A New Route to Roflumilast via Copper-Catalyzed Hydroxylation

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Abstract: A new route to Roflumilast, a selective phosphodiesterase type 4 (PDE 4) inhibitor, is described. The synthetic procedure starts from 4-hydroxy-3-iodobenzoic acid to access the key intermediate 3-(cyclopropylmethoxy)-4-(difluoromethoxy)benzoic acid via copper-catalyzed hydroxylation and utilizes amide coupling to accomplish the synthesis of Roflumilast in 80% overall yield.

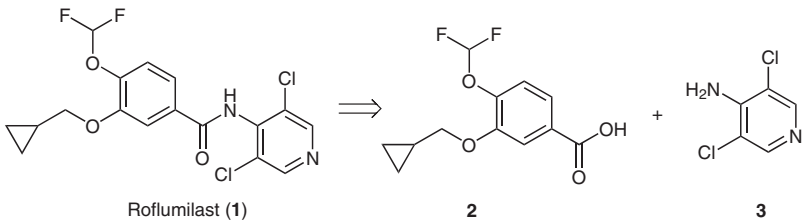
Key words: Roflumiast, PDE4 inhibitor, preparation, hydroxylation, copper catalyzed

Roflumilast (**1**),[1] a selective phosphodiesterase type 4 (PDE 4) inhibitor developed by Nycomed® for the treatment of chronic obstructive pulmonary diseases (COPD),[2] was launched as Daxas® on the European market in June 2010. Soon after, it was approved by the FDA for the treatment of patients with COPD in the U.S.A. in February 2011.[1a] Roflumilast treats COPD by a new mechanism; it inhibits PDE4 to reduce the breakdown of cAMP, which in turn down-regulates the inflammatory process.[1b]

Several synthetic routes to Roflumilast have been disclosed in the literature,[3,4] in which this amide compound was finally prepared through an efficient coupling[3] of the key intermediate, 3-(cyclopropylmethoxy)-4-(difluoromethoxy)benzoic acid (**2**) (Scheme 1). However, the preparation of the key intermediate **2** proved to be a challenge.[4] The reported routes to intermediate **2** have certain disadvantages: (a) low overall yields (15–41%) due to poor selectivity in the alkylation of the catechol;[3a,4a,b] (b) tedious purification processes, such as column chromatography and multiple distillation;[4] and (c) the use of expensive reagents and harsh conditions.[3a] Obviously, these methods can not satisfy the increasing need for the manufacture of this promising drug. A new synthetic method is urgently required.

Recently, several copper-catalyzed processes[5] have allowed the cross-coupling of aryl halides with hydroxide salts to provide phenols under relatively mild conditions. Due to the low cost, air- and moisture-stability of the copper catalyst, and reliability of the reaction system, the process constitutes a practical, general, and efficient method for the synthesis of phenols. Herein, we report a new route for the synthesis of Roflumilast using a copper-catalyzed hydroxylation process. This route avoids the use of expensive reagents, harsh conditions, and tedious purification processes, and it has the advantage of high yields than previously reported approaches.[3,4]

In our initial study, 4-hydroxybenzoic acid was readily prepared in the presence of copper(I) iodide and 1,10-phenanthroline from 4-iodobenzoic acid in 84% of yield,[5b] which encouraged us to use this process to synthesize Roflumilast. A tentative route (Scheme 2) was designed starting from 4-hydroxy-3-iodobenzoic acid (**4**), which was prepared in 81% yield according to a known procedure.[6] After esterification of **4** followed by etherification, the hydroxylation precursor **5** was prepared in 99% yield. To our surprise, the standard hydroxylation conditions[5b] produced an undesired byproduct, 3,4-dihydroxybenzoic acid (**7**), instead of **6**. It was proposed that compound **7** was generated by the hydrolysis of the difluoromethyl ether **6** in hot aqueous potassium hydroxide solution. A recent study[7] showed that the difluoromethyl ether tends to be hydrolyzed in a basic aqueous environment. The failure in the hydroxylation of 3-iodobenzoic ester **5** prompted us to investigate an alternative route.



