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Stereoselective Synthesis of a Dioxa-bicyclo[3.2.1]octane SGLT2 Inhibitor

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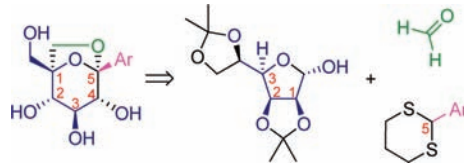
ABSTRACT



A promising class of SGLT2 inhibitors bearing a unique dioxa-bicyclo[3.2.1]octane motif was recently disclosed. An improved stereoselective synthesis providing efficient access to one of the most potent and selective compounds from this class is reported. A one-pot deprotection/cyclization was used as the key step to form the dioxa-bicyclo[3.2.1]octane motif with full control of stereochemistry. Using an appropriately substituted aryl group, the route enables the synthesis of any given compound from the class.

Type 2 diabetes looms as a growing threat to human health worldwide, a fact supported by increasingly alarming statistics.[1] A considerable body of research has been carried out within the pharmaceutical industry to identify new antidiabetic medicines, but progress has been slow. Recently, sodium glucose cotransporter 2 (SGLT2) inhibition has emerged as a very promising approach to the treatment of Type 2 diabetes. Inhibition of this target, which is responsible for the bulk of glucose reuptake in the kidney, allows control of hyperglycemia in a glucose-dependent, insulin-independent manner.[2]

The *O*-aryl glucoside natural product phlorizin,[3,4] a nonselective inhibitor of SGLT1 and SGLT2, provided an interesting lead for the discovery of antidiabetic agents based on glucose transport inhibition (Figure 1).

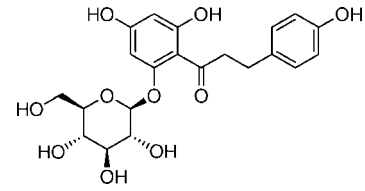


Figure 1. Structure of phlorizin (natural product).

Starting with phlorizin, elegant and fruitful lead optimization resulted in the identification of various *O*-aryl and *C*-aryl glucoside SGLT2 inhibitors.[5,6] Among these, several *C*-aryl glucosides (e.g., dapagliflozin and canagliflozin) are now in clinical development (Figure 2). Interestingly, so far the structures from the known agents in development are mostly *C*-aryl glucoside derivatives only differing by their aglycone residue.[5] No SGLT2 inhibitor has reached the market yet, and the pharmaceutical industry remains intensely focused on discovering differentiated agents.

(1) *Diabetes Atlas*, 4th ed.; International Diabetes Federation: Brussels, 2009.
(2) Neumiller, J. J.; White, J. R. Jr.; Campbell, R. K. *Drugs* **2010**, *70*, 377.
(3) Ehrenkranz, J. R. L.; Lewis, N. G.; Kahn, C. R.; Roth, J. *Diabetes Metab. Res. Rev.* **2005**, *21*, 31.
(4) White, J. R., Jr. *Clin. Diabetes* **2010**, *28*, 5.
(5) Washburn, W. N. *Expert Opin. Ther. Patents* **2009**, *19*, 1485.
(6) Washburn, W. N. *J. Med. Chem.* **2009**, *52*, 1785.
(7) Mascitti, V.; Collman, B. M. WO10023594, 2010.

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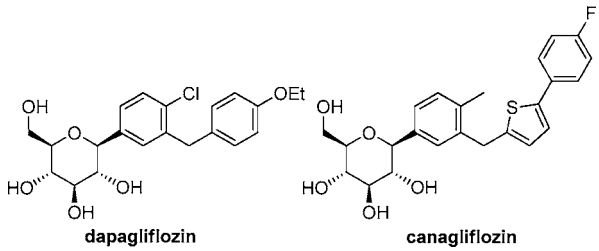


Figure 2. Structures of some *C*-aryl glucoside SGLT2 inhibitors.

