Synthesis of a Muscarinic Receptor Antagonist via a Diastereoselective Michael Reaction, Selective Deoxyfluorination and Aromatic Metal−Halogen Exchange Reaction

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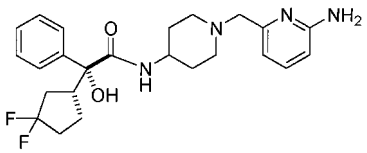
An efficient synthesis of a structurally unique, novel M_3 antagonist **1** is described. Compound **1** is conveniently disconnected retrosynthetically at the amide bond to reveal the acid portion **2** and the amine fragment **3**. The synthesis of key intermediate **2** is highlighted by a $ZnCl_2$−MAEP complex **19** catalyzed diastereoselective Michael reaction of dioxolane **7** with 2-cyclopenten-1-one (**5**) to establish the contiguous quaternary-tertiary chiral centers and a subsequent geminal difluorination of ketone **17** using Deoxofluor in the presence of catalytic BF_3·OEt_2. The synthesis of the amine moiety **3** is highlighted by the discovery of a novel *n*-Bu_3MgLi magnesium−halogen exchange reaction for selective functionalization of 2,6-dibromopyridine. This new and practical metalation protocol obviated cryogenic conditions and upon quenching with DMF gave 6-bromo-2-formylpyridine (**26**) in excellent yield. Further transformations afforded the amine fragment **3** via reductive amination with **35**, Pd-catalyzed aromatic amination, and deprotection. Finally, the highly convergent synthesis of **1** was accomplished by coupling of the two fragments. This synthesis has been used to prepare multi-kilogram quantities of the bulk drug.

Introduction

Over the past century classical muscarinic antagonists have been widely used for the treatment of certain diseases. However, their therapeutic applicability was limited, due to side effects in both the peripheral and central nervous system. In the past decade, this field has clearly been moving into the limelight due to the discovery of muscarinic receptors of distinctive subtypes, suggesting new therapeutic utility if ligands could be designed which selectively bind to each subtype. Five receptor subtypes have been so far identified and cloned (m1 to m5),[1] and among them, four receptor subtypes (m1 to m4) have been pharmacologically classified as M_1−M_4 on the basis of their response to selective antagonists. Our recent drug candidate (**1**) is a highly potent, orally active, long acting, selective M_3 antagonist and as such is being investigated for the treatment of chronic obstructive pulmonary diseases and urinary incontinence.[2]

In addition to the interesting biological profiles, **1** poses a number of interesting synthetic challenges including the contiguous quaternary-tertiary chiral centers as well as a *gem*-difluoro functionality. The heterocyclic amine portion contains no chiral centers; however, an economical and elegant synthesis is still a significant task. In this paper we describe an efficient and scalable synthesis of the target molecule **1** by virtue of the following discoveries: (a) a Zn−triamine complex catalyzed, highly diastereoselective Michael reaction that establishes both chiral centers in one operation, (b) a chemoselective deoxyfluorination reaction using the newly discovered reagent Deoxofluor and (c) a novel magnesium ate complex-induced metal−halogen exchange reaction which enables facile generation of a new, stable metallopyridine species at higher temperature.



1

I. Retrosynthetic Analysis

The final target compound **1** can be conveniently dissected at the amide bond to give two segments, the carbocyclic mandelic acid derivative **2** and the heterocyclic polyamine **3**. Typically, introduction of the *gem*-

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(1) (a) Kubo, T.; Fukuda, K.; Mikami, A.; Maeda, A.; Takahashi, H.; Mishina, M.; Haga, T.; Haga, K.; Ichiyama, A.; Kanagawa, K.; Kojiima, M.; Matsuo, H.; hirose, T.; Numa, S. *Nature* **1986**, *323*, 411−416. (b) Kubo, T.; Maeda, A.; Sugimoto, K.; Akiba, I.; Mikami, A.; Takahashi, H.; Haga, T.; Haga, K.; Ichiyama, A.; Kanagawa, K.; Matsuo, H.; Hirose, T.; Numa, S. *FEBS Lett.* **1986**, *209*, 367−372. (c) Peralta, E. G.; Ashkenawi, A.; Winslow, J. W.; Smith, D. H.; Ramachandran, J.; Capon, D. J. *EMBO J.* **1987**, *6*, 3923−3929. (d) Bonner, T. I.; Buckley, N.; Young, A. C.; Brann, M. R. *Science* **1987**, *237*, 527−532. (e) Bonner, T. I.; Young, A. C.; Brann, M. R.; Buckley, N. J. *Neuron* **1988**, *1*, 403−410.

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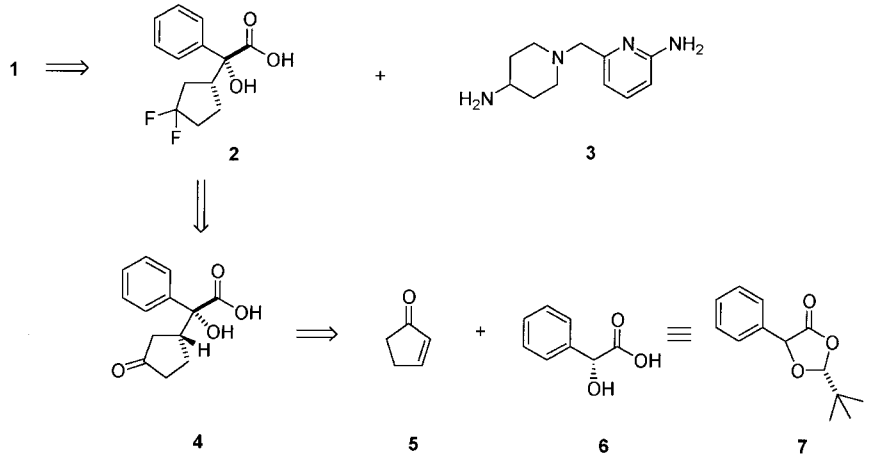
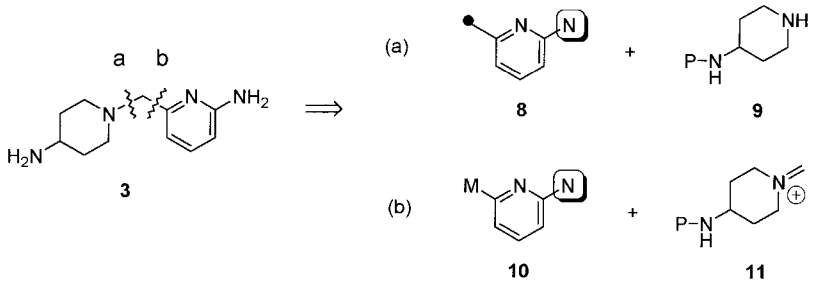
Scheme 1



Scheme 2



difluoro functionality could be envisioned by one of the following three ways:[3] (1) a fluorinated building block, (2) an electrophilic fluorination process,[4] or (3) a nucleophilic fluorination of a carbonyl group. We envisioned the latter approach to be the most efficient, thus generating the advanced ketone intermediate **4**, with its contiguous quaternary and tertiary chiral centers. Application of a retro-Michael transformation to ketone **4** generates the optically active mandelic acid (**6**) and the commercially available 2-cyclopenten-1-one (**5**) starting materials. In the forward, synthetic direction this analysis suggests the use of the Seebach chiral dioxolane **7**[5] as an appropriate functionalized Michael partner with 2-cyclopenten-1-one (**5**) (Scheme 1).

Our retrosynthetic analysis (Scheme 2) of the amine segment **3** reveals two key potential end game disconnections, (a) the C−N bond or (b) the C−C bond. The former suggests alkylation of the protected aminopiperidine **9** with a properly functionalized pyridine **8** by either reductive amination (with an aldehyde, R = CHO) or a simple N-alkylation type displacement (R = CH_2X). The C−C bond formation approach suggests a sequential homologation of **9**, for example via initial formation of the iminium cation **11** followed by treatment with a metalated pyridine **10**[6] (i.e., the Petasis protocol (M = $B(OH)_2$).[7] The aminopyridine moieties **8** or **10** could, in turn be made from the readily available and inexpensive 2,6-dibromopyridine (**13**) or 2-amino-6-picoline (**14**). In the case of **13**, the amino group on the pyridine ring could potentially be introduced by a transition metal catalyzed aromatic amination.

II. Synthesis of the Mandelic Acid Fragment 2

A. Synthesis of the Mandelic Acid Acetal 7. The preparation of acetal **7** from mandelic was readily accomplished in the laboratory at kilogram scale according to the literature procedure.[8] (*R*)-Mandelic acid (**6**), pivalaldehyde, and a catalytic amount of *p*-toluenesulfonic acid were heated at reflux in pentane while water was azeotropically removed by means of a Dean−Stark apparatus. The resulting solid was filtered and triturated in pentane at ambient temperature to afford the product

(2) (a) Mitsuya, M.; Kobayashi, K.; Kawakami, K.; Satoh, A.; Ogino, Y.; Kakikawa, T.; Ohtake, N.; Kimura, T.; Hirose, H.; Sato, A.; Numazawa, T.; Hasegawa, T.; Noguchi, K.; Mase, T. *J. Med. Chem.* **2000**, *43*, 5017−5029. (b) Mitsuya, M.; Ogino, Y.; Kawakami, K.; Uchiyama, M.; Kimura, T.; Numazawa, T.; Hasegawa, T.; Ohtake, N.; Noguchi, K.; Mase, T. *Bioorg. Med. Chem.* **2000**, *8*, 825−832. (c) Mitsuya, M.; Mase, T.; Tsuchiya, Y.; Kawakami, K.; Hattori, H.; Kobayashi, K.; Ogino, Y.; Fujikawa, T.; Satoh, A.; Kimura, T.; Noguchi, K.; Ohtake, N.; Tomimoto, K. *Bioorg. Med. Chem.* **1999**, *7*, 2555−2567. (d) Mitsuya, M.; Kawakami, K.; Ogino, Y.; Miura, K.; Mase, T. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2037−2038.

(3) Tozer, M. J.; Herpin, T. F. *Tetrahedron*. **1996**, *52*, 8619−8683.

(4) (a) Konas, D. W.; Coward, J. K. *Org. Lett.* **1999**, *1*, 2105−2107. (b) Lal, G. S.; Pez, G. P.; Syvret, R. G. *Chem. Rev.* **1996**, *96*, 1737−1755.

