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Process Research on a Phenoxybutyric Acid LTB4 Receptor Antagonist. Efficient Kilogram-Scale Synthesis of a 3,5-Bisarylphenol Core

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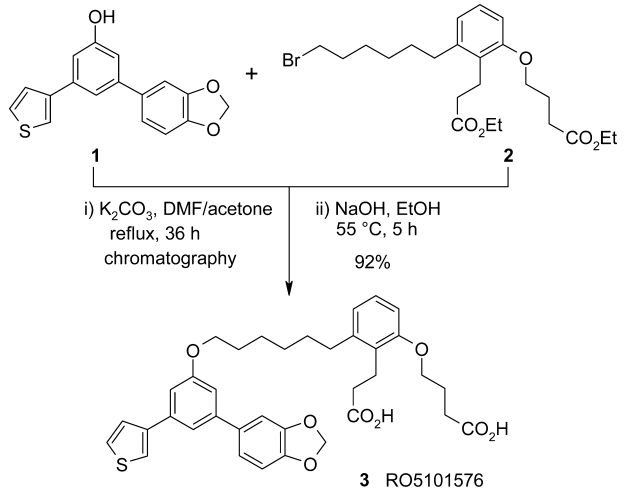
ABSTRACT: An improved, kilogram-scale synthesis of a LTB4 receptor antagonist is reported. The title compound was prepared in four linear steps (seven steps total) and 54% overall yield. The 3,5-bisarylphenol core was obtained in nearly quantitative yield by the condensation of 1-benzotriazol-1-ylpropan-2-one with a chalcone. Although all the intermediates were oils, no chromatography purification was required.

INTRODUCTION

Leukotriene B4 (LTB4) is an important mediator of acute and chronic inflammatory diseases. Elevated levels of LTB4 are observed in pulmonary tissues of patients suffering from a variety of pulmonary diseases, such as asthma, chronic obstructive pulmonary disease (COPD), and acute lung injury/acute respiratory distress syndrome (ALI/ARDS). It was hypothesized that blockade of LTB4 receptors could potentially provide a treatment for these diseases.[1] At Roche, RO5101576 (**3**) was identified as a potent LTB4 receptor antagonist.[2] In order to support the planned toxicology studies, process research was initiated to secure active pharmaceutical ingredient (API) supply on a kilogram scale.

In the original synthesis developed by the Discovery Chemistry group, **3** was prepared in two steps from 3,5-bisarylphenol **1** and bromide **2** in good yield (Scheme 1).[2b] The phenol, **1**, was initially prepared by one-pot Suzuki coupling of 3,5-dibromophenol (**4**) with boronic acids **5** and **6**. Bromide **2** was obtained in four steps from custom-synthesized benzyl bromide **7** (Scheme 2). While this synthesis is straightforward, several limitations prevented its use for large-scale production. First, except for the API, none of the intermediates was crystalline, and chromatographic purifications were required at almost every step. Second, the one-pot Suzuki coupling reactions of **4** with **5** and **6** produced **1** together with two symmetric Suzuki coupling products. The isolation of **1** from the reaction mixture was found to be tedious, and multiple chromatographic purifications were required to obtain **1** in reasonable purity. The synthesis of **2** was lengthy, and the bromination of **11** using carbon tetrabromide was undesirable due to poor atom economy. Herein, we report an efficient, kilogram-scale synthesis of **3** in 54% overall yield from bromide **7** without chromatography.

Scheme 1. Assembly of 3



RESULTS AND DISCUSSION

Preparation of the 3,5-Bisarylphenol Core, 1. The original Suzuki coupling of compounds **4**, **5**, and **6** in one pot gave **1** in only 37% yield due to the lack of coupling selectivity. A sequential approach that proceeds via a Kumada coupling, followed by a Suzuki coupling, was thus investigated (Scheme 3). Compound **13** was prepared in 93% yield from **12** as described in the literature.[3] Treatment of **13** with isopropyl magnesium chloride (1.06 equiv) generated the corresponding mono-Grignard reagent, which upon reaction with iodide **14** gave the PMB-protected phenol **15**, a crystalline intermediate, in 53−70% yield. Deprotection of **15** by treatment with ethanolic HCl then afforded phenol **16**, and Suzuki coupling of **16** with **5** produced the desired product **1** as an oil in 98% purity. While this new process eliminated the chromatographic purification of **1**, the overall yield from **12** was still in the suboptimal 31−41% range.

