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ORIGINAL PAPER

A new and improved process for *C*-aryl glucoside SGLT2 inhibitors

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Abstract A practical and scalable synthesis of *C*-glycosides identified as highly potent sodium-dependent glucose transporter 2 (SGLT2) inhibitors is described. Highlights of the synthetic process are a concise, ten-step synthesis of a structurally complex active pharmaceutical ingredient from a known intermediate via a selective and quantitative addition of an aryl species to the Weinreb amide, and the isomers of undesired *ortho*-products were avoided during the preparation. The chemistry developed has been applied to prepare SGLT2 inhibitors without recourse to chromatography.

Keywords Glycosides · Halogenation · Heterocycles

Introduction

Sodium glucose co-transporter 2 (SGLT2) plays a key role in maintaining glucose equilibrium in the human body [1, 2]. Much attention has been given to SGLT2 as a molecular target to directly enhance glucose excretion and to safely normalize plasma glucose in the treatment of type 2 diabetes [3, 4]. A promising subset of SGLT2 inhibitors explored was the carbon glycosides in which the bond between the glucose and aglycone is a carbon–carbon bond [5, 6]. It was reported that (1*S*,3′*R*,4′*R*,5′*S*,6′*R*)-5-chloro-6-[(4-ethylphenyl)methyl]-3′,4′,5′,6′-tetrahydro-6′-(hydroxymethyl)-spiro[isobenzofuran-1(3*H*),2′-[2*H*]pyran]-3′,4′,5′-triol (**12**) may be advancing to clinical development to directly increase glucose excretion and to safely normalize plasma glucose in the treatment of type 2 diabetes [7–16]. We were recently required to execute several hundred grams scale delivery of this active pharmaceutical ingredient (API). In this paper we report the development of a safe and scalable synthetic route that enabled the production of the required quantity of the target molecule.

Two synthetic routes have been used to synthesize **12**. One method is shown in Scheme 1. The key intermediate **7** was prepared by a Friedel–Crafts reaction, but the selectivity for the *para*-position over the *ortho*-position was low. In addition, compound **11** was synthesized by a coupling reaction between **10** and **13** in an unsatisfactory yield and the synthetic route required eleven steps, which was unsuitable for a large scale production [7–12]. For the other reported procedure, the target compound was synthesized from 1-bromo-4-chloro-2,5-dimethylbenzene with an unsatisfactory overall yield of 6 %. The synthetic sequence needed 12 steps and was not feasible for industrial scale-ups [13–16].

Recently, we have reported a new synthetic route to **12** on a very small scale via a Suzuki cross-coupling reaction between a benzylic halide and 4-ethylphenylboronic acid [17]. A set of experiments were performed in order to optimize the reaction conditions for this heterogeneous reaction. Nevertheless, the complexity of the product mixture obtained and the difficulty in purification of the product, which required chromatography and took long times for the reaction to reach completion, and 3500 ppm

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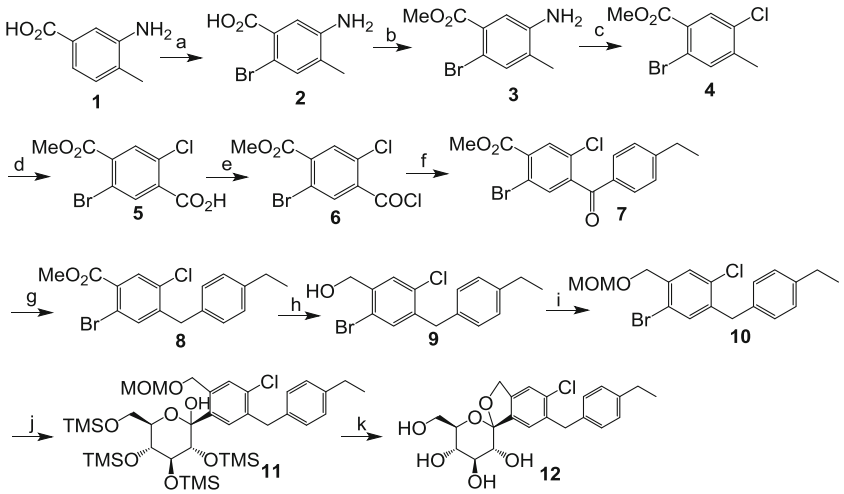
Scheme 1



