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Norbornyl Dipeptide Analogues: Mimics of Both a Transition State and a Torsionally Distorted Ground State

ROBERT M. SMITH,*,† DAVID P. WEINER,* NISHITH C. CHATURVEDI,* MICHAEL D. THIMBLIN, JR.,* SUSAN J. RAYMOND,* AND DAVID E. HANSEN*,†,[1]

*Department of Chemistry, Amherst College, Amherst, Massachusetts 01002, and †Program in Molecular and Cellular Biology, University of Massachusetts, Amherst, Massachusetts 01003

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The 1-amino-2-hydroxybicyclo[2.2.1]heptane-7-carboxylic acid derivatives **1–3** have been synthesized, the pivotal step being the use of an acyl nitrene-insertion reaction to introduce nitrogen functionality into the corresponding hydroxy ester. The analogues each mimic a distorted peptide ground state as well as the transition state for peptide bond hydrolysis. To enhance the immune response and to provide further sequence specificity, the analogues **1–3** have been coupled to at least one D-amino acid residue to yield the derivatives **21, 26,** and **27,** respectively. Antibodies elicited against these derivatives may catalyze the hydrolysis of the corresponding peptides both by straining the substrate ground state and by stabilizing the transition state.

INTRODUCTION

Analogues of amino acids and peptides are being utilized with increasing frequency in the study of biological systems. Unnatural amino acids can now be efficiently incorporated into peptides and proteins (*1*), a methodology that has facilitated the study of key residues in both catalytic and folding processes (*2*). Conformationally restricted peptide analogues (*3*) have been used to probe the biologically active conformations of peptides (*4*) and to model regions of defined structure such as β-sheet (*5*) or α-helix (*6*) initiation sites. A variety of enzymological studies have utilized peptide derivatives as mechanistic probes (*7*), and peptide-based transition state analogues can be potent protease inhibitors (*8*). Finally, most efforts directed toward the isolation of antibodies with peptidase activity have utilized peptide analogues as haptens (*9*). It is in this latter application that we have particular interest.

Since the first reports of antibody catalysis, the field has grown rapidly and has been extensively reviewed (*10*). While a number of promising reports have appeared (*11*), no *general* method has yet been developed for the elicitation of peptidolytic antibodies. Thus, we have been pursuing a new strategy for the isolation of antibody peptidases: immunization with analogues that mimic a distorted peptide ground

[1] To whom correspondence should be addressed.

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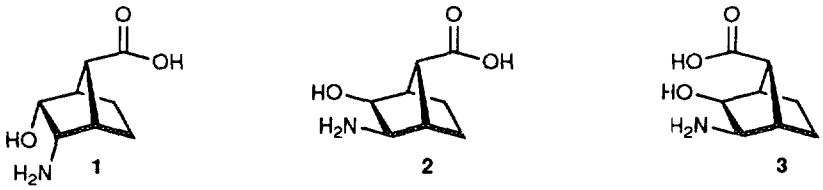


FIG. 1. Structures of the dipeptide analogues.

state in addition to the transition state for peptide bond hydrolysis. The antibodies elicited may catalyze hydrolysis of the corresponding peptide by both straining (or stressing (*12*)) the substrate ground state and by stabilizing the transition state. (Note that these two catalytic strategies are not, as has been discussed, independent (*13*).) We have described the detailed rationale for this approach elsewhere (*14*).

Here we report the synthesis of the 1-amino-2-hydroxybicyclo[2.2.1]heptane-7-carboxylic acid derivatives **1–3** (Fig. 1), each as a racemic mixture. As is shown in Fig. 2 for derivative **1,** the norbornyl framework is isosteric with both glycyl-glycine and glycyl-proline. The hydroxyethylene isostere mimics the transition state for peptide bond hydrolysis, while the norbornyl framework ensures that the peptide bond mimicked is distorted from planarity. Precedent for the use of these structural features comes from a variety of sources. Torsionally distorted amides, similar in geometry to the norbornyl derivatives here, have been shown to hydrolyze many orders of magnitude faster than their unstrained counterparts (*15*). The hydroxyethylene group has been demonstrated to be an effective transition state analogue: it is present in the pepsin inhibitor pepstatine (*16*), has been incorporated into potent HIV protease inhibitors (*17*), and has successfully been used to generate antibody catalysts, including those with esterase and imidase activity (*18, 11d*). (While tetrahedral phosphorus derivatives are arguably the best mimics of hydrolytic transition states, their incorporation into norbornyl derivatives is less than straightforward.) To enhance the immune response and to provide further sequence specificity, the analogues **1–3** have been coupled to additional amino acid residues to yield the derivatives **21, 26,** and **27,** respectively (Schemes 5 and 6).

The stereoisomers **1–3** differ in the relationship of the carboxylic acid and the

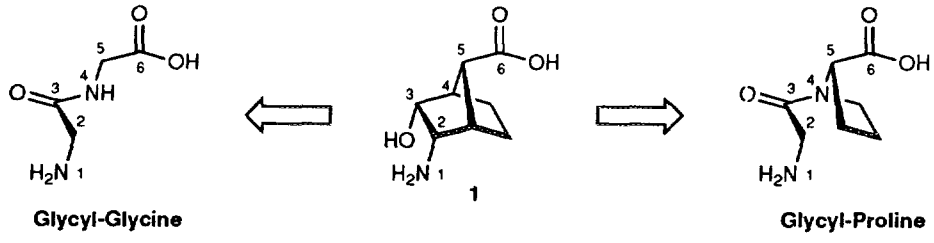
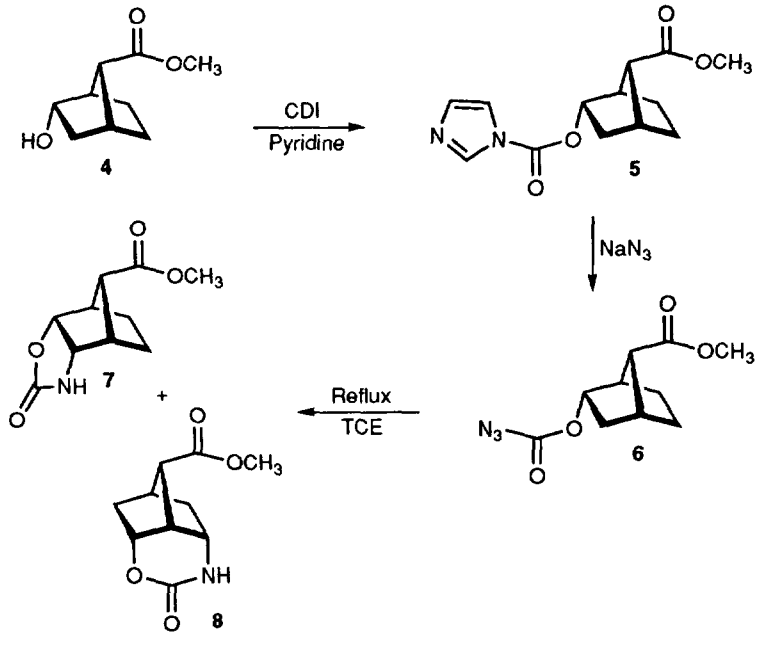


FIG. 2. Alignment of glycyl-glycine and glycyl-proline with analogue **1.**



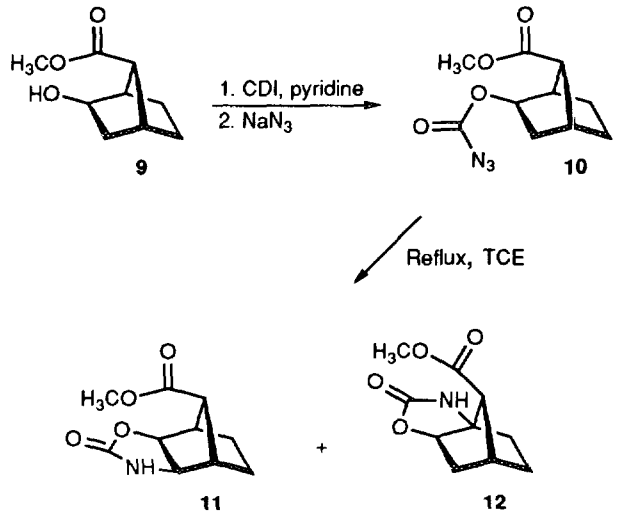
SCHEME 1

1,2-amino alcohol functionalities (*syn* versus *anti*), and in the relative orientation of the 1,2-amino alcohol functionality to the norbornyl ring (*endo* versus *exo*). The pivotal step in the preparation of these derivatives is the use of an intramolecular acyl nitrene-insertion reaction to introduce nitrogen functionality into the corresponding hydroxy methyl ester derivatives. Because of their reactive nature and the harsh conditions required for their formation, nitrenes have been used only occasionally in synthesis (*19*). Nonetheless, the results described here illustrate the utility of this reaction in the synthesis of dipeptide analogues. (We have also reported the use of this method to synthesize cyclobutyl and spiro[4.4]nonyl dipeptide analogues (*20*).)

