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A Diastereoselective Synthesis of Pseudo-C_2 -Symmetric 1,3-Diamino-2-propanols as Core Units in HIV Protease Inhibitors

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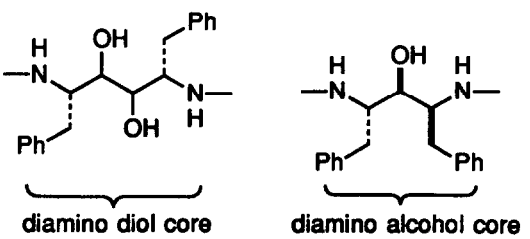
Abstract: Inhibitors of HIV-1 protease are effective against the proliferation of HIV-1 infection in vitro. Based on the inherent symmetry of the protease homodimer, C_2-symmetric and pseudo-C_2-symmetric inhibitors have been designed, synthesized, and demonstrated to be potent inhibitors of HIV-1 protease and effective in arresting the spread of HIV-1 in vitro. We now report a novel synthesis of the pseudo-C_2-symmetric 1,3-diamino-2-propanol core unit **12**, the key subunit in such HIV-1 protease inhibitors. Alkylation of the dianion of N-Boc hydroxylactam **1-3** is highly diastereoselective and provides **4** in moderate to good yield. Imide ring opening, Curtius rearrangement, and deprotection lead to the desired diamino alcohol core unit **12**. A number of substituents, aromatic and heteroaromatic, were included in the R^1 and R^2 side chains.

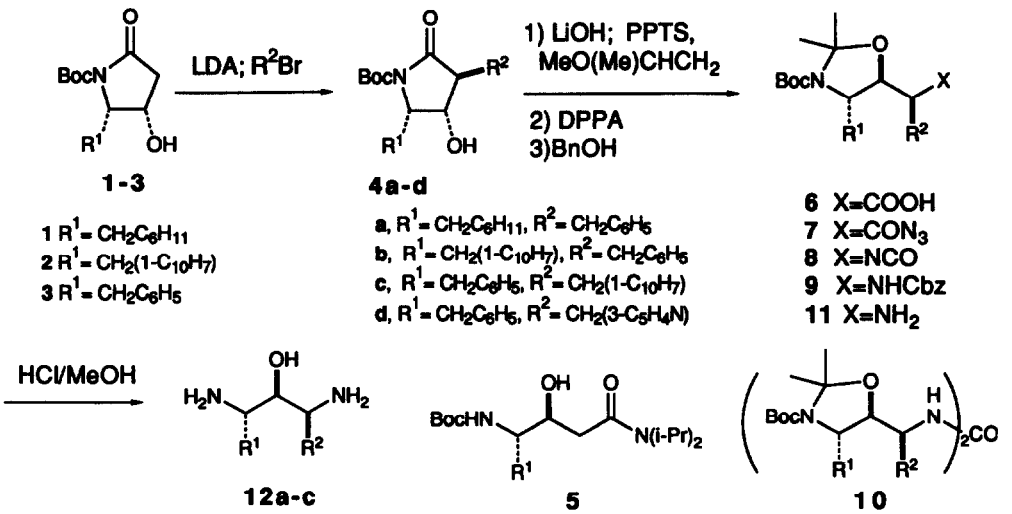
Inhibitors of the protease of the human immunodeficiency virus type-1 (HIV-1) have been shown to be effective agents against the proliferation of HIV infection in vitro.[1] A number of reports have appeared detailing the preparation of such inhibitors based upon known aspartic acid protease transition-state analogues as surrogates for the P_1/P_1' substrate cleavage site.[2] Recently, Erickson and coworkers disclosed a unique strategy for the design of HIV-1 protease inhibitors which recognized the symmetric nature of the enzyme.[3] They hypothesized that C_2-symmetric inhibitors comprised of a key diamino core unit flanked by acyl groups would be recognized and bound by this homodimeric retroviral protease. The preparation and in vitro binding of inhibitors of HIV-1 protease based on the C_2-symmetric diamino diol and pseudo-C_2-symmetric diamino alcohol core units have been reported (equation 1).[4,5]



(1)

We now report an alternate route to one series of these key diamino alcohol core units. This approach allows for assembly of core units that would be difficult to access via the published route of Kempf et. al.[4,5]

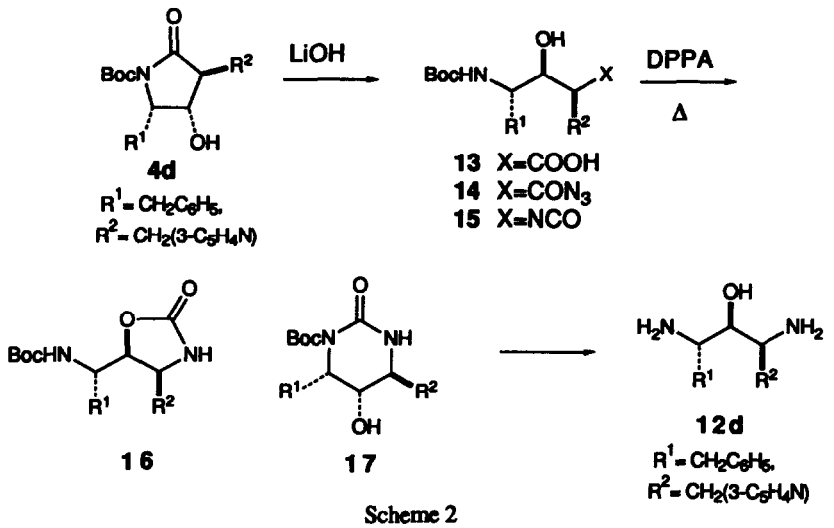
As in that approach the absolute stereochemistry was derived from an amino acid source, however the introduction of the secondary substituent (R^2) was accomplished through an alkylation reaction with R^2 participating as the electrophile. We were able to avoid oxidative conditions which allowed for preparation of a heteroaromatic containing core unit. The *threo*-5-substituted-4-hydroxypyrrolidin-2-ones **1-3** were prepared by the method of Jouin and Castro[6,7] (Scheme 1). Introduction of the C-3 substituent was accomplished by alkylation of the lithium dianion. The 3,5-disubstituted-4-hydroxypyrrolidin-2-ones **4a-d** were obtained in moderate to good chemical yield with excellent diastereoselectivity. The high diastereoselectivity observed was anticipated by analogy to our findings in the aldol reaction of the lithium dianion of **1** and isovaleraldehyde.[8] The α-face of the enolate system in the lithium dianion is congested due to the presence of the C-5 substituent and the C-4 lithium alkoxide with its associated ligands. Electrophilic attack on the sterically more accessible β-face of the enolate led to the observed products. Compounds **4a-c** were produced as single diastereomers and **4d** and **4d'** (epimeric at C-3) in an 11:1 ratio. When LDA was used as the base, substantial amounts (20-25%) of the addition product **5** could be isolated.[8] The addition side product could be eliminated through the use of the less nucleophilic LHMDS. However, the chemical yield was lower due to incomplete dianion formation (ca. 50% recovered starting material). This tendency for the carbonyl addition of LDA to N-Boc lactams was reported recently by Hagen.[9]