(a) NBS, DMF, 5 °C; (b) $SOCl_2$, MeOH, reflux; (c) $NaNO_2$, HCl, $CuCl_2$, 1,4-dioxane, H_2O, 0 °C; (d) $KMnO_4$, *t*-BuOH, 18-crown-6, H_2O, reflux; (e) $(COCl)_2$, DMF, DCM, r.t.; (f) $AlCl_3$, ethylbenzene, DCM, -5 °C; (g) Et_3SiH, CF_3SO_3H, TFA, reflux; (h) $NaBH_4$, MeOH, THF, reflux; (i) MOMCl, DIPEA, DCM, r.t.; (j) *n*-BuLi, THF, toluene, (3*R*,4*S*,5*R*,6*R*)-3,4,5-tris(trimethylsilyloxy)-6-[(trimethylsilyloxy)methyl]-tetrahydropyran-2-one (**13**), -78 °C; (k) CH_3SO_3H, MeOH, r.t..

of Pd, 400 ppm of iron impurities were also found, requiring that this liability to be addressed before larger scale production could be attempted. Moreover, the more high cost meant that this route would not be viable to manufacture kilogram quantities of API in a short time frame.

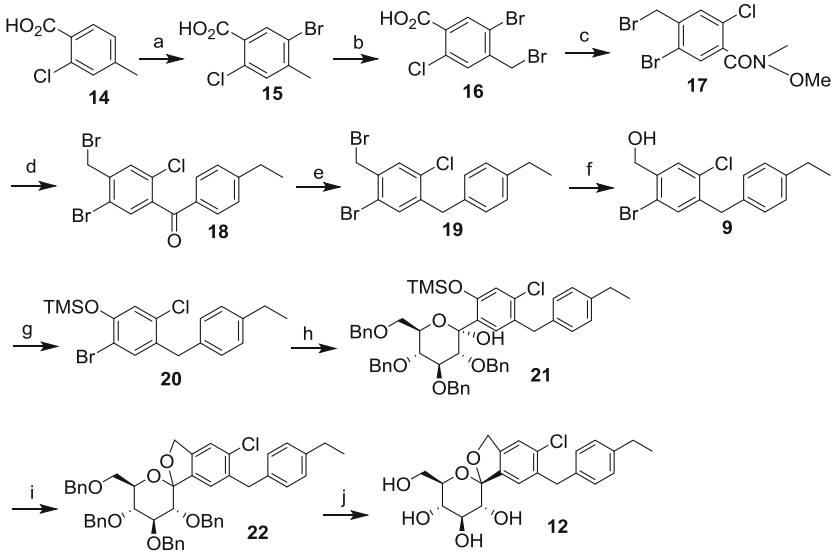
Results and discussion

As shown in Scheme 2, a practical and commercial process of preparing **12** was designed and studied by us. Compound **15** was readily prepared by reacting *N*-bromosuccimide (NBS) with the benzoic acid **14** in DMF. The treatment of **15** with NBS in the presence of azodiisobutyronitrile (AIBN) in CCl_4 gave **16**. Then **18** was prepared by the reactions of Weinreb amide **17** and Grignard reagent which the isomers of undesired *ortho*-products were avoided. Compound **18** was treated with Et_3SiH in trifluoroacetic acid to afford **19**, which was treated with NaOH in MeOH to give **9**. The treatment of **9** with trimethylsilyl chloride in THF gave silyl ether **20**, which was transformed to the glucopyranoside **22** in an excellent yield. Compound **22** was hydrogenated under 0.1 MPa of hydrogen in the presence of Pd/C at room temperature to produce **12** in about 31 % overall yield.

A screen of several solvents was carried out in the synthesis of **18**. For the coupling step diethyl ether remained the best solvent, with 2-methyltetrahydrofuran and THF as good alternatives. Since diethyl ether is not appropriate for scale-up, THF was selected as the most favorable solvent for both steps because it gave reasonably high yields and is commercially available in large quantities.

