Chirospecific Synthesis of the Tetrahydroimidazodiazepinol Aglycon of Pentostatin and Its Analogues

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A high-yield, versatile method is presented for the stereo- and regiospecific synthesis of the aglycon of pentostatin and its analogues using the L-vinylglycine 1 as the chiral educt. From this four-carbon asymmetric core, containing the contiguous carbons of the target ring system, the synthetic process proceeds with development of the *R* absolute stereochemistry for the hydroxyl group at *C*-8 and nitrogen or potential nitrogen functions at the other three carbons. Conversion of the α-amino ester to an α-amino nitrile is followed by formation of the 1,4,5-trisubstituted aminoimidazole. After generating another amine by reduction of an azide, the diazepine is then annealed by treatment with orthoformate. Using this process, a series of (8*R*)-8-hydroxy-substituted tetrahydroimidazodiazepinols has been prepared. The protecting group protocol allows specific deprotection at *N*-3 for subsequent glycosylation and other substitution.

Introduction

Pentostatin (2′-deoxycoformycin) and coformycin (Figure 1) are tight-binding naturally occurring inhibitors (K_i = 2.5 × 10^{-12} and 1.0 × 10^{-11}, respectively)[1] of adenosine deaminase, a ubiquitous mammalian enzyme with a central role in the purine salvage pathway.[2a] Recently, two additional analogues with similar activity have been isolated.[2b] They are the 2′-chloro-2′-deoxy compound adechlorin (Figure 1) and a carbocyclic analogue adecypenol (not shown). Pentostatin, a minor product from *Streptomyces antibioticus*,[3] has demonstrated oncologic chemotherapeutic activity against a variety of leukemias and non-Hodgkin's lymphomas,[4] most recently and dramatically in hairy cell leukemia.[5] Toxicities have limited the clinical use of pentostatin,[4,5] and the search for other adenosine deaminase inhibitors has been continuing.[6]

In planning our synthesis, we focused on the tetrahydroimidazodiazepinol aglycon. When appropriately protected, this target compound could provide the key substrate to which a wide series of substituents might subsequently be attached at *N*-3. Our plan was to derive the enantiomeric center bearing the hydroxyl group at *C*-8 from a chiral educt. Other syntheses[7-9] have introduced this center by diastereomer formation on reduction of an 8-keto function, influenced by the glycosidic moiety already at *N*-3. The result was a low yield and difficult separation with less variability at *N*-3.

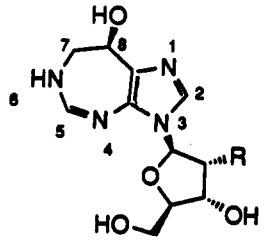

Figure 1. Pentostatin (R = H), coformycin (R = OH), and adechlorin (R = Cl).

Our synthesis centered on the four-carbon contiguous core of the tetrahydroimidazodiazepine. This core, *C*-7, *C*-8, *C*-8a, and *C*-3a, with the *R* absolute stereochemistry at the hydroxyl center at *C*-8 and amino or potential amino functions at the other three carbons, then was to be elaborated into a substituted amino imidazole to which would be fused the diazepine. Also required was a protection protocol that would allow specific deprotection at *N*-3. We now report the completion of such a synthesis and evidence that alkylation is highly regioselective at *N*-3.

Results and Discussion

Establishment of Hydroxyl Group Stereochemistry and Functionality in the Four-Carbon Core. An ideal educt on which to develop the appropriately functionalized four-carbon core is L-vinylglycine, now readily available in quantity from L-methionine as the *N*-CBZ methyl ester

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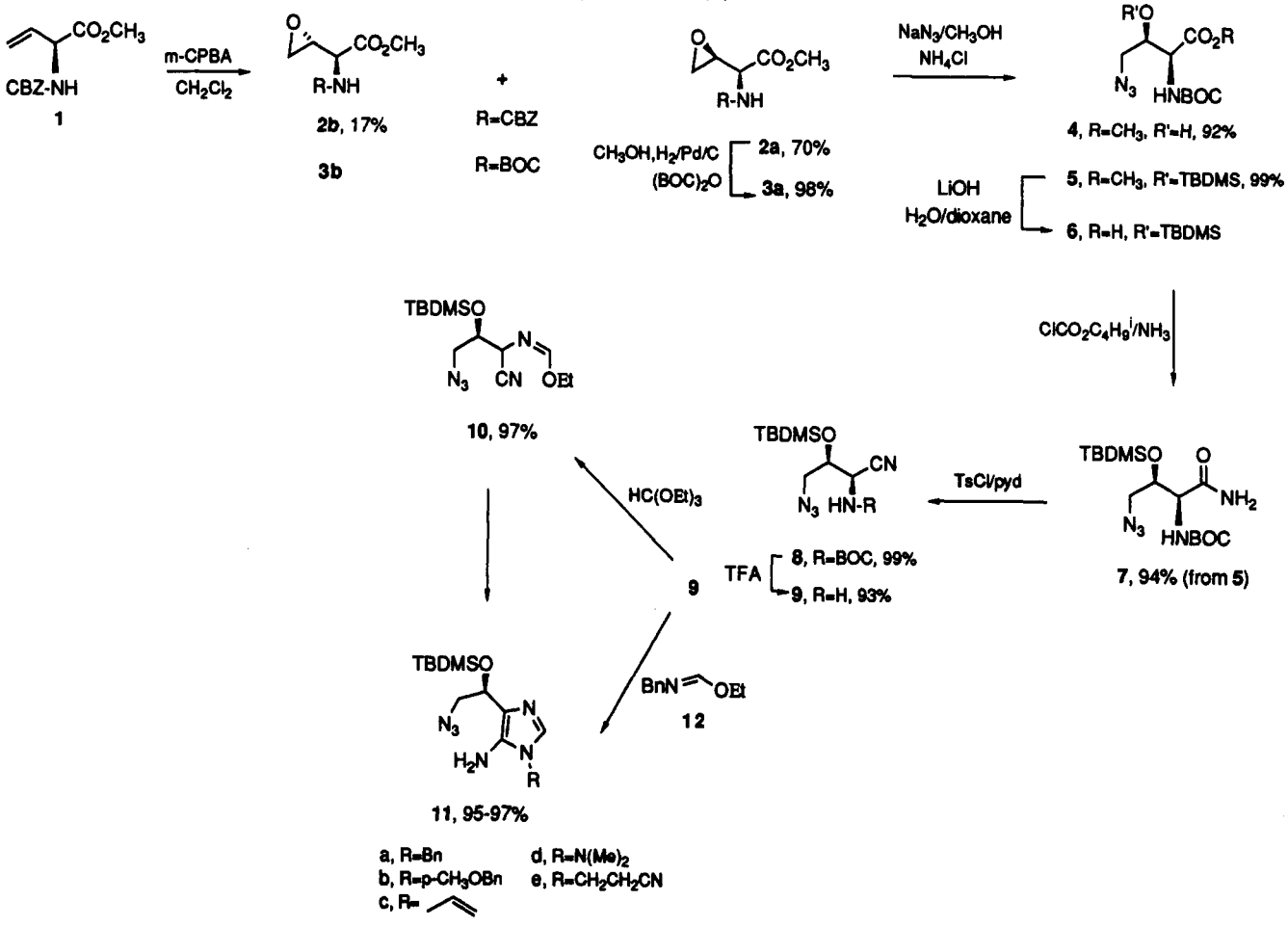
Scheme I. Synthesis of Asymmetric 1,4,5-Trisubstituted Imidazole



1.[10] Epoxidation with *m*-chloroperbenzoic acid has been shown to give a 4/1 mixture of diastereomers, with the major diastereomer having the requisite configuration.[11] Thus *N*-CBZ-L-vinylglycine methyl ester (1) was epoxidized and a mixture of *syn*- and *anti*-epoxides, **2a** and **2b**, respectively, was obtained in 95% yield.