Scheme 1

Elaboration to the final diamino alcohol core units was carried out by one of two routes. The first involved LiOH hydrolysis of the imide **4** according to the method of Grieco.[10] This product is an α–alkylated N-Boc "statine" analog.[11] An alternate approach to this class of compounds has appeared in the literature.[12] The crude N-Boc amino hydroxy acid was treated with 2-methoxypropene and catalytic PPTS to produce the acid **6** as the single product. Curtius rearrangement of the intermediate acyl azide **7** provided isocyanate **8** which was trapped in situ with benzyl alcohol to give the differentially protected diamine **9**. All attempts to

capture the isocyanate with *tert*-butyl alcohol to produce the bis(N-Boc) protected diamine failed, presumably due to the hindered environment surrounding the reactive center. Direct hydrolysis of the isocyanate under a variety of conditions produced what has been tentatively assigned as the dimeric urea **10**. Stepwise deprotection of **9** occurred without incident; catalytic hydrogenolysis removed the Cbz group and the surprisingly tlc-mobile amine **11** (again demonstrating the steric hindrance about the amino group) was treated with anhydrous hydrogen chloride in dioxane-methanol to remove both the N-Boc group and the acetonide to yield the key diamino alcohol core unit **12**.



Scheme 2

Alternatively, following LiOH hydrolysis of the 3,5-disubstituted-4-hydroxypyrrolidin-2-one **4**, the crude N-Boc amino hydroxy acid[11] **13** was converted into the acyl azide **14** and made to undergo the Curtius rearrangement to generate the isocyanate **15** (Scheme 2). Intramolecular trapping of the isocyanate moiety by the hydroxyl or the N-Boc nitrogen was competitive and yielded mixtures of the oxazolidinone **16** and urea **17** respectively. The oxazolidinone **16** was hydrolyzed with concomitant removal of the N-Boc protecting group using barium hydroxide in a refluxing dioxane-water mixture to give the diamino alcohol **12**. The urea **17**, when treated under the same conditions experienced only loss of the N-Boc protecting group. Acidic hydrolysis (6 N HCl, reflux) of **17** however was demonstrated to provide the desired **12**.

In conclusion, a new route to the key diamino alcohol core unit of the pseudo-C_c-symmetric inhibitors of HIV-1 protease has been developed. Noteworthy are the highly diastereoselective alkylations of *threo*-3-substituted-4-hydroxypyrrolidin-2-ones via their lithium dianions and the elaboration of these α-alkylated "statine" analog products via two distinct sequences to the title compounds.

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Experimental Section

Thin-layer chromatography was performed on precoated silica gel F-254 plates (0.25 mm; E. Merck) and was visualized with UV light and/or ceric ammonium sulfate stain. ^{1}HNMR spectra were measured on a GE QZ-300 (300 MHz) instrument using tetramethylsilane as an internal standard. ^{1}HNMR, mass spectra, and infrared spectra were measured by the Structural Chemistry Department at Abbott Laboratories. Elemental analyses were performed by either the Structural Chemistry Department at Abbott Laboratories or Oneida Research Services, Whitesboro, NY. Flash chromatography was performed on silica gel 60, 0.04-0.063 mm (E. Merck).

(4S,5R)-N-(((*tert*)-Butyloxy)carbonyl)-5-(cyclohexylmethyl)-4-hydroxy-2-pyrrolidinone (1). Prepared by the method of Jouin and Castro.[5] To a solution of N-Boc-cyclohexylalanine (8.76 g, 32.3 mmol), Meldrum's acid (i.e. 2,2-dimethyl-1,3-dioxane-4,6-dione, 4.89 g, 33.9 mmol) and DMAP (9.07 g, 74.2 mmol) in anhydrous dichloromethane (160 mL) at ca. -10°C was added isopropenyl chloroformate (3.80 g, 31.8 mmol) in anhydrous dichloromethane (7 mL) dropwise over 35 min. After 2 h at ca. -5° to 0°C the reaction was quenched by the addition of cold 5% $KHSO_4$ solution (200 mL). The layers were separated and the organics were washed with cold 5% $KHSO_4$ solution (200 mL). The combined aqueous portions were extracted with dichloromethane (50 mL) and the combined organics were washed with brine (100 mL) and dried ($MgSO_4$). Solvent evaporation left 12.41 g of the condensation adduct as a light yellow oil which was dissolved in ethyl acetate (350 mL) and heated to reflux for 30 min. The solution was allowed to cool and was extracted with half-saturated sodium bicarbonate solution (6 x 200 mL). The combined aqueous portions were carefully acidified to ca. pH 2 with powdered citric acid. The solution was extracted with ethyl acetate (3 x 200 mL) the organics were dried ($MgSO_4$), filtered and concentrated to give 10.26 g of the (5R)-N-(((*tert*)-butyloxy)carbonyl)-5-(cyclohexylmethyl)-2,4-pyrrolidindione as a thick yellow oil. The oil was dissolved in dichloromethane (150 mL) and glacial acetic acid (20 mL), chilled to ca. 0°C, and sodium borohydride (4.69 g, 124 mmol) was added in portions over 1 h. After stirring the resulting mixture for ca. 3 h, it was poured into ice water (300 mL) and stirred 10 min. The layers were separated and the aqueous portion was extracted with dichloromethane (2 x 100 mL). The organics were washed once with brine (300 mL) and then dried (Na_2SO_4). Evaporation left 9.0 g oil which was applied to a flash silica gel column (2" x 16") and eluted with 50% ethyl acetate/hexane, yielding after solvent removal 5.58 g of the desired (4S,5R)-N-(((*tert*)-butyloxy)carbonyl)-5-(cyclohexylmethyl)-4-hydroxy-2-pyrrolidinone (**1**); (58% overall) R_f = 0.35 (50% EA/Hexane); $[\alpha]^{21}_D$ = +40.9° (c=2.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.2-1.3(m, 2H), 1.4-1.55(m, 3H), 1.55(s, 9H), 1.6-1.9(m, 9H), 2.58(dd, *J*=8.4,17.4 Hz, 1H), 2.70(dd, *J*=7.5,17.4 Hz, 1H), 4.25(dddd, *J*=4.8,7.5,7.5,8.4 Hz, 1H), 4.54(ddd, *J*=7.5,7.5,7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 26.10, 26.15, 26.34, 27.91, 33.30, 33.65, 34.28, 35.74, 39.94, 59.13, 65.39, 83.10, 149.72, 172.43; MS (DCI/NH_3): $(M+H)^+$=298; IR: ($CDCl_3$) 3450, 1780, 1710 cm^{-1}.

