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Natural Product Synthesis

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Chemical Synthesis of the GHIJK Ring System and Further Experimental Support for the Originally Assigned Structure of Maitotoxin**

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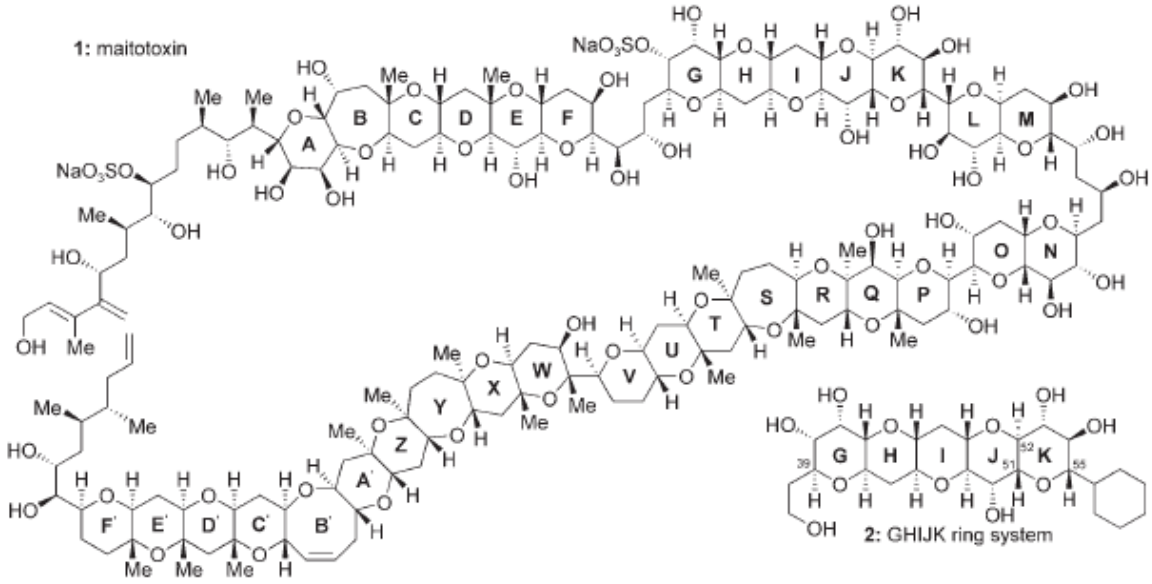
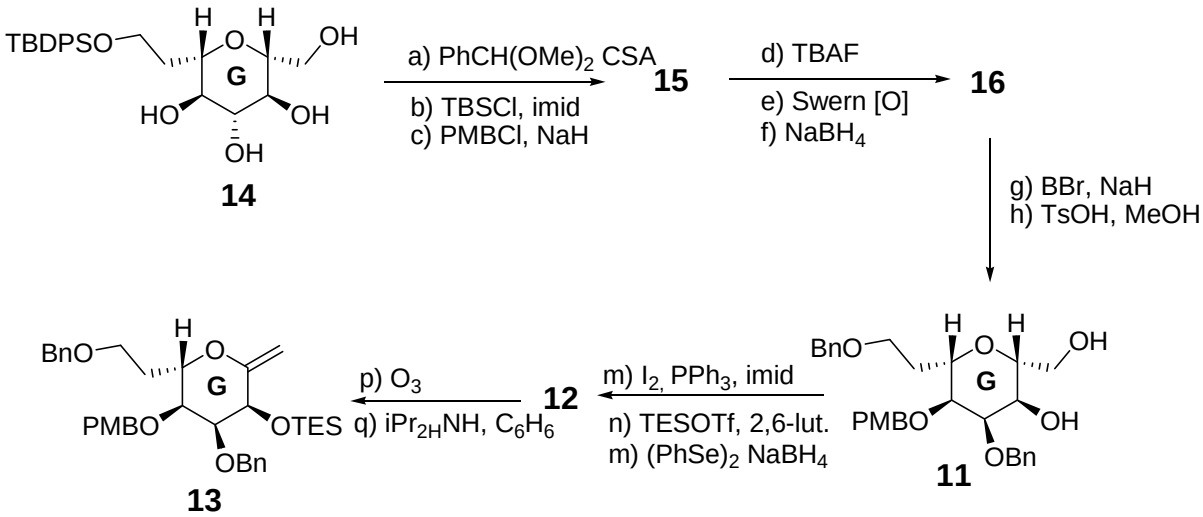


Scheme 1. Originally proposed structure of maitotoxin (**1**) and the targeted GHIJK ring system **2**.

