Synthesis of Five Nevirapine Metabolites

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Nevirapine (**1**) is a non-nucleoside reverse transcriptase inhibitor marketed for HIV treatment by Boehringer Ingelheim as Viramune® since 1996. *In vitro* studies of nevirapine biotransformation using human liver microsomes demonstrated the formation of five major metabolites. This paper describes the syntheses of these metabolites.

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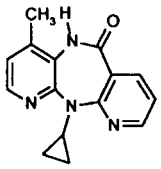
Introduction.

Nevirapine, a noncompetitive inhibitor of the enzyme Reverse Transcriptase (RT), demonstrated antiviral activity both in monotherapy and in combination with nucleoside RT-inhibitors such as Zidovudine, Didanosine and Zalcitabine [1]. Pharmacokinetic studies have shown that cytochrome P450 is responsible for the oxidative metabolism of nevirapine to five major metabolites: 2-hydroxy-(**2**), 3-hydroxy-(**3**), 4-hydroxymethyl-(**4**), 4-carboxy-(**5**) and 8-hydroxy-(**6**)-nevirapine [2,3]. To have sufficient material to develop a sensitive high-performance liquid chromatography (hplc) method which separates all metabolites from the main peak, and also to evaluate their toxicity, gram quantities of each metabolite was required. This paper describes various synthetic routes to prepare the five major metabolites.

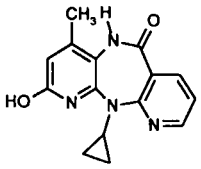
Results.

2-Hydroxy-nevirapine (**2**) (Scheme 1).

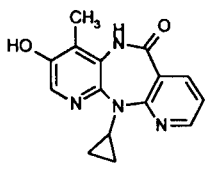
Our initial strategy to displace chlorine on the 2 position of **7** [4] with benzylamine at 180° C for up to 12 hours failed. Generally, displacement of chlorine on dipyridodiazepineones with benzylamines requires severe reaction conditions [5]. Heating **7** with an excess of *p*-methoxybenzylamine in a sealed tube to 180° C for 48 hours gave **8** (Scheme 1). De-benzylation of **8** using either palladium on activated carbon and hydrogen or using transfer hydrogenolysis conditions by refluxing **8** in cyclohexene and palladium hydroxide on carbon gave low yield of amine **9**. Amine **9** was obtained in higher yield by direct nitration of nevirapine (**1**) with nitronium tetrafluoroborate (NO_2BF_4) in acetonitrile at room temperature. Under



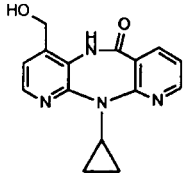
1
(Nevirapine)



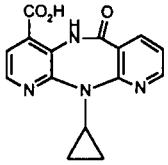
2
(2-Hydroxy-nevirapine)



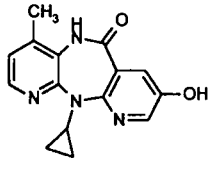
3
(3-Hydroxy-nevirapine)



4
(4-Hydroxymethyl-nevirapine)

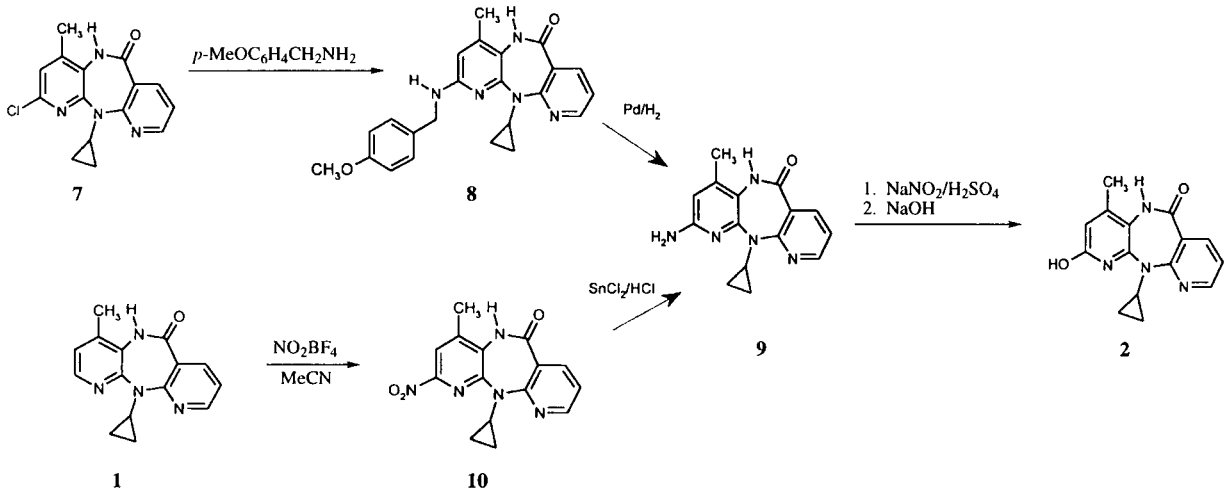


5
(4-Carboxy-nevirapine)



6
(8-Hydroxy-nevirapine)

Scheme 1



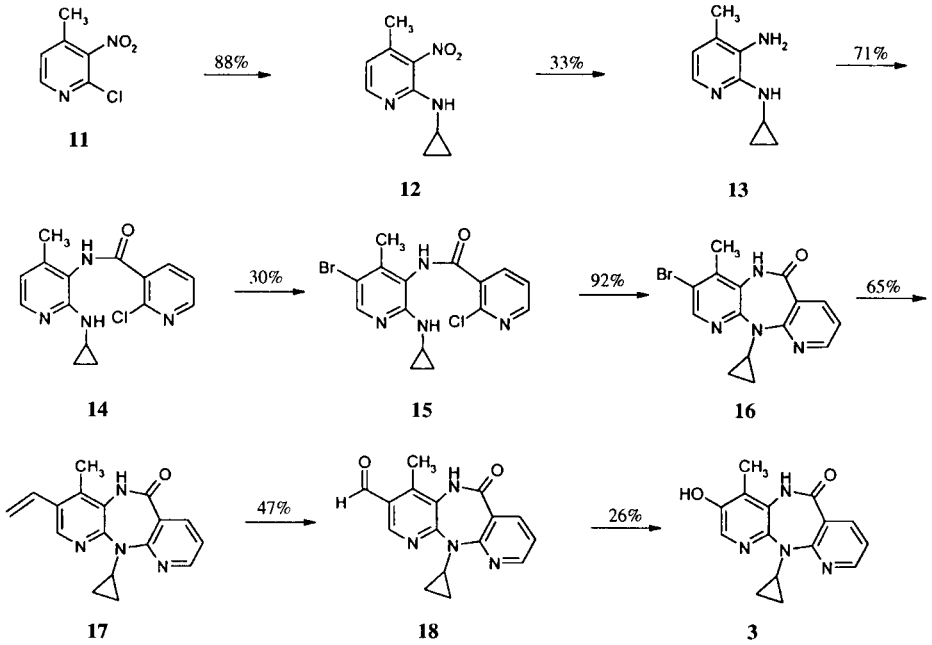
these conditions the 2-nitro derivative **10** was obtained as the sole regioisomer. Reduction of **10** using tin(II) chloride in hydrochloric acid gave the amine **9**. Diazotization of **9** followed by aqueous workup gave 2-hydroxy-nevirapine (**2**).

3-Hydroxy-nevirapine (**3**) (Scheme 2).

Recently Klunder [6] described the synthesis of 3-hydroxy-nevirapine (**3**) using a Sommelet-Hauser rearrangement of an ylide derived from 4-hydroxymethyl-nevirapine (**4**). To improve the yield, we developed an alternative route.