Alternatively, the Suzuki coupling of **15** with **5** gave **17** as an oil in 95% yield. However, the subsequent deprotection of **17** was found to be problematic. No reaction was observed under

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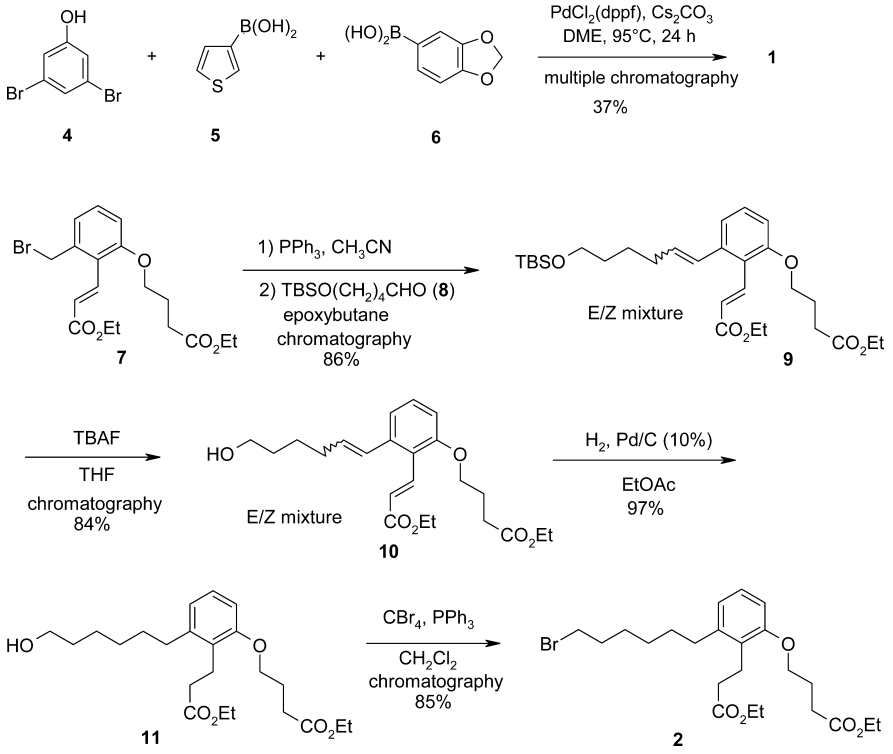
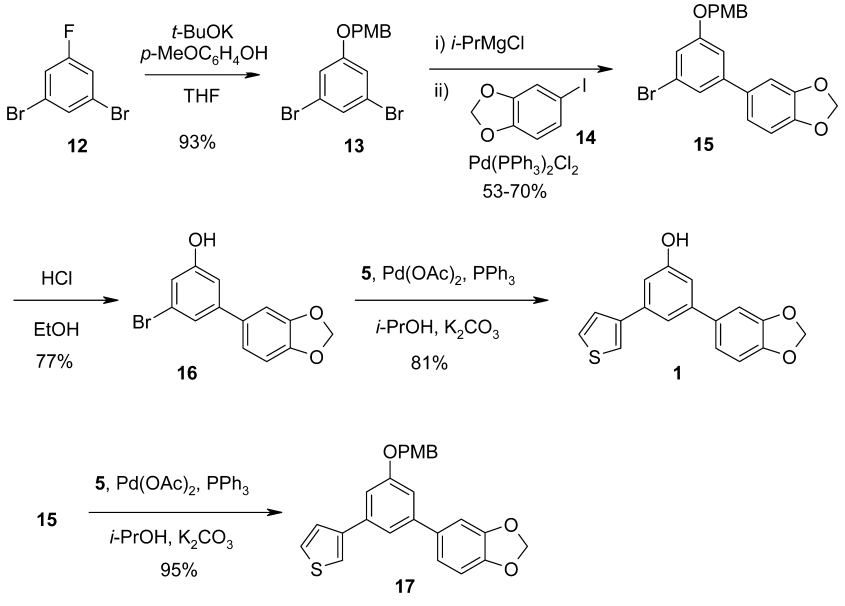
Scheme 2. Original synthesis of building blocks 1 and 2



Scheme 3. Preparation of 1 by sequential Kumada and Suzuki couplings



hydrogenolysis conditions using Pd/C or $Pd(OH)_2/C$ as catalyst. When **17** was treated with TFA in CH_2Cl_2, LC−MS analysis indicated formation of a 1:2:2 mixture of **1** plus two other peaks with a molecular weight of 416, possibly isomers of **17**.[4] The addition of a cation scavenger, anisole, as a cosolvent did not alter the product ratio.

