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Progress toward the Total Synthesis of Saudin: Development of a Tandem Stille-Oxa-Electrocyclization Reaction

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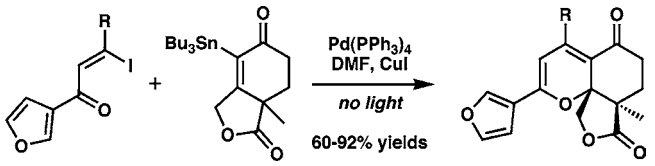
ABSTRACT



A diastereoselective tandem Stille-oxa-electrocyclization reaction provides access to the core of the diterpenoid natural product saudin. Additionally, this new reaction sequence was extended to the convergent preparation of related polycyclic pyran systems.

Diabetes mellitus, a group of diseases characterized by hyperglycemia, affects nearly 18.2 million people (6.3% of the population) and is the sixth leading cause of death in the United States (over 200,000 deaths per year).[1] The disease is controllable in most patients using a regimen of diet, insulin injections, and oral hypoglycemic agents.[2] In 1985, Mossa and Cassady disclosed the structure and biological activity of the novel caged diterpenoid saudin (**1**).[3] The chemical structure of **1** was proved unambiguously by single-crystal X-ray analysis to be that depicted in Figure 1.

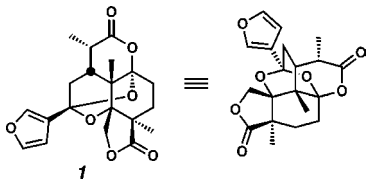


Figure 1. Structure of saudin (**1**).

Importantly, 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.

In the 20 years since the isolation of saudin, a substantial effort has been undertaken to complete its total synthesis. Recently, this effort resulted in the elegant syntheses of (±)-saudin by Winkler[4] and (−)-saudin by Boeckman.[5] 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.

Our retrosynthetic analysis of saudin is outlined in Scheme 1. The polycyclic structure of saudin (**1**) exhibits an impressive array of functionality and stereochemistry that includes eight oxygenated carbons, seven stereocenters (two

(1) 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.

(2) 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.

(3) 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.

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

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

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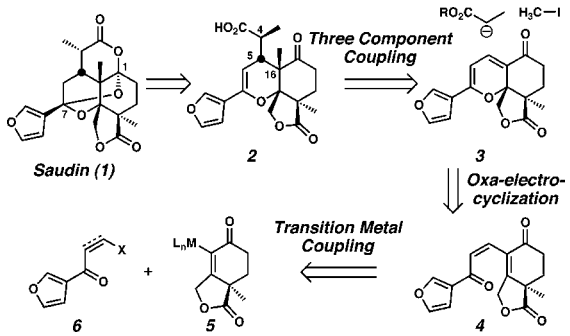
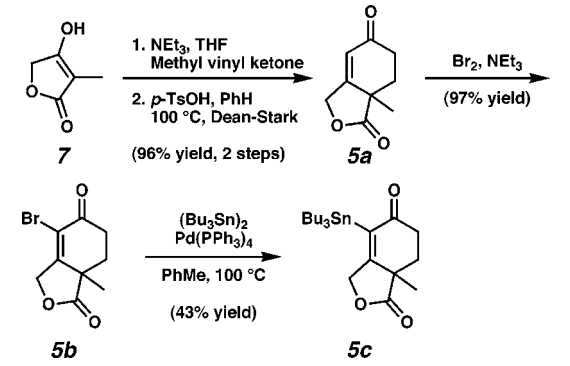
Scheme 1



of which are quaternary centers), two lactone rings, and a 3-substituted furan. Initial retrosynthetic disconnection of the C(1) and C(7) acetals exposes carboxylic acid **2** (Scheme 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 **3**. Opening the pyran ring of **3** in a retro-oxa-electrocyclization provides dienone **4**, 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, Heck) between enone **5** and furan **6**.

