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Chimica Oggi / Chemistry Today, March/April, 2015

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CHEMISTRY TODAY

The synthesis of gliflozins

Gerald L. Larson

GERALD L. LARSON
Gelest Inc., 11 East Steel Road, Morrisville, PA 19067, USA

MONOGRAPHIC SPECIAL issue

PEER REVIEWED

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KEYWORDS: Gliflozins, diabetes 2, glucose transporters, silane reductions.

Abstract Some of the general approaches to the key steps in the synthesis of gliflozins, a class of glucose transporters, are discussed. In particular the glycosidation step for the introduction of the key aryl moiety onto the glucose and the reduction steps are presented.

INTRODUCTION

Gliflozins constitute a class of compounds that is useful as sodium glucose co-transporter-2 (SGLT2) inhibitors. The gliflozins have shown particular expediency in the treatment of diabetes 2. They accomplish this through blocking of sodium glucose transport proteins, which, in turn, inhibit the kidneys from resorbing glucose back into the blood stream. The excess, non-resorbed glucose is then eliminated with the urine with the net result being a dosage-regulated glucose level. It has been shown that a key feature of the gliflozins is their ability to distinguish between the inhibition of the SGLT1 transporter, a low-capacity, high-affinity transporter that is expressed in the gut, heart and kidney, and the SGLT2 transporter, a high-capacity, low-affinity transporter expressed mostly in the kidney. It is estimated that by the year 2025 nearly 400 million people will suffer from diabetes 2 (1). Due in large part to this growing population of diabetes sufferers, considerable efforts have been and continue to be taken in the gliflozin approach towards addressing the diabetes 2 affliction. A significant part of these efforts has centered on various derivatives of the gliflozin class, represented by the general structure **1**. (Figure 1a) An excellent review of the structure activity relationship and some of the history of this class of drugs has appeared (2). This mini-review will look at some of the general approaches to the synthesis of the gliflozins with an emphasis on the glycosidation and the key reduction steps.

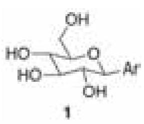

Figure 1a. General structure of typical Gliflozin.

As early as the 19th century phlorizin **2** was isolated and shown to inhibit both SGLT1 and SGLT2 and, thus, promote urinary excretion of glucose. Unfortunately, being a hemiacetal structure, phlorizin is subject to hydrolysis to phloretin **3** and glucose thus excluding it as a candidate for oral administration as the SGLT inhibitory activity of the phloretin is significantly reduced (3). (Figure 1b) Nevertheless, this led to investigations of structurally similar, more hydrolytically stable derivatives of phlorizin as SGLT2 inhibitors (4,5).

Figure 1b. Phloretin decomposition.

Five of the gliflozins have now been approved for prescribed use. These are dapagliflozin **4**, Farxica or Forxica, (Bristol Myers-Squibb/AstraZeneca), canagliflozin **5**, Invokana, (Janssen Pharmaceuticals), ipragliflozin **6**, Suglat, (Allesta Pharmaceuticals), empagliflozin **7**, Jardiance, (Boehringer-Ingelheim/Eli Lilly) and ertugliflozin **8**, Sitaglipton, (Pfizer/Merck) (Figure 1c).

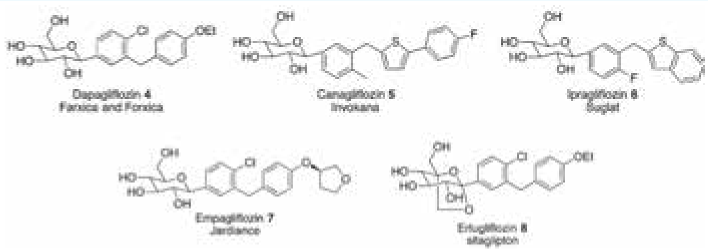

Figure 1c. Structures of five approved Gloflozins.

The general structures of the gliflozins have in common a glucose sugar to which is attached an aromatic group in the β−position at the anomeric carbon **1**. It will be noted that in addition to the glucose sugar moiety and the β−isomeric aryl substituent the aryl group is composed of a diarylmethylene structure. The differences in the structures are not large, *vis* the similarities in the structures of dapagliflozin, empagliflozin and ertugliflozin as well as those of canagliflozin and ipragliflozin.

SYNTHESIS OF GLIFLOZINS

The synthetic approaches to the gliflozins essentially consist of three general steps: 1) construction of the aryl substituent, 2) introduction of the aryl moiety onto the sugar or glucosylation of the aryl substituent, and 3) deprotection and modification of the arylated anomeric center of the sugar to the final desired product.