Moreover, the formation of the Grignard reagent **23** in THF with magnesium was straightforward with the aid of 1,2-dibromoethane as an initiator and it was used directly in the next step. This freshly prepared Grignard reagent

Scheme 2



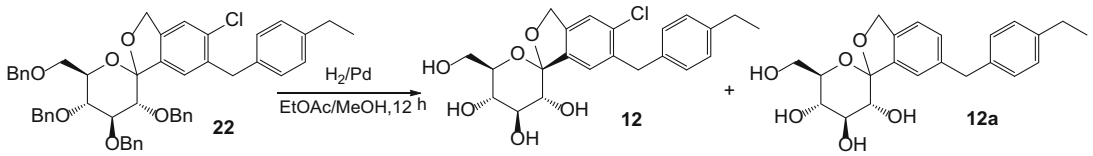
(a) DMF, NBS, 25 °C (94%); (b) CCl_4, NBS, AIBN, reflux (76%); (c) DMF / CDI / Et_3N / *N*-methoxymethanamine hydrochloride, 25 °C (98%); (d) THF / (4-ethylphenyl)magnesium bromide (**23**), 25 °C (91%); (e) Et_3SiH / TFA / CF_3SO_3H, reflux (85%); (f) MeOH, NaOH, 25 °C (86%); (g) THF, trimethylchlorosilane, r.t. (95%); (h) THF/toluene, (3*R*,4*S*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydropyran-2-one (**24**), -78 °C; (i) THF/toluene, $MeSO_3H$, r.t. (79%, two steps); (j) 10% Pd-C, MeOH, H_2 (0.1 MPa), 25 °C, 88%.

was added to a THF solution of **17** at 25 °C, and after quench and workup, a quantitative crude ketone **18** was obtained in a satisfactory yield.

In order to study the solvent effect in the deprotection reaction of the benzyl groups in **22**, a series of solvents were screened and the results are shown in Table 1. A mixture of **12** and **12a** were found when benzene, toluene, chlorobenzene, and 1,2-dichlorobenzene were used as solvents in the deprotection reaction. However, when 20 equiv. Of 1,2-dichlorobenzene was added in the reaction mixture, by-product **12a** could not be detected by LC–MS (Table 1, entry 4). It was also obtained in an excellent yield.

The final API exists as an amorphous foam that was inappropriate for isolation and purification by recrystallization. Herein, a simple and industrial feasible method for the isolation and purification of compound **12** was developed (Scheme 3). The solution of crude **12** (Scheme 1) was dissolved in CH_2Cl_2 and treated with Ac_2O followed by cooling and drying to provide **25**, then treatment of **25** in turn with LiOH and methanesulfonic acid in THF gave the target compound **12** in an excellent yield, and the purity of **12** was increased from 86.2 to 99.1 % according to the tested result of HPLC. Furthermore, we were also pleased to find that the residual palladium levels were reduced to <10 ppm in the isolated material.

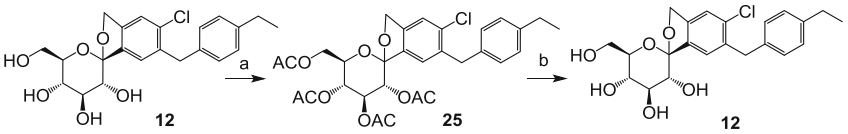
Table 1 Synthesis of compound **12** by deprotection of benzyl group



Entry	Solvent	Equimolar amounts	Compound **12** yield/%[a]	By-product **12a** yield/%[a]
1	Benzene	10	48	51
		20	47	52
2	Toluene	10	49	50
		20	48	50
3	Chlorobenzene	10	71	27
		20	80	19
4	1,2-Dichlorobenzene	10	91	7
		20	99	0

[a] Determined by HPLC analysis of crude products before purification

Scheme 3



(a) CH_2Cl_2, Ac_2O, r.t.; (b) THF/MeOH/H_2O, LiOH, $MeSO_3H$, r.t..

Conclusion

In conclusion, a more efficient synthetic route for the synthesis of **12** was developed. The overall yield of the sequence was about 31 % and the undesired *ortho*-products in the coupling reaction between the two aryl pieces in the previous reports were avoided using the current method.

