Organic Process Research & Development

Article

pubs.acs.org/OPRD

First- and Second-Generation Practical Syntheses of Chroman-4-one Derivative: A Key Intermediate for the Preparation of SERT/5-HT_{1A} Dual Inhibitors

Tomoaki Nishida,* Hidefumi Yoshinaga, and Tomohiro Toyoda

Chemistry Research Laboratories, Dainippon Sumitomo Pharma Co., Ltd., 3-1-98 Kasugade-naka, Konohana-ku, Osaka 554-0022, Japan

Minoru Toshima

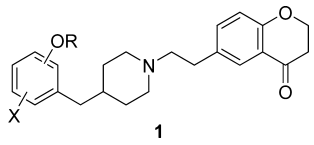
Process Chemistry Research and Development Laboratories, Dainippon Sumitomo Pharma Co., Ltd., 3-1-98 Kasugade-naka, Konohana-ku, Osaka 554-0022, Japan

Supporting Information

ABSTRACT: Two approaches to large-scale synthesis of the key intermediate **9**, a precursor of novel dual inhibitors of SERT/5-HT_{1A} receptor, are described. These two approaches each feature a mild and efficient method for construction of the chroman-4-one scaffold, which can be used with substrates containing base-sensitive functionalities and enable synthesis on kilogram scale without chromatographic purification. The first-generation synthesis enables quick delivery of a kilogram quantity of the key intermediate **9** with only one slurry purification step. On the other hand, the highly practical second-generation synthesis is suitable for the multikilogram campaign.

INTRODUCTION

Depression is a disease that affects millions of people worldwide. Although selective serotonin reuptake inhibitors (SSRIs) have widely been used for the treatment of depression, their slow onset action remains a problem. It has been reported that combination of SSRIs with 5-HT_{1A} antagonists can accelerate SSRIs onset action.[1] Accordingly, significant efforts have been devoted to identification of 5-HT_{1A} antagonists with serotonin reuptake inhibitory activity. In our search for such dual acting compounds, we have identified chroman-4-one derivatives (**1**, Figure 1) as potent dual inhibitors of the serotonin transporter (SERT) and 5-HT_{1A} receptor.[2] As these derivatives were considered to have potential efficacy in the treatment of depression, it was necessary to improve their synthetic route to supply the required amounts for preclinical pharmacology and safety studies.



1

Figure 1. Chemical structure of **1**.

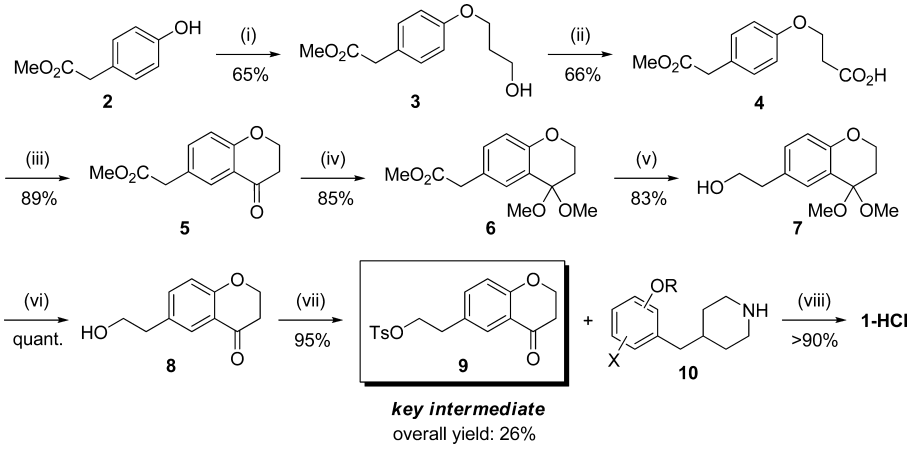
The synthetic route of **1** for medicinal chemistry work is shown in Scheme 1. A phenol moiety of the starting material **2** was alkylated with 3-bromo-1-propanol in the presence of potassium carbonate to give the alcohol **3** in 65% yield. Subsequent oxidation of this primary alcohol with pyridinium dichromate (PDC) afforded the propanoic acid **4** in 66% yield. The intramolecular Friedel–Crafts cyclization of **4** in polyphosphoric acid (PPA) provided the ester **5** in 89% yield. After protection of the ketone moiety of **5** as a ketal (**6**), the methyl ester was reduced to alcohol **7** by treatment with lithium aluminum hydride (LAH). Acidic deprotection of **7** gave compound **8**, which was treated with tosyl chloride in pyridine/CH_2Cl_2 to give the tosylate **9** as a crystalline solid. The overall yield of this key intermediate **9** was less than 26% in seven steps. *N*-Alkylation of the benzylpiperidine **10** with the tosylate **9** and potassium carbonate in CH_3CN gave the target molecules **1** in excellent yield (>90%). Finally, treatment of the crude **1** with conc. HCl in 2-propanol afforded the HCl salt of **1** as a solid. This synthesis enabled the supply of **1** for early-stage evaluation.

The aim of our medicinal chemistry work was to optimize the structure, and indeed, the tosylate **9** prepared by the above synthetic method was of great use in the preparation of various derivatives of **1**, since the tosylate **9** is chemically stable over months of storage. However, assessment of this initial synthetic route for large-scale synthesis of the common key intermediate **9** highlighted serious concerns in several reaction steps. A long reaction time was needed to complete *O*-alkylation of the commercially available **2**, and this step was poorly reproducible. In addition, production of the alcohol **3** was accompanied by multiple byproducts. Moreover, the subsequent oxidation step was conducted with the highly toxic PDC, giving a large amount of metal waste. Finally, the chemical yield of this alkylation–oxidation sequence was moderate, making this synthesis inefficient from a cost perspective. Other drawbacks

Received: December 8, 2011
Published: February 22, 2012

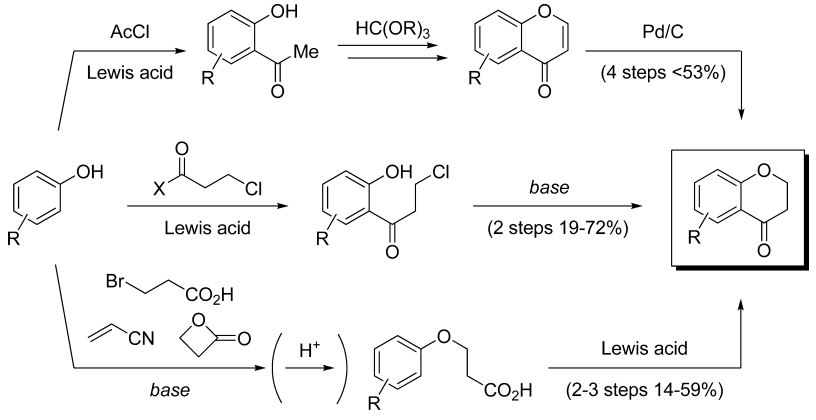
dx.doi.org/10.1021/op200357h | *Org. Process Res. Dev.* 2012, 16, 625–634

Scheme 1. Synthesis of 1 for medicinal chemistry work[a]



[a]Reagents and conditions: (i) 3-Bromo-1-propanol, K_2CO_3, CH_3CN, reflux, 14 h; (ii) PDC, MS4A, DMF, rt, 20 h; (iii) PPA, 80 °C, 2 h; (iv) trimethyl orthoformate, cat. TsOH-H_2O, MeOH, rt, 13 h; (v) LAH, THF, rt, 1.5 h; (vi) 3 M HCl, acetone, rt, 1.5 h; (vii) TsCl, pyridine, CH_2Cl_2, 0 °C, 18 h; (viii) K_2CO_3, CH_3CN, 60 °C, 15 h; then conc. HCl, 2-propanol.

