Chirospecific Syntheses of Conformationally Constrained 7-Azabicycloheptane Amino Acids by Transannular Alkylation

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A new method is reported for the chirospecific preparation of optically pure 1-carboxy-7-azabicycloheptane amino acids for the generation of peptidomimetics as conformational probes. The method allows for the multigram preparation of these amino acid analogues through use of a thiolactam sulfide contraction and a transannular alkylation sequence as the key C−C bond-forming steps, starting from L-glutamic acid. The route provides access to two common intermediates, 7-(benzyloxycarbonyl)-1-carboxy-7-azabicyclo[2.2.1]-3-heptane and (1*S*,4*R*)-7-(benzyloxycarbonyl)-1-carboxy-7-azabicyclo[2.2.1]-3-heptanone *tert*-butyl ester, for elaboration to symmetrical and chiral amino acid homologues, respectively. Decarboxylation of the C-1 carboxy unit of the latter intermediate also demonstrated the applicability of the method for a short, chirospecific preparation of a (+)-epibatidine intermediate, (1*S*,4*R*)-7-(*tert*-butyloxycarbonyl)-1-carboxy-7-azabicyclo[2.2.1]-3-heptanone.

Introduction

One tactic successful in overcoming some limitations of peptides as drugs has been the use of conformationally constrained peptidomimetics that mimic the receptor-bound conformation of the bioactive peptide. Studies have shown these analogues to be more protease-resistant as well as to have increased selectivity toward the receptor and thus fewer side effects.[1] Even if the receptor-bound conformation of the parent peptide is not known, substitution of conformationally constrained amino acids for the natural amino acids in the parent peptide can generate structurally defined peptides, possibly serving a dual role as conformational probes and bioactive peptidomimetics. Incorporation of conformationally constrained amino acid analogues, such as 1-carboxy-7-azabicyclo[2.2.1]heptane amino acids, containing the pendant side chain of the parent amino acid, into the backbone of a peptide in order to mimic the presumed bioactive conformation, might produce such an effective peptidomimetic.

Present paths to the 1-carboxy-7-azabicyclo[2.2.1]-heptane system include a Diels−Alder approach[2] involving simultaneous formation of C1−C4 bonds and free radical cyclization of a C-1 radical, generated from 1,5-hydrogen abstraction of an *o*-bromobenzoyl-protected 4-allyl-1-carboxyproline, forming the C1−C4 bond.[3] Both of these approaches, however, suffer from low generality for the incorporation of substituents and poor overall yields. The latter approach, although brief, demonstrates poor regiochemical control in formation of the 7-azabicyclo-[2.2.1]heptane system over the competing 8-azabicyclo-[3.2.1]octane system.

We now report a chirospecific route to conformationally constrained 1-carboxy-7-azabicyclo[2.2.1]heptane amino acids. The projected synthesis, shown in Figure 1, begins with the known sequence involving a two-carbon homologation of thiopyroglutamate **A** via a sulfide contraction sequence using methyl bromoacetate, followed by functional group manipulation involving two reductions to prepare (2*S*)-*cis*-1-benzyl-5-(2-hydroxyethyl)proline *tert*-butyl ester, a key precursor of **B**. Elaboration of this side chain to an unsubstituted or substituted bromoethyl unit of **B**, sets the stage for a key transannular alkylation to install the second and final C−C bond at C1−C2 of **C**, completing the formation of the bicyclic ring system. Substitution of the side chain of **B** with an H or OR moiety should allow the preparation of symmetrical or chiral amino acid analogues **D** via elaboration of the OR moiety of **C** to the appropriate amino acid **D** with side chain R′. Thus, the transannular cyclization of **B** allows the preparation of a symmetrical analogue **D** (where R′ = H), and also serves for the preparation of **D** where R′ = OR, the proposed precursor of the C-3 functionalized amino acid analogues. As examples, conversion of the 3-substituent (OR moiety) of **C** into a phenyl, methylguanidinyl, and 2-aminoethyl moieties, respectively, allows the preparation of conformationally constrained homophenylalanine, arginine, and lysine analogues.

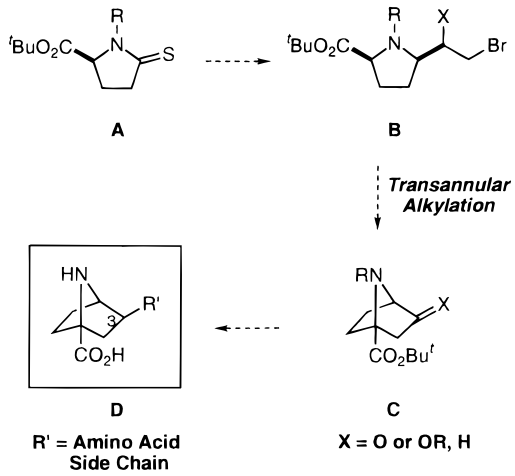

Figure 1. Proposed route to conformationally constrained 7-azabicyclo[2.2.1]heptane amino acids.

