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AN EFFICIENT AND PRACTICAL SYNTHESIS OF REMOGLIFLOZIN ETABONATE, A POTENT INHIBITOR OF LOW-AFFINITY Na^+-DEPENDENT GLUCOSE CO-TRANSPORTER (SGLT2)

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Abstract – A practical process for the preparation of remogliflozin etabonate, a prodrug of the selective low-affinity Na^+-dependent glucose co-transporter (SGLT2) inhibitor, remogliflozin, is described. We established a chemoselective synthetic route to 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-1-isopropyl-5-methyl-3*H*-pyrazol-3-one and an efficient *O*-glycosylation of this compound with 2,3,4,6-tetra-*O*-pivaloyl-α-D-glucopyranosyl bromide. This synthetic process provided remogliflozin etabonate in a 39% overall yield from commercially available 4-isopropoxybenzaldehyde.

INTRODUCTION

Remogliflozin etabonate (**1**; Figure 1) is the prodrug of remogliflozin (**2**), a highly selective inhibitor of the low-affinity Na^+-dependent glucose co-transporter SGLT2.[1,2] Two types of SGLT are known, namely SGLT1 and SGLT2, both of which act as transmembrane glucose transporters. Although SGLT1 (the high-affinity Na^+-dependent glucose co-transporter) is expressed to some extent in the kidney and contributes to glucose reabsorption, it is mainly expressed in the small intestine, where it plays an important role in glucose absorption.[3,4] In contrast, SGLT2 is specifically expressed in the kidney and plays an important role in renal glucose reabsorption in the proximal tubule.[5] As such, SGLT2 inhibitors are useful as preventative or therapeutic agents for diseases attributable to hyperglycemia, such as diabetes, complications related to diabetes, and obesity.[6,7]

In this context, we previously reported the synthesis of **1**.[8] However, to advance clinical studies into this compound, the development of a more efficient and practical synthesis of **1** is required. The

retrosynthetic approach for the preparation of **1** is outlined in Scheme 1, with this route constituting a more convergent synthetic approach than that previously reported.[8] From the retrosynthetic perspective, it is apparent that the development of a chemoselective synthetic route to 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-1-isopropyl-5-methyl-3*H*-pyrazol-3-one (**3**) and an efficient *O*-glycosylation of **3** with a glucosyl bromide **4a** or **4b** are required. Thus, we herein describe an efficient process for the preparation of **1** through the development of a chemoselective synthesis of **3** and an efficient *O*-glycosylation of **3** with **4a** or **4b**.

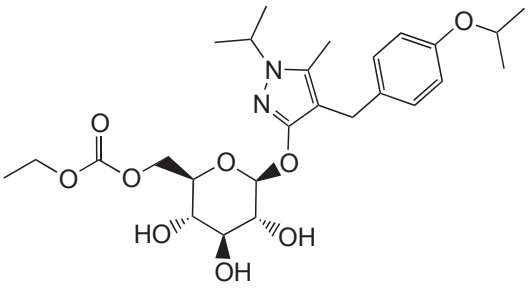
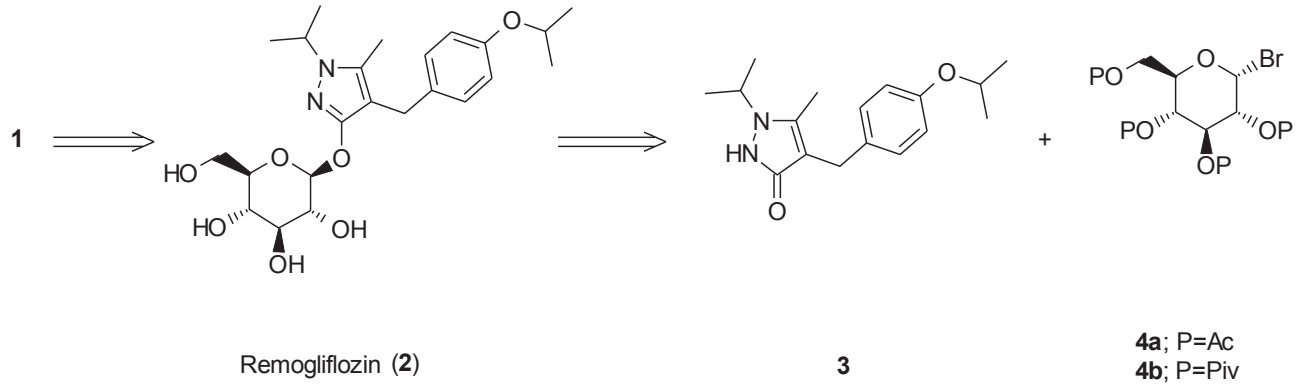


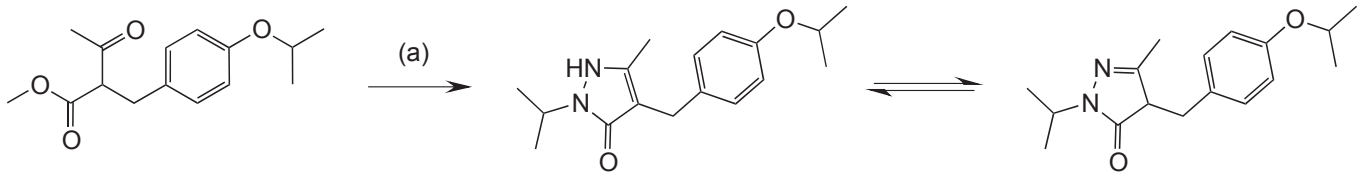
Figure 1. The chemical structure of remogliflozin etabonate (**1**)



Scheme 1. Retrosynthetic approach to remogliflozin etabonate (**1**)

RESULTS AND DISCUSSION

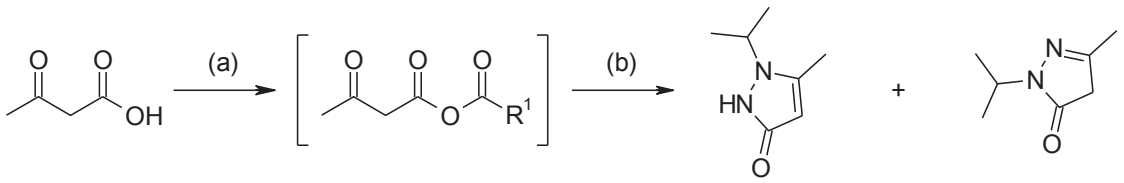
We previously reported that the condensation of β-keto ester derivative **5** with a hydrazine monohydrate is an effective approach to obtain 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one.[8] However, it is well known that the direct condensation of β-keto ester derivatives with alkyl hydrazines is not an effective approach to obtain N_1-alkylpyrazol-3-ones, as it leads predominantly to N_2-alkylpyrazol-3-ones.[9–11] Indeed, the direct condensation of **5** with isopropylhydrazine hydrochloride mainly provided N_2-isopropylpyrazol-3-one **6b** as the tautomeric form of **6a** (Scheme 2). We therefore investigated the condensation of β-keto ester derivatives with isopropylhydrazine to selectively obtain N_1-isopropylpyrazol-3-one.