Scheme 2. Reported approaches for construction of unsubstituted chroman-4-ones on aliphatic ring carbons



of the above synthetic route include the need for an excess amount of PPA (20 w/w) as the reaction solvent to fully convert the propanoic acid **4**, which required laborious workup process. Since the propanoic acid **4** did not dissolve in the reaction mixture, standard HPLC analysis was unsuitable to detect the remaining **4**. Furthermore, most intermediates except for **4** were obtained as oils, requiring purification by silica gel chromatography in several steps. In order to solve these problems, we focused our efforts on finding efficient and scalable syntheses of **5**.

Herein, we describe our successful establishment of two methodologies toward construction of the chroman-4-one scaffold, which can be used with substrates containing base-sensitive functionalities. First-generation synthesis enables the quick delivery of a kilogram quantity of the key intermediate **9**, while second-generation synthesis is suitable for a multikilogram campaign.

RESULTS AND DISCUSSION

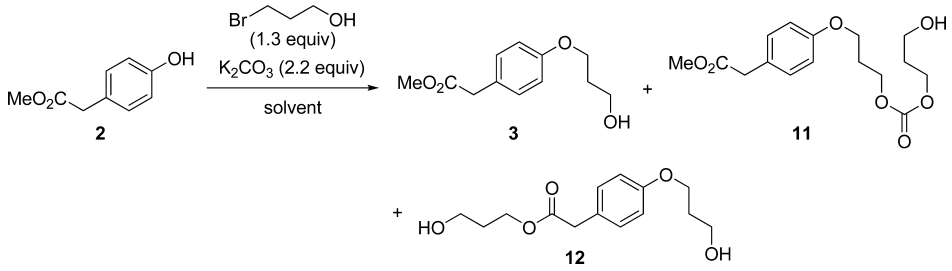
First-Generation Synthesis. Efforts related to synthesis of the chroman-4-one scaffold have been widely reported in the literature. However, there are relatively few accounts of synthetic methods toward construction of unsubstituted chroman-4-ones on the aliphatic ring carbons. These methods produce low-to-moderate chemical yield and require chromatographic purification (Scheme 2).[3] In addition, most of these methodologies require the use of strong basic and/or acidic conditions unsuitable for our substrate, since our starting material **2** contains a base-sensitive active methylene group and an ester functionality. Thus, it was necessary to establish a novel methodology to construct the chroman-4-one scaffold under mild conditions without chromatographic purification.

On the basis of the above, medicinal chemistry approach was designed to avoid strong basic conditions and successfully construct the chroman-4-one scaffold in 38% yield from the starting material **2** in three steps (Scheme 1). As the reported approaches were considered inappropriate for our purposes, we examined optimization of our medicinal chemistry route. Since transformation of **5** to the desired **9** was accomplished by simple modifications, we focused on a scalable method for the preparation of compound **5**.

In order to improve product yield and purity in the *O*-alkylation step of **2**, the stoichiometries of the reagents and reaction solvents were screened (Table 1). By the use of CH_3CN as a solvent, the starting material **2** was completely consumed to give the alcohol **3** with 92% HPLC purity in 3 h on 1-g scale (entry 1). We found that a reaction with less than 2 equiv of potassium carbonate did not reach completion, and prolonged reaction time caused a decrease in product purity. Reaction in acetone, 2-butanone or THF showed slow

dx.doi.org/10.1021/op200357h | Org. Process Res. Dev. 2012, 16, 625–634

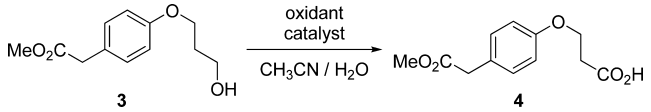
Table 1. Solvent screening in the *O*-alkylation of 2



			HPLC purity @ 3 h (%)			
entry[a]	solvent	temp., °C	**3**	**2**	**11**	**12**
1	CH_3CN	reflux	92	–	3.9	1.4
2	acetone	reflux	55	41	–	0.49
3	2-butanone	reflux	79	17	1.8	0.91
4	THF	reflux	12	82	–	–
5	DMF	80	61	17	16	0.62
6	DMSO	80	54	25	13	1.4
7[b,c]	CH_3CN	reflux	75	17	4.8	0.20
	(crude)[e]	reflux	83	0.43	12	0.24
8[b]	0.5% (v/v) H_2O/CH_3CN	reflux	94	0.32	1.9	1.7
9[b]	1.0% (v/v) H_2O/CH_3CN	reflux	96	–	1.2	1.7
10[b]	2.0% (v/v) H_2O/CH_3CN	reflux	93	–	0.46	2.4
11[b,d]	1.0% (v/v) H_2O/CH_3CN	reflux	95	–	0.66	0.44

[a]Screening was performed on 1-g scale in freshly opened CH_3CN. [b]Freshly opened potassium carbonate was used. [c]50-g scale. [d]75-g scale. [e]Refluxed for 9 h.

Table 2. Screening of conditions for oxidation of 3



entry[a]	oxidant (equiv)	catalyst (mol %)	yield (%)[b]
1	PDC (3.5)	none	66
2	$NaIO_4$ (4)	$RuCl_3$ (3)	85
3	DAIB (2)	TEMPO (10)	30
4	TCCA (2)	TEMPO (1)·NaBr (5)	<5
5	$NaClO_2$ (2)	TEMPO (7)·NaClO (2)	98

[a]Chromatographic purified alcohol **3** was used. [b]Isolated yield.

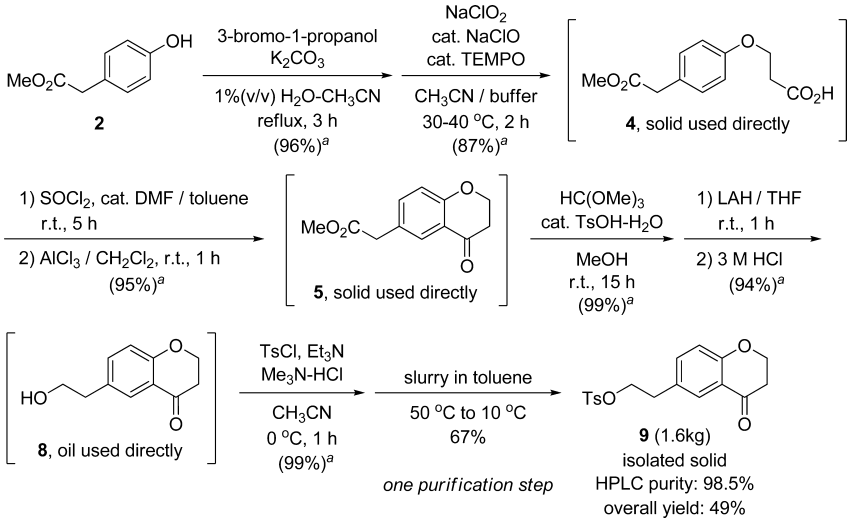
conversion rate and stalled at less than 80% conversion (entries 2–4). The use of an aprotic polar solvent such as DMF or DMSO gave significant levels of impurities (entries 5, 6).

On the basis of these results, CH_3CN was applied as a solvent for 50-g-scale synthesis of **3**. Unlike the result of entry 1, however, the reaction did not reach completion after 3 h, and compound **2** was still remaining even after 9 h together with a substantial amount of byproduct impurities (entry 7). Two of these impurities were identified as carbonate **11** and diol **12**. The carbonate **11** was one of the major byproduct on this scale which was caused by overreaction of the desired alcohol **3** with 3-bromo-1-propanol via potassium carbonate-promoted insertion of carbon dioxide.[4] On the other hand, the diol **12** was formed from **3** by a trans-esterification reaction. The increasing levels of these impurities caused not only degradation of product **3** but also lack of the reagent 3-bromo-1-propanol itself. This resulted in delay of the reaction completion and loss of product purity. Since the purification of the alcohol **3** from the accompanied impurities was considered difficult in light of the physical properties of **3**, reproducible conditions under which levels of impurities can be suppressed should be identified.

