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# Syntheses of C-5-spirocyclic C-glycoside SGLT2 inhibitors

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ABSTRACT

Several syntheses of C-5-spirocycle-containing C-glycosides are discussed. A multigram-scale synthesis capitalizing on a one-pot aldol-Cannizzaro sequence is described. Spiro oxetane formation using an unprotected penta-ol C-glycoside as substrate is also exemplified. Functional assessment of these compounds for potency and selectivity was evaluated at human SGLT2 and SGLT1.

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Sodium glucose transporter of type 2 (SGLT2) is a low affinity high capacity $Na^+$/glucose cotransporter of glucose which is found in the S1 domain of the proximal tubules in the kidney and is responsible for the transport of ~90% of the glucose in the urine back to the bloodstream.[1] SGLT2 inhibitors should theoretically promote weight loss and control hyperglycemia in a glucose-dependent yet insulin-independent manner, thereby making such therapeutic agents very compelling complements to the current arsenal of anti-diabetic agents.[2]

The early discovery that natural product phlorizin[3] (**1**, Fig. 1) induced glucosuria in humans[4] combined with the more recent full characterization[5] of SGLT2 triggered numerous research programs in the pharmaceutical industry over the past few years. These efforts produced several clinical candidates from two distinct series: O-aryl glycosides (e.g., remogliflozin[6] **2**) and C-aryl glycosides (e.g., dapagliflozin[7] **3**). SGLT2 inhibitors such as **4**, containing a spiro ring at the C-1 position of the pyranose (carbohydrate nomenclature) have also been reported.[8]

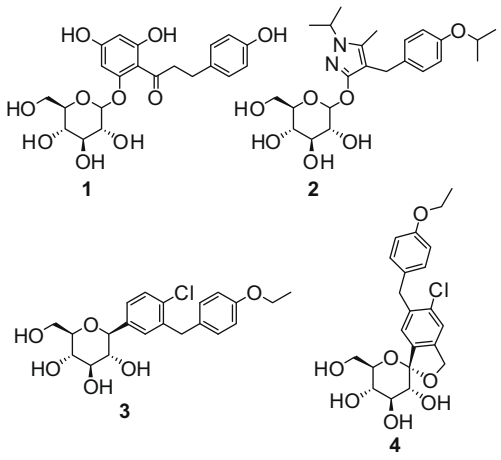
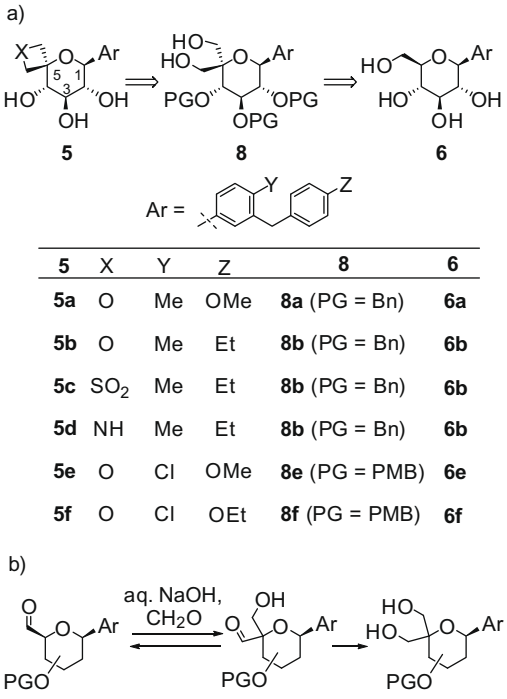


**Figure 1.** Structures of some SGLT2 inhibitors.



| 5 | X | Y | Z | 8 | 6 |
|---|---|---|---|---|---|
| **5a** | O | Me | OMe | **8a** (PG = Bn) | **6a** |
| **5b** | O | Me | Et | **8b** (PG = Bn) | **6b** |
| **5c** | $SO_2$ | Me | Et | **8b** (PG = Bn) | **6b** |
| **5d** | NH | Me | Et | **8b** (PG = Bn) | **6b** |
| **5e** | O | Cl | OMe | **8e** (PG = PMB) | **6e** |
| **5f** | O | Cl | OEt | **8f** (PG = PMB) | **6f** |

