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STEREOSELECTIVE SYNTHESIS OF THE GHI-RING OF MAITOTOXIN, A MARINE POLYCYCLIC ETHER

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Abstract – The GHI-ring of maitotoxin, a marine polycyclic ether, was stereoselectively synthesized by way of SmI_2-induced reductive cyclization of β-alkoxyacrylate and aldehyde.

Maitotoxin (**1**), isolated from the dinoflagellate *Gambierdiscus toxicus*, is the most toxic and largest natural product (MW 3422) so far known, except for biopolymers such as proteins or polysaccharides.[1] Maitotoxin (**1**) is implicated ciguatera food poisining and influences Ca^{2+}-dependent mechanisms in a wide range of cell types.[2] The full structure of maitotoxin (**1**) including a partial stereochemical assignment, was reported by Murata–Yasumoto group in 1993.[3] The relative stereochemistry of the remaining acyclic parts and the absolute structure of maitotoxin (**1**) were determined independently by Tachibana[4] and Kishi[5] and their colleagues in 1996.[6] The giant structure contains 32 fused ether rings, 28 hydroxy groups, 2 sulfates, and 98 chiral centers. The skeletal novelty, complexity, and biological activity have attracted the attention of both chemists and biologists, and partial syntheses of maitotoxin have been reported by Tachibana,[4,7] Kishi,[5] Nicolaou,[8] and our groups[9] so far. We now report the stereoselective synthesis of the GHI-ring of maitotoxin (**1**), by way of SmI_2-induced reductive cyclization of β-alkoxyacrylate and aldehyde.[10]

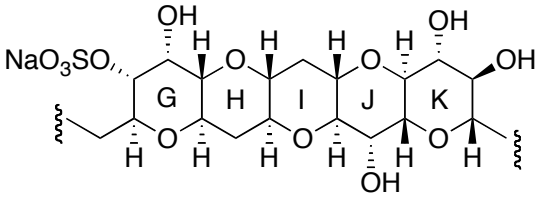
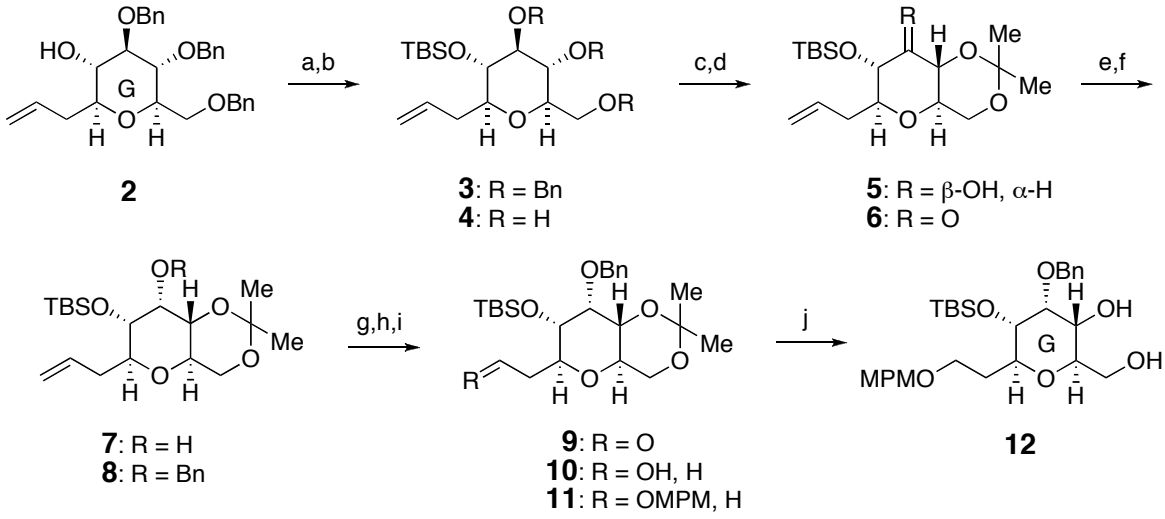


Figure 1. Partial structure of maitotoxin (**1**).

This paper is dedicated to Prof. Dr. Ekkhard Winterfeldt on the occasion of his 75th birthday.