(4S,5R)-N-(((*tert*)-Butyloxy)carbonyl)-4-hydroxy-5-(1-naphthylmethyl)-2-pyrrolidinone (2). Using the procedure for the preparation of **1** but with N-Boc-(1-naphthyl)alanine replacing N-Boc-cyclohexylalanine, the desired compound was provided; (63% overall) R_f = 0.77 (2:3:95 HOAc/MeOH/EA) and 0.04 (1:1:2 ether/CH_2Cl_2/Hexane); $[\alpha]^{24}_D$ = -59.5° (c=2.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.18(s, 9H), 2.12(d, *J*=5 Hz, 1H), 2.66(dd, *J*=7,17.4 Hz, 1H), 2.74(dd, *J*=6,17.4 Hz, 1H), 3.49(dd, *J*=7,14.1 Hz, 1H), 3.67(dd, *J*=7,14.1 Hz, 1H), 4.44(dddd, *J*=5,6,7,7 Hz, 1H), 4.68(ddd, *J*=7,7,7 Hz, 1H), 7.35-7.6(m, 4H), 7.77(d, *J*=7.2 Hz, 1H), 7.87(dd, *J*=1.5,7 Hz, 1H), 8.23(d, *J*=7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.27, 31.58, 39.99, 61.79, 65.71, 82.90, 123.77, 125.60, 125.63, 126.07, 127.40, 127.96, 128.77, 132.33,

133.86(2C's), 149.47, 172.36; MS (DCI/NH_3): $(M+NH_4)^+$=359, $(M+NH_4\text{-Boc})^+$=259, $(M+H\text{-Boc})^+$=242; IR: ($CDCl_3$) 3620, 3540, 1783, 1750, 1722 cm^{-1}; Anal. Calcd for $C_{20}H_{23}NO_4 \cdot 1/4H_2O$: C, 69.45; H, 6.85; N, 4.05. Found: C, 69.51; H, 6.83; N, 4.01.

(4S,5R)-N-(((*tert*)-Butyloxy)carbonyl)-5-benzyl-4-hydroxy-2-pyrrolidinone (3).[5] Using the procedure for the preparation of **1** but with N-Boc-phenylalanine replacing N-Boc-cyclohexylalanine the desired compound was provided.

Alkylation of (4S,5R)-N-(((*tert*)-Butyloxy)carbonyl)-5-substituted-4-hydroxy-2-pyrrolidinones. To a solution of LDA (prepared from diisopropylamine (0.68 mL, 4.85 mmol) and n-BuLi (3.45 mL, 4.66 mmol) in THF (8.0 mL) at -78°C) at 0°C was added HMPA (1.29 mL, 7.41 mmol). The vessel was rechilled to -78°C and the (4S,5R)-N-Boc-5-substituted-4-hydroxy-2-pyrrolidinone (1.85 mmol) was added in THF (7.0 mL). After 50 min, a solution of the bromide (9.3 mmol) in THF (5.0 mL) was added and the reaction was stirred at -78°C for 30 min before it was quenched by the addition of 1.0 N citric acid solution. The mixture was diluted with ether (100 mL) and washed with 1.0 N citric acid solution (2 x 50 mL). The combined aqueous portions were extracted with ether (1 x 50 mL) and discarded. The combined organics were washed with brine (3 x 50 mL) and dried ($MgSO_4$). Evaporation and flash silica gel chromatography provided the desired compound.

(3R,4S,5R)-N-(((*tert*)-Butyloxy)carbonyl)-3-benzyl-5-(cyclohexylmethyl)-4-hydroxy-2-pyrrolidinone (4a). (69% yield) R_f = 0.35 (1:2 EA/Hexane); $[\alpha]^{25}_D$ = +41.4° (c=3.01, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.8-1.8(m, 14H), 1.54(s, 9H), 2.75-2.9(m, 2H), 3.25-3.37(m, 1H), 4.15-4.3(m, 2H), 7.2-7.4(m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.25, 26.44, 28.03, 28.33, 33.43, 33.62, 34.20, 34.67, 36.61, 50.02, 56.34, 71.26, 83.18, 126.80, 128.90, 129.13, 138.23, 149.72, 172.26; MS (DCI/NH_3): $(M+NH_4)^+$=405, $(M+NH_4\text{-}H_2O)^+$=387; IR: ($CDCl_3$): 3600, 1780, 1715 cm^{-1}; Anal. Calcd for $C_{23}H_{33}NO_4$: C, 71.29; H, 8.58; N, 3.61. Found: C, 71.42; H, 8.30; N, 3.66.

