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Stereocontrolled Total Syntheses of Isodomoic Acids G and H via a Unified Strategy

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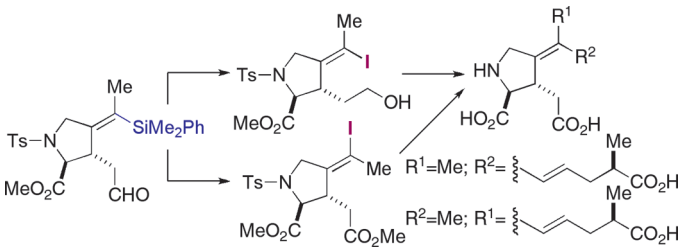

Marine neuroexcitatory compounds isodomoic acids G and H were efficiently synthesized from a common intermediate using a silicon-based cross-coupling reaction. Dividing each target compound into the core fragment and the side-chain fragment enabled the synthesis to be convergent. The *trans*-2,3-disubstituted pyrrolidine core fragment was accessed through a diastereoselective rhodium-catalyzed carbonylative silylcarbocyclization reaction of a vinylglycine-derived 1,6-enyne. A stereochemically divergent desilylative iodination reaction was developed to convert the cyclization product to both *E*- and *Z*-alkenyl iodides, which would eventually lead to isodomoic acid G and isodomoic acid H, respectively. The late-stage alkenyl−alkenyl silicon-based cross-coupling reaction uniting the core alkenyl iodides and the side-chain alkenylsilanol was achieved under mild conditions. Finally, two mild deprotections afforded the target molecules.

Introduction

Isodomoic acids belong to a class of nonproteinogenic amino acids known as kainoid amino acids,[1] a series of structurally related natural products bearing a 3-carboxymethylproline moiety. This family of natural products includes kainic acid, domoic acid, isodomoic acids, domoilactones, and acromelic acids (Figure 1). The first two members of this family isolated were kainic acid and allokainic acid from a Japanese alga *Digenea simplex* in 1953 by Murakami and co-workers.[2] Another important member of this family, domoic acid, was first isolated in 1958 from a Japanese red alga *Chondria armata* by Daigo and co-workers.[3] Domoic acid is a higher analogue of kainic acid, bearing a hexadienoic acid side-chain. However, not until much later were the congeners of domoic acids discovered. In the late 1980s, Nomoto and co-workers reported the isolation of isodomoic acids A, B, C,[4] and D[5] and domoilactones[6] from the same organism. Around the same time period, Wright and co-workers isolated domoic acid,[7] the C(5′)-epimer of domoic acid,[8] as well as isodomoic acids D−F,[9] from cultivated mussels *Mytilus edulis*, harvested in Prince Edward Island, Canada, during a shellfish poisoning outbreak that took place in 1989 in eastern Canada. These compounds were presumably produced by alga *Nitzschia pungens* and were accumulated in the

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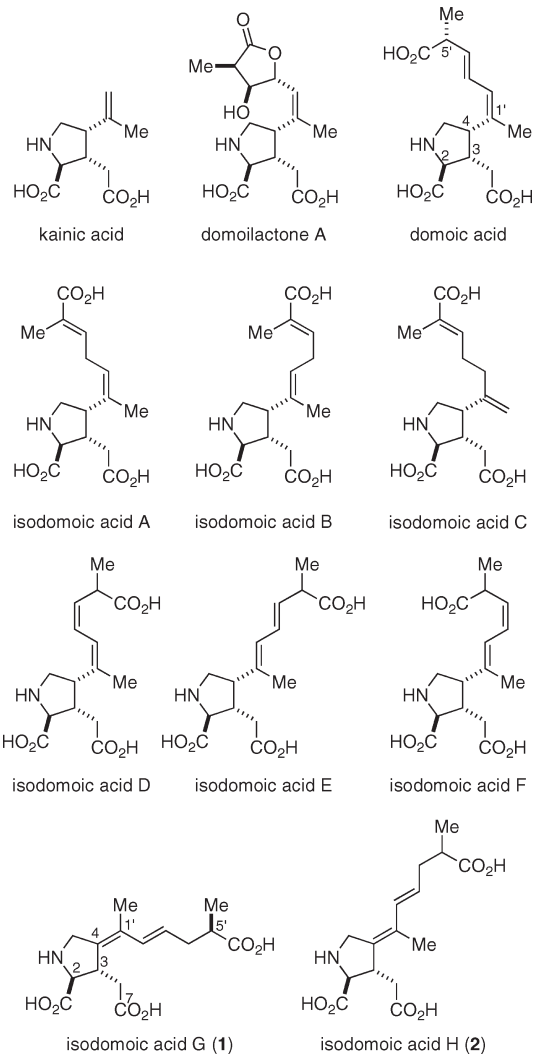

FIGURE 1. Kainoid amino acids.

tissue of mussels.[10] More recently, Arakawa and co-workers isolated isodomoic acids G (**1**) and H (**2**) from *Chondria armata*.[11] The authors did not, however, establish their absolute configuration. This determination was achieved unambiguously for isodomoic acid G by Montgomery and co-workers through the total synthesis of both C(5′) epimers, as well as NMR and CD analyses of both synthetic and authentic compounds.[12] Structurally, isodomoic acids differ from domoic acid in the position and the configuration of side-chain double bonds, and hence are constitutional isomers of domoic acid.

Kainoid amino acids have long been recognized as neuroexcitatory agents.[13] In general, they act as mimics of glutamic acid, a known neurotransmitter for the mammalian central nervous system, targeting ionotropic glutamate receptors. This binding causes neuronal depolarization and ultimately leads to neuronal death.[14] Interestingly, kainoid-containing algae such as *Chondria armata* and *Digenea simplex*, from which domoic acid analogues and kainic acid were isolated, are traditionally known in Japan as vermifuges.[4] In addition, domoic acid, as well as isodomoic acids A−C, have been shown to exhibit a very strong insecticidal property against American cockroaches *Periplaneta americana*.[4,5,15] Because of their interesting bioactivities and high potency, kainic amino acids are highly valuable for neuroscience and medicinal chemistry, especially since many kainoid derivatives are obtained in only minute quantities from natural sources. Therefore, a reliable supply of these natural products is highly pertinent. In fact, in 2000, the shortage of kainic acid threatened to hamper research projects in neurodegenerative diseases, and an urgent call for new supplies for isolation or synthesis was issued. Even now, the price of kainic acid remains extremely high.[16] In response, many syntheses of kainoid amino acids have been reported. For example, numerous total syntheses of kainic acid, the parent compound of this class, have been described, in enantiomerically enriched form,[1a] since the first by Oppolzer and co-workers in 1982.[17] For other analogues, on the other hand, synthetic studies are rare. To date, only one for domoic acid and isodomoic acid C, reported by Ohfune,[18] and Clayden,[19] respectively, are on record. Very recently, two syntheses of isodomoic acids G (**1**) and H (**2**) via two different approaches were disclosed independently from these laboratories[20] and from Montgomery and co-workers.[12]

We decided to embark on the total synthesis of isodomoic acid G (**1**) because this endeavor would showcase the sequential silylcarbocyclization/silicon-based cross-coupling technology that has been recently developed.[21−23] Silicon-based

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cross-coupling[24] is advantageous in the construction of C−C bonds for a number of reasons. The stability organosilanes gives them high functional group compatibility, and the mild reaction conditions employed in silicon-based cross-coupling reactions allows for their usage in a late stage of a total synthesis. When combined, these features not only allow for a highly convergent synthetic sequence but also obviate repetitive functional group manipulations. Additionally, the wide range of silicon-containing donors available makes it possible to prepare unnatural analogues of isodomoic acids for future studies. At the outset, isodomoic acid G (**1**) was targeted. Herein, we describe how this initial goal was achieved and the unexpected discovery that opened the possibility to synthesize isodomoic acid H (**2**), as well, via a common intermediate.

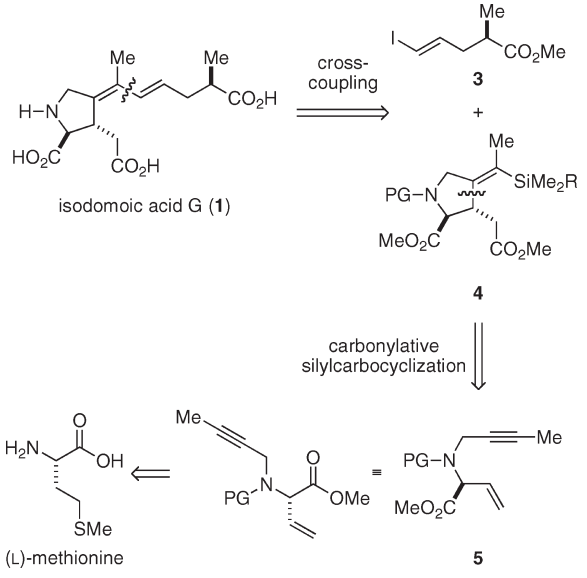
Results

1. Retrosynthetic Analysis. Isodomoic acid G (**1**) can be logically divided into two fragments: the substituted proline core fragment and the conjugated hexadienoic acid side-chain (Scheme 1). The conjugated diene on the side-chain provides a convenient point of disconnection. This conjugated diene could be formed by a silicon-based alkenyl−alkenyl cross-coupling reaction. The viability of this step is based on the successful applications of silicon-based cross-coupling on congested systems to prepare highly substituted olefins with a defined configuration.[21,25] The core fragment, featuring a 3-carboxymethyl-4-(*E*)-alkylidenepyrrolidine, closely resembles the structure generated from the silylcarbocyclization reaction of 1,6-enynes. Therefore, we envision that the silicon-containing donor will reside on the core fragment **4**, and this intermediate could be conveniently obtained by the silylcarbocyclization of substituted L-vinylglycine **5** with a suitable hydrosilane. The side-chain iodide **3** could be prepared in a straightforward manner using Evans' auxiliary-based alkylation from a chiral acyloxazolidinone[26] followed by the introduction of iodine. The formation of the vinyl group of **5** could be achieved by a simple oxidative elimination of a selenide or a sulfide. Finally, the synthesis would start from a chiral pool starting material, L-methionine.

As we embarked on the total synthesis of isodomoic acid G (**1**) according to the above retrosynthetic plan, several challenges were envisioned. First, vinylglycine derivatives are known to be both acid and base sensitive because, under these conditions, the vinyl double bond can easily isomerize into conjugation with the carbonyl group. Therefore, conditions used to prepare **5** have to be neutral and mild. Second, the application of carbonylative silylcarbocyclization to generate compounds as densely functionalized as **4** is unprecedented. The specific reaction conditions, such as catalyst, ligand, solvent, pressure, and temperature, required to achieve this transformation must be established. Also, the influence of the stereogenic center of **5** on the diastereoselectivity of the cyclization was unknown. Third, unlike silicon-based alkenyl−aryl and aryl−aryl cross-coupling, alkenyl−alkenyl cross-coupling is not as well developed. The cross-coupling of a highly congested, tetrasubstituted silanol or its equivalent is expected to be challenging, and any factor that might lead to double-bond isomerization must be avoided.

