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Total Syntheses of Isodomoic Acids G and H

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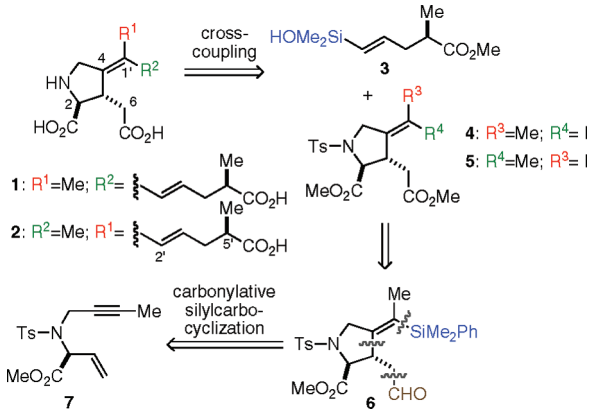
Isodomoic acids G (**1**) and H (**2**) were isolated in 1997 by Arakawa from red alga *Chondria armata*.[1] They belong to the family of kainoid amino acids, which includes kainic acid, domoic acid, and isodomoic acids, a series of structurally related natural products bearing a 3-carboxymethylproline moiety and a side chain on C(4). These compounds differ in the position and configuration of the double bond at C(4).[2] Kainoid amino acids have long been recognized as neuroexcitatory agents, and their high potency makes them extremely valuable as research tools in neuroscience as well as medicinal chemistry.[3] In fact, in 2000 the shortage of kainic acid threatened to hamper research projects in neurodegenerative diseases, and a call for new supplies for isolation or synthesis was issued.[4a] Even now, the price of kainic acid remains extremely high, and other kainoid derivatives are obtained in only minute quantities from natural sources.[4b] In response, many syntheses of kainic acid have been reported, whereas those of other kainoids have only been sparsely documented.[2] Notably, however, Montgomery recently disclosed an elegant synthesis of isodomoic acid G that also unambiguously established its absolute configuration.[5]

Our interest in developing a new synthetic route to these natural products stems from the desire (1) to showcase the synthetic utility of the sequential silylcarbocyclization/silicon-based cross-coupling technology recently developed in these laboratories[6] and (2) to potentially provide access to various analogues by a modular approach. We describe herein efficient, stereoselective total syntheses of **1** and **2** via a common intermediate.[7]

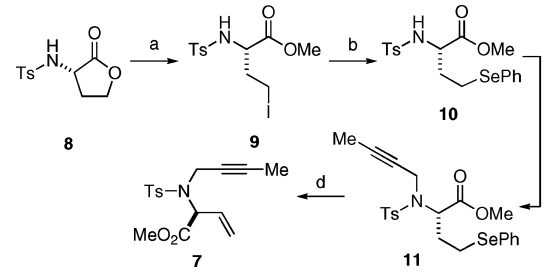
Scheme 1



An obvious disconnection of **1** and **2** is the division into the substituted proline core and side-chain fragments at C(1′)−C(2′) (Scheme 1). The construction of the conjugated diene would involve the silicon-based cross-coupling reaction of silanol **3**[8] with iodide **4** or **5**, both of which would be derived from aldehyde **6** via a stereodivergent iododesilylation. The proline moiety of **6** would be constructed via the carbonylative silylcarbocyclization of enyne **7**.[9,10]

The synthesis began by the opening of known amino lactone **8**,[11] derived from L-methionine, using TMSI followed by an in situ esterification with $SOCl_2$ and MeOH to afford iodinated amino ester **9** in 91% yield (Scheme 2). The conversion of iodide **9** to selenide **10** could be effected at room temperature with sodium phenylselenide in 88% yield, whereas the direct opening of **8** with this reagent required elevated temperatures that delivered **10** in racemic form.[12] The N-alkynylation of **10** was carried out under Mitsunobu conditions with 2-butyn-1-ol at ∼0 °C, to produce **11** in 93% yield. Oxidative elimination of the selenide moiety was accomplished by the treatment of **11** with H_2O_2 at room temperature.[13] As a result, the sensitive *N*-methylpropargyl L-vinylglycine ester **7** was isolated in a satisfying 95% yield.

