CHAPTER TWO

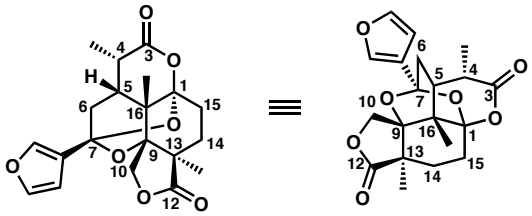
Progress Toward the Total Synthesis of Saudin: The Development of a Tandem Stille-Oxa-Electrocyclization Reaction[†]

2.1 Background

2.1.1 Introduction

We initiated research directed toward the total synthesis of the caged diterpenoid saudin (**1**) in late 2000. As described in Chapter 1, Mossa and Cassady disclosed the structure and biological activity of saudin 20 years ago.[1] The chemical structure of **1** was proved unambiguously by single crystal X-ray analysis to be that depicted in Figure 2.1.1. Importantly, saudin (**1**) was found to induce hypoglycemia in mice and therefore could be an appealing lead structure for the development of new agents to treat diabetes.

Figure 2.1.1



Saudin (1)

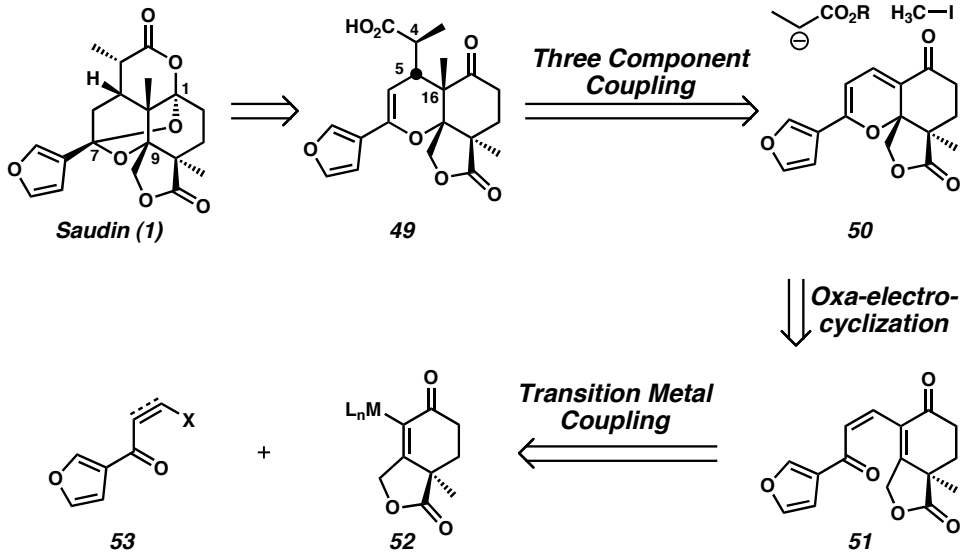
[†] This work was performed in collaboration with Dr. Taichi Kano, a postdoctoral scholar in the Stoltz group at the California Institute of Technology.

Our choice of saudin as a target molecule was based on its potent hypoglycemogenic bioactivity and unique structure. Additionally, we viewed this highly oxygenated, caged natural product as an ideal template for the discovery and development of new chemical reactions.

2.1.2 Retrosynthetic Analysis of Saudin

Our retrosynthetic analysis of saudin is outlined in Scheme 2.1.1. The polycyclic structure of saudin (**1**) exhibits an impressive array of functionality and stereochemistry that includes eight oxygenated carbons, seven stereocenters (two of which are quaternary centers and a total of five which are tetrasubstituted), two lactone rings, and a 3-substituted furan. Initial retrosynthetic disconnection of the C(1) and C(7) acetals exposes carboxylic acid **49** (Scheme 2.1.1), which, upon cleavage of the C(4)-C(5) linkage and removal of the C(16)-methyl in a retro three component coupling, arises from lactone **50**. Opening the pyran ring of **50** in a retro-oxa-electrocyclization provides dienone **51**, a substrate that is suited for disconnection across the C(16)-C(5) linkage via a number of possible transition metal-mediated coupling reactions (e.g., Stille, Suzuki, Sonogashira, and Heck) between enone **52** and furan **53**.

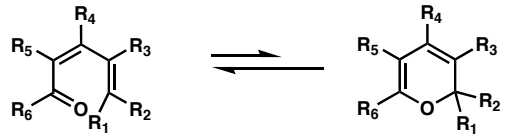
Scheme 2.1.1



2.1.3 Oxa-Electrocyclization Reactions in Natural Product Synthesis

The oxa-electrocyclization reaction is a relatively under-utilized transformation in organic synthesis.[2] This is primarily due to the existence of an unfavorable equilibrium in between the open *cis*-dienone (**54**) and the closed α-pyran (**54**) (Scheme 2.1.2). While the dienone structure is usually favored thermodynamically, in some cases the proper selection of functional groups and structural features in the molecule can control the equilibrium ratio to favor the α-pyran.[3]

Scheme 2.1.2



***cis*-dienone (54)** **α-pyran (55)**

Recently, thermodynamically favorable oxa-electrocyclization reactions have been exploited in the context of natural product synthesis, which has led to the total syntheses of torreyanic acid by Porco,[4] the epoxyquinols by Hayashi,[5] and the antimalarial naphthoquinones by Trauner.[6] Interestingly, an oxa-electrocyclization reaction was proposed to exist in the biosynthetic pathways for all these natural products. As described in Chapter 1, the putative biosynthetic pathway of saudin (**1**) does not involve an oxa-electrocyclization. In an attempt to expand the synthetic utility of this pericyclic transformation, we were interested in employing the oxa-electrocyclization in a more inconspicuous, non-biomimetic manner to rapidly synthesize the α-pyran core of saudin.

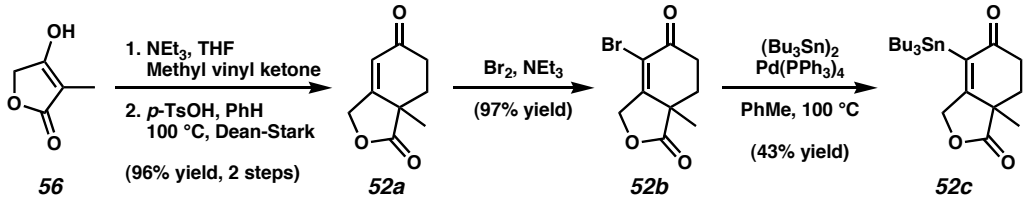
2.2 First Generation Strategy Based on a Michael Addition

2.2.1 Efficient Synthesis of the Core of Saudin

We initiated our study of the synthesis of saudin by preparing variants of enone **52** and furan **53**, with the hope that we would unite the two compounds through a

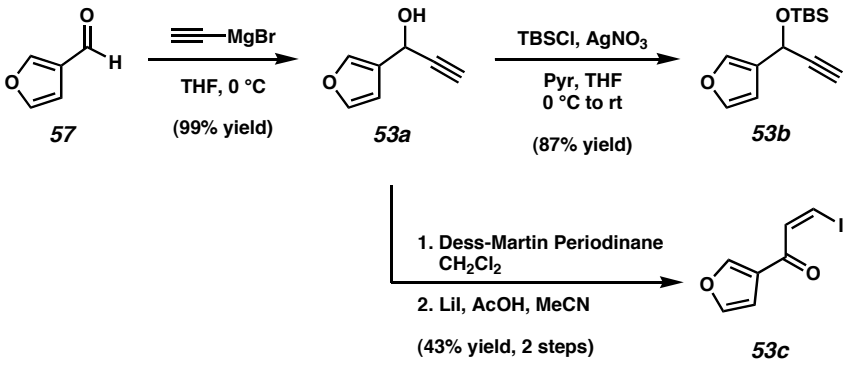
transition metal-catalyzed reaction. The preparation of enone **52a** proceeded via the Robinson annulation of tetronic acid **56** and methyl vinyl ketone (Scheme 2.2.1).[7] This enone was then cleanly converted to bromoenone **52b** by exposure to Br_2 and Et_3N.[8] The resulting product was easily transformed under Stille conditions to vinyl stannane **52c**,[9] albeit in modest yield, which was a viable intermediate for several transition metal-mediated couplings.

Scheme 2.2.1



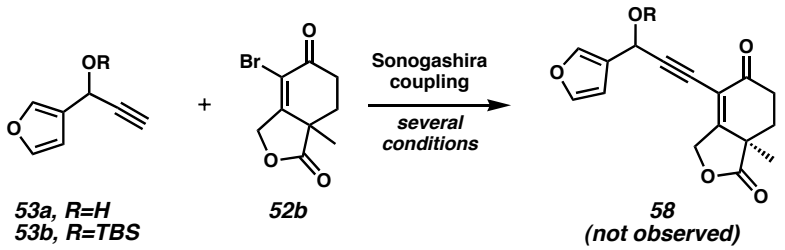
The other coupling partners for these metal-mediated coupling strategies were synthesized from furaldehyde **57** in a straightforward manner (Scheme 2.2.2). Treatment of this aldehyde with ethynyl Grignard produced propargyl alcohol **53a**, which was smoothly protected as the TBS-ether **53b**. Alternatively, the vinyl iodide derivate (**53c**) was synthesized in a two-step procedure from alcohol **53a**. Although oxidation of this alcohol failed under several conditions (Swern oxidation, Ley oxidation, and chromium-based oxidations), Dess-Martin periodinane[10] cleanly provided the desired ynone, which was then converted to vinyl iodide **53c** by treatment with LiI and AcOH in MeCN.[11]

Scheme 2.2.2



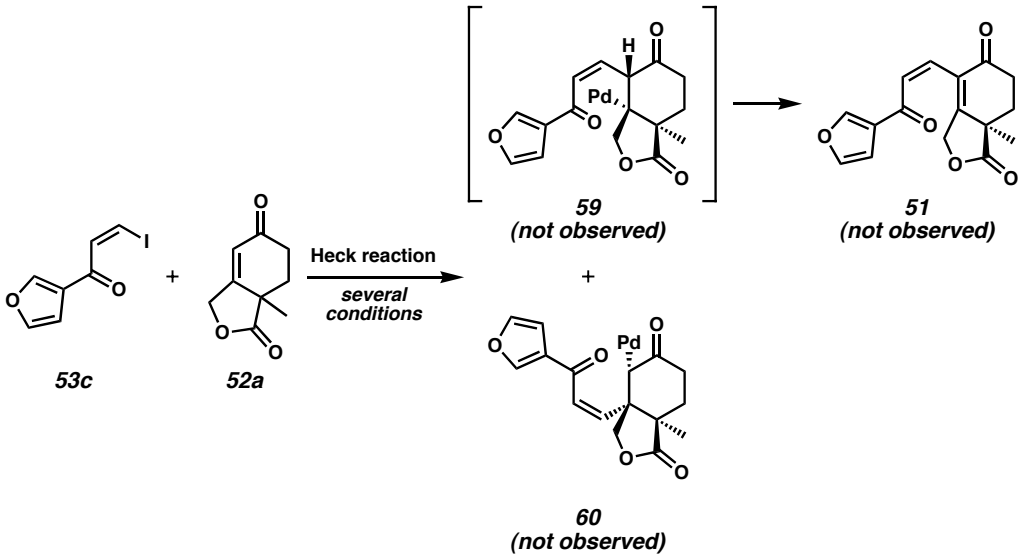
With these coupling partners in hand, a series of Sonogashira reactions were explored between bromoenone **52b** and alkynes **53a-b** (Scheme 2.2.3). Unfortunately, the coupling was not realized, though several conditions were tried. We discovered that analogs of bicyclic enone **52** are moderately unstable under a variety of basic conditions.

Scheme 2.2.3



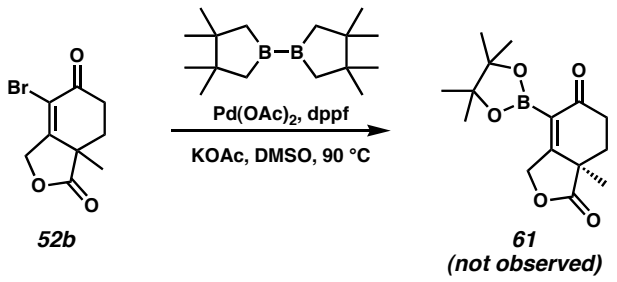
Alternatively, coupling via a Heck reaction of **53c** and **52a** was explored (Scheme 2.2.4).[12] Unfortunately, this strategy was not realized under either the standard Heck conditions or the modified Jeffery conditions.[13] The difficulty of this transformation may be attributed to the hindered Pd complex that would be generated by olefin insertion and the resulting anti relationship of the Pd and hydride in the cyclic structure[14] (i.e., **59**), along with the potential for regioisomeric insertion across the olefin (i.e., **60**).

Scheme 2.2.4



In an attempt to investigate Suzuki coupling reactions,[15] the conversion of vinyl bromide **52b** to the corresponding vinyl boronic ester **61** was attempted (Scheme 2.2.5). But, once again, the basic conditions of the reaction merely degraded the starting material.

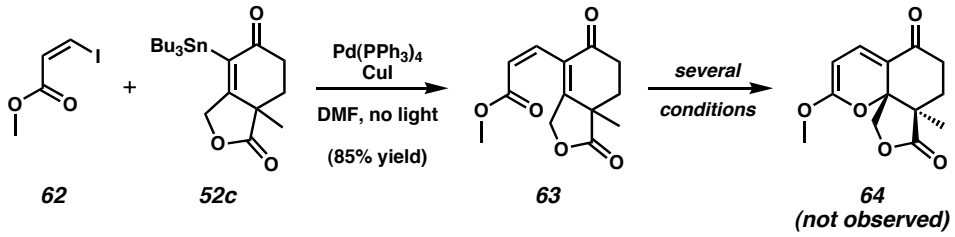
Scheme 2.2.5



Finally, we attempted to couple the two segments under Stille conditions.[16] Using a model system we were able to couple vinyl stannane **52c** with *cis*-vinyl iodide **62** under modified Stille conditions,[17] which yielded dienone **63** (Scheme 2.2.6). This result established that the bicyclic enone core structure was stable, at least under Stille

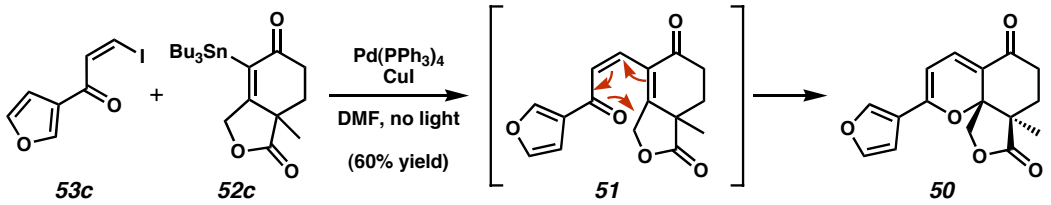
conditions. The oxa-electrocyclization of enone **63** was attempted under several conditions without success (heat, UV light, and Lewis acids).