Roflumilast (**1**) **2** **3**

Scheme 1 Roflumilast (**1**)

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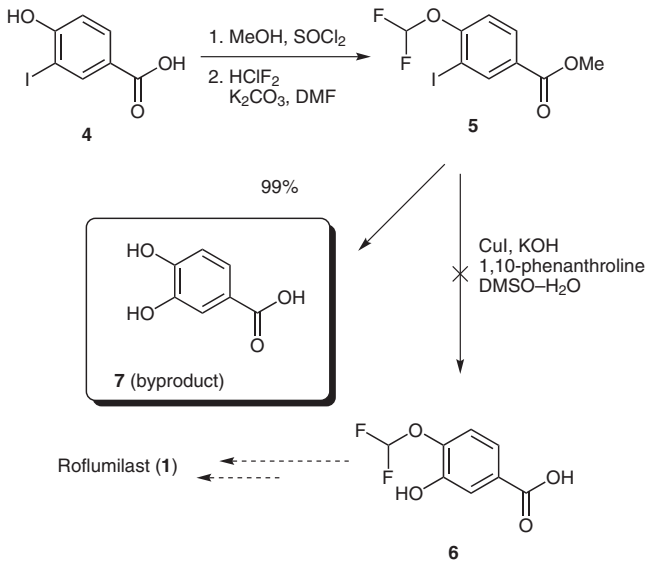


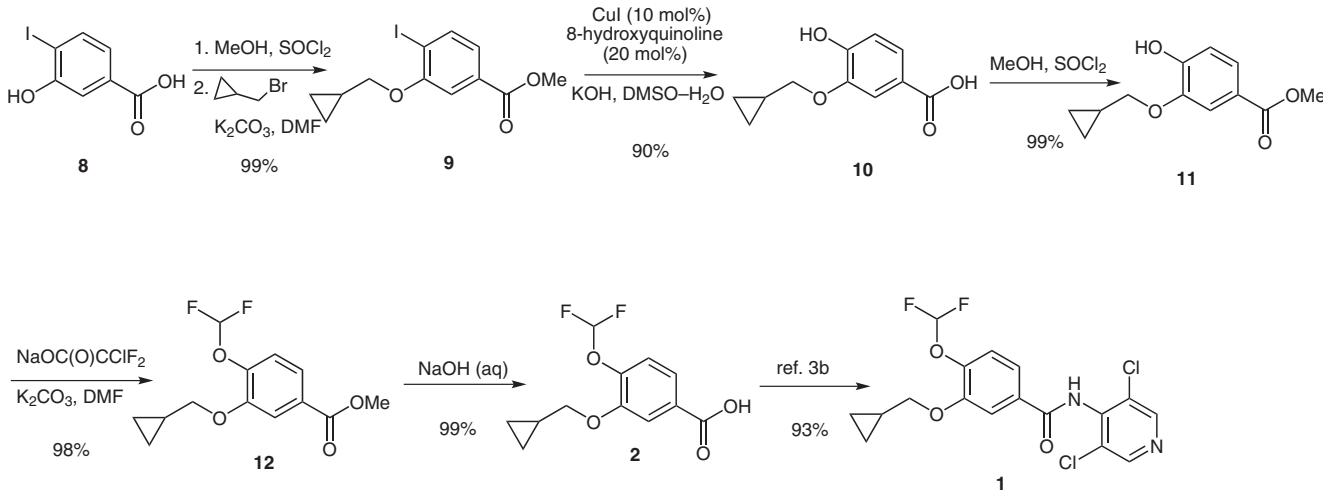
Scheme 2 Attempted synthesis of Roflumilast (**1**)

In the new route (Scheme 3), 3-hydroxy-4-iodobenzoic acid (**8**) was used as the starting material; it is easily prepared from 3-hydroxybenzoic acid in 90% yield.[8] The latter is an inexpensive chemical widely used in the synthesis of fungicides and in the pharmaceutical industry. This route allowed us to accumulate the starting material **8** without difficulty. The ^{1}H NMR spectrum indicated the iodination selective produced 3-hydroxy-4-iodobenzoic acid (**8**).[9] The hydroxylation precursor **9** was prepared uneventfully by esterification and then etherification in the presence of potassium carbonate.

