Organic Process Research & Development

ARTICLE

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A Large-Scale Synthesis of Potent Glucokinase Activator MK-0941 via Selective *O*-Arylation and *O*-Alkylation

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Supporting Information

ABSTRACT: An efficient, practical preparation of MK-0941, a potent glucokinase activator, is described. Keys to the success of the synthesis are a highly selective mono-*O*-arylation of methyl 3,5-dihydroxybenzoate with 2-ethanesulfonyl-5-chloropyridine and the choice of a proper protective group for the subsequent S_N2 *O*-alkylation. With the thorough understanding of the origins and fate of in-process impurities, the second-generation robust synthesis with a minimum number of operations reproducibly prepares MK-0941 in 56% overall yield with >99% purity.

INTRODUCTION

Glucokinase (GK) is a member of the hexokinase enzymes and catalyzes the phosphorylation of glucose to glucose-6-phosphate.[1] This enzyme is predominantly expressed in liver and pancreatic β-cells.[1] Acting as a glucose sensor of the insulin-producing pancreatic islet β-cells, glucokinase plays a key role in glucose homeostasis by controlling the conversion of glucose to glycogen and regulating hepatic glucose production.[1,2] To date, a number of GK activators have advanced into clinical trials for the treatment of type II diabetes.[2]

MK-0941 (**1**)[3] is a potent GK activator possessing a differentially substituted 3,5-dihydroxybenzamide structure. In order to support the drug development, an efficient synthesis suitable for large-scale preparation was required. The chemistry utilized at early stages of drug development is outlined in Scheme 1.[4] Although the overall synthetic strategy was straightforward, this synthesis had several major drawbacks. The *O*-arylation of dihydroxybenzoate **3** with chloropyridine **2**[3] had only moderate mono/bis selectivity and also suffered from poor reproducibility when scaled up. Attempts to isolate **4** as a crystalline solid were not successful due to the numerous in-process impurities generated in this step, which thus were carried through to the subsequent steps. As such, multiple recrystallizations of **7** were required to reject numerous impurities at the expense of a significant downgrade of its enantiomeric purity. Therefore, a subsequent recrystallization of **1** became necessary in order to improve its enantiomeric purity. In addition, the overall yield was highly variable, averaging around only ~20% upon scale up, as compared to 36% on a lab scale. Most importantly, significant variability observed from batch to batch resulted in the lack of control of the impurity profile of the final product **1**, which raised a serious concern about the robustness of the process.

In line with the current synthetic strategy, we envisioned that robust control of the impurity profile of the final API could be still attained, if the origin and fate of the process impurities could be understood fundamentally. This article describes our efforts to overcome all the issues encountered in the original synthesis, leading to the successful development of a highly efficient and practical-second generation synthesis of MK-0941 (**1**) in three pots in >99% purity with full control of the impurity profile.

RESULTS AND DISCUSSION

Selective Mono-*O*-arylation. Without involving extra manipulation steps, such as sequential protection/deprotection, selective and direct mono-*O*-arylation of resorcinol derivatives,[5−8] such as **3**, is challenging due to the competing formation of bis-arylated byproducts. Indeed, treatment of chloropyridine **2**[3] with 1.1 equiv of **3** and 2.2 equiv of *t*-BuOK in 1,3-dimethyl-2-imidazolidinone (DMI) at 100 °C resulted in a modest mono/bis selectivity (**4**:**9** = 3−4:1) along with the formation of numerous byproducts including impurity **10**, while the yield of the desired product **4** varied from 37% to 67%.

In order to probe the mono/bis selectivity, we first studied the formation of the bis-*O*-arylated byproduct **9** by treating **4** with chloropyridine **2** in the presence of *t*-BuOK (Scheme 2). The *O*-arylation of **4** was much slower than that of **3** under the same conditions[9] and generated numerous byproducts. The anion of dihydroxybenzoate **3** appeared to be more reactive than that of the mono *O*-arylated **4**,[9] which led us to believe that the reaction selectivity could be competitively improved by increasing the equivalents/concentration of benzoate **3**.

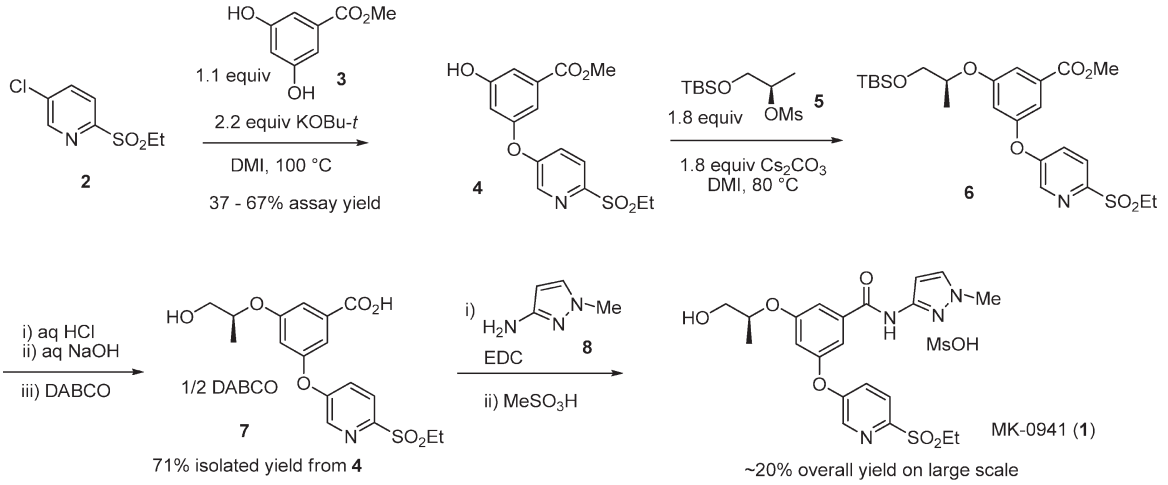
Thus, studies on selective mono-*O*-arylation of **3** with **2** were initiated in attempts to utilize the *O*-arylation reactivity differences between **3** and **4**. Interestingly, as the ratio of **3** vs **2** varied, the selectivity of the mono *O*-arylated **4** vs the bis *O*-arylayted byproduct **9** was significantly changed (Table 1). In addition, the use of excess of **3** also helped to suppress the formation of impurities and therefore enhanced the yield. We were pleased to find that the selectivity could be dramatically improved from 3:1 (**4**:**9**) to 28:1 in the presence of 2 equiv of *t*-BuOK, if the equivalents of **3** were increased from 1.1 equiv to 1.5 equiv. The use of 1.5 equiv of **3** was therefore determined to be optimal for the best balance of yield, selectivity, and overall cost.[10]