We recently disclosed a new class of such agents based on a unique dioxa-bicyclo[3.2.1]octane motif (Figure 3).[7]

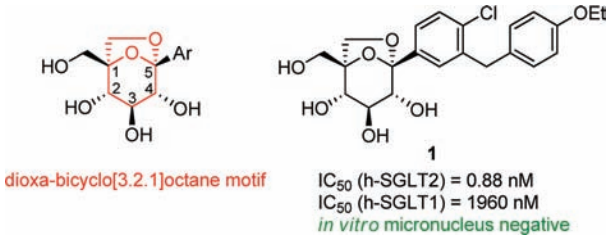


Figure 3. Dioxa-bicyclo[3.2.1]octane-based SGLT2 inhibitors.

Compound **1** is one of the most potent and selective SGLT2 inhibitors from this class and has demonstrated robust efficacy in preclinical rodent models.[7] It also has the potential safety advantage of lacking activity in the well-known in vitro micronucleus assay, a key distinction from certain SGLT2 inhibitors in development.[8] A compound from the class is currently in phase 2 clinical trials.

The original route to dioxa-bicyclo[3.2.1]octane SGLT2 inhibitors is depicted in Scheme 1. Starting from an acyclic Weinreb amide as an advanced intermediate,[9] the route capitalized on an unprecedented three-step protocol to assemble the desired [3.2.1]-bridged ketal system (Scheme 1).[7] This versatile synthetic sequence was a useful discovery tool, which enabled rapid analogue preparation and identification of compounds with optimal PK/PD[10] profiles; however, the route was not well suited for the synthesis of specific compounds on a larger scale. For example, it provided **1** in 0.3% overall yield over 13 linear steps starting from D-glucose including final HPLC separation of **1** from its epimer at C-4. These considerations prompted the development of a new stereoselective route that would provide efficient access to any specific compound from the class.

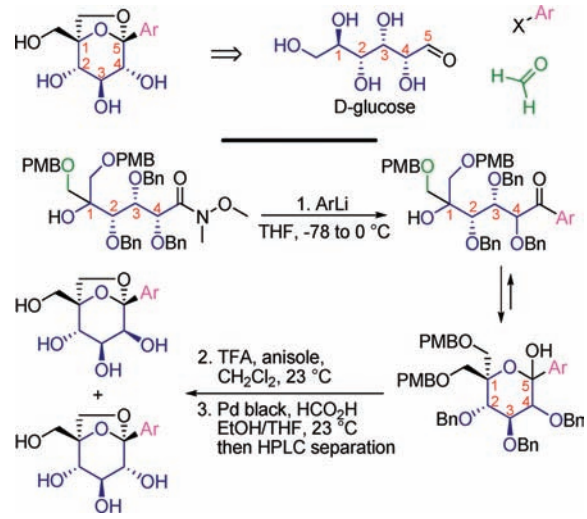
(8) *In Vitro* Mammalian Cell Micronucleus Test (MNvit). OECD Guideline for Testing of Chemicals No. 487, OECD, Paris, 2010. Available at: http://www.oecd.org/env/testguidelines. Compound **1** acts neither as an aneugen or clastogen in the micronucleus assay.

(9) Available in 10 steps starting from D-glucose.

(10) Pharmacokinetics/Pharmacodynamics.

(11) Corey, E. J.; Cheng, X. M. *The Logic of Chemical Synthesis*; Wiley: New York, 1989.

Scheme 1. Original Medicinal Chemistry Route



Retrosynthetic analysis[11] exploiting pseudo C_2-symmetry led to a D-mannose derivative as a readily available starting chiron,[12] formaldehyde and a dithiane intermediate serving as building blocks (Figure 4).

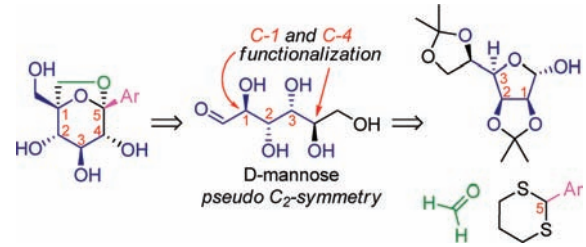


Figure 4. Retrosynthetic analysis.