Scheme 2. Direct condensation of **5** with isopropylhydrazine hydrochloride. Reagents and conditions: (a) Isopropylhydrazine hydrochloride, Et_3N, tetrahydrofuran (THF), toluene, reflux.

Initially, we evaluated the condensation of isopropylhydrazine with mixed acetoacetic anhydride derivatives **7**, which bear more reactive carboxyl moieties than the ester group. As outlined in Table 1, this high reactivity of **7** facilitated the formation of the desired N_1-isopropylpyrazol-3-one **8** (entry 2). However, hydrazone formation occurred more rapidly than the formation of the corresponding hydrazide, leading to the predominant formation of the undesired N_2-isopropylpyrazol-3-one **9**. It was therefore apparent that the carboxyl group remained insufficiently reactive for the desired transformation.

Table 1. Condensation of **7** with isopropylhydrazine

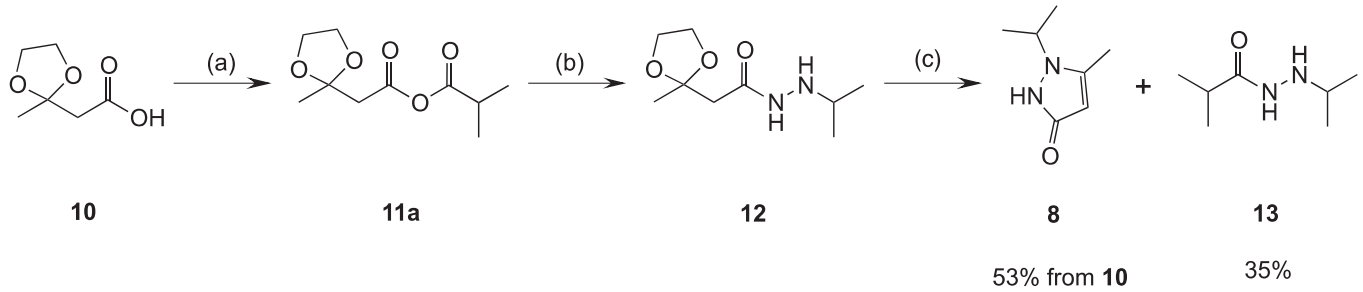


Entry	Mixed acetoacetic anhydride	Conditions[a)]	R^1	Ratio (**8**/**9**)[b)]
1	**7a**	A	*i*-Pr	7/93
2	**7b**	B	CF_3	16/84

a) A: (a) Isobutyryl chloride, pyridine, THF, toluene, 0 °C; (b) Isopropylhydrazine, Et_3N, THF, toluene, rt. B: (a) Trifluoroacetic anhydride, pyridine, THF, toluene, 0 °C; (b) Isopropylhydrazine, Et_3N, THF, toluene, rt.
b) Determined by ^1H NMR spectroscopy.

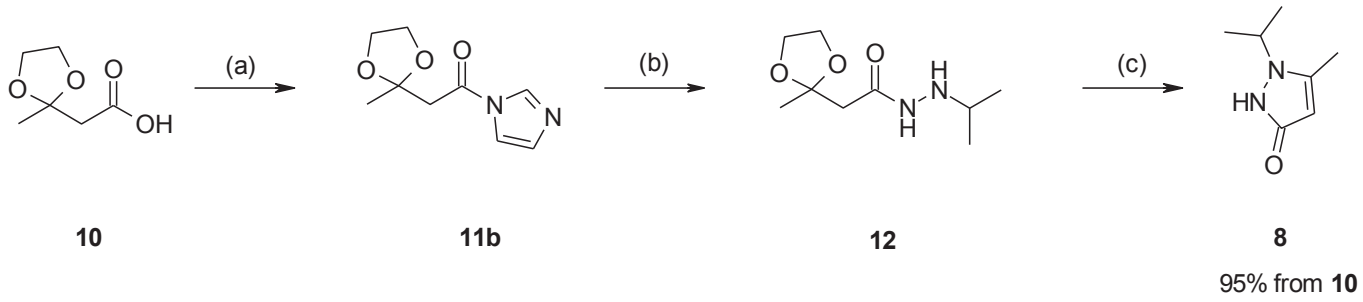
In an attempt to obtain the desired N_1-isopropylpyrazol-3-one **8** in a higher selectivity, we attempted the condensation of isopropylhydrazine with activated acetoacetic acid derivative **11a**, in which the carbonyl group was protected with ethylene glycol. Isobutyric 2-(2-methyl-1,3-dioxolan-2-yl)acetic anhydride (**11a**) was prepared by treating 2-(2-methyl-1,3-dioxolan-2-yl)acetic acid (**10**)[12] with isobutyryl chloride. Thus, the condensation of **11a** with isopropylhydrazine provided **8** as the main product, although trace amounts of **9** were observed. In addition, although the condensation of acetic anhydride with

methylhydrazine has been reported to provide the corresponding *N*-methylhydrazide,[13] we found this reaction to yield predominantly *N′*-isopropylhydrazide **12**. We therefore considered that nucleophilic attack of the unsubstituted nitrogen atom of isopropylhydrazine on the carbonyl carbon of **11a** occurred selectively due to the steric hindrance of the *N*-isopropyl group.[14] Unfortunately, the yield of the desired N_1-isopropyl- pyrazol-3-one **8** was moderate (53% from **10**) due to the concurrent formation of *N′*-isopropyl-isobutyric acid hydrazide (**13**) through acylation with isopropylhydrazine at the second carbonyl moiety of **11a**, as indicated in Scheme 3.



Scheme 3. Condensation of isopropylhydrazine with activated acetoacetic acid derivative **11a**. Reagents and conditions: (a) Isobutyryl chloride, pyridine, toluene, 0 °C; (b) Isopropylhydrazine, toluene, rt; (c) 1 M HCl, THF, 70 °C.

To prevent such undesired acylation at the second carbonyl moiety, we examined the condensation of isopropylhydrazine with imidazolide **11b**,[12] in which the carboxyl group was activated by *N,N′*-carbonyl-diimidazole (CDI). This method provided **8** in 95% yield from **10** and no formation of **9** was detected (Scheme 4).

