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Total Syntheses of Isodomoic Acids G and H: An Exercise in Tetrasubstituted Alkene Synthesis

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Abstract

A unified approach to the pyrrolidine triacid natural products isodomoic acids G and H has been developed. Total syntheses of both natural products were completed, and determination of the correct stereostructure of isodomoic acid G was established by comparing 5'(R) and 5'(S) isomers to a sample of authentic material. A nickel-catalyzed cyclization constructs the pyrrolidine ring while simultaneously establishing either the *E*- or *Z*-stereochemistry of an exocyclic tetrasubstituted alkene. The stereoselective assembly of both the *E*- and *Z*-alkenes of the natural products is made possible by a predictable strategy that alters the timing of substituent introduction to control alkene stereochemistry.

Keywords

nickel; domoic; kainic; olefination

Introduction

The kainoid family of marine natural products has attracted intense interest due to the important pharmacological properties of members of this group of natural products.¹ The parent member of the family, kainic acid (Scheme 1), has been the subject of many synthetic efforts, beginning from the impressive first synthesis from Oppolzer in 1982, and many total syntheses have since appeared.^{2,3} The interest in this target derives from its potent neuroexcitatory activity, by serving as a conformationally constrained analogue of glutamate.¹ By virtue of this bioactivity, it has served as a powerful pharmacological tool for the study of glutamate transmission. In the early 1990's, a shortage of natural kainic acid led to an increased emphasis on total synthesis approaches, although the scarcity of kainic acid has been relieved by the recent development of fermentation procedures for its isolation.⁴ The C-4 epimer of kainic acid, known as allokainic acid, exhibits considerably diminished neuroexcitatory properties. A number of efficient approaches to allokainic acid have appeared, but many of these routes require fundamentally different synthetic strategies than those described for the synthesis of kainic acid itself.² Interest in our group a decade ago focused on the formulation of a common approach to both kainic and allokainic acid, and the realization of that goal was allowed by development of complementary cyclizations of unsaturated acyl oxazolidinones with either mono-substituted allenes or internal alkynes possessing an oxazolidinone-containing tether.⁵

The more complex members of this family of natural products are typified by domoic acid (Scheme 1).⁶ This natural product is well known as the culprit in outbreaks of poisoning from

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SUPPORTING INFORMATION. Full experimental details including copies of ¹H NMR spectra, chiral HPLC analyses, and complete reference 7 (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

mussel toxins.⁷ The more complex C-4 side chain of domoic acid leads to increased toxicity compared with kainic acid. Numerous naturally occurring isomers of domoic acid have been identified, and the majority of those isomers differ from domoic acid itself by virtue of a change in stereochemistry or position of the 1,3-diene embedded within the C-4 side chain. The only synthesis of domoic acid, from Ohfuné, appeared in 1982 and presented a revision of the originally assigned structure.⁸ Since that time, three naturally occurring isomers of domoic acid have been prepared by total synthesis. In 2003, our group prepared isodomoic G and established its structure in a preliminary report of this work.^{9a} In 2005, Clayden completed a total synthesis of isodomoic acid C in an approach that allows construction of the pyrrolidine framework with the C-4 stereocenter installed, as seen in domoic acid and most naturally occurring isomers.^{9b} Most recently in 2009, Denmark established a general approach to both isodomoic acids G and H, wherein a stereodivergent alkenylsilane iodination allowed prepared of both isomers of the exocyclic alkene.^{9c} Additionally, several complex domoic acid analogues have been prepared in important advances from Baldwin.¹⁰

In addition to the intriguing and diverse biological activity of this family of natural products, we recognized that the various stereochemical orientations and positioning of sites of unsaturation of the C-4 substituents of members of the domoic acid family would provide an excellent platform for developing versatile synthetic entries to densely functionalized 1,3-dienes. In particular, selectively accessing both *E*- and *Z*-stereochemistries of the tetrasubstituted alkenes of isodomoic acids G and H poses a substantial challenge. To address these challenges in stereocontrolled synthesis of complex dienes, we set out to establish a common approach to isodomoic acids G and H.¹¹ The total syntheses of these two natural products are herein described.

