Practical Asymmetric Synthesis of Efavirenz (DMP 266), an HIV-1 Reverse Transcriptase Inhibitor

Michael E. Pierce,* Rodney L. Parsons, J r., Lilian A. Radesca, Young S. Lo, Stuart Silverman, James R. Moore, Qamrul Islam, Anusuya Choudhury, Joseph M. D. Fortunak, Dieu Nguyen, Chi Luo, Susan J. Morgan, Wayne P. Davis, and Pat N. Confalone

Chemical Process R&D Department, Process Research Facility, The DuPont Pharmaceuticals Company, Deepwater, New Jersey 08023-0999

Department of Process Research, Merck Research Laboratories, P.O. Box 2000, Rahway, New Jersey 07065

Received June 17, 1998

A highly enantioselective and practical synthesis of the HIV-1 reverse transcriptase inhibitor efavirenz (1) is described. The synthesis proceeds in 62% overall yield in seven steps from 4-chloroaniline (6) to give efavirenz (1) in excellent chemical and optical purity. A novel, enantioselective addition of Li-cyclopropyl acetylide (4a) to p-methoxybenzyl-protected ketoaniline 3a mediated by (1R,2S)-N-pyrrolidinylnorephedrine lithium alkoxide (5a) establishes the stereogenic center in the target with a remarkable level of stereocontrol.

Introduction

Inhibition of HIV-1 (human immunodeficiency virus type 1) reverse transcriptase by nucleosides such as AZT, DDC, DDI, D4T, and 3TC is a proven therapy for delaying the progression to AIDS. However, the rapid viral mutation to resistant strains requires the development of new therapeutic agents.1–3 The recent developments of both protease inhibitors and non-nucleoside reverse transcriptase inhibitors offer hope of effective treatment, especially when coadministered.4 Efavirenz (1) is a non-nucleoside reverse transcriptase inhibitor that shows high potency against a variety of HIV-1 mutant strains5 and is currently undergoing clinical studies.6 The importance of efavirenz has prompted us to design and develop a practical enantioselective synthesis of the compound.7–9

Results and Discussion

Establishment of the quarternary carbon center in an asymmetric manner presented a unique challenge during the synthesis of efavirenz. We envisioned that the most efficient route to efavirenz would involve enantioselective addition of a metal cyclopropylacetylide to a trifluoromethyl ketone 3 (with or without N-protection) mediated by a chiral additive as depicted in Scheme 1.10 The enantioselective addition of Li-acetylenes to cyclic N-acetylenketimines mediated by stoichiometric amounts of quinine Li-alkoxide has been reported previously.10a

Scheme 1

Subsequent studies on the use of chiral Li-alkoxides as mediators for addition of Li-cyclopropyl acetylide (4a) to ketones of general structure 3 identified (1R,2S)-N-pyrrolidinylnorephedrine Li-alkoxide (5a) as the optimal chiral mediator and the p-methoxybenzyl-protected ketoaniline 3a as the substrate of choice (Scheme 2). The enantioselective alkylation reaction proceeded rapidly and efficiently in THF at low temperature (<−50 °C) to give the product amino alcohol 2a with excellent enantioselectivity (96–98% ee). This key transformation is the cornerstone of an efficient asymmetric synthesis of efavirenz, which is described in detail in this paper.