With the precursor **9** in hand, the key reaction, hydroxylation, was carefully studied (Table 1). The reactions were carried out using copper(I) iodide (10 mol%) as the catalyst, ligand (20 mol%), potassium hydroxide (3–4 equiv), and substrate **9** (0.1 mol) in a mixed solvent of dimethyl sulfoxide–water at 100 °C for 30 hours. Product **10** was successfully obtained in the first attempt in 86% yield in the presence of copper(I) iodide (10 mol%) and 1,10-phenanthroline (20 mol%) (entry 1). Several ligands were then screened and 1,10-phenanthroline (**A**), L-proline (**C**), ethane-1,2-diamine (**D**), 2-hydroxyethylamine (**E**), picolinic acid (**F**), and 8-hydroxyquinoline (**B**) were all effective, but 8-hydroxyquinoline (**B**) gave the best results giving **10** in 90% isolated yield (entry 2).

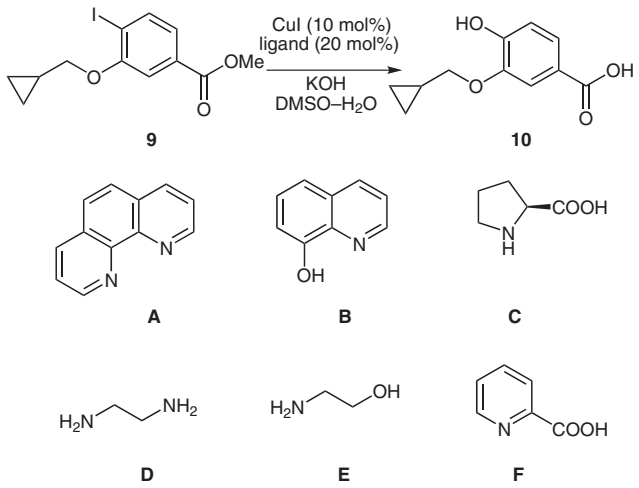
The reaction temperature and base were also investigated in order to improve the yield and practicality of the preparation of **10**. Generally, the reactions proceeded smoothly at 100 °C and were complete in 30 hours. The product **10** was isolated in much lower yields at low temperatures (90 °C) even if the reaction time was extended to 50 hours (entry 7). The yield fell to 79% when the reaction temperature was raised to 120 °C (entry 8); this is understandable as phenol is inclined toward oxidization under these elevated temperatures.[5e] These observation indicated that temperature plays a key role in the hydroxylation. To allow full conversion into the phenol product, potassium hydroxide (4 equiv) is essential. 3-(Cyclopropylmethoxy)-4-iodobenzoic acid (15%, from hydrolysis of the ester **9**) was isolated from the reaction mixture when only three equivalents of potassium hydroxide were used (entry 9).

From the results in Table 1, the optimized reaction conditions were determined to employ copper(I) iodide (10 mol%), 8-hydroxyquinoline (20 mol%), potassium hydroxide (4 equiv) as the base, and dimethyl sulfoxide–water as the solvent to provide the desired product **10** within 30 hours at a reaction temperature of 100 °C (see the experimental part). The optimized reaction condition proved highly efficient: compound **10** was collected as precipitation after removal of the copper catalyst by filtration followed by acidified with 1 M hydrochloric acid. Compound **10** was synthesized on a 200-gram scale without decrease in the yield, which was then esterified to give methyl ester **11**.



