New Synthetic Technology for the Construction of 9-Membered Ring Cyclic Ethers. Construction of the EFGH Ring Skeleton of Brevetoxin A

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The structure of the powerful neurotoxin brevetoxin A[1,2] (**1**, Figure 1) still stands as a formidable synthetic challenge despite much synthetic activity.[3−5] Synthetic strategies for the construction of several of its ring systems have been developed,[3−5] but clearly the most challenging region of the molecule must be its EFGH framework. The latter system contains three of the most difficult rings to construct, namely, a didehydrooxanonacane (E), a didehydrooxaoctacane (F), and an oxaoctacane (G). All previous attempts at the system fall short of an assembly of the complete EFGH framework. Herein, we report a solution to this problem, employing a new method for the construction of didehydrononacane systems. The reported strategy allowed the synthesis of the functionalized EFGH ring system **2** (Scheme 1) with complete stereochemical control of all its stereogenic centers as well as the observation of its unusual conformational properties[1,2,5m] by NMR spectroscopy.

The new strategy for the construction of the central didehydronooxanacane ring (E) is outlined in Scheme 1. Thus, it was anticipated that a tetrasubstituted didehydrooxanonacane (**I**) could be derived by reduction of a 6-membered endoperoxide (**II**), which in turn could be obtained from a conjugated diene system (**III**) via singlet oxygen addition. The latter system was envisioned to arise from a lactone-derived phosphate (**V** → **IV**) via palladium coupling chemistry, according to a method recently developed in these laboratories.[6] As demonstrated below, this strategy is both feasible and highly efficient.

Reaction of aldehyde **3**[4] with the ylide derived from **4** (LiHMDS; for abbreviations see legends in schemes) in toluene resulted in the stereoselective formation of **5** (84%), whose desilylation with TBAF led to diol **6** (82%). Exposure of **6** to the Dess−Martin reagent (1.3 equiv) resulted in selective oxidation of the primary alcohol, furnishing aldehyde **7** (87%), which was oxidized further to hydroxy acid **8** (96%) by the action[7] of $NaClO_4$−$NaHPO_4$ in the presence of 2-methyl-2-butene in *t*-BuOH:H_2O (5:1). Lactonization of **8** following the Yamaguchi protocol[8] then gave lactone **9** (70%). Applying our palladium-catalyzed methodology[6] for the conversion of lactones to cyclic enol ethers, we converted **9** to **11** via **10** [(i) KHMDS−$(PhO)_2POCl$, 90%; (ii) vinyltri-*n*-butyltin−$Pd(PPh_3)_4$ cat., 96%].

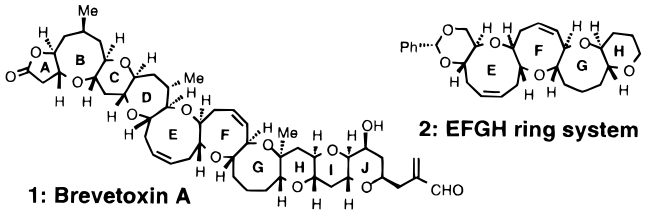
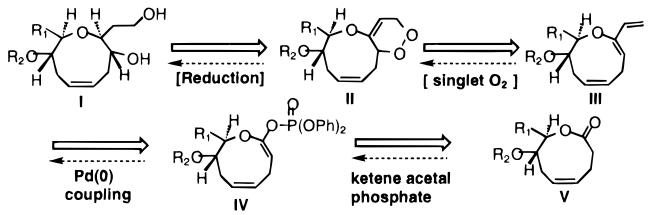


Figure 1. Structure of brevetoxin A (**1**) and EFGH ring system **2**.