**Preparation of Starting Materials.** The synthesis of efavirenz required the preparation of p-methoxybenzyl ketoaniline 3a, cyclopropylacetylene (4b), and (1R,2S)-N-pyrrolidinylnorephedrine (5b). The ketoaniline 3a was prepared from 4-chloroaniline (6) in 76% overall yield as shown in Scheme 3. Reaction of 4-chloroaniline with pivaloyl chloride in a two-phase mixture of tert-butyl methyl ether (MTBE) and aqueous sodium hydroxide afforded pivaloylamido 7 in 97% yield. Directed orthometalation of 7 (2 equiv of n-BuLi or n-hexyllLi, MTBE, TMEDA) generated the corresponding diion, which was quenched with ethyl trifluoroacetate to afford ketooamide 8. The use of MTBE avoids the competitive attack of n-butyllithium on THF at the required reaction temperature of 0 °C. Hydrolysis of the amide in situ (HOAc–HCl) provided the hydrochloride hydrate 9, which was directly crystallized from the reaction mixture at 5 °C and was isolated in 84% yield (from 4-chloroaniline) and >98% purity. Treatment of the salt 9 with aqueous NaOAc in MTBE provided the corresponding free base 3b in preparation for the p-methoxybenzyl protection. Previously, this transformation was carried out using p-methoxybenzyl chloride in the presence of basic alumina. A more efficient and economical method has been developed using p-methoxybenzyl alcohol under mild acid catalysis. Thus, a mixture of ketoaniline 3b and a catalytic amount of p-TsOH in acetonitrile was held at 70 °C while p-methoxybenzyl alcohol was slowly added (over 3 h). Slow addition was used to minimize the formation of p-methoxybenzyl alcohol self-condensation products. Under these conditions, p-methoxybenzyl alcohol is also converted into its symmetrical ether, however, this intermediate is an equally effective alkylating agent for the conversion 3b to 3a. The product 3a was then directly crystallized from the reaction mixture by addition of water and was isolated in 90% yield and in >99% purity. Alternatively, this p-methoxybenzylation reaction could be carried out using toluene as solvent and the product 3a employed directly in the next step, as a solution in toluene, without further purification. Although this method simplifies the processing, the procedure employing acetonitrile as solvent, and isolation of 3a, is preferred since the use of purified 3a leads to more reproducible results in the enantioselective addition reaction.

The preparation of (1R,2S)-N-pyrrolidinylnorephedrine (5b) and its application as a ligand in asymmetric synthesis has been reported in the literature. While the alkylation of (1R,2S)-norephedrine (10) with 1,4-dibromobutane using K2CO3 as base was reported to give 5b in only 33% yield, it was found that reproducibly excellent yields and product purity could be obtained using NaHCO3 as base and toluene as solvent (Scheme 4). At reaction completion, inorganic salts were filtered and the filtrate was washed with water to give the product 5b as a solution in toluene (97% yield, >99.9% purity). This solution can be used directly in the chiral addition step or may be solvent switched to heptane and the product 5b isolated by crystallization at <0 °C. Alternatively, the hydrochloride salt of 5b may be isolated by the addition of HCl and 2-propanol (96% yield, >99% purity).


(13) A similar acid-catalyzed benzylolation of amides was reported. Henneuse, C.; Boxus, T.; Tesolin, L.; Pantano, G.; Marchand-Brynaert, J. Synthesis 1996, 495.


(16) This simple and efficient alkylation procedure has now been used to prepare a wide variety of N,N-cycoalkyl derivatives of amino alcohols.
Pyrrolidinylnorephedrine Li-alkoxide (18) has been published. Alternative procedures from methyl cyclopropyl ketone have also been published. Procedures from alkylolithium reagent (7). Most importantly, it was shown that the alkoxide Li-cyclopropyl acetylide (Scheme 5) at this temperature was fully prepared by treating 5-chloropentane with 2 equiv of n-butyllithium or n-hexyllithium in cyclohexane or THF.17 Alternative procedures from methyl cyclopropyl ketone have also been published.18

### Enantioselective Alkynylation

The initial report describing the enantioselective alkynylation of ketoaniline 3a with Li-cyclopropyl acetylide (4a) in the presence of chiral additive 5a defined the key parameters leading to optimal results. In addition to the requirement for n-methoxycarbonyl protection, it was shown that 2 equiv of (1R,2S)-N-pyrrolidinylnorephedrine Li-alkoxide (5a) and 2 equiv of Li-cyclopropyl acetylide (4a) are required for maximum selectivity and conversion (>97%) and that THF is the solvent of choice (used as osolvent with hydrocarbons from alkylithium reagent). Most importantly, it was shown that the alkoxide–acetylide mixture is best generated at 25 to 0 °C in order to establish aggregate equilibration prior to reaction with the ketoaniline 3a. Generation of the alkoxide–acetylide mixture below -50 °C followed by reaction with 3a at this temperature provided the addition product 2a in only 82–85% ee. Finally, it was found that the reaction is complete within minutes of addition of the ketoaniline 3a to the prequillibrated alkoxide–acetylide mixture and shows some dependence of enantioselectivity on reaction temperature (Table 2).

