Synthesis of Hydroxyethylene Isosteres of the Transition State of the HIV Protease-Catalyzed Phe-Pro Hydrolysis: Reaction of 2-[(Boc)amino]-1-(2′-oxocyclopentyl)-3-phenylpropanols with Diethyl Phosphorocyanidate and Lithium Cyanide Followed by Samarium Iodide

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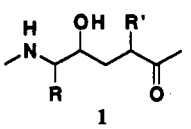
Received March 15, 1993

Reaction of cyclopentanone enolate (7) with Boc-L-phenylalaninal (6) afforded a mixture of four aldol products **5a–d** in a 3:3:1:1 ratio. Reaction of **5a** with diethyl phosphorocyanidate followed by samarium iodide reduction afforded lactone **13a** and phosphate **12**. The structure of **12** was confirmed by X-ray crystallography. Deprotection of **13a** gave (1*R*,1′*S*,2*S*,2′*S*)-2-(2′-amino-1′-hydroxy-3′-phenylpropyl)cyclopentanecarboxylic acid lactone (**14a**), which was transformed to a crystalline lactam **15a** under basic conditions. The structure of **15a** was also confirmed by X-ray analysis.

The *gag* and *pol* polyproteins of replication competent retroviruses, including HIV-1 and HIV-2, are cleaved into functional proteins by a protease.[1–3] Immature, uninfective forms of these viruses result from in vitro mutagenesis that produces defective protease.[4–6] The design and synthesis of potential protease inhibitors therefore constitutes a rational strategy for the development of anti-AIDS agents which is presently being pursued by a large number of research groups.

A successful strategy for the design of aspartic protease inhibitors has been the replacement of the cleaved amide bond in short substrate peptides with hydroxyethylene units 1 that mimic the transition state of the enzyme-catalyzed hydrolysis reaction.[7–14] Numerous pathways



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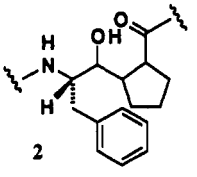

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leading to these types of compounds have been published.[15] Our efforts have been aimed at the synthesis of peptides containing a Phe-Pro analog unit **2** containing a cyclopentane ring.[14,16–18] The initially planned synthesis was based on the retrosynthetic analysis pathway shown in Scheme I.

Reaction of Boc-L-phenylalaninal (**6**)[19,20] with lithium cyclopentanone enolate (**7**) resulted in a mixture of four stereoisomers **5a–d** in a 3:3:1:1 ratio, respectively. As discussed below, the stereochemical assignments of these aldols **5a–d** are supported by the further transformation of two of them into crystalline compounds that were subjected to X-ray structure determination. The stereochemistry of the aldols was found to be rather labile; aldol **5a** can easily isomerize to **5c**. This isomerization was observed during column chromatographic separations. The fractions containing **5a** were always contaminated with **5c** and vice versa. Stirring a solution of **5a** with triethylamine or sodium carbonate resulted in the rapid formation of **5c**.

Several methods are known for the transformation of carbonyl compounds (R_2CO) into the next higher homologous nitriles or carboxylic acids ($R_2CHCOOH$). These include cyanation with tosylmethyl isocyanide in the presence of *t*-BuOK,[21] cyanation with (benzenesulfonyl)-hydrazones,[22] Darzen's condensation with chloroacetonitrile,[23] and cyanation with diethyl phosphorocyanidate

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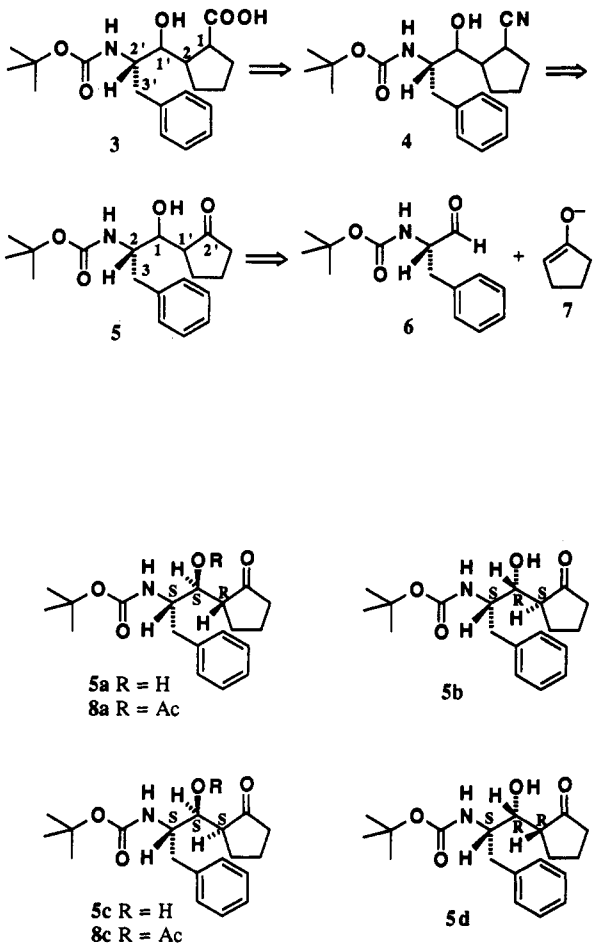
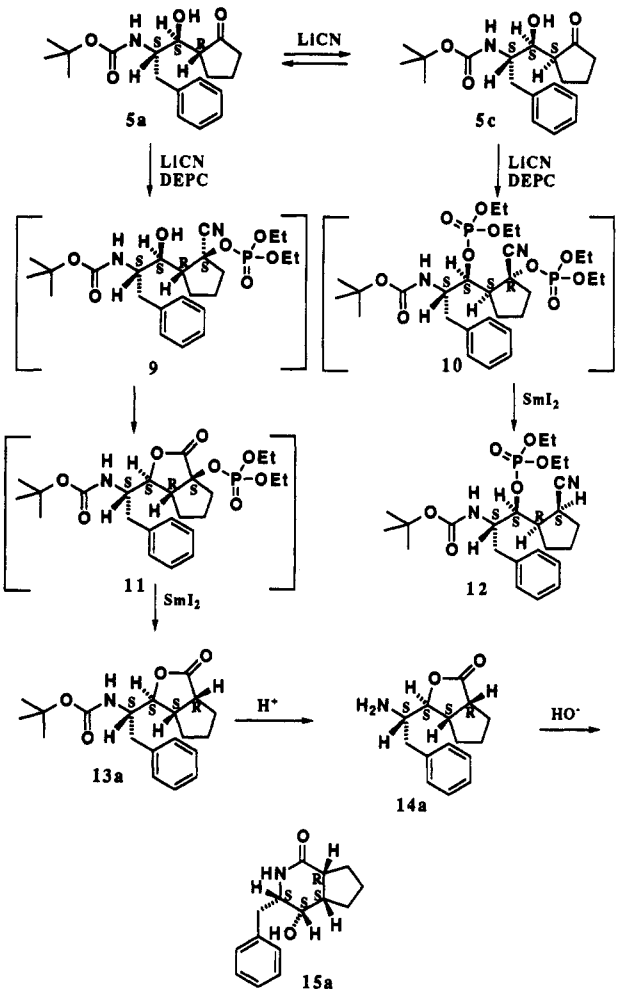
Scheme I



Scheme II



followed by reduction with samarium iodide.[24] We have chosen to employ the last method because of its versatility and the very mild conditions necessary for the transformation.