Among the various bases screened, the use of *t*-BuONa or *t*-BuOK was most effective in terms of the reaction yield. Solvent screening confirmed that the use of polar aprotic solvents was

Received: March 17, 2011
Published: May 03, 2011

dx.doi.org/10.1021/op200068c | *Org. Process Res. Dev.* 2011, 15, 824–830

Scheme 1. Initial synthesis of MK-0941 (1)



Scheme 2. *O*-Arylation of 3

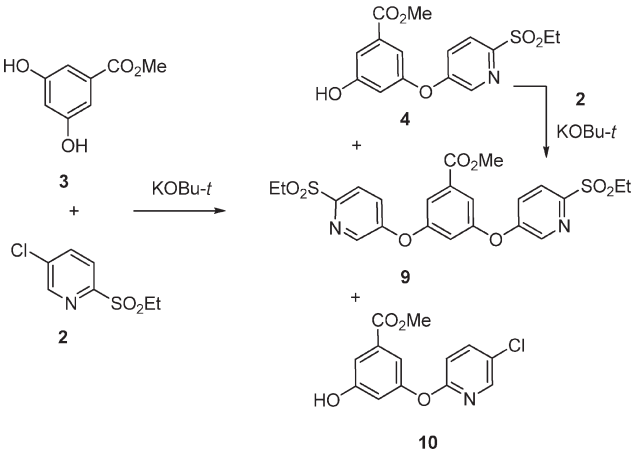


Table 1. Selected data for the effects of the amounts of 3 on *O*-arylation selectivity[a]

entry	3 (equiv)	yield of 4 (%)[b]	selectivity (4:9)
1	1.1	55	3:1
2	1.3	70	6:1
3	1.5	83	28:1

[a] Reaction conditions: $AcNMe_2$, 95 °C. Solid *t*-BuOK (2.0 equiv) was charged in portions. [b] Assay yield by HPLC.

crucial to obtain high yields. Thus, $AcNMe_2$ became our choice of solvent for further optimization. The reaction temperature also had a significant effect on the reactivity of *O*-arylation. Incomplete conversion was observed at <80 °C.

Although the mono/bis selectivity was substantially improved to a decent level (28:1) by increasing the charge of **3**, it was found that byproduct **9** was poorly rejected in the downstream chemistry. At this point, it was determined that the mono/bis selectivity (**4**:**9**) had to be further improved to >200:1 (i.e., <0.5% **9**), in order to practically prepare MK-0941 without introducing extra purification

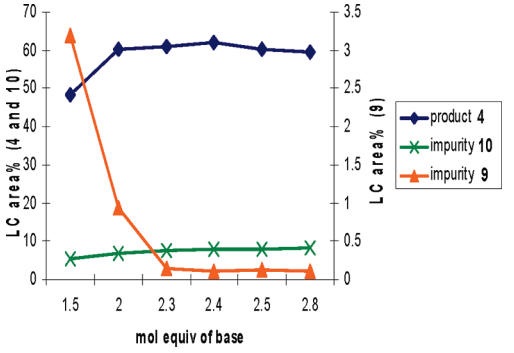


Figure 1. Effects of *t*-BuOK on *O*-arylation profile.

steps. Therefore, further development of this step focused on the enhancement of the mono/bis selectivity.

After several experiments, we found that the impurity profile of the reaction was sensitive to the amount of *t*-BuOK charged. Figure 1 depicts the correlation between the levels of byproducts **9** and **10** (Scheme 2) and the amount of *t*-BuOK. A significant decrease of the formation of **9** was achieved when the amount of *t*-BuOK was increased to >2.3 equiv. In contrast, the formation of **10**, which could be rejected easily through crystallization, was only subtly influenced by the increased charge of *t*-BuOK.

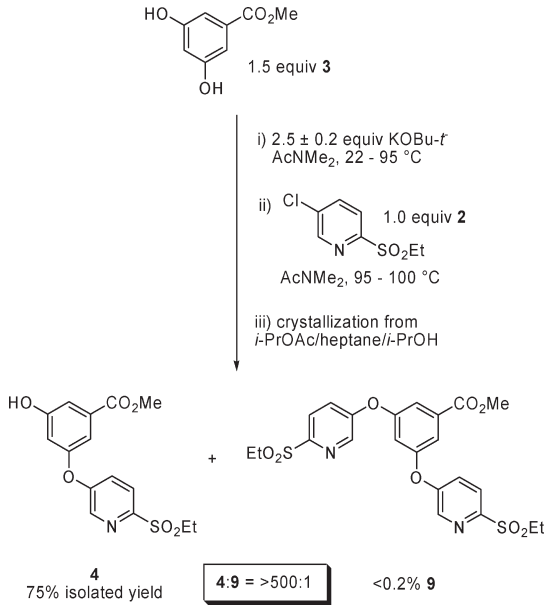
It is worthwhile to point out that the monoanion of **3** was very soluble in $AcNMe_2$, while the corresponding dianion potassium salt formed a slurry even at 80 °C.[11] Furthermore, if *t*-BuOK was charged as a solid, the unreacted/undigested *t*-BuOK would lead to variable results in terms of the reaction yield as well as the impurity profile. To circumvent these issues and achieve reproducible *O*-arylation, *t*-BuOK was dissolved in $AcNMe_2$ before it was charged into a solution of **2** at ambient temperature. The resulting slurry of the potassium salt of **3** was further agitated at 50 °C followed by 95 °C for several hours to ensure a complete digestion of *t*-BuOK (Scheme 3) and only then was chloropyridine **2** added. Applying this protocol instead of charging solid *t*-BuOK into the reaction mixture significantly improved the reproducibility and the reaction profile. Thus, the use of 2.5 ± 0.2 equiv of *t*-BuOK and 1.5 equiv of benzoate **3** in $AcNMe_2$ was determined to be optimal[12,13] to minimize the formation of **9** to <0.2%, while the assay yield of **4**

