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An Efficient Synthesis of a Multipotent Eicosanoid Pathway Modulator†

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Abstract:

An efficient, scalable synthesis of the multipotent eicosanoid pathway modulator 2-[3-[3[[5-ethyl-4′-fluoro-2-hydroxyl[1,1′-biphenyl]-4-yl]oxy]-propoxy]2-propoxylphenoxy]benzoic acid (1) is described. The process consists of nine chemical steps with the longest linear sequence having six isolations. Palladium metal-mediated cross-coupling assembles the biaryl fragment, and selective S_NAr chemistry is used to construct the resorcinol fragment. The synthesis converges at a phenolic coupling with an alkyl chloride to give the core structure of the active pharmaceutical ingredient (API). Further elaborations of the core and salt formation provides the final API. This process produced the drug candidate in 41% overall yield at multikilogram scale.

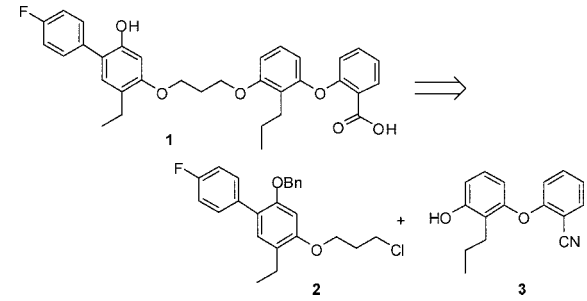
Introduction

Studies on the role of eicosanoids in tumor cell growth led to the examination of multipotent eicosanoid pathway modulator (MEPM), 2-[3-[3[[5-ethyl-4′-fluoro-2-hydroxyl[1,1′-biphenyl]-4-yl]oxy]-propoxy]2-propoxylphenoxy]benzoic acid (**1**), as an anticancer agent.[1] The compound has shown antiproliferative activity against a number of tumor cell lines at low micromolar concentrations, which are expected to be clinically attainable. As a single agent, the compound is active against BxPC3 xenograft tumors in mice, and it has been shown to enhance gemcitabine activity in vitro.[2] Compound **1** in combination with gemcitabine also showed increased activity over either compound alone. These results generated significant interest in clinically testing compound **1** both as a single agent and in combination therapy with gemcitabine.

Results and Discussion

First-Generation Synthesis. The first-generation synthesis was an efficient and practical multikilogram synthesis derived from the development of three methodologies: a robust Suzuki−Miyaura cross-coupling,[3] a ketone reduction, and an interesting biaryl ether formation. The development of these methodologies provided a practical, convergent synthesis of compound **1** to deliver early-stage material requirements.[4]

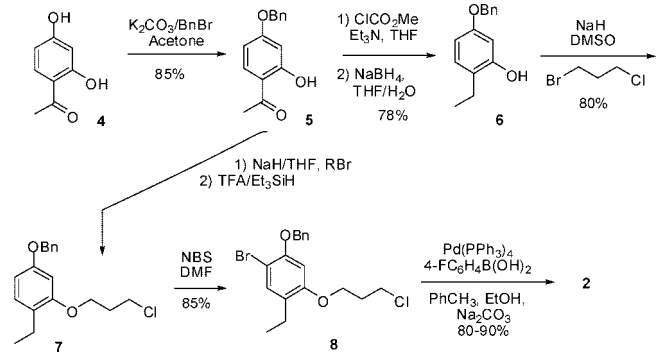
Scheme 1. **Retrosynthesis of compound 1**



A convergent strategy from the first-generation synthesis for compound **1** is outlined retrosynthetically in Scheme 1. Since the synthesis was intended to prepare bulk drug substance material, pivotal intermediates **2** and **3** required preparation from readily available starting materials. Therefore, a major challenge posed by this approach was establishing regiocontrol of each aryl substitution pattern. A Suzuki−Miyaura cross-coupling of a fluoro aryl boronic acid and a substituted resorcinol ether provided biphenyl **2**. Diaryl ether **3** was derived from coupling of propyl resorcinol and a suitable 2-halogenated benzonitrile. Coupling of the two pivotal intermediates followed by debenzylation and hydrolysis provided compound **1**.

The synthesis of fragment **2** is shown in Scheme 2. Commercially and readily available 2′,4′-dihydroxyacetophenone was selectively benzylated to provide **5** in >85% yield.[5] The resulting phenol was *O*-alkylated in quantitative yield with 1,3-bromochloropropane using sodium hydride as the base in THF.

Scheme 2. **Preparation of biphenyl 2**



Attempts at using various methods for ketone reduction to the hydrocarbon derivative gave poor yields for our purpose. For example, ionic hydrogenation[6] with triethylsilane and

† This paper is dedicated to the memory of our friend and former colleague Dr. Christopher R. Schmid.

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(3) (a) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513. (b) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, *15*, 2419.

(4) Sawyer, J. S.; Bach, N. J.; Baker, S. R.; Baldwin, R. F.; Borromeo, P. S.; Cockerham, S. L.; Fleisch, J. H.; Floreancig, P.; Froelich, L. L. *J. Med. Chem.* **1995**, *38*, 4411.

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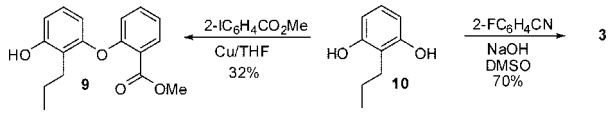
trifluoroacetic acid gave <60% yield. On a large scale, the major problem encountered was product isolation from silane byproduct. Variations in this methodology such as using other proton donor−proton acceptor pairs or addition of fluoride sources5 during workup did not enhance isolated yields. In view of the poor yields from ionic hydrogenation, we examined an alternate synthesis method. Reduction of 2-benzoylresorcinol and 2-*n*-propionylresorcinol to the alkylresorcinol has been reported with sodium borohydride after prior acylation with ethyl chloroformate in 55% and 22% yield, respectively.[7] In this manner, **5** was reacted with methyl chloroformate and triethylamine in THF to form the methyl carbonate. Addition of a solution of sodium borohydride followed by acidic workup provided the desired ethyl derivative **6** in 78% yield. This method of reduction was developed for a 300-gal scale.[8] The sodium alkoxide of **6** was reacted with 1,3-bromochloropropane to provide **7**. While initial studies used NaH to form the alkoxide, sodium *tert*-butoxide was preferred when the reaction was scaled up. Bromination of **7** with NBS along with the Suzuki−Miyaura cross coupling between **8** and 4-fluorophenyl boronic acid proceeded without incident to provide **2** in 90% yield.

