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AN EFFICIENT AND PRACTICAL PREPARATION OF A POTENT LOW-AFFINITY Na^+-DEPENDENT GLUCOSE COTRANSPORTER (SGLT2) INHIBITOR, SERGLIFLOZIN ETABONATE

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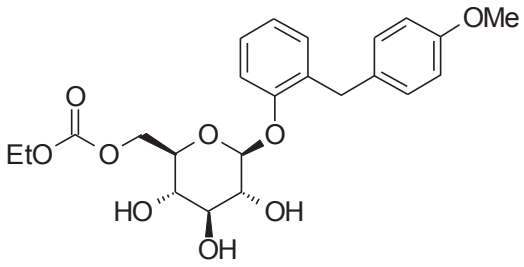
Abstract – The development of an efficient and practical process for the preparation of Sergliflozin etabonate (**1**), a prodrug of a novel selective low-affinity Na^+-dependent glucose cotransporter (SGLT2) inhibitor, Sergliflozin (**2**), is described. Its development required a suitable process for large-scale manufacturing. We established a chromatography-free approach for 2-[(4-methoxyphenyl)methyl]phenol (**5**), the efficient *O*-glycosylation of **5** with penta-*O*-acetyl-β-D-glucopyranose (**7**) without using a trichloroacetimidate intermediate (**9**), and efficient reaction conditions to introduce an ethoxycarbonyl group onto the primary alcohol of **2** with high selectivity. This process provided **1** with a 45% overall yield from anisole (**10**).

INTRODUCTION

Recently, low-affinity Na^+-dependent glucose cotransporter (SGLT2) inhibitors have been developed.[1] Two types of SGLT are known, SGLT1 and SGLT2; both act as transmembrane glucose transporters. Although SGLT1 (the high-affinity Na^+-dependent glucose cotransporter) is expressed to some extent in the kidney and contributes to glucose reabsorption, it is primarily expressed in the small intestine where it plays an important role in glucose absorption.[2,3] SGLT2 is specifically expressed in the kidney and plays an important role in renal glucose reabsorption in the proximal tubule.[4]

Serglifrozin (**2**), discovered at Kissei Pharmaceutical Co., Ltd., exhibits an inhibitory activity that is highly selective for SGLT2.

6-*O*-Ethoxycarbonyl-2-[(4-methoxyphenyl)methyl]phenyl-β-D-glucopyranoside (Sergliflozin etabonate (**1**); Figure 1), a prodrug of **2**, is metabolized to its active form **2** in the body, and may therefore be useful as a preventative or therapeutic agent for diseases attributable to hyperglycemia, such as diabetes, complications related to diabetes, and obesity.[5-8] Larger quantities of **1** must now be provided for preclinical and clinical evaluation as an antidiabetic agent. In this paper, we describe an efficient process for the preparation of **1**.

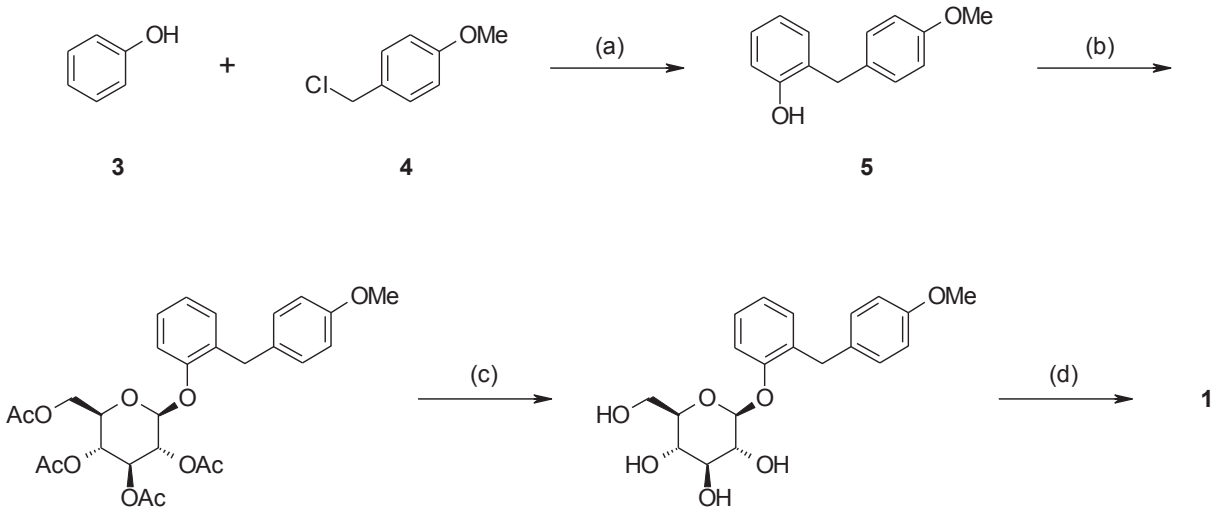


Sergliflozin etabonate (**1**)

Figure 1

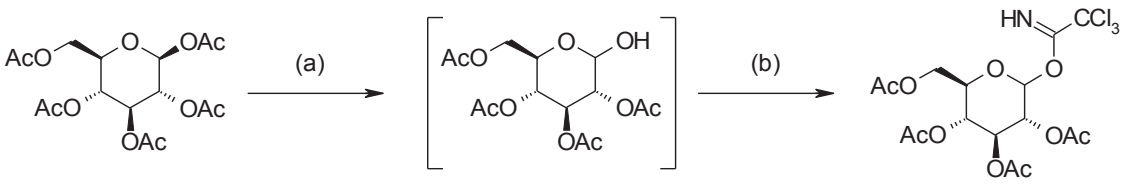
RESULTS AND DISCUSSION

Our initial synthetic route of Serglifrozin etabonate (**1**) in early development consisted of six steps, including synthesis of tetra-*O*-acetyl-D-glucopyranosyl trichloroacetimidate (**9**), as shown in Scheme 1 and Scheme 2.



Reagents: (a) LiOH・H_2O, benzene, reflux (30%); (b) **9**, BF_3・OEt_2, EtOAc, rt (77%); (c) NaOMe, MeOH, 50 °C (73%); (d) ethyl chloroformate, 2,6-lutidine, acetone, 15 °C (66%).

Scheme 1



7 **8** **9**

Reagents: (a) *N,N*-dimethylethylenediamine, THF, 20 °C (not isolated); (b) trichloroacetonitrile, K_2CO_3, EtOAc, 40 °C (crude product was used in the *O*-glycosylation step).

