

Improved preparation of C-aryl glucoside SGLT2 inhibitors

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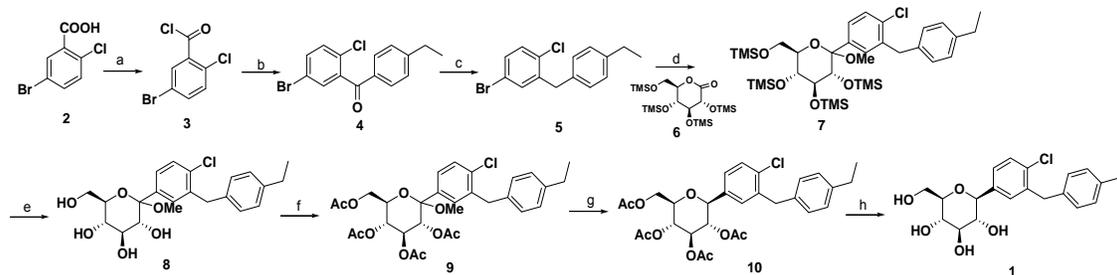
Abstract

A novel approach for the preparation of (2S,3R,4R,5S,6R)-2-(3-(4-ethylbenzyl)-4-chlorophenyl)-6-(hydroxymethyl)-tetrahydro-2H-pyran-3,4,5-triol **1** is developed. The target compound *via* six steps is synthesized from 5-bromo-2-chlorobenzoic acid and the isomers of undesired *ortho*-products were avoided during the preparation.

Keywords: Type 2 diabetes, sodium glucose co-transporter 2, inhibitor, preparation

Introduction

Sodium glucose co-transporter 2 (SGLT2) plays a key role in maintaining glucose equilibrium in the human body.¹ Much attention has been given to SGLT2 as a molecular target to directly induce glucose excretion and to safely normalize plasma glucose in the treatment of type 2 diabetes.² The reformative subset of SGLT2 inhibitors to be explored was the carbon glycosides in which the bond between the glucose and aglycone is a carbon-carbon bond.^{3,4} Recently, it was reported that (2S,3R,4R,5S,6R)-2-(3-(4-ethylbenzyl)-4-chlorophenyl)-6-(hydroxymethyl)-tetrahydro-2H-pyran-3,4,5-triol **1** may be advancing to clinical development to directly induce glucose excretion and to safely normalize plasma glucose in the treatment of type 2 diabetes. The reported synthetic route of **1** was shown in Scheme 1.^{5,6}

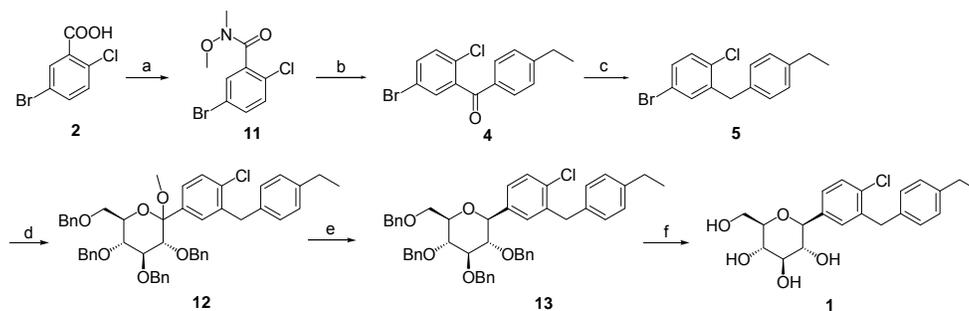


Scheme 1. Reagents and conditions: (a) SOCl_2 , dichloromethane (DCM), r.t.; (b) ethylbenzene, AlCl_3 , -15°C ; (c) Et_3SiH , TFA, $\text{CF}_3\text{SO}_3\text{H}$, reflux; (d) THF, toluene, *n*-BuLi, -55°C ; (e) CH_3OH , $\text{CH}_3\text{SO}_3\text{H}$, 20°C ; (f) diiso-propylethylamine, DMAP, Ac_2O , 20°C ; (g) DCM, Et_3SiH , $\text{BF}_3\cdot\text{Et}_2\text{O}$, -20°C ; (h) LiOH, CH_3OH , 20°C .

