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A Novel Enantioselective Alkylation and Its Application to the Synthesis of an Anticancer Agent

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Received March 24, 2003

Abstract: A novel enantioselective alkylation of double benzylic substrates with secondary electrophiles is reported. A simple norephedrine-based chiral ligand was synthesized that gives alkylation product in 95% yield and 95% ee. A unique water effect on the enantioselectivity was unveiled. Good to excellent ee values were obtained with a number of double benzylic substrates and secondary electrophiles. This novel reaction has been applied to the synthesis of a promising anticancer agent.

Lonafarnib (Sch 66336) is a potent farnesyl protein transferase inhibitor (FPTI) and is currently in clinical trial for the treatment of several types of cancer. FPT is a key enzyme that facilitates the signal transduction during cell proliferation.[1] Therefore, inhibition of FPT stops the progression of tumor cells.[2] These important clinical indications have stimulated research interests in developing synthetic routes. Several racemic syntheses were used for the initial supply of drug substance.[3] Those syntheses have more than 19 steps with poor yield. Furthermore, the late stage resolution resulted in more than 50% yield loss and the wrong enantiomer was very difficult to racemize. These shortcomings and the requirement of a large quantity of drug substance for clinical studies prompted our effort toward an efficient process. We now report the first example of an enantioselective alkylation of double benzylic substrates with secondary electrophiles and its application to the synthesis of Lonafarnib.

We envisioned, as a key step, an enantioselective alkylation for the formation of the benzylic chiral center starting from a tricycle **2a** and piperidine mesylate **1** shown in Figure 1. Various synthetic methods have been reported for carbon−carbon bond formation via enantioselective alklylation.[4,5] These reported methods can be divided into two types: those using a covalently bonded chiral auxiliary[4] and those using a noncovalently bonded chiral mediator.[5] We focused our attention on the straightforward chiral mediator-promoted alkylation. Most of the chiral mediator-promoted alkylation substrates reported bear a carbonyl-like group such as ketone, imine, and hydrazone. There are few examples of chiral mediator-promoted enantioselective alkylation of anions generated from benzylic compounds.[6] Those reported benzylic examples gave moderate yield and low ee values. Moreover, only primary electrophiles were used for the alkylation.

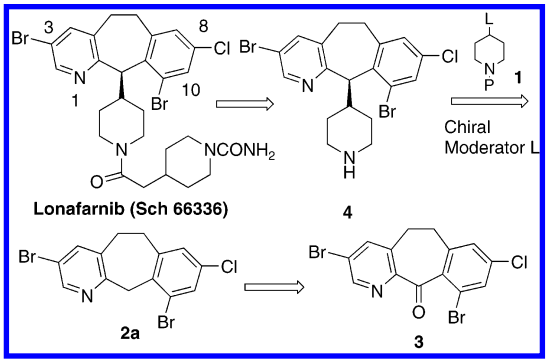

FIGURE 1. Retrosynthetic analysis.

For the preparation of **2a**, we have developed a zinc-promoted selective reduction of ketone **3** as shown in Scheme 1.[7] The three halogen substituents in ketone **3** remained essentially intact under the mild conditions. The precursor ketone **3** was prepared from a Grignard-promoted selective acylation.[8] We initially reduced ketone **3** to an alcohol in 80% ee with CBS reagent.[9] Attempts to convert the alcohol to a related leaving group followed by displacement with a nucleophile resulted in racemization of the chiral center. We therefore turned our effort to an alternative alkylation approach shown in Scheme 2.

