Organic Process Research & Development

Article

pubs.acs.org/OPRD

An Efficient Synthesis of 3-Substituted *N*-Glycoside Indoles Useful as Sodium-Dependent Glucose Transporter Inhibitors

Xun Li,* Kenneth M. Wells,* Shawn Branum, Sandra Damon, Scott Youells, Derek A. Beauchamp, David Palmer, Stephen Stefanick, Ronald K. Russell, and William Murray

Janssen Research and Development, L.L.C., Welsh and McKean Roads, Spring House, Pennsylvania 19477, United States

Supporting Information

ABSTRACT: A practical synthesis of two *N*-glycoside indoles **1** and **2**, identified as highly potent sodium-dependent glucose transporter (SGLT) inhibitors is described. Highlights of the synthetic process include a selective and quantitative Vilsmeier acylation and a high-yielding Grignard coupling reaction. The chemistry developed has been applied to prepare two separate SGLT inhibitors **1** and **2** for clinical evaluation without recourse to chromatography.

INTRODUCTION

One and a half million new cases of diabetes mellitus are diagnosed every year worldwide, and it is projected by the year 2050 that the number of individuals with diagnosed diabetes mellitus will increase by 165% in the United States alone.[1] Presently, there is a number of antidiabetic agents used in clinical treatment such as biguanide compounds, sulfonylurea compounds, insulin resistance-improving agents, and α-glucosidase inhibitors. These antidiabetic agents, while useful, have various serious undesired side effects.[2]

The crucial need for new diabetes mellitus treatment options with fewer or no unfavorable side effects have enticed pharmaceutical companies to develop novel treatment strategies. For example, by inhibiting the sodium-dependent glucose transporter 2 (SGLT2) present at the proximal convoluted tubule of the kidney, the reabsorption of glucose in the kidney is inhibited. The glucose is therefore excreted into the urine thus decreasing the blood glucose level.[3] Several potent SGLT2 inhibitors have entered clinical development (Figure 1).[3,4] Two

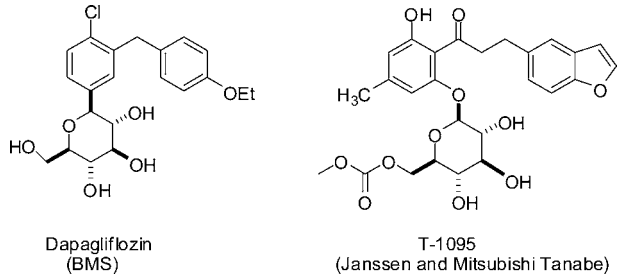


Figure 1. Examples of C- and O-glycosides as SGLT2 inhibitors that have entered clinical development.

N-glycosides inhibitors of SGLT2, **1**[5a] and **2**,[5b] have been identified as candidates for further development (Figure 2). Herein, we describe a safe, scaleable synthetic route to **1**, which has delivered several hundred grams to support early preclinical studies. The chemistry developed for **1** was applied successfully to the synthesis of **2** and was used to prepare material for preclinical study.

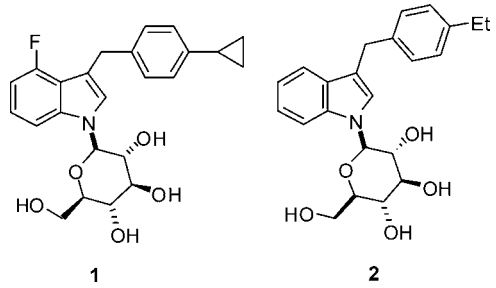


Figure 2. Examples of *N*-glycosides as SGLT2 inhibitors.

RESULTS AND DISCUSSION

The initial discovery synthesis of **1** described by the Mitsubishi Tanabe Pharma Corporation is shown in Scheme 1.[5a] Upon review of the discovery route, we identified scale-up issues that required synthesis improvements. For example, the Vilsmeier formylation conditions in step 1 gave 18−20% of the 2,3-diformyl **4a** impurity, which required removal by chromatography since recrystallization of the crude mixture could not afford pure 3-formyl indole **4**. Another issue was the poor isolated yield of 4−bromocyclopropylbenzene (**8**) (Scheme 3). Further complicating the scale-up was the chromatography burden, in which three column chromatographies were required to purify the intermediates **4**, **6**, and active pharmaceutical ingredient (API) **1** (see Table 1). Finally the crystallization of the **1** was not well developed, and the procedure relied on a difficult, slow conversion of an EtOH solvate to the desired hemihydrate, which was difficult to reproduce on large scale.

