J. Chem. Sci. (2020)132:42
https://doi.org/10.1007/s12039-020-1747-x
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RAPID COMMUNICATION

Synthesis of metabolites of dapagliflozin: an SGLT2 inhibitor

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MS received 7 July 2019; revised 21 December 2019; accepted 5 January 2020

Abstract. Dapagliflozin is one of the gliflozin class drugs, useful for the treatment of type-2 diabetes. Dapagliflozin undergoes extensive metabolism and transforms to metabolites in humans. The contribution of pharmacologically active metabolites in drug discovery and development is significant. A streamlined synthetic approach is devised to access three metabolites of dapagliflozin namely, benzylic hydroxy dapagliflozin, oxo dapagliflozin and desethyl dapagliflozin. Two synthetic protocols have been proposed for the synthesis of benzylic hydroxy dapagliflozin and oxo dapagliflozin. An enantioselective deethylation of dapagliflozin is also reported.

Keywords. Dapagliflozin; SGLT2 inhibitor; Anti diabetic drug; Metabolites; Synthesis.

Abbreviations

NBS	*N*-Bromosuccinimide
AIBN	Azobisisobutyronitrile
$LiOH.H_2O$	Lithium hydroxide momohydrate
PTSA	*p*-Toluene sulphonic acid
MeOH	Methanol
$BF_3.OEt_2$	Boron trifluoride diethyl etherate
Et_3SiH	Triethylsilane
MnO_2	Manganese dioxide
$NaBH_4$	Sodium borohydride
BBr_3	Boron tribromide
DCM	Dichloromethane
HBr	Hydrobromic acid

1. Introduction

Type-2 diabetes is a long-term metabolic disorder and chronic disease with worldwide prevalence. Type-2 diabetes is characterized by abnormally high blood sugar (hyperglycaemia) caused by a relative deficiency in insulin secretion, along with resistance to insulin, found to have a higher risk for the growth of microvascular complications.[1] Dapagliflozin (**1**) (Figure 1) is discovered and developed by Bristol-Myers Squibb Company, is identified as a potent and selective sodium-dependent glucose co-transporter (SGLT2) inhibitor which reduces blood glucose levels. Dapagliflozin is sold under the brand name FARXIGA®.

A drug metabolite is generated in the body as a byproduct by the biotransformation reactions of drugs. In general, active metabolites and their parent drugs have similar biochemical and pharmacological actions. Nevertheless, pharmacological action and therapeutic effects of active metabolites those are synergistic or inhibitory of the parent drugs. The active metabolites are also having an imperative role to understand the mechanism of action of drugs. In drug discovery, active metabolites are effectively useful as lead candidates during the period of lead optimization phase. Moreover, there are various active metabolites that are already established as drugs as a consequence of exhibiting superior pharmacological, pharmacodynamic,

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Electronic supplementary material: The online version of this article (https://doi.org/10.1007/s12039-020-1747-x) contains supplementary material, which is available to authorized users.

Published online: 13 February 2020

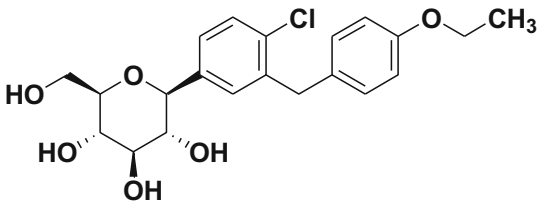


Figure 1. Chemical structure of dapagliflozin (**1**).

improved pharmacokinetic and safety profiles to their parent drugs. In clinical studies, identification of active metabolites is vital to understand the fundamental cause and to discover a superior study design where, enhanced *in vivo* pharmacological activity is exhibited by drug.[2]

Benzylic hydroxy dapagliflozin (**2**), oxo dapagliflozin (**3**) and desethyl dapagliflozin (**4**) (Figure 2) are disclosed as metabolites of dapagliflozin.[3–5] The isolation, characterization and metabolic pathway of benzylic hydroxy dapagliflozin (**2**) is described by Seed *et al.*[6] In addition, compounds **2**, **3** and **4** are listed as impurities of dapagliflozin drug product in another literature report.[7] Prior to biological investigation, these significant metabolites **2**–**4** should be made available in quantity. In this context, we report the simple methods for the synthesis of **2**, **3** and **4** using commercially accessible raw materials.

2. Experimental

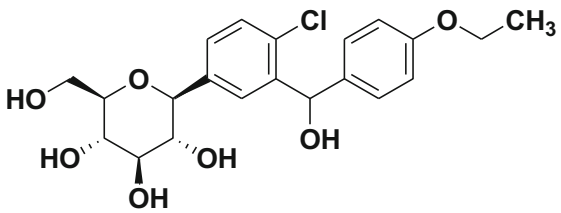
2.1 *General experimental methods*

^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 300 MHz and Varian 500 MHz spectrometer using TMS as an internal standard in DMSO-d_6, D_2O and CD_3OD solvents. The ^{1}H chemical shift values were reported in the δ scale relative to TMS (δ 0.00) and the ^{13}C chemical shift values were given relative to DMSO-d_6, D_2O and CD_3OD as internal standards. HRMS (High-resolution mass spectral) analysis was performed using electrospray ionization (ESI) method on Xevo G2 QTOF mass spectrometer. Specific optical rotation was recorded using an Anton Paar MCP 500 instrument. All the chemicals were purchased from commercial suppliers and used without any purification.

