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A method for preparing *C*-glycosides related to phlorizin

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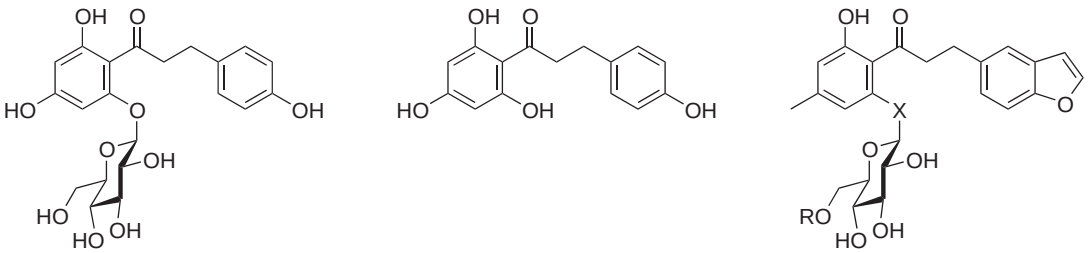
Abstract

Johnson's Suzuki coupling protocol was employed to prepare *C*-glycoside analogs of phlorizin (**1**). In vitro biological evaluation of these *C*-glycosides indicated the anomeric oxygen is important to the SGLT inhibitory activity of phlorizin (**1**) and related agents.

Noninsulin dependent diabetes mellitus (NIDDM) is a substantial and growing international health problem.[1] Treatments of the disease are sought by the development of pharmaceuticals which alleviate hyperglycemia.[2] One potential strategy is inhibition of the Na^+/glucose cotransporters (SGLTs) found in the kidney.[3] SGLTs mediate intestinal absorption and renal reabsorption of glucose.[4] Phlorizin (**1**), a β-aryl glucoside, is a specific inhibitor of SGLTs (Scheme 1).[5] Upon subcutaneous injection, phlorizin (**1**) has been demonstrated to lower blood glucose levels in diabetic animal models by promoting urinary glucose excretion.[6] One weakness of phlorizin (**1**) as an agent is its inactivation via conversion to phloretin (**2**) by β-glucosidases in the intestine.[3,7] Phloretin (**2**) is a weak SGLT inhibitor with the undesired effect of inhibiting the



1 phlorizin

2 phloretin

3 X=O, R=H T-1095A
4 X=O, R=CO_2Me T-1095
5 X=CH_2, R=H

Scheme 1.

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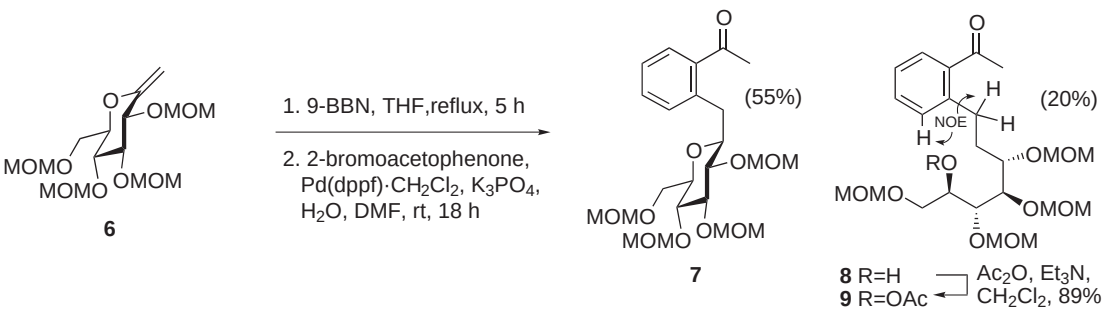
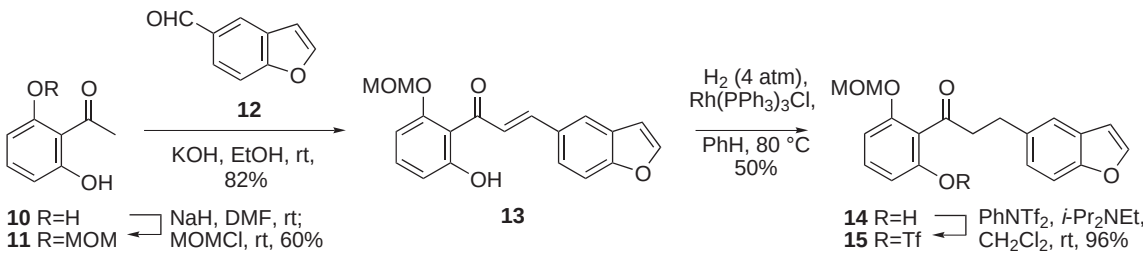
facilitated glucose transporters (GLUTs) which mediate the uptake of glucose into a variety of cells, most notably muscle. Researchers at Tanabe have studied analogs of phlorizin (**1**) and discovered T-1095A (**3**) and its prodrug T-1095 (**4**).[8] T-1095 (**4**) can be administered orally, is metabolized to T-1095A (**3**), and inhibits renal SGLTs, thereby inducing urinary glucose excretion and decreasing blood glucose levels in diabetic animal models. Spurred by these observations, we became interested in designing phlorizin (**1**) analogs in which the glycosidic bond was replaced by a more stable connection. One classic method for achieving this goal is to construct a related *C*-glycoside, e.g. **5**.[9] Such derivatives would be stable to glycosidases while maintaining a similar structure to phlorizin (**1**) or T-1095A (**3**). A short efficient method of synthesis amenable to analog production was required and Johnson's Suzuki cross-coupling protocol was selected.[10]

