Imine-Directed Metalation of o-Tolualdehyde: The Use of Catalytic Amine Base. A Route to 2-(8-Phenyloctyl)benzaldehyde

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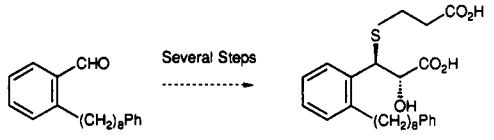
Much effort has been expended in the search for leukotriene antagonists in response to indications that leukotrienes are mediators in the biochemical sequence of events which give rise to asthma.[1] Intensive studies into the design and synthesis of potential antagonists has identified a series of [(phenyloctyl)phenyl]propionic acids that act as high affinity peptidoleukotriene antagonists. One of these, discovered within SmithKline Beecham, is SK&F104353 (2).[2] The first synthesis of 2 proceeded from 2-(8-phenyloctyl)benzaldehyde (1) *via* Darzen's chemistry, nonregioselective epoxide opening by thiopropionate anion and resolution with (*R*)-*p*-bromo-α-phenethylamine, giving the final product in low yield from aldehyde 1.[2] In addition, the original synthesis of 1 involved a lengthy sequence of reactions based on acetylene chemistry.[3] The use of these procedures to prepare the multikilogram quantities of SK&F104353 necessary to support the drug development process was clearly impractical, and this prompted the search for a more efficient synthesis.



1 2

Our objective was to establish a synthetic route to 1 which would be direct, efficient, low cost, and capable of producing multikilogram quantities. The two syntheses of 1 known at this time did not meet these criteria. One involved palladium-catalyzed cross-coupling of *o*-bromobenzaldehyde with 8-phenylocta-1,7-diyne derived from 6-hydroxyhex-1-yne, followed by hydrogenation.[3] The second involved addition of a Grignard reagent to an oxazoline derived from *o*-anisic acid, utilizing the methodology developed by Meyers. This approach required 1-bromo-8-phenyloctane, which was synthesized in five steps from cyclooctanone.[4] Our strategy was to use a "7 + 1" approach in constructing the phenyloctyl side chain in 1. We envisaged this could be achieved by functionalizing the methyl group of *o*-tolualdehyde and reacting it with a suitably terminally substituted phenylheptane. One such heptane is 1-bromo-7-phenylheptane (3), which is conveniently prepared in moderate (50%) yield by coupling benzylmagnesium chloride with excess 1,6-dibromohexane in the presence of a catalytic quantity of dilithium tetrachlorocuprate (Scheme 1).[5] We therefore required efficient methodology for coupling this precursor to *o*-tolualdehyde.

Functionalization of an aromatic methyl group can be facilitated by metalation in the presence of a number of different ortho substituents, as has been demonstrated with *o*-toluic acid,[6] *o*-toluamides,[7] 2-(*o*-methylaryl)oxazolines,[8] 2-(*o*-methylaryl)imidazolines,[9] and *o*-methylbenzylamines.[10] However, all of these substituents require additional chemical transformations if the desired product is an aromatic aldehyde. Other approaches have attempted to use simple aldehyde derivatives directly, and it has been shown that aromatic aldehydes can be substituted in the ortho position via *o*-lithiation using the directing groups 1,3-dimethylimidazolidine[11] and α-amino alkoxides.[12] Unfortunately, relatively expensive amines are required in these procedures (either *N,N'*-dimethyl- or *N,N,N'*-trimethylethylenediamine), as well as large excesses of base and alkylating agent. Both of these limitations were undesirable in our particular case.

