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Convergent synthesis of the FGHI ring system of yessotoxin: stereoselective construction of the G ring

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Abstract—A convergent synthetic route to the FGHI ring system of yessotoxin, a marine ladder polyether, has been developed. The synthesis features convergent coupling of the diol and the aldehyde to form α-cyano ethers via acetal formation followed by ring closing metathesis and reductive etherification to construct the oxocane ring G and tetrahydropyran ring H, respectively. The β-methyl group on the G ring was stereoselectively introduced by alkylation of the corresponding ketone.
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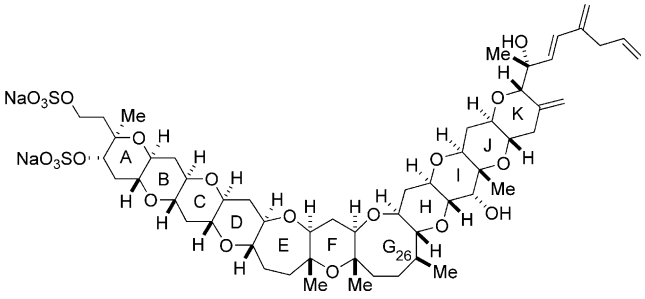
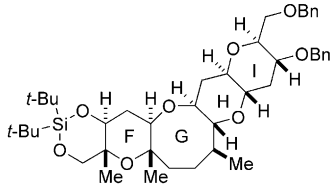
Yessotoxin (**1**)[1] is a marine polyether toxin produced by the dinoflagellate *Protoceratium reticulatum*.[2] Bivalve mollusks, such as scallops and mussels, accumulate **1** and its analogs[3] by filter feeding in waters containing blooms of the algae. Besides the potent acute toxicity against mice (LD_{50} = 286 μg/kg, ip),[4a] yessotoxins have recently been shown to exhibit intriguing biological activities in humans, that is, (i) modulation of cytosolic calcium levels of human lymphocytes,[4b] (ii) activation of caspases,[4c] and (iii) cytotoxicity against human tumor cell lines.[4d] The broad spectrum of biological activities of **1**, coupled with the unique arched molecular structure, prompted us to target its synthesis, although significant advancements[5] in the synthesis of **1** have already been reported by Nakata,[6] Mori,[7] and Kadota.[8] We have recently developed a novel convergent strategy via two-ring construction[9] for synthesis of *trans*-fused 6/*n*/6/6 (*n* = 7, 8) tetracyclic ether systems.[10] Herein, we describe a convergent synthesis of the FGHI ring system (**2**) of **1** via α-cyano ethers based on our methodology.



Yessotoxin (**1**)



FGHI ring system (**2**)

Scheme 1 outlines the synthesis plan of **2**. In the final stage, the tetrahydropyran ring H would be constructed by reductive etherification.[11] For the construction of the oxocane ring G, two synthetic routes (routes A and B) were envisaged by means of ring closing metathesis (RCM)[12] reaction of the diene **3** (or **4**), which could be derived from the α-cyano ether **5** (or **6**).

Synthesis of **5** and **6** commenced with the diol **8** prepared from **7**,[13] and aldehyde **9**[10] as shown in Scheme 2. Condensation of **9** using 1.4 equiv of **8** proceeded readily by treatment with $Sc(OTf)_3$[14] in benzene to give

Keywords: Yessotoxin; Convergent synthesis; Polyether; α-Cyano ether; Acetal cleavage; Ring closing metathesis; Alkylation; Reductive etherification.