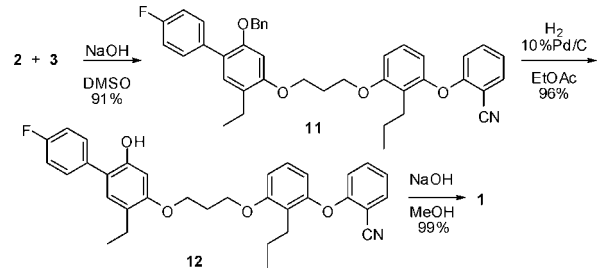
Ullmann reaction conditions[9] were explored for preparing biaryl ether **3** (Scheme 3). Reaction of 2-propyl resorcinol and 2-iodomethylbenzoate with copper in THF provided the biaryl ether **9** in 32% yield. This low yield was largely due to product isolation and purification of the resulting noncrystalline product. Since large quantities of **3** were required, we turned our attention to other means of preparation. We envisioned that nucleophilic aromatic substitution of 2-fluorobenzonitrile with 2-propyl resorcinol would provide an appropriate synthon. In this approach (Scheme 3), the nitrile moiety would play the dual role of activation for nucleophilic aromatic substitution and provide the carboxylic acid equivalent upon hydrolysis. Several conditions were developed for this transformation. In every case, more than 2 equiv of base was required for successful reaction. The optimum conditions developed used 2 equiv of solid sodium hydroxide in DMSO as solvent to provide **3** in 70% yield.

Scheme 3. **Synthesis of the biaryl ether**



Coupling of **2** and **3** with sodium hydroxide in DMSO furnished **11** in 91% yield (Scheme 4). To increase solubility upon nitrile hydrolysis, the phenol functionality of **11** was first deprotected using hydrogenolysis conditions. In several cases, concomitant reduction of the nitrile group was observed. Switching to hydrogen transfer methods using palladium on carbon as catalyst and ammonium formate gave the desired phenol **12** in 90% yield on small scale. However, due to concerns about the sublimation of ammonium carbonate and defluorination, this reaction was not implemented on pilot-plant scale.[10] Therefore, we decided to reinvestigate the hydrogenolysis conditions and found that the nitrile remained intact at 55−60 psi of hydrogen, with 10% palladium on carbon at 10−15 °C in ethanol for 10 h. Hydrolysis of **12** with 12.5 M sodium hydroxide in methanol provided compound **1** in almost quantitative yield.

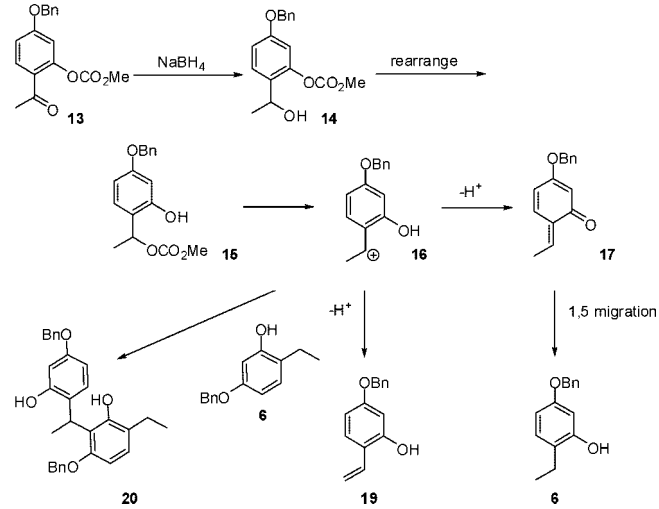
Scheme 4. **First-generation synthesis of API 1**



Although the first-generation synthesis of compound **1** provided multikilogram quantities in nine steps, control of reaction-critical process parameters was absent. This lack of detail for each step precluded complete impurity control. Therefore, process development of each step was investigated in order to understand each reaction sequence along with its impact on impurity control. Our process development focused on the following areas: (a) sodium borohydride/formate-mediated reduction of 2-hydroxyacetophenones, (b) the Suzuki−Miyaura cross-coupling, (c) selective S_NAr biaryl ether formation, (d) coupling of fragments **2** and **3**, and (e) further elucidation to the API.

Sodium Borohydride/Formate Reduction and Alkylation. Analysis of early lots of API found unacceptable levels (>0.1%) of impurities that originated from these first few steps of the synthesis. The main process impurities from this sequence were the styrene impurity **19**, the dimer **20**, and the bis-alkylated compound **21**. All three impurities were persistent throughout the rest of the synthesis and were difficult to remove during processing. The styrene and dimer compounds are formed during the quinone methide reduction as depicted in Scheme 5.

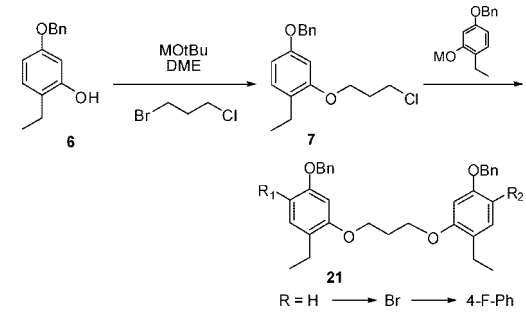
Scheme 5. **Mechanism of reduction and impurity generation**



(7) Stealey, M. A.; Shone, R. L.; Miyano, M. *Synth. Commun.* **1990**, *20*, 1869.
(8) Mitchell, D.; Doecke, C. W.; Hay, L. A.; Koenig, T. M.; Wirth, D. D. *Tetrahedron Lett.* **1995**, *36*, 5335.