(3R,4S,5R)-N-(((*tert*)-Butyloxy)carbonyl)-3-benzyl-4-hydroxy-5-(1-naphthylmethyl)-2-pyrrolidinone (4b). (56% yield) R_f = 0.25 (1:1:2 ether/CH_2Cl_2/Hexane); $[\alpha]^{20}_D$ = -17.4° (c=1.21, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.96(s, 9H), 1.45(d, *J*=3 Hz, 1H), 2.34(dd, *J*=7.5,13.5 Hz, 1H), 3.00(ddd, *J*=5.4,8.7,8.7 Hz, 1H), 3.08(dd, *J*=8.7,14 Hz, 1H), 3.35(dd, *J*=4.8,13.5 Hz, 1H), 3.75(dd, *J*=5.4,14 Hz, 1H), 4.30(ddd, *J*=3.0,8.7,12 Hz, 1H), 4.65(ddd, *J*=4.8,7.5,12 Hz, 1H), 7.25-7.5(m, 9H), 7.75(dd, *J*=2.5,7 Hz, 1H), 7.8-7.9(m, 1H), 8.0-8.1(m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.17, 32.28, 34.25, 49.95, 59.23, 71.41, 82.68, 122.84, 122.90, 125.59, 126.05, 126.86, 127.38, 127.93, 128.79, 128.93, 129.14, 132.26, 133.88, 134.03, 138.12, 149.06, 172.39; MS (DCI/NH_3): $(M+NH_4)^+$=449, $(M+NH_4\text{-Boc})^+$=349; IR: ($CDCl_3$) 3595, 3460, 1779, 1740, 1720 cm^{-1}; Anal. Calcd for $C_{27}H_{29}NO_4 \cdot 1/4H_2O$: C, 74.37; H, 6.82; N, 3.21. Found: C, 74.74; H, 6.99; N, 3.26.

(3R,4S,5R)-N-(((*tert*)-Butyloxy)carbonyl)-5-benzyl-4-hydroxy-3-(1-naphthylmethyl)-2-pyrrolidinone (4c). (43% yield) R_f = 0.39 (1:2 EA/Hexane); $[\alpha]^{25}_D$ = +36.3° (c=2.59, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.08(d, *J*=3 Hz, 1H), 1.49(s, 9H), 2.82(ddd, *J*=4.8,9,9 Hz, 1H), 2.88(dd, *J*=4.5,14.4 Hz, 1H), 2.99(dd, *J*=9,15 Hz, 1H), 3.07(dd, *J*=7,14.4 Hz, 1H), 3.85(dd, *J*=4.8,15 Hz, 1H), 4.30(ddd, *J*=3,9,10 Hz, 1H), 4.41(ddd, *J*=4.5,7,10 Hz, 1H), 7.1-7.2(m, 6H), 7.4-7.5(m, 1H), 7.5-7.6(m, 2H), 7.77(dd, *J*=3,7 Hz, 1H), 7.85-7.9(m, 1H), 7.95-8.0(m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.36, 30.81,33.85, 48.88, 60.48, 70.66, 83.05, 123.39, 125.12, 125.25, 125.78, 126.05, 127.02, 127.32, 127.99, 128.40, 129.64, 131.66, 133.52, 134.35, 137.61, 149.45, 173.48; MS (DCI/NH_3): $(M+NH_4)^+$=449, $(M+NH_4\text{-}H_2O)^+$=431; IR: ($CDCl_3$) 3600, 1782, 1742 cm^{-1}; Anal. Calcd for $C_{27}H_{29}NO_4 \cdot 1/2H_2O$: C, 73.61; H, 6.86; N, 3.18. Found: C, 73.22; H, 6.63; N, 3.12.

(3-(R,S),4S,5R)-N-(((*tert*)-Butyloxy)carbonyl)-5-benzyl-4-hydroxy-3-(3-picolyl)-2-pyrrolidin-one (4d and 4d'). The 3-picolyl bromide was prepared from the commercially available 3-pyridylcarbinol by a

procedure based on the work of Bixler and Niemann[13] and Sorm and Sedivy.[14] The following is representative: A mixture of 3-pyridylcarbinol (5.00 g, 45.8 mmol) and 48% HBr (45 mL, ca. 400 mmol) was heated at reflux for 4 h. The reaction mixture was then concentrated (water aspirator) with gentle warming to a thick light yellow oil. Absolute ethanol (ca. 25 mL) was added and the mixture was warmed to dissolve any precipitated solids. After overnight refrigeration (ca. +5°C) the solids were collected[15], washed with ice cold ethanol (20 mL) and dried in vacuo. After recrystallization from ethanol, 3.32 g of 3-picolyl bromide hyrdobromide was obtained. A portion of the above 3-picolyl bromide hyrdobromide (2.04 g, 8.07 mmol) was dissolved in a minimum amount of water (ca. 2 mL) and was covered with toluene (3 mL). To this biphasic mixture was added a solution of KOH (0.56 g, ca. 8.5 mmol) in water (ca. 1 mL) with vigorous stirring. After 15 min the darkly colored layers were separated and the aqueous portion was extracted with toluene (1 mL). The combined organics were washed with brine (1 mL), dried ($MgSO_4$ + activated carbon), and filtered though a pad of basic alumina (1"x 2"). The filtrate containing the free-based picolyl bromide was then added directly to the enolate reaction mixture (generated as for **4a-c**). In general, the picolyl bromide reactions were stirred at -78°C about 2 h and then warmed to ca. -40°C for about 2 h before water was added to quench the reaction. The layers were separated[16] and the aqueous portion was extracted with ether (2x). The combined organic phases were exhaustively washed with water (3x), then brine (2x) and dried (anhydrous K_2CO_3). After a few minutes 3-mercaptopropionic acid (1 mL, 11 mmol) was added to the solution and drying agent and the heterogeneous mixture was stirred at RT overnight.[17] Water was added, the layers were separated and the organic portion was extracted with saturated $NaHCO_3$ (2x). The combined aqueous layers were extracted with ether (2x) and the combined organics were again dried ($MgSO_4$). The products[18] were isolated by flash silica gel chromatography.

(3R,4S,5R)-N-(((*tert*)-Butyloxy)carbonyl)-5-benzyl-4-hydroxy-3-(3-picolyl)-2-pyrrolidinone (4d). (43% yield) R_f = 0.19 (EA); $[\alpha]^{25}_D$ = -28.0° (c=2.43, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.47(s, 9H); 2.84(ddd, *J*=3,6,8 Hz, 1H); 2.98(dd, *J*=3,13 Hz, 1H); 3.03(dd, *J*=6,13 Hz, 1H); 3.12(dd, *J*=4,14 Hz, 1H); 3.25(dd, *J*=8,14 Hz, 1H); 4.05(dd, *J*=8,12 Hz, 1H); 4.27(ddd, *J*=4,8,12 Hz, 1H); 6.12(br s, 1H); 7.1-7.4(m, 7H); 7.6-7.7(m, 1H); 8.32(d, *J*=2 Hz, 1H); MS (DCI/NH_3): $(M+H)^+$=383; IR: ($CDCl_3$) 3600, 1778, 1740, 1705 cm^{-1}; Anal. Calcd for $C_{22}H_{26}N_2O_4$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.11; H, 6.87; N, 7.31.