Results and Discussion

In considering alternative aldehyde derivatives which might be suitable, we decided to examine the possibility that an imine might serve as an appropriate aldehyde equivalent, since they are easily prepared and readily converted to aldehydes by hydrolysis. However, it was known that in general, imines function poorly as ortho directing groups in aromatic ring metalations, the typical reaction pathway being nucleophilic addition of the organolithium base to the imine.[13] We reasoned that if such nucleophilic attack could be suppressed, an appropriate imine of *o*-tolualdehyde might metalate the *o*-methyl substituent successfully, due to the enhanced acidity of the benzylic protons. At the start of our work the use of imines in such an application had not been reported, although a publication describing a similar approach has recently appeared.[14] We selected the *tert*-butylimine of *o*-tolualdehyde (4), since we anticipated the steric bulk of the *tert*-butyl group might yield the best possibility for disfavoring nucleophilic attack. This imine was readily prepared in 93% yield by condensing *tert*-butylamine with

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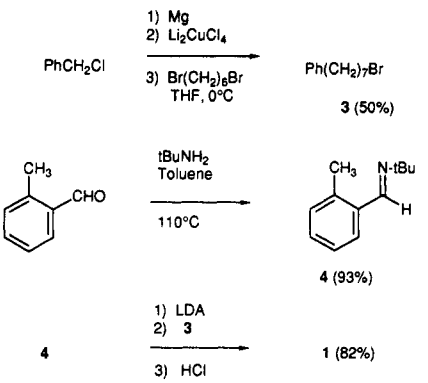
Scheme 1

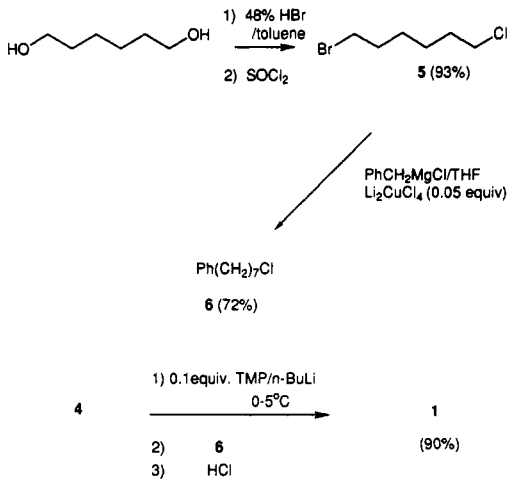


o-tolualdehyde under standard conditions (toluene, reflux). Furthermore, the imine 4 could be distilled *in vacuo* to give a product of high purity and could be stored for months with no sign of decomposition.

Treatment of imine 4 with lithium diisopropylamide [LDA] (1.0 equiv) in THF at −5 to 0 °C generated an anion, which was characterized by the generation of a deep purple solution. Treatment of the anion with bromide 3 (1.0 equiv) for an hour at 25 °C gave complete reaction (as determined by GC), at which point the anion color was discharged. Mild acid hydrolysis (aqueous 10% HCl, 0–25 °C) afforded aldehyde 1 in 82% yield, on the basis of the assay of the crude product. The high yield of 1 obtained showed that the hoped-for deprotonation of the methyl group of *o*-tolualdehyde *tert*-butylimine (4) is achieved extremely efficiently. This appears to contrast with a recent report wherein *o*-tolualdehyde, as its cyclohexyl imine, "gave incomplete metalation under a variety of conditions" with LDA.[14] We have shown that *o*-tolualdehyde cyclohexylimine is efficiently metalated with LDA under our conditions. We have formed the anion (1 equiv, −10 to 0 °C) and reacted it with bromide 3 to give 1 in 83% yield. These results demonstrate that under very mild and convenient conditions (avoiding low temperatures), deprotonation is specific and high yielding and allows elaboration of the methyl functionality. Our attempts to metalate 4 using alternate bases such as *n*-BuLi (with or without TMEDA), *s*-BuLi, and KH gave poorer yields.