Scheme 2[a]



[a] Conditions: (a) 1. TMSI, 2. $SOCl_2$, MeOH (91%); (b) $NaBH_4$, Ph_2Se_2 (88%); (c) 2-butyn-1-ol, PPh_3, DEAD (93%); (d) 30% H_2O_2 (95%).

The key carbonylative silylcarbocyclization of **7** was effected using $Rh(acac)(CO)_2$ at 120 °C under CO (500 psi), to afford aldehyde **6** in 77% yield as an inseparable mixture of 2,3-*trans*- and 2,3-*cis*-diastereomers in an 8:1 ratio (Scheme 3). To proceed forward with a pure trans isomer, **6** was reduced by $NaBH_4$ to afford alcohol *trans*-**12** which could be obtained free of the cis isomer in 85% yield. The conversion of **12** to a methyl ester through a CrO_3-catalyzed oxidation[14] and a subsequent methylation with diazomethane provided ester **13** in 81% yield. The iododesilylation of **13** using ICl proceeded smoothly in 1 h at room temperature with a complete *inversion* of double bond configuration to afford *Z*-alkenyl iodide **5** in 86% yield. This stereochemical outcome can be rationalized by the anchimeric participation of the C(7) carbonyl group.[15] As **13** reacts with ICl, the iodonium ion in intermediate **A** can be captured by the C(7) carbonyl group, to form oxocarbenium ion **B**. A simple bond rotation orients the silyl group antiperiplanar to the oxocarbenium C−O bond (conformer **B′**), and attack of chloride on the silicon atom regenerates the double bond *invertively* to furnish iodide **5**.

Optimization experiments for the key cross-coupling of **5** revealed that the hydration level of TBAF was critical to success,

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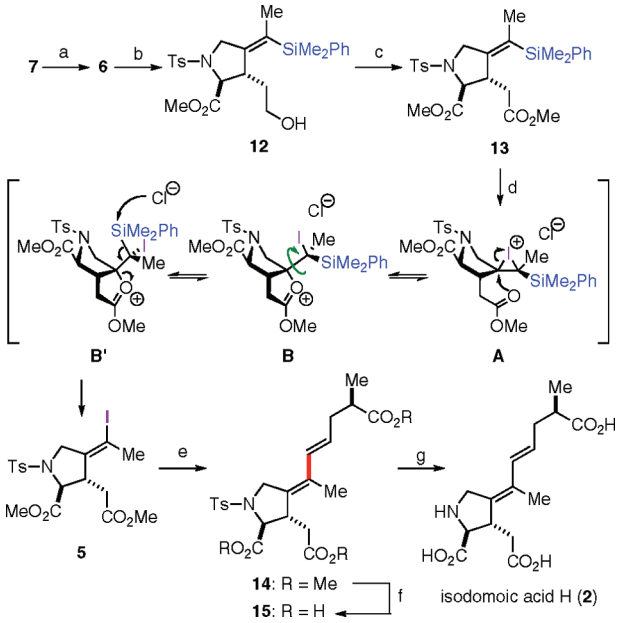
and TBAF·8H_2O gave the optimal results. Gratifyingly, when **3** and **5** were combined in the presence of $Pd_2(dba)_3$·$CHCl_3$ and TBAF·8H_2O, full conversion was observed within 1 h, and the fully protected isodomoic acid H (**14**) was isolated in 92% yield. The final deprotection was accomplished by the quantitative saponification of the three methyl esters using LiOH,[16] followed by the detosylation of the crude triacid **15** using sodium amalgam,[17] to thus afford 59 mg (56%) of isodomoic acid H (**2**) whose spectroscopic properties matched those of the natural material.[1]

Scheme 3[a]