Synthesis of the aryl group

The synthetic approach to the gliflozins first involves the construction of the aryl substituent with a suitable handle to allow its attachment to the sugar. There are two classical entries into the diarylmethylene units, namely, reaction of an organometallic reagent with an aldehyde to give the diaryl carbinol or a Friedel-Crafts acylation to provide a diaryl ketone. Both of these intermediates would then be followed by a reduction of the functionalized carbon to the requisite methylene. The former of these is exemplified in a synthetic route to **12** wherein aldehyde **9** was reacted with the Grignard reagent **10** to form the diarylmethanol **11**, which was then reduced with triethylsilane to the diarylmethane **12** (6).It is worth noting that organosilanes have been shown to be excellent reagents for the reduction of benzylic alcohols to the corresponding alkanes (7,8) (Figure 2a).

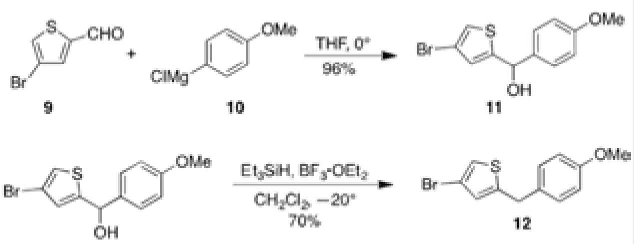

Figure 2a. Grignard approach to aryl portion of a Gloflozins.

A similar approach was employed in procuring the aryl substrate in a synthesis of ipragliflozin (9) (Figure 2b).

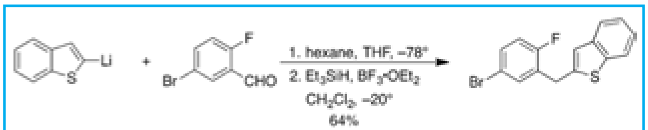

Figure 2b. Lithium reagent approach to aryl portion of a Gloflozins.

In an alternate approach to the diarylcarbinol precursor to the diarylmethane moiety Fürstner and Krause showed that the rhodium trichloride-catalyzed coupling of an aryl boronic acid with an aldehyde leads to the diaryl carbinol intermediates in high yields (10). Two of the 16 examples reported involved the preparation of an aryl bromide, indicating that the reaction can be carried out without competing aryl-aryl, Suzuki-type cross-coupling taking place. The resulting brominated diarylmethane could be converted to an organometallic reagent for reaction with the gluconolide leading to a gliflozin (Figure 2c).

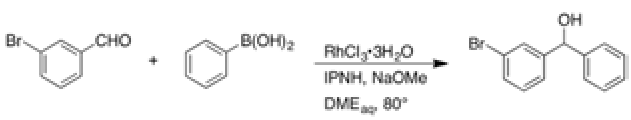

Figure 2c. Boronic acid approach to aryl portion of Gliflozins.

Alternatively, a Friedel-Crafts acylation/reduction sequence can be used as was employed in the preparation of **14** via the formation and reduction of intermediate **13**, in a synthesis of dapagliflozin, **4**. In this approach the acid chloride required for the Friedel Crafts acylation is prepared in-situ and reacted directly with ethylphenyl ether to give the required 4-acylated derivative (11). The direct organosilane reduction of ketone carbonyls, especially acetophenone derivatives, to a methylene group is well documented (12) (Figure 2d).

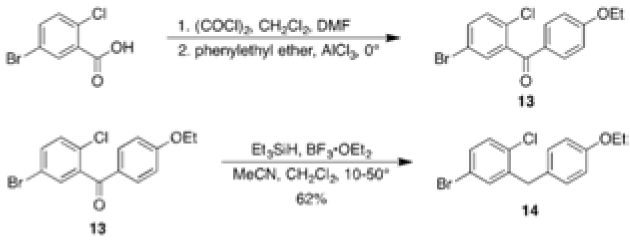

Figure 2d. Friedal-Crafts approach to aryl portion of Gliflozins.

Reduction of the carbonyl functionality to the methylene can be accomplished in a number of ways, but it has been shown that the reduction of aryl ketones to the corresponding methylenes can be conveniently done with an organosilane and an acid catalyst. The reduction of benzyl alcohols or aryl ketones to the corresponding methylene group is a particularly efficient process due in large part to the enhanced stability of the benzyl cationic intermediate. In a related case triethylsilane, and with greatly improved selectivity and the avoidance of a hazardous intermediate, tetramethyldisiloxane, TMDS, have been used in the reduction of an acetophenone derivative in the synthesis of the key intermediate **15** in a synthesis of ziprasidone, a Pfizer anti-psychotic drug (13). In this case the use of TMDS resulted in the avoidance of the hazardous chloromethyl ketone intermediate as well as the partially- and over-reduced by-products. Pentamethyldisiloxane and dimethylethoxysilane were less selective than TMDS for this process. Common catalysts for these organosilane reductions are trifluoroacetic acid or boron trifluoride etherate among others. The yields for these reductions are typically high and offer a facile isolation of the final product (Figure 3a).