This synthesis of 1 was satisfactory in most aspects except for the synthesis of 3 (Scheme 1). The moderate yield of 50% for 3 and the time factor involved in obtaining it pure by fractional distillation reduced its attractiveness for production of 3 on a commercial scale. These problems were circumvented by the more efficient synthesis[15] of an alternative precursor, 1-chloro-7-phenylheptane (6) (Scheme 2). However, reaction of the chloride 6 with the imine 4 anion under the conditions described for the bromo analogue 3 gave a very slow reaction, which was incomplete in 24 h, reflecting the lower reactivity of an alkyl chloride. What was more surprising was that on raising the temperature from 25 to 55 °C after the addition of chloride 6, all of 6 was consumed, but we only obtained a 45% yield

Scheme 2



of the required product; the major byproduct in this case was 7-phenyl-1-heptene, due to elimination of HCl.

It was clear to us at this point that the preparation of the chloride 6 according to Scheme 2 was a great deal more efficient than the preparation of the bromide 3 by Scheme 1, but that this benefit would only be realized if we could improve the yield of the subsequent alkylation step. Thus, controlling the reactivity of the imine anion to favor halide displacement instead of elimination became our major concern. The addition of inorganic salts (LiI, LiBr, $MgBr_2$) designed to acclerate the reaction through halogen exchange or the use of coordinating bases (e.g. TMEDA) to modify the nature of the anion in solution did not improve the yield. Alternative bases (*n*-BuLi, *s*-BuLi, lithium dicyclohexylamide, or LHMDS) similarly had no positive effect, except for the highly hindered LTMP where the yield was increased to 60%.

In thinking of other ways that the anion reactivity may be affected, we considered that the quantity of amine base used would be highly influential. It is well-known from the work of Seebach and others[16] that the reactivity of lithium carbanions, when generated using LDA, can be changed by removing the coordinating diisopropylamine to leave an "amine free" anion.[16] One way to generate a carbanion that is susbtantially free of amine is to use of a catalytic quantity, 10 mol %, of the secondary amine, in conjunction with an equivalent of alkyllithium. However, despite the fact that the effect of secondary amines on the reactivity of anions has been known for some time, the use of catalytic quantities of such secondary amines as outlined above has found surprisingly limited application in organic synthesis. To our knowledge the only reported instances are to facilitate the *o*-metalation of methoxypyridines[17] and, in the case of sp^3 carbon, the deprotonation of an *o*-toluamide and subsequent alkylation[18] and the generation of isobenzofuran from 3-methoxydihydroisochroman by elimination of methanol.[19] We decided to investigate this approach to the formation of imine 4 anion and examine the effect on its subsequent reactivity.

Our initial choice of amine base was tetramethylpiperidine (TMP) because it had given the highest yield to

(15) Our preparation of 5 is an extension of the synthesis of 6-bromohexan-1-ol reported by Sak-ku Kang *et al.* (*Synthesis*, **1985**, 1161) which used benzene for the azeotropic reflux with 48% HBr. Compound 5 has previously been synthesized by reaction of 6-chlorohexan-1-ol with PBr_3: Fusari, S. A.; Greenlee, K. W.; Brown, J. B. *J. Am. Oil Chemists' Soc.* **1951**, *28*, 416. Chloride 6 has been synthesized in low yield from the corresponding alcohol (Conant, J. B.; Kirner, W. R. *J. Am. Chem. Soc.* **1924**, *46*, 232) and by reaction of the Grignard from 1-chloro-4-phenylbutane and 3-chloropropyl *p*-toluene sulfonate (25% yield): Rossander, S. S.; Marvel, C. S. *J. Am. Chem. Soc.* **1928**, *50*, 1491.

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Table 1. Yield of 1 as a Function of the Temperature of Formation of Anion 4 and Amine Base

entry	temp (°C)	amine (mol %)	yield (%)
1	−5 to 0	10% TMP	87
2	25	10% TMP	86
3	−5 to 0	10% DIPA	55
4	25	10% DIPA	85
5	−5 to 0	10% dicyclohexylamine	48
6	25	10% dicyclohexylamine	83
7	−5 to 0	10% 2,5-dimethylpiperidine	72
8	20	10% 2,5-dimethylpiperidine	76
9	20	10% piperidine	67
10	0		45
11	25		77

