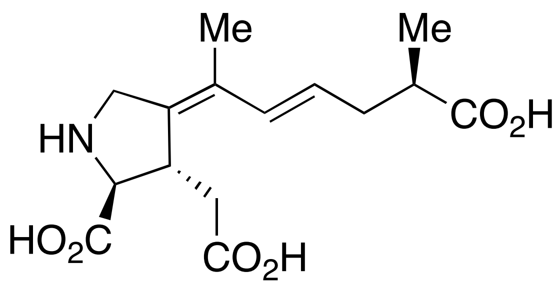
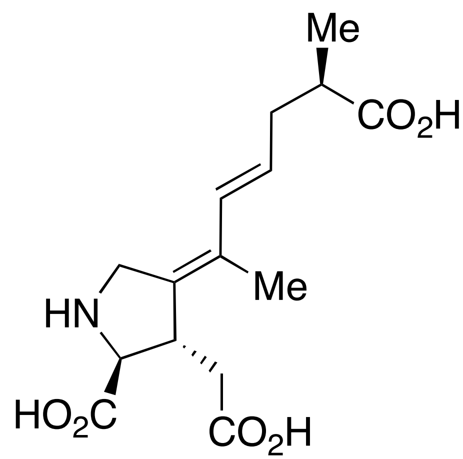
Total Syntheses of Isodomoic Acids G and H





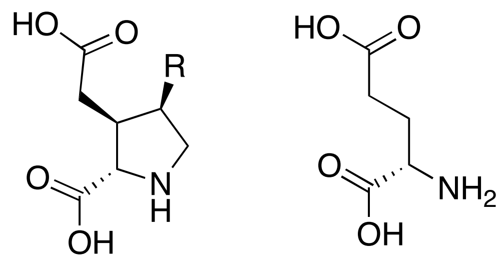
Scott E. Denmark, Jack Hung-Chang Liu, Joseck M. Muhuhi

J. Am. Chem. Soc. **2009**, *ASAP.*

Nate Ware, Wipf Group Current Literature 10/03/09

Kainoid Amino Acid Family

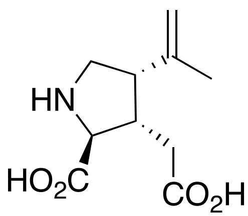
- Isolated from marine alga: *Digenea simplex* (kainic acid), *Chondria armata* (domoic acid and isodomoic acid isomers).
- One symptom of domoic acid poisoning is short-term memory loss, causeing “amnesic shellfish poisoning.”
- Kainoids also exhibit insecticidal, anthelmintic (anti-intestinal worm) as well as its neuroexcitatory properties.
- Biological activity believed to arise from structural similarities to glutamic acid.