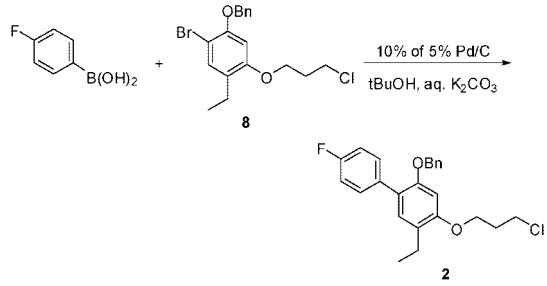
These impurities react in subsequent transformations and form additional impurities as well. Fortunately, the reduction impurities can be controlled by maintaining the addition rate to ensure sufficient borohydride is available for reaction. The bis-alkylated impurity **21** was routinely seen at ~3−5% levels during the alkylation reaction but could be controlled to <1% with careful crystallization of **7**. The control of **21** at this stage was important because, despite the fact that it is symmetrical, the reaction rates differed for the subsequent electrophilic bromination and Suzuki cross-coupling steps. As depicted in Scheme 6, if $R_1 \neq R_2$, this can give rise to a mixture of dimer impurities which proved difficult to reject downstream.

Scheme 6. **Formation of dimer impurity 21**



Suzuki−Miyaura Cross-Coupling. The final step required to complete the biaryl fragment was the Suzuki−Miyaura cross coupling of **8** with 4-fluorophenylboronic acid. Initially, Pd(0) was generated in situ from $Pd(OAc)_2$ and triphenylphosphine. This reaction was shown to be highly variable, depending on trace impurities in the arylbromide. Reaction completion could be achieved by adding more $Pd(OAc)_2$ and PPh_3, but control of residual metal became difficult and varied from >1000 ppm to ~20 ppm in the isolated products (Scheme 7). Recent communications have demonstrated the use of heterogeneous catalysis to effect similar couplings.[11] We found that Pd/C very cleanly produced the desired compound and controlled the Pd level to <20 ppm in the isolated biaryl fragment **2**.

Scheme 7. **Heterogeneous Pd coupling**



The heterogeneous coupling worked well with a variety of commercial hydrogenation catalysts in several solvents. Interestingly, the coupling did not work in DMF with solid K_2CO_3. Pretreatment of arylhalide **8** with Pd/C and filtration through a 0.45 μm filter before introduction of the boronic acid gave significant conversion (~15%) to the desired product, supporting other observations that these types of reactions are quasi-heterogeneous.[12] Very low levels of aryl halide homocoupling (<0.5%) was observed which could be further reduced with proper degassing. The choice of Pd/C catalyst was not crucial in this reaction (Figure 1). We found that either standard or eggshell dispersion catalysts were effective. Oddly, a higher Pd loading on the catalyst (10% vs 5%) did not increase the rate significantly, which also supports the theory that the forward reaction is due to a low level of dissolved Pd.

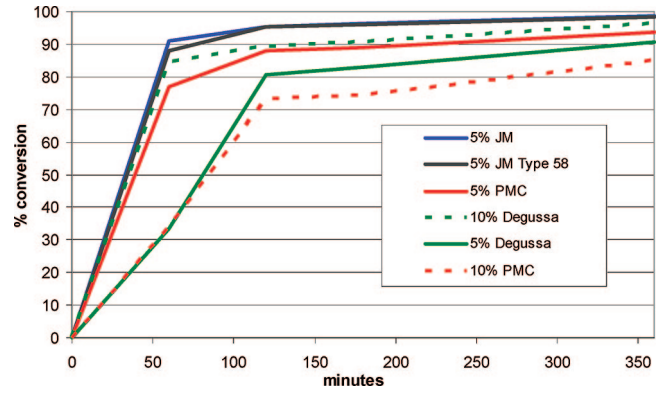


Figure 1. **Screen of different Pd/C catalysts.**

Several solvents were screened; the reaction worked well in alcohols with more than two carbons, but organic cosolvents such as toluene tended to slow the desired reaction (Figure 2).

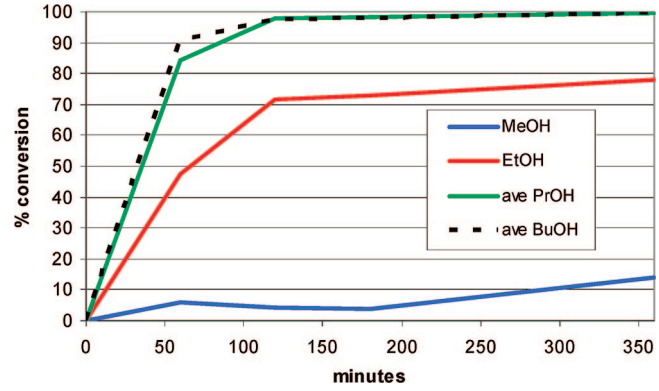


Figure 2. **Solvent effects on reaction completion (ave refers to the average of all isomers).**

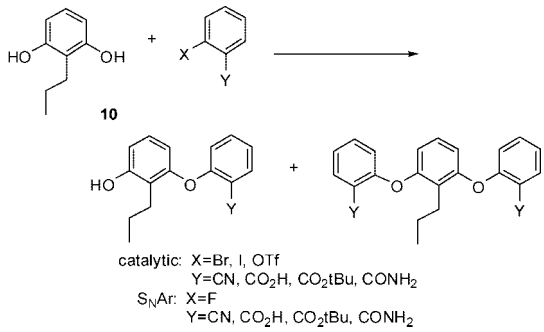
For ease of isolation we chose a biphasic solution of *tert*-butanol and 25% aq K_2CO_3 which allowed phase separation for removal of residual boronic acid.

Selective S_NAr Biaryl Ether Formation. The biaryl ether was originally made via a S_NAr reaction of 2-fluorobenzonitrile and 2-propyl resorcinol with NaH in DMSO. For environmental and safety reasons we were interested in exploring alternative systems to assemble this fragment. First, we wanted to confirm that these were the best fragments to bring together. Catalytic Buchwald−Hartwig conditions and additional S_NAr electrophiles were compared for selectivity and yield, and none were superior to 2-fluorobenzonitrile (Scheme 8).