**Figure 2.** (a) C-5-spirocyclic C-glycosides as SGLT2 inhibitors and (b) aldol-Cannizzaro one-pot sequence.

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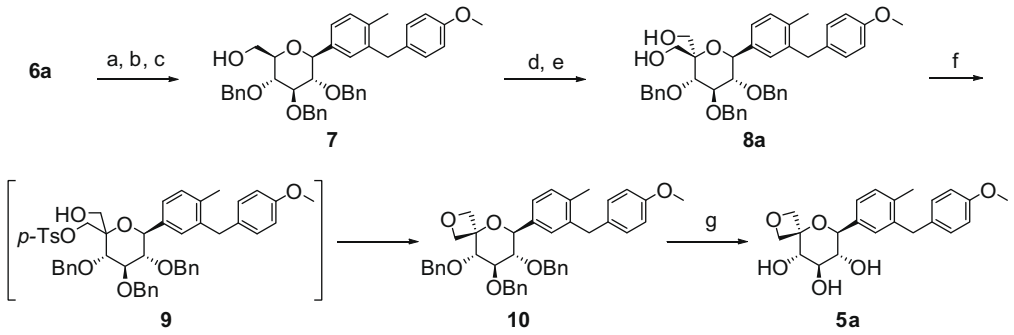
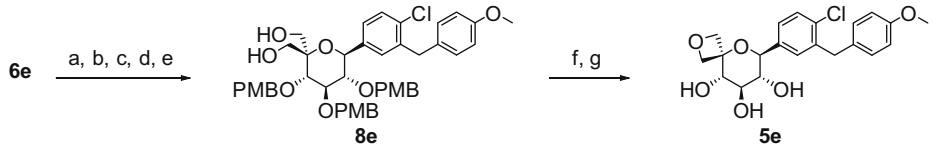



**Scheme 1.** Multigram-scale synthesis of spiro oxetane C-glycoside **5a**. Reagents and conditions: (a) $PhCH(OMe)_2$ (1.3 equiv), *p*-TsOH (cat.), DMF, 60 °C; (b) BnBr (3 equiv), NaH (3 equiv), DMF, 0–23 °C (82%, 2 steps); (c) $LiAlH_4$ (5 equiv), $AlCl_3$ (4 equiv), $Et_2O/CH_2Cl_2$, reflux (90%); (d) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$, −78 to −20 °C; (e) NaOH (1.5 equiv), $H_2CO$ (xs), $H_2O$/1,4-dioxane, 23 °C (45%, two steps); (f) *n*-BuLi (1 equiv), then *p*-TsCl, then *n*-BuLi (another 1 equiv), THF, 0–65 °C (65%); (g) Pd black (3 equiv), $HCO_2H$ (80 equiv), EtOH/THF, 23 °C (95%).

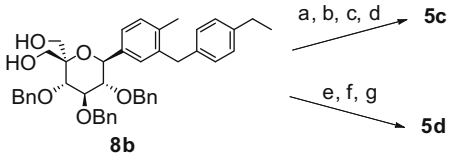



**Scheme 2.** Synthesis of spiro oxetane C-glycoside **5e**. Reagents and conditions: (a) $Ph_3CCl$ (2 equiv), pyridine (2.5 equiv), DMF, 0–23 °C (97%); (b) PMBBr (3.2 equiv), NaH (5 equiv), DMF, 10–50 °C (29%); (c) $BF_3$–$OEt_2$ (0.9 equiv), $CH_3OH/CH_2Cl_2$, 0 °C (86%); (d) Dess–Martin periodinane (2 equiv), $CH_2Cl_2$, 23 °C (89%); (e) NaOH (2 equiv), $H_2CO$ (20 equiv), *i*-PrOH/1,4-dioxane (2/1 vol.), 23 °C (48%); (f) *n*-BuLi (1 equiv), then *p*-TsCl, then *n*-BuLi (another 1 equiv), THF, 0–65 °C (70%); (g) TFA (30 equiv), anisole (5 equiv), $CH_2Cl_2$, 23 °C (83%).