dx.doi.org/10.1021/op200068c |*Org. Process Res. Dev.* 2011, 15, 824–830

was maintained at 85% (Figure 1). The mono/bis selectivity was finally improved up to >500:1, which was significantly above the targeted selectivity (>200:1).

Upon the completion of the reaction, the majority of the unconsumed benzoate **3** was effectively removed through *i*-PrOAc-aqueous workup.[10] With the improved selectivity of *O*-arylation, the desired **4** could be directly isolated as a crystalline solid from *i*-PrOAc/heptane/2-propanol[14] in 75% yield with >94% HPLC purity (Scheme 3). In contrast to the original process, the isolation of **4** at this stage rejected numerous impurities and improved the robustness of the synthesis.

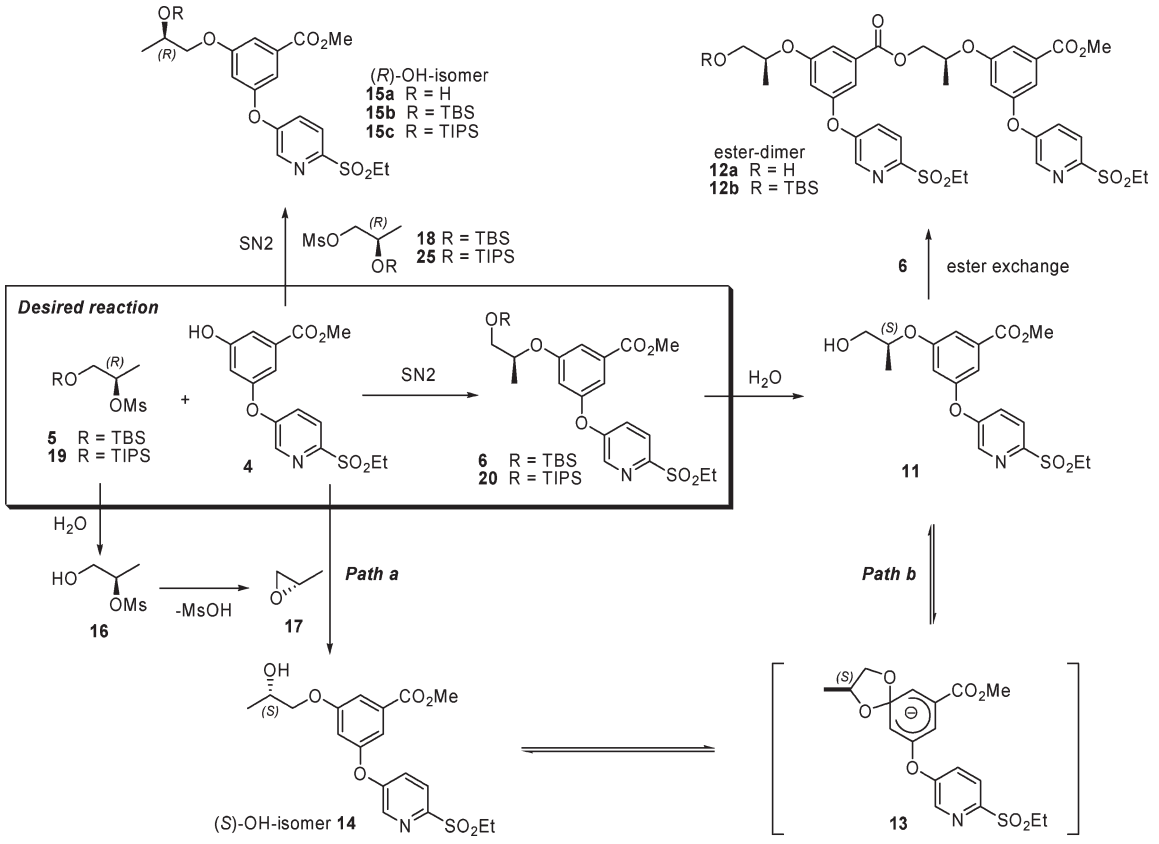
Scheme 3. Optimized process for selective mono-*O*-arylation



S_N2 *O*-Alkylation of 4. With the preparation of **4** established, we turned our attention to the subsequent S_N2 *O*-alkylation with mesylate **5**, which had also suffered from poor reproducibility along with the formation of several troublesome impurities. To understand the reaction pathways for the formation of these impurities, which are rejected poorly in the downstream chemistry, and to gain a control of their formation, their structures (Scheme 4) were unambiguously elucidated by NMR and LC/MS.