Scheme 3 A new route to Roflumilast (**1**)

Table 1 Optimization of the Hydroxylation[a]



Entry	Ligand	KOH (equiv)	Temp (°C)	Yield[b] (%)
1	**A**	4	100	86
2	**B**	4	100	90
3	**C**	4	100	76
4	**D**	4	100	34
5	**E**	4	100	41
6	**F**	4	100	83
7	**B**	4	90	75[c]
8	**B**	4	120	79
9	**B**	3	100	73

[a] Reaction conditions: **9** (0.1 mol), CuI (10 mol%), ligand (20 mol%), KOH (0.3–0.4 mol), DMSO–H_2O (1:1, 200 mL), 30 h.
[b] Isolated yield.
[c] The reaction was heated for 50 h.

In the early stage, chlorodifluoromethane was used as the difluoromethylation reagent[4b,c] for the synthesis of compound **12** due to its abundance and low cost. The reaction proceeded very quickly when chlorodifluoromethane was bubbled into the hot mixture of compound **11** in *N*,*N*-dimethylformamide. However, it is hard to apply this procedure to the 100-gram scale reaction for the following reasons: (a) dimer and trimer byproducts[10] are formed (see Figure 1); (b) the high toxicity of chlorodifluoromethane; and (c) unstable yields when using a procedure involving a gas in large-scale production. Sodium chlorodifluoroacetate is the reagent of choice for the difluoromethylation due to its stability and availability in bulk, it was also used by Wyeth® researchers to prepare methyl 4-(difluoromethoxy)-3-iodobenzoate,[7] a similar compound to the ester **12**. According to this procedure,[7] compound **12** was prepared successfully by adding a mixture of sodium chlorodifluoroacetate and **11** (2:1) in *N*,*N*-dimethylformamide into the hot slurry of potassium carbonate in *N*,*N*-dimethylformamide at 95 °C. This process largely avoided the formation of dimer and trimer byproducts by keeping the concentration of sodium chlorodifluoroacetate higher than the concentration of **11** throughout the course of the entire experiment.

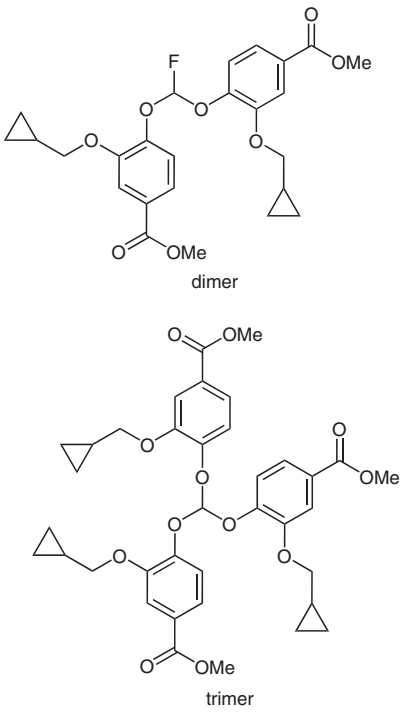


Figure 1 Dimer and trimer byproducts in difluoromethylation

The key intermediate **2** was readily prepared by heating in sodium hydroxide solution for three hours. The crude product was recrystallized from acetonitrile–petroleum ether (3:2)[3a] to give white crystals with 99.3% HPLC purity. Finally, Roflumilast (**1**) was prepared successfully through a potassium *tert*-butoxide mediated amide coupling[3b] in 93% yield.

^1H, ^{13}C, and ^{19}F NMR, IR, HRMS, and the melting point were used to confirm the final product (Roflumiast), which was synthesized by the procedure we developed; the melting point was identical with the reported data.[11]

In conclusion, we have demonstrated an efficient and practical synthesis of Roflumilast by using a copper-catalyzed hydroxylation. Roflumilast (**1**) was prepared from 3-hydroxy-4-iodobenzoic acid (**8**) in six steps in 80% overall yield. The whole process avoids using harsh condition and tedious purification procedures, thus it has considerable advantages over previously reported syntheses.

