APPENDIX FOUR

The Development and Scope of an Alternate Tandem Stille-Oxa-Electrocyclization Reaction[†]

A4.1 Background and Introduction

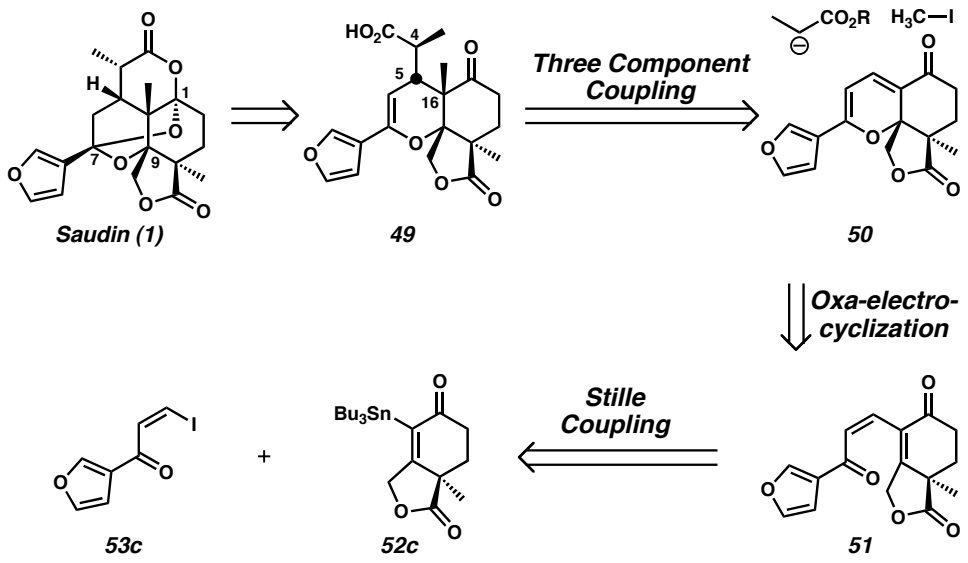
A4.1.1 Application of the Tandem Stille-Oxa-Electrocyclization Toward the Partial Synthesis of Saudin

Metal-mediated coupling reactions are essential tools for the synthetic chemist and are among the most important methods for forming carbon-carbon bonds. Tandem reactions are also useful since they can rapidly and efficiently build up complex molecular architectures. With these key features in mind, a palladium-catalyzed tandem Stille-oxa-electrocyclization has been developed in our group based upon work toward the total synthesis of saudin (**1**).[1]

The key disconnection in our synthetic strategy for saudin (**1**) is the opening of the 2H-pyran **50** via a retro-oxa-electrocyclization to reveal oxatriene **51**, followed by disconnection across the C(5)-C(16) bond via a Stille coupling (Scheme A4.1.1). This reveals the relatively simple coupling partners **52c** and **53c**.

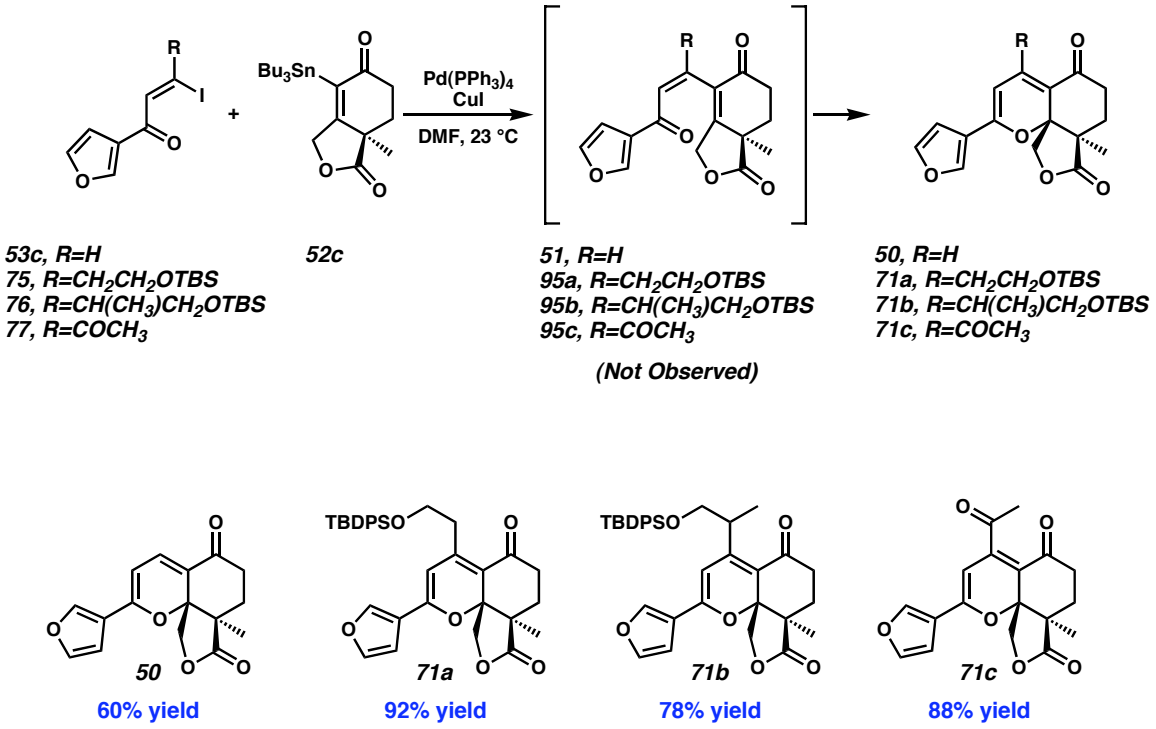
[†] This work was performed in collaboration with Taichi Kano, a postdoctoral scholar in the Stoltz group, and John F. Zepernick, a graduate student in the Stoltz group at the California Institute of Technology.

Scheme A4.1.1



When iodoenones **53c**, **75**, **76**, and **77** were treated with stannane **52c** under Cu(I)-accelerated Stille conditions, the desired coupling reactions occurred (Scheme A4.1.2). However, products **51** and **95a-c** were not observed. Instead, the substrates reacted further, undergoing an oxa-electrocyclization to yield substituted pyrans **50** and **71a-c**. This tandem reaction, which rapidly builds up the core structure of saudin, was selected for further investigation to evaluate its utility as a more general synthetic methodology.