Meanwhile, an alternative approach for the synthesis of 3,5-bisarylphenols, reported by Katritzky et al.,[5] was found to give very promising results. The condensation of chalcone **20** with 1-benzotriazolylacetone (**22**) afforded **1** in 83% yield after chromatographic purification (Scheme 4). This route was selected for further optimization.

While numerous conditions for Claisen−Schmidt condensation have been reported in the literature,[6] lithium hydroxide-catalyzed reaction described by Bhagat et al.[7] was found to give the desired product efficiently under very mild conditions. A suspension of ketone **19** in ethanol was treated with LiOH powder (0.1 equiv) for 5−10 min, and then aldehyde **18** was added. After the mixture was stirred at room temperature overnight and aqueous work-up, compound **20** was collected by filtration as a white solid in nearly quantitative yield and >99.9% purity.

Compound **22** was initially prepared in 53% yield by the reaction of benzotriazole with bromoacetone, according to the

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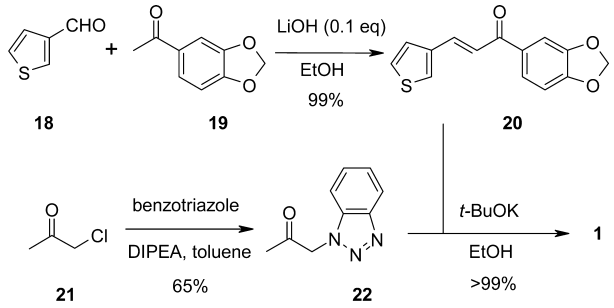
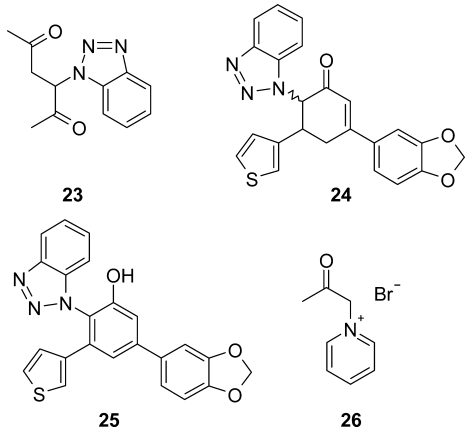
Scheme 4. Preparation of 1 via condensation of 20 and 22



reported procedure.[5] As bromoacetone is about 20 times more expensive than chloroacetone (**21**), the reaction of the latter was examined. Thus, a mixture of **21**, benzotriazole,[8] DIPEA, and toluene was heated to 90−100 °C.[9] HPLC analysis indicated the formation of **22** along with a byproduct with molecular weight of 231, possibly bis-adduct **23**. After aqueous workup, compound **22** was isolated by filtration as a white solid in 65% yield. Slow addition of DIPEA, or using potassium carbonate as the base, did not offer any advantage. No reaction occurred when sodium bicarbonate was used. While this process still requires development, it was deemed suitable for use at this early stage of development.



