Organic Process Research & Development **2008,** *12,* 1137–1141

A Practical Synthesis of a Diazepinylbenzoic Acid, a Retinoid X Receptor Antagonist

Xinglong Jiang,* George T. Lee, Kapa Prasad,* and Oljan Repič

Process Research & Development, Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, New Jersey 07936, U.S.A.

Abstract:

An optimized convergent synthetic route for the preparation of retinoid X receptor (RXR) antagonist (1) in an overall yield of 35% is described. The formation of the benzodiazepine was achieved in 85% yield using $POCl_3$ in toluene. The drug substance 14 was obtained by treatment of aryl bromide with vinyl butyl ether in the presence of palladium acetate, DPPP, and cesium carbonate This one-pot operation incorporating three chemical transformations (i.e., Heck reaction, hydrolysis of vinyl ether, and hydrolysis of ester) was achieved in 85% yield.

Introduction

Retinoid X receptor (RXR) is a nuclear receptor which forms heterodimers with peroxisome proliferator-activated receptors (PPARs). Such complexes can be activated by a ligand of either RXR or subtype of PPARs. Since PPAR regulates lipid metabolism, the antagonists of RXR could in principle provide opportunity for the treatment of diabetes and other metabolic diseases.[1−3] Several compounds binding to RXR/PPAR heterodimers have been studied in animal models.[2] On the basis of this study, compound **14** was selected as a promising drug candidate for further development. As multikilo quantities were needed for full evaluation, we investigated alternative synthesis, and these results are presented in this communication.

Results and Discussion

Evaluation of the Research Synthesis. The original synthesis that was used by medicinal chemists[2a] for preparing small quantities of **14** is shown in Schemes 1 and 2. This synthesis, although convergent, is lengthy (14 steps) and too cumbersome to be of practical value. Steps involving *N*-alkylation using ethyl iodide (**5**→**6**), and the conversion of the methoxy group to a triflate function via a hydroxyl group (**19**→**10**→**11**) had to be avoided to make the synthesis more efficient. In addition, undesirables such as chromatographic purifications and the use of toxic solvents and reagents such as CCl_4, CH_2Cl_2, and $SnCl_2$ needed to be eliminated.

Retrosynthesis. On the basis of retrosynthetic analysis, a new route to **14** shown in Scheme 3 was proposed. By choosing compounds **21** and **22** as starting materials, two major drawbacks, i.e. *N*-alkylation using ethyl iodide and the transformation of methoxy group to a triflate, were avoided.

Synthesis of Side Chain 8. In the original route (Scheme 2) compound **15** was converted to **8** in four steps. By changing the sequence as shown in Scheme 4, side chain **8** was made in two steps. Thus, the treatment of commercially available **15** with 1.1 equiv of TMSCl in methanol afforded compound **24** in 97% isolated yield. Oxidation of **24** to the corresponding carboxylic acid **8** initially proved to be problematic. Different oxidation conditions[4] were tried for converting **24** to **8** with little success. By optimizing conditions reported by Sasson,[5] we found that **24** can be oxidized with bleach in the presence of $RuCl_3$/sodium bicarbonate/TBAB/2,2′-bispyridine in a solvent mixture of acetonitrile, water, and heptane. Although the yield of isolated carboxylic acid **8** was only 30%, the unreacted **24** was efficiently recycled. It is worth noting that compound **8** was isolated by adjusting the pH of the aqueous phase to 3−3.5 while the minor byproduct (diacid) formed during oxidation was left in the mother liquor.

Main Sequence. Initially, we tried to use the less expensive 2,5-dibromonitrobenzene in place of 2-fluoro-5-bromonitrobenzene **22** for coupling with **21**. Coupling conditions, such as Buchwald's amination[6] with Pd (I)-dimer and *t*-BuONa at 100 °C for 5 h and $Pd_2(dba)_3$ and Cs_2CO_3 in the presence of DPPF at reflux,[7] were explored, but no desired product was detected. Direct treatment of 2,5-dibromonitrobenzene with **21** at 100−150 °C for 5 h[8] or the reaction of 2,5-dibromonitrobenzene with lithium amide[9] formed by treatment of **21** with *n*-BuLi at −40 °C, gave only about 10% of the desired product **20**. This necessitated the use of 2-fluoro-5-bromonitrobenzene (**22**) as an alternative in the present study. Coupling of **22** with **21** at 100−150 °C for 5 h in the absence of solvent resulted in a 50% yield of **20**. However, when **21** was treated with *n*-BuLi

* Authors for correspondence. E-mail: prasad.kapa@novartis.com.