[⊗] Abstract published in *Advance ACS Abstracts,* August 15, 1996.

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(3) (a) Sato, T.; Kugo, Y.; Nakaumi, E.; Hiroyuki, I.; Masazumi, I. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1801. (b) Sato, T.; Mori, T.; Tadakatsu, S.; Hiroyuki, I.; Masazumi, I. *Heterocycles* **1994**, *37*, 245.

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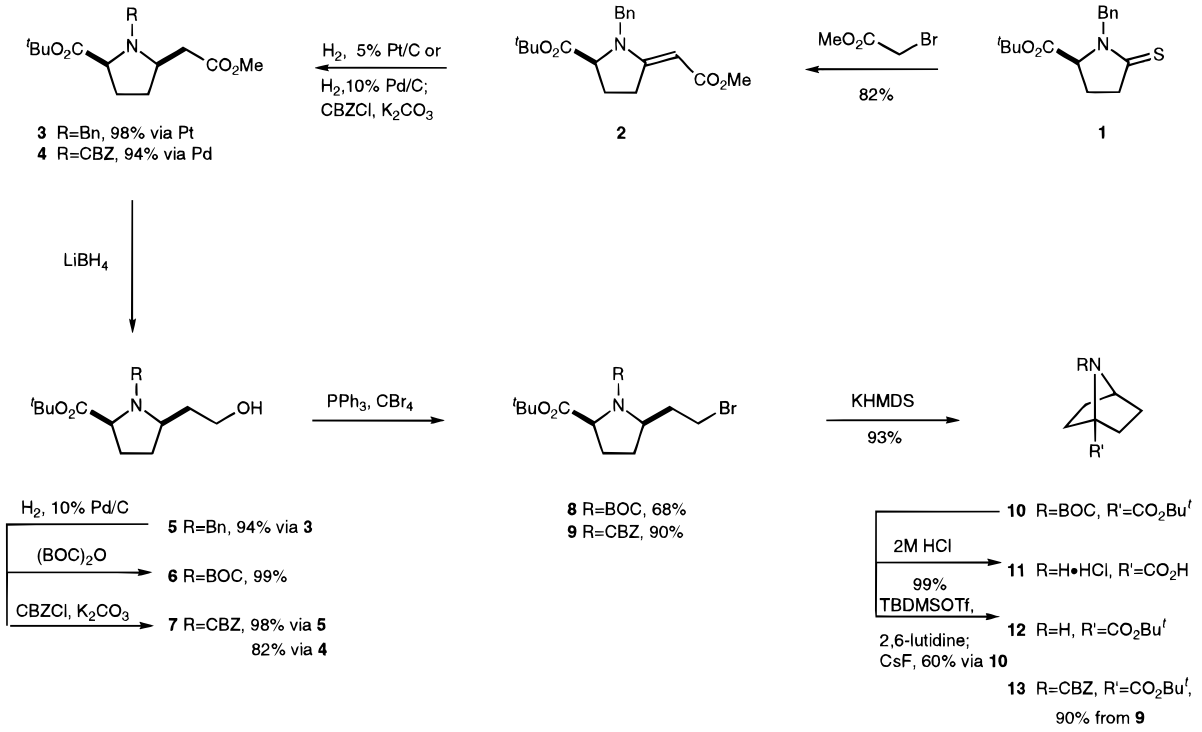
Scheme 1. Synthesis of the 7-Azabicyclo[2.2.1]heptane System by Transannular Alkylation



Results and Discussion

Preparation of Key Precursor (2*S*)-*cis*-1-Benzyl-5-(2-hydroxyethyl)proline *tert*-Butyl Ester (5). Central to the proposed synthesis is the efficacious preparation of (2*S*)-*cis*-1-benzyl-5-(2-hydroxyethyl)proline *tert*-butyl ester (**5**), a key precursor for incorporation of the functionalized ethyl side chain required for the transannular alkylation sequence. In an early synthesis of (−)-anatoxin, alcohol **5** was prepared in high enantiomeric purity (er ≥ 99/1) in three steps and 81% overall yield from *N*-benzylthiopyroglutamate **1**.[4] Some modifications of the synthesis, however, were necessary to allow reproducibility on a larger scale and resulted in an 83% yield of **2** after crystallization. This crystallization removed trace sulfur impurities and allowed hydrogenation essentially quantitatively to **3**. Removal of approximately 1% of *trans*-**3** and selective reduction of the resulting methyl ester of *cis*-**3** provided the key precursor **5** in 94% yield.