Vilsmeier Process Development. During initial observations of the Vilsmeier reaction on indole **3** with 3 equiv. of phosphorous(III) oxychloride and 6 equiv of DMF at 90 °C, a major impurity **4a** was observed which was confirmed by ^{1}H NMR and LC/MS (Scheme 2). Several reports of Vilsmeier reactions of these indoles in the literature all used DMF as a solvent and reaction temperatures of 90 °C which led in our

Received: May 23, 2012
Published: October 18, 2012

   dx.doi.org/10.1021/op3001355 | *Org. Process Res. Dev.* 2012, 16, 1727−1732

Scheme 1. Synthesis of SGLT2 inhibitor 1

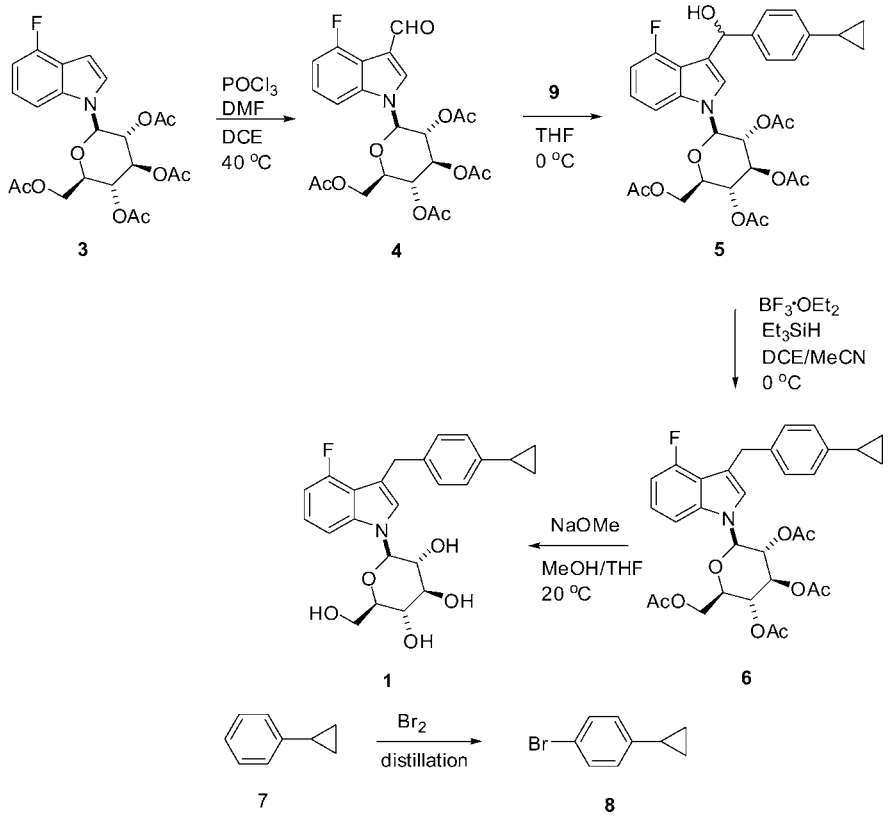
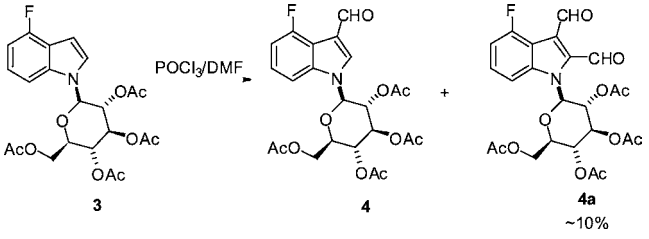


Table 1. Summary of the discovery and scale-up reaction yields for the preparation of SGLT2 inhibitor 1

route step	Mitsubishi Tanabe discovery[a,b]	scale-up of **1**
1	column chromatography, 79% of **4**, 18% of **4a**[c]	100% of **4**
2	(not isolated)	(not isolated)
3	column chromatography 89% of **6**	85% of **6**
4	column chromatography, 96% of **1**	98% of **1**

[a]Isolated yields from our laboratory using Mitsubishi Tanabe's conditions. [b]Three chromatographic purifications were required (steps 1, 3, and 4). [c]**4a** was isolated by this work.

Scheme 2. Vilsmeier impurity formation



hands to production of substantial amounts of impurity **4a**.[6a,b] In order to reduce or eliminate **4a**, the ratio of $POCl_3$/DMF used, as well as the effects of time and temperature, was studied (Figure 3).