Scheme 1. General Strategy for the Construction of Functionalized Didehydrononacanes



System **11** was transformed to phosphonium salt **20** with the proper stereochemistry, *via* the endoperoxide **12** as summarized in Scheme 2. Reaction of singlet oxygen with **11** gave endoperoxide **12** as a mixture of diastereoisomers (α:*β ca*. 1:1 ratio, 85%). Hydrogenation of **12** in the presence of Lindlar catalyst in MeOH furnished the corresponding diols (100%, α:*β ca*. 1:1), which were converted to monosilyl ethers **13** and **14** by the action of TBSCl−imidazole (imid.) (93%). The mixture was then oxidized with TPAP−NMO[9] to furnish enone **15** in 85% yield. The latter compound was then converted stereoselectively to the desired α-hydroxy compound **17** by a two-step sequence involving selective saturation of the exocyclic double bond $[(Ph_3P)CuH]_6$[10] (96%) and DIBAL reduction of the carbonyl function (87%). The conversion of **17** to **20** required pivalate formation to afford **18** (94%) followed by desilylation (TBAF, 91%), iodide formation (I_2, Ph_3P, imid.), and heating with Ph_3P (87% for two steps).

Coupling of the ylide derived from phosphonium salt **21**[4] (Scheme 3, *n*-BuLi, HMPA) with aldehyde **22**[11] gave *cis*-olefin **23** (56%). Desilylation of **23** with TBAF resulted in the formation of hydroxy dithioketal **24** (82%), which gave rise to oxocene **25** (72%) upon treatment with $AgClO_4$−$NaHCO_3$.[12] Reductive removal of the ethylthio group from **25** (Ph_3SnH−AIBN) established the desired oxocene framework **26** (81%). The benzylidene group was cleaved from **26** by hydrogenolysis (Pd/C, H_2, 94%), and the resulting diol (**27**) was selectively silylated with TBSCl-imid. to afford **28** (90%). Compound **28** was then oxidized with TPAP−NMO[9] to furnish ketone **29** (89%), the conversion of which to dithioketal **30** was achieved with EtSH−$Zn(OTf)_2$ (80%). Finally, desilylation of **30** with

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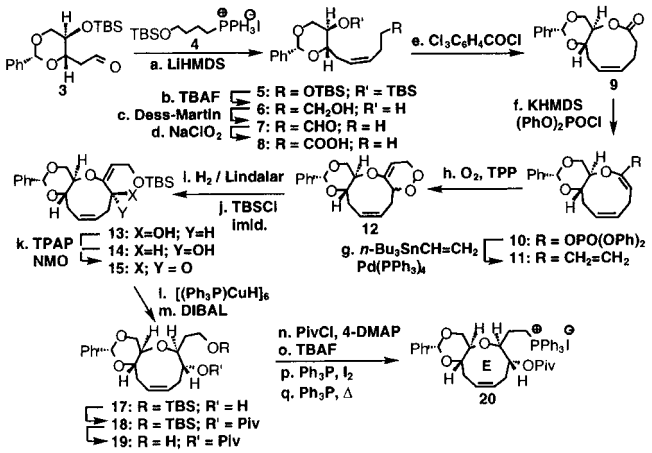
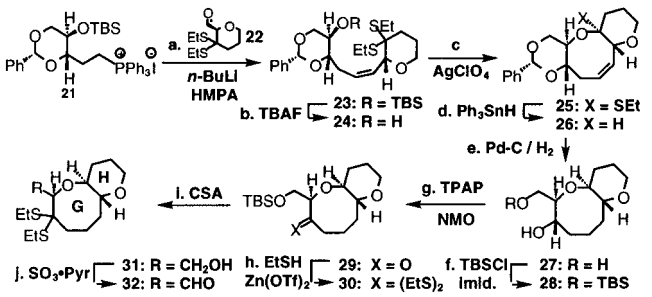
Scheme 2. Construction of the E ring phosphonium salt **20**[a]