Next, we examined the differences in experimental conditions between entry 1 and entry 7. As potassium carbonate from a freshly opened bottle was used for scale-up in entry 7 but not in entry 1, we hypothesized that water content in the reaction medium was a crucial factor for suppression of side reactions. In order to confirm this hypothesis, several conditions using CH_3CN with various amounts of water were screened. As shown in Table 1, addition of water was very effective for rapid conversion to the desired alcohol **3** and control of the generation of impurities (entries 8–10). In fact, generation of **11** was suppressed, depending on water content in the reaction medium, whereas the opposite was observed in the case of the diol **12**. Thus, CH_3CN containing 1.0% (v/v) of water was selected as a suitable solvent system for further scale-up studies. This condition reproducibly gave the alcohol **3** with >95% HPLC purity on 75-g scale (entry 11).[5] The obtained alcohol **3** was used for the next step without further purification.

dx.doi.org/10.1021/op200357h | *Org. Process Res. Dev.* 2012, 16, 625–634

Scheme 3. First-generation practical synthesis[a]



[a]Calculated yield.

With improved conditions developed for the *O*-alkylation step, our attention was directed toward optimization of the next oxidation step. In order to avoid the use of PDC and improve the chemical yield, we focused on finding a catalytic system that can directly oxidize **3** to the propanoic acid **4** (Table 2). With $RuCl_3$·$NaIO_4$ as a catalytic system, the oxidation of **3** proceeded to completion in 5 h, and the desired product **4** was obtained in 85% yield without the use of a chlorinated cosolvent (entry 2).[6] Encouraged by this result, we focused on metal-free catalytic oxidation of **3** using 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO). Although the use of (diacetoxyiodo)benzene (DAIB)[7a] or trichloroisocyanuric acid (TCCA)[7b] as oxidant gave a mixture of multiple byproducts (entries 3 and 4), utilizing $NaClO_2$ under the TEMPO·NaClO catalytic system[8] provided **4** in 98% yield (entry 5).

In spite of the excellent result described above (entry 5), this experimental procedure was relatively complicated, as both aqueous $NaClO_2$ solution and diluted NaClO had to be simultaneously added dropwise to the reaction mixture (mixing of aqueous $NaClO_2$ and diluted NaClO solutions prior to the addition is not recommended since the mixture appears to be unstable.[8]) We therefore started looking for a simpler and safer experimental procedure that can be applied for the large-scale preparation. Dropwise addition of diluted NaClO solution to a solution of alcohol **3**, TEMPO, and $NaClO_2$ in CH_3CN·phosphate buffer (0.67 M, pH = 6.7) at 22 °C on 1-g scale led to rapid oxidation into **4**; however, the reaction temperature rapidly increased to 42 °C within 10 min. This was due to acute decrease of the pH in the reaction mixture as the oxidation reaction progressed, and such a decrease of pH accelerated the rate of oxidation with acute elevation of temperature. Further investigation revealed that this elevation of temperature can be controlled by modification of the reaction conditions, namely a decrease in the phosphate buffer concentration from 0.67 to 0.25 M and gradual addition of aqueous $NaClO_2$ solution (over 1 h) to a solution of alcohol **3**, TEMPO, and NaClO in CH_3CN·phosphate buffer at 30−40 °C. Under these conditions, the oxidation successfully progressed to completion in 1 h on 50-g and 1-kg scales, and the reaction temperature could be controlled between 30 and 40 °C within jacket capabilities. When 0.10 M of phosphate buffer was used, the rate of oxidation of alcohol **3** was considerably slow, and the reaction did not reach completion even after 5 h. On the basis of these findings, we concluded that buffering capacity is important to control the reaction rate due to the pH-dependent nature of this oxidation. Thus, we could optimize the conditions for oxidation of alcohol **3** without using the toxic and metal waste-producing PDC.

Our next aim was to replace PPA in the intramolecular cyclization step, because its use would require not only a laborious and time-consuming process in the addition of PPA to the reaction vessel and the quench with water for workup but also additional investigation of appropriate analytical methods for detection of the remaining insoluble **4**. With the aim of avoiding the use of PPA, we tried to apply the traditional intramolecular Friedel−Crafts cyclization conditions. Acid chloride prepared from **4** with thionyl chloride and a catalytic amount of DMF in toluene was cyclized with $AlCl_3$ in CH_2Cl_2 at room temperature to give the desired **5** in 88% yield. This alternative method could overcome the problems associated with PPA. The unreacted acid chloride of **4** could be detected as the corresponding methyl ester by quenching a portion of the reaction mixture with methanol.

As described above, we established a robust synthetic route to compound **5** from the commercially available **2**. This improved process enabled synthesis of the key intermediate **5** with 93.8% HPLC purity without chromatographic purification on 50-g scale (Scheme 3). Effective purification of crude **5** proved to be difficult due to high solubility in various organic solvents; however, we found that the use of crude **5** did not cause major problems in the following reactions and could afford the tosylate **9** with high purity.

For the purpose of large-scale production, the synthetic method of the tosylate **9** from **5** was slightly modified. Protection of the ketone moiety of **5** with trimethyl orthoformate was effectively catalyzed by *p*-toluenesulfonic acid at room temperature in methanol. NMR analysis was used to determine the conversion rate instead of standard HPLC analysis, because the ketal **6** was highly susceptible to hydrolysis to ketone **5** even in neutral conditions.[9] After the ester moiety of the resulting ketal **6** was reduced to give alcohol **7** by LAH, acidic workup enabled obtaining the deprotected ketone **8**

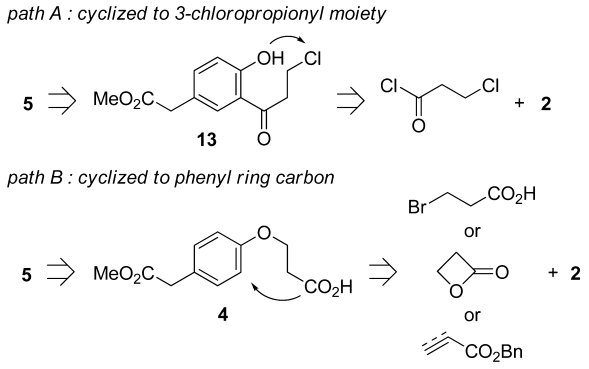
dx.doi.org/10.1021/op200357h | *Org. Process Res. Dev.* 2012, 16, 625−634

directly. Although tosylation of the hydroxyl group of **8** in pyridine/CH_2Cl_2 required more than 10 h to reach completion, a catalytic amount of trimethylamine hydrochloride (Me_3N·HCl) could highly accelerate this reaction to afford crude **9** (85.7% HPLC purity) within 1 h.[10] The crude **9** was accompanying several byproducts obtained in previous steps due to the lack of purifiable intermediate. These byproducts were effectively removed by the slurry method, i.e. stirring in toluene at 50 °C for 1 h, cooling to room temperature, and collecting the resulting solid by filtration. Thus, the desired tosylate **9** was prepared on 50-g scale with 98.5% HPLC purity.

As described above, we established a scalable and reproducible process to construct the chroman-4-one scaffold containing base-sensitive functionalities from starting material **2**. This method enabled us to avoid the use of PDC and PPA, and the overall yield was improved from 26% to 42% in seven synthetic steps without chromatographic purification. As a result of optimization in each step, the tosylate **9** was obtained with only one slurry purification step. A scale-up by this synthetic method afforded 1.6 kg of tosylate **9** in 49% yield with 98.5% HPLC purity, which was comparable to the result obtained on 50-g scale. In conclusion, we have established a synthetic method for supplying the common key intermediate **9** for preparation of the target compound **1** for preclinical studies.