We sought novel SGLT2 inhibitors of general structure **5** bearing a spirocyclic ring at the C-5 position (carbohydrate nomenclature) of the pyranose ring (Fig. 2a). To the best of our knowledge this constitutes the first example of SGLT2 inhibitors possessing such a structure.[9] Logical precursors to these targets were diols of general structure **8** which could be accessed via a one-pot aldol-Cannizzaro sequence[10] to forge the required tetrasubstituted carbon in C-5 (Fig. 2b).[11]

The multigram-scale synthesis of compound **5a** that was used to supply early in vivo toleration studies in rodents is shown in Scheme 1. Regioselective protection of **6a** by benzylidene masking the C-4 and C-6 hydroxyl groups was carried out under classical conditions using benzaldehyde dimethylacetal in the presence of a catalytic amount of *para*-toluenesulfonic acid. Subsequent protection of the remaining secondary C-2 and C-3 hydroxyl groups, followed by regioselective opening of the benzylidene acetal using the sterically demanding $AlCl_3/LiAlH_4$ reagent[12] led to intermediate **7** (74% yield over three steps). So revealed, the C-6 carbinol was oxidized under Swern conditions[13] to the corresponding aldehyde. Subsequent aldol-Cannizzaro reaction with formaldehyde produced advanced intermediate **8a** (45% yield over two steps[14]). This intermediate was then converted to the mono-tosylate intermediate **9** by treatment of the diol with 1 equiv of *n*-BuLi in THF followed by the addition of 1 equiv of *para*-toluenesulfonyl chloride; upon treatment with an additional equivalent of base and warming at 65 °C, oxetane **10** was formed cleanly in 65% yield.[15] Hydrogenolysis of the benzyl protective groups proceeded chemoselectively to produce the desired final product **5a** as a solid in 95% yield.[16] By this route, multigram quantities of compound **5a** could be produced; only three chromatographic purifications were required (intermediates **8a**, **10**, and final product **5a** were purified by flash chromatography over silica gel).

Compound **5b**[17] was synthesized following the same synthetic path whereas compounds such as **5e**[18] and **5f**[19], having an aryl chloride side chain, required a slightly different protective group strategy to avoid any potential problem of chemoselectivity in the final hydrogenolysis step (Scheme 2). For these derivatives,

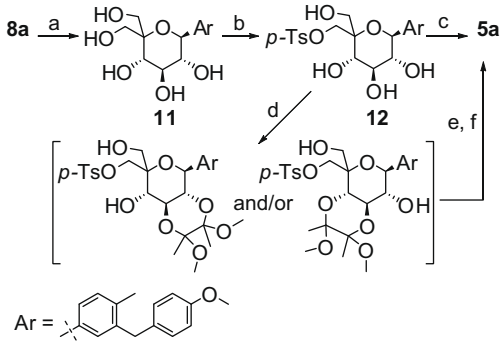



**Scheme 3.** Synthesis of spiro dioxathietane **5c** and spiro azetidine **5d**. Reagents and conditions: (a) MsCl (2.6 equiv), $Et_3N$ (3 equiv), $CH_2Cl_2$, −30 to −5 °C; (b) $Na_2S$ (1 equiv), DMF/$H_2O$, 200 °C (21%, 2 steps); (c) *m*-CPBA (40 equiv), $CHCl_3$, 23 °C (98%); (d) $Pd(OH)_2$ (0.75 equiv), $H_2$ (50 psi), EtOH, 23 °C (74%); (e) $Tf_2O$ (5 equiv), pyridine (30 equiv), $CH_2Cl_2$, −20 °C; (f) *i*-$Pr_2NEt$ (3 equiv), $BnNH_2$ (xs), 80 °C (75%); (g) Pd black (7 equiv), $HCO_2H$ (xs), EtOH/THF (2/1 vol.), 23 °C (63%).

the secondary hydroxyl groups were protected with *p*-methoxybenzyl groups (PMB). PMB deprotection using trifluoroacetic acid required the addition of anisole as a PMB cation scavenger to obtain the final products in both high yield and purity.[20]