Results and Discussion

The important intermediate **4** was prepared by Friedel-Crafts reaction but the selectivity of the *ortho*-position and *para*-position of the reaction was unsolved according to the procedure of William et al.⁶ In addition, compound **7** was synthesized by coupling reaction between **5** and **6** in unsatisfactory yield and the synthetic route needed eight steps which limited a large scale production.⁶

In this report a novel synthetic route was employed to prepare **4** by the reactions of Weinreb and Grignard at the first and second steps which the isomers of undesired *ortho*-products were avoided (Scheme 2). Then **5** was transformed to D-glucopyranoside **12** in excellent yield. Treatment of **12** with Et_3SiH and $\text{BF}_3\cdot\text{Et}_2\text{O}$ in DCM for 5 h afforded the compound **13**, which was hydrogenated under 0.1MPa hydrogen at room temperature to produce **1** in about 70.7% overall yield. The structure of the target compound was confirmed by elemental analysis, ^1H NMR, ^{13}C NMR and MS.

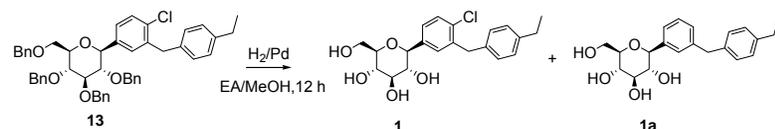


Scheme 2. Reagents and conditions: (a) DMF/CDI/ Et_3N / N-methoxymethanamine hydrochloride, 30°C ; (b) THF/(4-ethylphenyl)magnesium bromide, 30°C ; (c) Et_3SiH / TFA/ $\text{CF}_3\text{SO}_3\text{H}$, reflux; (d)

(1) THF/toluene, *n*-BuLi, -55°C; (2) (3*R*,4*S*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-pyran-2-one, -78°C; (e) DCM/CH₃CN/Et₃SiH/BF₃•Et₂O, below 0°C; (f) EA/MeOH/H₂; 0.1MPa, 25°C.

In order to demonstrate the influence of solvent, a series of solvents were used in this protocol for deprotection of **13** and the results are shown in Table 1. A mixture of **1** and **1a** were found in benzene, toluene, chlorobenzene and 1,2-dichlorobenzene during the deprotection reaction. However, when 1,2-dichlorobenzene was added (20 equimolar amounts) to the reaction system, by-product **1a** could not be detected by LC-MS (Table 1, Entry 4). Mechanically, the possible reason is in the existence of 1,2-dichlorobenzene in this protocol, its chlorine group can be reduced at first and the resultant hydrochloride can gradually inhibit reduction of the chlorine group of **1**.

Table 1. Synthesis of compound **1** by deprotection of benzyl group



Entry	Solvent	Equimolar amounts	Compound 1 Purity(%) ^a	By-product 1a Purity(%) ^a
1	Benzene	10	41.50	58.00
		20	40.50	58.50
2	Toluene	10	41.00	58.60
		20	40.30	58.40
3	Chlorobenzene	10	45.05	54.05
		20	49.40	49.50
4	1,2-Dichlorobenzene	10	87.32	10.32
		20	99.03	0

^aDetermined on HPLC analysis of crude products before purification.

In conclusion, a more novel, and effective approach for the synthesis **1** in about 71% overall yield was found. The undesired *ortho*-products were avoided for the preparation of intermediate **4** and two synthetic steps were reduced.