(3S,4S,5R)-N-(((*tert*)-Butyloxy)carbonyl)-5-benzyl-4-hydroxy-3-(3-picolyl)-2-pyrrolidinone (4d'). (4% yield) R_f = 0.25 (EA); $[\alpha]^{25}_D$ = -7.9° (c=0.36, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.60(s, 9H); 2.65(ddd, *J*=4,5,10 Hz, 1H); 2.85-3.0(m, 2H); 3.15(dd, *J*=4,15 Hz, 1H); 3.71(dd, *J*=4,13 Hz, 1H); 3.84(dd, *J*=4,4 Hz, 1H); 4.14(ddd, *J*=4,4,9 Hz, 1H); 7.1-7.3(m, 7H); 7.52(dt, *J*=2,8 Hz, 1H); 8.42(d, *J*=2 Hz, 1H); MS (DCI/NH_3): $(M+H)^+$=383; IR: ($CDCl_3$) 3600, 3440, 1780, 1715 cm^{-1}; Anal. Calcd for $C_{22}H_{26}N_2O_4 \cdot 1/10\ H_2O$: C, 68.77; H, 6.87; N, 7.29. Found: C, 68.82; H, 7.27; N, 7.45.

(2R,3S,4R)-4-(N-(((*tert*)-Butyloxy)carbonyl)-amino)-2-benzyl-5-cyclohexyl-3-hydroxy-pentanoic acid acetonide (6a). The following is a representative procedure for imide hydrolysis and acetonide formation outlined in Scheme 1: To a solution of **4a** (176 mg, 0.45 mmol) in THF (5.0 mL) was added 1M LiOH solution (1.35 mL, 1.35 mmol) and the resulting mixture was stirred 1.5 h at which point the solvents were removed in vacuo and the residue was partitioned between ethyl acetate and 1.0 N citric acid solution. The aqueous phase was extracted with ethyl acetate (2x) and the combined organics were dried (Na_2SO_4). Evaporation of solvent left 256 mg residue which was dissolved in CH_2Cl_2 (6 mL) and to which was added 2-methoxypropene (0.13 mL, 1.35 mmol) and PPTS (ca. 5 mg). After stirring 2 h at RT the mixture was concentrated and residue applied to a column of flash silica gel (1"x 5"; 5% to 25% ethyl acetate/hexane) to yield 192 mg of the desired compound **6a**; (95% yield) R_f = 0.38 (1:2 EA/Hexane); $[\alpha]^{20}_D$ = -10.1° (c=0.68, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.9-1.0(m, 2H), 1.05-1.3(m, 4H), 1.45(s, 9H), 1.5-1.8(m, 13H),

2.87(d, *J*=10 Hz, 1H), 2.96(d, *J*=10 Hz, 1H), 3.2-3.3(m, 1H), 3.75-3.85(m, 1H), 4.04(br d, *J*=10 Hz, 1H), 7.1-7.3(m, 5H).; MS (DCI/NH_3): $(M+NH_4)^+$=463, $(M+H)^+$=446; IR: ($CDCl_3$) 1702, 1688 cm^{-1}.

(2R,3S,4R)-4-(N-(((*tert*)-Butyloxy)carbonyl)-amino)-2-benzyl-3-hydroxy-5-(1-naphthyl)pentanoic acid acetonide (6b). (41% yield) R_f = 0.25 (1;2 EA/Hexane); $[\alpha]^{20}_D$ = -41.3° (c=0.15, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.52(s, ca. 0.5H) & 1.57(s, ca. 0.5H), 1.65(s, 3H), 1.73(s, 3H), 2.1-2.2(m, ca.0.5H) & 2.25-2.4(m, ca.0.5H), 2.6-2.7(m, 1H), 2.7-3.1(m, 2H), 3.8-3.9(m, ca.0.5H) & 4.15-4.4(m, ca.1.5H), 6.6-6.8(m, 1H), 7.0-7.7(m, 11H), 8.1-8.2(m, ca.0.5H) & 8.4-8.5(m, ca.0.5H); MS (DCI/NH_3): $(M+NH_4)^+$=507, $(M+H)^+$=490; IR: ($CDCl_3$) 3000, 1710, 1690 cm^{-1}.

(2R,3S,4R)-4-(N-(((*tert*)-Butyloxy)carbonyl)-amino)-3-hydroxy-2-(1-naphthylmethyl)-5-phenylpentanoic acid acetonide (6c). (60% yield) R_f = 0.34 (1:2 EA/Hexane); $[\alpha]^{24}_D$ = -53.4° (c=2.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz, @60°C) δ 1.53(s, 9H), 1.70(s, 6H), 2.8-2.95(m, 2H), 3.12(dd, *J*=2,8 Hz, 1H), 3.25(dd, *J*=7,9 Hz, 1H), 3.57(dd, *J*=3,9 Hz, 1H), 4.0-4.1(br s, 1H), 4.29(dd, *J*=3,5.4 Hz, 1H), 7.1-7.3(m, 7H), 7.4-7.45(m, 2H), 7.67(d, *J*=8.4 Hz, 1H), 7.68-7.72(m, 1H),7.95-8.0(m, 1H); MS (DCI/NH_3): $(M+NH_4)^+$= 507, $(M+H)^+$=490.