It was found that diformylation rate was very dependent on the temperature of the reaction. At temperatures below 40 °C, the diformylation product **4a** was not detectable even after extended aging. For example, treatment of indole **3** with lower amounts of both $POCl_3$/DMF produced no byproduct **4a**; however, 46% and 19% of unreacted **3** remained after 12 h. Optimization of $POCl_3$/DMF to 2.5 equiv/1.4 equiv resulted in complete conversion of **3** to the desired 3-formyl compound **4** as the sole product, at both 30 and 40 °C within 12 h. The reaction mixture was safely quenched by adding the reaction mixture over 75 min to warm aqueous sodium acetate. We were able to safely quench the reaction without any delayed exotherm that is typical when this reagent is used.[7] It is **absolutely imperative** to perform this quench between 35 °C and 40 °C. The addition rate of the crude reaction mixture must be adjusted accordingly to remain within this temperature range. This quench is extremely exothermic, and the recommended temperature range from data derived from the reaction calorimeter (RC-1) study of the quench guarantees instantaneous reaction of $POCl_3$ with water.[8] The instantaneous quenching prevents an accumulation of unreacted $POCl_3$ and the possibility of a runaway quench reaction. These conditions afforded **4** as a solid in high purity and quantitative yield and thus eliminated any need for chromatography.

Cyclopropylaryl Bromide and Subsequent Grignard Formation Process Development. Since aryl bromide **8** was not commercially available in bulk, the synthesis from cyclopropylbenzene was investigated. The discovery route followed the procedure outlined by Himmelsbach et al., which gave four products (Scheme 3/entry 1 of Table 2) and only a 38% yield of the desired **8** after careful fractional distillation.[9]

Similar conditions were reported by Lavey et al., where chromatography was used to purify the crude reaction mixture and likewise gave a 21% isolated yield of **8**.[10] Zeolite-catalysed bromination conditions of **7** also have been reported, but the reported yields (30%) of **8** offered no attractive alternative.[11]

dx.doi.org/10.1021/op3001355 | Org. Process Res. Dev. 2012, 16, 1727−1732

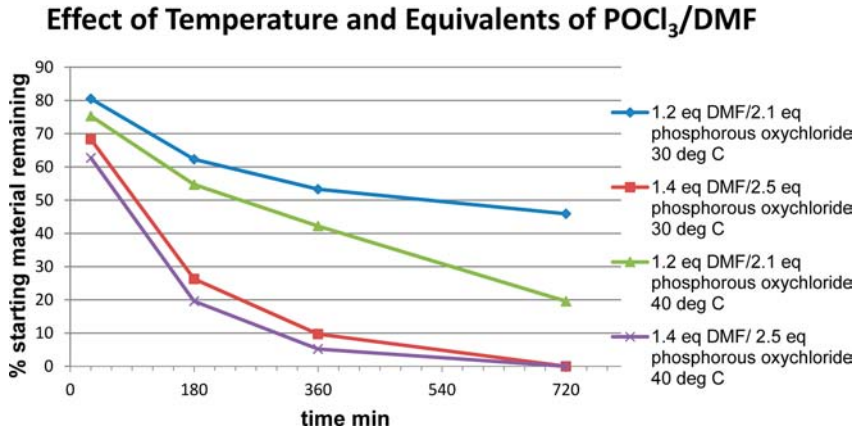


Figure 3. Vilsmeier optimization conditions.

Scheme 3. Original bromination conditions

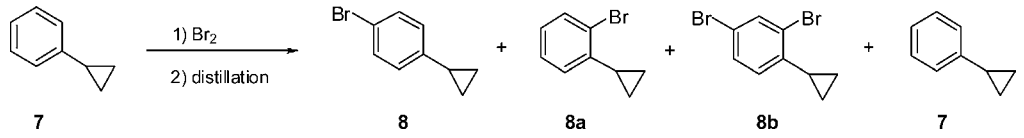


Table 2. Reaction conditions and the results for selective bromination of compound 7 to 8

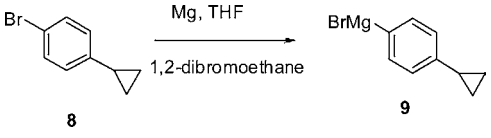
entry	7 (g)	temp (°C)	solvent	time (h)	crude mixture of 8/8a/8b/7/unknown (HPLC, area %)	isolated yield of 8 (g/ %)[a]
1[b]	5.0	0–10	HOAc	8	38/26/10/15/11[c]	3.2/38.5
2[d]	1.0		DMF		ND[e]	ND
3[f]	5.0	20	CH_2Cl_2	6	36/11/37/12/4[g]	ND
4[h]	5.0	−62	$CHCl_3$	3.5	69/9/14/8/0	5.7/69.0
5[h]	5.0	−76	CH_2Cl_2	3	82/6/8/2/2	6.1/73.0
6[h]	25.0	−76	CH_2Cl_2	4	73/7/10/6/4	30.1/74.5
7[h]	150.0	−76	CH_2Cl_2	5	81/6/8/5/0	195.0/81.0
8[h]	150.0	−76	CH_2Cl_2	5	87/3/5/5/0	210.0/90.0

[a]After distillation the product **8** purity was >94%. [b]1.0 equiv of Br_2, KOAc. [c]Mitsubishi Tanabe's synthetic process. [d]1.0 equiv NBS. [e]A complicated mixture. [f]1.12 equiv of Br_2, NaY Zeolite. [g]Could not be separated by distillation. [h]1.05 equiv of Br_2.

