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.

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 Winkler4 and (−)-saudin by Boeckman.5 Our choice of saudin as a target molecule was based on its potent hypoglycemic 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...

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.

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 and methyl vinyl ketone (Scheme 2).7 This enone was then cleanly converted to bromoenone 5b by exposure to Br3 and Et3N.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 Sonogashira, Heck, and Suzuki couplings. Nonetheless, we were able to couple vinyl stannane 5c with the cis-vinyl iodide 80 under modified Stille conditions,11 which yielded dienone 9 (Scheme 3). This result established that 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 Grignard produced propargyl alcohol 11. Although oxidation of this alcohol failed under several conditions (Swern oxidation, Ley oxidation, and chromium-based oxidations), Dess–Martin periodinane12 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

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produced. To our pleasant surprise, however, the combination of catalytic Pd(PPh₃)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-electrocyclization reaction (Scheme 5). Interestingly, the 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 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 polyycles 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 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 was converted to an alkynyl anion by the Corey-Fuchs procedure.¹⁶ Subsequent quenching of the anion with Weinreb amide 20 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

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(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:

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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).

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 intermediates en route to the natural product. 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.