First, we studied the racemic alkylation with substrate **2a**. Among the leaving groups (mesylate, brosylate, nosylate, and iodide) tested, mesylate was found to be the best for this alkylation. LDA was found to be an

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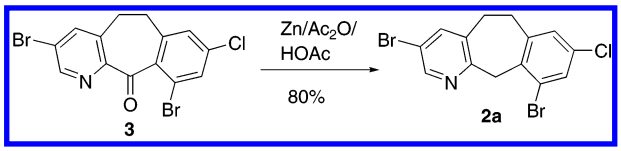
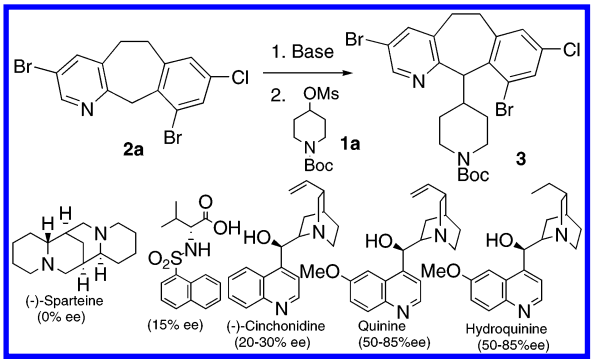
10.1021/jo034380t CCC: $25.00
Published on Web 05/10/2003

SCHEME 1. Reduction of 3 to 2a



SCHEME 2



effective base.[10] Reaction in THF generated only 15% of the alkylated product. Elimination of the mesylate was found to be the major pathway. Substitution of toluene, a lesser polar solvent, for THF minimized the elimination and increased the yield of alkylated product from 15% to 85%. This is not surprising as more polar solvents favor elimination.

With the success of racemic alkylation, we then studied its chiral version by screening commercially available chiral mediators. To test our secondary electrophiles, a general procedure was developed. Thus, to a mixture of **1a**, **2a**, and a chiral mediator in toluene was added LDA until a purple color was observed. Addition of a second equivalent of LDA completed the alkylation. The first equivalent of LDA neutralizes the alcohol in the mediator while the second one deprotonates the substrate. The ee of **4a** was determined by chiral HPLC. Over 40 commercially available mediators were screened and some selected results are summarized in Scheme 2. Sparteine did not give any chiral induction while D-valine sulfonamide produced **4a** in 15% ee. Cinchonidine induced 20−30% ee; however, its methoxy derivatives, quinine and hydroquinine, gave up to 85% ee. Apparently, the extra methoxy on the quinoline moiety exerts great influence on the enantioselectivity.

To improve the ee, we designed some mediators. On the basis of the results in Scheme 2, we postulated a three-point interaction between **2a** and quinine. The alkoxy and the bridgehead nitrogen are the first two sites to chelate with lithium. The third point of interaction comes from the π-stacking between the quinoline moiety and the pyridine ring in **2a**. The presence of an electron-donating methoxy group enriches the electron density on the aromatic ring and therefore enhances the π-stacking effect. Norephedrine was selected as the starting material for its easy derivatization. Both secondary and tertiary amines were prepared and tested as shown in Table 1. The ee values of **4a** with tertiary amines only ranged from 13 to 28%. The use of secondary amines produced much better ee values. Table 1 also indicates that (1) the

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TABLE 1. Norephedrine-Based Mediators

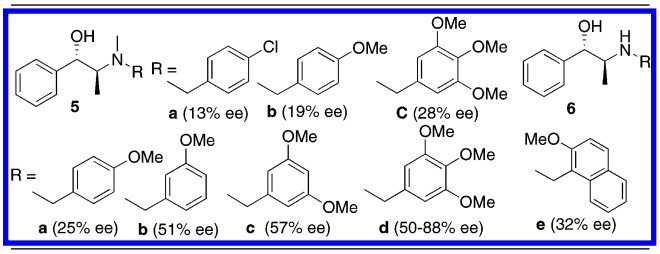


TABLE 2. Effect of Water on the Enantioselectivity

entry	**6d**, equiv	water, equiv	ee, %	yield, %
1	1.8	0.0	55	50
2	1.8	0.7	85	92
3	1.8	1.0	95	95

richer the electron density on the aromatic ring the better the ee and (2) meta substitution is better than ortho. The rationally designed mediator, **6d**, gave up to 88% ee.