Alternative Approaches to Synthesis of compound 5 without Oxidation. Although a kilogram of the tosylate **9** could be delivered by the first-generation synthesis described above (Scheme 3), use of the oxidation reaction for further scale-up synthesis was undesirable due to safety concerns. Therefore, robust approaches for synthesis of compound **5** excluding any oxidation step were investigated. As shown in Scheme 4, two methods were considered for the ring-closure

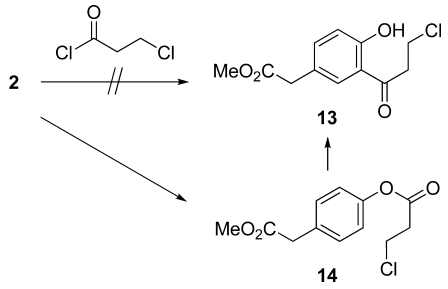
Scheme 4. Alternative approaches to synthesis of compound 5



reaction: *O*-alkylation with 3-chloropropionyl moiety (path A) or intramolecular Friedel–Crafts cyclization as in the case of first-generation synthesis (path B).

First, we focused on path A. Although treatment of **2** with 3-chloropropionyl chloride in the presence of $AlCl_3$ in refluxing CH_2Cl_2 or chlorobenzen did not give any amount of the expected meta-acylated **13** but afforded only undesired *O*-acylated product **14**,[11] treatment of **2** with 3-chloropropionyl chloride in TfOH afforded the desired **13** in 37% yield via Fries rearrangement of the *O*-acylated product **14** (Scheme 5). However, high concentration of TfOH was required for complete conversion of **14**, which resulted in a mixture of multiple byproducts. In addition, isolation of **13** without chromatographic purification was difficult, because **13** and the

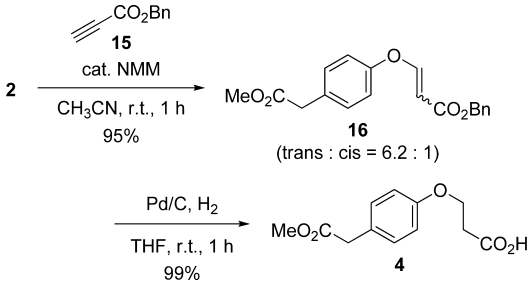
Scheme 5. *C*-Acylation of the starting material 2



accompanying byproducts have similar chemical properties. We therefore discontinued further work on this route.

Next, we examined path B. *O*-Alkylation of **2** with 3-bromopropanoic acid[3c] or *β*-propiolactone[12] in basic conditions (Cs_2CO_3 or KO^{t}Bu) resulted in a mixture of multiple byproducts due to competing reactions at the active methylene group. Michael addition of **2** with benzyl acrylate in the presence of DBU as a mild base[13] did not afford the desired product but gave unknown decomposed byproducts. In contrast, Michael addition of **2** with the benzyl propiolate **15** in the presence of *N*-methylmorpholine (NMM) afforded the benzyl acrylate **16** in high yield.[2c,14] Use of a catalytic amount of NMM in CH_3CN allowed the reaction to proceed to completion within 1 h at room temperature to give **16** as a mixture of stereoisomers in 95% yield (Scheme 6).[15] **16**,

Scheme 6. Oxidation-free synthesis of 4



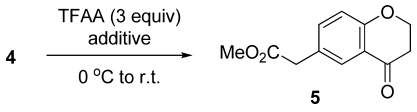
purified by silica gel chromatography, was successfully hydrogenated with Pd/C catalyst to give the propanoic acid **4** with 96.6% HPLC purity in 99% yield, achieving an efficient oxidation-free synthesis of **4**.[16]

Although the next cyclization of **4** with $AlCl_3$ via the corresponding acid chloride could overcome the resulting problems from PPA and was applied for a kilogram-scale synthesis, generation of a large amount of metal waste and inefficient two-step cyclization via the isolation of the corresponding acid chloride were still problems to be improved, upon considering further scale-up synthesis. Screening of one-step Friedel–Crafts cyclization conditions revealed that treatment with trifluoroacetic anhydride (TFAA) can afford the desired **5** from the carboxylic acid **4** via the corresponding mixed anhydride generated in situ (Table 3).[17] Addition of an acid accelerated the reaction rate, and the use of a catalytic amount of phosphoric acid gave excellent results in terms of both reaction rate and product purity. As a result on this improvement, the desired cyclized product **5** was obtained in 97% yield (entry 5).

Thus, we established a highly practical alternative route to construct the chroman-4-one scaffold under oxidation-free and

dx.doi.org/10.1021/op200357h | *Org. Process Res. Dev.* 2012, 16, 625–634

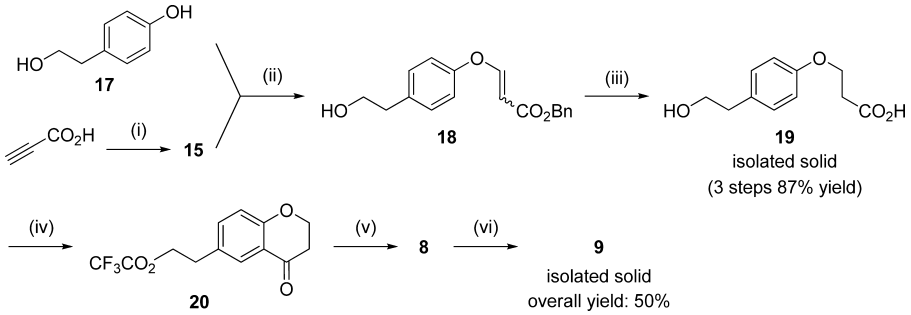
Table 3. Screening of one-step Friedel-Crafts cyclization of 4



entry	additive (equiv)	HPLC purity **5**/**4** @ 1 h (%)	isolated yield (%)
1[a]	–	94.6/–	88
2	none	2.72/95.2[b]	–
3	TFA (3)	90.2/7.41	–
4	TFA (0.1)	7.14/90.8[b]	–
5	H_3PO_4 (0.1)	98.1/–	97
6	AcOH (0.1)	5.12/92.9[b]	–

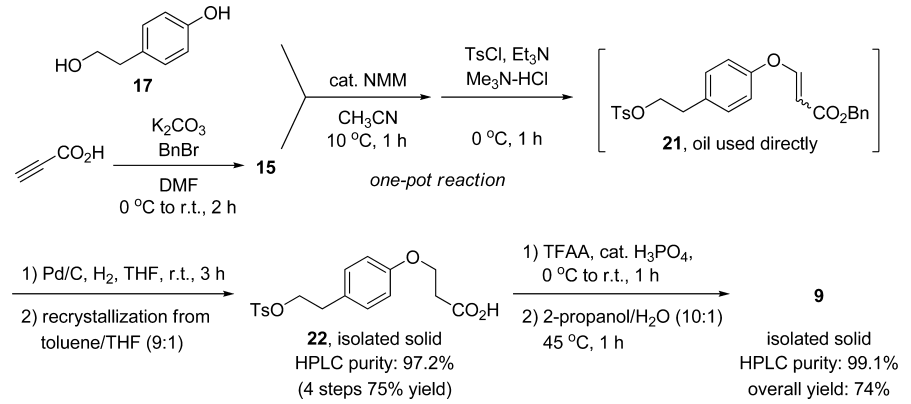
[a]Data obtained by the use of $AlCl_3$ in first-generation synthesis. [b]Reaction did not reach completion after 8 h.