Amination of the commercially available 2-chloro-4-methyl-3-nitropyridine (**11**) with cyclopropylamine gave **12** in 88% yield (Scheme 2). Reduction of **12** with hydrogen in the presence of Raney® nickel gave **13** in 33% yield. The diamine **13** was condensed with 2-chloronicotinoyl chloride in ethyl acetate in the presence of Hunig's base to **14** in 71% yield. Attempted regioselective nitration of **14** in the 3 position with nitronium tetrafluoroborate resulted in the loss of the cyclopropyl group. We then elected to regioselectively brominate **14** to **15** with bromine in acetic acid. Ring closure of **15** with sodium

Scheme 2

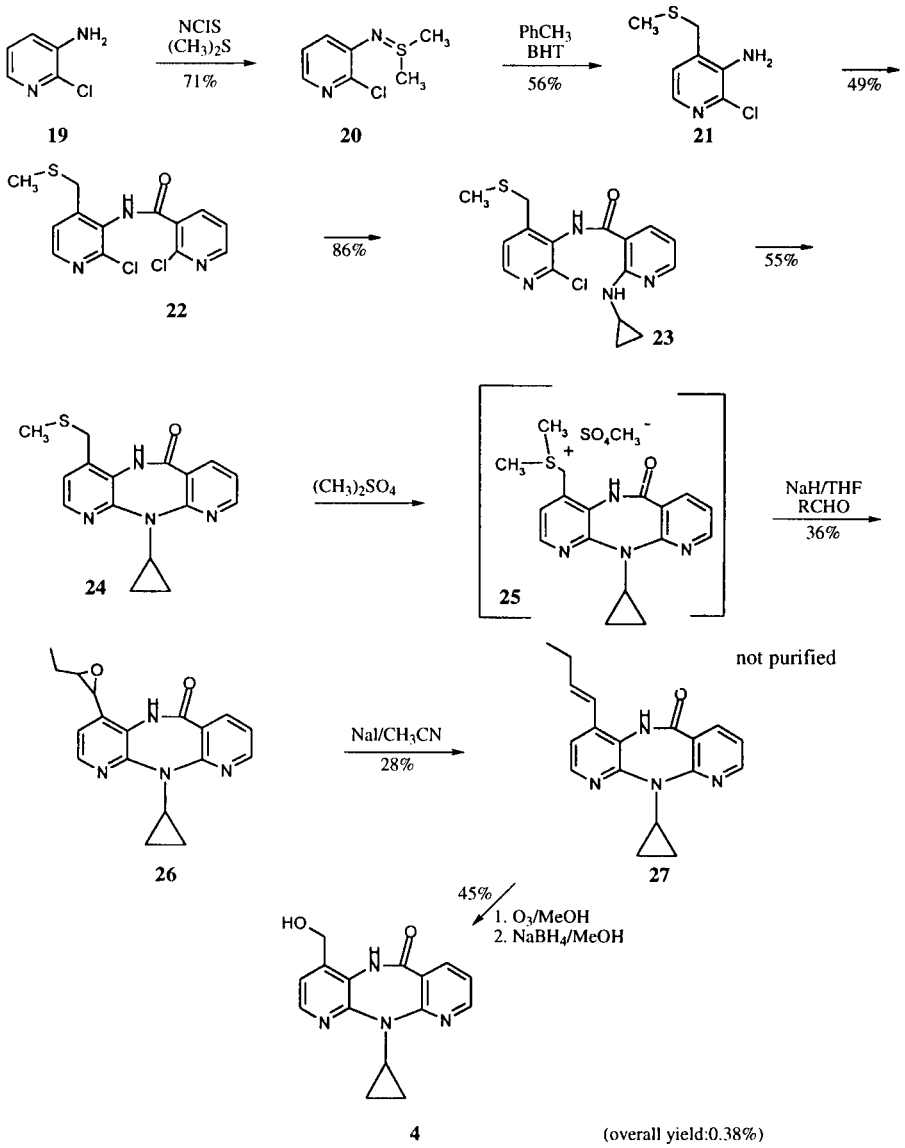


hydride in pyridine at 110° C gave 3-bromo-nevirapine **16** in 92% yield. The use of diglyme in this reaction lead to significant debromination resulting in the isolation of nevirapine (**1**). A palladium mediated cross coupling reaction of **16** with tributyl(vinyl)tin yielded the 3-vinyl derivative **17** in 65% yield. 3-Vinyl-nevirapine (**17**) was subjected to ozonolysis in dichloromethane to the corresponding aldehyde **18** in 47% yield. Baeyer-Villiger oxidation of **18** as reported [6] followed by hydrolysis of the formate ester, afforded the title compound **3** identical by ^{1}H nmr and tlc to an authentic sample [6].

4-Hydroxymethyl-nevirapine (**4**) (Scheme 3).

The preparation of metabolite **4**, as previously published [4] involved forming the dianion of nevirapine (**1**) with lithium diisopropylamide followed by oxidation with either oxygen at -40° C [4] or with oxodiperoxymolybdenum(pyridine)hexamethylphosphoramide (MoOPH) [7]. Alternatively to these published syntheses, we developed two additional synthetic procedures. Both started from the readily available 4-methylthiomethyl-nevirapine (**24**), which is obtained in a 5-step synthesis starting from the inexpensive 3-amino-2-chloropyridine (**19**). Formation of the sulfilimine **20** was accomplished by treatment of (**19**) with methyl sulfide and *N*-chlorosuccinimide in dichloromethane at 0° C to 5° C (Scheme 3). The sulfilimine **20** obtained in quantitative yield was converted to **21** by heating with 2-*tert*-butyl-4-methylphenol in toluene to 90-95° C for 30 minutes [8]. On workup, the minor product (6-methylthiomethyl isomer) crystallized from toluene

Scheme 3



and was removed by filtration (mp 72-73° C). The filtrate containing crude **21** was further purified by either high vacuum distillation or by column chromatography. Condensing **21** with 2-chloronicotinoyl chloride in toluene in the presence of a base gave **22**. Treatment of **22** with 4 equivalents of cyclopropylamine in xylene or in diglyme at 90-105° C in a closed vessel gave **23**. Ring closure of **23** with sodium hydride in pyridine gave 4-methylthiomethyl-nevirapine (**24**).

It should be noted here that desulfurization of 3-amino-2-chloro-4-methylthiomethyl pyridine (**21**) with Raney® nickel in ethanol resulted in 80% yield of 3-amino-2-chloro-4-methylpyridine [8], which is registered by the Food and Drug Administration (FDA) as the starting material of Nevirapine (**1**).

S-methylation of **24** with iodomethane or dimethyl sulfate in acetonitrile or in tetrahydrofuran was unsuccessful. However, when **24** was treated with dimethyl sulfate in trifluoroacetic acid for one week, the quaternary salt **25** was obtained in quantitative yield. Treatment of **25** with sodium hydride in tetrahydrofuran at -78° C, gave the sulfur ylide which was reacted *in situ* with propionaldehyde to form epoxide **26**. Epoxide **26** was treated with sodium iodide in the presence of trifluoroacetic acid to give **27**. 4-(1-Butenyl)-11-cyclopropyl-5,11-dihydro-6*H*-dipyrido-[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (**27**) was identified as a process related impurity in the production of Nevirapine **1** [9] and was requested by Quality Control (Q.C.) as an analytical standard. Olefin **27** was ozonized in methanol at 0° C and reduced *in situ* with sodium borohydride to afford 4-hydroxymethyl-nevirapine **4** in an overall yield of 0.38%.

An alternate approach to metabolite **4** is by oxidation of the thioether **24** with 3-chloroperoxybenzoic acid (MCPBA) to the corresponding sulfoxide **28** followed by reaction with perfluoropropionic anhydride (Scheme 4). Acetylation of the sulfoxide **28** under the conditions illustrated in Scheme 4 initiates the Pummerer rearrangement and leads to the formation of the acetoxy sulfide **29**. This intermediate is hydrolyzed in aqueous sodium bicarbonate solution and reduced *in situ* with sodium borohydride to **4** in 4% overall yield from 24.

4-Carboxy-nevirapine (**5**) (Scheme 5).

Our initial intention was to oxidize 4-hydroxymethyl-nevirapine (**4**) with tetrapropylammonium perruthenate (TPAP) and 4-methylmorpholine *N*-oxide (NMO) in dichloromethane [10] to the known 4-formyl-nevirapine intermediate [4], followed by further oxidation with potassium permanganate to the acid **5**. However, we observed that under the reaction conditions 4-hydroxymethy-nevirapine (**4**) is oxidized directly to the acid **5**. We noticed, however, that adding one or two equivalents of water to the reaction accelerated the oxidation to **5**.