Experimental Section

General Procedures. All the reagents were obtained from suppliers and were not purified. Melting points were measured on a PHMK179-2454 apparatus. Elemental analysis (C, H, N) was

determined with a Perkin-Elmer 240c instrument, their results were found to be in good agreement ($\pm 0.3\%$) with the calculated values. ^1H NMR was measured on a Bruker AM-400MHz spectro-meter, ^{13}C NMR was measured on a Bruker AM-300MHz spectro-meter. EI mass spectral measurement was carried out on a Waters alliance 2695 with acetonitrile and water as a mobile phase.

The **5** was synthesized according to Ref. 6. The **4**, **5**, are known compounds, which were characterized by Elemental analysis, ^1H NMR, EI mass spectral data compared with literature data reports.⁶

5-Bromo-2-chloro-N-methoxy-N-methylbenzamide (11). To a solution of 5-bromo-2-chlorobenzoic acid (23.5 g, 100 mmol) in 100 mL anhydrous DMF, *N,N'*-Carbonyldiimidazole (CDI) (18.3 g, 130 mmol) was added in portions. After all of the CDI was added, Et_3N (13.1 g, 130 mmol) was added to the mixture, stirred at 25°C for 1 h, then *N*-methoxymethanamine hydrochloride (12.7 g, 130 mmol) was added, the reaction mixture was stirred at 25°C for 10 h, then the mixture was poured into 1000 mL water and extracted with ether (1000 mL), the organic phase was separated and washed with water, brine and dried with anhydrous Na_2SO_4 , then was concentrated in *vacuo* to give a white solid (27.80 g, 99.8%). mp: $78\text{--}80^\circ\text{C}$. ^1H NMR (400 MHz, CDCl_3): $\delta=7.474$ (m, 2H), 7.286 (d, 1H, $J=8.0$ Hz), 3.572 (s, 3H), 3.345 (s, 3H); ^{13}C NMR (300MHz, CDCl_3): $\delta=167.05$, 137.32, 133.59, 131.38, 130.85, 129.88, 120.48, 61.85, 32.63; MS [EI]: m/z 280 [M^+]. Anal. Calcd for $\text{C}_9\text{H}_9\text{BrClNO}_2$: C 38.81, H 3.26, N 5.03; Found C 38.76, H 3.27, N 5.01.

(5-Bromo-2-chlorophenyl)(4-ethylphenyl)methanone (4). To a solution of **11** (13.9 g, 50 mmol) in anhydrous THF (100 mL), (4-ethylphenyl)magnesium bromide (1 M in THF, 60 mL) was added dropwise to the reactor below 30°C . The reaction mixture was stirred at 25°C for 2 h, then the reaction was quenched with saturated NH_4Cl , extracted with ethyl acetate (EA), washed with water, brine and dried with anhydrous Na_2SO_4 , and concentrated in *vacuo* to give an oil (16.89 g, 98.2%). ^1H NMR (400 MHz, CDCl_3) $\delta=7.73$ (d, 2H, $J=8.0$ Hz), 7.54 (dd, 1H, $J=2.4$ Hz, $J=8.8$ Hz), 7.49 (d, 1H, $J=2.4$ Hz), 7.33 (d, 2H, $J=8.4$ Hz), 7.29 (s, 1H), 2.73 (q, 2H, $J=7.6$), 1.272 (t, 3H, $J=7.6$ Hz); ^{13}C NMR (300MHz, CDCl_3): $\delta=193.0$, 149.2, 141.0, 136.0, 133.7, 134.3, 132.3, 129.8, 128.0, 128.7, 119.9, 29.1, 16.4; MS [EI]: m/z 323 [M^+]; Anal. Calcd for $\text{C}_{15}\text{H}_{12}\text{BrClO}$: C 55.67, H 3.74; Found C 55.61, H 3.75.