We found preparative-scale separation of the *syn*- and *anti*-*N*-CBZ epoxides **2a** and **2b** by medium-pressure liquid chromatography to be ineffective. Complete separation could be attained using preparative HPLC; however, the limited solubilities of the epoxides in the eluent severely restricted the quantity that could be separated per injection and made the process impractical. This problem was overcome by transforming the *N*-protected-CBZ-epoxide diastereomers **2a** and **2b** to the *N*-protected-BOC-epoxide diastereomers **3a** and **3b** (Scheme I). Complete separation of the *N*-protected-BOC-epoxides on a synthetically useful scale was attained by simple low-pressure chromatography, yielding pure *syn*-**3a** and *anti*-**3b** epoxide diastereomers.

A variety of oxidants and reaction conditions were explored in an effort to increase the proportion of the *syn*-epoxide **2a**. Indeed, monoperphthalic acid in toluene resulted in a tremendous increase in selectivity to a 40/1 mixture of *syn*-**2a** to *anti*-**2b**. The yield, however, was only 41% compared to 95% with *m*-chloroperbenzoic acid in methylene chloride, and the reaction time was increased 20-fold.

Having established the correct stereochemistry of the oxygen function in the four-carbon core **3a** as shown by conversion to the corresponding threonine,[11] we now turned to introduction of the other functionalities and closure of the imidazole ring (Scheme I). Opening the *syn*-*N*-BOC-epoxide **3a** with a solution of freshly activated sodium azide[12] in refluxing methanol provided the azido alcohol **4** in 92% yield. Protection of the azido alcohol **4** as its *tert*-butyldimethylsilyl (TBDMS) ether proceeded to a 99% chromatographed yield of ether **5**. The ester function of **5** could be directly transformed to amide (liquid NH_3/90 °C/4 d) in 95% yield. Although the α-center of **5** underwent epimerization under these conditions as shown by the formation of about 15% of the diastereomer, it was no concern since in subsequent ring closure to imidazole **11** the stereochemistry at this center is not preserved. A more convenient (for larger scale) transformation of ester **5** to amide **7** was accomplished in two steps under mild conditions with conservation of the α-chiral center. Ester **5** was hydrolyzed with lithium hydroxide in 1/1, dioxane/water at 5 °C to afford carboxylic acid **6**. Amide **7** was then readily obtained in 94% yield for the two-step procedure by activating with isobutyl chloroformate and then adding excess NH_3. Preservation of chirality at the α-center required that the activation-NH_3 sequence be conducted at −23 °C; higher temperatures led to epimerization.

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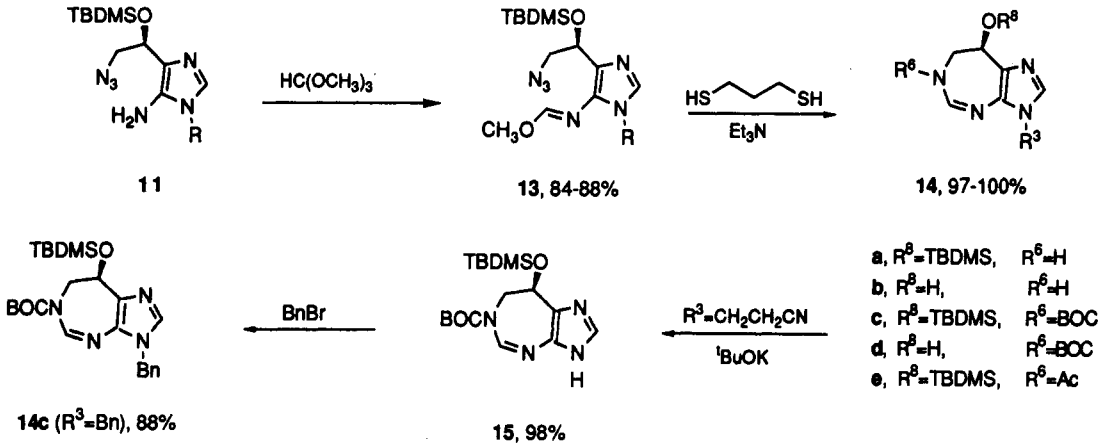
Scheme II. Imidazodiazepine Formation and Protection/Deprotection



Conversion to amino nitrile **9** was easily accomplished by first dehydration of amide **7** using tosyl chloride in pyridine to form *N*-BOC-amino nitrile **8**, followed by addition of TFA at 0 °C to selectively remove the BOC group; α-amino nitrile **9** was formed in 92% yield from **7**.

The first phase of our plan thus was achieved by the synthesis of the 2-amino-4-azido-3-hydroxybutyronitrile **9**, with the *R* configuration at *C*-3 and the necessary nitrogen functions at the other carbons.

Synthesis of Substituted 5-Aminoimidazole 11. The second phase of our general strategy involved closure of the five-membered ring to imidazole **11** with concomitant regiospecific introduction of an *N*-protecting group. Two routes were developed. In one route, the 2-amino group of amino nitrile **9** was treated with triethyl orthoformate, forming the imidate **10**. This imidate then was exposed to a variety of primary amines. The intermediate amidine thus formed underwent *in situ* addition to the nitrile, and the various 5-aminoimidazoles **11** resulted in 92–97% yields from **9**.

The amines, indicated as a–e in the products **11a–e**, were chosen so as to provide a variety of protecting groups, the conditions for the removal of which would be compatible with the presence of a number of other functions. 3-Aminopropionitrile was particularly attractive as one of the amines to provide the versatile 1-protected aminoimidazole **11e**, since the cyanoethyl group is easily removed with catalytic base. Although the presence of a second nitrile group created another potential site for ring closures to other bicyclic ring systems, none occurred; the product was solely **11e**.

The second route utilized conversion of the requisite amine to its imidate and then reaction with amino nitrile **9** to form the intermediate amidine followed by spontaneous ring closure to 5-aminoimidazole **11**. This method is illustrated with ethyl *N*-benzylformimidate (**12**), prepared from benzyl formamide and triethyloxonium tetrafluoroborate.[13] The product **11a** is identical with that obtained by the first route and the yields are equally high.

These two routes permit a wide variety of substituents at *N*-1 of the imidazole, subsequently to be *N*-3 of the tetrahydroimidazodiazepine. Either a permanent substituent may be introduced or a protecting group that can be removed later and replaced with a variety of substituents.

Tetrahydroimidazodiazepine Formation and Protection/Deprotection. The last phase of our synthesis is delineated in Scheme II. The best way to effect diazepine ring closure was to prepare imidate **13** from the various aminoimidazoles **11** by reaction with trimethyl orthoformate. The azido function then was reduced to amino most conveniently with 1,3-propanedithiol, and the intermediate amino imidate immediately ring closed to diazepine **14**. Yields were equally high for the various *N*-1-substituted imidazoles.

A new function had been introduced in this reaction, the amidine portion of the diazepine, and it was necessary to protect it to insure specific regiochemistry in later reactions. This was done with both a BOC group, forming **14c** and **14d**, and an acetyl group, forming **14e**.

To illustrate the potential application of these now fully protected tetrahydroimidazodiazepine aglycons to the synthesis of pentostatin analogues, the cyanoethyl group at *N*-3 of **14c** was removed on brief (1 min) treatment with ^{t}BuOK/^{t}BuOH in THF, forming the *NH* derivative **15**. This was alkylated in near quantitative yield with benzyl bromide, the regioselectivity being 9/1 in favor of the *N*-3 isomer **14c** as shown by direct comparison with the previously prepared sample.