(1) (a) Hashimoto, Y.; Miyachi, H. *Bioorg. Med. Chem.* **2005**, *13*, 5080. (b) Deng, T.; Shan, S.; Li, Z.-B.; Wu, Z.-W.; Liao, C.-Z.; Ko, B.; Lu, X.-P.; Cheng, J.; Ning, Z.-Q. *Biol. Pharm. Bull.* **2005**, *28* (7), 1192.

(2) (a) Sakaki, J.; Kishida, M.; Konishi, K.; Gunji, H.; Toyao, A.; Matsumoto, Y.; Kanazawa, T.; Uchiyama, H.; Fukaya, H.; Mitani, H.; Arai, Y.; Kimura, M. *Bioorg. Med. Chem.* **2007**, *17*, 4804. (b) Wan, Y. J.; Han, G.; Cai, Y.; Dai, T.; Konishi, T.; Leng, A. S. *Endocrinology* **2003**, *144* (2), 605. (c) Yotsumoto, T.; Naitoh, T.; Kanaki, T.; Tsurszoe, N. *Metab. Clin. Exp.* **2005**, *54*, 573. (d) Lehmann, J. M.; Moore, L. B.; Smith-Oliver, T. A.; Wilkison, W. O.; Willson, T. M.; Kliewer, S. A. *J. Biol. Chem.* **1995**, *270*, 12953. (e) Hashimoto, Y. *Mini. Rev. Med. Chem.* **2002**, *2*, 543. (f) Kagechika, H. *Curr. Med. Chem.* **2002**, *9*, 591.

(3) Total Prevalence of Diabetes and Pre-diabetes; American Diabetes Association, **2007**; http://www.shapeupsf.org.

(4) (a) Smith, M. B.; March, J. Advanced Organic Chemistry, 2007; p 1745. (b) Asanuma, N.; Yamakawa, K. JP 2000256252 A 20000919 CAN 133: 222444 AN 2000: 653714.

(5) Sasson, Y.; Zappi, G. D.; Neumann, R. *J. Org. Chem.* **1986**, *51*, 2880.

(6) (a) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131. (b) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125. (c) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805.

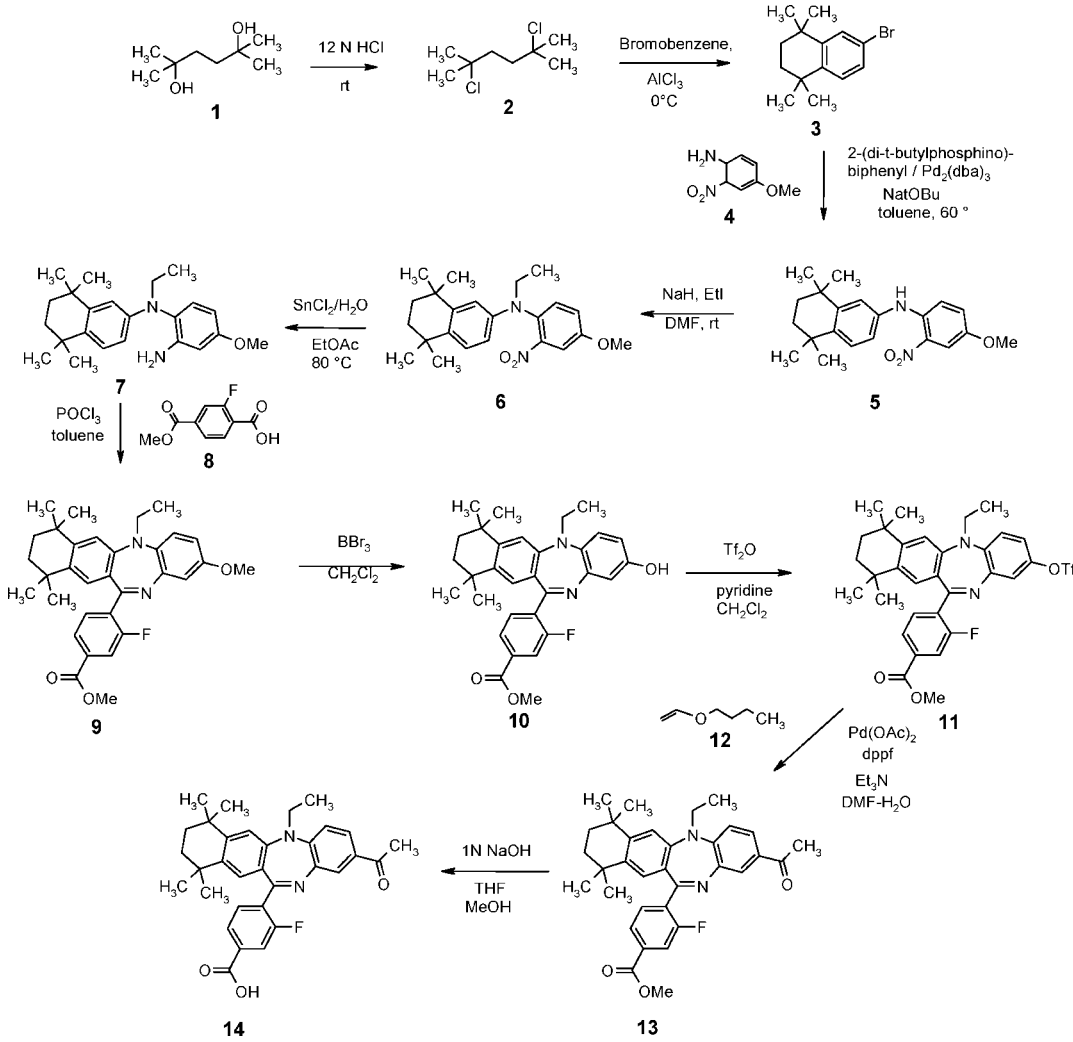
(7) (a) Beletskaya, I.; Bessmertnykh, A. G.; Guilard, R. *Synlett* **1999**, *9*, 1459. (b) Xu, Z.-B.; Lu, Y.; Guo, Z.-R. *Synlett* **2003**, *4*, 564.