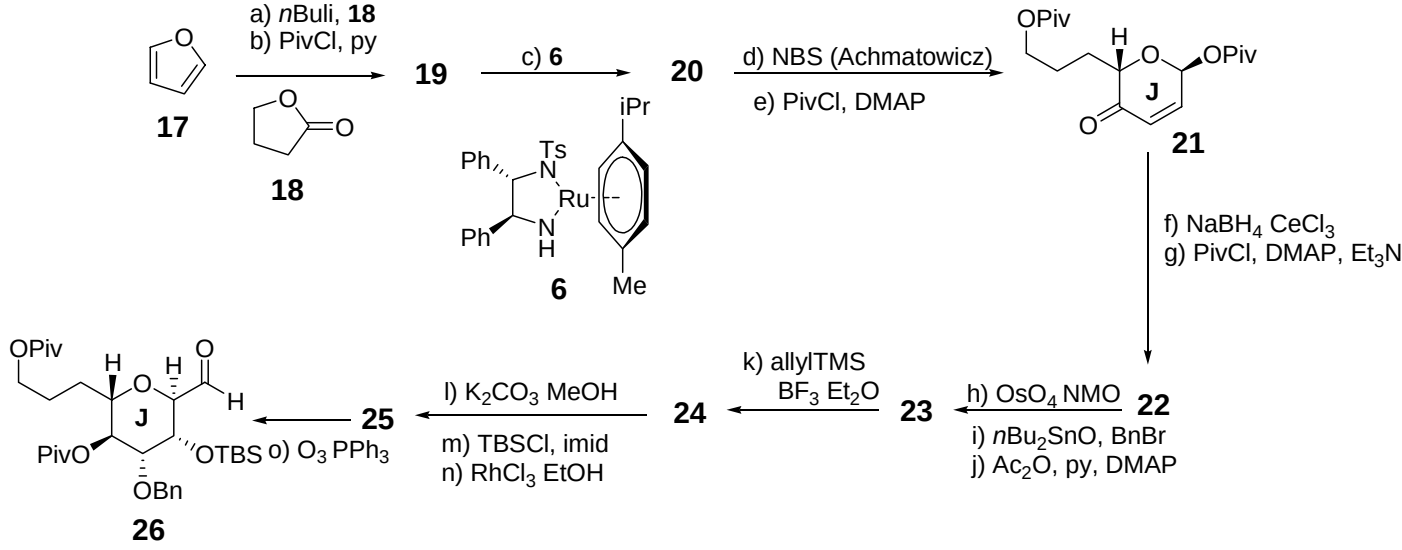
-Isolée en 1978 de l'algue marine *Gambierdicus toxicus.* Extrêmement toxique (LD_{50}= 50 ng/Kg).
-Structure déterminée en 1998. $C_{164}H_{256}O_{68}S_2Na_2$ Mw=3422 g.mol^{-1}

