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First Total Synthesis and Stereochemical Definition of Isodomoic Acid G

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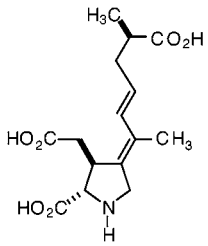
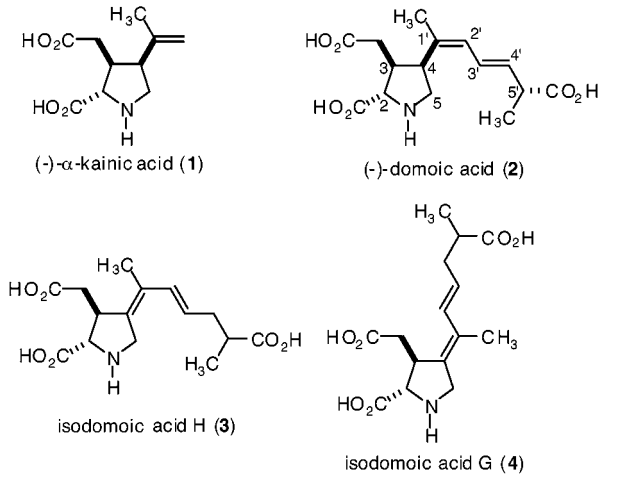
ABSTRACT



The first total synthesis and stereochemical definition of isodomoic acid G has been achieved. The key nickel-catalyzed coupling of an alkynyl enone with an alkenylzirconium allows formation of the pyrrolidine ring and most of the stereochemical features in a single step. This report provides the first total synthesis application of this new reaction and illustrates its utility in the stereoselective preparation of highly substituted 1,3-dienes.

The kainoid amino acids have attracted intense interest over recent years due to their potent neuroexcitatory activity, their utility as pharmacological probes, and their scarcity from natural sources.[1,2] The epimeric natural products kainic acid (**1**) and allokainic acid are the simplest members of this group of pyrrolidine di- and tricarboxylic acids,[3] and domoic acid (**2**)[4] and acromelic acid[5] are representative of the more complex members of this group (Scheme 1). Domoic acid was originally isolated from a marine algae in 1958,[4] and its structure was redefined in the first and only total synthesis reported by Ohfune and Tomita in 1982.[6] Numerous isomers of domoic acid have been isolated, and the observed structural variations include the position of the C4 side chain unsaturation and the chirality at the C5′ position.[7] No reports

Scheme 1



(1) (a) Tremblay, J.-F. *Chem. Eng. News* **2000**, *January 3rd*, 14. (b) Tremblay, J.-F. *Chem. Eng. News* **2001**, *January 29th*, 19.

(2) (a) Monaghan, D. T.; Bridges, R. J.; Cotman, C. W. *Annu. Rev. Pharmacol. Toxicol.* **1989**, *29*, 365. (b) Moloney, M. G. *Nat. Prod. Rep.* **1998**, 205. (c) Chamberlin, R.; Bridges, R. In *Drug Design For Neuroscience*; Kozikowski, A. P., Ed.; Raven Press, Ltd.: New York, 1993; pp 231−259. (d) McGeer, E. G.; Olney, J. W.; McGeer, P. L. *Kainic Acid as a Tool in Neurobiology*; Raven Press: New York, 1978.

(3) Murakami, S.; Takemoto, T.; Shimizu, Z. *J. Pharm. Soc. Jpn.* **1953**, *73*, 1026.

(4) Takemoto, T.; Daigo, K. *Chem. Pharm. Bull.* **1958**, *6*, 578.

(5) Konno, K.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1983**, *24*, 939.

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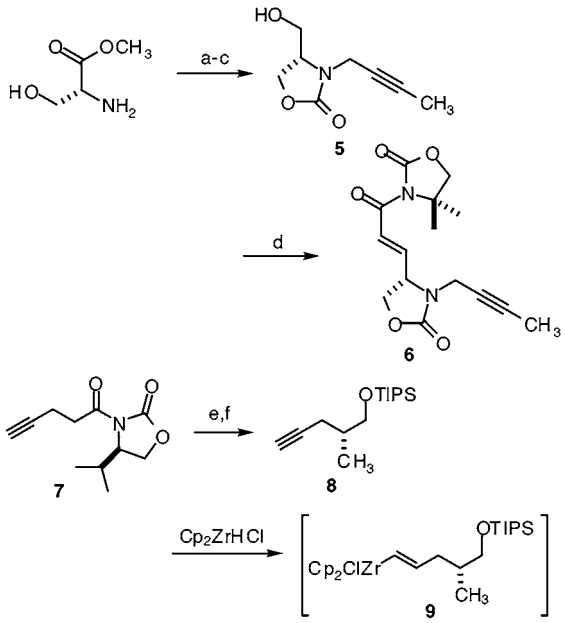
of the total synthesis of the naturally occurring isomers of domoic acid have appeared, although Baldwin has reported the synthesis of domoic acid analogues.[8] In 1997, two new isomers of domoic acid were isolated that were the first naturally occurring members of the kainoid amino acid group to possess a C4 exocyclic double bond.[9] These natural products, termed isodomoic acids H (**3**) and G (**4**), are identical aside from the *E* to *Z* variation of the exocyclic tetrasubstituted alkene stereochemistry (Scheme 1). Neither the relative stereochemistry of the C5′ position nor the overall absolute stereochemistry was established in the initial report. Given the structural novelty and the potentially interesting biological activity of isodomoic acids G and H, we set out to develop a synthetic strategy for their preparation. Herein, we report the first total synthesis of isodomoic acid G and establish its side chain stereochemistry as 5′(*R*).