(8) (a) Zhu, Y. F.; Lin, G. Q.; Chen, Y. Q. *Synthesis* **1990**, 430. (b) Schelz, D. *Helv. Chem. Acta* **1978**, *61* (7), 2452.

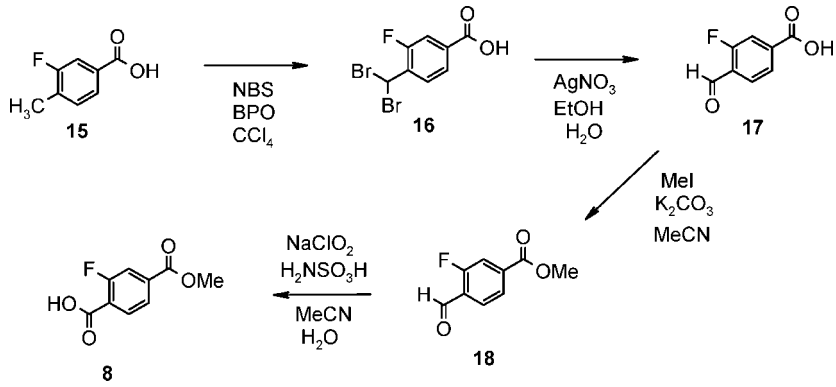
(9) Chakrabarti, J. K.; Hotten, T. M.; Pullar, I. A.; Tye, N. C. *J. Med. Chem.* **1989**, *32*, 2573.

10.1021/op800142b CCC: $40.75
Published on Web 09/23/2008

Scheme 1. **Research synthesis**



Scheme 2. **Research synthesis (cont.)**

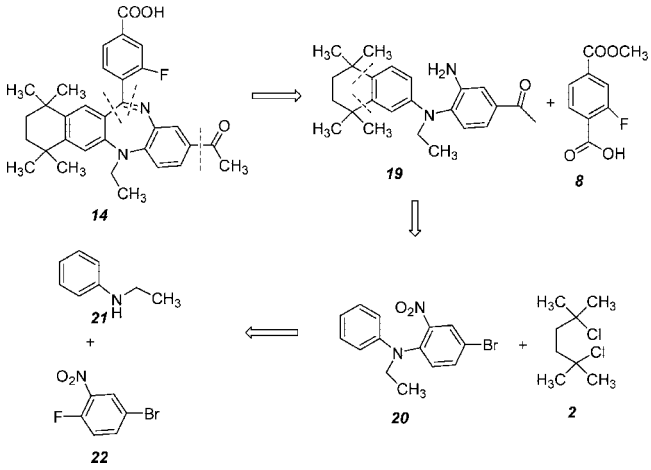


at −20 °C, followed by the addition of this lithium amide to **22** in THF, **20** was obtained in 90% yield. The above reaction was conducted by slowly adding lithium amide salt of **21** in THF (prepared by adding 1.3 equiv of *n*-BuLi at −20 °C) to **22** at −60 °C. Upon completion, the reaction was quenched by water and 2 N HCl. After recrystallization from isopropyl acetate and heptanes, **20** was isolated as a solid in 85% yield.