Finally, the derivatives described here may also find applications as probes of structure–function relationships in peptides and proteins; in particular, the rigid norbornyl ring system may give access to constrained peptide geometries that currently are unavailable. When a transition-state mimic is not required, the unprotected hydroxyl group may be oxidized to a ketone, resulting in the conversion of a hydrogen-bond donor to a hydrogen-bond acceptor.

RESULTS AND DISCUSSION

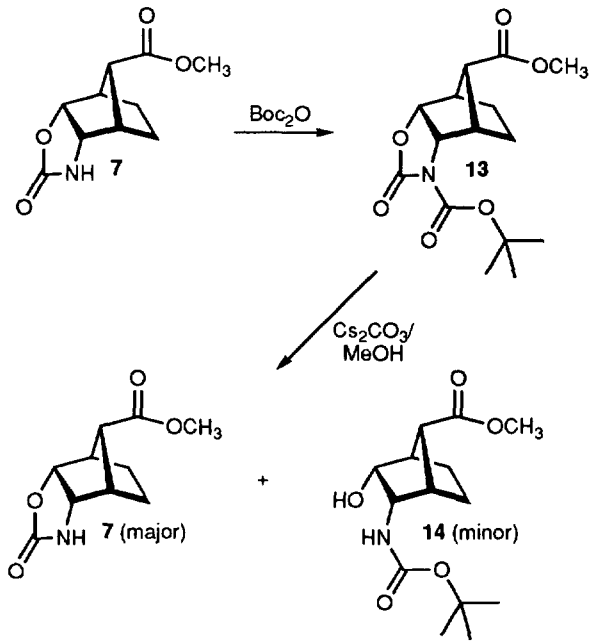
Preparation of azidocarbonate derivatives. As is outlined in Scheme 1, the norbornyl analogue **7** was synthesized, following the strategy of Lowe and Swain (*21*), from the corresponding hydroxy methyl ester **4** (*22*). The derivative **4** was treated



SCHEME 2

with carbonyldiimidazole (CDI) to give the carbonyl imidazole derivative **5,** which was reacted directly with NaN_3 to form the azidocarbonate derivative **6.** Both steps in this sequence were readily monitored by ^1H NMR, as each reaction is accompanied by a characteristic change in chemical shift of the carbinol proton: its resonance in the carbonyl imidazole derivative is approximately 0.8 ppm downfield from that in the reactant alcohol, and its resonance in the azidocarbonate derivative is approximately 0.3 ppm upfield relative to that in carbonyl imidazole derivative. Thermal decomposition, in refluxing 1,1,2,2-tetrachloroethane (TCE), of the azidocarbonate **6** yielded the cyclic carbamate **7** as the predominant product; a minor product was the six-membered cyclic carbamate **8.** In a similar fashion, the hydroxy ester precursor **9** (*23*), was elaborated into the azidocarbonate **10** (Scheme 2). Thermolysis yielded the two cyclic carbamates **11** and **12** in approximately equal yield. (Consistent with the geometrical constraints and with a previous study of the regiochemistry of carbene insertions in norbornyl derivatives (*24*), *exo*-insertion of the *endo*-azidocarbonate **6** or *endo*-insertion of the *exo*-azidocarbonate **10** was never observed.)

Thermolysis of azidocarbonates. Initial work in our laboratory on the azidocarbonate **6** and on azidocarbonates of two cyclobutyl derivatives (*20a*) involved thermolysis of a methylene chloride (CH_2Cl_2) solution in a sealed heavy-walled glass tube or in a Parr bomb reactor. Since dilute solutions of azide are required to avoid intermolecular insertion reactions, this method was limited in scale by the size of the commercially available apparatus. As both photolysis and thermolysis of the steroid derivative 3β-lanostenyl azidocarbonate had been reported to give the corresponding cyclic carbamate in similar yields (*25*), we investigated the photolysis reaction of azidocarbonate **10** as a means of increasing the yield of nitrene insertion.

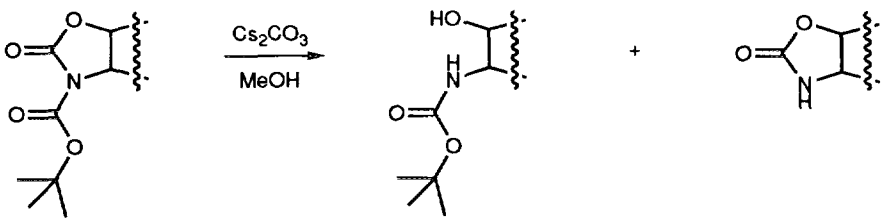


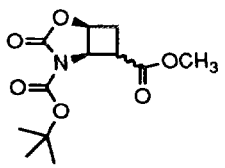
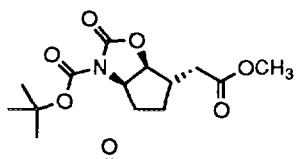
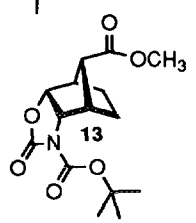
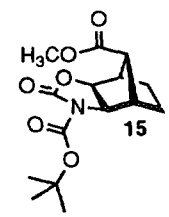
SCHEME 3

Unfortunately, the major product was the primary amino carbamate, presumably arising from proton abstraction from the solvent CH_2Cl_2, albeit a poor hydrogen donor. None of the desired cyclic carbamate was detected. Returning to the thermolysis reaction, we found that simply refluxing a dilute solution of an azidocarbonate in TCE (*19*), which has a boiling point of 147°C, for 30–60 min gave the desired product in comparable yield to high-pressure thermolysis without the limitation of scale. While these conditions are relatively harsh, closer investigation of the thermolysis of azidocarbonate **6** showed that the reaction was complete after 10 min; this shorter reaction time may be useful in the preparation of more labile compounds.

Cleavage of the cyclic carbamates. Prior to further elaboration, the carbamate derivatives had to be cleaved. Previously, with a series of cyclobutyl dipeptide analogues (*20a*), we reported cleavage of cyclic carbamates in high yield by the method of Ishizuka and Kunieda (*26a*). The carbamate was derivatized with di-*t*-butyloxycarbonyl anhydride (Boc_2O), followed by selective cleavage of the resulting dicarbamate with Cs_2CO_3. This method has the distinct advantage over direct carbamate hydrolysis in that mild conditions are employed. Furthermore, the amino functionality of the resulting dipeptide analogue is Boc-protected, facilitating elaboration into a longer peptide derivative, the next step in the synthesis. However, when we attempted to cleave the cyclic carbamate **7** using this procedure (Scheme 3), only a 26% yield of the desired ring-opened product **14** was obtained (the major product being regenerated starting carbamate **7**). More distressingly, as shown in

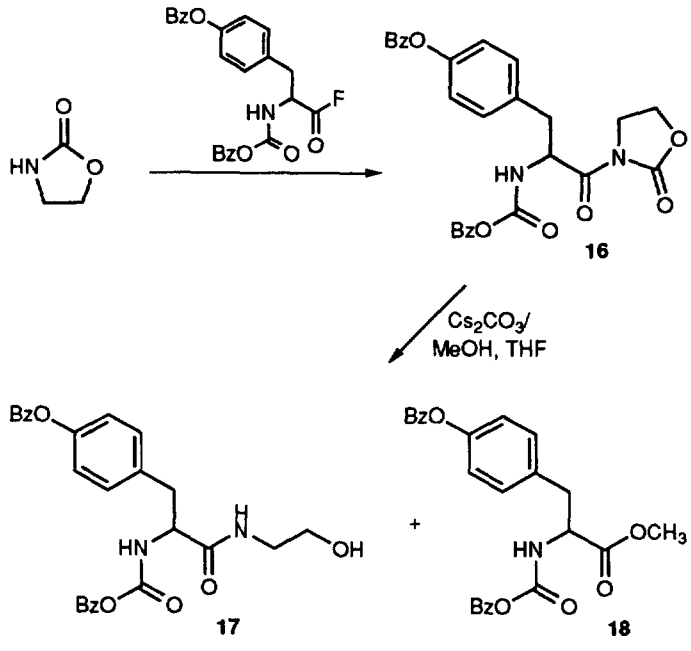
TABLE 1
Endocyclic versus Exocyclic Cleavage with Cs_2CO_3 in a Series of Dicarbamates



	100%[a]	0%[a]
	57%[b]	43%[b]
 13	37%	63%
 15	0%	100%

[a] Ref. (*20a*).
[b] D.P.W. and D.E.H., unpublished results.