Formation of Bicycles 10 and 13 via Transannular Cyclization of Bromides 8 and 9 (Scheme 1). Attempts to convert *N*-benzyl alcohol **5** into the corresponding bromide failed. Thus, treatment of **5** with CBr_4/PPh_3 formed the labile *N*-benzyl bromide analogue and HBr was produced upon concentration.[5] Presumably this was due to azetidine formation through intramolecular alkylation and *N*-debenzylation. Alternative alcohol substrates for use in the bromination reaction, the *N*-BOC and *N*-CBZ analogues **6** and **7**, were prepared in yields of 99% and 98%, respectively, from **5**, in a straightforward manner.

A simpler path to **7** was found in hydrogenation of the olefinic moiety of **2** with concomitant hydrogenolysis of the *N*-Bn group using 10% Pd/C in MeOH. Treatment with CBZCl then gave the corresponding *N*-CBZ ester *cis*-**4** in 93% yield, and reduction of the methyl ester of *cis*-**4** in 82% yield then gave **7**. Although the reaction of *N*-BOC alcohol **6** with CBr_4/PPh_3 gave *N*-BOC bromide **8** in only 68% yield, similar treatment of *N*-CBZ alcohol **7** gave *N*-CBZ bromide **9** in 90% yield.[5] The principal byproduct in the preparation of **8** is the 6-membered cyclic carbamate, resulting from displacement of the bromide by the carbamate carbonyl oxygen. Presumably, the increased formation of this intermediate via the closure of *N*-BOC bromide **8** results from the easy and irreversible loss of isobutylene.

The transannular alkylation with *N*-BOC bromide **8** or *N*-CBZ bromide **9** then was at hand. Cyclization of the potassium enolate of **8** in THF gave the desired *N*-BOC bicycle **10** in 93% yield.[6] Treatment of **10** in refluxing 2 M aqueous HCl for 24 h gave the fully unprotected crystalline symmetrical bicycle **11** in six steps and 47% overall from thiolactam **5**. Alternatively, selective removal of the *N*-BOC moiety was achieved using TBDMSOTf and 2,6-lutidine, followed by fluoride-mediated deprotection of the resulting silyl carbamate, gave amino *tert*-butyl ester **12** in 60% yield.[7] Although this selective procedure in a more highly functionalized example might not prove as satisfactory, the transannular alkylation of *N*-CBZ bromide **9** provided an answer, affording the orthogonally protected *N*-CBZ bicyclic *tert*-butyl ester **13** in 90% yield.

To further investigate the functionalization of the C1-carboxy unit of *N*-BOC and *N*-CBZ bicycles **10** and **13**, various analogues were prepared according to Scheme 2. Subjection of **11** to a benzyl esterification and *N*-BOC protection sequence afforded *N*-BOC benzyl ester **14** in 96% overall yield. To prepare an aldehyde analogue from **14**, a DibalH reduction of ester **14** was first attempted, affording aldehyde **15** and alcohol **16** in yields of 83% and 15%, respectively, after chromatography.[8] To avoid the necessity of chromatographic purification of aldehyde **15**

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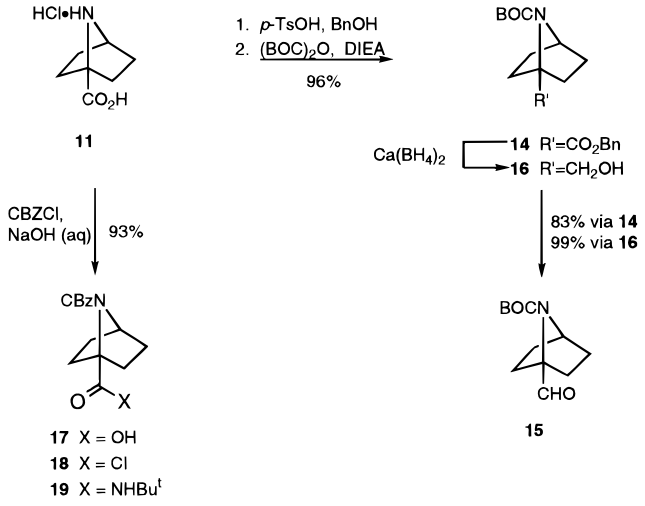
Scheme 2. Amino Acid and Amino Aldehyde Analogues in the 7-Azabicyclo[2.2.1]heptane System



from closely eluting alcohol **16**, the benzyl ester **14** was first reduced to primary alcohol **16** using $Ca(BH_4)_2$, then oxidized to aldehyde **15** in 99% overall yield.[9]

As an example of coupling of the C1-carboxy unit with a hindered amine, *tert*-butyl amide **19** was prepared from either hydrochloride salt **11** or *N*-CBZ *tert*-butyl ester **13**. Protection of **11** using CBZCl under modified Schotten-Baumann conditions gave the CBZ carbamate **17** in 93% yield.[10] Alternatively, TFA-mediated cleavage of the *tert*-butyl group of **13** gave **17** in quantitative yield. Surprisingly, preparation of the *N*-BOC analogue of **17** from amino acid **11** using $(BOC)_2O$ gave yields consistantly under 50%. Conversion of acid **17** to the acid chloride **18** using oxalyl chloride, followed by treatment with *tert*-butylamine in the presence of Et_3N/4-DMAP provided the desired hindered amide **19** in 97% yield.

