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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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%].

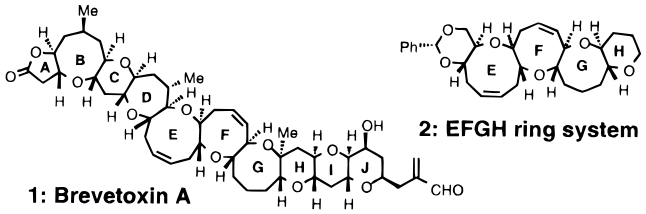
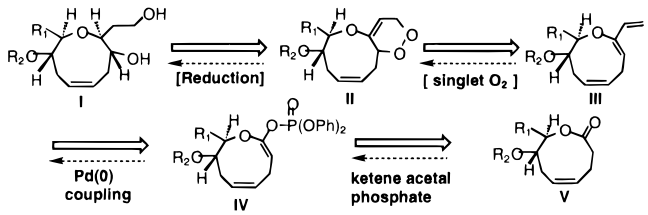


Figure 1. Structure of brevetoxin A (**1**) and EFGH ring system **2**.

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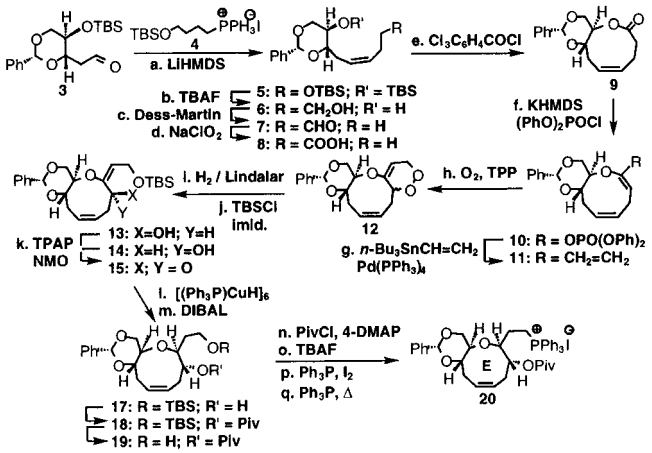
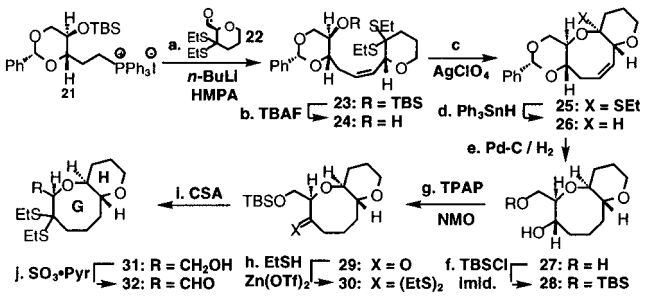
Scheme 2. Construction of the E ring phosphonium salt **20**[a]



[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,

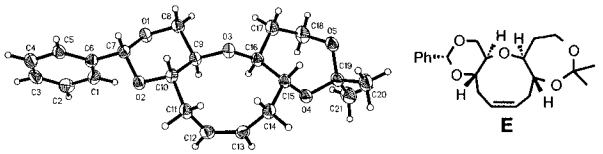
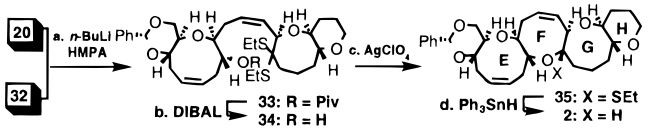


Figure 2. Crystal structure of E ring system.

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.

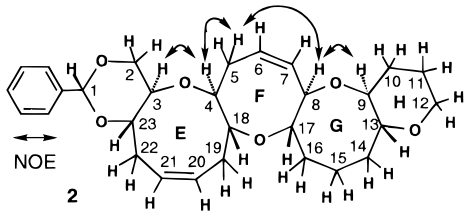


Figure 3. NOE correlations (^{1}H ROSEY) of selected protons in **2**.

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**).

Acknowledgment. We thank Dr. G. Siuzdak for Mass spectroscopic assistance. This work was supported by the National Institute of Health and The Skaggs Institute for Chemical Biology, fellowships from the George E. Hewitt Foundation (R.H.), the Austrian Science Foundation (an Erwin Schrödinger Postdoctoral Fellowship to P.G.), and the American Chemical Society (J.L.G.) and grants from Merck, DuPont-Merck, Schering Plough, Hoffmann La Roche, and Amgen.

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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