Scheme 2.2.6



Although the electrocyclization of model substrate **63** was unsuccessful, we decided to apply the Stille coupling strategy to fully elaborated substrates en route to saudin (**1**). A series of conditions were examined for the Stille coupling of vinyl stannane **52c** and vinyl iodide **53c**, and no product was observed with several common Pd sources, additives, and solvents. We then employed the conditions used in the model system to generate dienone **63** with the anticipation that the desired Stille product **51** would be produced. To our pleasant surprise, however, the combination of catalytic $Pd(PPh_3)_4$, CuI, and DMF with the exclusion of light facilitated the coupling of **52c** and **53a** to yield furan appended tricycle **50** – the result of a tandem Stille-oxa-electrocylization reaction – as a single diastereomer (Scheme 2.2.7). Interestingly, the presence of CuI and the absence of light were both essential for the success of this transformation.[18]

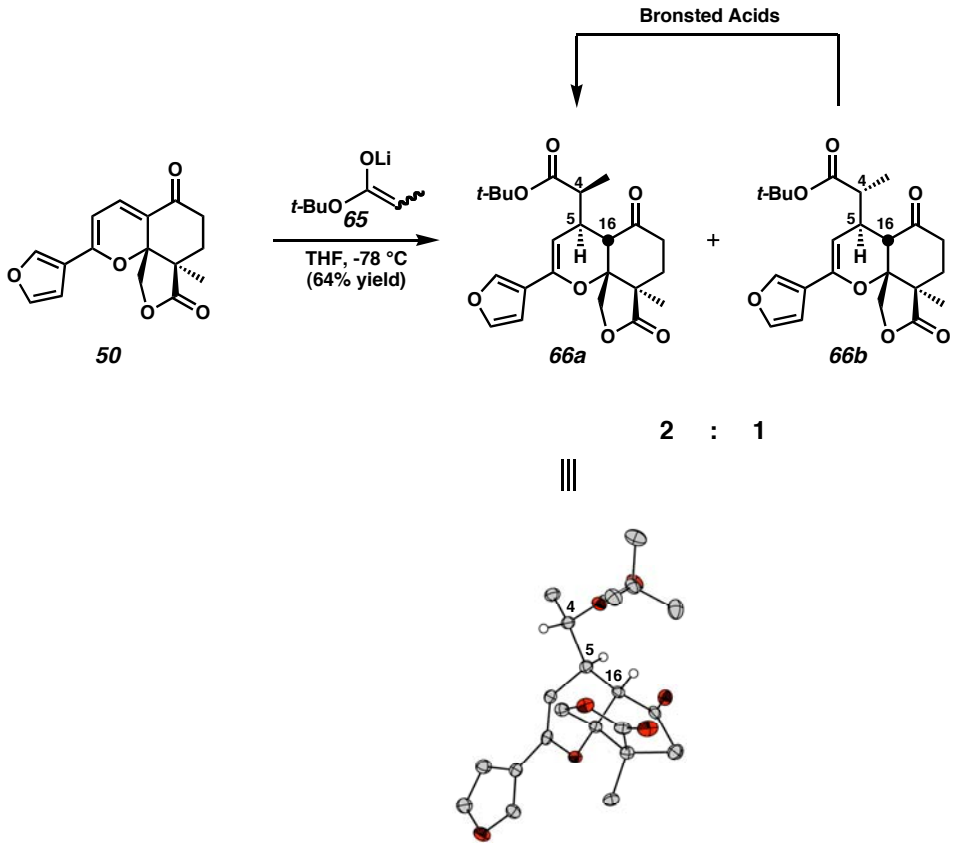
Scheme 2.2.7



2.2.2 Advancing Furan Appended Tricycle 50

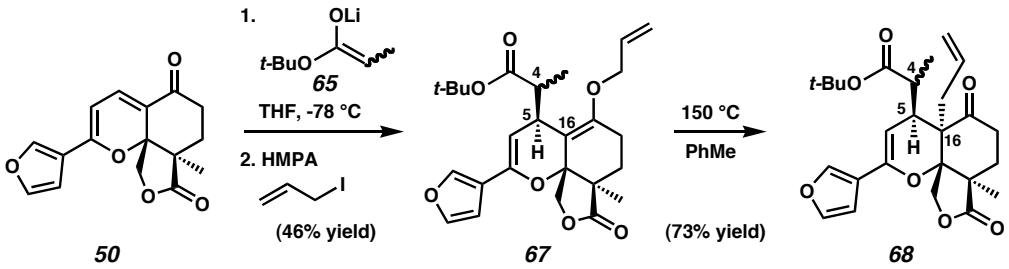
The synthesis of polycycle **50** represented an efficient diastereoselective route to the core structure of saudin. At this stage a series of 1,4-additions to this furan appended tricycle were explored. Under Mukaiyama-Michael conditions, the compound (**50**) decomposed.[19] Under anionic conditions, however, enolate **65** selectively reacted in a 1,4 fashion to yield a thermodynamic mixture of **66a** and **66b** (Scheme 2.2.8). Unfortunately, several attempts to react the carbon enolates of **66a-b** with methyl iodide and other electrophiles were unsuccessful.[20] X-ray structure analysis eventually revealed that the Michael addition product (**66a**) was actually the undesired diastereomer at C(5) than that which was needed for elaboration to saudin (Scheme 2.2.8).

Scheme 2.2.8



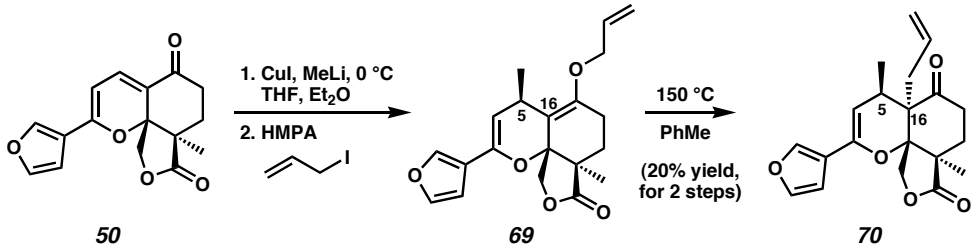
We envisioned that perhaps the stereochemistry at C(5) of ketoesters **66a** and **66b** sterically prohibited methylation at C(16), and an indirect C-alkylation could be achieved by O-allylation followed by a Claisen rearrangement. Treatment of polycycle **50** with enolate **65** followed by allyl iodide afforded the enol ether **67**, which rearranged thermally to ketone **68** (Scheme 2.2.9). The stereochemistry at the newly established quaternary carbon C(16) was most likely determined by the stereochemistry at C(5), as it was again inverted relative to the stereochemistry found in the natural product.

Scheme 2.2.9



While enolate equivalents like **65** attacked enone **50** from the β-face, we were hopeful that other nucleophiles would react from the α-face, which would map correctly onto the natural product. To test this hypothesis we reacted enone **50** with a simple methyl cuprate and then exposed the resulting enolate to allyl iodide and HMPA (Scheme 2.2.10). The vinyl allyl ether then underwent a thermal Claisen rearrangment. Unfortunately, the stereochemistry at both C(5) and C(16) were epimeric to that present in the natural product (i.e., **70**).

Scheme 2.2.10



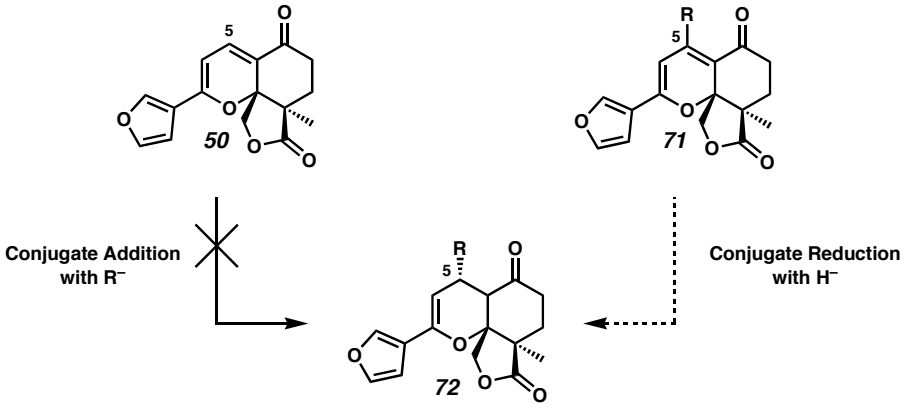
2.3 Second Generation Strategy Based on a 1,4-Reduction

2.3.1 Modified Strategy for the Synthesis of Saudin

Although we were disappointed by our inability to access the desired diastereomer of ketone **68** or **70**, there was enough flexibility in the synthetic strategy to investigate other potential solutions without abandoning the tandem Stille-oxa-electrocyclization approach.

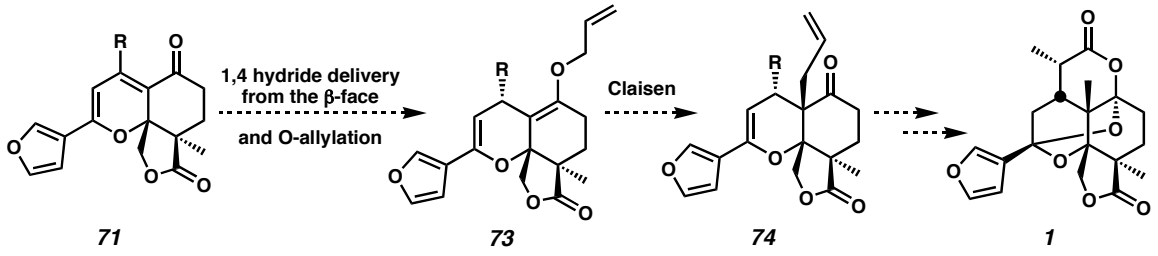
Initially our strategy for the synthesis of saudin called for a diastereoselective conjugate addition of a carbon nucleophile into enone **50** to access a C(5) substituted product (i.e., **72**, Scheme 2.3.1). The stereochemistry of the 1,4 additions to polycycle **50** suggested that the β-face may be preferred for nucleophiles adding in a conjugate fashion. This hypothesis could be tested by synthesizing a more functionalized polycycle (**71**), which would then be subjected to a 1,4 hydride reduction (Scheme 2.3.1). In addition to providing a more convergent route to saudin, this new strategy would also probe the generality of our tandem Stille-oxa-electrocyclization methodology.

Scheme 2.3.1



If the hydride also attacked from the β-face, the resulting product would have the correct stereochemistry at the β-position, which would hopefully lead to the correct stereochemistry at the α-position via a Claisen rearrangement (i.e., **74**, Scheme 2.3.2).

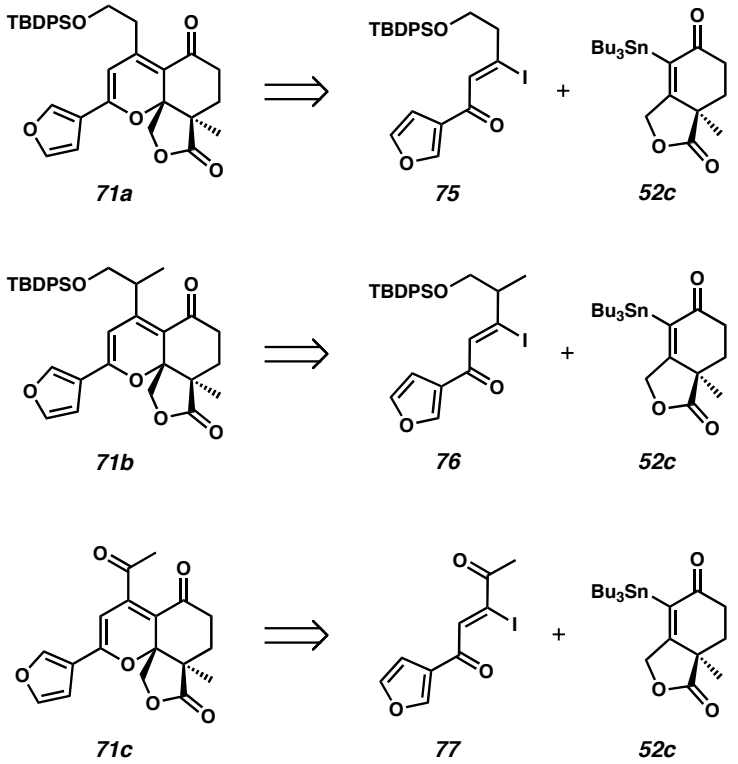
Scheme 2.3.2



2.3.2 Synthesis of Modified Furan Appended Tricycles

Initial exploration of the new strategy began with polycycles **71a-c**, which required the preparation of three new vinyl iodides (i.e., **75**, **76**, **77**, Scheme 2.3.3).

