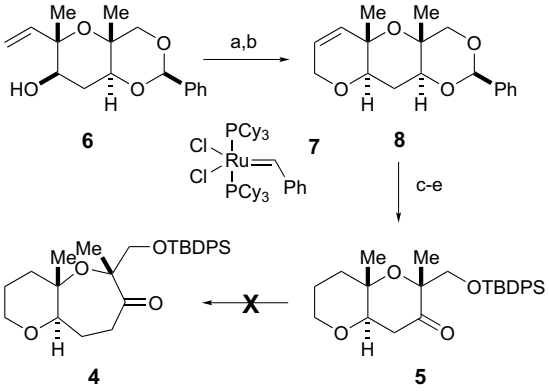
synthesis of a seven-membered ether ring system having 1,3-dimethyl substituents flanking the ether oxygen.[5]

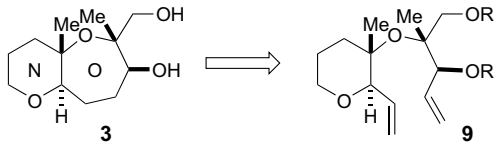
Initially, we planned to construct the O ring by ring expansion of tetrahydropyranyl ketone **5** according to the method of Mori et al.[6] (Scheme 1). The synthesis of **5** commenced with the known alcohol **6**[7] as illustrated in Scheme 2. Protection of **6** as its allyl ether followed by ring-closing metathesis (RCM) using Grubbs' catalyst **7**[8,9] afforded bicyclic ether **8** in 83% yield for the two steps. Hydrogenation of the double bond with concomitant removal of the benzylidene acetal group of **8** gave a diol. The primary alcohol was selectively protected as the *tert*-butyldiphenylsilyl (TBDPS) ether and the remaining secondary alcohol was oxidized with TPAP/NMO[10] to afford ketone **5** in 89% yield for the three steps. However, treatment of **5** with trimethylsilyldiazomethane in the presence of $BF_3{\cdot}OEt_2$ or Me_3Al yielded none of the desired ring expansion product **4** and unreacted **5** was recovered, presumably due to severe steric congestion of the axial methyl group at the α-position of the carbonyl.[11]



Scheme 1. Initial retrosynthetic plan for the NO ring model **3**.

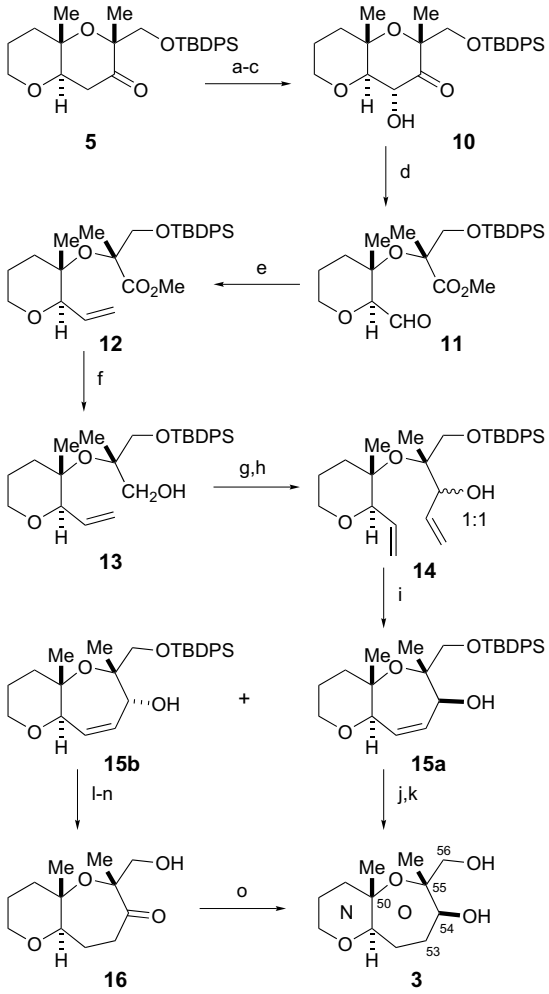


Scheme 2. Reagents and conditions: (a) NaH, allyl bromide, THF, rt, 83%; (b) Grubbs' catalyst (**7**), CH_2Cl_2, rt, quant.; (c) H_2, Pd–C, EtOAc, rt; (d) TBDPSCl, imidazole, DMF, rt, 89% (two steps); (e) TPAP, NMO, 4 Å MS, CH_2Cl_2, rt, quant.



Scheme 3.