Configurational Studies

Purity. The enantiomeric integrity at *C*-8 in these compounds was demonstrated by esterification of the hydroxyl group of **14d** with a chiral auxiliary and analysis of the resultant diastereomers using HPLC. Alcohol **14d** was obtained after protecting **14a** at *N*-6 with BOC, followed by cleavage of the TBDMS group of **14c**. Parallel esterifications of **14d** proceeded with both L- and DL-*N*-(phenylsulfonyl)prolyl chloride.[14] HPLC analysis of the esters established that the enantiomeric ratio of **14d** was >99/1.

Stability. It has been reported[15] that (8*R*)-deoxycoformycin epimerizes to its 8*S* epimer under conditions normally used for assay and storage, with the most rapid rate of epimerization being at pH 3. Therefore, the optical stability of the analogue **14b** (R^3 = benzyl instead of deoxyribosyl) was examined. Synthesis of **14b** was accomplished by desilylation of **14a** with aqueous HF/CH_3CN.

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Optical rotation was used to monitor the stability of analogue **14b** (R^3 = Bn) over 14 days in H_2O at pH 3, phosphate buffer, rt. Its specific rotation at day 0 was +101° and decreased in a straight line to +93.5° at day 14, a change of 0.5°/day. To determine whether this change was due to racemization, decomposition, or a combination of the two, the acidic solution of **14b** was made alkaline to pH 10 using excess 10% Na_2CO_3 and extracted with chloroform to give a quantitative recovery of material. TLC demonstrated a single spot with an R_f identical to that of **14b** and the proton NMR spectrum also was identical to that of **14b**. The aqueous layer showed no UV-active material. On these bases, we conclude that no decomposition had occurred and that racemization occurs at a rate of 0.5%/day.

Conclusion

Using L-vinylglycine **1** as a chiral educt, we have presented a high yield stereo- and regiospecific synthesis of variously protected, enantiomerically pure pentostatin aglycons. The ready removal of the cyanoethyl group at *N*-3 of tetrahydroimidazodiazepinol **14c** provides convenient access to the NH analogue **15** which is realkylated primarily at *N*-3. This process thus could permit the synthesis of a variety of coformycin analogues from aglycon **15**.

Experimental Section

General. Ether and THF were distilled from sodium/benzophenone immediately before use; acetonitrile, methylene-chloride, triethylamine; and benzylamine were distilled from CaH_2; methanol and pyridine were dried by distilling from Mg-$(OMe)_2$ and solid KOH, respectively. All reactions were performed under a static atmosphere (balloon) of nitrogen. Organic solvent solutions were dried over Na_2SO_4 before evaporation at reduced pressure with a Berkeley rotary evaporator. Melting points were determined on an open-capillary Buchi apparatus and are uncorrected. IR and ^1H NMR spectra were determined in $CDCl_3$ unless otherwise noted, and chemical shifts are reported in ppm (δ unit) downfield of internal tetramethylsilane (Me_4Si) with coupling constant(s) in hertz. ^{13}C NMR were obtained using a distortionless enhancement by polarization transfer (DEPT) pulse sequence experiments; the notation (i) is used to indicate inverted signals in the ^{13}C NMR-DEPT experiment. Elemental analyses were performed by the Analytical Laboratory, College of Chemistry, University of California, Berkeley, CA.

High-pressure liquid chromatography (HPLC) was done with the following stainless steel columns: A, Altex 3.2 × 250 mm, 5-μm LiChrosorb Si60, nonpolar normal phase (NP) silica gel; B, Whatman 150 × 450 mm, Partisil 10, NP silica gel. Low-pressure chromatography (LPC) was perfomed with 230–400 mesh silica gel. Analytical thin-layer chromatography (TLC) was done with aluminum-backed silica plates (E. Merck) and products were visualized by ultraviolet absorption or by spraying with a solution of ninhydrin [ninhydrin (400 mg) in absolute ethanol (200 mL)] or a solution of anisaldehyde [anisaldehyde (2.5 mL) in glacial acetic acid (5 mL), concentrated H_2SO_4 (2.5 mL), and absolute ethanol (450 mL)] and heating at 170 °C. The following chromatography solvent systems were used: a, ethyl acetate/hexane; b, ether/hexane; c, methanol/dichloromethane; d, triethylamine/ethyl acetate/hexane; e, triethylamine/ether/hexane; f, triethylamine/2-propanol/chloroform; g, ether/isooctane; h, triethylamine/ethylacetate; i, 2-propanol/chloroform; j, ethyl acetate; k, ethyl acetate/isooctane.

Methyl (2*S*,3*S*)-2-[[(benzyloxy)carbonyl]amino]-3,4-epoxybutanoate (2a) and methyl (2*S*,3*R*)-2-[[(benzyloxy)carbonyl]amino]-3,4-epoxybutanoate (2b) were prepared from vinylglycine derivative **1**[10] as described.[11] From 8.6 g of **1**, preparative HPLC (column B; solvent g, 3/7, 12 mL/min) using multiple injections (600 mg in Et_2O (5 mL)/injection) gave 6.40 g (70%) of **2a** and 1.58 g (17.3%) of **2b** as white solids: **2a**: mp 46–47 °C; ^1H NMR δ 7.34 (s, 5H), 5.36 (d, 1H, J = 8.4), 5.11 (s, 2H), 4.70 (d, 1H, J = 9.3), 3.80 (s, 3H), 3.45 (m, 1H), 2.77 (m, 1H), 2.67 (m, 1H). **2b**: mp 60–61 °C; ^1H NMR δ 7.35 (s, 5H), 5.58 (d, 1H, J = 6.5), 5.11 (s, 2H), 4.50 (dd, 1H, J = 5.1, 7.0), 3.79 (s, 3H), 3.23 (m, 1H), 2.79 (m, 2H).

Methyl (2*S*,3*S*)-2-[(*tert*-Butoxycarbonyl)amino]-3,4-epoxybutanoate (3a) and Methyl (2*S*,3*R*)-2-[(*tert*-Butoxycarbonyl)amino]-3,4-epoxybutanoate (3b). To a mixture of *syn*-*N*-CBZ epoxide **2a** (1.0 g, 3.8 mmol) in methanol (4.0 mL) and di-*tert*-butyl dicarbonate (4.1 g, 500 mol %) was added 10% Pd/C (200 mg) and hydrogen (balloon). The mixture was stirred at room temperature for 45 min and filtered through Celite which was washed with methanol (5 × 20 mL), and the combined filtrates were evaporated. Chromatography (solvent b, 1/3) gave 850 mg (98%) of the *syn*-*N*-BOC epoxide **3a** as a colorless oil: IR 3430, 2290, 1765, 1725 cm^{-1}; ^1H NMR δ 5.13 (d, 1H, J = 8.4), 4.64 (d, 1H, J = 8.1), 3.81 (s, 3H), 3.44 (d, 1H, J = 1.4), 2.81 (m, 1H), 2.68 (m, 1H), 1.44 (s, 9H). Anal. Calcd for $C_{10}H_{17}NO_5$: C, 51.9; H, 7.4; N, 6.1. Found: C, 52.0; H, 7.5; N, 6.1.

The same process applied to a mixture of *N*-CBZ epoxide diastereomers **2a** and **2b** gave, after chromatography (5.2 × 72.0 cm column, solvent b, 1/3), 6.72 g (77%) of the *syn*-*N*-BOC epoxide **3a** and 1.64 g (19%) of the *anti*-*N*-BOC epoxide **3b**: ^1H NMR δ 5.29 (d, 1H, J = 4.9), 4.43 (m, 1H), 3.81 (s, 3H), 3.22 (m, 1H), 2.80 (m, 2H), 1.45 (s, 9H).