This S_NAr reaction is a delicate balance between the reactivity needed for the acceptor and the selectivity of the bifunctional resorcinol to minimize impurity formation and

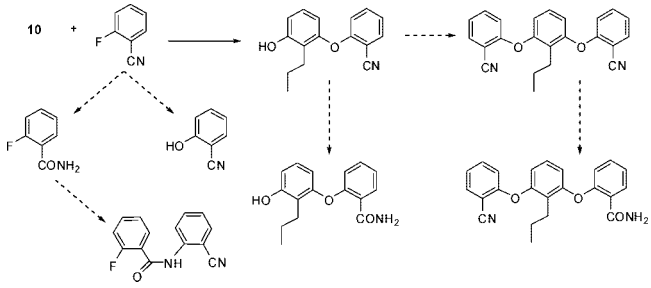
(9) (a) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2389. (b) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 853. (c) Jackson, W. T.; Froelich, L. L.; Gapinski, D. M.; Mallett, B. E.; Sawyer, J. S. *J. Med. Chem.* **1993**, *36*, 1726. (d) Sawyer, S. J.; Baldwin, R. F.; Saussy, D. L.; Froelich, L. L.; Jackson, W. T. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1985.

Scheme 8. **Alternative assembly of the aryl ether fragment**



maximize yield. We have identified several decomposition and/or side reactions that occur during the coupling (Scheme 9).

Scheme 9. **Impurity generation during S_NAr reaction**



A variety of bases and solvents were screened to take advantage of a counterion effect to increase selectivity (Table 1). The significant difference in response factors necessitated the use of in situ yield based on a standard curve to accurately assess each reaction. Not surprisingly, when hydrates were used, the 2-fluorobenzonitrile decomposed rapidly so that almost no product was formed. The use of KOH resulted in more decomposition of the 2-fluorobenzonitrile; however, the selectivity for product over dimer was ~10% higher, providing a significant yield increase.

Table 1. **Screen of bases in S_NAr reaction**

	in situ yield of product **3**	in situ yield of dimer	% dec F−CN
$Mg(OH)_2$	0.6	0.2	0.0
$Bu_4NOH \cdot 30\ H_2O$	1.2	0.3	94.5
$Me_4NOH \cdot 5\ H_2O$	12.6	0.1	89.8
LiOH	35.3	2.0	0.8
NaOH	79.9	11.0	1.7
$CsOH \cdot H_2O$	86.3	8.6	10.5
KOH	94.8	3.1	9.6
KOH w/PTC	97.5	2.5	4.8

At least 2 equiv of base is required to reduce dimer formation. With the use of 3 equiv of KOH, several solvents were screened for improved stability or selectivity (Table 2). NMP/DMSO was the only comparable result and was not likely to surpass pure DMSO.

Alkoxide bases and additional mixed toluene solvent systems were also tested and gave very high levels of dimer and inferior conversion. The data confirmed that KOH in DMSO are the preferred reaction conditions.[13] A fractional factorial was run to find optimal temperature, base equivalents, and reaction volumes (Figure 3). The reaction space that gave the highest yield was more dilute, with more base, at a lower temperature,

Table 2. **Screen of solvents in S_NAr reaction**

	in situ yield of pdt **3**	in situ yield of dimer	% dec F−CN
anisole	0.2	0.1	0.6
THF	0.4	0.2	1.2
IPA	1.1	0.2	56.2
diglyme	7.5	0.3	1.4
DMI	57.3	11.7	7.2
DMF	73.3	4.4	2.2
NMP	77.8	8.5	6.0
9:1 NMP/DMSO	81.7	9.5	3.5
DMSO	94.8	3.1	9.6

but these conditions resulted in more hydrolysis of the 2-fluorobenzonitrile. Since this may affect throughput, a careful cost analysis needs to be conducted before finalizing these conditions.

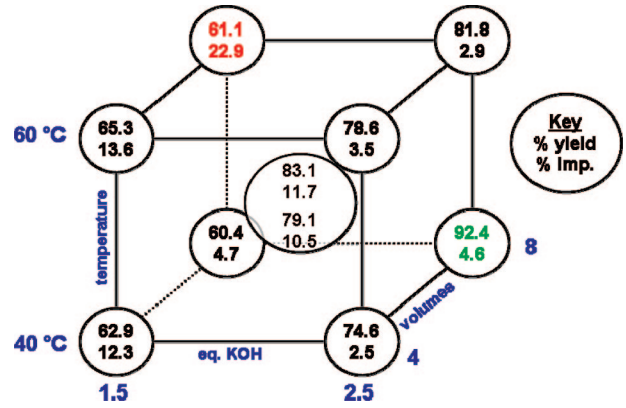
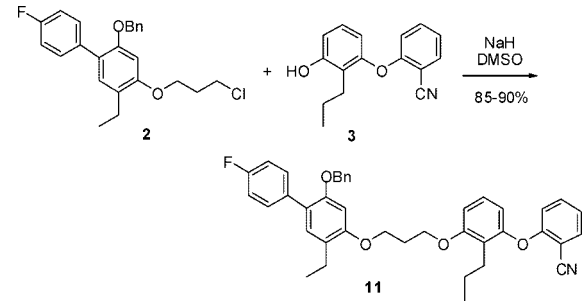


Figure 3. **Fraction factorial for S_NAr reaction.**

Coupling of 2 and 3. The convergence at step 7 is an ether formation to give the core structure of compound **1** (Scheme 10). This chemistry was also initially run in DMSO with NaH as the base.

Scheme 10. **Alkyl chloride coupling**



For environmental and safety concerns we needed to verify that these conditions were appropriate and address impurity control in this step. Hydrolysis of the nitrile, as seen in Step 6, is still a liability in this step (Scheme 11). The alkyl chloride of the biaryl fragment is also labile to hydrolysis or elimination. These process impurities were seen as high as 0.7% and 6.1%, respectively, under these conditions.

Alternative conditions of solvent, base, and temperature were screened. It was found that MeCN might be a suitable substitute for DMSO, but with it there is an additional liability of solvent hydrolysis giving acetamide, which is a known carcinogen.[14] There was no significant difference in the use of solid or

