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A general synthetic approach to the amnesic shellfish toxins: total synthesis of (–)-isodomoic acid B, (–)-isodomoic acid E and (–)-isodomoic acid F†

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The alkynylpyrrolidine **4** was made *via* a dearomatising cyclisation of an aromatic amide, and was elaborated by stannylcupration and palladium-catalysed coupling to achieve the first total synthesis of three members of the isodomoic acid family; the same alkyne can be envisaged as a precursor to several more of this class of amnesic shellfish toxins.

Domoic acid **1** and a group of related algal metabolites, the isodomoic acids **2** (Scheme 1),¹ are metabolites of the algae *Chondria armata* and *Pseudonitzschia spp.*² and are the causative agents of amnesic shellfish poisoning.³ Related in structure to the well-established neurotoxin kainic acid **3**,⁴ domoic acid has been the subject of extensive toxicological studies in both humans⁵ and marine animals.⁶ The hazard to human health posed by the consumption of shellfish contaminated with amnesic shellfish toxins⁷ has spurred the development of sensitive analytical methods for their environmental detection.⁸ Domoic acid exerts its effects by binding to the kainate subfamily of ionotropic glutamate receptors,⁹ and comparative studies have revealed differences in the bioactivity of the various isodomoic acids.¹⁰ Yet despite the environmental, biological and medicinal interest of these compounds, out of the eight known isodomoic acids A–H, only isodomoic acids C,¹¹ G^{12,13} and H¹³ have been synthesised.¹⁴

The remaining isodomoic acids A, B, D, E, F and domoic acid itself all contain a trisubstituted alkene variously substituted with a pyrrolidine ring, a carboxy-substituted unsaturated chain, and a methyl group. Current approaches to the isodomoic acids^{11–13} all rely on early introduction of the unsaturated side chain (R in Scheme 1), and do not address the challenge of controlling a trisubstituted double bond at C1' of this chain. They are therefore not readily generalisable to a broader synthetic approach to this class. We envisaged however that several members of the isodomoic acid family, and their non-natural analogues, would be available synthetically if

these substituents were added at a late stage by functionalisation of a common alkyne-containing precursor **4**. Metallation and alkylation of the alkyne would allow the choice of side chain to be made at a late stage, and established strategies for the stereoselective synthesis of trisubstituted double bonds from alkynes would allow the challenge of stereochemistry to be addressed. In this paper we report the preparation of **4** and we demonstrate its application to the first total synthesis of three of the isodomoic acids: B, E and F.

We have previously shown that a pyrrolidine ring with the substitution pattern and stereochemistry found in all kainoids,^{4a} including the isodomoic acids, can be constructed using the asymmetric dearomatising cyclisation of an *N*-benzyl benzamide.^{15–17} Our approach to alkyne **4** (Scheme 2) therefore began with amide **5**¹¹ which was enantioselectively deprotonated¹⁸ with lithium amide **6** to yield, after quenching at –20 °C, acidic work-up and recrystallisation, the bicyclic enone **7** in > 99:1 e.r. Conjugate addition of a trimethylsilyl group to this enone using (SiMe₃)₂CuCNLi₂¹⁹ gave the β-silyl ketone **8**. This transformation was crucial to the synthesis, as the newly introduced silyl group served to protect the enone from a subsequent Ru-catalysed oxidation, assisted the regioselectivity of a Baeyer–Villiger reaction, and promoted fragmentation of the resulting lactone. The relative stereochemistry of **8**, which was formed as a single diastereoisomer, was confirmed by X-ray crystallography.²⁰

Clean replacement of the cumyl group²¹ by Boc to yield **9** was achieved by solvolysis in trifluoroacetic acid and treatment with Boc₂O.²² Oxidation of the phenyl ring of **9** using a

Scheme 1 Amnesic shellfish toxins **1** and **2** from a common alkyne **4**.