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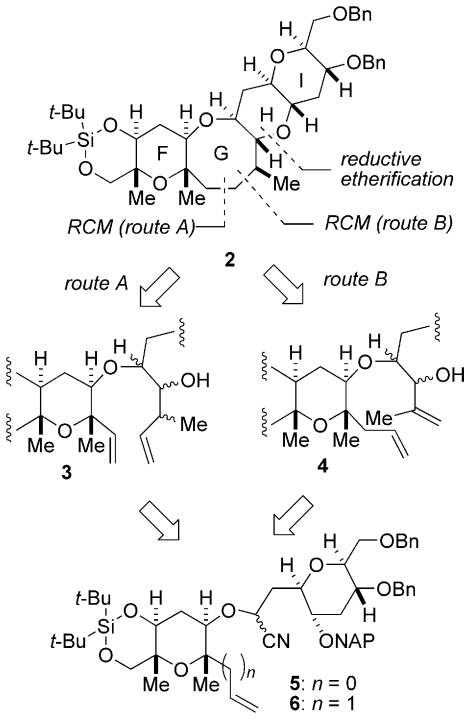
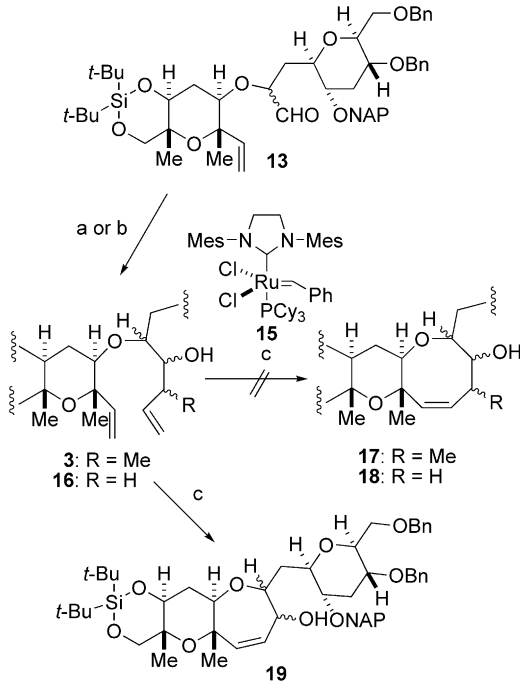


Scheme 1. Synthesis plan of the FGHI ring system **2**.

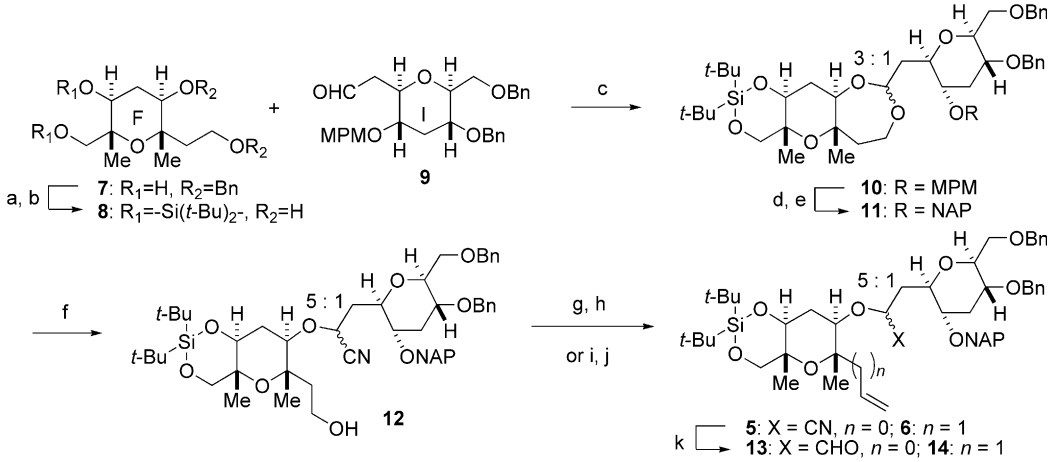


Scheme 3. Reagents and conditions: (a) 1-bromo-2-butene, $CrCl_2$, THF, 9 h, 92%; (b) $CH_2{=}CHCH_2MgBr$, THF, −40 °C, 1 h, 73%; (c) **15**, $ClCH_2CH_2Cl$, 60 °C.

seven-membered ring acetal **10** in 92% yield as a mixture of diastereomers (3:1) with respect to the stereogenic center on the acetal carbon.

After converting the MPM group of **10** to the NAP (2-naphthylmethyl) group,[15] regioselective opening of acetal **11** was successfully achieved by a modified method of the previous report[10] using TMSCN in the presence of $Sc(OTf)_3$ to afford α-cyano ether **12** in 89% yield as a mixture of diastereomers (5:1). Primary alcohol **12** was converted to terminal olefins **5** and **6** through elimination of the corresponding selenoxide[16] or by an oxidation/Wittig olefination sequence, and the resulting nitriles **5** and **6** were reduced with DIBAL-H at −78 °C to afford the aldehydes **13** and **14**, respectively.