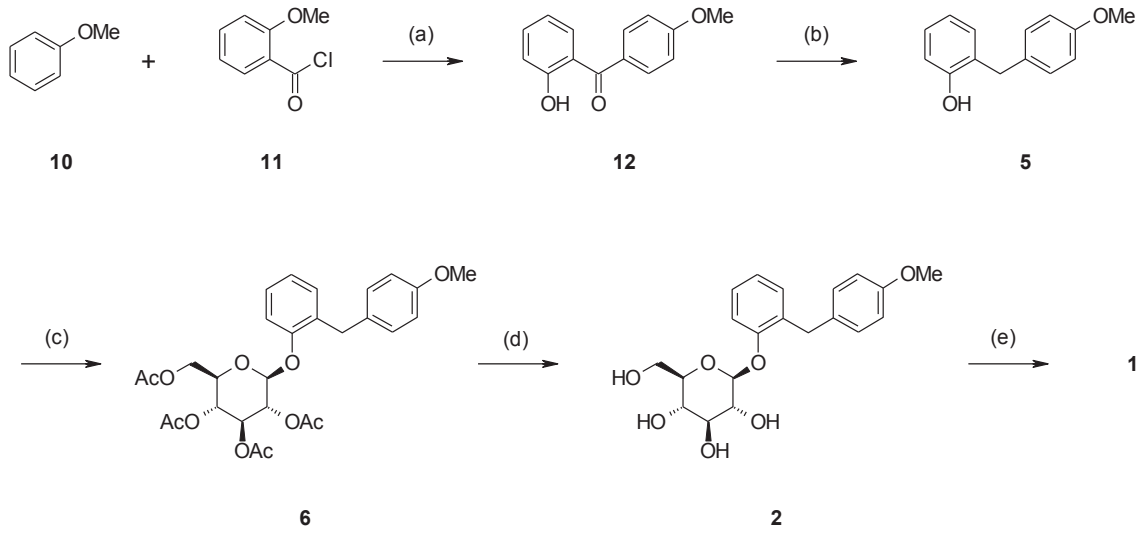
Scheme 2

The first step is the coupling reaction of phenol (**3**) and 4-methoxybenzyl chloride (**4**) in the presence of lithium hydroxide monohydrate ($LiOH \cdot H_2O$) to provide the aglycon **5** in a 30% yield following chromatographic purification (Scheme 1). We prepared **9** separately by mono-deacetylation of penta-*O*-acetyl-β-**D**-glucopyranose (**7**) with *N,N*-dimethylethylenediamine in THF followed by reaction of the crude product of **8** with trichloroacetonitrile in the presence of potassium carbonate (K_2CO_3) in ethyl acetate (EtOAc) (Scheme 2). Next, we carried out glycosylation of **5** with **9** in the presence of boron trifluoride diethyl etherate ($BF_3 \cdot OEt_2$) in EtOAc to produce **6** in a 77% yield. The obtained **6** was deacetylated with sodium methoxide (NaOMe) in MeOH to produce Serglifrozin (**2**) in a 73% yield, and reaction of the isolated **2** with ethyl chloroformate in the presence of 2,6-lutidine in acetone provided **1** in a 66% yield. The overall yield from **3** was 11%. While this route was capable of supplying small amounts of **1**, it suffered from several disadvantages.

The coupling reaction between **3** and **4** provided the aglycon **5** in low yield (30%); thus, chromatographic purification was required to obtain highly pure **5**. The trichloroimidation reaction of **8** is too hazardous for large-scale manufacturing, because an excess amount of trichloroacetonitrile, a volatile and highly toxic reagent, is required to obtain the trichloroacetimidate **9**. Furthermore, **9** is too unstable to use conveniently in large-scale manufacturing. Trichloroacetamide, a sublimation compound, is formed as a by-product from the glycosylation of **5** with **9**. Thus, the vacuum line and the vacuum pump of the manufacturing equipment would be polluted by trichloroacetamide.

Because of these issues, this synthetic method is unsuitable for large-scale manufacturing. Therefore, we investigated alternative processes for the preparation of **1**, suitable for large-scale manufacturing.

An improved synthetic method for **1** was achieved in a five-step procedure without purification of **6** (intermediate), as shown in Scheme 3.



Reagents: (a) $AlCl_3$, PhCl, 110 °C (78%); (b) 10% Pd/C (wet), H_2, EtOH, rt (88%); (c) **7**, $BF_3 \cdot OEt_2$, Et_3N, toluene, 40 °C; (d) NaOMe, MeOH, 15 °C (80% from **5**); ethyl chloroformate, 2,6-lutidine, pyridine, acetone, 0 °C (82%).

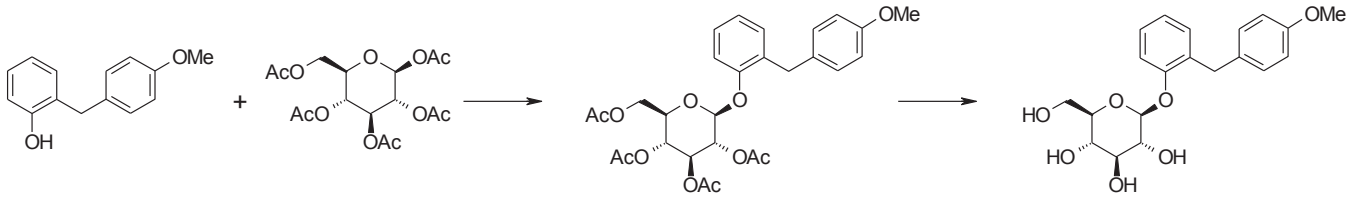
Scheme 3

The Friedel-Crafts acylation of anisole (**10**) with 2-methoxybenzoyl chloride (**11**) in the presence of aluminum chloride ($AlCl_3$) at 110 °C provided benzophenone (**12**), which was selectively demethylated on the methoxy group at the 2-position. The crude product of **12** was crystallized from MeOH to provide highly pure **12** in a 78% yield. Hydrogenation of **12** in EtOH with 0.3–0.4 MPa H_2 at room temperature in the presence of 10% Pd/C provided **5**. The crude product of **5** was crystallized from toluene/*n*-heptane to provide highly pure **5** in an 88% yield.