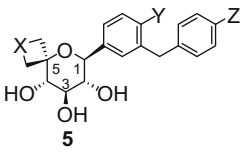
Having developed a robust synthesis of advanced intermediates of general structure **8**, we next explored the synthesis of the C-5 spirodioxathietane and azetidine (Scheme 3).[21] Treatment of intermediate **8b** with methanesulfonyl chloride in the presence of triethylamine led to the corresponding bis-mesylate. Reacting the crude bis-mesylate with sodium sulfide under relatively harsh conditions (200 °C, microwave reactor, 30 min) provided the corresponding thietane (21% yield over two steps). *m*-CPBA oxidation of the sulfide followed by hydrogenolysis cleanly produced the desired product **5c** in 73% yield over two steps.[22] Formation of the corresponding bis-triflate of **8b** under standard conditions followed by treatment of this intermediate with an excess of benzyl amine at 80 °C gave the benzyl-protected azetidine (75% yield over two steps). Hydrogenolysis of the benzyl protective groups gave **5d** (63% yield).[23]

Inspired by the developments in the field of glycosylation chemistry using unprotected glycosyl donors[24] and regioselective functionalization of monoprotected carbohydrates[25], we also explored the feasibility of synthesizing the oxetane motif found in **5a** starting from an unprotected penta alcohol intermediate such




**Scheme 4.** Synthesis of **5a** from an unprotected C-glycoside derivative. Reagents and conditions: (a) Pd black (3 equiv), $HCO_2H$ (30 equiv), EtOH/THF, 23 °C (97%); (b) *p*-TsCl (1.1 equiv), pyridine, 0–23 °C (57%, br sm); (c) NaHMDS (3 equiv), THF, 0–23 °C (15%); (d) 2,3-butadione, $MeC(OMe)_3$, $BF_3$–$OEt_2$, MeOH, 60 °C; (e) NaHMDS (2 equiv), THF, 0–23 °C; (f) TFA, $H_2O$, 23 °C (15%, three steps).

**Table 1**
Functional $IC_{50}$s against human SGLT2 and SGLT1



**5**

| 5 | X | Y | Z | SGLT2 $IC_{50}$ (nM) | SGLT1 $IC_{50}$ (nM) |
|---|---|---|---|---|---|
| **5a** | O | Me | OMe | 6.6 ± 2.5 (8) | 1540 ± 180 (7) |
| **5b** | O | Me | Et | 3.4 ± 0.8 (3) | 1500 (2) |
| **5c** | $SO_2$ | Me | Et | 14 (1) | >10,000 (1) |
| **5d** | NH | Me | Et | 5100 (1) | >10,000 (1) |
| **5e** | O | Cl | OMe | 23 ± 22 (5) | >9600 (5) |
| **5f** | O | Cl | OEt | 32 ± 79 (5) | 5600 ± 930 (4) |

as **11** (obtained in 97% yield by hydrogenolysis of **8a**; Scheme 4). When reacted with 1 equiv of *p*-TsCl, **11** provided **12** as a 2/1 mixture of primary mono-tosylates (57% yield based on recovered starting material). Treatment of this mixture of tosylates with 3 equiv of NaHMDS in THF from 0 to 23 °C gave **5a**, albeit in a modest 15% yield, after purification by flash chromatography over silica gel. Although the other products from this reaction were not identified, we hypothesize that these were byproducts arising from the intramolecular attack of the pendent C-3 and/or C-4 secondary hydroxyl groups on the primary tosylate. Unfortunately, masking these hydroxyls and locking the pyranose ring in a rigid *trans*-decaline-type conformation did not improve the overall yield of the sequence (15% overall yield, Scheme 4).

Functional assessment of these compounds for potency and selectivity was evaluated at human SGLT2 and SGLT1 (Table 1).[26] Despite the loss of an H-bond-donating group at C-5, compounds **5a**, **5b**, **5c**, **5e**, and **5f** proved to be potent and very selective SGLT2 inhibitors. On the other hand, azetidine **5d**, which is likely protonated at physiological pH, showed a marked decrease in potency indicating that a positively charged group may not be tolerated in this region of the molecule.[27]

In conclusion, we have described several routes to access SGLT2 inhibitors bearing various spirocyclic rings at the C-5 position of the pyranose. Most notably, a multigram-scale synthesis of potent and selective SGLT2 inhibitor **5a**, capitalizing on a one-pot aldol-Cannizzaro sequence, was developed. We have also demonstrated spiro oxetane formation using a fully unprotected penta-ol C-glycoside intermediate as substrate.