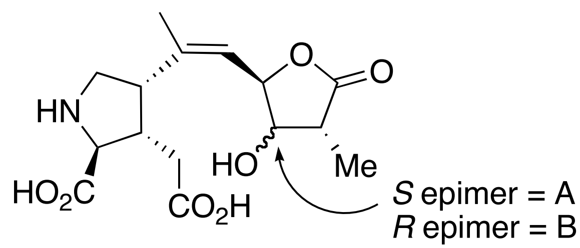
Kainoid Amino Acid   Glutamic Acid

Clayden *et al.* *Tetrahedron* **2005**, *61*, 5713

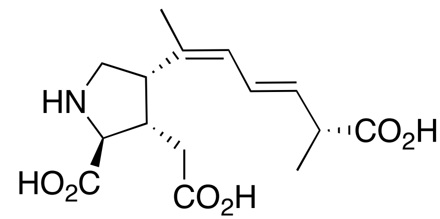
Kainoid Amino Acid Family



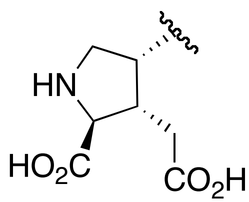
Kainic Acid



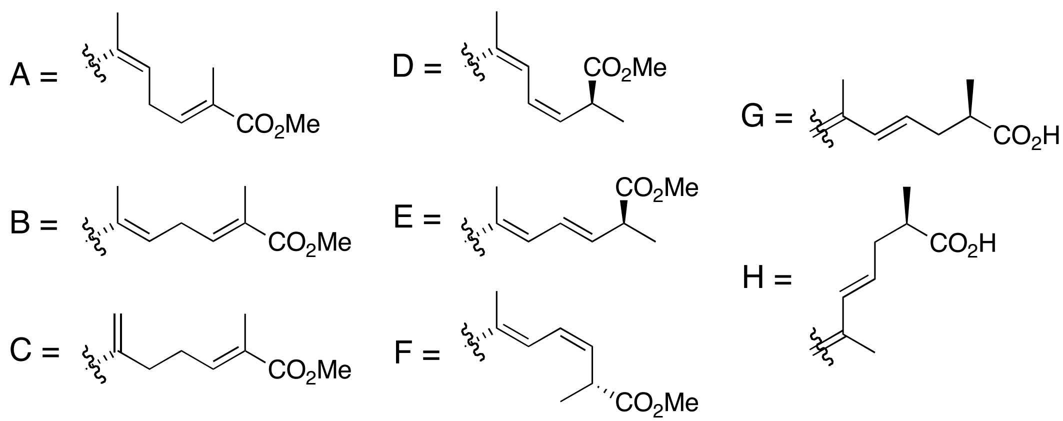
Domoilactones A and B



Domoic Acid

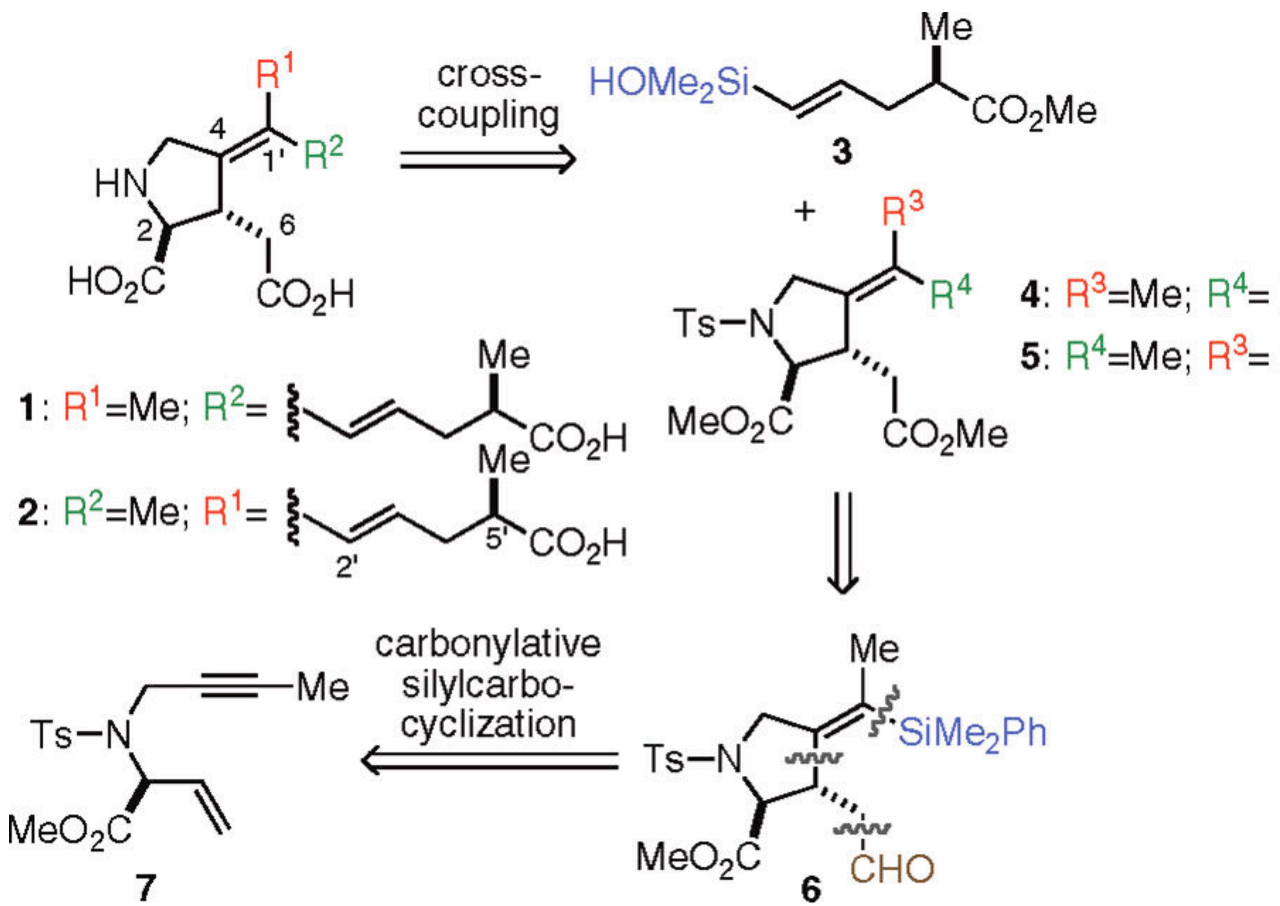


Isodomoic Acids



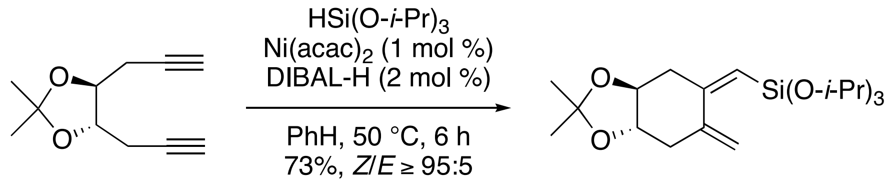
Clayden *et al.* *Tetrahedron* **2005**, *61*, 5713