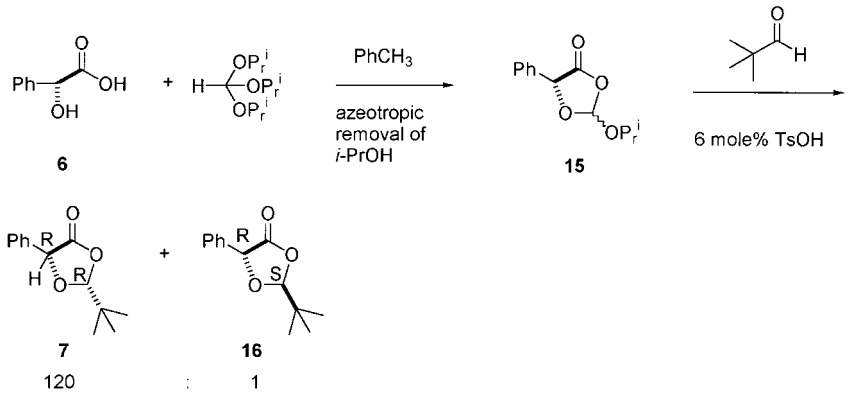
(5) Seebach, D.; Naef, R.; Carderari, G. *Tetrahedron* **1984**, *40*, 1313−1324.

(6) For classical iminium approaches: review, see (a) Kleinman, E. F. *Comprehensive Organic Synthesis*; Trost B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; vol. 2, pp 893−951. (b) Heaney, H. *Comprehensive Organic Synthesis*; Trost B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; vol. 2, pp 953−973. (c) Kleinman, E. F.; Volkmann, R. A. *Comprehensive Organic Synthesis*; Trost B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; vol. 2, pp 975−1006.

(7) (a) Petasis, N. A.; Akritopoulou, I. *Tetrahedron Lett.* **1993**, *34*, 583−586. (b) Petasis, N. A.; Zavialov, I. *J. Am. Chem. Soc.* **1997**, *119*, 445−446. (c) Petasis, N. A.; Zavialov, I. *J. Am. Chem. Soc.* **1998**, *120*, 11798−11799. (d) Harwood, L. M.; Currie, G. S.; Drew, M. G. B.; Luke, R. W. A. *Chem. Commun.* **1996**, 1953−1954.

(8) Several methods exist in the literature for the synthesis of lactic and mandelic acid dioxolanones: (a) Seebach, D.; Naef, R. *Helv. Chim. Acta*. **1981**, *64*, 2704−2710 and references therein. (b) Ortholand, J. Y.; Vicart, N.; Greiner, A. *J. Org. Chem.* **1995**, *60*, 1880−1884. (c) Ott, J.; Ramos Tombo, G. M.; Schmid, B.; Venanzi, L. M.; Wang, G.; Ward, T. R. *Tetrahedron Lett.* **1989**, *30*, 6151−6154.

Scheme 3



in 85% yield as a single diastereomer. Unfortunately, safety considerations precluded the use of pentane at pilot plant scale and mandated the discovery of new methodology for this condensation. Unfortunately, simple replacement of pentane with safer and higher boiling solvents gave rather poor ratios of **7**:**16**, making the isolation of the desired diastereomer challenging. Therefore, we explored a chemical rather than azeotropic means for removal of water in the acetal formation.

Reaction of (*R*)-mandelic acid **(6)** with triisopropyl orthoformate in toluene at ambient temperature afforded intermediate **15** as an equilibrium mixture with the starting acid (**15**:**6** = 4:1). Distillation under vacuum effectively removed *i*-PrOH, thus driving the reaction to completion and producing **15** as a mixture of anomeric isomers. Addition of pivalaldehyde and a catalytic amount of TsOH−H_2O (6 mol %) at ambient temperature afforded **7** and **16** in ratios exceeding 120:1 in favor of the desired isomer. Trituration from *n*-heptane then gave **7** as a pure diastereomer in 92% yield (Scheme 3). This impressive stereochemistry appears to be kinetic in origin and will be discussed in more detail elsewhere.

B. Synthesis of the Michael Adduct 17. Over the last two decades, study of the Michael reaction has been intense since appropriate design and implementation of the reaction affords a C−C bond and potentially two contiguous chiral centers.[9] The Heathcock group[10] and others,[11] in a series of elegant papers, have systematically addressed the mechanistic characteristics for the stereochemical course. However, the methodologies to construct contiguous stereogenic centers enantio- and diastereoselectively in one operation are limited.[9,14] Furthermore, the general strategy for complex substrates targeting pharmaceutical drugs and natural products is still to be established due to the fact that the stereoselectivity significantly depends on effects of enolate counterions, additives, solvents, and temperature. Therefore, we first screened representative metal enolates to find an appropriate metal counterion for our system (Table 1). As illustrated in Table 1, in all cases, as expected, the facial selectivity at the quarternary center was excellent (less than 10% **17b** was generated in all reactions).[12] It was also encouraging that the competing 1,2-addition to cyclopentenone **5** was not observed. However, the intrinsic diastereoselectivity of the reaction, as observed with Li, Na, K, Zr enolates, all favored the undesired isomer **17a**.[13] In an attempt to investigate the effects of noncoordinating or coordinatively saturated metals, the silyl ketene acetal (**enol-7**; M = SiR_3) was synthesized and reacted with **6** in the presence of Lewis acids.[10a,14] Interestingly, the results of this approach were unsatisfactory (entries 8−11), as the maximum ratio obtained was a marginal 2:1 favoring the desired compound. The best selectivity (**17**:**17a**) was achieved by the use of a Zn-enolate (entry 7), which gave a 3:1 ratio, favoring the desired product **17**.[15] It is intriguing to compare the difference between entries 4 and 5, both of which arise from Zr-enolates. With plain $ZrCl_4$, an unfavorable ratio of 1:3.2 was obtained, and with the use of Cp_2ZrCl_2, the ratio improved to 2.8:1. While it is not surprising that a conformational change in the Zr-enolate, by the introduction of the Cp ligand, could result in a different diastereoselectivity, the magnitude of the difference (ca. 9-fold) is quite significant. Thus, since the Zn-enolate gave the best selectivity in the screening experiments, we focused our efforts on the use additive ligands to further improve the selectivity.

The Zn-enolate was generated by addition of a sieve-dried solution of $ZnCl_2$ in THF to the Li-enolate at <−35 °C (eq 1). Addition of 1 equiv of TMEDA had no effect on

(9) (a) Schmalz, H.-G. *Comprehensive Organic Synthesis*; Semmelhach, M.; Trost, B. M., Eds.; Pergamon Press: Oxford, 1991; vol. 4, pp 199−236. (c) Evans, D. A.; Bilodeau, M. T.; Somers, T. C.; Clardy, J.; Cherry, D.; Kato, Y. *J. Org. Chem*. **1991**, *56*, 5750−5752. (d) Payne, S. G.; Dong, G.; Skelton, G. W.; White, A. H. *J. Org. Chem*. **1997**, *62*, 2337−2343. (e) Yasuda, K.; Shindo, M.; Koga, K. *Tetrahedron Lett*. **1997**, *38*, 3531−3534. (f) Aitken, R. A.; Thomas, A. W. *Synlett* **1998**, 102−104. (g) Yoshizaki, H.; Tanaka, T.; Yoshii, E.; Koizumi, T.; Takeda, K. *Tetrahedron Lett*. **1998**, *39*, 47−50. (h) Corey, E. J.; Noe, M. C.; Xu, F. *Tetrahedron Lett*. **1998**, *39*, 5347−5350. (i) Corey, E. J.; Houpis, I. N. *Tetrahedron Lett*. **1993**, *34***,** 2421−2424.

(10) Heathcock, C. H.; Norman, M. H.; Uehling, D. E. *J. Am. Chem. Soc*. **1985**, *107*, 2797−2799. (b) Heathcock, C. H.; Oare, D. A. *J. Org. Chem*. **1985**, *50*, 3022−3024. (c) Heathcock, C. H.; Henderson, M. A.; Oare, D. A.; Sanner, M. A. *J. Org. Chem*. **1985**, *50*, 3019−3022. (d) Oare, D. A.; Henderson, M. A.; Sanner, M. A.; Heathcock, C. H. *J. Org. Chem*. **1990**, *55*, 132−157. (e) Oare, D. A.; Heathcock, C. H. *J. Org. Chem*. **1990**, *55*, 157−172. (f) Stafford, J. A.; Heathcock, C. H. *J. Org. Chem*., **1990**, *55*, 5433−5434.

(11) For a theoretical study see: Bernardi, A.; Capelli, A. M.; Comotti, A.; Gennari, C.; Scolastico, C. *Tetrahedron Lett*. **1991**, *32*, 823−826.

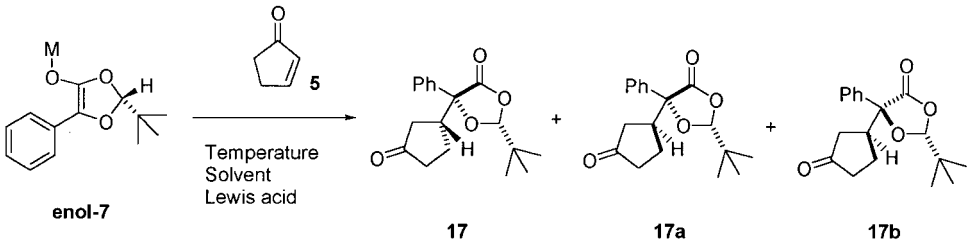
(12) For a recent example see: Visser, T. J.; Vanwaarde, A.; Jansen, T. J. H.; Visser, G. M.; Vandermark, T. W.; Kraan, J.; Ensing, K.; Vaalburg, W. *J. Med. Chem*. **1997**, *40*, 117−124.

(13) Stereochemical assignments for **17** and **17a**: see refs **3b** and **31**. For **17b**, it was determined by the fact that the free hydroxy acid derived from **17b** was identical with **17** in ^1H, ^{13}C, MS, IR spectral data. The diastereomer of **17b**, which should be defined as **17c**, appears at a very small level (below 1%). It was not discussed unnecessarily.

(14) For recent work on Mukaiyama−Michael reaction between silyl enol ethers and α,β-unsaturated ketones: see (a) Mukaiyama, T.; Tamura, M.; Kobayashi, S. *Chem. Lett*. **1986**, 1017−1020. (b) Evans, D. A.; Willis, M. C.; Johnston, J. N. *Org. Lett*. **1991**, *1*, 865−868. (c) Berl, V.; Helmchen, G.; Preston, S. *Tetrahedron Lett*. **1994**, *35*, 233−236.

(15) Unfortunately in this case there is some erosion of selectivity at the quaternary center and **17b** is produced in substantial amounts (ca. 20%).