A model coupling between 2-bromoacetophenone and *exo*-glycal **6**[10] was explored (Scheme 2).[11] Precedented stereoselective hydroboration of *exo*-glycal **6** with 9-BBN in refluxing THF, followed by Suzuki coupling of the resulting alkylborane yielded the β-*C*-glycoside **7** in 55% yield. In addition, a second product was isolated and has been assigned the structure **8**. Acetylation of **8** yielded the monoacetate **9** whose COSY and ROESY spectra support its assignment.[12] Although optimization of the reaction conditions to moderate (or eliminate) the production of **8** could be envisioned, we did not initiate such studies due to our desire to evaluate acyclic *C*-glycosides as potential SGLT inhibitors.



Scheme 2.

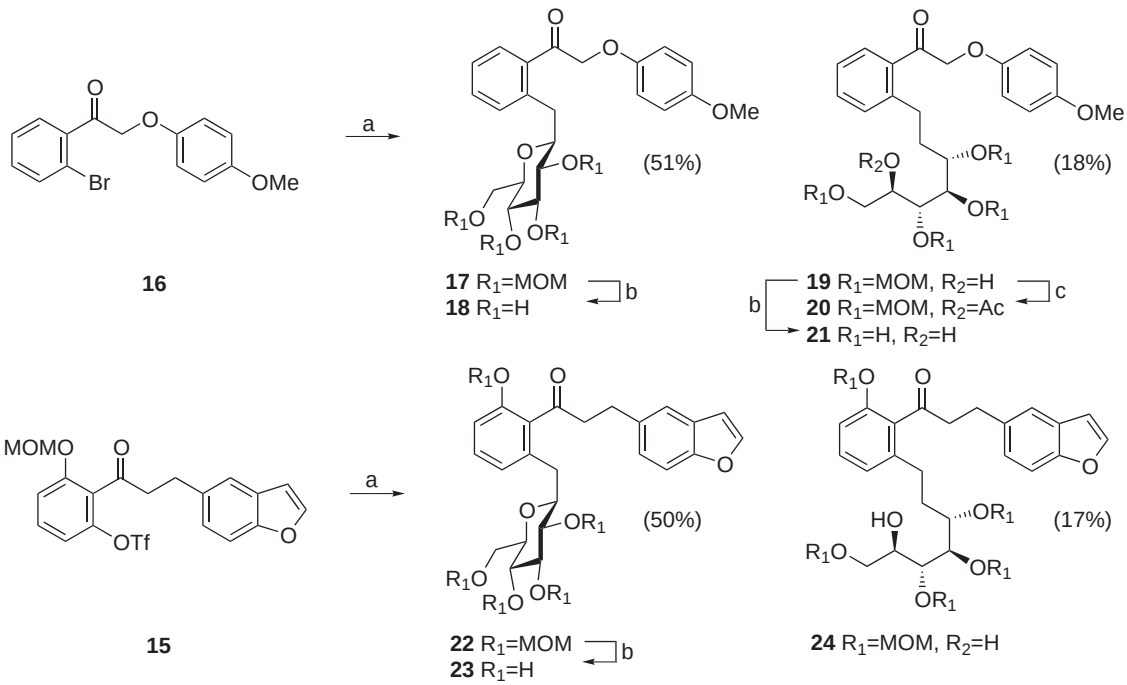
A concise preparation of an aglycone related to T-1095 (**4**) was also developed (Scheme 3). 2,6-Dihydroxy acetophenone **10** was monoprotected with MOMCl and condensed with aldehyde **12**[13] under basic aldol conditions to yield enone **13** in good yield. Standard hydrogenation conditions (H_2, Pd/C) reduced the alkene, dibenzofuran, and the benzylic ketone, so the milder Wilkinson's catalyst was employed and delivered the ketone **14** in moderate yield. Incomplete



Scheme 3.

conversion and ketone reduction accounted for the remainder of the material. Triflation of **14** then provided aglycone **15** suitable for Suzuki cross coupling.