All reagents were used as received from commercial sources without further purification or prepared as described in the literature. Melting points were determined on an electrothermal melting point apparatus and are uncorrected. NMR spectra were measured in $CDCl_3$ or DMSO-d_6 (all with TMS as internal standard) on a Bruker 400 MHz FT magnetic resonance spectrometers. Mass spectra were recorded on a Waters 2695+ZQ 2000 mass spectrometer. HRMS were recorded on an Agilent 6210 TOF mass spectrometer. Infrared spectra were measured on a Perkin-Elmer RX spectrophotometer. HPLC conditions for purity analysis of compounds **1** and **2**: AGILENT-LC1260; C_{18} column [5 μm, 4.6 mm (i.d.) × 150 mm];

phase A: MeOH, phase B: aq 10 mM NH_4OAc; flow rate: 1 mL/min at 30 °C.

Methyl 3-(Cyclopropylmethoxy)-4-iodobenzoate (9)

$SOCl_2$ (473.0 g, 4.0 mol) was added slowly to a soln of **8** (700.0 g, 2.6 mol) in MeOH (5 L) at 0 °C. The resulting mixture was stirred at 50 °C for 3 h. After completion of the reaction, the mixture was cooled to r.t. and then concentrated to provide crude methyl 3-hydroxy-4-iodobenzoate (740.0 g) as a white solid,[8a] which was used directly in the next step.

Cyclopropylmethyl bromide (522.0 g, 3.9 mol) was slowly added into a mixture of K_2CO_3 (646.0 g, 4.7 mol) and methyl 3-hydroxy-4-iodobenzoate (740.0 g, obtained in last step) in DMF (2 L), and the resulting mixture was heated to 80 °C for 2 h. The mixture was cooled to r.t. and diluted with H_2O (10 L). The resulting mixture was filtered and washed with H_2O (1 L) to afford ester **9** (871.1 g, 99%) as a white solid; mp 76.0–77.5 °C; R_f = 0.6 (hexane–EtOAc, 10:1).

IR (neat): 3447, 3092, 2953, 2885, 1711, 1585, 1400, 1235, 1257, 1115, 1015, 753 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 8.0 Hz, 1 H), 7.42 (s, 1 H), 7.37 (d, *J* = 8.0 Hz, 1 H), 3.98 (d, *J* = 6.4 Hz, 2 H), 3.93 (s, 3 H), 1.25–1.40 (m, 1 H), 0.60–0.75 (m, 2 H), 0.40–0.49 (m, 2 H).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 166.6, 157.7, 139.5, 131.4, 123.2, 112.7, 3.7, 73.7, 52.4, 10.1, 3.6, 3.3.

MS: *m*/*z* = 332.9 (M^+ + 1).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{14}IO_3$: 332.9988; found: 332.9981.

3-(Cyclopropylmethoxy)-4-hydroxybenzoic Acid (10)

A soln of KOH (22.4 g, 0.4 mol) in H_2O (0.1 L) was slowly added to a mixture of **9** (33.2 g, 0.1 mol), CuI (1.9 g, 0.01 mol), and 8-hydroxyquinoline (2.9 g, 0.02 mol) in DMSO (0.1 L), the mixture was stirred at 100 °C for 30 h under a N_2 atmosphere (TLC monitoring). The mixture was cooled to r.t. and the copper catalyst was filtered off. The resulting soln was acidified with aq 1 M HCl to pH 2. The precipitate was filtered off and the filtercake was washed with H_2O (50 mL) to give product **10** (20.1 g) as a yellow solid, which was purified by column chromatography (CH_2Cl_2–MeOH, 15:1) to afford **10** (18.7 g, 90%) as a light yellow powder; mp 145.5–147.2 °C; R_f = 0.5 (CH_2Cl_2–MeOH, 10:1). Crude **10** was used directly for the next step in a 200-gram scale preparation.

IR (neat): 3512, 3407, 3007, 1676, 1596, 1516, 1444, 1239, 1112, 834, 768 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 8.0 Hz, 1 H), 7.57 (s, 1 H), 7.00 (d, *J* = 8.0 Hz, 1 H), 3.97 (*J* = 6.4 Hz, 2 H), 1.19–1.37 (m, 1 H), 0.61–0.75 (m, 2 H), 0.32–0.45 (m, 2 H).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 171.8, 151.1, 145.6, 125.2, 121.2, 114.2, 113.3, 74.3, 10.2, 3.4 (2 C).