2. Preparation of Substituted Vinylglycine. 2.1. *N*-PMB Series. At the inception of the study, the PMB (*p*-methoxybenzyl) group was chosen as the nitrogen protecting group because of the successful silylcarbocyclization of benzylallyl(2-propargyl)-amine with benzyldimethylsilane.[21] In addition, unlike a benzyl group, which is normally cleaved via hydrogenolysis, a PMB group could be removed by the treatment using oxidizing agents such as 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) and ceric ammonium nitrate (CAN). Thus, L-methionine was first converted to methionine methyl ester hydrochloride (**6**) following literature conditions (Scheme 2).[27] The amino group of **6** was subsequently protected using *p*-anisaldehyde and sodium triacetoxyborohydride, affording *N*-PMB-protected methionine (**7**).[28] The protecting group was installed via reductive amination because of the discovery that the alkylation of the amino group in the presence of the methyl sulfide resulted in modest yield of the desired product, likely due to the competing *S*-alkylation and the

SCHEME 1



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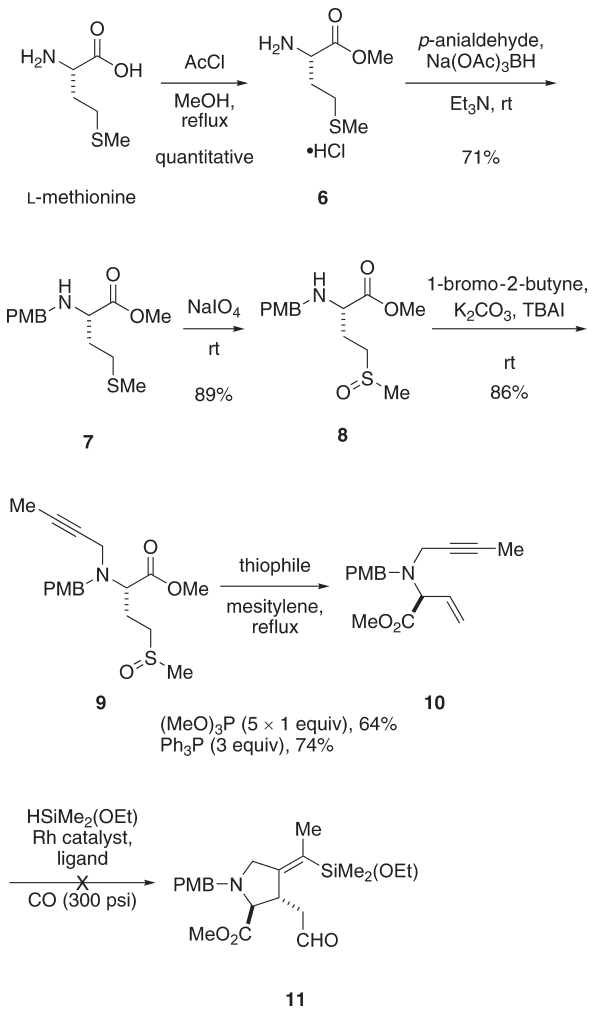
subsequent decomposition. Also for this reason, **7** was first oxidized to sulfoxide **8** using sodium periodate[29] before the alkynyl group was introduced. Then, the *N*-alkynylation of the **8** was achieved using 1-bromo-2-butyne, resulting in **9** in a satisfying 86% yield.[30]

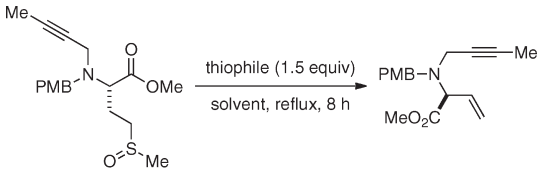
SCHEME 2



The pyrolysis of **9** was somewhat challenging. Two types of procedures of the pyrolysis of methionine sulfoxides can be found: (1) vacuum pyrolysis pioneered by Rapoport and co-workers[29a,b] and (2) prolonged heating in high-boiling solvents (e.g., refluxing xylene).[29c–e] However, most of the yields are modest, and unfortunately, no promising results were obtained when **9** was pyrolyzed following any of these procedures. This failure might stem from the lack of a thiophile in the reaction mixture to scavenge methylsulfenic acid that can react with the product, especially under elevated temperatures. Thus, in the initial experiment, a solution of **9** and 1 equiv of trimethyl phosphite were stirred in refluxing mesitylene to offer an approximately 50% conversion after 5 h, but decomposition became apparent after this point (Table 1, entry 1). This result suggested that under the reaction conditions, trimethyl phosphite was consumed through more than one pathway. Therefore, when the reaction mixture was replenished with 1 equiv of trimethyl phosphite every 2 h, 64% of **10** was isolated after 10 h of reflux (Scheme 2). These initial experimentations revealed that the presence of a thiophile such as trimethyl phosphite is critical to ensure a smooth pyrolysis, but a constant replenishment of the thiophile is hardly a practical solution. Therefore, to identify the optimal thiophile, various phosphines and phosphites were surveyed.

Among the thiophiles surveyed, triphenyl phosphite and tricyclohexylphosphine were not able to promote the pyrolysis of **9** (entries 2 and 3), whereas very little **10** was produced when tri-*n*-butylphosphine was employed (entry 4). The behavior of triphenylphosphine was markedly different, leading to an approximately 70% conversion after 8 h in refluxing mesitylene (entry 5), and more importantly, no replenishment of thiophile was necessary. To accelerate the pyrolysis, the reactions were carried out higher temperatures, but extensive decomposition was observed both when cymene (bp 177 °C) and *o*-dichlorobenzene (bp 188 °C) were used as solvent (entries 6 and 7). Finally, the effects of triphenylphosphine loading were examined, and the rate of

TABLE 1. Optimization of the Pyrolysis of 9[a]



					10/**9**[b]		
entry	thiophile	equiv	solvent	temp, °C	4 h	8 h	remark
1	$(MeO)_3P$	1.0	mesitylene	165	1/1		
2	$(PhO)_3P$	1.5	mesitylene	165			no **10** observed
3	Cy_3P	1.5	mesitylene	165			no **10** observed
4	Bu_3P	1.5	mesitylene	165	1/8	1/16	
5	Ph_3P	1.5	mesitylene	165	1/1	1/0.5	
6	Ph_3P	1.5	cymene	177			decomposition
7	Ph_3P	1.5	*o*-dichlorobenzene	188			complex mixture
8	Ph_3P	3.0	mesitylene	165	1/1.5	1/0.7	
9	Ph_3P	5.0	mesitylene	165	1/1.3	1/0.5	

[a]Reactions were carried out by refluxing a 0.2 M solution of **9** in the solvent indicated. [b]Estimated by no-D ^{1}H NMR integration ratio.

conversion was found to be similar regardless of the loading (entries 5, 8, and 9). For preparative purposes, however, a decision was made to employ 3.0 equiv of triphenylphosphine to ensure that it would not be depleted during the reaction period. Gratifyingly, on a 3.00 mmol scale, with 3 equiv of triphenylphosphine, and after 25 h of heating at reflux, **10** was isolated in 74% yield (Scheme 2).

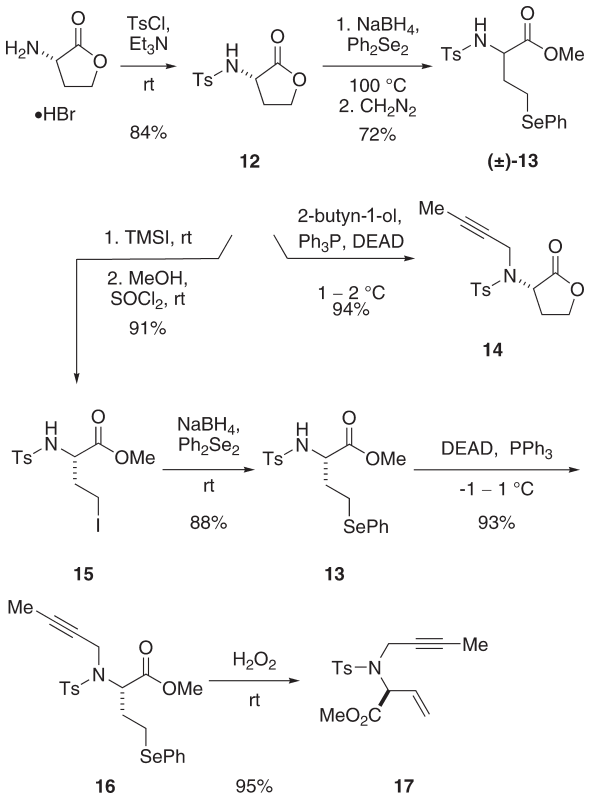
With **10** in hand, the carbonylative silylcarbocyclization reaction with ethoxydimethylsilane was attempted. To our disappointment, even after an extensive survey of conditions, desired product **11** was never observed. In all cases, complex mixtures were obtained, and ^{1}H NMR analysis of reaction mixtures revealed that very little CO insertion had taken place.

2.2. *N*-Tosyl Series. The failure of carbonylative silylcarbocyclization prompted the search for a different protecting group for nitrogen. Because the *N*-tosyl group is susceptible to nucleophilic attack by triphenylphosphine under the aforementioned pyrolysis conditions, the methyl sulfide moiety of L-methionine needed to be replaced with a leaving group capable of elimination under milder conditions. Thus, L-methionine was converted to L-homoserine lactone hydrobromide following the procedure developed by Angle and coworkers.[31] Subsequent protection afforded enantiomerically pure tosylamide **12** as determined by CSP SFC (chiral stationary phase supercritical fluid chromatography) analysis.[32] Unfortunately, direct selenylation of **12** following literature conditions gave *racemic* selenide **13** (Scheme 3).[33]

Clearly, the selenide functionality had to be introduced under milder conditions using a ring-opened intermediate. The initial attempts to open lactone by saponification **12** were unsuccessful. To avoid any complication caused by the acidity of the sulfonamide proton, the *N*-alkynyl group was introduced at this stage by a Mitsunobu alkylation.[34]

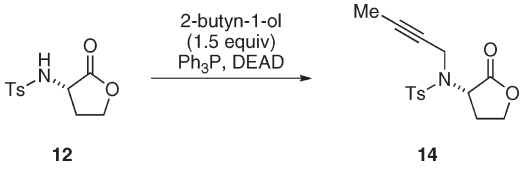
Accordingly, a solution of enantiomerically pure **12**, 1.5 equiv of 2-butyn-1-ol, and 1.5 equiv of triphenylphosphine was treated with 1.5 equiv of diethyl azodicarboxylate (DEAD) dropwise at rt to afford the alkynylated product **14** in 99% yield but as a *racemate* (Table 2, entry 1). However, when the loadings of triphenylphosphine and DEAD were both decreased to 0.95 equiv, the extent of racemization was attenuated (entry 2), indicating that at room temperature, the racemization of **14** and the alkylation of **12** were competitive. By maintaining the internal temperature between 2 and 3 °C, using 1.0 equiv of DEAD while keeping the loadings of **12**, triphenylphosphine, and 2-butyn-1-ol the same as in entry 1, no racemization was detected, but approximately 20% of **12** remained (entry 3). After the addition

SCHEME 3



of another 0.5 equiv of DEAD, although the conversion was completed, the enantiomeric ratio of **14** deteriorated somewhat to 95.4/4.6 (entry 4). To balance the trade-off between conversion and racemization, the reaction was carried out at 1−2 °C using only a slight excess (1.05 equiv) of triphenylphosphine and DEAD. As a result, **14** was isolated in a satisfying 94% yield virtually enantiomerically pure (entry 5).

