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Process Development of the PDE4 Inhibitor K-34

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ABSTRACT: A short and practical synthesis of the PDE4 inhibitor K-34 (**1**) was developed. This synthesis was achieved in four steps and with a 58% overall yield. The unique spiro acetal was created with exceptionally high yield by utilizing the neighbor carboxylic acid assistance. This synthesis also features efficient ketone construction with 4-pyridinylmethyl anion **9** and ester **18**, in which overreaction should be prohibited by quick in situ enolate formation. The overall synthesis was carried out under mild conditions and used a simple procedure suitable for large-scale production.

INTRODUCTION

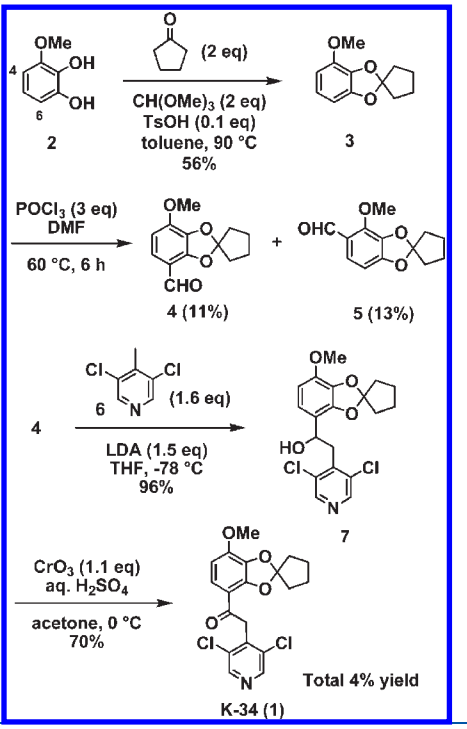
Among the c-AMP/c-GMP phosphodiesterases, the type 4 isozyme (PDE4) plays significant roles in regulating the functions of bronchial smooth muscle and inflammatory cells such as mast cells, neutrophils, eosinophils, T cells, B cells, and macrophages.[1] K-34 (**1**) was identified in Kyowa Hakko Kirin as a very potent and specific PDE4 inhibitor.[2] K-34 has been a potential anti-inflammatory drug candidate for the treatment of asthma or atopic dermatitis by intratracheal administration or by topical application, respectively.[3] To support further pharmacological evaluation and clinical trials, development of a practical synthesis method for the titled compound was required.

K-34 possesses a 3,5-dichloro-4-pyridyl moiety which is one of the essential structural components for its PDE4 inhibitory activity. The unique structural feature of this compound is that the linker between the pyridine unit and the benzene unit is a ketone, which is different from most of the other PDE4 inhibitors' linkers, which are amides.[4] Another unique feature is the spiro acetal moiety which is rarely seen in pharmaceutical compounds.[5] These novel structural features of K-34 therefore present us with interesting synthetic challenges.

Original Synthesis. The original synthesis used in the medicinal chemistry program is shown in Scheme 1.[2] Although the synthesis is very short, it includes significant disadvantages for large-scale production. It starts with moderate yield acetalization[6] of the 3-methoxycatechol **2** followed by a low chemo- and regioselective Vilsmeier reaction. After separation of isomer **5** by column chromatography, aldehyde **4** is coupled with the 4-pyridinylmethyl anion at −78 °C. Finally, Jones oxidation of alcohol **7** affords **1** in a total 4% yield. Therefore, we were forced to establish a practical synthesis of **1**, in which both the selective carbonyl introduction and oxidation-free ketone synthesis could be achieved.

Although the regioselectivity of electrophilic substitution on 3-methoxycatechol **2** is 6-position favored,[7] this is reversed after acetal formation.[8] Our initial attempts for functionalizing acetal **3**, such as bromination, also demonstrated that the undesired ortho-substitution to the methoxy group became favored. Moreover, the spiro acetal was not compatible with harsh reaction conditions such as Friedel−Crafts reaction. Therefore, we started new route exploration with 2,3,4-trimethoxybenzoic acid (**8**) which already bears the necessary atoms on a benzene ring.

Scheme 1. Original synthesis



Coupling Partner Selection. With the goal of achieving oxidation-free direct ketone synthesis, we first examined a model coupling study between 2,3,4-trimethoxybenzic acid derivative **10** and 4-pyridinylmethyl anion **9** which was formed by LDA treatment of **6** (Scheme 2).[9] Dimethylamide **10a** or Weinreb amide **10b** resulted in only recovery of the starting material.