Retrosynthesis

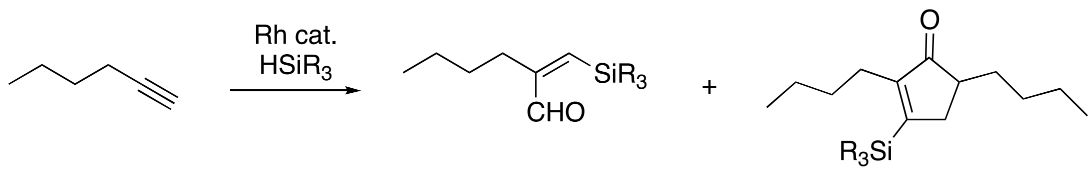


Denmark *et al. JACS* **2009**, *ASAP*

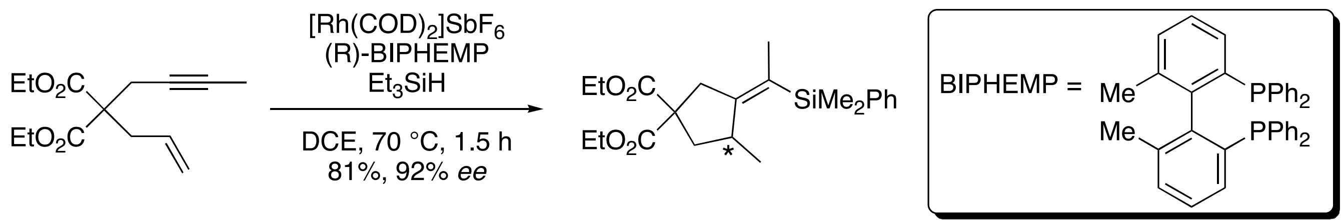
Silylcarbocyclization



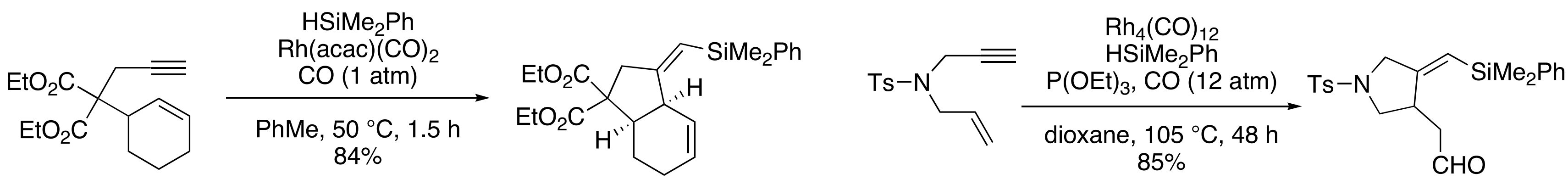
Tamao *et al.* *JACS* **1989**, *111*, 6478