1) synthèse du cycle **G**



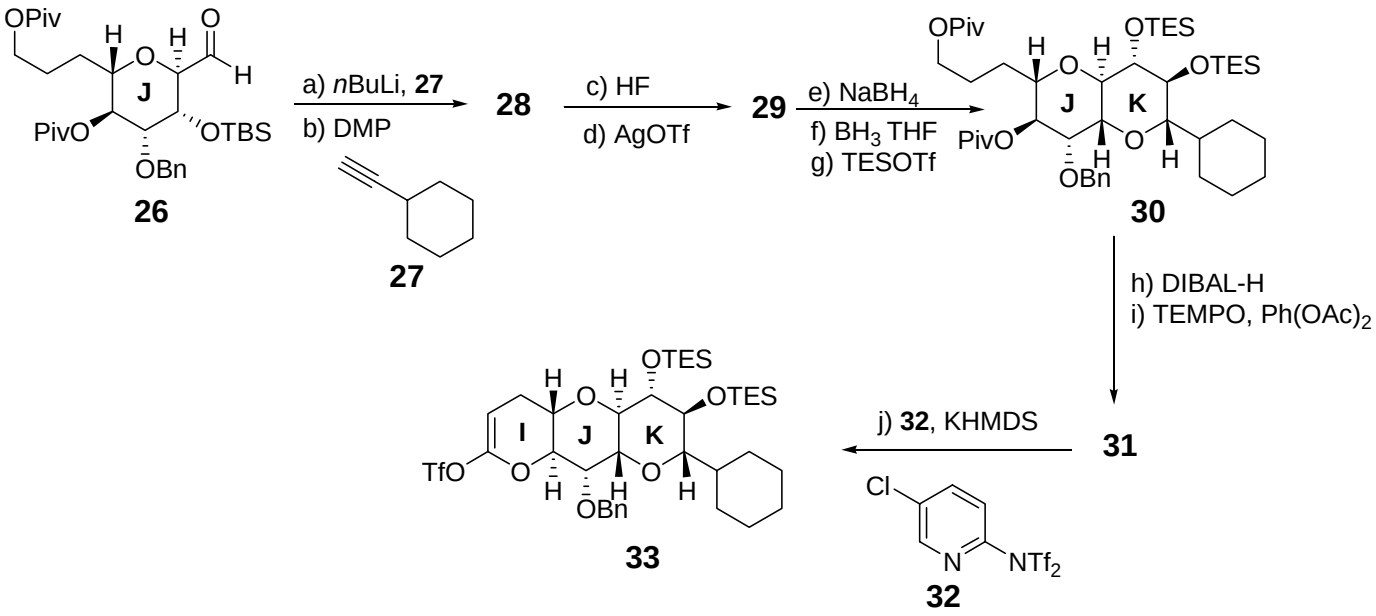
Construction of G ring system **13**. Reagents and conditions: a)$PhCH(OMe)_2$ (1.5 equiv), CSA (0.02 equiv), 4Å MS, CH_2Cl_2, 25°C, 2 h, 74%; b) TBSCl (2.0 equiv), imid. (3.0 equiv), DMF, 25°C, 18 h, 88%; c) PMBCl (10 equiv), TBAI (0.5 equiv), NaH (6.0 equiv), DMF, 25 °C, 18 h, 80%; d)TBAF (5.0 equiv), THF, 25°C, 18 h, 83%; e)$(COCl)_2$ (5.0 equiv), DMSO (10 equiv), CH_2Cl_2, -78 °C, 1 h; Et_3N (20 equiv), 0°C, 30 min; f)$NaBH_4$ (2.2 equiv), MeOH, 0°C, 86% over two steps; g) BnBr (7.0 equiv), TBAI (0.2 equiv), NaH (5.0 equiv), DMF, 25 °C, 18 h, 88%; h)TsOH (0.2 equiv), MeOH, 25°C, 18 h, 85%. m)I_2 (2.0 equiv), Ph_3P (2.0 equiv), imid. (2.0 equiv), THF, 25 °C, 2 h, 89%; n) TESOTf (2.0 equiv), 2,6-lut. (3.0 equiv), CH_2Cl_2, 0°C, 30 min, 93%; o)$(PhSe)_2$ (1.1 equiv), $NaBH_4$ (2.0 equiv), EtOH/THF (5:3), 0 to 25°C, 3 h; p) O_3, CH_2Cl_2/MeOH (5:1), -78°C, 10 min; q) iPr_2NH:C_6H_6 (1:10), 80°C, 3 h, 86% over three steps. TBDPS=tert-butyldiphenylsilyl, CSA=(±)-camphor-10-sulfonic acid, MS=molecular sieves, DMF=N,N-dimethylformamide, TBAI=tetra-n-butylammonium iodide, TBAF=tetra-n butylammonium fluoride, Bn=benzyl, TBS=tertbutyldimethylsilyl, THF=tetrahydrofuran, Piv=trimethylacetyl, lut.= lutidine, NBS=N-bromosuccinimide, PMB=para-methoxybenzyl, mCPBA=meta-chloroperbenzoic acid, DMSO=dimethyl sulfoxide, imid.=imidazole, TES=triethylsilyl, Tf=trifluoromethanesulfonyl.