[a] Reagents and conditions: (a) 1.2 equiv of **4**, 1.2 equiv of LiHMDS in THF, toluene, 0 °C; then 1.0 equiv of **3**, 8 h, 84%; (b) 2.4 equiv of TBAF, THF, 25 °C, 7 h, 82%; (c) 1.3 equiv of Dess−Martin reagent, CH_2Cl_2, 25 °C, 87%; (d) 3.0 equiv of $NaClO_2$, 1.2 equiv of NaH_2PO_4, 5.0 eqiuv of 2-methyl-2-butene, *t*-BuOH:H_2O (5:1), 25 °C 96%; (e) 1.2 equiv of trichlorobenzoyl chloride, 1.3 equiv of Et_3N, THF, 0 °C; then 6.0 equiv of 4-DMAP, benzene, 80 °C, 1 h, 70%; (f) 2.0 equiv of KHMDS, 2.0 equiv of $(PhO)_2POCl$, HMPA, THF, −78 °C, 90%; (g) 1.5 equiv of *n*-$Bu_3SnCH{=}CH_2$, 0.05 equiv of $Pd(PPh_3)_4$, 3.0 equiv of LiCl, THF, 80 °C, 95%; (h) 0.045 equiv of *meso*-tetraphenylporphine, CCl_4, O_2, *hν*, 0 °C, 85%; (i) H_2, Lindlar catalyst, MeOH, 25 °C, 100%; (j) 1.05 equiv of TBSCl, 1.2 equiv of imid., CH_2Cl_2, 25 °C, 93%; (k) TPAP, NMO, CH_2Cl_2, 25 °C, 1 h, 85%; (l) 2.0 equiv of $[(Ph_3P)CuH]_6$, benzene, 25 °C, 5 h, 96%; (m) 1.05 equiv of DIBAL, CH_2Cl_2, −78 °C, 2 h, 87%; (n) 3.0 equiv of PivCl, 4.0 equiv of 4-DMAP, CH_2Cl_2, 25 °C, 94%; (o) 1.5 equiv of TBAF, THF, 25 °C, 91%; (p) 2.0 equiv of imid., 2.0 equiv of Ph_3P, 1.05 equiv of I_2, CH_2Cl_2, 25 °C; (q) 10.0 equiv of Ph_3P, fusion (90 °C), 3 h, 87% for tw steps. LiHMDS = lithium bis(trimethylsilyl)amide; TBAF = tetra-*n*-butylammonium fluoride; 4-DMAP = 4-(dimethylamino)pyridine; KHMDS = potassium bis(trimethylsilyl)amide; HMPA = hexamethylphosphoramide; TBS = *tert*-butyldimethylsilyl.

Scheme 3. Construction of GH Ring Aldehyde **32**[a]



[a] Reagents and conditions: (a) 1.0 equiv of **21**, 1.05 equiv of *n*-BuLi, −78 °C, then 4.0 equiv of HMPA, 1.2 equiv of **22**, 8 h, 56%; (b) 1.2 equiv of TBAF, THF, 25 °C, 0.5 h, 82%; (c) 3.0 equiv of $AgClO_4$, 10.0 equiv of $NaHCO_3$, 4 Å MS, silica gel, $MeNO_2$, 25 °C, 2.5 h, 72%; (d) 4.0 equiv of Ph_3SnH, toluene, AIBN, 110 °C, 2 h, 81%; (e) Pd−C/H_2, MeOH, 25 °C, 17 h, 94%; (f) 1.1 equiv of TBSCl, 1.2 equiv of imid., CH_2Cl_2, 25 °C, 90%; (g) 0.05 equiv of TPAP, 1.5 equiv of NMO, CH_2Cl_2/MeCN (1:1), 25 °C, 89%; (h) 15 equiv of EtSH, CH_2Cl_2, 0.2 equiv of $Zn(OTf)_2$, 25 °C, 4 h; (i) 0.05 equiv of CSA, MeOH:CH_2Cl_2 (1:1), 1 h, 87%; (j) 3.0 equiv of SO_3·pyr, DMSO, Et_3N, CH_2Cl_2, 0 °C, 2 h, 89%. AIBN = 2,2′-azobisisobutyronitrile; CSA = 10-camphorsulfonic acid; DMSO = dimethyl sulfoxide; MS = molecular sieves.

CSA in MeOH−CH_2Cl_2 (87%), followed by SO_3·pyr (pyr = pyridine) oxidation, yielded aldehyde **32** (89%) via alcohol **31**.