However, a report by Lvina and Gembitskii of a high-yielding bromination of **7** using bromine at low temperatures in $CHCl_3$ led us to further explore these conditions.[12] Although these conditions (Table 2 entry 4) showed a much improved yield (69%) of **8** after distillation, a total of 23% of the competitive byproducts **8a** and **8b** were formed. However, since the reaction mixture in $CHCl_3$ (mp −63 °C) became a solid mass below −65 °C, CH_2Cl_2 (mp −97 °C) was chosen as an alternative solvent. Another benefit of the solvent switch is that the ICH guidance for residual $CHCl_3$ is 10 times lower than for CH_2Cl_2. The results (Table 2 entries 5–8) indicated that the reaction in CH_2Cl_2 at −76 °C resulted in a much higher ratio of the para versus the ortho position as well as an improved yield of **8** (90%) after distillation.

The formation of the Grignard reagent **9** in THF with magnesium was straightforward with the aid of 1,2-dibromoethane as an initiator (Scheme 4) and was used directly in the next step. This freshly prepared Grignard reagent was added to a THF solution of 3-formylindole **4** at 0 °C, and after quench and workup, a quantitative recovery of the crude alcohol **5** was obtained, which was used directly in the next reduction step without further purification.

Scheme 4. Grignard formation



Benzyl Alcohol Reduction and Protecting Group Removal. The hydroxy group of intermediate **5** was reduced (Et_3SiH/BF_3OEt_2) following the procedure outlined by the discovery team and gave good reproducibility of yield and quality of product. The product **6** was obtained in good yield (85%) and excellent purity after recrystallization from EtOH. Finally, the acetoxy protecting groups were removed with a catalytic amount of NaOMe in MeOH/THF, and the resulting crude **1** was recrystallized from aqueous EtOH to give a 97.5 LCAP of a pure EtOH/H_2O solvate of **1**. This solvate was slurried in warm H_2O and the solid-state form converted over 20 h to the desired hemihydrate form as a crystalline solid, which was confirmed by pXRD. All stereogenic centers on the N-substituted sugar moiety were confirmed by single crystal X-ray diffraction.[13]

■ CONCLUSIONS

A safe, reproducible, and nonchromatographic synthetic procedure has been developed for the preparation of multihundred grams of the SGLT2 inhibitor **1** in 73% overall

dx.doi.org/10.1021/op3001355 | Org. Process Res. Dev. 2012, 16, 1727–1732

yield. The Vilsmeier reaction conditions were defined for the formylation of *N*-glycoside indoles which produced quantitative isolated yields of **4** with excellent chemical purities (>99 LCAP). Further to our method was the use of a safe and convenient method for the quenching of the excess Vilsmeier reagents using warm aqueous sodium acetate that warrants further investigation by others. Our investigations also found an improved preparation of 4-bromocyclopropylbenzene (**8**), vastly improving the yield by lowering the reaction temperature using a compatible solvent. In addition, the final API **1** was prepared as a crystalline solid after recrystallization with 98.5% HPLC purity. The absolute stereochemistry of **1** was confirmed by X-ray diffraction study on a single crystal of **1**.

The preparation of SGLT2 inhibitor **1** was used as a prototype for optimizing the chemistry for a second SGLT2 inhibitor **2**, and the experimental details and scheme can be found in the Supporting Information. The original synthesis of **2** by discovery relied on a Friedel−Craft acylation followed by reduction of the resulting ketone and required several chromatographies to purify the intermediates.[14]

This chemistry was previously used to prepare several hundred grams of API for early toxicology studies but suffered from an exothermic quench of the excess $AlCl_3$ (2.3 equiv used in reaction) after the Friedel−Crafts reaction. The acid-sensitive acetoxy protecting groups were prone to cleavage under these conditions. In contrast, the efficient and high-yielding Grignard-based synthesis of **2** demonstrated important process advantages over the Friedel−Crafts route. No deprotection occurred during any of the synthetic steps, all chromatography was eliminated, and the overall yield was improved from 30% to 53%. Furthermore, the required Grignard reagent, 4-ethylbenzene magnesium bromide, was commercially available.

Therefore, taking all our experience and learning from the scale-up campaign of **1** just described, the Vilsmeier procedure developed for the previous compound **1** was successfully applied to the synthesis of the required 3-formylcarboxaldehyde intermediate. Similarly, the Grignard reaction of the 3-formylcarboxaldehyde intermediate with the commercially available Grignard reagent yielded the intermediate alcohol in 95% yield. The reduction of the alcohol intermediate, followed by the acetate deprotection were straightforward reactions and occurred without incident in a 60% yield of **2** over the two steps. Finally, crystallization of **2** with EtOH gave the EtOH solvate of **2** in 73% yield.