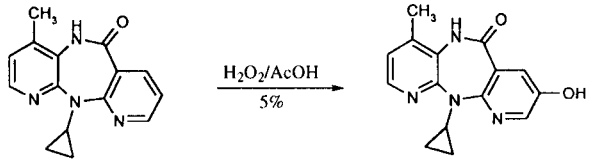
Scheme 5

4 **5**

8-Hydroxy-nevirapine (**6**) (Scheme 6).

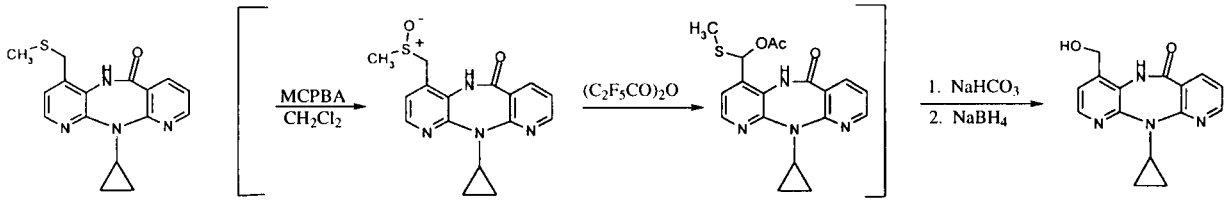
Oxidizing a solution of nevirapine (**1**) with hydrogen peroxide in acetic acid resulted in a mixture of several *N*-oxides [4]. Re-investigating this reaction, we repeated the published reaction conditions [4]. After purification by chromatography, we isolated 8-hydroxy-nevirapine (**6**) in 5% yield. To improve the yield of **6**, we deoxygenated the crude reaction mixture to convert possible *N*-oxide of **6** to 8-hydroxy-nevirapine (**6**). However, treatment of the crude reaction mixture with palladium on carbon under hydrogen did not improve the yield of **6**.

Scheme 6



1 **6**

Scheme 4



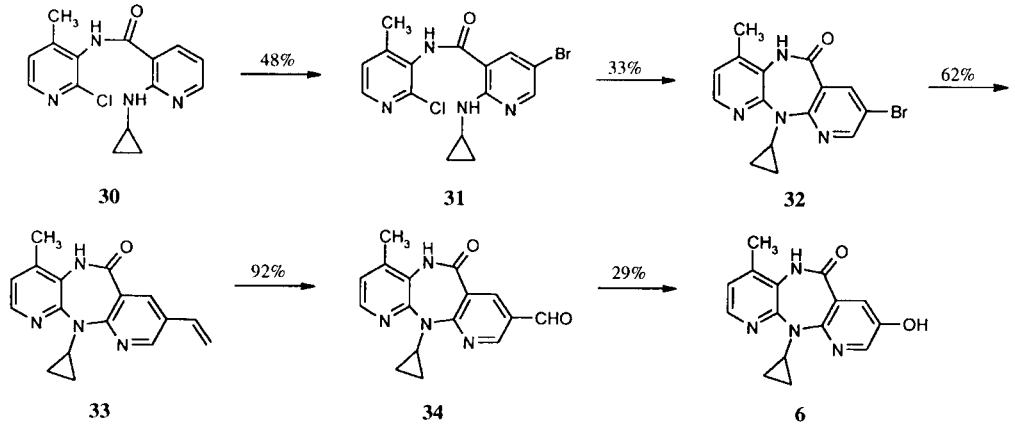
24 **28** **29** **4**

To find a scaleable route to **6**, we investigated two additional synthetic routes (Schemes 7 and 8). Both routes offer an easier workup over the direct oxidation (Scheme 6).

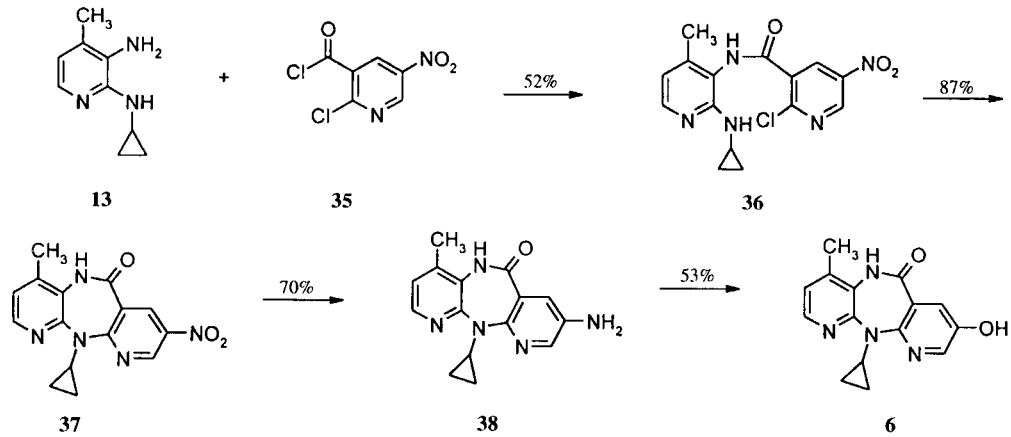
The synthesis of the 8-bromo analog started with the known *N*-(2-chloro-4-methyl-3-pyridyl)-2-(cyclopropylamino)-3-pyridinecarboxamide (**30**) [11] (Scheme 7). Regioselective bromination of **30** gave **31**. Formation of the diazepinone ring in the presence of sodium hydride/pyridine gave 8-bromonevirapine (**32**). Stille methodology was explored [12] and led to efficient coupling of **32** with tributyl(vinyl)tin to give **33**. Ozonolysis to the aldehyde **34**, followed by Baeyer-Villiger oxidation and *in situ* hydrolysis of the formate ester gave 8-hydroxynevirapine (**6**).

Another attempt to synthesize metabolite **6** was to regioselectively nitrate **30**. However, nitration even under mild conditions resulted in the loss of the cyclopropylamine group. For this reason we selected the following route: 3-amino-2-cylopropylamine-4-methylpyridine (**13**) (Scheme 2) was condensed with 2-chloro-5-nitronicotinoyl chloride (**35**) obtained by nitrating commercially available 2-hydroxynicotinic acid, followed by treatment with thionyl chloride [13]. Formation of the diazepinone ring **37** was accomplished by heating **36** in hexamethyldisilazane to 110° C. 8-Nitro-nevirapine (**37**) was reduced catalytically with Raney® nickel and hydrogen to 8-amino-nevirapine (**38**). Diazotization with sodium nitrite in tetrafluoroboric acid followed by acetolysis gave **6** in good yield.

Scheme 7



Scheme 8



Summary.

We have shown that five major metabolites of Nevirapine and one process impurity can be efficiently synthesized. These metabolites are useful for mechanistic pharmacokinetic studies and as analytical standards.

EXPERIMENTAL

Melting points were determined on a Büchi S10MP apparatus and are uncorrected. The ^{1}H nmr spectra were recorded in deuterated dimethylsulfoxide with tetramethylsilane as internal standard on a Varian EM 360, Brucker 270 and on a Brucker 400 MHz spectrometers, unless otherwise noted. Elemental analyses were performed by Quantitative Technologies, Inc., P.O. Box 470, Salem Industrial Park, Whitehouse, New Jersey 08888.

5,11-Dihydro-2-(4'-methoxybenzylamino)-4-methyl-6*H*-dipyrido-[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (**8**) from **7**.

A pressure tube was charged with **7** [4] (0.30 g, 1 mmole) and *p*-methoxybenzylamine (1.2 g, 10 mmoles), sealed and heated to 180° C in an oil bath for 48 hours. The mixture was allowed to cool to room temperature, diluted with water and acidified with 1 *M* hydrochloric acid. The mixture was extracted with dichloromethane, dried over magnesium sulfate and concentrated. The residue was purified by flash chromatography (dichloromethane/2% ethanol) followed by crystallization from ethyl acetate to give 0.24 g, (60%) of a beige colored solid of **8**, mp 192-195° C; ^{1}H nmr: δ 0.28 (m, 2H), 0.81 (m, 2H), 2.15 (s, 3H), 3.5 (m, 1H), 3.7 (s, 3H), 4.36 (m, 2H), 6.12 (s, 1H), 6.85 (m, 2H), 7.13 (m, 1H), 7.25 (m, 2H), 7.94 (m, 1H), 8.45 (m, 1H), 9.42 (s, 1H); ms: (CI) m/z 402 (MH^+).