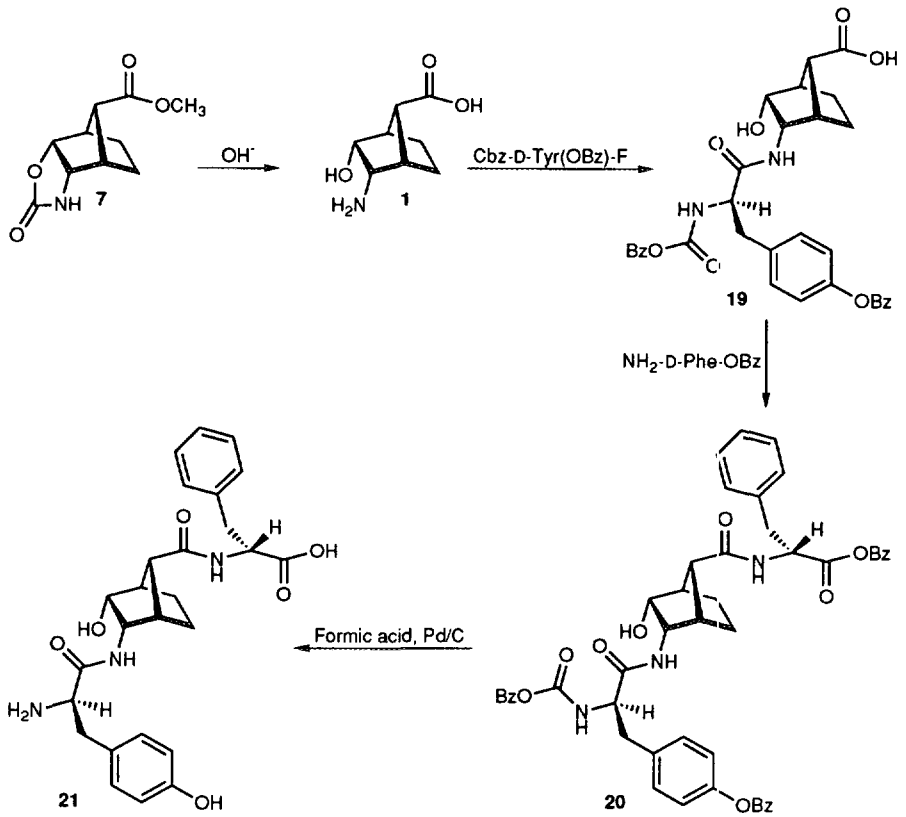
Table 1, with Boc-carbamate **15,** no ring-opened product was detected at all, the Cs_2CO_3 cleavage reaction yielding only starting carbamate. As is evident from the table, which also includes data obtained with a cyclobutyl and cyclopentyl derivative, Boc cleavage is favored over cyclic carbamate cleavage as steric crowding is in-



SCHEME 4

creased. Interestingly, blockage of one face of the cyclic carbamate apparently is sufficient to completely favor exocyclic carbamate cleavage. Regardless of the precise reasons, there is clearly a fine balance between endocyclic and exocyclic carbamate cleavage in sterically bulky derivatives, a balance that was not revealed in earlier studies of this reaction (*26*). Before turning to simple base-catalyzed hydrolysis of the carbamate, we explored a modification of Ishizuka and Kunieda's method: coupling of an amino acid residue to the carbamate, followed by selective cleavage. In a model study, Cbz-D-Tyr(Bzl)-F was coupled to oxazolidone to yield the product **16,** which was treated with Cs_2CO_3 in methanol (MeOH)/tetrahydrofuran (THF) (Scheme 4). However, the exocyclic cleavage again predominated, resulting in an approximately 1 to 5 ratio of the species **17** and **18.** (In a related system, Knapp *et al.* (*27*) found that benzoylcarbamates are also selectively hydrolyzed by LiOH at the benzoyl carbonyl group.)

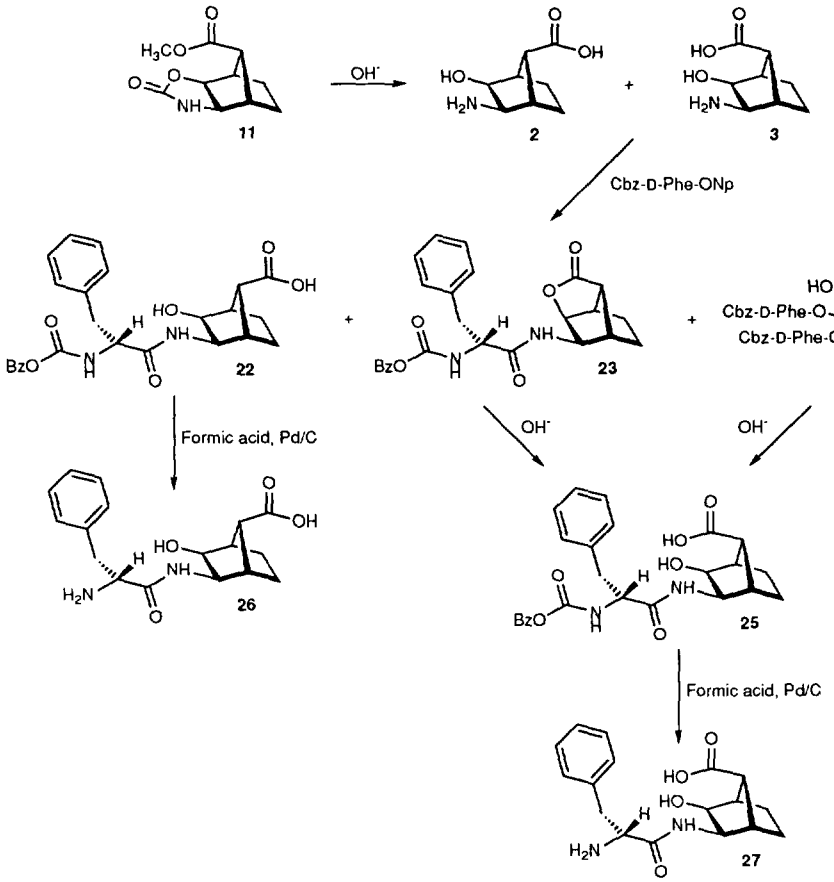
In view of the above results, we ultimately cleaved the carbamate esters in refluxing aqueous sodium hydroxide. As shown in Scheme 5, the carbamate ester **7** gave the expected dipeptide analogue **1.** As shown in Scheme 6, however, the carbamate ester **11** yielded both the anticipated *syn*-derivative **3** and the epimerized *anti*-derivative **2.** (Under identical conditions, no epimerization was observed during the hydrolysis of **7** above.) The observation of extensive epimerization in the hydrolysis of carbamate **11** illustrated the advantage of a mild method of carbamate



SCHEME 5

cleavage, such as the Cs_2CO_3/MeOH procedure described above. In this instance, however, the epimerization provided direct access to compound **2.**

Amino acid couplings. The dipeptide analogue **1** was coupled to Cbz-D-Tyr(Bzl)-F with triethylamine (TEA) in dimethylformamide (DMF) to yield the protected peptide derivative **19** (Scheme 5) as a mixture of diastereomers. (D-Amino acids were chosen so that the peptide derivatives would be more immunogenic. Clearly, if antibodies with activity against the corresponding peptides are obtained, derivatives incorporating only L-amino acids will be prepared and the experiment repeated.) $NaHCO_3$ in THF also provided effective conditions for the formation of coupled product **19** in high yield. However, a two-phase solvent system of aqueous bicarbonate and CH_2Cl_2 (1 : 1) gave only very low yields of **19,** presumably because of the low solubility of **1** in CH_2Cl_2. The coupling reaction was monitored by reverse-phase HPLC, which showed that no detectable coupling to the free hydroxyl group occurred in competition with the amino coupling. The tripeptide derivative **19** was then coupled using standard conditions (*28*) to D-phenylalanine benzyl ester to yield the derivative **20,** which upon deprotection yielded tetrapeptide analogue **21.**



SCHEME 6

In preparation for immunization, **21** was coupled to the heterobifunctional linker *N*-succinimidyl-6-maleimidocaproate, and the product conjugated to the carrier proteins bovine serum albumin and keyhole limpet hemocyanin.