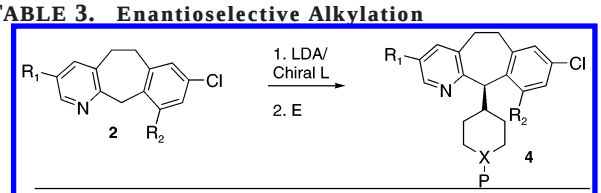
One of the issues associated with the reaction with both quinine and **6d** was the inconsistency of ee values obtained from run to run. We first suspected that water was detrimental to the LDA reaction. Counter-intuitively, a consistently lower range of ee values was observed when moisture was vigorously excluded from the system. To follow up on this unexpected observation, we then spiked different amounts of water to the reaction mixture prior to the addition of a second equivalent of LDA. To our delight, water had a pronounced positive effect on the ee as shown in Table 2. The higher the water contents the better the ee with an optimum being 1.0 equiv. The same trend was also true for the yield. With added water, 95% ee was consistently achieved with either **6d** or quinine. The added water was compensated by an equal equivalent of LDA. Interestingly, addition of solid LiOH, $B(OH)_3$, MeOH, and AcOH had no effect on the ee. The mechanism is under further investigation.

A number of substrates and electrophiles were subjected to the chiral alkylation with either **6d** or quinine and their results are listed in Table 3. The following points are worth noting. (1) The positive water effect has been observed for all reactions.(2) Good to excellent ee values were achieved for all the substrates. (3) This alkylation worked well for such a relatively symmetric substrate as des-10 bromo analogue, **2b**, (entries 7 and 8). (4) The substituent at the 4-position of the electrophile has a distinct effect on the ee.

To complete the reaction, the alkylated product **4a** was hydrolyzed in situ and crystallized as *N*-acetyl-L-phenylalanine salt, further enhancing the ee to >98%. Both quinine and **6d** can be readily recovered and recycled without loss of ee. The commercially available quinine was used for scale-up. After some practical modifications, this novel chiral alkylation was scaled up to a 33 kg batch size, producing more than 200 kg of **4**-salt in 99% ee and 80% isolated yield. To complete the synthesis, **4**-salt was coupled with *N*-Boc-piperidine-4-acetic acid followed by removal of the Boc and formation of the urea to give Lonafarnib in excellent overall yield as outlined in Scheme 3.

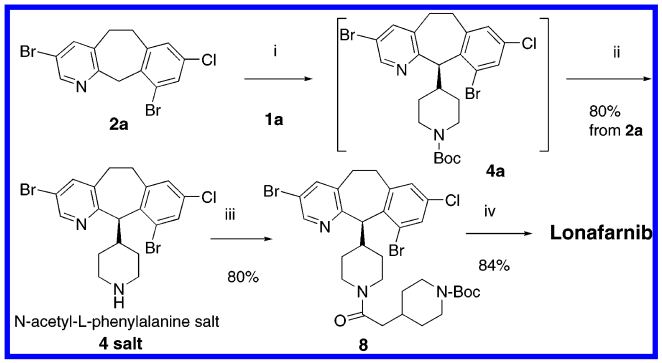
In summary, we have developed a novel enantioselective alkylation of benzylic derivatives with secondary

TABLE 3. Enantioselective Alkylation



entry	2	R_1	R_2	Chiral L	E	4	ee% No H_2O	ee% with H_2O
1	**2a**	Br	Br	**6d**	MsO-N·Boc-*t* **1a**	**4a**	58	95
2	**2a**	Br	Br	quinine	**1a**	**4a**	50	95
3	**2a**	Br	Br	quinine	MsO-N·COBu-*t* **1b**	**4b**	50	86
4	**2a**	Br	Br	quinine	MsO-N·CO_2Et **1c**	**4c**	64	81
5	**2a**	Br	Br	quinine	MsO-N·CONPr$_2$-*i* **1d**	**4d**	50	81
6	**2a**	Br	Br	quinine	MsO- **7**	**4e**	51	65
7	**2b**	Br	H	quinine	**1a**	**4f**	50	80
8	**2b**	Br	H	**6d**	**1a**	**4f**	50	80
9	**2c**	H	Br	quinine	**1a**	**4g**	N/A	85

SCHEME 3. Synthesis of Lonafarnib[a]



[a] Reagents and conditions: (i) LDA/quinine/toluene; (ii) H_2SO_4; (iii) *N*-Boc-piperidine acetic acid/HOBT/EDCl; (iv) HCl/urea/NMP.

electrophiles. We have also designed and synthesized a highly effective norephedrine-based mediator. In addition, we have discovered a unique water effect on the enantioselectivity. With the novel alkylation, we have not only achieved an 8-step synthesis of Lonafarnib but also scaled up production in the plant.