date (60%) in the reaction of imine 3 with chloride 6. Using only a catalytic quantity of amine meant that nucleophilic addition was possibly a major side reaction. In order to minimize this, the anion was formed by the reverse process of adding *n*-BuLi (1.0 equiv) to a mixture of imine 4 and tetramethylpiperidine (0.1 equiv) at 0 °C over 1 h. Reaction of this mixture with the chloride 6 (0.83 equiv) at 55 °C gave complete consumption of 6 in 3 h. No major side products were observed (phenylheptene 3% by GC) and after hydrolysis aldehyde 1 was obtained in 90% yield. Furthermore a yield of 89% was obtained when TMP was used at the 0.01 mol % level. The effectiveness of this procedure is remarkable. The deprotonation of TMP by the organolithium must be a great deal faster that the nucleophilic addition to the imine, and regeneration of the TMP by deprotonation of the imine must also be fast. Finally, there is a pronounced difference in the reactivity of the anion formed. Not only does it enhance the reaction rate but it also favors alkylation over elimination, giving a dramatically improved yield (90% instead of 60%).

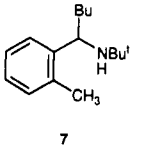
Extending the methodology to other amines gave varying results, and the temperature of anion formation had a profound effect on the effectiveness of the procedure (Table 1). In contrast to TMP (entry 1), diisopropylamine (DIPA) or dicyclohexylamine (0.1 equiv) under the same conditions of −5 to 0 °C gave only 45–50% yields (entries 3 and 5) of product 1. Considerable quantities of unreacted chloride 6 remained but little phenylheptene was formed, showing that elimination was not a problem under these conditions. Interestingly, when the temperature for the anion formation was raised to 25 °C with these bases, excellent yields of 1 were again obtained, 85 and 83%, respectively (entries 4 and 6). A similar temperature dependency was observed using *n*-BuLi with no added base, where the yields were 45 and 77% (entries 10 and 11). These differences in yield of 1 with temperature prompted us to investigate the formation of the imine 4 anion more closely. Under the conditions of formation for entry 3 (Table 1), if the imine 4 anion was quenched into water, analysis showed the presence of appreciable quantities of the addition products 7 and 8. These have been quantified and the results are shown in Table 2 (entry 1) along with the results for anion formation over a range of conditions. Entries 1 and 2 show that the difference in yield of 1 is due to the addition products 7 and 8 and consistent with the similar results (Table 1) showing a higher yield of 1 at higher temperatures. Of particular interest are the results where *n*-BuLi with no amine was used: at −50 °C 7 was the major addition product (entry 4) whereas at 0 °C 8 was the dominant addition component (entry 5). In addition, a smaller amount of the starting material 4 was consumed in formation of byproducts at

Table 2. Yields[a] of Addition Products 7 and 8 as a Function of Temperature of Formation of Anion 4

entry	temp (°C)	amine (mol %)	4 (%)	7 (%)	8 (%)
1	0	10% DIPA	68	10	22
2	25	10% DIPA	78.4	3.1	18.5
3	25	10% TMP	92.2	3.1	4.6
4	−50		62.9	33.8	1.4
5	−5 to 0		43.7	17.3	35.9
6	25		64.7	4.6	29.9

[a] Yields were determined by gas chromatography. All reactions were run for 3 h except for entry where the reaction was very slow. In this case the reaction was stopped after 5 h.

25 °C rather than 0 °C (entries 5 and 6). One possible explanation for this is that the presence of 7 and 8 could act as catalytic amine bases at the higher temperature and be the cause of the good yield of 1 in entry 11, Table 1. The results in Tables 1 and 2, which illustrate the dependence of yield of 1 with amine base and temperature, show there is a complex balance of rates for nucleophilic addition and deprotonation. Overall, TMP appears to be particularly effective as a catalytic amine base (Table 2, entry 3, and Table 1, entries 1 and 2).