The analogues **2** and **3,** which as discussed above were obtained as a mixture upon hydrolysis of the carbamate ester **11,** were elaborated only at the amino-terminus. Given the juxtaposition of the carboxylic acid functionality and the peptide bond mimicked in **3,** antibodies raised against this derivative may effect substrate-assisted exopeptide bond cleavage. That is, when bound to the antibody, the substrate may be held in a conformation that would allow its terminal carboxylate to participate in general base or nucleophilic catalysis. Such substrate-assisted catalysis cannot occur with antibodies elicited against the *anti*-derivative **2,** and these antibodies will provide an important control.

The mixture of **2** and **3** was directly coupled to Cbz-D-Phe-ONp in DMF. After workup and chromatography on silica gel, three products were obtained: the singly

coupled derivative **22,** the singly coupled lactone **23,** and the doubly coupled derivative **24,** each as a mixture of diastereomers. The stereochemistry of these derivatives was assigned as follows. The lactone **23,** which must be *syn,* was hydrolyzed under basic conditions to yield the hydroxy acid **25,** also presumably *syn.* Base-catalyzed hydrolysis of the ester functionality in the doubly coupled derivative **24** also yielded the *syn*-hydroxy acid **25.** The derivative **22** was therefore assigned as the *anti*-isomer. The derivatives **22** and **25** were deprotected by catalytic hydrogenation to yield the corresponding tripeptide derivatives **26** and **27.** The stereochemical assignment of these two materials was confirmed by difference NOE spectroscopy (*29*). For example, with the *syn*-isomer **27,** a large enhancement of the norbornyl 7-proton signal was observed upon irradiation of the *exo*-norbornyl 5- and 6-protons. This enhancement was not seen with the *anti*-isomer **26.** (The NOE intensities for the protected derivatives **22** and **25** in $CDCl_3$ or CD_3OD at 400 MHz were too small to be conclusive and were only slightly negative in ethylene glycol-d_6.) Finally, in the COSY spectrum of **27,** long-range "w-coupling" (*30*) between the norbornyl 7-proton and the *endo* 2- and 3-protons was observed, providing further evidence for the stereochemical assignments.

EXPERIMENTAL PROCEDURES

General experimental. Reagents were obtained from Aldrich or Sigma unless otherwise noted. Except where otherwise specified, all reactions were performed at room temperature. For all extractions, organic layers were dried over $MgSO_4$ and solvent was removed by evaporation under reduced pressure. Flash chromatographic separations were performed with Aldrich silica gel (200–400 mesh). Analytic reverse-phase HPLC analyses were performed on a Waters dual 501 system with a 150 × 4.6-mm econosphere C18 5U cartridge (Alltech) using water and acetonitrile mobile phases (Fisher) both containing 0.1% TFA (Pierce). Preparative HPLC was performed on a Waters 600E with a 250 × 22.5-mm econosil C18 10U column (Alltech) using the same mobile phases. Proton and carbon nuclear magnetic resonance spectra were recorded at 400 and 100 MHz, respectively, using a JEOL GSX-400 spectrometer. FAB mass spectral data were recorded at the Harvard Mass Spectrometry Facility (Cambridge, MA). Copies of all spectra are available from the authors.

Methyl endo-(2-azidoformyl)bicyclo[2.2.1]heptane-anti-7-carboxylate **(6).** To a stirred solution of *endo*-2-hydroxybicyclo[2.2.1]heptane-7-*anti*-methyl carboxylate **4** (0.58 g, 3.41 mmol) in benzene (10 ml), carbonyl diimidazole (CDI, 1.12 g, 6.91 mmol) and pyridine (0.34 ml, 4 mmol) were added. When the reaction was judged by ^1H NMR to be complete, the solvent was removed and the residue taken up in DMF (10 ml). To this solution was added NaN_3 (0.40 g, 6.15 mmol). The reaction mixture was then acidified to approximately pH 4 with concentrated HCl and stirred overnight. After removal of the solvent, the residue was slurried with EtOAc and the solution decanted from the remaining salts. This solution was washed with brine and dried, and the solvent was removed to afford the azidoformate **6** (0.61 g, 74%) as an amber oil. ^1H NMR ($CDCl_3$) δ 1.16–1.21 (m, 1 H), 1.34–1.42 (m, 1 H),

1.62–1.70 (m, 1 H), 1.76–1.86 (m, 2 H), 2.12–2.22 (m, 1 H), 2.52–2.56 (m, 2 H), 2.85–2.91 (m, 1 H), 3.67 (s, 3 H), 4.97–5.03 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 18.53, 26.92, 36.31, 38.52, 42.30, 51.00, 51.44, 77.68, 156.59, 171.16; IR ($CDCl_3$) cm^{-1} 3027, 2954, 2137, 1730, 1246; HRMS *m/z* 257.1261 $(M + NH_4)^+$ calcd for $C_{10}H_{17}N_4O_4$ 257.1250.

Methyl endo-(5-aza-4-oxo-3-oxo-3-oxa)tricyclo[5.2.1.0^{2,6}]decane-anti-10-carboxylate **(7)** *and methyl endo-(8-aza-7-oxo-6-oxa)tricyclo[3.3.1.1^{3,9}]decane-anti-10-carboxylate* **(8).** To a refluxing solution of tetrachloroethane (TCE, 1.5 liters) was added azidoformate **6** (500 mg, 2.09 mmol) dissolved in a small volume of TCE. The solution was refluxed for 30 min and allowed to cool, and the solvent was removed to yield a dark brown residue (620 mg). This crude material was purified by flash chromatography (eluting with EtOAc) to yield carbamate **7** (186 mg; 42%) and carbamate **8** (46.5 mg, 10.5%), each as a white solid. For carbamate **7:** ^{1}H NMR ($CDCl_3$) δ 1.64–1.82 (m, 4 H), 2.54–2.56 (m, 1 H), 2.68–2.71 (m, 1 H), 2.87–2.91 (m, 1 H), 3.71 (s, 3 H), 3.98–4.02 (dd, J = 10.2 and 4.2 Hz, 1 H), 4.79–4.83 (dd, J = 10.1 and 4.6 Hz, 1 H), 6.38 (broad s, 1 H); ^{13}C NMR ($CDCl_3$) δ 18.82, 19.90, 43.30, 50.42, 52.00, 54.96, 78.63, 159.66, 171,06; HRMS *m/z* $(M + H)^+$ 212.0919, calcd for $C_{10}H_{14}NO_4$ 212.0923. For carbamate **8:** ^{1}H NMR ($CDCl_3$) δ 1.40 (d, J = 13.4 Hz, 1 H), 1.48 (dd, J = 13.4 and 4.2 Hz, 1 H), 2.17–2.24 (m, 1 H), 3.34–2.41 (m, 1 H), 2.56–2.58 (m, 1 H), 2.66–2.26 (m, 2 H), 3.71 (s, 3 H), 4.12–4.17 (m, 1 H), 4.77–4.82 (m, 1 H), 5.86 (broad s, 1 H); ^{13}C NMR ($CDCl_3$) δ 37.36, 37.58, 38.13, 38.96, 48.26, 52.02, 52.60, 75.56, 151.22, 171.22; HRMS *m/z* 211.0849 $(M)^+$, calcd for $C_{10}H_{13}NO_4$ 211.0845.

Methyl exo-(2-azidoformyl)bicyclo[2.2.1]heptane-syn-7-carboxylate **(10).** Hydroxy ester **9** was subjected to the procedure described for hydroxy ester **4** except for the following. After the azidoformylation was judged to be complete by ^{1}H NMR, the solvent was removed. The residue remaining was taken up in EtOAc, dried, and then filtered over silica gel. Removal of the solvent then afforded the azide **10** (386 mg, 68%). ^{1}H NMR ($CDCl_3$) δ 1.13–1.27 (m, 2 H), 1.54–1.61 (m, 1 H), 1.69–1.79 (m, 1 H), 1.81–1.85 (m, 1 H), 2.00–2.06 (m, 1 H), 2.48 (s, 1 H), 2.63 (t, J = 4.4 Hz, 1 H), 2.81 (d, J = 4.9 Hz, 1 H), 3.68 (s, 3 H), 4.69 (dd, J = 7.33 and 2.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 24.44, 27.64, 36.99, 44.77, 51.47, 52.36, 81.63, 156.59, 172.43; HRMS *m/z* 239.0903 $(M)^+$, calcd for $C_{10}H_{13}N_3O_4$ 239.0906.

