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Señora
Alix Carmenza Céspedes de Verge
Jefe de División de Nuevas Creaciones
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
E. S. D.

Referencia: Expediente No. 07.021.230

Solicitud de Patente de Invención titulada: "Síntesis de benzoxazinona

Solicitante: Bristol-Myers Squibb Company

CAMBIO DE APODERADO

ALVARO CORREA ORDOÑEZ, mayor y vecino de Bogotá, D.C., identificado con la cédula de ciudadanía número 79.143.366 expedida en Bogotá, abogado inscrito con tarjeta profesional número 20.281 del Consejo Superior de la Judicatura, en mi carácter de apoderado de la sociedad de la referencia, presento poder otorgado por Bristol-Myers Squibb Company, el cual se encuentra radicado bajo el No. 08.129.339 del 04 de diciembre de 2008.

Atentamente,

ALVARO CORREA ORDOÑEZ
C.C.No.79.143.366 de Usaquén
T.P.20.281

BOGMVN/P2007/021230/MEMORIAL CAMBIO DE APODERADO

NOTARIA 38

COMPARECENCIA PERSONAL Y AUTENTICACIÓN DE FIRMA Y HUELLA

La Notaria Treinta y Ocho (38)(E) del Círculo de Bogotá D.C. da fe que en el anterior escrito dirigido a: _____

fue presentado personalmente por ALVARO CONCA ORDOÑEZ

quien exhibió la C.C. No. 79143366 de USAQUEN y T.P. No. 20281

y manifestó que la firma y la huella que aparecen en el presente documento son suyas, y que acepta el contenido del mismo.

FIRMA

25 JUN 2009

MONICA ZULMA BAUTISTA NAVARRO
NOTARIA TREINTA Y OCHO (38)(E)

ÍNDICE DERECHO DEL ROGADO

J. Org. Chem. **1998,** *63,* 8536−8543

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

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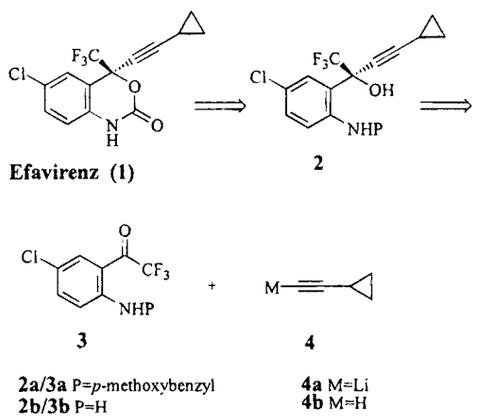
Received June 17, 1998

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 (1*R*,2*S*)-*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 strains[5] 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]

Scheme 1



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-acetylides to cyclic *N*-acetylketimines mediated by stoichiometric amounts of quinine Li-alkoxide has been reported previously.[10e]

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(4) De Clercq, E. *J. Med. Chem.* **1995**, *38*, 2491.
(5) Young, S. D.; Britcher, S. F.; Tran, L. O.; Payne, L. S.; Lumma, W. C.; Lyle, T. A.; Huff, J. R.; Anderson, P. S.; Olsen, D. B.; Carroll, S. S.; Pettibone, D. J.; O'Brien, J. A.; Ball, R. G.; Balani, S. K.; Lin, J. H.; Chen, I. W.; Schleif, W. A.; Sardana, V. V.; Long, W. J.; Byrnes, V. W.; Emini, E. A. *Antimicrob. Agents Chemother.* **1995**, *39*, 2602.
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(8) Thompson, A.; Corley, E. G.; Hungtington, M. F.; Grabowski, E. J. J.; Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 2028.
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(10) (a) Mukaiyama, T.; Suzuki, K.; Soai, K.; Sato, T. *Chem. Lett.* **1979**, 447. (b) Mukaiyama, T.; Suzuki, K. *Chem. Lett.* **1980**, 255. (c) Niwa, S.; Soai, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 937−943. (d) Tombo, G. M. R.; Didier, E.; Loubinoux, B. *Synlett* **1990**, 547−548. (e) Corey, E. J.; Cimprich, K. A. *J. Am. Chem. Soc.* **1994**, *116*, 3151−3152. (f) Huffman, M. A.; Nobuyoshi, Y.; DeCamp, A. D.; Grabowski, E. J. J. *J. Org. Chem.* **1995**, *60*, 1590.