Preparation of Homoserine and C-3 Fluorinated Amino Acid Analogues. The route allowing access to C-3 functionalized analogues is shown in Scheme 3 and uses *N*-CBZ alcohol **7** as the starting point. Conversion of the alcohol **7** to mesylate **20** using MsCl/Et_3N followed by displacement of the mesylate with sodium phenylselenide (prepared from diphenyl diselenide and $NaBH_4$/EtOH),[11] afforded selenide **21** cleanly in 95% yield. Although attempts to effect an oxidation−elimination sequence on selenide **20** when separately using $NaIO_4$ or 30% H_2O_2 at 55 °C only gave olefin **22** in 50−64% yield, these conditions used in combination provided the desired olefin **22** in 98% yield. Epoxidation of olefin **20** using *m*-CPBA[12] in CH_2Cl_2 at −10 → 0 °C gave the desired transannular cyclization precursor **23** as a 2.3/1 mixture of easily separable diastereomers, providing **23**β and **23**α in 61% and 27% isolated yields, respectively.

All attempts, however, to promote transannular cyclization of the potassium enolate of either the minor or major diastereomer of epoxide **23** failed, even in the presence of Lewis acid catalysis. Attention was then turned to preparation of the TES(triethylsilyl)-protected bromohydrin diastereomers of **23**, following the favorable cyclization results observed with bromides **8** and **9**. Thus, ring opening of either epoxide diastereomer of **23** with dibromotriphenylphosphorane,[13] followed by treatment of the resulting bromohydrin with Et_3SiCl/imidazole,[14] gave the TES ether of the corresponding bromohydrin **24** in 84−92% yield. Transannular cyclization of the potassium enolate of **24**β in THF, followed by desilylation using TBAF, gave the desired bicycle **25**β in 92% yield.

The corresponding minor diastereomer **24**α cyclized completely upon warming to room temperature only after 25−30 min, in contrast to **24**β, which cyclized within 5 min at room temperature. This prolonged warming at room temperature lowered the yield of the minor alcohol **25**α to only 68%. Alternatively, transannular cyclization of the potassium enolate mixture of TES ether diastereomers of **24** (−60 °C → rt), stirring for 20 min, followed by desilylation using TBAF, gave **25** in 84% yield as a 3/1 mixture of β/α alcohol diastereomers.[6] It was fortunate that **24**α, the isomer derived from the minor epoxide diastereomer **23**α, could be prepared exclusively from this mixture through use of an oxidation−reduction sequence. Thus, oxidation of the mixture of alcohols, **25**β/**25**α, followed by DibalH reduction of the resulting ketone **26**, afforded alcohol **25**α in 81% overall yield.[15] In this manner, differentially protected homoserine amino acid analogues **25**β and **25**α were both prepared in overall yields of 40% from *N*-benzylthiopyroglutamate **1** using either epoxide diastereomer **23**β or the **23**β/**23**α mixture of diastereomers.

Initial assignment of the C-3 stereochemistry of bicyclic alcohols **25**β and **25**α was simply made on the basis of the multiplicity and magnitude of the coupling constant of H-4, observed as a doublet ($J_{H4,H6exo}$ = 5.4 Hz) and triplet ($J_{H4,H3exo,H6exo}$ = 4.4 Hz), respectively. The lack of coupling between H-4, H-3endo, and H-6endo was clearly consistent with the 90° dihedral relationship of H-4 to H-3endo and H-6endo. In addition, the magnitude of the coupling constant between H-4 and H-6exo was consistent with a 30° relationship. For the endo alcohol **25**α, the 30° dihedral relationship of H-4 to H-3exo and H-6exo was consistent with the observed multiplicity and coupling data. A more rigorous proof of the assignment of stereochemistry was provided by the X-ray data for alcohol **25**β, as shown in Figure 2, definitively demonstrating the exo configuration of the alcohol moiety at C-3.[16]

Attempted DAST-mediated fluorine substitution with inversion of **25**α produced approximately a 1/1 mixture of easily separable exo and endo fluoro substituted bicycles, **26**β and **26**α, respectively.[6] Presumably, the exo fluoro analogue **26**β originates from the normal inversion pathway, whereas the endo fluoro compound **26**α is formed via anchimeric assistance involving the nitrogen moiety.[17] Thus, both fluoro-substituted bicycles were prepared from a single alcohol **25**α. Alternatively, treat-