Methyl exo-(5-aza-4-oxo-3-oxa)tricyclo[5.2.1.0^{2,6}]decane-syn-10-carboxylate **(11)** *and methyl exo-(2-aza-3-oxo-4-oxa)tricyclo[5.2.1.0^{1,5}]decane-syn-10-carboxylate* **(12).** The procedure reported for carbamate **7** was employed. Thermolysis of azidocarbonate **10** (386 mg, 1.83 mmol) in refluxing TCE (1.21) followed by flash chromatography on silica gel (EtOAc) yielded carbamates **11** (109 mg, 32%) and **12** (130 mg, 38%). For carbamate **11:** ^{1}H NMR ($CDCl_3$) δ 1.17 (d, J = 8.3 Hz, 2 H), 1.6–1.75 (m, 2 H), 2.63 (s, 1 H), 2.80 (d, J = 3.2 Hz, 1 H), 2.96 (d, J = 3.7, 1 H), 3.71 (s, 3 H), 3.83 (d, J = 7.1, 1 H), 4.57 (d, J = 7.1, 1 H), 6.23 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 23.81, 24.52, 42.19, 42.88, 51.29, 52.04, 59.93, 82.41, 159.24, 171.66; COSY and NOESY spectra were consistent with the structure of **11;** HRMS *m/z* 234.0751 $(M + Na)^+$, calcd for $C_{10}H_{13}NO_4Na$ 234.0743. For carbamate **12:** ^{1}H NMR ($CDCl_3$) δ 1.34–1.47 (m, 2 H), 1.76–1.83 (m, 1 H), 1.93–2.02 (m, 2 H), 2.34–2.40 (m, 1 H), 2.51 (s, 1 H), 2.61 (t, J = 3.7 Hz, 1 H), 3.71 (s, 3 H), 4.30 (dd, J = 7.4 and 4.0 Hz,

1 H), 6.06 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 25.36, 28.27, 35.73, 36.34, 51.94, 52.78, 70.78, 84.46, 159.82, 170.22; HRMS *m/z* 211.0841 $(M)^+$, calcd for $C_{10}H_{13}NO_4$ 211.0845.

Methyl N-(t-butoxycarbonyl)-endo-(5-aza-4-oxo-3-oxa)tricyclo[5.2.1.0^{2,6}]decane-anti-10-carboxylate ***(13).*** To a stirred solution of carbamate **7** (105 mg, 0.497 mmol) in THF (3 ml) was added di-*t*-butyl dicarbonate (220 mg, 1.01 mmol), 4-dimethylaminopyridine (22 mg, 0.142 mmol), and TEA (74 μl, 0.531 mmol). The reaction mixture was stirred overnight and the solvent was removed. The resultant solid was dissolved in EtOAc (75 ml), washed with 10% citric acid in brine (10 ml), followed by portions of saturated $NaHCO_3$ in brine (10 ml), until the washes remained basic. The solvent was removed to yield the Boc-carbamate **13** (136 mg, 88%) as a slightly yellow solid. ^{1}H NMR ($CDCl_3$) δ 1.54 (s, 9 H), 1.57–1.61 (m, 1 H), 1.68–1.76 (m, 3 H), 2.60 (s, 1 H), 2.88–2.91 (m, 1 H), 2.94–2.97 (m, 1 H), 3.72 (s, 3 H), 4.26 (ddd, J = 10.3, 4.0, and 0.7 Hz, 1 H), 4.63–4.68 (ddd, J = 10.3, 4.5, and 0.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 18.58, 19.82, 27.98, 43.06, 43.17, 50.11, 52.07, 57.88, 74.48, 83.93, 149.20, 152.57, 170.72, HRMS *m/z* 334.1264 $(M + Na)^+$, calcd for $C_{15}H_{21}NO_6Na$ 334.1267.

Methyl N-(t-butyloxycarbonyl)-endo-2-hydroxy-3-amino)bicyclo[2.2.1]heptane-anti-7-carboxylate ***(14).*** To a solution of Boc-carbamate **13** (290 mg, 0.932 mmol) in MeOH (7 ml) was added Cs_2CO_3 (61 mg, 0.186 mmol), and the reaction mixture was stirred overnight. The two products observed by TLC were separated by flash chromatography (EtOAc) to yield the desired product **14** (69.5 mg, 26%) as a slightly yellow solid and regenerated cyclic carbamate **7** (86.2 mg, 44%). ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9 H), 1.48–1.58 (m, 2 H), 1.83–1.95 (m, 2 H), 2.49 (s, 1 H), 2.65 (*app.* t, J = 3.9 Hz, 1 H), 2.72 (s, 1 H), 3.67 (s, 3 H), 3.73–3.80 (m, 1 H), 4.16–4.23 (m, 1 H), 5.14 (d, J = 4.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 17.88, 19.40, 28.23, 28.35, 43.30, 44.85, 48.85, 51.45, 51.65, 68.12, 156.08, 172.21; HRMS *m/z* 285.1568 $(M)^+$, calcd for $C_{14}H_{23}NO_5$ 285.1576.

Methyl N-(t-butoxycarbonyl)-exo-(5-aza-4-oxo-3-oxa)tricyclo[5.2.1.0^{2,6}]decane-syn-10-carboxylate ***(15).*** To a solution of carbamate **11** (109 mg, 0.516 mmol) in THF (8 ml) was added di-*t*-butyl dicarbonate (169 mg, 0.770 mmol), 4-dimethylaminopyridine (126 mg, 1.03 mmol), and TEA (180 μl, 1.78 mmol). The reaction mixture was stirred overnight and worked up as reported for Boc-carbamate **13** to yield **15** (239 mg, 93%). ^{1}H NMR ($CDCl_3$) δ 1.21–1.28 (m, 2 H), 1.57 (s, 9 H), 1.70–1.76 (m, 2 H), 2.62 (s, 1 H), 3.00 (d, J = 3.9 Hz, 1 H), 3.14 (d, J = 3.7 Hz, 1 H), 3.67 (s, 3 H), 4.12 (d, J = 7.1 Hz, 1 H), 4.44 (d, J = 7.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 23.4, 24.7, 27.9, 41.2, 42.9, 51.1, 52.3, 62.5, 78.6, 83.4, 149.1, 151.6, 171.0; HRMS *m/z* 334.1263 $(M + Na)^+$, calcd for $C_{15}H_{22}NO_6Na$ 334.1267.

N-[(N-Carbobenzyloxy-O-benzyl)-D-tyrosyl]-2-oxazolidone ***(16).*** To a solution of 2-oxazolidone (25 mg, 0.29 mmol) in THF (3 ml) was added Cbz-D-Tyr(OBz)-F (*20b*) (230 mg, 0.57 mmol), TEA (44 μl, 0.32 mmol), and DMAP (7.0 mg, 0.057 mmol), and the reaction mixture was stirred overnight. The solvent was dried and removed, and the product was recrystallized from EtOAc to yield **16** (100 mg, 74%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 2.73–2.80 (m, 1 H), 3.12–3.18 (m, 1 H), 3.88–3.96 (m, 1 H), 4.02–4.10 (m, 1 H), 4.33–4.46 (m, 2 H), 5.04 (s, 4 H), 5.30 (d, J = 7.7 Hz, 1 H), 5.70–5.76 (m, 1 H), 6.87–6.91 (d, J = 8.3 Hz, 2 H), 7.13 (d, J = 8.3 Hz, 2 H), 7.28–7.46 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 37.68, 42.57, 54.50, 62.53,

67.03, 70.01, 114.90, 127.41, 127.82, 127.98, 128.17, 128.21, 128.50, 128.63, 130.40, 136.31, 137.01, 152.89, 155.78, 158.00, 172.43; HRMS *m/z* (M + Na)$^+$ 497.1702, calcd for $C_{27}H_{26}O_6N_2Na$ 497.1689.