TABLE 2. Optimization of the Alkynylation of 14[a]



entry	Ph_3P, equiv	DEAD, equiv	temp, °C	conv, %[b]	er of **14**[c]
1	1.50	1.50	rt	100	50.6/49.4
2	0.95	0.95	rt	83	89.3/10.7
3	1.50	1.00	2−3	80	100.0/0.0
4	1.50	1.50	2−3	100	95.4/4.6
5	1.05	1.05	1−2	90	99.4/0.6

[a]Reactions were carried out on a 2.0 mmol scale. A solution of **14**, 2-butyn-1-ol (1.5 equiv), and Ph_3P in CH_2Cl_2 at the indicated temperature was treated with DEAD dropwise at a rate of 0.02 mL/min. [b]Estimated on the basis of ^{1}H NMR integration of **12** and **14**. [c]Determined by CSP SFC analysis using a Daicel Chiralpak AD column.

The ring-opening of **14** was again problematic. Lithium hydroxide led to nearly complete racemization of both **14** and the ring-opened product. Under acidic conditions, the reaction was complicated by the halogenation of the triple bond of the alkynyl group.

(29) (a) Afzali-Ardakani, A.; Rapoport, H. *J. Org. Chem.* **1980**, *45*, 4817–4820. (b) Carrasco, M.; Jones, R. J.; Kamel, S.; Rapoport, H.; Truong, T. *Organic Syntheses*; Wiley: New York, 1998; Vol. 9, pp 63−66. (c) Krebs, A.; Ludwig, V.; Pfizer, J.; Dürner, G.; Göbel, M. W. *Chem.—Eur. J.* **2004**, *10*, 544–553. (d) Kitamura, T.; Sato, Y.; Mori, M. *Tetrahedron* **2004**, *60*, 9649–9657. (e) Bartley, D. B.; Coward, J. K. *J. Org. Chem.* **2005**, *70*, 6757–6774.

(30) (a) Günter, M.; Gais, H.-J. *J. Org. Chem.* **2003**, *68*, 8037–8041. (b) Brummond, K. M.; Mitasev, B. *Org. Lett.* **2004**, *6*, 2245–2248.

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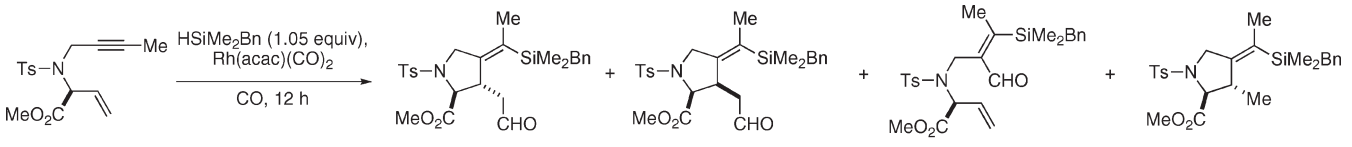
(34) (a) Hoffman, T.; Waibel, R.; Gmeiner, P. *J. Org. Chem.* **2003**, *68*, 62–69. (b) Li, L.-S.; Rader, C.; Matsushita, M.; Das, S.; Barbas, C. F., III; Lerner, R. A.; Sinha, S. *J. Med. Chem.* **2004**, *47*, 5630–5640. (c) Vallee, E.; Loemba, F.; Etheve-Quelquejeu, M.; Valéry, J.-M. *Tetrahedron Lett.* **2006**, *47*, 2191–2195.

TABLE 3. Optimization of the Carbonylative Silylcarbocyclization of 17[a]



17 *trans*-**18** *cis*-**18** **19** **20**

entry	Rh loading, mol %	solvent	temp, °C	pressure, psi	*trans*-**18**/*cis*-**18**/**19**/**20**[b]	remark
1	5	toluene	70	150	3/1/0.2/0.1	
2	5	toluene	70	200	3/1/0.6/0.3	
3	5	toluene	70	300	3/1/0/0	complex mixture
4	5	toluene	70	500	3/1/0/0	complex, a trace of **18** formed
5	5	toluene	70	700	3/1/0/0	complex, a trace of **18** formed
6	10	toluene	90	300	5/1/0.5/0.1	
7	10	toluene	90	500	5/1/0.6/0.3	
8	10	toluene	90	700	5/1/0.8/0.2	
9	5	toluene	120	200	5/1/0/1	
10	5	toluene	120	300	5/1/0/0.5	
11	5	toluene	120	500	5/1/0/0.3	
12	5	toluene	120	700	5/1/0/0.3	
13	5	toluene	150	150	5/1/0/1.6	some decomposition seen
14	5	toluene	150	200	5/1/0/1.4	some decomposition seen
15	5	toluene	150	300	4/1/0/1	some decomposition seen
16	5	THF	120	300	5/1/0/0.7	
17	5	*i*-PrCO$_2$Me	120	300		complex, some **20** observed
18	5	MeCN	120	300	16/1/0/0	complex, **17**/**18** = 0.6/1

[a]The reactions were carried out on a 0.50 mmol scale, under conditions described in each entry, in glass tubes that were placed in a six-well stainless steel autoclave. [b]Determined by ^{1}H NMR integration.

These setbacks prompted a return to the previous synthetic plan, in which the lactone opening of **12** *precedes* the *N*-alkynylation, but the lactone opening would have to take place under acidic conditions. Although the opening of homoserine lactones using strong Brønsted acids, including hydrochloric acid, hydrobromic acid, and hydroiodic acid, is known,[35,36] harsh conditions are often required under which a partial racemization of the product has been documented.[36a,c] It was therefore decided to investigate the ring-opening of **12** using a strong Lewis acid,[37] even though this method had only been applied to simpler γ-lactones. Gratifyingly, when **12** was treated with TMSI, the lactone was opened smoothly. The resulting carboxylic acid was esterified in situ in the presence of thionyl chloride and methanol to afford iodinated amino ester **15**, enantiomerically pure in 91% yield. As expected, the selenylation of **15** proceeded rapidly at room temperature to give an 88% yield of **13** without loss of enantiomeric purity as determined by CSP SFC analysis (Scheme 3). The *N*-alkynylation of **13** was carried out under conditions similar to those used with **12**. This reaction could be executed on a 50 mmol scale to afford a 93% yield of enantiomerically pure **16**. To gain access to the enyne substrate for the carbonylative silylcarbocyclization reaction, the oxidative elimination of the selenide was accomplished simply by stirring **16** in the presence of 30% aq H_2O_2 at room temperature. As a result, *N*-alkynyl vinylglycine ester **17** was isolated in 95% yield. Remarkably, the reaction conditions are the mildest and one of the highest yielding compared to all the conditions for the preparation of vinylglycine derivatives via selenoxide elimination.[35,38] As stated above, the side-chain double bond of vinylglycine derivatives easily isomerizes into conjugation with the carbonyl group under acidic or basic conditions, and not unexpectedly, **17** was found to be quite sensitive. As such, extreme care was taken during purification. A silica gel column was cooled by a coil of recirculating, ice-cold water and the eluent was kept in an ice bath. Only a trace of the isomerization product was detected with this protocol. When the flash chromatography was done without cooling, as much as 10% of the conjugated isomer of **17** had been observed.

3. Studies of Carbonylative Silylcarbocyclization. Investigation of the carbonylative silylcarbocyclization of **17** employed benzyldimethylsilane because an alkenylbenzylsilane serves effectively as a masked alkenylsilanol.[21,39] Three rhodium complexes known to catalyze carbonylative silylcarbocyclization, Rh(acac)(CO)$_2$, [Rh(COD)$_2$]BF$_4$, and Rh$_4$(CO)$_{12}$, were surveyed to identify the most active catalyst.[22] Heating a solution of Rh(acac)(CO)$_2$, **17**, and benzyldimethylsilane in toluene at 90 °C under 300 psi of CO for 12 h led to the clean formation of *trans*-**18** along with *cis*-**18**, **19**, and **20**. However, the use of

(35) (a) Pellicciari, R.; Natalini, B.; Marinozzi, M. *Synth. Commun.* **1988**, *18*, 1715–1721. (b) Bartley, D. M.; Coward, J. K. *J. Org. Chem.* **2005**, *70*, 6757–6774. (c) Feng, Y.; Coward, J. K. *J. Med. Chem.* **2006**, *49*, 770–788.

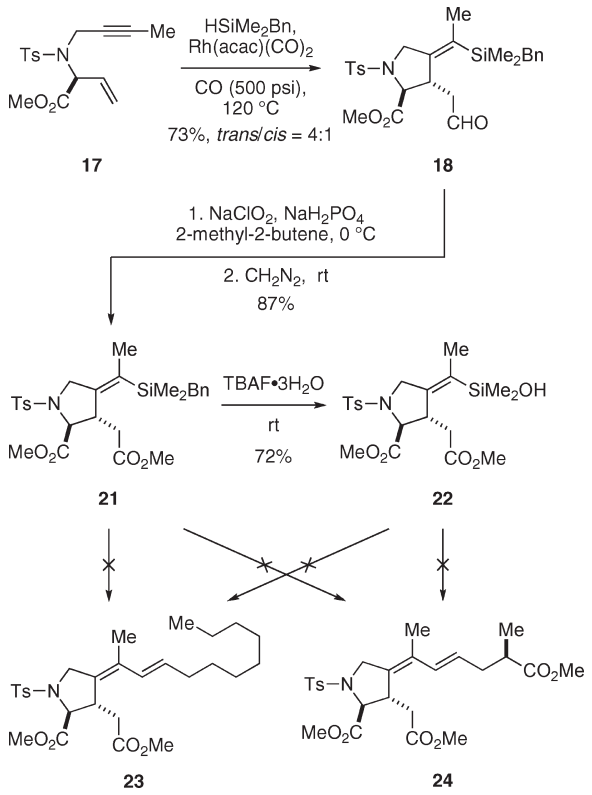
(36) (a) Bajgrowicz, J. A.; El Hallaoui, A.; Jacquier, R.; Pigière, C.; Viallefont, P. *Tetrahedron Lett.* **1984**, *25*, 2231–2234. (b) Baldwin, J. E.; North, M.; Flinn, A. *Tetrahedron* **1988**, *44*, 637–642. (c) Koch, T.; Buchardt, O. *Synthesis* **1993**, 1065–1067. (d) Wang, M.-C.; Zhang, Q.-J.; Zhao, W.-X.; Wang, X.-D.; Ding, X.; Jing, T.-T.; Song, M.-P. *J. Org. Chem.* **2008**, *73*, 168–176.

(37) (a) Kricheldorf, H. R. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 689–690. (b) Kolb, M.; Barth, J. *Synth. Commun.* **1981**, *11*, 763–767. (c) Schmidt, A. H.; Russ, M. *Chem. Ber.* **1981**, *114*, 1099–1110. (d) Larchevêque, M.; Henrot, S. *Tetrahedron Lett.* **1987**, *28*, 1781–1782. (e) Labrouillère, M.; Le Roux, C.; Ousaid, A.; Gaspard-Iloughmane, H.; Dubac, J. *Bull. Soc. Chim. Fr.* **1995**, *32*, 511–530.