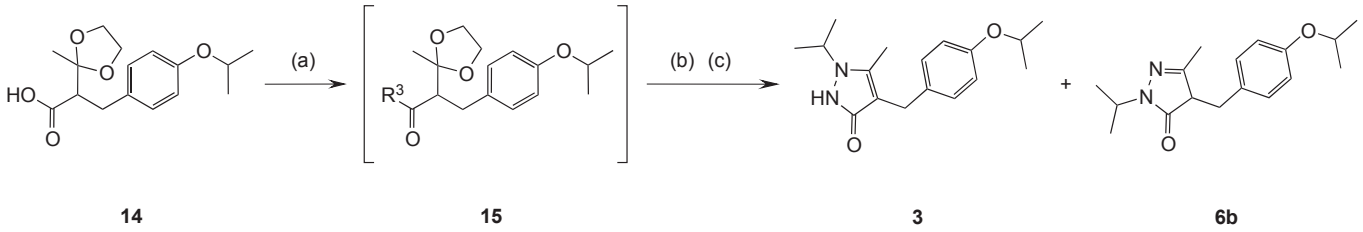


Scheme 4. Condensation of isopropylhydrazine with imidazolide **11b**. Reagents and conditions: (a) *N,N′*-carbonyldiimidazole (CDI), THF; (b) Isopropylhydrazine, toluene, 10 °C; (c) 2 M HCl, THF, 70 °C.

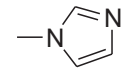
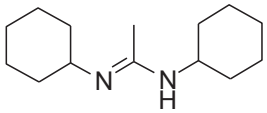
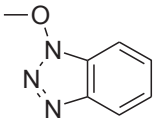
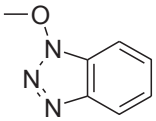
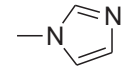
From the above results, it was apparent that the condensation of isopropylhydrazine with imidazolide **11b** bearing an ethylene glycol-protected carbonyl moiety is an efficient method to obtain the desired N_1-isopropylpyrazol-3-one derivative in high selectivity. To apply this method to the synthesis of **3**, we

examined the reaction of **14** with isopropylhydrazine hydrochloride, which is more readily available than isopropylhydrazine, and the results are summarized in Table 2.

Table 2. Condensation of **14** with isopropylhydrazine hydrochloride



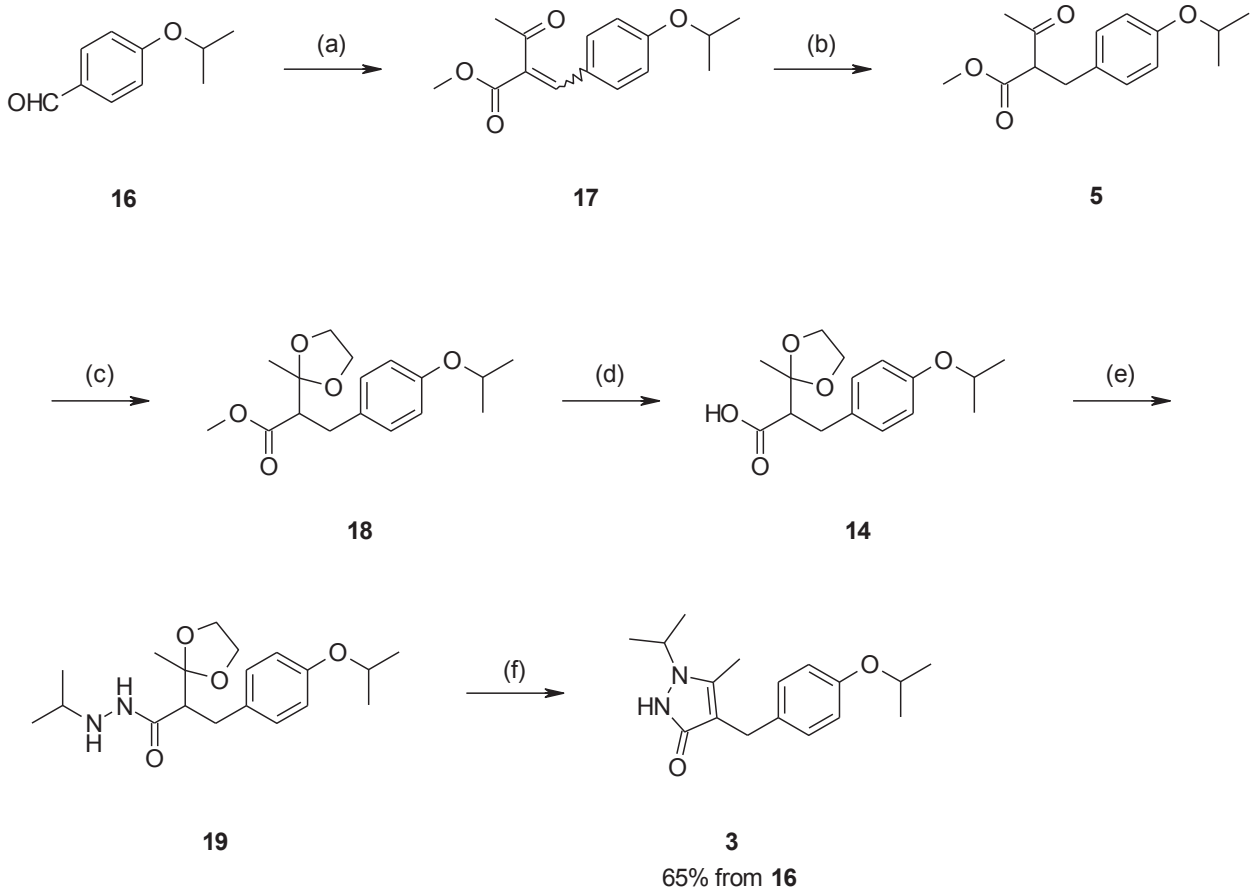
14 **15** **3** **6b**

Entry	Coupling Reagent	R^3	Conditions[a)]	Ratio (**3**/**6b**)[b)]	Yield of **3** (%)
1	CDI		A	99/1	90
2	DCC		A	97/3	28
3	DCC/HOBt		B	95/5	86
4	EDC·HCl/HOBt		C	99/1	76
5	TCDI		A	99.5/0.5	89

a) A: (a) Coupling reagent, THF, rt; (b) Isopropylhydrazine hydrochloride, Et_3N, dimethylformamide (DMF), 80 °C; (c) 10 M HCl aq., THF, DMF, 80 °C. B: (a) Coupling reagent, Et_3N, THF, DMF, rt; (b) Isopropylhydrazine hydrochloride, rt; (c) 10 M HCl aq., THF, DMF, 80 °C. C: (a) Coupling reagent, Et_3N, THF, DMF, rt; (b) Isopropylhydrazine hydrochloride, 80 °C; (c) 10 M HCl aq., THF, DMF, 80 °C.
b) Determined by HPLC.