Anal. Calcd. for C, 68.81; H, 5.78; N, 17.45. Found: C, 68.99; H, 5.98; N, 17.14.

2-Amino-5,11-dihydro-4-methyl-6*H*-dipyrido[3,2-*b*:2',3'-*e*][1,4] diazepin-6-one (**9**) from **8**.

A Parr hydrogenation flask was charged with **8** (0.2 g, 0.5 mmole), ethanol (10 ml) and 10% palladium on carbon (10 mg). The mixture was hydrogenated at 25 psi for 4 hours. The reaction mixture was filtered and concentrated. The residue was flash chromatographed to give 20 mg of **9**, identical by hplc, nmr and ms to the material obtained from **10**.

11-Cyclopropyl-5,11-dihydro-4-methyl-3-nitro-6*H*-dipyrido-[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (**10**) from Nevirapine (**1**).

Nevirapine (**1**) (25 g, 94 mmoles) was suspended in dry acetonitrile (200 ml) containing 4 Å molecular sieves (10 g). The suspension was cooled to 0° C, then nitronium tetrafluoroborate (25 g, 188 mmoles) was added in small portions over 90 minutes. The solution was stirred at 0° C for 20 minutes then poured into ice water (500 ml). The solution was neutralized with saturated sodium bicarbonate solution and extracted with dichloromethane. The organic phase was washed with brine and dried over sodium sulfate. The filtered organic extracts were concentrated under reduced pressure. Starting material precipitated upon concentration and was removed by filtration. The filtrate was chromatographed with 1% methanol in dichloromethane to give 6.0 g (20%) of a bright yellow solid of **10**, mp >300° C with decomposition; ^{1}H nmr: δ 0.4 (m, 2H), 0.9 (m, 2H), 2.5 (s, 3H), 3.6 (m, 1H), 5.7 (s, 1H), 7.2 (m, 1H), 8.0 (m, 1H), 8.5 (m, 1H), 10.3 (s, 1H).

2-Amino-5,11-dihydro-4-methyl-6*H*-dipyrido[3,2-*b*:2',3'-*e*][1,4]-diazepin-6-one (**9**) from **10**.

A solution of tin(II) chloride dihydrate (23.9 g, 106 mmoles) in concentrated hydrochloric acid (36%) (43 ml) was added to the solution of **10** (5.5 g, 17.6 mmoles) of acetic acid (80 ml). A precipitate formed, the suspension was stirred at room temperature overnight. The precipitate was collected by filtration and washed with a small amount of acetic acid. The collected solid was dissolved in water (100 ml) and basified with concentrated ammonium hydroxide. The resulting yellow precipitate was collected by filtration and washed with water followed by acetone and dried to give 4.3 g (86%) of a light tan solid of **9**, mp >300° C; ^{1}H nmr: δ 0.3 (m, 2H), 0.8 (m, 2H), 2.15 (s, 3H), 3.5 (m, 1H), 5.8 (s, 1H), 6.1 (s, 1H), 7.1 (m, 2H), 7.9 (m, 1H), 8.45 (m, 1H), 9.4 (s, 1H); ms: (CI) m/z 282 (MH^+).

5,11-Dihydro-2-hydroxy-4-methyl-4*H*-dipyrido[3,2-*b*:2',3'-*e*]-[1,4]diazepin-6-one (**2**) from **9**.

A solution of **9** (7.9 g, 25 mmoles) was suspended in 5% sulfuric acid (50 ml) and cooled to 0° C. An aqueous solution of sodium nitrite (5.25 g, 75 mmoles) was added to the solution of **9** over 15 minutes. The reaction mixture was stirred for 30 minutes, then neutralized with a 10% sodium hydroxide solution to *p*H 3-4 followed by the slow addition of solid sodium bicarbonate to *p*H 7-8. The resulting precipitate was collected by filtration and recrystallized from ethanol to give 2.4 g (30%) of a light yellow solid, mp >270° C; ^{1}H nmr: δ 0.35 (m, 2H), 0.85 (m, 2H), 2.25 (s, 3H), 3.32 (s, OH), 2.55 (m, 1H), 6.27 (s, 1H), 7.15 (m, 1H), 7.97 (m, 1H), 8.45 (m, 1H), 9.60 (s, 1H), 10.6 (s, NH); ms: (SP-EI) m/z 282 (M^+).

Anal. Calcd. for C, 63.82; H, 5.00; N, 19.85. Found: C, 63.74; H, 5.09; N, 19.57.

2-Cyclopropylamino-4-methyl-3-nitropyridine (**12**) from **11**.

A mixture of **11** (94 g, 0.55 mole), cyclopropylamine (125 g, 2.2 moles) and xylene (400 ml) was heated in a stirred autoclave to 75° C for 48 hours. After cooling to ambient temperature the mixture was poured into 1 liter of water. The product was extracted with ethyl acetate, dried over magnesium sulfate, filtered and concentrated to give a dark yellow oil of **12**, which solidified on standing, mp 50-52° C; ^{1}H nmr: δ 0.54 (m, 2H), 0.70 (m, 2H), 2.32 (s, 3H), 2.80 (m, 1H), 6.65 (d, J = 4.9 Hz, 1H), 7.61 (s, NH), 8.18 (d, J = 4.9 Hz, 1H); ms: m/z 194 (MH^+).

Anal. Calcd. for C, 55.95; H, 5.74; N, 21.75. Found: C, 55.94; H, 5.65; N, 21.72.

3-Amino-2-cyclopropylamino-4-methylpyridine (**13**) from **12**.

A solution of **12** (105 g, 0.54 mole) in ethanol (500 ml) containing 25 g of wet Raney® nickel catalyst was hydrogenated at 40 psi for 4 hours. The catalyst was removed by filtration and the filtrate evaporated to dryness. Addition of ethyl acetate gave 48.8 g (55%) of a white solid of **13**, mp 148-150° C; ^{1}H nmr (250 MHz, deuteriochloroform): δ 0.50 (m, 2H), 0.80 (m, 2H), 2.15 (s, 3H), 2.80 (m, 1H), 3.12 (bs, NH_2), 4.5 (bs, NH), 6.50 (m, 1H), 7.75 (m, 1H); ms: (CI) m/z 164 (MH^+).

Anal. Calcd. for C, 66.22; H, 8.03; N, 25.75. Found: C, 66.01; H, 8.10; N, 25.79.

2-Chloro-*N*-[(2'-cyclopropylamino)-4'-methyl-3'-pyridyl]-3-pyridinecarboxamide (**14**) from **13**.

A mixture of 2-chloronicotinic acid (47.3 g, 0.3 mole) in thionyl chloride (200 ml) was refluxed for 4 hours. After cooling and removal of excess thionyl chloride under vacuum, the crystalline acid chloride was dissolved in ethyl acetate (200 ml). The solution of 2-chloronicotinoyl chloride was slowly added to a solution of **13** (48.2 g, 0.29 mole) in ethyl acetate (500 ml) containing *N*,*N*-diisopropylethylamine (38.7 g, 0.3 mole) at room temperature. After stirring for 18 hours, the mixture was washed with water and brine, dried over magnesium sulfate and concentrated to give 63.7 g (71%) of a white crystalline solid of **14**, mp 177-179° C; ^{1}H nmr (400 MHz): δ 0.42 (m, 2H), 0.70 (m, 2H), 2.18 (s, 3H), 2.72 (m, 1H), 5.86 (d, J = 2 Hz, 1H), 6.57 (d, J = 5 Hz, 1H), 7.58 (m, 1H), 7.92 (d, J = 5 Hz, 1H), 8.26 (m, 1H), 8.54 (m, 1H), 9.70 (s, NH).