We initiated our study of the synthesis of saudin by preparing variants of enone **5** and furan **6**, with the hope that we would unite the two compounds through a transition metal-catalyzed reaction. The preparation of enone **5a** proceeded via the Robinson annulation of tetronic acid **7**[6] and methyl vinyl ketone (Scheme 2).[7] This enone was then

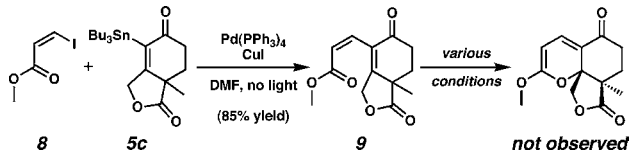
Scheme 2



cleanly converted to bromoenone **5b** by exposure to Br_2 and Et_3N.[8] The resulting product was easily transformed under Stille conditions to vinyl stannane **5c**,[9] which was a viable intermediate for transition metal-mediated coupling.

Initial model studies with variants of enone **5** revealed the inadequacy of several transition metal-mediated reactions, including Sonagashira, Heck, and Suzuki couplings. Nonetheless, we were able to couple vinyl stannane **5c** with the *cis*-vinyl iodide **8**[10] under modified Stille conditions,[11] which yielded dienone **9** (Scheme 3). This result established that

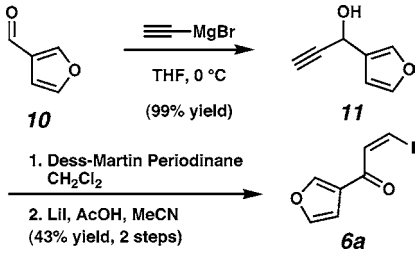
Scheme 3



the bicyclic enone core structure was stable at least under Stille conditions. The oxa-electrocyclization of enone **9** was attempted under several conditions without success (heat, UV light, Lewis acids).

Although the electrocyclization of model substrate **9** was unsuccessful, we decided to apply the Stille coupling strategy to fully elaborated substrates en route to saudin. The other component for the Stille reaction (i.e., vinyl iodide **6a**) was synthesized from furaldehyde **10** in a straightforward manner (Scheme 4). Treatment of this aldehyde with ethynyl

Scheme 4



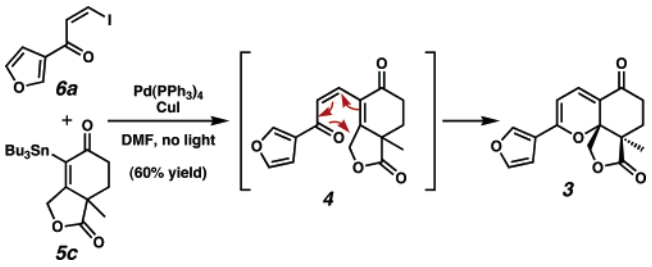
Grignard produced propargyl alcohol **11**. Although oxidation of this alcohol failed under several conditions (Swern oxidation, Ley oxidation, and chromium-based oxidations), Dess−Martin periodinane[12] cleanly provided the desired ynone, which was then converted to vinyl iodide **6a** by treatment with LiI and AcOH in MeCN.[13]

A series of conditions were examined for the Stille coupling of vinyl stannane **5c** and vinyl iodide **6a**, 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 **9** with the anticipation that the desired Stille product **4** would be

(6) For the synthesis of **7**, see: Knight, D. W.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1975**, 635−640.
(7) Prisbylla, M. P.; Takabe, K.; White, J. D. *J. Am. Chem. Soc.* **1979**, *101*, 762−763.
(8) Johnson, C. R.; Kozak, J. *J. Org. Chem.* **1994**, *59*, 2910−2912.
(9) Azizian, H.; Eaborn, C.; Pidcock, A. *J. Organomet. Chem.* **1981**, *215*, 49−58.
(10) For the synthesis of **8**, see: Piers, E.; Wong, T.; Coish, P. D.; Rogers, C. *Can. J. Chem.* **1994**, *72*, 1816−1819.
(11) Bellina, F.; Carpita, A.; De Santis, M.; Rossi, R. *Tetrahedron* **1994**, *50*, 12029−12046. (b) For a general review on the Stille reaction, see: Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1−652.
(12) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287.
(13) Ma, S.; Lu, X.; Li, Z. *J. Org. Chem.* **1992**, *57*, 709−713.