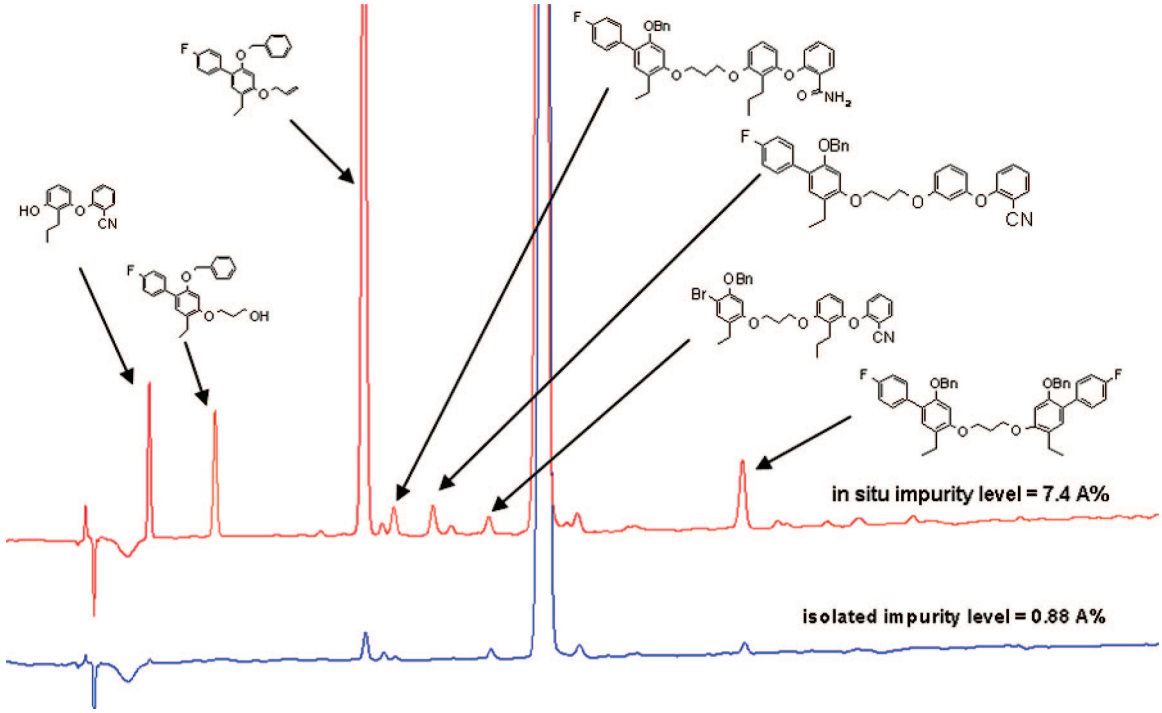
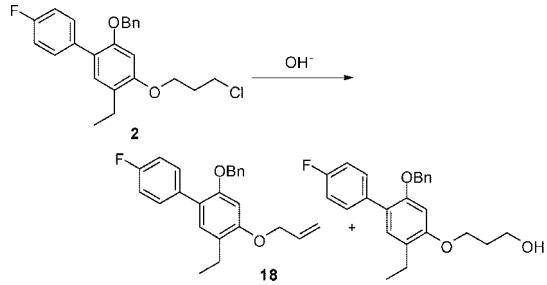


Figure 4. **Impurity rejection and control at coupled product 9.**

Scheme 11. **Impurity formation from alkyl chloride**



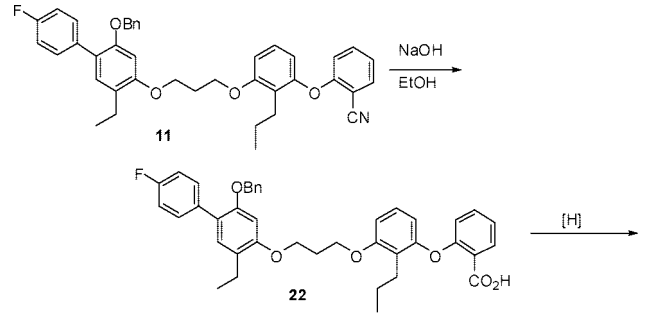
concentrated aqueous base solutions, but there was a 6% increase in yield for NaOH vs KOH. Alkoxide bases favored elimination to give the olefin **18** in a number of solvents and excess base led to the hydrolysis of the nitrile. Due to the nonpolar nature of the product, the isolation/purification was developed out of DMSO/methanol which effectively purges most of the impurities (Figure 4).

Further Elucidation to the API. The original process removed the benzyl protecting group by transfer hydrogenation and then hydrolyzed the nitrile. Due to the potential for oxidation of the free phenol and the harsh conditions needed to hydrolyze the nitrile, it was desirable to evaluate conversion to the acid and then benzyl protecting group removal (Scheme 12).

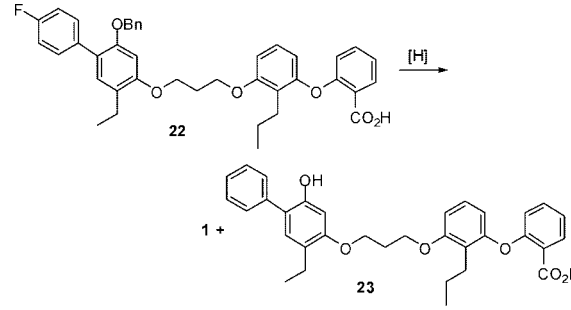
Amide hydrolysis was very straightforward in EtOH/NaOH with no side reactions or new impurities formed. During the hydrogenolysis of the benzyl group, the main impurity corresponded to defluorination (Scheme 13). This impurity was not eliminated during the isolation of **11** or subsequent salt formation.

The desfluoro impurity was seen sporadically from 0.04% to 5.14% when transfer hydrogenation was used. Initially, it was thought that catalyst type was responsible for its presence, but further experimentation revealed the same variability with a number of commercial catalysts. A likely explanation is