It was expected that protection of the hydroxy function of aldols **5** prior to cyanation would be advantageous, and compounds **5a** and **5c** were converted to the corresponding acetates **8a** and **8c** with acetyl chloride under basic conditions. No epimerization was detected during the acetylation, which was performed at room temperature with acetyl chloride and pyridine in methylene chloride. Reaction of acetyl derivative **8a** with lithium cyanide and diethyl phosphorocyanidate was sluggish. After 3 h at room temperature, 55% of the starting material was isolated from the mixture. After 16 h, significant amounts of derivative **8a** could still be detected by TLC, and a complex mixture of products had formed. In contrast, unprotected aldol **5a** reacted with lithium cyanide and diethyl phosphorocyanidate at 0 °C. The reaction was smooth, and the starting material disappeared in less than 20 min. Aldols **5b–d** behaved similarly. It was found that the reaction depends strongly on ratio of reagents. When aldol **5a**, lithium cyanide, and diethyl phosphorocyanidate were mixed in a 1:3:1.1 ratio, respectively, the reaction did not take place, but after the addition of a second equivalent of diethyl phosphorocyanidate, the ketone disappeared within 10 min. The reaction did not occur without lithium cyanide or with only a catalytic amount of the reagent.

Table I. Reaction Products Isolated after Treatment of Aldols 5a–c with Diethyl Phosphorocyanidate and Lithium Cyanide Followed by Samarium Iodide at 0 °C

aldol	lactone	phosphate
5a	**13a** (40%)	**12** (15%)
5a[a]	**13a** (28%)	**12** (46%)
5b	**13b** (30%)	
5c		**12** (50%)

[a] Reaction performed at room temperature.

Samarium iodide reduction of the products of cyanation resulted in formation of lactone **13a** and the phosphate **12** (Scheme II). Similar results were obtained for the other aldols. However, for aldols **5b** and **5d**, the products related to phosphate **12** could not be purified and were not fully analyzed. Table I lists compounds which were isolated pure. The structure of **12** was confirmed by X-ray crystallography. The *ORTEP-II* plot of the X-ray structure of **12** is shown in Figure 1.

The structure of **13a** was confirmed by removal of the Boc protecting group and intramolecular aminolysis of the lactone **14a** to form lactam **15a**, whose structure was also determined by X-ray analysis. The *ORTEP-II* plot of the X-ray structure of **15a** is depicted in Figure 2. The 2*R* configuration of phosphate **12**, opposite that of the corresponding aldol **5a**, evidently results from isomerization of aldol **5a** to **5c** in the presence of lithium cyanide. This is consistent with the observation that phosphate **12** is formed as the main product from aldol **5c** and that the yield of **12** from **5a** increases with an increase in the

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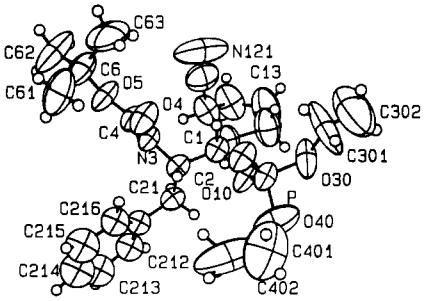


Figure 1. *ORTEP-II* plot of the X-ray structure of **12**.

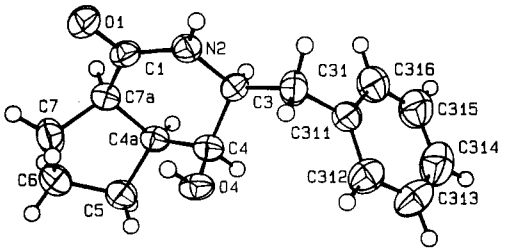


Figure 2. *ORTEP-II* plot of the X-ray structure of **15a**.

temperature. Lactone **14b** and rearrangement product **15b** were obtained from **13b** using chemistry outlined for **13a** in Scheme II.

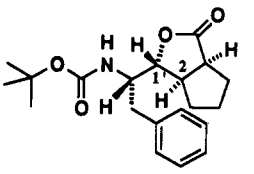
The structure of compound **13a** was given further support by comparison of its 500-MHz ^{1}H NMR spectrum ($CDCl_3$) with the 300-MHz ^{1}H NMR spectrum ($CDCl_3$) of compound **20**, which was prepared by a different route.[14] The 300-MHz spectrum of **20** was kindly provided to us by Dr. Wayne J. Thompson, Merck Research Laboratories. The spectra of **13a** and **20** were almost identical in the δ 4.8–1.2 ppm region, with minor variations clearly resulting from the different field strengths. On the other hand, the 300-MHz NMR spectrum ($CDCl_3$) of **21**[14] did not resemble the 500-MHz ^{1}H NMR spectra ($CDCl_3$) of either **13a** or **13b** in the δ 4.8–1.2 region.

The apparent stereoselectivity of cyanophosphate formation, as indicated by the transformation of **5a** to **13a** and **5c** to **12**, is noteworthy. Presumably, cyanohydrin formation is reversible and phosphorylation only occurs trans to the adjacent cyclopentane ring appendage. The apparent diphosphorylation of **5c** and monophosphorylation of **5a** and **5b** may be somewhat misleading, however, since the overall material balance in the reaction to form **13a** and **12** was only 55%. Several additional cyanated products were detected that have not been isolated and characterized.

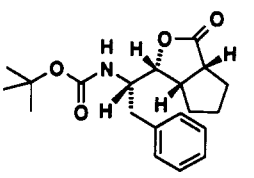
The structure of **13b**, which was derived from aldol **5b**, was established by ^{1}H NMR spectroscopy. Examination of molecular models reveals that **13b** can exist in a stable conformation having a dihedral angle between protons H-2 and H-1′ approximating 90°, which is consistent with the lack of coupling between these two protons in the ^{1}H NMR spectrum. Proton H-1′ appears at δ 4.01 as a doublet (J = 6.5 Hz) due to coupling to H-2′. This excludes the alternative structure **13c**, in which the dihedral angle between H-2 and H-1′ is approximately 20°.

The solid-state IR spectra of **13a** and **13b** were dependent on the crystallization solvent (chloroform vs hexane) and crystallization temperature. This was ascribed to the existence of distinct crystal forms.