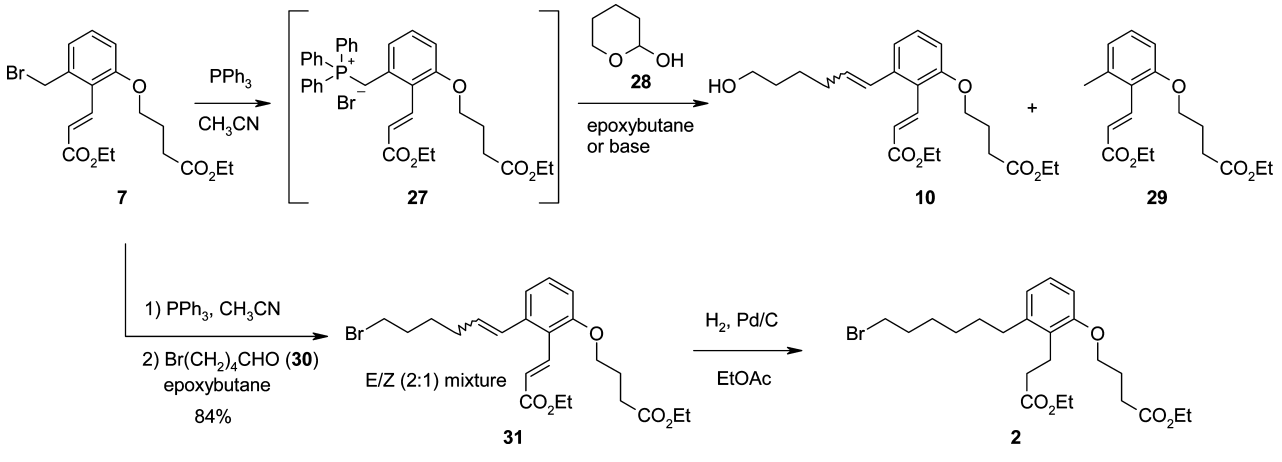
According to the literature procedure,[5] condensation of **22** with chalcones was accomplished in ethanol at reflux using aqueous sodium hydroxide as the base. Under these conditions, although pure **1** was isolated in up to 83% yield, column chromatography purification was required. Since **1** is an oil, it is necessary to improve the reaction so that the crude product could be directly used in the next step. The reaction was first tested in THF using DBU or KO*t*Bu as the base. Under both these conditions, the reaction stopped at the intermediate **24**, without further elimination of the benzotriazole. A much cleaner and complete conversion was subsequently achieved when the reaction was carried out in ethanol under anhydrous conditions, using KO*t*Bu as the base. Thus, to a suspension of **20** and **22** in ethanol was added KO*t*Bu (4 equiv) portionwise over 5−10 min. On a 100 g-scale reaction, an exotherm raised the temperature of the reaction mixture from 22 to 60 °C,[10] and HPLC analysis indicated the formation of **1**, along with intermediate **24**. A complete reaction was achieved after the mixture was heated to reflux for an additional 30 min. Upon aqueous wash and extractive work-up, compound **1** was obtained as a red oil in quantitative yield and >98% purity. Material of this quality could be used directly in the next step. The major impurity (~0.5%), with a molecular weight of 413, was presumed to be **25**, which is derived from the oxidation of **24**.

The condensation of **20** with **22** was successfully carried out at the scale of 848 g of **20**. The exotherm was well controlled by adding KO*t*Bu in portions over 30 min. Although both KOEt and NaOEt can be used in place of KO*t*Bu, the latter was preferred as it could be obtained in consistent quality from multiple commercial sources.

Since pyridinium salt **26** is commercially available and is known to undergo essentially the same chemistry to give 3,5-bisarylphenols,[11] its reaction with **20** was also briefly examined. Upon addition of KO*t*Bu to a mixture of **26** and **20** (1 g scale) in ethanol, a strong exotherm immediately ensued that brought the reaction mixture to reflux; HPLC analysis indicated complete reaction. While **1** was the major product, the reaction was not as clean as that of **22**.[12]

Preparation of Bromide 2. The four-step synthesis of **2** from benzyl bromide **7** presented a major challenge as all the intermediates were oils. Except for **11**, chromatographic purification was required for all intermediates. Originally, the five-carbon aliphatic chain was introduced via Wittig reaction of the TBS protected aldehyde **8** (Scheme 2). While a shorter synthesis of **2** was desired, it was also important to ensure that

Scheme 5. Improved synthesis of 2



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each individual step resulted in a crude product that could be used directly in the subsequent downstream processing.

The Wittig reaction of commercially available and inexpensive 2-hydroxytetrahydropyran (**28**)[13] was initially evaluated in an attempt to eliminate the TBS protection in **9** (Scheme 5). This reaction worked well on a gram scale under certain conditions but was not consistent on scale-up primarily due to competitive decomposition of the phosphonium salt **27** to give byproduct **29**.[14] In addition, the extractive removal of triphenylphosphine oxide from the reaction mixture was more difficult because of the increased solubility of **10** in the aqueous methanol phase as compared to that of **9**.