## Acknowledgments

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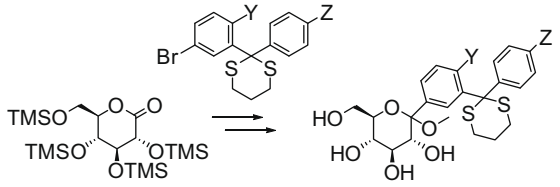
11. Compounds **6a**, **6b**, **6e**, and **6f** were prepared as described in the literature via addition of the appropriately substituted 3-benzylphenyllithium to 2,3,4,6-tetra-*O*-trimethylsilyl-β-D-gluconolactone; see for instance Ref. 7. Interestingly, nucleophilic additions onto an adequately protected form of gluconolactone using organometallic species derived from 1,3-dithiane-containing aryl bromides of the kind below led to moderate yields of the corresponding methyl ketal intermediate:

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14. A typical procedure is described below:
To a solution of oxalyl chloride (2 mL, 20 mmol) in dichloromethane (60 mL) at −78 °C was added dimethylsulfoxide (3.4 mL, 48 mmol). The resulting solution was stirred at −78 °C for 30 min. A solution of **7** (5.11 g, 7.92 mmol) in dichloromethane (40 mL) was then added drop-wise. The resulting mixture was stirred for 30 min allowing the temperature to rise to −60 °C. Triethylamine (10 mL, 72 mmol) was added and the mixture was allowed to warm to −20 °C over 1 h. The reaction was quenched by the addition of aqueous saturated ammonium chloride solution. The organic phase was dried over magnesium sulfate, filtered, and concentrated. The crude aldehyde was then dissolved in dioxane (80 mL), and 37 wt % aqueous formaldehyde (12 mL) followed by aqueous 1 M sodium hydroxide (12 mL) was added . The resulting mixture was stirred at room temperature for 4 days. The mixture was neutralized by the addition of aqueous 1 M hydrogen chloride solution and was extracted with ethyl acetate. The organic phase was separated, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by flash chromatography over silica gel eluting with a gradient of 20–40% ethyl acetate/heptane to afford the intermediate **8a** (2.41 g, 45%). MS: 675 ($M+H^+$; positive mode). $^1H$ NMR (400 MHz, chloroform-*d*) $\delta$ ppm 1.98 (dd, $J$ = 10.0, 4.1 Hz, 1H), 2.24–2.27 (m, 1H), 2.28 (s, 3H), 3.51–3.59 (m, 1H), 3.70–3.78 (m, 1H), 3.77 (s, 3H), 3.80–4.02 (m, 6H), 4.07 (d, $J$ = 4.3 Hz, 2H), 4.39 (d, $J$ = 10.5 Hz, 1H), 4.53 (d, $J$ = 9.8 Hz, 1H), 4.73 (d, $J$ = 11.1 Hz, 1H), 4.87 (d, 1H), 4.96 (d, $J$ = 10.9 Hz, 2H), 6.77 (d, $J$ = 8.8 Hz, 2H), 6.87–7.05 (m, 4H), 7.17–7.38 (m, 16H).