2.2 *Preparation of (2S,3R,4R,5S,6R)-2-(4-chloro-3-((4-ethoxyphenyl)(hydroxy)methyl)phenyl-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (benzylic hydroxy dapagliflozin) (2) (Scheme 1)*

To a stirred solution of tetra acetyl dapagliflozin (**5**) (15 g, 0.02 mol) in $CHCl_3$ (350 mL) under N_2, AIBN (0.42 g, 0.002 mol) and *N*-bromosuccinimide (7.4 g, 0.04 mol) were added. The mixture was warmed and stirred at gentle reflux for 16 h. The solution was cooled to ambient temperature and H_2O (150 mL) was added. The resultant slurry was stirred for 16 h at ambient temperature. The partitioned organic layer was washed with saturated aqueous $NaHCO_3$ (100 mL) and H_2O (100 mL). The organic layer was concentrated under reduced pressure to afford tetra acetyl benzylic hydroxy dapagliflozin (**6**) (16 g, 100%).

To a stirred solution of tetraacetyl benzylic hydroxy dapagliflozin (**6**) (15 g, 0.025 mol) in 1:1 MeOH/H_2O (100 mL) was added LiOH.H_2O (1.28 g, 0.03 mol). The reaction mixture was stirred for 16 h at 20–30 °C and the solvent was evaporated under reduced pressure. The residue, after dissolution in MTBE (300 mL), was subsequently washed with H_2O (75 mL) and brine (75 mL). The organic layer was concentrated under reduced pressure and the



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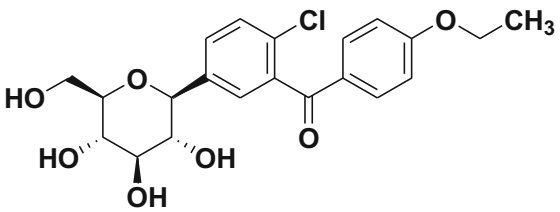

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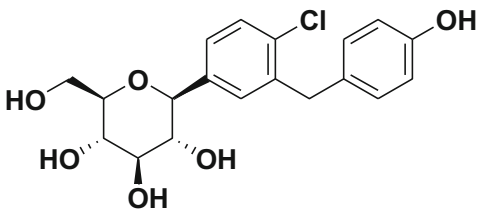

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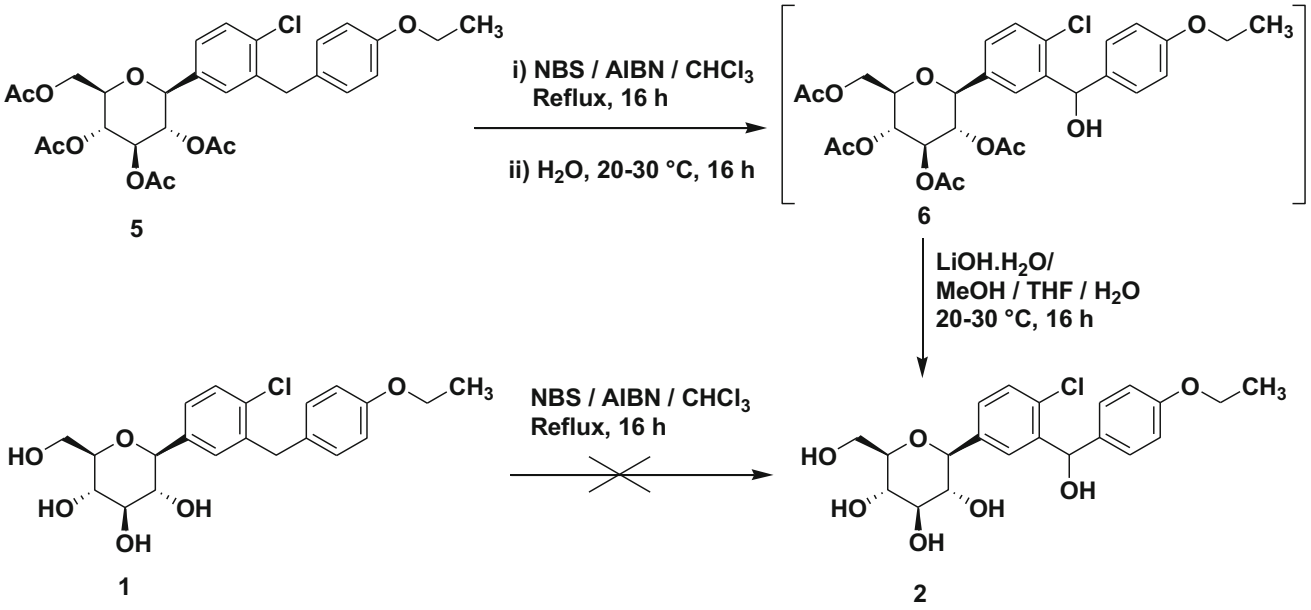
Figure 2. Chemical structures of benzylic hydroxy dapagliflozin (**2**), oxo dapagliflozin (**3**) and desethyl dapagliflozin (**4**).