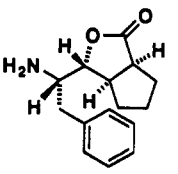
Overall, the results indicate some threo diastereoselectivity in the aldol reaction to form **5a–d**, but no "Cram" or "AntiCram" control. The aldol reactions of *N*-protected α-amino aldehydes are in general characterized by low diastereoselectivity.[25]



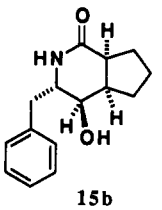
13b



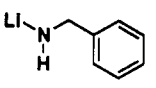
13c



14b



15b



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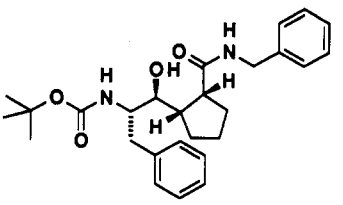
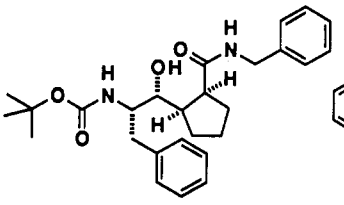
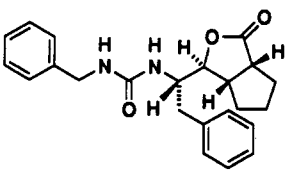


17a



17b



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Several attempts to open the lactone ring of **13a** with various amine derivatives to form amide derivatives of **3** failed. Finally, the reaction succeeded using a large excess of lithium benzylamide **16**.[14] The reaction was run in THF with the ratio of lactone **13a** to benzylamine to butyllithium being 1:10:6. Reaction of lactone **13a** with benzylamide **16** at −78 °C followed by column separation gave ring-opening product **17a** (78%) along with the starting lactone **13a** (15%). Small amounts (5%) of the urea derivative **18** were obtained along with **17a** (44%) when the reaction was performed at room temperature. Recyclization of hydroxy amide **17a** to amino lactone **14a** was observed during attempted deprotection of the amino group of amide **17a** with trifluoroacetic acid in methylene chloride. The stereochemistry of **17a** can be established by analogy to the conversion of **20** to **22**, since the structure of **22** has been determined by single-crystal X-ray analysis.[14]

Reaction of isomeric lactone **13b** with benzylamide **16** at −78 °C gave amide **17b** (24%) and the starting lactone **13b** (63%). Reaction of lactone **13b** with benzylamide **16** at room temperature gave amide **17b** (27%) and lactam **19** (30%). As in the case of the reaction of lactone **13a**,

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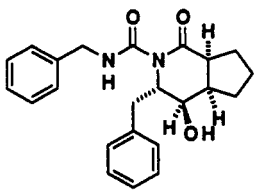

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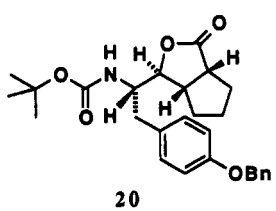

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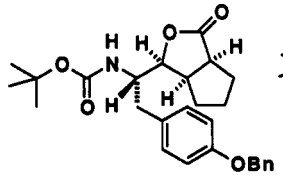

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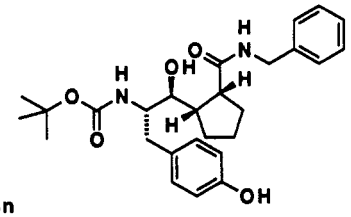

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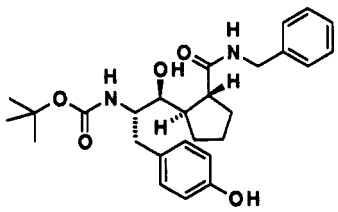

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an increase in temperature resulted in formation of Boc cleavage product.

Compounds **17a** and **17b** are closely related to hydroxyethylene isostere derivatives **22** and **23**, which were recently prepared by a different route.[14] The presently reported three-step synthesis of hydroxyethylene transition-state isosteres of this type from Boc-*N*-phenylalaninal (**6**) and cyclopentanone offers the advantages of being comparatively short and inexpensive.

Experimental Section

Melting points are uncorrected. ^{1}H NMR spectra were recorded at 500 MHz. Mass spectra were determined using an ionization potential of 70 eV. Low-resolution chemical ionization mass spectra (CIMS) were determined using ammonia or 2-methylpropane as the reagent gas. Microanalyses were performed by the Purdue Microanalytical Laboratory.

2-[(Boc)amino]-1-(2′-oxocyclopentyl)-3-phenylpropanols (5). A solution of cyclopentanone (1.77 mL, 20 mmol) in tetrahydrofuran (60 mL) was stirred with LDA (22 mmol) at −78 °C for 1.5 h. A solution of *N*-Boc-L-phenylalaninal (2.50 g, 10 mmol) in tetrahydrofuran (60 mL) was added, and stirring was continued for 5 min at −78 °C. The reaction mixture was quenched with water (25 mL) and extracted with ether (400 mL). The solution was washed with water (4 × 100 mL) and brine (1 × 100 mL), dried ($MgSO_4$), and evaporated. The residue was separated on a silica (300 g) column with a chloroform–ethyl acetate (5:1) solvent system to give four isomers:

(1*S*,1′*R*,2*S*)-2-[(Boc)amino]-1-(2′-oxocyclopentyl)-3-phenylpropanol (5a): yield 1.14 g (30%); mp 78–80 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16–7.32 (m, 5 H, Ph), 5.05 (d, J = 10 Hz, 1 H, NH), 4.45 (s, 1 H, OH), 3.78 (dd, J_{2-3a} = 6.6 Hz, J_{2-3b} = 9.2 Hz, 1 H, H-2), 3.54 (d, $J_{1-1'}$ = 8.6 Hz, 1 H, H-1), 2.92 (dd, J_{3a-3b} = 13.3 Hz, J_{2-3a} = 6.6 Hz, 1 H, H-3a), 2.88 (dd, J_{3a-3b} = 13.3 Hz, J_{2-3b} = 9.2 Hz, 1 H, H-3b), 2.25 (m, H-1′), 1.20–2.40 (m, 7 H, cyclopentanone), 1.40 (s, 9 H, Boc); IR (KBr) 3349, 1707, 1524, 1243, 1168 cm^{-1}; CIMS *m/e* (relative intensity) 334 (63), 278 (37), 234 (100), 216 (36). Anal. Calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.42; H, 8.45; N, 4.36.