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(16) The authors have deposited atomic coordinates for this structure 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, U.K.
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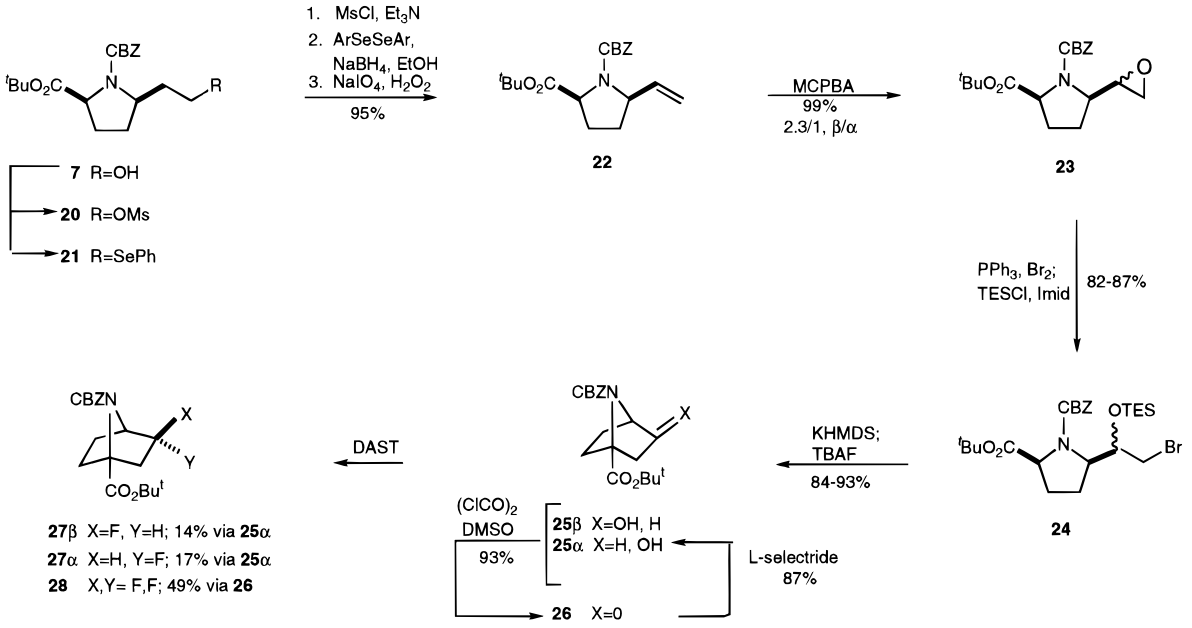
Scheme 3. Preparation of 1-Carboxy-2-fluoro- and -2,2-difluoro-7-azabicyclo[2.2.1]heptane Amino Acid Analogues



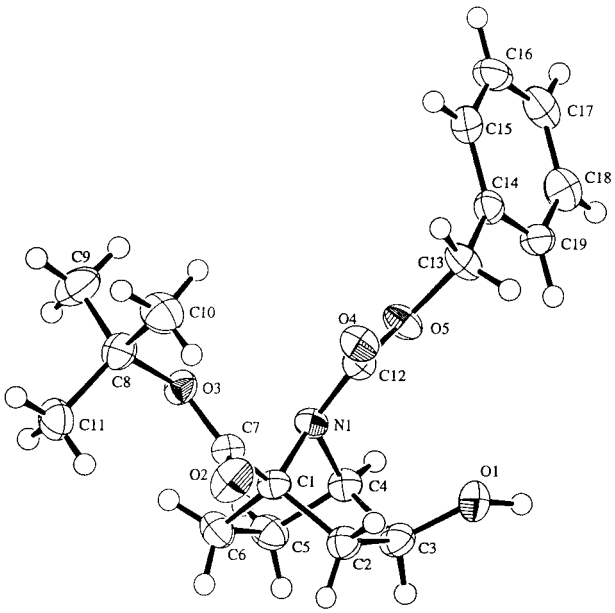


Figure 2. Structure of (1*S*,3*S*,4*R*)-*N*-(benzyloxycarbonyl)-1-carboxy-3-hydroxy-7-azabicyclo[2.2.1]heptane *tert*-butyl ester (**25***β*) as determined by X-ray crystallography.

ment of ketone **26** with DAST afforded the difluoro analogue **28** in 26% yield (49% based on unconverted **26**).