EXPERIMENTAL SECTION

Intermediates were analyzed on an Agilent 1100 HPLC system using the following conditions: 4.6 mm × 50 mm Luna C18 column, 5.0 μm, 254 nm, gradient elution (0.05% TFA/CH_3CN 20/80 water/0.05% TFA to 40% over 1 min, to 90% over 3 min and hold for 6 min). Retention times are as follows: **4**, 5.41 min; **5**, 4.38 min; **6**, 5.10 min; and **1**, 3.51 min. ^{1}H and ^{13}C NMR data were collected on either a Bruker AC-300 at 300 MHz for proton and 75 MHz for carbon, a Bruker AVANCE 600 at 600 MHz for proton and 125 MHz for carbon, or a Varian UNITYinova at 500 MHz for proton and 125 MHz for carbon. Compound **3** was commercially outsourced and was synthesized according the procedure outlined by Nomura et al.[14]

Preparation of 1-Bromo-4-cyclopropylbenzene (8). To a stirred solution of cyclopropylbenzene (**7**) (150.0 g, 1.23 mol) in CH_2Cl_2 (1.5 L) at −76 °C was added bromine (65.4 mL, 1.26 mol) in CH_2Cl_2 (0.75 L) over 2 h, and the mixture was stirred at −76 °C for 3 h. The mixture was warmed to −20 °C; then saturated aqueous $NaHCO_3$ solution (2.0 L) was added, and the mixture was stirred for 10 min. After phase separation, the organic phase was washed with brine (1.0 L) and concentrated under reduced pressure to afford 264.9 g of a crude mixture which after purification by short path distillation afforded 219 g (90% isolated yield) with 96 LCAP. ^{1}H NMR (DMSO-d_6, 300 MHz) 7.48 (d, J = 7.9 Hz, 2 H), 6.97 (d, J = 8.0 Hz, 2H), 1.85 (m, 1H), 0.94 (m, 2H), 0.62 (m, 2H). ^{13}C NMR (DMSO-d_6, 75.47 MHz) 143.1, 130.9 (2 C), 127.4 (2 C), 118.0, 14.6, 9.42 (2 C). LC−MS m/z MH^+ = 197, 199 (MH^+).

Preparation of (2*R*,3*R*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-(4-fluoro-3-formyl-1*H*-indol-1-yl)tetrahydro-2*H*-pyran-3,4,5-triyl Triacetate (4). To a stirred solution of indole **3** (225.0 g, 0.459 mol) and DMF (50.2 mL, 0.643 mol) in DCE (1.5 L) at 25 °C was added phosphoryl chloride (107.8 mL, 1.15 mol) over 75 min. After the addition was completed, the reaction mixture was stirred for 30 min, and then it was slowly warmed to 40 °C over 30 min. The reaction mixture was agitated at 40 °C for 12 h. The reaction mixture was slowly (**CAUTION**: this quench is very exothermic!) poured into a rapidly stirred warm (40 °C) 3 M aqueous NaOAc (3.0 L) solution over 45 min and was stirred for an additional 15 min after the addition was complete. The resulting mixture was extracted with CH_2Cl_2 (4.0 L), and the phases were separated. The aqueous phase was back-extracted with CH_2Cl_2 (1.0 L). The combined organic phases were washed with 0.05 M HCl (2.0 L) and de-ionized water (2.0 L) and then were dried ($MgSO_4$). The solvents were removed by rotaevaporation, and the resulting solid was dried at 40 °C to afford 230.0 g (100% isolated yield; LCAP 99%) of pure 3-formylindole **4** as a slightly yellow-brown solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.1 (s, 1H), 8.53 (s, 1H), 7.66 (d, J = 7.3 Hz, 1H), 7.38 (m, 1H), 7.10 (dd, J = 6.7, 6.9 Hz, 1H), 6.38 (d, J = 7.5 Hz, 1H), 5.68 (dd, J = 6.5, 6.6 Hz, 1H), 5.56 (t, J = 7.1 Hz, 1H), 5.32 (t, J = 7.2 Hz, 1H) 4.41 − 4.28 (m, 1H), 4.24 − 4.06 (m, 2H), 2.05 (s, 3H), 2.0 (s, 3H), 1.98 (s, 3H), 1.64 (s, 3H). ^{13}C NMR (DMSO-d_6, 75.47 MHz) δ 183.8, 169.9, 169.5, 169.3, 168.4, 155.8, 139.2, 135.7, 124.8, 117.7, 113.1, 108.3, 107.9, 81.9, 73.5, 72.1, 70.3, 67.6, 61.9, 20.4, 20.3, 20.1, 19.6. LC−MS m/z MH^+ = 494 (MH^+), 516 $[M + Na]^+$, 1009 $[2M + Na]^+$. $[\alpha]^{25}_D$ = −0.099 (c = 0.316, $CHCl_3$).