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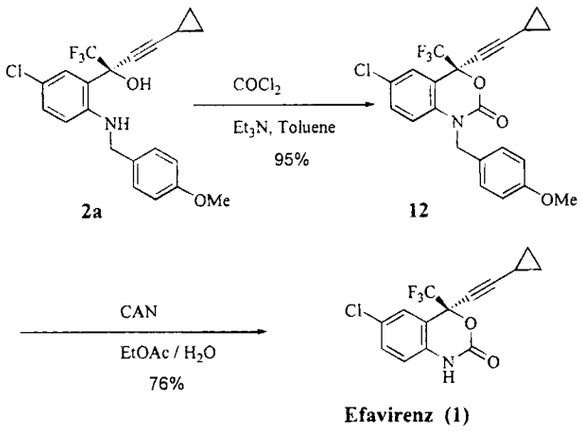
D1 198

Scheme 6

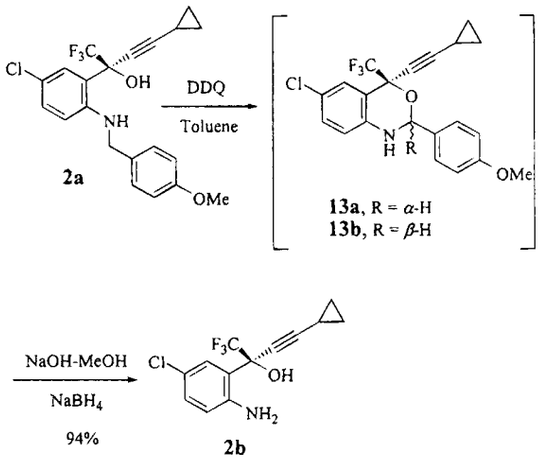


subsequent chiral addition reactions to give product **2a** with typical chemical and optical purity.

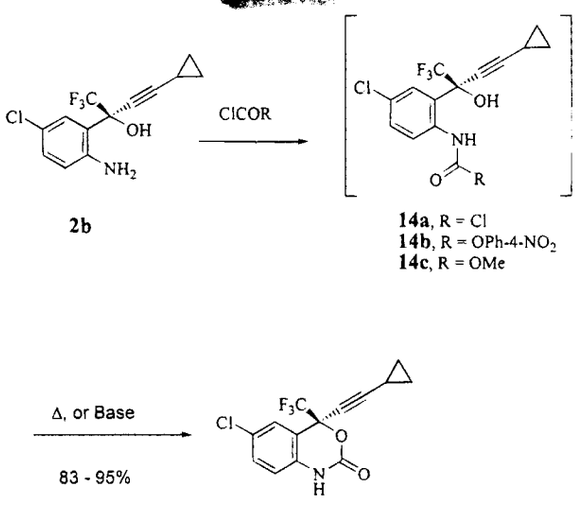
Completion of the Synthesis. Two routes were employed for conversion of the amino alcohol **2a** into the target compound, efavirenz. Initially, **2a** was converted into the benzoxazinone **12** ($COCl_2$, Et_3N, toluene), which was isolated in 95% yield upon crystallization from methanol. Compound **12** was then deprotected (CAN) to give efavirenz (Scheme 6).[7] 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).[22] 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**.[23] 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.[24] 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 ($NaBH_4$) to *p*-methoxybenzyl alcohol. The amino alcohol

Scheme 7



Scheme 8



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 $NaHCO_3$), efavirenz was crystallized from THF−heptane and was isolated in excellent yield (93−95%) and purity (>99.5% − 99.9% 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.[25] The organic layer was then washed with water, the solvent was switched to isopropyl alcohol

(22) The less expensive quinone chloranil was also used for the deprotection step. However, the initial oxidation of **2a** to give the cyclic aminals **13a/13b** is not as efficient as the reaction involving DDQ, and aminals **13a/13b** required purification (by crystallization) prior to conversion into the amino alcohol **2b**. The isolated yield of **2b** from this two-step procedure was 75−80%.