Anal. Calcd. for C, 59.51; H, 4.99; N, 18.51; Cl, 11.71. Found: C, 59.67; H, 4.76; N, 18.35; Cl, 11.84.

2-Chloro-*N*-[5'-bromo-4'-methyl-2'-cyclopropylamino-3'-pyridinyl]-3-pyridinecarboxamide (**15**) from **14**.

To a solution of **14** (45.3 g, 0.15 mole), potassium acetate (17.7 g, 0.18 mole) and acetic acid (600 ml) was added 24 g (0.15 mole) of bromine at room temperature over 30 minutes. After 1 hour, the mixture was diluted with water (2 liters). The product was extracted with ethyl acetate and dried over anhydrous magnesium sulfate. After filtration and removal of the solvent, the product was purified by flash chromatography on silica gel and crystallized from ethyl acetate/ether to afford 17.0 g (30%) of a white solid of **15**, mp 119-120° C; ^{1}H nmr: δ 0.60 (m, 2H), 0.85 (m, 2H), 2.32 (s, 3H), 2.70 (m, 1H), 4.15 (bs, NH), 7.55 (m, 1H), 8.20 (s, 1H), 8.30 (m, 1H), 8.50 (m, 1H); ms: (CI) m/z 381 (MH^+).

Anal. Calcd. for C, 47.21; H, 3.70; N, 14.68; Br, 20.94; Cl, 9.29. Found: C, 46.96; H, 3.62; N, 14.48; Br, 21.27; Cl, 9.56.

3-Bromo-11-cyclopropyl-5,11-dihydro-4-methyl-6*H*-dipyrido-[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (**16**) from **15**.

To a solution of **15** (10.6 g, 0.027 mole) in pyridine (80 ml) was added sodium hydride (50% dispersion in mineral oil, 0.081 mole) under nitrogen at 80° C. The mixture was heated to reflux for 30 minutes. After cooling, the mixture was poured on ice-water (500 ml), filtered, washed with water and dried to afford 8.9 g (92.7%) of **16**, mp 240-242° C; ^{1}H nmr: δ 0.35 (m, 2H), 0.85 (m, 2H), 2.30 (s, 3H), 3.60 (m, 1H), 7.20 (m, 1H), 7.95 (m, 1H), 8.30 (s, 1H), 8.50 (m, 1H), 10.05 (bs, 1H); ms: (CI) m/z 345 (MH^+).

Anal. Calcd. for C, 52.19; H, 3.81; N, 16.23. Found: C, 52.29; H, 3.77; N, 16.05.

11-Cyclopropyl-5,11-dihydro-4-methyl-3-vinyl-6*H*-dipyrido-[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (**17**) from **16**.

To a solution of **16** (7.1 g, 20.5 mmole) in *N*,*N*-dimethylformamide (100 ml) and tetrakis(triphenylphosphine)palladium (0.5 g, 0.43 mmole) was added tributyl(vinyl)tin (6.5 ml, 22 mmole). The mixture was heated to 90° C for 1.5 hours then poured into water (500 ml). The product was extracted with dichloromethane, dried over magnesium sulfate, filtered, concentrated and purified by flash chromatography on silica gel using ether-dichloromethane (9:1). The fractions were monitored by tlc. The first fractions eluted contained 2.1 g (39%) of unreacted **16**. The next product eluted was **17**. All fractions containing **17** were combined, concentrated and crystallized from petroleum ether to afford 3.9 g (64.9%) of a white solid of **17**, mp 219-222° C; ^{1}H nmr: δ 0.38 (m, 2H), 0.85 (m, 2H), 2.25 (s, 3H), 3.60 (m, 1H), 5.40 (d, 1H), 5.70 (d, 1H), 6.85 (dd, 1H), 7.20 (m, 1H), 8.0 (m, 1H), 8.3 (s, 1H), 8.50 (m, 1H), 9.95 (s, NH); ms: (CH_4CI) m/z 293 (MH^+).

Anal. Calcd. for C, 69.84; H, 5.52; N, 19.17. Found: C, 69.75; H, 5.46; N, 19.34.

11-Cyclopropyl-5,11-dihydro-3-formyl-4-methyl-6*H*-dipyrido-[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (**18**) from **17**.

A solution of **17** (1.0 g, 3.42 mmoles) in dichloromethane (20 ml) and methanol (20 ml) was cooled to -78° C. The solution was saturated with ozone, then allowed to warm to ambient temperature. The reaction was quenched with dimethyl sulfide. After concentrating the solvent, the residue was purified by flash chromatography on silica gel using dichloromethane/ethyl acetate (7:3) to give 0.47 g (47%) of a white solid of **18**, mp 250-253° C (lit. [6] 262-265° C); ^{1}H nmr: δ 0.40 (m, 2H), 0.94 (m, 2H), 2.50 (s, 3H), 3.68 (m, 1H), 7.25 (m, 1H), 8.05 (m, 1H), 8.55 (m, 1H), 8.62 (s, 1H), 10.03 (s, 1H), 10.17 (s, 1H); ms: (NH_3CI) m/z 295 (MH^+).

Anal. Calcd. for C, 65.29; H, 4.79; N, 19.04. Found: C, 65.13; H, 4.79; N, 18.97.

11-Cyclopropyl-5,11-dihydro-3-hydroxyl-4-methyl-6*H*-dipyrido-[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (**3**) from **18**.

To a solution of **18** (0.47 g, 1.6 mmoles) in dichloromethane (35 ml) was added 3-chloroperoxybenzoic acid (3.2 mmoles) at 10° C. The reaction mixture was stirred for 18 hours then quenched with a saturated sodium bicarbonate solution. The organic phase was washed with 10% sodium thiosulfate solution, dried over anhydrous magnesium sulfate, filtered and concentrated. The crude material was flash chromatographed on silica gel to give 120 mg (26%) of a white solid of **3**, mp 243-245° C (lit. [6] 255-258° C); ^{1}H nmr and ms are identical to an authentic sample [6].

S,*S*-Dimethyl-*N*-(3-pyridyl)sulfinimine (**20**) from **19**.

A solution of 2-chloro-3-aminopyridine (128.5 g, 1 mole) in dichloromethane (500 ml) was added to a stirred suspension of *N*-chlorosuccinimide (133.5 g, 1 mole) in dichloromethane (500 ml) at 0-5° C. To the resulting mixture was added dimethyl sulfide (74.6 g, 1.2 moles) over 1 hour; the reaction mixture was stirred at 0-5° C for an additional 1 hour. The mixture was poured into 10% sodium hydroxide solution (1 liter). The organic layer was separated and dried over sodium sulfate, filtered and concentrated. Addition of toluene (500 ml) afforded 133.8 g (71%) of a white solid of **20**, mp 114-117° C (lit. [8] 107-112° C); ^{1}H nmr (deuteriochloroform): δ 2.75, (s, 3H), 7.05-7.15 (m, 2H), 7.65- 7.78 (m, 1H).

3-Amino-2-chloro-4-methylthiomethylpyridine (**21**) from **20**.

A mixture of **20** (133 g, 0.70 mole), 2-*t*-butyl-4-methylphenol (6.0 g, 0.036 mole) in dry toluene (425 ml) was heated under nitrogen to 90-95° C for 2 hours. The toluene was removed under reduced pressure and the crude product was purified by flash chromatography using 2% ethyl acetate in dichloromethane. The fractions containing the product were concentrated to dryness to give 74.8 g (56%) of an amber colored oil of **21**; ^{1}H nmr (deuteriochloroform): δ 1.97 (s, 3H), 3.64 (s, 2H), 4.67 (bs, 2H), 6.92 (d, 1H, J = 4.76 Hz), 7.73 (d, 1H, J = 4.76 Hz).

N-(6-Chloro-4-methylthiomethyl-3-pyridinyl)-2-chloro-3-pyridinecarboxamide (**22**) from **21**.