The new synthesis, exemplified by the preparation of **1**, is summarized in Scheme 2. Diastereoselective addition of the lithium anion derived from crystalline dithiane **2**[13] to aldehyde **3** (readily available starting from diacetone-α-D-mannofuranose)[14] at low temperature in THF produced intermediate **4** as a single diastereomer via *Si* face addition to the aldehyde.[15]

(12) Hanessian, S. *The Total Synthesis of Natural Products: The Chiron Approach*; Pergamon Press: Oxford, 1983.

(13) For the synthesis and X-ray crystal structure of **2**, see: Samas, B.; Préville, C.; Thuma, B. A.; Mascitti, V. *Acta Crystallogr.* **2010**, *E66*, o1386.

(14) Brewster, K.; Harrison, J. M.; Inch, T. D.; Williams, N. *J. Chem. Soc., Perkin Trans. 1* **1987**, 21.

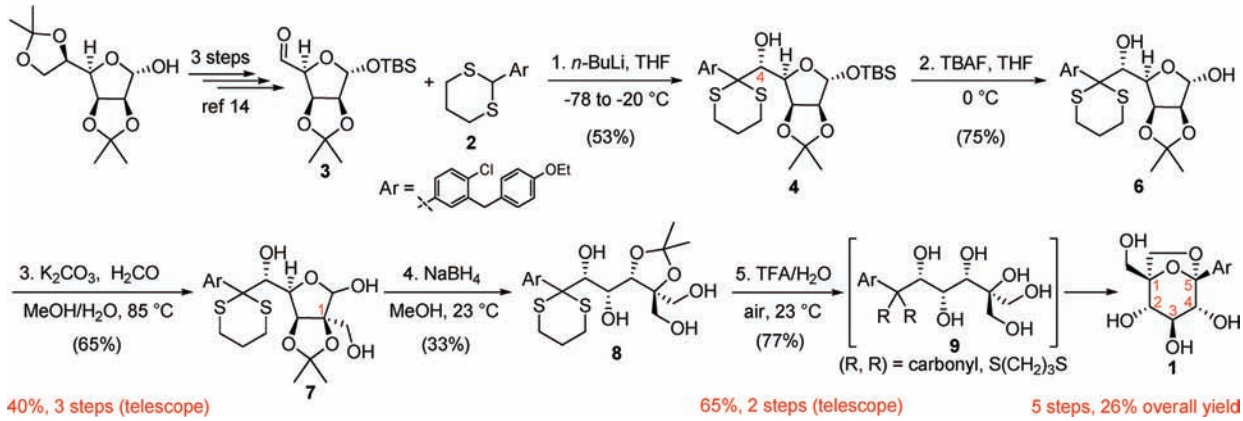
(15) Other methods, for instance, based on umpolung or biocatalysis, used to build this α-hydroxy ketone motif starting from a 4-chloro-3-(4-ethoxybenzyl)benzaldehyde derivative will be reported in due course.

(16) Readily available in two steps from intermediate **4**. See Supporting Information.

(17) Ho, P.-T. *Tetrahedron Lett.* **1978**, *19*, 1623.

(18) For an example of dithiane hydrolysis and acid-catalyzed spiroketalization, see: Smith, A. B., III.; Duan, J. J.-W.; Hull, K. G.; Salvatore, B. A. *Tetrahedron Lett.* **1991**, *32*, 4855.

Scheme 2. Synthesis of Compound **1**[a]



[a] The yield of each individual step is indicated in parentheses; the yield from the telescoped process is indicated in red.

The configuration of the newly created stereocenter was confirmed by single-crystal X-ray diffraction analysis of derivative **5** (Figure 5).[16] The high level of diastereoselectivity and preference for the *Si* face is consistent with a Cram chelate-type pretransition state assembly and unfavorable steric/stereoelectronic effects upon *Re* face attack of the bulky nucleophile via a Felkin−Anh pretransition state assembly.