Preparation of Ornithine, Arginine, Homophenylalanine, and Lysine Analogues. Ketone **26** proved to be a most versatile intermediate, allowing the preparation of differentially protected ornithine, arginine, homophenylalanine and lysine analogues, as shown in Scheme 4. Key to the strategy for the preparation of the ornithine, arginine, and lysine analogues was the elaboration of the methyl ester moiety of saturated ester **29**. This ester could be prepared from ketone **26** in either diastereomeric form at C-3, via two-carbon homologation−hydrogenation. Thus, reaction of **26** with trimethyl phosphonoacetate provided the corresponding unsaturated ester, which, upon reduction, afforded esters **29**α and **29***β* in yields of 77% and 21%, respectively.[18] Each isomer of **29** was converted to the corresponding ornithine and arginine isomer, **30** and **31**, respectively. Thus, subjection of **29**α and **29***β* to a hydrolysis−Curtius rearrangement sequence involving trapping of the intermediate isocyanate with 2-(trimethylsilyl)ethanol provided ornithine homologues **30**α and **30***β* in overall yields of 93% and 81%, respectively.[19] Deprotection of the *N*-TEOC [[(trimethylsilylethyl)oxy]carbonyl] moiety of **30**α and **30***β* using TBAF in THF, followed by capture of the resulting primary amine using *N*,*N*′-bis(*tert*-butoxycarbonyl)-*S*-methylisothiourea[20] in buffer solution afforded arginine analogues **31**α and **31***β* in overall yields of 89% and 72%, respectively.

The route to several differentially protected lysine analogues also starts from ester **29**, except that only the major isomer **29**α was taken through the sequence. Chemoselective reduction of the methyl ester of **29**α using $LiBH_4$ in Et_2O gave primary alcohol **32** in 74% yield.[4] Treatment of alcohol **32** with *tert*-butyl [[(2-trimethylsilyl)ethyl]sulfonyl]carbamate (SES-NHBOC) under Mitsunobu conditions afforded *N*-acylsulfonamide **33** in 95% yield.[21] Removal of the *N*-BOC and *tert*-butyl ester moieties was accomplished in a single operation using TFA, and CH_2N_2 treatment of the resulting acid **34** gave **35** in 78% yield.

To prepare the homophenylalanine analogues, ketone **26** was used as the starting point. The addition of PhLi to ketone **26** afforded alcohols **36** in 90% yield as a mixture of *β*/α diastereomers.[15] Dehydration of **36** using Ts_2O/pyridine afforded styrene analogue **37** in 82% yield and reduction of the double bond of **37** proceeded uneventfully, providing homophenylalanine analogues **38**α and **38***β* in yields of 74% and 20%, respectively. It is notable that treatment of **36** with $SOCl_2$/pyridine[22] and hydrogenolysis of the resulting mixture containing chloroolefin only afforded **38**, suggesting that anchimeric assistance by the nitrogen moiety during the chlorination step might be playing a role.[17]

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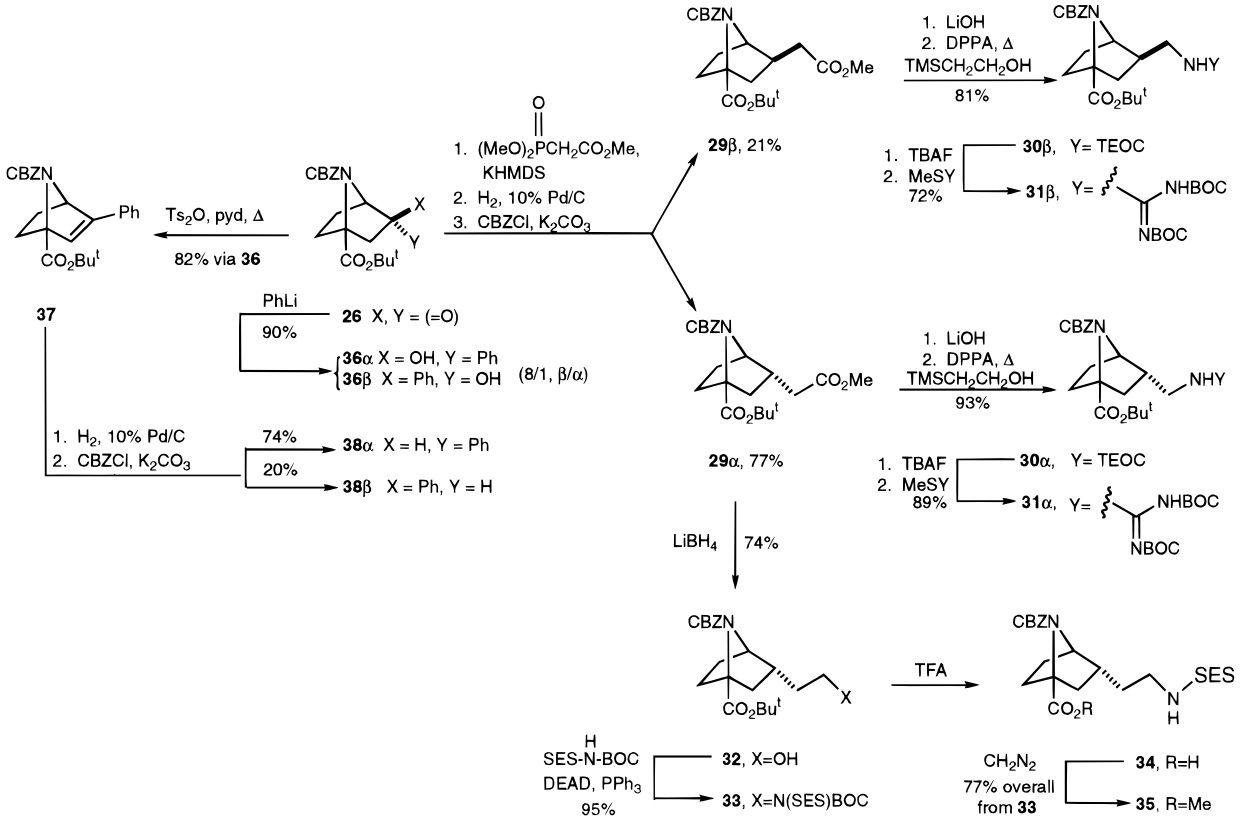
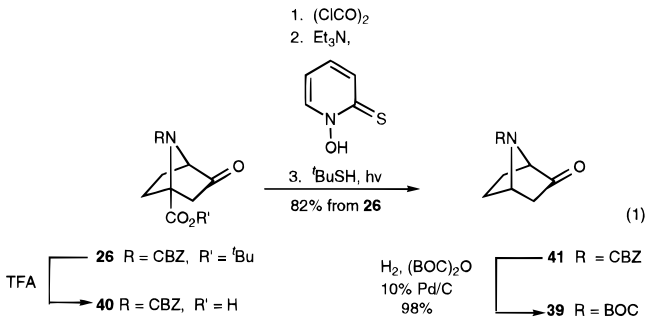
(21) (a) Campbell, J. A.; Hart, D. J. *J. Org. Chem.* **1993**, *58*, 2900. (b) Campbell, J. A.; Hart, D. J. *Tetrahedron Lett.* **1992**, 6247.
(22) Yoshifuji, S.; Kaname, M. *Chem. Pharm. Bull.* **1995**, *43*, 1302.