Experimental

All the reagents were obtained from suppliers and were not purified. Elemental analysis (C, H, N) was determined with a Perkin-Elmer 240c instrument, their results were found to be in good agreement (±0.3 %) with the calculated values. ^{1}H NMR and ^{13}C NMR were measured on a Bruker AM 300 MHz spectrometer. EI mass spectral measurement was carried out on a Waters alliance 2695 with acetonitrile and water as a mobile phase.

*5-Bromo-2-chloro-4-methylbenzoic acid (**15**, $C_8H_6BrClO_2$)*

To a solution of 0.75 kg 2-chloro-4-methylbenzoic acid (4.41 mol) in 7 dm^3 DMF at 80 °C was slowly added 0.94 kg NBS (5.3 mol) to maintain the temperature below 86 °C, and the reaction mixture was stirred for 16 h at 80 °C, and solvents were removed by rotaevaporation, cooled to room temperature, then de-ionized water was added, and then the resultant mixture was extracted with EtOAc, washed with de-ionized water and brine, dried with anhydrous sodium sulfate, and concentrated in vacuo. Subsequently it was recrystallized from 3 dm^3 MeOH to give colorless crystals (1.03 kg, 94 %). M.p.: 205–207 °C; IR (KBr): $\overline{\nu} = 3878, 2951, 1749, 1482$ cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.23$ (s, 1H), 7.52 (s, 1H), 2.38 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 165.8, 145.6, 135.2, 133.9, 131.2, 130.6, 122.6, 25.3$ ppm; MS: $m/z = 248$ (M^+), 271 ($[M + Na]^+$).

*5-Bromo-4-(bromomethyl)-2-chlorobenzoic acid (**16**, $C_8H_5Br_2ClO_2$)*

To a solution of 1.03 kg **15** (4.15 mol) in 12 dm^3 CCl_4 was added 0.89 kg NBS (5 mol) under argon, then 70 g AIBN (0.42 mol) was added under argon, and the mixture was stirred at reflux for 15 h, then the mixture was cooled to room temperature and filtered, and the filtrate was washed

with de-ionized water and brine, concentrated in vacuo to give a yellow oil (1.03 kg, 76 %). IR (KBr): $\overline{\nu} = 3894$, 2962, 1758, 1498 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.32$ (s, 1H), 7.48 (s, 1H), 4.62 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 165.7$, 144.8, 135.6, 134.9, 134.7, 130.8, 122.5, 33.4 ppm; MS: $m/z = 326$ (M^+), 349 ($[M + Na]^+$).

*5-Bromo-4-(bromomethyl)-2-chloro-N-methoxy-N-methylbenzamide (**17**, $C_{10}H_{10}Br_2ClNO_2$)*

To a solution of 1.03 kg **16** (3.2 mol) in 8 dm^3 anhydrous DMF, 0.67 kg *N*,*N*′-carbonyldiimidazole (CDI, 4.1 mol) was added in portions. After all of the CDI was added, 0.42 kg Et_3N (4.1 mol) was added to the mixture, stirred at 25 °C for 1 h, then 0.4 kg *N*-methoxymethanamine hydrochloride (4.1 mol) was added, the reaction mixture was stirred at 25 °C for 10 h. The product solution was distilled under vacuum, then the residual was poured into ice water and extracted with EtOAc, the organic phase was separated and washed with de-ionized water, concentrated in vacuo. Subsequently it was dried and recrystallized from 2.5 dm^3 MeOH to get a white solid (1.15 kg, 98 %). M.p.: 161–163 °C; IR (KBr): $\overline{\nu} = 2956$, 1782, 1640, 1488, 1193 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.10$ (s, 1H), 7.55 (s, 1H), 4.42 (s, 2H), 3.67 (s, 3H) 3.12 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 168.8$, 142.2, 134.6, 132.9, 131.7, 131.4, 68.6, 64.1, 35.6, 32.4 ppm; MS: $m/z = 369$ (M^+), 392 ($[M + Na]^+$).

