Drug Discovery

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Palladium-Catalyzed Arylation of Carbasugars Enables the Discovery of Potent and Selective SGLT2 Inhibitors

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Dedicated to Professor Stephen L. Buchwald

Abstract: *Selective inhibition of the transporter protein sodium-glucose cotransporter 2 (SGLT2) has emerged as a promising way to control blood glucose level in diabetes patients. Reported herein is a short and convergent synthetic route towards some small-molecule SGLT2 inhibitors by a chemo- and diastereospecific palladium-catalyzed arylation reaction. This synthetic strategy enabled the discovery of two highly selective and potent SGLT2 inhibitors, thereby paving the way towards the development of carbasugar SGLT2 inhibitors as potential antidiabetic/antitumor agents.*

Palladium-catalyzed C–N coupling reactions have been used extensively in the synthesis of many important pharmaceuticals.[1] It serves as a powerful method to synthesize amines which are not readily accessible by traditional synthetic transformations. Amino-carbasugars are biologically important compounds. For example, valienamine and acarbose were shown to exhibit strong glycosidase inhibitory activities.[2] Despite their biological importance, their syntheses remain challenging and are usually lengthy. The synthetic hurdle has prevented amino-carbasugars from being developed into valuable drug candidates.

Recently, we discovered a potent and selective inhibitor of the transporter protein sodium-glucose cotransporter 2 (SGLT2;[3] Figure 1, compound **4**). It is a carbasugar which contains a metabolically stable C–O bond. We postulate that the syntheses of their aza-analogues (e.g. amino-carbasugars **5** and **6**) could provide important insights into the structure–activity relationship (SAR) of these inhibitors,[4] thereby aiding the development of carbasugar SGLT2 inhibitors as antidiabetic[5] and antitumor[6] agents. The targeted amino-carbasugars **5** and **6**, the carbocyclic analogues of sergliflozin (**1**) and dapagliflozin (**2**), contain a C–N bond which is not easily accessible by traditional synthetic transformations (Figure 1). Thus, palladium-catalyzed arylation is ideal for such a challenging transformation (Figure 2). The β-hydride elimination of the [L_nPd(NHAlkyl)Ar] intermediate is a potential complication which may lead to the epimerization at C1 on the carbasugar core (Figure 2, pathway V). However, we envisioned that, with judicious choice of ligand and reaction conditions, the undesired β-hydride elimination pathway could be suppressed.

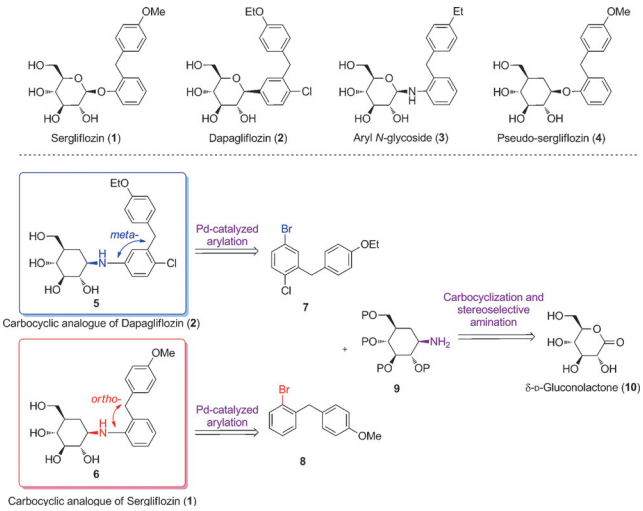

Figure 1. Retrosynthetic analysis of the two representative amino-carbasugars **5** and **6**.

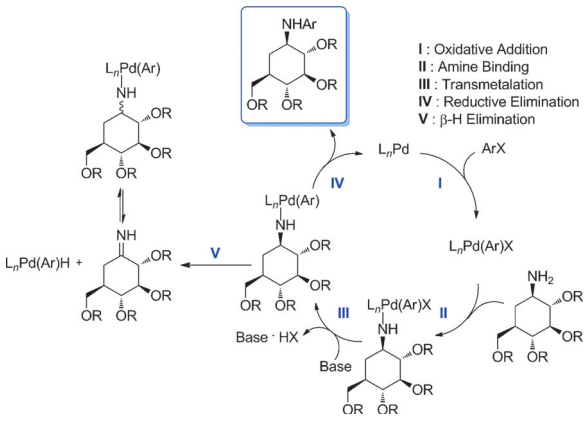

Figure 2. Mechanism of palladium-catalyzed arylation of a polyhydroxylated amino-carbasugar and potential complication by β-hydride elimination.