Table 1. Reaction of Enolates of Mandelic Acid Acetal 7 with 2-Cyclopenten-1-one (5)

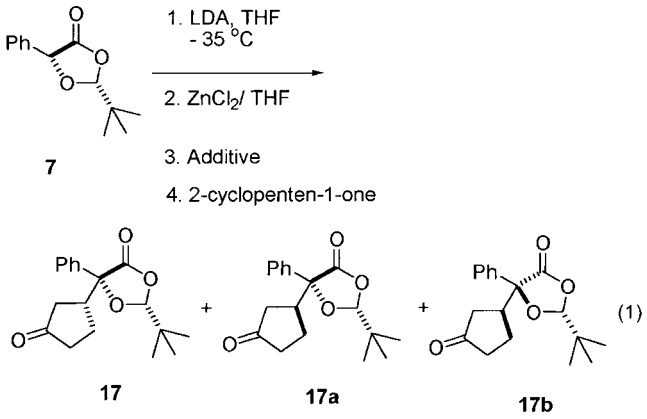


entry[a]	M	Lewis acid	solvent	ratio of **17**:**17a**[f]	yield, %[f]
1	Li	−	THF	1:1.5	89
2	Na	−	THF	1:2	92
3	K	−	THF/$PhCH_3$	1:2.5	92
4	Li	$ZrCl_4$[d]	THF	1:3.2	90
5	Li	Cp_2ZrCl_2	THF	2.8:1	88
6	Li	Cp_2TiCl_2	THF	1.5:1	90
7	Li	$ZnCl_2$	THF	3:1	75
8	TBS[c]	$TiCl_4$[e]	CH_2Cl_2	2.1:1	93
9[b]	TBS	Cp_2ZrCl_2	CH_2Cl_2	1.9:1	21
10	TBS	$ZrCl_2$	THF	1.9:1	98
11	TBS	$ZrCl_4$	CH_2Cl_2	1.3:1	93

[a] All reactions were carried out at −78 °C unless otherwise mentioned. [b]The reaction was carried out at 25 °C. [c]The *tert*-butyl dimethyl silyl (TBS) derivatives were generated from the Li enolate in THF followed by addition of TBS-Cl. The TMS derivetives were also preparared and gave similar results. [d]Metal enolates were prepared by using 1.2 equiv of additives to the lithium enolate. [e]The enone and Lewis acid were premixed in the appropriate solvent at the reaction temperature, followed by addition of a solution of the preformed silyl ketene acetal. [f]Ratios and yields were determined by HPLC.

the selectivity of the reaction; however, additional amounts of TMEDA showed a substantial increase in the selectivity with a maximum ratio of **17**:**17a** = 8.6:1 in the presence of 20 equiv of TMEDA.[16] Additional TMEDA (50 equiv) did not further enhance the selectivity. The fact that as much as 20 equiv of TMEDA was needed to secure the optimal diastereoselectivity strongly suggested solvent participation in the reaction. Since it is well-known that THF can coordinate strongly with Zn-enolate, it was postulated that a less-coordinating solvent might allow reduction of the necessary amount of ligand with enhancement of the selectivity. Therefore, we successively focused on optimization of the solvent system. A number of polar, nonpolar, ethereal, and hydrocarbon solvents were examined and interestingly, our findings suggested that a substantial proportion of a nonchelating hydrocarbon solvent to a chelating solvent was necessary for demonstration of the additive effect of the ligand. The optimal combination was found to be DME:toluene (1:1, wherein the maximum selectivity was obtained with only 4 equiv of TMEDA (vs 20 equiv in THF, **17**:**17a** = **11**:**1**, **17**:**17a**+**17b** = 8.4:1; reaction yield = 95%).

Finally, our optimization studies focused on the structure of the ligands (Table 2). Initial attempts with polydentate amine ligands, diol alkoxides,[17] aminoalkoxides,[18] and bis-amide and bis-sulfonamide anions were not effective, and low yields of **17** and poor ratios (**17**:**17a**+**17b)** were obtained. *However, to our great delight, unsymmetrical diamine ligands significantly increased the diastereoselectivity of this reaction.* Indeed, merely substitution of one of the dimethyl amino groups in TMEDA with the diethyl amino moiety resulted in a significant increase (entry 3) in the diastereomer ratio.



Furthermore enclosing the nitrogen in a ring (entries 4−6) further increased the selectivity in favor of the desired isomer. It is also worth noting that the largest effect observed is on the facial selectivity of the cyclopentenone (as expressed in the ratio of **17**:**17a**) while the face selectivity with respect to the enolate remains fairly constant (**17**+**17a**:**17b**). Thus, with TMEDA the ratio of **17**:**17a** is 11:1 while use of the piperazinyl-derivative **18** (entry 5) resulted in an increased ratio of **17**:**17a** to ca. 45:1. Interestingly, a symmetrical open-chain analogue did not perform satisfactorily in this reaction (entry 7). From the results in Table 2 we chose 1-(2-dimethylaminoethyl)-4-methylpiperazine (**18**, MAEP**)** as the preferred ligand for this reaction. Fortunately, this ligand was also the cheapest and most readily available.[19]

With satisfactory stereoselectivity for the Michael addition in hand, we modified this reaction condition to fit for the pilot plant implementation. Anhydrous $ZnCl_2$ is very hygroscopic and is not soluble in either DME or

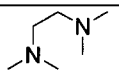
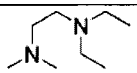
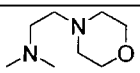
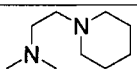
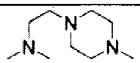
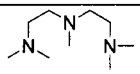
(16) With 5 equiv of TMEDA, the ratio is 5:1 and with 10 equiv of TMEDA, the ratio is 7:1.

(17) (a) Sasai, H.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1994**, *116*, 1571−1572. (b) Bolin, C.; Ewald, M. *Tetrahedron Lett.* **1990**, *31*, 5011−5012. (c) Asano, Y.; Iida, A.; Tomioka, K. *Tetrahedron Lett.* **1997**, *38*, 8973−8976.

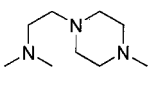
(18) (a) Huffman, M. A.; Yasuda, N.; DeCamp, A. E.; Grabowski, E. J. J. *J. Org. Chem.* **1995**, *60*, 1590−1594. (b) Thompson, A. S.; Corley, E. G.; Huntington, M. F.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 8937−8940.

(19) Ligand **18** is commercially available from TOSOH Co.

Table 2. Effect of the Structure of the Zn Ligand on the Diastereoselectivity of the Michael Reaction of 7 and 2-cyclopenten-1-one (eq 1)

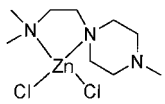
Entry	Ligand (4 equiv.)	Ratio **17** : **17a**	Ratio **17+17a** : **17b**
1	none	3 : 1	4 : 1
2		11 : 1	8.4 : 1
3		17 : 1	11 : 1
4		39 : 1	10 : 1
5		31 : 1	12 : 1
6		45 : 1	12 : 1
7		4.6 : 1	6.7 : 1

toluene. Further experimentation revealed that preformation of the complex **19**[20] is operationally advantageous as the complex is *not hygroscopic* and thus can be used directly in the water sensitive Michael reaction.[21] However, the reaction with **19** was heterogeneous and significant amount of solids were observed, and the solid was found to be the unreacted **19** itself.



MAEP

18



19

We therefore examined the possibility of using less than 1 equiv of the $ZnCl_2$−MAEP complex **19**. *Interestingly, only 15 mol % of **19** was needed to achieve an equal stereoselectivity and yield.* This very interesting finding translated to a reduction in the quantities of **19** employed in the reaction which in turn produced a homogeneous reaction mixture, reduced raw materials cost, facilitated reaction workup, and provided a more environmentally friendly waste stream. Further detailed investigation indicated that the lithium enolate of **7** was significantly more stable in the presence of **18**,[22] and the Zn−MAEP complex **19** could act as an catalyst. In contrast, the reaction of the lithium enolate of **7** with cyclopentenone **5** was a very fast reaction (complete in ≤3 min). To explain these results, a detailed kinetic study was initiated (the full data to be presented elsewhere) with preliminary indications showing that the "Zn enolate" reacts 7−10 times faster (in the presence of **18**) than the lithium enolate (with or without **18**).

Our typical procedure for this reaction is shown in Scheme 4. A mixture of LDA and **18** (4 equiv) in DME at −15 °C was treated with a solution of **7** at −15 to −10 °C. The resulting enolate, which is stable for several days at this temperature, was treated with **19** (15 mol %),[23] and toluene was added. The resulting heterogeneous mixture was allowed to stand for 1 h at 0 °C upon which time **19** completely dissolved to give a homogeneous reaction mixture. It should be noted that this last operation is critical, and failure to perform it results in diminished selectivity (**17**:**17a** + **17b** ≤ 4:1). The mixture was then cooled to −78 °C (where it remained homogeneous), and cyclopentenone was added over 1 h. Acid quench and extractive workup afforded **17** in 83% assay yield. Finally, the product was isolated from EtOH:H_2O (1:1) in 74% isolated yield with excellent chemical and diastereomeric purity on a 25 kg scale.

C. Difluorination of the Michael Adduct 17. In our initial attempts to convert **17** to the *gem*-difluoro compound **21**, we employed several literature deoxyfluorination procedures,[24] oxidative fluorination of ketone derivatives[25] and SF_4−HF.[26] Although some success was realized with these methods, safety and reproducibility concerns prompted us to investigate alternative approaches.[27]

Fortuitously, Air Products Inc. had just announced the commercialization of a new, safer, and more reactive

(20) The complex **19** was formed easily by adding **18** (1.2 equiv) to a solution of $ZnCl_2$ in THF (Aldrich) at 0 °C. A precipitate formed immediately and was filtered and worked with THF and dried at 40 °C in vacuo to afford **19** in 85−90% yield. An X-ray structure of **19** revealed that **18** acts as a bidentate ligand with the distal ring nitrogen not bound to Zn.