(2R,3S,4R)-4-(N-(((*tert*)-Butyloxy)carbonyl)-amino)-2-(N-((benzyloxy)carbonyl)-amino)-5-cyclohexyl-3-hydroxy-1-phenylpentane acetonide (9a). The following is a representative procedure for acyl azide preparation, Curtius rearrangement, and carbobenzyloxyamine synthesis: A solution of **6a** (150 mg, 336 μmole), triethylamine (0.093 mL, 667 μmole), and diphenylphosphoryl azide (0.11 mL, 510 μmole) in dry xylene (1.20 mL) was heated at ca. 90°C for 2 h. DMAP (ca. 10 mg) and benzyl alcohol (0.18 mL, 1.7 mmol) were then added and the reaction was stirred 15 h. It was allowed to cool to RT and evaporated. The residue was subject to flash chromatography (1"x 8"; 10% ethyl acetate/hexane) to give 141 mg of the desired compound; (76% yield) R_f = 0.48 (20% EA/Hexane); $[a]^{20}_D$ = +2.7° (c=1.11, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.8-1.8(m, 13H), 1.47(s, 9H), 1.62(s, 3H), 1.72(s, 3H), 2.35(dd, *J*=9,14 Hz, 1H), 3.10(dd, *J*=3,14 Hz, 1H), 3.65(br s, 1H), 3.9-4.0(m, 2H), 4.53(d, *J*=9 Hz, 1H), 5.02(s, 2H), 7.15-7.4(m, 10H); MS (DCI/NH_3): $(M+NH_4)^+$=568, $(M+H)^+$=551; IR: ($CDCl_3$) 1720, 1685 cm^{-1}; Anal. Calcd for $C_{33}H_{46}N_2O_5$: C, 71.97; H, 8.42; N, 5.09. Found: C, 71.95; H, 8.51; N, 5.09.

(2R,3S,4R)-4-(N-(((*tert*)-Butyloxy)carbonyl)-amino)-2-(N-((benzyloxy)carbonyl)-amino)-3-hydroxy-5-(1-naphthyl)-1-phenylpentane acetonide (9b). (80% yield) R_f = 0.36 (20% EA/Hexane); $[\alpha]^{20}_D$ = -58.4° (c=2.16, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.59(s, 3H), 1.60(s, 9H), 1.74(s, 3H), 2.45-2.5(m, 1H), 2.7-3.0(m, 2H), 3.3-3.4(m, 1H), 3.5-3.9(m, 2H), 4.3-4.45(m, 2H), 4.6-4.75(m, 1H),6.8-6.95(m, 1H), 7.0-7.4(m, 13H), 7.6-7.8(m, 2H), 8.15-8.25(m, 1H), 8.4-8.5(m, 1H); MS (DCI/NH_3): $(M+NH_4)^+$=612, $(M+H\text{-}Boc)^+$=495; IR: ($CDCl_3$) 3420, 1720, 1690 cm^{-1}; Anal. Calcd for $C_{37}H_{42}N_2O_5 \cdot 5/4H_2O$: C, 72.00; H, 7.27; N, 4.54. Found: C, 71.89; H, 6.97; N, 4.31.

(2R,3S,4R)-4-(N-(((*tert*)-Butyloxy)carbonyl)-amino)-2-(N-((benzyloxy)carbonyl)-amino)-3-hydroxy-1-(1-naphthyl)-5-phenylpentane acetonide (9c). (76% yield) R_f = 0.38 (20% EA/Hexane); $[\alpha]^{24}_D$ = -73.7° (c=2.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.54(s, 9H), 1.65(s, 3H),1.76(s, 3H), 2.6-2.9(m, 1H), 3.0-3.1(m, 1H), 3.1-3.2(m, 1H), 3.4-3.65(m, 1H), 3.9-4.2(m, 4H),4.82(d, *J*=13 Hz, 1H), 4.90(d, *J*=13 Hz, 1H), 6.95-7.5(m, 14H), 7.71(d, *J*=9 Hz, 1H), 7.80-7.85(m, 1H), 7.9-8.0(m, 1H); MS (DCI/NH_3): $(M+NH_4)^+$=612, $(M+H)^+$=595; IR: ($CDCl_3$) 3315, 1718, 1695 cm^{-1}; Anal. Calcd for $C_{37}H_{42}N_2O_5$: C, 74.52; H, 7.12; N, 4.71. Found: C, 74.79; H,; 7.22 N, 4.52.

(2R,3S,4R)-4-(N-(((*tert*)-Butyloxy)carbonyl)-amino)-2-amino-5-cyclohexyl-3-hydroxy-1-phenylpentane acetonide (11a). The following is a representative procedure for the carbobenzyloxy group removal: A mixture of **9a** (133 mg, 240 μmole), 10% Pd/carbon (0.13 g) and glacial acetic acid (ca. 6 mL) were stirred together under an atmosphere of hydrogen for 21 h. After filtration, the solvent was removed from the filtrate and the residue taken up in CH_2Cl_2 and washed with 1 M NaOH. The aqueous phase was

extracted twice and the combined organics were washed with brine (1x) and dried ($MgSO_4$). Filtration, evaporation and flash silica gel chromatography (1"x 6", 1:25:74 conc. NH_4OH/ethyl acetate/hexane) left 96.9 mg of the desired product; (96% yield) R_f = 0.41 (1:2 EA/Hexane); $[\alpha]^{20}_D$ = +3.8° (c=1.20, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.8-1.8(m, 14H), 1.47(s, 9H), 1.57(s, 3H), 1.70(s, 3H), 1.88(d, *J*=12 Hz, 1H), 2.39(dd, *J*=10,13.8 Hz, 1H), 3.02(ddd, *J*=3,9,9 Hz, 1H), 3.26(dd, *J*=3,13.8 Hz, 1H), 3.62(d, *J*=9 Hz, 1H), 4.03(m, 1H), 7.2-7.4(m, 5H); MS (DCI/NH_3): $(M+H)^+$=417; IR: ($CDCl_3$) 1682 cm^{-1}; Anal. Calcd for $C_{25}H_{40}N_2O_3$: C, 72.08; H, 9.68; N, 6.72. Found: C, 72.17; H, 9.59; N, 6.63.