Construction of the oxocane ring G via route A was examined as shown in Scheme 3. Treatment of the aldehyde **13** with 1-bromo-2-butene in the presence of $CrCl_2$[17] provided diene **3** in 92% yield as a mixture of two major diastereomers (the stereochemistry was not determined). Although diene **3** was subjected to RCM[12] using the second-generation Grubbs catalyst **15**,[18] cyclization did not occur and the starting material was recovered. Presumably, formation of the ruthenium–carbene intermediate was retarded due to the ste-



Scheme 2. Reagents and conditions: (a) t-$Bu_2Si(OTf)_2$, 2,6-lutidine, DMF, THF, 85%; (b) Pd/C, H_2, EtOAc, MeOH, 81%; (c) $Sc(OTf)_3$, benzene, 1.5 h, 92%; (d) DDQ, H_2O, CH_2Cl_2; (e) 2-naphthylmethyl bromide, NHMDS, TBAI, THF, DMF, 76% (two steps); (f) TMSCN, $Sc(OTf)_3$, CH_2Cl_2, rt, 58 h, then, K_2CO_3, MeOH, 89%; (g) 2-$NO_2C_6H_4SeCN$; Bu_3P, THF; (h) 30% H_2O_2, $NaHCO_3$ (aq), THF, 45 °C, 57% (two steps); (i) Dess–Martin periodinane, CH_2Cl_2, 2 h; (j) $Ph_3P^+CH_3Br^-$, NHMDS, THF, 0 °C, 40 min, 87% (two steps); (k) DIBAL-H, CH_2Cl_2, −78 °C, **13**: 90%, **14**: 88%.

ric hindrance arising from both the allylic methyl groups of **3**. Therefore, the less hindered diene **16**, derived from **13** in an analogous sequence using allylmagnesium bromide, was subjected to RCM. However, the reaction was still sluggish and the product, obtained in low yield, turned out to be not the desired **18** but the seven-membered ring ether **19**. The eight-membered ring formation might be retarded because of the proximity of the angular methyl group on the F ring to the terminal olefin, and isomerization[19] of the other terminal olefin occurred prior to the ring closure.

In the next stage, construction of the oxocane ring G via route B was examined starting with **14**, in which the terminal olefin was linked with one more carbon ($n = 1$) than **13** (Scheme 4). Addition of 2-propenyl lithium to aldehyde **14** gave diene **4**, which was subjected to RCM using Grubbs catalyst **15**. As expected, RCM reaction successfully proceeded to afford an eight-membered ring ether in 58% yield, which was further oxidized to give α,β-unsaturated ketone **21** as an inseparable mixture of epimers at the C28[20] position. Unfortunately, the major product turned out to possess undesirable stereochemistry (α-H:β-H = 1:8), as confirmed by subsequent transformations.

Attempts of isomerization to obtain the desirable epimer by heating with DBU were not successful to give an equilibrated mixture (α-H:β-H = 2:1). Alternatively, saturated ketone **23**, derived from **21** by hydrogenation with PtO_2, was subjected to base-induced epimerization. However, the reaction was too sluggish and did not converge on a desirable diastereomer (α-H:β-H = ~5:1 at C28, α-Me:β-Me = ~3:1 at C26). Based on these results, we next tried to introduce the methyl group under kinetic conditions.

In an analogous sequence, α,β-unsaturated ketone **22** was prepared by the addition of vinyl lithium to aldehyde **14**, followed by RCM of the diene and oxidation of the resulting alcohol. In contrast to the ketone **21**, epimerization of **22** proceeded completely, and concomitant isomerization of the C=C double bond occurred to afford β,γ-unsaturated ketone **24** as a single isomer in 54% yield. The structure of **24** was unambiguously determined by NOE experiments. The results of isomerization under thermodynamic controlled conditions were supported by an MM3* calculation on MacroModel® software as shown in Figure 1,[21] which shows