It was believed that the formation of these impurities was caused by the labile nature of the TBS-protection as depicted in Scheme 4. The cleavage of the TBS-ether in product **6** by a small amount of H_2O,[15] which could be generated under the alkylation conditions (Cs_2CO_3, 80 °C), could result in the formation of ester dimer **12** as well as des-TBS **11**. Similarly, (*R*)-OH-isomer **15a** could arise from desilylation of the corresponding **15b**, which was formed via *O*-alkylation of **4** with regioisomer mesylate **18**, a byproduct of selective TBS-protection of 1,2-propanediol during the preparation of **5**.[3] Indeed, treatment of **4** with **5** resulted in the formation of significant levels of des-TBS **11**, ester-dimer **12**, (*S*)-OH-isomer **14** and (*R*)-OH-isomer **15** (Table 2, entry 1). However, the observation of byproduct **14** intrigued us. In particular, the formation of (*S*)-OH-isomer **14** was also clearly observed upon exposure of the purified **6** to the same S_N2 *O*-alkylation conditions (Table 2, entry 2). Byproduct

Scheme 4. Plausible pathways for the formation of byproducts of S_N2 *O*-alkylation



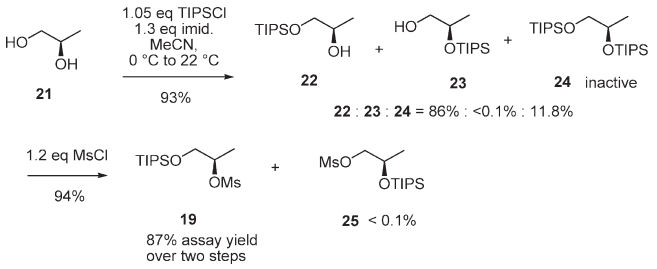
dx.doi.org/10.1021/op200068c |*Org. Process Res. Dev.* 2011, 15, 824–830

Table 2. Selected data for the effects of protective group on the *O*-alkylation of 4

entry	substrates	mesylates	time (h)	(*S*)-OH-isomer **14**(%)[a,b]	(*R*)-OH-isomer **15** (%)[a,b]	desilylation **11** (%)[a]	ester-dimer **12** (%)[a]
1	**4**	**5**	7	0.24	0.97	11.0	5.3
2	**6**	–	12[c]	0.73	n/d	–	–
3	**11**	–	12[c]	6.30	n/d	–	–
4	**4**	**19**	7	0.04	n/d	0.31	unknown
5	**20**	–	12[c]	0.13	n/d	–	–

[a] HPLC area%. [b] Determined by HPLC after saponification and desilylation to free acid of **7**. The percentages are reported as relative to the desired product. [c] Purified products (**6**, **11**, or **20**) were exposed to the alkylation conditions for 12 h (Cs_2CO_3, $AcNMe_2$, 80 °C) followed by aging for additional 12 h after addition of a small amount of H_2O to mimic the presence of water in the actual reaction system.[15]

Scheme 5. Through-process to prepare TIPS-mesylate 19[a]



[a] The ratio of **22**:**23**:**24** was determined by gas chromatography (GC) analysis (RTX-200 column) and did not represent the actual mole ratio without calibration.

14, in principle, could be generated from epoxide **17** via cleavage of the TBS group of mesylate **5** (path a); however, the results of the stress test (Table 2, entry 2) suggested that **14** was most likely formed via intermediate **13** through intramolecular nucleophilic attack to the aromatic ring (path b). This plausible ipso pathway was further supported by the fact that treatment of alcohol **11** under the same conditions (Cs_2CO_3, $AcNMe_2$, 80 °C, 12 h) resulted in an elevated level (6.3%) of **14** (Table 2, entry 3).

With these results in hand, we envisioned that the formation of these byproducts would be suppressed if the labile TBS group of **5** could be replaced with a more stable protective group such as triisopropylsilyl group (TIPS). Indeed, the use of TIPS-protected mesylate **19** dramatically suppressed the formation of all of these impurities as expected (Table 2, entry 4). The formation of OH-isomers **14** and **15** was controlled to <0.05%. Furthermore, exposure of the TIPS-protected product **20** to the same S_N2 *O*-alkylation conditions resulted in the formation of only negligible amount of **14** (Table 2, entry 5), which further confirmed that the increased stability of TIPS group shut down the degradation via pathway b (Scheme 4).

With the desired choice of protective group determined, we turned our attention to develop a process to prepare mesylate **19**. Most of the impurities including **14** formed during the S_N2 *O*-alkylation reaction were successfully suppressed by employing a more stable TIPS protective group. However, it was still crucial to minimize the formation of the regioisomer **23** and to convert **23** to the corresponding inactive bis-TIPS ether **24** (Scheme 5), because **23** could lead to the formation of (*R*)-OH-impurity **15** via the corresponding mesylate **25** (Scheme 4). Under the optimized conditions, treatment of **21** with 1.05 equiv of TIPSCl and 1.3 equiv of imidazole in MeCN at 0 °C followed by aging at 22 °C for 2 h afforded **22** in 93% yield along with 0.09% of **23** and 11.8% of **24** by GC analysis (see, footnote of Scheme 5). Upon aqueous workup, the unconsumed diol **21** (typically about 0.2% at the end of reaction, by GC analysis)[16] was also completely removed. The crude stream of **22** with 0.08% of **23** was subjected to the subsequent mesylation (1.2 equiv MsCl, 1.4 equiv Et_3N, 0 °C, 1 h) to afford the desired TIPS-mesylate **19** in 94% assay yield (87% yield over two steps). Therefore, the crude **19** in toluene with only <0.1% of **25** could be directly used for the subsequent *O*-alkylation reaction without further purification.

With the robust process for the preparation of **4** and TIPS-mesylate **19** in hand, a streamlined through-process to prepare DABCO salt **7** was then developed (Scheme 6). The use of TIPS protected mesylate **19** dramatically suppressed the formation of impurities such as desilylated byproducts, dimers, and OH-isomers, as discussed in Scheme 4. With the benefit of the stable TIPS protecting group, it became possible to lower the charge of the mesylate **19** and Cs_2CO_3 significantly without sacrificing the yield and purity profile. Since the S_N2 *O*-alkylation was carried out under heterogeneous conditions with dense Cs_2CO_3 salts, the reaction tended to be slower at high moisture levels or with slower agitation. A good mixing was essential to achieve >99% conversion. Under the optimized conditions (1.3 equiv **19**, 1.5 equiv Cs_2CO_3, 80 °C, 12 h), the alkylation reaction furnished the desired product **20** in 93% assay yield.[17]