Experimental Section

Zinc Reduction of Ketone 3 to 2a. To a mixture of the tricyclic ketone **3** (200 g, 0.5 mol) and acetic anhydride (360 mL) in THF (700 mL) at −25 °C were sequentially added zinc dust (113 g, 1.7 mol) and trifluoroacetic acid (84 mL, 1.1mol) dropwise over a 2-h period. The temperature of the mixture was slowly raised to 18 °C over a period of 2 h and kept at 18 °C for 20 h. A filter aid (Supercel) and toluene (200 mL) were added and the mixture was filtered. The extra zinc and inorganic residue were washed with toluene (40 mL). The filtrate and wash were combined, and washed with water (1 L), 10% NaOH (160 L), and water (1 L). After layer separation, the organic layer was concentrated to 600 mL. 2-Butanol (1.6 L) was added to the mixture, which was then concentrated to 600 mL under vacuum. Again, 800 mL of 2-butanol was added and the mixture was heated to reflux for 1 h. The mixture was cooled to between 0 and 5 °C and stirred for 4 h. The solid was filtrated and washed with 400 mL of 2-butanol. The wet cake was dried under vacuum at 70 °C to give 162 g (84%) of **2a** as a crystalline solid. Mp 163−164 °C. ^{1}H NMR ($CDCl_3$) δ 8.38 (d, J = 2.0 Hz, 1H), 7.46 (d, J = 2.0 Hz, 1H), 7.44 (d, J = 2.0 Hz, 1H), 7.14 (d, J = 2.0 Hz, 1H), 4.45 (s, 2H), 3.10−3.20 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 154.1, 148.5, 143.9, 141.7, 137.2, 135.8, 133.9, 131.6, 128.7, 125.5, 119.8, 41.7, 32.90, 32.7. Anal. Calcd for $C_{14}H_{10}Br_2ClN$: C, 43.37; H, 2.58; N, 3.61; Br, 41.31; Cl, 9.17. Found: C, 43.33; H, 2.66; N, 3.69; Br, 41.06; Cl, 9.11.

Method A. Enantioselective Alkylation with Quinine and 1a to 4a. A mixture of 6.0 g (15.5 mmol) of the tricycle, **2a**, and 5.0 g (17.9 mmol) of *N*-Boc-piperidine mesylate, **1a**, in 25 mL of toluene was heated to 40 °C until all solid dissolved (30 min). The solution was cooled to 25 °C and transferred to another flask containing 6.0 g (18.5 mmol) of quinine. To the resulting mixture at 5−10 °C was added 1.5 M of LDA∗monoTHF in cyclohexane (ca. 13.4 mL, 20.1 mmol) until a red solution was formed. To the red solution were sequentially added water (0.28 mL, 15.5 mmol) and 1.5 M of LDA∗monoTHF (10.3 mL, 15.5 mmol). The reaction mixture was allowed to warm to between 14 and 18 °C. To the mixture at 14−18 °C was added the same type of LDA (11.4 mL, 17.1 mmol) over a period of 3 h. The reaction mixture was allowed to warm to between 20 and 25 °C and agitated at this temperature for 18 h. The reaction was then quenched by an addition of 36 mL of water. The precipitated quinine was filtered and washed with 12 mL of toluene and 12 mL of water. The layers of the filtrate were separated and the organic phase was washed with 24 mL of 7.6% sulfuric acid. The toluene layer can be concentrate to give the *N*-Boc-protected product, **4a**, as a white solid (95% ee). Mp 172−174 °C. ^{1}H NMR ($CDCl_3$) δ 8.31 (d, J = 2.2 Hz, 1H), 7.40 (d, J = 2.2 Hz, 1H), 7.36 (d, J = 2.2 Hz, 1H), 7.00 (d, J = 2.2 Hz, 1H), 4.76 (d, J = 10.3 Hz, 1H), 3.94 (br s, 2H), 3.49 (td, J = 14.0, 7.0 Hz, 1H), 3.13 (dt, J = 13.3, 4.3 Hz, 1H), 2.84 (tt, J = 13.3, 4.3 Hz, 1H), 2.67 (dt, J = 14.9, 4.5 Hz, 1H), 2.32 (br s, 2H), 2.22−2.05 (m, 1H), 1.30 (br s, 9H), 1.25−1.05 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 115.1, 154.7, 147.3, 142.6, 141.3, 137.4, 135.1, 132.9, 131.0, 129.1, 127.2, 118.8, 79.4, 58.2, 43.6, 42.0, 32.0, 31.7, 31.4, 30.3, 28.4. Anal. Calcd for $C_{24}H_{27}Br_2ClN_2O_2$: C, 50.51; H, 4.77; N, 4.91. Found: C, 50.50; H, 4.73; N, 4.70.