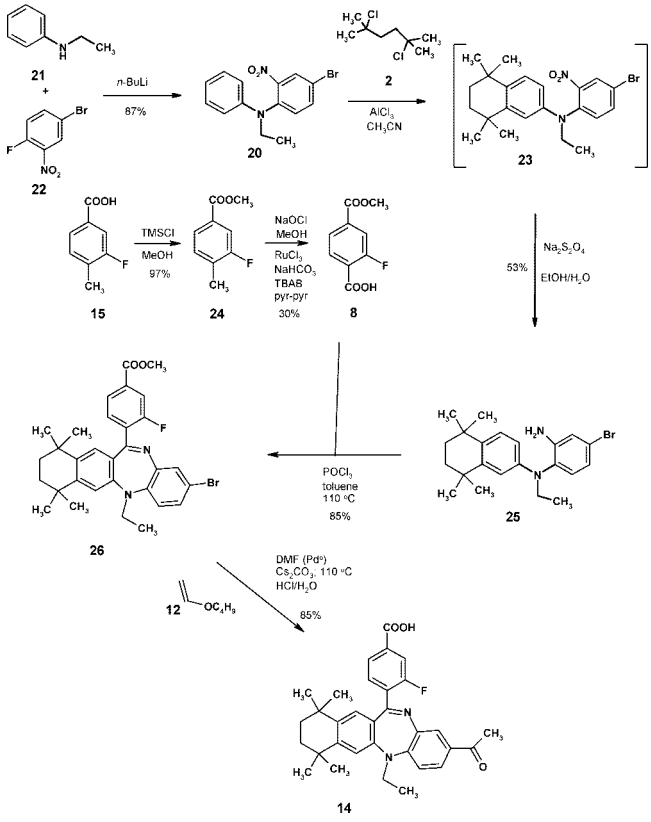
The double Friedel−Crafts alkylation[10] of **20** with 2,5-dichloro-2,5-dimethylhexane **2** proved to be problematic. Initial attempts to run this reaction in acetonitrile resulted in several byproducts although **20** was completely consumed. Attempted use of solvents such as toluene or $PhCF_3$ afforded very low conversion of **20** to **23** due to the precipitation of aluminium complex of compound **20** and aluminum chloride. On the basis of further optimization, the reaction was carried out by treatment of 1 equiv of **20** and 2 equiv of 2,5-dichloro-2,5-dimethylhexane **2** with 3 equiv of $AlCl_3$ in acetonitrile at 70 °C for 6 h. Initially, *i*-PrOAc was used to extract **23** from the reaction mixture, and this brought almost all impurities into the organic phase. Switching from *i*-PrOAc to heptanes resulted in removing most

(10) Hamada, Y.; Yamada, I.; Uenaka, M.; Sakata, T. PCT Int. Appl. WO 9114673 A1 19911003; CAN 116:105880; AN 1992: 105880, 1991.

Scheme 3. **Retrosynthesis of 14**



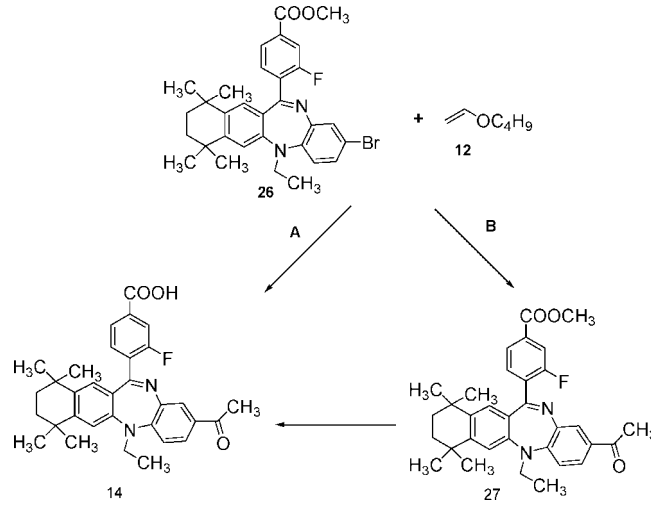
Scheme 4. **Current synthesis**



of the impurities, but some of the desired **23** was also lost in the tarry residue, resulting in low yield of **23**. Finally, toluene was used to extract **23** from the reaction mixture as most of the impurities remained in the aqueous phase. The crude product **23** was converted to **25** by reduction with sodium hydrosulfite[11] in ethanol and water at 75−80 °C. A little exotherm was observed by adding one portion of sodium hydrosulfite, but this could be overcome for a large-scale production by adding portions of sodium hydrosulfite. Recrystallization from ethanol/water (80/20, v/v) at 65 °C yielded pure **25** in a 53% overall yield from **20**.