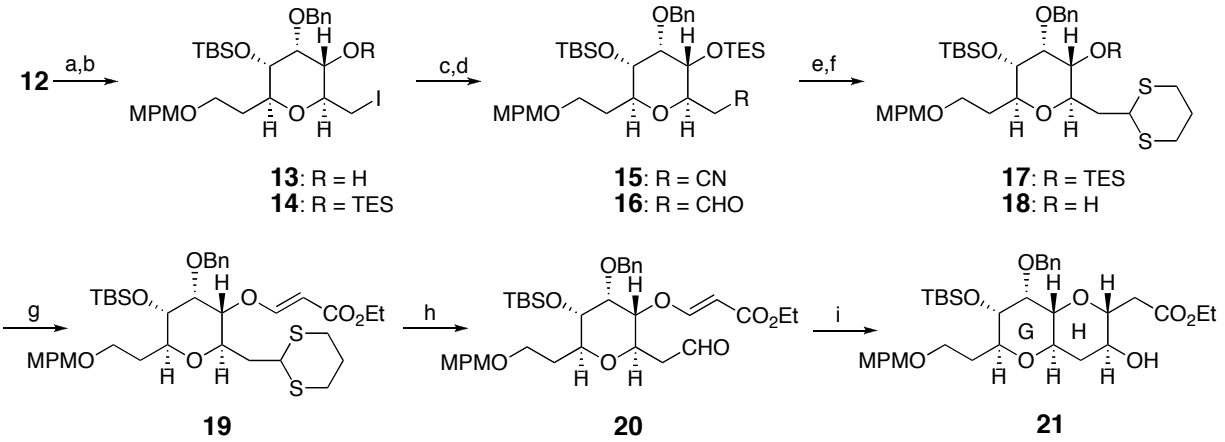
The synthesis started with the known alcohol (**2**),[11] prepared from 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose. First, glucose derivative **2** was transformed to the diol (**12**), corresponding to the G-ring, via inversion of β-*equatoria*l OH to α-*axial* OH (Scheme 1). Protection of the alcohol (**2**) as the TBS ether (**3**) (97%) followed by removal of all benzyl groups with lithium di-*tert*-butylbiphenylide (LiDBB)[12] afforded the triol (**4**) (86%), which was protected as an acetonide (**5**) (82%). Swern oxidation of **5** and reduction of the resulting ketone (**6**) with L-Selectride® gave the desired *axial* α-alcohol (**7**) in 84% yield (two steps). The configuration of the alcohol was confirmed as *axial* by ^{1}H-NMR coupling constant of the proton adjacent to OH; δ 4.05 (dd, J = 2.4, 2.4 Hz, 1H). After protection of **7** as the benzyl ether (95%), cleavage of olefin (**8**) with ozone provided the aldehyde (**9**), which was reduced with $NaBH_4$ to give the alcohol **10** in 99% yield (two steps). Protection of the alcohol (**10**) with *p*-methoxybenzyl chloride (MPMCl) and KH, followed by deprotection of the acetonide, afforded the diol (**12**) in 79% yield (two steps).



Scheme 1. Reagents and conditions; (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 97%; (b) LiDBB, THF, -78 °C, 86%; (c) $Me_2C(OMe)_2$, CSA, CH_2Cl_2, rt, 82%; (d) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C; Et_3N, -78 °C ~ rt; (e) L-Selectride®, THF, -78 °C, 84% (two steps); (f) NaH, BnBr, *n*-Bu_4NI, THF, 0 °C ~ rt, 95%; (g) O_3, CH_2Cl_2, –78 °C; Me_2S, –78 °C ~ rt; (h) $NaBH_4$, EtOH, rt, 99% (two steps); (i) KH, MPMCl, THF, rt; (j) CSA, MeOH, rt, 79% (two steps).

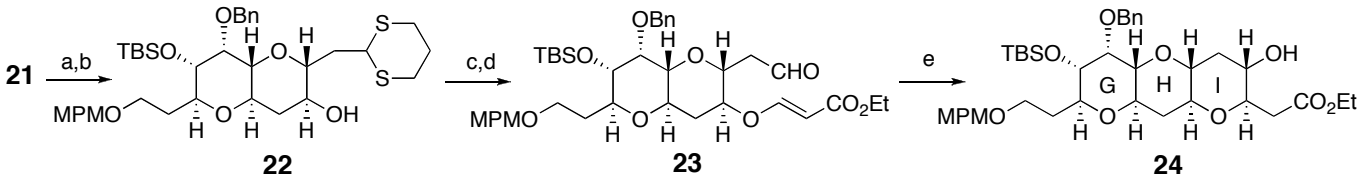
Next, the H-ring was constructed based on our developed SmI_2-induced reductive cyclization[10] for construction of 2,3-*trans*-tetrahydropyran ring (Scheme 2). Reaction of the diol (**12**) with I_2, Ph_3P, and imidazole afforded the mono-iodide (**13**) in 70% yield, and this was treated with triethylsilyl trifluoromethanesulfonate (TESOTf) and 2,6-lutidine to give the TES ether (**14**) (57%). Treatment of **14** with NaCN in DMSO afforded the nitrile (**15**) (91%), which was converted to thioacetal (**17**) (66%, two steps) via DIBAH reduction and thioacetalization. After removal of the TES group (86%), treatment of the resulting alcohol (**18**) with ethyl propiolate and *N*-methylmorpholine (NMM) effected hetero-Michael addition to give (**19**) (86%), the thioacetal of which was deprotected with MeI treatment to give the

aldehyde (**20**) in 82% yield. Treatment of **20** with SmI_2 in the presence of MeOH in THF at 0 °C effected reductive cyclization with complete stereoselectivity to give the GH-ring (**21**) in 86% yield.