Ojima *et al.* *JACS* **1992**, *114*, 6580

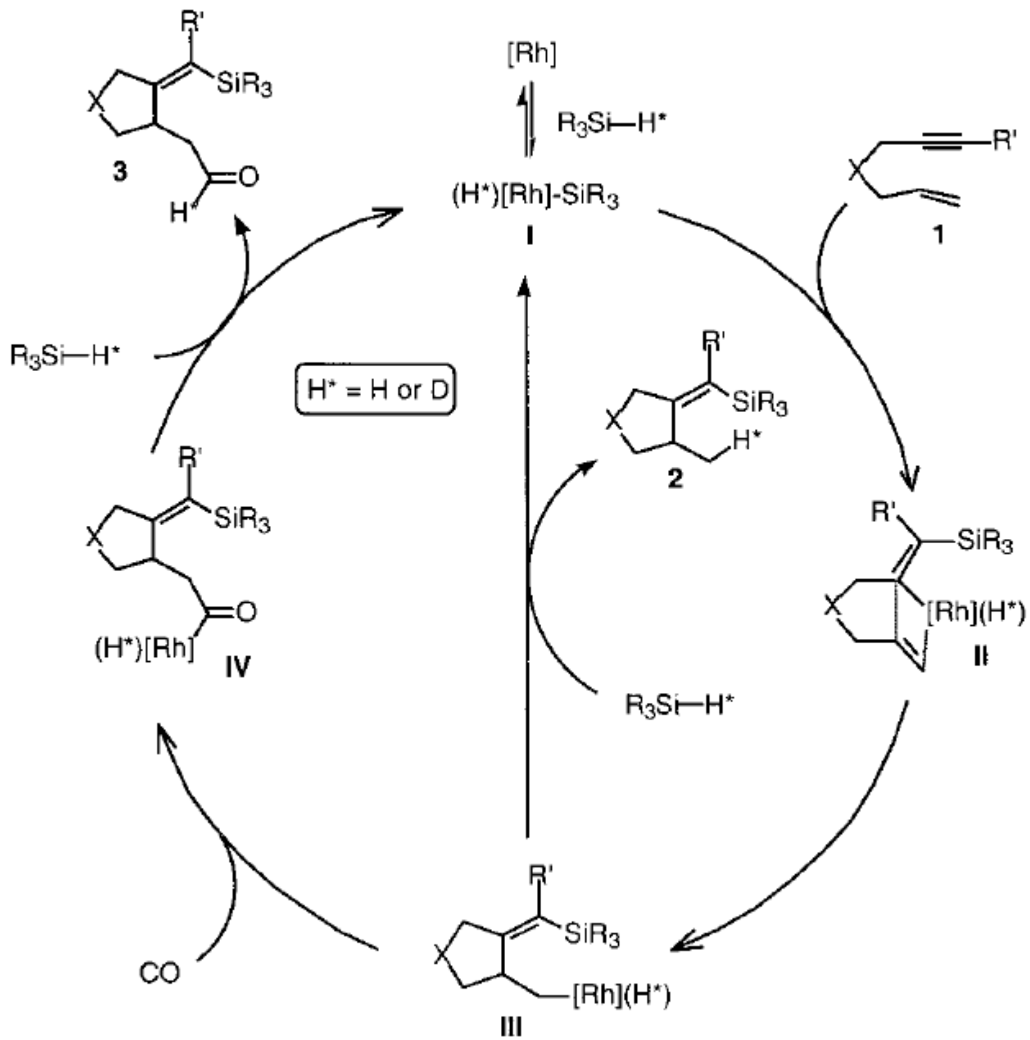


Widenhoefer *et al.* *OL* **2003**, *5*, 157



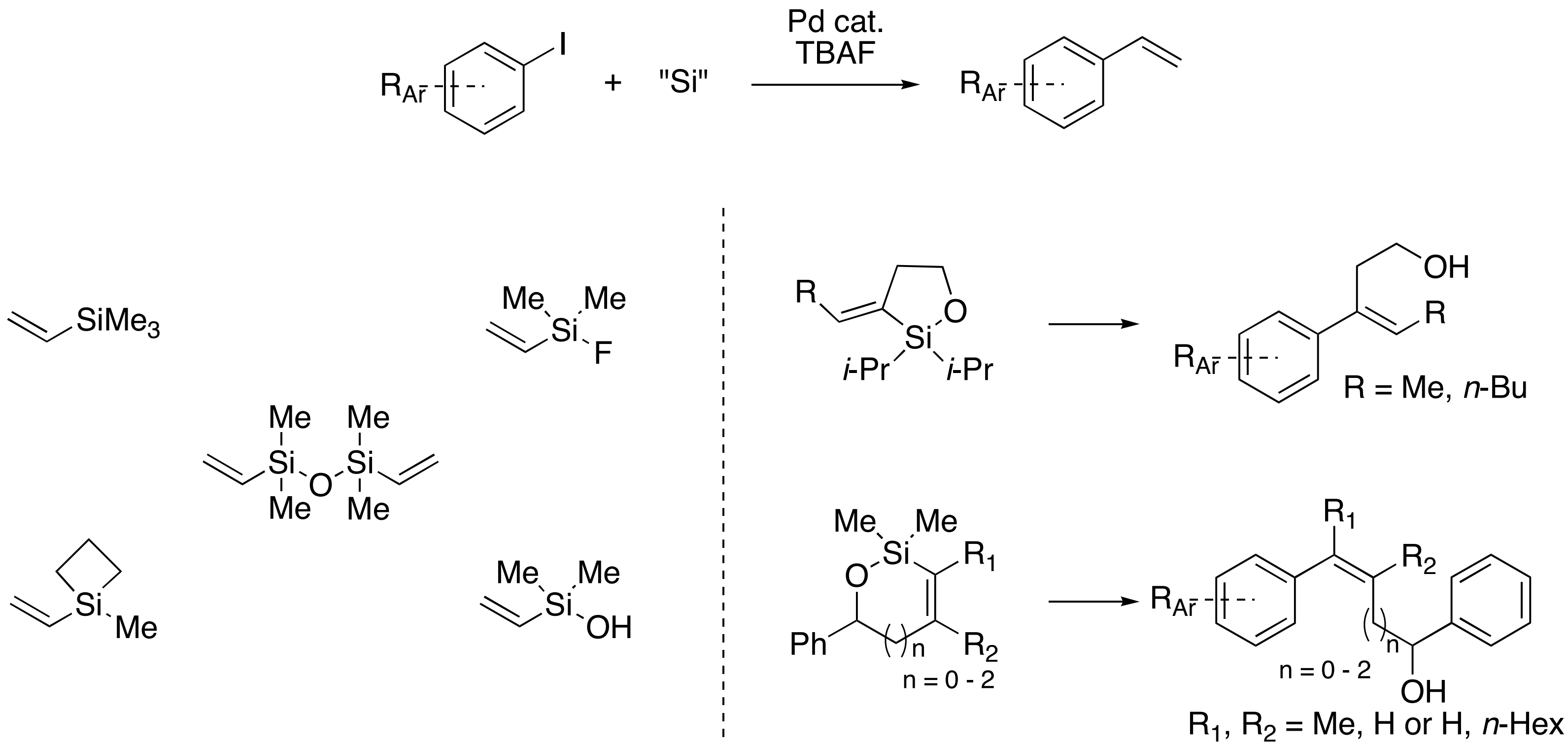
Ojima *et al.* *JACS* **2002**, *124*, 9164