(23) The structure of **13b** was determined by comprehensive heteronuclear NOE (HOESY) experiments. Yu, C.; Levy, G. C. *J. Am. Chem. Soc.* **1984**, *106*, 6533.

(24) Newman, M. S., Khanna, V. K. *Org. Prep. Proced. Int.* **1985**, *17*(6), 422−423.

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. ^{1}H, ^{13}C, and ^{19}F NMR spectra were collected at 300, 75, and 282 MHz, respectively. Analytical HPLC were run with Zorbax RX-C18 columns at 215, 240, or 250 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, NJ.

***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 trimethylacetyl 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 145 °C); ^{1}H 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); ^{13}C 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 *n*-butyllithium in hexane (10.2 kg, 39.3 mol) while the temperature was kept below 5 °C. The mixture 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 and concentrated by distilling approximately 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 heated to 65−70 °C and held for 4 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; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.65−7.5 (m, 2H), 7.1 (d, J = 8 Hz, 1H), 7.0 (brs, 3H); ^{19}F NMR (282 MHz, DMSO-d_6) δ −69.5; IR (cm^{-1}) 3201(broad), 1929, 1795 (weak), 1626, 1595, 1558, 1509, 1486, 1174. Anal. Calcd for $C_8H_8Cl_2F_3NO_2$: C, 34.56; H, 2.90; N, 5.04; Cl, 25.50. Found: C, 34.56; H, 2.76; N, 4.91; Cl, 25.26.

[25] Two bases are used in this reaction ($KHCO_3$, 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 $KHCO_3$ ensures pH < 8.5 and complete formation of the carbamate **14b** before addition of KOH to effect ring closure.

***N*-(4′-Methoxybenzyl)-4-chloro-2-(trifluoroacetyl)aniline (3a).** Into a 50 L extractor was charged a solution of sodium acetate (1.4 kg, 17.6 mol) in water (3.6 L) and *tert*-butyl methyl ether (18 L). The HCl salt **9** (3.0 kg, 10.8 mol) was added. The heterogeneous mixture was stirred at ambient temperature for 30 min or until solids disappeared. The pH of the aqueous layer should be in the range of 4.0−6.0, otherwise HCl (6 N) or NaOH (5 N) was used to adjust the pH to the desired range. The organic layer was separated, washed with water (3.6 L), and transferred to a 50 L, three-necked, round-bottom reaction flask equipped with mechanical stirrer and a thermocouple. The solution was concentrated to ~8 L and flushed with acetonitrile (2 × 12 L) to give ketoaniline **3b** (2.24 kg, 10.0 mol, 99% yield) as a free base in acetonitrile (8 L), which was directly used in the next step. A small sample of ketoaniline **3b** was isolated as yellow needles by crystallization from heptane: mp 98−99 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 2 Hz, 1 H), 7.32 (dd, J = 2. 9 Hz, 1H), 6.7 (d, J = 9 Hz, 1H), 6.44 (brs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.0, 151.6, 136.9, 1301.1, 120.9, 119.0, 116.8, 111.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ 70.3; IR (cm^{-1}) 3498, 3380, 1663, 1625, 1589, 1533, 1138; HRMS calcd for $C_8H_5ClF_3NO$ 223.0001, found 223.0012. Anal. Calcd for $C_8H_5ClF_3NO$: C, 42.98; H, 2.25; N, 6.26. Found: C, 43.01; H, 2.14; N, 6.09.

