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. 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. Importantly, saudin was found to induce hypoglycemia in mice, both in vitro and in vivo. Given its potent hypoglycemic activity and oral bioavailability, saudin is an appealing lead structure for the development of new agents to treat diabetes mellitus. Unlike many other hypoglycemic agents, saudin’s ability to reduce the glucose levels in mice and rats seems to be unrelated to the cellular 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. 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.


FIGURE 1. Structure of saudin (1).
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 and Boeckman’s synthesis of (−)-saudin in 2002. 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, 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 acetal in the natural product reveals carboxylic acid, which we envisioned accessible by a three component coupling of lactone, a propionate equivalent, and methyl iodide (Scheme 1). Opening the pyran ring of 3 in a retro-oxa-electrocyclization exposes diene 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. This is primarily due to the existence of a typically unfavorable equilibrium between the open cis-diene (7) and the closed α-pyran (8). While the diene 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.

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 epoxidequinols 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 (I), 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). This enone was then subjected to Br₂ and Et₃N, which yielded bromo enone

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

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 (to the ynone) followed by LiI and AcOH in MeCN.

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). Unfortunately, this intermolecular strategy was not realized under a variety of standard Heck conditions or the modified Jeffery conditions. 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 (i.e., 12), along with the potential for regioisomeric insertion across the olefin (i.e., 13).

To investigate Suzuki coupling reactions, 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. Initially, using a model system we were able to couple vinylstannane 5c with cis-vinyl iodide 15 under modified Stille conditions, which yielded diene 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 diene 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-electrocyclization reaction (Scheme 9). The presence of Cu and the absence of light were both essential for the success of this transformation. In the presence of light, cis-vinyl iodide 6c

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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 Mukaiyama-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. 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.

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 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 rearrangement 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.

(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 1:

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

(29) See the Supporting Information for complete X-ray data of 24c.
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 R-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 R-face, we believe it may be due to an intramolecular delivery of the hydride nucleophile. This mode of nucleophilic 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)-α-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.

(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 polycyclic 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 5e. A solution of bromoenone 5b (5.0 g, 20.4 mmol), (Bu3Sn)2 (20.6 mL, 40.8 mmol), Pd(PPh3)4 (306 mg, 0.265 mmol), and NaHCO3 (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 (pentaene eluent). The filtrate was concentrated in vacuo to an oil, which was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to give vinylstannane 5e as a yellow solid: 1H NMR (300 MHz, CDCl3) δ 7.26 (s, 1H), 6.91 (s, 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, 3H), 1.14 (s, 3H), 1.08 (d, J = 6.8 Hz, 3H); 13C NMR (125 MHz, CDCl3) δ 206.1, 178.5, 174.4, 145.9, 144.0, 140.3, 122.4, 107.6, 98.9, 83.5, 81.1, 74.7, 51.1, 46.7, 43.5, 34.7, 33.8, 30.3, 28.3, 17.3, 13.7; IR (thin film/NaCl) 2977.02, 1783, 1721, 1157 cm−1; HRMS (FAB+) m/z calcd for [C21H35O3Sn]+ 417.1913, found 417.1904.

Ketone 19b: Rf 0.54 (1:1 hexanes/EtOAc); mp 148 °C; 1H NMR (500 MHz, CDCl3) 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, 3H), 1.14 (s, 3H), 1.08 (d, J = 6.8 Hz, 3H); 13C NMR (125 MHz, CDCl3) δ 206.1, 178.5, 174.4, 145.9, 144.0, 140.3, 122.4, 107.6, 98.9, 83.5, 81.1, 74.7, 51.1, 46.7, 43.5, 34.7, 33.8, 30.3, 28.3, 17.3, 13.7; IR (thin film/NaCl) 2977.02, 1783, 1721, 1157 cm−1; HRMS (FAB+) m/z calcd for [C21H35O3Sn]+ 417.1913, found 417.1904.

Claisen Product 21. To a solution of HN(i-Pr2)2 (130 mL, 0.933 mmol) in THF (1.8 mL) cooled to 0 °C was added n-butyllithium (2.5 M in hexanes, 375 mL, 0.933 mmol). After 5 min, the mixture was cooled to −78 °C, and a solution of tert-butyl propionate (140 mL, 0.933 mmol) in THF (1.8 mL) was slowly added along the sides of the flask in a dropwise fashion. Following addition, the mixture was cooled to 50 °C and filtered through a short pad of Celite (pentaene eluent). The filtrate was concentrated in vacuo to an oil. For 19a, suitable crystals for X-ray diffraction were grown from EtO2O by slow evaporation.
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 H₂O (15 mL). The mixture was extracted with Et₂O (3 × 15 mL). The combined organic layers were dried over Na₂SO₄ 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 immediately used in the next step.

Enol ether 20 (32.6 mg, 0.0714 mmol) 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 Chaisen 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).

**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 H₂ bomb and stirred for 9 h under an atmosphere of pressurized H₂ (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 Et₂O by slow evaporation.

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**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.