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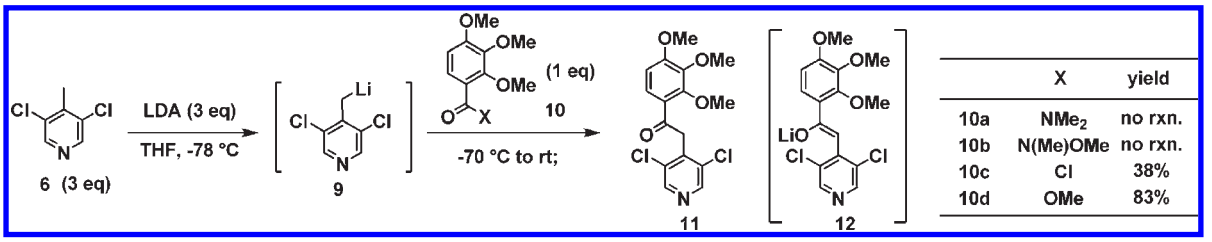
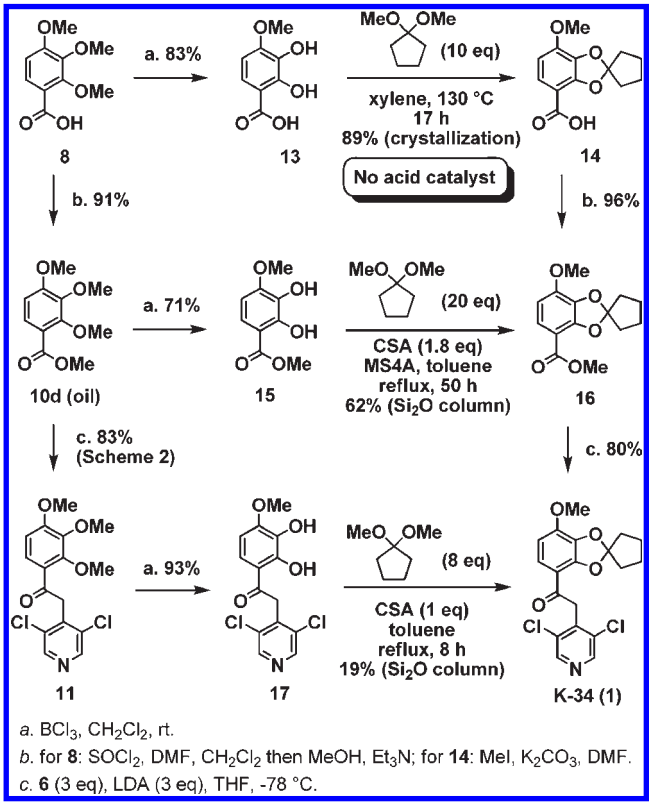
Scheme 2. Ketone synthesis



	X	yield
10a	NMe_2	no rxn.
10b	N(Me)OMe	no rxn.
10c	Cl	38%
10d	OMe	83%

Scheme 3. Route selection[a]



a. BCl_3, CH_2Cl_2, rt.
b. for **8**: $SOCl_2$, DMF, CH_2Cl_2 then MeOH, Et_3N; for **14**: MeI, K_2CO_3, DMF.
c. **6** (3 eq), LDA (3 eq), THF, -78 °C.

In response to the low nucleophilicity of anion **9**, more reactive acid derivatives were examined. Acid chloride **10c** gave the desired ketone **11**; however, it also yielded lots of byproduct. Methyl ester **10d** successfully afforded desired ketone **11** in a satisfactory yield without formation of a double alkylated byproduct.[10] This could be understood by the fact that 3 equiv of anion **9** was necessary for reaction completion, which implies the quick in situ formation of enolate **12**, which avoids further reaction of the ketone **11**.

Route Selection. Following the above successful ketone synthesis, we moved on to route selection. It was necessary to select from three possible routes which were realized in our initial examination (Scheme 3). BCl_3 mediated ortho- and meta-selective demethylation of 2,3,4-trimethoxyaryl carbonyl compounds such as **8** was known and was also successfully applied to **10d** or **11** (step a) to give diols **13**, **15**, and **17**, respectively.[11] The most critical step was identified as the acetalization step. Especially when 3-methoxycatechol was substituted at the 6-position, considerable slowing down of the reaction rate was observed. For example,

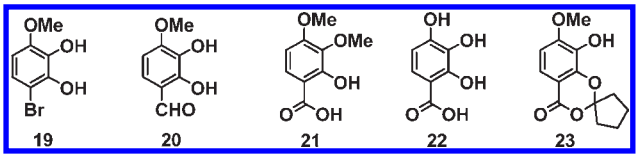


Figure 1.