In the total synthesis, the toluene layer was further processed as following. To the toluene phase was added 36 mL of 20% sulfuric acid while maintaining the temperature below 80 °C. The resulting mixture was heated to 85 °C for 4 h to complete the hydrolysis of the Boc group. After the mixture was cooled to 25 °C, 15.1 mL of 25% ammonium hydroxide was added. The layers were separated. The organic layer was concentrated under vacuum to 48 mL. To the concentrated mixture was added 114 mL of ethanol. The mixture was concentrated to a final volume of 48 mL and was then cooled to between 20 and 25 °C. To the resulting mixture was added 3 g of *N*-acetyl-L-phenylalanine dissolved in 120 mL of ethanol. The mixture was concentrated under vacuum to 48 mL. The concentrated batch was stirred at 70 °C for 1 h and cooled to room temperature. The precipitate was filtered and washed with *t*-BuOMe/EtOH (1:1) and dried at 55 °C under vacuum to give 10.5 g (80% yield, 98% ee) of **4**-salt. The corresponding free base was obtained by dissolving the salt in water, adjusting pH, and extracting with toluene. Characterization of the free base. Mp 179−182 °C. ^{1}H NMR ($CDCl_3$) δ 8.44 (d, J = 2.2 Hz, 1H), 7.53 (d, J = 2.2 Hz, 1H), 7.48 (d, J = 2.2 Hz, 1H), 7.12 (d, J = 2.2 Hz, 1H), 4.90 (d, J = 10.3 Hz, 1H), 3.64 (td, J = 13.9, 4.4 Hz, 1H), 3.27 (dt, J = 17.4, 4.4 Hz, 1H), 3.15−2.90 (m, 3H), 2.79 (dt, J = 14.8, 4.5 Hz, 1H), 2.49−2.41 (m, 2H), 2.32−2.20 (m, 1H), 1.55−1.40 (m, 2H), 1.35−1.20 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 155.8, 147.5, 142.9, 141.6, 138.0, 135.4, 133.1, 131.3, 129.4, 128.5, 127.6, 119.1, 59.2, 47.2, 47.0, 42.5, 33.3, 32.4, 32.1, 32.0. HRMS 470.9661 (MH^+), calcd for $C_{19}H_{20}Br_2ClN_2$ (MH^+) 470.9661.