To a stirred mixture of **21** (74.8 g, 0.396 mole) and anhydrous sodium carbonate: (83.3 g, 0.786 mole) in toluene (450 ml) at 90-100° C was added 2-chloronicotinoyl chloride (75.7 g, 0.43 mole) over 1 hour. The reaction mixture was kept at 90-100° C for 2 hours and allowed to cool to ambient temperature. The toluene was decanted and discarded. The solid was washed with water (1 liter) and dissolved in a mixture of dichloromethane/methanol (1.6 liters:0.4 liters), filtered and concentrated to near dryness. Addition of ether (1 liter) gave a solid which was filtered and dried at 60° C to yield: 63.5 g (49%), of a white solid of **22**, mp 157-160° C; ^{1}H nmr (deuteriochloroform): δ 2.05 (s, 3H), 3.82 (s, 2H), 7.35-7.60 (m, 2H), 8.20-8.67 (m, 4H).

N-(6-Chloro-4-methylthiomethyl-3-pyridinyl)-2-cyclopropyl-3-pyridinecarboxamide (**23**) from **22**.

A mixture of **22** (63 g, 0.192 mole), cyclopropylamine (43.8 g, 0.768 mole) and xylene (900 ml) in a sealed vessel was heated at 105° C for 3 days. The reaction mixture was cooled to room temperature and poured into water. The product was extracted with ethyl acetate (2 x 500 ml). The organic phase was dried over sodium sulfate, filtered, concentrated, and the residue recrystallized from ether to yield 56 g (83.6%) of off-white crystals of **23**, mp 115-120° C; ^{1}H nmr (deuteriochloroform): δ 0.5-1.0 (m, 4H), 2.8-3.2 (m, 1H), 3.70 (s, 3H), 6.6-6.8 (dd, 1H), 7.40 (d, 1H), 8.0-8.6 (m, 5H).

11-Cyclopropyl-5,11-dihydro-4-methylthiomethyl-6*H*-dipyrido-[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (**24**) from **23**.

To a suspension of sodium hydride (60% in mineral oil, 16 g, 0.4 mole) was added under nitrogen to a solution of **23** (45 g, 0.129 mole) in pyridine (200 ml) at 60-85° C over 90 minutes. The temperature was maintained for an additional 1 hour at 75-85° C and cooled to 10° C. The excess sodium hydride was quenched by the slow addition of water, neutralized with acetic acid and concentrated under reduced pressure. The residue was dissolved in *N*,*N*-dimethylformamide (300 ml), treated with charcoal, filtered and concentrated to 100 ml. Addition of water gave a yellow crystalline solid, dried at 100° C to afford 22.1 g (54%) of yellow crystals of **24**, mp 199-202° C; ^{1}H nmr: δ 0.38 (m, 2H), 0.88 (m, 2H), 1.90 (s, 3H), 3.62 (m, 2H), 4.18 (m, 1H), 7.14-7.22 (m, 2H), 8.02 (m, 1H), 8.16 (m, 1H), 8.52 (m, 1H), 9.9 (s, NH); ms: (CI) m/z: 213 (MH^+).

Anal. Calcd. for C, 61.52; H, 5.16; N, 17.93; S, 10.26. Found: C, 61.42; H, 5.16; N, 17.72; S, 10.28.

4-(1,2-Epoxybutyl)-11-cyclopropyl-5,11-dihydro-6*H*-dipyrido-[3,2-*b*:2',3'-*e*] [1,4]diazepin-6-one (**26**) from **24**.

To a solution of **24** (15 g, 0.048 mole) in trifluoroacetic acid (100 ml) was added dimethyl sulfate (4.5 ml, 0.047 mole). The mixture was stirred under nitrogen for one week and diluted with ether (200 ml). The liquid was decanted and the remaining residue in the flask was washed with additional ether (200 ml). After decanting the ether, the residue of crude methyl sulfate salt **25** was dried under vacuum. Without further purification, the crude salt (**25**) was suspended in dry tetrahydrofuran (200 ml), cooled to -78° C and treated with sodium hydride (60% in oil, 5.7 g, 0.14 mole). After 15 minutes at -78° C, propionaldehyde (7.2 g, 0.124 mole) was added and the dry ice-bath removed and the mixture was allowed to warm to room temperature. The reaction mixture was stirred at ambient temperature for an additional 1 hour. The excess sodium hydride was quenched with water, the mixture was concentrated to remove tetrahydrofuran. The remaining mixture was partitioned between water and ethyl acetate. The organic phase was dried over sodium sulfate, filtered, concentrated and purified by flash chromatography on silica gel (gradient toluene/isopropanol/acetic acid 98:1:1) to give 5.2 g (33%) of a beige solid of **24**, mp 162-172° C; ^{1}H nmr: δ 0.35 (m, 2H), 0.89 (m, 2H), 1.0 (m, 3H), 1.6 (m, 2H), 1.9 (m, 1H), 3.0-4.2 (m, 3H), 6.90 (m, 1H), 7.21 (m, 1H), 8.2 (m, 1H), 8.51-8.53 (m, 1H), 10.3 (m, 1H); ms: (CI) m/z: 323 (MH^+), 305 ($MH-H_2O$), 264 ($MH-C_3H_9O^+$).

Anal. Calcd. for C, 67.07; H, 5.63; N, 17.38. Found: C, 66.96; H, 5.69; N, 17.24.

4-(1-Butenyl)-11-cyclopropyl-5,11-dihydro-6*H*-dipyrido[3,2-*b*:2',3'-*e*] [1,4]diazepin-6-one (**27**) from **26**.

To a stirred mixture of **26** (5.2 g, 16 mmoles), sodium iodide (43 g, 0.287 mole) in acetonitrile (165 ml) at 0° C was added trifluoroacetic acid (5.2 ml, 16 mmoles). After warming to ambient temperature, the mixture was diluted with water (500 ml), the product was extracted with dichloromethane and dried over sodium sulfate. After filtration and evaporation of the solvent, the crude product was purified by flash chromatography on silica gel (eluent: toluene/isopropanol/acetic acid 98:1:1) to yield 1.4 g (28%), of a white solid of **27**, mp 220-230° C; ^{1}H nmr: δ 0.35 (m, 2H), 0.88 (m, 2H), 1.1 (m, 3H), 2.27 (m, 2H), 2.50 (s, 2H), 3.62 (m, 1H), 6.54 (m, 1H), 6.58 (m, 1H), 7.20 (m, 1H), 8.00 (m, 1H), 8.11 (m, 1H), 8.50 (m, 1H), 10.1 (s, NH); ms (CI) m/z: 307 (MH^+).

Anal. Calcd. for $C_{18}H_{18}N_4O$; C, 70.57; H, 5.92; N, 18.29. Found: C, 70.38; H, 5.85; N, 18.02.

11-Cyclopropyl-5,11-dihydro-4-(hydroxymethyl)-6*H*-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (**4**) from **27**.

A solution of **27** (30.6 mg, 0.1 mmole) was dissolved in methanol (2 ml) and cooled to -40° C. The solution was saturated with ozone and stirred an additional 10 minutes. The ozonide was quenched with methyl sulfide. To the mixture was added sodium borohydride (38 mg, 1 mmole) at 0° C. After 2 hours the reaction mixture was diluted with water, and extracted with dichloromethane, dried over magnesium sulfate, filtered, concentrated and flash chromatographed on silica gel to give after concentrating to dryness 12.7 mg (45%) of a white solid of **4**, mp 237-239° C, identical by nmr and tlc to an authentic sample [4].

11-Cyclopropyl-5,11-dihydro-4-(hydroxymethyl)-6*H*-dipyrido-[3,2-*b*:2',3'-*e*][1,4]diazopin-6-one (**4**) from **24**.