Many of these observations are now understood as a result of extensive 6Li NMR studies of the Li alkoxide–acetylide mixture.8 It is clear that the 2:2 alkoxide–acetylide mixture generated at low temperature exists as a complex mixture of species, which rapidly equilibrates to a single aggregate above -40 °C. This stable aggregate was fully characterized as the C2-symmetrical 2:2 cubic tetramer 11 (Scheme 5). Additionally, the level of asymmetric amplification observed in this reaction (Table 3) is very close to that predicted for reaction proceeding via cubic tetramer 11. It is clear from the above discussion that optimal reaction conversion and enantioselectivity require strict control of reagent stoichiometry and reaction conditions. Experimentally, the chiral complex 11 was prepared by reaction of n-butyllithium (N-hexyllithium) with a mixture of (1R,2S)-N-pyrrolidinylnorephedrine (5b) and cyclopropyl acetylene (4b) at -10 to 0 °C (aggregate equilibration) in a THF–toluene–hexane mixture (Scheme 5). After the mixture was cooled below -50 °C, ketoaniline 3a was added. After ~60 min, the reaction was quenched with aqueous citric acid. The organic layer was then solvent switched into toluene, and the product 2a was crystallized by the addition of heptane (91–93% isolated yield, >99.5% ee)21. The chiral additive 5b is easily recycled from the aqueous layer by basification with NaOH and extraction into toluene to give (1R,2S)-N-pyrrolidinylnorephedrine (5b) (99% purity, 98% yield). The ligand has been recycled up to nine times in this manner.

### Table 1. Asymmetric Addition of 4A to N-Protected Ketoanilines

<table>
<thead>
<tr>
<th>R group</th>
<th>solution (ee, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>p-methoxycarbonyl</td>
</tr>
<tr>
<td>b</td>
<td>hydrogen</td>
</tr>
<tr>
<td>c</td>
<td>3,4-dimethoxycarbonyl</td>
</tr>
<tr>
<td>d</td>
<td>triphenylmethyl</td>
</tr>
</tbody>
</table>

### Table 2. Effect of Temperature on Enantioselectivity

<table>
<thead>
<tr>
<th>T (°C)</th>
<th>2a (ee, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-30</td>
<td>91</td>
</tr>
<tr>
<td>-40</td>
<td>95</td>
</tr>
<tr>
<td>-50</td>
<td>97–98</td>
</tr>
<tr>
<td>-60</td>
<td>99</td>
</tr>
<tr>
<td>-70</td>
<td>99</td>
</tr>
</tbody>
</table>

### Table 3. Asymmetric Amplification

<table>
<thead>
<tr>
<th>additive 5b (ee, %)</th>
<th>product 2a (ee, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>99</td>
<td>98</td>
</tr>
<tr>
<td>90</td>
<td>95.5</td>
</tr>
<tr>
<td>80</td>
<td>91.5</td>
</tr>
<tr>
<td>70</td>
<td>88</td>
</tr>
<tr>
<td>50</td>
<td>77</td>
</tr>
</tbody>
</table>


(20) The reaction may alternately be quenched into 2 N aqueous HCl without loss of 2a into the aqueous phase. Aqueous HCl may also be used interchangeably with citric acid in purifying and recycling the ligand 5b.
(21) The product 2a readily upgrades in optical purity upon crystallization.
subsequent chiral addition reactions to give product 2a with typical chemical and optical purity.

Completion of the Synthesis. Two routes were employed for conversion of the amino alcohol 2a into the target compound, efavirenz. Initially, 2a was converted into the benzoxazinone 12 (COCl₂, Et₃N, toluene), which was isolated in 95% yield upon crystallization from methanol. Compound 12 was then deprotected (CAN) to give efavirenz (Scheme 6). Although this reaction proceeds cleanly and efficiently and is suitable for the small-scale synthesis of efavirenz, there were several features that are not attractive for the large-scale preparation of this drug. First, an equal amount of p-methoxybenzaldehyde was generated in this reaction, which was not efficiently removed from efavirenz upon crystallization. Also, a significant quantity of waste cerium salts was generated in the reaction, which is an environmental concern upon scale-up.