Scheme A4.1.2

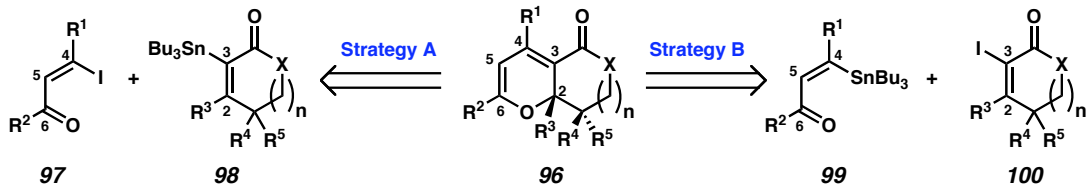


A4.1.2 An Alternate Tandem Stille-Oxa-Electrocyclization Strategy

The tandem Stille-oxa-electrocyclization has several interesting features: it is highly diastereoselective, convergent, and requires mild reaction conditions with low catalyst loading. These mild conditions are particularly noteworthy given the rather sterically hindered nature of the coupling partners. The reaction is also of interest since oxa-electrocyclizations are relatively under-utilized in organic synthesis. Recently there have been notable, though isolated, examples used in the syntheses of torreyanic acid by Porco[2], the epoxyquinols by Hayashi,[3] and the antimalarial naphthoquinones by Trauner.[4]

In pursuing this reaction as part of a general synthetic strategy for the formation of 2H-pyrans (**96**), we realized that there are two variants of this methodology: strategy A couples a 4-*cis*-iodoenone (**97**) with a 2-stannylenone (**98**), and strategy B couples a 4-*cis*-stannylenone (**99**) with a 2-iodoenone (**100**) (Scheme A4.1.3). Our earlier work had shown the viability of strategy A in the context of our synthetic efforts with saudin. Since different strategies may be better suited for different classes of pyrans, we were interested in expanding our tandem methodology by exploring the viability of strategy B. We were also interested in expanding the scope of this tandem reaction to include pyrans with varying substitution at positions 2, 3, and 6 of the ring system. We would like to now present our results on the development of a more general version of the tandem Stille-oxa-electrocyclization as a method for synthesizing highly substituted pyrans.

Scheme A4.1.3

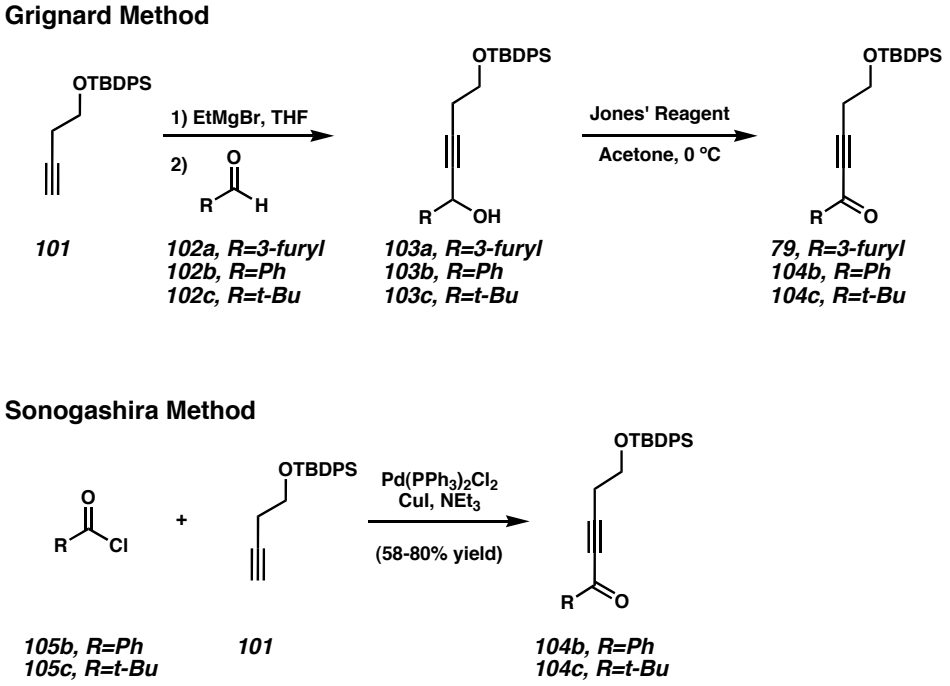


A4.2 Development of an Alternate Tandem Stille-Oxa-Electrocyclization Reaction

A4.2.1 Synthesis of the 4-*cis*-Stannylenone Substrates for the Tandem Stille-Oxa-Electrocyclization

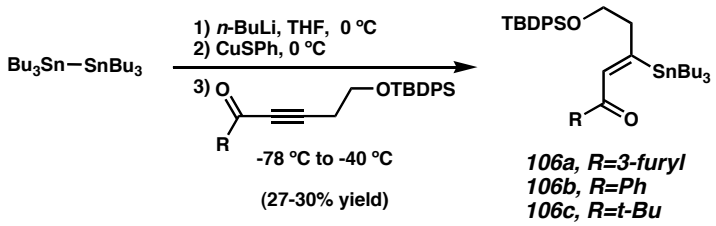
Two different routes were utilized to synthesize the 4-*cis*-stannylenone coupling partners for strategy B of our tandem methodology. The first route involved addition of a Grignard reagent into an aldehyde followed by a Jones' oxidation to form alkynones **79**, **104b**, and **104c** (Scheme A4.2.1). Alternatively, the same alkynones were made directly via a Sonogashira coupling between a terminal acetylene and an acid chloride (Scheme A4.2.1).[5]

Scheme A4.2.1



Alkynones **79**, **104b**, and **104c** were then converted to (Z)-vinyl stannanes (Scheme A4.2.2). Hexabutylditin was treated with *n*-butyl lithium, followed by the addition of copper thiophenol. This generated $(Bu_3Sn)CuSPhLi$ in situ, which was then reacted with alkynones **79**, **104b**, and **104c** to give vinyl stannanes **106a-c** with exclusively the desired olefin geometry.[6]