2-(4-Ethylbenzyl)-4-bromo-1-chlorobenzene (5). ^1H NMR (400 MHz, CDCl_3) $\delta=7.24\text{--}7.31$ (m, 3H), 7.176 (d, 2H, $J=8.0$ Hz), 7.13 (d, 2H, $J=8.4$ Hz), 4.055 (s, 2H), 2.664 (q, 2H, $J=7.6$ Hz), 1.267 (t, 3H, $J=7.6$ Hz); ^{13}C NMR (300MHz, CDCl_3): $\delta=142.9$, 141.6, 136.2, 134.2, 133.7, 131.4, 131.1, 129.4, 128.6, 121.0, 39.2, 29.0, 16.1; MS [EI]: m/z 309 [M^+]; Anal. Calcd for $\text{C}_{15}\text{H}_{14}\text{BrCl}$: C 58.19, H 4.56; Found C 58.11, H 4.57.

(3R,4S,5R,6R)-2-(3-(4-Ethylbenzyl)-4-chlorophenyl)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-2-methoxy-tetrahydro-2H-pyran (12). To a stirred -78°C solution of **5** (3.03 g, 9.8 mmol) in 15 mL of 1:2 anhydrous THF/toluene was slowly added 2.5 M *n*-BuLi (4.4 mL, 11 mmol) in hexane to maintain the temperature below -55°C .

After stirring for 10 min, this solution was transferred to a stirred -78°C solution of (3R,4S,5R,6R)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-pyran-2-one (5.28g, 9.8 mmol) in toluene (15 mL) below -55°C . The solution was stirred for 30 min at -78°C , quenched by addition of 10 mL of MeOH containing methanesulfonic acid (0.7 mL), the mixture was stirred at 20°C overnight. The reaction was quenched with saturated NaHCO_3 and extracted with EA. The organic phase was separated and washed with brine, dried (anhydrous Na_2SO_4) and concentrated in *vacuo* to give an oil, crystallization from EtOH (14mL) to get a light brown crystals $\square 6.22\text{g}$, 81% \square . mp: $97\text{--}99^{\circ}\text{C}$; ^1H NMR(400MHz, CDCl_3): $\delta=7.49$ (d, 1H, $J=1.5\text{Hz}$), 7.35~7.40 (m, 6H), 30~7.35 (m, 9H), 7.21~7.27 (m, 5H), 7.08 (d, 4H, $J=1.2\text{Hz}$), 7.04 (d, 2H, $J=8.4\text{Hz}$), 4.89~4.97 (m, 3H), 4.59~4.69 (m, 3H), 4.51 (d, 1H, $J=10.8\text{Hz}$), 4.14~4.21 (m, 2H), 3.98 (d, 1H, $J=8.4\text{Hz}$), 3.94 (s, 1H), 3.77~3.87 (m, 4H), 3.36 (d, 1H, $J=9.6\text{Hz}$), 3.11 (s, 3H), 2.61 (q, 2H, $J=7.6\text{Hz}$), 1.22 (t, 3H, $J=7.6\text{Hz}$); ^{13}C NMR (300MHz, CD_3OD): $\delta=139.0$, 138.8, 137.7, 130.9, 129.7, 129.1, 129.0, 128.9, 128.8, 128.6, 128.4, 128.3, 128.2, 128.1, 128.0, 127.4, 101.5, 85.8, 83.9, 78.8, 77.9, 77.5, 76.5, 76.2, 75.6, 73.9, 72.6, 69.2, 49.6, 39.4, 28.8, 16.0; MS [EI]: m/z 806 [$\text{M}^+ + \text{Na}^+$]; 801 [$\text{M}^+ + \text{H}_2\text{O}$]; 752 [$\text{M}^+ - \text{OMe}$]; Anal. Calcd for $\text{C}_{50}\text{H}_{51}\text{ClO}_6$: C 76.66, H 6.56; Found C 76.57, H 6.57.