A more practical route to efavirenz was realized by simply reversing the order of ring closure (benzoxazinone formation) and N-deprotection. The most efficient method for the de-p-methoxybenzylation of compound 2a involved oxidative cleavage using quinones, such as DDQ (Scheme 7). Reaction of compound 2a with 1 equiv of DDQ (toluene, 0–10 °C) proceeded quantitatively to give an 11.5:1 mixture of diastereomeric cyclic aminals 13a and 13b. The DDHQ (dichlorodicyanohydroquinone) byproduct from this reaction is essentially insoluble in toluene, enabling removal by filtration and efficient recycling back to DDQ using established literature procedures. The cyclic aminals 13a/13b were then directly converted into the desired amino alcohol 2b without isolation or further purification. Reaction of 13a/13b with NaOH in MeOH effected clean dissociation to the amino alcohol 2b (as its Na alkoxide) and p-methoxybenzaldehyde. Since direct isolation of 2b in the presence of p-methoxybenzaldehyde was not feasible, this was reduced in situ (NaBH₄) to p-methoxybenzyl alcohol. The amino alcohol 2b was then directly crystallized from the reaction mixture, upon neutralization (HOAc), and was isolated in 94% yield and >99.9% purity (after recrystallization from toluene–heptane).

Conversion of the amino alcohol 2b into efavirenz was most conveniently and economically accomplished using phosgene (THF–heptane, 0 to 25 °C) in the absence of base. This reaction presumably proceeds via intermediate 14a followed by ring closure (Scheme 8). After aqueous workup (aqueous NaHCO₃), efavirenz was crystallized from THF–heptane and was isolated in excellent yield (93–95%) and purity (>99.5%, >99.5% ee). Two nonphosgene, ring-closure methods using chloroformates were also developed (Scheme 8). A two-step procedure involving formation and isolation of the methyl carbamate 14c, followed by base-promoted ring closure, provided efavirenz in 83% overall yield. Aside from the lower yield, it was difficult to completely remove residual 14c from efavirenz prepared by this method. A more convenient one-pot process was also developed, involving formation of the p-nitrophenylcarbamate 14b followed by in situ ring closure. The organic layer was then washed with brine, the solvent was switched to isopropyl alcohol,
and the product was crystallized by addition of water to give efavirenz in 94% yield and >99.5% purity, free of the 14b intermediate.

**Summary**

A highly efficient, practical, enantioselective synthesis of the HIV reverse transcriptase inhibitor efavirenz is now available, which is suitable for the manufacture of this important compound. The synthesis provides analytically pure efavirenz in an overall yield of 62% in seven steps from 4-chloroaniline. A novel, chiral Li-alkoxide-mediated, enantioselective acetylide addition reaction is used to establish the chiral center in the target with a remarkable level of stereocontrol.

**Experimental Section**

**General Methods.** Melting points are uncorrected. 1H, 13C, and 19F NMR spectra were collected at 300, 75, and 282 MHz, respectively. Analytical HPLC were run with Zorbax RX-C18 columns at 215, 250, or 254 nm. Chiral HPLC were run with a Chiralpak AD column. All reactions were run under nitrogen, and all reagents were plant grade unless otherwise noted. Combustion analyses were performed by Quantitative Technologies, Inc., Bound Brook, N J.

**N-(4-Chlorophenyl)-2,2-dimethylpropanamide (7).** 4-Chloroaniline (6, 1.0 kg, 7.8 mol) was charged into a mixture of tert-butyl methyl ether (4.6 L) and 30% aqueous sodium hydroxide (1.17 kg, 8.78 mol), and the mixture was cooled to 15 °C. To the resulting slurry was added trimethylacetylene chloride (1.0 kg, 8.5 mol) over 1 h, keeping the temperature below 40 °C. After being stirred for 30 min at 30 °C, the slurry was cooled to −10 °C and held for 2 h. The product was collected by filtration, washed with a solution of 90/10 water/methanol (2.5 L) and water (5 L), and dried in vacuo to give pivaloylamide (7) (1.61 kg, 97% yield) as a crystalline solid: mp 152–153 °C (lit.11 mp 152 °C); 1H NMR (300 MHz, CDCl 3) δ 7.48 (d, J = 9 Hz, 2H), 7.37 (s, 1H), 7.28 (d, J = 9 Hz, 2H), 1.30 (s, 9H); 13C NMR (75 MHz, CDCl 3) δ 176.7, 136.6, 129.1, 128.9, 121.4, 39.6, 27.6.