The key step of the synthesis was the formation of the *O*-glycosylated product **6**. In the initial synthesis, it was necessary to isolate **6** to remove trichloroacetamide. Consequently, **2** was provided in a 56% yield from **5**. To obtain **6** efficiently without using the trichloroacetimidate (**9**), we evaluated several conditions for the direct *O*-glycosylation of **5** with **7**. The results are summarized in Table 1. The *O*-glycosylation of **5** with **7** (200 mol%) in the presence of boron trifluoride diethyl etherate ($BF_3 \cdot OEt_2$; 100 mol%) in dichloromethane (DCM) at room temperature provided the crude product of **6** with a good yield (80%) and β-selectivity (94/6), and then the deacetylation of the crude product of **6** in the presence of sodium methoxide (NaOMe) in MeOH proceeded almost quantitatively to provide **2** in a 71% isolated yield from **5** (run 1). Using this method, it was not necessary to isolate **6** because the excess amount of **7** was converted to glucose and removed to the aqueous layers in the deacetylation step. Use of DCM is undesirable for large-scale manufacturing because quenching of *O*-glycosylation with water is highly exothermic and washing of the DCM layer with water is a complicated procedure. Additionally, it is strongly desirable to avoid using DCM in a manufacturing process due to environmental issues. For the

reasons mentioned above, we attempted to use toluene as an alternative solvent. The *O*-glycosylation in the presence of $BF_3 \cdot OEt_2$ (100 mol%) in toluene at 30 °C did not proceed completely, and the yield of **6** was lower than run 1 (run 2). We concluded that the lower solubility of **7** in toluene, compared with DCM, caused the low yield. Because it was difficult to increase the amount of toluene from the perspective of manufacturing efficiency, we tried to improve its solubility by optimizing the reagent equivalent. Fortunately, we found that an excess amount of $BF_3 \cdot OEt_2$ enhanced the solubility of **7** in toluene, and using 300 mol% of $BF_3 \cdot OEt_2$ in toluene provided **6** in a good yield (80%), similar to that when using DCM (run 3). In contrast, reducing the amount of **7** provided **6** in an insufficient yield, and **2** was consequently provided in a lower yield (60%) (run 4). To achieve higher β-selectivity and an increased yield, triethylamine (Et_3N) was added to the *O*-glycosylation of **5** with **7** in the presence of $BF_3 \cdot OEt_2$, according to the method of Lee *et al*.[9] Addition of Et_3N (30 mol%) at 30 °C resulted in both higher yield (89%) and higher β-selectivity (97/3) to provide **2** with a 79% isolated yield (run 5). Increasing the amount of Et_3N to 60 mol% at 30 °C resulted in a lower yield (85%) of **6** compared with run 5, and the yield of **2** decreased (74%) (run 6). Increasing the reaction temperature to 40 °C in the presence of 60 mol% of Et_3N achieved the best results for both high yield (90%) and high β-selectivity (99/1) to provide **2** in an 80% yield (run 7).