(11) Kronenthal, D. R. B.; Bhandaru, R. S.; Shi, Z.; Mudryk, B. M. PCT Int. Appl. WO 2003041658; CAN 138:401763; AN 2003: 396674, 2003.

Scheme 5. **Possible routes to 14**



Benzodiazepine formation with $POCl_3$ has been reported; however, yields of products are generally low[12] under these conditions. With modified reaction conditions (i.e. the treatment of compounds **25** and **8** with 2.6 equiv of $POCl_3$ in toluene at 110 °C over 3−4 h and a careful quenching of the reaction mixture with ice−water) **26** was isolated in 85% yield.

Two possible alternatives were considered for transforming **26** to **14**. As shown in Scheme 5, alternative A is the one-pot reaction with three transformations, i.e. Heck coupling reaction, hydrolysis of vinyl ether and hydrolysis of methyl ester. On the other hand, alternative B is a stepwise transformation. Obviously, alternative A is more attractive since it is a one-pot operation.

The palladium-catalyzed arylation of vinyl butyl ether has been reported,[13] and the α- and β-regioselectivity has been shown to be dependent largely on the ligand and additives used for the reaction.[14] It has also been reported that aqueous DMF can accelerate the reaction.[15] On the basis of this information, we decided to couple **26** with vinyl butyl ether using 1,3-bis(diphenylphosphino)propane (DPPP) as the ligand in the presence of a base. Attempts to use triethylamine as a base in DMF afforded 40% of the desired product **14** after 3 days at 100 °C. Replacing triethylamine with cesium carbonate in DMF/water resulted in an 80% conversion at 100−116 °C in the presence of 5% $Pd(OAc)_2$. Increasing the catalyst loading from 5% to 8% dramatically reduced the reaction time from 20 to 8.5 h. A careful monitoring of the reaction progress by HPLC indicated that the Heck reaction was complete within 1 h with 8% $Pd(OAc)_2$, while it took more than 12 h with 5% $Pd(OAc)_2$. Also under these conditions it took about 6 h to hydrolyze the methyl ester to the corresponding carboxylic acid. After optimization of the reaction conditions, the reaction was carried

(12) Glamkowski, E. J.; Chiang, Y. *J. Heterocycl. Chem.* **1987**, *24*, 733.
(13) Hallberg, A.; Westfelt, L.; Holm, B. *J. Org. Chem.* **1981**, *46*, 5414.
(14) (a) Cabri, W.; Candiani, I.; Bedeschi, A.; Penco, S. *J. Org. Chem.* **1992**, *57*, 1481. (b) Xu, L.; Chen, W.; Ross, J.; Xiao, J. *Org. Lett.* **2001**, *3* (2), 295. (c) Larhed, M.; Anderson, C. M.; Hallberg, A. *Acta Chem. Scand.* **1993**, *47*, 212. (d) Grigg, R.; Loganathan, V.; Santhakumar, V.; Sridharan, V.; Teasdale, A. *Tetrahedron Lett.* **1991**, *32*, 687. (e) Karabelas, K.; Westerlund, C.; Hallberg, A. *J. Org. Chem.* **1985**, *50*, 3896.
(15) Vallin, K. S. A.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2001**, *66*, 4340.

out with 8 equiv of vinyl butyl ether and 8% $Pd(OAc)_2$ in the presence of DPPP at 116 °C in DMF/water, and the product **14** was isolated in 85% yield with >98% purity by HPLC. The Pd level could be reduced[16] from 1411 ppm to 8 ppm by pretreatment of *N*-acetylcysteine with 3 N NaOH, followed by addition of this solution into the suspension of the drug substance in EtOH at 40 °C.

Conclusions

The original synthesis of **14** from research was complicated by a long synthetic sequence (10 + 4 steps) and unacceptable reagents and intermediates, with a 10% overall yield. Our new synthesis described here is short (5 + 2 steps) with an overall yield of 35% and amenable to scale up. The drug substance **14** was obtained by treatment of compound **26** with vinyl butyl ether in the presence of palladium acetate, DPPP, and cesium carbonate in DMF/water at 110 °C. This one-pot operation incorporating three chemical transformations (i.e., Heck reaction, hydrolysis of vinyl ether, and hydrolysis of ester) was achieved in 85% yield.