2) synthèse du cycle **J**



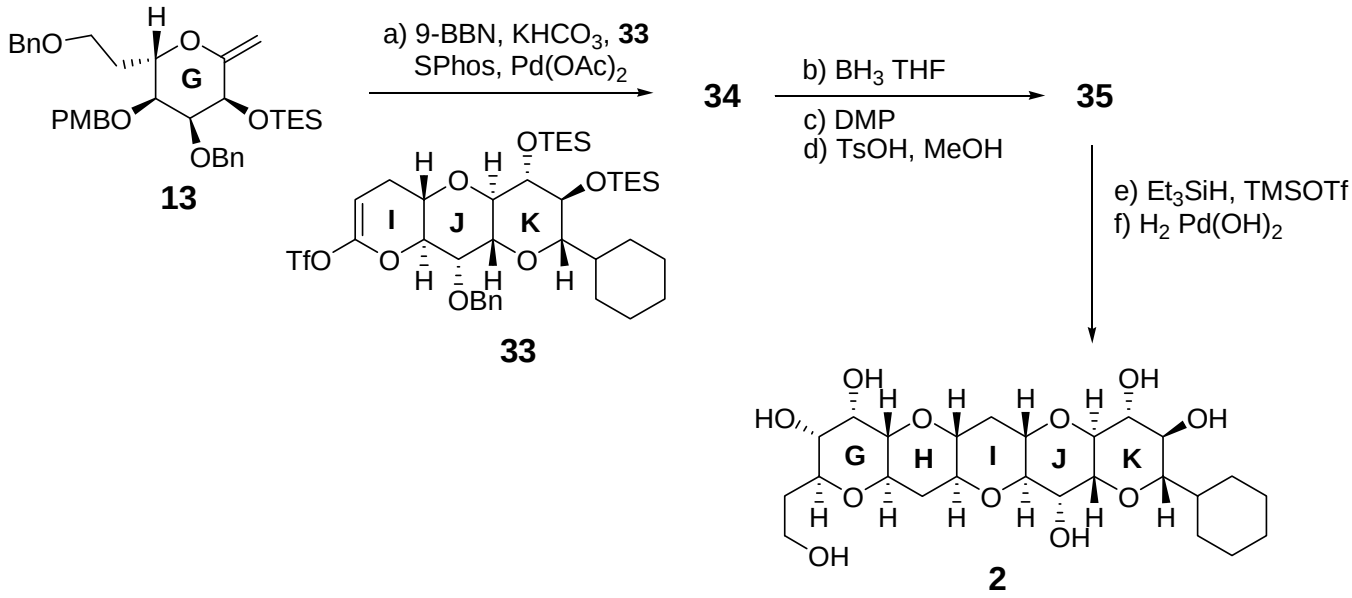
Construction of J ring aldehyde **26**. Reagents and conditions: a) nBuLi (1.05 equiv), THF, 0°C, 1 h; then **18** (2.0 equiv), -78 °C, 1 h, 58%; b) PivCl (1.25 equiv), py (3.0 equiv), CH_2Cl_2, 0°C,4 h, 86%, c) **6** (2.5 mol%), HCO_2H/Et_3N (5:2), 30 °C, 48 h, 89%(>95% ee); d) NBS (1.0 equiv), NaOAc (1.0 equiv), $NaHCO_3$ (2.0 equiv), THF/H_2O (3:1), 0°C, 1 h, 96%; e)PivCl (1.5 equiv), Et_3N (2.5 equiv), DMAP (0.05 equiv), CH_2Cl_2, -78 °C, 2 h, 64% (+20% other anomer); f) $CeCl_3 \cdot 7H_2O$ (0.5 equiv), $NaBH_4$ (1.0 equiv), MeOH/CH_2Cl_2 (1:1), -78°C, 30 min, 100%; g)PivCl (1.5 equiv), Et_3N (3.0 equiv), DMAP (0.05 equiv), CH_2Cl_2, 0°C, 6 h, 89%; h)OsO_4 (0.02 equiv), NMO (2.0 equiv), acetone/H_2O (10:1), 25°C, 48 h, 93%; i) nBu_2SnO (1.0 equiv), C_6H_6, reflux, 18 h; then BnBr (1.4 equiv), TBAI (1.0 equiv), 3 h, 98%; j) Ac_2O (4.0 equiv), DMAP (0.05 equiv), py (8.0 equiv), CH_2Cl_2, 25°C, 12 h, 97%; k)allylTMS (5.0 equiv), $BF_3 \cdot Et_2O$ (2.5 equiv), MeCN, 60 °C, 4 h, 87%; l)K_2CO_3 (0.1 equiv), MeOH, 25°C, 6 h, 84%; m) TBSCl (2.0 equiv), imid. (4.0 equiv), DMF, 40°C, 24 h, 85%; n)$RhCl_3 \cdot H_2O$ (0.05 equiv), EtOH, 80 °C, 3 h; o)O_3, CH_2Cl_2/ MeOH (5:1), -78°C, 5 min; then Ph_3P (1.5 equiv), 96% over two steps. py=pyridine, DMAP=4-dimethylaminopyridine, NMO=4-methylmorpholine N-oxide, TMS=trimethylsilyl.