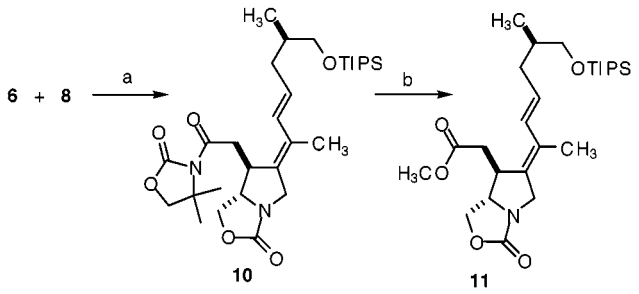
A recent report from our laboratory described the first examples of nickel-catalyzed cyclization of alkynyl enones with organozirconium reagents.[10] This new procedure efficiently assembles exocyclic dienes with a tetrasubstituted alkene component, and it appeared that the process was ideally suited to address the challenging issue of stereoselective diene introduction required in a total synthesis of isodomoic acid G. To assemble the required cyclization precursor, D-serine methyl ester was converted to the corresponding oxazolidinone upon treatment with triphosgene, and *N*-alkylation with butynyl mesylate followed by ester reduction with $NaBH_4$ afforded compound **5** (Scheme 2).[11] A Swern oxidation/Wittig olefination sequence then afforded substrate **6**. The requisite alkenylzirconium precursor **9** was then assembled by an Evans alkylation of acyloxazolidinone **7**.[12] Lithium borohydride reduction of the product of diastereoselective methylation followed by silylation provided TIPS-protected alkyne **8**. Hydrozirconation of **8** with Cp_2ZrHCl in THF to afford **9** in situ, followed by treatment with substrate **6** in the presence of 10 mol % $Ni(COD)_2$ and 20 mol % $ZnCl_2$, then afforded pyrrolidine **10** in 74% isolated yield with complete control of the C2−C3 relative stereochemistry (Scheme 3).[10,13] It should be stressed that this single step addresses most of the challenges associated with this total synthesis, including formation of the pyrrolidine ring, control of the C2−C3 relative stereochemistry, formation of the 1,3-diene, and control of stereochemistry of the C4−C1′ and C2′−C3′ alkenes.

Scheme 2 [a]



[a] Reagents and conditions: (a) triphosgene, THF, reflux, 99%. (b) KHMDS, butynyl mesylate, THF, 0 °C to rt, 72%. (c) $NaBH_4$, ethyl alcohol, 0 °C to rt, 90%. (d) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C; (ii) 4,4-dimethyl-3-[2-(triphenyl-phosphinio)-acetyl]-oxazolidin-2-one bromide, DMAP, 74% (two steps). (e) NaHMDS, MeI, THF, −78 ∼ −40 °C, 78% (dr > 98:2). (f) (i) $LiBH_4$, $EtOH/H_2O$; (ii) TIPSCl, imidazole, DMAP, CH_2Cl_2, 81% (two steps).

Scheme 3 [a]



[a] Reagents and conditions: (a) **8**, Cp_2ZrHCl, THF, rt; then **6**, $Ni(COD)_2$ (10 mol %), $ZnCl_2$ (20 mol %), THF, 0 °C, 74%. (b) MeOMgBr, MeOH, rt, 80%.

Methanolysis of the acyl oxazolidinone linkage of **10** with MeOMgBr afforded ester **11**.

The selective formation of compound **11** as a single isomer was complicated by the partial epimerization of the C2 stereocenter during the conversion of **5** to **6**. The extent of epimerization varied in amounts up to 20−30%. The most straightforward, albeit inelegant, way to avoid this complication was to employ a chiral oxazolidinone during the conversion, since the minor epimer of **12** was easily separated

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(11) For our earlier approaches to other members of the kainoid amino acids, see: (a) Chevliakov, M. V.; Montgomery, J. *Angew. Chem., Int. Ed.* **1998**, *37*, 3144. (b) Chevliakov, M. V.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 11139.