(1*R*,1′*S*,2*S*)-2-[(Boc)amino]-1-(2′-oxocyclopentyl)-3-phenylpropanol (5b): yield 1.14 (30%); mp 91–92 °C; NMR (500 MHz, $CDCl_3$) δ 7.18–7.30 (m, 5 H, Ph), 5.02 (d, J = 9.3 Hz, 1 H, NH), 4.15 (s, 1 H, OH), 3.89 (m, 1 H, H-2), 3.83 (d, $J_{1-1'}$ = 9.4 Hz, 1 H, H-1), 2.90 (dd, J_{2-3a} = 5.1 Hz, J_{3a-3b} = 14.1 Hz, 1 H, H-3a), 2.77 (dd, J_{2-3b} = 9.2 Hz, J_{3a-3b} = 14.1 Hz, 1 H, H-3b), 2.17 (m, H-1′), 1.3–2.42 (m, 7 H, cyclopentanone), 1.32 (s, 9 H, Boc); IR (KBr) 3373, 2972, 1736, 1699, 1519, 1263, 1170 cm^{-1}; CIMS *m/e* (relative intensity) 334 (61), 316 (45), 278 (32), 234 (100), 216 (65). Anal. Calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.44; H, 8.34; N, 4.32.

(1*S*,1′*S*,2*S*)-2-[(Boc)amino]-1-(2′-oxocyclopentyl)-3-phenylpropanol (5c): yield 0.38 g (10%); mp 138–140 °C; NMR (500 MHz, $CDCl_3$) δ 7.16–7.32 (m, 5 H, Ph), 4.75 (d, J = 9 Hz, 1 H, NH), 4.00 (m, 1 H, H-1), 3.90 (m, 1 H, H-2), 3.37 (d, J = 6.1 Hz, 1 H, OH), 2.91 (d, J_{2-3} = 7.3 Hz, 2 H, H-3), 1.60–2.40 (m, 7 H, cyclopentanone), 1.38 (s, 9 H, Boc); IR (KBr) 3462, 3384, 2970, 1733, 1660, 1528, 1168 cm^{-1}; CIMS *m/e* (relative intensity) 334 (13), 278 (44), 234 (100), 216 (27). Anal. Calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.27; H, 8.36; N, 4.13.

(1*R*,1′*R*,2*S*)-2-[(Boc)amino]-1-(2′-oxocyclopentyl)-3-phenylpropanol (5d): yield 0.38 g (10%); mp 95–97 °C; NMR (500 MHz, $CDCl_3$) δ 7.2–7.4 (m, 5 H, Ph), 4.37 (d, J = 8.8 Hz, 1 H, NH), 4.02 (m, 1 H, H-1), 3.94 (m, 1 H, H-2), 3.04 (dd, J_{3a-2} = 4.4 Hz, J_{3a-3b} = 14 Hz, 1 H, H-3a), 2.78 (m, J_{2-3b} = 7.5 Hz, 2 H, H-3b, OH), 1.5–2.5 (m, 9 H), 1.34 (s, 9 H, Boc); IR (KBr) 3359, 2979, 1732, 1688, 1518, 1167 cm^{-1}; CIMS *m/e* (relative intensity) 334 (58), 316 (21), 278 (48), 234 (82), 216 (100). Anal. Calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.19; H, 8.47; N, 4.44.

(1*S*,1′*R*,2*S*)-*O*-Acetyl-2-[(Boc)amino]-1-(2′-oxocyclopentyl)-3-phenylpropanol (8a). Pyridine (0.24 mL, 3 mmol) and acetyl chloride (0.1 mL, 1.5 mmol) were added to a solution of (1*S*,1′*R*,2*S*)-2-[(Boc)amino]-1-(2′-oxocyclopentyl)-3-phenylpropanol (**5a**, 167 mg, 0.5 mmol) in dry methylene chloride (5 mL). The suspension was stirred at rt for 7 h, the solvent was evaporated, and the residue was diluted with ethyl ether (40 mL) and extracted with sodium bicarbonate solution, water, and brine. The organic layer was dried over magnesium sulfate and evaporated, and the residue was purified on a silica gel (20 g) column in chloroform–ethyl acetate (20:1) solution to give 140 mg (75%) of product. The compound was crystallized from hexane to give 102 mg (54%) of white solid: mp 145–146 °C; NMR (200 MHz, $CDCl_3$) δ 7.2–7.4 (m, 5 H, Ph), 4.95 (d, J = 9.3 Hz, 1 H, H-1), 4.81 (d, J = 10 Hz, 1 H, NH), 4.07 (m, 1 H, H-2), 2.72 (m, 2 H, H-3), 1.3-2.45 (m, 7 H, cyclopentanone), 2.14 (s, 3 H, CH_3), 1.39 (s, 9H, Boc); IR (KBr) 3376, 2973, 1739, 1693, 1526, 1243, 1173, 1027 cm^{-1}; CIMS *m/e* (relative intensity) 376 (42), 320 (29), 276 (100), 216 (26). Anal. Calcd for $C_{21}H_{29}NO_5$: C, 67.18; H, 7.78; N, 3.73. Found: C, 67.54; H, 7.98; N, 3.91.

(1*S*,1′*S*,2*S*)-*O*-Acetyl-2-[(Boc)amino]-1-(2′-oxocyclopentyl)-3-phenylpropanol (8c). This compound was obtained analogously to acetyl derivative **8a** using aldol **5c** as starting material: yield 46%; mp 120–122 °C; NMR (200 MHz, $CDCl_3$) δ 7.2–7.4 (m, 5 H, Ph), 5.20 (apparent bt, 1 H, H-1), 4.65 (d, J = 9 Hz, 1 H, NH), 4.30 (m, 1 H, H-2), 2.76 (m, 2 H, CH_2Ph), 2.5–1.3 (m, 7 H, cyclopentanone), 2.05 (s, 3 H, CH_3), 1.35 (s, 9 H, Boc); IR (KBr) 3390, 2970, 1746, 1691, 1525, 1239 cm^{-1}; MS (CI) *m/e* (relative intensity) 376 (43), 358 (38), 320 (27), 302 (26), 276 (75), 258 (100). Anal. Calcd for $C_{21}H_{29}NO_5$: C, 67.18; H, 7.78; N, 3.73. Found: C, 66.84; H, 7.92; N, 3.50.