In order to eliminate the undesirable bromination of **11** in the original sequence, and to avoid the isolation issue encountered with **10**, the use of 5-bromopentanal (**30**), instead of the 5-hydroxypentanal derivative, was considered.

The phosphonium salt **27** was formed by heating a mixture of **7** and triphenylphosphine (1.1 equiv) in acetonitrile to reflux for 1 h. Treatment of **27** with a base (Table 1, entries 2–8) generated the ylide, which reacted with aldehyde **30** to afford **31**. Strong bases promoted the decomposition of the phosphonium salt **27** to **29** (Table 1, entries 3–5, 7, 8), or gave a messy mixture (Table 1, entry 6). On the other hand, when the acid scavenger 1,2-epoxybutane was used, the olefination reaction between **27** and **30** proceeded smoothly in the absence of base and overall gave the best result (Table 1, entry 1). These conditions were thus used for the first scale-up batches.

Table 1. Wittig reaction of 7 with 30

	ylides formation conditions			HPLC result (area %)		
entry	base	temp (°C)	time (h)	**31**	**29**	yield (%)
1	none[a]	reflux	18	95.2	1.5	79.4
2	NaOMe	−5 to rt	1	94.0	3.7	73.5
3	NaOEt	−5 to rt	1	92.1	5.6	81.8
4	NaOEt	−5	0.08	95.2	2.6	71.3
5	NaOEt	−35 to −15	0.25	81.0	6.3	–
6	LHMDS	−30	1	66.4	–	–
7	DBU	30	1	66.6	16.7	–
8	BuLi/DMSO	−20 to rt	0.25	90.9	8.3	85.6
9	Cs_2CO_3	reflux	1.2	96.5	1.0	89.2

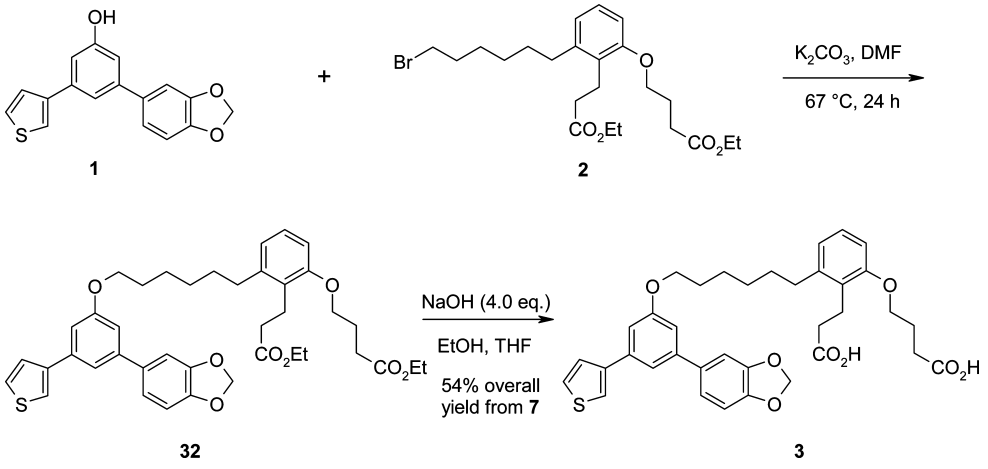
[a]Phosphonium salt **27** was used directly in the presence of an acid scavenger, 1,2-epoxybutane.

Due to the safety concern of the use of large quantities of 1,2-epoxybutane,[15] the Wittig reaction was revisited after the first scale-up campaign was complete. A significant improvement was realized when cesium carbonate was used, which allowed the reaction to be run more concentrated and to be completed within a shorter time (Table 1, entry 9). The yield and purity of **31** were also improved. This improved process was expected to replace the initial scale-up procedure using 1,2-epoxybutane.

In the hydrogenation step, triphenylphosphine carried over from the Wittig reaction is a catalyst poison. Thus, it was necessary to oxidize any residual material completely to triphenylphosphine oxide. The reaction mixture from the Wittig reaction was treated with 30% H_2O_2[16] at reflux, until HPLC analysis confirmed the absence of triphenylphosphine. After extractive work up to remove triphenylphosphine oxide, crude **31** was used directly in the subsequent hydrogenation step. With such treatment, the hydrogenation of **31** proceeded smoothly with 10% Pd/C (2 mol % Pd) under 500–550 psi of hydrogen pressure over 20 h. The crude product **2**, obtained as an oil, was used directly in the next step. On the contrary, when the H_2O_2 treatment was omitted, the hydrogenation was considerably slower, and only the double bond located in the 6-bromohexenyl chain could be reduced.