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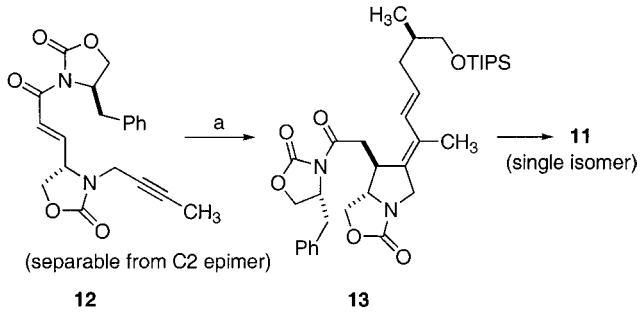
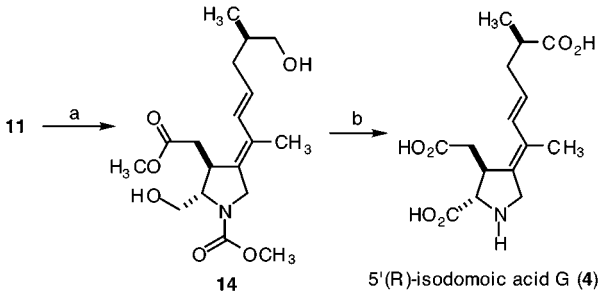
Scheme 4 [a]



[a] Reagents and conditions: (a) **8**, Cp_2ZrHCl, THF, rt; then **12**, $Ni(COD)_2$ (10 mol %), $ZnCl_2$ (20 mol %), THF, 0 °C, 70%.

Scheme 5 [a]



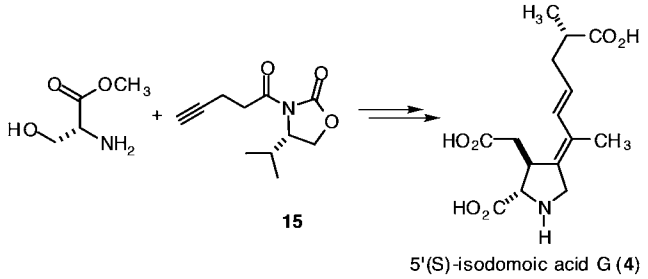
[a] Reagents and conditions: (a) (i) MeONa, MeOH, rt; (ii) TBAF, THF, rt, 95% (two steps). (b) (i) Dess Martin periodinane, CH_2Cl_2, rt; (ii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O, rt; (iii) NaOH, MeOH, H_2O, rt; (iv) ion-exchange chromatography (38% from **14**).

from the desired isomer (Scheme 4). The configuration of the chiral oxazolidinone does not affect the diastereoselectivity in the conversion of **12** to **13**.[14]

With compound **11** in hand, methanolysis of the remaining internal oxazolidinone with MeONa was accomplished (Scheme 5).[11] After *n*-Bu_4NF-mediated deprotection, the resulting diol **14** was oxidized to the corresponding diacid (Dess Martin followed by $NaClO_2$). Exhaustive hydrolysis and sequential ion exchange chromatographic separations afforded synthetic 5′(*R*)-isodomoic acid G (**4**) that displayed ^{1}H NMR spectral characteristics identical to the data provided in the original isolation report from Arakawa.[9]

(14) See Supporting Information for complete details.

Scheme 6



By repeating the entire sequence, starting from D-serine methylester and (*S*)-valine-derived **15**, we then prepared the 5′(*S*)-isomer of isodomoic acid G in essentially identical fashion (Scheme 6). Although the NMR spectra of the 5′(*R*) and 5′(*S*) synthetic samples were extremely similar, the ^{1}H NMR spectrum of a mixed sample of the synthetic 5′(*S*)-isomer and the natural product possessed subtle differences when compared with the pure natural product. A mixed sample of the 5′(*R*)-isomer and the natural product were indistinguishable from the pure natural product; *thus, the natural product side chain stereochemistry can be assigned as 5′(R)*. The absolute stereochemistry of isodomoic acid G was confirmed to be that shown on the basis of comparing CD spectra of synthetic 5′(*R*)-**4** and the natural product.

In summary, the first total synthesis and stereochemical definition of isodomoic acid G has been achieved. The key nickel-catalyzed coupling of an alkynyl enone with an alkenylzirconium allows formation of the pyrrolidine ring and most of the stereochemical features in a single step. This report provides the first total synthesis application of this new reaction and illustrates its utility in the stereoselective preparation of highly substituted 1,3-dienes.

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Supporting Information Available: Full experimental details and copies of NMR spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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