Stereocontrolled synthesis of the HIJ ring system of ciguatoxin

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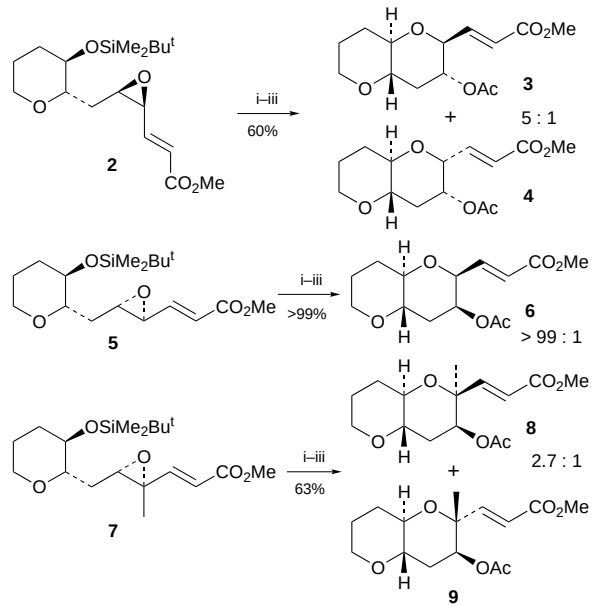
Divergent synthesis of the HIJ ring framework 21 of ciguatoxin 1 starting with oxocane 10 is achieved using the palladium- and acid-catalysed cyclization reactions of hydroxy epoxides.

Ciguatoxin **1** is the principal toxin which causes ciguatera poisoning.[1] Its unique structure and agonist activity against Na^+ channels have attracted considerable attention from synthetic organic chemists.[2] Although numerous synthetic studies of fragments of **1** have been reported, the central medium rings, such as the F and I rings, have eluded synthesis until very recently.[3,4] We describe herein the first divergent synthesis of the HIJ ring system of **1** *via* stereocontrolled palladium-[5] and acid-catalysed[6] cyclization reactions of hydroxy epoxides starting with the methyl oxocane I ring.[3]

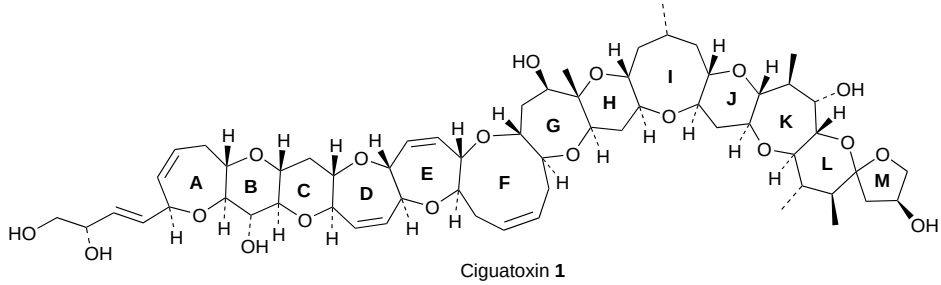
The palladium-catalysed cyclization procedure[5] was examined first to construct the H and J rings. *cis*-Epoxide **2** and *trans*-epoxide **5**, and trisubstituted *trans*-epoxide **7** were subjected to a cyclization reaction as models for constructing the J and H rings, respectively (Scheme 1).† While complete stereocontrol was realized for **5** to give **6** (> 99 : 1), lower selectivities were observed for **2** and **7** to give mixtures of **3** and **4** (5 : 1), and **8** and **9** (2.7 : 1), respectively. The *trans*-epoxide **15** was therefore used to construct the J ring, and we chose acid-catalysed cyclization technology to prepare the H ring.