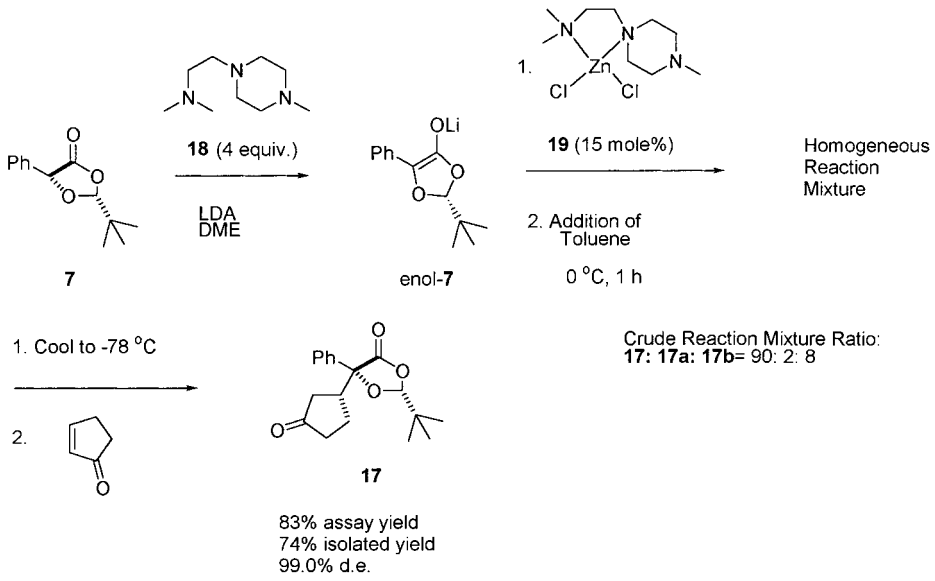
(21) In cases when $ZnCl_2$ in THF was used, the solution was dried overnight over 4 Å molecular sieves. Studies showed that under these conditions there is substantial change in the chloride titration indicating some instability of this solution on storage.

(22) The lithium enolate in the presence of MAEP ($t_{1/2}$ = 24 h at −10 °C is more stable than the lithium enolate itself ($t_{1/2}$ = 12 h at −35 °C) in DME−toluene.

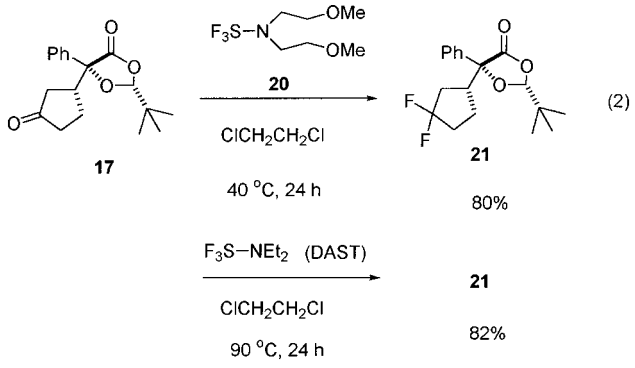
(23) The ratio of **17**:**17a**:**17b** = 90:2:8 is the same when 1 equiv of **19** is used.

(24) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574−578.

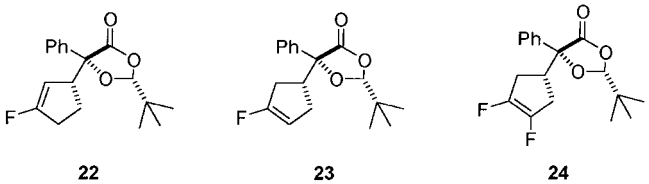
Scheme 4



reagent for the conversion of carbonyls to *gem*-difluoro derivatives: Deoxofluor (**20**). Differential scanning cal-



orimetry data indicated this compound might be safer than DAST or morpholino-DAST.[28] Moreover, when **17** was reacted with **20** (2.5 equiv) in 1,2-dichloroethane at 40 °C, complete conversion to the difluoroacetal **21** was realized in ca. 24 h (80% assay yield). In comparison, temperatures of ca. 90 °C were required with DAST in order to obtain similar results. Despite the good yield of **21**, two issues remained problematic. First the requirement for 2.5 equiv dramatically increased the cost of this step, and second, three major impurities were generated (**22**−**24**).



For the reaction described above (eq 2), 1.5% each of **22** and **23** as well as ca. 5% of **24** were formed. Moreover, these impurities could not be easily removed at this or later stages in the synthesis.

Table 3. Effect of Additives to the Difluorination Reaction of 17 with Deoxofluor

				yield (%)			
entry	additives	temp (°C)	time (h)[c]	21	22	23	24
1	none[1]	40	24	80	1.5	1.5	5
2	H_2O (20%)[a]	40	16	85	0.7	0.7	2.0
3	CF_3CO_2H (20%)[a]	40	14	83	0.7	0.7	2.5
4	$BF_3{\cdot}OEt_2$ (5%)[b]	55	36	92	0.3	0.3	0.4

[a] 2.5 equiv of Deoxofluor were required for these reaction conditions. [b] 1.4 equiv of Deoxofluor were used. [c] Time to >95% conversion.

To overcome these problems, we investigated reports in the literature that protic acids accelerate the deoxyfluorination reaction and thus may allow reduction of equivalents of Deoxofluor required. Hopefully, the increase in the rate of the desired reaction would also generate less of the impurities **22**−**24**. Addition of H_2O (20 mol %) to the reaction mixture, to generate HF in situ, or an anhydrous protonic acid (trifluoroacetic acid, 20 mol %) produced only a marginal rate increase (Table 3, entries 2, 3). More importantly these additives reduced the level of impurities **22**−**24** formed to approximately half of the amounts produced in the original reaction.

To our surprise, even small amounts of (5−10 mol %) of Lewis acids such as $BF_3{\cdot}OEt_2$[29] substantially retarded the rate of the reaction (70% conversion in 36 h at 40 °C and 95% conversion in 36 hat 55 °C). However, the yield of **21** improved by 10−12% (entry 4) and only trace amounts of **22**−**24** were formed; moreover, 1.4 equiv of Deoxofluor were sufficient to drive the reaction to completion. A typical procedure (eq 3) involved slow addition of $BF_3{\cdot}OEt_2$ to a cold (0 °C) solution of **20** in toluene followed by allowing the mixture to stand for 1 h at 0 °C. A solution of **17** in toluene was added over 3 h, and the mixture was heated to 55 °C for 36 h. Careful quench

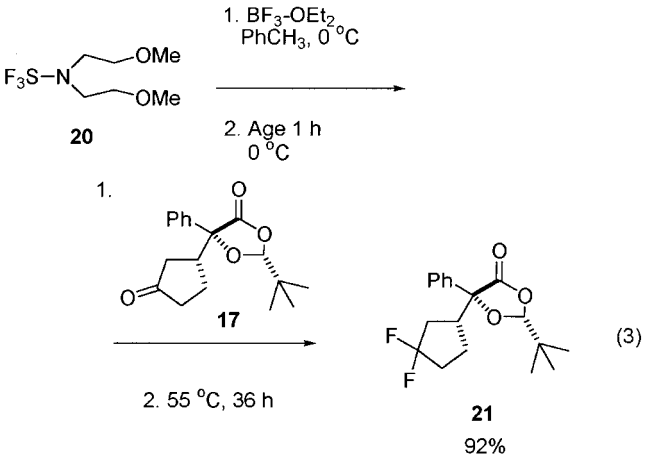
(25) (a) Kuroboshi, M.; Hiyama, T. *Synlett*. **1991**, 909−910. (b) Sondej, S. C.; Katzenellenbogen, I. A. *J. Org. Chem*. **1986**, *51*, 3508−3513. (c) Motherwell, W. B.; Wilkinson, J. A. *Synlett*. **1991**, 191−192. (d) Rozen, S.; Brand, M.; Zamir, D.; Hebel, D. *J. Am. Chem. Soc*. **1987**, *109*, 896−897. (e) Rozen, S.; Zamir, D. *J. Org. Chem*. **1991**, *56*, 4695−4700. (f) York, C.; Prakash, G. K. S.; Wang, A.; Olah, G. A. *Synlett* **1994**, 425−426.

(26) Hammond, G. B.; Plevey, R. G. *J. Fluorine Chem*. **1993**, *63*, 13 and references therein.

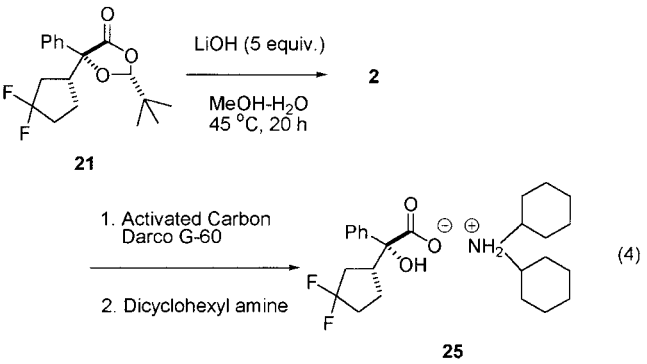
(27) Messina, P. A.; Mange, K. C.; Middleton, W. J. *J. Fluorine Chem*. **1989**, *42*, 137−143.

(28) Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M.; Cheng, H. *J. Org. Chem*. **1999**, *64*, 7048−7054.

into a NaOH solution, while constantly maintaining basic pH, followed by extractive workup afforded **21** in ca. 92% assay yield.



D. Hydrolysis of the Acetal 21. Hydrolysis of crude **21** to give the key acid fragment **2** was accomplished conveniently under basic conditions (eq 4). Treatment of



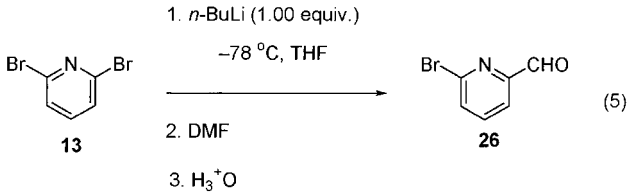
the deep brown solution of **21** in MeOH with 5 equiv of aqueous LiOH (1 M) at 45 °C effected a rapid methanolysis of the acetal to produce the methyl ester and a subsequent slow hydrolysis (45 °C, 20 h) to give the desired hydroxy acid **2**. Compound **2** was treated with dicyclohexylamine (DCHA) to give the crude DCHA salt **25** which was recrystallized from MeOH−H_2O (1:1) to give pure **25** in 75% yield from **21**.[30] The purity of this compound by HPLC analysis was ≥99%.

It is noteworthy that we have been unable to effect the hydrolysis of **21** under acidic conditions even though the starting acetal **7** was fairly easily hydrolyzed in acidic methanol solutions. Heating of **21** with H_2SO_4 (2 M) in MeOH or EtOH at reflux resulted in recovery of the starting material (97%).[31]

II. Amine Synthesis

Since a number of attempts[6,7] to effect coupling of the iminium cation species with metallopyridines gave unsatisfactory results (Scheme 2), we focused our attention on the C−N retrosynthesis path (b), Scheme 2. To prepare the bromomethyl pyridine (**8**: R = CH_2Br) from 2-amino-6-picoline (**14**), radical bromination of 2-Boc-amino-6-picoline with NBS/AIBN was examined.[32] However, considerable amounts of the corresponding dibromo side product were obtained, and it was difficult to suppress the undesired path even after many attempts. We therefore turned our attention to selective formylation of 2,6-dibromopyridine (**13**) for the reductive amination protocol with a protected amino piperidine.