(2S,3S,4R,5R,6R)-2-(3-(4-ethylbenzyl)-4-chlorophenyl)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2H-pyran (13). A stirred solution of **12** (3.92 g, 5 mmol) in 20mL solution ($\text{DCM}/\text{CH}_3\text{CN}=1:1$; v/v) containing Et_3SiH (1.16 g, 9.97 mmol) was cooled to -20°C . Prior to addition of $\text{BF}_3\cdot\text{Et}_2\text{O}$ (1.1 g, 7.7 mmol) below 0°C , and then, the reaction was stirred for 5 h below 25°C . The saturated solution of NaHCO_3 was added until pH to above 7. The organic phase was separated, and the water phase was extracted with $3\times 60\text{mL}$ DCM, the combined organic phase was washed with saturated NaHCO_3 , dried with anhydrous Na_2SO_4 , and concentrated in *vacuo* to give an oil. $\square 3.57\text{g}$, 95% \square . ^1H NMR (400MHz, CDCl_3): $\delta=7.41$ (m,1H), 7.27~7.37 (m, 16H), 7.20~7.26 (m,4H), 7.05~7.15 (m,4H), 6.93 (d, 2H, $J=8.4\text{Hz}$), 4.77~4.97 (m, 3H), 4.55~4.69 (m, 3H), 4.40~4.51 (m, 1H), 4.04~4.21 (m, 4H), 3.75~3.89 (m, 4H), 3.42~3.62 (m, 2H), 2.61(q, 2H, $J=7.6\text{Hz}$), 1.22 (t, 3H, $J=7.6\text{Hz}$); ^{13}C NMR (300MHz, CD_3OD) $\delta=142.0$, 138.6, 138.2, 138.1, 137.5, 136.5, 130.6, 129.5, 129.0, 128.7, 128.4, 128.3, 128.2, 128.0, 127.7, 126.7, 86.7, 84.1, 80.9, 79.4, 78.3, 77.4, 76.6, 75.7, 75.1, 75.0, 73.4, 69.0, 38.8, 28.4, 15.5; MS [EI]: m/z 776 [$\text{M}^+ + \text{Na}^+$]; 771 [$\text{M}^+ + \text{H}_2\text{O}$]; 753 [M^+]; Anal. Calcd for $\text{C}_{49}\text{H}_{49}\text{ClO}_5$: C 78.12, H 6.56; Found C 78.05, H 6.57

(2S,3R,4R,5S,6R)-2-(3-(4-Ethylbenzyl)-4-chlorophenyl)-6-(hydroxymethyl)-tetrahydro-2H-pyran-3,4,5-triol (1). To a solution of **13** (2.51 g, 3.33mmol) in 2:3 EA/MeOH (30 mL), 0.25g Palladium on carbon and 10mL 1,2-Dichlorobenzene was added in turn. The air of reactor is removed by argon, then the 0.1MPa H_2 was added for 12 h at 25°C . The solvent was filtrated, filter cake was washed by EA, the filtrate was concentrated in *vacuo* to give an oil. The oil was purified with silicon column to get a glassy off white solid (1.24g, 95%). mp: $46\text{--}48^{\circ}\text{C}$, Yield 96%, ^1H NMR (400 MHz, CD_3OD , δ ppm) :7.34 (m, 2H), 7.263 (dd, 1H, $J=2.0$ Hz, $J=8.0$ Hz), 7.08 (m, 4H), 4.056 (m, 3H), 3.86 (d, 1H, $J=12.4$ Hz), 3.67 (m, 1H), 3.37-3.46 (m, 3H), 3.264 (d, 1H, $J=8.8$ Hz), 2.578 (q, 2H, $J=7.6$ Hz), 1.186 (t, 3H, $J=7.6$ Hz); ^{13}C NMR(300 MHz, CD_3OD , δ ppm): 143.2, 140.0, 139.7, 138.1, 134.5, 131.98, 130.1, 129.8, 128.8, 128.2, 82.8, 82.14, 79.7, 76.4, 71.9,

63.1, 39.7, 29.4, 16.25; MS [ESI]: m/z 393 [M^+]; 410 [$M^+ + H_2O$]; 786 2[M^+]; Anal. Calcd for $C_{21}H_{25}ClO_5$: C 64.20, H 6.41; Found C 64.11, H 6.43.

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