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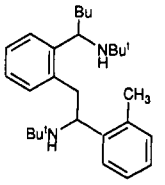

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Our work has demonstrated that *o*-tolualdehyde can be cleanly metalated and alkylated *via* its *tert*-butylimine, thus providing a direct and efficient synthesis of 2-(8-phenyloctyl)benzaldehyde. We have shown that the use of a catalytic amount of amine base can be used in conjunction with BuLi to generate the anion of imine 4, even though this imine is susceptible to nucleophilic attack by the organolithium. This "catalytic amine base" protocol gives an anion with profoundly different reactivity and selectivity to the corresponding anion prepared using a stoichiometric amount of lithium amide base. In our case, this led to substantially higher yields of the alkylated product on reaction with the alkyl halide 6. The temperature dependence of this "catalytic amine base" procedure has also been demonstrated with certain amines. Other applications of this "catalytic amine base" method are currently under investigation within our laboratories.

Experimental Section

Unless otherwise noted, reagents were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran, if used as a reaction solvent, was dried over 4A molecular sieves or used as supplied. All other solvents were obtained from commercial suppliers as reagent grade and were used without further purification. All nonaqueous reactions were performed under an atmosphere of dry nitrogen.

NMR spectra were recorded on JEOL GX 270, Bruker WM 360, or Bruker AM 400 spectrometers. Chemical shifts are reported in ppm (δ) downfield from tetramethylsilane. IR spectra were recorded on a Perkin-Elmer Model 283 infrared spectrophotometer. Combustion analyses were run on a Perkin-Elmer 240 C elemental analyzer.

1-Bromo-7-phenylheptane (3). To a stirred solution of 134.4 g (1.0 mol) of anhydrous copper(II) chloride in 3.0 L of tetrahydrofuran at ambient temperature was added 84.4 g (2.0 mol) of anhydrous lithium chloride in several portions. The dark-

red homogeneous solution was stirred at ambient temperature for 30 min, treated with 4.88 kg (20.0 mol) of 1,6-dibromohexane, and then cooled to −10 °C. While stirring vigorously and maintaining the reaction temperature at 0 °C, 5.0 L (10.0 mol) of 2 M benzylmagnesium chloride in tetrahydrofuran was added over a 2-h period. The reaction mixture was stirred at 0 °C for 90 min, and then the reaction was quenched carefully with 8.0 L of saturated aqueous ammonium chloride. The internal reaction temperature was kept below 30 °C during the quench. The layers were separated, and the organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo* at 45–50 °C to an amber oil. Purification by fractional vacuum distillation through a 12-in. vacuum jacketed Vigreux column gave 1276 g (50%) of the desired product as a colorless oil. An analytical sample was prepared by redistillation: bp 123–124 °C (1.5 mmHg) lit.[20] bp 110–114 °C (0.1 mmHg); IR (neat film) 3100–2800, 2000–1700, 1604, 1496, 748, 699, 644 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.29–7.16 (m, 5H), 3.40 (t, 2H), 2.60 (t, 2H), 1.88–1.81 (m, 2H), 1.63–1.60 (m, 2H), 1.43–1.32 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.70, 128.37, 128.23, 125.60, 35.90, 33.99, 32.77, 31.36, 29.07, 28.62, 28.08. Anal. Calcd for $C_{13}H_{19}Br$: C, 61.19; H, 7.50; Br, 31.31. Found: C, 61.25; H, 7.59; Br, 31.47.