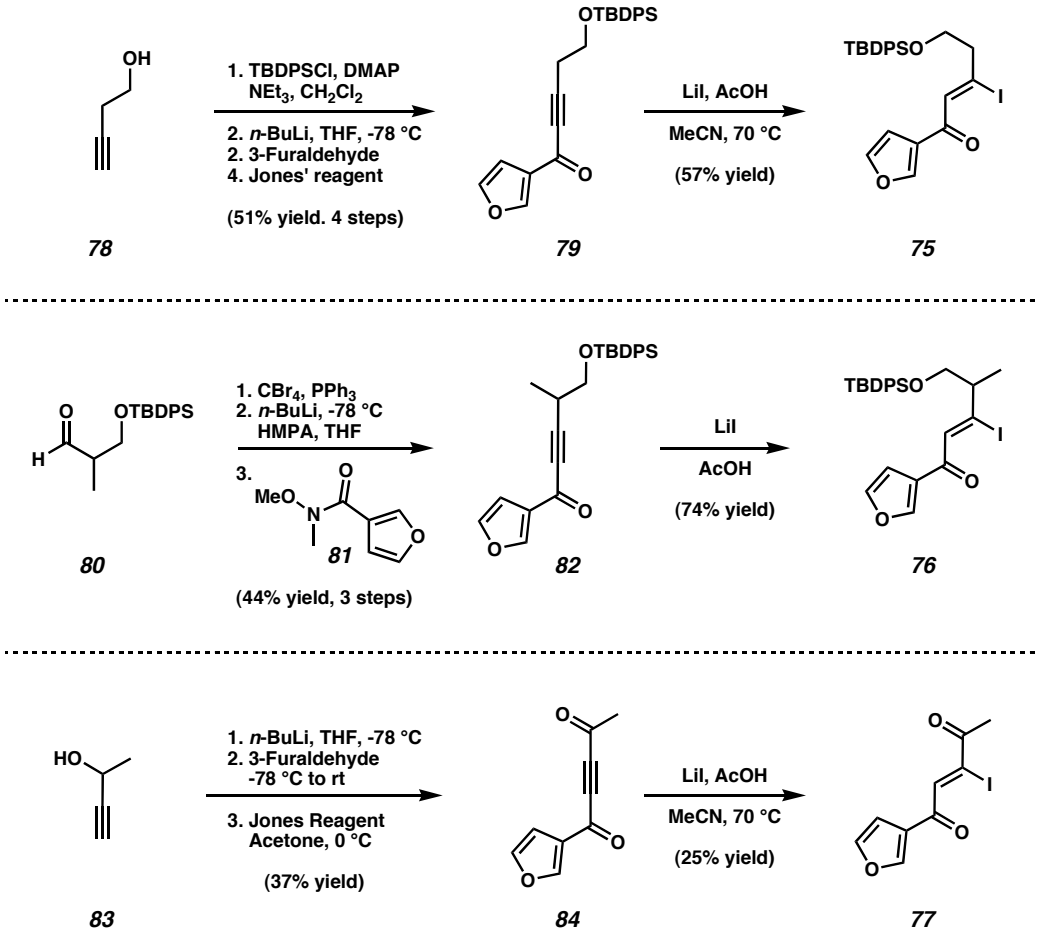
Scheme 2.3.3



The synthesis of vinyl iodide **75** commenced with the silyl protection of alcohol **78** (Scheme 2.3.4). Subsequent treatment with *n*-butyllithium followed by 3-furaldehyde yielded the coupled alcohol, which was oxidized with Jones' reagent to produce ynone **79**. Conversion of **79** to vinyl iodide **75** was effected by treatment of the ynone (**79**) with LiI and AcOH in MeCN to generate the desired *cis*-vinyl iodide (**75**) in good yield and as a single olefin isomer. The synthesis of vinyl iodide **76** is also depicted in Scheme 2.3.4. Aldehyde **80** was converted to an alkynyl anion by the Corey-Fuchs procedure.[21] Subsequent quenching of the anion with Weinreb amide **81** yielded ynone **82**, which was readily converted to vinyl iodide **76** as a single olefin isomer with LiI and AcOH. Vinyl iodide **77** was rapidly synthesized from 1-butyn-3-ol (**83**), which was first coupled to 3-

furaldehyde (Scheme 2.3.4). Double oxidation of the resulting propargylic diol furnished ynone **84**, which was treated with LiI and AcOH in MeCN to yield the desired vinyl iodide **77**.

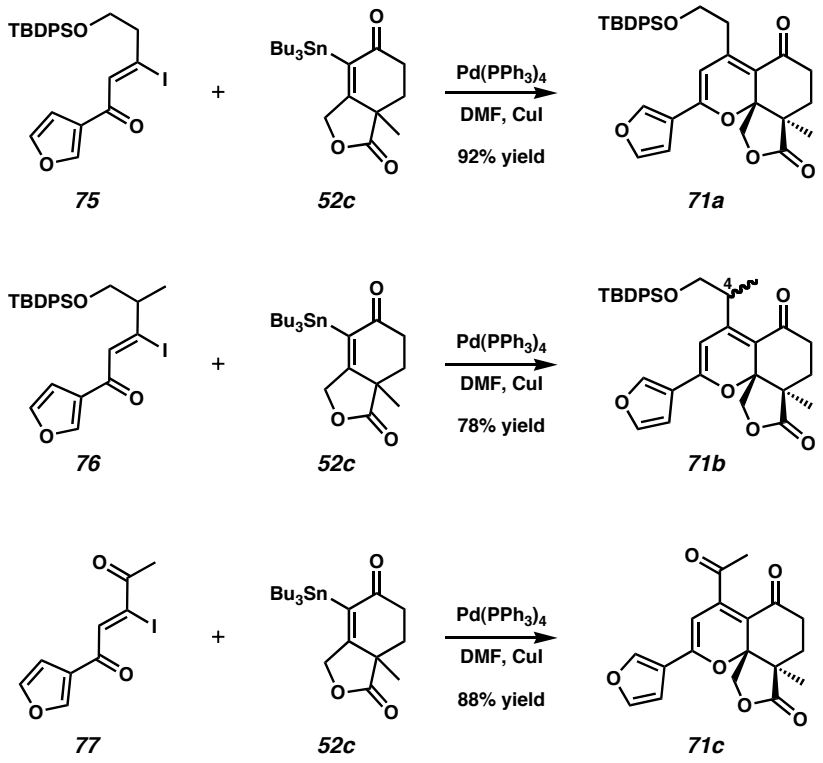
Scheme 2.3.4



With these three new vinyl iodides in hand (**75-77**), the key Stille-oxa-electrocyclization reactions were attempted. Under previously optimized conditions, smooth coupling occurred between stannane **52c** and vinyl iodides **75**, **76**, and **77** to form the desired polycycles **71a**, **71b**, and **71c** in 92%, 78%, and 88% yield, respectively

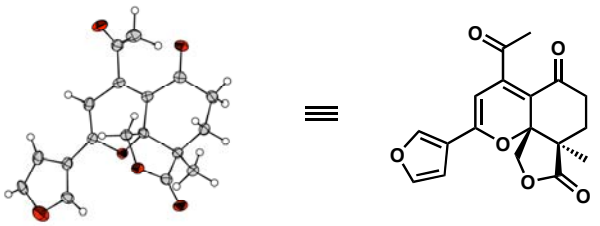
(Scheme 2.3.5). Products **71a** and **71c** were formed as single diastereomers, whereas **71b** was produced as a 1:1 mixture of diastereomers at C(4).

Scheme 2.3.5



The bond connectivity and relative stereochemistry of **71c** were unambiguously confirmed by single crystal X-ray diffraction of the diketone (Figure 2.3.1).

Figure 2.3.1

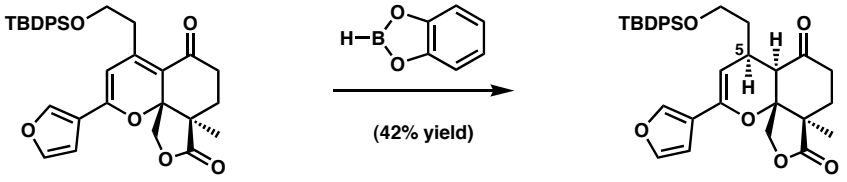


71c

2.3.3 1,4-Reduction of Substituted Enone 71a

At this point, although the 1,4 addition of carbon nucleophiles to enone **50** seemed to give the C(5)-α-H-diastereomer, we were ready to test our hypothesis on the diastereoselective 1,4-reduction of enone **71a**. To realize the 1,4 hydride reduction product, polycycle **71a** was subjected to a variety of conditions. In most cases the sterically hindered starting material was unreactive.[22] Treatment with catecholborane resulted in a 1,4-reduction, but surprisingly the hydride was delivered from the α-face of the enone (i.e., **85**, Scheme 2.3.6).[23] When polycycle **71a** was reacted with a multitude of in situ generated "Cu–H" species, the resulting ketone did exhibit the desired C(5) stereochemistry needed for elaboration to the natural product. Unfortunately, the yields of these reactions were prohibitively low.

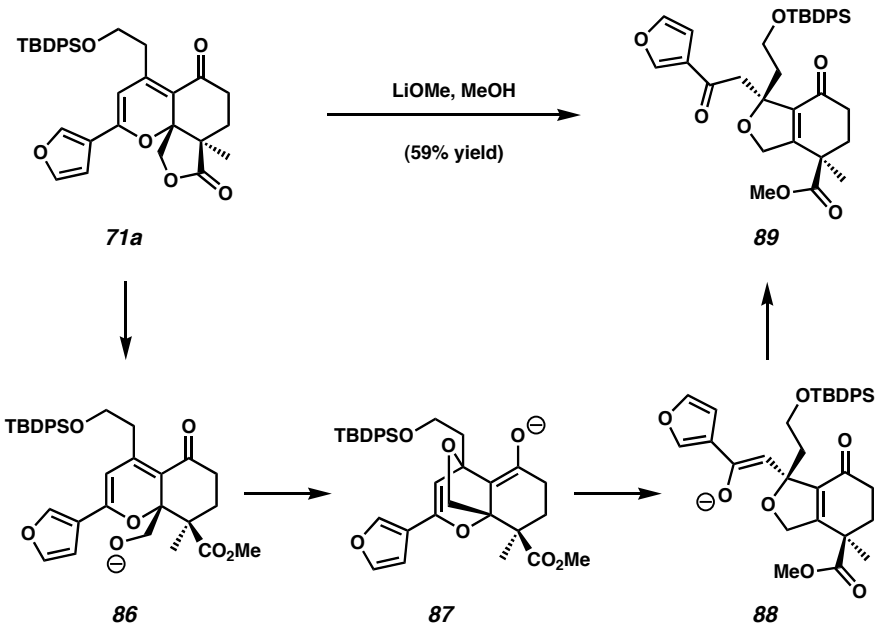
Scheme 2.3.6



71a ***85***

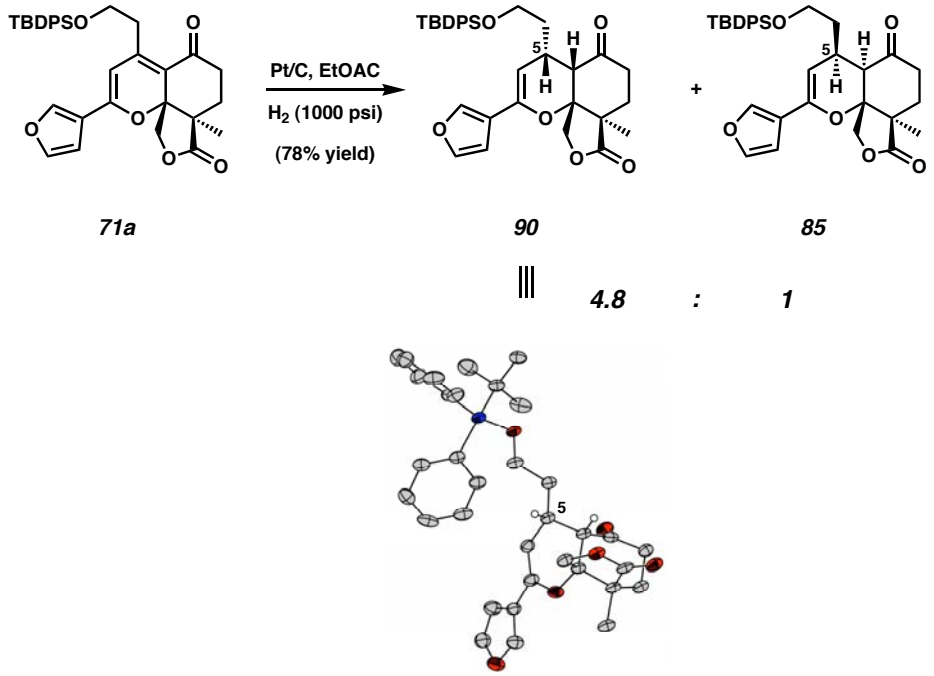
Presumably, the 1,4-reduction of enone **71a** from the β-face was hindered by the caged nature of the lactone functionality. We reasoned that this steric obstacle could be reduced by modifying the topology of our polycyclic structures. Specifically, we wanted to open the lactone in enone **71a**, with the hope of drastically changing the steric environment around the tetrasubstituted olefin. Although treating enone **71a** with LiOMe led to the opening of the lactone, the liberated alkoxide then underwent an undesired intramolecular 1,4-addition, followed by a β-elimination, to generate diketone **89** (Scheme 2.3.7). We concluded from this result that the selective opening of the lactone was not a trivial transformation given the dense array of functionality in the products of our tandem Stille-oxa-electrocyclization reaction.

Scheme 2.3.7



Finally, after much investigation, we obtained the desired ketone (**90**) in good yield by treating enone **71a** with Pt/C under a high pressure atmosphere of hydrogen gas (Scheme 2.3.8). This constituted a diastereoselective reduction of a tetrasubstituted olefin. The stereochemistry of the major product (**90**) was established by single crystal X-ray diffraction.