More specifically, when CDI was employed as the coupling reagent, the condensation reaction provided an excellent yield of **3** in high selectivity (90%, entry 1) via intermediate **15**. However, the use of *N*,*N*′-dicyclohexylcarbodiimide (DCC) was less effective, resulting in a low yield (28%, entry 2). The yield of **3** was improved once again upon the addition of 1-hydroxybenzotriazole (HOBt) to carbodiimide crosslinkers DCC and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl), although the obtained yields remained lower than that achieved using CDI (86 and 76%, entries 3 and 4, respectively). Although CDI appears to be the most efficient coupling reagent for this condensation, its use in larger scale syntheses is undesirable in terms of cost, as CDI is a relatively expensive reagent. We therefore attempted to replace CDI with *N*,*N*′-thionyldiimidazole (TCDI), as this reagent can be prepared

from the inexpensive reagents imidazole and thionyl chloride.[15,16] Interestingly, a comparable result was obtained (89% yield, entry 5), thereby allowing the selective preparation of N_1-isopropylpyrazol-3-one **3** via a 6-step sequence starting from commercially available 4-isopropoxybenzaldehyde (**16**), and without the use of expensive reagents (Scheme 5).



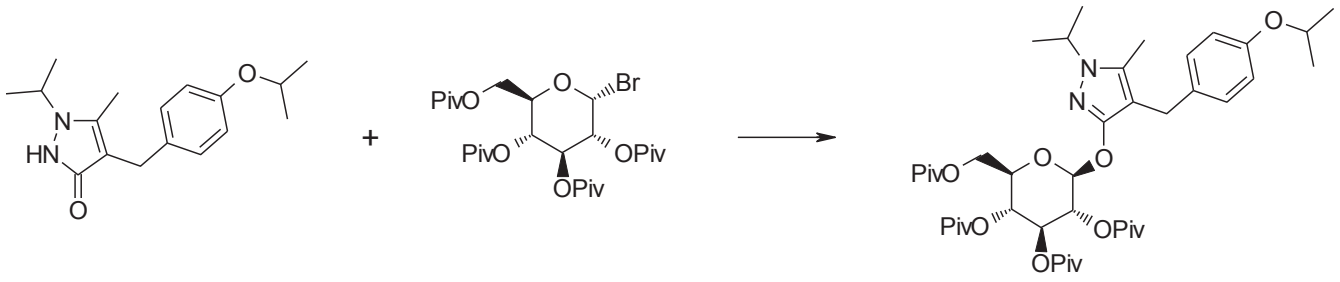
Scheme 5. Application of the developed method in the synthesis of **3** from **16**. Reagents and conditions: (a) methyl acetoacetate, pyridine/acetic acid, rt; (b) H_2, 10% Pd/C, 2-propanol (2-PrOH), rt; (c) ethylene glycol, *p*-toluenesulfonic acid (TsOH)/toluene, reflux; (d) NaOH, MeOH, reflux; (e) (i) *N,N*′-thionyldiimidazole (TCDI)/THF, rt, (ii) isopropylhydrazine hydrochloride, Et_3N/DMF, 80 °C; (f) 6 M HCl, 80 °C.

More specifically, treatment of **16** with methyl acetoacetate under Knoevenagel conditions provided **17**, and subsequent hydrogenation of the crude product **17** in the presence of Pd/C gave **5**. Following protection of the carbonyl group of **5** with ethylene glycol, the crude product **18** was hydrolyzed using aqueous NaOH in methanol (MeOH) to provide **14**. Condensation of **14** with isopropylhydrazine hydrochloride under the aforementioned conditions using TCDI as the coupling reagent followed by *in situ* deprotection of the carbonyl group of **19** in the presence of hydrochloric acid provided **3**. Overall, this synthetic process provided **3** in 65% yield from **16** without isolation of the various synthetic intermediates.

To complete the synthesis of **1**, an efficient method for the *O*-glycosylation of **3** with **4** was required. Indeed, we previously reported that the *O*-glycosylation of N_1-alkylated pyrazol-3-one with **4a** proceeded in a low yield,[8] and so we herein wished to re-investigate the *O*-glycosylation of **3** with **4** to achieve an efficient synthetic route to the target compound, **1**.

As the glycosidic linkage of **1** is unstable under acidic conditions, the *O*-glycosylation reaction must be performed under basic conditions. Although 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**4a**) is generally used as an effective glycosyl donor, it is relatively unstable, and so requires storage below −20 °C. We therefore selected 2,3,4,6-tetra-*O*-pivaloyl-α-D-glucopyranosyl bromide (**4b**) for the purpose of this study, as this glycosyl donor is stable, and so can be stored at room temperature without special caution.[8] Thus, the results obtained in the *O*-glycosylation of **3** with **4b** are summarized in Table 3.

Table 3. Optimization of the reaction conditions for the *O*-glycosylation of **3** with **4b**



3 **4b** **20**

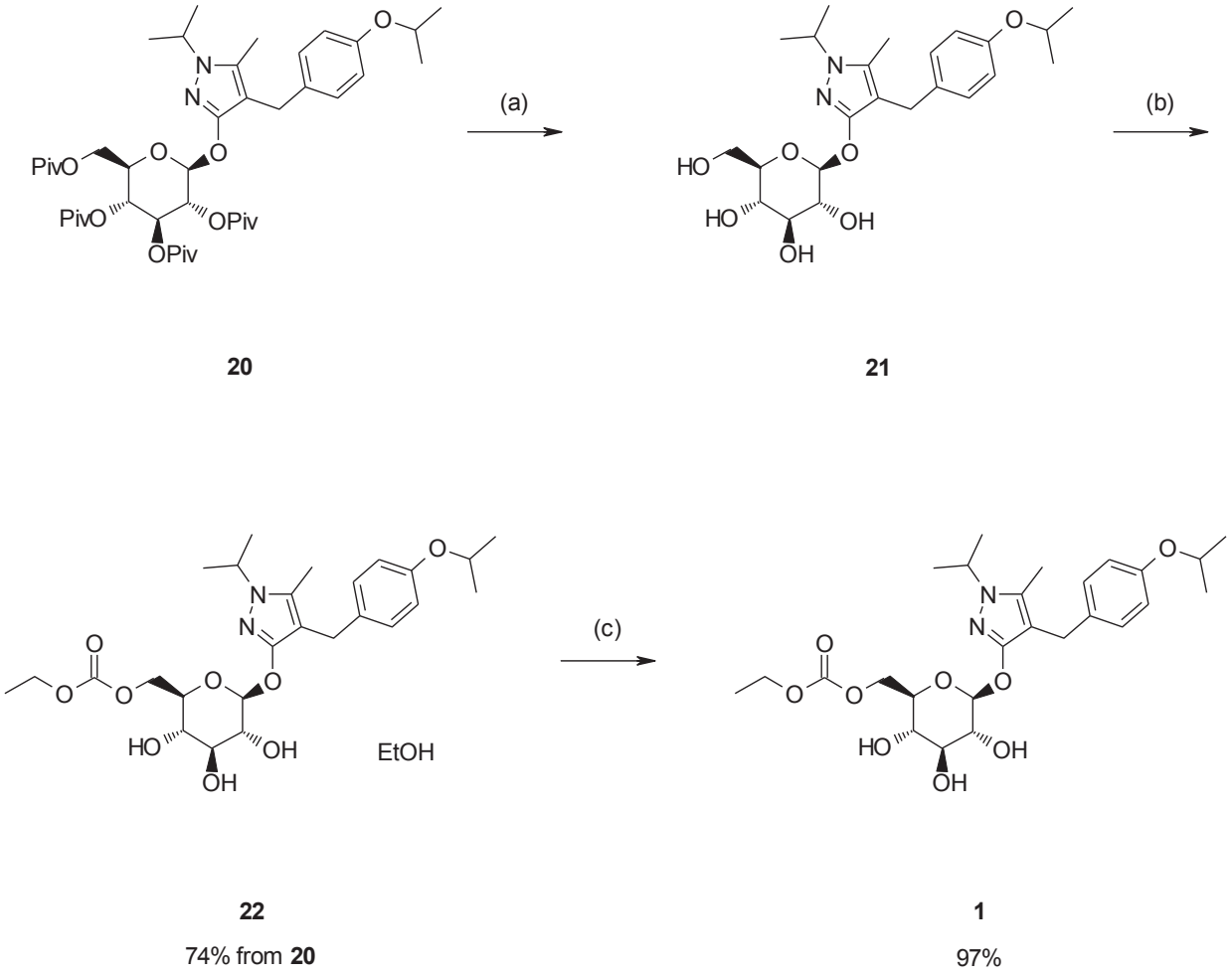
Entry	Solvent	Base	Temp. (°C)	Conversion (%)[a),b)]
1	MeCN	K_2CO_3	55	51
2	DMAc	NaH	rt	26
3	MeCN/2-PrOH (1:1)	K_2CO_3	50	79
4	MeCN/2-PrOH (1:1)	Cs_2CO_3	50	95
5	MeCN/2-PrOH (1:1)	KOH	rt	70
6	MeCN/2-PrOH (1:3)	Cs_2CO_3	50	97[c)]
7	2-PrOH	Cs_2CO_3	50	95
8	MeCN/*t*-BuOH (1:3)	Cs_2CO_3	50	95