Coupling and Hydrolysis to the Final Product (3). A mixture of phenol **1** and potassium carbonate in DMF was heated to 45 °C to generate the potassium salt of **1**; then bromide **2** was added and the mixture was heated to 67 °C (Scheme 6). The reaction was complete in 24 h as compared to 40 h when acetone was used as solvent in the original synthesis. Upon extractive workup and treatment with charcoal, crude **32** was obtained as an oil. Ester hydrolysis was accomplished by treating a THF/ethanol mixture of **32** with 2 M NaOH. The resulting solution was extracted with methyl *tert*-butyl ether to remove nonpolar impurities. The aqueous phase was then acidified with hydrochloric acid and extracted with ethyl acetate. After an aqueous wash and solvent exchange to acetonitrile, **3** precipitated and was isolated by filtration. A recrystallization in acetonitrile afforded **3** in 98% purity and 54% overall yield from **7**.

Scheme 6. Final coupling and hydrolysis to 3



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CONCLUSION

We have developed an efficient synthesis of LTB4 receptor antagonist **3** in four linear steps (seven steps in total). The key building block, 3,5-bisarylphenol **1**, was prepared in high yield from readily available starting materials. A streamlined preparation of the requisite bromide **2** was also developed. Although all the intermediates were oils, the title compound was prepared in 54% overall yield and 98% purity without any chromatographic purifications. While safety evaluations were required for further development, this process was successfully utilized for the preparation of the initial 1.26 kg of **3** for the toxicology studies.

EXPERIMENTAL SECTION

General. HPLC analysis was performed on Cadenza CD-C18 (100 × 3 mm, 3 μm) column with 50−100% CH_3CN/H_2O (+0.1% HCO_2H) as mobile phase at flow rate of 0.5 mL/min over 10 min, and held for 7 min. Compound **7** was prepared by a contract supplier following a previously reported synthesis.[2b]

(*E*)-1-Benzo[1,3]dioxol-5-yl-3-thiophen-3-ylpropenone (20). A mixture of **19** (1.89 kg, 11.5 mol), ethanol (11.3 L), and anhydrous LiOH (28.0 g, pre-ground) was stirred at room temperature for 10 min, and then **18** (1.29 kg, 11.5 mol) was added in one portion. The resulting yellow suspension was stirred at room temperature overnight and then diluted with water (6 L) and filtered. The collected solid was washed with ethanol−water (1:1, v/v, 6 L) and water (11.3 L), then dried in a vacuum oven at 40 °C/120 mmHg to give **20**[17] (2.93 kg, 99% yield) as a white solid in >99.9% purity.

1-Benzotriazol-1-ylpropan-2-one (22). A mixture of **21** (1.02 kg, 11.0 mol), benzotriazole (1.33 kg, 11.2 mol) (**CAUTION**: Benzotriazole is explosive under certain conditions—do not repeat this experiment without sufficient safety awareness and precautions.), and toluene (5.1 L) was heated to 80 °C; DIPEA (2.31 L) was then added at 80−90 °C over 70 min. The reaction mixture was stirred at 90−95 °C for 1.5 h, then cooled to 60 °C, and diluted with water (5 L). After the mixture was cooled to room temperature, the resulting suspension was filtered, and the filter cake was washed with water (3 × 5.1 L) and toluene (3 × 3.5 L). The resulting wet cake was reslurried in toluene (5 L) at room temperature for 30 min. The solid was filtered, washed with toluene (2 × 1 L), and dried to give **22**[5] (1.25 kg, 65% yield) as a white solid in 99% purity.