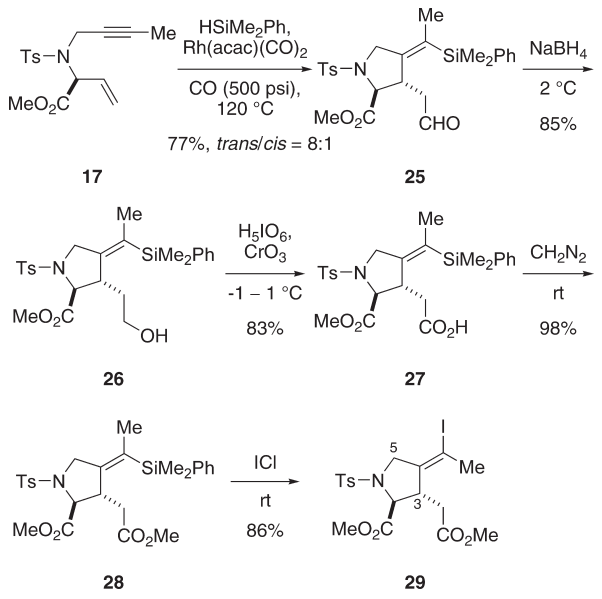
(38) (a) Barton, D. H. R.; Chrich, D.; Hervé, Y.; Potier, P.; Thierry, J. *Tetrahedron* **1985**, *41*, 4347–4357. (b) Pedersen, M. L.; Berkowitz, D. B. *J. Org. Chem.* **1993**, *58*, 6966–6975. (c) Itaya, T.; Shimizu, S.; Nakagawa, S.; Morisue, M. *Chem. Pharm. Bull.* **1994**, *42*, 1927–1930. (d) Berkowitz, D. B.; Smith, M. K. *Synthesis* **1996**, 39–41. (e) Siebum, A. H. G.; Woo, W. S.; Raap, J.; Lugtenburg, J. *Eur. J. Org. Chem.* **2004**, 2905–2913.

(39) (a) Trost, B. M.; Machacek, M. R.; Ball, Z. T. *Org. Lett.* **2003**, *5*, 1895–1898. (b) Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2005**, *127*, 17644–17655. (c) Denmark, S. E.; Tymonko, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 8004–8005. (d) Trost, B. M.; Machacek, M. R.; Faulk, B. D. *J. Am. Chem. Soc.* **2006**, *128*, 6745–6754.

SCHEME 4



SCHEME 5



$[Rh(COD)_2]BF_4$ under otherwise identical conditions produced the desired aldehyde **18** accompanied by some decomposition. Unexpectedly, under previously developed conditions with $Rh_4(CO)_{12}$,[21] no cyclization of **17** took place but instead only the isomerization of its double bond was observed. Therefore, $Rh(acac)(CO)_2$ was used for all further optimizations.

The silylcarbocyclization reaction of **17** with benzyldimethylsilane was carried out using $Rh(acac)(CO)_2$ in toluene under a range of temperatures and CO pressures (Table 3). At 70 and 150 °C, the reaction either proceeded with a significant amount of decomposition (entries 3−5, 13−15) or afforded considerable amounts of the undesired silylformylation product **19** (entries 1 and 2). At both 90 and 120 °C, the formation of **20** was reduced as the CO pressure increased (entries 7−13). However, the *trans*-**18**/**20** ratio did not improve above 500 psi at 120 °C (entries 11 and 12). At both temperatures, the ratio of *trans*-**18**/*cis*-**18** was 5:1, but **19** was not observed at 120 °C (entries 9−12).

More strongly coordinating solvents such as THF, methyl isobutanoate, and acetonitrile were also surveyed to explore the solvent effects on the *trans*-**18**/*cis*-**18** ratio. Unfortunately, when THF was used, no improvement was seen (entry 16), and when methyl isobutanoate and acetonitrile were used, the reactions resulted in complex mixtures (entries 17 and 18). In summary, the optimal conditions found involved the use of toluene at 120 °C under 500 psi of CO. Upon scaling to 6.6 mmol, **18** was isolated in a 73% yield as a mixture of *trans*- and *cis*-diastereomers in a 4:1 ratio (Scheme 4). Further purification of this mixture afforded 59% of pure *trans*-**18**, thus meeting the second synthetic challenge.

4. Studies of the Alkenyl−Alkenyl Cross-Coupling Using Tetrasubstituted Silanes. The sensitive formyl group in **18** was oxidized to the carboxylic acid by a Pinnick oxidation and then was protected as a methyl ester using diazomethane to afford an 87% yield of methyl ester **21** (Scheme 4).[12,40] Forming the methyl ester **21** facilitated purification and provided functional group compatibility during the cross-coupling. Silanol **22** was prepared by simply treating **21** with TBAF for the study of the cross-coupling reaction under fluoride-free conditions.[24m,n]

The TBAF-promoted cross-coupling using benzylsilane **21** and the fluoride-free cross-coupling using silanol **22** (activated by strong Brønsted bases including NaH, KH, and KO*t*-Bu) were carried out with both **3**[41] and 1-(*E*)-iododecene model substrate. After an extensive survey of reaction parameters including palladium catalysts, ligands, additives, solvents, temperatures, and Brønsted bases, in no instance was either cross-coupling products **23** or **24** formed. The only identifiable product observed resulted from the reduction of **3** and the protodesilylation of **21** (Scheme 4).

To address the failure of **21** and **22** to undergo cross-coupling, a tactical change was investigated to reverse the polarity of cross-coupling partners. Namely, the side-chain fragment would carry the silicon-containing donor and the alkenyl iodide electrophile would reside on the pyrrolidine fragment. To introduce iodine to the pyrrolidine fragment, the silylcarbocyclization product was subjected to an electrophilic iodination reagent for a desilylative iodination reaction.[42] However, to avoid any complication caused by the benzyl group of **21**, the carbonylative silylcarbocyclization of enyne **17** was carried out with dimethyl*phenyl*silane under the previously optimized conditions (Scheme 5). Interestingly, an improved diastereoselectivity was observed and aldehyde **25** was isolated in 77% yield as an 8:1 mixture of *trans*- and *cis*-diastereomers. To obtain pure

(40) For a review on Pinnick oxidation, see: Raach, A.; Reiser, O. *J. Prakt. Chem.* **2000**, *342*, 605–608.

(41) For the synthesis of **3**, see the Supporting Information.

(42) (a) Zakarian, A.; Batch, A.; Holton, R. A. *J. Am. Chem. Soc.* **2003**, *125*, 7822–7824. (b) Fuwa, H.; Ebine, M.; Sasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 9648–9650. (c) Fuwa, H.; Ebine, M.; Bourdelais, A. J.; Baden, D. G.; Sasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 16989–16999. (d) Lu, C.-D.; Zakarian, A. *Org. Lett.* **2007**, *9*, 3161–3163.

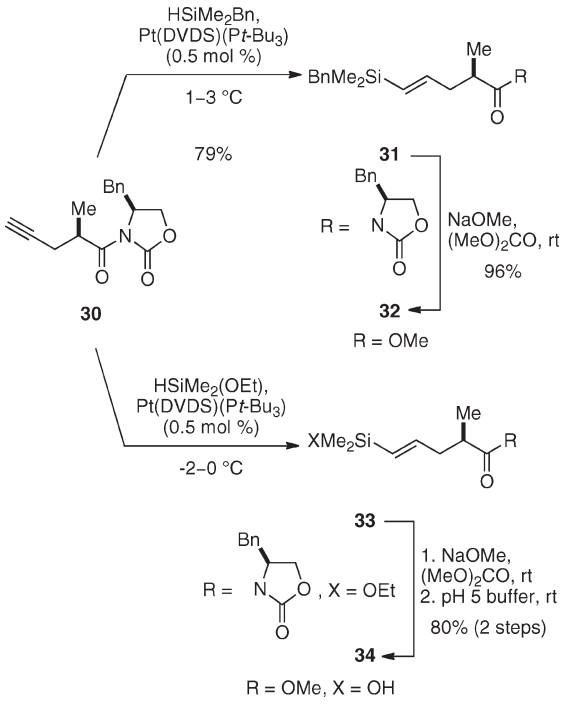
trans-2,3-disubstituted intermediates, the mixture of aldehydes **25** was reduced using sodium borohydride from which pure alcohol *trans*-**26** could be separated in 85% yield.[43] The conversion of **26** to carboxylic ester **28** was achieved by chromium trioxide-catalyzed oxidation with periodic acid followed by esterification of **27** with diazomethane.

The desilylative iodination of **28** employing *N*-iodosuccinimide (NIS) following known procedures for that of trisubstituted alkenyldimethylphenylsilanes failed.[42] However, when treating **28** with iodine monochloride, this reaction proceeded smoothly at room temperature within 1 h. Surprisingly, the iodination proceeded with complete *inversion* of double-bond configuration, affording *Z*-alkenyl iodide **29** in 86% yield. The double-bond configuration was established unambiguously by NOE experiments. When the C(5) methylene protons were irradiated, the only enhancement seen was the tosyl group protons. Additionally, when the C(3) methine protons were irradiated, the enhancement of the allylic methyl proton signal was clearly seen.[44]

Although the inability of **21** and **22** to engage in cross-coupling as well as the unexpected stereochemical outcome in the iododesilylation of **28** may initially seem disappointing, the clean and complete inversion of the double-bond configuration of **28** nevertheless opened up a new vista in isodomoic acid synthesis. First, by the virtue of its double-bond configuration, **29** can act as a precursor to isodomoic acid H (**2**). Second, the modular nature of silicon-based cross-coupling reactions implies that if an isomer of **29** bearing *E*-alkenyl iodide can be prepared, both isodomoic acids G (**1**) and H (**2**) could be synthesized through the cross-coupling with a common partner, thus expanding the initial objective. Furthermore, by employing other cross-coupling partners, a large array of structurally diverse unnatural analogues of isodomoic acids can be prepared. Because the configuration of **2** has not been unambiguously determined and an authentic sample was no longer available from the isolationists, (5′*R*)-**2** was to be synthesized, by analogy to the configuration of isodomoic G established by Montgomery and co-workers.[12]

To examine the cross-coupling of **29** under both fluoride-promoted and fluoride-free conditions, the side-chain fragment bearing a benzylsilane and a silanol functionality were both synthesized (Scheme 6). Acyloxazolidinone **30**, used previously for the side-chain iodide synthesis, was subjected to a platinum-catalyzed hydrosilylation reaction with benzyldimethylsilane as well as ethoxydimethylsilane.[39c,45] The internal temperature must be carefully maintained at approximately 0 °C, for the reaction proceeded with almost perfect constitutional selectivity, affording terminal alkenylsilanes **31** and **33**. To obtain the side-chain benzylsilane **32**, the oxazolidinone was conveniently exchanged with a methoxy group following the method of Kanomata.[46] For the synthesis of silanol **34**, crude **33** was not purified because of its hydrolytic sensitivity. Instead, it was first subjected to auxiliary cleavage as above followed by the hydrolysis of the silyl ether moiety to afford side-chain silanol **34** in 80% overall yield.

SCHEME 6



The first stage in the evaluation of cross-coupling partners involved the combination of **29** and **32**. A number of palladium sources such as $Pd_2(dba)_3 \cdot CHCl_3$, $[(\pi\text{-allyl})PdCl]_2$, and $Pd((4,4'\text{-}(OMe)_2dba)_2$,[47] as well as ligands such as triphenylarsine, trifurylphosphine, and $4,4'\text{-}(CF_3)_2dba$,[47] were used. Unfortunately, in most cases, very little, if any, product was observed. The cross-coupling reaction of **29** with **32** under fluoride-free conditions led only to the decomposition of **29**. However, complete consumption of **29** and the formation of **35**, the fully protected isodomoic acid H, were observed when **29** was stirred with 1.5 equiv of **32**, 25 mol % of $Pd_2(dba)_3 \cdot CHCl_3$, and 3 equiv of $TBAF \cdot 3H_2O$ in THF at room temperature. This result was extremely encouraging, in spite of the high catalyst loading. Therefore, $Pd_2(dba)_3 \cdot CHCl_3$ was used in all subsequent optimizations. Because the reactivity and basicity of a fluoride salt depend heavily on the counterion and the hydration level, the TBAF, tetraethylammonium fluoride (TEAF), and tetramethylammonium fluoride (TMAF) were surveyed, and their levels of hydration were investigated (Table 4).[48,49] Fluoride sources

(43) The Pinnick oxidation of **25** and the subsequent methylation following previously developed procedures proceeded well, but the separation of the diastereomers proved difficult at every stage along this route.