With fragments **20** and **32** at hand, the construction of the targeted system **2** proceeded smoothly and expediently, as shown in Scheme 4. Thus, Wittig coupling (*n*-BuLi, HMPA) of **20** and **32** furnished, stereoselectively and in high yield (77%), *cis*-olefin **33** from which the pivalate group was removed by DIBAL reduction, furnishing hydroxy dithioketal **34** (84%). Finally,

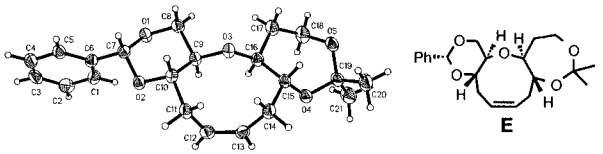
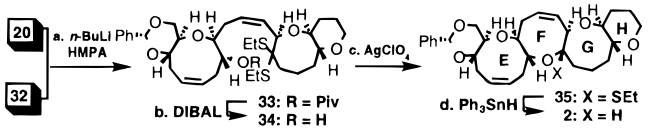


Figure 2. Crystal structure of E ring system.

Scheme 4. Synthesis of EFGH Ring System **2**[a]



[a] Reagents and conditions: (a) 1.0 equiv of **20**, 1.05 equiv of *n*-BuLi, THF, −78 °C; then 4.0 equiv of HMPA, 1.2 equiv of **32**, −78 °C, 1 h; then 25 °C, 8 h, 77%; (b) 1.05 equiv of DIBAL, CH_2Cl_2, −78 °C, 84%; (c) 2.5 equiv of $AgClO_4$, 10.0 equiv of $NaHCO_3$, 4 Å MS, silica gel, $MeNO_2$, 25 °C, 1 h, 81%; (d) 15 equiv of Ph_3SnH, 0.1 equiv of AIBN, toluene, Δ, 80%. TPAP = tetra-*n*-propylammonium perruthenate; NMO = 4-methylmorpholine *N*-oxide; DIBAL = diisobutylaluminum hydride.

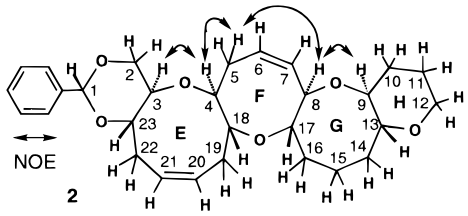


Figure 3. NOE correlations (^{1}H ROSEY) of selected protons in **2**.

ring closure of **34** under the standard $AgClO_4$−$NaHCO_3$ conditions[12] led to **35** (81% yield), from which the ethylthio group was removed by reaction with Ph_3SnH−AIBN to afford the desired EFGH ring system **2** in 80% yield.

The framework of **2** was established by ^{1}H-COSY, ^{1}H ROESY, ^{1}H−^{13}C HMQC, and HMBC NMR, as well as by X-ray crystallographic techniques (Supporting Information). Thus, the stereochemistry around ring E was confirmed by X-ray analysis of intermediate **E** (mp 144−145 °C, EtOAc−hexane) obtained from **17** by desilylation followed by acetonide formation (Figure 2). The relationship between the tri-*O*-acetyl-D-glucal-derived stereocenters C9,C13 and C8,C17 was deduced from ^{1}H ROESY experiments. Indeed, the ^{1}H ROESY experiment (Figure 3) revealed a strong NOE between H-8 (δ 4.08) and H-9 (δ 3.09) indicating a *syn* relationship between these protons. The absence of NOE between H-8 (δ 4.08) and H-17 (δ 3.33) and between H-9 (δ 3.09) and H-13 (δ 2.99) supported *trans* relationships at these fusions. Further study using E.COSY techniques demonstrated that the coupling constant (J) between H-8 and H-17 is 10.0 Hz, supporting a *trans* arrangement between these two protons. Additional NOE correlations were in support of structure **2** (see Figure 3).

The described chemistry provides the basis for the final approach toward brevetoxin A (**1**).

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Supporting Information Available: A scheme for the synthesis of compound **22**, procedures for the preparation of compounds **12**−**14**, **16**, **17**, **25**, **26**, **32**, **33**, **35** and **2**, a listing of selected data for the above compounds, NMR spectra for compound **2**, and X-ray crystallographic data for compound **E** (39 pages). See any current masthead page for ordering and Internet access instructions.

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