Scheme 7. Alternative approach for synthesis of the tosylate 9[a]



[a]Reagents and conditions: (i) Benzyl bromide, K_2CO_3, DMF, 0 °C, 3 h; (ii) cat. NMM, CH_3CN, 10 to 25 °C, 1.5 h; (iii) H_2, Pd/C, THF, 25 °C, 3 h; then slurry in toluene, 25 °C, 1 h; (iv) TFAA, cat. H_3PO_4, 0 °C, 2 h; (v) K_2CO_3, MeOH, 25 °C, 1 h; (vi) TsCl, Et_3N, Me_3N·HCl, CH_3CN, 0 °C, 1 h; then slurry in toluene, 50 °C, 1 h.

Scheme 8. Second-generation practical synthesis



mild conditions. Compound **5** was obtained from the phenol **2** in 91% yield, far exceeding the yield in first-generation synthesis (73–78%). Each of the three steps reached completion within 1 h at room temperature; moreover, we could avoid the use of the environmentally undesired $AlCl_3$ and CH_2Cl_2.

Second-Generation Synthesis. From a cost perspective, the 4-(2-hydroxyethyl)phenol **17** looks highly desired as an alternative starting material.[18] In addition, the use of this compound can help avoid the reduction step of the ester moiety and the treatment of the unstable intermediate **6** which can readily be hydrolyzed to the ketone **5** with exposure to moisture. Despite these advantages of compound **17**, it was not applied for the first-generation synthesis due to its primary hydroxyl group which would be easily oxidized to carboxylic acid in the second oxidation step. Selective protection of the primary hydroxyl group of **17** over the phenol moiety was considered difficult and inefficient; hence, efforts for the synthesis of the tosylate **9** had been concentrated on using **2** as the starting material. As the above Michael addition route (Scheme 6) became available, however, the alternative approach to **9** from **17** for the multikilogram campaign was reconsidered.

Use of Michael addition enabled selective introduction of the propanoic acid unit without protection of the primary hydroxyl group to give the acrylate **18** (Scheme 7).[2c] Surprisingly, we found that benzyl propiolate **15** was highly reactive to afford the Michael adduct on the less active primary hydroxyl group as well as on the desired phenol moiety, which resulted in the generation of diacrylated byproduct. When 1.2 equiv of **15** was used in this reaction at 25 °C, the obtained **18** was

dx.doi.org/10.1021/op200357h | Org. Process Res. Dev. 2012, 16, 625–634

accompanying 27.7% (HPLC purity) of diacrylated byproduct. The use of an equimolar amount of **15** at 10 °C successfully suppressed this side reaction, and **18** was obtained with 93.5% HPLC purity accompanying 3.22% (HPLC purity) of diacrylated byproduct. The obtained acrylate **18** was hydrogenated with Pd/C catalyst and then purified in toluene by slurry method to give the propanoic acid **19** in 87% yield as a sole product in three steps from propiolic acid. Treatment of **19** with TFAA and a catalytic amount of phosphoric acid gave **20** as the trifluoroacetate of the alcohol **8**. Hydrolysis of **20** with potassium carbonate in methanol afforded the alcohol **8**, which was led to the tosylate **9** in 58% yield. Thus, we identified an alternative approach from desired starting material **17** in 50% overall yield.

In order to improve this alternative synthesis, we considered that hydrolysis of **20** could be avoided by transformation of the primary hydroxyl group of **19** into a tosylate before Friedel–Crafts cyclization. Although tosylation of **19** resulted in a mixture of multiple side products, the acrylate **18** was successfully tosylated in a one-pot reaction without isolation after the Michael addition (Scheme 8). Subsequent hydrogenation followed by recrystallization from toluene·THF (9:1) afforded the penultimate **22** with 97.2% HPLC purity as an isolated solid in 75% yield in four steps from propiolic acid. The tosyl functionality was well tolerated in the Friedel–Crafts cyclization step, and the resulting crude product was purified by slurry method with 2-propanol·H_2O (10:1) to give the tosylate **9** with 99.1% HPLC purity in 98% yield.

In this way, we have succeeded in developing a practical second-generation synthesis for the tosylate **9**. This synthetic method allowed us to overcome the problems identified in the first-generation synthesis. Using **17** as starting material, we obtained **9** on 10-g scale with 99.1% HPLC purity in 74% overall yield with five synthetic steps without having to use chromatographic purification. As a consequence, we could avoid the oxidation step, the unstable intermediate **6**, and the use of LAH and $AlCl_3$ which would result in a large amount of metal waste. We also obtained in this synthesis penultimate **22**, an appropriate intermediate that can be easily purified for impurity control. Further optimization of this alternative route for multikilogram campaign is currently under investigation.[19]

CONCLUSION

We have successfully developed two approaches for large-scale synthesis of the key intermediate **9**, a precursor of novel dual inhibitors of SERT/5-HT_{1A} receptor. These two approaches feature a mild and efficient method for construction of the chroman-4-one scaffold, which can be used with substrates containing base-sensitive functionalities, and enable synthesis on kilogram scale without chromatographic purification. Chroman-4-one derivatives are well-known not only as natural products, but also as key building blocks with a ketone functionality. Since our methodologies are applicable even in the presence of labile functionalities, we anticipate the use of these methods in the synthesis of various chroman-4-one derivatives.

EXPERIMENTAL SECTION

General. HPLC was performed on a Shimadzu UFLC system; shim-pack XR-ODS column (3.0 mm i.d. × 100 mm); gradient elution (0.05% TFA·H_2O/0.05% TFA·CH_3CN 90:10 to 10:90 over 6 min, hold 2 min); flow rate = 1.0 mL/min, T = 40 °C, UV detection at 220 nm. The purity listed is determined by area %. Melting points were determined on an electrothermal apparatus without correction. NMR spectra were recorded on a JEOL JNM-LA300 spectrometer. Chemical shifts (δ) are given in parts per million, and tetramethylsilane was used as the internal standard for spectra obtained in $CDCl_3$ or DMSO-d_6. IR spectra were recorded on a JEOL JIR-SPX60 spectrometer as ATR. High-resolution MS spectra were recorded on a Thermo Fisher Scientific LTQ orbitrap Discovery MS equipment. Elemental analysis was performed on a CE Instrument EA1110 and a Yokokawa analytical system IC7000. Column chromatography was carried out using a Yamazen W-prep system. All reactions were carried out under nitrogen atmosphere unless otherwise mentioned. Reagents and solvents were used as obtained from commercial suppliers without further purification.

First-Generation Synthesis (Scheme 3). *Methyl [4-(3-Hydroxypropoxy)phenyl]acetate (**3**).* To a solution of methyl (4-hydroxyphenyl)acetate **2** (964 g, 5.80 mol) in CH_3CN (15.2 kg) was added water (193 kg), and the mixture was stirred for 15 min at ambient temperature; then potassium carbonate (1.76 kg, 12.8 mol, 2.2 equiv) and 3-bromo-1-propanol (1.05 kg, 7.55 mol, 1.3 equiv) were added. The mixture was refluxed for 3 h and then allowed to cool to ambient temperature. The precipitate was filtered off and washed with CH_3CN (3.80 kg). The combined filtrates were concentrated in vacuo. Then toluene (8.34 kg) and water (4.82 kg) were added to the residue, and the layers were separated. The aqueous layer was extracted with toluene (3.58 kg). The combined organic layers were washed with 0.5 M NaOH (1.93 kg) and 1% aqueous $KHSO_4$ solution (1.93 kg) and then concentrated in vacuo to give **3** (1.27 kg) as a yellow oil. In total 2.09 kg of **3** was prepared according to the above-described procedure. It was used for the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 4.00 (t, J = 6.1 Hz, 2H), 3.72 (t, J = 5.9 Hz, 2H), 3.62 (s, 3H), 3.51 (s, 2H), 3.44 (br, 1H), 1.94 (t, J = 6.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 157.6, 129.9, 125.6, 114.1, 64.6, 58.9, 51.6, 39.7, 31.6; IR (ATR) 3390, 1732, 1512 cm^{-1}; HRMS (ESI) m/z calcd for $C_{12}H_{17}O_4$ $[M + H]^+$ 225.1121, found 225.1117.