Experimental Section

General. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. NMR spectra were recorded on a Bruker AVANCE DPX-300 spectrometer (^{1}H NMR and ^{13}C NMR at 300 MHz). HPLC method: Dynamax model SD-200; column: Symmetry, C18/5 μm, 4.6 mm × 250 mm; Flow rate: 1.0 mL/min; Eluents: A:B = 90%:10%, isocratic, A is water with 0.05% TFA (v/v), B is acetonitrile with 0.05%TFA (v/v). Retention times for compounds are as follows: **20**, 17.2 min; **23**, 29.6 min; **8**, 10.3 min; **25**, 28.5 min; **26**, 39.1 min; **14**, 18.4 min. Reactions were carried out under an atmosphere of nitrogen unless stated otherwise.

Preparation of Methyl 3-Fluoro-4-methylbenzoate 12. To a suspension of 3-fluoro-4-methylbenzoic acid **15** (250 g, 97% purity, 1.57 mol) and methanol (900 mL) was slowly added chlorotrimethylsilane (188 g, 1.7 mol) at 20−23 °C over 30 min. The hazy contents were warmed to 47 °C and refluxed at 47−52 °C for 30 min to give a homogeneous mixture. The reaction mixture was stirred at rt for 18 h. The mixture was concentrated at 35 °C *in vacuo* to a thick suspension. Isopropyl acetate (1.7 L) and saturated $NaHCO_3$ solution (420 mL) were added, and the mixture was stirred for 10 min. The top organic layer was washed with saturated NaCl aqueous solution (2 × 420 mL). The organic layer was separated and dried and concentrated at 55 °C *in vacuo* to give methyl 3-fluoro-4-methylbenzoate[17] as an off-white solid (257 g, 97% yield). ^{1}H NMR (300 MHz, CD_3OD) δ 2.32 (s, 3 H), 3.88 (s, 3 H), 7.34 (t, J = 7.9 Hz, 1 H), 7.50−7.78, (m, 2 H).

Preparation of 2-Fluoroterephthalic Acid 4-Methyl Ester 8. To a solution of methyl 3-fluoro-4-methylbenzoate **24** (200 g, 1.19 mol) in acetonitrile (1 L) were added ruthenium trichloride hydrate (2.4 g), 2,2′-bispyridyl (3.7 g, 23.8 mmol), tetrabutylammonium bromide (3.8 g, 11.9 mmol), and sodium bicarbonate (300 g, 3.57 mol). The mixture was cooled to 5 °C, and a 6% sodium hypochlorite aqueous solution (8.77 kg, 7.06 mol) was added at 7−10 °C over 15 min. The contents were stirred at 7−10 °C for 8 h. Heptane (2 L), saturated Na_2SO_3 solution (400 mL), and saturated Na_2CO_3 (150 mL) solutions were added in sequence at 10−20 °C to quench all unreacted sodium hypochlorite, and the pH of the mixture was adjusted to 10. The top organic layer was washed with saturated NaCl solution (300 mL) and concentrated at 50 °C *in vacuo* to recover methyl 3-fluoro-4-methylbenzoate (110 g) as a pale-yellow solid. The bottom aqueous layer was acidified slowly with conc HCl (37%) to pH 3−3.5. Isopropyl acetate (4 L) was added to the suspension, and the mixture was stirred for 5 min. The organic layer was separated and washed with saturated NaCl solution (500 mL) and water (200 mL). The organic layer was concentrated at 50 °C *in vacuo* to give **8** as a white solid (67 g, 30% yield). ^{1}H NMR (300 MHz, CD_3OD) δ 3.93 (s, 3 H), 4.95 (br, 1 H), 7.76 (dd, J = 11.1 Hz, 1.35 Hz, 1 H), 7.86 (dd, J = 1.50, 8.1 Hz, 1 H), 8.00 (t, J = 7.9 Hz, 1 H); ^{13}C NMR (300 MHz, CD_3OD) δ 53.57, 119.02, 124.95, 126.2, 133.92, 137.34, 161.54, 164.97, 166.80.