Preparation of (2*R*,3*R*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-(3-((4-cyclopropylphenyl)(hydroxy)methyl)-4-fluoro-1*H*-indol-1-yl)tetrahydro-2*H*-pyran-3,4,5-triyl Triacetate (5). To a stirred suspension of magnesium (17.8 g, 0.725 mol) in anhydrous THF (420 mL) was added a solution of 1,2-dibromoethane (0.53 mL, 6.1 mmol) and **8** (142.1 g, 0.685 mol) in THF (110 mL) dropwise over 20 min at 20 °C. (**CAUTION**: this experimental is designed to avoid a runaway reaction, but a delay in initiation may cause the solvent to boil.) 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. After the reaction temperature declined to 16 °C, the water bath was removed, and the mixture was stirred at 20 °C for an additional 10−20 min to give the Grignard reagent **9** as a gray-yellow solution, which was immediately used in the next step.

To a stirred 0 °C solution of 3-formylindole **4** (230 g, 0.457 mol) in anhydrous THF (4.2 L) was added the above freshly

dx.doi.org/10.1021/op3001355 | *Org. Process Res. Dev.* 2012, 16, 1727−1732

prepared Grignard reagent **9** in THF (530 mL) over 20 min, while the internal temperature was maintained between 0 and 8 °C by adjusting the rate of addition. The resultant mixture was stirred at 0 °C for 30 min. The reaction was quenched with saturated aqueous NH_4Cl (5.4 L) solution, and then extracted with EtOAc (4.0 L) twice. The combined organic phase was washed with brine and dried ($MgSO_4$). After filtration, the filtrate was concentrated at 66 °C under house vacuum to afford 334.6 g (contained 82 LCAP of the desired **5**, 0.7 LCAP of starting **4**, and 2.2 LCAP of bromide **8** as a yellowish solid which was used in next step without further purification. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.49 (dd, J = 7.9, 1.4 Hz, 1H), 7.41 (dd, J = 8.0, 1.0 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.18 (dd, J = 7.3, 1.6 Hz, 2H), 7,15 (m, 1H), 6.97 (dd, J = 7.4, 1.6 Hz, 2H), 6.78 (dd, J = 2.7, 1.6 Hz, 1H), 6.18 (dd, J = 7.8, 2.6 Hz, 1H), 5.94 (m, 1H), 5.65 (dd, J = 7.9, 1.5 Hz, 1H), 5.59−5.45 (m, 1H), 5.24 (dd, J = 7.9, 8.3 Hz, 1H), 4.36 − 4.24 (m, 1H), 4.20−4.04 (m, 2H), 2.05 (s, 3H), 2.01 (s, 3H), 1.98 (s, 3H), 1.84 (m, 1H), 1.66 (s, 3H), 0.92 (m, 2H), 0.61 (m, 2H). ^{13}C NMR (DMSO-d_6, 75.47 MHz): δ 170.1, 170.0, 169.9, 169.3, 156.1, 140.9 139.0, 137.9, 128.0 (2 C), 125.2 (2 C), 124.2, 122.6, 116.3, 114.6, 107.4, 105.2, 81.5, 76.8, 73.0, 72.6, 70.1, 68.2, 62.0, 20.6, 20.4, 20.2, 19.8, 14.8, 8.96 (2 C) . LC−MS m/z MH^+ = 612 (MH^+), 634 $[M + Na]^+$.