bromide **19** gave the corresponding acetal in a 30% yield, but aldehyde **20** did not afford the desired product (Figure 1). In a similar fashion, both methyl ester **15** and ketone **17** resulted in low to moderate yield even when using an excess of the sulfonic acid catalyst. In contrast, benzoic acid **13** exhibited smooth completion of the acetalization when xylene or chlorobenzene was used as a reflux solvent. Moreover, the sulfonic acid catalyst was found to have no effect on the reaction progression. We investigated this unique high reactivity for acetalization as well as the non-necessity of the acid catalyst. A small amount of hemiacetal **23** was isolated and was assumed to be an active intermediate. However, **23** was not converted to **14** under the same acetalization condition, which indicated that **23** was just a byproduct (Figure 1). Thus, we concluded that the neighboring carboxylic acid moiety acts as an activating group for the phenol as well as an acid catalyst. Thus, acetal **14** was obtained in 89% yield with a simple crystallization by cooling the reaction mixture. Subsequent treatment with methyl iodide and K_2CO_3 afforded methyl ester **16** which was then subjected to the above ketone synthesis method to successfully afford **1** in an 80% yield. The total yield was dramatically improved, and the oxidation step was eliminated. We next moved on to optimization of this route in order to make it possible to carry out multikilogram-scale production.

Route Optimization. First, replacement of the volatile and toxic BCl_3 was requested in the demethylation step. Other demethylating reagents, e.g., $AlCl_3$, TMSI, HBr, or thiols, were less reactive and less selective than BCl_3. Only aqueous HI treatment in acetic acid exhibited the potential to be an alternative for BCl_3, and was investigated in detail. Monitoring the reaction progress with HPLC proved that demethylation proceeds in sequence from the 2-, 3-, then the 4-position (**21**, **13**, then **22**). This reactivity order could be understood with regard to possible hydrogen bond activation of either oxygen atom by the neighboring carboxylic acid or phenol. A higher reaction temperature or longer reaction time yielded considerable full demethylation product **22**. Fortunately, the desired diol **13** was found to precipitate as the reaction proceeded, and this became an advantage for preventing the overreaction. The optimal condition is shown in Scheme 4. Simple crystallization from the reaction mixture by addition of water afforded **13** in a 73% yield. The generated methyliodide was >96% trapped by

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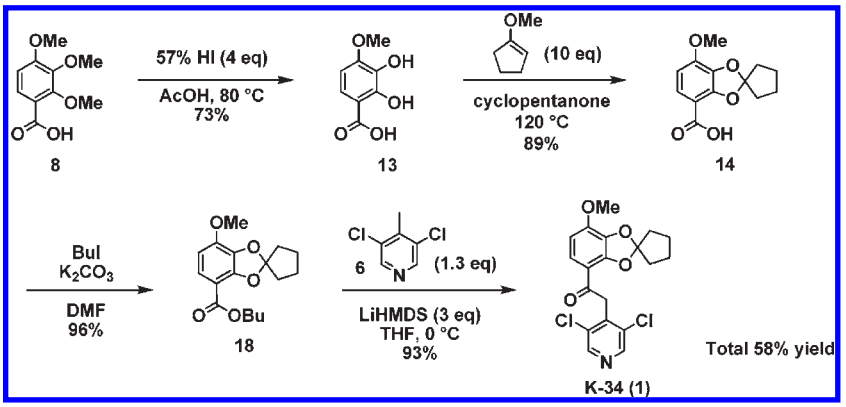
Scheme 4. Optimal process synthesis



a combination of a reflux condenser, cold trap, and an alkaline scrubber.

In the acetalization step, elimination of the generated methanol had become a rate-determining factor in the large-scale synthesis (5 L, 100-g scale). Therefore, the acetalization reagent was changed to 1-methoxycyclopentene, which generates half the amount of methanol and also acts as a methanol trapping reagent. Cyclopentanone was selected as a highly dissolvable solvent instead of xylene. The reproducibility was good on the pilot-plant scale.

Because the methyl ester **16** did not exhibit good crystallinity or a sufficient crystallization yield, other esters were examined. Next, butyl ester **18** was selected because of its equivalent reactivity to **16** and proper crystallinity, which made it possible to achieve direct crystallization by adding water to the reaction. In the final ketone synthesis, LDA was able to be substituted by LiHMDS, and the overall temperature could be settled at 0 °C. However, the assay yield was around 70% and therefore was not satisfactory. The reason was identified to be the relatively rapid degradation rate of anion **9** at 0 °C ($T_{1/2}$ = ~8 h). In order to minimize the handling time of **9**, the procedure was changed to dropwise addition of LiHMDS into the 0 °C mixture of ester **18** and pyridine **6**. The reaction was completed within 0.5 h after the completion of LiHMDS addition. The in situ enolate formation was confirmed by a deuterium oxide quenching experiment to obtain ~60% deuterated **1** at the methylene position. The yield was thus dramatically improved and amount of **6** was reduced to 1.3 equiv by this change. Finally, a recrystallization of the crude mixture from acetone−water afforded pure **1** in a 97% yield.