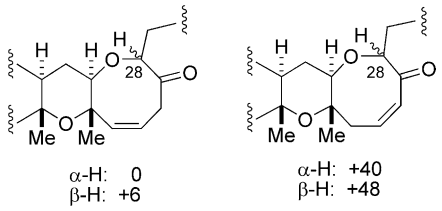
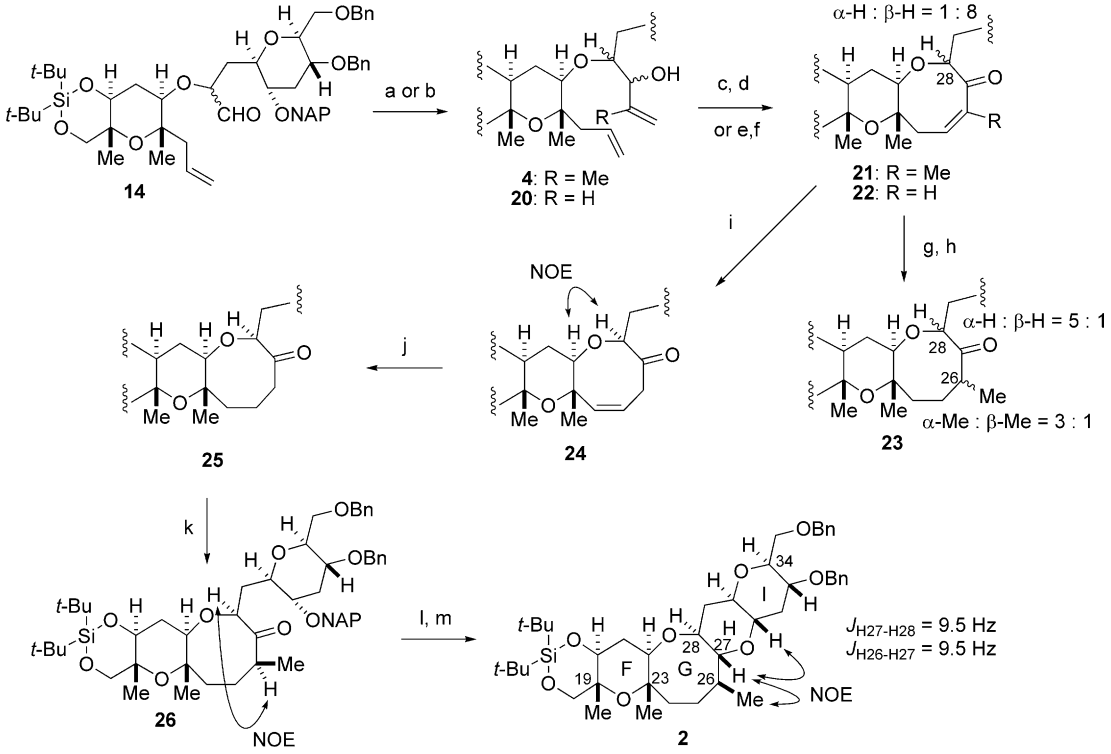


Figure 1. Differences of the steric energies (kJ/mol) between **24** and its isomers by MM3* calculation.



Scheme 4. Reagents and conditions: (a) 2-bromopropene, *t*-BuLi, THF, −78 °C, 89%; (b) $(CH_2{=}CH)_4Sn$, MeLi, THF, −78 °C, 80%; (c) **15**, $(CH_2Cl)_2$, 60 °C, 2 h, 58%; (d) Dess–Martin periodinane, CH_2Cl_2, 90%; (e) Dess–Martin periodinane, CH_2Cl_2; (f) **15**, toluene, 100 °C, 3 h, 66% (two steps); (g) PtO_2, H_2, EtOAc, 2 h; (h) DBU, toluene, 80 °C, 60 h, 60% (two steps); (i) DBU, toluene, reflux, 18 h, 54%; (j) PtO_2, H_2, EtOAc, 4 h, 85%; (k) MeI, LHMDS, THF, −78 to −20 °C, 5 h, 61% (recovery of **26**, 8%); (l) DDQ, CH_2Cl_2, H_2O; (m) Et_3SiH, TMSOTf, CH_2Cl_2, −60 to −30 °C, 1 h, 74% (two steps).

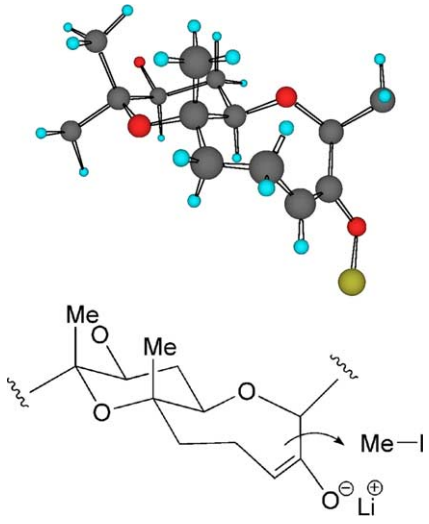


Figure 2. Working model of the stereoselective alkylation.

that the desirable isomer **24** is most stable among the regio- and stereoisomers.