Scheme 4. Preparation of Ornithine, Arginine, Homophenylalanine, and Lysine Analogues of the 1-Carboxy-7-azabicyclo[2.2.1]heptane Ring System



Preparation of (1*S*4*R*)-7-(*tert*-Butyloxycarbonyl)-1-carboxy-7-azabicyclo[2.2.1]-3-heptanone (39), an (+)-Epibatidine Precursor. A variation in the route to the bicyclic amino acids also makes the method amenable to the chirospecific synthesis of epibatidine precursor, **39**.[15] This sequence uses reductive radical decarboxylation of the C-1 carboxy group and the resulting ketone **26** as the starting point. Cleavage of the *tert*-butyl ester (TFA) of **26** afforded acid **40** in essentially quantitative yield. Coupling of the acid chloride of **40** (prepared by treatment of **40** with oxalyl chloride) with *N*-hydroxy-2-thiopyridone in the presence of Et_3N afforded the corresponding *O*-acyl thiohydroxamate, which was photolyzed with *tert*-butyl thiol using two 100 W tungsten lamps to afford **41** in 81% overall yield.[23] Hydrogenolysis (10% Pd/C) of **41** in MeOH containing $(BOC)_2O$ afforded **39** in 98% yield (eq 1). This method,



constituting a formal synthesis of epibatidine, may also be amenable to the synthesis of other natural products. Thus, use of a three- and four-carbon sulfur extrusion homologation sequence, instead of the two-carbon extrusion homologation sequence demonstrated in this study, should provide access to natural products containing the 8-azabicyclo[3.2.1]octane and 9-azibicyclo[4.2.1]nonane framework.[24]

Conclusion

We report a new method for the chirospecific preparation of enantiomerically pure 1-carboxy-7-azabicycloheptanes, amino acids for the generation of peptidomimetics as conformational probes and bioactive agents. The method allows for the multigram preparation of these conformationally constrained amino acid analogues through a sulfide contraction and transannular alkylation sequence as the key C−C bond-forming steps, starting from L-glutamic acid. The route provides access to two common intermediates, 7-(benzyloxycarbonyl)-1-carboxy-7-azabicyclo[2.2.1]-3-heptane and (1*S*,4*R*)-7-(benzylocarbonyl)-1-carboxy-7-azabicyclo[2.2.1]-3-heptanone *tert*-butyl ester, for elaboration to symmetrical and chiral amino acid analogues. Decarboxylation of the C-1 carboxy unit of the latter intermediate also demonstrated the potential applicability of the method for natural product synthesis, with the short chirospecific preparation of (1*S*,4*R*)-7-(*tert*-butyloxycarbonyl)-1-carboxy-7-azabicyclo[2.2.1]-3-heptanone, an (+)-epibatidine precursor.