*[5-Bromo-4-(bromomethyl)-2-chlorophenyl](4-ethylphenyl)methanone (**18**, $C_{16}H_{13}Br_2ClO$)*

To a stirred suspension of 88.51 g magnesium (3.6 mol) in 2.8 dm^3 anhydrous THF was added a solution of 2.6 cm^3 1,2-dibromoethane (0.03 mol) and 629 g 1-bromo-4-ethylbenzene (3.4 mol) in 0.8 dm^3 THF dropwise over 20 min at 20 °C. When the temperature was 26 °C, the reaction was placed in a cold-water bath, and the temperature continued to increase to 32 °C; ice was added to the water bath to maintain the temperature between 40 and 48 °C with vigorous stirring (CAUTION: this experimental is designed to avoid a runaway reaction, but a delay in initiation may cause the solvent to boil). After the reaction temperature declined to 20 °C, the water bath was removed, and the mixture was stirred at 20 °C for an additional 20 min to give the Grignard reagent, which was immediately used in the next step.

To a solution of 1.15 kg **17** (3.1 mol) in 10 dm^3 anhydrous THF, the air of the reactor was removed by argon, and above freshly prepared Grignard reagent (4-ethylphenyl)magnesium bromide (1 M in THF, 3.4 dm^3) was added dropwise slowly to the reactor below 30 °C. The reaction mixture was stirred at 25 °C for 2 h, and the reaction was quenched with saturated NH_4Cl, extracted with ethyl acetate (EtOAc), washed with de-ionized water, then the organic layer was dried over sodium sulfate, and drying agent was filtered. The residue was distilled under reduced pressure, and the fraction boiling at 196–202 °C/2 mm Hg was collected to give **18** (1.17 kg, 91 %) as a colorless oil. IR (KBr): $\overline{\nu} = 2916$, 2863, 1701, 1459 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.86$ (s, 1H), 7.72 (d, $J = 8.0$ Hz, 2H), 7.50 (s, 1H), 7.01 (d, $J = 8.0$ Hz, 2H), 4.61 (s, 2H), 2.58 (q, $J = 7.8$ Hz, 2H), 1.23 (t, $J = 7.8$ Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 197.1$, 148.1, 142.6, 138.9, 135.7, 135.4, 134.8, 130.8, 130.1, 128.1, 121.8, 33.4, 28.8, 14.9 ppm; MS: $m/z = 414$ (M^+), 437 ($[M + Na]^+$).

*1-Bromo-2-(bromomethyl)-4-chloro-5-(4-ethylbenzyl)benzene (**19**, $C_{16}H_{15}Br_2Cl$)*

To a stirred solution of 1.17 kg **18** (2.8 mol) and 0.69 kg Et_3SiH (5.9 mol) in 7 dm^3 TFA, 2.6 g CF_3SO_3H (0.017 mol) was added dropwise slowly to the reactor below 45 °C. Within minutes the temperature increased causing the solution to reflux. After 1 h at reflux, 40 g Et_3SiH was added, and the solution was stirred at reflux for 12 h. The product solution was distilled under vacuum, and the mixture was poured into water and extracted with hexane, washed with de-ionized water and concentrated in vacuo to give an oil (0.96 kg, 85 %). IR (KBr): $\overline{\nu} = 2921$, 2869, 1452 cm^{-1}; ^1H NMR (300 MHz, CD_3OD): $\delta = 7.96$ (s, 1H), 7.54 (s, 1H), 7.22 (d, $J = 7.8$ Hz, 2H), 7.11 (d, $J = 7.8$ Hz, 2H), 4.53 (s, 2H), 4.11 (s, 2H), 2.62 (q, $J = 7.8$ Hz, 2H), 1.26 (t, $J = 7.8$ Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 146.6$, 142.6, 139.1, 135.9, 135.1, 133.4, 131.8, 130.1, 129.2, 122.1, 36.5, 33.2, 28.5, 14.6 ppm; MS: $m/z = 400$ (M^+), 423 ($[M + Na]^+$).