a) Determined by HPLC.
b) Conversion = 100 × **20**/(**3**+**20**).
c) Isolated yield = 85%.

More specifically, in acetonitrile (MeCN) and in the presence of K_2CO_3, the reaction proceeded to give **20** in a low conversion (51%, entry 1), as reported previously.[8] Although the use of a stronger base was

expected to facilitate the formation of the imidic acid salt of **3**, NaH was found to be less effective than K_2CO_3 (26%, entry 2). In addition, in the presence of K_2CO_3 in a mixture of MeCN and 2-propanol (2-PrOH) (1:1), **20** was obtained in 79% conversion (entry 3). Furthermore, the use of Cs_2CO_3 was more effective than K_2CO_3 (95%, entry 4), while KOH produced a lower conversion than Cs_2CO_3 (70%, entry 5). It was therefore apparent that the combination of Cs_2CO_3 with an alcoholic solvent provided optimal results, with **20** being obtained in high conversions (95–97%, entries 4, 6, 7, and 8). In particular, the *O*-glycosylation of **3** with **4b** in the presence of Cs_2CO_3 in a mixture of MeCN and 2-PrOH (1:3) gave the highest conversion of 97% (entry 6). Formation of the α-anomer and glucoside-orthoester was not observed in either case. We therefore considered that *O*-glycosylation proceeds through a direct S_N2-type displacement reaction.

Achievement of the efficient *O*-glycosylation of **3** with **4b** made it possible to complete the synthesis of **1** from **3**. Thus, we have previously reported that remogliflozin etabonate **1** was prepared via a three-step sequence starting from **20**, as outlined in Scheme 6.[8]



20 **21**

22
74% from **20**

1
97%

Scheme 6. Completion of the preparation of **1** from **20**. Reagents and conditions: (a) MeONa, MeOH, 55 °C; (b) (i) ethyl chloroformate, 2,6-lutidine, pyridine/MeCN, 0 °C, (ii) recrystallization (EtOH, *n*-heptane); (c) recrystallization (MTBE, *n*-heptane).

The subsequent treatment of **20** with sodium methoxide (MeONa) in MeOH provided **21**, which was reacted in its crude form with ethyl chloroformate in the presence of 2,6-lutidine and a catalytic amount of pyridine[17] in MeCN to provide **1**, and subsequent recrystallization of the crude product **1** from a mixture of ethanol (EtOH) and *n*-heptane gave highly pure **22** as an ethanol solvate of **1** in 74% yield. Finally, **22** was recrystallized from a mixture of methyl *t*-butyl ether (MTBE) and *n*-heptane to provide **1** in an excellent yield of 97%.

In conclusion, we established an efficient and practical synthesis of remogliflozin etabonate (**1**) based on a chemoselective synthesis of **3** and an efficient *O*-glycosylation of **3** with **4b**. This synthetic process was achieved in 10 steps with an overall yield of 39% from commercially available 4-isopropoxy-benzaldehyde. Importantly, this result is superior to that previously reported for the preparation of **1**, which was completed in a 28% overall yield.[8] We could therefore conclude that the process described herein provided a considerable improvement in the overall yield of **1**. As such, we propose that this methodology could be applicable to the preparation of **1** on a larger scale to ultimately advance clinical trials on this selective low-affinity Na^+-dependent glucose co-transporter inhibitor.

EXPERIMENTAL

All melting points were measured using a Yanagimoto MP-J3 melting point apparatus and are uncorrected. Fourier transform infrared (FTIR) spectra were recorded on a Nicolet AVATAR 320 FT-IR spectrometer. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AV-400M spectrometer at 400 and 100 MHz, respectively, using tetramethylsilane as the internal standard. High resolution mass spectrometry (MS) was carried out on an Agilent Technologies QToF 6520 mass spectrometer.