CONCLUSION

In summary, a short, practical, and scalable synthesis procedure for the PDE4 inhibitor K-34 (**1**) was developed. The synthesis was achieved in four steps and with a 58% overall yield. The unique spiro acetal was created by utilizing assistance from the neighboring carboxylic acid, that is the sequence of the selective bis-demethylation and following exceptionally high-yielding acetalization. This synthesis also features the efficient ketone construction with 4-pyridinylmethyl anion **9** and ester **18**, in which excess LiHMDS suppressed over addition to the resulting ketone via in situ protection as the corresponding enolate. Overall, harsh reagents and cryogenic conditions were eliminated, and all intermediates were isolated by direct crystallization from the reaction solutions. Multikilogram quantities of **1** have now been successfully produced in our laboratories using this procedure.

EXPERIMENTAL SECTION

General Information. All reagents and solvents are commercially available (from Tokyo Kasei Kogyo Co., Ltd., Sigma-Aldrich Co.) and used without further purification. ^{1}H NMR spectra were obtained on a JEOL JNM-LA300 spectrometer (300 MHz) or Bruker AVANCE 500 spectrometer (500 MHz). Chemical shifts (δ) are reported in ppm. Multiplicities are given as: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), m (multiplet), br s (broad singlet). Proton-decoupled ^{13}C NMR spectra were obtained on a JEOL JNM-LA300 spectrometer (75 MHz) or Bruker AVANCE 500 spectrometer (125 MHz). IR frequencies are given in cm^{-1} and spectra were obtained on a Shimadzu FT-IR8700 spectrometer. Mass spectra were obtained on a JEOL JMS-DX303. Melting points (mp) were determined on a Mettler FP61. Elemental analysis was performed on a Perkin Elmer series II CHNS/O analyzer 2400. HPLC analyses were performed on a Hitachi L-4000 system. GC analyses were performed on a Shimadzu GC-14A equipped with a capillary column GL Sciences TC-1.

Route Scouting. Methyl 2,3,4-Trimethylbenzoate (10d). To a solution of **8** (2.00 g, 9.43 mmol) and DMF (0.87 mL, 11.3 mmol, 1.2 equiv) in CH_2Cl_2 (10 mL) under N_2 was added $SOCl_2$ (0.78 mL, 11.0 mmol, 1.2 equiv) at 0 °C. The reaction mixture was stirred at room temperature for 4 h. The acid chloride solution was added dropwise to a solution of triethylamine (6.6 mL, 47.1 mmol, 5 equiv) in methanol (20 mL) at 0 °C. The resulting mixture was diluted with ethyl acetate and washed with aqueous sodium bicarbonate and brine. The organic layer was dried over sodium sulfate and evaporated to afford **10d** (1.93 g, 8.53 mmol, 91% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.61 (d, J = 8.8 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 3.94 (s, 3H), 3.91 (s, 3H), 3.89 (s, 3H), 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 166.0, 157.1, 154.7, 142.9, 126.9, 117.8, 106.9, 61.8, 61.0, 56.0, 51.9; IR (film) 2945, 2843, 1724, 1682, 1595, 1495, 1466, 1431, 1412, 1273, 1219, 1188, 1138, 1036, 982, 780, 750, 696 cm^{-1}; MS/EI m/z 226 [M]$^+$.

2-(3,5-Dichloro-4-pyridyl)-1-(2,3,4-trimethoxyphenyl)-ethanone (11). To a solution of **6** (215 mg, 1.3 mmol, 3 equiv) in THF (2 mL) under N_2 was added LDA (2 mol/L in THF, 0.66 mL, 1.3 mmol, 3 equiv) at −78 °C. The solution was stirred at this temperature for 30 min, and **10d** (100 mg, 0.44 mmol) in THF (1 mL) was added. The mixture was allowed to warm to

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room temperature over 3 h, poured into aqueous ammonium chloride, and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified on a silica gel column chromatography eluting with hexane/ethyl acetate (4/1) to afford **11** (130 mg, 0.36 mmol, 83% yield) as a white solid: mp 110−112 °C; ^{1}H NMR ($CDCl_3$) δ 8.50 (s, 2H), 7.63 (d, J = 8.9 Hz, 1H), 6.77 (d, J = 8.9 Hz, 1H), 4.69 (s, 2H), 4.10 (s, 3H), 3.94 (s, 3H), 3.92 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 192.6, 158.1, 154.4, 147.2, 142.1, 141.6, 133.5, 126.0, 124.4, 107.4, 61.5, 60.9, 56.2, 44.9; IR (KBr) 2950, 1670, 1590, 1470, 1295, 1100 cm^{-1}; MS/EI m/z 355 $[M]^+$.

