# Convergent and Diastereoselective Synthesis of the Polycyclic Pyran Core of Saudin

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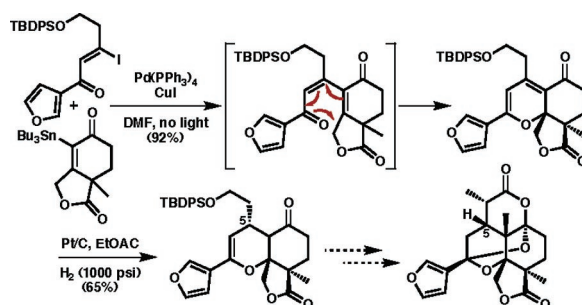
The natural product saudin was found to induce hypoglycemia in mice and, therefore, could be an appealing lead structure for the development of new agents to treat diabetes. A diastereoselective tandem Stille-oxa-electrocyclization reaction has been developed which provides access to the core structure of saudin in a rapid and convergent manner. This new reaction has been extended to the convergent preparation of a series of polycyclic pyran systems. Progress has been made on the advancement of these complex pyran systems toward the natural product. A complete account of these synthetic efforts is presented.

Introduction and Background

The caged diterpenoid saudin (**1**) was isolated in 1985 by Mossa and Cassady from the leaves of the *Clutia richardiana (L.)* family Euphorbiaceae, a toxic plant indigenous to the western and southern mountains of Saudi Arabia.[1] The complex polycyclic architecture was delineated by single-crystal X-ray analysis and shown to be that depicted in Figure 1. This unusual polycyclic natural product is presumably related to the labdane diterpenes.

Three years after isolating and disclosing the structure of saudin (**1**), Mossa and co-workers reported the biological activity of this novel caged diterpenoid.[2] Importantly, saudin was found to induce hypoglycemia in mice, both in vitro and in vivo. Given its potent hypoglycemogenic activity and oral bioavailability, saudin is an appealing lead structure for the development of new agents to treat diabetes mellitus. Unlike many other hypoglycemogenic agents, saudin's ability to reduce the glucose levels in mice and rats seems to be unrelated to the cellular
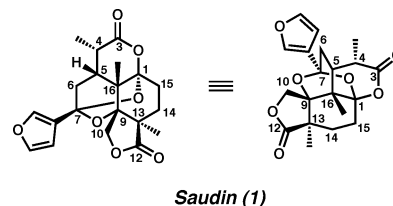

FIGURE 1. Structure of saudin (**1**).

pathways for insulin secretion. This unique mode of action may provide a complementary form of treatment for diabetes mellitus, specifically in cases where other hypoglycemic agents have failed.

Diabetes mellitus affects over 18 million people and is one of the leading causes of death in the United States.[3] In most cases, it is the result of defective insulin metabolism by the body. The disease is usually controlled in patients by a combination of diet, insulin injections, and oral hypoglycemic agents.[4]

(1) Mossa, J. S.; Cassady, J. M.; Antoun, M. D.; Byrn, S. R.; McKenzie, A. T.; Kozlowski, J. F.; Main, P. *J. Org. Chem.* **1985**, *50*, 916−918.

(2) Mossa, J. S.; El-Denshary, E. S. M.; Hindawi, R.; Ageel, A. M. *Int. J. Crude Drug Res.* **1988**, *26*, 81−87.

(3) Centers for Disease Control and Prevention. National Diabetes Fact Sheet: General Information and National Estimates on Diabetes in the United States, 2003. Rev ed. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2004.
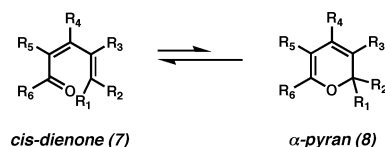
SCHEME 1

SCHEME 2

SCHEME 3
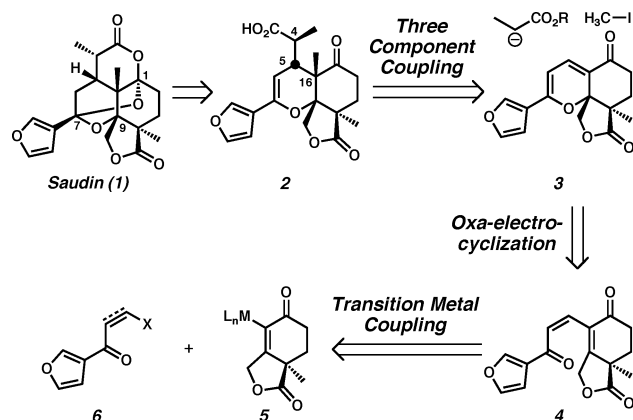
Since the isolation of saudin in 1985, there have been two total syntheses of the natural product, including Winkler's synthesis of (±)-saudin in 1999[5] and Boeckman's synthesis of (−)-saudin in 2002.[6] In these aforementioned synthetic studies, saudin's unique structural complexity has served as the inspiration for the development of innovative chemistry. Although the strategies developed to construct saudin have been elegant and efficient, we were interested in developing an alternative method that would build the core structure of the natural product in a potentially more direct and convergent manner.