To the solution of ketoaniline **3b** in acetonitrile, under nitrogen, was added *p*-toluenesulfonic acid monohydrate (28.65 g, 0.15 mol). The reaction mixture was heated to 70 °C with stirring. 4-Methoxybenzyl alcohol (1.53 kg, 11.0 mol) in acetonitrile (3 L) was added over 4−5 h, keeping the reaction temperature at 70 °C. The reaction was monitored by HPLC until reaction completion (typically 2 h after the addition of the alcohol). The batch was cooled to room temperature and seeded. A bright yellow crystalline solid gradually formed. The slurry was then aged at ambient temperature for 1−2 h with stirring. Water (11 L) was added slowly over 2 h. After being aged at room temperature for another 1−2 h, the solid was filtered and washed with 50/50 acetonitrile/water (2 × 10 L). The wet cake was dried under vacuum (50 °C, 70 mmHg, 24 h) to give ketoaniline **3a** (3.17 kg, 90% yield) as a bright yellow solid: mp 82−84 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.04 (s, 1H), 7.74 (d, J = 2 Hz, 1H), 7.35 (dd, J = 2, 9 Hz, 1H), 7.24 (d, J = 8 Hz, 2H), 6.91 (d, J = 8 Hz, 2H), 6.75 (d, J = 9 Hz, 1H), 4.43 (d, J = 6 Hz, 2H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.5, 159.2, 151.9, 137.4, 130.8, 128.9, 128.4, 119.9, 117.0, 114.5, 114.4, 111.3, 55.3, 46.6; IR (cm^{-1}) 3355, 1659, 1608, 1565, 1510, 1431, 1407, 1357, 1245, 1160, 1133; HRMS calcd for $C_{16}H_{13}ClF_3NO_2$ 343.0587, found 343.0588. Anal. Calcd for $C_{16}H_{13}ClF_3NO_2$: C, 55.91; H, 3.81; N, 4.07. Found: C, 56.07; H, 3.87; N, 3.99.

***N*-(3′,4′-Dimethoxybenzyl)-4-chloro-2-(trifluoroacetyl)aniline (3c).** Compound **3a** (4.96 g, 40 mmol) and 3,4-dimethoxybenzyl alcohol (7.39 g, 44 mmol) were added to 2-propanol (40 mL). TsOH (76 mg, 0.4 mmol) was added and the mixture heated to 60 °C and held 3.5 h. The solution was concentrated in vacuo to one half the original volume, diluted with water (10 mL), and stirred at 25 °C. The resulting slurry was filtered and the product dried in vacuo at 30 °C to give 10.16 g (68%) of **3c** as a yellow powder. An analytically pure sample was obtained by recrystallization from acetonitrile: mp 82−84 °C; ^{1}H NMR ($CDCl_3$) δ 9.05 (brs, 1H), 7.75 (brt, J = 2 Hz, 1H), 7.35 (dd, J = 2, 8 Hz, 1H), 6.8 (d, J = 8 Hz, 3H), 6.75 (d, J = 8 Hz, 1H), 4.43 (d, J = 5 Hz, 2H), 3.88 (s, 3H), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 179.9, 151.9, 149.4, 148.7, 137.4, 130.8, 130.8, 130.7, 129.4, 119.4, 114.5, 111.5, 111.4, 110.3, 56.1, 56.0, 47.0; ^{19}F NMR ($CDCl_3$) δ −69.61; IR (cm^{-1}) 3343, 1656, 1612, 1566, 1512, 1464, 1141, 1264, 1195, 1140, 1028; HRMS calcd for $C_{17}H_{15}F_3ClNO_3$ 373.0692, found 373.0698.

***N*-(Triphenylmethyl)-4-chloro-2-(trifluoroacetyl)aniline (3d).** To a solution of NaOAc (1.42 kg, 17.3 mol) in water (3.6 L) was added *tert*-butyl methyl ether (5.0 L), cyclohexane (13.7 L), and compound **9** (3.00 kg, 10.8 mol). After dissolution the phases were separated. The organic phase was partially concentrated by distilling 7.5 L of solvent. Trityl alcohol (3.03 kg, 11.6 mol) and *p*-TsOH (20 g, 0.11 mol) were added and the mixture heated to reflux with distillation of 6.5 L of solvent