Methyl (2*S*,3*R*)-4-Azido-2-[(*tert*-butoxycarbonyl)amino]-3-hydroxybutanoate (4). A mixture of epoxide **3a** (13.40 g, 58 mmol), freshly activated sodium azide (11.30 g, 300 mol%),[12] and ammonium chloride (4.65 g, 150 mol %) in methanol (450 mL) was stirred at room temperature for 2 h. The homogeneous mixture was brought to reflux for 4 h then cooled to room temperature, and the solvent was evaporated to give a white solid. This residue was digested with hot $CHCl_3$ (500 mL), the digest was filtered, the insoluble portion was washed with hot $CHCl_3$ (3 × 200 mL), and the combined filtrates were evaporated to give a pale yellow oil. Chromatography (solvent b, 1/1) provided 14.7 g (92%) of azide **4**: IR 3600, 3400, 2980, 2110, 1710 cm^{-1}; ^1H NMR δ 5.45 (d, 1H, J = 8.9), 4.40 (d, 1H, J = 9.1), 4.26 (d, 1H, J = 4.4), 3.80 (s, 3H), 3.41 (m, 2H), 1.46 (s, 9H). Anal. Calcd for $C_{10}H_{18}N_4O_5$: C, 43.8; H, 6.6; N, 20.4. Found: C, 43.4; H, 6.5; N, 20.6.

Methyl (2*S*,3*R*)-4-Azido-2-[(*tert*-butoxycarbonyl)amino]-3-[(*tert*-butyldimethylsilyl)oxy]butanoate (5). To a stirred solution of azido alcohol **4** (4.75 g, 17.3 mmol) in DMF (40 mL) was added *tert*-butyldimethylsilyl chloride (13.0 g, 500 mol %) and imidazole (11.8 g, 1000 mol %). The mixture was stirred at room temperature for 4 d and then partitioned between dichloromethane (300 mL) and water (200 mL). The aqueous layer was extracted with dichloromethane (2 × 150 mL), and the combined organic layer was washed with water (5 × 300 mL), dried, and evaporated to give a yellow oil. Chromatography (solvent a, 1/3) gave 6.65 g (99%) of **5**: IR 3460, 2950, 2110, 1720 cm^{-1}; ^1H NMR δ 5.11 (d, 1H, J = 10.0), 4.50 (d, 1H, J = 9.4), 4.26 (m, 1H), 3.75 (s, 3H), 3.42 (m, 2H), 1.47 (s, 9H), 0.86 (s, 9H), 0.10 (s, 3H), 0.01 (s, 3H). Anal. Calcd for $C_{16}H_{32}N_4O_5Si$: C, 49.5; H, 8.3; N, 14.4. Found: C, 49.3; H, 8.4; N, 14.0.

(2*S*,3*R*)-4-Azido-2-[(*tert*-butoxycarbonyl)amino]-3-[(*tert*-butyldimethylsilyl)oxy]butanamide (7). To a stirred solution of ester **5** (16.0 g, 41.2 mmol) in dioxane (150 mL) at 5 °C was added dropwise a solution of lithium hydroxide monohydrate (24.7 g, 1000 mol%) in water (150 mL). The mixture was stirred at 5 °C for 3 h, acidified with cold 1.0 M H_3PO_4 to pH 4, and extracted with chloroform (3 × 500 mL). The combined extract was washed with water (2 × 1000 mL), dried, and evaporated to give **(2*S*,3*R*)-4-Azido-2-[(*tert*-butoxycarbonyl)amino]-3-[(*tert*-butyldimethylsilyl)oxy]butanoic acid (6**, 15.1 g, 98%) as a yellow oil: IR 3450, 3400–3200, 2950, 2100, 1730, 1650 cm^{-1}; ^1H NMR δ 5.17 (d, 1H, J = 9.2), 4.50 (m, 1H), 4.34 (m, 1H), 3.40 (m, 2H), 1.47 (s, 9H), 0.87 (s, 9H), 0.12 (s, 3H), 0.06 (s, 3H).

To carboxylic acid **6** (9.2 g, 24.6 mmol) in THF (47 mL) at −23 °C was added *N*-methylmorpholine (2.7 g, 2.9 mL, 110 mmol %), followed by isobutyl chloroformate (3.7 g, 3.5 mL, 110 mol %). The mixture was stirred at −23 °C for 90 s and ammonia was

bubbled through the inlet bubbler for approximately 1 h. After being stirred at −23 °C for an additional 2 h, the mixture was warmed to room temperature, 5% citric acid (300 mL) was added, and the mixture was extracted with ethyl acetate (5 × 200 mL). The combined extract was washed with $NaHCO_3$ (600 mL) and NaCl (600 mL), dried, and evaporated to give a yellow oil. Chromatography (solvent a, 1/1) afforded 8.8 g (96%) of amide 7: IR 3500, 3400, 2950, 2100, 1685 cm^{-1}; ^{1}H NMR δ 6.25 (s, 1H), 5.60 (s, 1H), 5.46 (d, 1H, J = 7.6), 4.34 (m, 1H), 4.19 (m, 1H), 3.50 (dd, 1H, J = 3.7, 13.1), 3.38 (dd, 1H, J = 3.7, 13.2), 1.45 (s, 9H); 0.91 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H). Anal. Calcd for $C_{15}H_{31}N_5O_4Si$: C, 48.2; H, 8.4; N, 18.7. Found: C, 48.0; H, 8.5; N, 18.4.

(2*S*,3*R*)-4-Azido-2-[(*tert*-butoxycarbonyl)amino]-3-[(*tert*-butyldimethylsilyl)oxy]butyronitrile (8). To a solution of amide 7 (12.2 g, 32.7 mmol) in dichloromethane (40 mL) was added *p*-toluenesulfonyl chloride (12.5 g, 200 mol %) and pyridine (13.2 mL, 500 mol %). After stirring the reaction mixture at room temperature for 4 d, it was added to saturated $NaHCO_3$ (380 mL), stirred for 1 h, and diluted with CH_2Cl_2 (130 mL). The organic phase was washed with 1.0 M H_3PO_4 (960 mL), dried, and evaporated to give an oily residue. Chromatography (solvent a, 1/3) provided 8 (11.5 g, 99%) as a colorless oil: IR 3430, 2930, 2240, 2100, 1710 cm^{-1}; ^{1}H NMR δ 5.08 (d, 1H, J = 8.7), 4.79 (d, 1H, J = 8.6), 4.06 (m, 1H), 3.41 (m, 2H), 1.49 (s, 9H), 0.94 (s, 9H), 0.22 (s, 3H), 0.17 (s, 3H). Anal. Calcd for $C_{15}H_{29}N_5O_3Si$: C, 50.6; H, 8.2; N, 19.7. Found: C, 50.5; H, 8.3; N, 19.8.

(2*S*,3*R*)-2-Amino-4-azido-3-[(*tert*-butyldimethylsilyl)oxy]-butyronitrile (9). The protected amine 8 (5.45 g, 15.3 mmol) in CH_2Cl_2 (47 mL) was added dropwise to a solution of trifluoroacetic acid (47 mL, 4000 mol %) and water (0.47 mL). After stirring a 0 °C for 45 min, the reaction mixture was poured onto a cold solution of NH_4OH (600 mL) and H_2O (1200 mL), extracted with CH_2Cl_2 (5 × 300 mL), dried, and evaporated to give a yellow oil. Chromatography (solvent a, 1/3) afforded 3.68 g (93%) of 9 as a colorless oil: IR 3420, 2950, 2250, 2110 cm^{-1}; ^{1}H NMR δ 3.95 (m, 1H), 3.84 (d, 1H, J = 2.6), 3.59 (dd, 1H, J = 7.1, 12.3), 3.37 (dd, 1H, J = 5.4, 12.3), 1.67 (br s, 2H), 0.93 (s, 9H), 0.20 (s, 3H), 0.16 (s, 3H). Anal. Calcd for $C_{10}H_{21}N_5OSi$: C, 47.0; H, 8.3; N, 27.4. Found: C, 47.0; H, 8.4; N, 27.2.