At the onset of our synthetic studies, we viewed the unique structure of saudin as an ideal template for the discovery and development of new chemical reactions. Recently, we reported the development of a tandem Stille-oxa-electrocyclization reaction for the synthesis of polycyclic pyran systems,[7] which was initially inspired by the structure of saudin. Herein, we describe a complete account of the application of this novel reaction sequence toward the convergent and diastereoselective synthesis of the core structure of saudin.

1. Retrosynthetic Analysis of Saudin. The polycyclic structure of saudin (**1**) contains a dense array of functionality and stereochemistry. This includes eight oxygenated carbons and seven stereocenters (two of which are quaternary centers and a total of five which are tetrasubstituted). Retrosynthetic unraveling of the two acetals in the natural product reveals carboxylic acid **2**, which we envisioned accessible by a three component coupling of lactone **3**, a propionate equivalent, and methyl iodide (Scheme 1). Opening the pyran ring of **3** in a retro-oxa-electrocyclization exposes dienone **4**, which may be synthesized by a variety of possible transition metal-mediated coupling reactions between enone **5** and furan **6**.

2. Oxa-Electrocyclization Reactions in Natural Product Synthesis. The oxa-electrocyclization reaction is a relatively underutilized transformation in organic synthesis.[8] This is primarily due to the existence of a typically unfavorable equilibrium between the open *cis*-dienone (**7**) and the closed
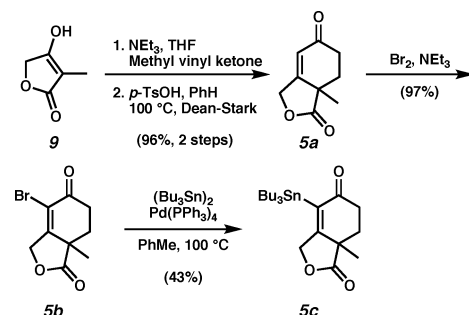
α-pyran (**8**) (Scheme 2). While the dienone structure is usually favored thermodynamically, in some cases the proper selection of functional groups and structural features in the molecule can control the equilibrium ratio to favor the α-pyran.[9]

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,[10] the epoxyquinols by Hayashi,[11] the antimalarial naphthoquinones by Trauner,[12] EI-1941-2 by Porco,[13] and Hsung's approach to a number of natural products including rhododaurichromanic acids A and B and arisugacin A.[14]

Interestingly, an oxa-electrocyclization reaction was proposed to exist in the biosynthetic pathways for all of these natural products. The putative biosynthetic pathway of saudin (**1**), which was proposed by the authors of the original isolation paper,[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, nonbiomimetic manner to rapidly synthesize the α-pyran core of saudin.

Results and Discussion

1. First-Generation Strategy Based on a Michael Addition

1.1. Efficient Synthesis of the Core of Saudin. Enone **5a** was synthesized by an efficient Robinson annulation between tetronic acid **9** and methyl vinyl ketone (Scheme 3).[15] This enone was then subjected to Br₂ and Et₃N, which yielded bromo enone

(4) Davis, S. N.; Granner, D. K. Insulin, Oral Hypoglycemic Agents, and the Pharmacology of the Endocrine Panceas. In *Goodman & Gilman's The Pharmacological Basis of Therapeutics*; Hardman, J. G., Limbard, L. E., Eds.; McGraw-Hill: New York, 1996; pp 1487−1517.

(5) Winkler, J. D.; Doherty, E. M. *J. Am. Chem. Soc.* **1999**, *121*, 7425−7426.

(6) Boeckman, R. K.; Ferreira, M. R. R.; Mitchell, L. H.; Shao, P. *J. Am. Chem. Soc.* **2002**, *124*, 190−191.

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

(8) Marvell, E. N. *Thermal Electrocyclic Reactions*; Academic Press: New York, 1980; pp 260−375.

(9) For an early example of the isomerization of dienones to α-pyrans, see: Büchi, G.; Yang, N. C. *J. Am. Chem. Soc.* **1957**, *79*, 2318−2323.

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

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

(12) (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. (c) Beaudry, C. M.; Malerich, J. P.; Trauner, D. *Chem. Rev.* **2005**, *105*, 4757−4778.

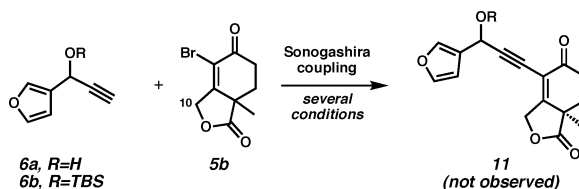(13) Kleinke, A. S.; Li, C.; Rabasso, N.; Porco, J. A., Jr. *Org. Lett.* **2006**, *8*, 2847−2850.

(14) Hsung, R. P.; Kurdyumov, A. V.; Sydorenko, N. *Eur. J. Org. Chem.* **2005**, 23−44.