MS: *m*/*z* = 209.1 (M^+ + 1).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{13}O_4$: 209.0814; found: 209.0814.

Methyl 3-(Cyclopropylmethoxy)-4-hydroxybenzoate (11)

$SOCl_2$ (16.0 g, 0.14 mol) was added slowly to a soln of **10** (18.7 g, 90 mmol) in MeOH (0.1 L) at 0 °C. The resulting mixture was stirred at 50 °C for 3 h. After completion of the reaction, the mixture was cooled to r.t. and then concentrated to provide crude phenol **11**, which was purified by column chromatography to afford **11** (19.8 g, 99%) as a colorless oil;[4b] R_f = 0.7 (hexane–EtOAc, 2:1).

IR (neat): 3420, 2952, 1711, 1597, 1513, 1441, 1288, 1218, 1102, 1010, 765 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 8.0 Hz, 1 H), 7.52 (s, 1 H), 6.97 (d, *J* = 8.0 Hz, 1 H), 3.95 (d, *J* = 6.4 Hz, 2 H), 3.90 (s, 3 H), 1.18–1.37 (m, 1 H), 0.60–0.75 (m, 2 H), 0.31–0.45 (m, 2 H).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 166.9, 150.3, 145.5, 124.2, 122.2, 114.0, 112.9, 74.2, 52.2, 10.2, 3.4 (2 C).

Methyl 3-(Cyclopropylmethoxy)-4-(difluoromethoxy)benzoate (12)

A soln of sodium chlorodifluoroacetate (27.0 g, 0.18 mol) and phenol **11** (19.8 g, 89 mmol) in DMF (60 mL) was added slowly over a period of 1 h to a suspension of K_2CO_3 (18.4 g, 0.13 mol) in DMF (40 mL) at 95 °C. When the addition was complete, the suspension was stirred for a further 15 min and then cooled to 15 °C. H_2O (0.3 L) was added and the resulting mixture was extracted with toluene (0.1 L). The organic layer was washed with sat. aq NaCl soln (30 mL), dried, and concentrated to afford crude **12**, which was purified by column chromatography to provide **12** (23.7 g, 98%) as a white crystalline solid;[4b] mp 44.5–46.4 °C; R_f = 0.7 (hexane–EtOAc, 10:1).

IR (neat): 3446, 2954, 1722, 1601, 1439, 1291, 1099, 1025, 756 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 8.0 Hz, 1 H), 7.62 (s, 1 H), 7.20 (s, *J* = 8.0 Hz, 1 H), 6.73 (t, *J* = 76.0 Hz, 1 H), 3.94 (d, *J* = 6.4 Hz, 2 H), 3.92 (s, 3 H), 1.19–1.36 (m, 1 H), 0.61–0.75 (m, 2 H), 0.32–0.45 (m, 2 H).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 167.0, 150.1, 144.0, 128.2, 122.8, 121.8, 115.1 (t, $OCHF_2$), 114.6, 74.0, 52.3, 10.2, 3.2 (2 C).

MS: *m*/*z* = 273.1 (M^+ + 1).

3-(Cyclopropylmethoxy)-4-(difluoromethoxy)benzoic Acid (2)

A soln of **12** (23.7 g, 87 mmol) in MeOH (60 mL) and 3 M NaOH (80 mL) was heated at 50 °C for 3 h. The mixture was cooled to r.t. and concentrated to remove MeOH. The resulting mixture was diluted with H_2O (30 mL) and acidified with aq 4 M HCl to pH 2. After cooling at 5 °C for 5 h, the precipitate was filtered off and washed with H_2O to give product **2** as a white crystalline solid (22.3 g, 99%). The crystalline solid was further purified by crystallization (MeCN–petroleum ether, 3:2) to give white crystals; HPLC purity: 99.3%; mp 120.0–120.9 °C (lit.[11] mp 118–118.5 °C); R_f = 0.3 (hexane–EtOAc, 1:1).