(44) See the Supporting Information for full details of the structural assignment.

(45) (a) Murphy, P. J.; Spencer, J. L.; Proctor, G. *Tetrahedron Lett*. **1990**, *31*, 1051–1054. (b) Kahle, K.; Murphy, P. J.; Scott, J.; Tamagni, R. *J. Chem. Soc., Perkin Trans. 1* **1997**, 997–999. (c) Arsenyan, P.; Oberte, K.; Rubina, K.; Belyakov, S. *Tetrahedron Lett*. **2005**, *46*, 1001–1003. (d) Lowe, J. T.; Youngsaye, W.; Panek, J. S. *J. Org. Chem*. **2006**, *71*, 3639–3642. (e) Su, Q.; Dakin, L. A.; Panek, J. S. *J. Org. Chem*. **2007**, *72*, 2–24.

(46) Kanomata, N.; Maruyama, S.; Tomono, K.; Anada, S. *Tetrahedron Lett*. **2003**, *44*, 3599–3603.

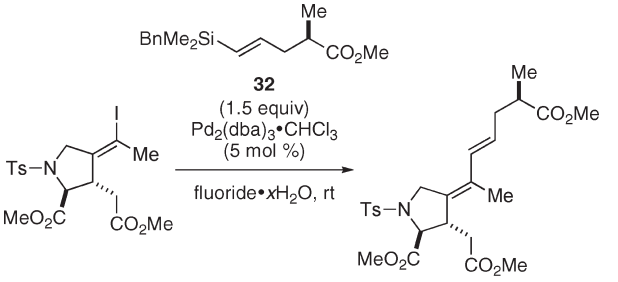
(47) Fairlamb, I. J. S.; Kapdi, A. R.; Lee, A. F. *Org. Lett*. **2004**, *6*, 4435–4438.

(48) (a) Landini, D.; Maia, A.; Rampoldi, A. *J. Org. Chem*. **1989**, *54*, 328–332. (b) Albanese, D.; Ladini, D.; Penso, M. *J. Org. Chem*. **1998**, *63*, 9587–9589.

(49) The structures of hydrated tetraalkylammonium ions have been the subject of careful investigation for many years. A continuum of structures has been identified (depending upon ion structure and hydration level) that ranges from pure anions clathrates through framework structures through hydrogen bonded networks and finally to discrete polyhedral cluster anions; see: (a) Jeffrey, G. A.; Mak, T. C. W. *Science* **1965**, *149*, 178–179. (b) McLean, W. J.; Jeffrey, G. A. *J. Chem. Phys*. **1967**, *47*, 414–417. (c) Gennick, I.; Harmon, K. M.; Potvin, M. M. *Inorg. Chem*. **1977**, *16*, 2033–2040.

containing four or six waters of hydration produced very similar rates of conversion regardless of the fluoride used. Moreover, the conversion stalled within 2 h under these conditions (Table 4, entries 1, 2, and 5−7). In stark contrast, with TBAF·8H_2O the reaction rate improved dramatically and **29** was largely consumed within 4 h. Furthermore, a higher loading of TBAF·8H_2O helped accelerate the cross-coupling reaction (entries 3 and 4).

TABLE 4. Effects of Fluoride Sources and Hydration Levels[a]



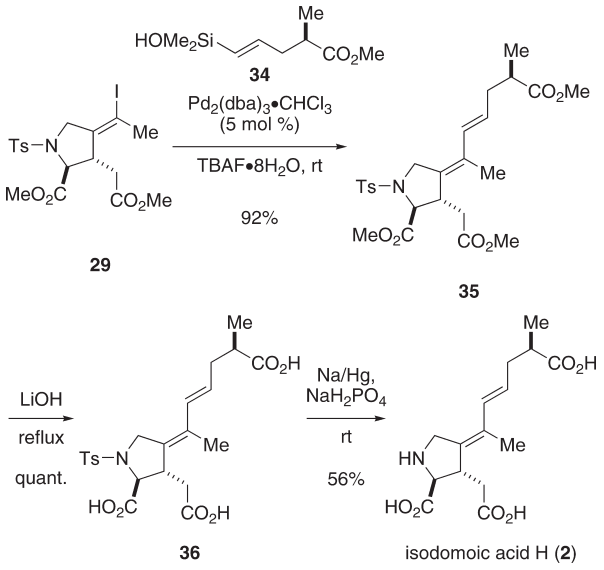
			29/35[b]	
entry	fluoride	equiv	2 h	4 h
1	TBAF·4H_2O	3	69/31	69/31
2	TBAF·6H_2O	3	75/25	75/25
3	TBAF·8H_2O	3	14/86	8/92
4[c]	TBAF·8H_2O	5	10/90	4/96
5	TEAF·4H_2O[d]	3	65/35	60/40
6	TEAF·6H_2O	3	68/32	65/35
7	TMAF·4H_2O[e]	3	70/30	68/32

[a]Reactions were carried out on 0.02 mmol scale with 1.5 equiv of **32**. [b]Ratio determined on the basis of the peak areas of **29** and **35** from HPLC analyses. [c]Reaction carried out on 0.06 mmol scale. [d]TEAF = tetraethylammonium fluoride. [e]TMAF = tetramethylammonium fluoride.

A close inspection of a reaction mixture developed using the conditions of entry 4 revealed a 2:1 mixture of **35** and **32**. No appreciable amounts of silanol **34** or the corresponding disiloxane were detected by ^{1}H NMR analysis. This observation indicates that at a high level of hydration the cleavage of the benzyl group of **32** is very likely rate limiting and that the silanol or disiloxane generated in situ is quickly consumed as soon as it is formed. This hypothesis led to the obvious conclusion that if *silanol* **34** were used instead of *benzylsilane* **32**, the cross-coupling reaction would be more rapid and thus minimize the occurrence of other side reactions. This assertion was indeed confirmed when **29** and **35** (1.2 equiv) were combined in the presence of 5 mol % of $Pd_2(dba)_3 \cdot CHCl_3$ and 3.0 equiv of TBAF·8H_2O. The consumption **29** was complete within 1 h, and **35** was isolated in 92% yield (Scheme 7).

5. Completion of the Total Synthesis of Isodomoic Acid H (2). To complete the synthesis of isodomoic acid H, the protecting groups needed to be removed from **35**. This maneuver was accomplished by the saponification of the three methyl esters using LiOH[50] to afford triacid **36** in quantitative yield (Scheme 7). Crude **36** was then subjected to the detosylation reaction using finely ground 5% sodium amalgam.[51] The heterogeneous nature of sodium amalgam presented challenges for optimization. First, the loading required was scale dependent. Additionally, the formation of mercury droplets in the course of the reaction, which can reamalgamate unreacted sodium, substantially reduced the efficacy of the reagent. Because of these complications, a large excess of sodium amalgam was employed rather than batch wise charges of smaller equivalents. Thus, 0.34 mmol of **36** was treated with 50 equiv of 20% sodium amalgam to afford the target molecule, isodomoic acid H (**2**) in 56% yield, after purification by ion-exchange chromatography. Notably, sodium amalgam did not cause isomerization or reduction of the conjugated diene in the detosylation reaction.

SCHEME 7



6. Total Synthesis of Isodomoic Acid G (1). As discussed above, the unexpected discovery of an invertive desilylative iodination of **28** enabled the total synthesis of isodomoic acid H (**2**). In this reaction, the interaction between the C(7) carbonyl group and the intermediate iodonium ion in the iodination reaction was believed to cause the inversion of the double-bond geometry. Conversely, if this interaction could be suppressed, the iodination product with retention of double configuration could be secured. The strategy devised to achieve this objective was to install a protecting group that would prevent the participation of the functionality on C(7). Therefore, **26** was protected with a TIPS (triisopropylsilyl) group using chlorotriisopropylsilane (TIPSCl) and imidazole at room temperature (Scheme 8). Protected substrate **37** was subjected to desilylative iodination using iodine monochloride followed by TIPS group cleavage in the same flask using 4.9% hydrofluoric acid, which delivered *E*-alkenyl iodide **38** in 73% yield with exclusive *retention* of double-bond configuration. The double-bond configuration of **38** was established unambiguously by NOE experiments.[44] When the C(5) methylene protons were irradiated, the signal of C(1′) methyl protons was enhanced. To complete the total synthesis of isodomoic acid G, **38** was first converted by methyl ester **40** in 79% yield by a chromium-catalyzed

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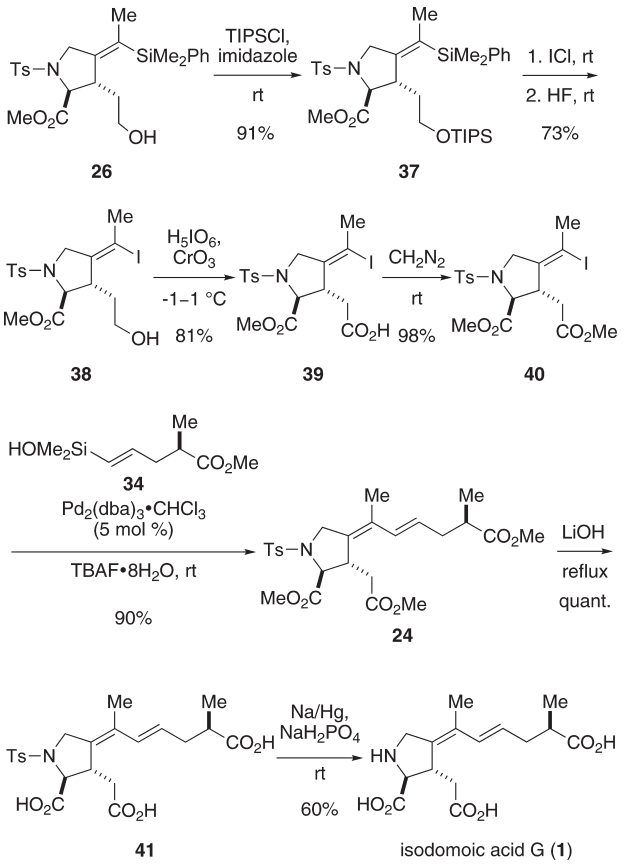
(51) (a) Pyne, S. G.; Hensel, M. J.; Byrn, S. R.; McKenzie, A. T.; Fuchs, P. L. *J. Am. Chem. Soc*. **1980**, *102*, 5962–5964. (b) Pyne, S. G.; Hensel, M. J.; Fuchs, P. L. *J. Am. Chem. Soc*. **1982**, *104*, 5719–5728. (c) Yamada, H.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem*. **1991**, *56*, 4569–4574.

periodate oxidation followed by a methylation of carboxylic acid **39** with diazomethane. The optimized cross-coupling conditions for **29** utilizing TBAF·$8H_2O$ were equally applicable for **40** to afford fully protected isodomoic acid G, **24**, in 90% yield. The same sequence of deprotection was carried out as described above, resulting in isodomoic acid G (**1**) in 60% yield.

SCHEME 8



Discussion

Valuable insights in synthetic design and reaction optimization have been garnered in the course of this synthesis. The key steps discussed below include: (1) the synthesis of vinylglycine derivatives, (2) the carbonylative silylcarbocyclization, (3) the stereodivergent desilylative iodination, and (4) the alkenyl−alkenyl cross-coupling.