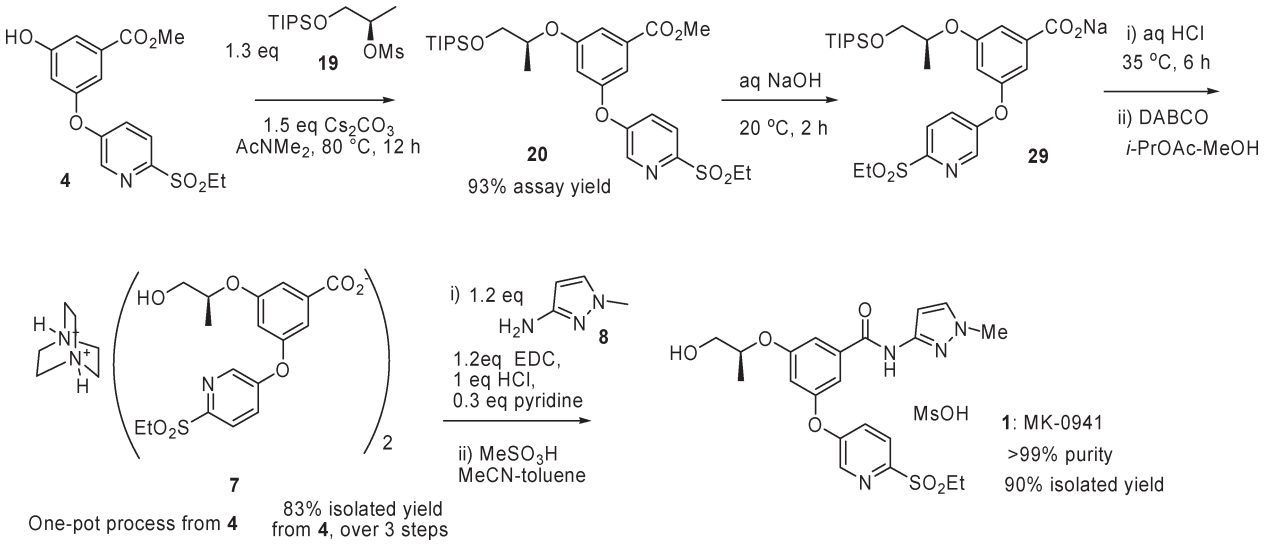
It is worthwhile to note that the unconsumed **4**, ~1% at the end of the alkylation, would be converted in the subsequent steps to the corresponding impurities, which were difficult to reject.[18] After several experiments, we found that the unconsumed **4** could be selectively partitioned/rejected in the aqueous $AcNMe_2$ layer during the workup, if the ratio of $AcNMe_2$:H_2O was adjusted to approximately 3:2 (v/v). The product **20** could be selectively extracted with MTBE.

In the initial synthesis, the deprotection of the silyl ether was performed before the saponification of the methyl ester (Scheme 1). However, the corresponding desilylated alcohol **11** from **20** could react[19] with the unconsumed excess mesylate **19**, which was carried through from the previous *O*-alkylation step, to form byproducts in the subsequent saponification step. To circumvent this issue, the order of this sequence was reversed. In practice, the crude **20** was hydrolyzed first with aqueous NaOH (5 N, 1.6 equiv) in THF/MeOH, while the residual mesylate **19** was also quenched under this condition. In one pot the resulting crude **29** was subsequently treated with aqueous HCl at 35 °C for 8 h to afford the free acid **7**. As such, the hydrolysis−deprotection proceeded in near quantitative yield.

With implementation of the process described above, free acid **7** was converted to the corresponding DABCO salt and effectively isolated in 83% yield over three steps with >99% purity (Scheme 6). Multiple recrystallizations of **7** were no longer needed to meet the purity specifications. More importantly, the new process performed with greatly improved robustness

dx.doi.org/10.1021/op200068c |*Org. Process Res. Dev.* 2011, 15, 824–830

Scheme 6. One-pot through-process to prepare DABCO salt 7 and endgame



and reliability to produce consistent results even on an industrial scale.

Endgame. In the initial synthesis, the free acid was liberated from the corresponding DABCO salt through an acidic aqueous extraction, prior to the final EDC coupling with **8**. To streamline the process, elimination of this salt break step without sacrificing the efficiency and yield of the EDC coupling was desired. After several experiments, we found that the addition mode was important to achieve this goal. A slow addition of 1 equiv of aqueous HCl to a solution of the DABCO salt **7**, amine **8**, and EDC in aqueous MeCN in the presence of a catalytic amount of pyridine gave the desired MK-0941 effectively and cleanly. Without introducing HCl, the reaction stalled at ~60% conversion. Finally, MK-0941 was isolated as its methanesulfonate salt in 90% yield and >99% purity.

The process was successfully scaled up on industrial scale and produced >1 tonne API without sacrificing yield and purity.

CONCLUSION

In summary, we have developed an efficient and robust process for the large-scale synthesis of MK-0941. The success of the development is attributed to two key accomplishments, a highly selective mono-*O*-arylation and the selection of TIPS-protected mesylate **19** for S_N2 *O*-alkylation. The selectivity of the mono/bis *O*-arylation was improved from 3−4:1 to >500:1. The direct isolation of **4** greatly improved the robustness of the synthesis by facilitating the rejection of numerous impurities. The use of TIPS-protected mesylate **19** in the *O*-alkylation step was crucial to suppress the formation of OH-isomers, which were difficult to reject in the downstream chemistry. By applying an improved through process, DABCO salt **7** was efficiently obtained with >99% purity in a reproducible manner. In contrast to ~20% overall yield in the first generation synthesis, the highly efficient second generation synthesis produces MK-0941 in 56% overall yield and >99% purity with minimal operations/isolations. More importantly, based on fundamental understanding the origins and fate of the impurities, a robust control of the impurity profile of the final product was finally achieved without any recrystallizations or chromatographic purification.