Aryl bromide **16**[14] and aryl triflate **15** behaved similarly to 2-bromoacetophenone in the Suzuki coupling reaction (Scheme 4). Coupling of bromide **16** with the hydroboration products of *exo*-glycal **6** provided the protected *C*-glycoside **17** and its acyclic relative **19**. The assignment of the structure of **19** was supported by the formation of monoacetate **20** under acetylation conditions. The MOM protecting groups were cleanly removed from **17** and **19** to yield *C*-glycoside **18** and the pentaol **21**. Triflate **15** also underwent Suzuki coupling to provide **22** and **24**. In this case, deprotection also unmasked a phenol which has been shown to be critical to phlorizin's (**1**) in vivo activity.[15]



Scheme 4. (a) **6**, Pd(dppf)·CH_2Cl_2, K_3PO_4, H_2O, DMF, rt, 18 h; (b) HCl, MeOH, H_2O, 91–95%; (c) Ac_2O, Et_3N, CH_2Cl_2, 85%

In vitro examination of *C*-glycosides **18** and **23** in several assays indicated these compounds were much weaker inhibitors of SGLT than phlorizin (**1**), indicating the importance of the glycosidic oxygen in this family of SGLT inhibitors.[16]

Acknowledgements

The help rendered by Dr T. S. Pagano and Dr L. Seif in NMR studies and in high pressure hydrogenation experiments, respectively, is greatly appreciated. Dr C. Lin, Dr B. Dayton, and Dr B. Cool are acknowledged for their determination of the biological activity of analogs. Dr B. Szczepankiewicz is thanked for thoughtful discussions.