(15) Prisbylla, M. P.; Takabe, K.; White, J. D. *J. Am. Chem. Soc.* **1979**, *101*, 762−763.
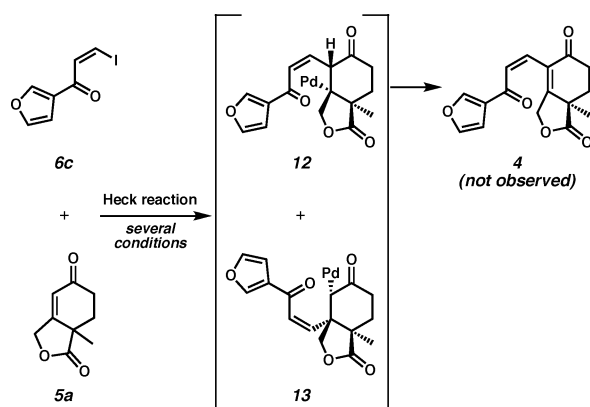
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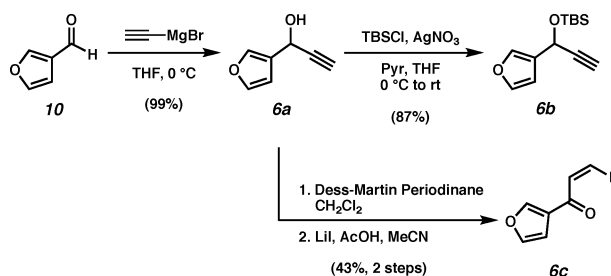
SCHEME 5

5b in 97% yield.[16] The brominated product (**5b**) was then transformed to vinyl stannane **5c** in a single step, albeit in a modest, 43% yield.[17]

Variants of furan **6** were synthesized from furaldehyde **10** by rapid two- or three-step sequences (Scheme 4). For example, addition of ethynyl Grignard into aldehyde **10** yielded propargyl alcohol **6a**, which was protected as the TBS-ether **6b**. Alternatively, *cis*-vinyl iodide **6c** could be synthesized from alcohol **6a** by sequential exposure to Dess–Martin periodinane[18] (to the ynone) followed by LiI and AcOH in MeCN.[19]
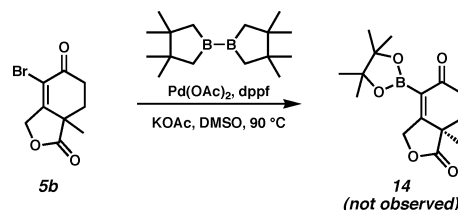
With these coupling partners in hand, a series of Sonogashira reactions were explored between bromoenone **5b** and alkynes **6a,b** (Scheme 5). In the course of these investigations, it was discovered that bicyclic enones **5a**−**c** are moderately unstable under a variety of basic conditions due to the acidic nature of the C(10) position. Despite extensive experimentation with different Pd sources, bases, and Cu salts, the Sonogashira coupling was not realized.

Alternatively, coupling via a Heck reaction of vinyl iodide **6c** and enone **5a** was explored (Scheme 6).[20] Unfortunately, this intermolecular strategy was not realized under a variety of standard Heck conditions or the modified Jeffery conditions.[21] 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[22] (i.e., **12**), along with the potential for regioisomeric insertion across the olefin (i.e., **13**).
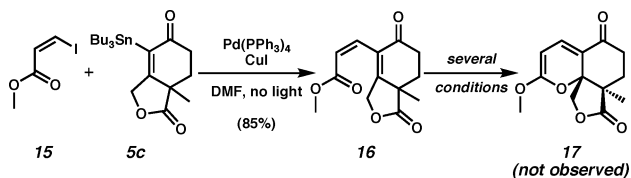
(16) Johnson, C. R.; Kozak, J. *J. Org. Chem.* **1994**, *59*, 2910−2912.

(17) Azizian, H.; Eaborn, C.; Pidcock, A. *J. Organomet. Chem.* **1981**, *215*, 49−58.

(18) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287.

(19) Ma, S.; Lu, X.; Li, Z. *J. Org. Chem.* **1992**, *57*, 709−713.

(20) For a general review on Heck reactions, see: Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009−3066.

(21) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113−10130.

(22) 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.

SCHEME 6

SCHEME 7

SCHEME 8

To investigate Suzuki coupling reactions,[23] we attempted the conversion of vinyl bromide **5b** to the corresponding vinyl boronic ester **14** (Scheme 7). But, once again, the basic conditions of the reaction merely degraded the starting material by deprotonation at C(10).

Finally, we attempted to couple the two segments under Stille conditions.[24] Initially, using a model system we were able to couple vinylstannane **5c** with *cis*-vinyl iodide **15** under modified Stille conditions,[25] which yielded dienone **16** (Scheme 8). Unfortunately, despite several attempts, we were never able to realize the oxa-electrocyclization of model enone **16**. This is presumably due to an unfavorable equilibrium, since the ester resonance energy in dienone **16** would be lost in the formation of pyran **17**.