Silylcarbocyclization Mechanism



Ojima *et al. JACS* **2002**, *124*, 9164

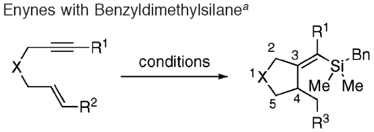
Fluorine Promoted Silicon Cross-Couplings



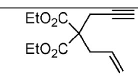
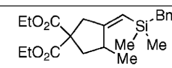
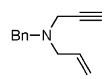
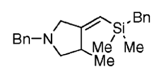
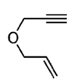
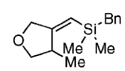
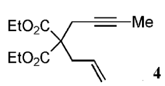
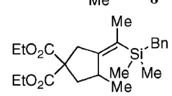
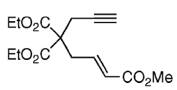
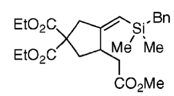
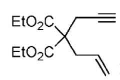
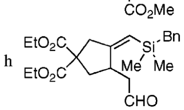
Hiyama *et al. JOC.* **1988**, *53*, 918
Denmark *et al. Acc. Chem. Res.* **2002**, *35*, 835

Previous Work Developing Silylcarbocyclization/ Silicon-Based Cross-Coupling Reactions

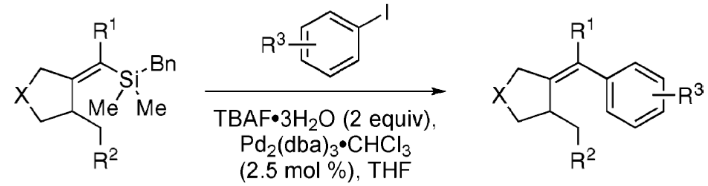
Table 1. Results of Silylcarbocyclization of Enynes with Benzyldimethylsilane[a]



1-5 → 6-11

entry	substrate	silane loading, equiv	catalyst loading,[b] mol %	temperature, °C	atmosphere	time	product	yield,[c] %
1	 **1**	1.5	0.5	rt	CO (1 atm)	10 min	 **6**	84
2	 **2**	1.5	0.5	rt	CO (1 atm)	15 min	 **7**	95
3[d]	 **3**	1.5	5	70	CO (1 atm)	20 min	 **8**	53
4	 **4**	2.0	2	50	CO (1 atm)	15 min	 **9**	81
5	 **5**	1.5	2	rt	CO (8 mol %)/Ar	3.5 h	 **10**	87
6[e]	 **1**	1.05	1	105	CO (20 atm)	48 h	 **11**	83

[a] All reactions run in hexane unless otherwise specified. [b] $Rh_4(CO)_{12}$ used unless otherwise specified. [c] Yields of analytically pure products. [d] Reaction run in toluene; catalyst, $Rh(acac)(CO)_2$. [e] Reaction run in dioxane; 20 mol % of $P(OEt)_3$ was used in addition to $Rh_4(CO)_{12}$.