Enantioselective Alkylation of 2b with Quinine as a Ligand. Mehtod A was followed with 0.5 g of des-3-bromo **2b** analogue and **1a** to give **4f** in 80% ee. The alkylated product was purified on a silica gel column, eluting with hexanes/EtOAc (1:1), to give des-10-bromo **4f** as a white solid. Mp 85−90 °C. ^{1}H NMR ($CDCl_3$) δ 8.32 (d, J = 2.0 Hz, 1H), 7.49 (s, 1H), 7.06 (d, J = 2.0 Hz, 1H), 7.03 (dd, J = 8.1, 2.1 Hz, 1H), 6.99 (d, J = 8.1 Hz, 1H), 4.12−3.95 (m, 2H), 3.81 (d, J = 10.2 Hz, 1H), 3.47−

3.15 (m, 2H), 2.90−2.70 (m, 2H), 2.58−2.35 (m, 2H), 2.25−2.08 (m, 1H), 1.36 (s, 9H), 1.35−1.00 (m, 3H).

Enantioselective Alkylation of 2c with Quinine as a Ligand. Mehtod A was followed with 0.8 g of **2c** and **1a** to give **4g** in 85% ee. The crude product was chromatographed on silica gel, eluting with hexanes/EtOAC (4:1), to give 0.97 g (76%) of **4g** as a white solid. Mp 80−85 °C. ^{1}H NMR ($CDCl_3$) δ 8.32 (d, J = 3.8 Hz, 1 H), 7.39 (d, J = 1.4 Hz, 1H), 7.29 (d, J = 7.5 Hz, 1H), 7.05 (s, 1H), 7.00 (dd, J = 7.5, 3.8 Hz, 1H), 4.85 (d, J = 10.3 Hz, 1H), 4.00 (br s, 2H), 3.58 (td, J = 14.3, 2.6 Hz, 1H), 3.23−3.19 (m, 1H), 3.00−2.80 (m, 1H), 2.78−2.60 (m, 1H), 2.46 (br s, 2H), 2.35−2.15 (m, 2H), 1.36 (br s, 9H), 1.34−1.20 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 156.8, 155.1, 146.8, 143.4, 139.7, 138.4, 133.6, 133.1, 131.2, 129.5, 127.6, 122.4, 79.7, 59.3, 42.6, 32.6, 32.5, 31.8, 30.8, 28.8. MS (MH^+): 491. Calcd for $C_{24}H_{29}BrClN_2O_2$ (MH^+): 491.

Enantioselective Alkylation with Quinine to 4b, 4c, and 4d. These alkylation products were all converted to the free amine **4** for charaterization.

Alkylation with Cyclohexyl Mesylate with Quinine to 4e. Mehtod A was followed and **4e** was isolated with silica gel column, eluting with hexanes/ethyl acetate (1:1) to give the alkylated product as a white solid in 65% ee. Mp 165−167 °C. ^{1}H NMR ($CDCl_3$) δ 8.36 (d, J = 2.2 Hz, 1H), 7.44 (dd, J = 2.2, 1.1 Hz, 1H), 7.03 (d, J = 2.2 Hz, 1H), 4.77 (d, J = 10.3 Hz, 1H), 3.59 (td, J = 13.2, 4.5 Hz, 1H), 3.34 (dt, J = 17.4, 4.5 Hz, 1H), 2.88 (td, J = 13.2, 4.7 Hz, 1H), 2.69 (dt, J = 14.8, 4.7 Hz, 1H), 2.12−2.04 (m, 1H), 1.70−1.23 (m, 4H), 1.22−0.95 (m, 6H). ^{13}C NMR ($CDCl_3$) δ 156.5, 147.5, 142.9, 141.6, 138.8, 135.4, 133.0, 131.2, 129.4, 127.6, 119.0, 59.3, 43.9, 32.7, 32.3, 32.0, 31.8, 27.0, 26.8, 26.5. MS (MH^+): 468. Calcd for $C_{20}H_{21}Br_2ClN$ (MH^+): 468.