Optically active oxocane **10**[3] was converted to **11** *via* protection of the primary alcohol as a benzyloxymethyl (BOM) ether, removal of the acyl groups and subsequent protection of the 1,3-diol as the acetonide and of the remaining secondary alcohol as a triisopropylsilyl ether in 83% overall yield (Scheme 2). The BOM group of **11** was removed by hydrogenolysis and the resulting primary alcohol was converted to the trifluoromethanesulfonate, which was immediately treated with the lithium acetylide generated from **22** in THF–dimethylpropyleneurea (DMPU) (6 : 1) at −78 °C[7] to give the adduct **12** in 68% overall yield. Selective removal of the ethoxyethyl (EE) group with pyridinium toluene-*p*-sulfonate (PPTS) in propanol[8] produced **13** in quantitative yield. The prop-2-ynyl alcohol **13** was partially reduced with sodium dihydrobis(2-methoxyethoxy)aluminate (Red-Al)[9] to give the *trans*-allylic alcohol **14**. Sharpless asymmetric epoxidation of **14** using D-(−)-diethyl tartrate (DET) gave the corresponding α-epoxide exclusively, and successive oxidation of the primary alcohol with a SO_3–pyridine complex and Wittig olefination gave **15** in 88% overall yield. Stereospecific construction of the J ring was achieved by the palladium-catalysed cyclization.[5] Treatment of **15** with tetrabutylammonium fluoride in THF, followed by solvent exchange to CH_2Cl_2 and addition of a catalytic amount of $Pd(PPh_3)_4$, gave **16** within 5 min as a single diastereoisomer in 93% yield in two steps.‡ The stereochemistry of the resulting alcohol with a non-natural orientation could be readily inverted by reduction of the corresponding ketone with $NaBH_4$.[10]

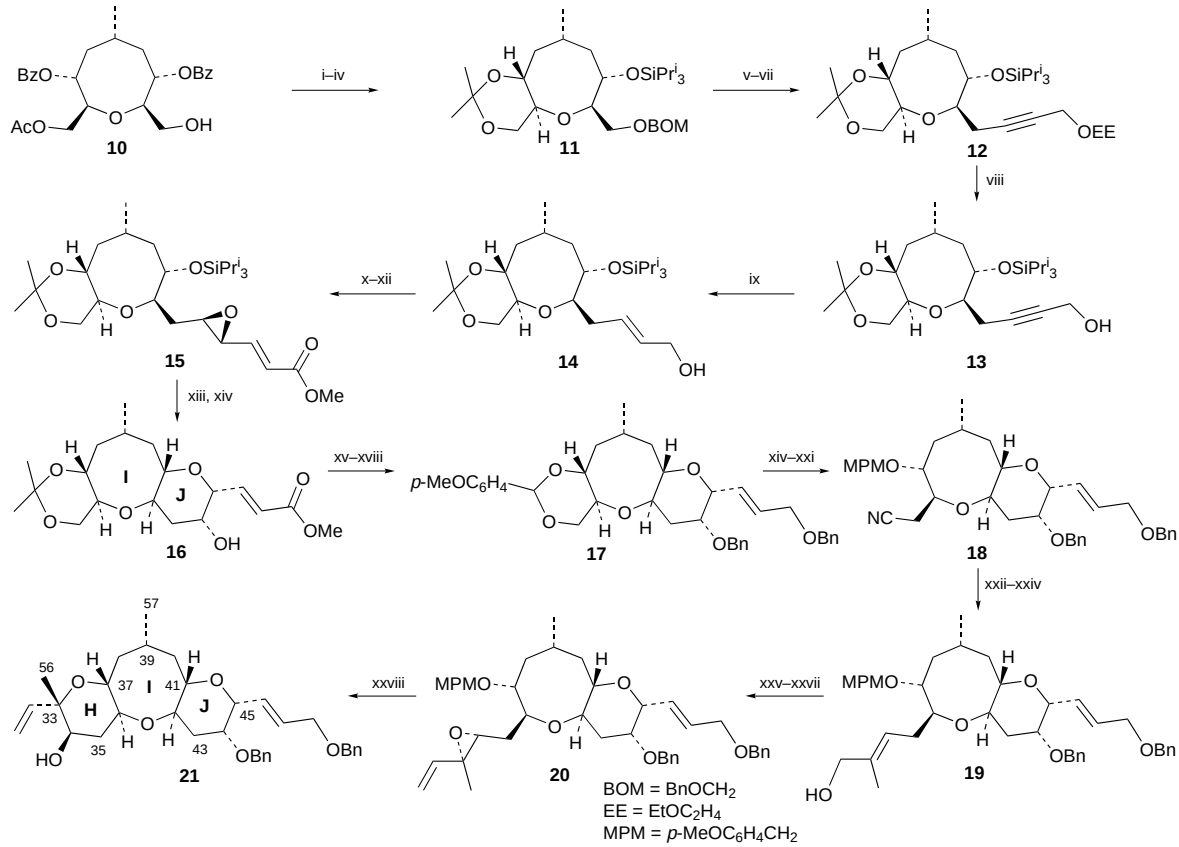
Having completed the synthesis of the I and J ring system, we were now in a position to construct the H ring. The ester **16** was reduced with DIBAL-H, the resulting alcohols were protected as benzyl ethers, and transformation of the acetonide into *p*-methoxybenzylidene acetal gave **17** in 90% overall yield. Regiospecific reductive cleavage of the benzylidene acetal with DIBAL-H furnished the *p*-methoxybenzyl (MPM) ether, and the resulting primary alcohol was converted to the methanesulfonate, which was then treated with sodium cyanide to yield the nitrile **18** in 91% overall yield. Extension of the side chain *via* DIBAL-H reduction and Wittig olefination with (carbethoxyethylene)triphenylphosphorane gave the α,β-unsaturated ester, which was reduced to allylic alcohol **19** in 98% overall yield. Sharpless asymmetric epoxidation of **19** furnished the corresponding hydroxy epoxide and further oxidation to the aldehyde and Wittig olefination gave **20** in 75% overall yield. Finally, treatment of **20** with 2,3-dichloro-5,6-dicyano-