(1*R*,1′*S*,2*S*,2′*S*)-2-[2′-[(Boc)amino]-1′-hydroxy-3′-phenylpropyl]cyclopentanecarboxylic Acid Lactone (13a). A solution of diethyl phosphorocyanidate (0.23 mL, 1.5 mmol) and lithium cyanide (50 mg, 1.5 mmol) in dry THF (10 mL) was cooled to 0 °C. Aldol **5a** (167 mg, 0.5 mmol) was added, and the solution was stirred at 0 °C for 20 min. Water (10 mL) was added to the solution, and the mixture was extracted with hexane–ethyl acetate (1:1) solution (50 mL). The extract was washed with brine (2 × 20 mL), dried ($MgSO_4$), and evaporated to dryness. The IR spectrum (film) of the oily residue demonstrated absorptions at 3321, 2980, 2207, 1789, 1710, 1523, 1367, 1269, 1168, and 1029 cm^{-1}. The residue was carefully dried, deoxygenated, dissolved in dry, oxygen free THF (7 mL), and cooled to 0 °C. *tert*-Butyl alcohol (37 mg, 0.5 mmol) and samarium

iodide (23 mL of 0.1 M solution in THF, 2.3 mmol) were added, and the cooled solution was stirred for 1 h. The reaction was quenched by addition of 10% HCl (10 mL) and diluted with ethyl ether (100 mL). The organic layer was washed with 5% sodium thiosulfate (10 mL), water (3 × 50 mL), and brine (50 mL) and dried ($MgSO_4$). The solvent was evaporated and the residue separated on a silica gel (25 g) column using chloroform–ethyl acetate (50:1) solution to give two products. Compound **13a** was obtained as a white solid, yield 68 mg (40%), IR (KBr) 3398, 2977, 1790, 1690, 1516, 1169 cm^{-1}. The NMR analysis of this material did not reveal any significant impurities, and it was used in the subsequent aminolysis to afford **17a**. The analytical sample was crystallized from hexane to give 41 mg of solid: mp 145–146 °C; NMR (500 MHz, $CDCl_3$) δ 7.15–7.36 (m, 5 H, Ph), 4.50 (d, J = 9.6 Hz, 1 H, NH), 4.08 (q, $J_{2'-3'}$ = 7.9 Hz, $J_{2'-NH}$ = 9.6 Hz, 1 H, H-2'), 4.05 (d, $J_{1'-2}$ = 3.3 Hz, 1 H, H-1'), 3.02 (ddd, J = 9.5, 9.5, and 2.4 Hz, 1 H, H-1), 2.88 (d, $J_{2'-3'}$ = 7.9 Hz, 2 H, CH_2Ph), 2.80 (m, 1 H, H-2), 1.2–2.11 (m, 6 H, cyclopentane), 1.35 (s, 9 H, Boc); IR (KBr) 3338, 2975, 1771, 1701, 1363, 1180, 1020 cm^{-1}; CIMS m/e (relative intensity) 346 (1), 328 (3), 290 (100), 246 (4). Anal. Calcd for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88; N, 4.05. Found: C, 69.22; H, 8.03; N, 4.09.

(1*S*,2*S*,1'*R*,2'*S*)-2-[(Boc)amino]-1-(2'-cyanocyclopentyl)-3-phenylpropyl Diethyl Phosphate (12). Compound **12** was also obtained from the silica gel column chromatography above as a solid: yield 15%, mp 120–121 °C; NMR (500 MHz, $CDCl_3$) δ 7.2–7.35 (m, 5 H, Ph), 4.78 (d, J = 10 Hz, 1 H, NH), 4.56 (dd, $J_{1-1'}$ = 10 Hz, J_{1-P} = 9.7 Hz, 1 H, H-1), 4.18 (m, 1 H, H-2), 4.18 (m, 4 H, OCH_2), 3.27 (dt, J = 6.95 Hz, J= 1.8 Hz, 1 H, H-2'), 3.02 (dd, J_{3a-3b} = 14 Hz, J_{3a-2} = 5.4 Hz, 1 H, H-3a), 2.89 (dd, J_{3a-3b} = 14 Hz, J_{3b-2} = 9.7 Hz, 1 H, H-3b), 2.31 (m, 1 H, H-1'), 1.64–2.10 (m, 6 H, cyclopentane), 1.29 (s, 9 H, Boc); IR (KBr) 3266, 2979, 2234, 1703, 1541, 1245, 1029, 1007 cm^{-1}; CIMS m/e (relative intensity) 481 (2), 423 (4), 381 (100). Anal. Calcd for $C_{24}H_{37}N_2O_6P$: C, 59.98; H, 7.76; N, 5.83. Found: C, 59.93; H, 8.22; N, 5.77.

(1*S*,1'*R*,2*R*,2'*S*)-2-[2'-[(Boc)amino]-1'-hydroxy-3'-phenylpropyl]cyclopentanecarboxylic Acid Lactone (13b). Aldol **5b** was reacted with diethyl phosphorocyanidate and lithium cyanide using the procedure described above for **5a**. The crude product of cyanation (before reduction with SmI_2) demonstrated IR (film) 3319, 2982, 2208, 1787, 1711, 1269, 1167, 1029 cm^{-1}. The reduction product was purified on a silica column (chloroform–ethyl acetate (50:1)) to give **13b** as a white solid, yield 30%, IR (KBr) 3370, 2965, 1774, 1688, 1526, 1170 cm^{-1}. Crystallization of **13b** from hexane gave the product (60%) as a colorless solid: mp 131–132 °C; NMR (500 MHz, $CDCl_3$) δ 7.15–7.35 (m, 5 H, Ph), 4.47 (d, J = 8.7 Hz, 1 H, NH), 4.01 (d, $J_{1'-2'}$ = 6.5 Hz, 1 H, H-1'), 3.95 (m, 1 H, H-2'), 3.08 (ddd, J = 9.5, 9.5, 2.5 Hz, 1 H, H-1), 2.98 (dd, $J_{2'-3'a}$ = 4.3 Hz, $J_{3'a-3'b}$ = 14 Hz, 1 H, H-3'a), 2.80 (m, 2 H, H-3'b, H-2), 1.20–2.20 (m, 6 H, cyclopentane), 1.35 (s, 9 H, Boc); IR (KBr) 3430, 3327, 2972, 1744, 1704, 1542, 1283, 1210, 1165, 1029 cm^{-1}; CIMS m/e (relative intensity) 346 (3), 330 (4), 290 (100). Anal. Calcd for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88; N, 4.05. Found: C, 69.78; H, 8.24; N, 4.29.

Reaction of (1*S*,1'*S*,2*S*)-2-[(Boc)amino]-1-(2'-oxocyclopentyl)-3-phenylpropanol (5c) with Diethyl Phosphorocyanidate To Afford Phosphate 12. Aldol **5c** was cyanated using the procedure described for **5a**. The products were purified on a silica gel column (chloroform–ethyl acetate (50:1)) to give **12**, yield 50%. The analytical data were identical with those given for **12** obtained from aldol **5a**.