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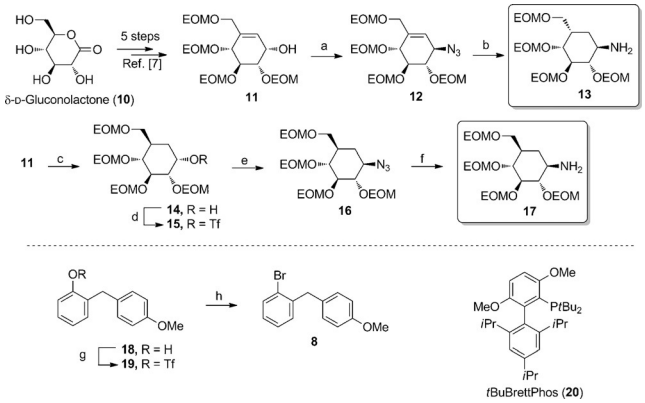
Herein, we report a novel synthetic strategy towards the syntheses of these biologically active amino-carbasugars using a palladium-catalyzed arylation of a polyhydroxylated carbocyclic amine as the key step. This synthetic strategy enabled the short and convergent syntheses of these optically pure amino-carbasugars without any epimerization. Two of these compounds turned out to show strong SGLT2 inhibitory activity in a cell-based glucose uptake assay. This arylation reaction also enabled the syntheses of conformationally distinct amino-carbasugars, thereby allowing study of their SARs and guiding the future design of clinically valuable drug candidates.

We first set out to synthesize the carbocyclic amine **17** as a coupling partner (Scheme 1). In our first attempt, the α-allylic alcohol **11**, readily accessible from D-gluconolactone,[7] was converted into the allylic azide **12** by displacement of the corresponding mesylate LiN_3. Unfortunately, Raney nickel catalyzed hydrogenation of the azide and alkene moieties in **12** provided the carbocyclic amine **13** with the undesired α-L-idose configuration. Nevertheless, **13** proved to be useful in our subsequent SAR study.

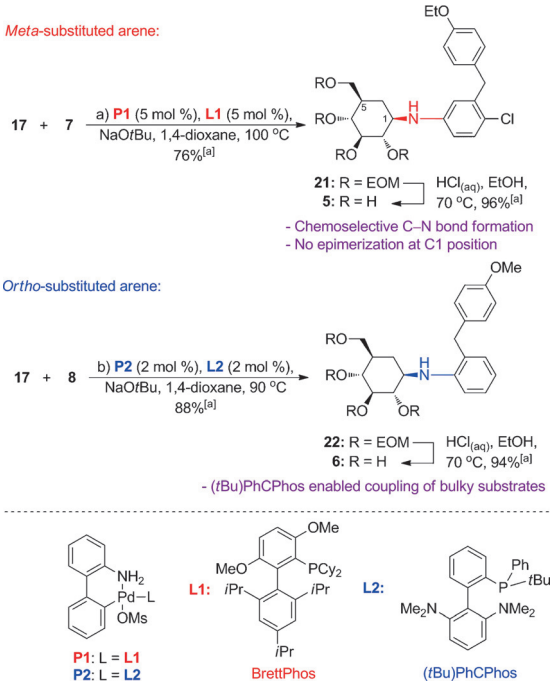


Scheme 1. Syntheses of the carbocyclic amines **13** and **17**, and aryl bromide **8** for subsequent palladium-catalyzed N-arylation. a) 1. MsCl, Et_3N, CH_2Cl_2; 2. LiN_3, DMF, 71% over 2 steps; b) Raney Ni (cat.), H_2, 1,4-dioxane, RT, 88%; c) Raney Ni (cat.), H_2, EtOH, RT; d) Tf_2O, py, CH_2Cl_2, 0°C; e) NaN_3, DMF, RT; f) Raney Ni (cat.), H_2, EtOH, RT, 38% from **14**; g) Tf_2O, py, CH_2Cl_2, −78°C to RT, 94%; h) $[Pd_2(dba)_3]$ (8 mol%), **20** (24 mol%), KF, KBr, 1,4-dioxane, 100°C, 70%. DMF = *N*,*N*-dimethylformamide, EOM = ethoxymethyl, Ms = methanesulfonyl, py = pyridine, Tf = trifluoromethanesulfonyl.