Scheme 1. Synthesis of benzylic hydroxy dapagliflozin (**2**).

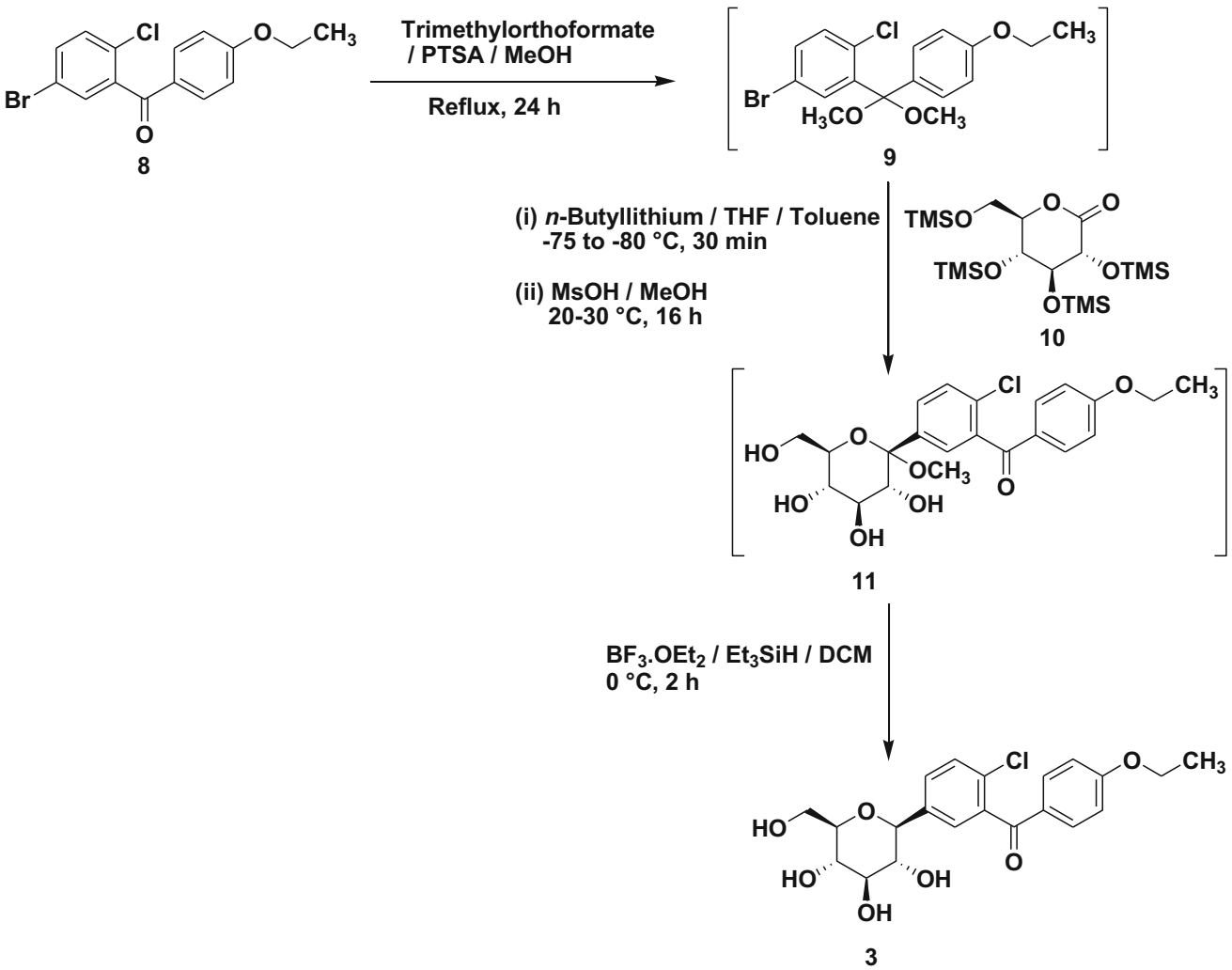
residue was purified by column chromatography to afford pure benzylic hydroxy dapagliflozin (**2**) (1.7 g, 15%) as a glassy off-white amorphous solid. $[\alpha]_D^{20}$: +10.9° (c = 0.2 in methanol); ^{1}H NMR (D_2O) (500 MHz): 1.35–1.38 (t, 3H), 3.57–3.64 (m, 2H), 3.78–3.92 (m, 2H), 4.11–4.09 (m, 2H), 4.36–4.34 (d, 1H, *J* = 9.5Hz), 6.20 (s, 1H), 6.99–6.97 (d, 2H, *J* = 9Hz), 7.35–7.34 (d, 2H, *J* = 8.5Hz), 7.41–7.39 (m, 1H), 7.48–7.46 (dd, 1H), 7.73–7.72 (d, 1H, *J* = 2.5Hz); ^{13}C NMR (D_2O) (300 MHz): 16.74, 28.77, 51.58, 63.69, 67.22, 72.54, 74.51, 77.01, 80.08, 82.85, 84.12, 117.62, 129.65, 129.88, 131.05, 131.72, 131.79, 132.72, 134.92, 137.10, 139.94, 143.54, 160.50; MASS (ESI) for $C_{21}H_{25}ClO_7$ $(M - H)^+$ 423.1210, found: 423.1200;