Accordingly, we next investigated an alternative route, which features construction of the O ring by RCM of diene **9** that would be derived from **5** (Scheme 3).[12,13] Thus, the ketone **5** was converted into the corresponding silyl enol ether, which was oxidized with *m*-CPBA in the presence of $NaHCO_3$ to give, after acidic treatment, α-hydroxy ketone **10** as the sole product in 95% overall yield (Scheme 4). Oxidative cleavage of **10** with $Pb(OAc)_4$ led to aldehyde **11**, which was then subjected to Wittig reaction to afford olefin ester **12** in 54% yield for the two steps. DIBALH reduction gave alcohol **13** (88% yield), which was oxidized under Swern conditions to the aldehyde and subsequently treated with a vinyl Grignard reagent to afford allyl alcohol **14** as a 1:1 mixture of diastereomers in 92% yield over the two



Scheme 4. Reagents and conditions: (a) TMSCl, LiHMDS, Et_3N, THF, −78 °C; (b) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, rt; (c) PPTS, MeOH, rt, 95% (three steps); (d) $Pb(OAc)_4$, benzene/MeOH, rt; (e) Ph_3PMeBr, NaHMDS, THF, 0 °C → rt, 54% (two steps); (f) DIBALH, CH_2Cl_2, −78 °C, 88%; (g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C → rt; (h) $CH_2{=}CHMgBr$, THF, 0 °C, 92% (two steps); (i) Grubbs' catalyst (**7**), CH_2Cl_2, 35 °C, 40% for **15a**, 44% for **15b**; (j) H_2, Pd–C, EtOAc, rt; (k) TBAF, THF, rt, 74% (two steps); (l) TPAP, NMO, 4 Å MS, CH_2Cl_2, 82%; (m) H_2, Pd–C, EtOAc, rt; (n) TBAF, HOAc, THF, rt; (o) $MeN_4BH(OAc)_3$, MeCN/AcOH, −20 °C, 65% (three steps).

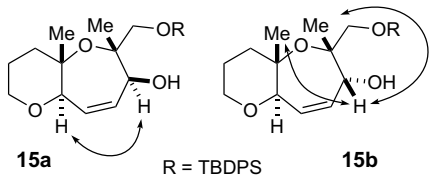


Figure 2. NOE experiments of **15a** and **b**.

Table 1. Selected NMR data for model **3** and gymnocin-B (**1**)[a]

Position	3		Gymnocin-B (1)	
	^{1}H	^{13}C	^{1}H	^{13}C
53	1.76	27.7	1.75	27.5
	1.84	—	1.85	—
54	3.75	72.4	3.76	72.2
55	—	81.0	—	81.2
56	3.17	71.2	3.17	71.1
	3.35	—	3.34	—
55-Me	1.27	20.5	1.27	20.5

[a] 600 MHz, $CDCl_3$.

steps. RCM reaction of **14** using **7** under unoptimized conditions (5 mM in CH_2Cl_2, 35 °C, 4 days) proceeded cleanly to generate seven-membered ether **15a** and **b** in 40% and 44% yield, respectively. The stereochemistry of **15a** and **b** was unambiguously established by NOE experiments as shown in Figure 2. Finally, hydrogenation of the double bond followed by desilylation of **15a** completed the synthesis of the NO ring model **3** in 74 % yield for the two steps. On the other hand, diastereomeric alcohol **15b** was also converted to **3** by a four-step sequence, including oxidation to the enone, hydrogenation and desilylation to ketone **16**, and diastereoselective reduction using $Me_4NBH(OAc)_3$.[6,14] The ^{1}H and ^{13}C NMR data around the O ring of **3** matched well with those of natural **1** (Table 1).[15]

In summary, we have established a synthetic route to the NO ring model **3** having 1,3-dimethyl groups on the seven-membered ether ring. Further studies directed toward the total synthesis of gymnocin-B (**1**) are in progress and will be reported in due course.

Acknowledgments

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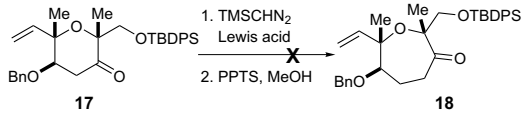

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15. Selected data for compound **3**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 3.88 (ddd, J = 11.2, 5.0, <1 Hz, 1H), 3.78 (ddd, J = 6.5, <1, <1 Hz, 1H), 3.38 (dd, J = 10.3, 2.3 Hz, 1H), 3.30 (ddd, J = 11.2, 11.2, 2.6 Hz, 1H), 3.20 (dd, J = 10.2, 7.6 Hz, 1H), 2.96 (dd, J = 11.4, 3.5 Hz, 1H), 2.26 (br, 1H), 1.93–1.85 (m, 2H), 1.82–1.45 (m, 7H), 1.42 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 84.9, 81.0, 76.2, 72.4, 71.2, 68.3, 40.5, 27.7, 24.4, 24.3, 20.5, 16.9; HRMS (FAB) calcd for $C_{12}H_{22}O_4Na$ [$(M+Na)^+$]: 253.1426. Found 253.1422.