We then amended our synthetic route to obtain the desired β-D-glucose-configured amine **17** (Scheme 1). The alkene moiety in **11** was first reduced diastereoselectively to give **14**, which was converted into the triflate **15**. Nucleophilic substitution of the triflate group with NaN_3 then yielded the carbocyclic azide **16**. Owing to the instability of **16**,[8] the crude product was subjected to Raney nickel catalyzed hydrogenation without purification. Thus, the desired cyclohexylamine **17** was obtained in 38% yield from **14** by a telescoping approach.

Next, we prepared the aryl bromide precursor to the aglycone of sergliflozin (Scheme 1, bottom). The aryl triflate **19** was prepared in 94% yield from the phenol **18**, which was readily obtained from commercial starting materials by a one-pot procedure.[3] Palladium-catalyzed bromination of **19** was then achieved by using *t*BuBrettPhos as the ligand, thus providing **8** in 70% yield.[9]

With the desired coupling partners in hand, we performed the key palladium-catalyzed arylation reaction using the palladium precatalysts **P1** and **P2** (Scheme 2).[10] The N-arylation of **17** with the *meta*-substituted bromochlorobenzene **7** was accomplished by using the bulky dialkylbiaryl phosphine ligand BrettPhos (**L1**). The reaction proceeded with good chemoselectively for coupling at the aryl bromide.[11] In addition, there was no epimerization at C1 on the carbasugar core resulting from β-hydride elimination of the $[L_nPd(NHAlkyl)Ar]$ intermediate. Thus, the coupled product **21** was isolated in 76% yield as a single diastereomer. Finally, acid hydrolysis yielded the tetraol **6**. For our SAR studies on this class of amino-carbasugars, the C5 epimer of **21** was also prepared using the same synthetic sequence by starting from the carbocyclic amine **13** and arene **7** (see the Supporting Information).

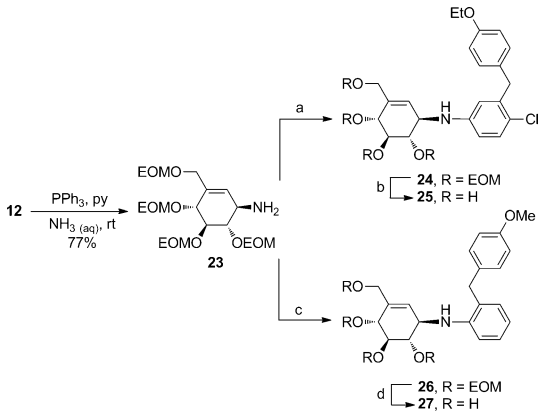


Scheme 2. Palladium-catalyzed N-arylation of the cyclohexylamine **17** and subsequent global deprotection reactions. a) **P1** (5 mol%), **L1** (5 mol%), NaO*t*Bu, 1,4-dioxane, 90°C, 4 h, 76%; b) $HCl_{(aq)}$, EtOH, 70°C, 2 h, 96%; c) **P2** (2 mol%), **L2** (2 mol%), NaO*t*Bu, 1,4-dioxane, 90°C, 4 h, 88%; d) $HCl_{(aq)}$, EtOH, 70°C, 2 h, 94% Yield of the isolated product.

Subsequently, we coupled the *ortho*-substituted aryl bromide **8** with **17** to synthesize the sergliflozin analogue. We first used the optimized reaction conditions of the coupling reaction involving **7**. However, the desired product was not formed and the starting materials were recovered. We recognized that this N-arylation reaction was very challenging because of the bulk of both the *ortho*-substituted arene and the carbocyclic amine. After extensive optimization, we found

that the recently developed catalyst system[12] based on (*t*Bu)PhCPhos effectively promoted this transformation at a catalytic loading as low as 2 mol%. The N-arylated product **22** was obtained in 88% yield, again without any epimerization at C1. Acid hydrolysis of **22** yielded **6**, a carbocyclic aza-analogue of sergliflozin, for subsequent biological evaluation. The C5 epimer of **6** was also prepared using these reaction conditions (see the Supporting Information).