(1*R*,1'*S*,2*S*,2'*S*)-2-(2'-Amino-1'-hydroxy-3'-phenylpropyl)-cyclopentanecarboxylic Acid Lactone (14a). A solution of (1*R*,1'*S*,2*S*,2'*S*)-2-(2'-[(Boc)amino]-1'-hydroxy-3'-phenylpropyl]-cyclopentanecarboxylic acid lactone (**13a**) (120 mg, 0.35 mmol) and trifluoroacetic acid (1 mL) in methylene chloride (2 mL) was stirred at room temperature for 1 h. The solution was evaporated, and the residue was either washed with dry ether to give the colorless noncrystalline trifluoroacetate salt (100 mg, 88%) of **14a**, IR (KBr) 3436, 2958, 1776, 1678, 1200, 1136 cm^{-1}, or dissolved in methylene chloride (20 mL), washed with saturated sodium bicarbonate (10 mL) and brine (10 mL), and dried ($MgSO_4$). Evaporation of the solution gave **14a** as a colorless oil (76 mg, 90%): NMR (200 MHz, $CDCl_3$) δ 7.2–7.35 (m, 5 H, Ph), 4.00 (apparent t, J = 3.8 Hz, 1 H, H-1'), 2.70–3.20 (m, 4 H), 2.60 (dd, $J_{3'a-3'b}$ = 13.1 Hz, $J_{2'-3}$ = 9.0 Hz, 1 H, H-3), 1.20–2.20 (m, 6 H); IR (KBr) 3380, 2953, 1766, 1602, 1452, 1192 cm^{-1}; CIMS m/e (relative intensity) 246 (100), 154 (5). Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.80; N, 5.70. Found: C, 73.29; H, 8.03; N, 5.51.

(1*S*,1'*R*,2*R*,2'*S*)-2-(2'-Amino-1'-hydroxy-3'-phenylpropyl)-cyclopentanecarboxylic Acid Lactone (14b). Deprotected lactone **14b** was prepared from (1*S*,1'*R*,2*R*,2'*S*)-2-[2'-[(Boc)-amino]-1'-hydroxy-3'-phenylpropyl]cyclopentanecarboxylic acid lactone (**13b**) using the procedure described above for **14a**, yield 90%. For **14b** trifluoroacetate: IR (KBr) 3432, 2959, 1777, 1678, 1628, 1200, 1135 cm^{-1}. For **14b**: IR (KBr) 3379, 2954, 1766, 1603, 1453, 1195 cm^{-1}; NMR (500 MHz, $CDCl_3$) δ 7.15–7.40 (m, 5 H, Ph), 4.05 (dd, $J_{1'-2'}$ = 4.8 Hz, $J_{1'-2}$ = 3.6 Hz, 1 H, H-1'), 3.38 (bd, $J_{2'-3'b}$ = 9.1 Hz, 1 H, H-2'), 3.11 (dd, J = 9.6, 2.6 Hz, 1 H, H-1), 2.95 (m, 2 H, H-3'a, H-2), 2.62 (dd, $J_{2'-3'b}$ = 9.1 Hz, $J_{3'a-3'b}$ = 13.6 Hz, 1 H, H-3'b), 2.2 (bs, 1 H, NH), 1.5–2.1 (m, 6 H, cyclopentane). Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.80; N, 5.70. Found: C, 73.19; H, 7.91; N, 5.42.

(1*R*,1'*S*,2*S*,2'*S*)-2-(2'-Amino-1'-hydroxy-3'-phenylpropyl)-cyclopentanecarboxylic Acid Lactam (15a). The crude trifluoroacetate salt of **14a** (90 mg, 0.25 mmol) was dissolved in methanol (4 mL), sodium hydroxide (1 mL of 0.5 M solution) was added, and the solution was stirred for 4 h at rt. The solution was concentrated on a rotary evaporator to give a suspension of white solid. The suspension was diluted with water (2 mL), filtered, and washed with water to give lactam **15a** (37 mg, 60%). Crystallization from hexane–chloroform gave white crystals, mp 164–166 °C. The structure of **15a** was established by X-ray crystallography: NMR (500 MHz, $CDCl_3$) δ 7.15–7.40 (m, 5 H, Ph), 5.90 (bs, 1 H, NH), 3.75 (d, $J_{1'-2}$ = 3.3 Hz, 1 H, H-1'), 3.67 (dd, $J_{3'a-2'}$ = 6.7 Hz, $J_{3'b-2'}$ = 8.1 Hz, H-2'), 3.00 (dd, $J_{3'a-3'b}$ = 13.5 Hz, $J_{3'a-2'}$ = 6.7 Hz, 1 H, H-3'a), 2.88 (dd, $J_{3'a-3'b}$ = 13.5 Hz, $J_{3'b-2'}$ = 8.1 Hz, 1 H, H-3'b), 2.68 (q, J = 9.0 Hz, 1 H, H-1), 2.54 (bs, 1H, OH), 2.40 (m, 1 H, H-2), 2.18 (m, 2 H, cyclopentane), 1.80 (m, 4 H, cyclopentane); IR (KBr) 3431, 2930 1664 cm^{-1}; CIMS m/e (rel intensity) 246 (100), 154 (3). Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.80; N, 5.70. Found: C, 73.62; H, 7.81; N, 5.55.

(1*S*,1'*R*,2*R*,2'*S*)-2-(2'-Amino-1'-hydroxy-3'-phenylpropyl)-cyclopentanecarboxylic Acid Lactam (15b). Lactam **15b** was prepared from amino lactone **14b** using the procedure described above for **15a**: yield 68%, mp 175–176 °C (after crystallization from hexane–chloroform); NMR (500 MHz, $CDCl_3$) δ 7.16–7.39 (m, 5 H, Ph), 5.56 (s, 1 H, NH), 3.90 (dd, $J_{1'-2}$ = 5.0 Hz, $J_{1'-2'}$ = 8.0 Hz, 1 H, H-1'), 3.60 (m, 1 H, H-2'), 3.25 (dd, $J_{3'a-3'b}$ = 13.7 Hz, $J_{3'a-2'}$ = 3.7 Hz, 1 H, H-3'a), 2.81 (dt, J = 8.8 and 5.5 Hz, 1 H, H-1), 2.55 (m, 1 H, H-2), 2.50 (m, 1 H, H-3'b), 2.41 (s, 1 H, OH), 2.1 (m, 1 H), 1.88 (m, 2 H), 1.5–1.76 (m, 3 H); IR (KBr) 3293, 2954, 1629, 1588 cm^{-1}; CIMS m/e (relative intensity) 246 (100), 228 (2), 154 (9). Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.80; N, 5.70. Found: C, 73.18; H, 7.87; N, 5.35.