Table 1. Optimization of *O*-glycosylation of **5** with **7**



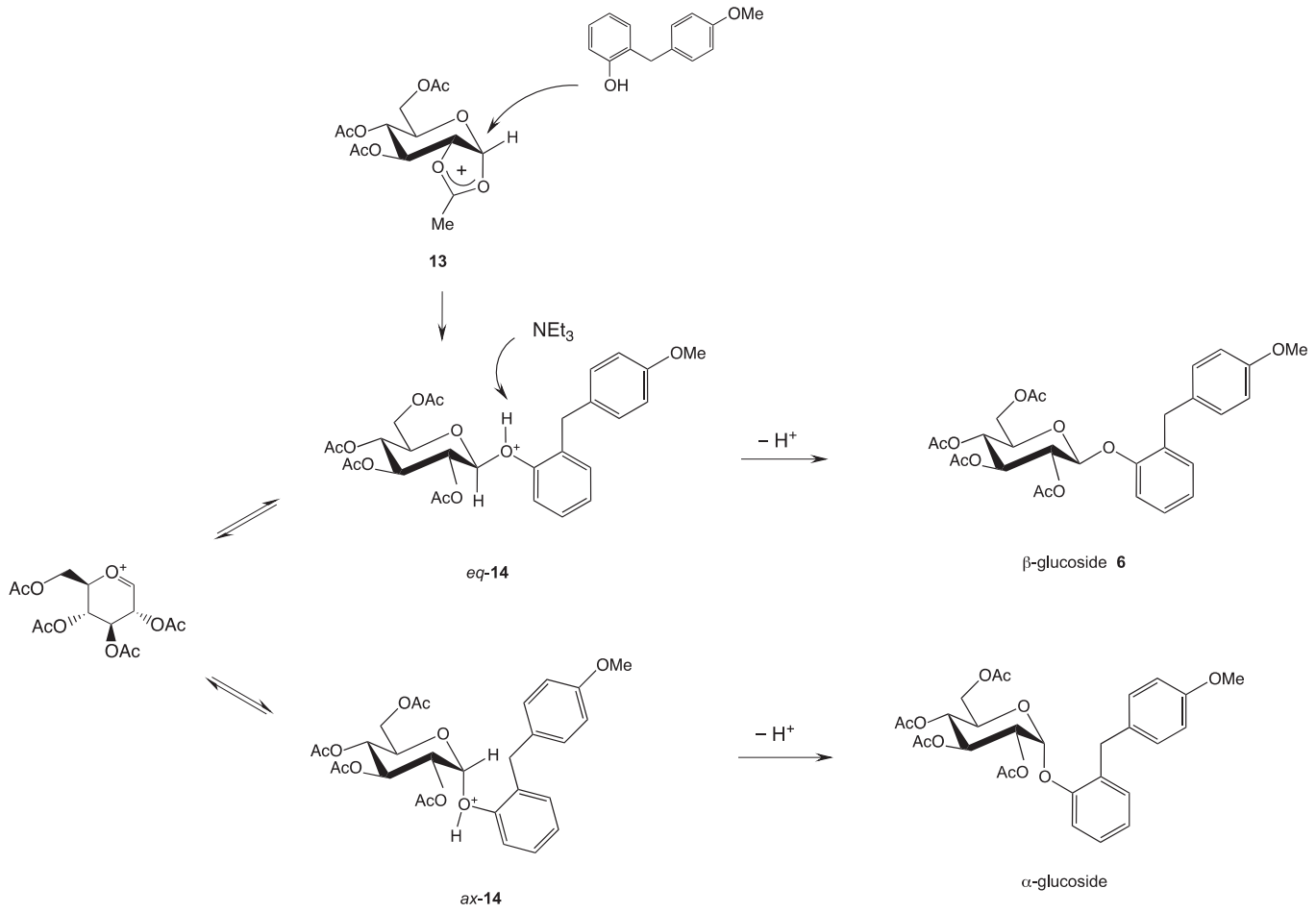
5 **7** **6** **2**

run	**7** (mol%)	$BF_3 \cdot OEt_2$ (mol%)	Base (mol%)	Solvent	Temp (°C)	**6**		**2**
						yield (%)[a]	Ratio (β/α)[b]	Isolated yield (%)
1	200	100	none	DCM	rt	80	94/6	71
2	200	100	none	toluene	30	74	92/8	62
3	200	300	none	toluene	30	80	92/8	71
4	150	300	none	toluene	30	73	90/10	60
5	200	300	Et_3N (30)	toluene	30	89	97/3	79
6	200	300	Et_3N (60)	toluene	30	85	98/2	74
7	200	300	Et_3N (60)	toluene	40	90	99/1	80

a) Determined by HPLC. Area % of product **6**.

b) Determined by HPLC.

Scheme 4 provides an explanation for the high β-selectivity. It is well-known that the glycosylation of phenol derivatives with **7** provides β-glucosides as major products, because the attack of a phenolic oxygen on the oxonium intermediate **13** takes place kinetically from the equatorial site. In the absence of Et_3N, interconversion to some extent of the kinetically stable *eq*-**14** into the thermodynamically stable *ax*-**14** occurs during the glycosylation reaction, and the formation of thermodynamically more stable α-glucoside causes lower β-selectivity. In the presence of Et_3N, the proton is rapidly removed from *eq*-**14** to provide β-glucoside at a higher selectivity.[10]

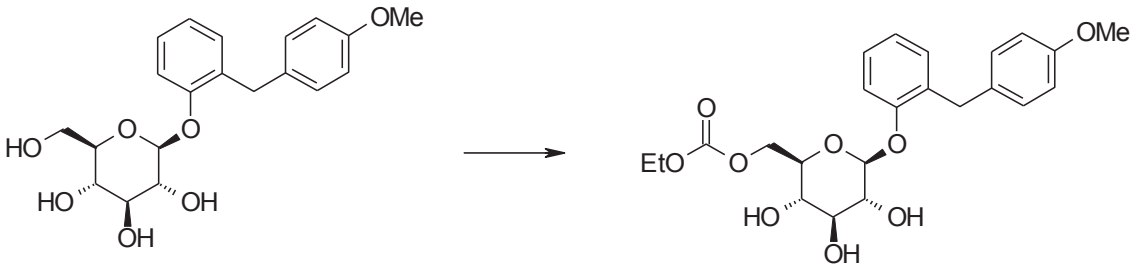


Scheme 4

To complete the synthesis, we optimized the ethoxycarbonylation condition of **2**. Yamamoto *et al.* reported that a sterically hindered amine was suitable for the selective acylation of the primary alcohols.[11] The 6-*O*-ethoxycarbonyl derivative **1** was prepared by treatment of **2** with ethyl chloroformate in the presence of 2,6-lutidine as a sterically hindered amine. In the initial synthesis, the reaction of **2** with ethyl chloroformate (125 mol%) in the presence of 2,6-lutidine (175 mol%) in acetone at 15 °C for 23 h provided **1** in a 66% isolated yield and ratio **1**/bis-ethoxycarbonylated derivatives (2,6-, 3,6-, and

4,6-bis-*O*-ethoxycarbonyl derivatives) of 78/22 (Table 2, run 1). However, the required reaction time fluctuated from several hours to 23 h. We investigated the cause of this fluctuation and found that the content of 3-picoline as an impurity of 2,6-lutidine varied from 0.06% to 0.6%, and the different contained quantities of 3-picoline affected the reaction time. Specifically, the reaction was accelerated dramatically by the addition of a small amount of 3-picoline, which required lower reaction temperatures and considerably shorter reaction times, and thus, the reaction was completed with a smaller amount of ethyl chloroformate. The reaction of **2** with ethyl chloroformate (115 mol%) in the presence of 2,6-lutidine (150 mol%) and 3-picoline (2.4 mol%) at 0 °C proceeded completely in 4 h and achieved high **1**/bis-ethoxycarbonylated derivative selectivity (90/10), to provide **1** in an 80% yield (run 2). The addition of pyridine was more effective than the addition of 3-picoline, and the reaction was completed in 2 h (82% yield, run 3). In contrast, the reaction using pyridine as a base provided **1** in a low yield (52%) because of a significant amount of recovered **2** and the production of some by-products (run 4).

Table 2. Optimization of Ethoxycarbonylation of **2**



2 **1**

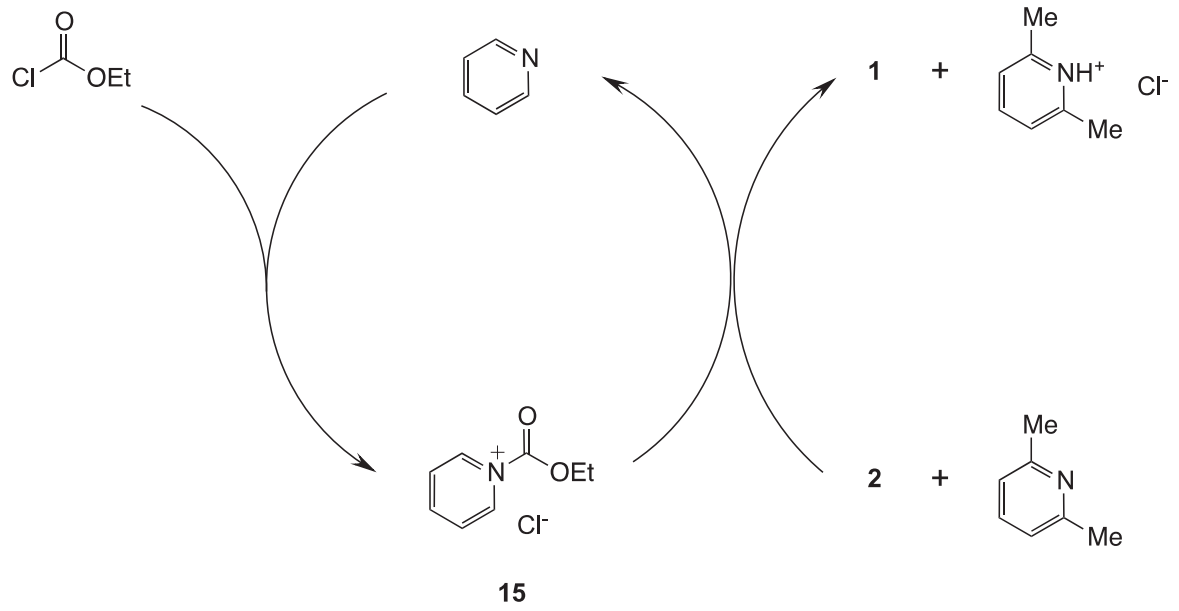
run	Base (mol%)	Additive (mol%)	$ClCO_2Et$ (mol%)	Temp. (°C)	Time (h)	Ratio (**1**/Bis-ethoxycarbonylated derivatives)[a) b)]	**1** (% yield)
1	2,6-lutidine (175)	none	125	15	23	78/22	66
2	2,6-lutidine (150)	3-picoline (2.4)	115	0	4	90/10	80
3	2,6-lutidine (150)	pyridine (2.4)	115	0	2	91/9	82
4	pyridine (130)	none	110	0	1	81/19	52[c)]