Scheme 12. **Preferred deprotection order**



Scheme 13. **Defluorination during hydrogenolysis**

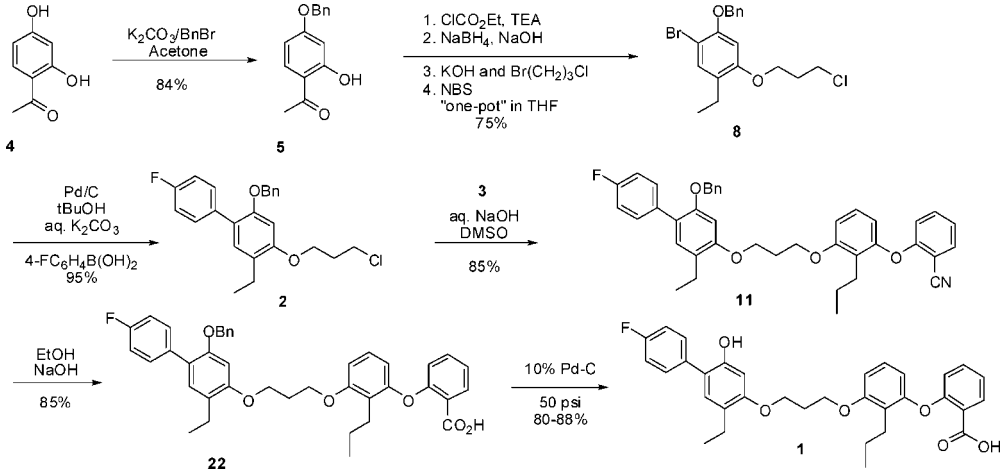


variability in the amount of reducing agent available for the desired reaction which may lead to "hydrogen-starved" conditions allowing oxidative insertion of the palladium.[15] While pressure hydrogenolysis (~50 psi) limits what equipment can be used, in this case it significantly reduced the level of defluorination. A screen of commercially available catalysts (5% Pd/C 50% wet) in several solvent combinations gave conditions that successfully eliminated the formation of **23**.

Conclusions

A robust synthesis of compound **1** has been developed. The synthetic robustness is attributable to improvements made in

Scheme 14. **Final synthesis**



the aryl ketone reduction, cross coupling, and aryl ether-forming transformations. The ketone reduction offers a strategy that circumvents a problematic purification requirement. In the cross-coupling, simplified catalyst systems that are readily available may be utilized. A S_NAr reaction was adopted for preparing the biaryl ether moiety.

In addition to the synthetic sequence each reaction parameter was examined to determine byproduct(s) formation. This investigation contributed to an overall impurity-control strategy along with addressing potential safety parameters. The above development resulted in a modified and improved process which provides compound **1** with six isolations in a 41% overall yield from **4** (Scheme 14).

Experimental Section

All reagents were obtained from commercial suppliers and used without further purification. Solvents, including tetrahydrofuran, *tert*-butylmethyl ether (MTBE), and dimethoxymethane, were used without drying or further purification. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR data were obtained on a QE-300 instrument. Elemental analyses were provided by the Physical Chemistry Department of the Lilly Research Laboratories. Due to the timing of the project, not all of the optimized procedures were scaled up to pilot scale; thus, the procedures below represent the largest-scale demonstration of these procedures.

4-Benzyloxy-2-hydroxyacetophenone (5). A slurry of compound **4** (45 kg, 295.8 mol), potassium carbonate (51.1 kg, 369.7 mol), and acetone (300 L) was stirred at 40−45 °C for 45 min. Benzyl bromide (50.6 kg, 295.8 mol) was added to the slurry and the resulting mixture stirred at 40−45 °C for 5 h. Progress of the reaction was monitored by HPLC (such as 4.6 × 25 cm Zorbax Rx-C8, acetonitrile/0.01 N sulfuric acid, 75/25 as eluent system; 1.0 mL/min). After being cooled to room temperature, 2 N hydrochloric acid was slowly added until the pH was 7.0−7.5. The mixture was cooled to 0 °C and then filtered. The resulting product cake was washed with water (149 L), isopropyl alcohol (225 L), and finally with heptane (225 L) to provide 58.6 kg (84%) of compound **5**, mp 101−103 °C. IR ($CHCl_3$) 3705, 3590, 2975, 1631, 1579, 1507, 1371, 1253, 1135, 1067 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.74 (s, 1 H), 7.62 (d, J =9.49 Hz, 1 H), 7.25−7.46 (m, 5 H), 6.54−6.50 (m, 3 H), 5.09 (s, 2 H), 2.57 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 202.6, 165.2, 135.9, 132.4, 128.7, 128.3, 127.5, 114.1, 108.1, 101.9, 70.2, 26.2; mass spectrum *m/z* (relative intensity) 242 (M^+, 100). Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.77; H, 5.34.

1-Bromo-2-(phenylmethoxy)-4-[(3-chloropropyl)oxy]-5-ethylbenzene (8). Ethyl chloroformate (53.3 kg, 491 mol) was added to a solution of THF (91 kg), triethylamine (50 kg, 500 mol), and compound **5** (91.0 kg, 375.6 mol) at 20−25 °C. Progress of the reaction was monitored by HPLC (such as 4.6 × 25 cm Zorbax Rx-C8, acetonitrile/ 0.01 N sulfuric acid, 65/35 as eluent system; 1.0 mL/min). The reaction mixture was stirred for 1 h at 20−25 °C before quenching with water (220 L). The organic portion was separated and added to a basic solution of $NaBH_4$ (30 kg, 793 mol); two additional portions of $NaBH_4$ were added (20 kg in 70 kg of water and 10 kg in 60 kg of DI water). These solutions were added to achieve

(10) Defluorination is discussed later in this paper, and there are safety concerns with ammonium carbonate plugging condensers upon scale up. For more information see: Slade, J.; Parker, D. J.; Girgis, M.; Mueller, M.; Vivelo, J.; Liu, H.; Bajwa, J. S.; Chen, G. P.; Carosi, J.; Lee, P.; Chaudhary, A.; Wambser, D.; Prasad, K.; Bracken, K.; Dean, K.; Boehnke, H.; Repič, O.; Blacklock, T. J. *Org. Process Res. Dev.* **2006**, *10*, 78.

(11) First example: Marck, G.; Villiger, A.; Buchecker, R. *Tetrahedron Lett.* **1994**, *35*, 3277. For a recent review see: Yin, L.; Liebscher, J. *Chem. Rev.* **2007**, *107*, 133.

(12) For an excellent discussion of the nature of these reactions see: Davies, I. W.; Matty, L.; David, L.; Hughes, D. L.; Reider, P. J. *J. Am. Chem. Soc.,* **2001**, *123*, 10139. Conlon, D. A.; Pipik, B.; Ferdinand, S.; LeBlond, C. R.; Sowa, J. R., Jr.; Izzo, B.; Collins, P. C.; Ho, G. J.; Williams, J. M.; Shi, Y. J.; Sun, Y. *Adv. Synth. Catal.* **2003**, *345*, 931.

(13) Although in Table 1 KOH with PTC gave slightly better results, it was not felt that the added complexity was worth the slight improvement in yield, especially since most of the yield loss was due to hydrolysis and not dimerization.