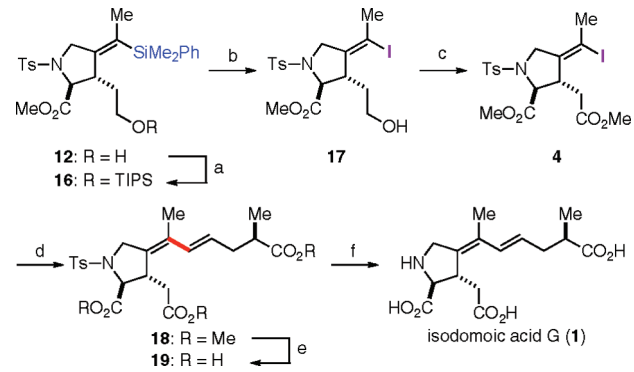


[a] Conditions: (a) $HSiMe_2Ph$, $Rh(acac)(CO)_2$ (5 mol %), CO (500 psi), 120 °C (77%, *trans*/*cis*, 8:1); (b) $NaBH_4$ (85%); (c) 1. CrO_3, H_5IO_6, 2. CH_2N_2 (81%); (d) ICl (86%); (e) **3**, $Pd_2(dba)_3$·$CHCl_3$ (5 mol %), TBAF·8H_2O (92%); (f) LiOH (quant.); (g) 20% Na/Hg, NaH_2PO_4 (56%).

As discussed above, the invertive iododesilylation of **13** resulted from the anchimeric assistance of a proximal participating group. Conversely, by employing a substrate bearing a nonparticipating functional group at C(7), the iodination reaction would become *retentive*, thus enabling the synthesis of **1**. To this end, **12** was protected as a triisopropylsilyl ether (**16**) (Scheme 4). Gratifyingly, exposure of **16** to ICl under previously developed conditions followed by an in situ deprotection using aqueous HF cleanly produced *E*-alkenyl iodide **17** in 73% yield. The synthesis of **1** was completed through the same sequence of oxidation (79%), cross-coupling (90%), and deprotection (60% for two steps) under conditions developed earlier to furnish 93 mg of **1**, whose spectroscopic properties matched those of the natural and previously synthesized materials.[1,5]

In conclusion, the total syntheses of isodomoic acids G (**1**) and H (**2**) have been accomplished expediently through a unified strategy. The rhodium-catalyzed carbonylative silylcarbocyclization of **7** afforded the densely substituted pyrrolidine core. Importantly, the double bond configuration of **4** and **5** was controlled by judicious selection of the C(6) substituent. The fluoride-promoted cross-coupling uniting **4** and **5** with side-chain silanol **3** could be achieved under mild conditions by modulating the hydration level of the TBAF. This exercise serves to illustrate the flexibility of the silicon-based cross-coupling reaction as enabling strategies in the synthesis of sensitive natural products. Further illustrations will be reported in due course.

Scheme 4[a]



[a] Conditions: (a) TIPSCl, imidazole (91%); (b) 1. ICl, 2. HF (73%); (c) 1. CrO_3, H_5IO_6, 2. CH_2N_2 (79%); (d) **3**, $Pd_2(dba)_3$·$CHCl_3$ (5 mol %), TBAF·8H_2O (90%); (e) LiOH (quant.); (f) 20% Na/Hg, NaH_2PO_4 (60%).

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Supporting Information Available: Full experimental procedures and characterization data for intermediates and synthetic natural product described. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Because the configuration of isodomoic acid H has not been unambiguously determined and an authentic sample was no longer available, (5′*R*)-isodomoic acid H was synthesized by analogy to the configuration of isodomoic G as determined by Montgomery and co-workers.[5]
(8) For the preparation of **3**, see the Supporting Information.
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(10) The original cross-coupling reaction designed to implement this strategic disconnection involved a silicon-based donor related to **6** and a 5-iodopentenoate acceptor related to **3**. The failure to effect this coupling led to a change in the roles of the donor and the acceptor and will be described in detail in a full account of this work.
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