a) Determined by HPLC.

b) Bis-ethoxycarbonylated derivatives contained 2,6-, 3,6- and 4,6-bis-*O*-ethoxycarbonyl derivatives.

c) Isolated by column chromatography.

The proposed mechanism for the reaction is shown in Scheme 5. 2,6-Lutidine did not form acyl pyridinium salt with ethyl chloroformate because of steric hindrance from the 2,6-dimethyl groups. 2,6-Lutidine acted as a scavenger of hydrogen chloride. The addition of a catalytic amount of pyridine formed the acyl pyridinium salt **15**, which is a more reactive species than ethyl chloroformate, and the reaction was accelerated.



Scheme 5

In conclusion, we overcame the disadvantages of the initial synthetic route of **1**, and developed an efficient and practical process for the large-scale preparation of Sergliflozin etabonate (**1**). The benefits of our new process are: 1) a chromatography-free approach to obtain highly pure **5**; 2) a high yield and high β-selective *O*-glycosylation of **5** with **7**; 3) avoidance of highly toxic reagents such as trichloroacetonitrile, unstable intermediates such as trichloroacetimidate (**9**), and halogenated solvents such as DCM; and 4) an efficient ethoxycarbonylation condition onto the primary alcohol of **2** with high selectivity by the addition of a catalytic amount of pyridine.

The results revealed that the optimized process described here improved the overall yield of the synthesis of **1** from 11% to 45%.

EXPERIMENTAL

All melting points were determined using a Yanagimoto melting point apparatus and are uncorrected. Optical rotations were recorded on a JASCO P-2300 polarimeter. IR spectra were recorded on a Nicolet AVATAR 320 FT-IR spectrometer. ^{1}H and ^{13}C-NMR spectra were recorded on a Bruker AV-400M (400 MHz) or DRX-500 (500 MHz) spectrometer using TMS as the internal standard. High-resolution MS spectra were recorded on an Agilent Technologies QToF 6520 mass spectrometer. HPLC analysis was carried out using a Shimadzu 10A-VP.

Initial synthetic procedures

2-[(4-Methoxyphenyl)methyl]phenol (5). The mixture of LiOH·H_2O (210 mg, 5.0 mmol) and phenol

(**3**) (471 mg, 5.0 mmol) in benzene (3 mL) was refluxed for 1 h. 4-Methoxybenzyl chloride (**4**) (882 mg, 5.25 mmol) was then added to the reaction mixture. The mixture was refluxed with stirring for an additional 3 h and then cooled to room temperature. Water (3 mL) and EtOAc (10 mL) were added to the reaction mixture, and the biphasic solution was transferred to a separating funnel for phase separation. The organic layer was dried over Na_2SO_4 and the filtrate concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluent EtOAc:*n*-hexane, 1/7) to provide **5** (323 mg, 30% yield), which was identified using NMR spectra compared with reference data.[12] ^{1}H-NMR ($CDCl_3$) δ: 3.78 (3H, s), 3.93 (2H, s), 4.66 (1H, s), 6.77–6.91 (4H, m), 7.10–7.15 (4H, m).

Tetra-*O*-acetyl-D-glucopyranosyl trichloroacetimidate (9). *N,N*-Dimethylethylenediamine (63.4 g, 0.719 mol) was added to a solution of penta-*O*-acetyl-β-D-glucopyranose (**7**) (200 g, 0.512 mol) in a mixed solvent of EtOAc (400 g) and THF (400 g). The reaction mixture was stirred at 20 °C overnight. EtOAc (200 g) and an aqueous solution of 15% phosphoric acid (607 g) were added to the reaction mixture, and the biphasic solution was transferred to a separating funnel for phase separation. The organic layer was washed successively with an aqueous solution of 10% NaCl (400 g), an aqueous solution of 5% $NaHCO_3$ (400 g), and an aqueous solution of 18% NaCl (196 g). The organic layer was dried over Na_2SO_4 and the filtrate concentrated under reduced pressure. The residue was then dissolved in EtOAc (400 g). The solution was concentrated under reduced pressure to provide **8** as an oil. The residue was dissolved in EtOAc (500 g). Trichloroacetonitrile (298 g, 2.06 mol) and K_2CO_3 (10.9 g, 78.9 mmol) were added to the EtOAc solution of **8**. The reaction mixture was stirred at 40 °C for 7 h and then aged at 20 °C overnight. Inorganic salt was removed by filtration through Celite, and the filter cake was washed with EtOAc (400 g). The filtrate was concentrated under reduced pressure, and the residue was dissolved in EtOAc (400 g). The solution was concentrated under reduced pressure. The obtained residue was dissolved in EtOAc (200 g) to provide **9** as an EtOAc solution. The solution was used in the next step without further purification. **9** was identified using ^{1}H-NMR spectra compared with reference data.[13] ^{1}H-NMR analysis indicated an α-amoner/β-anomer ratio of 1/4. ^{1}H-NMR ($CDCl_3$) δ: (α-amoner) δ: 2.02 (3H, s), 2.04 (3H, s), 2.05 (3H, s), 2.08 (3H, s), 4.10–4.25 (2H, m), 4.25–4.35 (1H, m), 5.10–5.25 (2H, m), 5.50–5.65 (1H, m), 6.56 (1H, d, *J*=3.5 Hz), 8.70 (1H, s); ^{1}H-NMR ($CDCl_3$) (β-amoner) δ: 2.02 (3H, s), 2.03 (3H, s), 2.04 (3H, s), 2.09 (3H, s), 3.85–3.95 (1H, m), 4.10–4.20 (1H, m), 4.25–4.35 (1H, m), 5.15–5.35 (3H, m), 5.85–5.95 (1H, m), 8.72 (1H, s).

