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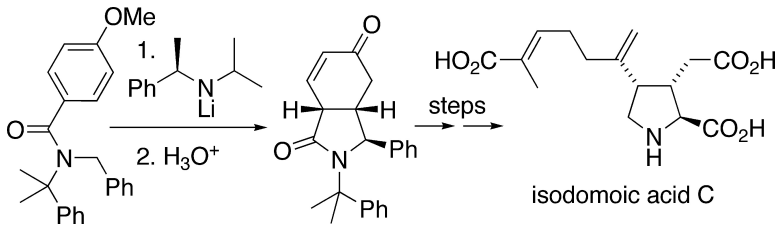

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The Synthesis of (−)-Isodomoic Acid C

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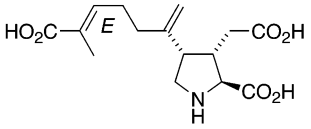
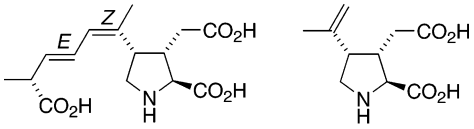
Isodomoic acid C **1**[1] is a member of a 10-strong family[2] of isomers of domoic acid **2**,[3] all of which are cyclic kainoid amino acids[4] isolable from the marine organisms *Nitzschia pungens* and *Chondria armata*. Domoic acid has powerful neuroexcitatory properties,[5] and isodomoic acids are insecticidal.[1] Domoic acid and the isodomoic acids have, on occasion, been found in the edible parts of the mussel, *Mytilus edulis*,[2d] posing a threat to both humans and marine mammals and birds.[6] The syndrome known as amnesic shellfish poisoning has been ascribed to ingestion of shellfish containing domoic and isodomoic acids,[7] and there have been numerous recent developments in methods for analysis of domoic acid.[8]



isodomoic acid C **1**



domoic acid **2**

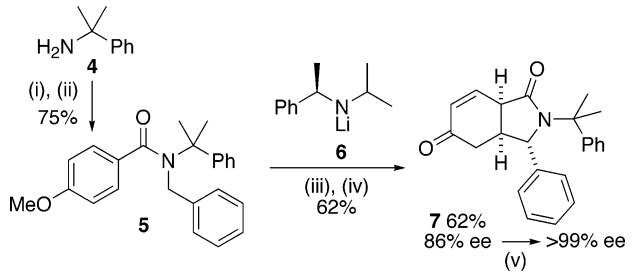
kainic acid **3**

Domoic acid has been synthesized on one occasion,[3b] and only one of the family of isodomoic acids, isodomoic acid G, has so far been made,[9] though domoic acid has been isomerized photochemically to a mixture of the isodomoic acids;[2b] moreover, Baldwin[10] has successfully synthesized a series of non-natural domoic acid analogues.[11] In this paper, we describe the first total synthesis of (−)-isodomoic acid C **1** in 15 steps from a simple aromatic amide **5**. The key step in our strategy is the asymmetric dearomatizing cyclization of this *N*-benzyl benzamide **5**,[12] a reaction we have employed in the synthesis of the structurally related (−)-kainic acid **3**.[13] This work had shown that the stereochemistry of the bicyclic product **7** of the cyclization was correct for the biologically active kainoids,[4] and that chemoselective Ru(VIII) oxidation of the aryl ring and regioselective Baeyer−Villiger oxidation of the cyclohexanone ring accomplished two of the key transformations required for the conversion of **7** into a target kainoid.

To employ this cyclization in the synthesis of isodomoic acid C, we made amide **5** from cumylamine[14] **4** on a 10−20 g scale and cyclized it in 2.5 g batches. Treatment of **5** in THF at −78 °C with *N*-lithioamine **6**[15] by our published method[13a] promoted asymmetric deprotonation and cyclization to an enol ether which was hydrolyzed[16] in situ to yield enone **7** (Scheme 1) in 86% ee (by HPLC). Recrystallization of **7** from ethyl acetate improved the enantiomeric excess to >99%.