1. Synthesis of Vinylglycine Derivatives. The strongly electron-withdrawing nature of the tosyl protecting group significantly enhances the acidity of the nitrogen-bearing methine, and consequently, all the intermediates along the synthetic sequence are base sensitive. This factor had a profound implication on the choice of reaction conditions and reagents along the route to the natural product. The base sensitivity was first manifested in production of racemic selenide **13** by treatment of homoserine lactone **12** with a mixture of sodium borohydride and diphenyl diselenide at elevated temperature (Scheme 3). In addition, when both lactones **12** and **14** were subjected to the basic saponification conditions, decomposition or racemization ensued. In contrast, upon treatment of **14** with TMSI, no loss of enantiomeric integrity in iodinated amino ester **15** was detected.

Another step where racemization presented a serious problem was the *N*-alkylation of **12**. From the results shown in Table 2, under Mitsunobu conditions at both rt and approximately 0 °C, the erosion of enantiomeric purity of **14** started to occur before **12** was completely consumed. Clearly, some basic species must be present to cause racemization. This outcome is surprising because none of the reagents in Mitsunobu reaction, including DEAD, triphenylphosphine, and 2-butyn-1-ol, is a strong Brønsted base. However, as part of the mechanism of the Mitsunobu reaction, the zwitterionic adduct of DEAD and triphenylphosphine likely serves as the base for the observed racemization.[52]

2. Carbonylative Silylcarbocyclization. The difference between the reactivity of vinylglycinates, PMB-protected **10**, and tosyl-protected **17** is intriguing (Schemes 2 and 4). Whereas the latter underwent carbonylative silylcarbocyclization under 500 psi of CO at elevated temperatures to afford aldehyde **18**, subjecting the former to similar conditions resulted in little CO insertion. This striking difference may be attributed to the electronic character of the nitrogen atom in these two compounds. A PMB-protected nitrogen atom is electron rich and is therefore capable of coordinating to the rhodium center under the reaction conditions. This coordination likely disrupts the cyclization and the CO insertion. In contrast, the electron-withdrawing nature of tosyl group, renders the nitrogen in **17** electron poor with a diminished ability to bind to rhodium, thus allowing the CO insertion to proceed smoothly.

The successful construction of the substituted pyrrolidine core of isodomoic acids depends on the *trans* selectivity in the carbonylative silylcarbocyclization reaction with respect to the resident stereogenic center. This kind of diastereoselectivity is documented in a study conducted by Ojima and coworkers, wherein both the silylcarbocyclization or the carbonylative silylcarbocyclization of dienyne **42** demonstrated excellent diastereoselectivity, giving tetrahydrofurans **43** and **44** with exclusively 2,3-*trans* substitution (Scheme 9).[53]

In the cyclization of **17**, the observed preference for the formation of aldehydes *trans*-**18** and *trans*-**25** can be rationalized in the following manner. When enyne **17** and a hydrosilane are stirred in the presence of $Rh(acac)(CO)_2$, the silylrhodation of the alkyne moiety occurs first, where the silyl group occupies the terminal position (Scheme 10). Then, π-complexation of the olefin to the rhodium center takes place. Two intermediates can be generated depending on which face of the olefin coordinates to the rhodium center. If the olefin binds to the rhodium center on the *Re*-face, intermediate **A** is generated, but alternatively, if it binds to the rhodium center on the *Si*-face, intermediate **B** is formed instead. Both **A** and **B** are depicted in Scheme 10 in the most stable pseudochair conformation. Intermediates **A** and **B** may be in equilibrium through the dissociation and reassociation of the olefin to the rhodium center. The subsequent step is the olefin insertion that effects the five-membered ring formation through transition structures **C** and **D**, respectively, that are presumably similar to **A** and **B** in structure. These transition structures lead to two diastereomeric alkylrhodium species **E** and **F**, and following CO insertion and reductive elimination of the rhodium center, *trans*- and *cis*-**18** and **25** are produced.

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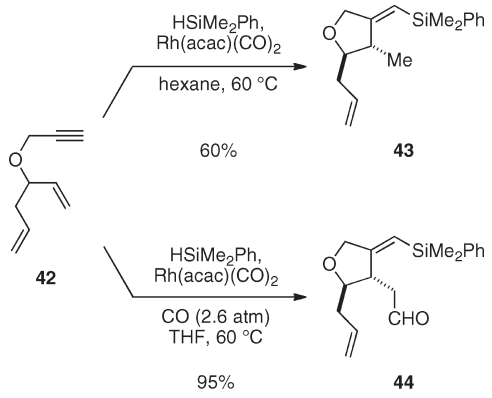
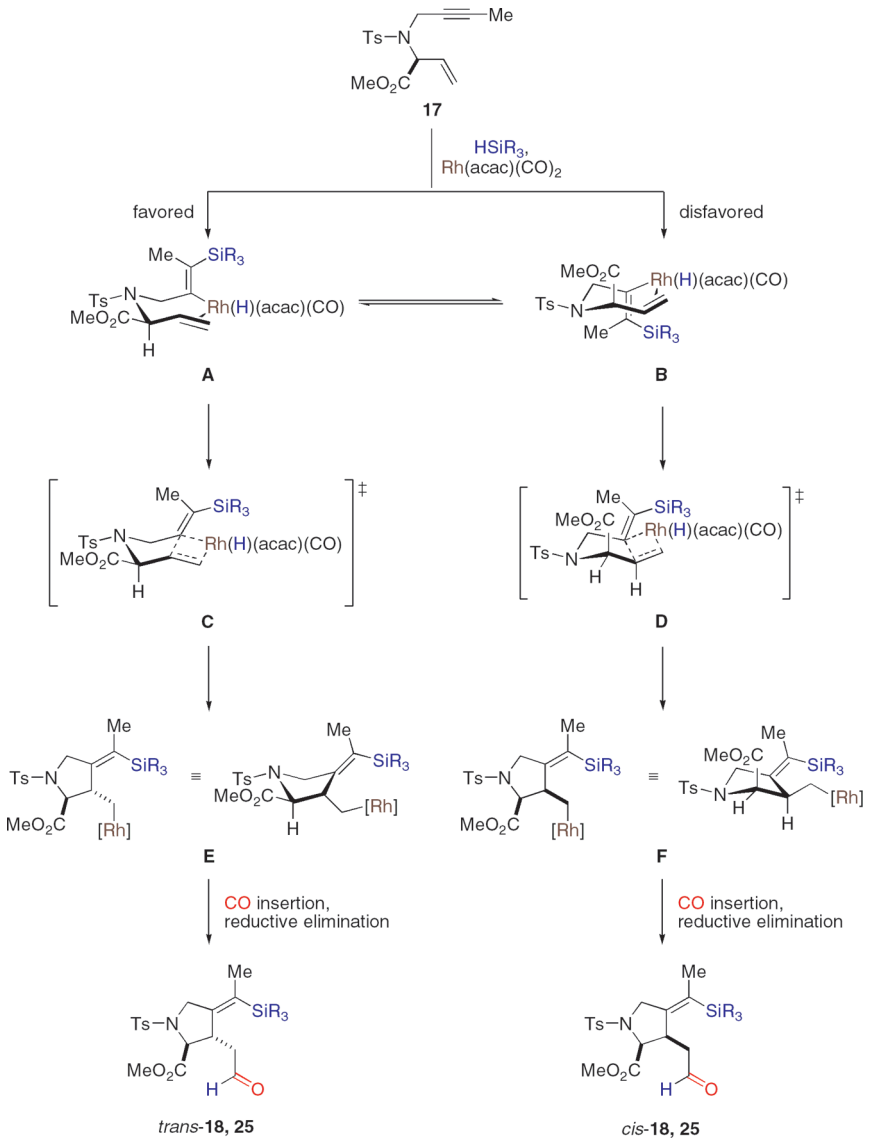
The formation of **A** is favored compared to **B** on the grounds of $A^{1,3}$ allylic strain. In the lowest energy conformation, the vinyl group of **A** either eclipses or is synclinal to the allylic proton, depending on the rhodium−olefin bond length, thereby minimizing $A^{1,3}$ allylic strain. Notably, the methyl ester group of **A** adopts a pseudoequatorial position, and it is anticlinal or antiperiplanar to the vinyl group. However, in a pseudochair conformation, the methyl ester group of **B** is not only pseudoaxial but also eclipses or is synclinal to the vinyl group. Therefore, **B** is expected to be higher in energy than **A**. More importantly, because of the structural similarity between transition structures **C** and **D** and intermediates **A** and **B**, **F** is likewise higher in energy than **E**. Overall, the pathway leading to the formation of intermediates **B**, **F**, and ultimately, *cis*-**18** and **25** is disfavored. Consequently, *trans*-**18** and *trans*-**25** are the major products.

SCHEME 9

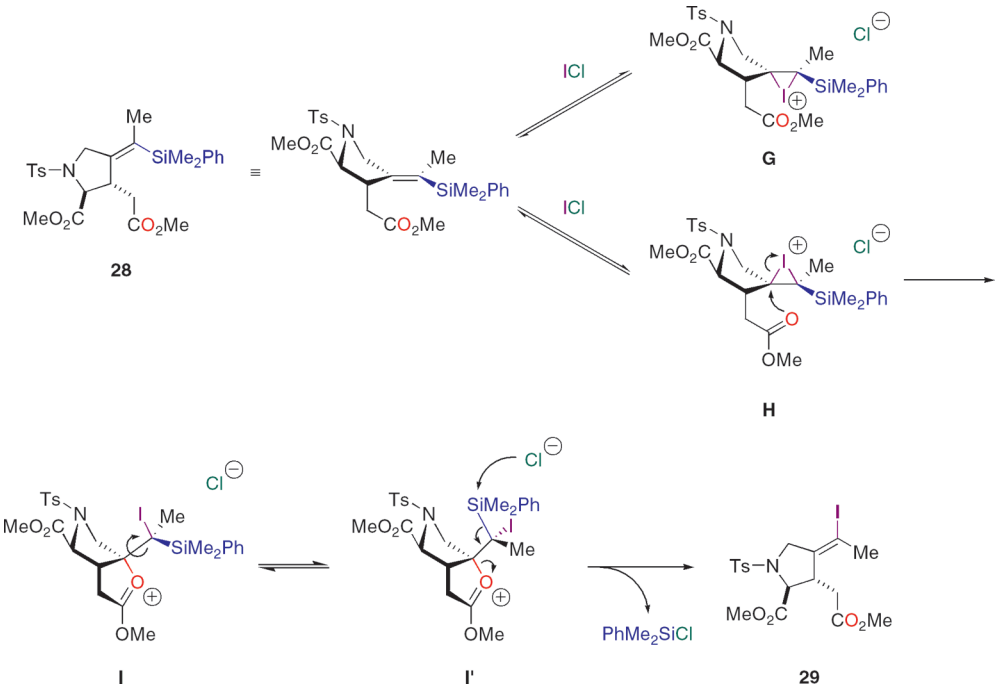


3. Desilylative Iodination. Complete control of the double-bond configuration in the desilylative iodination reaction was critical to the success of the total syntheses of both isodomoic acids G (**1**) and H (**2**). Inversion of double-bond configuration from *E* (silane **28**) to *Z* (iodide **29**) can be understood by an anchimeric participation of the neighboring carbonyl group at C(7) (Scheme 5).[54] In the reaction of **28** with iodine monochloride, the electrophilic iodine atom can