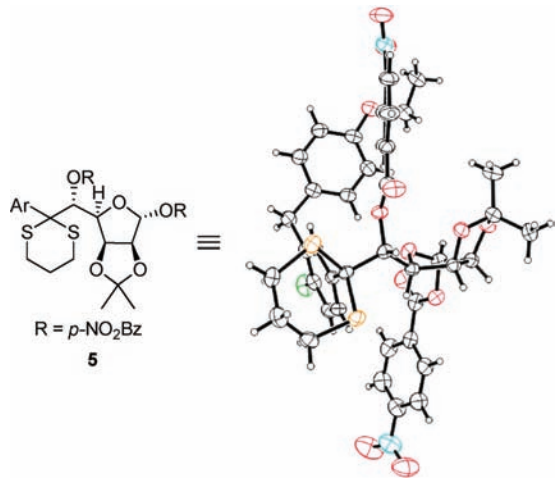


Figure 5. ORTEP representation of the X-ray structure of **5**.

Having installed the stereocenter found at C-4 of the final product, we next built the tetrasubstituted carbon C-1. This task was accomplished by first reacting **4** with TBAF in THF at 0 °C to produce lactol **6** in 75% yield; treatment of a solution of **6** in MeOH/H_2O at 85 °C with excess formaldehyde in the presence of K_2CO_3 provided intermediate **7** in 65% yield.[17] The overall yield was 26% over three steps if each intermediate was isolated. This overall yield could be dramatically improved by carrying on the crude material (telescoping) through the three steps to produce intermediate **7** in both high yield (40%) and purity (>95% by HPLC). Reduction of lactol **7** with sodium borohydride in MeOH at 23 °C produced acyclic advanced intermediate **8**, which was primed for validation of the key synthetic transformation into **1**.

When **8** was stirred at 23 °C in a mixture of TFA/H_2O (9/1 vol.) under air, deprotection/cyclization occurred to cleanly produce **1** as a single isomer in 77% yield. This reaction is believed to occur by cleavage of the acetonide to lead to intermediate **9**, followed by attack of the unprotected hydroxyl group(s) onto the unmasked ketone (or a putative thionium ion) to produce the desired bridged ketal under thermodynamic control.[18,19] Notably, the cyclization occurred without any epimerization at C-4, in contrast to the original discovery route. At this point, the next challenge was to improve the overall yield of the reduction−(deprotection/cyclization) sequence. We reasoned that the modest isolated yield of **8** was due to formation of a strong borate complex that was only partially broken under the original workup conditions (neutralization with an aqueous solution of NH_4Cl). Thus, rather than isolating **8**, the crude material was exposed directly to the conditions for deprotection/cyclization, conditions that also would favor complete hydrolysis of residual borate complex. In practice, telescoping of the two steps led to a dramatically improved yield (65%). Compound **1** was purified by flash chromatography over silica gel and could be isolated as the L-pyroglutamic acid cocrystal.[7]

In conclusion, the stereoselective synthesis described in this Letter provides **1** in 26% overall yield over five steps starting from readily available materials. This constitutes a major improvement over the original route. Noteworthy features of this improved synthesis include (1) exploitation of pseudo C_2-symmetry to identify the readily available diacetone-α-D-mannofuranose starting material, (2) a

(19) On the basis of our observations and preliminary investigations, the presence of a stream of air is believed to help drive the equilibrium towards the formation of the desired product by scavenging thiol-based byproducts into a putative 1,2-dithiolane intermediate which then oligomerizes. See: Ranganathan, S.; Jayaraman, N. *J. Chem. Soc., Chem. Commun.* **1991**, 934.

highly stereoselective dithiane anion addition onto an aldehyde, (3) a deprotection/cyclization sequence to produce the dioxa-bicyclo[3.2.1]octane-2,3,4-triol motif in high yield and with exclusive stereocontrol, and (4) telescoping of several steps to add elements of practicality (only one intermediate, **7**, is isolated). Using an appropriately substituted aryl group, this route also allows for the efficient synthesis of any given compound from this class of SGLT2 inhibitors. Lastly, the route provides rapid access to C-1 and C-5 substituted dioxa-bicyclo[3.2.1]octane-2,3,4-triol derivatives that could find additional applications as biologically active compounds.

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Supporting Information Available: Experimental procedures and characterization data for the process shown in Scheme 2 (PDF). X-ray crystallographic data for **5** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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