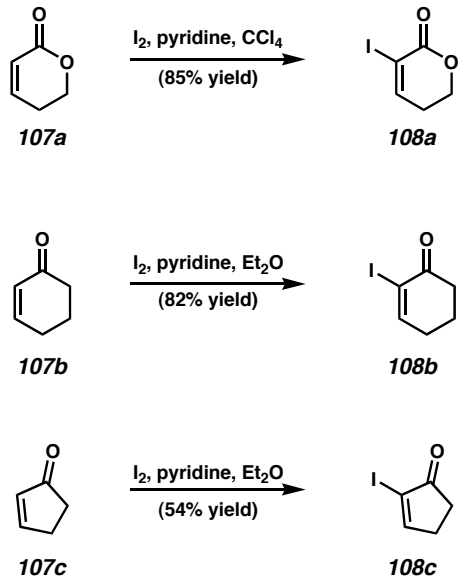
Scheme A4.2.2



A4.2.2 Synthesis of the 2-Iodoenone Substrates for the Tandem Stille-Oxa-Electrocyclization

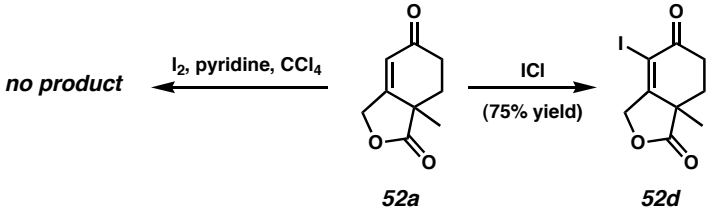
In order to examine the scope of the reaction, vinyl iodides **108a-c** were synthesized from the readily available enones **107a-c** (Scheme A4.2.3). These iodoenones feature varying ring sizes and differing amounts of steric bulk around the ring. In addition, vinyl iodide **108a** contains a lactone.

Scheme A4.2.3



Subjection of enone **52a** to the standard iodination conditions did not yield the desired product (Scheme A4.2.4). However, treatment with ICl provided iodoenone **52d** in good yield.

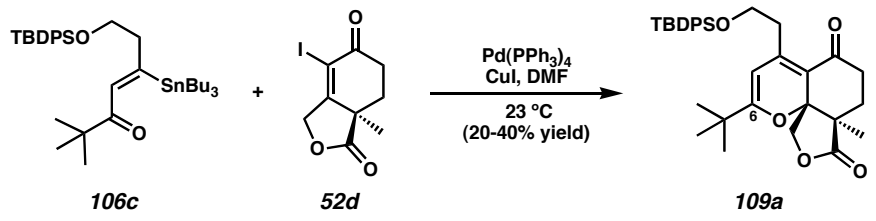
Scheme A4.2.4



A4.2.3 Optimization of the Alternate Tandem Stille-Oxa-Electrocyclization

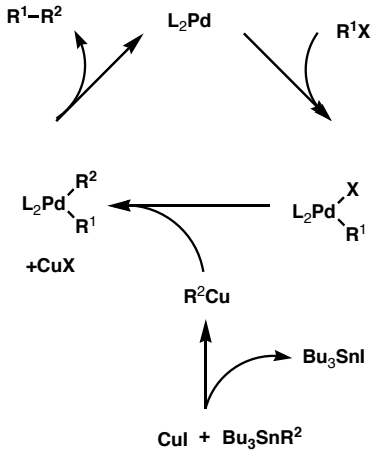
With a variety of stannanes and iodoenones in hand, the efficiency of the reaction was investigated. The bicyclic iodoenone **52d** served as a good test substrate to examine various substituents in the 6-position of the resulting 2H-pyran. Stannane **106c** successfully underwent both the Stille coupling and the oxa-electrocyclization in tandem when coupled to iodoenone **52d**. However, the reaction conditions that worked so well for strategy A of our tandem reaction were less successful for strategy B (Scheme A4.2.5). Pyran **109a** was produced in low and variable yields, presumably because of decomposition of 4-stannyl enone **106c**.

Scheme A4.2.5



Previous studies in our group demonstrated that copper(I) iodide was necessary for this Stille coupling to proceed. This copper effect in Stille couplings has been well studied,[7,8] and different mechanisms have been proposed depending upon the reaction medium.[9,10] In the case of very polar solvents such as DMF or NMP, copper(I) salts are believed to undergo Cu/Sn transmetallation, resulting in the formation of an organocopper species (Scheme A4.2.6).

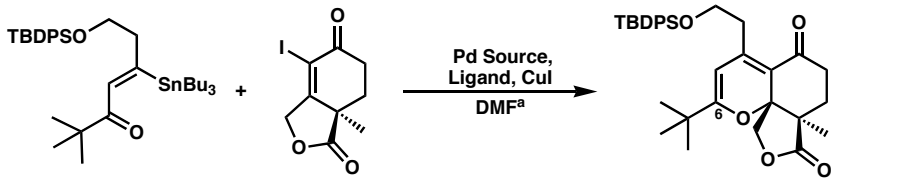
Scheme A4.2.6



In an attempt to further optimize our reaction, the amount of copper(I) iodide was varied. When substoichiometric amounts of copper(I) iodide were used, the stannane was not consumed, which suggested that somehow the presence of stoichiometric copper was leading to an undesired side reaction of the vinyl stannane (Table A4.2.1, entries 2 and 3). In two control experiments, iodoenone **52d** was excluded from the reaction (Table A4.2.1, entries 4 and 5). Decomposition of vinyl stannane **106c** was observed in the presence of copper(I) iodide (Table A4.2.1, entry 4), while no decomposition was seen in the absence of copper(I) iodide (Table A4.2.1, entry 5). From these results, it was

hypothesized that copper(I) was undergoing oxidation to a copper(II) species, which is known to facilitate the homocoupling of vinyl stannanes.[11] In order to test this hypothesis, the reaction was run in an inert atmosphere glovebox, thus rigorously excluding oxygen. To our delight, the desired product was obtained in high yield (Table A4.2.1, entry 6).