Results and Discussion

Overview of Strategy

Considering the structural similarity of isodomoic acids G and H, we were attracted to the notion of developing a unified synthetic strategy that allows synthesis of both isomers from a set of common intermediates. Only the stereochemistry of the exocyclic tetrasubstituted alkene differs between these two natural products. In addressing this challenge, we anticipated that enone-alkyne alkylative cyclizations developed previously in our lab could be utilized to access both isomers simply by altering the sequence of substituent introduction.¹² The nickel-catalyzed cyclization of a tethered enone-alkyne substrate allows efficient construction of an exocyclic tetrasubstituted alkene, and simply swapping the identity of the R² and R³ substituents allows synthesis of both *E*- and *Z*-isomers of the tetrasubstituted alkene product (eq 1).

(1)

Significantly, this strategy allows kinetic control of alkene geometry to produce either stereoisomer without relying on thermodynamic preferences.

As depicted below, we anticipated that the *E*-stereochemistry of isodomoic acid G could be directly accessed by cyclization of substrate **6** with vinyl zirconium reagent **7** (Scheme 2). Oxazolidinone **6** could be prepared by N-butynylation of compound **8**, whereas zirconium species **7** should be easily derived from hydrozirconation of terminal alkyne **9**. The strategy to prepare isodomoic acid H would then involve a similar sequence, wherein the timing of methyl

and alkenyl substituent introduction would be reversed. Nickel-catalyzed cyclization of substrate **10** with dimethylzinc would afford the Z-stereochemistry of isodomoic acid H. The required enyne **10** could be accessed by Sonogashira coupling of terminal alkyne **11** with *E*-vinyl iodide **12**. Compound **11** should be readily accessed from compound **8** by N-propargylation, whereas vinyl iodide **12** should be available from zirconium species **7** utilized in the isodomoic acid G synthesis.

Routes to Cyclization Precursors

The desired strategy for synthesis of isodomoic acids G and H requires the synthesis of N-propargylated oxazolidinone intermediates (Scheme 3). The route originally employed in our prior syntheses of kainic acid, allokainic acid, and isodomoic acid G involved the conversion of D-serine methyl ester (**13**) to oxazolidinone **14**, followed by N-alkylation to **15**, and then ester reduction with NaBH₄ to afford alcohol **16**.¹³ Swern oxidation followed by Wittig olefination afforded unsaturated acyl oxazolidinone **17** for exploring nickel-catalyzed cyclizations. Our prior studies had demonstrated that unsaturated acyl oxazolidinones were far superior substrates than enoates in nickel-catalyzed reactions of this type.¹⁴ While this sequence was chemically efficient, as we noted in our communication of isodomoic acid G,^{9a} this route led to variable levels of epimerization of the stereocenter embedded within the oxazolidinone. Evaluating the enantiopurity of each intermediate during the sequence illustrated that oxazolidinone **14** was obtained in >99% ee, and that a slight erosion of enantiopurity occurred during N-alkylation to afford N-butynylated intermediate **15** in 91% ee. The major source of epimerization, however, was NaBH₄ reduction of this species to alcohol **16**.¹⁵ Depending on the rate of addition of NaBH₄ and internal temperature, this step proceeded with variable extents of epimerization, with ee's ranging from approximately 60–85%.

Given the sensitive nature of this early sequence, the route was modified so that initial NaBH₄ reduction of oxazolidinone **14** at –5 °C was followed by THP protection to afford **18** followed by N-butynylation and PPTS deprotection of the THP moiety to afford **16**. While adding two steps to the overall conversion of **13** to **17**, this sequence proceeded in good overall yield and reliably furnished unsaturated acyl oxazolidinone **17** in 90–95 % ee. A similar sequence involving N-propargylation of **18** instead of N-butynylation afforded cyclization substrate **20** via alcohol **19**.