SCHEME 10



SCHEME 11



approach either face of the double bond leading to two iodonium species, **G** and **H** (Scheme 11). Whereas **H** can be rapidly trapped via an intramolecular backside attack at the iodonium ion by the carbonyl group, **G** lacks a suitable geometry for this process. Because iodonium ion formation is reversible, all of the substrate reacts through the intermediacy of **H**, which leads directly to oxocarbenium ion **I**. In the first conformation shown, the carbon−iodine bond and the carbon−oxygen bond are arranged in an antiperiplanar fashion, and thus cannot lead to desilylation. However, with a simple bond rotation that orients the silyl group antiperiplanar to the oxocarbenium ion, as depicted in conformer **I′**, attack of chloride on the silicon gives **29**, the iodinated product bearing an inverted *Z*-double bond.[55]

With this mechanistic insight, it was not difficult to devise a strategy for *retention* of the double-bond configuration by suppressing the aforementioned anchimeric participation (Scheme 12). The sterically encumbered TIPS group was employed for this purpose because it disfavors interaction between the Lewis basic oxygen atom on C(7) with an electrophilic center elsewhere in the molecule. In the reaction of silane **37** with iodine monochloride, two intermediate iodonium ions **J** and **K** can exist in equilibrium with tertiary carbocations **L** and **M**, respectively, since a nucleophilic neighboring group is absent. It is noteworthy that these carbocations are maximally stabilized when the carbon−silicon bond is synplanar with the empty p-orbital. This stereoelectronically preferred alignment can be achieved through a least-motion bond rotation (∼60°), as depicted in conformers **L′** and **M′**. This stabilization by the *β*-silyl group originates from the hyperconjugative interaction between the carbon−silicon *σ*-bond and the empty p-orbital of the carbocation.[56] The nucleophilic attack of chloride anion on the silyl group of both **L′** and **M′** results in the formation *E*-alkenyl iodide **45**, with *retention* of double-bond configuration.

4. Cross-Coupling. The failure of benzylsilane **21** and silanol **22** to cross-couple with alkenyl iodide **3** or (*E*)-1-iododecene to any extent can be attributed to two factors (Scheme 4): (1) the inability of the substrates to undergo transmetalation under fluoride-promoted conditions and (2) the base sensitivity of the substrates.

Recent kinetic studies from these laboratories revealed that in the fluoride-promoted silicon-based cross-coupling, the turnover-limiting step is the silicon-to-palladium transmetalation, although the molecular details of this event are not well understood.[57] For alkenylsilane substrates, this kinetic behavior translates to the sensitivity to steric crowding around the olefin, particularly to the geminal substituent of the silicon-containing moiety.[25,58,59] The more sterically congested substrates often require more forcing conditions or higher catalyst loadings to be consumed completely while affording products in somewhat attenuated yields due to the competing side reactions. This effect is clearly illustrated in the cross-coupling of cyclic silyl ether **46a** with ethyl 4-iodobenzoate, which was complete within 10 min, affording product **47a** in 90% yield (Scheme 13). However, for

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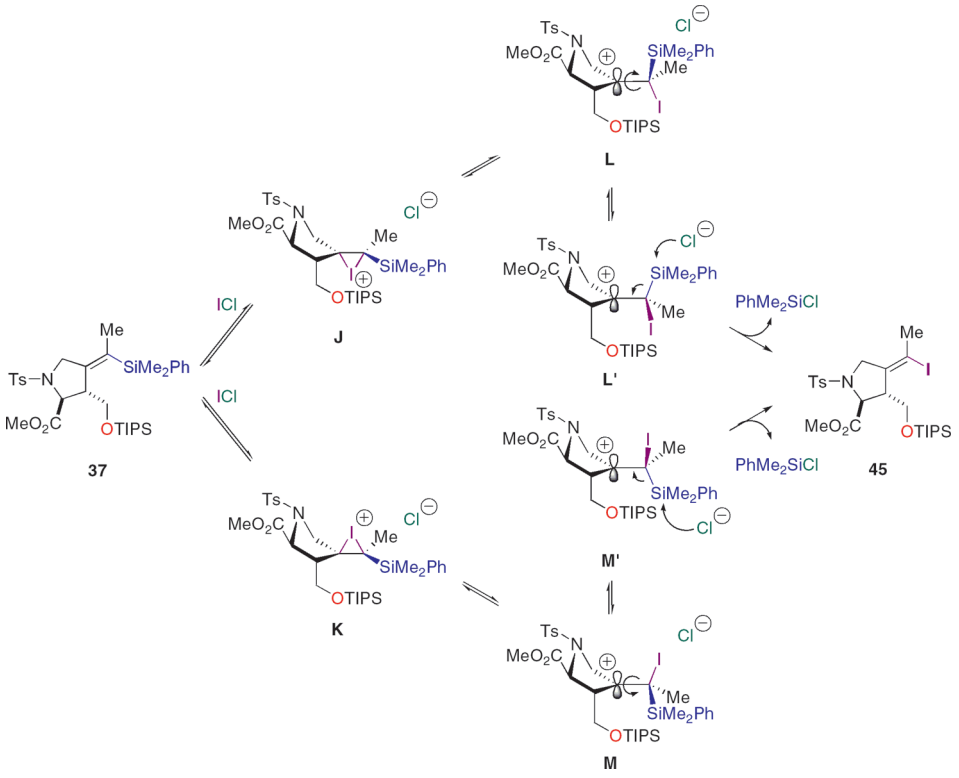
SCHEME 12



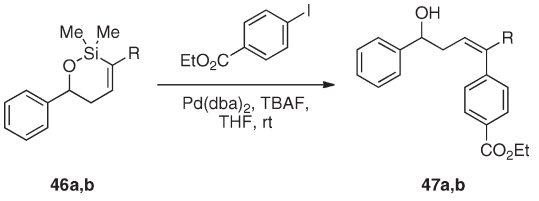
analogue **46b**, bearing a hexyl group geminal to the silicon, the reaction proceeded much more sluggishly. Portionwise additions of the catalyst as well as the iodide were required to minimize undesired homocoupling of the iodide and catalyst deactivation. Despite these efforts, the yield of **47b** was somewhat modest (81%) compared to **47a**.[59]

In the present system, both benzylsilane **21** and silanol **22** bear a tetrasubstituted alkenylsilyl group, and the substituent *cis* to the silyl group is capable of providing both steric congestion and coordination to the palladium center. Although a clear picture of the transition state of transmetalation is presently lacking, it is possible to speculate that the tetrasubstituted alkenyl silyl group of **21** and **22** is too hindered to transfer to the palladium center. In stark contrast, when the polarity of the two components was reversed, the disubstituted alkenylsilanes **32** and **34** had no difficulty reacting with alkenyl iodides **29** and **40** at room temperature (Table 4, Schemes 7 and 8).

As discussed above, the strongly electron-withdrawing nature of the *N*-tosyl group significantly acidifies of HC(2) of intermediates along the synthetic sequence. Under fluoride-promoted conditions, the fluoride anion can act as a Brønsted base to deprotonate the HC(2) of **21** and **22**. For **22**, under the fluoride-free cross-coupling conditions, i.e., in the presence of strong Brønsted bases such as NaH, KH, and KO*t*-Bu, both the silanol moiety and the HC(2) can be deprotonated by the strong Brønsted base employed. Therefore, in addition to the unfavorable steric environment, the base sensitivity of **21** and **22** may also have contributed to the failure of this cross-coupling through substrate decomposition and catalyst deactivation.

The problem of fluoride basicity is evident in the stalling of the reaction when TBAF was used in low hydration levels for

SCHEME 13



46a,b **47a,b**

46a, **47a**: R = H, $Pd(dba)_2$ (5 mol %), 10 min, 90%
46b, **47b**: R = C_6H_{13}, $Pd(dba)_2$ (4 × 2.5 mol %), 24 h, 81%

the cross-coupling reactions of **29** with **32**. Therefore, the attenuation of the basicity was indeed the key to the optimization of this cross-coupling reaction. From Table 4, it is apparent, by considering the rate of conversion, that the counterion of the fluoride has only a minimal effect, even though tetramethylammonium ion and tetraethylammonium ion associate to fluoride more tightly than tetra-*n*-butylammonium ion by the virtue of lesser insulation of the positive charge (entries 1, 5, and 7).[60] The most effective means found to attenuate fluoride basicity is the augmentation of the hydration level, and the difference between the results using TBAF·$6H_2O$ and TBAF·$8H_2O$ is indeed striking (entries 2 and 3).[48] Notably, as similar beneficial effects have been observed for fluoride-promoted silicon-based cross-couplings of base-sensitive substrates such as aryl triflates, aryl nonaflates, as well as silyl ethers bearing an ester functionality.[61]

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(61) (a) Denmark, S. E.; Sweis, R. F. *Org. Lett.* **2002**, *4*, 3771–3774. (b) Denmark, S. E.; Muhuhi, J. M. *J. Am. Chem. Soc.* **2010**, *132*, 11768–11778.

Conclusion

The total syntheses of isodomoic acids G (**1**) and H (**2**) have been achieved via a common intermediate, alkenylsilane **26**, and through an efficient sequence (12-step longest linear sequence) that addressed three important synthetic challenges. Key intermediate **17**, a sensitive vinylglycine derivative, was prepared in excellent yield under mild conditions and without loss of enantiomeric purity. The rhodium-catalyzed carbonylative silylcarbocyclization reaction of **17** with dimethylphenylsilane afforded a densely substituted pyrrolidine **25** in good yield. A setback was encountered when the core silanes **21** and **22** failed to undergo cross-coupling with side-chain iodide **3**, prompting the reversal the polarity, which led to the discovery of a stereochemically divergent desilylative iodination. The ability to invert the double-bond configuration allowed us to expand the initial objective and include isodomoic acid H (**2**) as a target molecule. In the process of the optimizing the cross-coupling of alkenyl iodide **29**, an important insight was garnered for the cross-coupling of base-sensitive substrates. The hydration level was found critical to moderate the basicity of fluoride, thus avoiding the substrate decomposition as well as catalyst deactivation. Notably, the completion of this exercise was accompanied with deepened knowledge of two underutilized catalytic synthetic transformations, silylcarbocyclization and silicon-based cross-coupling, in complex molecule syntheses.