Table A4.2.1



106c *52d* *109a*

Entry	Pd Source	Ligand	CuI (mol%)	Other	Stannane consumed?	Yield
1	$Pd_2(dba)_3$	PPh_3	100%		yes	45%[b]
2	$Pd_2(dba)_3$	PPh_3	5%		no	trace
3	$Pd(PPh_3)_4$		0%		no	no reaction
4	$Pd(PPh_3)_4$		100%	no iodoenone 5a	yes	decomposition
5	$Pd(PPh_3)_4$		0%	no iodoenone 5a	no	no reaction
6	$Pd(PPh_3)_4$		100%	in glovebox	no	94%[b]

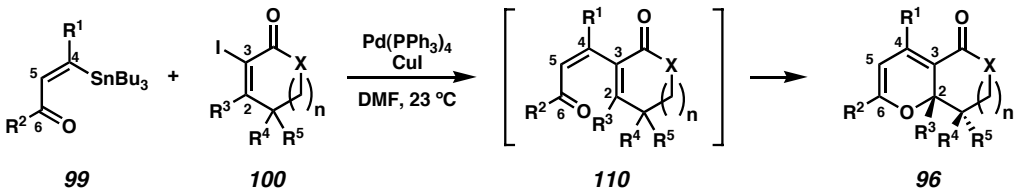
[a] 5 mol% Pd, 20 mol% ligand, 0.1 M in **5a**, 1 equiv **5a**, 1.2 equiv **14c**. [b] Isolated yield.

A4.2.4 Substrate Scope of the Alternate Tandem Stille-Oxa-Electrocyclization

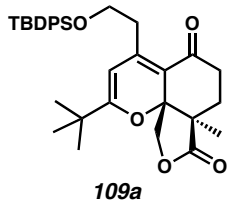
Having found that rigorously anaerobic conditions were optimal for this reaction, we examined other substrates. Vinyl stannes **106a**, **106b**, and **106c** (Scheme A4.2.2)

were successfully coupled with vinyl iodides **108a** (Scheme A4.2.3) and **52d** (Scheme A4.2.4) to produce pyrans **109a-e** and **71a** in good to excellent yields (Scheme A4.2.7).

Scheme A4.2.7

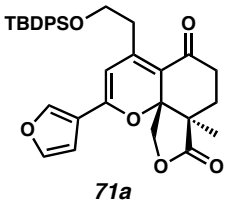


99 ***100*** ***110*** ***96***



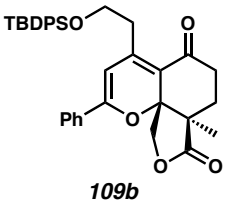
109a

94% yield



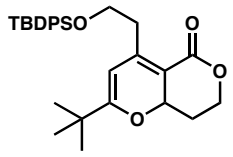
71a

92% yield



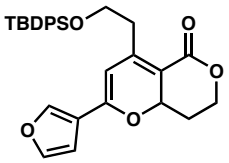
109b

94% yield



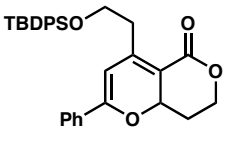
109c

67% yield



109d

65% yield



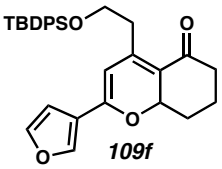
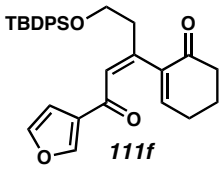
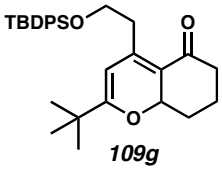
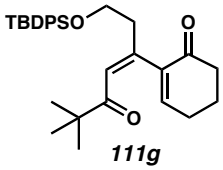
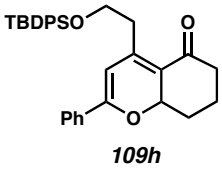
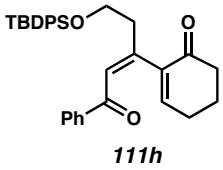
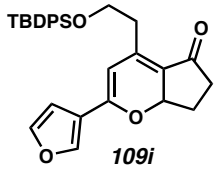
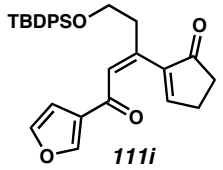
109e

92% yield

When we subjected vinyl iodides **108b** and **108c** (Scheme A4.2.3) to our tandem reaction conditions with various vinyl stannanes, the Stille couplings were successful, but the oxa-electrocyclizations yielded an equilibrium mixture of products (Table A4.2.2). These equilibrium mixtures were difficult to characterize because the species in solution were rapidly interconverting on the NMR timescale, causing the peaks in the NMR spectrum to be very broad. To alleviate this problem, the ^{1}H NMR spectra were taken at

–30 ºC. These products were obtained in useful yields and often in a good ratio of cyclized to uncyclized product.

Table A4.2.2

Cyclized Product	Uncyclized Product	Ratio (Cyclized:Uncyclized)[a]	Yieldb
 *109f*	 *111f*	7 : 1	90%
 *109g*	 *111g*	10 : 1	66%
 *109h*	 *111h*	10 : 1	73%
 *109i*	 *111i*	1 : 3	62%

[a] Ratio determined by 1H NMR spectroscopy. b Isolated yield.

A4.3 Theoretical Studies on the Tandem Stille-Oxa-Electrocyclization

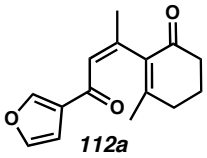
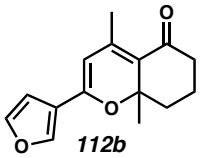
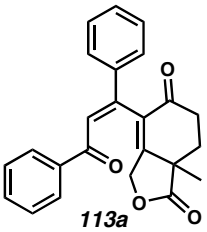
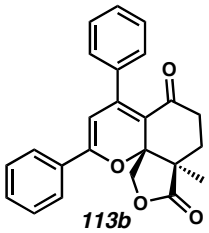
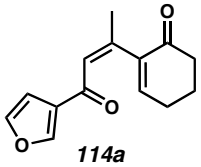
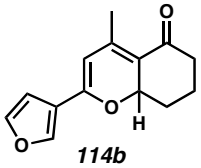
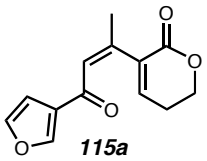
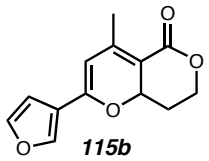
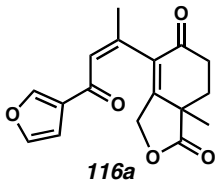
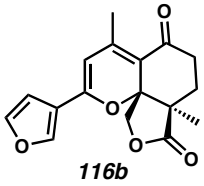
One of the key difficulties in developing the oxa-electrocyclization as a useful synthetic tool is a typically small – or even unfavorable – thermodynamic driving force

for the reaction. This often leads to the formation uncyclized products or equilibrium mixtures of products. Rather than relying solely on trial and error, we turned to theoretical calculations to examine substrates for the tandem Stille-oxa-electrocyclization reaction.