2.3 *Preparation of (2-chloro-5-((2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)-tetrahydro-2H-pyran-2-yl)phenyl)ethoxyphenyl)methanone (oxo dapagliflozin) (**3**) (Scheme 2)*

To a stirred solution of 5-bromo-2-chloro-4′-ethoxybenzophenone (**8**) (10 g, 0.03 mol) in MeOH (100 mL), PTSA (3 g, 0.01 mol) was added. To this reaction mass, trimethylorthoformate (50 mL) was added potion wise over 20 min. The mixture was warmed and stirred at a gentle reflux for 24 h. The mixture was cooled to ambient temperature subsequently EtOAc (300 mL) and saturated aqueous $NaHCO_3$ solution were added. The separated organic layer was washed with brine (30 mL), prior to the concentration under reduced pressure to yield **9** (9 g) as a white solid.

To a stirred −75 to −80 °C solution of **9** (9 g, 0.233 mol) in 1:4 THF/toluene (90 mL) under N_2, *n*-BuLi (15% w/v in hexanes, 16 mL, 0.256 mol) was added while keeping the temperature between −75 to −80 °C. After 30 min, 2,3,4,6-tetra-*O*-trimethylsilyl-*β*-*D*-glucolactone (**10**) (13.3 g, 0.256 mol) solution in toluene (54 mL) was added by maintaining the reaction at −75 to −80 °C. After 60 min, methanesulfonic acid (4.9 g, 0.406 mol) solution in MeOH (54 mL) was added; whereupon, the reaction was allowed slowly to 20–30 °C and stirred for 16 h. The reaction was then quenched with saturated aqueous $NaHCO_3$ (90 mL). After extraction with EtOAc (90 mL), the organic layer was washed with brine prior to concentration under reduced pressure to afford methoxy oxo dapagliflozin (**11**) (3.5 g, 35%).

To a stirred −40 to −45 °C solution of methoxy oxo dapagliflozin (**11**) (3.5 g, 0.01 mol) in CH_2Cl_2 (20 mL), Et_3SiH (3.0 g, 0.027 mol) followed by $BF_3{\cdot}OEt_2$ (3.8 g, 0.027 mol) were added by maintaining the reaction temperature between −40 and −45 °C. The solution was allowed to warm to 0 °C over 2 h and stirred for 2 h, prior to quenching with saturated aqueous $NaHCO_3$ (35 mL). After removal of solvent under reduced pressure, the residue was partitioned between EtOAc (35 mL) and H_2O (35 mL). Following extraction of the aqueous layer with EtOAc (35 mL), the combined organic layers were washed with H_2O (10 mL) and brine (10 mL). The organic phase was concentrated under reduced pressure and the residue was purified by column chromatography to yield oxo dapagliflozin **(3)** (2.6 g, 80%) as an off-white amorphous solid. $[\alpha]_D^{20}$: +9.4° (c = 0.2 in methanol); ^{1}H NMR (D_2O) (500 MHz): 1.44–1.39 (t, 3H), 3.25–3.48 (m, 4H), 3.67–3.90 (m, 2H), 4.10–4.21 (m, 3H), 4.10–4.17 (m, 2H), 4.18–4.21 (d, 1H, *J* = 9.3Hz), 6.98–7.01 (m, 2H), 7.46–7.44 (m, 1H), 7.49 (s, 1H), 7.55–7.59 (dd, 1H), 7.76–7.74 (m, 2H); ^{13}C NMR (CD_3OD) (300 MHz): 14.44, 14.94,



Scheme 2. Preparation of oxo dapagliflozin (**3**).

20.89, 30.87, 61.51, 62.87, 65.03, 71.56, 76.43, 79.51, 82.00, 82.15, 115.49, 129.11, 130.19, 130.46, 130.99, 131.47, 133.69, 139.63, 140.23, 165.26, 172.99, 195.75; HRMS (ESI) calculated for $C_{21}H_{23}ClO_7$ $(M + H)^+$: 423.1210, found: 423.1198;

2.4 *Preparation of (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-hydroxybenzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (desethyl dapagliflozin) (**4**)*