Preparation of (2*R*,3*R*,4*S*,5*R*,6*R*)-2-(acetoxymethyl)-6-(3-(4-cyclopropylbenzyl)-4-fluoro-1*H*-indol-1-yl)-tetrahydro-2*H*-pyran-3,4,5-triyl Triacetate (6). To a stirred solution of **5** (82%, 334.6 g, 0.449 mol) in DCE (1.14 L) and MeCN (2.28 L) at 0 °C was added Et_3SiH (108.6 mL, 0.671 mol) followed by the addition of boron trifluoride etherate (68.8 mL, 0.539 mol) dropwise over 10 min. After completion of the reaction, saturated aqueous $NaHCO_3$ solution (4.2 L) was added to the mixture, which was extracted twice with EtOAc (4 L). The solvents were removed by rotoevaporation to afford 315.0 g (contained 84% LCAP of the desired product **6**). The resulting crude **6** (315.0 g) was slurried with EtOH (2.1 L) at 76 °C and cooled to 20 °C over 30 min and stirred for 1 h. The solid was collected by filtration, washed with cold (0 °C) EtOH (200 mL), and dried in a vacuum oven at 60 °C. There was obtained 228.6 g (85% isolated yield, 98.4 LCAP) of pure **6** as an off-white crystalline solid. Mp 168−169 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.47 (d, J = 7.2 Hz, 1H), 7.22 (s, 1H), 7.20−7.10 (m, 1H), 7.06 (d, J = 8.1, 2H), 6.95 (d, J = 8.1 Hz, 2H), 6.78 (dd, J = 7.3, 7.0 Hz, 1H), 6.16 (d, J = 7.1 Hz, 1H), 5.61−5.48 (m, 2H), 5.21 (t, J = 7.3, 7.1 Hz, 1H), 4.34 − 4.25 (m, 1H), 4.18−4.04 (m, 2H), 4.0 (s, 2H), 2.04 (s, 3H), 1.97 (s, 3H), 1.95 (s, 3H), 1.84 (m, 1H), 1.61 (s, 3H), 0.89 (m, 2H), 0.61 (m, 2H). ^{13}C NMR (DMSO-d_6, 75.47 MHz): δ 169.9, 169.5, 169.3, 168.3, 156.2, 140.9, 139.0, 137.9, 128.0 (2 C), 125.2 (2 C), 124.2, 122.7, 116.1, 114.1, 107.2, 105.0, 81.7, 73.0, 72.5, 69.8, 68.0, 62.0, 31.2, 20.4, 20.3, 20.2, 19.7, 14.6, 8.93 (2 C). HRMS: m/z = 596.2261 $[M - 1]^+$. $[\alpha]^{25}_D$ = −0.008 (c = 0.306, $CHCl_3$).

Preparation of (2*R*,3*R*,4*S*,5*S*,6*R*)-2-(3-(4-Cyclopropyl-benzyl)-4-fluoro-1*H*-indol-1-yl)-6-(hydroxymethyl)-tetrahydro-2*H*-pyran-3,4,5-triol (1). To a solution of compound **6** (250 g, 0.413 mol) in MeOH (1.2 L) and THF (2.4 L) was added sodium methoxide (2.5 mL, 0.012 mol), and the reaction was stirred at 20 °C for 3 h. The solvent was removed by rotaevaporation, and EtOAc (8.0 L) was added. The resulting solution was washed with brine (800 mL × 2) and dried ($MgSO_4$). The filtrate was concentrated by rotaevaporation, and EtOH (900 mL) was added. The solution was heated to 76 °C and de-ionized H_2O (1800 mL) was added in a small stream over 20 min that resulted in a slightly yellowish clear solution, which was gradually cooled to 40 °C over 20 min with stirring while seeded. The resulting slightly white-yellowish suspension was stirred at 20 °C for 20 h, the solids were collected by filtration, washed with cold (0 °C) EtOH/H_2O (1:4), and dried by air-suction for 6 h with a gentle stream of N_2. There was obtained 198.5 g (97.5% isolated yield based on free base form; 98.8 LCAP) of **1** EtOH/H_2O solvate as an off-white crystalline solid. A slurry of the EtOH/H_2O solvate **1** (198.5 g, 0.399 mol) in de-ionized H_2O (3.2 L,) was warmed to 76 °C, and then the slurry was gradually cooled to 20 °C over 30 min. The white suspension was stirred at 20 °C for 20 min and then at 10 °C for 1 h. The solid was collected by filtration, washed with de-ionized H_2O (100 mL × 2), dried in an oven at 50 °C for 20 h and further at 60 °C for 3 h to afford 177.4 g, (99.8% isolated yield, 98.6 LCAP) of **1** hemihydrate as an off-white crystalline solid, of which the ^{1}H NMR showed no EtOH residue and the powder X-ray diffraction (pXRD) confirmed that it was a crystalline solid. TGA indicated it contained 2.3% of water. Mp = 108−111 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.36 (d, J = 8.2 Hz, 1 H), 7.22 (s, 1 H), 7.14 (d, J = 8.1, 2 H), 7.10−7.0 (m, 1 H), 6.96 (d, J = 8.1 Hz, 2 H), 6.73 (dd, J = 7.5, 7.7 Hz, 1 H), 5.38 (d, J = 7.7 Hz, 1 H), 5.21 (d, J = 6.9 Hz, 1 H), 5.18 (d, J = 6.8 Hz, 1 H), 5.10 (d, J = 6.9 Hz, 1 H), 4.54 (t, J = 6.9, 1.8 Hz, 1 H), 4.04 (s, 2 H), 3.75−3.60 (m, 2 H), 3.52−3.30 (m, 3 H), 3.20−3.17 (m, 1 H), 1.84 (m, 1 H), 0.89 (m, 2 H), 0.61 (m, 2 H). ^{13}C NMR (DMSO-d_6, 75.47 MHz): δ 156.2, 140.8, 139.4, 138.2, 128.2 (2 C), 125.2 (2 C), 124.4, 121.8, 115.9, 112.8, 107.4, 104.2, 84.8, 79.3, 77.4, 71.7, 69.8, 60.8, 31.3, 14.6, 8.92 (2 C). LC−MS m/z MH^+ = 428 (MH^+), 450 $[M + Na]^+$, 877 $[2M + Na]^+$. $[\alpha]^{25}_D$ = −0.026 (c = 0.302, CH_3OH). Anal. Calc'd for $C_{24}H_{26}NFO_5 \cdot 0.54\ H_2O$: C, 65.93; H, 6.24; N, 3.20; F, 4.35, H_2O, 2.23. Found: C, 65.66; H, 6.16; N, 3.05; F, 4.18, H_2O, 2.26.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Scheme and experimental data for the synthesis of **2**. $POCl_3$ RC-1 reaction quench into sodium acetate study in the RC-1. X-ray crystallographic data for compound **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*(X.L.) Telephone: +1-215-628-7829. Fax: +1-215-540-4611. E-mail: xli6@its.jnj.com; (K.M.W.) Telephone: +1-215-628-7814. Fax: +1-215-540-4611. E-mail: kwells1@its.jnj.com.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to Brigitte Segmuller and Richard Dunphy for analytical assistance. We are also grateful to Christopher Teleha for manuscript review.