Using Spartan '02 for Macintosh, AM1 calculations were performed to evaluate the enthalpy of reaction for the conversion of 1,3,5-oxatriene to 2H-pyran (Table A4.3.1). In order to simplify the calculations, methyl groups were used to approximate longer alkyl groups in the 4-position of the pyran ring. The theoretical results agreed well with the experimental observations. In the cases where the calculated enthalpy was endothermic, the analogous 2H-pyran products were not observed experimentally (Table A4.3.1, entries 1 and 2). In the cases where the calculated enthalpy was exothermic, the 2H-pyrans were obtained as the major products from the tandem Stille-oxa-electrocyclization process (Table A4.3.1, entries 3, 4, and 5). While these methods are not as precise as higher level calculations,[12] they offer some degree of predictive power for evaluating potential oxa-electrocyclization substrates.

Table A4.3.1

Enthalpy of Reaction for Oxaelectrocyclizations

Entry	1,3,5-oxatriene	2H-pyran	ΔH (kcal/mol)[a]
1	 ***112a***	 ***112b***	2.046
2	 ***113a***	 ***113b***	0.083
3	 ***114a***	 ***114b***	-3.71
4	 ***115a***	 ***115b***	-3.84
5	 ***116a***	 ***116b***	-1.62

[a] AM1 result based on lowest energy conformation of 1,3,5-hexatriene and 2H-pyran.

A4.4 Conclusion

The tandem Stille-oxa-electrocyclization reaction is a general method for the synthesis of highly substituted 2H-pyrans. Versatility in this methodology has been

shown by developing both variants of this reaction (strategy A and strategy B). This work demonstrates the utility of tandem reactions for the construction of complex molecular architectures and also shows the potential of using oxa-electrocyclizations in synthesis.

A4.5 Experimental Section

A4.5.1 Materials and Methods

Unless stated otherwise, reactions were performed in flame-dried glassware sealed with rubber septa under a nitrogen atmosphere using anhydrous, deoxygenated solvents. Commercially obtained reagents were used as received. Solvents were dried by passage through an activated alumina column under argon. Liquids and solutions were transferred via syringe. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized using a combination of UV, anisaldehyde, ceric ammonium molybdate, and potassium permanganate staining. ICN silica gel (particle size 0.032 - 0.063 mm) was used for flash chromatography. ^{1}H NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz) or a Varian Inova 500 (at 500 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 75 MHz) or a

Varian Inova 500 (at 125 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{13}C NMR spectra are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Spectrum BXII spectrometer or a Perkin Elmer Paragon 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). High resolution mass spectra were obtained from the California Institute of Technology Mass Spectral Facility.

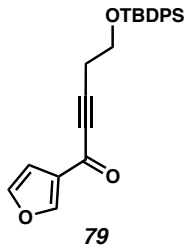
A4.5.2 Preparative Procedures

General Procedure for the Preparation of Propargyl Alcohols. A terminal alkyne (18 mmol, 1 equiv) was added to a stirred solution of ethyl magnesium bromide (18 mmol, 1 equiv) in Et_2O (10 mL) at 23 ºC. This reaction mixture was stirred for 30 min. Aldehyde (21 mmol, 1.2 equiv) was then added dropwise, and the reaction mixture was stirred until the reaction reached completion as determined by TLC. After quenching with 1 N HCl, the organic layer was washed three times with water and once with brine. The organic layer was separated and dried over $MgSO_4$. Following concentration in vacuo, the resulting crude mixture was carried on to the oxidation step without further purification.

General Procedure for the Preparation of Ynones by Jones' Oxidation. The crude propargyl alcohol (7.2 mmol, 1 equiv) was dissolved in acetone (15 mL). This solution was cooled to 0 ºC, and Jones' reagent (15 mmol, 2.1 equiv) was added slowly. After stirring for 30 min, the excess Jones' reagent was quenched with isopropanol. The

reaction mixture was extracted three times with Et_2O. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine. After drying over $MgSO_4$ and concentrating in vacuo, the crude ynone was purified by flash chromatography.

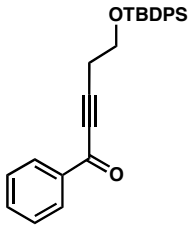
General Procedure for the Preparation of Ynones via the Sonogashira Reaction. A Schlenk tube was charged with CuI (0.2mmol, 2 mol%), $Pd(PPh_3)_2Cl_2$ (0.06 mmol, 0.5 mol%), and the terminal alkyne (10.8 mmol, 1 equiv). Next, NEt_3 (22 mL) was added to the Schlenk tube, and the mixture was degassed by the freeze-pump-thaw method. An acid chloride (14.2 mmol, 1.3 equiv) was then added dropwise to the reaction mixture at 23 ºC. After stirring for 12 h, water was added to the mixture, which was then extracted three times with pentane. The combined organic layers were washed thrice with water and once with brine and dried over $MgSO_4$. After concentrating in vacuo, the crude ynone was purified by flash chromatography.



79

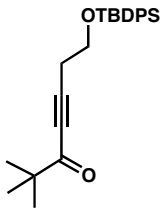
Ynone 79. Purification by flash chromatography (30:1 hexanes/EtOAc eluent) provided ynone **79** (51% yield) as a clear oil: ^{1}H NMR (300 MHz, CDCl3) δ 8.10 (dd, J = 1.3, 0.8 Hz, 1H), 7.75-7.66 (m, 5H), 7.48-7.35 (m, 6H), 6.81 (dd, J = 1.9, 0.8 Hz, 1H), 3.88 (t, J = 6.6 Hz, 2H), 2.68 (t, J = 6.5 Hz, 2H), 1.08 (s, 9H); ^{13}C NMR (75 MHz,

CDCl3) δ 171.3, 150.6, 144.6, 135.7, 135.0, 133.4, 130.1, 129.8, 129.4, 128.0, 127.9, 108.6, 90.6, 80.8, 61.7, 27.0, 26.8, 23.4, 19.4; IR (thin film/NaCl) 2931, 2858, 2217, 1642, 1428, 1308, 1164, 1112 cm^{-1}; HRMS (EI+) m/z calc'd for $[C_{25}H_{26}O_3Si]$+: 402.1651, found 402.1664.