(14) Acetamide is listed by IARC as a Level IIb compound: "There is sufficient evidence in experimental animals for the carcinogenicity of acetamide." *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*; International Agency for Research on Cancer: Lyon, France, 1999; Vol. 71, pp 1211−1221.

(15) Similar phenomena have been noted by other groups; see: Brands, K. M. J.; Krska, S. W.; Rosner, T.; Conrad, K.; Corley, E. G.; Kaba, M.; Larsen, R. D.; Reamer, R. A.; Sun, Y.; Tsay, F.-R. *Org. Process Res. Dev.* **2006**, *10*, 109–117.

reaction completion. The biphasic solution was filtered and the aqueous layer discarded. To the organic layer was added 1-bromo-3-chloropropane (148 kg, 940 mol) and solid potassium hydroxide (33 kg, 825 mol). The mixture was heated at reflux for 3 h and reaction completion confirmed. The reaction mixture was cooled to <25 °C and phosphoric acid was added to adjust the pH to 6.5−7.5 before cooling to 0 °C. *N*-Bromosuccinimide (1.15 equiv) was added in portions while maintaining the temperature at less than 15 °C. After bromination was complete (as determined by HPLC), the mixture was treated with solid sodium sulfite until a negative starch/iodide test was obtained. At ambient temperature the slurry was filtered to remove insoluble salts, and the lower aqueous layer was separated. The organic layer was concentrated at atmospheric pressure until constant temperature reached 85 °C. Methanol was added, and additional distillate was removed. After more methanol was added, the solution was cooled to 30−35 °C and seeded, then cooled to 0−5 °C, filtered,and rinsed before drying overnight in vacuo at 35 °C. The yield was 36.6 kg (78%) of compound **8**, mp 55−57 °C. IR ($CHCl_3$) 2969, 2934, 2876, 1602, 1575, 1500, 1468, 1398, 1282, 1251, 1163, 1081, 1060, 1028, 887 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.55−7.28 (m, 7 H), 5.13 (s, 2 H), 4.03 (t, J = 5.78 Hz, 2 H), 3.73 (t, J = 6.30 Hz, 2 H), 2.54 (q, J = 7.55 Hz, 2 H), 2.20 (qn, J = 6.0 Hz, 2 H), 1.15 (t, J = 7.25 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.3, 153.7, 136.7, 132.7, 128.60, 128.0, 127.2, 102.9, 100, 71.5, 64.6, 41.5, 32.2, 22.4, 14.2; mass spectrum *m/z* (relative intensity) 384, 382 (M^+, 100); Anal. Calcd for C18H20BrClO2: C, 56.34; H, 5.25; Br, 20.82; Cl, 9.24; O, 8.34. Found: C, 56.62; H, 5.31; Br, 20.60; Cl, 9.03.

5-Fluorophenyl-4-benzyloxy-2-(3-chloropropyloxy)ethylbenzene (2). Compound **8** (53.1 g, 138.4 mmol), *tert*-butanol (5 vol), 4-fluorobenzeneboronic acid (20 g, 143 mmol), and aq 25% (w/w) K_2CO_3 (5 vol) were added to a reaction vessel. The resulting solution was degassed and heated to 80 °C before introduction of Pd/C as an aqueous slurry. The mixture was heated for 3 h and sampled for reaction completion (<99.5% conversion). Toluene (1 vol) was added and the mixture filtered to remove catalyst. The lower aqueous phase was separated and the organic layer washed with 25% K_2CO_3 (5 vol). The organic layer was concentrated to remove 3.5 vol before adding back methanol (3.5 vol). Distillation was continued at reduced pressure at 40−45 °C. After solvent exchange to MeOH was completed, the solution was cooled to 20 °C, and 3.5 vol of water was added and held for 1 h. The solid was filtered and dried in a vacuum oven at 40−45 °C to give compound **2** as a white solid, mp 63−65 °C. IR ($CHCl_3$) 2969, 1612, 1579, 1496, 1469, 1454, 1387, 1317, 1296, 1274, 12311, 1143, 1039, 839 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.6−7.46 (m, 2 H), 7.41−7.20 (m, 5 H), 7.15−7.05 (m, 3 H), 6.60 (s, 1 H), 5.04 (s, 2 H), 4.12 (t, J =5.74 Hz, 2 H), 3.78 (t, J = 6.31 Hz, 2 H), 2.62 (q, J = 7.47 Hz, 2 H), 2.28 (qn, J = 6.0 Hz, 2 H), 1.22 (t, J = 7.53 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.4, 160.11, 156.4, 154.4, 137.2, 134.5, 131.1, 128.5, 127.8, 127.0, 125.7, 122.7, 114.9, 114.6, 99.1, 71.3, 64.5, 41.6, 32.3, 22.7, 14.5; mass spectrum *m/e* (relative intensity) 398 (M^+, 100). Anal. Calcd for $C_{24}H_{24}ClFO_2$: C, 72.26; H, 6.06; Cl, 8.89; F, 4.76. Found: C, 72.27; H, 6.14; Cl, 9.45; F, 5.16.

3-(2-Cyanophenoxy)-2-propylphenol (3). To an appropriate reactor was added DMSO (214.7 g, 195 mL, 4 vol), 2-propylresorcinol (48.7 g), 2-fluorobenzonitrile (40.7 g, 35.7 mL, 1.05 equiv), and KOH (40.8 g, 2.0 equiv). The mixture was heated to 40 °C for 6 h. After cooling to 20 °C, DI water (633 mL) and Celite (6.3 g) were added. The mixture was filtered and the wet cake washed with 1:1 DMSO/DI water (40.7 g, 37 mL). To the filtrate was added 1.0 M HCl (319 mL, 1.0 equiv, 6.6 vol) over 3 h to pH 8.0−8.5, crystallizing the product. The product was filtered, washed with 1:1 DMSO/DI water (80.4 g, 73 mL, 1.5 vol), followed by DI water (3 × 65 g, 4 vol). The product was dried to a constant weight at 35−40 °C under vacuum (10 mBar), to afford **3** (62.0 g, 76.5% yield), mp 116−118 °C. IR ($CHCl_3$) 3601, 3008, 2965, 2934, 2233, 1600, 1577, 1495, 1449, 1280, 1248, 1161, 1108, 1097, 1037, 979 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.65 (dd, J = 7.5 Hz, J = 1.43 Hz, 1 H), 7.44 (dt, J = 7.11 Hz, J = 1.48 Hz, 1 H), 7.15−7.0 (m, 2 H), 6.77 (d, J = 8.51 Hz, 1 H), 6.70 (d, J = 8.0 Hz, 1 H), 6.54 (d, J = 8.1 Hz, 1H), 5.25 (s, 1 H), 2.59 (t, J = 7.42 Hz, 2 H), 1.57 (qn, J = 7.38 Hz, 2 H), 0.95 (t, 7.35 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.2, 155.6, 153.7, 134.4, 133.8, 127.1, 122.3, 121.7, 116.10, 116, 112.6, 112.4, 102.7, 25.7, 22.5, 14.10; mass spectrum *m/z* (relative intensity) 253 (M^+, 100). Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.77; N, 5.53. Found: C, 75.75; H, 5.79; N, 5.58.