Although the electrocyclization of model substrate **16** was unsuccessful, we decided to apply the Stille coupling strategy to fully elaborated substrates en route to saudin (**1**). When stannyl enone **5c** and vinyl iodide **6c** were subjected to the Stille conditions used in our model system, we did not observe any Stille product **4**. Instead, we isolated pyran **3** as a single diastereomer, which was the result of a tandem Stille-oxa-electrocylization reaction (Scheme 9). The presence of CuI and the absence of light were both essential for the success of this transformation. In the presence of light, *cis*-vinyl iodide **6c**

(23) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147−168.
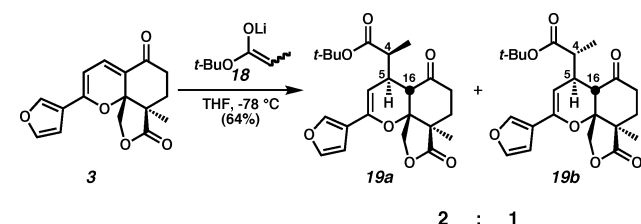
(24) For a general review on the Stille reaction, see: Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1−652.

(25) Bellina, F.; Carpita, A.; De Santis, M.; Rossi, R. *Tetrahedron* **1994**, *50*, 12029−12046.
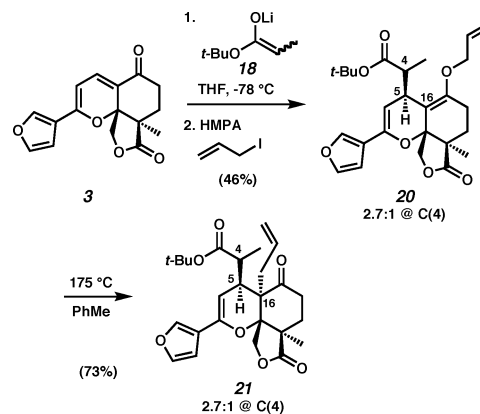
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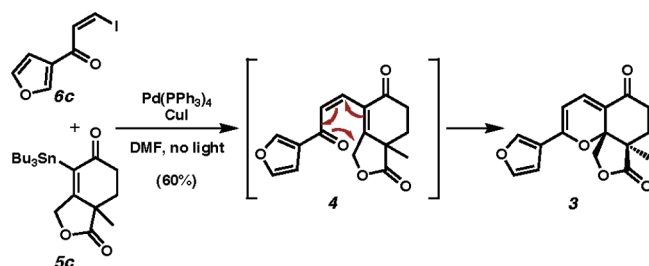
SCHEME 10

isomerized to the trans isomer, thus preventing the transient formation of the oxa-electrocyclization substrate **4**.
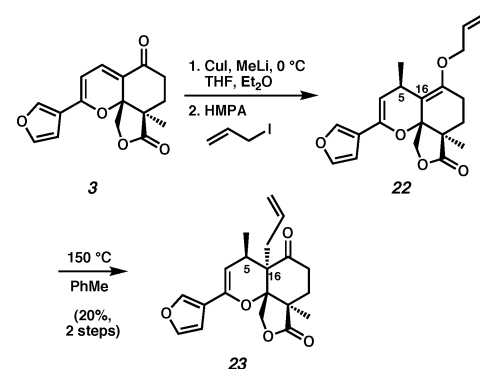
1.2. Advancing Furan Appended Tricycle 3. The synthesis of polycycle **3** represented an efficient and diastereoselective route to the core structure of saudin. At this stage, a series of 1,4-additions to this furan appended tricycle were explored. Under Mukaiyama-Michael conditions, the compound (**3**) decomposed. While it appeared that silyl ketene acetals underwent 1,4-additions into enone **3**, the Lewis acidic Mukaiyam-Michael conditions resulted in a subsequent decomposition of the pyran ring system, presumably by complexation of the Lewis acid the pyran oxygen. Under anionic conditions, however, enolate **18** selectively reacted in a 1,4-fashion to yield a mixture of **19a** and **19b** (Scheme 10). Since we assume that the initial Michael addition is irreversible, the mixture of diastereomers at C(4) may be due to the initial presence of both *E*- and *Z*-enolates **18**. Both isomers of **18** preferred to approach enone **3** from the β-face, with subsequent protonation at C(16) from the β-face as well. Unfortunately, several attempts to react the carbon enolates of **19a,b** with methyl iodide and other electrophiles were unsuccessful.[26] X-ray structure analysis eventually revealed that the Michael addition product (**19a**) was, in fact, the undesired diastereomer at C(5) with relative stereochemistry opposite to that necessary for elaboration to saudin.[27]

We envisioned that perhaps the stereochemistry at C(5) of ketoesters **19a** and **19b** sterically prohibited direct methylation at C(16) and an indirect C-alkylation could be achieved by O-allylation followed by a Claisen rearrangement. Treatment of polycycle **3** with enolate **18** followed by allyl iodide and HMPA afforded the enol ether **20**, which rearranged thermally

(26) 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 **i**:

(27) See the Supporting Information for complete X-ray data of **19a**.