2,3-Dihydroxy-4-methoxybenzoic Acid (13). To a solution of 2,3,4-trimethoxybenzoic acid (**8**) (4.25 g, 20 mmol) in CH_2Cl_2 (15 mL) under N_2 was added BCl_3 (1 mol/L in CH_2Cl_2, 20 mL, 20 mmol, 1.0 equiv) at 0 °C. The mixture was stirred at room temperature for 1 h, and another portion of BCl_3 (1 mol/L in CH_2Cl_2, 30 mL, 30 mmol, 1.5 equiv) was added. After stirring 10 h at room temperature, water and ethyl acetate were added. The mixture was neutralized (pH 8) with 1 mol/L NaOH (40 mL) and saturated aqueous sodium bicarbonate (10 mL). The separated aqueous layer was acidified with 6 mol/L HCl (45 mL) and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated in vacuo. The residue was diluted with methanol (20 mL), heated under reflux for 30 min, and cooled to 0 °C. The precipitate was filtered, washed with methanol, and dried to give **13** (2.15 g, 58% yield) as a white solid. The mother liquor was concentrated in vacuo, and recrystallized from water (33 mL) to afford another crop of **13** (0.92 g, 25% yield) as a white solid.

7-Methoxyspiro(1,3-benzodioxol-2,1′-cyclopentane)-4-carboxylic Acid (14). To a solution of cyclopentanone (841 g, 10.0 mol) and *p*-toluenesulfonic acid monohydrate (9.5 g, 50 mmol, 0.5 mol %) in methanol (2.5 L) was added trimethyl orthoformate (1.15 L, 10.5 mol, 1.05 equiv) at 5 °C. The mixture was stirred at the same temperature for 30 min and then neutralized with sodium methoxide (28 wt % in methanol, 38.6 g, 0.20 mol, 2 mol %). Xylene (4.0 L) and water (2.0 L) were added to the mixture, and then the organic layer was separated to give 1,1-dimethoxycyclopentane as a xylene solution (5.7 L, net 1209 g, 1.64 mol/L, 9.29 mol, 93% yield). To the xylene solution of 1,1-dimethoxycyclopentane (3.32 L, net 707 g, 5.43 mol, 10 equiv) was added **13** (100 g, 543 mmol). The reaction mixture was heated at 130 °C for 17 h, continuously removing methanol and methyl formate by Dean−Stark apparatus. Then the resultant mixture was slowly cooled to 5 °C over 2 h. The precipitate was collected by filtration and washed with toluene and then dried to give **14** (120.8 g, 483 mmol, 89%) as a white solid.

Methyl 2,3-Dihydroxy-4-methoxybenzoate (15). To a solution of **10d** (8.80 g, 38.9 mmol) in CH_2Cl_2 (20 mL) under N_2 was added BCl_3 (1 mol/L in CH_2Cl_2, 98 mL, 98 mmol, 2.5 equiv) at 0 °C. The mixture was stirred at room temperature for 1 h, then diluted with ethyl acetate and washed with water. The separated organic layer was dried over magnesium sulfate and evaporated. The residue was recrystallized from methanol (6 mL) to afford **15** (5.44 g, 27.4 mmol, 71% yield) as a white solid: mp 93 °C; ^{1}H NMR ($CDCl_3$) δ 10.84 (s, 1H), 7.41 (d, J = 9.0 Hz, 1H), 6.50 (d, J = 9.0 Hz, 1H), 5.49 (br s, 1H), 3.95 (s, 3H), 3.93 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.4, 151.5, 149.3, 133.3, 121.3, 106.7, 102.9, 56.2, 52.1; IR (KBr) 3450, 3373, 2955, 1670, 1628, 1508, 1479, 1440, 1364, 1292, 1261, 1213, 1198, 1161, 1096, 1076, 1018, 779, 770, 719 cm^{-1}; MS/EI m/z 198 $[M]^+$.