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Scheme 2 Synthesis of alkyne **4** via dearomatising cyclisation. Reagents and conditions: (a) (i) **6**, THF, -78°C to -20°C ; (ii) HCl (3M); (b) (i) $(\text{SiMe}_3)_2\text{CuCNLi}_2$, -78°C , THF, Me_3SiCl , 30 min; (ii) HCl (1M), THF; (c) $\text{CF}_3\text{CO}_2\text{H}$, reflux, 1 h; (d) Boc_2O , CH_2Cl_2 , DMAP (cat.), Et_3N , r.t., 18 h; (e) (i) RuCl_3 (10 mol%), NaIO_4 , EtOAc , H_2O , CH_3CN , r.t., 24 h; (ii) *tert* butanol, DCC, Et_3N , CH_2Cl_2 , r.t., 15 h; (f) (i) LiEt_3BH , THF, 0°C , 1 h; (ii) Et_3SiH , $\text{BF}_3\cdot\text{OEt}_2$, THF, -78°C , 2 h; (g) Dess–Martin periodinane, CH_2Cl_2 , r.t., 2 h; (h) *m*-CPBA, CH_2Cl_2 , r.t., 48 h; (i) (i) Bu_4NF , 0°C , THF, 1 h; (ii) Boc_2O , DMAP, *tert* butanol, r.t., 2 h; (j) (i) O_3 , CH_2Cl_2 , -78°C ; (ii) Me_2S , r.t., 24 h; (k) Ohira–Bestmann reagent $(\text{MeO})_2\text{P}(\text{O})\text{C}(\text{N}_2)\text{COMe}$, MeONa , THF, -78°C , 1 h.

modification^{16b} of Sharpless' conditions²³ gave a carboxylic acid which was protected as its *t*-butyl ester.²⁴ Reduction of the amide was achieved in two steps, with the concomitant reduction of the cyclohexanone reversed by a final treatment with Dess–Martin periodinane to yield the ketone **11**.

Bicyclic ketones related to **11** are known to undergo regioselective Baeyer–Villiger oxidation,^{11,16b} and with the additional assistance of the trimethylsilyl group,²⁵ the treatment of **11** with *m*-CPBA returned a single lactone **12** in which the β -silylalkyl group had undergone migration to oxygen. Fragmentation of silyl lactone **12** with TBAF ²⁶ and protection of the resulting acid as its *tert*-butyl ester gave alkene **13**.

A number of methods for the overall dehydrogenation of **13** to alkyne **4** were investigated, but the most effective turned out to be ozonolysis of the vinyl group to yield aldehyde **14** followed by chain extension to give the alkyne **4** using the Ohira–Bestmann reagent,²⁷ $(\text{MeO})_2\text{P}(\text{O})\text{C}(\text{N}_2)\text{COMe}$. As has been previously noted by others,^{28a} the use of NaOMe (equimolar with the Ohira–Bestmann reagent) allowed us to avoid the epimerisation of the sensitive aldehyde which resulted when potassium carbonate in methanol was used as the base.²⁸

Application of alkyne **4** to the stereoselective formation of the trisubstituted double bonds of the targets was achieved by *syn* stannylcupration with $\text{Bu}_3\text{SnCu}(\text{Bu})\text{CNLi}_2$ using the conditions of Lipshutz (Scheme 3).²⁹ Unlike many of the other alkyne metallation methods which we surveyed for this transformation, this procedure was tolerant of the presence of a nitrogen carbamate protecting group.³⁰ The presumed vinyl copper intermediate was methylated *in situ* to generate

the vinylstannane **15** as a single regio- and stereoisomer (by NMR) in 65% yield. We found that the stannane **15** was stable at -18°C and could be stored for weeks in a freezer. Treatment of the stannane with TFA led to protodestannylation and global deprotection to yield (–)-kainic acid **3**,³¹ confirming the relative and absolute stereochemistry of the alkyne **4** and the regiochemistry of the stannylcupration.

Side chains **16**, *E*-**18** and *Z*-**18** were prepared for coupling with the vinylstannane by reported routes³² from 2-bromopropionic acid or (S)-Roche ester. Stirring **15** and **16** in DMF in the presence of 3 mol% of $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ ³³ gave a diene **17B** which was purified and treated with TFA to give a sample of (–)-isodomoic acid **B 2B**.

Similar treatment of **15** with *E*-**18** gave a diene which was purified and treated with TFA to give a sample of (–)-isodomoic acid **E 2E**. Likewise **15** and *Z*-**18** were coupled under the same conditions to give a diene which was deprotected with TFA to yield (–)-isodomoic acid **F 2F**.

The spectroscopic characteristics of the synthetic samples in each case matched those reported for natural material.³⁴ The availability of **4** and the simplicity of its subsequent transformations of alkyne **4** suggests that it will prove a valuable intermediate for the synthesis of further naturally-occurring members of the domoic acid family and their synthetic analogues, and will facilitate further biological and environmental studies of this class of molecules.

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Scheme 3 Alkyne **4** as precursor to kainic and isodomoic acids. Reagents and conditions: (a) (i) $\text{Bu}_3\text{SnCu}(\text{Bu})\text{CNLi}_2$, THF -78°C , 1 h, (ii) MeI ; (b) TFA, CH_2Cl_2 , r.t.; (c) $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ (3 mol%), DMF, 50°C , 5–48 h.

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