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11. Characterization data. (**7**) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, $J=7.5$ Hz, 1H), 7.36 (m, 2H), 7.27 (m, 1H), 4.97 (d, $J=6.5$ Hz, 1H), 4.87 (d, $J=6.1$ Hz, 1H), 4.85 (d, $J=6.1$ Hz, 1H), 4.82 (d, $J=6.4$ Hz, 1H), 4.78 (d, $J=6.8$ Hz, 1H), 4.71 (d, $J=6.4$ Hz, 1H), 4.54 (d, $J=6.4$ Hz, 1H), 4.50 (d, $J=6.4$ Hz, 1H), 3.50–3.72 (m, 4H), 3.49 (s, 3H), 3.46 (m, 1H), 3.45 (s, 3H), 3.39 (s, 3H), 3.36 (m, 2H), 3.26 (s, 3H), 3.21 (m, 1H), 2.84 (dd, $J=14.2$, 9.8 Hz, 1H), 2.58 (s, 3H); MS (APCI) $(M+H_2O)^+$ at m/z 490. (**8**) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (dd, $J=7.1$, 1.4 Hz, 1H), 7.40 (m, 1H), 7.24–7.31 (m, 2H), 4.88 (d, $J=6.5$ Hz, 1H), 4.66–4.84 (m, 7H), 3.77–4.01 (m, 6H), 3.66 (dd, $J=10.5$, 5.8 Hz, 1H), 3.46 (s, 3H), 3.44 (s, 3H), 3.41 (s, 3H), 3.39 (s, 3H), 3.03 (m, 1H), 2.87 (m, 1H), 2.57 (s, 3H), 1.87 (m, 2H); MS (APCI) $(M+Cl)^-$ at m/z 509. (**9**) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (dd, $J=7.8$, 1.4 Hz, 1H), 7.40 (m, 1H), 7.32 (m, 1H), 7.26 (m, 1H), 5.24 (m, 1H), 4.80 (d, $J=6.8$ Hz, 1H), 4.75 (s, 2H), 4.72 (m, 3H), 4.64 (d, $J=6.4$ Hz, 1H), 4.60 (d, $J=6.4$ Hz, 1H), 4.00 (dd, $J=6.1$, 4.1 Hz, 1H), 3.90 (dd, $J=11.2$, 3.4 Hz, 1H), 3.86 (m, 1H), 3.76 (m, 2H), 3.45 (s, 3H), 3.41 (s, 3H), 3.36 (s, 3H), 3.35 (s, 3H), 3.35 (s, 3H), 3.07 (m, 1H), 2.88 (m, 1H), 2.58 (s, 3H), 2.09 (s, 3H), 1.99 (m, 2H); MS (APCI) $(M+H_2O)^+$ at m/z 534. (**13**) ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.91 (s, 1H), 7.92 (m, 2H), 7.84 (d, $J=1.3$ Hz, 1H), 7.67 (d, $J=2.0$ Hz, 1H), 7.61 (dd, $J=8.8$, 1.7 Hz, 1H), 7.54 (d, $J=8.8$ Hz, 1H), 7.35 (t, $J=8.5$ Hz, 1H), 6.81 (dd, $J=2.4$, 0.8 Hz, 1H), 6.68 (dd, $J=8.4$, 0.8 Hz, 1H), 6.62 (dd, $J=8.4$, 0.8 Hz, 1H), 5.32 (s, 2H), 3.54 (s, 3H); MS (ESI) $(M+H)^+$ at m/z 325. (**14**) ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.03 (s, 1H), 7.60 (d, $J=2.4$ Hz, 2H), 7.46 (m, 1H), 7.42 (d, $J=8.5$ Hz, 1H), 7.31 (t, $J=8.5$ Hz, 1H), 7.17 (dd, $J=8.5$, 1.7 Hz, 1H), 6.72 (m, 1H), 6.61 (m, 2H), 5.25 (s, 2H), 3.47 (t, $J=7.4$ Hz, 2H), 3.46 (s, 3H), 3.13 (t, $J=7.4$ Hz, 2H); MS (ESI) $(M+H)^+$ at m/z 327. (**15**) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, $J=2.4$ Hz, 1H), 7.35–7.45 (m, 3H), 7.18 (m, 2H), 6.98 (d, $J=8.4$ Hz, 1H), 6.71 (m, 1H), 5.07 (s, 2H), 3.36 (s, 3H), 3.19 (m, 4H); MS (ESI) $(M+H_2O)^+$ at m/z 476. (**16**) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (m, 1H), 7.32–7.47 (m, 3H), 6.84 (m, 4H), 5.09 (s, 2H), 3.76 (s, 3H); MS (APCI) $(M)^+$ at m/z 321. (**17**) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (dd, $J=7.9$, 1.0 Hz, 1H), 7.39 (m, 2H), 7.28 (m, 1H), 6.88 (d, $J=9.5$ Hz, 2H), 6.81 (d, $J=9.5$ Hz, 2H), 5.11 (s, 2H), 4.92 (d, $J=6.4$ Hz, 1H), 4.84 (s, 2H), 4.81 (d, $J=6.4$ Hz, 1H), 4.74 (d, $J=6.4$ Hz, 1H), 4.69 (d, $J=6.4$ Hz, 1H), 4.48 (d, $J=6.6$ Hz, 1H), 4.45 (d, $J=6.6$ Hz, 1H), 3.76 (s, 3H), 3.47–3.70 (m, 4H), 3.44 (s, 6H), 3.39–3.43 (m, 1H), 3.38 (s, 3H), 3.26–3.35 (m, 3H), 3.20 (s, 3H), 2.92 (dd, $J=14.1$, 9.7 Hz, 1H); MS (APCI) $(M+H_2O)^+$ at m/z 612. (**18**) ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.67 (d, $J=7.2$ Hz, 1H), 7.43 (m, 2H), 7.31 (dt, $J=7.6$, 1.7, 1H), 6.93 (d, $J=9.3$ Hz, 2H), 6.84 (d, $J=9.3$ Hz, 2H), 5.33 (d, $J=18.2$ Hz, 2H), 5.27 (d, $J=18.2$ Hz, 1H), 3.72 (s, 3H), 3.58 (dd, $J=11.4$, 1.7 Hz, 1H), 2.70–3.34 (m, 8H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 201.0, 153.5, 151.9, 138.3, 137.6, 131.1, 130.6, 126.8, 125.7, 115.5, 114.4, 80.7, 80.2, 78.0, 73.6, 72.1, 70.5, 61.3, 55.3, 33.7; HRMS (FAB) m/e 418.1620 (418.1628 calcd for $C_{22}H_{26}O_8$). Anal. calcd for $C_{22}H_{26}O_8(H_2O)_{0.05}(CF_3CO_2H)_{0.55}$: C, 57.56; H, 5.57; Found: C, 57.53; H, 5.58. (**19**) ^{1}H NMR (300 MHz, $CDCl_3$) d 7.64 (dd, $J=7.8$, 1.0 Hz, 1H), 7.45 (dt, $J=7.5$, 1.8 Hz, 1H), 7.35 (dd, $J=7.5$, 1.0 Hz, 1H), 7.30 (dd, $J=7.5$, 1.0 Hz, 1H), 6.82 (m, 4H), 4.63–4.86 (m, 10H), 3.76 (s, 3H), 3.34–4.00 (m, 6H), 3.44 (s, 3H), 3.42 (s, 3H), 3.39 (s, 3H), 3.36 (s, 3H), 2.98 (m, 1H), 2.84 (m, 1H), 1.98 (m,