Reaction of 13a with 16 at −78 °C To Afford (1*R*,1'*S*,2*S*,2'*S*)-2-[2'-[(Boc)amino]-1'-hydroxy-3'-phenylpropyl]cyclopentanecarboxylic Acid *N*-Benzylamide (17a). A solution of benzylamine (0.3 mL, 2.8 mmol) and *n*-butyllithium (1.1 mL of 1.6 M solution in hexanes, 1.7 mmol) in THF (9 mL) was stirred at −78 °C for 30 min, and **13a** (95 mg, 0.28 mmol) in THF (2 mL) was added. The solution was stirred at −78 °C for 5 h, quenched with 2 N HCl (5 mL), and extracted with ethyl ether (50 mL). The ethereal solution was washed with 2 N HCl (2 × 10 mL), sodium bicarbonate solution (1 × 10 mL), water (3 × 10 mL), and brine (1 × 10 mL) and dried ($MgSO_4$). The solution was evaporated and the residue separated on silica column in chloroform–ethyl acetate (5:1) solution to give **13a** (15 mg, 15%), IR (KBr) 3336, 2960, 1770, 1701, 1362, 1180, 1020 cm^{-1}, and **17a** (97 mg, 78%): mp 120–121 °C; NMR (500 MHz, $CDCl_3$) δ 7.15–7.35 (m, 10 H, 2 Ph), 6.08 (bs, 1 H, amide NH), 4.91 (d, 1 H, $J_{NH-2'}$ = 8.9 Hz, BocNH), 4.43 (dd, 1 H, J_1 = 14.7 Hz, J_2 = 5.7 Hz, H_a-benzylamide), 4.34 (dd, 1 H, J_1 = 14.7 Hz, J_2 = 5.3 Hz, H_b-benzylamide), 3.67 (m, 1 H, H-2'), 3.44 (d, 1 H, $J_{1'-2}$ = 10.35 Hz, H-1'), 2.95 (dd, 1 H, $J_{3'a-3'b}$ = 13.5 Hz, $J_{3'a-2'}$ = 7.5 Hz, H-3'a), 2.92 (m, 1 H, H-1), 2.83 (dd, 1 H, $J_{3'b-2'}$ = 7.3 Hz, $J_{3'a-3'b}$ = 13.4 Hz, H-3'b), 2.25 (m, 1 H, $J_{2-1'}$ = 9 Hz, H-2), 1.96–1.45, (m, 7 H, cyclopentane + OH), 1.39 (s, 9 H, Boc); NMR (500 MHz, C_6D_6) δ 7.0–7.2 (m, 10 H, Ph), 5.52 (t, 1 H, amide NH), 4.91 (s, 2 H, Boc

NH + OH), 3.78 (q, J = 7.7 Hz, 1 H, H-2'), 3.62 (dd, $J_{1'-2}$ = 1.4 Hz, $J_{1'-2}$ = 10 Hz, 1 H, H-1'), 3.13 (dd, $J_{3'a-3'b}$ = 13.4 Hz, $J_{3'a-2'}$ = 7.4 Hz, 1 H, H-3'a), 2.89 (dd, $J_{3'a-3'b}$ = 13.4 Hz, $J_{3'b-2'}$ = 7.3 Hz, 1 H, H-3'b), 2.58 (m, J_{1-2} = 7.4 Hz, 1 H, H-1), 2.26 (m, 1 H, H-2), 1.1–1.7 (m, 6 H, cyclopentane), 1.40 (s, 9 H, Boc). IR (KBr) 3311, 2973, 1684, 1640, 1542, 1391, 1366, 1170, 699 cm^{-1}; CIMS m/e (relative intensity) 453 (100), 435 (55), 379 (29), 353 (94). Anal. Calcd for $C_{27}H_{36}N_2O_4$: C, 71.65; H, 8.02; N, 6.19. Found: C, 71.84; H, 8.25; N, 6.07.

Reaction of 13a with 16 at Room Temperature to Afford (1*R*,1'*S*,2*S*,2'*S*)-2-[2'-[(Boc)amino]-1'-hydroxy-3'-phenylpropyl]cyclopentanecarboxylic Acid N-Benzylamide (17a) and 2-[2'-[(benzylaminocarbonyl)amino]-1'-hydroxy-3'-phenylpropyl]cyclopentanecarboxylic Acid Lactone (18). A solution of benzylamine (0.1 mL, 1 mmol) and n-butyllithium (0.38 mL of 1.6 M solution in hexanes, 0.6 mmol) in THF (3 mL) was stirred at −78 °C for 30 min, and **13a** (35 mg, 0.1 mmol) in THF (1 mL) was added. The solution was stirred at −78 °C for 1.5 h and then for 1 h at rt. The mixture was quenched with 2 N HCl (3 mL) and extracted with ethyl ether (20 mL). The ethereal solution was washed with 2 N HCl (2 × 5 mL), sodium bicarbonate solution (1 × 5 mL), water (3 × 10 mL), and brine (1 × 10 mL) and dried ($MgSO_4$). The solution was evaporated and the residue separated on a silica gel column in chloroform–ethyl acetate (5:1) solution to give **17a** (20 mg, 44%) and **18** (2 mg, 5%): mp 73–74 °C; NMR (500 MHz, $CDCl_3$) δ 7.0–7.3 (m, 10 H, Ph), 6.1 (t, 1 H, NH), 4.78 (s, 1 H, NH), 4.36 (m, J = 6 Hz, 2 H, benzyl), 4.12 (dd, $J_{1'-2'}$ = 5 Hz, $J_{1'-2}$ = 10.8 Hz, 1 H, H-1'), 3.62 (m, 1 H, H-2'), 2.75 (m, 2 H, H-3'a + H-1), 2.53 (dd, $J_{3'a-3'b}$ = 13.5 Hz, $J_{3'b-2'}$ = 9.6 Hz, 1 H, H-3'b), 2.20 (m, 1 H, H-2), 1.1–2.05 (m 6 H, cyclopentane); IR (KBr) 3313, 2940, 1754, 1654, 1543, 1238, 1002, 700 cm^{-1}; CIMS m/e 379. Anal. Calcd for $C_{23}H_{26}N_2O_3$: C, 72.99; H, 6.92; N, 7.40. Found: C, 72.69; H, 6.73; N, 7.84.