A mixture of dapagliflozin (**1**) (5 g, 0.012 mol) and aqueous HBr (12.6 g, 0.073 mol, 48% w/w) were warmed and stirred under a gentle reflux for 16 h. The reaction mass was cooled to an ambient temperature and partitioned between MTBE (50 mL) and H_2O (50 mL). Following extraction of aqueous layer with MTBE (50 mL), the combined organic layers were neutralized with aqueous NaOH solution. The organic layer was separated, washed with H_2O (50 mL) and concentrated. The residue was then treated with EtOH (20 mL) and the precipitated salts were removed by celite bed filtration. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography to afford pure desethyl dapagliflozin (**4**) (1.6 g) as a glassy off-white amorphous solid. $[\alpha]_D^{20}$: +5.5° (c = 0.2 in methanol); ^{1}H NMR (D_2O) (500 MHz): 3.46–3.59 (m, 4H), 3.73 & 3.84 (2dd, 2H), 3.95 (s, 2H), 4.15–4.18 (d, 1H, *J* = 9.3Hz), 6.74–6.76 (d, 2H, *J* = 6Hz), 7.05–7.07 (d, 2H, *J* = 6Hz), 7.22–7.23 (d, 1H, *J* = 3Hz), 7.26 (s, 1H), 7.30 (s, 1H), 7.37–7.40 (d, 1H, *J* = 9Hz); HRMS (ESI) calculated for $C_{19}H_{21}ClO_6$ $(M- H)^+$: 379.0948, found: 379.0936;

2.5 *Preparation of tetraacetyl oxodapagliflozin (**7**) (Scheme 3)*

To a stirred solution of tetraacetyl dapagliflozin (**5**) (10 g, 0.01 mol) in $CHCl_3$ (1000 mL), activated MnO_2 (150 g, 1.72 mol) was added. The reaction mass was warmed and

stirred under a gentle reflux for 12 h. The reaction mass was cooled to ambient temperature and the insolubles were removed by celite bed filtration. The filtrate was concentrated under reduced pressure, and the residue was crystallized from a mixture of MeOH (100 mL) and $CHCl_3$ (20 mL) to afford tetraacetyl oxo dapagliflozin (**7**) (8.3 g, 81%) as a white solid. ^{1}H NMR (DMSO-d_6) (300 MHz): 1.32–1.37 (t, 3H, J = 7Hz), 2.48 (s, 3H), 1.93 (s, 3H), 1.98–2.01 (d, 6H, J = 6.6Hz), 4.05–4.17 (m, 5H), 4.75–4.79 (d, 1H, J = 9.6Hz), 4.96–5.13 (m, 2H), 5.33–5.40 (t, 1H, J = 9.4Hz), 7.03–7.07 (m, 2H), 7.41 (d, 1H, J = 1.8Hz), 7.50–7.65 (m, 4H); ^{13}C NMR (DMSO-d_6) (300 MHz): 20.10, 20.23, 20.35, 20.46, 38.66, 38.94, 39.21, 39.49, 39.77, 40.05, 40.33, 62.33, 63.76, 68.38, 72.35, 73.02, 74.72, 77.00, 114.66, 127.22, 128.36, 129.48, 129.67, 129.75, 132.04, 136.46, 138.40, 163.34, 168.62, 169.34, 169.56, 170.04, 192.49; HRMS (ESI) calculated for $C_{29}H_{31}ClO_{11}$ $(M + NH_4)^+$: 608.1987, found: 608.2007;

2.6 *Preparation of oxo dapagliflozin (**3**) (Scheme 3)*

To a stirred solution of tetra acetyl oxo dapagliflozin (**7**) (6 g, 0.01mol) in 1:2:3 H_2O/THF/MeOH (72 mL) was added LiOH.H_2O (0.5 g, 0.012 mol). After the mixture was stirred for 16 h at 20–30 °C, the reaction mass was concentrated under reduced pressure. The residue was portioned between 60 mL each of EtOAc and H_2O. The organic layer was washed with H_2O (30 mL) and concentrated under reduced pressure to afford oxo dapagliflozin (**3**) as a glassy off-white amorphous solid (3.6 g, 84%) (see above).