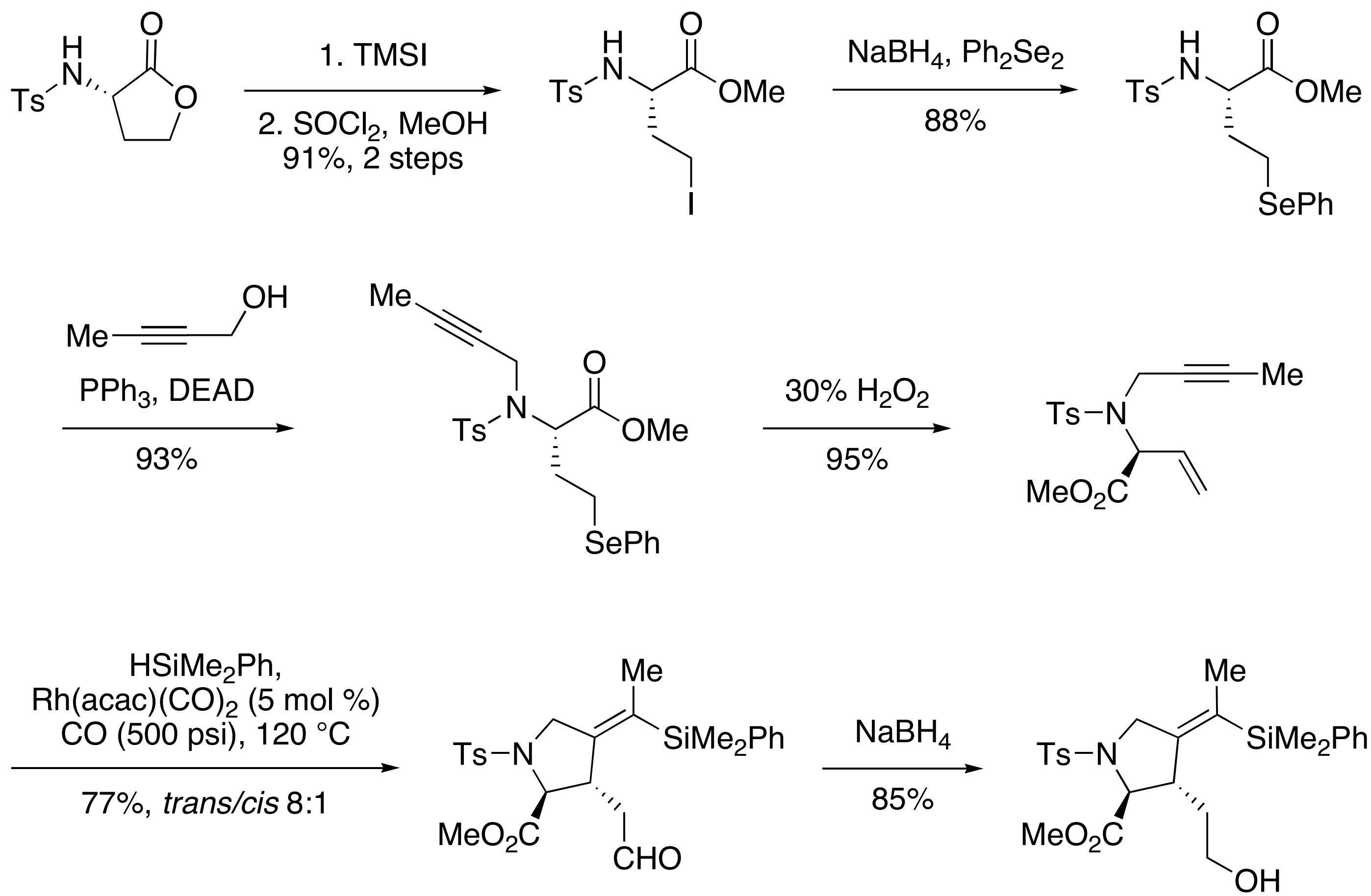
7-10 → **19-22**

entry	substrate	X	R^1	R^2	R^3	temp, °C	product	yield,[b] %
1	**7**	N-Bn	H	H	4-CO_2Et	rt	**19a**	72[c]
2	**7**	N-Bn	H	H	4-OMe	rt	**19b**	90[c]
3	**7**	N-Bn	H	H	2-Me	rt	**19c**	85[c]
4	**8**	O	H	H	4-CO_2Et	rt	**20a**	88[c]
5	**8**	O	H	H	4-OMe	rt	**20b**	89[c]
6	**8**	O	H	H	2-Me	rt	**20c**	77
7	**9**	$C(CO_2Et)_2$	Me	H	4-CO_2Et	35	**21a**	72
8	**9**	$C(CO_2Et)_2$	Me	H	4-OMe	35	**21b**	74
9	**9**	$C(CO_2Et)_2$	Me	H	2-Me	35	**21c**	64
10	**10**	$C(CO_2Et)_2$	H	CO_2Me	4-CO_2Et	rt	**22a**	74
11	**10**	$C(CO_2Et)_2$	H	CO_2Me	4-OMe	rt	**22b**	77
12	**10**	$C(CO_2Et)_2$	H	CO_2Me	2-Me	rt	**22c**	73

[a] All reactions performed in 1.0 M TBAF solution in THF with 1.1 equiv of substrate, 1.0 equiv of aryl iodide, and 2.5 mol % of $Pd_2(dba)_3$•$CHCl_3$ at 1.0 mmol scale under an Ar atmosphere at the specified temperature. [b] Yields of analytically pure products unless otherwise specified. [c] Yields of chromatographically homogeneous materials.