Method B. Enantioselective Alkylation with Norephedrin-Based Ligand 6d to 4a. The tricyclic methylene compound **2a** (50 g, 0.13 mol), trimethoxybenzyl-norephedrine ligand **6d** (77 g in 436 mL of toluene solution, 1.8 equiv), and *N*-Boc piperidine mesylate **1a** (43.2 g, 1.2 equiv) were dissolved in toluene (1 L). To the mixture at between 0 and 5 °C were sequentially added lithium diisopropyl amide mono(tetrahydrofuran) solution (1.5 M in cyclohexane) (155 mL, 1.8 equiv) in 20 min and water (2.3 mL, 1 equiv) over 10 min. The remaining LDA (172 mL, 2 equiv) was added slowly over 4 to 5 h at between 15 and 20 °C. The reaction mixture was stirred at 25 °C for another 4 h as monitored by HPLC. Once the reaction is completed, 1 N hydrochloric acid (1.2 L) was added to precipitate the chiral inducing ligand as hydrochloric acid salt. The solid was filtered and the layers were separated. The organic layer was concentrated and the residue was separated on a silica gel column to give **4a** (95% yield and 95% ee) as a solid. Without addition of the water into the reaction mixture the ee ranged from 50 to 88%.

Preparation of Norephederine-Based Ligand 6d. A mixture of (1*R*,2*S*)-(−)-norephedrine (100 g) and 3,4,5-trimethoxybenzaldehyde (143 g) was dissolved in ethanol (1 L). The resulting solution was brought to a gentle reflux for 4−5 h. The reaction mixture was then cooled with an ice batch, and sodium borohydride (37 g) was added protionwise. The reaction mixture was stirred at room temperature overnight. Once reduction was completed, excess sodium borohydride was destroyed by adding water (25 mL). The organic solvent was evaporated and the product was extracted with ethyl acetate. The organic layer was concentrated to give a colorless oil. The oil was dissolved in 400 mL of ethanol. To the resulting solution was added slowly aqueous hydrobromic acid (48%, 73 mL). The precipitate was stirred at room temperature for 1 h and filtered to give crude **6d** as HBr salt. The crude salt was recrystallized in a mixture of methanol/diethyl ether (12:1). The recrystallized salt was converted to a free base with diluted aqueous sodium hydroxide. The free base was extracted with toluene. The toluene was then removed to give 114 g of **6d** (87%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.25−7.33 (m, 5H), 6.56 (s, 2H), 4.80 (d, J = 3.8 Hz, 1H), 3.86 (s, 6H), 3.84 (s, 3H), 3.82 (s, 2H), 3.00 (qd, J = 6.5, 3.8 Hz, 1H), 0.89 (d, J = 6.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 154.3, 142.2, 139.0, 136.4, 129.1, 128.2, 127.10, 106.0, 74.4, 62.0, 59.1, 57.3, 52.7, 15.8. Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.68; H, 7.74; N, 4.30.

Conversion of 4-salt to 8. To a 500-mL flask were sequentially charged 10 g (14.4 mmol) of **4**-salt, 100 mL of toluene, 50 mL of 25% NaOH, and 100 mL of water. The resulting mixture was agitated for 30 min and 1 g of Celite was added. The mixture was filtered and washed with 10 mL of toluene. The layers were separated and the organic layer was washed with 4 × 50 mL of water. To the organic layer were added 40 mL of DMF, 0.20 g (14.7 mmol) of 1-hydroxybenzotriazole (HOBT), 3.2 g (16.6 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide∗HCl (EDCl∗Cl), and 4.0 g of 1-*N*-*tert*-butoxy-carbonylpiperidinyl-4-acetic acid. The mixture was stirred at room temperature to completion (about 18 h) as monitored by HPLC. To the reaction mixture was added 50 mL of water and the layers were separated. The organic layer was sequentially washed with 20 mL of 10% acetic acid solution, 40 mL of water, 3% NaOH solution, 3 × 40 mL of water, and 40 mL of brine. The organic layer was concentrated to 60 mL and chromatographed on silica gel, eluting with EtOAc/toluene (1:1). The fractions containing the product were combined, concentrated, and treated with 3.5 g of activated basic alumina. The mixture was filtered and washed with toluene. The filtrate was concentrated and treated with EtOAc and heptane to give after filtration 8.0 g (80%) of **8** as a solid. Mp 171−173 °C. ^{1}H NMR ($CDCl_3$) δ 8.44 (d, J = 2.0 Hz, 1H), 7.55 (dd, J = 5.0, 2.0 Hz, 1H), 7.49 (t, J = 2.0 Hz, 1H), 4.89 (dd, J = 10.3, 3.5 Hz, 1H), 4.63−4.57 (m, 1H), 4.18−3.98 (m, 2H), 3.82 (t, J = 12.7 Hz, 1H), 3.64 (tt, J = 13.8, 3.6 Hz, 1H), 3.60 (dt, J = 17.7, 4.3 Hz, 1H), 2.98 (tt, J = 13.8, 3.6 Hz, 1H), 2.90−2.75 (m, 2H), 2.75−2.60 (m, 2H), 2.45−2.30 (m, 2H), 2.30−2.15 (m, 2H), 2.05−1.90 (m, 1H), 1.80−1.20 (m, 6H), 1.45 (s, 9H), 1.20−1.05 (m, 2H).