Total Synthesis of Isodomoic Acid G

As described in our preliminary report,^{9a} the synthesis of isodomoic acid G requires the coupling of butynylated oxazolidinone **17** with vinyl zirconium species **23**. Reagent **23** was therefore obtained by an Evans alkylation of acyl oxazolidinone **21** with methyl iodide,¹⁶ followed by oxazolidinone reduction with LiBH₄ and alcohol protection as the TIPS (triisopropylsilyl) ether **22** (Scheme 4). Hydrozirconation¹⁷ of alkyne **22** in THF was directly followed by treatment with substrate **17** in the presence of 10 mol % Ni(COD)₂ and 20 mol % ZnCl₂ to afford pyrrolidine **24** in 74% isolated yield with complete control of the C2-C3 relative stereochemistry.¹⁸ 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.

Methanolysis of the acyl oxazolidinone linkage of **24** with MeOMgBr then afforded ester **25**. With compound **25** in hand, methanolysis of the remaining internal oxazolidinone with MeONa was accomplished (Scheme 4). This two-step procedure proceeded in higher yield than a one-step procedure with either reagent. Additionally, compound **25** was a useful structure for NMR characterization before rotamer-derived spectral complexities were introduced by installation of an acyclic carbamate. After *n*-Bu₄NF-mediated deprotection, the resulting diol **26** 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 (**5**) that displayed ^1H NMR spectral characteristics identical to the data provided in the original isolation report from Arakawa.¹¹

By repeating the entire sequence, starting from D-serine methylester and (S)-valine-derived **27**, we then prepared the 5'(S) isomer of isodomoic acid G (**28**) in essentially identical fashion (eq 2).

(2)

As observed in our earlier report, although the NMR spectra of the 5'(R) and 5'(S) synthetic samples **5** and **28** were extremely similar, the ^1H NMR spectrum of a mixed sample of the synthetic 5'(S) isomer **28** and the authentic natural product possessed subtle differences when compared with the pure natural product. A mixed sample of the 5'(R) isomer **5** 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 naturally occurring isodomoic acid G was confirmed to be that shown for synthetic **5** on the basis of comparing CD spectra of synthetic 5'(R)-**5** and the natural product.

Total Synthesis of Isodomoic Acid H

The total synthesis of isodomoic acid H requires that a highly functionalized conjugated enyne substrate undergoes Ni(0)-catalyzed cyclization with dimethylzinc. As noted above, the timing of installation of alkenyl and methyl groups must be reversed in comparison with the isodomoic acid G synthesis. Accomplishing this reversal simply requires that the previously utilized vinyl zirconium reagent **23** is converted to *E*-vinyl iodide **29** upon treatment with *N*-iodosuccinimide (Scheme 5). This sequence proceeds in 71% isolated yield from alkyne **22**. At this stage, Sonogashira coupling¹⁹ of vinyl iodide **29** with terminal alkyne **20** proceeds in 83% isolated yield to afford conjugated enyne **30**, which possesses all of the carbons of isodomoic acid H except the C-1' methyl group. Cyclization of enyne **30** proceeded cleanly upon exposure to dimethylzinc with 10 mol % $\text{Ni}(\text{COD})_2$ to afford product **31** in 77% isolated yield as a single isomer. Comparison of the NMR spectrum of compound **31**, which possesses the *Z*-exocyclic alkene, with compound **24**, which possesses the *E*-exocyclic alkene, illustrates that the tetrasubstituted alkene is installed with complete stereocontrol in both cases.

After assembly of the key pyrrolidine framework, the synthesis proceeded as described for isodomoic acid G. Methanolysis of the acyloxazolidinone, followed by internal methanolysis of the remaining oxazolidinone afforded ester **32** after desilylation of the TIPS ether. Dess-Martin oxidation followed by NaClO_2 oxidation and global hydrolysis afforded 5'(R)-isodomoic acid H (**4**), which was purified by ion exchange chromatography. As we only had access to naturally occurring isodomoic acid G, we were unable to secure natural isodomoic acid H for confirmation of C5' stereochemistry.