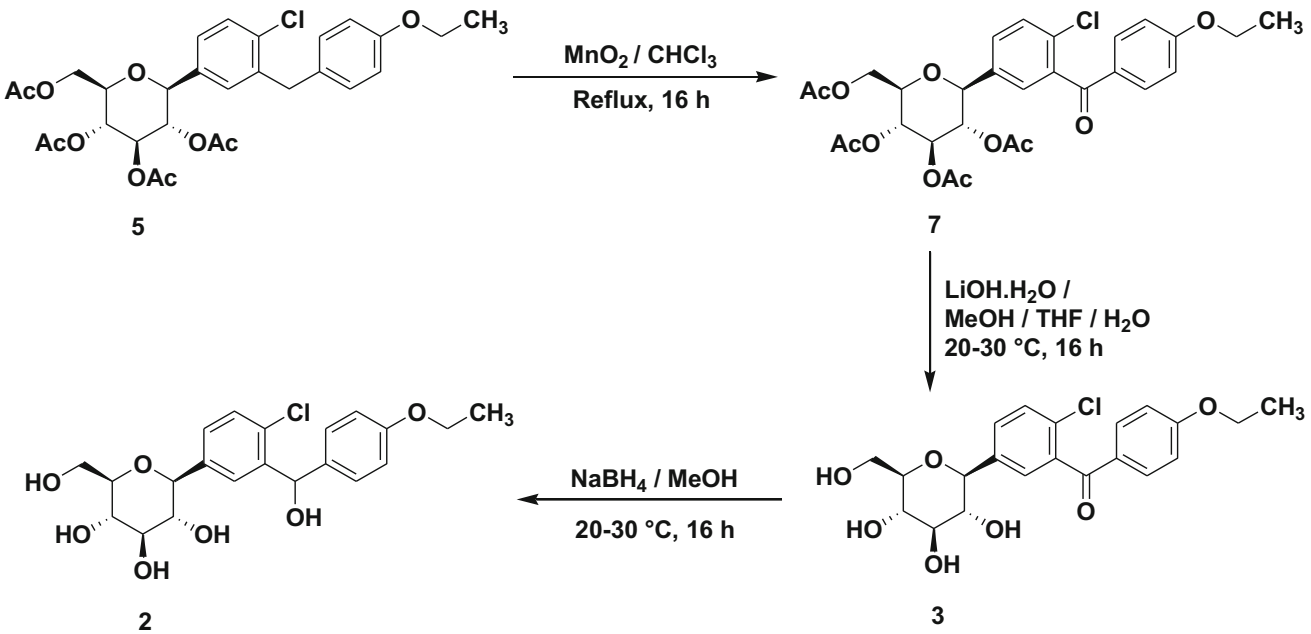
2.7 *Preparation of benzylic hydroxy dapagliflozin (**2**) (Scheme 3)*

To a stirred 0 °C solution of oxo dapagliflozin (**3**) (2 g, 0.004 mol) in MeOH (10 mL), $NaBH_4$ (0.2 g, 0.004 mol) was added portion-wise over 20 min. The mixture was warmed to 20–30 °C and stirred for 16 h. The mixture was cooled to 0–5 °C and acidified with aqueous HCl solution. The solvent was evaporated under reduced pressure, the residue was partitioned between MTBE (40 mL) and H_2O (10 mL). The organic layer was concentrated under reduced pressure to afford benzylic hydroxy dapagliflozin (**2**) (3.7 g, 85%) as a glassy off-white amorphous solid (See above).