Reaction of 13b with 16 at −78 °C To Afford (1*S*,1'*R*,2*R*,2'*S*)-2-[2'-[(Boc)amino]-1'-hydroxy-3'-phenylpropyl]cyclopentanecarboxylic Acid *N*-Benzylamide (17b). A solution of benzylamine (0.1 mL, 1 mmol) and n-butyllithium (0.38 mL of 1.6 M solution in hexanes, 0.6 mmol) in THF (3 mL) was stirred at −78 °C for 30 min, and **13b** (35 mg, 0.1 mmol) in THF (1 mL) was added. The solution was stirred at −78 °C for 24 h, quenched with 2 N HCl (3 mL), and extracted with ethyl ether (20 mL). The ethereal solution was washed with 2 N HCl (2 × 5 mL), sodium bicarbonate solution (1 × 5 mL), water (3 × 10 mL), and brine (1 × 10 mL) and dried ($MgSO_4$). The solution was evaporated and the residue separated on a silica gel column in chloforom–ethyl acetate (5:1) solution to give **13b** (22 mg, 63%) and **17b** (11 mg, 24%): mp 186–187 °C; NMR (500 MHz, $CDCl_3$) δ 7.36–7.14 (m, 10 H, 2 Ph), 6.44 (bs, 1 H, NH), 4.64 (d, 1 H, J = 7.9 Hz, BocNH), 4.46 (d, 2 H, J = 5.0 Hz, amide CH_2), 3.69 (m, 1 H, H-2'), 3.57 (bs, 1 H, H-1'), 2.93 (dd, 1 H, $J_{3'a-3'b}$ = 14 Hz, $J_{3'a-2'}$ = 3.9 Hz, H-3'a), 2.88 (m, 1 H, H-1), 2.80 (bt, 1 H, H-3'b), 2.27 (m, 1 H, H-2), 1.4–2.0 (m, 6 H, cyclopentane), 1.32 (s, 9 H, Boc); NMR (500 MHz, C_6D_6) δ 7.0–7.2 (m, 10 H, Ph), 6.08 (bs, 1 H, amide NH), 5.24 (d, J = 6.6 Hz, 1 H, OH), 4.36 (dd, J_1 = 14.7 Hz, J_2 = 5.9 Hz, 1 H, amide benzyl), 4.20 (dd, J_1 = 14.7 Hz, J_2 = 5.6 Hz, 1 H, amide benzyl), 4.16 (d, J = 10.8 Hz, 1 H, Boc NH), 3.78 (m, $J_{2'-NH}$ = 11 Hz, 1 H, H-2'), 3.54 (m, 1 H, H-1'), 3.05 (dd, $J_{3'a-3'b}$ = 13.8 Hz, $J_{3'a-2'}$ = 3.6 Hz, 1 H, H-3'a), 2.86 (dd, $J_{3'a-3'b}$ = 13.8 Hz, $J_{3'b-2'}$ = 9.3 Hz, 1 H, H-3'b), 2.64 (m, 1 H, H-2), 2.12 (m, 1 H, H-1), 1.2–2.1 (m, 6 H, cyclopentane), 1.33 (s, 9 H, Boc); IR (KBr) 3361, 2933, 1673, 1648, 1535, 1249, 1170, 699 cm^{-1}; CIMS m/e (relative intensity) 453 (100), 397 (49), 379 (97), 353 (29). Anal. Calcd for $C_{27}H_{36}N_2O_4$: C, 71.65; H, 8.02; N, 6.19. Found: C, 71.57; H, 8.18; N, 5.94.

Reaction of 13b with 16 at Room Temperature To Afford (1*S*,1'*R*,2*R*,2'*S*)-2-[2'-[(Benzylaminocarbonyl)amino]-1'-hydroxy-3'-phenylpropyl]cyclopentanecarboxylic Acid Lactam 19 and 17b. A solution of benzylamine (0.15 mL, 1.5 mmol) and n-butyllithium (0.55 mL of 1.6 M solution in hexanes, 0.88 mmol) in THF (5 mL) was stirred at −78 °C for 30 min, and **13b** (50 mg, 0.145 mmol) in THF (2 mL) was added. The solution was stirred at −78 °C for 1 h and for another hour at room temperature. The mixture was quenched with 2 N HCl (5 mL) and extracted with ethyl ether (40 mL). The ethereal solution was washed with 2 N HCl (2 × 10 mL), sodium bicarbonate solution (1 × 10 mL), water (3 × 10 mL), and brine (1 × 10 mL) and dried ($MgSO_4$). The solution was evaporated and the residue separated on silica column in chloroform–ethyl acetate (5:1) solution to give **19** (17 mg, 30%): mp 170–171 °C; NMR (500 MHz, $CDCl_3$) δ 7.3–7.0 (m, 10 H, 2 Ph), 6.57 (t, 1 H, amide NH), 4.35 (dd, 1 H, J_1 = 15 Hz, J_2 = 6 Hz, amide CH_a), 4.28 (dd, 1 H, J_1 = 15 Hz, J_2 = 6 Hz, amide CH_b), 3.79 (bs, dd after exchange with D_2O, 1 H, $J_{1'-2'}$ = 5.7 Hz, $J_{1'-2'}$ = 5.7 Hz, H-1'), 3.34 (dd, 1 H, $J_{3'a-3'b}$ = 13 Hz, $J_{3'a-2'}$ = 3.5 Hz, H-3'a), 3.37 (m, 1 H, H-2'), 2.49 (dd, 1 H, $J_{3'b-2'}$ = 13 Hz, $J_{3'a-3'b}$ = 13 Hz, H-3'b), 2.3–1.7 (m, 8 H, cyclopentane); IR (KBr) 3295, 1676, 1630, 1545, 1453, 1333, 701 cm^{-1}; CIMS 379. Anal. Calcd for $C_{23}H_{26}N_2O_3$: C, 72.99; H, 6.92; N, 7.40. Found: C, 72.52; H, 6.90; N, 7.24. Amide **17b** (18 mg, 27%) was eluted as a second fraction.

Crystal Structures. Crystals of **12** and **15a** were mounted on a glass fiber in random orientation and data collected on an Enraf-Nonius CAD4 diffractometer. Cell constants were refined from 25 reflections in the range $14 \leq 2\theta < 21°$. ω scans of several intense reflections were measured; the widths at half-height were less than 1° with a take-off angle of 2.95° indicating good crystal quality. From the systematic absences and from subsequent least-squares refinements, the space groups were determined. Data were collected using $\omega - 2\theta$ scan technique; scan rate varied from 2 to 20° min^{-1} (in ω). Three standard reflections were measured every hour of X-ray exposure; no crystal decay was detected. Lorentz and polarization corrections based on the method of Walker and Stuart[26] were applied on both data; no absorption corrections were necessary to either structure.

The structures were solved using the structure solution program *SHELXS86*,[27] and the remaining atoms were located in succeeding difference Fourier syntheses. Except as noted in the table of positional parameters, hydrogen atoms were located and added to the structure factor calculations but not refined. The structures were refined by full-matrix least-squares methods using MolEN[28] where the function minimized was $\sum w(|F_o| - |F_c|)^2$ and the weight w is defined by the Killean and Lawrence method with terms of 0.020 and 1.0.[29] Atomic scattering factors and the values for f' and f'' were taken from Cromer[30] and anomalous dispersion effects were included in F_c as described by Ibers and Hamilton.[31] Plots of $\sum w(|F_o| - |F_c|)^2$ versus $|F_o|$, reflection order in data collection, $\sin\theta/\lambda$, and various classes of indices showed no unusual trends.

Figures 1 and 2 are *ORTEP-II* drawings[32] of the two structures showing thermal ellipsoids of non-hydrogen atoms scaled to 50% probability level. The larger ellipsoids in Figure 1 are probably due to disorder in the ethoxy side chains.[33]

Acknowledgment. The authors wish to thank Dr. P. E. Fanwick, Department of Chemistry, Purdue University, for his assistance and the use of the Enfraf-Nonius CAD-4 diffractometer. This investigation was supported by contract NO1-CM-17513, awarded by the National Cancer Institute, DHHS. We are grateful to Dr. Wayne J. Thompson, Merck Research Laboratories, for providing 300-MHz ^{1}H NMR spectra of compounds **6**, **7**, **12**, and **15** in ref 14.

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(33) The authors have deposited atomic coordinates for **12** and **15a** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.