SCHEME 11

SCHEME 12

to ketone **21** (Scheme 11). Unfortunately, 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.

While enolate equivalents such as **18** attacked enone **3** 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 **3** with a simple methyl cuprate and then exposed the resulting enolate to allyl iodide and HMPA (Scheme 12). The vinyl allyl ether (**22**) then underwent a thermal Claisen rearrangment to produce keto lactone **23**. Despite the differences in the type of nucleophile employed, the stereochemistry at C(5) again mirrored that previously observed, and both C(5) and C(16) were again epimeric to that present in the natural product (i.e., **23**).

Our hypothesis for the observed diastereoselective 1,4-addition of carbon nucleophiles to enone **3** from the β-face is based on a stereoelectronic argument. Since these 1,4-additions are assumed to be irreversible in our system, the formation of the C(5) stereocenter must be kinetically controlled. In our original retrosynthetic analysis, we predicted that the lactone functionality in enone **3** would sterically block the β-face from nucleophilic attack. The unexpected 1,4-additions from the β-face may be explained by torsional strain in the pyran ring system. Specifically, to avoid an eclipsing interaction between the C(5)−H and the C(6)−H bonds, which would result from α-face attack, carbon nucleophiles may prefer to approach from the β-face.
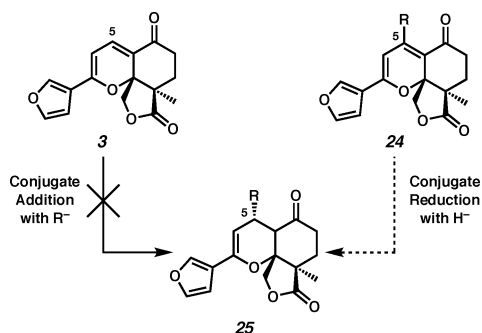
2. Second Generation Strategy Based on a 1,4-Reduction

2.1 Modified Strategy for the Synthesis of Saudin. Although we were disappointed by our inability to access the
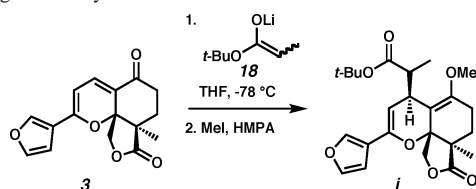
SCHEME 13

SCHEME 14

SCHEME 15

SCHEME 16
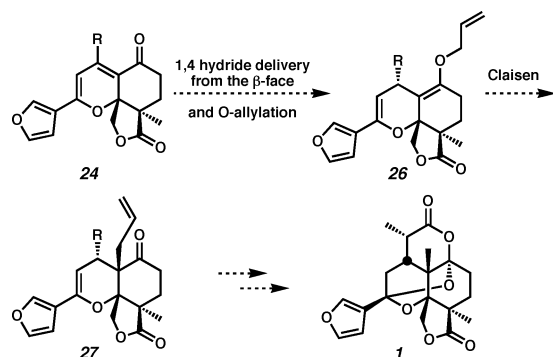
desired diastereomer of ketone **21** or **23**, there was enough flexibility in the synthetic strategy to investigate other potential solutions without abandoning the tandem Stille-oxa-electrocyclization approach.

The stereochemistry of the 1,4-additions to polycycle **3** strongly 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 bearing a side chain (i.e., **24**), which would then be subjected to a 1,4-hydride reduction (Scheme 13). If a hydride nucleophile also preferred to approach from the β-face, we would be able to access ketone **25** with the desired relative stereochemistry.
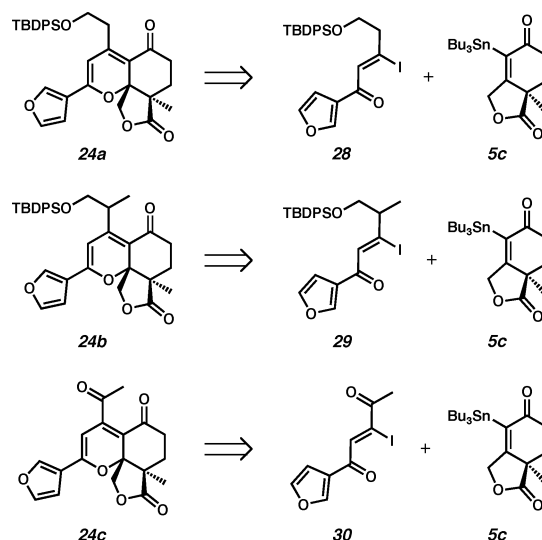
Additionally, if the hydride attacked from the β-face, the resulting enolate could be trapped with allyl iodide to generate enol ether **26**. This intermediate would hopefully undergo a diastereoselective Claisen rearrangement to generate the desired stereochemistry at C(16) (i.e., **27**, Scheme 14).

2.2. Synthesis of Modified Furan-Appended Tricycles. To investigate our second-generation strategy for the synthesis of saudin, we needed to access polycycles **24a**−**c**, which required the preparation of three new vinyl iodides (i.e., **28**, **29**, and **30**, Scheme 15).

