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ORIGINAL PAPER

Convenient synthesis of [3*R*-(3α,4β,5α,6β)]-2-[7-chloro-1-(4-ethylbenzyl)-5-methyl-1*H*-indol-3-yl]-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol

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Abstract A novel and convenient approach for the preparation of [3*R*-(3α,4β,5α,6β)]-2-[7-chloro-1-(4-ethylbenzyl)-5-methyl-1*H*-indol-3-yl]-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol is developed. It has been achieved in about 72% overall yield.

Keywords Glycosides · Halogenation · Heterocycles

Introduction

Sodium glucose co-transporter 2 (SGLT2) plays a key role in maintaining glucose equilibrium in the human body [1–3]. 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 [4–7]. 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 [8–12]. It was reported that [3*R*-(3α,4β,5α,6β)]-2-[7-chloro-1-(4-ethylbenzyl)-5-methyl-1*H*-indol-3-yl]-6-(hydroxymethyl)-tetrahydro-2*H*-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 [13, 14]. The reported synthetic route of **1** is shown in Scheme 1 [14].

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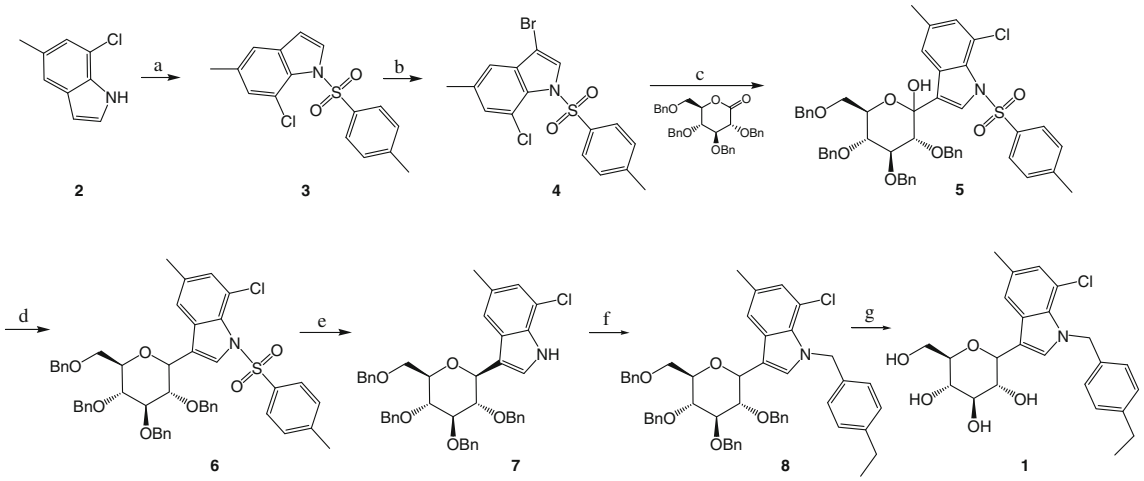
Results and discussion

The important intermediate **4** was synthesized by bromination of **3** in dichloromethane at 0 °C. However, the 3-halo- and even more so the 2-haloindoles are unstable and must be utilized as soon as they are prepared [15]. Accordingly, it is very difficult to handle compound **4** at scale up level, and it requires more attention to avoid exposure to air, especially at the time of product filtration and drying. Moreover, compound **5** was prepared by coupling reaction between **4** and [3*R*-(3α,4β,5α,6β)]-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)tetrahydropyran-2-one in unsatisfactory yield, and the synthetic route needed seven steps, which limited a large-scale production according to the procedure of Yonekubo et al. [14].

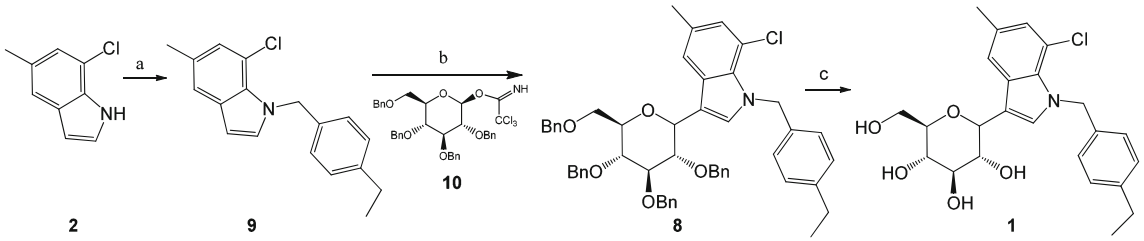
Herein we report the facile synthesis of **1** by three steps. The synthetic route is depicted in Scheme 2. Firstly, the coupling reaction between **2** and 1-(bromomethyl)-4-ethylbenzene gave **9** in the presence of cesium carbonate. Moreover, **10** can be easily prepared by treatment of [2*R*-(2α,3β,4α,5β,6α)]-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2*H*-pyran-2-ol with trichloroacetonitrile for 4 h at room temperature. Then the coupling reaction between **9** and **10** in anhydrous dichloromethane for 30 min at −78 °C afforded **8** in a high yield of 83%, which was hydrogenated under 0.1 MPa hydrogen at room temperature to produce **1** in about 72% overall yield.