EXPERIMENTAL SECTION

General. Degassing was conducted where specified by repeating an evacuation/nitrogen refill cycle. HPLC assays were performed using a reverse phase column eluted with 0.1% H_3PO_4 (aq) and acetonitrile. The levels of OH-isomers **14** and **15** were determined after saponification and desilylation to free acid of **7** by chiral HPLC analysis: ChiralPak IC; mobile phase: isocratic 0.1% H_3PO_4 (aq)−acetonitrile; column temperature: 40 °C; flow: 1.0 mL/min; 23% acetonitrile for 15 min, increased to 30% acetonitrile in the next 15 min, and then hold at 30% acetonitrile for the next 5 min. Retention times (R_t): minor enantiomer, 19.8 min; free acid **7**, 21.3 min; (*R*)-OH-isomer (free acid of **15a**), 24.1 min; (*S*)-OH-isomer (free acid of **14**), 27.3 min. The ratio of **22**:**23**:**24** was determined by gas chromatography (GC) analysis: Column: RTX-200 30 m × 0.32 mm × 1.0 μm; constant flow: 3.3 mL/min; carrier gas: He; inlet temperature: 240 °C; detection: FID; oven program: 75 °C (3 min), ramp 20 °C/min to 190 °C, ramp 35 °C/min to 285 °C, and hold for 2 min. Retention times (R_t): diol **21**, 2.7 min; **22**, 8.6 min; **23**, 8.8 min; **24**, 10.8 min.

3-(6-Ethanesulfonyl-pyridin-3-yloxy)-5-hydroxy-benzoic Acid Methyl Ester (4). To a degassed solution of **3** (50.6 kg, 291.9 mol) in $AcNMe_2$ (280 L) at 20−25 °C under N_2 atmosphere was added a degassed solution of *t*-BuOK (57.4 kg) in $AcNMe_2$ (400 L) dropwise over 2 h at <25 °C. The slurry was agitated at 20−25 °C for 1 h, 50 °C for 1 h, and 95 °C for 0.5−1 h. A degassed solution of chloropyridine **2**[3] (40 kg, 194.5 mol) in $AcNMe_2$ (120 L) was added at 95−100 °C over 5 h. After additional 2 h age at 95 °C, the batch was cooled to 20 °C and quenched into 1 M HCl (640 L) at <30 °C. The pH of the quenched solution was adjusted to 2−3 with 1 M HCl and extracted twice with *i*-PrOAc (800 L + 600 L). The combined organic phase was washed with 5% NaCl (3 × 400 L). The organic phase was azeotropically concentrated (jacket temperature <50 °C) to ~240 L followed by addition of 2-propanol (24 L). The batch was seeded, and the slurry was aged at 25−30 °C for 6 h. Heptane (420 L) was added over 10 h, and the batch was cooled to 20 °C and agitated for 2−4 h before filtration. The wet cake was washed with 30% *i*-PrOAc in heptane (2 × 200 L) followed by 25% *i*-PrOAc in heptane (200 L). Vacuum oven dry at 45 °C afforded **4** (53 kg) as a white solid. 75% yield. Analytically

dx.doi.org/10.1021/op200068c |*Org. Process Res. Dev.* 2011, 15, 824–830

pure sample was prepared by recrystallization. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (d, J = 2.8 Hz, 1 H), 8.05 (d, J = 8.2 Hz, 1 H), 7.48 (dd, J = 2.3, 1.4 Hz, 1 H), 7.43 (dd, J = 2.3, 1.4 Hz, 1 H), 7.28 (dd, J = 2.3, 1.4 Hz, 1 H), 6.84 (t, J = 2.3 Hz, 1 H), 3.82 (s, 3 H), 3.42 (q, J = 7.4 Hz, 2 H), 1.33 (t, J = 7.4 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.14, 158.09, 156.82, 155.36, 149.79, 141.01, 133.07, 124.99, 124.26, 114.10, 112.59, 112.07, 52.63, 46.93, 6.87. Anal. Calcd for $C_{15}H_{15}NO_6S$: C, 53.40; H, 4.48; N, 4.15. Found: C, 53.42; H, 4.23; N, 4.01.

(*R*)-1-(Triisopropylsilyloxy)propan-2-ol (22). To a solution of (*R*)-1,2-propanediol (**21**, 10 kg, 131.4 mol) and imidazole (11.6 kg, 170.8 mol) in acetonitrile (60 L) at 0 °C was added triisopropylchlorosilane (26.6 kg, 138 mol) over 3 h at 0−5 °C. The resulting slurry was stirred at 0−5 °C for additional 1 h followed by at 20−25 °C for 1−3 h until the reaction was deemed complete (1,2-propanediol <1.0% by GC). The reaction was quenched by addition of 15% NaCl (100 L) and toluene (80 L). The organic layer was separated and washed with 15% NaCl (50 L). GC assay: 28.28 kg of **22**. 93% yield. Analytically pure sample could be prepared by distillation under reduced pressure. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98−3.80 (m, 1 H), 3.68 (dd, J = 9.7, 3.6 Hz, 1 H), 3.44 (dd, J = 9.7, 7.7 Hz, 1 H), 2.50 (br, 1 H), 1.15−1.04 (m, 21 H), 1.13 (d, J = 6.4 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.81, 68.05, 18.14, 17.91, 11.86. Anal. Calcd for $C_{12}H_{28}O_2Si$: C, 62.01; H, 12.14. Found: C, 61.78; H, 12.26.