3-Benzo[1,3]dioxol-5-yl-5-thiophen-3-ylphenol (1). Two 22-L flasks were each charged with **20** (848 g, 3.28 mol), **22** (575 g, 3.28 mol), and ethanol (8.4 L). To each of the resulting suspensions was added, portionwise, potassium *tert*-butoxide (1.55 kg, 13.8 mol) over 30 min. (**CAUTION**: Beware of the exotherm if addition is too fast.) An exotherm ensued that increased the batch temperature from 22 to 66 °C. The resulting solutions were heated to reflux for 30 min. After cooling to room temperature, conc. HCl (1.64 L) was added to each flask at ≤25 °C. The resulting suspensions were combined and filtered. The solid cake was then washed with MTBE (2 × 3.3 L). The filtrate and washes were combined and concentrated. The resulting brown oil was redissolved in MTBE (12 L) and diluted with heptane (6 L). After stirring at room temperature for 20 min, the resulting solid was removed by filtration, and the collected solids were washed with a mixture of MTBE/heptane (2:1, v/v, 3 L). The filtrate and wash were combined in an extractor and washed with 2 M HCl (8.4 L), followed by water (8.9 L). The organic phase was then concentrated at 50 °C/75 mmHg to give **1**[2b] (1.95 kg, >99% yield) as a brown oil in 98% purity.

5-Bromopentanal (30). A 12 L round-bottom flask was charged with sodium hypochlorite (10−13%, 7.0 L) and potassium carbonate (675 g). The mixture was stirred for 15 min and then filtered to give the solution of bleach used below.

Two flasks were each charged with 5-bromopentanol (879 g, 4.99 mol), KBr (133 g), Bu_4NHSO_4 (94.4 g), water (1.8 L), CH_2Cl_2 (4.0 L), and TEMPO (8.88 g, 56.3 mmol). The reaction mixtures were cooled to 0 °C, and to each flask was added the bleach solution (3.3 L) from above at ±1 °C over 1.5 h. After GC analysis indicated complete reaction (~3.5% starting material remaining),[18] the contents of the two flasks were combined in an extractor, and diluted with hexane (17.8 L). The organic layer was separated and washed successively with 1 M NaOH (5.3 L) and water (2 × 6.7 L) and then dried over sodium sulfate (700 g). The mixture was filtered and the filtrate was concentrated at 35 °C/10 mmHg to give **30**[19] (1.71 kg, 86% GC purity, 84% yield) as a red oil, which was used directly in the next step.

4-[3-(6-Bromohex-1-enyl)-2-(2-ethoxycarbonylvinyl)-phenoxy]butyric Acid Ethyl Ester (31). (*Important Note*: The procedure described in this step was used for the initial scale-up at early stage of development. Although no problems occurred over multiple runs, this procedure should not be used for large-scale preparation without sufficient safety evaluation. The Cs_2CO_3-promoted Wittig reaction which is safe and more efficient should be used instead.) Two flasks were each charged with **7** (651 g, 1.63 mol), triphenylphosphine (477 g, 1.82 mol), and acetonitrile (5.4 L). The mixtures were stirred at reflux for 1 h. After the mixtures cooled to 40 °C, **30** (296 g, 1.79 mol) and 1,2-epoxybutane[15] (8.2 L, 95.2 mol) were added to each flask. The dark solutions were heated to reflux for 18 h, and then H_2O_2[16] (272 mL, 30 wt %) was added to each flask over 10 min. The reaction mixtures were heated to reflux for an additional 2.5 h while maintaining a N_2 flow. After cooling to room temperature, the contents of the two flasks were combined and concentrated at 35 °C/10 mmHg. (**CAUTION**: The reaction mixture should be tested to be free of residual H_2O_2 before concentration.) The residual suspension was diluted with *n*-heptane/EtOAc (3:1, v/v, 15.0 L) and washed with MeOH/H_2O (2:1, v/v, 7.1 L). The aqueous bottom layer was separated and back extracted with *n*-heptane/EtOAc (3:1, v/v, 2 × 3.5 L). The combined organic layers were washed with MeOH/H_2O (2:1, v/v, 2 × 7.0 L) and then with H_2O (7.3 L); this mixture was concentrated at 40 °C/10 mmHg to give **31**[20] (1.28 kg, 84% yield) as an orange oil, which was used directly in the next step.

4-[3-(6-Bromohexyl)-2-(2-ethoxycarbonylethyl)-phenoxy]butyric Acid Ethyl Ester (2). A 20-L autoclave was charged with **31** (1.67 kg, 3.57 mol), 10% Pd/C (166 g, 53% water wet, 73.3 mmol), and EtOAc (5.0 L). The mixture was stirred at 40 °C under 550 psi of hydrogen for 20 h until LC−MS analysis indicated complete reaction. The reaction mixture was then filtered through a thin layer of Celite, and the Celite pad was washed with EtOAc (3 × 100 mL). The combined filtrate and washes were concentrated at 40 °C/10 mmHg to give crude **2**[2b] (overweight, 3.57 mol in theory) as a light-yellow oil, which was used directly in the next step.