■ REFERENCES

(1) (a) Narayan, K. M.; Boyle, J. P; Thompson, T. J.; Sorensen, S. W.; Williamson, D. F. *JAMA, J. Am. Med. Assoc.* **2003**, *290*, 1884. (b) Boyle, J. P.; Honeycutt, A. A.; Venkat Narayan, K. M.; Hoerger, T. J.; Geiss, L. S.; Chen, H.; Thompson, T. J. *Diabetes Care* **2001**, *24*,

1936−1940. (c) International Diabetes Federation. *Diabetes Atlas*, 3rd ed.; International Diabetes Federation: Brussels, Belgium, 2006.
(2) Bell, D. S. H. *South. Med. J.* **2002**, *95*, 24.
(3) Oku, A.; Ueta, K.; Arakawa, K.; Ishihara, T.; Nawano, M.; Kuronuma, Y.; Matsumoto, M.; Saito, A.; Tsujihara, K.; Anai, M.; Asano, T.; Kanai, Y.; Endou, H. *Diabetes* **1999**, *48*, 1794.
(4) Meng, W.; Ellsworth, B. A.; Nirschl, A. A.; McCann, P. J.; Patel, M.; Girotra, R. N.; Wu, G; Sher, P. M.; Morrison, E. P.; Biller, S. A.; Zahler, R.; Deshpande, P. P.; Pullockaran, A.; Hagan, D. L.; Morgan, N.; Taylor, J. R.; Obermeier, M. T.; Humphreys, W. G.; Khanna, A.; Discenza, L.; Robertson, J. G.; Wang, A.; Han, S.; Wetterau, J. R.; Janovitz, E. B.; Flint, O. P.; Whaley, J. M.; Washburn, W. N. *J. Med. Chem.* **2008**, *51*, 1145.
(5) (a) Nomura, S.; Sakamaki, S. WO/2008/013322, 2008. (b) Nomura, S.; Kawanishi, E; Ueta, K. WO/2005/012326, 2005.
(6) (a) Preobrazhenskaya, M.; Tolkachev, V.; Geling, O.; Kostyuchenko, P. *Zh. Org. Khim.* **1974**, *10*, 1764. (b) Humenik, M; Dzurilla, M.; Kutschy, P.; Solcaniova, E.; Kovacik, V.; Bekesova, S. *Collect. Czech. Chem. Commun.* **2004**, *69*, 1657.
(7) Achmatowicz, M.; Thiel, O.; Colyer, J; Hu, J.; Elipe, M; Tomaskevitch, J.; Tedrow, J.; Larsen, R. *Org. Process Res. Dev.* **2010**, *14*, 1490.
(8) RC-1 Study of the $POCl_3$ quench is included in the Supporting Information.
(9) Himmelsbach, F.; Ruden Von, T.; Dahmann, G.; Metz, T. WO/1996/07657, 1996.
(10) Lavey, B. J.; Kozlowski, J. A.; Shankar, B. B.; Spitler, J. M.; Zhou, G.; Yang, D.; Shu, Y.; Wong, M. C. K.; Wong, S.; Shih, N.; Wu, J.; McCombie, S. W.; Rizvi, R.; Wolin, R. L.; Lunn, C. A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3760.
(11) Esakkidurai, T.; Kumarraja, M.; Pitchumani, K. *Catal. Lett.* **2004**, *92*, 169.
(12) Lvina, R. Y.; Gembitskii, P. A. *Zh. Obshch. Khim.* **1961**, *31*, 3480.
(13) X-ray crystallographic data is included in the Supporting Information.
(14) Internal communications.
(15) Nomura, S.; Yamamoto, Y. WO/2006/080577, 2006.