(2*S*,3*R*)-4-Azido-3-[(*tert*-butyldimethylsilyl)oxy]-2[(ethoxymethylene)amino]butyronitrile (10). To a 250-mL two-necked round-bottomed flask equipped with a short distillation head was added α-amino nitrile 9 (4.6 g, 18.0 mmol) followed by triethyl orthoformate (150 mL). The mixture was refluxed 2 h, until ethanol was completely distilled, at which time the residue was cooled to room temperature and subjected to Kugelrohr distillation (0.3 Torr, 60 °C, 1 h) in order to remove the remaining triethyl orthoformate. The residue was dissolved in isooctane (30 mL) and allowed to stand at −15 °C for 2 d to give imidate 10 (5.4 g, 97%) as a colorless solid: mp 110–112 °C; IR 2950, 2260, 2110, 1660 cm^{-1}; ^{1}H NMR δ 7.73 (s, 1H), 4.40 (d, 1H, J = 5.3), 4.19 (q, 2H, J = 7.0), 3.97 (m, 1H), 3.54 (dd, 1H, J = 4.1, 12.8), 3.39 (dd, 1H, J = 5.8, 12.8), 1.28 (t, 3H, J = 7.0), 0.92 (s, 9H), 0.14 (d, 6H, J = 6.0). Anal. Calcd for $C_{13}H_{25}N_5O_2Si$: C, 50.1; H, 8.1; N, 22.5. Found: C, 50.2; H, 8.1; N, 22.3.

5-Amino-1-benzyl-4-[(1′*R*)-[(2-azido-1′-*tert*-butyldimethylsilyl)oxy]ethyl]imidazole (11a). A. From Amino Nitrile 9. To a stirred solution of ethyl *N*-benzylformimidate (12, 351 mg, 500 mol %) in acetonitrile (2 mL) and 5-Å molecular sieves (372 mg) was added dropwise a solution of α-amino nitrile 9 (100 mol %) in acetonitrile (2 mL). The mixture was refluxed for 27 h, cooled to room temperature, diluted with CH_2Cl_2 (30 mL), filtered, and washed with CH_2Cl_2 (2 × 50 mL). The combined filtrates were rotary evaporated and the residue was purified by column chromatography (solvent d, 1/3/6) to afford imidazole 11a as a brown oil in 96% yield: IR 3700, 3430, 2950, 2110 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.99 (m, 2H), 8.93 (d, 1H, J = 7.3), 8.85 (s, 1H), 8.81 (d, 2H, J = 7.3), 6.71 (s, 2H), 6.58 (dd, 1H, J = 3.8, 8.8), 6.10 (s, 2 H), 5.29 (dd, 1H, J = 8.8, 12.4), 4.8 (dd, 1H, J = 3.8, 12.4), 2.49 (s, 9H), 1.7 (s, 3H), 1.53 (s, 3H); ^{13}C NMR δ 137.8, 134.1, 130.4, 128.3, 127.2, 126.9, 120.0, 68.1, 55.9 (i), 45.8(i), 25.9, 25.8, 25.6, 17.8, −4.9, −5.1. Anal. Calcd for $C_{18}H_{28}N_6OSi$: C, 58.0; H, 7.6; N, 22.6. Found: C, 57.8; H, 7.7; N, 22.5.

B. From Imidate 10. General Procedure. To a stirred solution of α-formimidate nitrile 10 (1.0 g, 100 mol %) and 5-Å molecular sieves (5.0 g) in acetonitrile (50 mL) was added the appropriate primary amine (500 mol %). After refluxing the reaction mixture for 2 h, it was cooled to room temperature, filtered, and washed with CH_3CN (3 × 50 mL). The combined filtrates were evaporated, and the residue was chromatographed.

5-Amino-1-benzyl-4-[(1′*R*)-[(2′-azido-1′-*tert*-butyldimethylsilyl)oxy]ethyl]imidazole (11a). was obtained in 96% yield using benzylamine, identical with imidazole 11a obtained from amino nitrile 9.

5-Amino-1-(*p*-methoxybenzyl)-4-[(1′*R*)-[(2′-azido-1′-*tert*-butyldimethylsilyl)oxy]ethyl]imidazole (11b) was obtained using *p*-methoxybenzylamine. Purification by column chromatography (solvent d, 1/10/10) gave 11b as a brown oil in 96% yield: IR 3400, 2950, 2110, 1750, 1670, 1610 cm^{-1}; ^{1}H NMR δ 7.13 (s, 1H), 7.06 (d, 2H, J = 6.7), 6.87 (d, 2H, J = 6.7), 4.96 (m, 1H), 4.92 (s, 2H), 3.79 (s, 3H), 3.40 (m, 2H), 3.35 (s, 2H), 0.88 (s, 9H), 0.12 (s, 3H), 0.01 (s, 3H). Anal. Calcd for $C_{19}H_{30}N_6O_2Si$: C, 56.7; H, 7.5; N, 20.9. Found: C, 56.9; H, 7.2; N, 21.0.

1-Allyl-5-amino-4-[(1′*R*)-[(2′-azido-1′-*tert*-butyldimethylsilyl)oxy]ethyl]imidazole (11c). Allylamine was used and purification by column chromatography (solvent d, 1/10/10) provided 11c as a brown oil in 97% yield: IR 3420, 2950, 2110, 1750, 1665, 1625 cm^{-1}; ^{1}H NMR δ 7.07 (s, 1H), 5.96 (m, 1H), 5.25 (m, 1H), 5.05 (m, 2H), 4.42 (m, 2H), 3.48 (s, 2H), 3.42 (m, 2H), 0.91 (s, 9H), 0.14 (s, 3H), 0.03 (s, 3H). Anal. Calcd for $C_{14}H_{28}N_6OSi$: C, 52.1; H, 8.1; N, 26.1. Found: C, 52.1; H, 8.1; N, 26.2

5-Amino-1-(*N*,*N*-dimethylamino)-4-[(1′*R*)-[(2′-azido-1′-*tert*-butyldimethylsilyl)oxy]ethyl]imidazole (11d) was obtained using *N*,*N*-dimethylhydrazine. Chromatography (solvent d, 1/10/10) gave 11d as a brown oil in 96% yield: ^{1}H NMR δ 7.35 (s, 1H), 4.88 (dd, 1H, J = 3.8, 7.0), 3.89 (br s, 2H), 3.45 (m, 2H), 2.84 (s, 6H), 0.90 (s, 9H), 0.18 (s, 3H), 0.12 (s, 3H); ^{13}C NMR-DEPT δ 132.5, 122.7, 116.1, 71.4, 56.7 (i), 47.6, 25.7, 25.5, 18.1, −5.2, −5.3. Anal. Calcd for $C_{13}H_{27}N_7OSi$: C, 48.0; H, 8.4; N, 30.1. Found: C, 47.6; H, 8.3; N, 30.4.

5-Amino-4-[(1′*R*)-[(2′-azido-1′-*tert*-butyldimethylsilyl)oxy]ethyl]-1-(2′-cyanoethyl)imidazole (11e) was obtained using 3-aminopropionitrile. Purification by column chromatography (solvent i, 1/3) gave 11e as a brown oil in 97% yield: IR 3420, 3340, 2960–2860, 2260, 2110, 1760, 1680, 1630, 1610 cm^{-1}; ^{1}H NMR δ 7.20 (s, 1H), 4.96 (t, 1H, J = 4.9), 4.13 (t, 2H, J = 6.6), 3.50 (br s, 2H), 3.43 (d, 2H, J = 4.9), 2.83 (t, 2H, J = 6.6), 0.91 (s, 9H), 0.14 (s, 3H), 0.02 (s, 3H). Anal. Calcd for $C_{14}H_{25}N_7OSi$: C, 50.1; H, 7.5; N, 29.2. Found: C, 49.8; H, 7.2; N, 29.4.