104b

Ynone 104b. Purification by flash chromatography (8:1 hexanes:EtOAc eluent). Provided ynone **104b** (27% yield) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17-8.14 (m, 2H), 7.73-7.69 (m, 4H), 7.583 (tt, *J* = 9.6, 1.5 Hz, 1H), 7.47-7.35 (m, 8H), 3.92 (t, *J* = 6.6 Hz, 2H), 2.748 (t, *J* = 6.6 Hz, 2H), 1.12 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.1, 136.8, 135.6, 134.0, 133.2, 129.9, 129.7, 128.5, 127.8, 93.8, 80.4, 61.5, 26.8, 23.5, 19.2; IR (thin film/NaCl) 2931, 2858, 2238, 2207, 1645, 1645, 1264, 1113 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[C_{27}H_{27}O_2Si]^+$: 411.1780, found 411.1792.

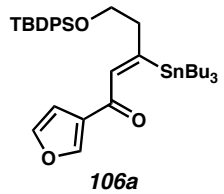


104c

Ynone 104c. Purification by flash chromatography (1:1 hexanes:DCM eluent) provided ynone **104c** (58% yield) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70-7.66 (m, 4H), 7.4-7.36 (m, 6H), 3.83 (t, *J* = 6.6 Hz, 2H), 2.63 (t, *J* = 6.6 Hz, 2H), 1.20 (s, 9H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.3, 135.6, 133.3, 129.8, 127.8, 92.6, 79.5, 61.5, 44.6, 26.8, 26.1, 23.3, 19.2; IR (thin film/NaCl) 2932, 2859, 2211, 1810, 1670 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[C_{25}H_{31}O_2Si]^+$: 391.2093, found 391.2098.

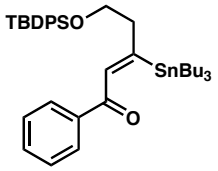
General Procedure for the Preparation of (Z)-Vinyl Stannanes. To a stirred solution of bis(tributyltin) (4.5 mmol, 1.2 equiv) in THF (40 mL) at 0 ºC was added *n*-butyllithium (4.5 mmol, 1.2 equiv). After stirring for 30 min, CuSPh (4.5 mmol, 1.2 equiv) was added. After an additional 30 min of stirring, the reaction mixture was cooled to –78 ºC. Alkynone (3.8 mmol, 1 equiv) was added slowly to the reaction mixture, which was stirred for 30 min at –78 ºC. The reaction was then warmed to –40 ºC, stirred for 1 h, and allowed to warm to room temperature. Saturated aqueous NH_4Cl was added to quench the reaction, and the mixture was extracted with Et_2O. To the separated organic layer was added methanol, forming a yellow slurry that was filtered through

celite. The filtrate was concentrated in vacuo to provide the crude (Z)-vinyl stannane, which was then purified by flash column chromatography.



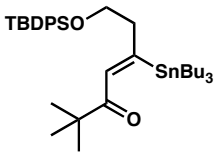
106a

Stannane 106a. Purification by flash chromatography (100:1 hexanes:EtOAc → 25:1 hexanes:EtOAc eluent) provided stannane **106a** (49% yield) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.70-7.64 (m, 5H), 7.46-7.34 (m, 6H), 7.22 (s, 1H), 6.83 (d, *J* = 1.1 Hz, 1H), 3.75 (t, *J* = 6.6 Hz, 2H), 2.76 (t, *J* = 6.2 Hz, 2H), 1.58-1.35 (m, 6H), 1.35-1.19 (m, 6H), 1.05 (s, 9H), 0.96-0.77 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.8, 173.7, 147.7, 144.2, 135.8, 135.4, 134.0, 129.9, 128.6, 127.9, 109.3, 62.9, 43.4, 29.5, 27.7, 27.1, 14.0, 11.3, 9.0; IR (thin film/NaCl) 2955.89, 2925.30, 1651.69, 1559.99, 1157.70, 1111.94 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[C_{37}H_{53}O_3SiSn]^+$: 693.2786, found 693.2779.



106b

Stannane 106b. Purification by flash chromatography (10:1 hexanes:EtOAc → 6:1 hexanes:EtOAc eluent) provided stannane **106b** (31% yield) as a clear clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98-7.95 (m, 2H), 7.70-7.67 (m, 4H), 7.63 (s, 1H), 7.55 (m, 1H), 7.48-7.35 (m, 8H), 3.79 (t, *J* = 6.6 Hz, 2H), 2.83 (t, *J* = 6.6 Hz, 2H), 1.48-1.42 (m, 6H), 1.29-1.25 (m, 6H), 1.06 (s, 9H), 0.99-0.93 (m, 6H), 0.85 (t, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.5, 175.4, 138.3, 135.6, 134.1, 133.8, 132.6, 129.7, 128.5, 128.5, 127.7, 62.9, 43.5, 29.3, 27.5, 26.9, 19.3, 13.8, 11.2; IR (thin film/NaCl) 1651 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[C_{39}H_{55}O_2SiSn]^+$: 703.2993, found 703.3007.

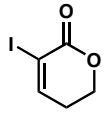


106c

Stannane 106c. Purification by flash chromatography (50:1 hexanes:EtOAc eluent) provided stannane **106c** (28% yield) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72-7.68 (m, 4H), 7.46-7.35 (m, 6H), 7.11 (s, 1H), 3.70 (t, *J* = 6.65 Hz, 2H), 2.69 (t, *J* = 6.65 Hz, 2H), 1.44-1.34 (m, 6H), 1.26-1.22 (m, 7H), 1.13 (s, 9H), 1.04 (s, 9H), 0.89-0.81 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.6, 171.4, 135.6, 133.8, 133.6, 129.6, 127.7,

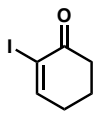
62.9, 43.2, 42.5, 29.3, 27.5, 26.9, 26.4, 19.2, 13.7, 11.0; IR (thin film/NaCl) 2956, 2857, 1671, 1113 cm^{-1}; HRMS (EI+) *m/z* calc'd for $[C_{33}H_{51}O_2SiSn]^+$: 627.2680, found 627.2666.

General Procedure for the Preparation of Iodoenones from I_2/Pyridine. The enone (1.16 mmol) was dissolved in CCl_4 or Et_2O (1 ml) and pyridine (1 ml). A solution of iodine (0.9 g, 3.4 mmol) in 1:1 pyridine : CCl_4 or Et_2O (6 mL) was then slowly added at 0 ºC. The reaction was quenched with aqueous sodium thiosulfate and the mixture was extracted with CH_2Cl_2. The organic layer was then washed once with brine and dried over $MgSO_4$. Following concentration in vacuo, the crude product was purified by flash chromatography.