To a cooled solution of **24** (8.2 g, 26.2 mmoles) in dichloromethane (138 ml) was added 3-chloroperoxybenzoic acid (60%, 9.0 g, 31.3 mmoles) at -5 to 0° C over 30 minutes. The mixture was stirred for an additional 20 minutes, then diluted with saturated aqueous sodium bicarbonate (138 ml). The product was extracted with dichloromethane (50 ml), dried over magnesium sulfate, and concentrated to an oil. The crude sulfoxide (**28**) was dissolved in dichloromethane (75 ml) and pentafluoropropionic anhydride (16 ml, 134 mmoles) was added with cooling over 20 minutes at 20° C. The mixture was stirred at room temperature for an additional hour, concentrated to dryness, dissolved in dichloromethane (80 ml) and added over 30 minutes to a stirred solu-

tion of sodium borohydride (12.5 g, 330 mmoles) in methanol (500 ml) containing a saturated aqueous sodium bicarbonate solution (150 ml). After stirring overnight, the mixture was concentrated, diluted with water, and extracted with dichloromethane (3 x 100 ml). The organic phase was dried over magnesium sulfate, filtered and concentrated; the residue was purified by flash chromatography (dichloromethane to 5% methanol gradient). The product was monitored by tlc, the fractions containing the product were combined and recrystallized from a mixture of methanol/ethyl acetate (1:1) to give 1.5 g (20%) of a white solid of **4**, identical by nmr, hplc and tlc to an authentic sample [4].

4-(11-Cyclopropyl-5,11-dihydro-6*H*-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one)carboxylic Acid (**5**) from **4**.

A solution of **4** (3.5 g, 12.4 mmoles) and 4-methylmorpholine *N*-oxide (2.93 g, 25 mmoles) was dissolved in 200 ml of a mixture of acetonitrile/dioxane (1:3). Tetrapropylammonium perruthenate (0.21 g, 0.6 mmole) was then added in small portions. The reaction was stirred overnight, then quenched with aqueous sodium metabisulfite. The dark mixture was concentrated to near dryness and redissolved in 19:1 dichloromethane/methanol, and passed through a silica gel column. The fractions were combined and concentrated, the residue was dissolved in water and acidified with 2*N* hydrochloric acid. The precipitate was filtered, washed with water, and dried at 30° C under reduced pressure to give 1.7 g (41%) of a white solid of **5**, mp >260° C (dec). The product crystallized with 1/4 mole water; ^{1}H nmr: δ 0.35 (m, 2H), 0.85 (m, 2H), 3.65 (m, 1H), 7.20 (m, 1H), 7.55 (m, 1H), 8.05 (m, 1H), 8.30 (m, 1H), 8.55 (m, 1H), 10.25 (s, 1H); ms: m/z: 297 (MH^+).

Anal. Calcd. for C, 59.89; H, 4.19; N, 18.63. Found: C, 60.10; H, 4.19; N, 18.66.

11-Cyclopropyl-5,11-dihydro-8-hydroxy-6*H*-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (**6**) from Nevirapine (**1**).

To a mixture of **1** (100 g, 0.363 mole) in 0.8 liter of acetic acid at 100° C was added dropwise hydrogen peroxide (120 ml) over 2 hours. After 24 hours at 95-100° C, an additional 120 ml hydrogen peroxide was added and stirred for 24 hours. The dark mixture was poured into 3 liters of water and extracted with ethyl acetate. The combined organic extracts were concentrated and treated with 5% palladium on carbon (1.0 g) and hydrogen at 40 psi for 6 hours. The catalyst was filtered and the mixture purified by column chromatography on 2 kg of silica gel (230-400 mesh) eluting with dichloromethane/ethanol (98:2). Fractions containing 8-hydroxynevirapine (monitored by tlc) were combined and crystallized from methanol to give 5.2 g (5%) of a white solid of **6**, mp 278-280° C; ^{1}H nmr: δ 0.30 (m, 2H), 0.80 (m, 2H), 2.30 (s, 3H), 3.20 (MeOH), 3.40 (m, 1H), 4.15 MeOH), 7.00 (s, 1H), 7.40 (s, 1H), 8.10 (m, 2H), 9.8 (s, 1H), 9.9 (bs, 1H); ms: sp (solid probe) EI m/z 282 (M^+).

Anal. Calcd. with 0.5 mole CH_3OH for C, 62.41; H, 5.41; N, 18.78. Found: C, 62.24; H, 5.24; N, 18.60.

5-Bromo-2-(cyclopropylamino)-*N*-[2'-chloro-4'-methyl-3'-pyridinyl]-3-pyridinecarboxamide (**31**) from **30**.

To a stirred solution of **30** (31.6 g, 0.090 mole), potassium acetate (10.6 g, 0.108 mole) and glacial acetic acid (355 ml) was added a solution of bromine (5.8 ml, 0.113 mole) in 20 ml glacial acetic acid dropwise over 10 minutes at room temperature. After 20 minutes, additional bromine (1.2 ml, 0.023 mole) was added. Stirring was continued for an additional 20 minutes. Water (200 ml) was added to the reaction mixture forming a precipitate which was filtered. The filter cake was washed with water (3 x 100 ml). Additional product was obtained by concentrating the filtrate under reduced pressure to a small volume; the solids were filtered and washed with water. The combined solids were dried at 40° C in a vacuum oven overnight to yield 16.5 g (48%) of beige crystals of **31**, mp 134-170° C (dec.); ^{1}H nmr: δ 10.37 (s, 1H), 8.45 (m, 2H), 8.25 (m, 2H), 7.42 (d, J = 3 Hz, 1H), 2.79 (m, 1H), 2.27 (s, 3H), 0.77 (m, 2H), 0.43 (m, 2H); ms: m/z (CI^+) 381 ($M+H$).

Anal. Calcd. with 0.5 mole CH_3COOH for C, 46.68; H, 3.92; N, 13.61. Found: C, 46.68; H, 3.85; N, 13.21.

8-Bromo-11-cyclopropyl-5,11-dihydro-4-methyl-6*H*-dipyrido-[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (**32**) from **31**.

To a stirred solution of **31** (22.97 g, 0.060 moles) in dry pyridine (115 ml) was added at room temperature and under nitrogen a 1.0 *M* solution of sodium bis(trimethylsilyl)amide (132 ml, 0.13 moles) in tetrahydrofuran dropwise over 20 minutes. The temperature increased to 36° C. The dark orange solution was heated to 80-85° C for 16 hours. The reaction was incomplete by tlc (1:1 hexane/ethyl acetate). After cooling the reaction mixture to room temperature, an additional charge of a 1 *M* solution of sodium bis(trimethylsilyl)amide (58 ml, 0.060 moles) was added. After heating the reaction for 1 hour at 80-85° C, tlc indicated complete conversion. The mixture was cooled to room temperature and poured into water (2 liters). The *p*H of the solution was adjusted to 5-6 with acetic acid, the mixture was stirred over the weekend, and the precipitate was filtered and washed with water. The solid was dissolved in 200 ml warm acetic acid and passed through a pad of silica gel. After removing the acetic acid under vacuum, the remaining oil was diluted with water (500 ml) and the solid was filtered, washed with water and dried under high vacuum at 40° C to yield 6.9 g (33%) of off-white crystals of **32**, mp 220-224° C; ^{1}H nmr (deuteriochloroform): δ 8.58 (s, 1H), 8.23 (m, 3H), 6.99 (m, 1H), 3.74 (m, 1H), 2.42 (s, 3H), 1.01 (m, 2H), 0.50 (m, 2H); ms: m/z 345 ($M+H$).

Anal. Calcd. with 0.5 mole water for C, 50.99; H, 3.96; N, 15.86. Found: C, 51.48; H, 3.94; N, 15.73.

11-Cyclopropyl-5,11-dihydro-4-methyl-8-vinyl-6*H*-dipyrido-[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (**33**) from **32**.

To a suspension of **32** (1.73 g, 5 mmoles) in anhydrous *N*,*N*-dimethylformamide (25 ml) under nitrogen was added tetrakis(triphenylphosphine)palladium (0.116 g, 2 mole %) and tributyl(vinyl)tin (1.55 ml, 5.3 mmoles). The mixture was heated to 90° C for 1.5 hours, cooled to room temperature and poured into water (100 ml). The product was extracted with dichloromethane (3 x 25 ml), the combined organic layer was washed with 50% ammonium hydroxide solution (25 ml) followed by brine (25 ml) and dried over sodium sulfate, filtered and concentrated. The residue was purified on a silica gel column, eluting with 3:1 hexane/ethyl acetate followed by 1:1 hexane/ethyl acetate to give 0.9 g (62%) of a yellow solid of **33**, mp 215-218° C (dec.); ^{1}H nmr: δ 9.92 (s, 1H), 8.58 (d, 1H, J = 2.3), 8.12 (d, 1H, J = 2.3), 8.08 (d, 2H, J = 4.8), 7.07 (d, 1H, J = 4.8), 6.75 (dd, 1H, J = 17.7), 5.91 (d, 1H, J = 17.7), 5.65 (d, 1H, J = 11), 3.62 (m, 1H), 2.34 (s, 3H), 0.88 (m, 2H); ms: m/z 293.3 (MH^+).