**4-Chloro-2-trifluoroacetylaniline, Hydrochloride Hydrate (9).** Compound 7 (3.7 kg, 17.3 mol) was charged to a solution of TMEDA (2.0 kg, 17.4 mol) in anhydrous tert-butyl methyl ether (35 L), and the mixture was cooled to −20 °C. To the cold slurry was added 2.7 N HCl (13.7 L), and compound 7 was aged at 0–5 °C for 2 h and cooled below −15 °C, and ethyl trifluoroacetate (3.45 kg, 24.3 mol) was added rapidly. After 30 min, the resulting solution was quenched into 3 N HCl (20 L, 58.9 mol), keeping the temperature below 25 °C. The organic solution was separated by distillation approx. 20 L of solvent. Acetic acid (33 L) was added while 35 L of solvent was distilled under vacuum (~100 mmHg). The solution was cooled to 30 °C, 12 N HCl (3.6 L, 43.4 mol) was added, and the mixture was aged at 0–5 °C and held for 2 h. The resulting slurry was cooled to 5 °C, and the product was collected by filtration, washed with ethyl acetate (5.5 L), and dried in vacuo to give 4.2 kg (87%) of the salt 9 as a white crystalline solid: mp 159–162 °C dec; 1H NMR (300 MHz, DMSO-d 6) δ 7.65–7.5 (m, 2H), 7.1 (d, J = 8 Hz, 1H), 7.0 (brs, 3H); 13C NMR (282 MHz, DMSO-d 6) δ −69.5; IR (cm−1) 3201(broad), 1529, 1795 (weak), 1626, 1595, 1558, 1509, 1486, 1174. Anal. Calc. for C14H9F3ClNO3: C, 41.61; H, 2.80; N, 5.04; Cl, 25.50. Found: C, 43.56; H, 2.76; N, 4.91; Cl, 25.26.

(25) Two bases are used in this reaction (KHCOP, followed by KOH), since the reaction does not proceed to completion if run at initially high pH (pH > 11). In this case, ring closure is rapid and K-nitrophenylate competes with 2b for nitrophenyl chloroformate (forming nitrophenyl carbonate as a byproduct). Use of KHCOP ensures pH < 8.5 and complete formation of the carbamate 14b before addition of KOH to effect ring closure.
over 6 h. Diisopropylethylamine (28 g, 0.22 mol) and aceto-

nitrile (125.5 L) were added followed by distillation of 7.5 L of

solvent. The mixture was cooled to −5 °C and the product

isolated by filtration to give 4.4 kg (88%) of 3d as a bright yellow solid. An analytically pure sample was obtained by recrystallization from acetonitrile: mp 165−167 °C; 1H NMR (CDCl3) δ 10.4 (brs, 1H), 7.71 (brt, J = 2 Hz, 1H), 7.3 (brs, 15 H), 6.98 (d, J = 8 Hz, 1H), 6.48 (s, 1H), 3.75 (s, 3H), 1.42 (s, 18 H); 13C NMR (75 MHz, CDCl3) δ 158.9, 145.5, 130.3, 130.2, 128.6, 124.0, 121.6, 119.5, 114.8, 114.1, 94.0, 75.0, 70.6, 55.3, 48.0, 8.6, 8.5, −0.6; 19F NMR (282 MHz, CDCl3) δ −80.19; IR (cm−1) 3428, 3294, 2235, 1601, 1574, 1507, 1459, 1323, 1305, 1256, 1233, 1166, 1135. Anal. Calcd for C22H3F3ClINO: C, 61.54; H, 4.67; N, 3.42. Found: C, 61.26; H, 4.62; N, 3.24.