***N*-[(2-Methylphenyl)methylene]-1,1-dimethylethanamine (4).**[21] A stirred solution of 810.0 g (6.67 mol) of *o*-tolualdehyde, 900.0 g (12.3 mol) of *tert*-butylamine, and 5.0 L of toluene was heated to reflux temperature. After 20 h at reflux, ^1H NMR analysis of a small aliquot indicated residual aldehyde. An additional 122 g (1.67 mol) of *tert*-butylamine was added and heating was continued for another 4 h. The reaction mixture was cooled to ambient temperature and concentrated *in vacuo*. Purification by vacuum distillation gave 1081 g (93%) of the desired product: bp 70–73 °C (0.6 mmHg); IR (neat film) 2980, 1690, 1605, 1210 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.56 (s, 1H), 7.86–7.83 (m, 1H), 7.25–7.11 (m, 3H), 2.46 (s, 3H), 1.30 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.7, 137.1, 135.1, 130.5, 129.6, 127.1, 126.4, 57.5, 29.8, 19.2.

1-Bromo-6-chlorohexane (5).[15] A mixture of 1,6-hexanediol (30 kg, 254 mol), 48% hydrobromic acid (51.0 kg, 302 mol), and toluene (508 L) was heated to reflux. Water (34.5 kg) was removed under azeotropic conditions. When distillation had ceased the mixture was cooled to 20 °C and extracted with a solution made up of concentrated hydrochloric acid (69.9 kg) and water (60 L). The phases were separated and the organic phase was dried by reheating and removing water by azeotropic distillation. The mixture was cooled to 65 °C and dimethylformamide (1.11 kg) added. Thionyl chloride (31.41 kg, 264 mol) was added over 45 min while maintaining the temperature between 65 and 68 °C. The mixture was heated to 109 °C over 1.25 h and cooled to 20 °C. It was then washed successively with 20% sodium hydroxide solution (100 L) and water (2 × 150 L, 1 × 100 L). Toluene (400 L) was removed under vacuum to leave the bromochlorohexane as a toluene solution (85.5 kg, 55% w/w by assay, 93% yield). The purity was 90% as determined by GC. An analytical sample was prepared by distillation (107–110 °C, 2 mmHg). ^1H NMR ($CDCl_3$, 270 MHz): 3.58–3.48 (t, 2H), 3.45–3.35 (t, 2H), 1.95–1.70 (m, 4H), 1.55–1.35 (m, 4H).

7-Chloro-1-phenylheptane (6).[15] A solution of lithium tetrachlorocuprate [THF (33 L), lithium chloride (0.87 kg, 19.3 mol), and cupric chloride (1.4 kg, 10.4 mol)] was added to a THF solution of benzylmagnesium chloride (160 L of 1.86 M, 298 mol) at 15 °C, and the mixture was stirred for 30 min. Chloride 5 in toluene (85.5 kg of solution, 55% w/w by assay, 47.1 kg, 236 mol) was added over 3 h while maintaining the temperature between 15 and 20 °C. Stirring was continued for a further 1.25 h. A 10% ammonium chloride solution (263 L) was added over 1 h, maintaining the temperature below 30 °C. The phases were separated and the organic phase was further washed with an ammonium chloride solution (170 L) and a 20% sodium chloride solution (3 × 197 L). The organic solution was concentrated under vacuum to leave an oil. This was purified by fractional distillation (129–132 °C, 2 mmHg) to give 36.0 kg (72.4% yield) of the product of 99% purity by GC. ^1H HMR ($CDCl_3$, 270 MHz): 7.35–7.1 (m, 5H), 3.55–3.45 (m, 2H × 5), 2.65–2.55 (t, 2H), 1.82–1.70 (m, 2H), 1.30–1.55 (m, 2H), 1.52–1.22 (m, 6H).