Synthesis of 5-[(Methoxymethylene)amino]-1,4-Substituted Imidazoles 13. General Procedure. To a boiling solution of trimethyl orthoformate (100 mL), trifluoroacetic acid (0.05 mL), and 5-Å molecular sieves (10.0 g) was added in one portion of a mixture of the appropriate 5-amino 1,4-substituted imidazole 11 (1.0 g) in trimethyl orthoformate (50 mL). The reaction was refluxed for approximatley 3 h and then cooled to rt, triethylamine (10 mL) was added, and the mixture was filteed. The insoluble material was washed with CH_3CN (3 × 50 mL), the combined filtrates were evaporated, and the residue was chromatographed.

5-[(Methoxymethylene)amino]-1-benzyl-4-[(1′*R*)-[(2′-azido-1′-*tert*-butyldimethylsilyl)oxy]ethyl]imidazole (13, R = Bn). The starting material was 5-amino-1-benzyl-4-[(1′*R*)-[(2′-azido-1′-*tert*-butyldimethylsilyl)oxy]ethyl]imidazole (11a) and chromatography (solvent d, 1/10/10) afforded 13 (R = Bn) as a yellow oil in 86% yield: IR 2950, 2100, 1640 cm^{-1}; ^{1}H NMR δ 8.25 (s, 1H), 7.39 (m, 4H), 7.19 (m, 2H), 5.10 (s, 2H), 4.90 (m, 1H), 3.89 (s, 3H), 3.62 (m, 1H), 3.51 (m, 1H), 0.91 (s, 9H), 0.10 (s, 3H), 0.06 (s, 3H). Anal. Calcd for $C_{20}H_{30}N_6OSi$: C, 58.0; H, 7.3; N, 20.2. Found: C, 58.2; H, 7.3; N, 19.8.

5-[(Methoxymethylene)amino]-1-(*p*-methoxybenzyl)-4-[(1′*R*)-[(2′-azido-1′-*tert*-butyldimethylsilyl)oxy]ethyl]imidazole (13, R = *p*-CH_3OBn) was obtained from 5-amino-1-(*p*-methoxybenzyl)-4-[(1′*R*)-[(2′-azido-1′-*tert*-butyldimethylsilyl)oxy]ethyl]imdiazole (11b). Chromatography (solvent d, 1/10/10) gave 13 (R = *p*-CH_3OBn) as a brown oil in 84% yield: IR 2950–2850, 2100, 1640 cm^{-1}; ^{1}H NMR δ 8.26 (s, 1H), 7.37 (s, 1H), 7.17 (d, 2H, J = 8.7), 6.92 (d, 2H, J = 8.7), 5.05 (s, 2H), 4.92 (dd, 1H, J = 5.0, 7.6), 3.91 (s, 3H), 3.86 (s, 3H), 3.65 (dd, 1H, J = 7.6, 12.4), 3.49 (dd, 1H, J = 5.0, 12.4), 0.93 (s, 9H), 0.11 (s, 3H), 0.01 (s, 3H).

5-[(Methoxymethylene)amino]-4-[(1′*R*)-[(2′-azido-1′-*tert*-butyldimethylsilyl)oxy]ethyl]-1-(2′-cyanoethyl)imidazole (13, R = CH_2CH_2CN) was prepared from 5-amino-4-[(1′*R*)-[(2′-azido-1′-*tert*-butyldimethylsilyl)oxy]ethyl]-1-(2′-cyanoethyl)imidazole (11e). Chromatography (solvent j) provided 13 (R = CH_2CH_2CN) as a yellow oil in 88% yield: IR 2960–2860, 2260, 2110, 1645 cm^{-1}; ^1H NMR δ 8.42 (s, 1H), 7.43 (s, 1H), 4.92 (dd, 1H, *J* = 5.1, 7.0), 4.21 (t, 2H, *J* = 6.9), 3.95 (s, 3H), 3.60 (dd, 1H, *J* = 7.0, 12.4), 3.48 (dd, 1H, *J* = 5.1, 12.4), 2.87 (t, 2H, *J* = 6.8), 0.90 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H). Anal. Calcd for $C_{16}H_{27}N_7O_2Si$: C, 50.9; H, 7.2; N, 26.0. Found: C, 50.9; H, 7.2; N, 25.9.

Reductive Cyclization to Form the Imidazodiazepine 14. General Procedure. To a stirred solution of the 5-[(methoxymethylene)amino]-1,4-substituted imidazole 13, (1.0 g) in methanol (5.0 mL) and triethylamine (1000 mol %) was added in one portion 1,3-propanedithiol (1000 mol %). The mixture was stirred overnight at rt under a nitrogen atmosphere, followed by rotary evaporation and purification.

(8*R*)-3-Benzyl-8-[(*tert*-butyldimethylsilyl)oxy]-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepine (14a, R^3 = Bn) was prepared from 5-[(methoxymethylene)amino]-1-benzyl-4-[(1′*R*)-[(2′-azido-1′-*tert*-butyldimethylsilyl)oxy]ethyl]imidazole (13, R = Bn). Chromatography (solvent d, 1/9/10) afforded 14a (R^3 = Bn) as a yellow oil in 99% yield: IR 3450, 2960–2860, 1640 cm^{-1}; ^1H NMR δ 7.37 (m, 3H), 7.29 (m, 3H), 7.12 (d, 1H, *J* = 4.1), 5.59 (s, 1H), 5.30 (s, 1H), 5.21 (s, 2H), 3.45 (m, 2H), 0.93 (s, 9H), 0.22 (s, 3H), 0.06 (s, 3H); ^{13}C NMR δ 206.1, 147.6, 139.8, 132.4, 129.2, 128.2, 128.0, 70.2, 49.8 (i), 46.7 (i), 26.3, 18.8, –0.3, –4.0, –4.5. Anal. Calcd for $C_{19}H_{18}N_4OSi$: C, 64.0; H, 7.9; N, 15.7. Found: C, 64.1; H, 8.0; N, 15.6.

(8*R*)-3-(*p*-Methoxybenzyl)-8-[(*tert*-butyldimethylsilyl)oxy]-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepine (14a, R^3 = *p*-CH_3OBn) was prepared from 5-[(methoxymethylene)amino]-1-(*p*-methoxybenzyl)-4-[(1′*R*)-(2′-azido-1′-*tert*-butyldimethylsilyl)oxy]ethyl]imidazole (13, R = *p*-CH_3OBn). Chromatography (solvent d, 1/10/10) gave 14a (R^3 = *p*-CH_3OBn) as a yellow oil in 98% yield: IR 3440, 2960–2860, 1635 cm^{-1}; ^1H NMR δ 7.16 (s, 1H), 7.14 (d, 2H, *J* = 8.7), 7.06 (d, 1H, *J* = 4.3), 6.85 (d, 2H, *J* = 8.7), 6.16 (s, 1H), 5.22 (br, s, 1H), 5.06 (s, 2H), 3.76 (s, 3H), 3.35 (m, 2H), 0.85 (s, 9H), 0.14 (s, 3H), –0.07 (s, 3H). Anal. Calcd for $C_{20}H_{30}N_4O_2Si$: C, 62.1; H, 7.8; N, 14.5. Found: C, 62.2; H, 8.1; N, 14.5.

