## 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.<sup>1</sup> Its unique structure and agonist activity against Na<sup>+</sup> channels have attracted considerable attention from synthetic organic chemists.<sup>2</sup> 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.<sup>3,4</sup> We describe herein the first divergent synthesis of the HIJ ring system of 1 *via* stereocontrolled palladium-<sup>5</sup> and acid-catalysed<sup>6</sup> cyclization reactions of hydroxy epoxides starting with the methyl oxocane I ring.<sup>3</sup>

The palladium-catalysed cyclization procedure<sup>5</sup> 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).<sup>†</sup> 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 lithium acetylide generated from 22 in the THFdimethylpropyleneurea (DMPU) (6:1) at -78 °C<sup>7</sup> to give the adduct 12 in 68% overall yield. Selective removal of the ethoxyethyl (EE) group with pyridinium toluene-p-sulfonate (PPTS) in propanol<sup>8</sup> 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  $\alpha$ -epoxide exclusively, and successive oxidation of the primary alcohol with a SO<sub>3</sub>-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<sub>2</sub>Cl<sub>2</sub> and addition of a catalytic amount of Pd(PPh<sub>3</sub>)<sub>4</sub>, gave **16** within 5 min as a single diastereoisomer in 93% yield in two steps.<sup>‡</sup> The stereochemistry of the resulting alcohol with a non-natural orientation could be readily inverted by reduction of the corresponding ketone with NaBH<sub>4</sub>.<sup>10</sup>

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  $\alpha,\beta$ -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



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Scheme 2 *Reagents and conditions*: i, BnOCH<sub>2</sub>Cl, Pri<sub>2</sub>EtN, Bu<sub>4</sub>NI (cat.), (CH<sub>2</sub>Cl)<sub>2</sub>, 40 °C, 99%; ii, K<sub>2</sub>CO<sub>3</sub>, MeOH, 99%; iii, 2,2-dimethoxypropane, PPTS (cat.), MeCN, 85%; iv, Pri<sub>3</sub>SiOSO<sub>2</sub>CF<sub>2</sub>, 2,6-lutidine, (CH<sub>2</sub>Cl)<sub>2</sub>, -30 °C, quant; v, H<sub>2</sub>, Pd(OH)<sub>2</sub>–C (cat.), AcOEt, 87%; vi, (CF<sub>3</sub>SO<sub>2</sub>)<sub>2</sub>O, Et<sub>3</sub>N, (CH<sub>2</sub>Cl)<sub>2</sub>, -15 °C; vii, HC=CCH<sub>2</sub>C<sub>2</sub>H<sub>4</sub>OEt **22**, BuLi, THF–DMPU (6:1), -78 °C, 78% (2 steps); viii, PPTS (cat.), PrOH; ix, Red-Al, Et<sub>2</sub>O, 0 °C to room temp., 97% (2 steps); x, (-)-DET, Ti(OPri)<sub>4</sub>, Bu<sup>4</sup>OOH, molecular sieves 4A, CH<sub>2</sub>Cl<sub>2</sub>, -20 °C, 97%; xi, SO<sub>3</sub>-pyridine, Et<sub>3</sub>N, DMSO, (CH<sub>2</sub>Cl)<sub>2</sub>, 0 °C to room temp.; xii, Ph<sub>3</sub>P=CHCO<sub>2</sub>Me, toluene, 94% (2 steps); xiii, Bu<sub>4</sub>NF, THF; xiv, Pd(PPh<sub>3</sub>)<sub>4</sub> (cat.), PPh<sub>3</sub> (cat.), CH<sub>2</sub>Cl<sub>2</sub>, 93% (2 steps); xv, DIBAL-H, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, 98%; xvi, BnBr, NaH, DMF–THF (1 : 1), 0 °C, 92%; xvii, *p*-MeC<sub>6</sub>H<sub>4</sub>SO<sub>3</sub>H·H<sub>2</sub>O (cat.), MeOH; xviii, *p*-MeC<sub>6</sub>H<sub>4</sub>CH(OMe)<sub>2</sub>, PPTS (cat.), OF, 90°, C or 0, 97%; xxi, DIBAL-H, CH<sub>2</sub>Cl<sub>2</sub>, -40 °C, 97%; xxi, MeSO<sub>2</sub>Cl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, quant; xvi, NaCN, 18-crown-6 (cat.), DMF, 50 °C, 94%; xxii, DIBAL-H, CH<sub>2</sub>Cl<sub>2</sub>, -60 °C; xxiii, Ph<sub>3</sub>P=CMeCO<sub>2</sub>Et, toluene, 94% (2 steps); xviv, DIBAL-H, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, quant; xvii, (-)-DET, Ti(OPri)<sub>4</sub>, Bu<sup>4</sup>OH, molecular sieves 4A, CH<sub>2</sub>Cl<sub>2</sub>, -60 °C; xxiii, Ph<sub>3</sub>P=CMeCO<sub>2</sub>Et, toluene, 94% (2 steps); xviv, DIBAL-H, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, quant; xviv, (-)-DET, Ti(OPri)<sub>4</sub>, Bu<sup>4</sup>OH, molecular sieves 4A, CH<sub>2</sub>Cl<sub>2</sub>, -20 °C, 90%; xviv, SO<sub>3</sub>-pyridine, Et<sub>3</sub>N, DMSO, (CH<sub>2</sub>Cl<sub>2</sub>)<sub>2</sub>, 0 °C to room temp.; xviii, Ph<sub>3</sub>P=CMeCO<sub>2</sub>Et, toluene, 94% (2 steps); xviv, DIBAL-H, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, quant; xvvii, Ph<sub>3</sub>P=CH<sub>3</sub>Br<sup>-</sup>, NaN(SiMe<sub>3</sub>)<sub>2</sub>, THF, 0 °C, 83% (2 steps); xviii, DDQ, CH<sub>2</sub>Cl<sub>2</sub>–H<sub>2</sub>O (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 ( $\geq$ 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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- $\dagger$  Epoxides **2**, **5** and **7** were prepared from (2*S*,3*R*)-2-ethenyl-3-hydroxy-tetrahydropyran (ref. 6).

<sup>‡</sup> 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<sub>3</sub>); <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$  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.

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