(Recycle of (1R,2S)-N-Pyrrolidinynorephedrine (5b). A 22 L three-necked round-bottom flask equipped with a mechanical stirrer, a condenser, and a thermometer was heated under reflux (110 °C) for 60 min and quenched by addition into 1 M citric acid (92 mL). The organic layer was separated, dried with sodium sulfate, and concentrated to an oil. Crystallization from toluene gave 6.34 g (60%) of 5b as a pale yellow solid.

(5)-(5-Chloro-(cyclopropylethynyl)-2-[(3,4-dimethoxyphenyl) methyl] amino)-[(trifluoromethyl)benzenemethanol (2c). A 22 L three-necked round-bottom flask equipped with a mechanical stirrer, a condenser, and a thermometer was heated under reflux (110 °C) for 60 min and quenched by addition into 1 M citric acid (92 mL). The organic layer was separated, dried with sodium sulfate, and concentrated to an oil. Crystallization from toluene gave 6.34 g (60%) of 5b as a pale yellow solid.

(1R,2S)-N-Pyrrolidinynorephedrine (5b). A 22 L three-necked round-bottom flask equipped with a mechanical stirrer, a condenser, and a thermometer was heated under reflux (110 °C) for 60 min and quenched by addition into 1 M citric acid (92 mL). The organic layer was separated, dried with sodium sulfate, and concentrated to an oil. Crystallization from toluene gave 6.34 g (60%) of 5b as a pale yellow solid.

(1R,2S)-N-Pyrrolidinynorephedrine (5b). A 22 L three-necked round-bottom flask equipped with a mechanical stirrer, a condenser, and a thermometer was heated under reflux (110 °C) for 60 min and quenched by addition into 1 M citric acid (92 mL). The organic layer was separated, dried with sodium sulfate, and concentrated to an oil. Crystallization from toluene gave 6.34 g (60%) of 5b as a pale yellow solid.
A 20% solution of phosgene (0.84 kg, 8.5 mol) in toluene (4 L) was added at a rate that the temperature remained below 25 °C. The mixture was aged at this temperature for 1 h, and methanol (90 g, 2.8 mol) was added to quench excess phosgene. After 15 min, water (9.0 L) was added, and the layers were separated. The organic layer was washed with water (6.0 L) and concentrated by distilling about 14 L of solvent in vacuo. Methanol (29 L) was added, and the mixture was concentrated by distilling about 18.5 L of solvent. The mixture was aged at ambient temperature for 1 h, and the residue was crystallized from EtOAc (700 g), and the mixture was aged at ambient temperature for 1 h. The solid (mainly DDHQ) was washed with toluene (3 L) and was charged dropwise to a slurry of the PMB-protected 4a-(cyclopentylethynyl)benzenemethanol (2b). Aqueous 10° C and was charged dropwise to a slurry of the PMB-protected 4a-(cyclopentylethynyl)benzenemethanol (2b). The mixture was aged at this temperature for 1 h, and the residue was crystallized from EtOAc (700 g), and the mixture was aged at ambient temperature for 1 h. The solid (mainly DDHQ) was washed with toluene (3 L) and was charged dropwise to a slurry of the PMB-protected 4a-(cyclopentylethynyl)benzenemethanol (2b). The mixture was aged at this temperature for 1 h, and the residue was crystallized from EtOAc (700 g), and the mixture was aged at ambient temperature for 1 h. The resulting slurry was aged at ambient temperature for 1 h. The solvent was collected by filtration, washed with heptane (1 L), and dried in vacuo to give crude amino alcohol 2b as a pale yellow solid (1.04 kg). The crude product was dissolved in toluene (2.7 L) and MTBE (0.85 L). The solution was concentrated in vacuo to ~1.5 L. Heptane (2.6 L) was added over 1 h. The resulting slurry was aged at ambient temperature for 1 h. The solution was collected by filtration, washed with heptane, and dried in vacuo to give 1.0 kg (94% yield) of the amino alcohol 2b as a white solid: mp 141–143 °C; [α]D 25 = −28.3 (c 0.106, MeOH); 1H NMR (300 MHz, CDCl3) δ (7.5 Hz, 1H), 7.13 (d, J = 9.2 Hz, 1H), 6.61 (d, J = 9Hz, 1H), 4.50 (bs, 1H), 1.44–1.35 (m, 1H), 0.94–0.78 (m, 2H), 0.72–0.68 (m, 2H); 13C NMR (75 MHz, DMSO-d6) δ 167.7, 129.4, 129.0, 124.3, 118.4, 118.05, 92.3, 72.6, 71.0, 8.2, 8.1, -1.1; 19F NMR (282 MHz, CDCl3) δ = –80.5; 1H NMR (300 MHz, CDCl3) δ = 3421, 3331, 2237, 1612, 1490, 1289, 1264, 1199, 1092; HRMS calcd for C13H11NO2ClF3: 289.0481, found 289.0497. Anal. Calcd for C15H13NO2ClF3: C, 53.80; H, 3.77; N, 4.72. Found: C, 53.65; H, 3.63; N, 3.02. 8542 J. Org. Chem., Vol. 63, No. 23, 1998