(*R*)-1-(Triisopropylsilyloxy)propan-2-yl Methanesulfonate (19). The crude solution of **22** (28.28 kg assay, 121.7 mol) was azeotropically concentrated (batch temperature <60 °C) to ∼50 L and diluted with toluene to 310 L. The resulting solution was cooled to 0 °C. Triethylamine (17.2 kg, 170.3 mol) was charged followed by addition of methanesulfonyl chloride (16.7 kg, 146 mol) over 2 h at 0−5 °C. The resulting slurry was stirred at 0−5 °C until the reaction was deemed complete by GC assay. The reaction was quenched by addition of water (170 L), and the resulting mixture was allowed to warm to 20−25 °C. The organic layer was washed with H_2O (85 L). The resulting solution was azeotropically concentrated under vacuum (batch temperature <60 °C) to give **19** as a clear solution (GC assay: 60.6 wt %, 35.5 kg of **19**, 94% yield). Analytically pure sample could be prepared by silica gel chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82−4.74 (m, 1 H), 3.81 (dd, J = 11.1, 6.9 Hz, 1 H), 3.74 (dd, J = 11.1, 3.8 Hz, 1 H), 3.04 (s, 3 H), 1.41 (d, J = 6.5 Hz, 3 H), 1.10−1.05 (m, 21 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 80.63, 66.35, 38.37, 17.92, 17.82, 11.88. HRMS: m/z $[M + H]^+$ calcd for $C_{13}H_{30}O_4SSi$: 311.1712. Found: 311.1713.

3-(6-Ethanesulfonyl-pyridin-3-yloxy)-5-((*S*)-2-hydroxy-1-methyl-ethoxy)-benzoic Acid DABCO salt (2:1) (7). A crude solution of **19** in toluene (19.57 kg, 60.6 wt %, 38.2 mol) was diluted with dry $AcNMe_2$ (59.5 L). Cesium carbonate (powdered, 14.36 kg, 44.1 mol) was charged followed by **4** (9.91 kg, 29.4 mol) while maintaining a vigorous agitation. The reaction mixture was stirred vigorously at 80 °C for 8−12 h until >99% conversion was achieved. The reaction mixture was then cooled to 0 °C and diluted with MTBE (79 L). H_2O (40 L) was charged slowly at <10 °C. After a phase cut at ambient temperature, the organic phase (HPLC assay: 15.15 kg of **20**, 93% yield) was solvent switched to THF at a final volume of 89 L. MeOH (30 L) was added and the batch was cooled to 0 °C. NaOH (5 N, 8.8 L, 43.9 mol) was charged at <5 °C. The resulting solution was stirred at 0−5 °C for 1 h followed by at 20−25 °C for 2−6 h until >99.5% conversion was achieved. HCl (4 M, 27.5 L, 109.8 mol) was added. The resulting hazy solution of the free acid of **29** was stirred at 35 °C for 6−8 h until >99.5% of free acid **29** was converted to the corresponding free acid **7**. The batch was cooled to ambient temperature and *i*-PrOAc (75 L) and 15% NaCl (40 L) were added. The aqueous layer was separated and extracted with *i*-PrOAc (40 L). The combined organic layer was washed with 15% NaCl (75 L).

The above solution was azeotropically dried (batch temperature <25 °C) with *i*-PrOAc. The solution was filtered to remove a small amount of inorganic salts and diluted with *i*-PrOAc to 97 L and MeOH (16 L). The batch was heated to 50 °C. 6.4 L of a DABCO solution, prepared by dissolving DABCO (2.03 kg, 18.1 mol) in *i*-PrOAc (43 L), was charged. A well-dispersed slurry of **7** (200 g) in *i*-PrOAc (2 L) was charged as seed, and the resulting slurry was stirred at 50 °C for 2 h to form a seed bed. The remaining DABCO solution was added at 50 °C over 6 h. The resulting slurry was aged at 50 °C for 1 h and then cooled to 22 °C over 1 h. After aging at 22 °C for 5 h, the solid was collected by filtration. The wet cake was washed with 5% MeOH/*i*-PrOAc (20 L) followed by *i*-PrOAc (70 L). Drying in vacuum under nitrogen at 40 °C afforded **7** (11.9 kg) as an off-white solid. 98.5% purity. >98.8% ee. 89% yield from **4**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (d, J = 2.8 Hz, 1 H), 8.04 (d, J = 8.7 Hz, 1 H), 7.61 (dd, J = 8.7, 2.8 Hz, 1 H), 7.36 (dd, J = 2.4, 1.2 Hz, 1 H), 7.16 (dd, J = 2.4, 1.2 Hz, 1 H), 6.98 (t, J = 2.4 Hz, 1 H), 4.53−4.45 (m, 1 H), 3.54 (dd, J = 11.5, 5.8 Hz, 1 H), 3.48 (dd, J = 11.5, 4.7 Hz, 1 H), 3.41 (d, J = 7.4 Hz, 2 H), 2.97 (s, 6 H), 1.21 (d, J = 6.2 Hz, 3 H), 1.14 (t, J = 7.4 Hz, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.52, 159.38, 156.53, 155.16, 149.86, 141.10, 137.83, 125.50, 124.25, 113.11, 112.08, 110.53, 75.16, 64.13, 46.22, 44.21, 16.39, 6.81. Anal. Calcd for $C_{20}H_{25}N_2O_7S$: C, 54.91; H, 5.76; N, 6.40. Found: C, 54.86; H, 5.51; N, 6.36.