*Methyl [4-(3-{[(3-Hydroxypropoxy)carbonyl]oxy}propoxy)-phenyl]acetate (**11**).* Analytically pure **11** was obtained by silica gel chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.3 Hz, 2H), 4.33 (t, J = 6.2 Hz, 2H), 4.27 (t, J = 6.2 Hz, 2H), 4.04 (t, J = 6.0 Hz, 2H), 3.73–3.65 (m, 2H), 3.67 (s, 3H), 3.56 (s, 2H), 2.42 (br, 1H), 2.13 (quin, J = 6.1 Hz, 2H), 1.89 (quin, J = 6.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 157.6, 155.2, 130.1, 126.0, 114.4, 64.8, 64.6, 63.7, 58.6, 51.9, 40.1, 31.4, 28.4; IR (ATR) 3446, 1736, 1512 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{23}O_7$ $[M + H]^+$ 327.1438, found 327.1433.

*3-Hydroxypropyl [4-(3-Hydroxypropoxy)phenyl]acetate (**12**).* Analytically pure **12** was obtained by silica gel chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 4.20 (t, J = 6.2 Hz, 2H), 4.06 (t, J = 6.1 Hz, 2H), 3.79 (t, J = 5.4 Hz, 2H), 3.63–3.55 (m, 2H), 3.54 (s, 2H), 2.80–2.60 (m, 2H), 1.99 (quin, J = 6.1 Hz, 2H), 1.81 (quin, J = 6.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 157.8, 130.1, 126.0, 114.5, 65.3, 61.8, 59.8, 58.8, 40.3, 31.8, 31.4; IR (ATR) 3358, 1718, 1512 cm^{-1}; HRMS (ESI) m/z calcd for $C_{14}H_{21}O_5$ $[M + H]^+$ 269.1384, found 269.1379.

dx.doi.org/10.1021/op200357h | Org. Process Res. Dev. 2012, 16, 625–634

*3-[4-(2-Methoxy-2-oxoethyl)phenoxy]propanoic Acid (**4**).* To a solution of KH_2PO_4 (319 g, 2.34 mol) and $Na_2HPO_4{\cdot}12H_2O$ (838 g, 2.34 mol) in water (18.1 kg) were successively added **3** (1.27 kg, 5.65 mol) in CH_3CN (14.7 kg), TEMPO (111 g, 0.708 mol, 0.13 equiv), and NaClO (5% solution) (169 g, 0.113 mol, 0.02 equiv). After the mixture was heated to 30−40 °C (internal temperature), a solution of $NaClO_2$ (80%) (1.28 kg, 11.3 mol, 2 equiv) in water (5.63 kg) was slowly added over 1 h. Then the mixture was kept at 30−40 °C for 2.5 h and cooled to 0−5 °C. A solution of 20% aqueous $NaHSO_3$ solution (9.38 kg) was added dropwise over 1 h, keeping the temperature lower than 10 °C during the addition (**CAUTION**: generated sulfur dioxide should be trapped by aqueous NaOH solution.). The mixture was warmed to room temperature, and then the biphasic system was separated. The aqueous layer was extracted with EtOAc (8.46 kg), and the combined organic layers were concentrated in vacuo. The resultant precipitate was added to water (2.82 kg), collected by filtration, washed with water (2 × 1.41 kg), and dried in vacuo to give **4** (1.11 kg) as a white solid. In total 1.93 kg of **4** was prepared according to the above-described procedure. It was used for the next step without further purification. Mp 112 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.39 (br, 1H), 7.17 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 4.14 (t, J = 6.0 Hz, 2H), 3.60 (s, 3H), 3.60 (s, 2H), 2.69 (t, J = 6.1 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.4, 172.0, 157.3, 130.5, 126.5, 114.3, 63.6, 51.7, 39.3, 34.2; IR (ATR) 1734, 1691, 1514 cm^{-1}; HRMS (ESI) m/z calcd for $C_{12}H_{15}O_5$ $[M + H]^+$ 239.0914, found 239.0910; Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.50; H, 5.83.

*Methyl (4-Oxo-3,4-dihydro-2H-chromen-6-yl)acetate (**5**).* Thionyl chloride (1.16 kg, 9.74 mol, 1.2 equiv) was added dropwise over 0.5 h to a suspension of **4** (1.93 kg, 8.11 mol) in toluene (16.7 kg) and DMF (18.3 g). The mixture was stirred at ambient temperature for 5 h and concentrated in vacuo. Toluene (8.60 kg) was added to the residue, and the resultant solution was concentrated in vacuo (twice) to give the corresponding acid chloride (2.08 kg) as a yellow oil. The residue was dissolved in CH_2Cl_2 (8.28 kg), and then added dropwise over 1 h to a suspension of $AlCl_3$ (2.16 kg, 16.2 mol, 2 equiv) in CH_2Cl_2 (19.3 kg) at ambient temperature. The mixture was stirred for 1.5 h and added dropwise over 2 h to cooled (0−5 °C) 2 M HCl (20.8 kg), keeping the temperature lower than 20 °C during the addition. The mixture was warmed to ambient temperature, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5.52 kg). The combined organic layers were successively washed with water (4.15 kg), 5% aqueous $NaHCO_3$ solution (4.16 kg), and water (4.16 kg), and then concentrated in vacuo. MeOH (3.28 kg) was added to the residue, and the mixture was concentrated in vacuo to give **5** (1.71 kg) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, J = 2.4 Hz, 1H), 7.41 (dd, J = 8.5, 2.3 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 4.52 (t, J = 6.5 Hz, 2H), 3.69 (s, 3H), 3.59 (s, 2H), 2.80 (t, J = 6.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.5, 171.6, 160.9, 136.9, 127.4, 127.0, 121.0, 118.1, 66.9, 52.0, 39.9, 37.5; IR (ATR) 1720, 1682, 1140 cm^{-1}; HRMS (ESI) m/z calcd for $C_{12}H_{13}O_4$ $[M + H]^+$ 221.0808, found 221.0805.

*6-(2-Hydroxyethyl)-2,3-dihydro-4H-chromen-4-one (**8**).* To a suspension of **5** (1.71 kg, 7.72 mol) in MeOH (4.03 kg) were added trimethyl orthoformate (9.89 kg) and $TsOH{\cdot}H_2O$ (146 g, 0.766 mol, 0.1 equiv), and the reaction mixture was stirred 15 h at room temperature. After 5% aqueous $NaHCO_3$ solution (8.50 kg) was cooled down to 0−10 °C, the reaction mixture was added dropwise to that solution over 1 h. After the reaction mixture was warmed to room temperature, toluene (7.36 kg) was added, and then the layers were separated. The aqueous layer was washed with toluene (4.42 kg), and the combined organic layers were washed with water (3.40 kg) and then concentrated in vacuo. Toluene (1.50 kg) was added to the residue and concentrated in vacuo to give **6** (2.05 kg) as a yellow oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.36 (d, J = 2.2 Hz, 1H), 7.11 (dd, J = 8.4, 2.2 Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 4.25 (t, J = 5.7 Hz, 2H), 3.61 (s, 2H), 3.59 (s, 3H), 3.17 (s, 6H), 2.09 (t, J = 5.8 Hz, 2H).