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 solution was cooled to −15 °C, and the resulting solids were filtered, washed with cold methanol (2 L), and dried in vacuo at 50 °C to give 2.82 kg (91%) of benzoxazinone **12** as a white solid: mp 115−116.5 °C; $[\alpha]^{25}_D$ −93.67° (*c* 0.300, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (m, 1H), 7.26 (dd, J = 9, 2 Hz, 1H), 7.17 (d, J = 9 Hz, 2H), 6.85 (d, J = 9 Hz, 2H), 6.83 (d, J = 9 Hz, 1H), 5.08 (s, 2H), 3.77 (s, 3H), 1.40 (m, 1H), 0.96−0.82 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.6, 147.5, 134.9, 131.8, 128.1, 127.8, 127.0, 126.7, 122.1, 117.3, 116.6, 114.1, 96.0, 76.8, 65.6, 54.9, 46.6, 8.5, 8.4, −1.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −81; IR (cm^{-1}) 2248, 1735, 1605, 1515, 1497, 1314, 1252, 1187; HRMS calcd for $C_{22}H_{18}ClF_3NO_3$ (M + H) 436.0927, found 436.0931. Anal. Calcd for $C_{22}H_{17}ClF_3NO_3$: C, 60.62; H, 3.90; N, 3.21. Found: C, 60.51; H, 3.89; N, 3.18.

(*S*)-6-Chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2*H*-3,1-benzoxazin-2-one (1). To a solution of compound **12** (250 g, 0.57 mol) in acetonitrile (2.5 L) was added a solution of CAN (960 g, 1.75 mol) in water (1 L). The mixture was stirred at ambient temperature for 1 h and quenched with $Na_2S_2O_5$ (200 g) to remove anisaldehyde. The organic layer was separated and washed with 1 L of water. To the organic solution was added another portion of $Na_2S_2O_5$ (700 g), and the mixture was aged at ambient temperature for 12 h to give a slurry. The slurry was filtered, and the waste cake was washed with EtOAc (2 L). The filtrate was concentrated in vacuo, and the residue was crystallized from EtOAc−heptane (5/95) to give efavirenz (**1**, 140 g, 76% yield) as white solid.

(*S*)-5-Chloro-α-(cyclopropylethynyl)-2-amino-α-(trifluoromethyl)benzenemethanol (2b). DDQ (0.85 kg, 3.74 mol) was dissolved in toluene (4.52 L, 5.31 mL/1 g of DDQ) at 30 °C and was charged dropwise to a slurry of the PMB-protected amino alcohol **2a** (1.51 kg, 3.68 mol) in toluene (6.62 L) at 0 °C over 20 min. The resulting mixture was aged at ambient temperature for 2 h. The mixture was filtered, and the waste solid (mainly DDHQ) was washed with toluene (3 × 0.5 L). The filtrate and wash were combined and washed with aqueous 5% $NaHCO_3$ (3.3 L). The resulting toluene solution contained mainly the cyclic aminals **13**: ^{1}H NMR (major isomer, 300 MHz, DMSO-d_6) δ 7.46 (d, J = 9 Hz, 2H), 7.28−7.21 (m, 3H), 7.0 (d, J = 9 Hz, 2H), 6.85 (d, J = 9 Hz, 1H), 5.52 (s, 1H), 3.78 (s, 3H), 1.52−1.47 (m, 1H), 0.90−0.84 (m, 2H), 0.72−0.68 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.3, 143.8, 129.6, 129.3, 128.9, 125.8, 123.1, 121.7, 118.1, 117.8, 113.8, 93.6, 80.9, 74.1, 70.3, 55.2, 8.5, 8.4, −1.07; ^{19}F NMR (282 MHz, $CDCl_3$) δ −80.9; IR (cm^{-1}) 2226, 1610, 1513, 1492, 1458, 1303, 1279, 1256, 1174. HRMS calcd for $C_{21}H_{17}NO_2ClF_3$ 407.0899, found 407.0885. Anal. Calcd for $C_{21}H_{17}NO_2ClF_3$: C, 61.99; H, 3.89; N, 3.41. Found: C, 61.68; H, 4.16; N, 3.34.