2,4-Dihydro-4-[(4-isopropoxyphenyl)methyl]-2-isopropyl-5-methyl-3*H*-pyrazol-3-one (6b). A mixture of **5** (0.264 g, 1.0 mmol), isopropylhydrazine hydrochloride (0.166 g, 1.5 mmol), and Et_3N (0.202 g, 2.0 mmol) in a mixture of THF (3 mL) and toluene (3 mL) was refluxed for 12 h. After the reaction mixture was cooled to room temperature, the resulting triethylamine hydrochloride was removed by filtration. The filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (eluent EtOAc:MeOH, 100:0 → 85:15) to provide **6b** (0.210 g, 73%). An analytical sample of **6b** was obtained as a white solid by recrystallization from a mixture of EtOAc (2 mL) and *n*-hexane (4 mL). mp 120–121 °C. IR (KBr) cm^{-1}: 2974, 2930, 1599, 1560, 1508, 1464, 1424, 1375, 1368, 1290, 1244, 1182, 1121. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, d, *J*=6.8 Hz), 1.22 (3H, d, *J*=6.8 Hz), 1.28 (3H, d, *J*=3.3 Hz), 1.30 (3H, d, *J*=3.3 Hz), 2.01 (3H, d, *J*=0.5 Hz), 3.07–3.16 (2H, m), 3.25 (1H, t, *J*=5.3 Hz), 4.26–4.36 (1H, m), 4.44–4.53 (1H, m), 6.76 (2H, d, *J*=8.8 Hz), 7.05 (2H, d,

J=8.5 Hz). ^{13}C-NMR ($CDCl_3$) δ: 16.2 (q), 20.4 (q), 20.6 (q), 21.9 (q), 22.0 (q), 32.5 (t), 44.6 (d), 53.1 (d), 69.9 (d), 115.9 (d×2), 128.1 (s), 129.9 (d×2), 156.9 (s), 158.4 (s), 173.4 (s). HRMS (ESI) *m/z*: 289.1910 $[M+H]^+$ (Calcd for $C_{17}H_{25}N_2O_2$: 289.1911).

General Procedure for Reaction of 7 with Isopropylhydrazine. A solution of acylating agent (1.96 mmol) in toluene (0.5 mL) was added dropwise to a mixture of acetoacetic acid (200 mg, 1.96 mmol) and pyridine (158 mg, 2.00 mmol) in a mixture of toluene (1.9 mL) and THF (1.2 mL) while maintaining the temperature < 5 °C, and the resulting mixture was stirred for 1 h at 0 °C. After this time, the reaction mixture was added dropwise to a solution of isopropylhydrazine (294 mg, 3.97 mmol) and Et_3N (200 mg, 1.98 mmol) in toluene (1.5 mL) and stirring continued for 15 h at room temperature. After this time, the reaction mixture was diluted with toluene (20 mL) and washed with H_2O (2 × 15 mL). The resulting organic layer was dried over anhydrous $MgSO_4$ and the filtrate was concentrated under reduced pressure. The ratios of **8**/**9** was determined by ^{1}H NMR spectroscopy. **8**: ^{1}H-NMR ($CDCl_3$) δ: 1.42 (6H, d, *J*=6.9 Hz), 2.19 (3H, d, *J*=0.7 Hz), 4.27 (1H, m), 5.36 (1H, d, *J*=0.6 Hz). **9**: ^{1}H-NMR ($CDCl_3$) δ: 1.28 (6H, d, *J*=6.6 Hz), 2.10 (3H, s), 3.21 (2H, s), 4.42 (1H, m).

Procedure for Reaction of 11a with Isopropylhydrazine. A solution of isobutyryl chloride (0.875 g, 8.21 mmol) in toluene (15 mL) was added dropwise to a mixture of **10** (1.04 g, 7.14 mmol) and pyridine (0.650 g, 8.21 mmol) in toluene (5 mL) while maintaining the temperature < 5 °C, and the resulting mixture was stirred for 2 h at 0 °C. After this time, the reaction mixture was added dropwise to a solution of isopropylhydrazine (1.06 g, 14.3 mmol) in toluene (10 mL) and stirring continued for 2 h at room temperature. The reaction mixture was concentrated under reduced pressure. Subsequently, a mixture of the obtained residue and 1 M HCl (20 mL) in THF (15 mL) was stirred for 2 h at 70 °C. After cooling to room temperature, sodium hydrogencarbonate ($NaHCO_3$) (1.8 g) was added to the reaction mixture, and ethyl acetate (EtOAc) (20 mL) was then added to the reaction mixture. Following separation of the aqueous and organic layers, the aqueous layer was then extracted with EtOAc (3 × 20 mL) and the organic layers were combined. After this time, the obtained organic layer was dried over anhydrous $MgSO_4$ and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (eluent EtOAc:MeOH, 100:0 → 95:5) to provide **8** (0.528 g, 53%).

Procedure for Reaction of 11b with Isopropylhydrazine. A mixture of **10** (2.00 g, 13.7 mmol) and CDI (2.44 g, 15.0 mmol) in THF (16 mL) was stirred for 0.5 h at room temperature, and the reaction mixture was concentrated under reduced pressure. A solution of the obtained residue in toluene (10 mL)

was added to dropwise to a solution of isopropylhydrazine (2.03 g, 27.4 mmol) in toluene (10 mL), and stirring continued for 1 h at 10 °C. The reaction mixture was concentrated under reduced pressure. Subsequently, a mixture of the obtained residue and 2 M HCl (29 mL) in THF (28 mL) was stirred for 2 h at 70 °C. After cooling to room temperature, $NaHCO_3$ (2.32 g) was added to the reaction mixture, and EtOAc (20 mL) was then added to the reaction mixture. Following separation of the aqueous and organic layers, the aqueous layer was then extracted with EtOAc (3 × 20 mL) and the organic layers were combined. After this time, the obtained organic layer was dried over anhydrous $MgSO_4$ and the filtrate was concentrated under reduced pressure to provide **8** (1.82 g, 95%).

Methyl 2-[(4-isopropoxyphenyl)methyl]-3-oxobutanoate (5). A mixture of **16** (10.0 g, 60.9 mmol), methyl acetoacetate (14.0 g, 121 mmol), piperidine (1.60 g, 18.8 mmol), and acetic acid (5.0 g, 83.3 mmol) was stirred for 115 h at room temperature prior to the addition of 2-PrOH (80 g) to the reaction mixture. Subsequently, the obtained solution was hydrogenated over 10% Pd/C (50% wet with water for safety, 3.2 g) for 6 h at room temperature under atmospheric pressure. After this time, the Pd/C was removed by filtration, and the filtrate was concentrated under reduced pressure. EtOAc (60 g) was then added to the residue and the mixture was washed successively with H_2O (60 g), a 5% aqueous solution of $NaHCO_3$ (60 g), and a 10% aqueous solution of NaCl (60 g). The resulting organic layer was dried over anhydrous $MgSO_4$ and the filtrate was concentrated under reduced pressure. The obtained crude residue weighed 19.1 g and was used in the next step without further purification. An analytical sample of **5** was obtained as a colorless oil by purification using silica gel column chromatography (eluent EtOAc:*n*-hexane, 2:98 → 35:65). IR (NaCl) cm^{-1}: 2981, 1747, 1718, 1612, 1511, 1436, 1384, 1373, 1360. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (6H, d, J=6.0 Hz), 2.17 (3H, s), 3.09 (2H, d, J=7.8 Hz), 3.69 (3H, s), 3.75 (1H, t, J=7.8 Hz), 4.45–4.54 (1H, m), 6.79 (2H, d, J=8.7 Hz), 7.06 (2H, d, J=8.7 Hz). ^{13}C-NMR ($CDCl_3$) δ: 22.0 (q×2), 29.8 (q), 33.3 (t), 52.4 (q), 61.4 (d), 69.8 (d), 116.0 (d×2), 129.77 (d×2), 129.80 (s), 156.7 (s), 169.7 (s), 202.7 (s). HRMS (ESI) *m/z*: 287.1255 $[M+Na]^+$ (Calcd for $C_{15}H_{20}NaO_4$: 287.1254).