Summary and Conclusions

In summary, efficient approaches to isodomoic acids G and H have been developed, using a suite of metal-catalyzed processes to establish nearly all of the structural complexity of the targeted natural products. Zirconium, palladium, and nickel-based processes are key steps in the approach. Notably, a metallated reagent may be directly transferred during the nickel-catalyzed cyclization as illustrated in the isodomoic acid G synthesis, whereas an iodination / Sonogashira coupling sequence using the same metallated reagent installs this group before the nickel-catalyzed cyclization as illustrated in the isodomoic acid H synthesis. This altered timing sequence changes the stereochemistry of the tetrasubstituted alkene that is installed. In both syntheses, the *E*- or *Z*-tetrasubstituted alkene is selectively and predictably obtained depending on the order of substituent introduction. In combination with earlier published approaches to kainic acid and allokainic acid, the generality of nickel-catalyzed reactions to establish the stereochemistry of densely-functionalized pyrrolidines while positioning the site and stereochemistry of side chain unsaturation has been demonstrated. The combination of these syntheses provides a versatile synthetic strategy for many members of the kainic acid and domoic acid family of natural products.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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(-)- α -kainic acid (**1**)

(-)- α -allokainic acid (**2**)

(-)-domoic acid (**3**)

isodomoic acid H (**4**)

isodomoic acid G (**5**)

Scheme 1.
Kainoid Natural Products

Scheme 2.
Retrosynthetic Analysis.

Route A

Route B

Scheme 3. Preparation of Cyclization Precursors

^aConditions: (a) triphosgene, THF, reflux, 98%; (b) KHMDS, 1-bromo-2-butyne, THF, 0 °C to rt, 74%; (c) NaBH₄, ethanol, 0 °C to rt, 90%; (d) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -78 °C; then 4,4-dimethyl-3-[2-(triphenylphosphinio)acetyl]oxazolidin-2-one bromide, DMAP, -15 °C, 90% (two steps); (e) NaBH₄, ethanol, -5 °C, 90%; (f) dihydropyran, PPTS, CH₂Cl₂, 40 °C, 88%; (g) procedure b, 77%; (h) PPTS, ethanol, 55 °C, 87%; (i) KHMDS, propargyl bromide, THF, 0 °C to rt, 88%; (j) PPTS, ethanol, 55 °C, 90%; (k) procedure d, 90%.

Scheme 4. Synthesis of Isodomoic Acid G.^a

^aConditions: (a) NaHMDS, MeI, THF, -78 to -40 °C, 78% (dr > 98:2); (b) LiBH_4 , EtOH/ H_2O ; then TIPSCl, imid, DMAP, CH_2Cl_2 , 77% (2 steps); (c) **22**, Cp_2ZrHCl , THF, rt; then **17**, $\text{Ni}(\text{COD})_2$ (10 mol %), ZnCl_2 (20 mol %), THF, 0 °C, 74%; (d) MeOMgBr , MeOH, rt, 66%; (e) MeONa , MeOH, rt; then TBAF, THF, rt, 81% (two steps); (f) Dess Martin periodinane, CH_2Cl_2 , rt; then NaClO_2 , NaH_2PO_4 , 2-methyl-2-butene, *t*-BuOH, H_2O , rt; then NaOH, MeOH, H_2O , rt; ion-exchange chromatography, (38% from **26**).

Scheme 5. Synthesis of Isodomoic Acid H

^aConditions: (a) Cp_2ZrHCl , THF, rt; then *N*-iodosuccinimide, 71%; (b) $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, CuI , $i\text{Pr}_2\text{NH}$, THF, 0 °C, 83%; (c) $\text{Ni}(\text{COD})_2$, Me_2Zn , THF, 0 °C, 77%. (d) MeOMgBr , MeOH, rt, 70%; then MeONa , MeOH, rt; then TBAF, THF, rt, 75% (two steps); (e) Dess-Martin periodinane, CH_2Cl_2 , rt; then NaClO_2 , NaH_2PO_4 , 2-methyl-2-butene, *t*-BuOH, H_2O , rt; then NaOH, MeOH, H_2O , rt; ion-exchange chromatography, (21% from **32**).