(5) 6-Chloro-4(cyclopropylthiophenyl)-1,4-dihydro-4-(trifluoromethyl)-1H,3,1-benzoxazin-2-one (1) – Phosphogene. Compound 2b (1.57 kg, 5.43 mol) was dissolved in a mixture of heptane (4 L) and THF (6 L), and the solution was cooled to below –10 °C. Phosgene (0.8 kg, 8.0 mol) was directly fed below the surface over about 1 h, keeping the temperature below 0 °C. The resulting slurry was warmed to 20–25 °C and held for 1 h. Methanol (0.65 kg, 20.3 mol) was added and the solution stirred for ~30 min. Heptanes (14 L) was added, and ~14 L of solvent was distilled under reduced pressure. Heptanes (14 L) and THF (2.5 L) were added, and the solution was washed with 5% aqueous sodium bicarbonate (1.5 L) followed by water (1.5 L). The solution was warmed to 50 °C and filtered into a clean reactor, followed by a 5 L heptanes rinse. The solution was concentrated under reduced pressure, diluted with heptanes (2.5 L) and cooled below –10 °C. The product was filtered, washed with heptanes (4.5 L), and dried in vacuo at 90–100 °C to give 1.6 kg (95% yield) of compound 1 as a white solid: mp 139–141 °C; [α]D 25 = −94.1° (c 0.300, MeOH); 1H NMR (400 MHz, DMSO-d6) δ 11.05 (s, 1H), 7.54 (d, J = 2.5, 7.1 Hz), 7.43 (d, J = 2.5 Hz, 1H), 6.99 (d, J = 7 Hz, 1H), 1.58 (m, 1H), 0.92 (m, 2H), 0.77 (m, 2H); 13C NMR (100 MHz, DMSO-d6) δ 146.3, 134.7, 131.4, 126.9, 125.7, 122.4, 116.3; 1H NMR (400 MHz, DMSO-d6) δ 6.89 (d, J = 7 Hz, 1H), 1.58 (m, 1H), 0.92 (m, 2H), 0.77 (m, 2H); 13C NMR (100 MHz, DMSO-d6) δ 146.3, 134.7, 131.4, 126.9, 125.7, 122.4, 116.3; 1H NMR (400 MHz, DMSO-d6) δ 6.89 (d, J = 7 Hz, 1H), 1.58 (m, 1H), 0.92 (m, 2H), 0.77 (m, 2H); 13C NMR (100 MHz, DMSO-d6) δ 146.3, 134.7, 131.4, 126.9, 125.7, 122.4, 116.3; 1H NMR (400 MHz, DMSO-d6) δ 6.89 (d, J = 7 Hz, 1H), 1.58 (m, 1H), 0.92 (m, 2H), 0.77 (m, 2H). The solution should be concentrated to approximately 10% toluene/90% heptane and a final volume of 100 mL. After filtration, the solution was concentrated to 50–60 °C under vacuum, and heptane was added to adjust the final solvent to approximately 10% toluene/90% heptane and a final volume of 100 mL. During the solvent ratio adjustment, the methyl carbamate (2c) was crystallized. After the slurry was aged at 20–25 °C for approximately 30 min, the material was filtered, and the cake was washed with one cake volume of heptane. The solid was dried by suction to give 11.32 g of methyl carbamate 14c (92% yield) as a white solid: mp 112.5–114.5 °C; 1H NMR (300 MHz, CDCl3) δ 8.70 (bs, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.67 (d, J = 2.4 Hz, 1H), 7.32 (dd, J = 8.9, 2.5 Hz, 1H), 4.54 (bs, 1H), 3.76 (s, 3H), 3.16 (m, 1H), 0.90 (m, 2H), 0.81 (m, 2H); 13C NMR (75 MHz, CDCl3) δ 154.7, 136.2, 130.2, 130.1, 124.1, 124.3 (q, J = 269.6 Hz, 1H), 122.9, 94.7, 74.8 (q, J = 33.5, 1C), 69.6, 52.7, 85.5, 8.4, -0.7. To a solution of methyl carbamate 14c (32.55 mmol, 11.32 g) in MTBE (170 mL) was added a solution of LiO-t-Bu in hexanes (1 equiv, 32.6 mL of a 1 M solution). The reaction mixture immediately became a slurry, which became a clear