Methyl 7-Methoxyspiro(1,3-benzodioxol-2,1′-cyclopentane)-4-carboxylate (16) from 14. To a suspension of **14** (15.0 g, 60 mmol) and K_2CO_3 (9.9 g 72 mmol, 1.2 equiv) in DMF (150 mL) under N_2 was added methyliodide (4.1 mL, 66 mmol, 1.1 equiv). The mixture was stirred at room temperature for 1 h, then poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was dissolved in methanol−water (5:1, 180 mL) at 40 °C and cooled to 10 °C. Water (120 mL) was added, and the slurry was aged for 1 h. The precipitate was filtered, washed with methanol−water (1/1), and dried to give **16** (15.1 g, 57 mmol, 96% yield) as a white solid: mp 47 °C; ^{1}H NMR ($CDCl_3$) δ 7.40 (d, J = 9.0 Hz, 1H), 6.52 (d, J = 9.0 Hz, 1H), 3.94 (s, 3H), 3.88 (s, 3H), 2.28−2.11 (m, 4H), 1.93−1.83 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 165.1, 149.6, 146.7, 135.6, 129.8, 123.5, 106.6, 106.0, 56.4, 51.8, 37.3, 23.4; IR (KBr) 2955, 1713, 1638, 1508, 1433, 1101, 1020, 768 cm^{-1}; MS/EI m/z 264 $[M]^+$.

16 from 15. To a solution of cyclopentanone (50.0 g, 0.59 mol) and trimethyl orthoformate (75 mL, 0.71 mol, 1.2 equiv) in methanol (300 mL) was added *p*-toluenesulfonic acid monohydrate (0.56 g, 2.9 mmol, 0.5 mol %) at room temperature. The mixture was stirred at the same temperature for 30 min and then neutralized with sodium methoxide (28 wt % in methanol, 2.3 g, 1.2 mol, 2 mol %). Hexane and water were added to the mixture. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated to give 1,1-dimethoxycyclopentane as a pale-yellow oil (47.9 g, 0.37 mol, 62% yield). To a solution of **15** (1.0 g, 5.04 mmol) and 1,1-dimethoxycyclopentane (2.63 g, 20.2 mmol, 4 equiv) in toluene (50 mL) was added camphorsulfonic acid (1.17 g, 5.04 mmol, 1 equiv). A dropping funnel was charged with MS4A (10 g) and installed between the reaction flask and reflux condenser. The mixture was then heated under reflux. About every 6 h, 1,1-dimethoxycyclopentane (1.32 g, 10.1 mmol, 2 equiv) and camphorsulfonic acid (0.12 g, 0.50 mmol, 0.1 equiv) were added (eight times). After 50 h, the resultant mixture was washed with saturated aqueous sodium bicarbonate and brine, dried over sodium sulfate, and concentrated. The residue was purified on a silica gel column chromatography eluting with hexane/ethyl acetate (9:1) to afford **16** as a white solid (0.82 g, 3.10 mmol, 62% yield).

K-34 (1) from 16 using LDA. To a solution of **6** (53 mg, 0.33 mmol, 3 equiv) in THF (1 mL) under N_2 was added LDA (2 mol/L in THF, 0.17 mL, 0.34 mmol, 3 equiv) at −78 °C. The solution was stirred at this temperature for 50 min, and **10d** (28.7 mg, 0.11 mmol) in THF (1 mL) was added. The mixture was allowed to warm to room temperature over 3 h, poured into aqueous ammonium chloride, and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluting with hexane/ethyl acetate (5:1) to afford **1** (34.4 mg, 0.087 mmol, 80% yield) as a white solid.

2-(3,5-Dichloro-4-pyridyl)-1-(2,3-dihydroxy-4-methylphenyl)ethanone (17). To a solution of **11** (1.84 g, 5.17 mmol) in CH_2Cl_2 (30 mL) under N_2 was added BCl_3 (1 mol/L in CH_2Cl_2, 10.4 mL, 10.4 mmol, 2 equiv) at 0 °C. The mixture was stirred at room temperature for 12 h, and another portion of BCl_3 (1 mol/L in CH_2Cl_2, 5.2 mL, 5.2 mmol, 1 equiv) was added. The mixture was stirred again at room temperature for 12 h, and then diluted with ethyl acetate and washed with aqueous sodium

bicarbonate and brine. The separated organic layer was dried over magnesium sulfate and evaporated. The residue was recrystallized from hexane/ethyl acetate to afford **17** (1.57 g, 4.78 mmol, 93% yield) as a white solid: mp 190−192 °C; ^{1}H NMR ($CDCl_3$) δ 11.90 (s, 1H), 8.54 (s, 2H), 7.51 (d, J = 9.1 Hz, 1H), 6.62 (d, J = 9.1 Hz, 1H), 5.59 (br s, 1H), 4.68 (s, 2H), 4.00 (s, 3H); IR (KBr) 3400, 3100, 1635, 1505, 1310, 1260 cm^{-1}; MS/EI m/z 327 $[M]^+$.