***N*-(4-Bromo-2-nitrophenyl)-*N*-ethylphenylamine, 20.** A 5-L flask was charged with ethylphenylamine **21** (141.57 g, 1.17 mol) and anhydrous tetrahydrofuran (THF, 2 L). The resulting solution was cooled to −20 °C, and 2.5 M *n*-BuLi in hexane (491.4 mL, 1.228 mol) was slowly added and solution was warmed to 10 °C. This solution was slowly added to another flask containing 2-fluoro-5-bromonitrobenzene **22** (198 g, 0.9 mol) in THF (500 mL, anhydrous) at −60 °C. The reaction was monitored by HPLC. After the reaction was completed, 2 N HCl (250 mL) and water (250 mL) were added and the product was extracted with isopropyl acetate (750 mL). The organic phase was washed with 2 N HCl (3 × 250 mL), water (250 mL), and brine (500 mL). The solvent was evaporated to give the crude compound **20** as dark-red solid (252 g) in 87% yield after recrystallization from *i*-PrOAc and heptanes(1 g of compound **20**/10 mL of *i*-PrOAc/15 mL of heptanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, J = 7.14 Hz, 3 H), 3.76 (q, J = 7.14 Hz, 2 H), 6.74 (d, J = 7.7 Hz, 2 H), 6.87 (t, J = 7.4 Hz, 1 H), 7.20 (m, 3 H), 7.23 (d, J = 5.28 Hz, 1 H), 7.25 (s, 1 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 13.0, 47.3, 116.2, 117.8, 121.7, 128.9, 129.2, 129.9, 136.6, 140.2, 146.3, 146.5; *m/e* (M + 1) = 322.

***N*-(4-Bromo-2-nitrophenyl)-ethyl-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-amine, 23.** A flask was charged with compound **20** (380 g, 1.18 mol), compound **2** (433.2 g, 2.37 mol, 2 equiv), and acetonitrile (700 mL). The suspension was stirred, and the temperature was dropped from 22 to 12 °C. Three equal portions of aluminum chloride (anhydrous, 473.3 g, 7.11 mol, 3.0 equiv) were slowly added and the temperature was raised to 65 °C. The reaction mixture was heated to 70 °C and maintained at this temp for 6 h. The reaction was monitored by HPLC until compound **20** was consumed completely. The cooled reaction mixture was slowly added to a flask containing toluene (3.0 L) and water (4.5 L). The phases were separated, and the organic phase was washed with water (1000 g), saturated $NaHCO_3$ (1.0 L), and brine (1.0 L) and was evaporated to dryness to give 465 g (91%, it

(16) Garrett, C.; Prasad, K. *Adv. Synth. Catal.* **2003**, *346*, 889.
(17) Gauuan, P. F.; Trova, M. P.; Gregor-Boros, L.; Bocckino, S. B.; Crapo, J. D.; Day, B. J. *Bioorg. Med. Chem.* **2002**, *10* (9), 3013.

contained 20−30% impurities) of the crude compound **23** which was used directly in the next step.

4-Bromo-*N*-ethyl-*N*-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzen-1,2-diamine, 25. A flask was charged with compound **23** (155 g, crude, 0.36 mol), ethanol (2.6 L, 95%), and water (800 mL). The resulting reaction mixture was heated to 75−80 °C, and sodium hydrosulfite (252 g, 1.44 mol, 4.01 equiv) was added in one portion. The reaction mixture was stirred at this temperature for 30 min and monitored by HPLC. After the completion of the reaction, the reaction mixture was extracted with ethyl acetate (750 mL) and washed with water (300 mL) followed by brine (300 mL). The solution was concentrated to give crude **25** as a semisolid. Dissolving the crude in ethanol (750 mL) at 65 °C, followed by adding water (175 mL) and cooling to 20 °C, afforded solids which were isolated by filtration to give 76 g of pure compound **25** in 53% yield based on **20**; mp: 123−124 °C; *m*/*z* (M + 1): 402; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (m, 15 H), 1.64 (s, 4 H), 3.57 (q, J = 6.96 Hz, 2 H), 3.85 (bs, 2 H), 6.39 (d, J = 5.85 Hz, 1 H), 6.56 (s, 1 H), 6.84 (d, J = 5.85 Hz, 1 H), 6.87 (s, 1 H), 6.92 (d, J = 8.64 Hz, 1 H), 7.10 (d, J = 8.64 Hz, 1 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 12.67, 31.82, 31.91, 33.41, 34.35, 35.20, 35.28, 44.67, 110.73, 112.03, 118.33, 120.22, 121.69, 127.14, 131.10, 131.37, 134.21, 145.06, 145.50, 145.98.