1H), 1.86 (m, 1H); MS (APCI) $(M+H_2O)^+$ at m/z 614. (**21**) ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.35 (dd, $J=7.5$, 1.7 Hz, 1H), 7.09–7.25 (m, 3H), 6.95 (d, $J=9.5$ Hz, 2H), 6.86 (d, $J=9.5$ Hz, 2H), 4.72 (m, 1H), 4.55 (d, $J=10.0$, 1H), 4.42 (d, $J=10.0$ Hz, 1H), 4.36 (m, 1H), 3.71 (s, 3H), 3.62 (m, 2H), 2.80 (m, 2H), 1.88 (m, 2H); MS (ESI) $(M)^+$ at m/z 420. (**22**) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (m, 1H), 7.47 (br s, 1H), 7.45 (m, 1H), 7.19 (m, 2H), 6.96 (m, 2H), 6.71 (m, 1H), 4.99 (s, 2H), 4.84 (m, 4H), 4.69 (m, 2H), 4.43 (s, 2H), 3.68 (m, 1H), 3.57 (m, 2H), 3.44 (s, 3H), 3.41 (s, 3H), 3.39 (s, 3H), 3.32 (s, 3H), 3.21 (s, 3H), 3.14 (m, 4H), 2.48 (m, 1H), 1.28 (m, 2H); MS (APCI) $(M+H_2O)^+$ at m/z 680. (**23**) ^{1}H NMR (300 MHz, $CDCl_3$, DMSO-d_6) δ 9.31 (br s, 1H), 7.62 (d, $J=2.2$ Hz, 1H), 7.46 (d, $J=1.1$, 1H), 7.38 (d, $J=8.4$ Hz, 1H), 7.17 (dd, $J=8.4$, 1.6 Hz, 1H), 7.08 (t, $J=7.6$ Hz, 1H), 6.84 (d, $J=7.3$ Hz, 1H), 6.73 (m, 2H), 3.54–3.85 (m, 2H), 3.22–3.38 (m, 5H), 3.00–3.18 (m, 5H), 2.51 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, DMSO-d_6) δ 207.3, 153.1, 152.4, 144.2, 135.9, 135.0, 129.3, 128.7, 126.4, 124.0, 120.6, 119.62, 112.7, 109.9, 105.54, 79.3, 78.5, 77.5, 77.4, 72.7, 70.23, 61.6, 45.5, 33.6, 28.5; HRMS (FAB) $(M+H)^+$ m/e 443.1701 (443.1706 calcd for $C_{22}H_{26}O_8$). (**24**) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (m, 1H), 7.45 (m, 1H), 7.38 (m, 1H), 7.21 (m, 1H), 7.17 (m, 1H), 6.96 (m, 1H), 6.89 (m, 1H), 6.71 (m, 1H), 5.01 (s, 2H), 4.56–4.85 (m, 8H), 3.60–4.10 (m, 6H), 3.32–3.47 (m, 12H), 3.14 (s, 3H), 1.50–2.51 (m, 8H); MS (APCI) $(M+H_2O)^+$ at m/z 682.

12. An NOE signal in the ROESY spectrum between the marked aryl and benzylic protons allowed their assignment (Scheme 2). The COSY spectrum lead to the assignment of the remainder of the signals including the homobenzylic protons (δ 1.98 ppm).
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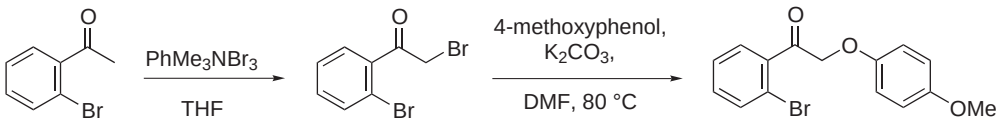
14. Aryl bromide **16** was prepared by converting 2-bromo-acetophenone to the corresponding α-bromoketone followed by reaction with 4-methoxyphenoxide.



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16. *C*-glycosides **18** and **23** were greater than tenfold weaker than phlorizin (**1**) in their ability to displace [^{3}H]-phlorizin from pig kidney membrane preparations and in their capacity to inhibit uptake of [^{14}C]-α-methyl-D-glucose into rat brush-border membrane vesicles.