2-[(4-Methoxyphenyl)methyl]phenyl-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (6). EtOAc was added to the EtOAc solution of crude **9**, and the weight was adjusted to 630 g. **5** (67.0 g, 313 mmol) was added to the solution, and a solution of $BF_3{\cdot}OEt_2$ (13.4 g, 94.4 mmol) in EtOAc (130 g) was then

added at 20 °C. The reaction mixture was stirred at 40 °C for 2 h and then cooled to 20 °C. An aqueous solution of 18% NaCl (268 g) was added to the reaction mixture and the biphasic solution transferred to a separating funnel for phase separation. The organic layer was washed successively with an aqueous solution of 18% NaCl (268 g × 3), a solution of $NaHCO_3$ (3.4 g) and NaCl (24 g) in water (170 g), and an aqueous solution of 18% NaCl (268 g). The organic layer was dried over Na_2SO_4 and the filtrate concentrated under reduced pressure. EtOAc was added to the residue, and the weight was adjusted to 402 g. MeOH (469 g) was added, and the resulting slurry was heated to 40 °C to dissolve solids. The solution was cooled to 28 °C and seeded with **6**. The solution was aged for 1.5 h at 28 °C, during which time the product began to crystallize. The slurry was cooled to 20 °C and then stirred for 1 h at 20 °C. The slurry was cooled to 0 °C and then stirred for 1 h at 2 °C. The slurry was filtered, and the wet cake was washed with MeOH (80 g × 2). The precipitate was dried *in vacuo* at 70 °C to give 131 g (77% yield) of **6** as a white solid. mp 116–117 °C. $[\alpha]_D^{20}$ -29.7 (*c* 1.0, DMSO). IR (KBr) cm^{-1}: 1744, 1512, 1493, 1368, 1239. ^{1}H-NMR ($CDCl_3$) δ: 1.91 (3H, s), 2.03 (3H, s), 2.05 (3H, s), 2.07 (3H, s), 3.77 (3H, s), 3.85–3.89 (3H, m), 4.17 (1H, dd, *J*=2.5, 12.4 Hz), 4.28 (1H, dd, *J*=5.5, 12.3 Hz), 5.11 (1H, d, *J*=7.6 Hz), 5.18 (1H, t, *J*=9.5 Hz), 5.27–5.37 (2H, m), 6.78–6.82 (2H, m), 6.97–7.08 (5H, m), 7.14–7.19 (1H, m). ^{13}C-NMR ($CDCl_3$) δ: 20.5 (q), 20.6 (q×2), 20.7 (q), 34.3 (t), 55.2 (q), 62.0 (t), 68.4 (d), 71.1 (d), 72.0 (d), 72.9 (d), 99.1 (d), 113.82 (d×2), 115.1 (d), 123.4 (d), 127.3 (d), 129.9 (d×2), 130.7 (d), 131.4 (s), 132.4 (s), 154.5 (s), 157.9 (s), 169.2 (s), 169.4 (s), 170.3 (s), 170.6 (s). HRMS (ESI) *m/z*: 562.2288 $[M+NH_4]^+$ (Calcd for $C_{28}H_{36}NO_{11}$: 562.2283).

2-[(4-Methoxyphenyl)methyl]phenyl-β-D-glucopyranoside (2). A methanolic solution of 1% NaOMe (13.5 g, 2.5 mmol) was added to a suspension of **6** (27.2 g, 50 mmol) in a mixed solvent of EtOH (68 g) and MeOH (27 g) at room temperature. The reaction mixture was stirred at 50 °C for 1 h and then quenched by the addition of acetic acid (150 mg, 2.5mmol). EtOH (95 g) was added to the reaction mixture at 50 °C. The solution was cooled to 35 °C and seeded with **2**. The solution was aged for 1 h at 35 °C, during which time the product began to crystallize. The solution was allowed to cool slowly over 1 h to 3 °C and was stirred for 1.5 h at 3 °C. The slurry was filtered, and the wet cake was washed successively with a mixed solvent of EtOH (27 g) and MeOH (5 g) and *i*-Pr_2O (27 g). The precipitate was dried *in vacuo* at 80 °C to give 13.8 g (73% yield) of **2** as a white solid. mp 112–113 °C. $[\alpha]_D^{20}$ -42.4 (*c* 1.0, DMSO). IR (KBr) cm^{-1}: 3363, 1513, 1491, 1453, 1301, 1238. ^{1}H-NMR (DMSO-d_6) δ: 3.16–3.20 (1H, m), 3.25–3.35 (3H, m), 3.44–3.51 (1H, m), 3.70–3.73 (4H, m), 3.81 (1H, d, *J*=14.5 Hz), 3.99 (1H, d, *J*=14.6 Hz), 4.56 (1H, t, *J*=5.8 Hz), 4.80 (1H, d, *J*=7.3 Hz), 5.01 (1H, d, *J*=5.3 Hz), 5.08 (1H, d, *J*=4.8 Hz), 5.29 (1H, d, *J*=5.3 Hz), 6.79 (2H, m), 6.90 (1H, dt, *J*=1.3, 7.4 Hz), 7.06–7.15 (3H, m), 7.18–7.22 (2H, m). ^{13}C-NMR (DMSO-d_6) δ: 34.0 (t), 54.9 (q), 60.7 (t), 69.8 (d), 73.4 (d), 76.7 (d), 77.0

(d), 101.4 (d), 113.6 (d×2), 115.0 (d), 121.7 (d), 127.1 (d), 129.7 (d), 129.9 (d×2), 130.9 (s), 133.0 (s), 155.2 (s), 157.3 (s). HRMS (ESI) *m/z*: 394.1853 $[M+NH_4]^+$ (Calcd for $C_{20}H_{28}NO_7$: 394.1860).