The toluene solution was concentrated in vacuo to ~3 L at ~40 °C. MeOH (9 L) was added portionwise, and the solution was concentrated in vacuo to ~3 L (toluene content 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 $NaBH_4$ (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 **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 solid was collected by filtration, washed with heptane (1 L), and dried in vacuo to give 1.0 kg (94% yield) of the amino alcohol **2b** as a white solid: mp 141−143 °C; $[\alpha]^{25}_D$ −28.3° (*c* 0.106, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, J = 2 Hz, 1H), 7.13 (dd, J = 9, 2 Hz, 1H), 6.61 (d, J = 9 Hz, 1H), 4.50 (brs, 3H), 1.44−1.35 (m, 1H), 0.94−0.78 (m, 2H), 0.72−0.68 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 146.7, 129.4, 129.0, 124.3, 118.4, 118.07, 118.05, 92.3, 72.6, 71.0, 8.2, 8.1, −1.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ −80.5; IR (cm^{-1}) 3421, 3331, 2237, 1612, 1490, 1410, 1289, 1264, 1169, 1092; HRMS calcd for $C_{13}H_{11}NOClF_3$ 289.0481, found 289.0497. Anal. Calcd for $C_{13}H_{11}NOClF_3$: C, 53.80; H, 3.77; N, 4.72. Found: C, 53.65; H, 3.63; N, 4.81.

(*S*)-6-Chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2*H*-3,1-benzoxazin-2-one (1)−Phosgene. Compound **2b** (1.57 kg, 5.43 mol) was dissolved in a mixture of heptanes (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 **1** as white solid: mp 139−141 °C; $[\alpha]^{25}_D$ −94.1° (*c* 0.300, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.05 (s, 1H), 7.54 (dd, J = 2.5, 7 Hz, 1H), 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); ^{13}C NMR (100 MHz, DMSO-d_6) δ 146.23, 134.71, 132.04, 126.93, 126.57, 122.24, 116.83, 114.08, 95.63, 77.62, 65.85, 8.48, 8.44, −1.32; ^{19}F NMR (282 MHz, DMSO-d_6) δ −81.1; IR (cm^{-1}) 3316, 2250, 1752, 1602, 1498, 1196, 1186; HRMS calcd for $C_{14}H_{10}F_3ClNO_2$ (M + H) 316.0352, found 316.0338. Anal. Calcd for $C_{14}H_9F_3ClNO_2$: C, 53.27; H, 2.87; N, 4.45; Cl 11.23; F, 18.05. Found: C, 53.15; H, 2.73; N, 4.37; Cl, 11.10; F, 17.84

(*S*)-6-Chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2*H*-3,1-benzoxazin-2-one (1)−Nonphosgene. To a solution of the amino alcohol **2b** (35.38 mmol, 10.25 g) in toluene (100 mL) were added water (100 mL), potassium bicarbonate (2 equiv, 7.08 g), and methyl chloroformate (2 equiv, 5.46 mL). The biphasic mixture was stirred vigorously at 20−25 °C until <0.5% amino alcohol **2b** remained by HPLC analysis (approximately 8.5 h). The layers were separated, and the organic layer was washed with brine (100 mL) and dried over magnesium sulfate. After filtration, the solution was concentrated (50−60 °C under vacuum), and heptane was added to adjust the final solvent ratio to approximately 10% toluene/90% heptane and a final volume of 100 mL. During the solvent ratio adjustment, the methyl carbamate **14c** 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; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (brs, 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 (brs, 1H), 3.76 (s, 3H), 1.36 (m, 1H), 0.90 (m, 2H), 0.81 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 136.2, 130.2, 130.1, 128.1, 124.3, 123.6 (q, J = 286.9, 1C), 122.9, 94.7, 74.8 (q, J = 33.5, 1C), 69.6, 52.7, 8.5, 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

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)-2*H*-3,1-benzoxazin-2-one (1)−Nonphosgene. To a three necked round-bottom flask equipped with a mechanical stirrer, N_2 line, and thermocouple were charged amino alcohol **2b** (500 g, 1.73 mol), MTBE (2.5 L), water (5.0 L), and solid $KHCO_3$ (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). H_2O (5.7 L) was added to crystallize compound **1** (94% yield) as a white solid.

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