N-[(N-Carbobenzyloxy-O-benzyl)-D-tyrosyl]-2-ethanolamine **(17)** *and (N-carbobenzyloxy-O-benzyl)-D-tyrosyl-methyl ester* **(18).** To a solution of **16** (20 mg, 0.042 mmol) in methanol (7 ml) and THF (8 ml) was added Cs_2CO_3 (3.5 mg, 0.011 mmol). The reaction mixture was stirred overnight, and the solvent removed. The resultant solid was taken up in EtOAc, and the solution washed with brine and dried. Removal of solvent gave a crude white solid, which after flash chromatography (EtOAc), afforded the alcohol **17** (2.7 mg, 14%) and the methyl ester **18** (10.7 mg, 62%). For alcohol **17:** ^{1}H NMR ($CDCl_3$) δ 2.92–3.12 (m, 2 H), 3.24 (m, 2 H), 3.50–3.58 (m, 2 H), 4.24–4.32 (m, 1 H) 5.04 (s, 2 H), 5.10 (s, 2 H), 5.24–5.30 (m, 1 H), 5.96 (d, J = 5.3 Hz, 1 H), 6.90 (d, J = 8.3 Hz, 2 H), 7.10 (d, J = 8.3 Hz, 2 H), 7.30–7.44 (m, 10 H). ^{13}C NMR ($CDCl_3$) δ 37.83, 41.75, 42.25, 56.67, 61.85, 67.18, 69.98, 115.14, 115.32, 127.43, 127.46, 128.01, 128.12, 128.30, 128.48, 128.56, 128.59, 130.32, 136.00, 136.84, 157.92, 171.69. HRMS *m/z* 471.1909 (M + Na)$^+$, calcd for $C_{26}H_{28}O_5N_2Na$ 471.1896. For methyl ester **18:** ^{1}H NMR ($CDCl_3$) δ 3.00–3.11 (m, 2 H), 3.70 (s, 3 H), 4.60–4.65 (m, 1 H), 5.04 (s, 2 H), 5.10 (s, 2 H), 5.16–5.22 (m, 1 H), 6.88 (d, J = 8.2 Hz, 2 H), 7.02 (d, J = 8.2 Hz, 2 H), 7.30–7.44 (m, 10 H). ^{13}C NMR ($CDCl_3$) δ 37.46, 52.38, 54.90, 66.90, 70.02, 115.04, 127.42, 127.86, 127.91, 128.11, 128.23, 128.53, 128.60, 130.31, 136.19, 136.97, 155.60, 157.92, 172.05. HRMS (M + Na)$^+$ 442.1638, calcd for $C_{25}H_{25}O_5NNa$ 442.1630.

endo-(2-Hydroxy-3-amino)bicyclo[2.2.1]heptane-anti-7-carboxylic acid **(1).** Carbamate **7** (200 mg, 0.948 mmol) was dissolved in aqueous NaOH (40 ml, 0.95%), and the solution stirred at 75°C for 15 h. The solution was allowed to cool and then acidified to approximately pH 2 with 1 M HCl. Lyophilization yielded a white solid composed of the dipeptide analogue **1** and NaCl. ^{1}H NMR (D_2O) δ 1.42–1.56 (m, 2 H), 1.63–1.73 (m, 1 H), 1.76–1.85 (m, 1 H), 2.52 (*app.* t, J = 4.0 Hz, 1 H), 2.56 (*app.* t, J = 1.5 Hz, 1 H), 2.61 (*app.* t, J = 4.3 Hz, 1 H), 3.52 (ddd, J = 9.4, 4.5, 1.5 Hz, 1 H), 4.23 (ddd, J = 9.4, 4.4, 1.0 Hz, 1 H); ^{13}C NMR (D_2O) δ 18.36, 19.95, 42.73, 45.25, 52.03, 52.36, 67.49, 179.71; HRMS *m/z* 172.0972 (M + H)$^+$, calcd for $C_8H_{14}NO_3$ 172.0974.

exo-(2-Hydroxy-3-amino)bicyclo[2.2.1]heptane-anti-7-carboxylic acid **(2)** and *exo-(2-hydroxy-3-amino)bicyclo[2.2.1]heptane-syn-7-carboxylic acid* **(3).** Carbamate **11** (100 mg, 0.47 mmol) was dissolved in aqueous NaOH (20 ml, 0.69%) and heated to reflux for 7 h. The solution was allowed to cool and was then acidified to pH 1.5 with 1 M HCl. Lyophilization yielded a mixture of the *anti-* and *syn-*derivatives **2** and **3,** respectively, and NaCl. ^{1}H NMR (D_2O) δ 1.21–1.38 (m, 4 H), 1.61–1.92 (m, 4 H), 2.46 (d, J = 3.9 Hz, 1 H), 2.55 (d, J = 3.4 Hz, 1 H), 2.66 (d, J = 3.7 Hz, 1 H), 2.71 (s, 2 H), 3.23 (s, 1 H), 3.25 (d, J = 6.6 Hz, 1 H), 3.37 (d, J = 6.4 Hz, 1 H), 3.96 (d, J = 6.6 Hz, 1 H), 4.08 (d, J = 6.3, 1 H); ^{13}C NMR (D_2O) δ 17.68, 22.17, 23.67, 25.22, 27.00, 41.58, 42.77, 46.68, 49.01, 49.41, 51.82, 53.11, 56.76, 56.92, 58.31, 67.40, 72.60, 73.94, 177.14, 179.95; HRMS *m/z* 172.0977 (M + H)$^+$, calcd for $C_8H_{14}NO_3$ 172.0974.

N-[(N-Carbobenzyloxy-O-benzyl)-D-tyrosyl]-endo-(2-hydroxy-3-amino)bicyclo [2.2.1]heptane-anti-7-carboxylic acid **(19).** To a solution of derivative **1** (200 mg,

0.948 mmol) in DMF (60 ml) was added a Cbz-D-Tyr(OBz)-F (*20b*) (450 mg, 1.100 mmol). The pH was then raised to between 9 and 10 with TEA, and the reaction mixture was allowed to stir overnight. The solvent was removed, and the resultant solid taken up in EtOAc. This solution was washed with 5% HCl, and the crude product was purified by preparative HPLC using a linear gradient of 50–100% acetonitrile in 40 min to yield the protected tripeptide analogue **19** (391 mg, 74%) as a white gum composed of a 1:1 mixture of diastereomers. ^{1}H NMR ($CDCl_3$) δ 1.42–1.74 (m, 4 H), 2.43 (s, 1/2 H), 2.47 (s, 1/2 H), 2.53–2.55 (m, 1/2 H), 2.58–2.64 (m, 1 H), 2.69–2.71 (m, 1/2 H), 2.82–3.17 (m, 2 H), 3.73–3.83 (m, 1 H), 3.88–3.96 (m, 1/2 H), 4.06–4.14 (m, 1/2 H), 4.32–4.37 (m, 1 H), 5.02–5.08 (m, 4 H), 5.08–5.11 (m, 1 H), 5.45–5.50 (m, 1 H), 6.10 (d, J = 5.86 Hz, 1/2 H), 6.29 (d, J = 7.7 Hz, 1 H), 6.88–7.91 (m, 2 H), 7.09–7.12 (m, 2 H), 7.32–7.43 (m, 10 H) ^{13}C NMR ($CDCl_3$) δ 17.83, 17.95, 19.34, 37.95, 42.90, 42.94, 44.48, 44.54, 48.85, 48.92, 50.42, 50.50, 56.52, 56.56, 66.97, 67.05, 67.76, 67.86, 69.85, 69.89, 115.00, 127.36, 127.83, 127.87, 127.96, 128.11, 128.16, 128.46, 128.50, 128.56, 128.69, 130.26, 130.38, 136.02, 136.83, 136.91, 156.11, 156.41, 157.64, 157.76, 171.68, 172.21, 175.68, 175.74; HRMS *m/z* 559.2451 $(M + H)^+$, calcd for $C_{32}H_{35}N_2O_7$ 559.2444.