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16. Compound **5a**: MS: 431 ($M + HCO_2^-$; negative mode). $^1$H NMR (400 MHz, methanol-$d_4$) $\delta$ ppm 2.19 (s, 3H), 3.25–3.38 (m, 3H), 3.74 (s, 3H), 3.92 (s, 2H), 4.04 (d, $J$ = 8.8 Hz, 1H), 4.49 (d, $J$ = 6.8 Hz, 1H), 4.63 (d, $J$ = 6.4 Hz, 1H), 4.82 (d, $J$ = 6.6 Hz, 1H), 4.93 (d, $J$ = 6.6 Hz, 1H), 6.79 (d, $J$ = 8.8 Hz, 2H), 7.03 (d, $J$ = 8.8 Hz, 2H), 7.11–7.19 (m, 3H).
17. Compound **5b**: MS: 429.2 ($M+HCO_2^-$; negative mode). $^1$H NMR (400 MHz, methanol-$d_4$) $\delta$ ppm 7.16–6.96 (m, 7H), 4.89 (d, 1H, $J$ = 6.8 Hz), 4.79 (d, 1H, $J$ = 6.8 Hz), 4.59 (d, 1H, $J$ = 6.4 Hz), 4.45 (d, 1H, $J$ = 7.2 Hz), 4.00 (d, 1H, $J$ = 9.6 Hz), 3.92 (s, 2H), 3.36–3.20 (m, 3H), 2.54 (q, 2H, $J$ = 7.6 Hz), 2.16 (s, 3H), 1.15 (t, 3H, $J$ = 7.6 Hz).
18. Compound **5e**: MS: 451 ($M+HCO_2^-$; negative mode). $^1$H NMR (400 MHz, methanol-$d_4$): $\delta$ ppm 3.20–3.28 (m, 2H), 3.34–3.38 (m, 1H), 3.75 (s, 3H), 3.99–4.08 (m, 3H), 4.48 (d, $J$ = 6.6 Hz, 1H), 4.60 (d, $J$ = 6.8 Hz, 1H), 4.82 (d, $J$ = 6.8 Hz, 1H), 4.92 (d, $J$ = 6.8 Hz, 1H), 6.79–6.84 (m, 2H), 7.09–7.11 (m, 2H), 7.23–7.29 (m, 2H), 7.36 (d, $J$ = 8.1 Hz, 1H).
19. Compound **5f**: MS: 465 ($M+HCO_2^-$; negative mode). $^1$H NMR (400 MHz, methanol-$d_4$) $\delta$ ppm 1.35 (t, $J$ = 7.0 Hz, 3H), 3.20–3.34 (m, 3H), 3.92–4.09 (m, 5H), 4.48 (d, $J$ = 6.6 Hz, 1H), 4.60 (d, $J$ = 6.6 Hz, 1H), 4.82 (d, $J$ = 6.6 Hz, 1H), 4.92 (d, $J$ = 6.8 Hz, 1H), 6.76–6.86 (m, 2H), 7.02–7.13 (m, 2H), 7.21–7.30 (m, 2H), 7.36 (d, $J$ = 8.2 Hz, 1H).
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22. Compound **5c**: MS: 450 ($M+NH_4^+$; positive mode); 477 ($M+HCO_2^-$; negative mode). $^1$H NMR (400 MHz, methanol-$d_4$) $\delta$ ppm 7.22–6.99 (m, 7H), 4.55 (d, 1H, $J$ = 13.6 Hz), 4.46 (d, 1H, $J$ = 14 Hz), 4.20 (dd, 1H, $J$ = 13.6 and 4.8 Hz), 4.15 (d, 1H, $J$ = 9.6 Hz), 4.03 (dd, 1H, $J$ = 14 and 4.8 Hz), 3.96 (s, 2H), 3.53 (d, 1H, $J$ = 9.6 Hz), 3.41 (t, 1H, $J$ = 9.2 Hz), 3.23 (t, 1H, $J$ = 9.2 Hz), 2.58 (q, 2H, $J$ = 7.6 Hz), 2.19 (s, 3H), 1.17 (t, 3H, $J$ = 7 Hz).
23. Compound **5d**: MS: 384.3 ($M+H^+$). $^1$H NMR (400 MHz, methanol-$d_4$) $\delta$ ppm 8.43 (s, 1H), 7.19–6.99 (m, 7H), 4.37 (d, 1H, $J$ = 11.0 Hz), 4.28 (d, 1H, $J$ = 11.1 Hz), 4.12–4.06 (m, 2H), 3.99–3.91 (m, 3H), 3.48–3.33 (m, 3H), 2.58 (q, 2H, $J$ = 7.6 Hz), 2.20 (s, 3H), 1.19 (t, 3H, $J$ = 7.6 Hz).
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