(8*R*)-3-(2′-Cyanoethyl)-8-[(*tert*-butyldimethylsilyl)oxy]-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepine (14a, R^3 = CH_2CH_2CN) was prepared from 5-[(methoxymethylene)amino]-4-[(1′*R*)-(2′-azido-1′-*tert*-butyldimethylsilyl)oxy]ethyl-1-(2′-cyanoethyl)imidazole (13, R^3 = CH_2CH_2CN). Chromatography (solvent h, 1/10) gave 14a (R^3 = CH_2CH_2CN) as a yellow oil in 99% yield: IR 3450, 2960–2860, 2270, 1640 cm^{-1}; ^1H NMR δ 7.37 (s, 1H), 7.12 (d, 1H, *J* = 4.4), 5.71 (br s, 1H), 5.28 (m, 1H), 4.28 (t, 2H, *J* = 6.8), 3.46 (m, 2H), 2.96 (t, 2H, *J* = 6.8), 0.93 (s, 9H), 0.23 (s, 3H), 0.07 (s, 3H). Anal. Calcd for $C_{15}H_{25}N_5OSi$: C, 56.4; H, 7.9; N, 21.9. Found: C, 56.1; H, 8.1; N, 21.6.

Synthesis of the Fully Protected Imidazole-Fused Diazepine System 14c Using $(BOC)_2O$. General Procedure. To a stirred solution of the appropriate (8*R*)-3*N*-substituted-8-*O*-TBDMS-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepine (14a, 500 mg) in methanol (5 mL) was added di-*tert*-butyl dicarbonate (1000 mol %). The mixture was stirred overnight at room temperature under a nitrogen atmosphere, followed by evaporation and purification.

(8*R*)-3-Benzyl-6-(*tert*-butoxycarbonyl)-8-[(*tert*-butyldimethylsilyl)oxy]-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepine (14c, R^3 = Bn) was prepared from (8*R*)-3-benzyl-8-[(*tert*-butyldimethylsilyl)oxy]-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepine (14a, R^3 = Bn). Chromatography (solvent e, 1/5/14) gave a yellow oil which was crystallized from isooctane at 0 °C to obtain 14c (R^3 = Bn) in 97% yield as a white solid: mp 123–124 °C; IR 3000–2860, 1720; 1625 cm^{-1}; ^1H NMR δ 7.86 (s, 1H), 7.35 (m, 4H), 7.20 (m, 2H), 5.19 (d, 2H, *J* = 2.6), 5.15 (m, 1H), 4.50 (m, 1H), 3.14 (m, 1H), 1.54 (s, 9H), 0.89 (s, 9H), 0.20 (s, 3H), 0.05 (s, 3H). Anal. Calcd for $C_{24}H_{36}N_4O_3Si$: C, 63.1; H, 8.0; N, 12.3. Found: C, 63.3; H, 8.0; N, 12.3.

(8*R*)-3-Allyl-6-(*tert*-butoxycarbonyl)-8-[(*tert*-butyldimethylsilyl)oxy]-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepine (14c, R^3 = $CH_2CH{=}CH_2$) was prepared from (8*R*)-3-allyl-8-[(*tert*-butyldimethylsilyl)oxy]-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepine (14a, R^3 = $CH_2CH{=}CH_2$). Chromatography (solvent b, 1/1) gave 14c (R^3 = $CH_2CH{=}CH_2$) as a white solid in 98% yield: mp 107–108 °C; IR 2960–2860, 1720, 1630 cm^{-1}; ^1H NMR δ 7.85 (s, 1H), 7.36 (s, 1H), 6.0 (m, 1H), 5.24 (m, 2H), 5.20 (m, 1H), 4.62 (d, 2H, *J* = 5.5), 4.52 (m, 1H), 3.10 (m, 1H), 1.54 (s, 9H), 0.88 (s, 9H), 0.20 (s, 3H), 0.05 (s, 3H). Anal. Calcd for $C_{20}H_{34}N_4O_3Si$: C, 59.1; H, 8.4; N, 13.8. Found: C, 59.1; H, 8.2; N, 13.7.

(8*R*)-6-(*tert*-Butoxycarbonyl)-3-(2′-cyanoethyl)-8-[(*tert*-butyldimethylsilyl)oxy]-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepine (14c, R^3 = CH_2CH_2CN) was prepared from (8*R*)-3-(2′-cyanoethyl)-8-[(*tert*-butyldimethylsilyl)oxy]-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepine (14c, R^3 = CH_2CH_2CN). Chromatography (solvent j) gave 14c (R^3 = CH_2CH_2CN) as a white solid in 99% yield: mp 119–120 °C; IR 2960–2860, 2260, 1720, 1630 cm^{-1}; ^1H NMR δ 7.85 (s, 1H), 7.45 (s, 1H), 5.13 (d, 1H, *J* = 5.0) 4.52 (m, 1H), 4.29 (t, 2H, *J* = 6.7), 3.11 (d, 1H, *J* = 13.8), 2.88 (m, 2H), 1.55 (s, 9H), 0.89 (s, 9H), 0.20 (s, 3H), 0.07 (s, 3H). Anal. Calcd for $C_{20}H_{33}N_5O_3Si$: C, 57.3; H, 7.9; N, 16.7. Found: C, 57.2; H, 8.0; N, 16.5.

Synthesis of the Fully Protected Imidazole-Fused Diazepine System 14e Using Acetic Anhydride. General Procedure. To a stirred solution of the appropriate (8*R*)-3-*N*-substituted-8-*O*-TBDMS-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]-diazepine (14a, 500 mg) in pyridine (22 mL) was added in one portion acetic anhydride (8 mL). After the mixture was stirred at rt for 10 min, it was evaporated and purified.

(8*R*)-6-Acetyl-3-benzyl-8-[(*tert*-butyldimethylsilyl)oxy]-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepine (14e, R^3 = Bn) was prepared from (8*R*)-3-benzyl-8-[(*tert*-butyldimethylsilyl)-oxy]-3,6,7,8-tetrahydroimidazo[4,5*d*][1,3]diazepine (14a, R^3 = Bn). Chromatography (solvent d, 1/10/10) gave 14e, R^3 = Bn, as a white solid in 99% yield: mp 99–101 °C; IR 2960–2860, 1690, 1620 cm^{-1}; ^1H NMR δ 7.91 (s, 1H), 7.81 (s, 1H), 7.38 (m, 3H), 7.27 (m, 2H), 5.38 (m, 1H), 5.27 (s, 2H), 4.7 (br s, 1H), 3.12 (d, 1H, *J* = 13.8), 2.43 (s, 3H), 0.87 (s, 9H), 0.21 (s, 3H), 0.04 (s, 3H). Anal. Calcd for $C_{21}H_{30}N_4O_2Si$: C, 63.3; H, 7.6; N, 14.0. Found: C, 63.2; H, 7.6; N, 13.9.

(8*R*)-6-Acetyl-3-(*p*-methoxybenzyl)-8-[(*tert*-butyldimethylsilyl)oxy]-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]-diazepine (14e, R^3 = *p*-CH_3OBn) was prepared from (8*R*)-3-(*p*-methoxybenzyl)-8-[(*tert*-butyldimethylsilyl)oxy]-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepine (14a, R^3 = *p*-CH_3OBn). Chromatography (solvent d, 1/10/10) gave 14e, R^3 = *p*-CH_3OBn, as a white solid in 100% yield: mp 101–102 °C; IR 2960–2860, 1690, 1620 cm^{-1}; ^1H NMR δ 7.85 (s, 1H), 7.38 (s, 1H), 7.18 (d, 2H, *J* = 8.7), 6.87 (d, 2H, *J* = 8.7), 5.16 (m, 1H), 5.15 (s, 2H), 4.60 (br s, 1H), 3.80 (s, 3H), 3.14 (d, 1H, *J* = 13.7), 2.39 (s, 3H), 0.87 (s, 9H), 0.20 (s, 3H), 0.01 (s, 3H). Anal. Calcd for $C_{22}H_{32}N_4O_3Si$: C, 61.7; H, 7.5; N, 13.1. Found: C, 61.7; H, 7.6; N, 12.9.