The mixture contained in the final solution should be ~2 vol%). The total volume of the solution was adjusted to 6.6 L with methanol. The solution was heated at 40 °C, and 5 N NaOH (3.3 L) was added over 10 min. The resulting clear solution was held at 40 °C for 30 min. A solution of NaBH4 (39.1 g, 1.03 mol) in 0.5 N NaOH (390 mL) was added dropwise, maintaining the temperature at 40–45 °C. The mixture was stirred at ambient temperature for 15 min and cooled to 19 °C. The solution was neutralized with glacial acetic acid (~1.0 L) to pH 8.4, keeping the temperature at 20–25 °C. Water (10 L) was added dropwise over 30 min. The mixture was aged at ambient temperature for 1 h and filtered. The solid was washed with water (1 L) and dried in vacuo to give crude amino alcohol 2a as a pale yellow solid (1.04 kg).
yellow solution within 30 min. The reaction mixture was aged at 20–25 °C until <0.3% methyl carbamate 14c remained by HPLC analysis (approximately 16 h). The reaction was quenched into 0.5 N HCl (150 mL), the layers were separated, and the organic layer was washed with brine (150 mL), dried over magnesium sulfate, and filtered. The solution was solvent switched into IPA (56 mL), and the product was crystallized by the addition of water (106 mL). The product was filtered and dried to give 9.22 g (90% yield, 83% from 2b) of 1. 

(S)-6-Chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one (1) — Nonphogene. To a three necked round-bottom flask equipped with a mechanical stirrer, N2 line, and thermocouple were charged amino alcohol 2b (500 g, 1.73 mol), MTBE (2.5 L), water (5.0 L), and solid KHCO3 (225 g, 2.25 mol). The resulting mixture was stirred at ambient temperature, and then solid 4-nitrophenyl chloroformate (365 g, 1.82 mol) was added over 3 h. The mixture was stirred at 20–25 °C for 1 h. The pH of the reaction was adjusted to 11 by addition of aqueous KOH (1.94 M). At approximately pH 9.2, the carbamate dissolved. More KOH was added until the pH was 11–11.5. The resulting two-phase mixture was stirred vigorously at 25 °C. The total aqueous volume was adjusted to 100 mL by addition of water. The layers were separated, and 2.5 L of brine (15 wt %) was added to the organic phase. HOAc (0.1 N) was added until the pH was 6–7 (approximately 350–700 mL of HOAc was added). The organic layer was then washed with 2.5 L of brine and solvent switched to IPA (3 L). H2O (5.7 L) was added to crystallize compound 1 (94% yield) as a white solid.

Acknowledgment. DuPont Pharmaceuticals: We are thankful to Dr. Rodger Stringham, Barbara Lord, Bill Cummings, and Tom Sholz for their analytical support and to Hank Jackson and Dr. Charles Ray for performing thermochemical hazards analyses throughout the process. Merck: We would like to acknowledge the efforts of Charles Moeder, Tom O’Brien, and Dr. P. Yehl in Analytical Research and J. Kukura for the development of the isopropyl alcohol–water crystallization of efavirenz.

J O981170L