The reactivity of enone **7** allowed us to introduce a precursor to the required side chain of isodomoic acid C by conjugate addition

Scheme 1. Asymmetric Dearomatizing Cyclization[a]



[a] Reagents: (i) *p*-$MeOC_6H_4COCl$, Et_3N, CH_2Cl_2, 0 °C; (ii) NaH, DMF, BnBr; (iii) **6**, THF, −78 to 20 °C; (iv) HCl, H_2O; (v) recryst (EtOAc).

of a mixed cuprate formed from the protected iodo alcohol **8**, yielding ketone **9** in 79% yield as a single diastereoisomer. Although inconsequential for the synthesis overall, we assume that **9** forms with the stereochemistry shown, by virtue of *exo* attack of the cuprate on the bicyclic system. Removal of the cumyl protecting group with formic acid[17] led additionally to desilylation and formylation of the primary hydroxyl group. Reprotection of the secondary lactam as an *N*-Boc derivative yielded **10** in 81% yield from **9**.

The benzyl group of **5** is essential for clean cyclization; few alternative cyclizing groups are as effective.[13b] However, the resulting phenyl substituent requires conversion to the C2 carboxyl group of the target, and the vigorously oxidizing conditions required for such a reaction[18] leave little room for manoeuvre chemoselectively. Ketone **10** is one of few compounds in the synthetic sequence in which chemoselective oxidation of Ph is feasible, and treatment of **10** with sodium periodate in the presence of catalytic ruthenium(III) chloride yielded, after methylation with trimethylsilyldiazomethane, ester **11**. Reprotection of the primary hydroxyl group with TBDPS gave **12**.

The way was now clear for cleavage of the six-membered ring of **12**, whose *cis* fusion with the lactam ring will generate the necessary *syn* relationship between the C3 and C4 substituents of isodomoic acid C. Following the precedent[13] that similar 6,5-fused systems undergo surprisingly regioselective Baeyer−Villiger oxidation,[19] we treated ketone **12** with *m*-CPBA. As we had hoped, lactone **13** was formed quantitatively as a single regioisomer. Careful methanolysis of lactone **13** by slow addition of sodium methoxide avoided epimerization of the hard-earned *cis* stereochemistry and returned the hydroxyester **14** as the C3,C4-*cis* stereoisomer.

Elimination of water from **14** to give the unsaturated compound **15** was achieved via oxidation of the corresponding selenide using the method of Grieco.[20] Despite the presence of four carbonyl groups in **15**, we found that the slow addition of DIBAL to **15** in THF allowed the selective reduction of the amide carbonyl group, and treatment of the product with triethylsilane and boron trifluoride gave the *N*-Boc pyrrolidine **16**.

Elaboration to the isodomoic acid C side chain was achieved by fluoride-promoted deprotection of the silylated hydroxyl group,