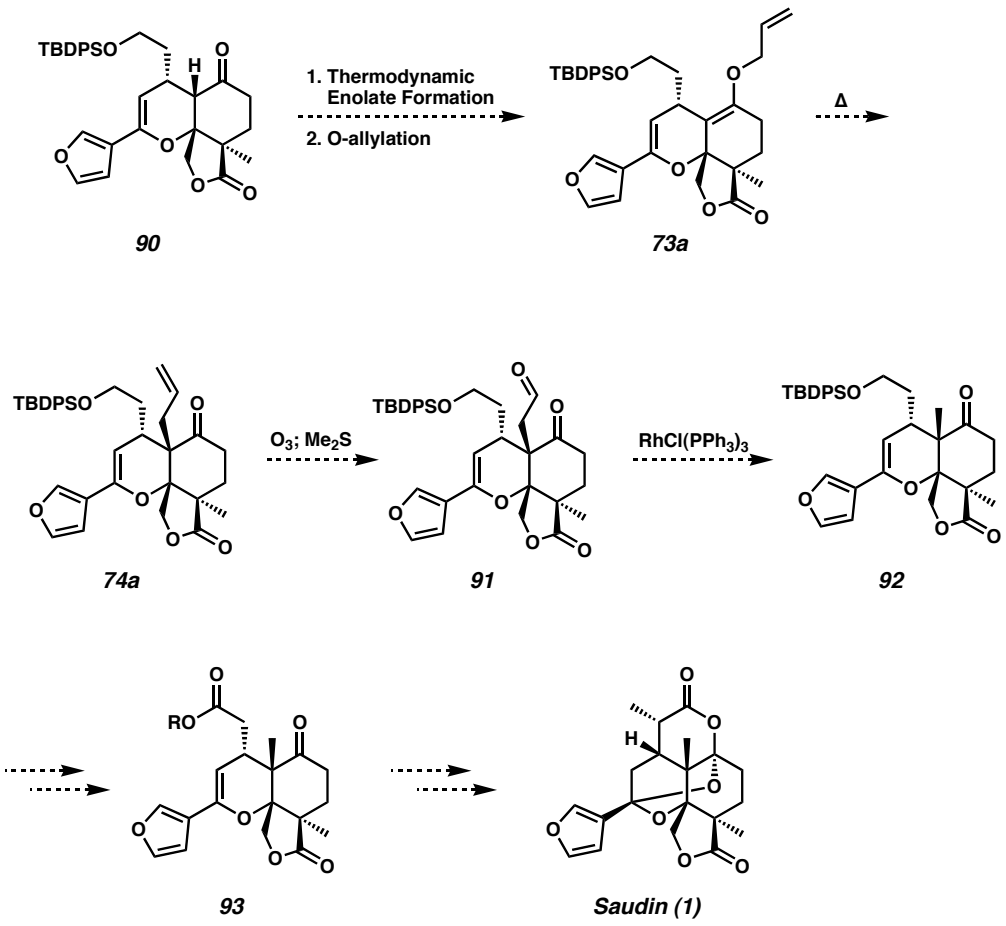
Scheme 2.3.8



2.3.4 Proposal For the Completion of Saudin

With access to ketone **90**, future work will target the installation of the α-quaternary carbon at C(16) via the Claisen rearrangement strategy and other more direct C-alkylation methods. One potential strategy for the completion of saudin (**1**) is shown in Scheme 2.3.9. If the thermodynamic enolate of ketone **90** can be formed, this intermediate will be treated with allyl iodide to generate enol ether **73a**, which could undergo a thermal Claisen rearrangement to generate ketone **74a**. Oxidation of the terminal olefin in ketone **74a** to an aldehyde, followed by Rh(I) catalyzed decarbonylation, could yield α-methyl ketone **92**. Facile functional group interconversions would then lead to ketoester **93**, which could be transformed easily to the natural product saudin (**1**).

Schem 2.3.9



2.4 Conclusion

Our studies toward the total synthesis of (±)-saudin (**1**) have produced an efficient, rapid, and diastereoselective construction of the natural product's core. While conjugate additions to polycycle **50** yielded products of undesired stereochemistry, intermediate **71a** was advanced to a structure with the desired stereochemistry for

elaboration to saudin (i.e., **90**). In the process of our work, we have also developed a novel tandem Stille-oxa-electrocyclization sequence that delivers a wide range of pyran structures in a convergent and rapid fashion. Current efforts are focused on expanding the substrate scope of this tandem reaction sequence as well as advancing ketone **90** to saudin.

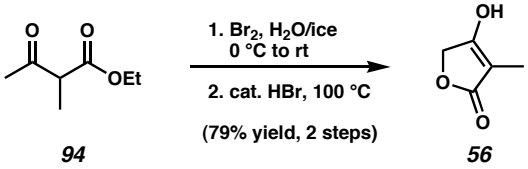
2.5 Experimental Section

2.5.1 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. X-ray crystallographic structures were obtained by Mr. Larry M. Henling and Dr. Mike W. Day at the California Institute of Technology Beckman Institute X-Ray Crystallography Laboratory.

2.5.2 Preparative Procedures

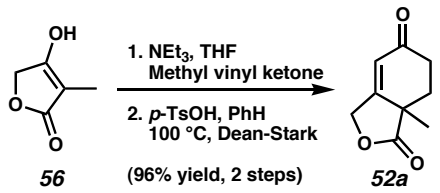


94 *56*

Methyl tetronic acid 56. This is a modification of a known literature procedure.[24] To a solution of ethylmethyl acetoacetate **94** (50 mL, 353 mmol) in deionized water (100 mL) cooled to 0 °C was slowly added bromine (18 mL, 353 mmol) in a dropwise fashion over 2 h. Following addition, the ice bath was allowed to warm to 23 °C, and the reaction mixture was stirred for 12 h. The organic layer was separated and dried over Na_2SO_4 and evaporated in vacuo to provide the desired bromoketone (81.08 g, 353 mmol) as a clear oil, which was used in the next step without further purification: ^1H

NMR (300 MHz, $CDCl_3$) δ 4.28 (dq, J = 7.2, 0.9 Hz, 1H), 2.43 (s, 3H), 1.97 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H).

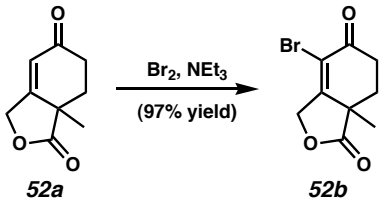
To the bromoketone from the previous step (81.08 g, 353 mmol) was added 12 drops of HBr (48% *w*/*v* in H_2O) in a dropwise fashion. Following addition, the reaction mixture was refluxed at 100 °C and allowed to stir for 12 h. The reaction was cooled to 23 °C. The precipitate was vacuum filtered and rinsed with ethyl acetate. The concentrated filtrate was resubmitted to the reaction conditions twice. The filtrates from the three reaction cycles were combined to yield methyl tetronic acid **56** (31.86 g, 79% yield) as a white solid: mp 185 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.74 (s, 1H), 4.55 (s, 2H), 1.57 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 175.3, 173.0, 94.5, 66.6, 6.0; IR (KBr pellet) 2984, 2695, 1598, 1448 cm^{-1}; HRMS (EI$^+$) calc'd for $[C_5H_6O_3]^+$: m/z 114.0317, found 114.0313.



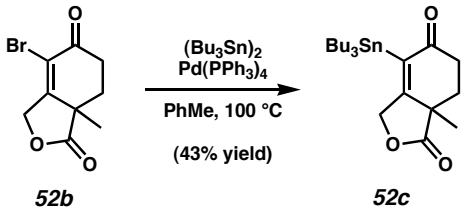
Enone 52a. To a cooled (0 °C) solution of methyl tetronic acid **56** (150 g, 1.31 mol) in THF (1.3 L) was added Et_3N (366 mL, 2.63 mol). Methyl vinyl ketone (131 mL, 1.58 mol) was then slowly added over 15 min. After stirring for 30 min, the reaction mixture was washed with 1 N HCl (1 L). The organic layer was separated, dried over Na_2SO_4, and evaporated in vacuo to provide the conjugate addition product (242.2 g, 1.31

mol) as a yellow oil, which was used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.73 (d, *J* = 16.8 Hz, 1H), 4.63 (d, *J* = 16.8 Hz, 1H), 2.56 (t, *J* = 7.2 Hz, 2H), 2.12 (s, 3H), 2.09-1.95 (m, 2H), 1.31 (s, 3H).

To a solution of this conjugate addition product (242.2 g, 1.31 mol) in benzene (650 mL) was added *p*-TsOH (24.9 g, 131 mol). The mixture was refluxed with azeotropic removal of H_2O (Dean-Stark trap). After stirring for 40 h, the reaction mixture was allowed to cool to 23 °C and concentrated in vacuo. The resulting oil was dissolved in CH_2Cl_2 (300 mL) and washed with water (200 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 40 mL). The combined organic layers were dried over Na_2SO_4. After filtration, the residue was concentrated under reduced pressure. Purification by flash chromatography (2:1 hexanes/EtOAc eluent) provided enone **52a** (211 g, 96% yield over 2 steps) as a clear oil: R_F 0.40 (1:3 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88 (s, 1H), 5.01 (dd, *J* = 14.6, 2.1 Hz, 1H), 4.83 (d, *J* = 14.6 Hz, 1H), 2.60-2.36 (m, 2H), 2.22-1.92 (m, 2H), 1.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.4, 177.5, 161.6, 122.2, 68.2, 41.3, 32.6, 29.5, 20.7; IR (thin film/NaCl) 2940, 1780, 1676 cm^{-1}; HRMS (EI$^+$) calc'd for $[C_9H_{10}O_3]^+$: *m/z* 166.0630, found 166.0629.

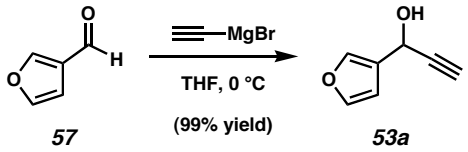


Bromoenone 52b. To a solution of enone **52a** (5.0 g, 30 mmol) in CH_2Cl_2 (60 mL) cooled to 0 °C was added a solution of Br_2 (1.7 mL, 33 mmol) in CH_2Cl_2 (30 mL) in a dropwise fashion over 15 min. When the addition was complete, Et_3N (4.6 mL, 33 mmol) was quickly added. After stirring for 5 min, the reaction mixture was washed with water (3 x 50 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (3:1 hexanes/EtOAc eluent) provided bromoenone **52b** (7.16 g, 97% yield) as a clear oil: R_F 0.30 (2:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.00 (s, 2H), 2.83-2.77 (m, 2H), 2.33-2.14 (m, 2H), 1.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.6, 176.7, 160.2, 117.8, 69.4, 45.2, 33.3, 29.5, 21.7; IR (thin film/NaCl) 2935, 1782, 1689, 1655 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_9H_9O_3Br]^+$: 243.9735, found 243.9732.



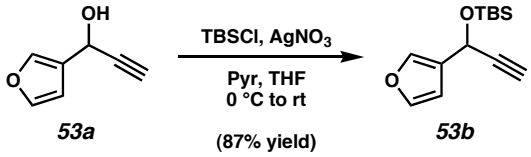
Vinyl stannane 52c. A solution of bromoenone **52b** (5.0 g, 20.4 mmol), $(Bu_3Sn)_2$ (20.6 mL, 40.8 mmol), $Pd(PPh_3)_4$ (306 mg, 0.265 mmol), and $NaHCO_3$ (8.57 g,

102 mol) in toluene (200 mL) was stirred at -78 °C under reduced pressure for 30 min. The mixture was then stirred at reflux. After 24 h, the reaction mixture was allowed to cool to 23 °C and filtered through a short pad of Celite (pentane eluent). The filtrate was concentrated in vacuo to an oil, which was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to give vinyl stannane **52c** as a clear oil (4.0 g, 43% yield): R_F 0.45 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.03 (d, *J* = 14.7 Hz, 1H), 4.79 (d, *J* = 14.7 Hz, 1H), 2.67-2.47 (m, 2H), 2.23 (ddd, *J* = 13.3, 5.3, 2.1 Hz, 1H), 2.04 (td, *J* = 13.3, 6.6 Hz, 1H), 1.48 (s, 3H), 1.47-1.24 (m, 13H), 1.03-0.86 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.4, 178.4, 169.6, 139.5, 69.9, 42.2, 32.1, 29.2, 28.3, 27.2, 21.6, 13.7, 11.0; IR (thin film/NaCl) 2956, 2926, 1785, 1655, 1625 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[C_{21}H_{35}O_3Sn]^+$: 455.1608, found 455.1603.



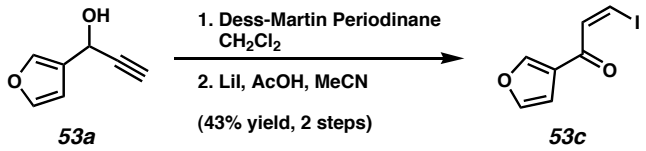
Alcohol 53a. To a solution of 3-furaldehyde **57** (17.3 mL, 200 mmol) in THF (170 mL) cooled to 0 °C was added ethynyl magnesium bromide (0.5 M in Et_2O, 500 mL, 250 mmol) slowly via an addition funnel over 2 h. Following addition, the ice bath was allowed to warm to 23 °C, and the mixture was stirred for 5 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (500 mL) and extracted with Et_2O (2 x 400 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (2:1

hexanes/EtOAc eluent) provided alcohol **53a** (25.41 g, 99% yield) as a clear oil: R_F 0.25 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (t, *J* = 0.8 Hz, 1H), 7.37 (t, *J* = 1.7 Hz, 1H), 6.48 (d, *J* = 0.8 Hz, 1H), 5.35 (d, *J* = 1.3 Hz, 1H), 3.14 (s, 1H), 2.58 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7, 140.4, 126.0, 109.2, 83.2, 73.5, 57.0; IR (thin film/NaCl) 3293, 1505, 1158, 1021 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_7H_6O_2]^+$: 122.0368, found 122.0367.



TBS-ether 53b. To a cooled (0 °C) solution of alcohol **53a** (235.2 mg, 2.00 mmol) in THF (9.6 mL) were added $AgNO_3$ (491 mg, 2.89 mmol), Pyridine (623 μl, 7.70 mmol), and TBSCl (435 mg, 2.89 mmol). After 5 min, the reaction mixture was warmed to 23 °C. The reaction was stirred for 10 h and then passed through a short pad of Celite (Et_2O eluent). The solution was washed with water (15 mL). The aqueous layer was extracted with Et_2O (2 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (10:1 hexanes/EtOAc eluent) provided TBS-ether **53b** (411.6 mg, 87% yield) as a clear oil: R_F 0.68 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 0.8 Hz, 1H), 7.20 (t, *J* = 1.7 Hz, 1H), 6.28 (d, *J* = 1.1 Hz, 1H), 5.28 (d, *J* = 1.1 Hz, 1H), 2.35 (d, *J* = 2.1 Hz, 1H), 0.77 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 139.8, 127.2, 109.3, 84.0, 72.9, 58.2, 25.9, 18.5, -4.4, -4.8; IR (thin film/NaCl)

3309, 2957, 2931, 2858, 1254, 1087, 1062 cm^{-1}; HRMS (EI^+) *m*/*z* calc'd for $[C_{13}H_{20}O_2Si]^+$: 236.1233, found 236.1232.