Obtained **6** (2.05 kg, 7.70 mol) in THF (3.64 kg) was added dropwise over 40 min to a suspension of LAH (439 g, 11.6 mol, 1.5 equiv) in THF (23.7 kg) at such a rate that the reaction temperature stayed in the range 20−30 °C. The mixture was stirred for 2 h and cooled down to around 5 °C. Water (294 g) in THF (145 g) and 3 M HCl (20.5 kg) were successively added dropwise over 2.5 h, keeping the reaction temperature lower than 15 °C during the addition. Toluene (17.7 kg) was added to the reaction mixture, and the layers were separated. The aqueous layer was washed with toluene (17.7 kg), and the combined organic layers were washed with 3 M HCl (4.1 kg) and water (8.2 kg) and then concentrated in vacuo to give **8** (1.39 kg) as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 2.2 Hz, 1H), 7.35 (dd, J = 8.4, 2.4 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 4.48 (t, J = 6.4 Hz, 2H), 3.81 (t, J = 6.7 Hz, 2H), 2.86 (br, 1H), 2.81 (t, J = 6.7 Hz, 2H), 2.75 (t, J = 6.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.1, 160.3, 136.9, 131.7, 126.6, 120.8, 117.8, 66.7, 63.0, 37.9, 37.5; IR (ATR) 3404, 1682, 1616 cm^{-1}; HRMS (ESI) m/z calcd for $C_{11}H_{13}O_3$ $[M + H]^+$ 193.0859, found 193.0856.

*2-(4-Oxo-3,4-dihydro-2H-chromen-6-yl)ethyl 4-methylbenzenesulfonate (**9**).* To a solution of **8** (1.39 kg, 7.21 mol) in CH_3CN (10.9 kg) were added $Me_3N{\cdot}HCl$ (68.9 g, 0.721 mol, 0.1 equiv) and triethylamine (1.46 kg, 14.4 mol, 2 equiv). The mixture was cooled down to around 5 °C, and then tosyl chloride (1.65 kg, 8.64 mol, 1.2 equiv) in CH_3CN (5.44 kg) was added dropwise over 1 h. The reaction mixture was stirred for an additional 2 h, and then 5% aqueous $NaHCO_3$ solution (10.4 kg) was added dropwise over 1 h. Toluene (8.98 kg) and water (6.92 kg) were added, and the layers were separated. The aqueous layer was washed with toluene (8.98 kg), and the combined organic layers were washed with 1% aqueous $KHSO_4$ solution (10.4 kg) and 10% aqueous NaCl solution (10.3 kg) and then were dried over $MgSO_4$ (750 g). The solid was filtered off and washed with toluene, and then the filtrate was concentrated in vacuo to 7.2-fold volumes of estimated quantity of **9** (slurry in 6.46 kg of toluene). The suspension was then stirred at 50 °C for 1 h and cooled down to 10 °C over 1 h, held for 2 h, and then filtered. The solid was washed with cooled (5−10 °C) toluene (2 × 1.30 kg) and dried in a vacuum oven at 50 °C. The target compound **9** (1.64 kg, 49% yield) was obtained as a pale-yellow solid (98.5% area purity by HPLC). Mp 125 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 8.3 Hz, 2H), 7.60 (d, J = 2.2 Hz, 1H), 7.30 (d, J = 8.1 Hz, 2H), 7.25 (dd, J = 8.4, 2.4 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 4.51 (t, J = 6.4 Hz, 2H), 4.18 (t, J = 6.9 Hz, 2H), 2.90 (t, J = 6.9 Hz, 2H), 2.78 (t, J = 6.4 Hz, 2H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.5, 160.7, 144.7, 136.7, 132.7, 129.7, 129.2, 127.7, 126.8, 121.0, 118.1, 70.2, 66.9, 37.6, 34.2, 21.5; IR (ATR) 1684, 1493, 1169 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{19}O_5S$ $[M + H]^+$ 347.0948, found 347.0938.

dx.doi.org/10.1021/op200357h | Org. Process Res. Dev. 2012, 16, 625−634

Alternative Approach for the Synthesis of 9 (Scheme 6). *3-[4-(2-Hydroxyethyl)phenoxy]propanoic Acid (**19**).* To a solution of 4-(2-hydroxyethyl)phenol **17** (2.00 g, 14.5 mmol) in CH_3CN (15 mL) were added NMM (159 μL, 1.45 mmol, 0.10 equiv) and a solution of **15** (2.32 g, 14.5 mmol, 1.0 equiv) in CH_3CN (5 mL) at 10 °C. This reaction mixture was stirred for 1.5 h at 25 °C and then concentrated in vacuo. Toluene (20 mL) was added to the residue, and the resulting solution was washed with 5% aqueous $NaHCO_3$ solution (10 mL) and 5% aqueous NaCl solution (10 mL) and then dried over Na_2SO_4. After filtration, the solvent was removed in vacuo to give **18** as a yellow oil.

To a solution of obtained **18** in THF (40 mL) was added 10% Pd/C (50% wet) (802 mg), and the mixture was stirred under hydrogen atmosphere (1 atm) at 25 °C for 3 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated in vacuo. The residue was purified by slurry in toluene (40 mL) at 25 °C for 1 h and filtered. The solid was washed with cooled (0−5 °C) toluene (10 mL) and dried in vacuo to give **19** (2.66 g, 87% yield) as a white solid. Mp 137 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.35 (br, 1H), 7.11 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.4 Hz, 2H), 4.60 (br, 1H), 4.12 (t, J = 6.1 Hz, 2H), 3.54 (t, J = 7.2 Hz, 2H), 2.67 (t, J = 6.1 Hz, 2H), 2.64 (t, J = 6.7 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.3, 156.6, 131.6, 129.8, 114.1, 63.5, 62.5, 38.2, 34.2; IR (ATR) 3385, 1722, 1043 cm^{-1}; HRMS (ESI) m/z calcd for $C_{11}H_{15}O_4$ $[M + H]^+$ 211.0965, found 211.0960; Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 62.95; H, 6.59.

Second-Generation Synthesis (Scheme 7). *3-[4-(2-{[(4-Methylphenyl)sulfonyl]oxy}ethyl)phenoxy]propanoic Acid (**22**).* To a suspension of potassium carbonate (12.0 g, 86.9 mmol, 1.2 equiv) in DMF (40 mL) were added propiolic acid (6.09 g, 86.9 mmol, 1.2 equiv) in DMF (20 mL) at 0−5 °C, and the reaction mixture was stirred for 10 min. Benzyl bromide (12.4 g, 72.4 mmol, 1.0 equiv) was added, and the mixture was warmed to 25 °C and stirred for 2 h. Then water (90 mL) was added to the residue at 0−5 °C. EtOAc·hexane (1:1) (60 mL) was added to the residue at 25 °C, and the layers were separated. The aqueous layer was extracted with EtOAc·hexane (1:1) (30 mL). The combined organic layers were washed with 5% aqueous NaCl solution (2 × 30 mL) and dried over Na_2SO_4. After filtration, the solvent was removed in vacuo to give **15** as a yellow oil.

To a solution of 4-(2-hydroxyethyl)phenol **17** (10.0 g, 72.4 mmol) in CH_3CN (100 mL) were added NMM (796 μL, 7.24 mmol, 0.10 equiv) and a solution of obtained **15** in CH_3CN (20 mL) at 10 °C, and the reaction mixture was stirred for 1 h at 25 °C. The mixture was cooled down to 0−5 °C, and then triethylamine (20.1 mL, 145 mmol, 2.0 equiv), Me_3N·HCl (346 mg, 3.62 mmol, 0.050 equiv), and tosyl chloride (16.6 g, 86.9 mmol, 1.2 equiv) were added. The reaction mixture was stirred for additional 1 h at 0−5 °C, and then 3% aqueous $NaHCO_3$ solution (100 mL) was added. The organic solvent was removed in vacuo, toluene (100 mL) was added to the residue, and the layers were then separated. The aqueous layer was extracted with toluene (50 mL). The combined organic layers were washed with 5% aqueous NaCl solution (50 mL), 5% aqueous $KHSO_4$ solution (50 mL), and 5% aqueous NaCl solution (50 mL), and then dried over $MgSO_4$. After filtration, the solvent was removed in vacuo to give **21** as a yellow oil.