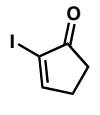
108a

Iodopyranone 108a. Purification by flash chromatography (10:1 hexanes:EtOAc eluent) provided iodopyranone **108a** (85% yield) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (t, *J* = 4.65 Hz, 1H), 4.48 (t, *J* = 6 Hz, 2H), 2.52 (dt, *J* = 4.65, 6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 154.4, 89.5, 67.0, 28.2; IR (thin film/NaCl) 1724 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[C_5H_6O_2I]^+$: 224.9413, found 224.9405.



108b

Iodocyclohexenone 108b. Purification by flash chromatography (4:1 hexanes:EtOAc eluent) provided iodocyclohexenone **108b** (82% yield) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (t, *J* = 4.5 Hz, 1H), 2.70-2.66 (m, 2H), 2.47 (dt, *J* = 4.5, 6 Hz, 2H), 2.15-2.06 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.2, 159.5, 103.9, 37.3, 30.0, 22.9; HRMS (FAB+) *m/z* calc'd for $[C_6H_8OI]^+$: 222.9620, found 222.9622.

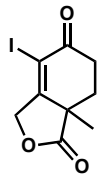


108c

Iodocyclopentenone 108c. Purification by flash chromatography (4:1 hexanes:EtOAc eluent) provided iodocyclopentenone **108c** (54% yield) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (dt, *J* = 0.9, 3 Hz, 1H), 2.78-2.74 (m, 2H), 2.50-2.46 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.1, 169.7, 102. 9, 31.3, 31.0.

General Procedure for the Preparation of Iodoenones from ICl. The enone (6 mmol) was dissolved in CH_2Cl_2 (12 ml). A solution of ICl (1.0 M in CH_2Cl_2, 9.9 mL, 9.9 mmol) was then slowly added at 0 ºC. After 4 h, NEt_3 (1.4 mL, 9.9 mmol) was added at

0 °C. The mixture was washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$. Following concentration in vacuo, the crude product was purified by flash chromatography.

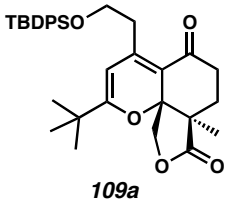


52d

Bicyclic Iodoenone 52d. Purification by flash chromatography (4:1 hexanes:EtOAc eluent) provided iodoenone **52d** (75% yield) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.97 (d, *J* = 15 Hz, 1H), 4.83 (d, *J* = 15 Hz, 1H), 2.86-2.81 (m, 2H), 2.31-2.13 (m, 2H), 1.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.2, 176.8, 166.5, 99.1, 73.2, 46.0, 32.0, 29.5, 21.6; HRMS (FAB+) *m/z* calc'd for $[C_9H_{10}O_3I]^+$: 292.9675, found 292.9685.

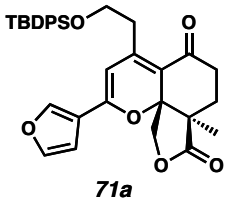
General Procedure for Tandem Stille-oxa-electrocyclization Reactions. $Pd(PPh_3)_4$ (0.0033 mmol, 5 mol%), CuI (0.057 mmol, 1 equiv), and the iodoenone (0.057 mmol, 1 equiv) were weighed into an oven-dried vial. The stannane (0.068 mmol, 1.2 equiv) was concentrated in vacuo from benzene in a separate flask. These materials were taken into the glovebox. The stannane was dissolved in DMF (0.7 mL), and the resulting solution was transferred into the vial containing the other reagents. The reaction was

stirred for 24 h. Water was then added, and the reaction mixture was extracted with Et_2O. The organic layer was dried by passing it through a short pad of silica gel. The material was concentrated in vacuo to yield the crude product, which could then be purified by flash column chromatography. Sometimes after flashing a compound, some alkyl tin contaminants remained. These were removed by dissolving the material in acetonitrile and washing three times with hexanes. Concentrating the acetonitrile layer in vacuo produced the desired product free of alkyl tin byproducts.



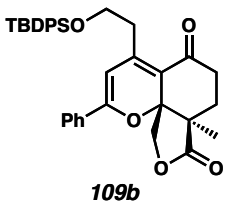
109a

***tert*-Butyl Appended Tricycle 109a.** Purification by flash chromatography (hexanes → 5:1 hexanes/EtOAc eluent) provided polycycle **109a** (94% yield) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66-7.62 (m, 4H), 7.46-7.33 (m, 6H), 5.45 (s, 1H), 4.64 (d, *J* = 10.8 Hz, 1H), 3.97-3.83 (m, 3H), 3.11 (dt, *J* = 12.0, 5.0 Hz, 1H), 2.84-2.75 (m, 1H), 2.62-2.46 (m, 1H), 2.38 (dt, 1H), 1.95 (q, *J* = 5 Hz, 2H), 1.47 (s, 3H), 1.11 (s, 9H), 1.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.8, 179.4, 168.7, 151.8, 135.6, 133.7, 129.7, 127.7, 112.9, 103.4, 86.0, 71.4, 63.5, 44.9, 36.7, 35.7, 35.0, 27.8, 27.2, 26.9, 19.3, 14.7; IR (thin film/NaCl) 2932, 2858, 1787, 1663 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[C_{34}H_{43}O_5Si]^+$: 559.2880, found 559.2878.



71a

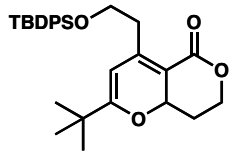
Furan Appended Tricycle 71a. Purification by flash chromatography (10:1 hexanes:EtOAc → 7:1 hexanes:EtOAc eluent) provided polycycle **71a** (92% yield) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.66-7.61 (m, 4H), 7.45-7.32 (m, 7H), 6.46 (d, *J* = 2.1 Hz, 1H), 5.82 (s, 1H), 4.74 (d, *J* = 11.1 Hz, 1H), 3.97-3.88 (m, 3H), 3.10 (dt, *J* = 2.4, 6.0 Hz, 2H), 2.68-2.23 (m, 2H), 2.04-2.00 (m, 2H), 1.54 (s, 3H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.7, 179.2, 151.5, 144.3, 143.1, 135.6, 133.7, 133.6, 129.7, 172.7, 120.7, 113.9, 107.3, 105.5, 86.5, 71.5, 63.3, 44.9, 36.6, 35.0, 27.8, 26.9, 19.3, 14.9; IR (thin film/NaCl) 2932, 2858, 1785, 1659, 1112 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[C_{34}H_{37}O_6Si]^+$: 569.2359, found 569.2346.