3-(6-Ethanesulfonyl-pyridin-3-yloxy)-5-((*S*)-2-hydroxy-1-methyl-ethoxy)-*N*-(1-methyl-1*H*-pyrazol-3-yl)-benzamide Methanesulfonic Acid Salt (MK-0941, 1). To a solution of **7** (20 kg, 45.7 mol) in MeCN (120 L) and H_2O (80 L) at 0−5 °C, were added pyridine (1.1 kg, 13.7 mol) and 3-amino-1-methylpyrazole (**8**, 5.3 kg, 54.86 mol). EDC-HCl (10.5 kg, 54.86 mol) was charged, and the resulting solution was aged at 0−5 °C for 30 min. HCl (1 M, 45.7 L, 45.72 mol) was charged at 0−5 °C over 3 h. The resulting biphasic solution was stirred at 0−5 °C for 2−4 h. The reaction was allowed to warm to 22 °C and diluted with *i*-PrOAc (160 L), H_2O (140 L) and 1 M HCl (13.7 L). The aqueous layer was separated and extracted with *i*-PrOAc (160 L). The combined organic layer was washed with 2% citric acid/20% NaCl (prepared from 2.4 kg of citric acid, 24 kg of NaCl, and 93.6 kg of H_2O) followed by 25% NaCl (100 L). The solution was concentrated and azeotropically dried with MeCN (batch temperature <25 °C). The resulting mixture was filtered to remove inorganic salts and diluted with MeCN (∼24 wt % of **1**). Toluene (80 L) was added, and the batch was heated to 30 °C, followed by charging methanesulfonic acid (1.1 kg, 11.43 mol). The resulting solution was seeded (1.3 kg of MK-0941 MsOH salt), and the resulting mixture was stirred at 25−35 °C for 2 h to form a seed bed. A solution of methanesulfonic acid (3.7 kg, 38.86 mol) in MeCN (40 L) and toluene (40 L) was charged at 25−35 °C over 12 h. The resulting slurry was stirred at 25−35 °C for 1 h and allowed to cool to 5−10 °C over 2 h, followed by stirring at 5−10 °C for 6 h before filtration. The wet cake was displacement washed with cold 1:1 MeCN/toluene (80 L, 5−10 °C), 1:9 MeCN/toluene (80 L) and MTBE (160 L) and dried in vacuum oven at 45 °C to afford **1** (22.9 kg) as an off-white solid with >99% purity. 90% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.63 (d, J = 2.8 Hz, 1 H), 8.15 (brs, 2 H), 8.06 (d, J = 8.7 Hz, 1 H), 7.66 (dd, J = 8.7, 2.8 Hz, 1 H), 7.61 (d, J = 2.3 Hz, 1 H), 7.57−7.50

(m, 1 H), 7.37−7.35 (m, 1 H), 7.02 (t, J = 2.0 Hz, 1 H), 6.57 (d, J = 2.3 Hz, 1 H), 4.64−4.56 (m, 1 H), 3.77 (s, 3 H), 3.55 (dd, J = 11.3, 5.8 Hz, 1 H), 3.51 (dd, J = 11.3, 4.6 Hz, 1 H), 3.41 (q, J = 7.3 Hz, 2 H), 2.48 (s, 3 H), 1.24 (d, J = 6.2 Hz, 3 H), 1.14 (t, J = 7.3 Hz, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.13, 159.77, 156.46, 155.52, 150.10, 146.81, 141.27, 137.05, 131.31, 125.95, 124.38, 111.63, 111.06, 97.56, 75.34, 64.28, 46.36, 39.76, 38.48, 16.54, 6.95. Anal. Calcd for $C_{22}H_{28}N_4O_9S_2$: C, 47.47; H, 5.07; N, 10.07. Found: C, 47.35; H, 5.18; N, 10.08.

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

We thank Dr. P. Dormer for assistance with NMR studies and Dr. T. Chasse and Ms. E. Kolodziej for analytical assistance.

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(9) This is consistent with the observed trend of the ratio of **4**:**9**. Further discussion about the reaction kinetics is beyond the scope of this manuscript, because the kinetic profile is affected by multiple components including the reactivity of the mono- and di- anion of **3** and related multiple acid−base equilibriums.

(10) The use of a larger excess of **3** resulted in increased levels of **10** and could also cause difficulties in the removal of unconsumed **3**.

(11) The monoanion of **3** seemed to be more reactive or at least as effective as the corresponding dianion for S_NAr displacement, which could be attributed to its solubility or actual concentration of the species in the reaction solution, as the *O*-arylation still gave >98% conversion and ∼75% yield even with a mole ratio for *t*-BuOK/**3** as low as 1.4:1. As evidence, the use of a large excess of monoanion of **3** gave an excellent conversion and selectivity, although it was not practical.

(12) In line with this conclusion, the formation of **9** also depended on the water content in the reaction mixture, which partially quenched *t*-BuOK. However, the reaction could still tolerate a moisture level (KF) of up to ∼1700 ppm under optimal conditions, while the formation of **9** was suppressed to <0.5%.

(13) Interestingly, higher levels of impurity **9** were also observed when the reaction was conducted in the presence of air, implying that the formation of **9** could occur via radical-type mechanism. This would rationalize the fact that reducing the amount of base to less than 2 mol equiv made the radical pathway more competitive and hence generated substantially higher levels of **9**.

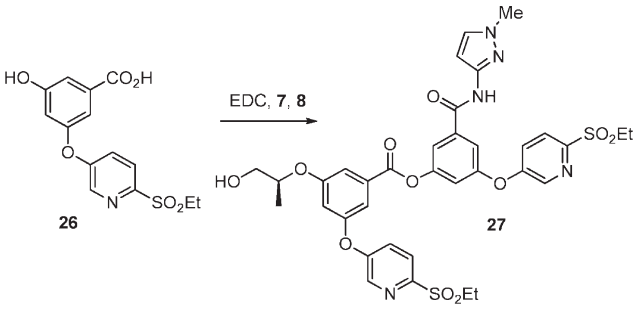
(14) The use of 2-propanol (∼10%) made the crystallization of **4** reproducible, presumably by keeping the unconsumed **3** from precipitating out.

(15) Upon heating, $CsHCO_3$ could turn into Cs_2CO_3 and water with evolution of CO_2. See: Pushnyakova, V. A.; Berger, A. S.; Kirgintsev, A. N. *Zh. Neorg. Khim.* **1973**, *18*, 311.

(16) 1,2-Propandiol could be converted to the corresponding bismesylate in the subsequent step, which could then react with **4** to generate (*R*)-OH-isomer **15**.

(17) The use of other bases such as Na_2CO_3 or DBU gave lower conversions. The use of 2 equiv of powered K_2CO_3 and 1.3 equiv of **19** in $AcNMe_2$ at 100 °C afforded **20** in 83% assay yield (10% lower than the use of Cs_2CO_3) after 20 h. However, the formation of **11** was increased to 3% (vs <1% with Cs_2CO_3).

(18) The unconsumed **4** could be transformed to **26** upon hydrolysis, which could further react with **7** and **8** to form **27**, subsequently.



(19) For example, byproduct **28** could be formed.