The next task was the stereoselective introduction of the methyl group to the G ring. The β,γ-unsaturated ketone **24** was converted to the saturated ketone **25** by hydrogenation using PtO_2. The lithium enolate, generated from **25** with LHMDS, was treated with methyl iodide. Fortunately, the alkylation proceeded regio- and stereoselectively to afford the desired β-oriented diastereomer **26** (as determined by NOE) in 61% yield. The stereochemical outcome can be rationalized as follows. Under kinetically controlled conditions, deprotonation would occur at the less hindered C26 position of the ketone **25** to form the (*E*)-enolate with the electrophile approaching from the less hindered side of the enolate in the boat-chair conformation of the G ring (Fig. 2). Finally, construction of the H ring was achieved through oxidative removal of the NAP group with DDQ, followed by reductive etherification[11] with Et_3SiH/TMSOTf to afford the FGHI ring system **2** in 74% yield for two steps. The stereochemistry of **2** was supported by NOE experiments and coupling constants ($J_{H27–H28}$ = 9.5 Hz, $J_{H26–H27}$ = 9.5 Hz).[22] ^1H and ^{13}C NMR signals of **2** corresponding to the C22–C28 part of yessotoxin (**1**) resemble closely those of the natural product as shown in Table 1.[1a]

Table 1. Selected ^1H and ^{13}C NMR chemical shifts of yessotoxin (**1**) and the FGHI ring system (**2**) in CD_3OD

Position	^1H (500 MHz)		^{13}C (125 MHz)	
	1	**2**	**1**	**2**
22	3.53	3.52	87.3	87.3
23	—	—	77.0	78.3
23-Me	1.20	1.21	20.7	21.0
24	1.54	1.48	47.0	46.6
24	1.77	1.73		
25	1.51	1.48	32.8	32.9
25	1.75	1.70		
26	1.74	1.65	40.8	40.8
26-Me	1.07	0.99	22.4	22.4
27	2.81	2.71	89.4	88.6
28	3.34	3.32	84.1	84.3

In conclusion, we have established a highly convergent route to the FGHI ring system of yessotoxin via α-cyano ethers. The present synthesis features construction of the central GH ring system based on ring closing metathesis, stereoselective alkylation, and reductive etherification. Further studies directed towards the total synthesis of yessotoxin are currently in progress in our laboratory.

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22. Compound **2**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98 (3H, d, J = 7.0 Hz, Me-26), 1.01 (9H, s, *t*-Bu), 1.09 (9H, s, *t*-Bu), 1.20 (3H, s, Me), 1.39 (1H, ddd, J = 11.5, 11.5, 11.5 Hz, $H32_{ax}$), 1.42 (3H, s, Me), 1.44–1.52 (3H, m, H24, H25), 1.58 (1H, ddd, J = 11.5, 11.5, 11.5 Hz, $H29_{ax}$), 1.61–1.68 (1H, m, H26), 1.74 (1H, dd, J = 14.0, 9.0 Hz, H24), 1.79 (1H, ddd, J = 12.0, 12.0, 12.0 Hz, $H21_{ax}$), 1.91 (1H, dt, J = 12.0, 4.0 Hz, $H21_{eq}$), 2.28 (1H, dt, J = 11.5, 4.5 Hz, $H29_{eq}$), 2.52 (1H, dt, J = 11.5, 4.5 Hz, $H32_{eq}$), 2.68 (1H, dd, J = 9.5, 9.5 Hz, H27), 2.87 (1H, ddd, J = 11.5, 9.0, 4.5 Hz, H31), 3.03 (1H, ddd, J = 11.5, 9.0, 4.5 Hz, H30), 3.22 (1H, ddd, J = 11.5, 9.5, 4.5 Hz, H28), 3.37 (1H, dd, J = 12.0, 4.0 Hz, H22), 3.39 (1H, ddd, J = 9.5, 5.0, 2.0 Hz, H34), 3.49 (1H, ddd, J = 11.5, 9.5, 4.5 Hz, H33), 3.64 (1H, dd, J = 10.5, 5.0 Hz, H35), 3.66 (1H, d, J = 10.0 Hz, H18), 3.81 (1H, d, J = 10.0 Hz, H18), 3.74 (1H, dd, J = 10.5, 2.0 Hz, H35), 3.87 (1H, dd, J = 12.0, 4.0 Hz, H20), 4.36 (1H, d, J = 11.5 Hz, benzyl), 4.53 (1H, d, J = 12.0 Hz, benzyl), 4.56 (1H, d, J = 11.5 Hz, benzyl), 4.60 (1H, d, J = 12.0 Hz, benzyl), 7.18–7.33 (10H, m, Ph); ESI-MS 736 ($M+Na^+$).