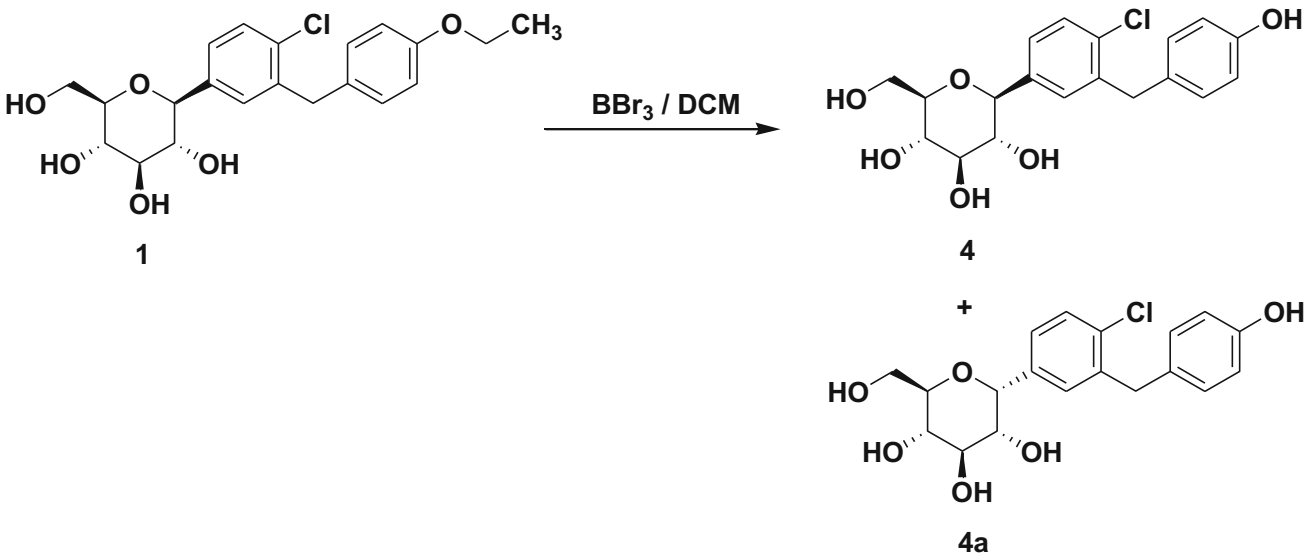
3. Results and Discussion

3.1 *Preparation of benzylic hydroxy dapagliflozin (**2**) (Scheme 1)*

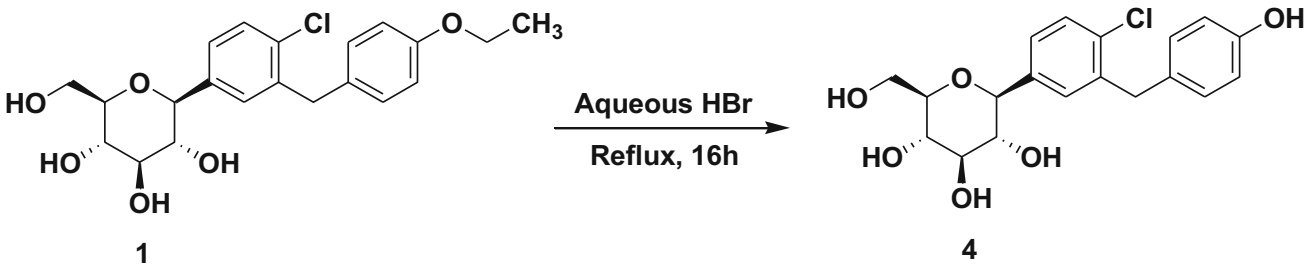
The synthesis of benzylic hydroxy dapagliflozin (**2**) was commenced with tetra acetyl dapagliflozin (**5**).[8] Wohl–Ziegler reaction[9] of tetra acetyl dapagliflozin (**5**) with *N*-bromosuccinimide (NBS) in the presence of Azobisisobutyronitrile (AIBN), subsequent treatment with H_2O furnished the synthesis of tetra acetyl benzylic hydroxy dapagliflozin (**6**). The hydrolysis of tetra acetyl benzylic hydroxy dapagliflozin (**6**) with LiOH.H_2O generated benzylic hydroxy dapagliflozin (**2**). The pure benzylic hydroxy dapagliflozin (**2**) was isolated by column chromatography. During the initial



Scheme 3. Alternative synthesis of benzylic hydroxy dapagliflozin (**2**) and oxo dapagliflozin (**3**).



Scheme 4. Reported synthesis of desethyl dapagliflozin (**4**).



Scheme 5. Proposed synthesis of desethyl dapagliflozin (**4**).

development, an attempt to prepare **2** from **1** instead of **5** was unsuccessful.

3.2 *Preparation of oxo dapagliflozin (**3**) (Scheme 2)*

The synthesis of oxo dapagliflozin (**3**) was initiated with 5-bromo-2-chloro-4′-ethoxybenzophenone (**8**).[8] The reaction of 5-bromo-2-chloro-4′-ethoxybenzophenone (**8**) with trimethylorthoformate[10] in the presence of *p*-toluenesulphonic acid (PTSA) afforded corresponding ketal i.e. 4-bromo-1-chloro-2-((4-ethoxyphenyl)dimethoxymethyl)benzene (**9**). Lithium halogen exchange of **9**, followed by addition of the nascent lithiated aromatic to 2,3,4,6-tetra-*O*-trimethylsilyl-*β*-*D*-glucolactone (**10**)[8] generated a mixture of lactols, which were desilylated *in situ* to afford methoxy oxo dapagliflozin (**11**) by treatment with methanesulphonic acid (MsOH) in methanol. Reductive elimination of methoxy oxo dapagliflozin **11** using triethylsilane and $BF_3.OEt_2$ afforded oxo dapagliflozin (**3**). The pure product was isolated by column chromatography. During our initial development, an attempt to prepare **3** using 5-bromo-2-chloro-4′-ethoxydiphenylmethane[8] instead of **8** was unsuccessful.

3.3 *Alternative synthesis of benzylic hydroxy dapagliflozin (**2**) and oxo dapagliflozin (**3**)*

In spite of the fact that the above proposed synthetic approaches were promising enough to synthesize benzylic hydroxy dapagliflozin (**2**) and oxo dapagliflozin (**3**), there was a constraint for alternative synthesis that could avoid chromatographic purifications and lengthier synthetic sequence. Consequently, we proposed an alternative synthetic pathway to resolve the aforementioned issues (Scheme 3).

The proposed concise synthetic approach permitted the simultaneous synthesis of the two metabolites (**2** and **3**) from tetra acetyl dapagliflozin (**7**). The total synthesis began with the oxidation of the diarylmethane group in tetra acetyl dapagliflozin (**5**) with MnO_2[11] to afford tetra acetyl oxo dapagliflozin (**7**). The pure tetra acetyl oxo dapagliflozin (**7**) was isolated by crystallization in a mixture of MeOH and $CHCl_3$. The hydrolysis of tetra acetyl oxo dapagliflozin (**7**) with $LiOH.H_2O$ generated oxo dapagliflozin (**3**). Subsequent reduction of diaryl ketone group in oxo dapagliflozin (**3**), in the presence of $NaBH_4$ yielded benzylic hydroxy dapagliflozin (**2**).

3.4 *Preparation of desethyl dapagliflozin (**4**)*

Prior to our synthesis, two synthetic approaches were reported for desethyl dapagliflozin (**4**) from dapagliflozin (**1**) using BBr_3 (Scheme 4).[12,13] We evaluated the suitability of these synthetic routes in order to satisfy our material needs and encountered a major challenge. Both these synthetic routes yielded a mixture of α-isomer (**4a**) and β-isomer (**4**) (Scheme 4). Nevertheless, β-isomer was the required metabolite of dapagliflozin.