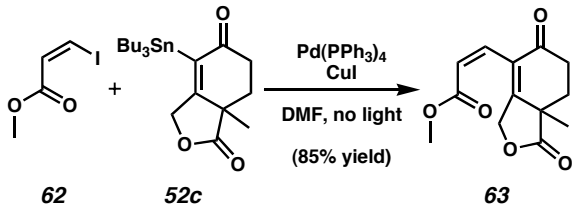


53a *53c*

Vinyl Iodide 53c. To a solution of Dess-Martin Periodinane (1.91 g, 4.50 mmol) in CH_2Cl_2 (18 mL) cooled to 0 °C was added alcohol **53a** (500 mg, 4.09 mmol) in CH_2Cl_2 (3 mL). After 1 h the reaction was quenched by addition of a 1:1 mixture of saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$ (20 mL). The mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under a slight reduction of pressure (produced by a water aspirator) while submerged in a cold bath (0 °C). The resulting oil was purified by flash chromatography on silica gel (3:1 petroleum ether/ether eluent) to provide the volatile ynone product (442 mg, 3.68 mmol) as a yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 8.20-8.19 (m, 1H), 7.46-7.45 (m, 1H), 6.83-6.82 (m, 1H), 3.26 (d, *J* = 1.2 Hz, 1H).

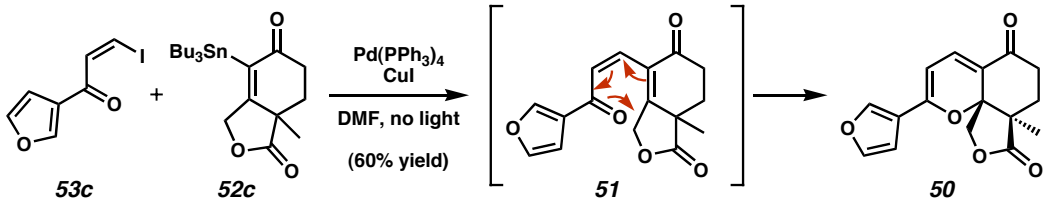
To a solution of the volatile ynone (5 g, 41.6 mmol) and LiI (6.13 g, 45.8 mmol) in MeCN (42 mL) was added glacial AcOH (2.63 mL, 45.8 mmol). Following addition, the mixture was stirred for 2 h and then poured into ice water (75 mL). Solid K_2CO_3 was added until bubbling ceased, and the mixture was extracted with Et_2O (2 x 75 mL). The combined organic layers were dried over $MgSO_4$. After filtration, the residue was

concentrated under reduced pressure. Purification by flash chromatography (10:1 pentane/ether eluent) provided vinyl iodide **53c** (5.46 g, 43% yield over 2 steps) as a yellow solid: R_F 0.29 (5:1 pentane/ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (dd, *J* = 1.4, 0.8 Hz, 1H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.47 (dd, *J* = 1.9, 1.4 Hz, 1H), 7.44 (d, *J* = 8.8 Hz, 1H), 6.85 (dd, *J* = 1.9, 0.8 Hz, 1H); ^{13}C NMR (75 MHz, C_6D_6) δ 183.0, 147.7, 144.8, 133.9, 129.0, 109.3, 91.6; IR (thin film/NaCl) 3130, 1655, 1295 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_7H_5O_2I]^+$: 247.9335, found 247.9346.



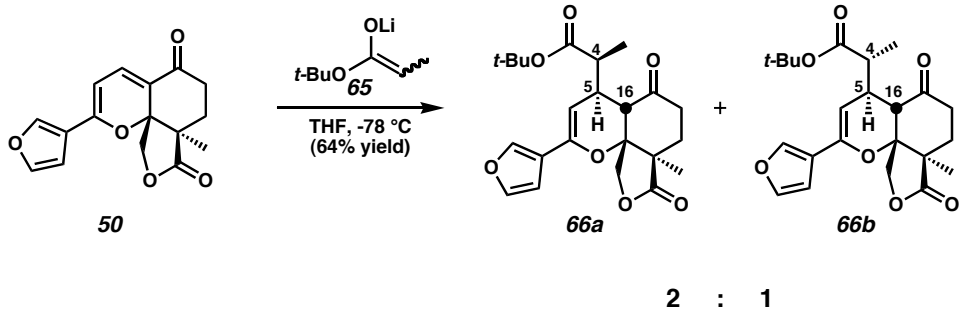
Enone 63. To a mixture of $Pd(PPh_3)_4$ (14 mg, 0.012 mmol), vinyl stannane **52c** (50 mg, 0.12 mmol), and vinyl iodide **62**[25] (30 mg, 0.12 mmol) was added DMF (2.5 mL). CuI (17.5 mg, 0.09 mmol) was added, and the flask was protected from ambient light. After stirring for 9 h, the mixture was diluted with water (10 mL) and extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over Na_2SO_4. After filtration, the residue was concentrated under reduced pressure. Purification by flash chromatography (1:1 hexanes/EtOAc eluent) provided enone **63** (25.5 mg, 85% yield): R_F 0.25 (1:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.62 (ddd, *J* = 12.2, 1.9, 0.8 Hz, 1H), 6.15 (d, *J* = 12.2 Hz, 1H), 5.02 (dd, *J* = 15.0, 2.0 Hz, 1H), 4.72 (dd, *J* = 15.0, 0.7 Hz, 1H), 3.69 (s, 3H), 2.77-2.53 (m, 2H), 2.32-2.11 (m, 2H), 1.61 (s, 3H); ^{13}C NMR (75

MHz, $CDCl_3$) δ 195.4, 177.9, 165.5, 158.7, 136.0, 128.7, 125.6, 77.7, 68.6, 51.9, 42.0, 33.0, 29.9, 21.0; IR (thin film/NaCl) 2952, 1781, 1722, 1675, 1197, 1179 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{13}H_{14}O_5]^+$: 250.0841, found 250.0844.



Polycycle 50. To a mixture of $Pd(PPh_3)_4$ (1.16 g, 1.0 mmol), vinyl stannane **52c** (9.0 g, 20.0 mmol), and vinyl iodide **53a** (6.13 g, 24.7 mmol) was added DMF (100 mL). Freshly recrystallized CuI[26] (3.81 g, 20.0 mmol) was added, and the flask was cooled to -78 °C under vacuum. The reaction mixture was protected from ambient light. After 30 min of degassing, the mixture was allowed to warm to 23 °C under N_2. After stirring for 12 h, the mixture was diluted with water (200 mL) and extracted with Et_2O (2 x 200 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (3:2 hexanes/EtOAc eluent) provided polycycle **50** (3.37g, 60% yield) as an orange solid: R_F 0.31 (1:1 hexanes/EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.44 (t, *J* = 1.7 Hz, 1H), 7.33 (d, *J* = 6.8 Hz, 1H), 6.53 (d, *J* = 2.0 Hz, 1H), 5.88 (d, *J* = 6.3 Hz, 1H), 4.78 (d, *J* = 10.7 Hz, 1H), 4.07 (d, *J* = 10.7 Hz, 1H), 2.59-2.45 (m, 2H), 2.09-2.02 (m, 2H), 1.49 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.7, 179.1, 153.8, 144.6, 143.3, 134.7, 121.1, 118.3, 107.5, 99.5, 85.8, 71.9, 44.8, 33.2, 28.0, 14.5; IR (thin film/NaCl) 3131, 2947,

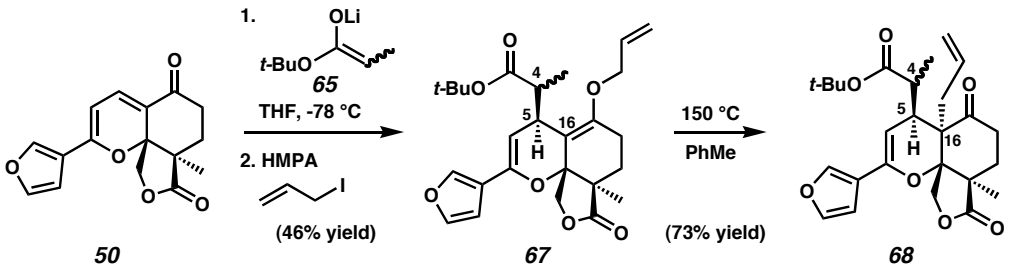
1782, 1673, 1561, 1526, 1160, 1015 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{16}H_{14}O_5]^+$: 286.0841, found 286.0838.



Michael Products 66a-b. To a solution of $HN(i\text{-}Pr)_2$ (610 μL, 4.38 mmol) in THF (4.4 mL) cooled to 0 °C was added *n*-butyllithium (2.2 M in hexanes, 2.08 mL, 4.38 mmol). After 5 min the mixture was cooled to -78 °C, and a solution of *t*-butyl propionate (657 μL, 4.38 mmol) in THF (4.4 mL) was slowly added along the sides of the flask in a dropwise fashion. Following addition, the mixture was stirred for 30 min, and then a solution of polycycle **50** (250 mg, 0.875 mmol) in THF (4.4 mL) was slowly added over 2 min. After 15 min the reaction was quenched with 1 N HCl (10 mL) and the cold bath was removed. After 1 h of stirring, the mixture was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (4:1 hexanes/EtOAc eluent) provided a 2 : 1 mixture of ketone **66a** as a white solid and its C(4) epimer **66b** as an oil (232.1 mg combined, 64% yield). For **66a**, suitable crystals for X-ray diffraction were grown from Et_2O by slow evaporation.

*Ketone **66a**:* R_F 0.45 (1:1 hexanes/EtOAc); mp 148 °C; ^{1}H NMR (500 MHz, C_6D_6) δ 7.03-7.02 (m, 1H), 6.23-6.21 (m, 2H), 4.91 (d, *J* = 2.4 Hz, 1H), 3.84 (d, *J* = 10.3 Hz, 1H), 3.77 (d, *J* = 10.7 Hz, 1H), 3.34-3.30 (m, 1H), 2.80 (d, *J* = 7.8 Hz, 1H), 2.49-2.43 (m, 1H), 2.42-2.35 (m, 1H), 1.95-1.88 (m, 1H), 1.65-1.61 (m, 2H), 1.45 (s, 9H), 1.25 (s, 3H), 1.12 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 206.6, 178.8, 173.5, 145.9, 144.0, 140.3, 122.4, 107.6, 98.9, 83.5, 81.1, 74.4, 50.3, 46.7, 43.8, 34.7, 34.2, 30.2, 28.3, 17.3, 13.7; IR (thin film/NaCl) 2977, 1783, 1722, 1160 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{23}H_{29}O_7]^+$: 417.1913, found 417.1904.

*Ketone **66b**:* R_F 0.54 (1:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, C_6D_6) δ 7.26 (s, 1H), 6.91 (t, *J* = 1.7 Hz, 1H), 6.10-6.08 (m, 1H), 5.05 (d, *J* = 2.9 Hz, 1H), 3.82 (d, *J* = 10.3 Hz, 1H), 3.72 (d, *J* = 10.7 Hz, 1H), 3.35-3.31 (m, 1H), 2.60 (d, *J* = 6.8 Hz, 1H), 2.47-2.40 (m, 1H), 2.19-2.11 (m, 1H), 1.86-1.79 (m, 1H), 1.59-1.51 (m, 1H), 1.48-1.41 (m, 1H), 1.33 (s, 9H), 1.14 (s, 3H), 1.08 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 206.1, 178.5, 174.4, 145.9, 144.0, 140.3, 122.5, 107.6, 96.8, 83.5, 81.1, 74.1, 51.1, 46.7, 43.5, 34.7, 33.8, 30.3, 28.3, 17.3, 13.6; IR (thin film/NaCl) 2977.02, 1783, 1721, 1157 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{23}H_{29}O_7]^+$: 417.1913, found 417.1926.



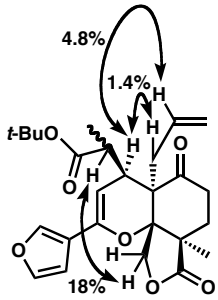
Claisen Product 68. To a solution of HN(*i*-Pr)$_2$ (130 μL, 0.933 mmol) in THF (1.8 mL) cooled to 0 °C was added *n*-butyllithium (2.5 M in hexanes, 375 μL, 0.933 mmol). After 5 min the mixture was cooled to -78 °C, and a solution of *t*-butyl propionate (140 μL, 0.933 mL) in THF (1.8 mL) was slowly added along the sides of the flask in a dropwise fashion. Following addition, the mixture was stirred for 25 min, and then a solution of polycycle **50** (50 mg, 0.175 mmol) in THF (1.8 mL) was slowly added over 2 min. After 15 min the reaction was transferred via cannula into a 23 °C solution of allyl iodide (900 μL) and HMPA (900 μL). Following addition, the mixture was stirred for 80 min and then quenched with H_2O (15 mL). The mixture was extracted with Et_2O (3 x 15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (10:1 hexanes/EtOAc eluent) provided enol ether **67** (37.1 mg, 46% yield) as a clear oil, which was used immediately in the next step.

Enol ether **67** (32.6 mg, 0.0714 mmol) in toluene (4 mL) was transferred to a sealable flask. The flask was sealed, and the reaction vessel was heated to 175 °C behind a blast shield. After 2.5 h the mixture was cooled to 23 °C and concentrated in vacuo. Purification by preparatory thin layer chromatography on silica gel (0.5 mm, 3:1

hexanes/EtOAc eluent) provided a 2.7:1 diastereomeric mixture (Diastereomer 1 : Diastereomer 2) of Claisen products **68** (23.8 mg combined, 73% yield) as clear oils.