(8*R*)-6-Acetyl-3-(*N*,*N*-dimethylamino)-8-[(*tert*-butyldimethylsilyl)oxy]-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]-diazepine (14e, R^3 = $N(CH_3)_2$) was prepared from (8*R*)-3-(*N*,*N*-dimethylamino)-8-[(*tert*-butyldimethylsilyl)oxy]-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepine (14a, R^3 = $N(CH_3)_2$). Chromatography (solvent d, 1/10/10) gave 14e, R^3 = $N(CH_3)_2$, in 100% yield: IR 2960–2860, 1690, 1620 cm^{-1}; ^1H NMR δ 7.85 (s, 1H), 7.54 (s, 1H), 5.09 (d, 1H, *J* = 4.6), 4.55 (br s, 1H), 3.15 (d, 1H, *J* = 13.7), 3.03 (s, 6H), 2.38 (s, 3H), 0.85 (s, 9H), 0.18 (s, 3H), 0.01 (s, 3H). Anal. Calcd for $C_{16}H_{29}N_5O_2Si$: C, 54.7; H, 8.3; N, 19.9. Found: C, 54.5; H, 8.4; N, 20.0.

(8*R*)-3-Benzyl-6-(*tert*-butoxycarbonyl)-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepin-8-ol (14d, R^3 = Bn). To a solution of 1.0 M *n*-Bu_4NF/THF (10 mL) was added (8*R*)-3-benzyl-6-(*tert*-butyloxycarbonyl)-8-[(*tert*-butyldimethylsilyl)-oxy]-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepine (14c, R^3 = Bn, 320 mg, 0.7 mmol). The mixture was stirred at rt for 2 h, the solvent was evaporated, and the residue was chromatographed (solvent f, 5/1/15) to give 14d, R^3 = Bn, as a pale yellow oil (238 mg, 99% yield): IR 3500–3000, 2980, 1720, 1630 cm^{-1}; ^1H NMR δ 7.83 (s, 1H), 7.40 (s, 1H), 7.25 (m, 5H), 5.19 (s, 2H), 5.05 (d, 1H, *J* = 5.3), 4.75 (s, 1H), 3.98 (dd, 1H, *J* = 5.9, 13.5), 3.70 (d, 1H, *J* = 13.5), 1.54 (s, 9H). Anal. Calcd for $C_{18}H_{22}N_4O_3$: C, 63.1; H, 6.5; N, 16.4. Found: C, 63.3; H, 6.8; N, 16.0.

(8*R*)-3-Benzyl-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]-diazepin-8-ol (14b, R³ = Bn). To a Teflon cylinder containing (8*R*)-3-benzyl-8-[(*tert*-butyldimethylsilyl)oxy]-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepine (**14a**, R³ = Bn, 200 mg, 0.56 mmol) in acetonitrile (10 mL) was added a mixture of 49% HF (10 mL) in acetonitrile (30 mL). The reaction was stirred at rt for 3 h, diluted with $CHCl_3$ (50 mL), and partitioned between saturated Na_2CO_3 (200 mL) and $CHCl_3$ (100 mL). The aqueous phase was extracted with 1/3 2-propanol/$CHCl_3$ (5 × 100 mL), the combined extracts were dried and evaporated, and the residue was chromatographed (solvent c, 1/9) affording **14b**, R³ = Bn, as an amorphous solid (135 mg, 99% yield): $[\alpha]^{20}_D$ +84.2° (*c* 0.95, CH_3OH); IR 3700–3100, 2940, 1630 cm^{-1}; ^1H NMR (CD_3OD) δ 7.37 (s, 1H), 7.27 (m, 5H), 7.07 (s, 1H), 5.15 (s, 2H), 5.05 (m, 1H), 3.39 (dd, 1H, *J* = 4.5, 13.2), 3.28 (d, 1H, *J* = 13.7); ^{13}C NMR δ 149.8, 139.0, 137.0, 133.9, 130.2, 129.6, 128.6, 128.4, 68.4, 49.1 (i), 47.6 (i). Anal. Calcd for $C_{13}H_{14}N_4O$: C, 64.4; H, 5.8; N, 23.1. Found: C, 64.0; H, 5.9; N, 22.7.

(8*R*)-6-(*tert*-Butoxycarbonyl)-8-[(*tert*-butyldimethylsilyl)oxy]-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepine (15). To a stirred solution of (8*R*)-6-(*tert*-butoxycarbonyl)-3-(2′-cyanoethyl)-8-[(*tert*-butyldimethylsilyl)oxy]-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepine (**14c**, R³ = CH_2CH_2CN, 200 mg, 0.48 mmol) in THF (5 mL) was added a concentrated mixture of potassium *tert*-butoxide in *tert*-butyl alcohol (1 mL). After stirring the reaction mixture at room temperature for 1 min it was evaporated. The residue was digested with Et_2O (50 mL), the mixture was filtered, washing with Et_2O (5 × 30 mL), and the combined filtrates were evaporated and chromatographed using ethyl acetate as eluant to give **15** as a white solid (172 mg, 99.4% yield): mp 157–158 °C; IR 3450, 2960–2860, 1725, 1630 cm^{-1}; ^1H NMR δ 10.97 (br s, 1H), 7.88 (s, 1H), 7.48 (s, 1H), 5.17 (br s, 1H), 4.54 (br s, 1H), 3.12 (br s, 1H), 1.54 (s, 9H), 0.88 (s, 9H), 0.20 (s, 3H), 0.06 (s, 3H). Anal. Calcd for $C_{17}H_{30}N_4O_3Si$: C, 55.7; H, 8.3; N, 15.3. Found: C, 55.6; H, 8.3; N, 15.3.

Benzylation of (8*R*)-6-(*tert*-Butoxycarbonyl)-8-[(*tert*-butyldimethylsilyl)oxy]-3,6,7,8-tetrahydroimidazo[4,5-*d*]-[1,3]diazepine (15) to form 14c, R³ = Bn. To a solution of **15** (20 mg, 0.05 mmol) in THF (5 mL) and triethylamine (80 μL, 1000 mol %) was added benzyl bromide (30 μL, 500 mol %). After being refluxed for 3 h, the mixture was cooled to room temperature, evaporated, and chromatographed (solvent a, 1/1) to give a 9/1 mixture of **14c**, R³ = Bn, and its 1-*N* isomer as established by comparison with material prepared above and by NMR (24.0 mg, 98% yield): ^1H NMR δ 7.86 (s, 2H), 7.35 (m, 10H), 5.20 (m, 6H), 4.50 (m, 1H), 4.13 (m, 1H), 3.75 (m, 1H), 3.14 (m, 1H), 1.54 (s, 9H), 1.52 (s, 9H), 0.88 (s, 9H), 0.74 (s, 9H), 0.18 (s, 3H), 0.05 (s, 3H), −0.01 (s, 3H), −0.3 (s, 3H).

Enantiomeric Purity Studies of 14d, R³ = Bn. To a stirred solution of (8*R*)-3-benzyl-6-(*tert*-butoxycarbonyl)-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepin-8-ol (**14d**, R³ = Bn, 10.0 mg, 0.03 mmol) and *N*-methylmorpholine (3.5 μL, 110 mol %) in THF (2 mL) at −23 °C was added *N*-(phenylsulfonyl)prolyl chloride[14] (8.8 mg, 110 mol %) in THF (3 mL). After being stirred for 12 h at −23 °C, the reaction mixture was added to 5% citric acid (50 mL) and extracted with EtOAc (3 × 10 mL). The combined extracts were washed with saturated $NaHCO_3$ (2 × 20 mL), dried, and evaporated. The resulting equal mixture of the diastereomeric esters of **14d**, R³ = Bn, from DL-*N*-(phenylsulfonyl)prolyl chloride was separable by HPLC (column A; solvent k, 7/3; 0.95 mL/min); t_R 1.75 h, 2.75 h. Reaction with L-*N*-(phenylsulfonyl)prolyl chloride gave a single peak eluting at t_R 2.75 h; therefore **14d**, R³ = Bn, was ≥99% enantiomerically pure (limit of detection).

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