(2R,3S,4R)-2-Amino-4-(N-(((*tert*)-utyloxy)carbonyl)-amino)-3-hydroxy-5-(1-naphthyl)-1-phenylpentane acetonide (11b). (46% yield) R_f = 0.22 (1:2 EA/Hexane); $[\alpha]^{20}_D$ = -62.2° (c=0.83, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.48(s, 9H), 1.67(s, 3H), 1.74(s, 3H), 1.9-2.05(m, 1H), 2.3-2.5(m, 1H), 2.7-2.8(m, 1H), 2.9-3.1(m, 1H), 3.75-3.85(m, 1H), 3.9-4.0(m, 1H), 4.15-4.25(m, 1H), 4.42(dt, *J*=11.4,3.6 Hz, 1H), 6.7-6.8(m, 2H), 7.1-7.9(m, 9H), 8.2-8.3(m, 1H), 8.45-8.55(m, 1H); MS (DCI/NH_3): $(M+H)^+$=461; IR: ($CDCl_3$) 1690, 1390 cm^{-1}; Anal. Calcd for $C_{29}H_{36}N_2O_3 \cdot 1/4H_2O$: C, 74.89; H, 7.91; N, 6.02. Found: C, 74.90; H, 7.58; N, 5.91.

(2R,3S,4R)-4-(N-(((*tert*)-Butyloxy)carbonyl)-amino)-2-amino-3-hydroxy-1-(1-naphthyl)-5-phenylpentane acetonide (11c). (78% yield) R_f = 0.52 (1:2 EA/Hexane); $[\alpha]^{24}_D$ = -60.6° (c=1.04, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.30(br s, 2H), 1.54(s, 9H), 1.68(s, 3H), 1.78(s, 3H), 2.45-2.65(m, 1H), 2.7-3.1(m, 2H), 3.33(d, *J*=12 Hz, 1H), 3.54(d, *J*=14 Hz, 1H), 4.15-4.25(m, 1H), 7.2-7.5(m, 9H), 7.72(d, *J*=9 Hz, 1H), 7.8-7.85(m, 1H), 7.9-7.95(m, 1H); MS (DCI/NH_3): $(M+H)^+$=461; IR: ($CDCl_3$) 1690 cm^{-1}; Anal. Calcd for $C_{29}H_{36}N_2O_3$: C, 75.62; H, 7.88; N, 6.08. Found: C, 75.42; H, 8.02; N, 5.89.

(2R,3S,4R)-5-Cyclohexyl-2,4-diamino-3-hydroxy-1-phenylpentane (12a). The following is a representative procedure for the removal of the N-Boc and acetonide moieties: To a solution of **11a** (79 mg, 189 μmole) in MeOH (1.50 mL) at 0°C was added 4.8 M HCl/dioxane (0.40 mL, 1.9 mmol). The reaction was stirred ca. 2 h then allowed to warm slowly to RT over ca. 23 h. After flushing the solution with N_2 for several minutes, solid sodium carbonate was added and stirred 10 min. The mixture was diluted with CH_2Cl_2 (ca. 2x volume) and filtered though Celite. Evaporation left 80 mg yellow glass which was purified by flash silica gel chromatography (1/2"x 4"; 1:10:89 conc. NH_4OH/MeOH/CH_2Cl_2) to give 41 mg desired product; (79% yield) R_f = 0.05 (7% MeOH/CH_2Cl_2); $[\alpha]^{20}_D$ = -32.0° (c=0.67, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.8-1.45(m, 8H), 1.6-1.85(m, 5H), 1.9-2.2(br s, 5H), 2.50(dd, *J*=10.5,13.8 Hz, 1H), 2.95(dd, *J*=4,13.8 Hz, 1H), 3.1-3.2(m, 2H), 3.25(t, *J*=4.5 Hz, 1H), 7.1-7.4(m, 5H); MS (DCI/NH_3): $(M+H)^+$=277, exact mass: *m/z* calc'd for $C_{17}H_{29}N_2O$: 277.2280, found: 277.2278; IR: ($CDCl_3$) 3390 cm^{-1}.

(2R,3S,4R)-2,4-Diamino-3-hydroxy-5-(1-naphthyl)-1-phenylpentane (12b). (76% yield) R_f = 0.32 (1:15:84 conc.NH_4OH/MeOH/CH_2Cl_2); $[\alpha]^{20}_D$ = -6.8° (c=0.56, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.15(br s, 5H), 2.54(dd, *J*=9,13.5 Hz, 1H), 2.94(dd, *J*=4,13.5 Hz, 1H), 3.13(dd, *J*=9,14 Hz, 1H), 3.23(ddd, *J*=4,5.4,9 Hz, 1H), 3.42(dd, *J*=5.4,14 Hz, 1H), 3.48(dd, *J*=2.4,5.4 Hz, 1H), 3.57(ddd, *J*=2.4,5.4,9 Hz, 1H), 7.1-7.6(m, 9H), 7.76(d, *J*=8.7 Hz, 1H), 7.85-7.9(m, 1H), 8.06(d, *J*=8.7 Hz, 1H); MS (DCI/NH_3): $(M+H)^+$=321, exact mass: *m/z* calc'd for $C_{21}H_{24}N_2O$: 321.1967, found: 321.1965; IR: ($CDCl_3$) 3380, 3320, 1595 cm^{-1}.

(2R,3S,4R)-2,4-Diamino-3-hydroxy-1-(1-naphthyl)-5-phenylpentane (12c). (64% yield) R_f = 0.14 (1:10:89 conc.NH_4OH/MeOH/CH_2Cl_2); $[\alpha]^{20}_D$ = -33.5° (c=1.07, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.1(br s, 5H), 2.72(dd, *J*=10,14 Hz, 1H), 2.82(dd, *J*=10.5,14.8 Hz, 1H), 2.96(dd, *J*=6,14 Hz, 1H), 3.28(ddd, *J*=3,6,10 Hz, 1H), 3.45(m, 2H), 3.63(dd, *J*=3,14 Hz, 1H), 7.2-7.55(m, 9H), 7.74(d, *J*=9 Hz, 1H), 7.8-7.9(m, 1H), 8.0-8.1(m, 1H); MS (DCI/NH_3): $(M+H)^+$=321, exact mass: *m/z* calc'd for $C_{21}H_{24}N_2O$: 321.1967, found: 321.1969; IR: ($CDCl_3$) 3390, 3020, 1590 cm^{-1}.