Diastereomer 1: R_F 0.31 (2:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, C_6D_6) δ 7.26 (s, 1H), 6.93 (t, *J* = 1.7 Hz, 1H), 6.10 (dd, *J* = 1.9, 0.8 Hz, 1H), 5.77-5.60 (m, 1H), 4.98-4.86 (m, 2H), 4.82 (d, *J* = 5.8 Hz, 1H), 3.93 (d, *J* = 10.5 Hz, 1H), 3.52 (t, *J* = 6.5 Hz, 1H), 3.30 (d, *J* = 10.5 Hz, 1H), 2.33 (t, *J* = 6.5 Hz, 1H), 2.17 (t, *J* = 7.4 Hz, 1H), 2.12-1.98 (m, 1H), 1.78-1.69 (m, 1H), 1.63 (s, 9H), 1.37 (s, 3H), 1.30-1.27 (m, 1H), 1.01 (d, *J* = 7.7 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 206.1, 178.6, 175.8, 143.9, 143.0, 140.1, 132.4, 122.4, 119.1, 107.8, 99.0, 86.0, 80.2, 69.9, 56.7, 46.0, 41.5, 38.9, 36.5, 35.3, 30.2, 28.6, 17.5, 17.0; IR (thin film/NaCl) 2977, 1784, 1722, 1156 cm^{-1}; HRMS (FAB$^+$) *m*/*z* calc'd for $[C_{26}H_{31}O_7]^+$: 455.2070, found 455.2089.

Claisen product **68** *(Diastereomer 1)* was assigned the indicated relative stereochemistry based on the shown nOe interactions.

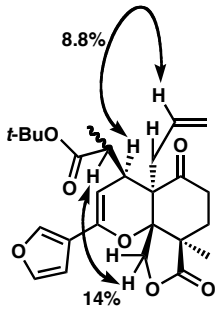


68 (Diastereomer 1)

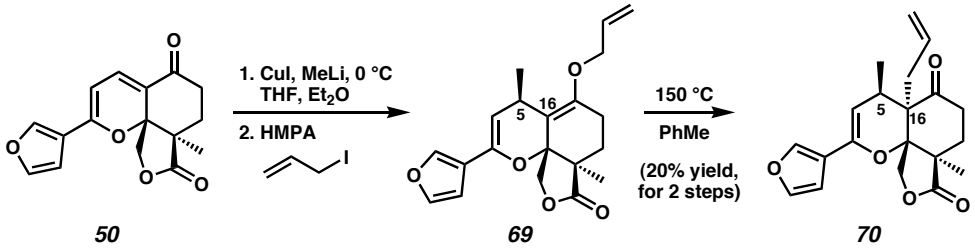
Diastereomer 2: R_F 0.38 (2:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, C_6D_6) δ 7.27 (s, 1H), 6.91 (t, *J* = 1.8 Hz, 1H), 6.17 (dd, *J* = 1.7, 0.8 Hz, 1H), 5.50-5.36 (m, 1H), 5.32 (d, *J* = 5.5 Hz, 1H), 4.94-4.74 (m, 3H), 3.88 (d, *J* = 11.6 Hz, 1H), 2.54-2.41 (m, 2H), 2.36-2.15 (m, 2H), 2.07-1.95 (m, 1H), 1.69 (d, *J* = 6.6 Hz, 3H), 1.55-1.41 (m, 1H), 1.37

(s, 3H), 1.27 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 206.3, 179.4, 174.3, 144.0, 142.7, 140.4, 132.1, 122.4, 119.8, 107.7, 99.4, 85.0, 80.9, 72.7, 57.2, 46.2, 43.2, 41.7, 38.5, 36.1, 30.5, 28.3, 21.8, 18.4; IR (thin film/NaCl) 2977, 1782, 1719, 1150 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{26}H_{33}O_7]^+$: 457.2226, found 457.2213.

Claisen product **68** *(Diastereomer 2)* was assigned the indicated relative stereochemistry based on the shown nOe interactions.



68 (Diastereomer 2)



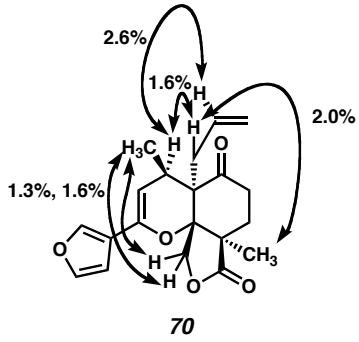
50 ***69*** ***70***

Methyl Claisen Product 70. A solution of MeLi in Et_2O (1.29 mL, 2.07 mmol) was slowly added to a mixture of CuI (197 mg, 1.03 mmol) in Et_2O (2.5 mL) at 0 °C in a dropwise fashion. Following addition, the mixture was stirred for 10 min at 0 °C, and then a solution of polycycle **50** (60 mg, 0.210 mmol) in THF (2 mL) was added. After 30 min the reaction was transferred via cannula into a flask at 23 °C containing allyl iodide

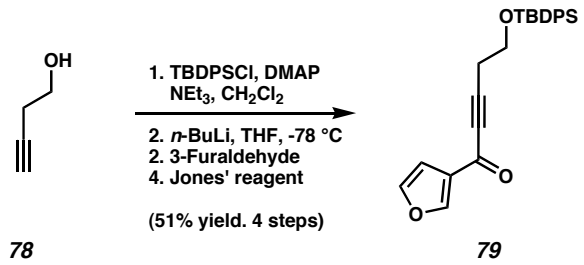
(500 μL) and HMPA (500 μL). Following addition the mixture was stirred for 2 h and then quenched with brine (10 mL). The mixture was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (8:1 hexanes/EtOAc eluent) provided enol ether **69** (14.1 mg, 20% yield) as a clear oil, which was used immediately in the next step.

Enol ether **69** (14.1 mg, 0.412 mmol) in toluene (1 mL) was transferred to a sealable flask. The flask was sealed, and the reaction vessel was heated at 150 °C behind a blast shield. After 4.5 h, the mixture was cooled to 23 °C and concentrated under reduced pressure to provide Claisen product **70** (14.1 mg, 100% yield) as a clear oil: R_F 0.67 (1:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, C_6D_6) δ 7.29 (s, 1H), 6.98 (t, *J* = 2.0 Hz, 1H), 6.16-6.14 (m, 1H), 5.55-5.46 (m, 1H), 4.96-4.92 (m, 1H), 4.84-4.78 (m, 1H), 4.73 (d, *J* = 5.4 Hz, 1H), 4.10 (d, *J* = 10.7 Hz, 1H), 3.42 (d, *J* = 10.7 Hz, 1H), 2.53-2.46 (m, 1H), 2.28 (d, *J* = 7.3 Hz, 2H), 2.05-1.97 (m, 1H), 1.73-1.65 (m, 1H), 1.60-1.52 (m, 1H), 1.41-1.37 (m, 1H), 1.36 (s, 3H), 0.91 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 206.0, 179.5, 143.9, 142.3, 140.2, 132.7, 122.6, 119.2, 107.8, 103.5, 85.1, 72.6, 55.4, 46.0, 38.0, 36.0, 31.7, 30.5, 18.9, 17.3; IR (thin film/NaCl) 2944, 1779, 1712, 1113 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{20}H_{22}O_5]^+$: 342.1467, found 342.1462.

Methyl Claisen product **70** was assigned the indicated relative stereochemistry based on the shown nOe interactions.



70



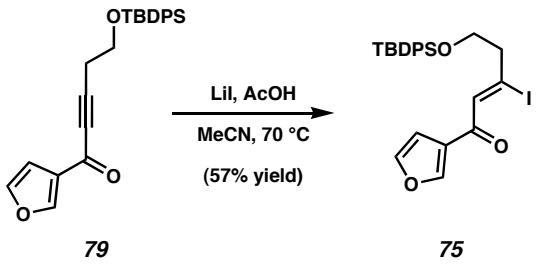
78 *79*

Ynone 79. To a solution of alcohol **78** (1.73 mL, 22.9 mmol), *t*-butyldiphenylsilyl chloride (5.72 g, 22 mmol), and DMAP (98 mg, 0.8 mmol) in CH_2Cl_2 (20 mL) was added Et_3N (3.1 mL, 22 mmol). After stirring for 1 h, the reaction was washed with H_2O (20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was dissolved in benzene (10 mL) and concentrated in vacuo to azeotropically remove water, and the resulting protected alcohol was taken on to the next step without further purification.

The product from the previous step was dissolved in THF (40 mL) and cooled to –78 °C. To this solution was slowly added *n*-butyllithium (2.5 M in hexanes, 8.8 mL, 22

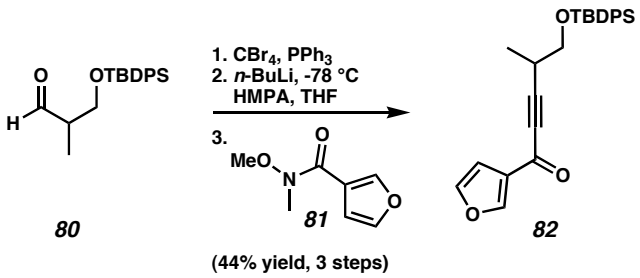
mmol). After 20 min 3-furaldehyde (1.9 mL, 22 mmol) was slowly added. Following addition, the mixture was warmed to 23 °C and stirred for 10 min. The reaction was quenched with 1 N HCl (40 mL). The mixture was concentrated in vacuo to remove THF, and the resulting solution was extracted with ether (2 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure, and the resulting coupled alcohol was taken onto the next step without further purification.

The crude product from the previous step was dissolved in acetone (40 mL) and cooled to 0 °C. To this solution was added Jones' reagent[27] (2.67 M, 15 mL, 40 mmol). After stirring for 10 min, *i*-PrOH (5 mL) was added to quench the remaining oxidant. The reaction was diluted with ether (100 mL) and extracted with a 1:1 mixture of brine and saturated aqueous $NaHCO_3$ (100 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography (30:1 hexanes/EtOAc eluent) provided ynone **79** (4.47 g, 51% yield): R_F 0.56 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) 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, $CDCl_3$) 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.



79 *75*

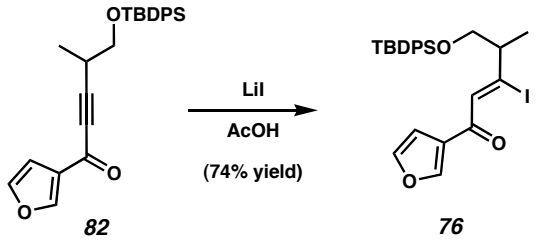
Vinyl Iodide 75. To a solution of ynone **79** (402 mg, 1.0 mmol) and LiI (147 g, 1.1 mmol) in MeCN (1.0 mL) was added glacial AcOH (63 μL, 1.1 mmol). Following addition, the mixture was refluxed for 20 h. The mixture was concentrated in vacuo and purified by flash chromatography (50:1 to 4:1 hexanes/EtOAc eluent) to provide vinyl iodide **75** (302 mg, 57% yield): R_F 0.45 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, C_6D_6) δ 7.75-7.68 (m, 4H), 7.45 (dd, *J* = 1.3, 0.8 Hz, 1H), 7.25-7.19 (m, 6H), 6.77 (t, *J* = 1.7 Hz, 1H), 6.72 (t, *J* = 1.1 Hz, 1H), 6.68 (dd, *J* = 1.9, 0.8 Hz, 1H), 3.71 (t, *J* = 6.0 Hz, 2H), 2.61 (dt, *J* = 5.9, 0.9 Hz, 2H), 1.10 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6) δ 182.5, 147.4, 144.7, 136.4, 136.3, 135.6, 134.1, 132.0, 130.5, 130.2, 129.2, 128.5, 128.2, 113.6, 109.6, 62.7, 51.2, 27.4, 27.3, 27.1, 19.8, 19.6; IR (thin film/NaCl) 2930, 2857, 1662, 1591, 1428, 1157, 1112 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{25}H_{28}O_3SiI]^+$: 531.0853, found 531.0856.



Ynone 82. To a solution of PPh_3 (8.53 g, 32.5 mmol) in CH_2Cl_2 (10 mL) cooled to 0 °C was added a solution of CBr_4 (5.4 g, 16.3 mmol) in CH_2Cl_2 (4 mL). After 10 min, aldehyde **80**[28] (2.66 g, 8.13 mmol) in CH_2Cl_2 (6 mL) was slowly added. Following addition, the reaction was stirred for 4 h at 0 °C. A small scoop of Celite was added to the reaction mixture, which was then slowly poured onto a stirring solution of Celite in petroleum ether (500 mL). The mixture was filtered, and the filtrate was concentrated in vacuo and purified by flash chromatography on silica gel (20:1 petroleum ether/EtOAc eluent) to provide the vinyl dibromide (3.46 g, 91% yield) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (m, 4H), 7.41 (m, 6H), 6.27 (d, J = 8.7 Hz, 1H), 3.55 (m, 2H), 2.69 (m, 1H), 1.06 (s, 9H), 1.04 (d, J = 6.9 Hz, 3H).

To a solution of the resulting vinyl dibromide (2.29 mg, 4.91 mmol) in THF (25 mL) cooled to -78 °C was slowly added *n*-butyllithium (2.5 M in hexanes, 4.3 mL, 10.8 mmol). After 15 min, the mixture was warmed to 0 °C. The reaction was stirred for 30 min at this temperature and then cooled back to -78 °C. HMPA (2.5 mL) was added, and the mixture was stirred for 20 min. The reaction was then warmed to -40 °C, and a solution of Weinreb amide **81**[29] (1.73 g, 11.1 mmol) in THF (12.5 mL) was slowly added. The cold bath was allowed to warm to 23 °C, and after 2.5 h the reaction was quenched with saturated aqueous NH_4Cl (50 mL). The mixture was extracted with ether (3 x 50

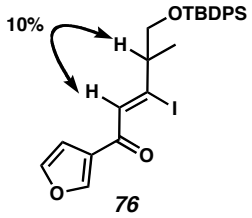
mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (15:1 hexanes/EtOAc eluent) provided ynone **82** (989.2 mg, 48% yield, 44% yield over 2 steps) as a clear oil: R_F 0.54 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (dd, *J* = 1.3, 0.8 Hz, 1H), 7.70-7.65 (m, 4H), 7.47-7.34 (m, 7H), 6.80 (dd, *J* = 1.9, 0.8 Hz, 1H), 3.78 (dd, *J* = 9.8, 6.1 Hz, 1H), 3.67 (dd, *J* = 9.7, 6.5 Hz, 1H), 2.95-2.82 (m, 1H), 1.30 (d, *J* = 6.9 Hz, 3H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 150.6, 144.6, 135.8, 133.4, 133.4, 130.1, 129.4, 128.0, 108.6, 95.1, 80.6, 77.4, 67.0, 29.7, 27.0, 19.5, 16.7; IR (thin film/NaCl) 2932, 2858, 2215, 1643, 1113 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{26}H_{27}O_3Si]^+$: 415.1730, found 415.1727.