The carbocyclic allylic analogues of sergliflozin and dapagliflozin were also prepared for biological evaluation (Scheme 3). Staudinger reduction of the β-allylic azide **12**

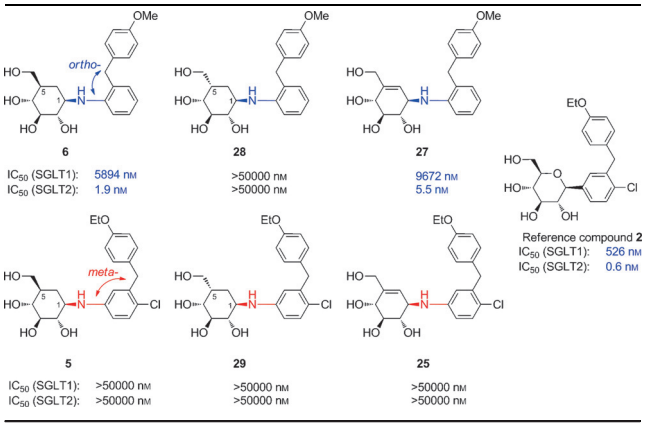


Scheme 3. Preparation of the allylic amine **23** and the subsequent transformations. a) **P2** (5 mol%), **L2** (5 mol %), NaO*t*Bu, 1,4-dioxane, 90°C, 45 min, 69%; b) $HCl_{(aq)}$, EtOH, 70°C, 2 h, 93%; c) **P2** (5 mol%), **L2** (5 mol%), NaO*t*Bu, 1,4-dioxane, 90°C, 45 min, 43%; d) $HCl_{(aq)}$, EtOH, 70°C, 2 h, 98%.

furnished the coupling precursor **23** in 77% yield. With **23** in hand, we then performed the palladium-catalyzed N-arylation reaction using the (*t*Bu)PhCPhos-based catalytic system. We found that an increased catalytic loading (5 mol%) was essential for full conversion of **23**, and a shorter reaction time (45 min) was essential to minimize the formation of side products. Successful N-arylation reactions gave the secondary allylic amines **24** and **26** in 43 and 69% yield, respectively. Lastly, acid hydrolysis furnished the amines **25** and **27**, which were carbocyclic allylic analogues of sergliflozin and dapagliflozin, respectively.

A cell-based ^{14}C-α-methyl-D-glucopyranoside (^{14}C-AMG) uptake assay was used to evaluate the SGLT2/SGLT1 inhibitory activities of the six novel amino-carbasugars. The results from the uptake assay are summarized in Table 1. The amino-carbasugar **6**, the carbocyclic aza-analogue of **1**, was found to be a highly selective and potent SGLT2 inhibitor. Its IC_{50} value is 1.9 nM, thus showing that it is as potent as its aryl O-pseudoglycoside counterpart **4**.[3] It also demonstrates an over 3000-fold SGLT2/SGLT1 inhibitory selectivity. Surprisingly, **5** showed almost no SGLT2/SGLT1 inhibitory activities, even though it consists of a β-D-glucose-configured core and the aglycone of **2**. This brief SAR study revealed that the amine functionality and the distal aromatic ring must be positioned at the *ortho*-position of the amino group to show a high SGLT2 inhibitory activity.

Table 1: IC_{50} values for the six novel amino-carbasugars with SGLT1 and SGLT2.



In line with the SARs in aryl O-pseudoglycosides,[3] the D-idose-configured **28** was also inactive, thus suggesting that the inversion of the stereocenter at C5 is not tolerated in carbasugar SGLT2 inhibitors. However, the allylic amine **27** showed nanomolar inhibitory activity (5.5 nM) and high selectivity (>1700-fold), despite the fact that it adopts a distorted chair conformation.

In conclusion, we have developed a facile synthetic route towards some amino-carbasugars, and it features a key palladium-catalyzed arylation of a polyhydroxylated amino-carbasugar. The arylation reactions showed completed chemo- and disastereoselectivities. Two of the amino-carbasugars, **6** and **27**, were identified to be highly selective and potent SGLT2 inhibitors through a cell-based radioactive assay. With the streamlined synthetic route and SARs of these carbasugar SGLT2 inhibitors, we envision the further exploration of this new family of SGLT2 inhibitors as antidiabetic/antitumor agents.

Acknowledgments

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