Scheme 1 *Reagents and conditions*: i, Bu_4NF, THF; ii, $Pd(PPh_3)_4$ (cat.), PPh_3 (cat.), CH_2Cl_2; iii, Ac_2O, pyridine



Ciguatoxin **1**



Scheme 2 *Reagents and conditions*: i, $BnOCH_2Cl$, Pr^i_2EtN, Bu_4NI (cat.), $(CH_2Cl)_2$, 40 °C, 99%; ii, K_2CO_3, MeOH, 99%; iii, 2,2-dimethoxypropane, PPTS (cat.), MeCN, 85%; iv, $Pr^i_3SiOSO_2CF_2$, 2,6-lutidine, $(CH_2Cl)_2$, −30 °C, quant.; v, H_2, $Pd(OH)_2$–C (cat.), AcOEt, 87%; vi, $(CF_3SO_2)_2O$, Et_3N, $(CH_2Cl)_2$, −15 °C; vii, HC≡$CCH_2C_2H_4OEt$ **22**, BuLi, THF–DMPU (6 : 1), −78 °C, 78% (2 steps); viii, PPTS (cat.), PrOH; ix, Red-Al, Et_2O, 0 °C to room temp., 97% (2 steps); x, (−)-DET, $Ti(OPr^i)_4$, Bu^tOOH, molecular sieves 4A, CH_2Cl_2, −20 °C, 97%; xi, SO_3·pyridine, Et_3N, DMSO, $(CH_2Cl)_2$, 0 °C to room temp.; xii, Ph_3P=$CHCO_2Me$, toluene, 94% (2 steps); xiii, Bu_4NF, THF; xiv, $Pd(PPh_3)_4$ (cat.), PPh_3 (cat.), CH_2Cl_2, 93% (2 steps); xv, DIBAL-H, CH_2Cl_2, −78 °C, 98%; xvi, BnBr, NaH, DMF–THF (1 : 1), 0 °C, 92%; xvii, *p*-$MeC_6H_4SO_3H$·H_2O (cat.), MeOH; xviii, *p*-$MeOC_6H_4CH(OMe)_2$, PPTS (cat.), $(CH_2Cl)_2$, quant. (2 steps); xix, DIBAL-H, CH_2Cl_2, −40 °C, 97%; xx, $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C, quant.; xxi, NaCN, 18-crown-6 (cat.), DMF, 50 °C, 94%; xxii, DIBAL-H, CH_2Cl_2, −60 °C; xxiii, Ph_3P=$CMeCO_2Et$, toluene, 98% (2 steps); xxiv, DIBAL-H, CH_2Cl_2, −78 °C, quant.; xxv, (−)-DET, $Ti(OPr^i)_4$, Bu^tOOH, molecular sieves 4A, CH_2Cl_2, −20 °C, 90%; xxvi, SO_3·pyridine, Et_3N, DMSO, $(CH_2Cl)_2$, 0 °C to room temp.; xxvii, $Ph_3P^+CH_3Br^-$, $NaN(SiMe_3)_2$, THF, 0 °C, 83% (2 steps); xxviii, DDQ, CH_2Cl_2–H_2O (20 : 1), 88%.

1,4-benzoquinone (DDQ) in CH_2Cl_2 and water (20 : 1) resulted in cleavage of the MPM ether, and spontaneous cyclization of the resulting hydroxy epoxide prevailed under the weakly acidic conditions to afford **21** in 88% yield.§ The overall yield of **21** from **10** was 25% in 28 steps. Thus each step effectively proceeded in good yield (⩾95% yield).