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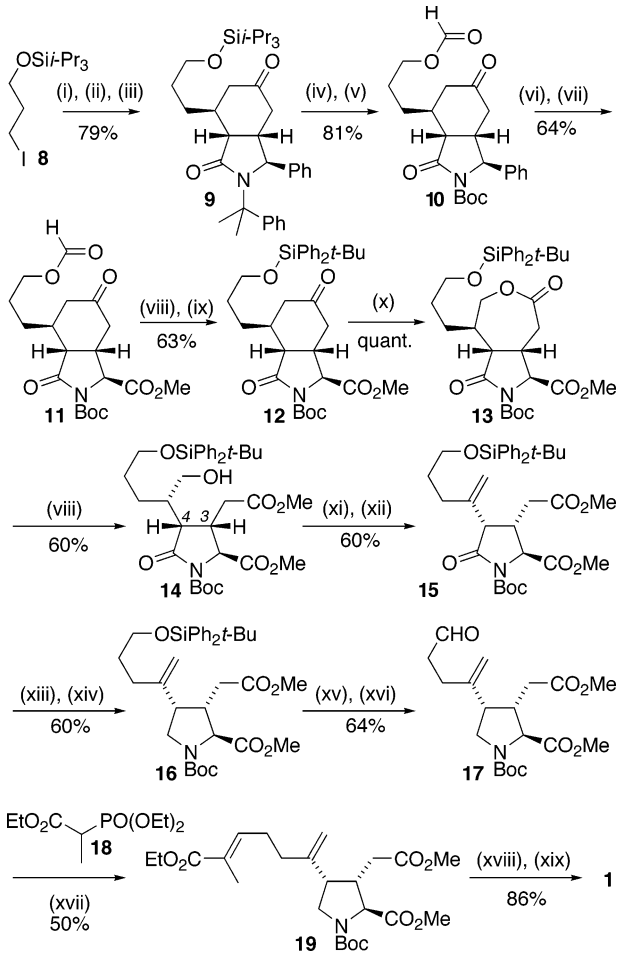
Scheme 2. Synthesis of (−)-Isodomoic Acid C[a]



[a] Reagents: (i) *t*-BuLi, −78 °C, Et_2O; (ii) MeLi, CuCN, Et_2O, −78 to 25 °C; (iii) **7**, −78 °C; (iv) HCO_2H, reflux, 30 min; (v) Boc_2O, Et_3N, DMAP, CH_2Cl_2, 25 °C, 18 h; (vi) $NaIO_4$, $RuCl_3$, H_2O, MeCN, EtOAc, 18 h; (vii) Me_3SiCHN_2, toluene, MeOH, 20 °C, 5 min; (viii) NaOMe, MeOH, −78 °C, 1 h; (ix) *t*-$BuPh_2SiCl$, imid, CH_2Cl_2, 20 °C, 18 h; (x) *m*-CPBA (70%), CH_2Cl_2, 25 °C, 72 h; (xi) *o*-$NO_2C_6H_4SeCN$, Bu_3P, THF, 20 °C, 2 h; (xii) H_2O_2, py, −40 to 25 °C, 12 h; (xiii) *i*-Bu_2AlH, PhMe, THF, −78 °C, 1 h; (xiv) Et_3SiH, BF_3/OEt_2, −78 °C, 2.5 h; (xv) Bu_4NF, THF, 25 °C, 2 h; (xvi) Dess−Martin, CH_2Cl_2, 25 °C, 30 min; (xvii) **18**, DBU, LiCl, MeCN, 25 °C, 1 h; (xviii) LiOH, H_2O, THF, 25 °C, 12 h; (xix) CF_3CO_2H, CH_2Cl_2, Δ, 2 h.

Dess−Martin[21] oxidation to aldehyde **17**, and Horner−Wadsworth−Emmons olefination. Under Masamune's conditions,[22] **17** reacted with ethyl 2-triethylphosphonopropionate **18** to yield a single stereoisomer of the trisubstituted alkene **19**. Deprotection by treatment with lithium hydroxide followed by trifluoroacetic acid yielded, after purification by ion exchange and reverse-phase HPLC, the target natural product (−)-isodomoic acid C **1**, $[\alpha]^{20}_D = -30 \pm 10$ ($c = 0.02$, H_2O) [lit.[1] $[\alpha]^{20}_D = -30$ ($c = 0.015$, H_2O)]. Comparison of the ^1H and ^{13}C NMR spectra of the product with those of authentic naturally derived isodomoic acid C[23] indicated an exact match.

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Supporting Information Available: Experimental procedures and characterization of all new compounds. ^1H and ^{13}C NMR spectra of key intermediates and spectroscopic comparison of natural and synthetic (−)-isodomoic acid C. This material is available free of charge via the Internet at http://pubs.acs.org.

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