6-*O*-Ethoxycarbonyl-2-[(4-methoxyphenyl)methyl]phenyl-β-D-glucopyranoside (1). Ethyl chloroformate (407 mg, 3.75 mol) was added drop-wise to the mixture of **2** (1.13 g, 3.0 mmol) and 2,6-lutidine (563 mg, 5.25 mmol) in acetone (4 mL) while maintaining the temperature between 12 and 18 °C. The reaction mixture was stirred at 15 °C for 23 h. Water (5 mL) was added drop-wise while maintaining the temperature below 30 °C, and EtOAc (10 mL) was then added to the mixture. The biphasic solution was transferred to a separating funnel for phase separation. The aqueous layer was extracted with EtOAc (5 mL). The EtOAc layers were combined, washed successively with an aqueous solution of 10% citric acid (5 mL × 2), an aqueous solution of 10% NaCl (5 mL), an aqueous solution of 5% $NaHCO_3$ (5 mL × 2), and an aqueous solution of 10% NaCl (5 mL). They were then dried over Na_2SO_4 and the filtrate was concentrated under reduced pressure. EtOH was added to the residue, and the weight was adjusted to 7.2 g. The mixture was heated to 65 °C to dissolve solids. The solution was cooled to 55 °C and seeded with **1**. The solution was aged for 1 h at 50 °C, during which time the product began to crystallize. After the slurry was cooled to 25 °C, *n*-heptane (11 mL) was added drop-wise to the slurry at 25 °C followed by stirring for 1 h at 25 °C. The slurry was cooled to 3 °C and then stirred for 2 h at 3 °C. The slurry was filtered, and the wet cake was washed with a mixed solvent of EtOH (1.5 mL) and *n*-heptane (3 mL). The precipitate was dried *in vacuo* at 70 °C to give 888 mg (66% yield) of **1** as a white solid. $[\alpha]_D^{20}$ -43.5 (*c* 1.0, DMSO). IR (KBr) cm^{-1}: 3495, 1744, 1514, 1488, 1454, 1467, 1411, 1372, 1340, 1266. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, t, *J*=7.0 Hz), 2.00 (1H, d, *J*=1.6 Hz), 3.46–3.54 (3H, m), 3.56–3.61 (2H, m), 3.72 (1H, d, *J*=2.1 Hz), 3.75 (3H, s), 3.82 (1H, d, *J*=15.5 Hz), 4.03 (1H, d, *J*=15.5 Hz), 4.11–4.22 (2H, m), 4.42 (2H, d, *J*=3.8 Hz), 4.69 (1H, d, *J*=7.4 Hz), 6.79–6.83 (2H, m), 6.97–7.02 (2H, m), 7.04–7.07 (2H, m), 7.15–7.22 (2H, m). ^{13}C-NMR ($CDCl_3$) δ: 14.2 (q), 36.1 (t), 55.4 (q), 64.4 (t), 66.4 (t), 69.6 (d), 73.4 (d), 73.8 (d), 75.7 (d), 100.8 (d), 114.1 (d×2), 114.4 (d), 122.7 (d), 128.0 (d), 129.2 (d×2), 130.0 (s), 131.1 (d), 133.4 (s), 155.2 (s), 155.4 (s), 157.8 (s). HRMS (ESI) *m/z*: 466.2070 $[M+NH_4]^+$ (Calcd for $C_{23}H_{32}NO_9$: 466.2072).

Efficient and practical synthetic procedures

2-Hydroxy-4'-methoxybenzophenone (12). 2-Methoxybenzoyl chloride (**11**) (78.9 g, 0.462 mol) was added drop-wise to a mixture of $AlCl_3$ (anhydrous) (67.8 g, 0.506 mol) and anisole (**10**) (50.0 g, 0.462 mol) in chlorobenzene (250 ml) maintaining the temperature between 0 and 10 °C. The reaction mixture was stirred at 110 °C for 1.5 h and then cooled to room temperature. After the reaction mixture was added drop-wise to the mixture of toluene (600 mL) and 4 M HCl (1500 mL), maintaining the

temperature between 0 and 20 °C, the mixture was stirred at room temperature for 1.5 h. The resulting insoluble material was removed by filtration through Celite, and the filter cake was washed with toluene (300 mL × 2). The biphasic filtrate was transferred to a separating funnel for phase separation. The toluene layer was washed successively with water (750 mL), an aqueous solution of 10% K_2CO_3 (750 mL), water (750 mL), and an aqueous solution of 20% NaCl (750 mL). The resulting organic layer was dried over Na_2SO_4, and the filtrate was concentrated under reduced pressure. The residue was dissolved in MeOH (315 mL) at 60 °C. The solution was seeded with **12** and stirred at 20 °C overnight. The resulting slurry was further stirred at 0 °C for 2 h. The slurry was filtered, and the wet cake was washed with *n*-heptane (100 mL × 2). The precipitate was dried *in vacuo* at 35 °C to give 82.2 g (78% yield) of **12** as a yellow solid. mp 53 °C. IR (KBr) cm^{-1}: 1625, 1590, 1507, 1484, 1458, 1336, 1301, 1255, 1224. ^{1}H-NMR ($CDCl_3$) δ: 3.90 (3H, s), 6.86–6.90 (1H, m), 6.98–7.02 (2H, m), 7.06 (1H, dd, J=0.9, 8.4 Hz), 7.47–7.51 (1H, m), 7.63 (1H, dd, J=1.5, 7.9 Hz), 7.70–7.74 (2H, m), 11.98 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 55.5 (q), 113.7 (d×2), 118.3 (d), 118.5 (d), 119.4 (s), 130.3 (s), 131.9 (d×2), 133.3 (d), 135.8 (d), 162.9 (s×2), 200.1 (s). HRMS (ESI) *m/z*: 229.0873 $[M+H]^+$ (Calcd for $C_{14}H_{13}O_3$: 229.0859).

2-[(4-Methoxyphenyl)methyl]phenol (5). A solution of **12** (10 g, 0.0438 mol) in EtOH (50 mL) was hydrogenated over 10% Pd-C (50% wet, 2.2 g) for 5 h at room temperature under 0.35 MPa of H_2. The Pd-C was removed by filtration through Celite, and the filter cake was washed with EtOH (10 mL × 2). The filtrate was concentrated under reduced pressure. The residue was dissolved in toluene (100 mL) at 50 °C. Activated carbon was added to the solution and stirred for 0.5 h. The activated carbon was removed by filtration through Celite, and the filter cake was washed with toluene (10 mL × 2). The filtrate was concentrated under reduced pressure. The residue was dissolved in toluene (40 mL) at 25 °C. After the solution was seeded with **5**, *n*-heptane (80 mL) was added drop-wise to the solution over a 0.2 h period at 25 °C, during which time the product began to crystallize. The resulting slurry was stirred at 25 °C overnight and further stirred at 0 °C for 1 h. The slurry was filtered, and the wet cake was washed with *n*-heptane (20 mL × 2). The precipitate was dried *in vacuo* at 40 °C to give 8.21 g (88% yield) of **5** as a yellow solid.