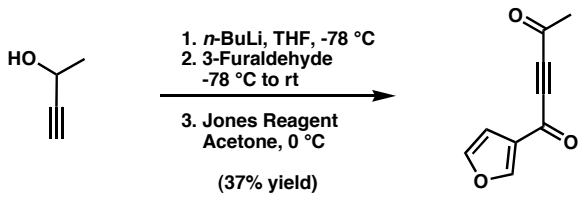
Vinyl Iodide 76. To a solution of ynone **82** (387 mg, 0.929 mmol) in glacial AcOH (10 mL) was added LiI (250 mg, 1.86 mmol). Following addition, the mixture was stirred for 10 h and then poured onto ice water (50 mL). Solid K_2CO_3 was added until bubbling ceased, and the mixture was extracted with Et_2O (4 x 50 mL). The combined organic layers were dried over Na_2SO_4. After filtration, the residue was concentrated under reduced pressure. Purification by flash chromatography (20:1

hexanes/EtOAc eluent) provided vinyl iodide **76** (373.5 mg, 74% yield) as a yellow oil: R_F 0.50 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, C_6D_6) δ 7.78-7.71 (m, 4H), 7.54 (dd, *J* = 1.3, 0.8 Hz, 1H), 7.27-7.20 (m, 6H), 6.83 (d, *J* = 0.8 Hz, 1H), 6.79 (t, *J* = 1.7 Hz, 1H), 6.70 (dd, *J* = 1.9, 0.8 Hz, 1H), 3.68 (dd, *J* = 10.2, 7.6 Hz, 1H), 3.51 (dd, *J* = 10.1, 5.1 Hz, 1H), 2.31-2.19 (m, 1H), 1.12 (s, 9H), 0.82 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 183.4, 147.7, 144.7, 136.5, 136.3, 136.3, 134.3, 134.1, 131.1, 130.5, 130.5, 130.5, 129.0, 128.5, 123.4, 109.6, 67.9, 51.2, 27.4, 27.4, 19.9, 17.9; IR (thin film/NaCl) 2931, 2858, 1664, 1590, 1156, 1112 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{26}H_{30}O_3SiI]^+$: 545.1009, found 545.0997.

Vinyl iodide **76** was assigned the (Z) stereochemistry based on a 10% nOe interaction between the vinyl hydrogen and the allylic hydrogen.



76

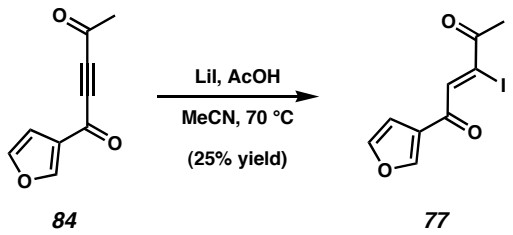


83 ***84***

Ynone 84. Alcohol **83** (3.14 mL, 40 mmol) was dissolved in THF (80 mL) and cooled to -78 °C. To this solution was slowly added *n*-butyllithium (2.5 M in hexanes, 32

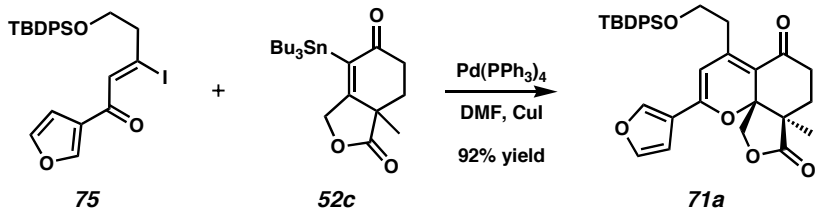
mL, 80 mmol) over 5 min. After 20 min, 3-furaldehyde (3.63 mL, 42 mmol) was slowly added. Following addition, the mixture was warmed to 23 °C and stirred for 10 min. The reaction was quenched with 1 N HCl (100). The mixture was concentrated in vacuo to remove THF, and the resulting solution was extracted with ether (2 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting coupled alcohol was taken onto the next step without further purification.

The product from the previous step was dissolved in acetone (100 mL) and cooled to 0 °C. To this solution was added Jones' reagent (2.67 M, 35 mL, 93 mmol). After stirring for 10 min, *i*-PrOH (5 mL) was added to quench the remaining oxidant. The reaction was diluted with ether (150 mL) and extracted with a 1:1 mixture of brine and saturated aqueous $NaHCO_3$ (150 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography (9:1 hexanes/EtOAc eluent) provided ynone **84** (2.37 g, 37% yield): R_F 0.37 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (dd, *J* = 1.6, 0.8 Hz, 1H), 7.49 (t, *J* = 1.7 Hz, 1H), 6.83 (dd, *J* = 1.9, 0.8 Hz, 1H), 2.48 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.1, 169.4, 151.4, 145.4, 128.6, 108.3, 83.6, 83.0, 32.8; IR (thin film/NaCl) 3133, 1681, 1641, 1556, 1510, 1305, 1200, 1156 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_9H_6O_3]^+$: 162.0317, found 162.0321.



84 *77*

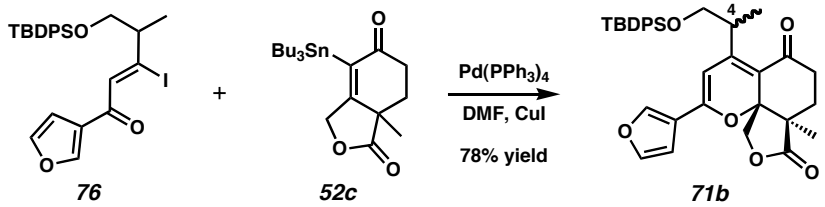
Vinyl Iodide 77. To a solution of ynone **84** (2.37 g, 14.6 mmol) and LiI (2.15 g, 16.1 mmol) in MeCN (160 mL) was added glacial AcOH (922 μL, 1.1 mmol). Following addition, the mixture was refluxed for 20 h. The mixture was concentrated in vacuo and purified by flash chromatography (6:1 hexanes/EtOAc eluent) to provide vinyl iodide **77** (1.0 g, 25% yield): R_F 0.27 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, C_6D_6) δ 6.86 (dd, *J* = 1.3, 0.8 Hz, 1H), 6.65 (dd, *J* = 2.0, 1.5 Hz, 1H), 6.50 (s, 1H), 6.41 (dd, *J* = 2.1, 0.8 Hz, 1H), 2.21 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 198.8, 180.7, 148.5, 144.8, 135.4, 127.4, 118.1, 109.2, 25.6; IR (thin film/NaCl) 3134, 1706, 1654, 1576, 1512, 1156 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_9H_7O_3I]^+$: 289.9440, found 289.9432.



75 *52c* *71a*

Polycycle 71a. Vinyl stannane **52c** (1.78 g, 3.90 mmol) and vinyl iodide **75** (2.07 g, 3.90 mmol) were subjected to the tandem Stille-oxa-electrocyclization conditions, as described above for the synthesis of polycycle **50**. Purification by flash chromatography

(3:1 hexanes/EtOAc eluent) provided polycycle **71a** (2.05 g, 3.59 mmol) as an orange solid: R_F 0.26 (3:1 hexanes/EtOAc); ^{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 Hz, 2H), 2.68-2.37 (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, 127.7, 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.

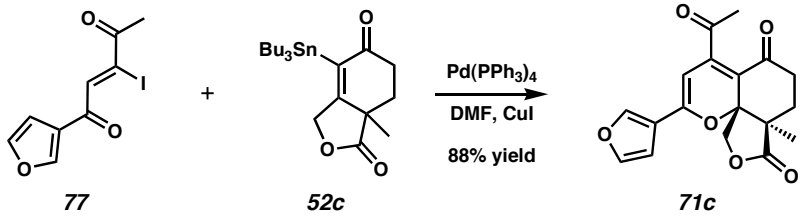


Polycycle 71b. Vinyl stannane **52c** (611 mg, 1.34 mmol) and vinyl iodide **76** (665 mg, 1.22 mmol) were subjected to the tandem Stille-oxa-electrocyclization conditions, as described above for the synthesis of polycycle **50**. Purification by flash chromatography (3:1 hexanes/EtOAc eluent) provided a 1:1 diastereomeric mixture of polycycle **71b** (554 mg, 78% yield) as an orange oil.

Diastereomer 1: R_F 0.27 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, C_6D_6) δ 7.71-7.63 (m, 4H), 7.28 (d, *J* = 0.8 Hz, 1H); 7.21-7.18 (m, 6H), 6.85 (t, *J* = 1.7 Hz, 1H), 6.15 (s, 1H), 6.06 (dd, *J* = 1.9, 0.8 Hz, 1H), 5.74 (s, 1H), 4.80-4.66 (m, 1H), 4.28 (d, *J* = 11.0 Hz, 1H), 3.69-3.55 (m, 2H), 3.30 (d, *J* = 11.0 Hz, 1H), 2.31-2.04 (m, 2H), 1.54-1.43

(m, 2H), 1.40 (s, 3H), 1.18-1.10 (m, 2H), 1.06 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 195.2, 178.8, 153.7, 152.3, 144.5, 143.4, 136.3, 136.2, 134.3, 134.2, 130.4, 130.3, 128.7, 128.5, 128.4, 128.3, 121.7, 116.5, 107.9, 99.8, 87.3, 71.0, 67.6, 45.5, 36.2, 36.0, 28.4, 27.3, 19.8, 15.6, 15.4; IR (thin film/NaCl) 2930, 1784, 1654, 1522, 1110 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{35}H_{39}O_6Si]^+$: 583.2516, found 583.2534.

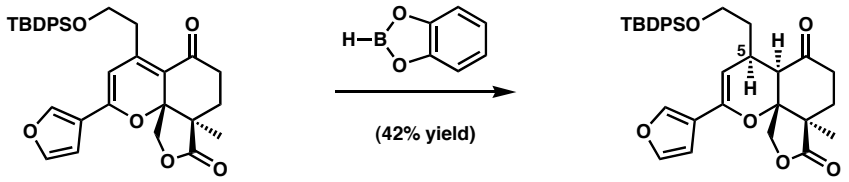
Diastereomer 2: R_F 0.23 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, C_6D_6) δ 7.84-7.75 (m, 4H), 7.28-7.20 (m, 6H), 6.83 (t, *J* = 1.8 Hz, 1H), 6.14 (s, 1H), 6.07 (t, *J* = 1.1 Hz, 1H), 5.93 (s, 1H), 4.72-4.62 (m, 1H), 4.47 (d, *J* = 11.0 Hz, 1H), 3.91 (d, *J* = 5.8 Hz, 2H), 3.48 (d, *J* = 11.0 Hz, 1H), 2.15-1.99 (m, 2H), 1.44-1.36 (m, 2H), 1.30 (s, 3H), 1.16 (s, 9H), 1.05 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 194.7, 178.7, 155.2, 152.3, 144.6, 143.5, 136.5, 136.4, 134.3, 134.3, 130.5, 121.7, 115.2, 107.7, 101.0, 87.5, 74.9, 71.1, 68.6, 45.3, 36.2, 35.8, 33.4, 28.0, 27.6, 27.5, 20.0, 15.9, 15.2; IR (thin film/NaCl) 2931, 1784, 1657, 1515, 1112 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{35}H_{39}O_6Si]^+$: 583.2516, found 583.2533.



77 ***52c*** ***71c***

Polycycle 71c. Vinyl stannane **52c** (1.57 g, 3.45 mmol) and vinyl iodide **77** (1.0 g, 3.45 mmol) were subjected to the tandem Stille-oxa-electrocyclization conditions, as described above for the synthesis of polycycle **50**. Purification by flash chromatography

(2:1 hexanes/EtOAc eluent) provided polycycle **71c** (1.0 g, 88% yield) as an orange solid. Suitable crystals for X-ray diffraction were grown from 1:1 hexanes/EtOAc by slow evaporation: R_F 0.24 (1:1 hexanes/EtOAc); mp 142 °C; ^{1}H NMR (300 MHz, C_6D_6) δ 6.78 (t, *J* = 1.7 Hz, 1H), 6.18 (s, 1H), 5.90 (dd, *J* = 1.9, 0.8 Hz, 1H), 5.36 (s, 1H), 4.19 (d, *J* = 11.4 Hz, 1H), 3.20 (d, *J* = 11.2 Hz, 1H), 2.17 (s, 3H), 1.95-1.88 (m, 2H), 1.40-1.22 (m, 2H), 1.18 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 201.9, 192.8, 178.1, 154.9, 149.9, 145.1, 144.8, 144.2, 107.7, 98.3, 86.3, 70.5, 44.8, 33.4, 29.1, 27.7, 26.6, 14.4; IR (thin film/NaCl) 3135, 2918, 1782, 1705, 1668, 1560, 1519, 1499, 1161 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{18}H_{16}O_6]^+$: 328.0947, found 328.0946.