In order to demonstrate the influence of solvent, a series of solvents were used in this protocol for deprotection of **8**, and the result is shown in Table 1. A mixture of **1** and **1a** was found in benzene, ethyl acetate (EtOAc), chlorobenzene, and 1,2-dichlorobenzene during deprotection reaction. However, when 20 equivalents of 1,2-dichlorobenzene were added to the reaction system, by-product **1a** could not be detected by LC–MS (Table 1, entry 4). A



(a) DMF, 4-toluenesulfonyl chloride, 25 °C; (b) dichloromethane, bromine, 0 °C; (c) *n*-butyl lithium, [3*R*-(3α,4β,5α,6β)]-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydropyran-2-one, -78 °C; (d) triethylsilane, acetonitrile, -15 °C; (e) tetrahydrofuran, potassium hydroxide, 50 °C; (f) DMF, 1-(bromomethyl)-4-ethylbenzene, 0 °C; (g) 10% Pd-C, MeOH, H_2, 25 °C.

Scheme 1



(a) DMF, 1-(bromomethyl)-4-ethylbenzene, Cs_2CO_3, 60 °C; (b) CH_2Cl_2, [2*S*-(2α,3β,4α,5β,6α)]-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2*H*-pyran-2-yl 2,2,2-trichloroacetimidate (**10**), -78 °C; (c) 10% Pd-C, 1,2-dichlorobenzene, MeOH, H_2, 25 °C.

Scheme 2

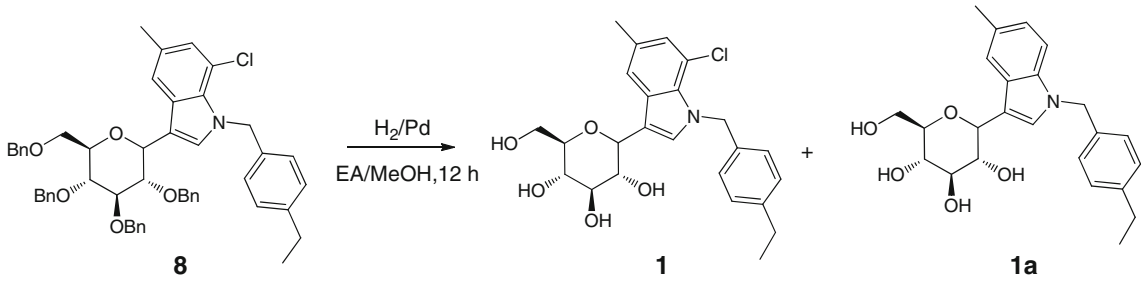
possible reason for the effect of 1,2-dichlorobenzene in this protocol could be that its chlorine group can be reduced first, and the resultant hydrochloride can gradually inhibit the reduction of the chlorine atom of **1**.

In conclusion, a more convenient and effective approach for synthesis **1** was found. It has been achieved in about 72% overall yield.

Experimental

Compound **2** was purchased from Sigma-Aldrich, and all reagents were obtained from suppliers and were not purified. Melting points were measured on a PHMK179-2454 apparatus. Elemental analyses (C, H, N) were determined with a Perkin-Elmer 240c instrument; their results were

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



8 **1** **1a**

Entry	Solvent	Equivalents	Product **1** yield (%)[a]	By-product **1a** yield (%)[a]
1	Benzene	10	51	48
		20	51	49
2	Ethyl acetate	10	51	49
		20	51	48
3	Chlorobenzene	10	74	25
		20	81	18
4	1,2-Dichlorobenzene	10	92	6
		20	99	0

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

found to be in good agreement (±0.2%) with the calculated values. ^{1}H NMR and ^{13}C NMR were measured on a Bruker AM-300 spectrometer. EI mass spectral measurement was carried out on a Waters alliance 2695 with acetonitrile and water as a mobile phase. Column chromatography was conducted under low pressure by elution of the columns filled with silica gel (0.040–0.063 mm, Merck).