Methyl 3-[(4-isopropoxyphenyl)methyl]-2-(2-methyl-1,3-dioxolan-2-yl)propionate (18). A mixture of crude product **5** from the preceding step, ethylene glycol (18.0 g, 290 mmol), and *p*-toluenesulfonic acid monohydrate (0.232 g, 1.22 mmol) in toluene (160 g) was refluxed for 8 h with azeotropic drying. After this time, the reaction mixture was cooled to room temperature and washed successively with a 5% aqueous solution of $NaHCO_3$ (80 g) and with H_2O (40 g). The organic layer was concentrated under reduced pressure. The obtained crude residue weighed 23.0 g and was used in the next step without further purification. An analytical sample of **18** was obtained as a colorless oil by purification using

silica gel chromatography (eluent EtOAc:*n*-hexane, 2:98 → 40:60). IR (NaCl) cm^{-1}: 2975, 1739, 1612, 1510, 1436, 1383, 1356. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (6H, d, *J*=6.0 Hz), 1.46 (3H, s), 2.87–3.00 (3H, m), 3.56 (3H, s), 3.96–4.06 (4H, m), 4.45–4.54 (1H, m), 6.78 (2H, d, *J*=8.8 Hz), 7.05 (2H, d, *J*=8.5 Hz). ^{13}C-NMR ($CDCl_3$) δ: 21.7 (q), 22.1 (q×2), 33.3 (t), 51.6 (q), 56.7 (d), 64.86 (t), 64.92 (t), 69.8 (d), 109.4 (s), 115.9 (d×2), 129.6 (d×2), 131.1 (s), 156.4 (s), 172.6 (s). HRMS (ESI) *m/z*: 309.1705 $[M+H]^+$ (Calcd for $C_{17}H_{25}O_5$: 309.1697).

3-[(4-Isopropoxyphenyl)methyl]-2-(2-methyl-1,3-dioxolan-2-yl)propionic acid (14). A mixture of crude product **18** from the preceding step and a 25 w/v% aqueous solution of NaOH (14 mL, 89.7 mmol) in MeOH (19 g) was refluxed for 7 h. After this time, the reaction mixture was concentrated under reduced pressure, and the resulting residue was dissolved in H_2O (57 g) and MTBE (95 g). Following separation of the aqueous and organic layers, the aqueous layer was washed with MTBE (95 g), while MTBE (95 g) and 2 M HCl (37 mL) were added to the aqueous layer, and the layers were separated once again. The organic layer was then washed with a 10% aqueous solution of NaCl (57 g) and dried over anhydrous $MgSO_4$. The filtrate was concentrated under reduced pressure to provide **14** as a colorless oil (15.2 g, 85% yield from **16**). IR (NaCl) cm^{-1}: 2977, 2936, 2893, 1737, 1711, 1611, 1508, 1448, 1383, 1334. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (6H, d, *J*=6.0 Hz), 1.47 (3H, s), 2.88–3.00 (3H, m), 3.97–4.07 (4H, m), 4.45–4.54 (1H, m), 6.78 (2H, d, *J*=8.5 Hz), 7.08 (2H, d, *J*=8.5 Hz). ^{13}C-NMR ($CDCl_3$) δ: 21.8 (q), 22.1 (q×2), 33.0 (t), 56.6 (d), 64.89 (t), 64.94 (t), 69.8 (d), 109.3 (s), 115.9 (d×2), 129.7 (d×2), 130.8 (s), 156.5 (s), 177.3 (s). HRMS (ESI) *m/z*: 295.1546 $[M+H]^+$ (Calcd for $C_{16}H_{23}O_5$: 295.1540).

***N*′-Isopropyl-3-[(4isopropoxyphenyl)methyl]-2-(2-methyl-1,3-dioxolan-2-yl)propanohydrazide (19).** Thionyl chloride (6.79 g, 57.1 mmol) was added dropwise to a mixture of imidazole (7.76 g, 114 mmol) and pyridine (9.02 g, 114 mmol) in THF (150 g) while maintaining the temperature between 0 and 10 °C and the reaction mixture stirred for 1 h at 5 °C. Subsequently, a solution of **14** (15.2 g, 51.6 mmol) in THF (60 g) was added dropwise to the reaction mixture, and stirring continued for 1 h at room temperature. After this time, DMF (31 g), Et_3N (10.5 g, 104 mmol), and isopropylhydrazine hydrochloride (8.61 g, 77.9 mmol) were added successively to the reaction mixture, and stirring continued for 6 h at 80 °C. The reaction mixture was then cooled to room temperature and used directly in the next step without further purification. An analytical sample of **19** was obtained as a colorless solid by purification using silica gel column chromatography (eluent EtOAc:*n*-hexane, 40:60 → 100:0). mp 104–106 °C. IR(KBr) cm^{-1}: 3298, 2977, 1635, 1613, 1512, 1381, 1251, 1209, 1121, 1050. ^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, d, *J*=6.2 Hz), 0.95 (3H, d, *J*=6.2 Hz), 1.30 (6H, d, *J*=6.1 Hz), 1.42 (3H, s), 2.54 (1H, dd, *J*=3.2, 11.6 Hz), 2.87–3.05 (3H, m), 3.94–4.05 (4H, m), 4.43–4.52 (1H, m), 6.76 (2H, d,

J=8.7 Hz), 7.08 (2H, d, *J*=8.7 Hz). ^{13}C-NMR ($CDCl_3$) δ: 20.5 (q), 20.6 (q), 21.6 (q), 22.1 (q×2), 32.7 (t), 50.9 (d), 56.9 (d), 64.8 (t), 64.9 (t), 69.9 (d), 109.5 (s), 115.9 (d×2), 129.8 (d×2), 131.5 (s), 156.4 (s), 170.8 (s). HRMS (ESI) *m/z*: 351.2279 $[M+H]^+$ (Calcd for $C_{19}H_{31}N_2O_4$: 351.2278).