To a solution of obtained **21** in THF (300 mL) was added 10% Pd/C (50% wet) (6.00 g), and the mixture was stirred under hydrogen atmosphere (1 atm) at 25 °C for 3 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated in vacuo. The resulting solid was purified by recrystallization from toluene·THF (9:1) (300 mL) at 70 °C, and cooled down to 0−5 °C over 2 h and held for 1 h. The solid was filtered, washed with cooled (<5 °C) toluene, and dried in vacuo to give **22** (19.8 g, 75% yield) as a white solid (97.2% area purity by HPLC). Mp 119 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J = 8.3 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 7.01 (d, J = 8.4 Hz, 2H), 6.78 (d, J = 8.6 Hz, 2H), 4.21 (t, J = 6.1 Hz, 2H), 4.16 (t, J = 7.1 Hz, 2H), 2.88 (t, J = 6.8 Hz, 2H), 2.84 (t, J = 6.1 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.9, 157.3, 144.6, 132.9, 129.9, 129.7, 128.7, 127.8, 114.7, 70.8, 63.0, 34.4, 34.3, 21.6; IR (ATR) 1695, 1512, 1171 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{21}O_6S$ $[M + H]^+$ 365.1053, found 365.1045.

*2-(4-Oxo-3,4-dihydro-2H-chromen-6-yl)ethyl 4-methylbenzenesulfonate (**9**).* To a solution of TFAA (26.8 mL) and phosphoric acid (85%) (316 mg, 2.74 mmol, 0.10 equiv) was added **22** (10.0 g, 27.4 mmol) at 0−5 °C, and the mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated in vacuo. Toluene·THF (2:1) (150 mL) and water (100 mL) were added to the residue, and the layers were separated. The aqueous layer was extracted with toluene (50 mL). The combined organic layers were washed with 5% aqueous $NaHCO_3$ solution (2 × 50 mL) and 5% aqueous NaCl solution (50 mL) and dried over $MgSO_4$. After filtration, the solvent was removed in vacuo. To the resulting solid was added 2-propanol·H_2O (10:1) (55 mL), and the suspension was warmed to 45 °C and held for 1 h. After the mixture was cooled to 25 °C, water (95 mL) was added and stirred at 25 °C for 1 h. The mixture was cooled to 0−5 °C, held for 1 h, and then filtered. The solid was washed with water (20 mL) and dried in vacuo to give **9** (9.32 g, 98% yield) as a white solid (99.1% area purity by HPLC). Obtained analytical data are in complete accord with that of **9** obtained through first-generation synthesis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of NMR spectra of important intermediates in the first- and second-generation synthesis. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Telephone: +81-6-6466-5203. Fax: +81-6-6466-5484. E-mail: tomoaki-nishida@ds-pharma.co.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We express our thanks to Ms. K. Bando for performing the elemental analysis and to Ms. M. Honma for recording high-resolution MS spectra.

■ REFERENCES

(1) (a) Artigas, F.; Perez, V.; Alvarez, E. *Arch. Gen. Psychiatry* **1994**, *51*, 248−251. (b) Zhou, D.; Stack, G. P.; Lo, J.; Failli, A. A.; Evrard, D. A.; Harrison, B. L.; Hatzenbuhler, N. T.; Tran, M.; Croce, S.; Yi, S.; Golembieski, J.; Hornby, G. A.; Lai, M.; Lin, Q.; Schechter, L. E.; Smith, D. L.; Shilling, A. D.; Huselton, C.; Mitchell, P.; Beyer, C. E.; Andree, T. H. *J. Med. Chem.* **2009**, *52*, 4955−4959.

(2) (a) Toyoda, T.; Yoshinaga, H. PCT Int. Appl. WO 2009/099087, 2009. (b) Toyoda, T.; Nishida, T; Yoshinaga, H. PCT Int. Appl. WO 2011/016468, 2011. (c) Kojima, M.; Nishida, T. Jpn. Kokai Tokkyo Koho, JP 2010/150247, 2010.
(3) (a) Cohen, N.; Bizzarro, F. T.; May, W. P.; Toth, K.; Lee, F. K.; Heslin, P. H.; Holland, G. W.; Kwoh, S. C.; Franco, L. S.; Simko, B. A.; Yagaloff, K. A. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2883−2888. (b) Cube, R. V.; Vernier, J. M.; Hutchinson, J. H.; Gardner, M. F.; James, J. K.; Rowe, B. A.; Schaffhauser, H.; Daggett, L.; Pinkerton, A. B. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2389−2393. (c) Vu, A. T.; Campbell, A. N.; Harris, H. A.; Unwalla, R. J.; Manas, E. S.; Mewshaw, R. E. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4053−4056. (d) Siddaiah, V.; Maheswara, M.; Rao, C. V.; Venkateswarlu, S.; Subbaraju, G. V. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1288−1290.
(4) Cella, J. A.; Bacon, S. W. *J. Org. Chem.* **1984**, *49*, 1122−1125.
(5) The amounts of impurities **11** and **12** were different between entries 9 and 11. Since water content in the reaction mixture and the mixing conditions were similar between both experiments except for the scale of the reaction, the reason for accounting this difference was not identified.
(6) Kim, Y. J.; Wang, P.; Navarro-Villalobos, M.; Rohde, B. D.; DerryBerry, J.; Gin, D. Y. *J. Am. Chem. Soc.* **2006**, *128*, 11906−11915.
(7) (a) Rozners, E.; Liu, Y. *J. Org. Chem.* **2005**, *70*, 9841−9848. (b) Luca, L. D.; Giacomelli, G.; Masala, S.; Porcheddu, A. *J. Org. Chem.* **2003**, *68*, 4999−5001.
(8) Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1999**, *64*, 2564−2566.
(9) NMR analysis was conducted in DMSO-d_6, since ketal **6** was gradually deprotected in $CDCl_3$.
(10) Yoshida, Y.; Sakakura, Y.; Aso, N.; Okada, S.; Tanabe, Y. *Tetrahedron* **1999**, *55*, 2183−2192.
(11) Alagha, A.; Moman, E.; Adamo, M. F.; Nolan, K. B.; Chubb, A. J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4213−4216.
(12) Rassias, G.; Stevenson, N. G.; Curtis, N. R.; Northall, J. M.; Gray, M.; Prodger, J. C.; Walker, A. J. *Org. Process Res. Dev.* **2010**, *14*, 92−98.
(13) Tatsuta, K.; Kasai, S.; Amano, Y.; Yamaguchi, T.; Seki, M.; Hosokawa, S. *Chem. Lett.* **2007**, *36*, 10−11.
(14) Shinozuka, T.; Shimada, K.; Matsui, S.; Yamane, T.; Ama, M.; Fukuda, T.; Taki, M.; Takeda, Y.; Otsuka, E.; Yamato, M.; Mochizuki, S.; Ohhata, K.; Naito, S. *Bioorg. Med. Chem.* **2006**, *14*, 6789−6806.
(15) HPLC purity of the obtained **16** was 86.0% as a mixture of stereoisomers.
(16) Although hydrogenation of some of 3-aryloxyacrylic acid derivatives is reported to need no less than one week to reach completion even under increased pressure, our substrates **16**, **18**, and **21** are readily hydrogenated in a few hours under ordinary pressure (THF, 25 °C).
(17) (a) Kawasaki, M.; Kakuda, H.; Goto, M.; Kawabata, S.; Kometani, T. *Tetrahedron: Asymmetry* **2003**, *14*, 1529−1534. (b) Galli, C. *Synthesis* **1979**, *4*, 303−304.
(18) Catalogue prices from TCI-US: 4-(2-hydroxyethyl)phenol **17**, \$176/500 g; methyl(4-hydroxyphenyl)acetate **2**, \$250/500 g.
(19) Subsequent work to identify the suitable salt of API **1** and optimize a more suitable process for preparing **9** and the endgame will be the subject of a future publication.