3) synthèse des cycles I, **J** et **K**



Construction of IJK ring system **33**. Reagents and conditions: a) nBuLi (2.0 equiv), **27** (2.0 equiv), THF, -78°C, 1 h; then **26** (1.0 equiv), 15 min, 93%; b) DMP (1.5 equiv), CH_2Cl_2, 25°C, 1 h, 96%; c)48 % aq HF/MeCN (1:3), 25 °C, 18 h, 94%; d)AgOTf (0.1 equiv), CH_2Cl_2, 40°C, 18 h, 89%; e)$CeCl_3 \cdot 7H_2O$ (0.2 equiv), $NaBH_4$ (1.1 equiv), MeOH/CH_2Cl_2 (1:1), 0°C, 15 min; f)$BH_3 \cdot$THF (1.0m in THF, 10 equiv), THF, 0°C, 3 h; then NaOH (1.0M aq), H_2O_2 (35% aq), 1 h, 71% over two steps; g)TESOTf (15 equiv), 2,6-lut. (20 equiv), CH_2Cl_2, 0°C, 2 h, 92%; h)DIBAL-H (1.0M in CH_2Cl_2, 10 equiv), CH_2Cl_2, -78 °C, 10 min; i)TEMPO (0.1 equiv), PhI(OAc)2 (3.0 equiv), CH_2Cl_2, 25°C, 18 h, 82% over two steps; j) **32** (2.0 equiv), KHMDS (0.5m in THF, 2.0 equiv), THF, -78 °C, 10 min, 93%. DMP=Dess–Martin periodinane, DIBAL-H=diisobutylaluminum hydride, TEMPO=2,2,6,6-tetramethyl-1-piperidinyloxy, KHMDS=potassium bis(trimethylsilyl)amide.

4) synthèse des cycles **G, H,** I, **J** et **K**



Completion of the synthesis of GHIJK ring system **2**. Reagents and conditions: a) **13** (2.0 equiv), 9-BBN (4.0 equiv), THF, 50°C, 3 h; then $KHCO_3$ (1.0M aq, 20 equiv), **33** (1.0 equiv), SPhos (0.2 equiv), $Pd(OAc)_2$ (0.1 equiv), 25°C, 48 h, 78%; b)BH_3·THF (1.0m in THF, 10 equiv), THF, 0°C, 18 h; then NaOH (1.0m aq), H_2O_2 (35% aq), 1 h, 71%; c) DMP (1.5 equiv), CH_2Cl_2, 25°C, 2 h, 95%; d)TsOH (1.0 equiv), MeOH, 50°C, 48 h, 85%; e)Et_3SiH (5.0 equiv), TMSOTf (2.0 equiv), MeCN, 0°C, 15 min, 98%; f)H_2, 20% $Pd(OH)_2$/C (25% w/w), EtOH, 25 °C, 18 h, 70%. 9-BBN=9-borabicyclo[3.3.1]nonane, SPhos=2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl, Ts=p-toluenesulfonyl.