109b

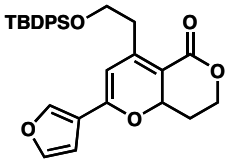
Phenyl Appended Tricycle 109b. Purification by flash chromatography (hexanes → 5:1 hexanes/EtOAc eluent) provided polycycle **109b** (94% yield) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (m, 5H), 7.39 (m, 10H), 6.15 (s, 1H), 4.76 (d, *J* =

11 Hz, 1H), 3.95 (m, 3H), 3.10 (t, *J* = 6 Hz, 2H), 2.58 (m, 1H), 2.44 (dt, *J* = 7.4, 13.5 Hz, 1H), 2.05 (m, 2H), 1.57 (s, 3H), 1.03 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.9, 179.3, 156.4, 151.5, 135.6, 133.7, 132.1, 131.0, 129.7, 128.8, 127.7, 126.1, 114.2, 105.5, 86.7, 71.5, 63.3, 45.0, 36.7, 35.0, 27.8, 26.9, 19.3, 14.9; IR (thin film/NaCl) 2931, 2857, 1786, 1662 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[C_{36}H_{39}O_5Si]^+$: 579.2567, found 579.2565.



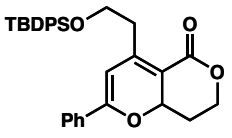
109c

***tert*-Butyl Appended Bicycle 109c.** Purification by flash chromatography (hexanes → 5:1 hexanes:EtOAc eluent) provided bicycle **109c** (67% yield) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67-7.64 (m, 4H), 7.44-7.33 (m, 6H), 5.54 (s, 1H), 4.44 (t, *J* = 5.3 Hz, 1H), 4.32 (m, *J* = 6 Hz, 1H), 4.18 (m, 1H), 3.07 (m, 1H), 2.88 (m 1H), 2.26 (q, *J* = 5.3 Hz, 2H), 1.12 (s, 9H), 1.0 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 164.9, 153.2, 135.7, 133.8, 129.6, 127.6, 105.0, 104.0, 72.8, 63.7, 63.5, 35.7, 35.6, 29.0, 27.9, 26.9, 19.2; IR (thin film/NaCl) 2960, 2858, 1706, 1543, 1113 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[C_{30}H_{37}O_4Si]^+$: 489.2461, found 489.2473.



109d

Furan Appended Bicycle 109d. Purification by flash chromatography (hexanes → 10:1 hexanes:EtOAc eluent) provided polycycle **109d** (65% yield) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.65 (d, *J* = 6.5 Hz, 4H), 7.41-7.26 (m, 7H), 6.49 (s, 1H), 5.91 (s, 1H), 4.67 (t, *J* = 5.0 Hz, 1H), 4.37-4.22 (m, 2H), 3.93 (t, *J* = 6.0 Hz, 2H), 3.11-3.01 (m, 2H), 2.33 (q, *J* = 5.0 Hz, 2H), 1.03 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0, 153.9, 153.1, 144.2, 143.0, 135.9, 134.0, 131.1, 129.8, 127.9, 120.8, 108.0, 106.4, 73.1, 63.9, 63.3764, 35.9, 29.3, 27.1, 19.4; IR (thin film/NaCl) 2931, 2857, 1703, 1530, 1113 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[C_{30}H_{33}O_5Si]^+$: 501.2097, found 501.2105.



109e

Phenyl Appended Bicycle 109e. Purification by flash chromatography (hexanes → 5:1 hexanes/EtOAc eluent) provided polycycle **109e** (92% yield) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63-7.67 (m, 5H), 7.31-7.42 (m, 10H), 6.25 (s, 1H), 4.70 (t, *J* = 5.5 Hz, 1H), 4.39 (m, 1H), 4.26 (m, 1H), 3.95 (t, *J* = 6.0 Hz, 2H), 3.15 (m, 1H), 3.05 (m, 1H), 2.39 (t, *J* = 6.0 Hz, 2H), 1.03 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0,

159.1, 153.1, 135.9, 134.0, 132.4, 130.7, 129.8, 128.8, 127.9, 126.4, 106.5, 106.4, 73.3, 63.9, 63.6, 35.9, 29.3, 27.1, 19.4; IR (thin film/NaCl) 2931, 2857, 1703, 1532, 1104 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[C_{32}H_{35}O_4Si]^+$: 511.2305, found 511.2315.

A4.6 Notes and References

(1) Tambar, U. K.; Kano, T.; Stoltz, B. M. *Org. Lett.* **2005**, *7*, 2413-2416.

(2) (a) Li, C.; Lobkovsky, E.; Porco, J. A. *J. Am. Chem. Soc.* **2000**, *122*, 10484-10485. (b) Li, C.; Johnson, R. P.; Porco, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 5095-5106.

(3) Shoji, M.; Yamaguchi, J.; Kakeya, H.; Osada, H.; Hayashi, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 3192-3194.

(4) (a) Malerich, J. P.; Trauner, D. *J. Am. Chem. Soc.* **2003**, *125*, 9554-9555. (b) Malerich, J. P.; Maimone, T. J.; Elliott, G. I.; Trauner, D. *J. Am. Chem. Soc.* **2005**, *127*, 6276-6283.

(5) Tohda, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1977**, 777-778.

(6) For similar reaction conditions, see: Nielsen, T. E.; Cubillo de Dios, M. A.; Tanner, D. *J. Org. Chem.* **2002**, *67*, 7309-7313.

(7) Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359-5364.

(8) Han, X.; Stoltz, B.M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600-7605.

(9) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905-5911.

(10) A. L. Casado, Espinet, P. *Organometallics* **2003**, *22*, 1305-1309.

(11) Han, X.; Corey, E. J. *Org. Lett.* **1999**, *1*, 1871-1872.

(12) For more rigorous calculations of simpler 1,3,5-oxatriene systems, see: Rodriguez-Otero, J. *J. Org. Chem.* **1999**, *64*, 6842-6848.