Scheme 2. Reagents and conditions; (a) I_2, Ph_3P, imidazole, THF-MeCN (3:1), rt, 70%; (b) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 57%; (c) NaCN, MS4A, DMSO, 80 °C, 91%; (d) DIBAH, toluene, -78 °C; (e) $HS(CH_2)_3SH$, $Zn(OTf)_2$, CH_2Cl_2, 0 °C, 66% (two steps); (f) CSA, MeOH, 0 °C, 86%; (g) ethyl propiolate, NMM, CH_2Cl_2, rt, 86%; (h) MeI, $NaHCO_3$, aq. MeCN, rt, 82%; (i) SmI_2, MeOH, THF, 0 °C, 86%.

The GH-ring (**21**) was transformed to the GHI-ring (**24**) through the same strategy as described above (Scheme 3). Reduction of **21** with DIBAH followed by thioacetalization afforded **22** in 64% yield (two steps). After hetero-Michael addition of **22** with ethyl propiolate (74%), removal of thioacetal gave the aldehyde (**23**) in 76% yield. Finally, treatment of **23** with SmI_2 again effected completely stereoselective cyclization to give the desired GHI-ring (**24**)[13] in 90% yield. The stereostructure of **24** was confirmed by NOE-measurement of the corresponding acetate of **24** (Fig. 2).



Scheme 3. (a) DIBAH, toluene, -78 °C; (b) $HS(CH_2)_3SH$, $Zn(OTf)_2$, CH_2Cl_2, 0 °C, 64% (two steps); (c) ethyl propiolate, NMM, CH_2Cl_2, rt, 74%; (d) MeI, $NaHCO_3$, aq. MeCN, rt, 76%; (e) SmI_2, MeOH, THF, 0 °C, 90%.

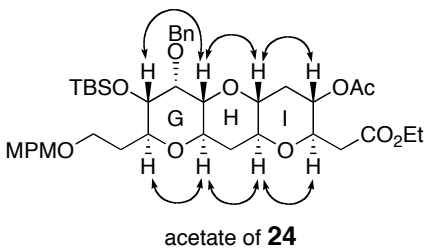


Figure 2. Observed NOE of the corresponding acetate of **24**.

In summary, the GHI-ring of maitotoxin was stereoselectively synthesized starting from 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose through our SmI_2-induced reductive cyclization, which was developed for the construction of polycyclic ethers.

ACKNOWLEDGEMENTS

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13. Data for **24**: $[\alpha]_D^{20}$ –36.2 (*c* 0.265, $CHCl_3$), IR (neat) 3446, 2929, 1738, 1613, 1513, 1456, 1249, 1182, 1094, 830, 755, 699 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.33-7.24 (m, 7H), 6.87-6.85 (m, 2H), 4.64 (d, *J* = 11.8 Hz, 1H), 4.45 (d, *J* = 11.5 Hz, 1H), 4.39 (d, *J* = 11.8 Hz, 1H), 4.37 (d, *J* = 11.5 Hz, 1H), 4.34 (br s, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.81-3.78 (m, 1H), 3.80 (s, 3H), 3.61 (ddd, *J* = 11.5, 9.5, 4.4 Hz, 1H), 3.57-3.51 (m, 2H), 3.49 (m, 1H), 3.04 (dd, *J* = 9.5, 1.8 Hz, 1H), 3.04-2.96 (m, 2H), 2.87 (dd, *J* = 9.5, 1.8 Hz, 1H), 2.79 (dd, *J* = 15.4, 4.6 Hz, 1H), 2.53 (dd, *J* = 15.4, 7.2 Hz, 1H), 2.39 (ddd, *J* = 11.5, 4.4, 4.4 Hz, 1H), 2.24 (ddd, *J* = 11.3, 4.4, 4.4 Hz, 1H), 2.18-2.13 (m, 1H), 2.12 (br d, *J* = 6.7 Hz, 1H), 1.59-1.53 (m, 1H), 1.49 (ddd, *J* = 11.3, 11.3, 11.3 Hz, 1H), 1.31 (ddd, *J* = 11.3, 11.3, 11.3 Hz, 1H), 1.27 (t, *J* = 7.2 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.9, 159.0, 137.8, 130.8, 129.3 (2C), 128.3 (2C), 128.0 (2C), 127.7, 113.7 (2C), 79.6, 79.3, 78.7, 76.6, 76.0, 72.4, 71.6, 70.8, 69.9, 68.4, 67.1, 66.6, 60.8, 55.3, 38.6, 38.2, 34.9, 31.8, 25.9 (3C), 18.5, 14.2, –4.2, –4.7; HRMS (FAB) calcd for $C_{38}H_{56}O_{10}Si$ ($M+H^+$) 701.3721, found 701.3718.