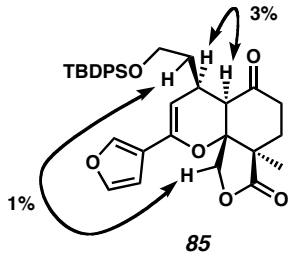


71a *85*

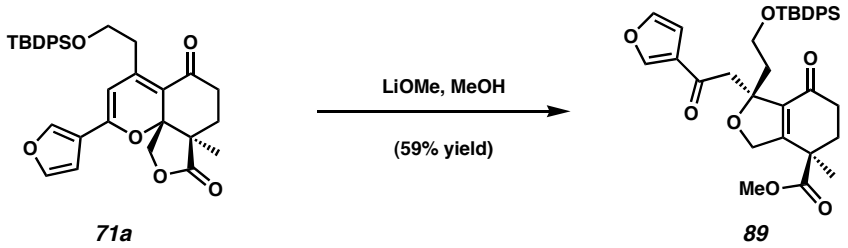
Ketone 85. To a solution of enone **71a** (36.7 mg, 0.0645 mmol) in THF (500 μL) was added catecholborane (20 μL, 0.194 mmol). The mixture was stirred for 90 min and then quenched with MeOH (500 μL). The mixture was diluted with Et_2O (20 mL) and extracted with a 2:1 mixture of 1 N NaOH and saturated aqueous NH_4Cl (4 x 7 mL). The combined aqueous layers were extrated with Et_2O (10 mL). The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4. After filtration, the residue was concentrated under reduced pressure. Purification by preparatory thin layer chromatography on silica gel (0.5 mm, 3:1 hexanes/EtOAc eluent) provided ketone **85**

(15.5 mg, 42% yield) as a clear oil: R_F 0.27 (2:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74-7.67 (m, 5H), 7.48-7.34 (m, 7H), 6.32 (s, 1H), 5.31 (d, *J* = 5.5 Hz, 1H), 4.37 (d, *J* = 11.0 Hz, 1H), 4.09 (d, *J* = 10.4 Hz, 1H), 3.86 (t, *J* = 6.0 Hz, 2H), 3.00 (d, *J* = 4.9 Hz, 1H), 2.91-2.82 (m, 1H), 2.69-2.54 (m, 1H), 2.50-2.28 (m, 2H), 2.10-1.97 (m, 3H), 1.51 (s, 3H), 1.09 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6) δ 203.4, 178.3, 143.8, 143.2, 140.2, 136.5, 136.4, 134.6, 134.5, 130.5, 130.5, 122.9, 107.8, 101.6, 84.8, 78.0, 71.3, 63.5, 49.7, 45.9, 36.2, 35.0, 30.2, 27.9, 27.5, 19.9, 13.8; IR (thin film/NaCl) 2931, 1784, 1719, 1105 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{34}H_{39}O_6Si]^+$: 571.2516, found 571.2492.

Ketone **85** was assigned the indicated relative stereochemistry based on the shown nOe interactions.



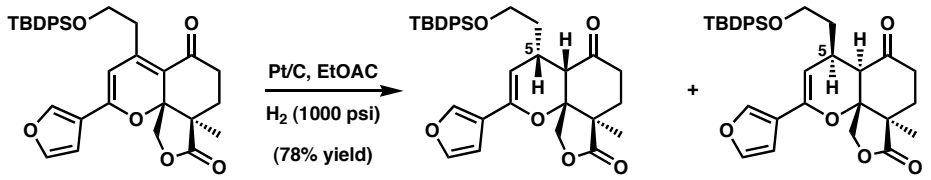
85



71a ***89***

Diketone 89. To a solution of lactone **71a** (75.7 mg, 0.133 mmol) in MeOH (1.75 mL) was added LiOH (32 mg, 1.33 mmol). The mixture was stirred for 30 min and then quenched with saturated aqueous NH_4Cl (5 mL). The mixture was extracted with EtOAc

(3 x 5 mL). The combined organic layers were dried over Na_2SO_4. After filtration the residue was concentrated under reduced pressure. Purification by flash chromatography (4:1 hexanes/EtOAc eluent) provided diketone **89** (47.0 mg, 59% yield) as a clear oil: R_F 0.52 (1:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 1.5, 0.7 Hz, 1H), 7.69-7.60 (m, 5H), 7.42-7.35 (m, 6H), 6.69 (dd, *J* = 1.9, 0.8 Hz, 1H), 4.58 (d, *J* = 16.0 Hz, 1H), 4.47 (d, *J* = 15.7 Hz, 1H), 3.86-3.73 (m, 1H), 3.52-3.44 (m, 1H), 3.37 (s, 3H), 3.24-3.20 (m, 3H), 2.38-2.20 (m, 4H), 1.92-1.81 (m, 1H), 1.29 (s, 3H), 1.01 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.9, 192.9, 173.6, 159.4, 148.4, 144.2, 135.7, 133.9, 129.7, 129.0, 127.9, 108.7, 90.2, 74.2, 60.0, 52.6, 48.7, 43.9, 42.4, 35.7, 35.0, 27.0, 26.9, 23.0, 19.3; IR (thin film/NaCl) 2930, 1735, 1675, 1111 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{35}H_{41}O_7Si]^+$: 601.2622, found 601.2631.



71a ***90*** ***85***

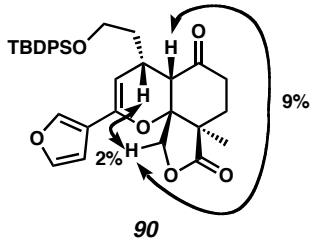
4.8 : 1

Ketone 90. Two batches of enone **71a** (2.3348 g, 4.105 mmol each) were separately dissolved in EtOAc (11 mL each). To these mixtures were added 10% Pt/C (560 mg in each mixture). The mixtures were then transferred to a H_2 bomb and stirred for 9 h under an atmosphere of pressurized H_2 (1000 psi). The two mixtures were then combined and passed through a short pad of silica gel to remove the Pt/C (EtOAc eluent).

Purification by flash chromatography (5:1 hexanes/EtOAc eluent) provided ketone **90** (1.287 g, 27.5% yield) as a white solid, the C(16) epimer of ketone **90** (1.745 g, 37.2% yield) as a clear oil,[30] and ketone **85** (0.627 g, 13.4% yield) as a clear oil. For **90**, suitable crystals for X-ray diffraction were grown from Et_2O by slow evaporation.

*Ketone **90**:* R_F 0.45 (2:1 hexanes/EtOAc); mp 131 °C; ^{1}H NMR (300 MHz, C_6D_6) δ 7.79-7.71 (m, 5H), 7.32-7.21 (m, 6H), 6.97 (t, *J* = 1.7 Hz, 1H), 6.15-6.12 (m, 1H), 4.94 (s, 1H), 3.93 (d, *J* = 9.6 Hz, 1H), 3.82-3.72 (m, 1H), 3.67-3.57 (m, 2H), 3.26 (q, *J* = 7.0 Hz, 2H), 2.75-2.65 (m, 1H), 2.47 (d, *J* = 4.3 Hz, 1H), 2.26-2.16 (m, 2H), 1.92-1.83 (m, 2H), 1.18 (s, 9H), 0.98 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 205.6, 177.9, 143.8, 143.6, 139.5, 136.4, 136.3, 134.2, 134.1, 130.6, 130.5, 122.9, 107.9, 101.2, 84.5, 73.3, 62.7, 47.1, 46.3, 37.3, 34.2, 30.9, 28.2, 27.5, 27.3, 19.8, 18.8; IR (thin film/NaCl) 2931, 2858, 1784, 1727, 1111 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{34}H_{39}O_6Si]^+$: 571.2516, found 571.2502.

Ketone **90** was assigned the indicated relative stereochemistry based on the shown nOe interactions.



90

2.6 Notes and References

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(14) In our analysis of the failed Heck strategy, we are ignoring the possibility of anti-β-hydride elimination. Although there are isolated examples of this phenomenon, these cases are usually limited to exceptionally activated olefin systems. For recent examples of anti-β-hydride elimination, see: (a) Lautens, M.; Fang, Y. Q. *Org. Lett.* **2003**, *5*, 3679-3682. (b) Maeda, K.; Farrington, E. J.; Galardon, E.; John, B. D.; Brown, J. M. *Adv. Synth. Catal.* **2002**, *344*, 104-109. (c) Shea, K. M.; Lee, K. L.; Danheiser, R. L. *Org. Lett.* **2000**, *2*, 2353-2356.

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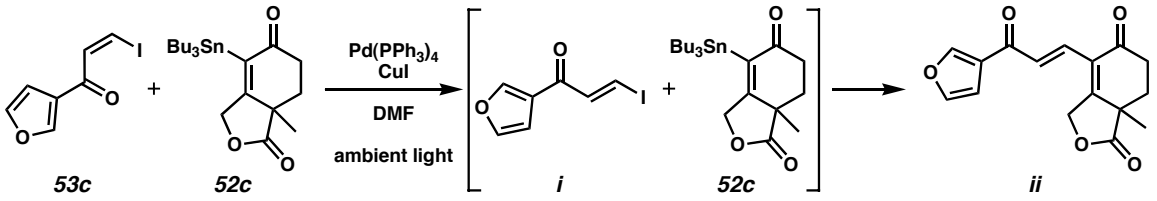
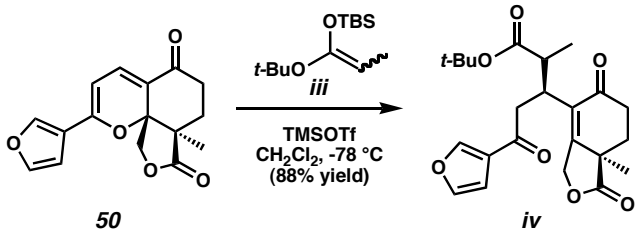
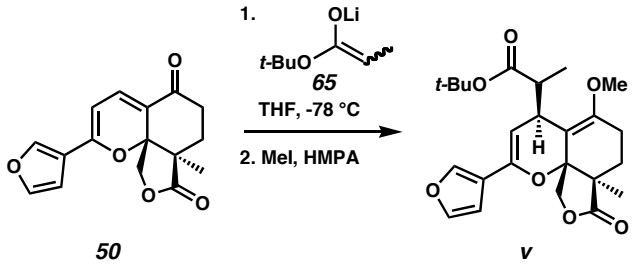
(18) In the presence of light, *trans*-dienone ***ii*** was formed, presumably as a result of cis-trans isomerization of vinyl iodide **53a** to ***i***, followed by Stille coupling:



(19) Specifically, polycycle **50** underwent 1,4-addition, but unfortunately proceeded with undesired β-hydroxy elimination to cleave the pyran substructure:



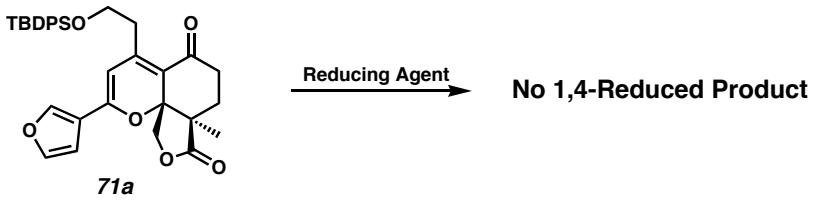
(20) Interestingly, when methyl iodide was added in the presence of HMPA, the enolate product was methylated on oxygen, not carbon, thus producing the methyl enol ether ***v***:



50 ***v***

(21) Panek, J. S.; Hu, T. *J. Org. Chem.* **1997**, *62*, 4912-4913.

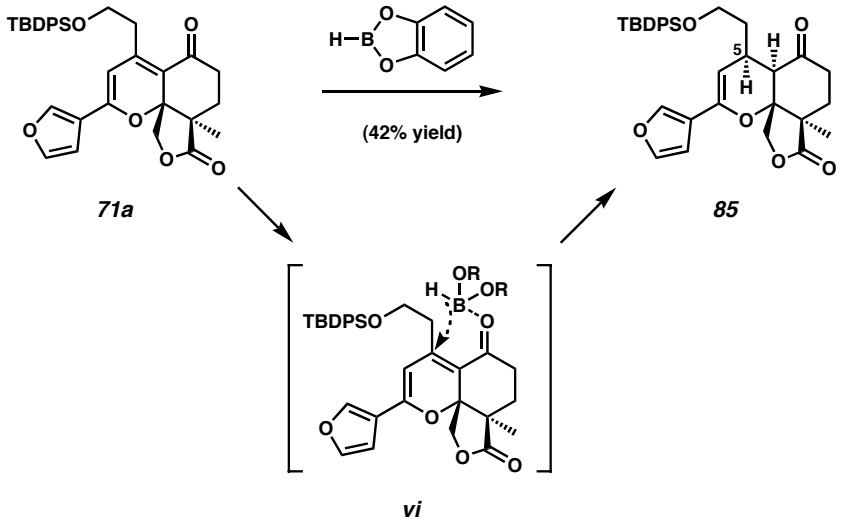
(22) Several conjugate reduction conditions were explored. Unfortunately, in most cases the tetrasubstituted olefin was resitant to reduction. Some of the unsuccessful condition reduction conditions are listed below:



71a

Reducing Agent	
Li/NH_3	$[CuH(PPh_3)]_6/R_3SiH$
HN=NH	$RhCl(PPh_3)_3$/Catecholborane
CuI-$LiAlH_4$	Pd/C, H_2 (with varying H_2 pressures)
$NaBH_4$	Pd black, H_2 (with varying H_2 pressures)
L--selectride	PtO_2, H_2 (with varying H_2 pressures)
K-selectride	$RhCl(PPh_3)_3$, H_2 (with varying H_2 pressures)
$Pd(PPh_3)_4/Bu_3SnH$	Rh/Alumina, H_2 (with varying H_2 pressures)

(23) Although we do not have a detailed explanation for why catecholborane delivers a hydride from the α-face, we believe it may due to an intramolecular delivery of the hydride nucleophile (i.e., ***vi***). This mode of nucleophillic attack differs from the putative intermolecular delivery of carbon nucleophiles from the β-face, which was discussed earlier in the chapter.



(24) For the synthesis of **56**, see: Knight, D. W.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1975**, 635-640.

(25) For the synthesis of **62**, see: Piers, E.; Wong, T.; Coish, P.; Rogers, C. *Can. J. Chem.* **1994**, *72*, 1816-1819.

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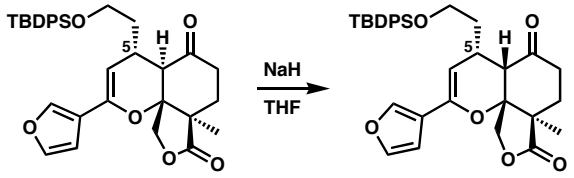
(29) For the synthesis of **81**, see: Kinoshita, T.; Ichinari, D.; Sinya, J. *J. Heterocycl. Chem.* **1996**, *33*, 1313-1317.

(30) The C(16) epimer of ketone **90** (i.e., ***vii***) was easily converted to ketone **90** by simple bases such as NaH:



vii ***90***