K-34 (1) from 17. A solution of **17** (92 mg, 0.28 mmol), 1,1-dimethoxycyclopentane (0.40 mL, 0.29 mmol, 1 equiv), and camphorsulfonic acid (65 mg, 0.28 mmol, 1 equiv) in toluene (4.6 mL) was heated under reflux for 8 h. 1,1-Dimethoxycyclopentane (0.40 mL, 0.29 mmol, 1 equiv) was added every hour (seven times) until reaction stopped. The resultant mixture was washed with saturated aqueous sodium bicarbonate and brine, dried over sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography eluting with hexane/ethyl acetate (9:1) to afford **1** as a pale-yellow solid (21 mg, 0.053 mmol, 19% yield).

3,4-Dimethoxy-2-hydroxybenzoic Acid (21): white solid: mp 164 °C; ^{1}H NMR ($CDCl_3$) δ 7.90 (d, J = 9.9 Hz, 1H), 6.55 (d, J = 9.9 Hz, 1H), 3.94 (s, 3H), 3.91 (s, 3H); IR (KBr) 2943, 2548, 1651, 1605, 1504, 1460, 1275, 1103 cm^{-1}; MS/EI m/z 198 $[M]^+$.

8-Hydroxy-7-methoxyspiro[4H-4-oxo-1,3-benzodioxin-2,1′-cyclopentane] (23):. white solid: mp 117 °C; ^{1}H NMR ($CDCl_3$) δ 7.56 (d, J = 8.6 Hz, 1H), 6.69 (d, J = 8.6 Hz, 1H), 5.45 (br s, 1H), 3.98 (s, 3H), 2.22−2.17 (m, 4H), 1.89−1.81 (m, 4H), 3.92 (s, 3H); IR (KBr) 3419, 2934, 1726, 1620, 1508, 1323, 1194, 1119, 1076 cm^{-1}; MS/EI m/z 250 $[M]^+$.

Optimal Process Route . 2,3-Dihydroxy-4-methoxybenzoic Acid (13). To a solution of 2,3,4-trimethoxybenzoic acid (**8**) (300.0 g, 1.41 mol) in acetic acid (1.8 L) under N_2 was added 57% HI (750 mL, 5.69 mol, 4.0 equiv) at 20 °C. The mixture was gradually heated to 80 °C over 6 h and stirred at the same temperature for 7 h. Generated methyl iodide was trapped by a sequentially connected Dean−Stark apparatus, a dry-ice-cooled trap, and a NaOH (5 mol/L) bubbling trap. The resulting mixture was cooled to 20 °C and partially neutralized (pH 1.5) by NaOH (5 mol/L, 600 mL). The precipitate was collected by filtration, washed with water (1.8 L), and dried to give **13** (191.0 g, 1.04 mol, 73.4% yield) as a white solid: mp 234 °C; ^{1}H NMR (DMSO-d_6) δ 7.29 (d, J = 8.9 Hz, 1H), 6.57 (d, J = 8.9 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 172.4, 152.8, 150.7, 133.8, 120.8, 106.7, 103.4, 55.9; IR (KBr) 3350, 2818, 1655, 1618, 1508, 1283, 1090, 772 cm^{-1}; MS/EI m/z 184 $[M]^+$.

7-Methoxyspiro(1,3-benzodioxol-2,1′-cyclopentane)-4-carboxylic Acid (14). To a solution of cyclopentanone (1262 g, 15.0 mol) and p-toluenesulfonic acid monohydrate (14.3 g, 75 mmol, 0.5 mol %) in methanol (1262 mL) was added trimethyl orthoformate (1723 mL, 15.8 mol, 1.05 equiv) at 5 °C. The mixture was stirred at the same temperature for 30 min, then slowly heated to 130 °C over 4 h, and stirred at the same temperature for 22 h under nitrogen gas flow (50−100 mL/min). The resultant mixture was concentrated and distilled (70 °C/70−75 mmHg) to give 1-methoxycyclopentene (926 g, 7.5 mol, 50% yield) as colorless oil. A suspension of **13** (138.0 g, 0.75 mol) and 1-methoxycyclopentene (926 g, 7.5 mol, 10 equiv) in cyclopentanone (828 mL) was heated 120 °C for 6 h under N_2 flow. The reaction mixture was cooled to 70 °C, and volatile components were removed (∼1.6 L) under reduced pressure (70−75 mmHg). The residue was diluted with toluene (1.6 L), and the resulting slurry was heated at 90 °C for 1 h and then cooled to 0 °C. The precipitate was collected by filtration, washed with cold toluene (0.4 L), and dried to give **14** (166.2 g, 0.66 mol, 88.6% yield) as a white solid: mp 215 °C; ^{1}H NMR ($CDCl_3$) δ 7.47 (d, J = 9.1 Hz, 1H), 6.56 (d, J = 9.1 Hz, 1H), 3.96 (s, 3H), 2.26−2.12 (m, 4H), 1.92−1.86 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 169.6, 150.2, 147.4, 135.6, 130.1, 124.3, 106.4, 105.7, 56.5, 37.4, 23.4; IR (KBr) 2990, 1678, 1639, 1452, 1286, 1111, 766 cm^{-1}; MS/EI m/z 250 $[M]^+$.