*[2-Bromo-5-chloro-4-(4-ethylbenzyl)phenyl]methanol (**9**, $C_{16}H_{16}BrClO$)*

To a solution of 0.96 kg **19** (2.39 mol) in 10 dm^3 MeOH, 2.63 dm^3 1 M NaOH (2.63 mol) was added slowly, and the mixture was stirring for 5 h at 25 °C, and the product solution was distilled under vacuum, and the isolated oil was pouring into water. The resultant mixture was extracted with EtOAc, washed with de-ionized water and brine, dried over anhydrous sodium sulfate and concentrated in vacuo. Subsequently it was recrystallized from 3 dm^3 EtOH/hexane (v:v = 1:2) to get a white solid (0.7 kg, 86 %). M.p.: 44–46 °C; IR (KBr): $\overline{\nu} = 3679$, 2913, 2871, 1458 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.85$ (s, 1H), 7.44 (s, 1H), 7.15 (d, $J = 7.8$ Hz, 2H), 7.09 (d, $J = 7.8$ Hz, 2H), 4.53 (s, 2H), 4.05 (s, 2H), 2.63 (q, $J = 7.8$ Hz, 2H), 1.24 (t, $J = 7.8$ Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 142.5$, 141.6, 136.6, 135.8, 134.2, 132.9, 130.8, 129.6, 128.4, 121.2, 64.6, 38.6, 29.6, 16.8 ppm; MS: $m/z = 338$ (M^+), 361 ($[M + Na]^+$).

*[4-(4-Ethylbenzyl)-2-bromo-5-chlorobenzyloxy]trimethylsilane (**20**, $C_{18}H_{22}BrClOSi$)*

To a stirred 0 °C solution of 0.7 kg **9** (2.05 mol) and 3.37 kg 4-methylmorpholine (4.1 mol) in 10 dm^3 THF was added slowly 0.55 kg trimethylchlorosilane (5.1 mol), and reaction mixture was stirred for 12 h at r.t., then it was poured into ice water, extracted with EtOAc, washed with de-ionized water, brine and concentrated in vacuo to give a slightly yellow oil (0.78 kg, 95 %). IR (KBr): $\overline{\nu} = 2918$, 2867, 1451, 1083 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.85$ (s, 1H), 7.44 (s, 1H), 7.15 (d, $J = 7.8$ Hz, 2H), 7.09 (d, $J = 7.8$ Hz, 2H), 4.05 (s, 2H), 2.63 (q, $J = 7.8$ Hz, 2H), 1.24 (t, $J = 7.8$ Hz, 3H), 0.27 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 4.5$, 14.9, 28.5, 36.8, 120.9, 128.4, 129.1, 129.8, 132.9, 134.8, 137.8, 138.6, 142.3, 144.7 ppm; MS: $m/z = 396$ (M^+), 419 ($[M + Na]^+$).

*(3′R,4′S,5′R,6′R)-3′,4′,5′-Tris(benzyloxy)-6′-(benzyloxymethyl)-5-chloro-6-(4-ethylbenzyl)-3′,4′,5′,6′-tetrahydro-3H-spiro[isobenzofuran-1,2′-pyran] (**22**, $C_{50}H_{49}ClO_6$)*

To a stirred −78 °C solution of 0.78 kg **20** (1.9 mol) in 15 dm^3 anhydrous THF/toluene (1:2) was slowly added 1.9 dm^3 1.1 M *n*-BuLi (2.1 mol) in hexane to maintain the temperature below −70 °C. After stirring for 10 min at −78 °C, the reaction mixture was added dropwise a solution of 1.21 kg (3*R*,4*S*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-pyran-2-one (2.27 mol) in 8 dm^3 of toluene at −78 °C. The solution was stirred for 5 h at the same temperature prior to quenching by addition of a solution of 405 g methanesulfonic acid (4.16 mol) in 8 dm^3 of THF. The reaction was stirred for 24 h as the temperature rose to 25 °C, and then quenched with saturated $NaHCO_3$. The mixture was extracted with EtOAc, washed with water and brine, dried with anhydrous sodium sulfate, and concentrated in vacuo. Subsequently it was recrystallized from 10 dm^3 EtOH to get light yellow crystals (1.17 kg, 79 %). M.p.: 81–83 °C; IR (KBr): $\overline{\nu} = 2912$, 2831, 1467, 1291 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.52$ (d, 1H, $J = 1.5$ Hz), 7.38–7.42 (m, 6H), 7.29–7.32 (m, 9H), 7.17–7.21 (m, 4H), 7.11 (d, 4H, $J = 1.2$ Hz), 7.08 (d, 2H, $J = 8.4$ Hz), 4.88–4.96 (m, 3H), 4.72 (s, 2H), 4.56–4.67 (m, 3H), 4.46 (d, 1H, $J = 10.8$ Hz), 4.16–4.22 (m, 2H), 3.88 (d, 1H, $J = 8.4$ Hz), 3.82 (s, 1H), 3.66–3.77 (m, 4H), 3.36 (d, 1H, $J = 9.6$ Hz), 2.60 (q, 2H, $J = 7.6$ Hz), 1.24 (t, 3H, $J = 7.6$ Hz) ppm; ^{13}C NMR (100 MHz, CD_3OD): $\delta = 139.8$, 138.6, 137.6, 130.5, 129.5, 129.1, 129.0, 128.9, 128.8, 128.6, 128.4, 128.3, 128.2, 128.1, 128.0, 127.4, 101.2, 85.6, 84.9, 79.8, 78.9, 78.5, 77.5, 76.4, 75.6, 74.9, 73.6, 70.2, 62.7, 39.4, 28.8, 16.0 ppm; MS: $m/z = 780$ (M^+), 803 ($[M + Na]^+$).