2-[3-[3[[5-Ethyl-4′-fluoro-2-(phenylmethoxy)[1,1′-biphenyl]-4-yl]oxy]-propoxy]2-propoxylphenoxy]benzonitrile (11). A 25-mL three-necked round-bottomed flask was set up with an overhead mechanical stirrer, water-cooled condenser, thermocouple, heating mantle, and nitrogen inlet. To the flask was charged **2** (2.08 g, 0.00495 mol, 1 equiv), **3** (1.27 g, 0.00501 mol, 1.01 equiv), followed by DMSO (12 mL, 6 vol), and 50% NaOH (0.42 g, 0.00525 mol, 1.06 equiv). The mixture was stirred under a nitrogen purge for 1 min. The reaction solution was heated to 60 °C and stirred for 8 h. The reaction was then allowed to cool to room temperature and filtered through a fine scintered glass funnel to remove the precipitated salt. The reaction flask and the filter cake/funnel were rinsed with hot methanol (60 °C, 10 mL). The filtrate was transferred to a 50 mL three-necked round-bottomed flask equipped with an overhead mechanical stirrer, water-cooled condenser, thermocouple, heating mantle, and nitrogen inlet. To the flask was charged methanol (14 mL), and the solution was heated to 40 °C to ensure dissolution of any precipitated product. The solution was allowed to cool, and the crystallized product was isolated by suction−filtration and washed with cold methanol (5 °C, 15 mL). The product (**11**) was dried in vacuo at 60 °C overnight. Yield: 85%, mp 75−77 °C. IR ($CHCl_3$) 2965, 2952, 2871, 2226, 1604, 1577, 1496, 1449, 1317, 1251, 1116, 1060, 839 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.63 (dd, J = 7.75 Hz, J = 1.47 Hz, 1 H), 7.60−6.90 (m, 13 H), 6.77 (d, J = 8.04 Hz, 1 H), 6.72 (d, J = 8.65 Hz, 1 H), 6.58 (t, J = 3.5 Hz, 2 H), 5.0 (s, 1 H), 4.24−4.16 (m, 4 H), 2.61 (q, J = 7.70 Hz, 4 H), 2.35−2.28 (m, 2 H), 1.62−1.43 (m, 2 H), 1.20 (t, J = 7.43 Hz, 3 H), 0.89 (t, J = 7.32 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.3, 160.2, 158.4, 156.6, 154.4, 153.4, 137.1, 134.5, 134.1, 133.8, 131.1, 130.9, 128.5, 127.7, 127.2, 126.9, 125.7, 123.8, 122.5, 122.2, 116.1, 115.9, 114.9, 114.6, 112.9,

108.2, 99.0, 71.2, 64.59, 64.8, 29.5, 25.7, 22.7, 22.6, 14.5, 14.3; mass spectrum *m/z* (relative intensity) 615 (M^+, 100). Anal. Calcd for $C_{40}H_{38}FNO_4$: C, 78.03; H, 6.22; F, 3.09; N, 2.27. Found: C, 77.78; H, 6.22; F, 2.94; N, 2.36.

2-[3-[3[[5-Ethyl-4′-fluoro-2-hydroxyl[1,1′-biphenyl]-4-yl]oxy]-propoxy]2-propoxylphenoxy]benzoic Acid (1). To a methanolic (46 L) solution of compound **12** (2.3 kg, 4.39 mol) was added sodium hydroxide (12.5 M, 24 L). This reaction mixture was refluxed at 80 °C, for 12.5 h. After cooling to 5 °C, the reaction mixture was acidified to pH 0.44 with 12 N hydrochloric acid (20 L). Methyl *tert*-butyl ether (3 × 30 L) was used to extract the aqueous solution, and the combined extracts were concentrated to a residue. The residue was crystallized from acetonitrile (17.5 L) to provide 2.3 kg (99%) of **1** as a white solid, mp 68−70 °C. IR ($CHCl_3$) 3588, 3375, 2965, 2935, 2890, 1739, 1625, 1604, 1577, 1496, 1454, 1376, 1328, 1271, 1110, 1062, 843 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.23 (dd, $J = 7.86$ Hz, $J = 1.73$ Hz, 1 H), 7.55−7.05 (m, 7 H), 6.90 (s, 1 H), 6.81 (d, $J = 8.39$ Hz, 1 H), 6.71 (d, $J = 8.45$ Hz, 1 H), 6.62 (d, $J = 8.10$ Hz, 1 H), 6.55 (s, 1 H), 5.01 (br s, 1 H), 4.24 (t, $J = 6.27$ Hz, 2 H), 4.20 (t, $J = 6.22$ Hz, 2 H), 2.58 (m, 4 H), 2.4 (m, 2 H), 1.52 (m, 2 H), 1.17 (t, $J = 7.56$ Hz, 3 H), 0.90 (t, $J = 7.35$ Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.1, 163.8, 158.5, 157.7, 157.1, 152.5, 151.3, 134.9, 133.6, 133.3, 130.9, 130.8, 130.2, 127.5, 125.2, 124.2, 123.1, 118.9, 118.5, 116.3, 116.2, 113.2, 108.7, 99.7, 64.9, 64.3, 29.40, 25.8, 22.8, 22.7, 14.5, 14.2; mass spectrum *m/z* (relative intensity) 544 (M^+, 100). Anal. Calcd for $C_{33}H_{33}FO_6$: C, 72.78; H, 6.11; F, 3.49. Found: C, 72.76; H, 6.07; F, 3.22.

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