A. Synthesis of 6-Bromo-2-formylpyridine (26). Selective monometalation of 2,6-dibromopyridine (**13**) is a useful way to produce diversely functionalized pyridine derivatives and thus has received considerable attention. Lithium−bromide exchange of **13** with 1.00 equiv of BuLi proceeded cleanly in THF at −78 °C to give the monolithiated compound, and addition of DMF followed by aqueous workup afforded the product **26** in excellent yield (eq 5).[33]



However, cryogenic temperatures (≤−70 °C) and pinpoint accuracy of the BuLi charge were essential for the success of the above metalation/formylation reaction.[33] The latter was particularly crucial and was also the most difficult parameter to control on scale-up (Scheme 5). The need for perfect control of the BuLi charge lies in the fact that exposure of the monolithiated species **27** to excess BuLi readily affords the bis-lithiated species **28** which eventually produces **29**. On the other hand, a slight deficiency in BuLi results in reaction of **27** with unreacted **13** to give the ortho-lithiated product **30** and 2-bromopyridine (**31**). Reaction of **30** with DMF affords **32**. Interestingly, replacement of THF with CH_2Cl_2[34] or $PhCH_3$[35] allowed the use a slight excess of BuLi (1.05−1.1 equiv). However, cryogenic conditions were still necessary as intermediate **27** was not stable at temperatures above −50 °C.

To prepare a more stable intermediate, we next focused on the magnesium−bromine exchange reaction. Magnesium−halogen exchange reactions are also well established,[36] and Quéguiner et al have recently reported the magnesium−bromine exchange of 2,6-dibromopyridine (**13**) using *i*-PrMgCl.[37] On the basis of this procedure, we aggressively refined the reaction conditions. However,

(29) Other Lewis acids studied include $AlCl_3$; $EtAlCl_2$; Et_2AlCl, $Ti(OPr^i)_4$; and $GaCl_3$. BF_3·OEt_2 was optimal for reduction of impurities **22**−**24**.

(30) The dicyclohexylamine salt was optimal for isolation.

(31) For earlier synthetic work from our medicinal chemistry division, see: Mitsuya, M.; Ogino, Y.; Ohtake, N.; Mase, T. *Tetrahedron* **2000**, *56*, 9901−9907.

(32) (a) Maris, V. P.; Goswami, S.; Hamilton, A. D. *J. Heterocycl. Chem.* **1995**, *32*, 675−681. (b) Goswami, S.; Hamilton, A. D.; Engen, D. V. *J. Am. Chem. Soc.* **1989**, *111*, 3425−3426.

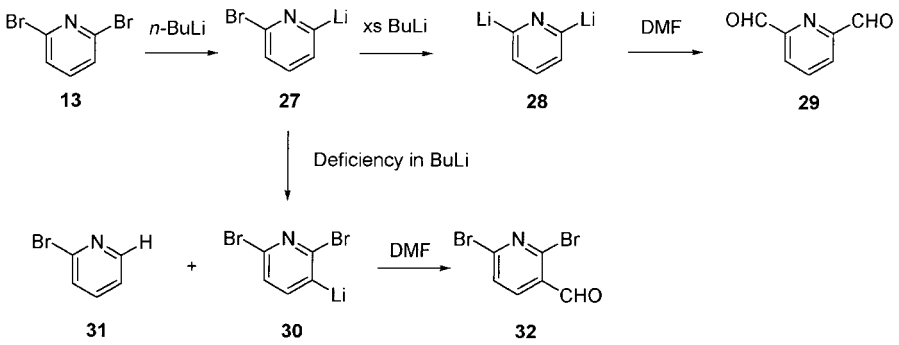
(33) Cai, D.; Hughes, D. L.; Verhoeven, T. R. *Tetrahedron Lett.* **1996**, *37*, 2537−2540.

(34) Peterson, M. A.; Mitchell, J. R. *J. Org. Chem.* **1997**, *62*, 8237−8239.

(35) Unpublished result from our laboratory: The exchange reaction with 2,6-dibromopyridine occurred very cleanly below −40 °C.

(36) (a) Furukawa, N.; Shibutani, T.; Fujihara, H. *Tetrahedron Lett.* **1987**, *28*, 5845−5848. (b) Nishiyama, H.; Isaka, K.; Itoh, K.; Ohno, K.; Nagase, H.; Matsumoto, K.; Yoshiwara, H. *J. Org. Chem.* **1992**, *57*, 407−410. (c) Shinokubo, H.; Miki, H.; Yokoo, T.; Oshima, K.; Utimoto, K. *Tetrahedron* **1995**, 11681−11692. (d) Bérillon, L.; Leprêtre, A.; Turck, A.; Plé, N.; Quéguiner, G.; Cahiez, G.; Knochel, P. *Synlett* **1998**, 1359−1360. (e) Boymond, L.; Rottländer, M.; Cahiez, G.; Knochel, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 1701−1703. (f) Rottländer, M.; Boymond, L.; Cahiez, G.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 1080−1081. (g) Abarbri, M.; Knochel, P. *Synlett.* **1999**, 1577−1578.

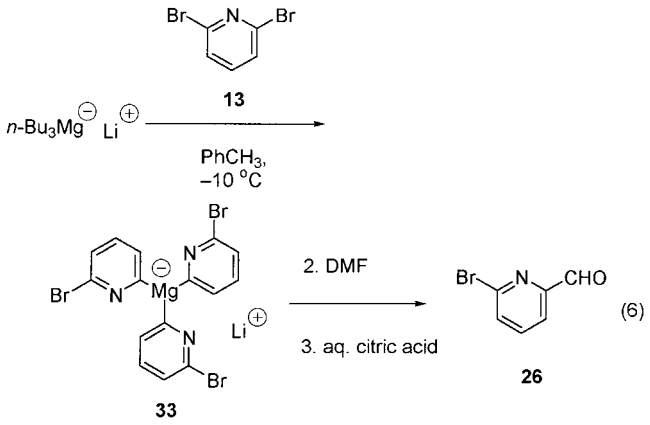
Scheme 5



even after optimization, the reaction was relatively sluggish and required excess *i*-PrMgCl for completion. In addition, formation of the side product 2-formyl-6-isopropylpyridine after treatment with DMF could not be ignored (more than 5%). Interestingly, the metalated mono-bromopyridine intermediate from *i*-PrMgCl was quite stable at 20 °C even after standing for a long time (>24 h). It should also be noted that Knochel et al. have reported the *i*-Pr_2Mg-induced exchange reaction of 2,6-dibromopyridine (**13**) (albeit a sluggish reaction).[38]

These results prompted us to devise a new metalation protocol that addressed both issues of low temperature and stoichiometry. Ideally, this solution requires that the desired metalated species should have stability similar to the RMgX and R_2Mg species; however, its reactivity should be greater. With this in mind, we envisioned that a magnesium ate complex such as R_3MgLi, would possess the necessary reactivity difference, between BuLi and RMgX/R_2Mg, and might also exhibit the requisite stability profile. To our best knowledge, no report on a magnesium ate complex induced metal−halogen exchange reaction had been published at that time, although several examples with other metal-based ate complexes are known.[39] Furthermore, in all cases reported, only one alkyl on the metal was active in the exchange reaction.

After several attempts, *we were pleased to find that the halogen−metal exchange reaction of* ***13*** *cleanly proceeded at −10 °C in toluene with only 0.35 equiv of n-Bu₃MgLi* (prepared by mixing *n*-Bu_2Mg and *n*-BuLi according to the literatures).[40] However, since it is known that *n*-Bu_2Mg can be prepared from *n*-BuMgCl and *n*-BuLi,[41] we chose to prepare the speculated ate complex by direct reaction of *n*-BuMgCl and n-BuLi as a more convenient and safer alternative method. Indeed, the reagent prepared from mixing *n*-BuMgCl (0.35 equiv to **13**) and *n*-BuLi (0.70 equiv to **13**) in a ratio of 1:2 in toluene at −10 °C showed similar reactivity to the one prepared from *n*-Bu_2Mg. Treatment of the above prepared, R_3MgLi species with **13**, in toluene, resulted in complete consumption of the starting dibromopyridine, indicating conversion to the desired mono-bromopyridine derived ate complex **33** and upon subsequent quenching yielded 2-bromopyridine (**31**), quantitatively. Analogously, when the reaction mixture was treated with DMF at −10 °C, the desired 6-bromo-2-formylpyridine (**26**) was formed in 94−97% assay yield (eq 6).



(6)

This remarkable metal−bromine exchange at higher temperature did not occur cleanly with either of the components alone. Extensive decomposition occurred with *n*-BuLi at −10 °C, and *n*-BuMgCl and *n*-Bu_2Mg were much less active. In addition, this exchange is not sensitive to the accuracy of the reagent charge, unlike the original lithium−bromine exchange. The combination of various amounts of *n*-BuMgCl and *n*-BuLi were comparable to the typical procedure (0.35/0.7equiv) and afforded **26** in 96% yield.

In conclusion, this novel, *n*-Bu_3MgLi metal−halogen exchange reaction provides a robust, scaleable process for selective functionlization of 2,6-dibromopyridine.[42] Detailed studies using *n*-Bu_3MgLi and related complexes will be reported elsewhere.

(37) Trécourt, F.; Breton, G.; Bonnet, V.; Mongin, F.; Marsais, F.; Quéguiner, G. *Tetrahedron Lett.* **1999**, *40*, 4339−4342.

(38) Abarbri, M.; Dehmel, F.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 7499−7453.