Considering the limitations of the reported procedures for the synthesis of **4**, it was indispensable to develop a new synthetic route to overcome the disadvantages associated with the previously described procedures. Consequently, we focused to evaluate enantioselective synthetic protocols for desethyl dapagliflozin (**4**) from dapagliflozin (**1**). Surprisingly, simple hydrolysis of aryl ethyl ether group in dapagliflozin in the presence of aqueous HBr[14] afforded desired desethyl dapagliflozin (**4**). Subsequently, the pure product was isolated by column chromatography (Scheme 5).

4. Conclusions

In summary, we successfully demonstrated the synthesis of **2**, **3** and **4**, and the metabolites of dapagliflozin. In addition, we developed a concise, efficient and alternative synthesis of **2** and **3**. A simple enantioselective deethylation of dapagliflozin was also described.

Supplementary Information (SI)

^{1}H NMR, ^{13}C NMR and HRMS spectra of all compounds are available at www.ias.ac.in/chemsci.

Acknowledgements

We are grateful to the management of Aurobindo Pharma Limited., for the generous support and constant encouragement. We are also thankful to the chemical and analytical research departments for their co-operation.

References

1. Meng W, Bruce A E, Alexandra A N, Peggy J M, Manorama P, Ravindar N G, Gang W, Philip M S, Eamonn P M, Scott A B, Robert Z, Prashant P D, Annie P, Deborah L H, Nathan M, Joseph R T, Mary T O, William G H, Ashish K, Lorell D, James G R, Aiying W, Songping H, John R W, Evan B J, Oliver P F, Jean M W and William N W 2008 Discovery of dapagliflozin: a potent, selective renal sodium-dependent glucose cotransporter 2 (SGLT2) inhibitor for the treatment of type-2 diabetes *J. Med. Chem.* **51** 1145
2. Fura A 2006 Role of pharmacologically active metabolites in drug discovery and development *Drug Discov. Today* **11** 133
3. Obermeier M, Yao M, Khanna A, Koplowitz B, Zhu M, Li W, Komoroski B, Kasichayanula S, Discenza L, Washburn W, Meng W, Ellsworth B A, Whaley J M and Humphreys W G 2010 In vitro characterization and pharmacokinetics of dapagliflozin (BMS-512148), a potent sodium-glucose co transporter type II inhibitor, in animals and humans *Drug Metab. Dispos.* **38** 405
4. Timothy P R, Michael J G, Evan B J, Thomas E D, Craig F, Francis L, Jian C, Tai W, Jean M W and Mark T 2014 Carcinogenicity risk assessment supports the chronic safety of dapagliflozin, an inhibitor of sodium-glucose co-transporter 2, in the treatment of type 2 diabetes mellitus *Diabetes Ther.* **5** 73
5. Japan Pharmaceutical interview form, 2015, 5th edition.
6. Seed B, Lv B, Roberge J Y, Chen Y, Peng K, Dong J, Xu B, Du J, Zhang L, Tang X, Xu G, Feng Y and Xu M 2015 Preparation of deuterated benzyl-benzene glycosides having an inhibitory effect on sodium-dependent glucose co-transporter U.S. Patent 9061060B2
7. TLC Pharmaceutical Standards Ltd. http://www.tlcstandards.com/ProductsList.aspx?key=DAPAGLIFLOZIN accessed on: 12th July, 2019
8. Bruce E, William N W, Philip M S, Gang W and Wei M 2003 C-aryl glucoside SGLT2 inhibitors and method U.S. Patent 6,515,117 B2
9. Djerassi C 1948 Brominations with N-bromosuccinimide and related compounds. The Wohl–Ziegler reaction *Chem. Rev.* **43** 271
10. Ghosh S and Ghatak U R 1988 Carbon–carbon bond formation and annulation reactions using trimethyl and triethylorthoformates *Proc. India Acad. Sci. (Chem. Sci)* **100** 235
11. Ernest F P and Stuart P S 1963 Oxidation by solids II. The preparation of either tetraarylethanes or diaryl ketones by the oxidation of diarylmethanes with manganese dioxide *J. Org. Chem.* **28** 638
12. Xu B, Feng Y, Cheng H, Song Y, Lv B, Wu Y, Wang C, Li S, Xu M, Du J, Peng K, Dong J, Zhang W, Zhang T,

Zhu L, Ding H, Sheng Z, Welihinda A, Roberge J Y, Seed B and Chen Y 2011 C-Aryl glucosides substituted at the 4′-position as potent and selective renal sodium-dependent glucose co-transporter 2 (SGLT2) inhibitors for the treatment of type 2 diabetes *Bioorg. Med. Chem. Lett.* **21** 4465

13. Chen Y, Cheng H, Li S, Wu Y, Feng Y, Lv B, Xu B, Seed B, Hadd M J, Du J, Wang C and Roberge J Y 2009 Benzylbenzene derivatives and methods of use PCT Int. Appl. 2009026537A1
14. Ranu B C and Bhar S 1996 Dealkylation of ethers. A review *Org. Prep. Proced. Int.* **28** 371