4-[3-[6-(3-Benzo[1,3]dioxol-5-yl-5-thiophen-3-ylphenoxy)hexyl]-2-(2-ethoxycarbonylethyl)phenoxy]-

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butyric Acid Ethyl Ester (32). A mixture of **1** (1.03 kg, 3.47 mol), DMF (3.2 L) and K_2CO_3 (1.08 kg, 7.81 mol) was heated to 45 °C and stirred for 20 min; then a solution of **2** (crude oil, containing 3.57 mol of **2** in theory) in DMF (2.0 L) was added. The mixture was stirred at 65−67 °C for 24 h and then diluted with H_2O (16 L), MTBE (24 L), and heptane (2.4 L). The organic phase was separated and washed with aqueous K_2CO_3 (1.2 wt %, 2 × 8 L). Charcoal (350 g) was added, and the resulting mixture was stirred for 20 min and then filtered through a pad of Celite (750 g); the Celite pad was then washed with MTBE (4.0 L). The combined filtrate and wash were concentrated to give **32**[2b] (2.47 kg, 3.47 mol in theory) as an oily foam which was used directly in the next step.

4-[3-[6-(3-Benzo[1,3]dioxol-5-yl-5-thiophen-3-ylphenoxy)hexyl]-2-(2-carboxyethyl)phen-oxy]butyric Acid (3). Two flasks were each charged with **32** (1.11 kg of oil, containing 1.56 mol of **32** in theory), THF (4.5 L), and ethanol (2.0 L). To each solution was added 2 M NaOH (3.25 L, 6.50 mol). The mixtures were stirred at 19−23 °C for 16 h to obtain clear, brownish solutions. The contents of the two flasks were combined and concentrated at 40 °C/10 mmHg to remove THF. The residue was diluted with water (14 L) and MTBE (18 L). The aqueous layer was separated and acidified with 4 M HCl (3.0 L) to pH ∼1.2, while cooling with an ice−water bath. The mixture was then diluted with EtOAc (16 L). The organic layer was separated, washed with water (4 × 10 L), and concentrated at 35 °C/10 mmHg. The residual oil was diluted with CH_3CN (7.5 L) and further concentrated to near dryness. The resulting oil was diluted with CH_3CN (8.5 L) and stirred at 19−23 °C for 3 h. The precipitated solid was isolated by filtration to give crude **3** (1.53 kg) as an off-white solid.

Crude **3** (1.53 kg) and CH_3CN (4.0 L) were heated to reflux to obtain a light-brown solution. This solution was gradually cooled to room temperature with stirring to complete the crystallization. The resulting solid was isolated by filtration, washed with CH_3CN (2 × 1 L), and dried to give **3**[2b] (1.26 kg, 64% yield from **31**) as a white solid in 98% purity.

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Notes

The authors declare no competing financial interest.

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(10) The exotherm was primarily caused by mixing KO*t*Bu with ethanol. When KOEt or NaOEt was used, only a mild exotherm was observed.

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(12) This approach was not further investigated due to the termination of the project.

(13) For an example of Wittig reaction of **28**, see Ohloff, G.; Vial, C.; Näf, F.; Pawlak, M. *Helv. Chim. Acta* **1977**, *60*, 1161.

(14) For an example of the decomposition of phosphonium salt, see Grayson, M.; Keough, P. T. *J. Am. Chem. Soc.* **1960**, *82*, 3919.

(15) 1,2-Epoxybutane is highly flammable, and it could polymerize and generate heat under certain conditions. Although it has been widely used in Wittig reactions as acid scavenger and solvent, *it is not recommended for use at large scale*.

(16) Oxidation using H_2O_2 in flammable solvent is potentially hazardous. It is important to maintain a constant flow of inert gas to prevent oxygen from building up in the reaction vessel. For safe scale-up of oxidation by H_2O_2 in flammable solvents, see Astbury, G. R. *Org. Process Res. Dev.* **2002**, *6*, 893.

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