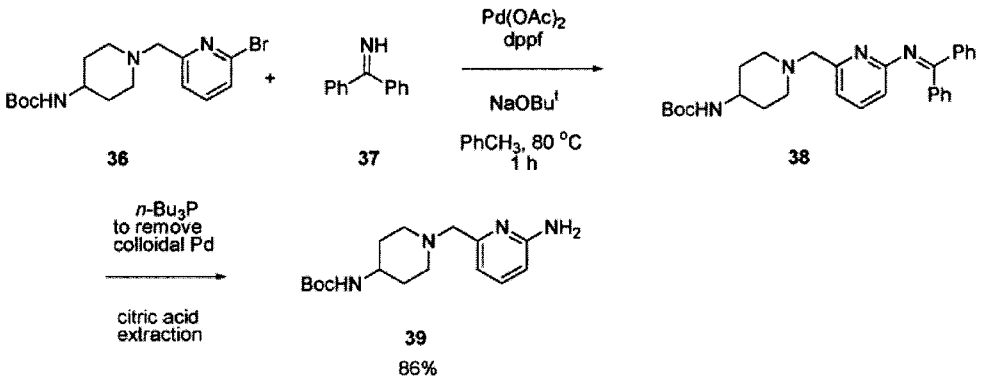
(39) Ate complex-induced halogen−metal exchange reactions: (a) Harada, T.; Katsuhira, T.; R. Hattori, K.; Oku, A. *J. Org. Chem.* **1993**, *58*, 2958−2965. (b) Harada, T.; Katsuhira, T.; Hara, D.; Kotani, Y.; Maejima, K.; Kaji, R.; Oku, A. *J. Org. Chem.* **1993**, *58*, 2958−2965. (c) Uchiyama, M.; Koike, M.; Kameda, M.; Kondo, Y.; Sakamoto, T. *J. Am. Chem. Soc.* **1996**, *118*, 8733−8734. (d) Kondo, Y.; Matsudaira, T.; Sato, J.; Murata, N.; Sakamoto, T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 736−738. (e) Inoue, R.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **1996**, *37*, 5377−5380. (f) Inoue, R.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **1998**, *63*, 910−911. (g) Hojo, M.; Harada, H.; Ito, H.; Hosomi, A. *J. Am. Chem. Soc.* **1997**, *119*, 5459−5460. (h) Hojo, M.; Hosomi, A. *Chem. Commun.* **1997**, 2077−2078.

(40) (a) Malpass, D. B.; Eastham, J. F. *J. Org. Chem.* **1973**, *38*, 3718. (b) Ashby, E. C.; Chao, L.-C.; Laemmle, J. *J. Org. Chem.* **1974**, *39*, 3258.

(41) For preparation of *n*-Bu_2Mg: see Wakefield, B. J. *Organomagnesium Methods in Organic Synthesis*; Academic Press: New York, 1995; pp 61−71.

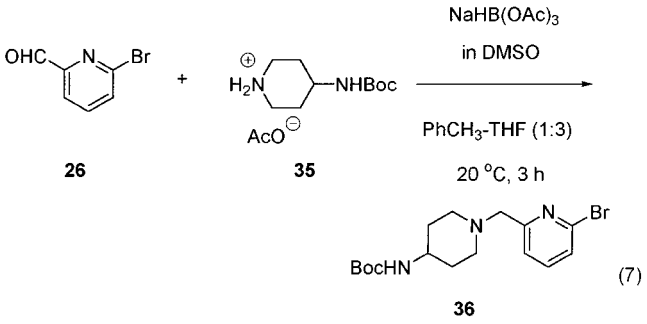
(42) A patent application was filed: Iida, T.; Wada, T.; Mase T., Japan Application No. JP 2000-024613 20000202. During the preparation of this manuscript, an analogous metal−halogen exchange using R_3MgLi has been published: Kitagawa, K.; Inoue, A.; Shinokubo, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 2481−2483. They used 3 equiv of the organometallic reagents in most cases.

Scheme 6



B. Reductive Amination Reaction to form 36

The preparation of the key bromopyridine intermediate **36** was accomplished by reductive amination of aldehyde **26** with readily available 4-Boc-aminopiperidine **35**[43] (eq 7). The aldehyde and piperidine acetic acid salt were mixed in toluene:THF(1:1), and $NaHB(OAc)_3$[44] was introduced slowly as a DMSO solution over 3 h. The crude reaction mixture was partitioned between toluene and water and crystallized to give **36** in 82% overall yield (from **13**).

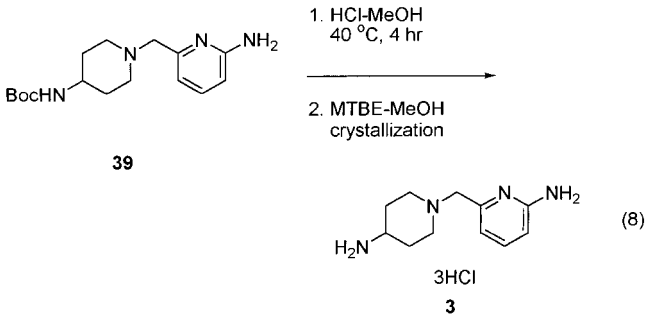


(7)

C. Aromatic Amination To Form 39. Amination of aromatic halides under transition metal catalysis has received considerable attention in the past few years,[45] and a bigger challenge involves the introduction of the unsubstituted "NH_2" group. Although direct methods including classical copper-catalyzed amination with ammonia exsist, they are mechanistically ill defined and generally employ harsh or inconvenient conditions.[46,47] Several ingenious procedures have been developed to introduce variably substituted amine surrogates.[48] Among them, benzophenone imine (**37**) appears to be optimal due to its facile hydrolysis to NH_2,[49] despite economic and volumetric productivity issues. We examined several more available ammonia equivalents using Pd, Ni, or Cu based catalysts without much success. Consequently, benzophenone imine (**37**) was used for the amination (Scheme 6).

Typically, bromopyridine **36** in toluene was treated with 0.25 mol % of $Pd(OAc)_2$ and 0.5 mol % of diphenylphosphino ferrocene (dppf) followed by 1.1 equiv of *t*-BuONa and the imine **37**. The mixture was heated to 80 °C for 1 h, *n*-Bu_3P was added,[50] and the toluene solution was stirred with aqueous citric acid to effect hydrolysis of the imine of **38** while leaving the Boc protecting group intact. The benzophenone byproduct and most of the palladium remain in the organic layer and are easily removed. The product **39** was isolated from the aqueous layer by basification and extraction. Crystallization from *i*-PrOAc/*n*-heptane (1:2.5) afforded **39** in 86% yield.

D. Boc-Deprotection Reaction To Form 3. Deprotection of the Boc group was readily achieved by treatment of **39** with excess anhydrous (or aqueous concentrated) HCl in methanol at 40 °C for 4 h. The tris-HCl salt thus produced was isolated by removal of the volatile components followed by crystallization from MeOH:*t*-BuOMe (1:2) in 92% yield and 99.9% purity (eq 8).[51]

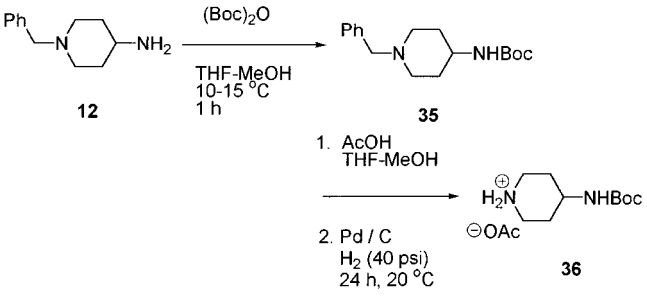


(8)

III. Final Coupling

A streamlined protocol for coupling of the dicyclohexylamine salt **25** was also developed. A solution of **25** in H_2O

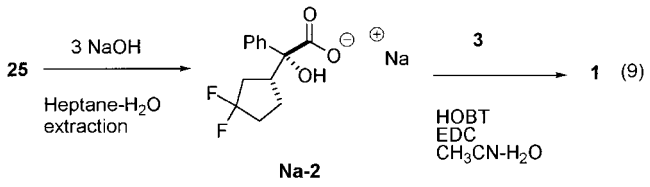
(43) The piperidine moiety was readily synthesized from commercially available *N*-benzyl amino piperidine (**12**). Protection of the primary amine as the carbamate was accomplished by brief exposure (1 h) of **12** to Boc_2O in THF/MeOH at 10−15 °C to give the intermediate **34** in nearly quantitative yield.



Heterogeneous catalytic hydrogenolysis of the benzyl group in **34** at the free amine stage proved problematic requiring 50 wt % of Pd/C and long reaction times. However, addition of 1 equiv of acetic acid to the crude solution of **34** (in MeOH/THF) followed by hydrogenation with 5 wt % of Pd/C at 40 psi H_2, afforded **35** in >95% crude yield. After filtration through Solka-Floc, to remove the catalyst, and evaporation of the solvent, **35** was isolated in pure enough form to be used directly in the next step.

(44) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849−3862.

is treated with 3 equiv of NaOH and extracted with heptane. The organic phase, containing free dicyclohexylamine, is removed, and the remaining aqueous solution of the sodium salt of **2** (an extra 2 equiv of base) is treated with **3** in CH_3CN. The excess NaOH neutralizes two equiv of acid from **3**, and the mixture is treated with HOBT and EDC. The resulting homogeneous mixture is stirred for 16 h at ambient temperature to produce **1** in 80−85% yield after extractive workup and *i*-PrOAc/*n*-heptane crystallization (eq 9).



(9)

Conclusion

A highly efficient and convergent synthesis of drug candidate **1** was accomplished in excellent overall yield. The synthesis is highlighted by the following transformations: (1) a triisopropyl orthoformate-induced acetalization was used as an alternative to the usual azeotropic approach to give the desired mandelic acid derived dioxolane with unprecedented stereoselectivity, (2) a novel zinc−MAEP complex was demonstrated to catalyze a selective lithium enolate Michael reaction (which was itself inactivated by MAEP) to produce the desired adduct with high diastereoselectivity (this finding is in contrast to the usual case where a transition-metal catalytically activates inactive Zn-containing organometallics), (3) Deoxofluor/BF_3·OEt_2 was demonstrated as a highly efficient and selective reagent for the conversion of functionalized ketones to their corresponding geminally difluorinated derivatives (this reagent proved to be superior to DAST in suppression of vinyl fluoride side product formation), (4) *n*-Bu_3MgLi was shown to be a highly effective reagent for selective metal−halogen exchange of 2,6-dihalopyridines and obviated the need for cryogenic reaction conditions (as required with the alkyllithium reagents). This approach should be widely applicable to other aryl or vinyl halides. This work enabled us to provide multi-kilograms of highly pure bulk drug without the use of chromatographic purification.