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 **5c** and **6** to yield the furan appended tricycle **3**—the result of a tandem Stille-oxa-electrocylization reaction (Scheme 5). Interestingly, the

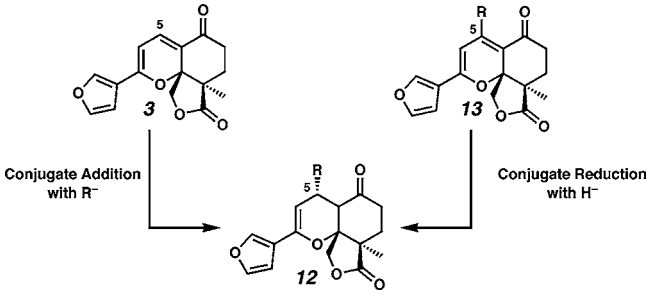
Scheme 5



presence of CuI and the absence of light were both essential for the success of this transformation.[14]

Initially, our strategy for the synthesis of saudin called for a diastereoselective conjugate addition of a carbon nucleophile into enone **3** to access a C(5) substituted product (**12**, Scheme 6). Alternatively, we hypothesized that an

Scheme 6

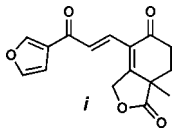


appropriately substituted enone **13** could undergo a diastereoselective conjugate reduction to furnish a similar intermediate. In addition to providing a more convergent route to saudin, this new strategy would also give us a better sense of the generality of our tandem Stille-oxa-electrocyclization methodology.

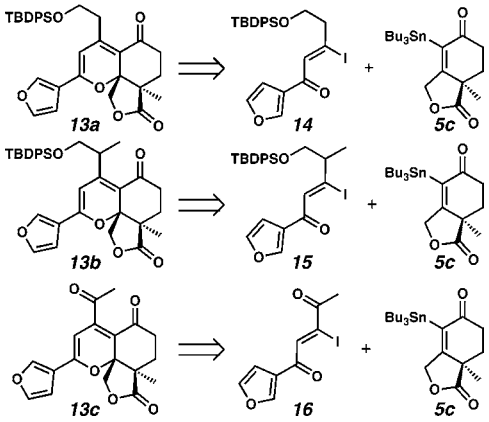
Initial exploration of the new strategy began with polycycles **13a**−**c**, which required the generation of three new vinyl iodides (i.e., **14**, **15**, **16**, Scheme 7).

The synthesis of vinyl iodide **14** commenced with the silyl protection of alcohol **17** (Scheme 8). Subsequent treatment

(14) In the presence of light, *trans*-dienone ***i*** was formed, presumably as a result of cis−trans isomerization of vinyl iodide **6a** followed by Stille coupling:



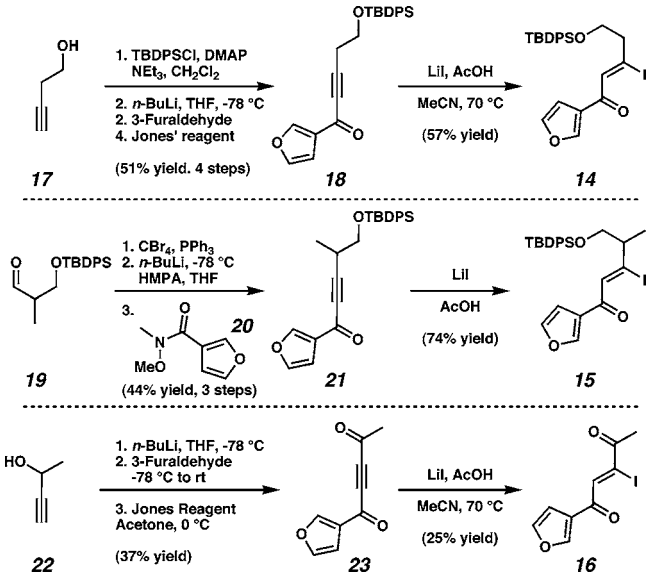
Scheme 7



with *n*-butyllithium followed by 3-furaldehyde yielded the coupled alcohol, which was oxidized with Jones' reagent to produce ynone **18**. Conversion of **18** to vinyl iodide **14** was affected by treatment of the ynone with LiI and AcOH in MeCN to generate the desired *cis*-vinyl iodide in good yield and as a single isomer. The synthesis of vinyl iodide **15** is also depicted in Scheme 8. Aldehyde **19**[15] was converted to an alkynyl anion by the Corey-Fuchs procedure.[16] Subsequent quenching of the anion with Weinreb amide **20**[17] yielded ynone **21**, which was readily converted to vinyl iodide **15** as a single olefin isomer with LiI and AcOH. Vinyl iodide **16** was rapidly synthesized from 1-butyn-3-ol (**22**), which was first coupled to 3-furaldehyde (Scheme 8). Oxidation of the resulting propargylic alcohol furnished ynone **23**, which was treated with LiI and AcOH in MeCN to yield the desired vinyl iodide **16**.