Oxazolidinone 16 and Urea 17. The following procedure is representative for the transformation of the imide **4d** to the oxazolidinone **16** and urea **17**: To a rapidly stirred solution of the imide **4d** (140 mg, 0.366 mmol) in THF (2.5 mL) was added 1 M LiOH (1.10 mL). After 2 h the solvents were removed in vacuo and the solid residue was extracted with 10% i-PrOH/$CHCl_3$ (3x 4 mL - until extract no longer showed the presence of any UV-active material by tlc) and the combined extracts were filtered though Celite and concentrated to give 150 mg of the crude lithium carboxylate as a yellow foam which was dissolved in THF (7.5 mL). Triethylamine (0.12 mL, 0.86 mmol), DMAP (ca. 5 mg), and DPPA (0.12 mL, 0.56 mmol) were added and the mixture was heated at 65°C for ca. 20 h. After cooling to RT the solvents were evaporated and the residue partitioned between water and 10% i-PrOH/$CHCl_3$. Following the usual extractive work up, flash silica gel chromatography provided the oxazolidinone **16** and urea **17**.

5R-[2-Phenethyl-1S-(N-(((*tert*)-butyloxy)carbonyl)-amino)]-4S-(3-picolyl)oxazolidin-2-one (16). (59% yield) R_f = 0.73 (1:20:79 conc. NH_4OH/ MeOH/CH_2Cl_2); $[\alpha]^{22}_D$ = -47.1° (c=1.31, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.40(s, 9H); 2.85-3.05(m, 4H); 4.03(ddd, *J*=5,8,9 Hz, 1H); 4.27(ddd, *J*=6,8,9 Hz, 1H); 4.68(d, *J*=8 Hz, 1H); 4.98(s, 1H); 5.05(d, *J*=10 Hz, 1H); 7.2-7.4(m, 6H); 7.48(dt, *J*=8,1 Hz, 1H); 8.42(s, 1H); 8.52(dd, *J*=1,5 Hz, 1H); MS (DCI/NH_3): $(M+NH_4)^+$=415, $(M+H)^+$=398; IR: ($CDCl_3$) 3430, 1760,1695 cm^{-1}.

(4S,5S,6S)-1-(N-(((*tert*)-Butyloxy)carbonyl)-)-6-benzyl-5-hydroxy-4-(3-picolyl)-(3*H*)-tetrahydro-2-pyrimidinone (17). (23% yield) R_f = 0.78 (1:20:79 conc. NH_4OH/MeOH/CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.40(s, 9H); 2.67(dd, *J*=8,14 Hz, 1H); 2.75-2.9(m, 2H); 2.96(dd, *J*=7,14 Hz, 1H); 3.9-4.0(m, 2H); 4.19(d, *J*=7 Hz, 1H); 4.80(d, *J*=9 Hz, 1H); 5.12(s, 1H); 7.15-7.4(m, 7H); 8.35(d, *J*=2 Hz, 1H); 8.50(dd, *J*=1,5 Hz, 1H); MS (DCI/NH_3): $(M+H)^+$=398; IR: ($CDCl_3$) 3435, 3260, 1760, 1705 cm^{-1}; Anal. Calcd for $C_{22}H_{27}N_3O_4 \cdot 1/2H_2O$: C, 65.01; H, 6.94; N, 10.34. Found: C, 64.95; H, 6.79; N, 10.09.

Oxazolidinone hydrolysis to diamine 12. A solution of the oxazolidinone **16** (28 mg, 70 μmole) and $Ba(OH)_2 \cdot 8H_2O$ (70 mg, 221 μmole) in dioxane (0.6 mL) and water (0.4 mL) was heated at reflux 4 h. Tlc indicated that some intermediate amino oxazolidinone remained so more barium hydroxide (ca. 20 mg) was added and heating continued 1 h longer. The reaction mixture was cooled to RT and filtered through a glass wool plug (10% i-PrOH/$CHCl_3$) and the solvents were evaporated. The solid residue was triturated with 10% i-PrOH/$CHCl_3$, refiltered and concentrated. Flash silica gel chromatography (10% MeOH/CH_2Cl_2 to 1:20:70 conc. NH_4OH/ MeOH/CH_2Cl_2) gave the desired diamino alcohol **12d**.

(2R,3S,4R)-2,4-Diamino-3-hydroxy-1-phenyl-5-(3-picolyl)pentane (12d). (56% yield) R_f = 0.20 (1:20:79 conc. NH_4OH/MeOH/ CH_2Cl_2); $[\alpha]^{22}_D$ = -14.0° (c=0.53, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.1-1.6(br s, 5H); 2.52(dd, *J*=9.6,13.8 Hz, 1H); 2.66(dd, *J*=9.6,13.4 Hz, 1H); 2.89(dd, *J*=5.4,13.4 Hz, 1H); 3.00(dd, *J*=3.6,13.8 Hz, 1H); 3.08(ddd, *J*=3.6, 6.0,9.6 Hz, 1H); 3.31(dd, *J*=2.6,6.0, Hz, 1H); 3.37(ddd, *J*=2.6,5.4,9.6 Hz, 1H); 7.1-7.4(m, 6H); 7.52(dt, *J*=7.5,2.0 Hz, 1H); 8.4-8.5(m, 2H); MS (DCI/NH_3): $(M+H)^+$=272, exact mass: *m/z* calc'd for $C_{16}H_{21}N_3O$: 272.1763, found: 272.1763; IR: ($CDCl_3$) 3380, 3320 cm^{-1}; Anal. Calcd for $C_{16}H_{21}N_3O \cdot 1/2H_2O$: C, 68.54; H, 7.91; N, 14.99. Found: C, 68.23; H, 7.50; N, 14.75.

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11 Perhaps these intermediates are more appropiately referred to as an α–alkylated "ACHPA" ((3S,4S)-4-amino-5-cyclohexyl-3-hydroxypentanoic acid) analogs.
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15. Care should be taken when the picolyl bromide hyrdobromides are isolated as they are very powerful lachrymators.
16. The work up should be carried out in a well ventilated fume hood because picolyl bromides are powerful lachrymators.
17. Without this treatment, upon concentration of the mixture, the excess picolyl bromide alkylates the pyridyl nitrogen in the product and very low yields are realized. The amino acid resulting from S-alkylation of the 3-mercaptopropionic acid by the picolyl bromide can easily be washed out by aqueous extraction.
18. Unlike the benzyl and napthyl bromide alkylations, the picolyl bromide alkylations produced two diastereomeric products which were apparent by tlc prior to the anhydrous K_2CO_3/3-mercaptopropionic acid treatment.