Experimental Section

Acetal Formation: (2*R*,5*R*)-2-*tert*-Butyl-5-phenyl-1,3-dioxolan-4-one (7). A slurry of (*R*)-mandelic acid (**6**) (7.00 kg) in toluene (70 L) was treated with triisopropyl orthoformate (10.51 kg) added dropwise at 24 °C. The batch was stirred at 24 °C for 2 h, until NMR monitoring showed a ratio of **15**:**6** of 82:18). Toluene (70 L) was added (to 170 L total volume), and the batch was distilled maintaining a constant volume of 170 L by gradual addition of toluene. NMR analysis showed complete consumption of **6** at this time. The batch was concentrated to 70 L at 16 °C under vacuum. Gas chromatographic analysis showed <1.5% of *i*-PrOH. *p*-Toluenesulfonic acid (6 mol %, 525 g) and a solution of pivalaldehyde (5151 g) in toluene (35 L) were added at 25−28 °C over a period of 50 min, and the reaction mixture was stirred at 28 °C for 30 min. After confirming the completion of the reaction, by HPLC analysis, the batch was diluted with toluene (90 L) to 200 L and was washed with 5% aqueous sodium bicarbonate solution (70 L) and 30% aqueous NaCl solution. The organic layer was concentrated in vacuo to a minimum stirrable volume, *n*-heptane was added (50 L), and the batch was further concentrated to a volume of 25 L. The same procedure was repeated three times to switch the solvent to *n*-heptane. The resulting slurry was filtered, washed with *n*-heptane (2 × 25 L), and dried under reduced pressure to give the desired compound **7** (9.3 kg, 92% yield, 98.8% purity).[5,53]

Michael Addition: (2*R*,5*R*)-2-*tert*-Butyl-5-[(1*R*)-4-oxo-2-cyclopentyl]-5-phenyl-1,3-dioxolan-4-one (17). A 3000 mL three-neck flask was equipped with mechanical stirrer and temperature probe. Dimethoxyethane (DME, 350 mL) and **18** (176 mL) were mixed at room temperature and cooled to −20 °C. A solution of LDA (2.0 M, 159 mL) was added over 10 min while keeping the temperature below −10 °C. The resulting solution was cooled to −20 °C, and a solution of **7** (50.0 g) in DME (470 mL, heating to 35 °C is required for complete dissolution) was added dropwise over 45 min while keeping the temperature below −15 °C. The resulting solution was allowed to stand for 15 min at −15 °C. The $ZnCl_2$−MAEP complex **19** (20.9 g) and toluene (820 mL) were added sequentially. The temperature was raised to 0 °C, and the mixture was allowed to stand for 2 h. The reaction mixture was then cooled to −78 °C, and a solution of 2-cyclopenten-1-one (20.9 mL) in toluene (82 mL) was added dropwise over 50 min while

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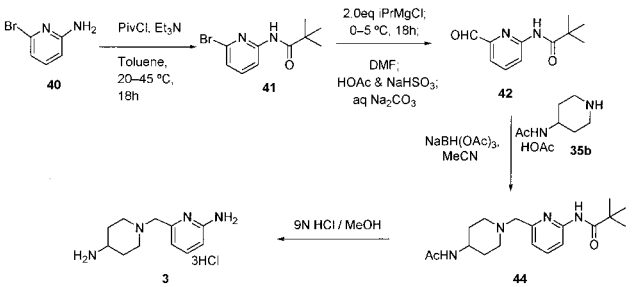
(51) Alternatively, amine moiety **3** could also be prepared from commercially available 2-amino-6-bromopyridine **(40)**. Conversion to pivalamide **41** (quantitative) and metal−halogen exchange with *i*-PrMgCl followed by quenching with DMF provided the aldehyde **42** (87−90%). Reductive amination with *N*-acyl-protected piperidine **35b** gave **43** which was readily deprotected in the presence of acid to furnish the desired tris-HCl salt amine coupling partner **3** (86%).



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(53) All spectral data (^1H, ^{13}C NMR, IR, HR-MS, elemental analysis, melting point and optical rotation) obtained were identical with those of authentic samples.

keeping the temperature between −75 to −70 °C. After 20 min HPLC analysis indicated that the reaction was complete. H_2SO_4 (4 M, 25 mL) was added over 5 min (the temperature of the reaction mixture increased to about −50 °C), and the reaction mixture was allowed to warm to −20 °C and transferred slowly into H_2SO_4 (4 M, 475 mL, precooled to −10 °C) while controlling the temperature below 10 °C. The two-phase mixture was allowed to warm to room temperature and was stirred for 20 min. The layers were separated (the pH of aqueous layer was between 1 and 3), and the organic layer was washed sequentially with 250 mL water, 500 mL 5% $NaHCO_3$ and 2 × 250 mL water. The final aqueous wash pH was 5 to 7.

The worked-up solution from above was solvent-switched to EtOH by repeated concentrations and additions of EtOH, and the concentration of the solution was adjusted to ca. 5 mL/g (ca. 275 mL). The solvent amount was checked by NMR (EtOH:Michael adduct molar ratio = 20:1.). The mixture was heated to 50 °C to effect complete dissolution and then cooled to 40 °C and seeded (2−5 wt %). The resulting slurry was allowed to cool to 18 °C and 20 mL/g EtOH:MeOH:H_2O (1:1:2) (275 mL:275 mL:550 mL) was added over 2 h. The slurry was allowed to stand at ambient temperature for 18 h and then cooled to 0 °C for 6 h. The slurry was then filtered at 0 °C, and the filter cake washed with 3 mL/g of cold (0 °C) EtOH:MeOH:H_2O (2:1:2) (165 mL × 2) and dried in vacuo under a N_2 stream. The yield of **17** was 50.8 g (74%).[2b,53]

Difluorination: (2*R*,5*R*)-2-*tert*-Butyl-5-[(1*R*)-3,3-difluorocyclopentyl]-5-phenyl-1,3-dioxolan-4-one (21). Toluene (27 L) was charged to a Teflon-coated 50 gallon reactor, followed by a Deoxofluor **20** (10.25 kg, 8.5 L). The batch temperature was lowered to 5 °C and boron trifluoride diethyl etherate (0.47 kg, 0.4 L) was charged into the reactor as a solution in toluene (3.5 L). The resulting mixture was allowed to stand for 2 h at 5 °C. **[The addition of Boron trifluoride to Deoxofluor is exothermic, so care must be taken to keep the temperature between 5−15 °C].** The Michael adduct **17** (10.0 kg) was charged to the vessel as a toluene solution (25 L). The temperature of the batch was gradually raised to 55 °C, and the batch was allowed to stand for 36 h at this temperature. HPLC analysis indicated 3% residual starting material remained. A separate 200 gal Teflon-lined vessel was charged with 2 N NaOH (200 L) and toluene (190 L), and the mixture was cooled to 0 °C with agitation. The reaction mixture was added slowly to the basic solution while maintaining the temperature below 18 °C. After the transfer was complete, the mixture was agitated for 30 min. The two layers were allowed to settle, and the aqueous layer was separated. The remaining organic layer was washed with 2 N NaOH (100 L) and deionized water (100 L). HPLC assay of the organic layer showed 90% yield.[2a,53]

Hydrolysis of 21 and Salt Formation: (2*R*)-2-[(1*R*)-3,3-Difluorocyclopentyl]-2-hydroxy-2-phenylacetic Acid (25). The solution of **21** in toluene (from the previous step) was charged into a 100 gallon reactor, where the batch was distilled to a minimum volume (in vacuo). Methanol was added and distilled until the toluene content was 2−5%. The volume of the mixture was adjusted to 110 L. To that methanolic solution, 2 N LiOH (81 L) was added, and the reaction mixture was heated to 40 °C for 20 h. The mixture was cooled to ambient temperature, and heptane (100 L) was added. The batch was agitated for 30 min and allowed to settle. The aqueous layer (ca. 120 L) was transferred to a 200 gallon reactor where it was cooled to 7 °C, and *i*-PrOAc was added. The chilled, agitated mixture was treated with 2 N HCl (75 L, added at such a rate so that the temperature did not exceeding 15 °C). The pH of the aqueous layer was checked to ensure it was 2.5−3.0. The layers were separated, and the organic phase was washed with deionized water (100 L). HPLC assay of the organic layer verified the formation of **2** (7.55 kg, 99%).

The above brown solution of **2** in *i*-PrOAc (containing 5% H_2O and 5% MeOH, as determined by gas chromatographic assay) was treated with Darco G60 (5 kg), and the resulting suspension was stirred at room temperature for 60 min. At the end of this time, the batch was filtered through an Estrella filter (prepacked with 10 kg of solka floc) and the cake was washed with additional *i*-PrOAc (50 L). The resulting light yellow solution was subjected to azeotropic distillation at constant volume to lower the water content of the mixture to 160 μg/mL. This dry toluene solution of **2** was treated with dicyclohexylamine (DCHA, 1.4 kg) at ambient temperature. After 1 h, initial crystallization was observed and the remainder of the DCHA (5.6 kg) was added over 110 min. The resulting slurry was allowed to stand for 17 h. The slurry was filtered through a DeDeitrich pressure filter, and the filter cake was washed with fresh *i*-PrOAc (10 kg). The wet cake was strained under nitrogen for 60 min and then dried for 15 h at 28−30 °C, to give crude **25** (86% recovery, 93.6 A% purity). This material and 99 kg of methanol were charged to a 100 gallon glass-lined vessel. The resulting slurry was heated to 60 °C for 1 h to give a homogeneous solution. Water (33 kg) was added over 30 min, maintaining the temperature between 58 and 62 °C. The batch was seeded with 100 g of pure DCHA salt and allowed to stand for 2 h at 60 °C. Water was charged in the following sequence: 15 kg over 4.5 h, 35 kg over 3 h and finally 42 kg over 1.5 h. The slurry was then cooled to 20 °C over 3 h and allowed to stand at this temperature for another 8 h. After this age, the batch was filtered via a DeDeitrich pressure filter and washed with 23 kg of 1:1 = MeOH:H_2O. The wet cake was strained under nitrogen for 30 min and dried for 67 h at 20−25 °C, under nitrogen. 8.7 kg of 99.5% pure **25** were obtained (87% yield).[2a,31,53]

6-Bromo-2-formylpyridine (26). Dry toluene (45.3kg) and *n*-BuLi (1.63 M in hexane, 1230 g, 2.97 mol) were charged to a 800 L reactor and cooled to −10 °C. *n*-BuMgCl (1.95 M in THF, 26.9 kg, 54.6 mol) was added over 30 min, while maintaining the temperature at −10 to 0 °C, and the mixture was stirred at −10 °C for 30 min. A solution of 2,6-dibromopyridine (34.92 kg, 144.8 mol) in toluene (30.2 kg, KF = 69 ppm) was added dropwise over a period of 1 h while keeping the temperature of the mixture below −5 °C. The resulting suspension was stirred at −10 °C for 2.5 h. The mixture was transferred via cannula to a cooled solution (−10 °C) of DMF (14 kg, 188.9 mol) in toluene (43.2 kg) while maintaining the temperature below 10 °C. The solution was allowed to stand at −5 to −10 °C for 30 min and then transferred via a Teflon cannula to an aqueous citric acid solution (56.6 kg in 105 L of water) while maintaining the temperature of the mixture below 20 °C. After stirring the mixture below 20 °C for 10 min, the organic layer was separated and washed with water (105 L). The organic layer was concentrated to ca. 130 L, in vacuo, and was used in the next step. HPLC analysis showed that the desired product was obtained in 91% assay yield (25.0 kg).[32,33]