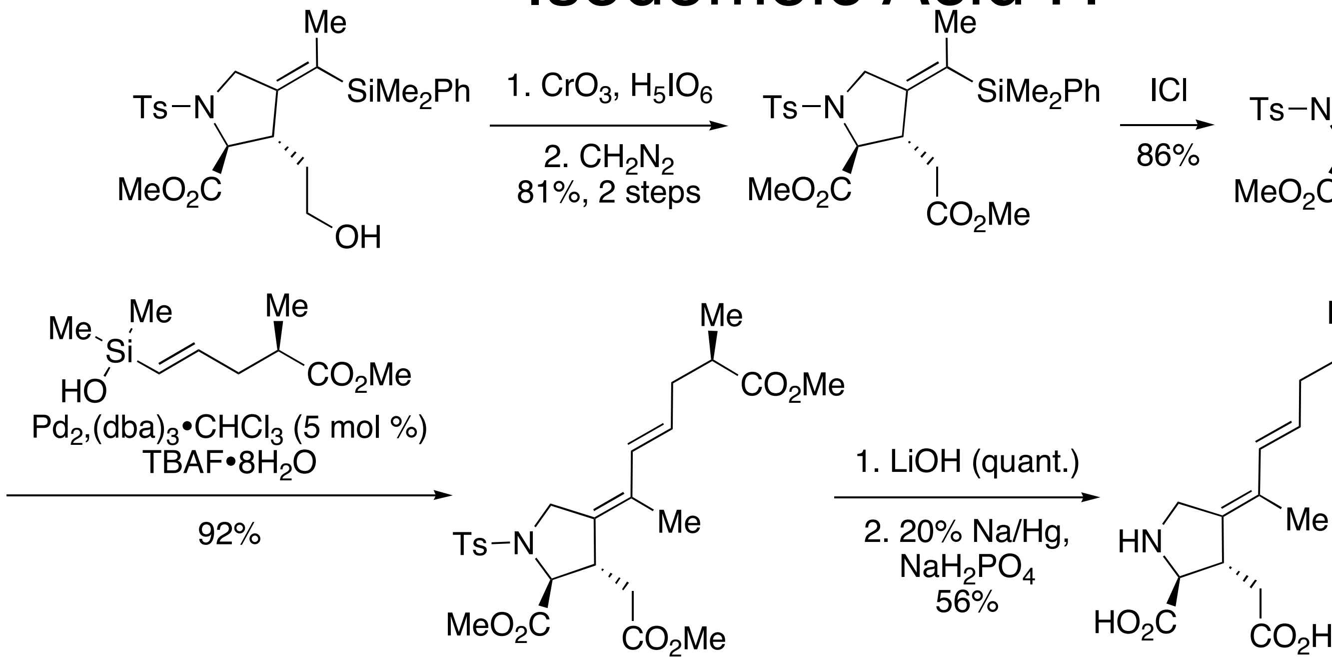
Denmark *et al. JACS* **2007**, *129*, 3737