1,2-Dihydro-4-[(4-isopropoxyphenyl)methyl]-1-isopropyl-5-methyl-3*H*-pyrazol-3-one (3). To the above reaction mixture was added 6 M HCl (65 mL) and the resulting mixture allowed to stir for 17 h at 80 °C. After cooling to room temperature, $NaHCO_3$ (35 g) was added to the reaction mixture and the layers were separated. The aqueous layer was then extracted with toluene (72 g) and the organic layers were combined. The obtained organic layer was concentrated under reduced pressure, and the resulting residue was dissolved in MeCN (36 g) at 80 °C. Subsequently, H_2O (36 g) was added dropwise at 60 °C, and the obtained slurry was cooled to room temperature. Similarly, H_2O (18 g) was added dropwise, and the slurry was stirred for 3 h at room temperature. After this time, the slurry was filtered and the cake was washed twice with a mixture of MeCN (9.0 g) and H_2O (9.0 g). The precipitate was dried under reduced pressure to provide **3** as a white solid (11.3 g, 65% yield from **16**). mp 141–142 °C. IR (KBr) cm^{-1}: 2978, 2933, 1613, 1532, 1508, 1285, 1273, 1242, 1203, 1184, 1125. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (6H, d, *J*=6.3 Hz), 1.39 (6H, d, *J*=6.8 Hz), 2.05 (3H, s), 3.62 (2H, s), 4.19–4.29 (1H, m), 4.43–4.52 (1H, m), 6.77 (2H, d, *J*=8.9 Hz), 7.14 (2H, d, *J*=8.9 Hz), 11.96 (1H, bs). ^{13}C-NMR ($CDCl_3$) δ: 9.7 (q), 22.1 (q×4), 27.1 (t), 48.9 (d), 69.9 (d), 101.3 (s), 115.7 (d×2), 129.2 (d×2), 133.9 (s), 136.2 (s), 155.9 (s), 160.0 (s). HRMS (ESI) *m/z*: 289.1909 $[M+H]^+$ (Calcd for $C_{17}H_{25}N_2O_2$: 289.1911).

4-[(4-Isopropoxyphenyl)methyl]-1-isopropyl-5-methyl-3-(2,3,4,6-tetra-*O*-pivaloyl-β-D-glucopyranosyloxy)-1*H*-pyrazole (20). A mixture of **3** (5.00 g, 17.3 mmol), **4b** (13.1 g, 22.6 mmol), and Cs_2CO_3 (11.3 g, 34.5 mmol) in a mixture of MeCN (13 g) and 2-PrOH (39 g) was stirred for 3 h at 50 °C. After this time, the reaction mixture was concentrated under reduced pressure and toluene (50 g) was added to the residue prior to washing with H_2O (2 × 30 g). Subsequently, the organic layer was concentrated under reduced pressure, the obtained residue was dissolved in 2-PrOH (50 g) and concentrated under reduced pressure. 2-PrOH was then added to the residue to adjust the weight to 50 g. The mixture was then heated to 50 °C to dissolve all solids, and the resulting solution was cooled to room temperature prior to seeding with **20** and stirring for 2 h at room temperature. The resulting slurry was cooled to 3 °C, a mixture of 2-PrOH (10 g) and *n*-heptane (10 g) was added dropwise, and the slurry was cooled to −5 °C and stirred for 2 h. After this time, the slurry was filtered, and the wet cake was washed with 2-PrOH (2 × 5.0 g). The precipitate was dried under reduced pressure to provide **20** as a white solid (11.6 g, 85%). The analytical results agreed with literature values.[8]

3-(β-D-Glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-1-isopropyl-5-methyl-1*H*-pyrazole (21). A 28% methanolic solution of MeONa (2.69 g, 14.0 mmol) was added to a suspension of **20** (11.0 g, 14.0 mmol) in MeOH (85 g) at room temperature and the resulting mixture was stirred for 3 h at 55 °C. After this time, the reaction mixture was cooled to room temperature, and a methanolic solution of 40% phosphoric acid (20.5 g, 8.39 mmol) was added dropwise. The reaction mixture was then concentrated under reduced pressure to evaporate any methyl pivalate present in the mixture. Subsequently, MeCN (55 g) was added to the residue, the resulting inorganic salts were removed by filtration through Celite®, and the filtrate was concentrated under reduced pressure to provide **21** as a pale brown oil, which was used in the next step without purification. The analytical results agreed with literature values.[8]

5-Methyl-4-[4-(1-methylethoxy)benzyl]-1-(1-methylethyl)-1*H*-pyrazol-3-yl-6-*O*-(ethoxycarbonyl)-β-D-glucopyranoside ethanolate (22). A solution of ethyl chloroformate (1.74 g, 16.1 mmol) in MeCN (3 g) was added dropwise to a mixture of **21** (6.30 g, 14.0 mmol), 2,6-lutidine (2.25 g, 21.0 mmol), and pyridine (44 mg, 0.56 mmol) in MeCN (18 g) while maintaining the temperature between −3 and 3 °C. Following complete addition of this solution, the reaction mixture was stirred at 0 °C for 2 h, after which time glacial acetic acid (378 mg, 6.29 mmol) was added and the mixture allowed to warm to room temperature. The reaction mixture was then diluted with MTBE (20 g) and a 10% aqueous solution of NaCl (13 g), and the layers separated. The organic layer was washed twice with a 10% aqueous solution of NaCl (13 g), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained residue was dissolved in EtOH (40 g) and concentrated under reduced pressure. EtOH was then added to the residue to adjust the weight to 37.8 g. To the resulting EtOH solution, *n*-heptane (13 g) was added and this mixture heated to 60 °C to dissolve all solids. After cooling to 45 °C and stirring for 1 h at this temperature, stirring was continued for an additional 1 h at 0–5 °C. The resulting slurry was filtered, and the wet cake washed with a mixture of EtOH (3.2 g) and *n*-heptane (6.3 g) cooled to 0 °C, then washed with *n*-heptane (6.3 g). The precipitate was dried under reduced pressure at room temperature to give **22** as a white solid (5.88 g, 74%). The analytical results agreed with literature values.[8]

5-Methyl-4-[4-(1-methylethoxy)benzyl]-1-(1-methylethyl)-1*H*-pyrazol-3-yl-6-*O*-(ethoxycarbonyl)-β-D-glucopyranoside (1). Compound **22** (5.50 g, 9.67 mmol) was dissolved in MTBE (28 g) at 45 °C and the resulting solution concentrated under reduced pressure to remove the EtOH from the ethanolate. MTBE was then added to the residue to adjust the weight to 33 g. Subsequently, H_2O (0.061 mL) and *n*-heptane (13 g) were added to the solution at 40 °C and the solution cooled to 25 °C. After seeding this solution with **1** and stirring at 25 °C for 3 h, the resulting slurry was warmed to 40 °C, and a mixture of MTBE (1.6 g) and *n*-heptane (9.0 g) was added dropwise while maintaining the temperature between 37

and 43 °C. The slurry then was stirred at 40 °C for 1 h and for an additional 3 h at 10 °C. The slurry was filtered and the wet cake washed successively with a mixture of MTBE (5.5 g) and *n*-heptane (5.5 g) followed by *n*-heptane (11 g). The precipitate was dried under reduced pressure at room temperature to give **1** as a white solid (4.91 g, 97%). The analytical results agreed with literature values.[8]

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