IR (neat): 3421, 3015, 2931, 2879, 1690, 1601, 1517, 1442, 1297, 1215, 1095, 886, 846, 766 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.0 Hz, 1 H), 7.70 (s, 1 H), 7.26 (d, *J* = 8.0 Hz, 1 H), 6.77 (t, *J* = 76.0 Hz, 1 H), 3.97 (d, *J* = 7.2 Hz, 2 H), 1.18–1.42 (m, 1 H), 0.63–0.78 (m, 2 H), 0.36–0.49 (m, 2 H).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 171.6, 150.1, 144.8, 127.2, 123.7, 121.7, 115.7, 115.5 (t, $OCHF_2$), 74.1, 10.0, 3.3 (2 C).

^{19}F NMR (400 MHz, $CDCl_3$): δ = –82.0 (d, *J* = 78.8 Hz, 2 F).

HRMS (ESI): *m*/*z* $[M – H]^+$ calcd for $C_{12}H_{11}F_2O_4$: 257.0625; found: 257.0623.

Roflumilast (1)

Roflumilast (**1**) was prepared according to the procedure[3b] developed by Nycomed®; yield: 122.0 g (93%); HPLC purity: 99.4%; mp 158.1–159.9 °C (lit.[11] mp 159 °C); R_f = 0.5 (hexane–EtOAc, 2:1).

IR (neat): 3448, 3259, 2940, 2878, 1653, 1596, 1557, 1502, 1402, 1305, 1199, 1156, 1008, 808, 748 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 10.67 (s, 1 H), 8.78 (s, 2 H), 7.71 (s, 1 H), 7.66 (d, *J* = 8.0 Hz, 1 H), 7.37 (d, *J* = 8.0 Hz, 1 H), 7.25 (t, *J* = 76.0 Hz, 1 H), 3.99 (d, *J* = 8.0 Hz, 2 H), 1.19–1.40 (m, 1 H), 0.63–0.76 (m, 2 H), 0.32–0.46 (m, 2 H).

^{13}C NMR (400 MHz, DMSO-d_6): δ = 164.3, 150.2, 148.8 (2 C), 143.5, 141.6, 131.2 (2 C), 130.8, 121.4, 120.9, 117.0 (t, $OCHF_2$), 114.1, 73.8, 10.4, 3.5 (2 C).

^{19}F NMR (400 MHz, DMSO-d_6): δ = –81.8 (d, *J* = 79.2 Hz, 2 F).

HRMS (ESI): *m*/*z* $[M - H]^+$ calcd for $C_{17}H_{13}Cl_2F_2N_2O_4$: 401.0271; found: 401.0277.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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(9) The standard sample was purchased from Sigma-Aldrich. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.04 (br, 1 H), 10.80 (s, 1 H), 7.80 (d, *J* = 8.0 Hz, 1 H), 7.43 (s, 1 H), 7.13 (d, *J* = 8.0 Hz, 1 H).

(10) The byproducts were isolated by column chromatography (hexane–EtOAc, 10:1) and confirmed by ^{1}H NMR. Dimer byproducts: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 8.0 Hz, 2 H), 7.61 (s, 2 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 6.97 (d, *J* = 76.0 Hz, 1 H), 3.92 (s, 6 H), 3.90 (d, *J* = 6.4 Hz, 4 H), 1.16–1.36 (m, 2 H), 0.55–0.68 (m, 4 H), 0.28–0.37 (m, 4 H). Trimer byproducts: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 8.0 Hz, 3 H), 7.56 (s, 3 H), 7.52 (d, *J* = 8.0 Hz, 3 H), 7.06 (s, 1 H), 3.91 (s, 9 H), 3.78 (d, *J* = 6.4 Hz, 6 H), 1.10–1.26 (m, 3 H), 0.53–0.65 (m, 6 H), 0.27–0.36 (m, 6 H).

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