Silylcarbocyclization



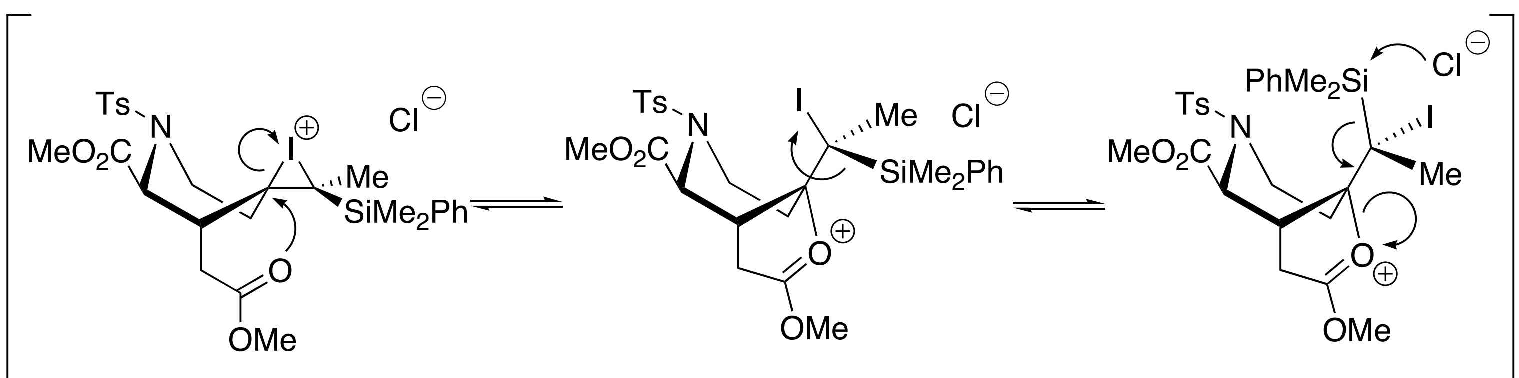
Denmark *et al. JACS* **2009**, *ASAP*

Isomerization of the Olefin and Synthesis of Isodomoic Acid H



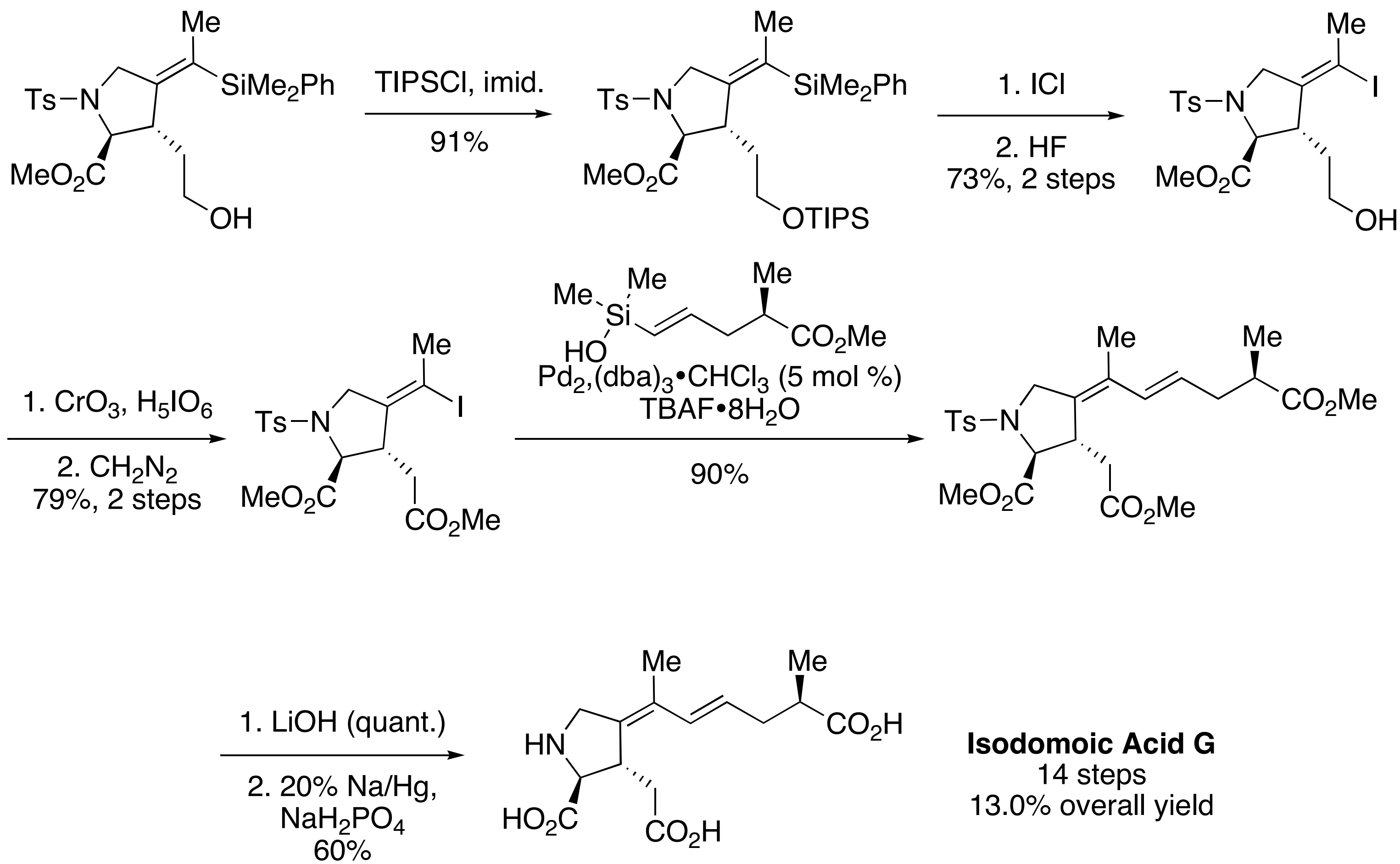
Isodomoic Acid H
12 steps
16.6% overall yield

Rational for Iodine Selectivity:



Zhao *et al. TL.* **1998**, *39*, 5323
Kishi *et al TL.* **1996**, *37*, 8647

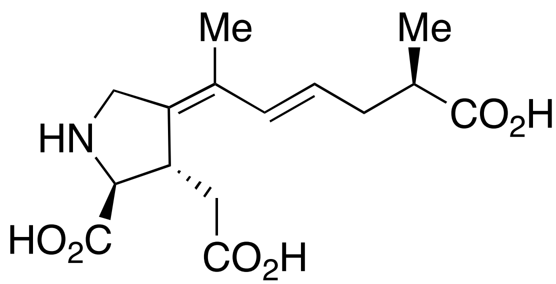
Synthesis of Isodomoic Acid G

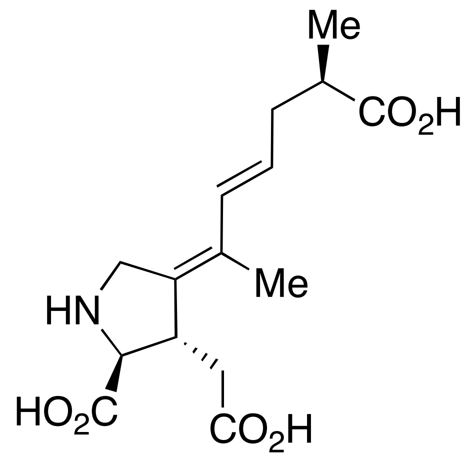


Isodomoic Acid G
14 steps
13.0% overall yield

Kishi *et al TL.* **1996**, *37*, 8647

Summary





- Synthesized isodomoic acids G and H in 14 and 12 steps respectively.
- Utilized a silylcarbocyclization/silicon based cross coupling sequence developed in the Denmark labs.
- Very efficient syntheses with average yields of 87% per step for each of the products.