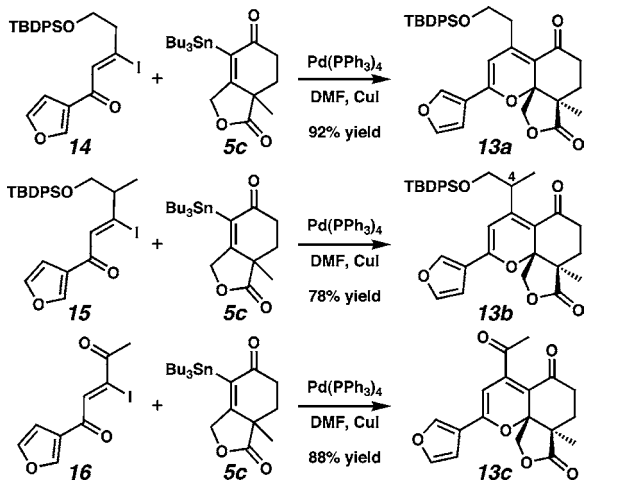
With these three new vinyl iodides in hand, the key Stille-oxa-electrocyclization reactions were attempted. Under identical conditions, smooth coupling occurred between stannane

Scheme 8



5c and vinyl iodides **14**, **15**, and **16** to form the desired polycycles **13a**, **13b**, and **13c** in 92%, 78%, and 88% yield, respectively (Scheme 9). Products **13a** and **13c** were formed as single diastereomers, whereas **13b** was produced as a 1:1 mixture of diastereomers at C(4).

Scheme 9



The bond connectivity and relative stereochemistry in **13c** were unambiguously confirmed by single-crystal X-ray diffraction of the diketone (Figure 2).

In summary, we have developed a tandem Stille-oxa-electrocyclization reaction that delivers the polycyclic pyran core of the diterpenoid saudin in a convergent and rapid fashion. We have also demonstrated the versatility of this methodology toward the preparation of related polycyclic pyran systems that may serve as useful synthetic intermedi-

(15) For the synthesis of **19**, see: Kiyooka, S.; Shahid, K. A.; Goto, F.; Okazaki, M.; Shuto, Y. *J. Org. Chem.* **2003**, *68*, 7967−7978.

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

(17) For the synthesis of **20**, see: Kinoshita, T.; Ichinari, D.; Sinya, J. *J. Heterocycl. Chem.* **1996**, *33*, 1313−1317.

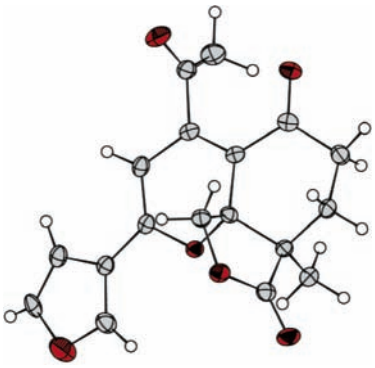


Figure 2. X-ray crystal structure of pyran intermediate **13c**.

ates en route to the natural product.[18] Current efforts are focused on expanding the substrate scope of this tandem reaction sequence, as well as advancing the aforementioned pyran intermediates (**3**, **13a**, **13b**, and **13c**) to saudin.

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Supporting Information Available: Experimental details and characterization data for all new compounds including X-ray data for **13c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Toward this end, we have encountered some level of difficulty implementing the three component coupling chemistry outlined in Scheme 1. In particular C−C bond formation at the sterically congested C(16) center has been difficult. We are currently developing catalytic asymmetric methods to synthesize hindered quaternary carbon centers, and plan to apply these strategies to override any inherent steric and stereochemical bias of the pyran systems prepared in this study. For an example, see: Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044−15045.