4-(2-Bromo-5-ethyl-7,7,10,10-tetramethyl-7,8-9,10-tetrahydro-5H-5,13-diazabenzo[4,5]cyclohepta[1,2-*b*]naphthalene-12-yl)-3-fluorobenzoic Acid Methyl Ester, 26. A flask was charged with **25** (120.42 g, 0.3 mol), **8** (59.46 g, 0.3 mol), and toluene (780 mL). $POCl_3$ (138 g, 0.90 mol, 3 equiv) was slowly added to the reaction mixture which was heated to 110 °C and held at this temperature for 4 h. The reaction mixture was cooled and slowly added to a flask containing ice (900 g) and water (600 g). After stirring for 2 h at 20 °C, the solids were filtered, washed with water (300 g), and dried at 55 °C for 16 h to give 144 g of compound **26** in 85% yield; mp: 145−146 °C; *m*/*z* (M+1) 563.5; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (s, 3 H), 1.03 (S, 3 H), 1.19 (s, 3 H), 1.24 (t, J = 6.9 Hz, 3 H), 1.28 (s, 3 H), 1.59−1.61 (m, 4 H), 3.50−3.59 (m, 1 H), 3.62−3.74 (m, 1 H), 3.96 (s, 3 H), 6.75 (s, 1 H), 8.83 (d, J = 8.8 Hz, 1 H), 6.85 (s, 1 H), 7.26 (s, 1 H), 7.45 (s, 1 H), 7.74 (dd, J = 2.25 Hz, 8.85 Hz, 1 H), 7.92 (s, 1 H), 7.84−7.95 (m, 1 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 13.09, 21.83, 31.33, 31.58, 31.63, 31.69, 33.70, 34.66, 34.76, 42.78, 52.54, 116.4, 117.2, 120.25, 125.09, 125.14, 128.16, 129.74, 130.39, 131.76, 133.26, 133.36, 140.35, 143.94, 145.56, 149.60, 152.05, 158.83, 162.19, 165.71, 166.44.

4-(2-Acetyl-5-ethyl-7,7,10,10-tetramethyl-7,8-9,10-tetrahydro-5H-5,13-diazabenzo[4,5]cyclohepta[1,2-*b*]naphthalene-12-yl)-3-fluorobenzoic Acid, 14. A flask was charged with compound **26** (112.7 g, 0.2 mol), cesium carbonate (195.5 g, 0.60 mol), DMF (835 mL), and water (111 mL). After purging the flask with nitrogen, palladium acetate (3.59 g, 16 mmol), DPPP (20.4 g, 48 mmol, 97%), and vinyl butyl ether **12** (160.4 g, 1.60 mol) were added. The reaction mixture was heated to 110 °C and maintained at this temperature for 2 h. Water (100 mL) was added, and the reaction was held at 110 °C for 7 h. The reaction was monitored by HPLC. The reaction mixture was cooled to <10 °C, and then 2 N HCl (600 mL), water (500 mL), and ethyl acetate (1000 mL) were added. The two layers were separated, and the organic phase was washed with water (2 × 200 mL) and brine (300 mL). The organic layer was concentrated to give 87 g of compound **14** in 85% yield; *m*/*z* (M + 1) 512.5; mp: 177−178 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.16 (s, 6 H), 1.21 (t, J = 7.6 Hz, 3 H), 1.22 (s, 3 H), 1.27 (s, 3 H), 1.55−1.58 (m, 4 H), 2.52 (s, 3 H), 3.52−3.70 (m, 1 H), 3.71−3.86 (m, 1 H), 6.77 (s, 1 H), 7.02 (s, 1 H), 7.16 (d, J = 8.49 Hz, 1 H), 7.72 (d, J = 8.5 Hz, 1 H), 7.78 (s, 1 H), 7.80 (dd, J = 8.5, 2.07 Hz, 1 H), 7.91−8.00 (m, 2 H), 13.00 (br, 1 H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 12.85, 26.51, 30.87, 31.07, 31.32, 33.25, 34.01, 34.15, 34.26, 40.26, 41.99, 116.37, 116.72, 119.09, 125.21, 126.81, 127.05, 127.82, 131.82, 132.17, 132.34, 132.57, 134.42, 139.95, 141.62, 148.99, 150.70, 158.09, 161.42, 165.11, 165.82, 196.42.

Removal of Residual Palladium. A flask was charged with 10 g of **14** (19.5 mmol) and 250 mL of ethanol (200 proof). The reaction mixture was heated to 40 °C, and a preprepared solution containing 3.5 g of *N*-acetylcysteine (21.4 mmol) and 20.8 mL of 3 N NaOH (62.4 mmol) was added. The mixture wasa stirred at 40 °C for 1 h, seeds of **14** were added, and the solution was cooled to 2−5 °C. The mixture was stirred and held at 2−5 °C for 1 h; solids were collected by filtration and washed with 50% ethanol in water. The solids were dried at 60 °C under vacuum for 16 h to give 8.5 g of **14** in 85% recovery yield; mp: 177−178 °C; Pd: 8 ppm.

Received for review June 19, 2008.

OP800142B