In conclusion, we have demonstrated that the appropriate combination of stereoselective pyran formation methodologies allows us to synthesize the central HIJ ring system of **1** starting with oxocane **10**. Further synthetic studies directed towards **1** are in progress in our laboratory. We thank the Uehara Memorial Foundation, The Naito Foundation, and the Ministry of Education, Science and Culture, Japan for financial support.

Footnotes

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† Epoxides **2**, **5** and **7** were prepared from (2*S*,3*R*)-2-ethenyl-3-hydroxytetrahydropyran (ref. 6).

‡ On the other hand, acid-catalysed cyclization (ref. 6) of the **15** gave the 5-*exo* cyclization product (tetrahydrofuran) exclusively.

§ *Representative data* for **21**: $[\alpha]_D^{25}$ −2.14 (*c* 0.35, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.04 (3 H, d, *J* 7.2 Hz, H57), 1.26 (3 H, s, H56), 1.51 (1 H, ddd, *J* 13.5, 11.2, 2.7 Hz, H43ax), 1.52 (1 H, ddd, *J* 14.3, 9.5, 6.2 Hz, H38ax), 1.59 (1 H, d, *J* 3.6 Hz, OH), 1.63 (1 H, td, *J* 12.2, 11.0 Hz, H35ax), 1.74 (1 H, ddd, *J* 14.4, 10.6, 8.0 Hz, H40ax), 1.84 (1 H, br dd, *J* 14.3, 3.6 Hz, H38eq), 1.84–1.89 (1 H, m, H39), 1.88 (1 H, br d, *J* 14.4 Hz, H40eq), 2.12 (1 H, ddd, *J* 12.2, 5.0, 4.6 Hz, H35eq), 2.28 (1 H, ddd, *J* 13.5, 4.7, 3.1 Hz, H43eq), 3.20 (1 H, ddd, *J* 10.6, 9.2, 3.1 Hz, H41), 3.23 (1 H, ddd, *J* 11.0, 10.5, 5.0 Hz, H36), 3.40 (1 H, ddd, *J* 10.5, 9.5, 3.6 Hz, H37), 3.46 (1 H, ddd, *J* 12.2, 4.6, 3.6 Hz, H34), 3.52 (1 H, ddd, *J* 11.2, 9.2, 4.7 Hz, H42), 3.56–3.58 (1 H, m, H44), 3.86–3.88 (1 H, m, H45). The relative stereochemistry was unambiguously determined by NOE experiments.

References

1 M. Murata, A. M. Legrand, Y. Ishibashi and T. Yasumoto, *J. Am. Chem. Soc*., 1989, **111**, 8929; M. Murata, A. M. Legrand, Y. Ishibashi, M. Fukui, and T. Yasumoto, *J. Am. Chem. Soc.*, 1990, **112**, 4380.

2 E. Alvarez, M.-L. Candenas, R. Pérez, J. L. Ravelo and J. D. Martín, *Chem. Rev.*, 1995, **95**, 1953 and references cited therin; H. Oguri, S. Hishiyama, T. Oishi and M. Hirama, *Synlett*, 1995, 1252; H. Oguri, S. Hishiyama, O. Sato, T. Oishi, M. Hirama, M. Murata, T. Yasumoto and N. Harada, *Tetrahedron*, 1997, **53**, 3057.

3 Oishi, M. Shoji, K. Maeda, N. Kumahara and M. Hirama, *Synlett*, 1996, 1165.

4 M. Inoue, M. Sasaki and K. Tachibana, *Tetrahedron Lett.*, 1997, **38**, 1611.

5 T. Suzuki, O. Sato and M. Hirama, *Tetrahedron Lett.*, 1990, **31**, 4747.

6 K. C. Nicolaou, C. V. C. Prasad, P. K. Somers and C.-K. Hwang, *J. Am. Chem. Soc.*, 1989, **111**, 5330.

7 H. Kotsuki, I. Kadota and M. Ochi, *Tetrahedron Lett.*, 1990, **31**, 4609.

8 H. A. Tius and A. H. Faug, *J. Am. Chem. Soc.*, 1986, **108**, 1035.

9 S. E. Denmark and T. K. Jones, *J. Org. Chem.*, 1982, **47**, 4595.

10 Y. Mori, K. Yaegashi and H. Furukawa, *J. Am. Chem. Soc.*, 1996, **118**, 8158.

Received in Cambridge, UK, 1st April 1997; Com. 7/02158E