Vinyl iodide **28** was synthesized from alcohol **31** (Scheme 16). Silyl protection of **31** followed by coupling with 3-furaldehyde yielded the propargylic alcohol product, which was then oxidized with Jones' reagent to produce ynone **32**. Treatment of the ynone (**32**) with LiI and AcOH produced the desired *cis*-vinyl iodide (**28**) as a single olefin isomer. The synthesis of vinyl iodide **29** commenced with aldehyde **33** (Scheme 16), which was converted to an alkynyl anion[28] and coupled with Weinreb amide **34**. The resulting ynone (**35**) was converted to vinyl iodide **29** as a single olefin isomer with LiI and AcOH. Finally, vinyl iodide **30** was prepared from 1-butyn-3-ol (**36**),
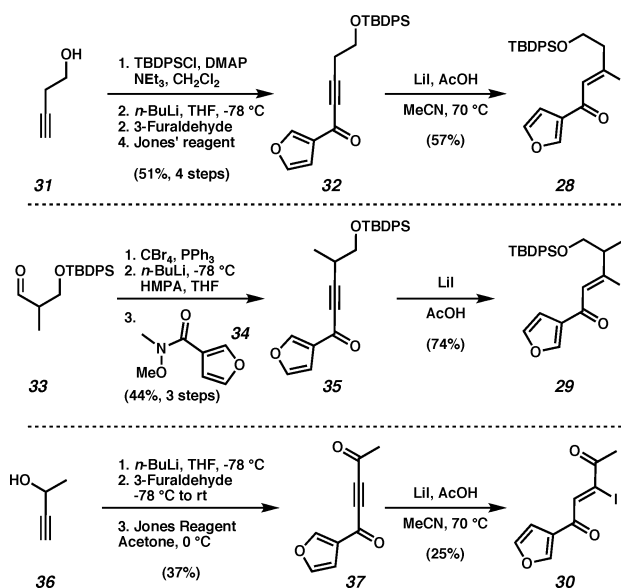
which was coupled to 3-furaldehyde and doubly oxidized to yield ynone **37** (Scheme 16). This product was then transformed into the desired vinyl iodide **30**.
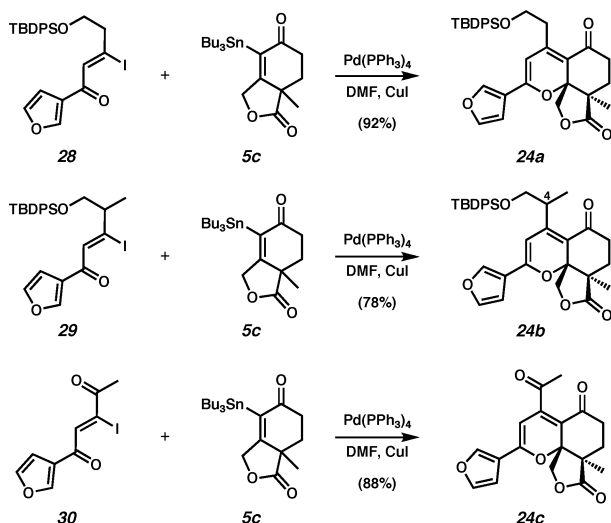
With these three new vinyl iodides in hand (**28**−**30**), the key Stille-oxa-electrocyclization reactions were performed. Smooth coupling occurred between stannane **5c** and vinyl iodides **28**, **29**, and **30** to form the desired polycycles **24a**, **24b**, and **24c** (Scheme 17). Products **24a** and **24c** were formed as single diastereomers, whereas **24b** was produced as a 1:1 mixture of diastereomers at C(4).

The structure of **24c** was unambiguously verified by single-crystal X-ray diffraction of the diketone.[29] In addition to verifying the general bond connectivity of our Stille-oxa-electrocyclization products, this crystal structure also supported our hypothesis for the observed diastereoselectivity in 1,4-additions to enone **3** (Schemes 10−12). The dihedral angle between the C(5)−C(4) bond and the C(6)−H bond in **24c** revealed a potential eclipsing interaction that would develop if
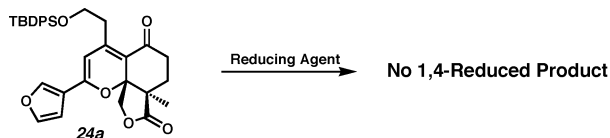
(28) Panek, J. S.; Hu, T. *J. Org. Chem.* **1997**, *62*, 4912−4913.

(29) See the Supporting Information for complete X-ray data of **24c**.