Experimental Section

Preparation of (2*S*,3*S*,4*E*)-1-[(4-Methylphenyl)sulfonyl]-2-methoxycarbonyl-4-[(phenyldimethylsilyl)ethylidene]-3-pyrrolidineacetaldehyde (25). To an oven-dried glass liner (∅ = 3 cm) in a drybox was added 64.6 mg (0.25 mmol, 5 mol %) of $Rh(acac)(CO)_2$. The glass liner was sealed with a septum and was taken out. $Rh(acac)(CO)_2$ was then dissolved in 10 mL of toluene, resulting in a light green solution. A solution of 1.607 g (5.00 mmol) of **17** and 0.80 mL (5.25 mmol, 1.05 equiv) of $HSiMe_2Ph$ in 40 mL of toluene was transferred via cannula to the glass liner under Ar. The color of the mixture quickly turned to light yellow. The glass tube was opened and was quickly placed in a stainless steel bomb. The bomb was sealed and then placed on a rocker. The bomb was purged with CO by pressurizing to ∼500 psi followed by venting three times. Finally, the bomb was then pressurized with 500 psi of CO. The bomb was heated to 120 °C in the course of ∼1 h, and it was rocked at this temperature for 12 h. At the end of the reaction period, the autoclave was cooled to rt, and the pressure was released. The glass liner was taken out, and the red-orange reaction mixture was treated with a solution of 76.1 mg (1.00 mmol, 20 mol %) of thiourea in 4 mL of EtOH. Upon treatment, this mixture quickly became a suspension, and the color gradually darkened from yellow to brown. It was stirred at rt under air for 40 min before it was filtered through a layer of silica gel. The silica gel was eluted with 100 mL of EtOAc, and the combined filtrates were concentrated under reduced pressure. The crude product was purified using flash chromatography (silica gel (240 g),hexanes/EtOAc, 10/1 (2 L), 5/1 (2 L), 3/1 (3 L)) to afford in total 1.860 g (77%) of *trans*-**25** and *cis*-**25** (*trans*-**25**/*cis*-**25** = 8:1) as a light yellow liquid. Data for *trans*-**25**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.26 (s, 1 H, HC(7)), 7.71 (d, J = 8.2 Hz, 2 H, HC(2″), HC(6″)), 7.42 (dd, J = 7.7, 1.6 Hz, 2 H, HC(8″), HC(12″)), 7.39−7.25 (m, 5 H, HC(Aryl)), 4.23 (s, 1 H, HC(2)), 4.09 (d, J = 14.3 Hz, 1 H, HC(5)), 4.03 (d, J = 14.1 Hz, 1 H, HC(5)), 3.57 (s, 3 H, OCH_3), 3.19 (d, J = 10.9 Hz, 1 H, HC(3)), 2.42 (s, 3 H, ArylCH_3), 2.17 (dd, J = 18.2, 11.4 Hz, 1 H, HC(6)), 1.79 (dd, J = 18.5, 2.3 Hz, 1 H, HC(6)), 1.70 (s, 3 H, $H_3C(2')$), 0.35 (s, 3 H, H_3CSi), 0.35 (s, 3 H, H_3CSi); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.1 (C(7)), 170.8 (CO_2), 147.4 (C(1″)), 143.8 (C(4)), 138.4 (C(1′)), 136.3 (C(4″)), 134.0 (C(8″), C(12″)), 129.76 (C(3″), C(5″)), 129.6 (C(10″)), 128.4 (C(7″)), 128.3 (C(9″), C(11″)), 127.4 (C(2″), C(6″)), 64.8 (C(2)), 52.5 (C(5)), 49.8 (OCH_3), 47.5 (C(6)), 42.0 (C(3)), 21.8 (ArylCH_3), 19.7 (C(2′)), −1.5 ($SiCH_3$), −2.3 ($SiCH_3$); IR (neat) ν_{max} 2484 (w), 2954 (m), 1746 (s), 1722 (m), 1349 (s), 1162 (s), 1109 (s), 818 (m), 667 (s), 596 (s) cm^{-1}; LRMS (CI) m/z 135.1 (29.5), 210.1 (46.1), 270.1 (16.2), 330.2 (39.5), 408.1 (21.6), 426.2 (32.6), 470.2 (10.2), 486.2 (100.0, $[M + H]^+$); HRMS (CI, $[M + H]^+$) m/z calcd 486.1770, found 486.1767; TLC R_f 0.30 (silica gel, hexanes/EtOAc, 3/1, UV); $[\alpha]_D$ −22.3 (c = 0.5, EtOH).

Preparation of Methyl (2*S*,3*S*,4*Z*)-1-[(4-Methylphenyl)sulfonyl]-2-methoxycarbonyl-4-[(iodo)ethylidene]-3-pyrrolidineacetate (29). In a flame-dried, 50-mL, round-bottomed flask equipped with a magnetic stir bar and a gas inlet adaptor was dissolved 793.3 mg (1.54 mmol) of **28** in 10 mL of CH_2Cl_2. To this solution was added 499.7 mg (3.08 mmol, 2.0 equiv) of ICl. An exotherm was observed, and the reaction mixture, a dark-purple solution, was stirred at rt for 1 h. Then the reaction was quenched by adding 10 mL of satd aq $Na_2S_2O_3$ solution. The purple color quickly faded, and this mixture became a yellow suspension. The quenched reaction mixture was transferred to a 60 mL separatory funnel. The aqueous layer was extracted with 3 × 10 mL of CH_2Cl_2. The combined organic layers were washed with 30 mL of satd aq $Na_2S_2O_3$ solution and 30 mL of brine, dried over anhydrous $MgSO_4$, filtered, and were concentrated under reduced pressure. The crude product was purified using flash chromatography (silica gel (90 g), hexanes/EtOAc, 5/1 (1 L), 4/1 (1 L), 3/1 (1 L)) to afford 672.9 mg (86%) of **29** as an off-white solid. Data for **29**: mp 82−83 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J = 8.1 Hz, 2 H, HC(2″), HC(6″)), 7.33 (d, J = 8.0 Hz, 2 H, HC(3″), HC(5″)), 4.67 (s, 1 H, HC(2)), 4.09 (ddd, J = 14.5, 1.9, 1.9 Hz, 1 H, HC(5)), 3.95 (dd, J = 14.5, 1.9 Hz, 1 H, HC(5)), 3.72 (s, 3 H, C(8)O_2CH_3), 3.60 (s, 3 H, C(7)O_2CH_3), 3.41 (dd, J = 8.7, 6.1 Hz, 1 H, HC(3)), 2.45 (s, 3 H, ArylCH_3), 2.44 (s, 3 H, $H_3C(2')$), 2.34 (d, J = 5.4 Hz, 1 H, HC(6)), 2.33 (dd, J = 9.5 Hz, 1 H, HC(6)); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2 (C(7)), 170.8 (C(8)), 144.0 (C(1″)), 141.7 (C(4)), 136.0 (C(4″)), 129.9 (C(3″), C(5″)), 127.5 (C(2″), C(6″)), 91.9 (C(1′)), 66.5 (C(2)), 57.8 (C(5)), 52.7 (C(7)O2CH_3), 52.4 (C(8)O_2CH_3), 43.4 (C(3)), 36.9 (C(6)), 30.0 (ArylCH_3), 21.8 (C(2′)); IR (thin film) ν_{max} 3447 (w), 2955 (m), 2255 (w), 1667 (w), 1560 (w), 1436 (m), 1351 (m), 1261 (m), 1209 (m), 1161 (s), 1096 (s), 913 (w), 816 (w), 730 (w), 666 (m) cm^{-1}; LRMS (ESI) m/z 508.0 ($[M + H]^+$), 530.0 ($[M + Na]^+$), 545.9 (100.0, ($[M + K]^+$)); HRMS (ESI, $[M + H]^+$) calcd 508.0291, found 508.0276; TLC R_f 0.24 (silica gel, hexanes/EtOAc, 2:1, UV); $[\alpha]_D$ −7.8 (c = 0.5, EtOH). Anal. Calcd for $C_{18}H_{22}INO_6S$: C, 42.61; H, 4.37; N, 2.76. Found: C, 42.92; H, 4.24; N, 2.71.

Preparation of Methyl (2*S*,3*S*,4*Z*)-1-(4-Methylphenylsulfonyl)-2-methoxycarbonyl-4-[(2*E*,5*R*)-5-methoxycarbonyl-1-methyl-2-hexen-1-ylidene]-3-pyrrolidineacetate (35). To a 50-mL Schlenk flask equipped with a magnetic stir bar was added 59.5 mg (0.057 mmol, 5 mol %) of $Pd_2(dba)_3 \cdot CHCl_3$. The Schlenk flask was evacuated and purged with Ar three times. In another 50 mL, round-bottomed flask equipped with a magnetic stir bar and a gas inlet adaptor, 578.2 mg (1.14 mmol) of **29** and 276.7 mg (1.37 mmol, 1.2 equiv) of **34** were dissolved in 11 mL of THF. To this solution were added 0.31 mL (17.10 mmol, 15.0 equiv) of H_2O and 3.4 mL (3.4 mmol, 3.0 equiv) of TBAF$\cdot 3H_2O$ solution (1.0 M in THF) sequentially. The resulting orange-brown solution was transferred via cannula to the Schlenk flask under Ar. The reaction mixture quickly turned from dark-purple to dark-green, and it was stirred at rt under Ar for 1 h. Then the reaction

mixture was filtered through a layer of silica gel, and the silica gel was eluted with 20 mL of EtOAc. The filtrate was concentrated under reduced pressure. The crude product was adsorbed onto ~5 g of silica gel, and this silica gel was loaded onto a packed silica gel column for the purification by flash chromatography (silica gel (60 g), hexanes/EtOAc, 4/1 (1 L), 2/1 (1 L)) to afford 534.4 mg (92%) of **35** as a light-yellow liquid. A small portion of the chromatographed product was further purified using a second column (silica gel (15 g), hexanes/Et_2O, 1/1) for characterization. Data for **35**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, J = 8.1 Hz, 2 H, HC(2″), HC(6″)), 7.32 (d, J = 8.0 Hz, 2 H, HC(3″), HC(5″)), 5.99 (d, J = 15.4 Hz, 1 H, HC(2′)), 5.67−5.54 (ddd, J = 15.4, 7.4, 7.4 Hz, 1 H, HC(3′)), 4.51 (s, 1 H, HC(2)), 4.21 (d, J = 13.6 Hz, 1 H, HC(5)), 4.16 (d, J = 14.5 Hz, 1 H, HC(5)), 3.72 (s, 3 H, C(8)O_2CH_3), 3.66 (s, 3 H, C(6′)O_2CH_3), 3.59 (s, 3 H, C(7)O_2CH_3), 3.39 (dd, J = 10.8, 3.3 Hz, 1 H, HC(3)), 2.59−2.50 (m, 1 H, HC(5′)), 2.50−2.45 (m, 1 H, HC(4′)), 2.44 (s, 3 H, ArylCH_3), 2.30 (dd, J = 16.3, 3.7 Hz, 1 H, HC(6)), 2.27−2.16 (m, 1 H, HC(4′)), 2.22 (d, J = 16.0 Hz, 1 H, HC(6)), 1.71 (s, 3 H, H_3CC(1′)), 1.16 (d, J = 6.9 Hz, 3 H, H_3CC(5′)); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.5 (C(6′)), 171.7 (C(7)), 171.2 (C(8)), 143.8 (C(1″)), 136.1 (C(4″)), 133.1 (C(1′)), 130.7 C(2′)), 129.8 (C(3″), C(5″)), 128.4 (C(3′)), 127.6 (C(4)), 127.5 (C(2″), C(6″)), 64.9 (C(2)), 52.6 (C(7)O_2CH_3), 52.2 (C(8)O_2CH_3), 51.8 (C(6′)O_2CH_3), 49.2 (C(5)), 43.7 (C(3)), 39.8 (C(5′)), 37.4 (C(4′)/C(6)), 37.2 (C(4′)/C(6)), 21.8 (ArylCH_3), 16.9 (C(5′)CH_3), 15.2 (C(1′)CH_3); IR (neat) ν_{max} 3455 (w), 2954 (m), 1738 (s), 1598 (w), 1495 (w), 1436 (m), 1350 (s), 1206 (s), 1164 (s), 1096 (s), 1070 (m), 1018 (m), 966 (m), 817 (w), 736 (w), 708 (w), 669 (s), 602 (s) cm^{-1}; LRMS (ESI) m/z 139.0, 267.1, 305.1, 337.1, 448.1, 476.1, 508.1 (100.0, $[M + H]^+$), 530.1 ($[M + Na]^+$), 546.1 ($[M + K]^+$); HRMS (ESI, $[M + H]^+$) m/z calcd 508.2005, found 508.1993; TLC R_f 0.24 (silica gel, hexanes/EtOAc, 2:1, UV); $[\alpha]_D$ −1.0 (c = 0.5, EtOH).

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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.