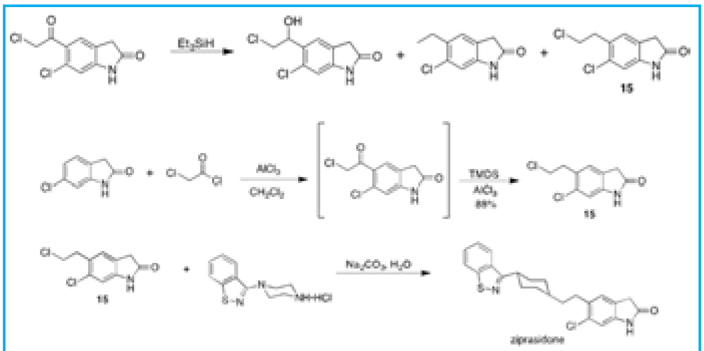

Figure 3a. Reduction of the benzoyl carbonyl in the synthesis of Ziprasidone.

Addition of the aryl group to the glucose

The second aspect in the synthesis of the gliflozins is that of glucosylation of the aryl moiety with the final stereochemistry being that wherein the aryl group occupies a β−position. One early approach to the gliflozins is illustrated for the synthesis of **17** as a general entry into the C1-aryl gluconosides.

It had been shown that the reaction of an aryllithium reagent with gluconolactone resulted in the hemiketal, which could in turn be reduced with triethylsilane (14). Thus, lithium-bromine exchange of **12** and reaction of the lithium reagent with gluconolactone **16** followed by triethylsilane reduction provided the C1-arylated glycopyranoside **17** (9). In a similar vein lithium reagent **19** was reacted with trimethylsilyl-protected gluconolactone **18** and the resulting hemiketal reduced with triethylsilane to dapagliflozin **4**. The reduction step is based on the findings of Kraus and Molina as well as those of Kishi and coworkers, who showed that triethylsilane reduction of glucose hemiketals leads to β−C-glycopyranosides with high stereoselectivity (6,15). The selective reduction of ketals and hemiketals as well as aminals and hemiaminals with the weakly hydridic organosilanes is well documented and can be attributed to the stability of the resulting α−oxygenated carbocationic intermediate (12) (Figure 3b/4a).
Thus, the triethylsilane reduction of the initially formed hemiketal followed by deprotection provided the desired gliflozin derivative. This reduction has been studied in a number of cases with varying degrees of stereoselectivity with triethylsilane/ BF_3•OEt_2 giving rather poor β:α ratios and the more hindered triisopropylsilane providing a high β:α ratio (16) (Figure 4a).

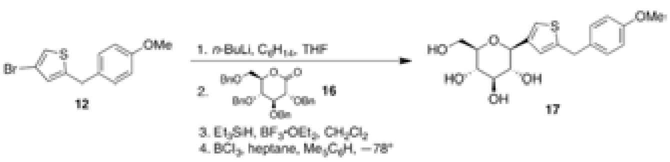

Figure 3b. Lithium reagent approach to arylation of glucose derivative.

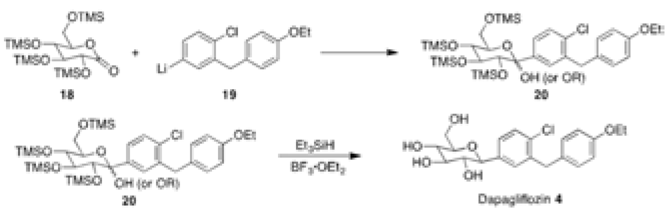

Figure 4a. Lithium reagent - silane reduction approach to arylation of glucose derivative.

Finally, the tetramethyldisiloxane, TMDS, silane reducing agent has been employed in the successful reduction of a hemiketal to the corresponding furan derivative as shown in the reduction of the protected precursor to canagliflozin, which is based on some earlier work by Kraus and coworkers who demonstrated the silane reduction of sugar hemiketals (17-20).