Anal. Calcd. for C, 69.85; H, 5.52; N, 19.17. Found: C, 69.98; H, 5.58; N, 18.71.

11-Cyclopropyl-5,11-dihydro-8-formyl-4-methyl-6*H*-dipyrido-[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (**34**) from **33**.

A solution of **33** in dichloromethane (10 ml) was diluted with methanol (10 ml) and cooled to -78° C. The solution was saturated with ozone and stirred for an additional 5 minutes. The reaction mixture was warmed to room temperature and quenched with methyl sulfide (2 ml). The solvent was evaporated under reduced pressure and the yellow solid remaining was stirred with hexane, the precipitate was filtered and washed with hexane to give 0.65 g (92%) of a white solid of **34** as the monohydrate; ^{1}H nmr: δ 10.08 (s, 1H), 10.01 (s, 1H), 8.99 (d, 1H, J = 2.7), 8.43 (d, 1H, J = 2.7), 8.14 (m, 1H), 7.16 (m, 1H), 2.39 (s, 3H), 0.95 (m, 2H), 0.42 (m, 2H); ms: m/z 295 (MH^+).

Anal. Calcd. for C, 61.53; H, 5.16; N, 17.26. Found: C, 61.23; H, 4.78; N, 17.21.

11-Cyclopropyl-5,11-dihydro-8-hydroxy-4-methyl-6*H*-dipyrido-[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (**6**) from **34**.

A solution of purified 3-chloroperoxybenzoic acid in dichloromethane (0.094 mmole) titrated to 90% purity, was added to the monohydrate of **34** (0.21 g, 0.71 mmole) in dichloromethane (10 ml) at 0° C. After 15 minutes, the cooling bath was removed and the solution allowed to warm to room temperature and stirred 16 hours. Since tlc indicated that starting material was still present; an additional 3-chloroperoxybenzoic acid (0.094 mmole) in dichloromethane solution was added and the mixture was stirred for an additional 16 hours, quenched with 4 ml methanol and 4 ml of a saturated sodium bicarbonate solution. After stirring for 2 hours the *p*H was adjusted to 7 and the layers were separated. The aqueous layer was washed with dichloromethane and the combined organic layers were washed with 10% sodium thiosulfate solution until potassium iodide-starch paper was negative to peroxides. The organic layer was washed with brine, dried over magnesium sulfate and concentrated, the residue was purified by flash chromatography (eluent 90:5:5 toluene:ethanol:acetic acid) to yield 40 mg (20%) of a white solid of **6**. The compound was identical by nmr, ms and hplc to an authentic sample obtained by Scheme 6.

2-Chloro-*N*-[(2'-cyclopropylamino)-4'-methyl-3'-pyridyl]-8-nitro-3-pyridinecarboxamide (**36**) from **13**.

A solution of 2-chloro-5-nicotinoyl chloride [12] (71.4 g, 0.37 mole) in ethyl acetate (300 ml) was added over 2 hours to a cooled stirred mixture of **13** (60.4 g, 0.37 mole), *N*,*N*-diisopropylethylamine (47.8 g, 0.37 mole) and ethyl acetate (700 ml). The mixture was stirred for 48 hours at room temperature, washed with water followed with brine and dried over magnesium sulfate. After filtering and concentrating *in vacuo*, the residue was purified on a silica gel column, eluting with 5% ethanol/dichloromethane resulted in 67 g (52%) of a beige solid of **36**, mp 185-186° C; ^{1}H nmr: δ 0.40 (m, 2H), 0.70 (m, 2H), 2.20 (s, 3H), 3.4 (m, 1H), 6.35 (s, 1H), 6.50 (m, 1H), 7.90 (m, 1H), 9.25 (s, 1H), 9.32 (s, 1H), 9.90 (s, 1H); ms: (PB-NH_3Cl) m/z 348 (MH^+).

Anal. Calcd. for C, 51.81; H, 4.06; N, 20.14; Cl, 10.19. Found: C, 52.01; H, 4.33; N, 20.17; Cl, 10.07.

11-Cyclopropyl-5,11-dihydro-4-methyl-8-nitro-6*H*-dipyrido-[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (**37**) from **36**.

A solution of **36** (34.9 g, 0.1 mole) in 1,1,1,3,3,3-hexamethyldisilazane (250 ml) was heated to 110° C for 24 hours. After concentration *in vacuo*, the mixture was dissolved in ether (300 ml), filtered and stirred with 1*N* hydrochloric acid solution (150 ml) for 2 hours at room temperature. The yellow crystalline material was filtered and dried to give 21.1 g (87.1%) of yellow crystals of **37**, mp 259-266° C; ^{1}H nmr: δ 0.45 (m, 2H), 0.95 (m, 2H), 2.30 (s, 3H), 3.60 (m, 1H), 7.15 (m, 1H), 8.10 (m, 1H), 8.60 (m, 1H), 9.3 (m, 1H), 10.10 (bs, 1H); ms: (SP-NH_3Cl) m/z 344.

Anal. Calcd. for C, 57.87; H, 4.21; N, 22.50. Found: C, 57.73; H, 4.20; N, 22.20.

8-Amino-11-cyclopropyl-5,11-dihydro-4-methyl-6*H*-dipyrido [3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (**38**) from **37**.

A suspension of **37** (29 g, 0.093 mole) in methanol (500 ml) and tetrahydrofuran (500 ml) containing approximately 10 g wet Raney® nickel catalyst was hydrogenated at 30 psi for 4 hours. The catalyst was removed by filtration through celite and the filtrate evaporated to dryness under reduced pressure to give 23.6 g (90%) of a yellow solid of **38**, mp 294-296° C; ^{1}H nmr: δ 0.30 (m, 2H), 0.80 (m, 2H), 2.25 (s, 3H), 3.50 (m, 1H), 5.20 (bs, NH_2), 6.95 (m, 1H), 7.20 (m, 1H), 7.80 (m, 1H), 8.02 (m, 1H), 9.65 (s, NH); ms: (PP-NH^+_4Cl) m/z 282 (MH^+).

Anal. Calcd. for 1/4 mole H_2O: C, 63.05; H, 5.42; N, 24.51. Found: C, 62.88; H, 5.30; N, 24.45.

11-Cyclopropyl-5,11-dihydro-8-hydroxy-4-methyl-6*H*-dipyrido-[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (**6**) from (**38**).

To a stirred suspension of **38** (13 g, 46.6 mmoles) in tetrafluoroboric acid (48%, 75 ml) at 0° C was added a solution of sodium nitrite (3.7 g, 53.6 mmole) in water (50 ml) over 20 minutes. The mixture dissolved and after a few minutes the diazonium salt precipitated. After 30 minutes, the diazonium salt was filtered and washed with ether. The wet diazonium salt was slowly added to a stirred acetic acid (75 ml) solution at 100° C. After the evolution of gas stopped, the mixture was cooled and concentrated to dryness under reduced pressure. The residue was diluted with water (100 ml) and the *p*H adjusted to 7-7.5 by addition of ammonium hydroxide. The crude acetoxy derivative was extracted with ethyl acetate, dried, concentrated to dryness, dissolved in methanol (100 ml) and hydrolyzed by addition of sodium methoxide until the *p*H of the solution was >9. The mixture was allowed to stir overnight, and concentrated *in vacuo*. The residue was diluted with water (200 ml) and neutralized with acetic acid. The crude material was filtered and purified on a silica gel column, the product was eluted with toluene/ethanol/acetic acid (90:5:5) to give 3.7 g (53%) of a white solid of **6**, mp 280-282° C, identical by ms, ^{1}H nmr, hplc to an authentic sample obtained from Scheme 6.

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