2-(8-Phenyloctyl)benzaldehyde (1).[3] **a. From Bromide 3.** A stirred solution of 292 g (2.89 mol) of diisopropylamine in 4.65 L of tetrahydrofuran was cooled to −5 °C and treated dropwise with 1.14 L (2.86 mol) of 2.5 M *n*-butyllithium in hexanes. The *n*-butyllithium was added at such a rate that the internal temperature was kept below 10 °C. After the addition was complete, the solution was stirred for 15 min while cooling back to −5 °C. A solution of 500 g (2.86 mol) of imine 4 in 600 mL of tetrahydrofuran was added dropwise at such a rate that the reaction temperature was kept below 5 °C. The deep purple solution of the anion was cooled to −5 °C and stirred for 15 min. A solution of 729 g (2.86 mol) of bromide 3 in 750 mL of tetrahydrofuran was then added fairly rapidly, such that the reaction temperature rose to 15–20 °C. The reaction was stirred for approximately 1 h with cooling (internal temperature returned to 0 °C), the cooling bath was removed, and stirring was continued for an additional 14 h at ambient temperature. The mixture was transferred via cannula into 2.5 L of cold (−5 °C) aqueous 10% hydrochloric acid. During the quench, the temperature of the aqueous hydrochloric acid rose to approximately 25 °C. The quenched reaction was stirred for 1 h with cooling (solution temperature returned to 0 °C), the cooling bath was removed, and stirring was continued at ambient temperature for 14 h. The reaction mixture was diluted with 5 L of dichloromethane and stirred for 5 min, and the layers were separated. The aqueous layer was extracted with 4 L of methylene chloride. The combined organic extracts were washed with two 5-L portions of aqueous 10% hydrochloric acid and 3.5 L of saturated aqueous sodium chloride and concentrated *in vacuo*. The resulting oil was passed through a 4-in. Pope still (100 °C, 0.2 mmHg) to remove unreacted *o*-tolualdehyde. The residue from this distillation was slurried for 10 min in 4 L of hexane, and the hexane was decanted away from insoluble material. The hexane slurry and decantation was repeated two times. The combined hexane washings were filtered through Celite and concentrated in vacuo to afford 725.1 g (92.4% purity, 82% yield) of the desired aldehyde. This material was generally used without purification in the synthesis of 2. For analytical purposes, a small sample was further purified by Kugelrohr distillation (oven temperature 250 °C, 0.1 mmHg): bp 250–255 °C (0.2 mmHg); IR (neat film) 2920, 2880, 1695, 1600, 1455 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 10.25 (s, 1 H), 7.80 (dd, 1 H, J = 1.2 and 7.7 Hz), 7.45 (m, 1 H), 7.33–7.13 (m, 7 H), 2.98 (t, 2H, J = 7.7 Hz), 2.58 (t, 2 H, J = 7.7 Hz), 1.58 (m, 4H), 1.30 (m, 8 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 192.2, 145.7, 142.8, 133.68, 133.59, 131.34, 130.89, 128.34, 128.17, 126.31, 125.51, 35.91, 32.434, 32.36, 31.44, 29.47, 29.38, 29.34, 29.23.

b. From Chloride 6. A stirred solution of imine 4 (11.2 g, 64 mmol) and 2,2,6,6-tetramethylpiperidine (0.9 g, 6.4 mmol) in tetrahydrofuran (40 mL) was cooled to −5 °C. To this was added *n*-BuLi (1.6 M, 40 mL, 64 mmol) over 60 min from a syringe pump such that the temperature was maintained below 0 °C. The mixture was stirred for 30 min and chloride 6 [11.23 g, 53 mmol (12.54 g of 89.5% pure material)] in tetrahydrofuran (20 mL) was quickly added. The reaction mixture was heated at 50–55 °C for 2 h. The reaction mixture was cooled to 40 °C and quenched by the slow addition of dilute hydrochloric acid (100 mL of concd acid diluted with 300 mL of water). Hydrolysis was completed by heating the mixture at 50–60 °C for 2.5 h. The mixture was cooled to ambient temperature and the organic phase was separated. The aqueous phase was extracted with hexane (100 mL) and the combined organic extracts were washed with water (100 mL). The extracts were dried over magnesium sulfate and after filtering and washing the filter cake with hexane, the organic solution was concentrated under vacuum to give 1 as an oil (14.5 g, 69.3% pure by HPLC assay, 87% corrected yield). This material can be purified by short path distillation (220 °C, 2 mmHg) to give 95% pure material in an 78% overall yield.

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