N-[(N-Carbobenzyloxy-O-benzyl)-D-tyrosyl]-endo-(2-hydroxy-3-amino)bicyclo [2.2.1]heptane-anti-7-carboxoyl-D-phenylalanine benzyl ester **(20).** To a solution of tripeptide analogue **19** (179 mg, 0.320 mmol) in THF (30 ml) was added NH_2-D-Phe-OBz [BACHEM] (148 mg, 0.346 mmol) followed by EDC (74 mg, 0.390 mmol), TEA (70 μl, 0.950 mmol), and HOBt (8 mg, 0.059 mmol). The reaction mixture was stirred overnight, and then the solvent was removed. The residue was taken up in EtOAc, and this solution washed with brine. The crude product was purified by flash chromatography (1:1 EtOAc/hexanes, 5% AcOH) to yield **20** (226 mg, 89%) as a white foamy gum composed of a 1:1 mixture of diastereomers. ^{1}H NMR ($CDCl_3$) δ 0.94–1.44 (m, 2 H), 1.56–1.82 (m, 2 H), 2.26 (s, 1/2 H), 2.30 (s, 1/2 H), 2.44 (s, 1/2 H), 2.48 (s, 1/2 H), 2.52 (*app.* t, J = 3.91 Hz, 1/2 H), 2.56 (*app.* t, J = 3.78 Hz, 1/2 H), 2.86–3.17 (m, 4 H), 3.68–3.83 (m, 1 H), 3.83–3.90 (m, 1/2 H), 3.97–4.04 (m, 1/2 H), 4.33–4.42 (m, 1 H), 4.87–4.95 (m, 1 H), 5.00–5.18 (m, 6 H), 5.45 (d, J = 7.57 Hz, 1/2 H), 5.54 (d, J = 7.57 Hz, 1/2 H), 5.94 (d, J = 8.06 Hz, 1/2 H), 6.00 (d, J = 7.81 Hz, 1/2 H), 6.21 (d, J = 5.61 Hz, 1/2 H), 6.45 (d, J = 6.35 Hz, 1/2 H), 6.86–6.90 (m, 2 H), 6.97–7.02 (m, 2 H), 7.07–7.11 (m, 2 H), 7.20–7.44 (m, 18 H); ^{13}C NMR ($CDCl_3$) δ 17.70, 17.79, 19.30, 37.70, 37.83, 37.87, 38.20, 42.98, 43.17, 44.58, 49.92, 49.99, 50.57, 50.69, 52.76, 66.75, 67.04, 67.29, 67.78, 67.83, 69.88, 69.96, 115.08, 126.80, 127.11, 127.40, 127.91, 127.98, 128.01, 128.09, 128.17, 128.21, 128.37, 128.40, 128.50, 128.53, 128.56, 128.59, 129.09, 129.27, 130.24, 130.42, 134.97, 135.00, 135.47, 135.63, 135.66, 136.09, 136.13, 136.84, 136.93, 136.96, 157.69, 157.84, 170.22, 170.32, 170.96, 171.29, 171.38, 171.50; HRMS *m/z* 796.3593 $(M + H)^+$, calcd for $C_{48}H_{50}N_3O_8$ 796.3598.

N-(D-Tyrosyl)-endo-(2-hydroxy-3-amino)bicyclo[2.2.1]heptane-anti-7-carboxoyl-D-phenylalanine **(21).** To a solution of the protected tetrapeptide analogue **20** in 3 ml of a THF/formic acid solution (10:1 w/w) was added a suspension of Pd black (50 mg) in water (3 ml). Analytical HPLC revealed that after 15 min the reaction had not gone to completion; after 2 h, however, only the two fully deprotected diastereomeric products were present. The reaction mixture was filtered through

glass wool, and the solvent was removed to give the product **21** in quantitative yield. (This reaction was performed three times, and on one occasion a side product was obtained in addition to the desired deprotected product. Although the formic acid deprotection reaction yielded only the expected diastereomeric products as judged by HPLC, upon removal of the solvent, two additional products were observed. These new products were identified as the diastereomeric tyrosyl formate esters.) For tetrapeptide derivative **21** (as a 1 : 1 mixture of diastereomers); ^{1}H NMR (CD_3OD) δ 0.90–1.10 (m, 1 1/2 H), 1.26–1.42 (m, 1 1/2 H), 1.61–1.78 (m, 1 H), 2.39–2.48 (m, 2 1/2 H), 2.59–2.63 (m, 1/2 H), 2.90–3.04 (m, 2 1/2 H), 3.11–3.16 (m, 1/2 H), 3.22–3.27 (m, 1 H), 3.85 (dd, J = 9.5, 4.2 Hz), 3.93 (dd, J = 9.2, 3.3 Hz), 4.03–4.10 (m, 1 H), 4.16–4.21 (m, 1 H), 4.63–4.69 (m, 1 H), 6.74–6.79 (m, 2 H), 7.09–7.14 (m, 2 H), 7.16–7.34 (m, 5 H); ^{13}C NMR (CD_3OD) δ 18.69, 18.75, 20.40, 20.43, 38.00, 38.10, 38.44, 38.47, 44.40, 44.66, 46.13, 46.55, 51.00, 52.31, 55.19, 55.73, 66.83, 68.73, 68.83, 116.85, 116.90, 126.12, 126.22, 127.64, 127.67, 128.45, 129.37, 129.40, 129.98, 130.24, 130.43, 131.52, 131.58, 138.93, 158.21, 166.19, 169.85, 169.98, 173.42, HRMS m/z 504.2094 (M + Na)$^+$, calcd for $C_{26}H_{31}N_3O_6Na$ 504.2111.

N-[N-(Carbobenzyloxy)-D-phenylalanyl]-exo-(2-hydroxy-3-amino)bicyclo[2.2.1] heptane-anti-7-carboxylic acid **(22)**, *N-[N-(Carbobenzyloxy)-D-phenylalanyl]-exo-6-amino-4-oxa-3-oxotricyclo[4.3.0.0^{2,7}]nonane* **(23)**, *and O,N-Di-[N-(carbobenzyloxy)-D-phenylalanyl]-exo-(2-hydroxy-3-amino)bicyclo[2.2.1]heptane-syn-7-carboxylic acid* **(24)**. To the lyophilized mixture of derivatives **2** and **3** was added DMF (10 ml) and TEA (80 μl, 0.58 mmol), followed by Cbz-D-Phe-ONp (245 mg, 0.58 mmol). The reaction mixture was allowed to stir for 2 days. The solvent was removed, and brine (15 ml) was added to the resultant solid. The solution acidified to pH 1.5 with 1 M HCl and then extracted with EtOAc (3 × 25 ml). TLC (1 : 3 EtOAc : hexanes containing 5% acetic acid) showed a highly impure mixture. Flash chromatography in the same solvent system, followed by preparative HPLC using a gradient of 30% CH_3CN to 100% CH_3CN in 30 min, yielded the compounds **22, 23,** and **24,** each as a mixture of diastereomers (30% overall; 3 : 1 : 1, respectively). For hydroxy acid **22:** ^{1}H NMR ($CDCl_3$) δ 1.10 (m, 1 H), 1.23 (m, 1 H), 1.73 (m, 2 H), 2.23 (s, 1 H), 2.36, (s, 1 H), 2.54, (s, 1 H), 2.95–3.07 (m, 2 H), 3.63 (t, J = 6.0 Hz, 1 H), 3.79 (d, J = 6.4, 1 H), 4.40–4.46 (m, 1 H), 4.99–5.04 (m, 2 H), 5.83 (d, J = 7.6, 1 H), 6.72 (d, J = 5.6, 1 H), 7.17–7.35 (m, 10 H). ^{13}C NMR ($CDCl_3$) δ 22.55, 24.78, 29.69, 38.97, 43.88, 46.01, 48.63, 50.82, 56.40, 56.51, 67.13, 73.92, 77.61, 127.06, 128.00, 128.19, 128.51, 128.71, 129.24, 135.97, 136.29, 156.37, 171.34, 176.62. For lactone **23** (mixture of diastereomers, 3 : 1): ^{1}H NMR ($CDCl_3$) δ 1.43–1.51 (m, 1 H), 1.68–1.76 (m, 2 H), 1.91–1.97 (m, 1 H), 2.17 (broad s, 1/4 H), 2.28 (broad s, 3/4 H), 2.54 (s, 1/4 H), 2.59 (s, 3/4 H), 2.95 (d, J = 2.0 Hz, 1 H), 2.99–3.07 (m, 3 H), 3.80 (d, J = 2.2 Hz, 1 H), 3.77–3.80 (m, 1 H) 4.35–4.38 (m, 1 H), 4.43 (s, 1 H), 4.60 (broad s, 1 H), 5.03–5.11 (m, 2 H), 5.26 (broad s, 1 H), 6.14 (broad s, 1 H), 7.16 (d, J = 6.8, 1 H), 7.23–7.38 (m, 9 H). ^{13}C NMR ($CDCl_3$) δ 19.58, 31.25, 31.32, 38.67. 45.59, 45.75, 51.07, 52.08, 52.12, 53.94, 54.01, 56.10, 67.10, 67.15, 76.84, 77.32, 82.15, 82.18, 127.09, 127.17, 128.01, 128.09, 128.48, 128.72, 129.13, 136.00, 136.10, 136.18, 155.85, 171.59, 175.97, 176.16, 176.20; HRMS m/z 457.1755 (M + Na)$^+$, calcd for $C_{25}H_{26}N_2O_5Na$ 457.1740. For doubly coupled derivative **24:** ^{1}H NMR ($CDCl_3$) δ 1.23–1.36 (m, 4 H), 1.47–1.51 (m, 2 H), 1.68–1.75 (m, 2 H), 2.23 (s, 1