2-[(4-Methoxyphenyl)methyl]phenyl-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (6). $BF_3 \cdot OEt_2$ (100 g, 0.705 mol) was added drop-wise to the mixture of **5** (50.0 g, 0.233 mol), penta-*O*-acetyl-β-D-glucopyranose (**7**) (182 g, 0.466 mol), and Et_3N (14.0 g, 0.138 mol) in toluene (460 mL), maintaining the temperature between 15 and 40 °C. The reaction mixture was stirred at 40 °C for 6 h and then cooled to 20 °C. The mixture was aged for 12 h at 10–30 °C. Water (200 mL) was added drop-wise, maintaining the temperature below 40 °C, and the mixture was stirred at 40 °C until the

resulting inorganic salts were dissolved. After cooling to 25 °C, the biphasic solution was transferred to a separating funnel for phase separation. The toluene layer was washed successively with water (200 mL × 3), an aqueous solution of 5% $NaHCO_3$ (100 g), and water (50 g). The toluene layer was concentrated under reduced pressure. The residue was dissolved in MeOH (1 L) at 50 °C and then cooled to room temperature. HPLC analysis indicated the yield of **6** was 90% (117 g).[14] The solution was used in the next step without further purification.

2-[(4-Methoxyphenyl)methyl]phenyl-β-D-glucopyranoside (2). A methanol solution of 10% NaOMe (19.7 g, 0.0348 mol) was added drop-wise to the methanol solution of **6** from the preceding step, maintaining the temperature between 23 and 27 °C. The reaction mixture was stirred for 1 h at 12–18 °C, and then the reaction was quenched by the addition of acetic acid (2.10 g, 0.0350 mol) in MeOH (16 mL). The mixture was concentrated under reduced pressure. The residue was dissolved in water (190 g) and EtOAc (490 mL) at 55 °C and then cooled to 35 °C. The biphasic solution was transferred to a separating funnel for phase separation. The aqueous layer was extracted with EtOAc (70 mL). The EtOAc layers were combined and washed successively with water (130 g), an aqueous solution of 10% NaCl (130 g), and water (130 g). The EtOAc layer was concentrated under reduced pressure, and the residue was dissolved in EtOH (810 mL) at 70 °C. The solution was concentrated under reduced pressure until more than 350 mL distillate was collected. EtOH was added to the residue, and the weight was adjusted to 587 g. Water (17 g) was added, and the resulting slurry was heated to 70 °C to dissolve solids. The solution was cooled to 50 °C and seeded with **2**. The solution was aged for 1 h at 45 °C, during which time the product began to crystallize. The slurry was allowed to cool slowly over 1 h to 3 °C and was stirred for 1.5 h at 3 °C. The slurry was filtered, and the wet cake was washed successively with EtOH (160 mL) and *i*-Pr_2O (180 mL). The precipitate was dried *in vacuo* at 80 °C to give 70.4 g (80% yield) of **2** as a white solid.

6-*O*-Ethoxycarbonyl-2-[(4-methoxyphenyl)methyl]phenyl-β-D-glucopyranoside (1). Ethyl chloroformate (21.6 g, 0.199 mol) was added drop-wise to the mixture of **2** (65.0 g, 0.173 mol), 2,6-lutidine (27.8 g, 0.259 mol) and pyridine (0.33 g, 4.2 mmol) in acetone (210 mL), maintaining the temperature between -1 and 5 °C. The reaction mixture was stirred at 0 °C for 2 h. The reaction was monitored by HPLC.[15] Water (200 mL) was added drop-wise, maintaining the temperature below 30 °C, and then EtOAc (220 mL) was added to the mixture. The biphasic solution was transferred to a separating funnel for phase separation. The aqueous layer was extracted with EtOAc (140 mL). The EtOAc layers were combined, washed successively with an aqueous solution of 10% citric acid (180 mL × 2), an aqueous solution of 10% NaCl (66 g), an aqueous solution of 5% $NaHCO_3$ (65 g × 2), and an

aqueous solution of 10% NaCl (100 g), and then dried over Na_2SO_4 (65 g). After acetic acid (10 g, 0.167 mol) was added to the filtrate, the mixture was concentrated under reduced pressure. The residue was dissolved in EtOH (660 mL) at 65 °C. The solution was concentrated under reduced pressure until more than 330 mL distillate had been collected. EtOH was added to the residue, and the weight was adjusted to 370 g. *n*-Heptane (120 mL) was added, and the resulting slurry was heated to 65 °C to dissolve solids. The solution was cooled to 55 °C and seeded with **1**. The solution was aged for 1 h at 50 °C, during which time the product began to crystallize. *n*-Heptane (480 mL) was added drop-wise to the slurry, maintaining the temperature between 50 and 60 °C, and the slurry was stirred for 0.5 h at 55 °C. The slurry was allowed to cool slowly over 2.5 h to 30 °C, then cooled to 3 °C, and then stirred for 1.5 h at 3 °C. The slurry was filtered, and the wet cake was washed with a mixed solvent of EtOH (80 mL) and *n*-heptane (180 mL). The precipitate was dried *in vacuo* at 70 °C to give 63.6 g (82% yield) of **1** as a white solid.

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14. HPLC conditions: column, Inertsil ODS-3 (5 μm) 4.6 mm × 250 mm (GL Science Inc.); mobile phase, isocratic elution with acetonitrile / 0.02 M KH_2PO_4, pH 3 = 6/4; flow rate, 1.0 mL/min; column oven temperature, 40 °C; wave length, 225 nm; retention times, **5** = 16 min, α-anomer of **5** =

18 min.

15. HPLC conditions: column, Inertsil ODS-3 (5 μm) 4.6 mm × 250 mm (GL Science Inc.); mobile phase, gradient elution with 5 min 4/6 → 15 min 6/4 → 30 min 6/4 of acetonitrile/0.02 M KH_2PO_4, pH 3; flow rate, 1.0 mL/min; column oven temperature, 40 °C; wavelength, 225 nm; retention times, **1** = 17 min, 2,6- and 4,6-bis-*O*-ethoxycarbonyl derivatives = 24 min, 3,6-bis-*O*-ethoxycarbonyl derivative = 25 min.