4-(*tert*-Butoxycarbonylamino)-1-(6-bromopyridin-2-ylmethyl)piperidine (36). The toluene solution of 6-bromo-2-formylpyridine (**26**), obtained from previous step, was added to a suspension of 4-Boc-aminopiperidine AcOH salt **35**[52] (38.55 kg, 4.07 mol) in THF (46.6 kg) at ambient temperature, and the mixture was stirred at 15 to 20 °C for 30 min. A solution of $NaBH(OAc)_3$ (33.04 kg, mol) in DMSO (100 kg) was added at 15 to 20 °C over a period of 3 h, and the mixture was further stirred at 15 to 20 °C for 2.5 h. After cooling the reaction mixture to 10 °C, an aqueous NaOH solution (1 N, 8 L) was added while maintaining the temperature below 25 °C. A solution of phthalic anhydride (4.18 kg, mol) in DMSO (20 L) was added at 15 to 20 °C, and the mixture was further stirred at 15 to 20 °C for 1 h. After cooling to 10 °C, aqueous NaOH solution (1 N, 291 L) was added while maintaining the temperature below 25 °C, and the mixture was warmed to ambient temperature. The organic layer was separated and washed with brine (20%, 146 L). The resulting solution was concentrated to ca. 80 L at 60 °C (bath temperature) in vacuo, and then *n*-heptane (569.7 kg) was added at 70 °C over a period of 1 h. The mixture was allowed to cool to ambient temperature and stand overnight at 0 °C for 2 h. The resulting slurry was filtered, and the cake was washed with *n*-heptane (47.44 kg) twice. Drying the white crystalline solid under reduced pressure with nitrogen stream at ambient temperature gave the

desired product **36** (43.5 kg, 80% yield). ^{1}H NMR($CDCl_3$, ppm) δ 1.44 (s, 9H), 1.38−1.53 (m, 2H), 1.91−1.94 (m, 3H), 2.21 (td, J = 2.0, 11.2 Hz, 2H), 2.78−2.83 (m, 2H), 3.62 (s, 2H), 4.45 (bs, 1H), 7.35 (d, J = 7.6 Hz, 1H), 7.41 (d, J = 7.3 Hz, 1H), 7.52 (dd, J = 7.3 and 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, ppm) δ 28.4, 32.5, 52.4, 63.7, 121.5, 126.2, 138.7, 141.3, 160.8. Anal. Calcd for $C_{16}H_{24}BrN_3O_2$: C, 51.90; H, 6.53; N, 11.35. Found: C, 51.96; H, 7.09; N, 11.37.

4-(*tert*-Butoxycarbonylamino)-1-(6-aminopyridin-2-ylmethyl)piperidine (39). Dry toluene (50.4 L) was introduced into a 80 L reactor, and the mixture was degassed (vaccum/N_2 cycle, three times). Mono-bromopyridine **36** (5290 g, 95 wt %), dppf (75.5 g), NaO^{t}Bu (1570 g), $Pd(OAc)_2$ (15.3 g), and benzophenone imine (3021 g) were charged, and the mixture was heated at such a rate that the inner temperature rose to 78−82 °C within 30−60 min. The reaction mixture was agitated for 1h at 78−82 °C. The mixture was allowed to cool to ambient temperature −15−20 °C) and then allowed to stand for 10 min. Tri *n*-butylphosphine (306 g) was added to the mixture which was allowed to stand for 10 min. The toluene solution was then poured into 5% aq citric acid (91 L) and allowed to stand for 30 min at ambient temperature. The aqueous layer was washed with *i*-PrOAc (25.2L), and the organic layer was discarded (after HPLC analysis to ensure no product loss to this layer). The citric acid layer was treated with *i*-PrOAc (62.6 L) and 5 N NaOH (12.1 L) at 15−20 °C. The organic layer was washed with 7% aq NaCl (10.1 L) and then dried over anhydrous sodium sulfate (6000 g). The resulting solution was pretreated with activated carbon (417 g, Shirasagi P) for 1 h at ambient temperature and then filtered through Celite to remove activated carbon, and the filter cake was washed with isopropyl acetate (9 L). The filtrate was concentrated to ca. 25 L under reduced pressure. Crystallization was induced by seeding, and the resultant slurry was allowed to stand for 1 h at 20−25 °C. *n*-Heptane (50.1L) was added over a period of 30 min, and the mixture was agitated for 1 h at 15−20 °C. The slurry was filtered through a glass filter, and the filter cake was washed with *n*-heptane/*i*-PrOAc = 2.5/1 (12.5 L) and dried at 40 °C under reduced pressure with a nitrogen stream for 20 h to give 3600 g of **39** (86% yield) as white crystals (mp 139.5 °C). ^{1}H NMR ($CDCl_3$, ppm) δ 1.44 (s, 9H), 1.40−1.58 (m, 2H), 1.87−1.93 (m, 3H), 2.14 (td, J = 2.3, 11.6 Hz, 2H), 2.81−2.86 (m, 2H), 3.44 (s, 2H), 3.46 (bs, 1H), 4.44 (bs, 2H), 6.37 (d, J = 7.9 Hz, 1H), 6.69 (d, J = 7.3 Hz, 1H), 7.38 (dd, J = 7.3, 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, ppm) δ 28.4, 32.5, 52.6, 64.6, 106.9, 138.0. Anal. Calcd for $C_{16}H_{26}N_4O_2$: C, 62.72; H, 8.55; N, 18.29. Found: C, 62.84; H, 8.76; N, 18.25.

4-Amino-1-(6-aminopyridin-2-ylmethyl)piperidine Trihydrochloride Salt (3). To a solution of **39** (7100 g, 23.17 mol) in methanol (24.9 L) was added a mixture of concentrated HCl (10.2 L, 115.86 mol) and methanol (10.2 L), over a period of 30 min, while maintaining the temperature of the mixture below 30 °C. The mixture was warmed to 40 °C over ca. 30 min and stirred at 40 °C for 4 h. The resulting solution was cooled to ambient temperature and then concentrated to ca. 9.5 L. MeOH (11.8 L) was added, and the solution was again concentrated to 11 L. After being seeded, the solution was allowed to stand at ambient temperature for 1 h to make a seed bed, and methyl *tert*-butyl ether (7.1 L) was added to the slurry over a period of 30 min. After allowing to stand at ambient temperature overnight the resulting slurry was filtered. The filter cake was washed with methanol- methyl *tert*-butyl ether (2:1) (14.2 L) and then dried at room temperature under reduced pressure with a nitrogen sweep for 12 h to give **3** (6580 g, 90% yield) as white crystals (mp 258 °C).[2a] ^{1}H NMR (DSS in D_2O, ppm) δ 0.60−0.66 (m, 1H), 1.74−1.79 (m, 1H), 1.96−2.11 (m, 2H), 2.39 (d, J = 13.5 Hz, 2H), 2.88−2.94 (m, 1H), 3.30−3.39 (m, 2H), 3.76 (d, J = 12.2 Hz, 2H), 4.49 (s, 2H), 4.80 (bs, 2H), 7.14 (d, J = 5.9 Hz, 1H), 7.14 (d, J = 6.6 Hz, 1H), 7.95 (dd, J = 5.9, 6.6 Hz, 1H); ^{13}C NMR (DSS in D_2O, ppm) δ 21.8, 29.4, 47.7, 53.7, 57.0, 58.7, 118.5, 119.4, 119.4, 138.1, 146.6. Anal. Calcd for $C_{11}H_{21}Cl_3N_4$: C, 41.85; H, 6.71; N, 17.75. Found: C, 41.96; H, 6.98; N, 17.83.

Final Coupling: (2*R*)-*N*-[1-(6-Aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1*R*)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylactamide (1). In a separation vessel, the DCHA salt **25** (3102 g, 8.15 mol) was mixed with 1.02 N NaOH (20.3 L, 2.54 equiv) and *n*-heptane (15.5 L). The two layers were separated, and the aqueous layer was re-extracted with *n*-heptane (15.5 L). The aqueous layer was mixed with CH_3-CN (20.2 L) and HOBT (958 g), and amine trihydrochloride **3** (2350 g) was added sequentially. After all of the solids were dissolved, EDC (1631 g) was added. The resulting homogeneous solution had a pH of about 6−6.5. The batch was allowed to stand at 30 °C for 6 h until HPLC indicated <2 area % of the acid **2** remained. The batch was cooled to ≤20 °C and charged with 5 N NaOH (4.3 L, 3 equiv) and MTBE (20.2 L), and the two layers were separated. The organic layer was washed with 1 N NaOH (12.4 L) and 2 N HCl (14.1 L, 3 equiv), and the layers were separated. The organic layer was discarded. The aqueous layer was mixed with MTBE (20.2 L) and cooled to ≤20 °C, and then 50% NaOH solution (2.4 kg) was added. The pH of the aqueous layer was ≥11. The two layers were separated, the organic layer was washed with brine (12.4 L), solvent was switched with *i*-PrOAc and treated with activated charcoal Darco G-60 (155 g), and the mixture was stirred for 1 h. Filtration through Celite afforded a clear solution. The Celite cake was washed with additional *i*-PrOAc (3.1 L). The filtrate was concentrated in vacuo to about 23.5 L total volume. The resulting slurry was heated to 60 °C, to dissolve the solid, and then *n*-heptane was added while keeping the temperature of the batch at 60 °C. After *n*-heptane (1.6 L) addition, the batch was seeded and allowed to stand for 30 min until crystallization initiated. The remainder of the *n*-heptane (total of 44.9 L, 2× of the *i*-PrOAc volume) was added over 30 min. The batch was allowed to cool to ambient temperature (20−25 °C) and allowed to stand overnight. The solid product was collected by filtration and the cake washed with 2:1 *n*-heptane/*i*-PrOAc (9.3 L) and then *n*-heptane (7.8 L). The product was dried at in a vacuum oven under nitrogen sweep at 45 °C overnight to afford **1** (2612 g, 83% from **25**).[2a]

Supporting Information Available: Experimental procedures and spectroscopic data of compounds **34**, **35**, **41**, **42**, **35b**, **43**, and **3** (from alternative synthesis). This material is available free of charge via the Internet at http://pubs.acs.org.

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