Butyl 7-Methoxyspiro(1,3-benzodioxol-2,1′-cyclopentane)-4-carboxylate (18). To a solution of **14** (50.0 g, 0.20 mol) in DMF (500 mL) under N_2 were added K_2CO_3 (27.6 g,0.20 mol, 1.0 equiv) and butyliodide (25.0 mL, 0.22 mol, 1.1 equiv). The mixture was stirred at 50 °C for 5 h then cooled to 20 °C. Water (500 mL) was added, and the mixture was cooled and stirred for 1 h at 5 °C. The precipitate was filtered, washed with water (500 mL), and dried to give **18** (58.5 g, 0.19 mol, 95.5% yield) as a white solid: mp 51 °C; ^{1}H NMR ($CDCl_3$) δ 7.39 (d, J = 9.1 Hz, 1H), 6.51 (d, J = 9.1 Hz, 1H), 4.29 (t, J = 6.5 Hz, 2H), 3.93 (s, 3H), 2.25−2.10 (m, 4H), 1.92−1.81 (m, 4H), 1.72 (tt, J = 6.5, 8.0 Hz, 2H), 1.48 (tq, J = 8.0, 7.4 Hz, 2H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 164.6, 149.6, 146.5, 135.6, 129.5, 123.4, 107.0, 105.9, 64.3, 56.3, 37.2, 30.7, 23.3, 19.2, 13.7; IR (KBr) 2955, 1701, 1639, 1450, 1339, 1285, 1215, 1138, 1107 cm^{-1}; MS/EI m/z 306 $[M]^+$.

2-(3,5-Dichloro-4-pyridyl)-1-(7-methoxyspiro[1,3-benzodioxol-2,1′-cyclopentane]-4-yl)ethanone (K-34, 1). To a solution of **18** (4.50 kg, 14.7 mol) and 3,5-dichloro-4-methylpyridine **6** (3.10 kg, 19.1 mol, 1.3 equiv) in THF (45 L) under N_2 was added dropwise LiHMDS (1.05 mol/L in THF, 42.0 L, 44.1 mol, 3.0 equiv) at 0 °C over 30 min. The mixture was stirred at 0 °C for 1 h and then quenched with aqueous ammonium chloride (60 L). The organic layer was separated, washed with brine, and concentrated in vacuo. The residue was diluted with acetone (36 L) and concentrated again. The residue was dissolved in acetone (45 L) at 50 °C, and active carbon (225 g) was added with acetone (2 L). After 30 min of agitation, the active carbon was filtered off and washed with hot acetone (13.5 L) at the same temperature. The filtrate was diluted with water (67.5 L) and cooled to 10 °C. The formed precipitate was filtered, washed with acetone/water (1:1, 20 L), and dried to afford **1** (5.40 kg, 13.7 mol, 93.2% yield) as a white solid: mp 149 °C; ^{1}H NMR ($CDCl_3$) δ 8.50 (s, 2H), 7.47 (d, J = 9.1 Hz, 1H), 6.61 (d, J = 9.1 Hz, 1H), 4.59 (s, 2H), 3.97 (s, 3H), 2.27−2.22 (m, 4H), 1.93−1.88 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 189.3, 149.3, 147.5, 147.2, 141.2, 135.4, 133.5, 129.9, 122.3, 113.4, 107.0, 56.5, 44.0, 37.4, 23.4; IR (KBr) 2968, 1685, 1635, 1505, 1310, 1260 cm^{-1}; MS/EI m/z 393 $[M]^+$; Anal. Calcd for $C_{19}H_{17}Cl_2NO_4$: C, 57.88; H, 4.35; N, 3.55. Found: C, 58.05; H, 4.32; N, 3.52.

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