A highly stereoselective introduction of the aryl moiety can be accomplished via the cross-coupling of an aryl zinc reagent, using the well-developed organozinc chemistry of Knochel and co-workers, with the bromo-functionalized glucose **21** (21). Thus, zinc reagent **21** was reacted with bromopyran **22** to introduce the aryl group in the β−position assisted by the neighboring group participation of the pivaloyl group. Other ester protecting groups for the hydroxyls on the sugar also worked, but the pivalate protection was shown to be preferred for reasons of selectivity and yield. Deprotection led to dapagliflozin **4** (Figure 4b).

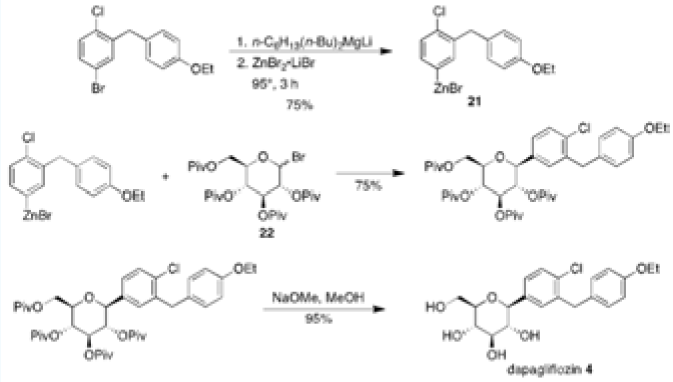

Figure 4b. Zinc cross-coupling approach to Dapagliflozin.

The tribenzyl glycal **23** was converted to the gliflozin structures in a couple of ways. One of these is via the corresponding epoxide **24**, which serves to place the 3-hydroxyl group on the sugar as well as provide a route for the introduction of the aryl unit (22). Reaction of **24** with 2-lithiofuran leads to the β−substituted benzyl-protected glucose **25**. On the other hand reaction of the epoxide with the corresponding zinc reagent **26** results in the introduction of the aryl group in the α−position. This is based on the earlier work of Halcomb and Danishefsky (23) (Figure 5a).

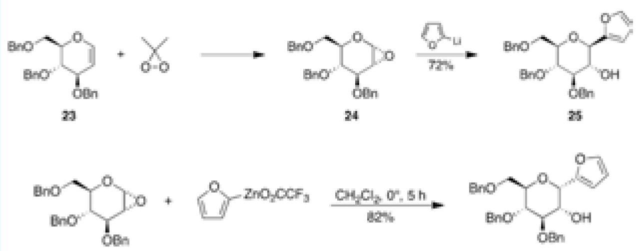

Figure 5a. Epoxide approach to arylation of glucose.

The di-tert-butylsilylene-protected dihydropyran **27** was subjected to a Stille cross-coupling reaction with an aryl sulfonyl chloride to show that this approach will work to introduce an aryl group to the sugar. Introduction of the requisite 3-hydroxyl group in the α−position was then accomplished via hydroboration/oxidation to provide the β−arylated sugar derivative **29** (24) (Figure 5b).

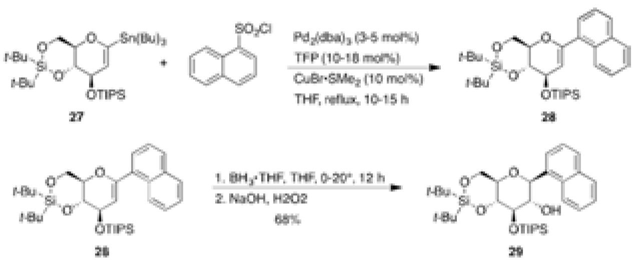

Figure 5b. Stille cross-coupling approach to Gliflozins.

Gong and Gagné have shown that the reaction of arylzinc reagents with suitably-protected glucosyl bromides under Ni(0) catalysis results in the C1-aryl glucoside with good β−selectivity (25) (Figure 5c).

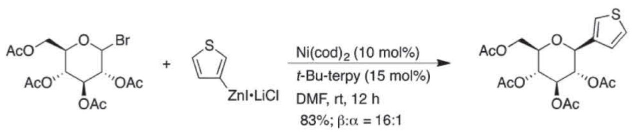

Figure 5c. Organozinc cross-coupling approach to Gliflozins.

CONCLUSIONS

A number of gliflozins has now been approved for prescription use in the dosage control of diabetes 2. The most general and flexible synthetic approaches to this class of drugs are outlined herein and follow a similar three-step sequence of preparation of the appropriate aryl substituent, attachment of the aryl moiety to a protected glucose followed by deprotection and modification of the anomeric center of the arylated glucose. The use of the gluconolactone intermediate does have the disadvantage of carrying out an oxidation step to the lactone and a subsequent reduction step, usually carried out with an organosilane.

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