H), 2.45 (s, 2 H), 2.61 (d, J = 4.4 Hz, 2 H), 2.89 (dd, J = 13.7 and 9.8 Hz, 1 H), 3.00–3.13 (m, 4 H), 3.33–3.26 (m, 2 H), 4.31–4.35 (m, 1 H), 4.46–4.52 (m, 3 H), 4.81–4.84 (m, 2 H), 4.95–5.07 (m, 6 H), 5.46 (d, J = 8.8 Hz, 1 H), 6.28 (d, J = 8.8, 1 H), 7.09–7.30 40 H); ^{13}C NMR ($CDCl_3$) δ 23.76, 23.97, 27.00, 27.12, 27.30, 36.71, 37.08, 37.31, 38.53, 42.43, 45.48, 46.79, 52.67, 52.74, 54.55, 54.80, 55.64, 55.72, 57.04, 57.83, 66.71, 67.02, 67.59, 68.41, 76.35, 77.95, 126.54, 126.69, 126.95, 126.98, 127.12, 127.24, 127.30, 127.75, 127.80, 127.96, 128.04, 128.22, 128.34, 128.38, 128.43, 128.50, 128.67, 128.74, 128.90, 129.00, 129.08, 129.18, 129.35, 129.47, 135.71, 135.83, 135.97, 136.07, 136.31, 136.57, 137.15, 137.33, 156.16, 156.27, 156.47, 156.58, 156.64, 156.85, 158.03, 169.80, 169.95, 170.32, 170.80, 175.21, 175.28; HRMS (M + Na)$^+$ m/z 756.2903, calcd for $C_{42}H_{43}N_3O_9Na$ 756.2897.

N-[N-(Carbobenzyloxy)-D-phenylalanyl]-exo-(2-hydroxy-3-amino)bicyclo[2.2.1]heptane-syn-7-carboxylic acid **(25).** To a stirred solution of 2 N NaOH/1,4-dioxane (10 ml, 1.75 : 1) was added doubly coupled carboxylic acid **24** (114 mg, 0.155 mmol). The reaction mixture was allowed to stir for 20 min, at which point it was acidified to pH 1.5 with 1 M HCl and lyophylized. The resultant solid was slurried in $CHCl_3$, and the solution decanted. Purification by HPLC yielded the protected tripeptide derivative **25** (33 mg, 67%) as a 1 : 1 mixture of diastereomers: ^{1}H NMR (CD_3OD) δ 0.96–0.99 (m, 1 H), 1.24–1.35, (m, 1 H), 1.56–1.65 (m, 1 H), 1.72–1.79 (m, 1 H), 2.28 (d, J = 2.7 Hz, 1/2 H), 2.46 (d, J = 2.4 Hz, 1/2 H), 2.54 (s, 1/2 H), 2.57 (s, 1/2 H), 2.65 (s, 1/2 H), 2.66 (s, 1/2 H), 2.85–2.91 (m, 1 H), 3.26 (d, J = 4.9 Hz, 1/2 H), 3.28 (d, J = 4.6 Hz, 1/2 H), 3.92–3.98 (m, 2 H), 4.31–4.38 (m, 1 H), 4.97–5.10 (m, 2 H), 7.23–7.36 (m, 10 H); ^{13}C NMR (CD_3OD) δ 20.09, 25.74, 29.08, 31.47, 39.53, 45.00, 58.25, 58.37, 59.42, 59.55, 68.42, 76.91, 77.09, 128.47, 129.33, 129.41, 129.62, 130.20, 130.25, 131.04, 131.12, 138.94, 138.97, 139.79, 139.91, 159.32, 159.25, 174.19, 174.04. HRMS (M + Na)$^+$ m/z 475.1825, calcd for $C_{25}H_{28}N_2O_6Na$ 475.1845.

N-(D-Phenylalanyl)-exo-(2-hydroxy-3-amino)bicyclo[2.2.1]heptane-anti-7-carboxylic acid **(26).** To a stirred solution of the protected tripeptide derivative **22** (49 mg, 0.108 mmol) in THF with 10% formic acid (2 ml) was added Pd/black (50 mg) suspended in H_2O (1.5 ml). The reaction mixture was allowed to stir for 20 min and filtered, and the solvent was removed. Purification by HPLC yielded the tripeptide derivative **26** (32 mg, 92%) as a slightly yellow oil. Isomer from first fraction: ^{1}H NMR (CD_3OD) δ 1.16–1.28 (m, 2 H), 1.69–1.79 (m, 2 H), 2.18 (d, J = 2.4 Hz, 1 H), 2.29 (d, J = 3.7 Hz, 1 H), 2.49 (d, J = 1.2 Hz, 1 H), 3.09–3.21 (m, 2 H), 3.63 (d, J = 6.8 Hz, 1 H), 3.79 (d, J = 6.8 Hz, 1 H), 4.19–4.22 (m, 1 H), 7.31–7.43 (m, 5 H); ^{13}C NMR (CD_3OD) δ 24.24, 26.37, 39.58, 45.72, 48.44, 56.41, 58.36, 74.98, 129.67, 131.01, 131.28, 136.53, 169.76, 177.29. Isomer from second fraction: ^{1}H NMR (CD_3OD) δ 1.12–1.18 (m, 1 H), 1.25–1.35 (m, 1 H), 1.76–1.91 (m, 2 H), 2.33 (d, J = 2.2 Hz, 1 H), 2.36 (d, J = 2.0 Hz, 1 H), 2.84 (s, 1 H), 2.94–3.00 (m, 1 H), 3.16–3.22 (m, 1 H), 3.63, (d, J = 6.8 Hz, 1 H), 3.78 (d, J = 6.8 Hz, 1 H), 3.98–4.02 (m, 1 H), 7.28–7.40 (m, 5 H); ^{13}C NMR (CD_3OD) δ 24.21, 26.55, 30.32, 39.64, 46.41, 48.41, 56.55, 56.91, 58.62, 75.15, 129.70, 130.96, 131.01, 131.25, 136.56, 170.14, 177.45. HRMS (M + H)$^+$ m/z 319.1663, calcd for $C_{17}H_{23}N_2O_4$ 319.1663.

N-(D-Phenylalanyl)-exo-(2-hydroxy-3-amino)bicyclo[2.2.1]heptane-syn-7-carboxylic acid **(27).** To a stirred solution of the protected tripeptide **25** (23 mg, 0.051 mmol) in THF with 10% formic acid (1 ml) was added Pd/black (25 mg) suspended

in H_2O (1 ml). The reaction mixture was allowed to stir for 20 min and filtered, and the solvent was removed under reduced pressure. Purification by HPLC yielded the deprotected tripeptide derivative **27** (14 mg, 88%) as a 2:1 mixture of diastereomers. ^1H NMR (CD_3OD) δ 1.33–1.6 (m, 2/3 H), 1.53–1.62 (m, 1 H), 1.75–1.93 (m, 2 1/3 H), 2.11 (s, 2/3 H), 2.41 (s, 1/3 H), 2.67 (s, 2/3 H), 2.73 (s, 1/3 H), 2.99–3.27 (m, 3 H), 3.76 (d, J = 2.2 Hz, 2/3 H), 3.81 (d, 2.0 Hz, 1/3 H), 4.12–4.17 (m, 1 H), 4.77 (s, 1/3 H), 4.81 (s, 2/3 H), 7.30–7.45 (m, 5 H); ^{13}C NMR (CD_3OD) δ 21.15, 33.04, 33.18, 39.64, 46.52, 46.67, 53.26, 53.34, 54.77, 54.85, 56.08, 56.97, 57.03, 84.00, 84.37, 129.75, 130.93, 130.99, 131.27, 136.32, 136.39, 170.72, 171.04, 174.87, 179.27, 186.61.

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