Conversion of 8 to Lonafarnib. To a 250-mL flask were added 7.07 g (10.2 mmol) of **8** and 35 mL of ethanol. To the above solution was added slowly 42 mL of 3 N HCl while maintaining the temperature below 25 °C with an ice bath. The mixture was stirred at room temperature for about 6 h to complete the hydrolysis. The reaction mixture was concentrated under vacuum to about 35 mL. To the concentrated mixture was added 17.5 mL of 1-methyl-2-pyrrolidinone and the pH was carefully adjusted to 9 with 3 N NaOH. To the resulting mixture was added 28.0 g of urea. The mixture was heated to 110 °C for about 10 h and cooled to 50 °C. The pH of the reaction mixture was adjusted to 6 with 3 N HCl. The precipitate was filtered and washed with 140 mL of water to give after drying 5.44 g (84%) of Lonafarnib. Mp 222−223 °C. δ ^{1}H NMR ($CDCl_3$) 8.38 (d, J = 2.2 Hz, 1H), 7.48 (dd, J = 4.8, 2.0 Hz, 1H), 7.43 (d, J = 2.0 Hz, 1H), 7.08 (d, J = 2.2 Hz, 1H), 4.82 (dd, J = 10.3, 4.2 Hz, 1H), 4.53 (t, J = 7.4 Hz, 1H), 4.34 (s, 2H), 3.90−3.70 (m, 3H), 3.55 (tt, J = 13.8, 4.3 Hz, 1H), 3.20 (dt, J = 17.6, 4.2 Hz, 1H), 2.95−2.82 (m, 1H), 2.80−2.70 (m, 4H), 2.37−2.30 (m, 2H), 2.20−2.15 (m, 2H), 2.00−1.95 (m, 1H), 1.70 (d, J = 12.8 Hz, 2H), 1.48−1.00 (m, 6H). ^{13}C NMR ($CDCl_3$, two rotamers) 169.5, 158.3, 155.1, 155.0, 146.8, 144.1, 144.1, 137.8, 137.7, 136.3, 136.2, 132.4, 130.4, 129.8, 129.7, 126.7, 126.7, 118.8, 58.3, 58.2, 45.4, 45.3, 43.9, 41.4, 41.2, 40.8, 39.0, 38.9, 33.1, 32.7, 32.0, 31.8, 31.4, 31.3, 30.8, 30.6. Anal. Calcd for $C_{27}H_{31}Br_2ClN_4O_2$: C, 50.76; H, 4.89; N, 8.77. Found C, 50.84; H, 4.77; N, 8.73.

Acknowledgment. We thank Mr. Zhixing Ding, Dr. Mingsheng Huang, Jie Xie, and Ms. Jacqueline Klug for their help on this project and Drs. Doris Schumacher and Michael Mitchell for their support and proof-reading of the manuscript.

Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for compounds **2a**,**b**,**c**, **4a**, **4**, **4**-salt, **4e**,**f**,**g**, **5a**,**b**,**c**, **6a**,**b**,**c**,**d**,**e**, **8**, and Lonafarnib and a chiral HPLC chromatogram for **4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO034380T