SCHEME 17

SCHEME 18

| Reducing Agent	
Li/NH$_3$	[CuH(PPh$_3$)]$_6$/R$_3$SiH
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$_3$SnH	Rh/Alumina, H$_2$ (with varying H$_2$ pressures)

SCHEME 19
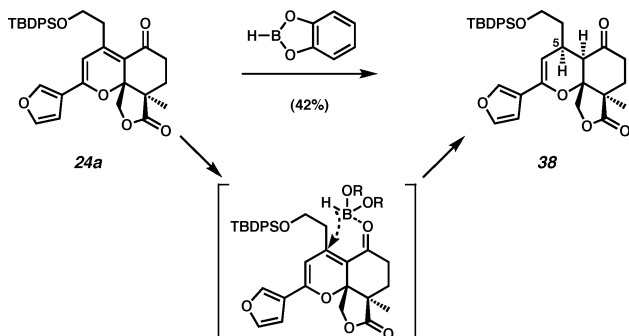
nucleophiles attacked polycycle pyran systems **3** and **24a−c** from the α-face at C(5).

2.3. 1,4-Reduction of Substituted Enone 24a. At this point, although the 1,4-addition of carbon nucleophiles to enone **3** seemed to give the C(5)-α-H-diastereomer, we were ready to test our hypothesis on the diastereoselective 1,4-reduction of enone **24a**. To realize the 1,4-hydride reduction product, we subjected polycycle **24a** to a variety of conditions. In most cases, the sterically hindered starting material was unreactive. Some of the unsuccessful reduction conditions tried are listed in Scheme 18.

Treatment of enone **24a** with catecholborane resulted in a 1,4-reduction, but surprisingly the hydride was delivered from the α-face of the enone (i.e., **38**, Scheme 19). Although we do not have a detailed explanation for why catecholborane delivers a hydride from the α-face, we believe it may be due to an intramolecular delivery of the hydride nucleophile. This mode

SCHEME 20
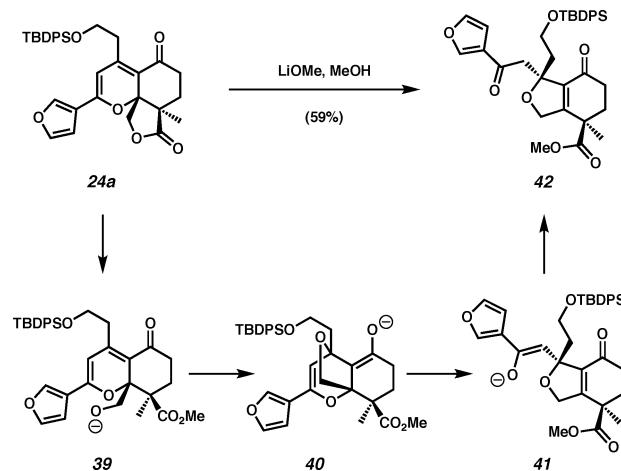
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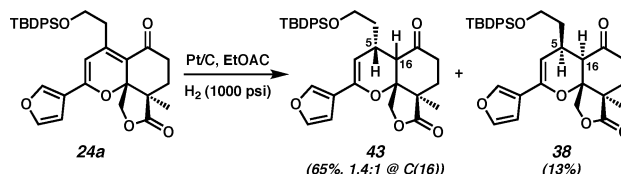
of nucleophillic attack differs from the putative intermolecular delivery of carbon nucleophiles from the β-face, which was discussed earlier.

Gratifyingly, when polycycle **24a** 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 such reactions were prohibitively low.

Presumably, the 1,4-reduction of enone **24a** 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 **24a**, with the hope of drastically changing the steric environment around the tetrasubstituted olefin. Although treating enone **24a** with LiOMe led to the opening of the lactone, the liberated alkoxide underwent an undesired intramolecular 1,4-addition, followed by a β-elimination, to generate diketone **42** (Scheme 20). The pseudoaxial orientation of the lactone at C(9) in the crystal structure of **24c** suggests the potential proximity of the liberated alkoxide in **39** to the electrophilic site at C(5). The formation of this interesting rearrangement product was confirmed by diagnostic NMR and IR data. 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.

Finally, after extensive investigation, we obtained the desired ketone **43** as a mixture of C(16) epimers in good yield by high-pressure hydrogenation of enone **24a** over Pt/C in EtOAc, resulting in a chemo- and diastereoselective reduction of the tetrasubstituted olefin (Scheme 21). The structure and stereochemistry of the desired product (i.e., ketone **43**) was established by single-crystal X-ray diffraction of the C(16)-β-H epimer.[30] Both C(16) epimers of ketone **43** can be utilized in the strategy outlined in Scheme 14, since the formation of enol ether **26**

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(30) See the Supporting Information for complete X-ray data of **43**.

will eliminate the stereocenter at C(16). Nevertheless, it is interesting to note that these C(16) epimers can be easily interconverted by exposure to simple bases such as sodium hydride followed by an aqueous workup.

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 **3** yielded products of undesired stereochemistry, intermediate **24a** was advanced to a structure with the desired stereochemistry for elaboration to saudin (i.e., **43**). 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 **43** to saudin.

Experimental Section

Vinylstannane 5c. A solution of bromoenone **5b** (5.0 g, 20.4 mmol), (Bu$_3$Sn)$_2$ (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 vinylstannane **5c** 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 calcd for [C$_{21}$H$_{35}$O$_3$Sn]$^+$ 455.1608, found 455.1603.