7-Chloro-1-(4-ethylbenzyl)-5-methyl-1H-indole (**9**, $C_{18}H_{18}ClN$)

To a solution of 1.66 g **2** (10 mmol) in 10 cm^3 anhydrous DMF, 2.19 g 1-(bromomethyl)-4-ethylbenzene (11 mmol) was added, and the mixture was stirred for 5 h at 50 °C. Then the reaction mixture was poured into ice water and extracted with EtOAc. The organic phase was washed with water and brine, dried with anhydrous sodium sulfate, and concentrated in vacuo to give **9** as yellow solid (2.76 g, 97%). M.p.: 61–62 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.17$ (3H, t, $J = 7.5$ Hz), 2.37 (3H, s), 2.57 (2H, q, $J = 7.8$ Hz), 5.61 (2H, s), 6.49 (1H, m), 6.72–6.83 (2H, m), 6.91–6.94 (1H, m), 6.94–7.04 (2H, m), 7.30 (1H, s), 7.46–7.51 (1H, m) ppm; ^{13}C NMR (300 MHz, CD_3OD): $\delta = 137.2, 136.6, 134.9, 132.3, 129.2, 129.1, 127.8, 127.7, 120.7, 119.3, 116.2, 102.4, 60.8, 28.6, 20.8, 16.1$ ppm; MS: $m/z = 283\ [M]^+, 306\ [M + Na]^+$.

7-Chloro-1-(4-ethylbenzyl)-5-methyl-3-[[3S-(3α,4β,5α,6β)]-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2H-pyran-2-yl]-1H-indole (**8**, $C_{52}H_{52}ClNO_5$)

To a stirred solution of 6 g **10** (8.8 mmol) in 150 cm^3 anhydrous dichloromethane at −78 °C, 9.9 g **9** (35.1 mmol) was slowly added. The solution was stirred for 30 min at −78 °C, quenched with saturated $NaHCO_3$, and extracted with EtOAc. The organic phase was separated and washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give a crude oil. The oil was purified by column chromatography (petroleum ether/EtOAc, 6:1, v/v) to give the pure product **8** as colorless oil (5.8 g, 83%). $R_f = 0.35$ (petroleum ether/EtOAc, 8:1, v/v); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.17$ (3H, t, $J = 7.8$ Hz), 2.37 (3H, s), 2.60 (2H, q, $J = 7.8$ Hz), 3.43–3.52 (3H, m), 3.65–3.90 (7H, m), 3.97–4.10 (2H, m), 4.43 (1H, d, $J = 9.6$ Hz), 4.47–4.99 (8H, m), 5.26 (2H, s), 6.93–6.96 (3H, m), 7.08 (1H, d, $J = 7.8$ Hz), 7.07–7.30 (21H, m), 7.46 (1H, s) ppm; ^{13}C NMR (300 MHz, $CDCl_3$): $\delta = 142.8, 135.4, 131.2, 130.6, 130.4, 129.8, 128.8, 128.6, 128.2, 128.0, 127.8, 127.6, 127.2, 126.6, 120.8, 120.6, 119.4, 118.2, 94.6, 87.8, 79.8, 75.5, 75.1, 75.0, 74.6, 74.3, 73.4, 66.6, 55.2, 28.6, 22.4, 15.5$ ppm; MS: $m/z = 805\ [M]^+, 828\ [M + Na]^+$.

[3R-(3α,4β,5α,6β)]-2-[7-Chloro-1-(4-ethylbenzyl)-5-methyl-1H-indol-3-yl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (**1**, $C_{24}H_{28}ClNO_5$)

To a solution of 5 g **8** (6.21 mmol) in 50 cm^3 EtOAc/MeOH (1:4) in a 150 cm^3 autoclave reactor, 0.5 g palladium on carbon and 15 cm^3 1,2-dichlorobenzene were added in turn. The air in the reactor was removed by argon, then 0.1 MPa H_2 was added for 12 h at 25 °C. The solvent was filtrated, the filter cake was washed by EtOAc, and the filtrate was concentrated in vacuo to give an oil. The oil was purified by column chromatography (MeOH/EtOAc,

1:4, v/v) to get **1** as light yellow oil (2.46 g, 89%). $R_f = 0.30$ (MeOH/EtOAc, 1:5, v/v); ^{1}H NMR (300 MHz, CD_3OD): $\delta = 1.17$ (3H, t, $J = 7.5$ Hz), 2.37 (3H, s), 2.57 (2H, q, $J = 7.8$ Hz), 3.43–3.52 (3H, m), 3.65–3.71 (2H, m), 3.86–3.91 (1H, m), 4.46 (1H, d, $J = 9.6$ Hz), 5.26 (2H, s), 6.93–6.96 (3H, m), 7.08 (2H, d, $J = 7.8$ Hz), 7.29 (1H, s), 7.46 (1H, s) ppm; ^{13}C NMR (300 MHz, CD_3OD): $\delta = 142.4$, 138.5, 133.3, 130.7, 129.0, 128.6, 128.2, 126.8, 120.6, 119.9, 117.8, 116.2, 90.6, 85.8, 78.8, 71.6, 71.3, 62.6, 55.2, 29.6, 23.2, 16.5 ppm; MS: $m/z = 445$ $[M]^+$, 468 $[M + Na]^+$.

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