*(1S,3′R,4′R,5′S,6′R)-5-Chloro-6-[(4-ethylphenyl)methyl]-3′,4′,5′6′-tetrahydro-6′-(hydroxymethyl)-spiro[isobenzofuran-1(3H),2′-[2H]pyran]-3′,4′,5′-triol (**12**, $C_{22}H_{25}ClO_6$)*

To a solution of 1.17 kg **22** (1.49 mol) in 13 dm^3 EtOAc/MeOH (2:3), 115 g palladium on carbon and 4.5 dm^3 1,2-dichlorobenzene were added in turn. The air of reactor was removed by argon, then 0.1 MPa H_2 was added for 12 h at 25 °C. The solvent was filtrated, filter cake was washed by EtOAc, and the filtrate was concentrated in vacuo to give a crude **12** as an yellow oil.

A stirred solution of crude **12** in 2 dm^3 CH_2Cl_2 containing 1.4 kg diisopropylethylamine (10.8 mol) and 1.5 g DMAP (12.3 mol) was cooled to 0 °C. Acetic anhydride (978 g, 9.57 mol) was slowly added at such a rate that the temperature did not exceed 5 °C, and then the solution was warmed to 20 °C and stirred for 10 h, and quenched with saturated $NaHCO_3$. The mixture was extracted with EtOAc, washed with water and brine, dried with anhydrous sodium sulfate and concentrated in vacuo to give an oil, crystallization from 10 dm^3 EtOH yielded the tetraacetylated *C*-glucoside **25** as a white solid. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.24$ (s, 2H), 7.09 (dd, 4H, $J = 8.4$, 13.7 Hz), 5.51–5.62 (m, 2H), 5.24 (dd, 1H, $J = 8.8$, 9.5 Hz), 5.11 (dd, 2H, $J = 12.2$, 13.0 Hz), 4.22–4.33 (m, 2H), 4.01–4.12 (m, 3H), 2.61 (q, 2H, $J = 7.6$ Hz), 2.04 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H), 1.75 (s, 3H), 1.21 (t, 3H, $J = 7.6$ Hz) ppm.

To a stirred solution of **25** in 6 dm^3 THF/MeOH (2:3) under N_2 at 25 °C was added 58.8 g $LiOH{\cdot}H_2O$ (1.47 mol) in 2 dm^3 H_2O, then the solution was stirred for 12 h at 25 °C, and 96.1 g methylsulfonic acid (1 mol) was added slowly and stirred for 1 h at 25 °C, and then quenched with saturated $NaHCO_3$. The product solution was filtered and distilled under vacuum, and the isolated oil was pouring into de-ionized water. The resultant mixture was extracted with EtOAc, washed with de-ionized water and brine, dried over anhydrous sodium sulfate and concentrated in vacuo to get **12** as a glassy off white solid (0.55 kg, 88 %). $[\alpha]_D^{20} = -26.5°$ cm^2 g^{-1} ($c = 1$, methanol); IR (KBr): $\overline{\nu} = 3858$, 2919, 2842, 1478, 1281 cm^{-1}; ^1H NMR, ^{13}C NMR, and mass spectra were identical with those described in Refs. [7–16].

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