Vinyl Iodide 6c. To a solution of Dess–Martin periodinane (1.91 g, 4.50 mmol) in CH$_2$Cl$_2$ (18 mL) cooled to 0 °C was added alcohol **6a** (500 mg, 4.09 mmol) in CH$_2$Cl$_2$ (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$_2$S$_2$O$_3$ (20 mL). The mixture was extracted with CH$_2$Cl$_2$ (3 × 20 mL). The combined organic layers were dried over Na$_2$SO$_4$, 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: ^{1}H NMR (300 MHz, CDCl3) 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$_2$CO$_3$ was added until bubbling ceased, and the mixture was extracted with Et$_2$O (2 × 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 **6c** (5.46 g, 43% yield over two steps) as a yellow solid: R_f 0.29 (5:1 pentane/ether); mp 69–70 °C; ^{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$_6$D$_6$) 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 calcd for [C$_7$H$_5$O$_2$I]$^+$ 247.9335, found 247.9346.

Polycycle 3. To a mixture of Pd(PPh$_3$)$_4$ (1.16 g, 1.0 mmol), vinylstannane **5c** (9.0 g, 20.0 mmol), and vinyl iodide **6c** (6.13 g, 24.7 mmol) was added DMF (100 mL). Freshly recrystallized CuI[31] (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 being stirred for 12 h, the mixture was diluted with water (200 mL) and extracted with Et$_2$O (2 × 200 mL). The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (3:2 hexanes/EtOAc eluent) provided polycycle **3** (3.37 g, 60% yield) as an orange solid: R_f 0.31 (1:1 hexanes/EtOAc); mp 109–111 °C; ^{1}H 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, CDCl3) 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 calcd for [C$_{16}$H$_{14}$O$_5$]$^+$ 286.0841, found 286.0838.

Michael Products 19a,b. To a solution of HN(i-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 $tert$-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 **3** (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$_2$O (3 × 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 separable 2:1 mixture of ketone **19a** (154 mg, 42% yield) as a white solid and its C(4) epimer **19b** (78 mg, 22% yield) as an oil. For **19a**, suitable crystals for X-ray diffraction were grown from Et$_2$O by slow evaporation.

Ketone 19a: R_f 0.45 (1:1 hexanes/EtOAc); mp 148 °C; ^{1}H NMR (500 MHz, C$_6$D$_6$) 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$_6$D$_6$) 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 calcd for [C$_{23}$H$_{29}$O$_7$]$^+$ 417.1913, found 417.1904.

Ketone 19b: R_f 0.54 (1:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, C$_6$D$_6$) 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$_6$D$_6$) 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 calcd for [C$_{23}$H$_{29}$O$_7$]$^+$ 417.1913, found 417.1926.

Claisen Product 21. 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 $tert$-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

(31) Dieter, R. K.; Silks, L. A.; Fishpaugh, J. A.; Kastner, M. E. *J. Am. Chem. Soc.* **1985**, *107*, 4679–4692.

was stirred for 25 min, and then a solution of polycycle **3** (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 × 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 **20** (37.1 mg, 46% yield) as a clear oil, which was used immediately in the next step.

Enol ether **20** (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. The 2.7:1 diastereomeric mixture (diastereomer 1/diastereomer 2) of Claisen products **21** was purified and separated by preparatory thin-layer chromatography on silica gel (0.5 mm, 3:1 hexanes/EtOAc eluent) to provide diastereomer 1 (17.4 mg, 53% yield) and diastereomer 2 (6.4 mg, 20% yield) as two clear oils (23.8 mg combined, 73% yield).

Diastereomer 1: R_f 0.31 (2:1 hexanes/EtOAc); ^1H 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* calcd for $[C_{26}H_{31}O_7]^+$ 455.2070, found 455.2089.

Diastereomer 2: R_f 0.38 (2:1 hexanes/EtOAc); ^1H 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* calcd for $[C_{26}H_{33}O_7]^+$ 457.2226, found 457.2213.

Ketone 43. Two batches of enone **24a** (2.33 g, 4.105 mmol each) were separately dissolved in EtOAc (11 mL each). To these solutions 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 the C(16) β-H epimer of ketone **43** (1.29 g, 27.5% yield) as a white solid, the C(16) α-H epimer of ketone **43** (1.75 g, 37.2% yield) as a clear oil, and ketone **38** (0.627 g, 13.4% yield) as a clear oil. For the C(16) β-H epimer of **43**, suitable crystals for X-ray diffraction were grown from Et_2O by slow evaporation.

Ketone 43 C(16) β-H: R_f 0.45 (2:1 hexanes/EtOAc); mp 131 °C; ^1H 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* calcd for $[C_{34}H_{39}O_6Si]^+$ 571.2516, found 571.2502.

Supporting Information Available: Experimental details and characterization data for all new compounds including X-ray data for **19a**, **24c**, and **43**. This material is available free of charge via the Internet at http://pubs.acs.org.

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