Experimental Section

General Procedures. All melting points are uncorrected. NMR spectra were taken in $CDCl_3$ and are referenced to internal TMS unless otherwise noted; ^{13}C NMR chemical shifts are followed by multiplicity as determined from DEPT. *J* values are given in Hs. Solvents were dried and purified prior

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to use: THF and NMP were distilled from sodium metal; CH_2Cl_2, DMF, hexane, and pyridine were distilled from CaH_2; CH_3CN was distilled from P_2O_5 and then CaH_2. Reactions were conducted under Ar or N_2. For isolation, the organic phase was dried over $MgSO_4$ unless otherwise noted and evaporated under reduced pressure using a Berkeley rotary evaporator. TLC analysis was performed on aluminum-backed silica gel 60 F_{254}, 0.2 mm plates (MCB Reagents), visualized with UV light (254 nm), followed by heating with ethanolic phosphomolybdic acid. Chromatography was carried out using 230−400 mesh silica gel. The diameter of the column corresponded to the amount of of silica gel used in the separation: (a) 1.6 cm width, 0−20 g silica, (b) 3 cm width, 20−90 g, (c) 5-cm width, 90−360 g, (d) 8-cm width; 360−500 g. Elemental analyses were determined by Microanalytical Laboratories, University of California at Berkeley.

(2*S*)-1-Benzyl-(*E*)-5-[(methoxycarbonyl)methylidene]-proline *tert*-Butyl Ester (2). A solution of thiolactam **1**[1] (40 g, 137 mmol) and methyl bromoacetate (26 g, 170 mmol) in CH_3CN (80 mL) was stirred for 42 h and then cooled to −5 °C, and a solution of PPh_3 (43.2 g, 165 mmol) in CH_2Cl_2 (640 mL) was added over 20 min, followed by 18.4 mL (151 mmol) of NMP. The mixture was stirred for 30 h and then poured into 1 M aqueous $KHSO_4$ (300 mL), and the aqueous layer was washed with additional CH_2Cl_2 (3 × 80 mL). The combined organic extracts were washed with 1 M aqueous KH_2PO_4 (200 mL) and then H_2O (100 mL), dried, and evaporated. This solid residue was triturated with 550 mL of 25% EtOAc/hexane for 10 min and then cooled for 24 h at 0 °C. The resulting slurry was filtered to remove Ph_3PS, the filtrate was evaporated, and the residue was chromatographed twice (450 g of silica gel, eluted with 8% then 15% EtOAc/hexane) to afford the nearly pure vinylogous ester. This material was recrystallized from the minimum amount of hexane (~1 mL of hexane/gram of ester) at 0 °C to afford a total (three crops) of 37.7 g (83%) of pure vinylogous carbamate **2**. The analytical data were identical to those reported.[4]

(2*S*)-*cis*-1-Benzyl-5-[(methoxycarbonyl)methyl]proline *tert*-Butyl Ester (3). A solution of 12.2 g (36.6 mmol) of vinylogous carbamate **2** in 120 mL of EtOAc was degassed (Ar), and 3.5 g of 5% Pt/C was added. The resulting slurry was degassed once more and then hydrogenated (60 psig) over 16 h. The slurry was filtered through Celite, the Celite pad was washed with 500 mL of CH_2Cl_2, the filtrate was evaporated, and the residue was chromatographed (450 g of silica gel, eluted with 5% then 12% EtOAc/hexane) to afford 45 mg (0.4%) of *trans*-**3**, 200 mg (1.6%) of a mixture of *trans*-**3** and *cis*-**3**, followed by 12.0 g (98%) of *cis*-**3**. The analytical data were identical to those reported.[4]

(2*S*)-*cis*-1-(Benzyloxycarbonyl)-5-[(methoxycarbonyl)-methyl]proline *tert*-Butyl Ester (4). To a solution of 0.95 g (2.85 mmol) of **2** in 25 mL of degassed (Ar) MeOH was added 550 mg of 10% Pd/C, and the mixture was hydrogenated at 60 psi for 36 h. The slurry was filtered through Celite, and the Celite pad was washed with 50 mL of MeOH and then 200 mL of CH_2Cl_2. The filtrate was evaporated, the residue was immediately dissolved in 14 mL of 50% EtOAc/H_2O, and 560 mg (4 mmol) of calcined K_2CO_3 was added, followed by 422 mL (9 mmol) of CBZCl, added dropwise over 5 min. The mixture was stirred for 1 h, and the aqueous layer was extracted with EtOAc (4 × 40 mL). The combined EtOAc layers were washed with 40 mL of 2 M aqueous HCl, dried, and evaporated. The residue was chromatographed (40 g silica gel, eluted with 10% EtOAc/hexane) to afford 954 mg (94%) of carbamate **4**: mp 43−44 °C; $[\alpha]^{20}_D$ −20.5° (*c* 1.1, $CHCl_3$); IR (CH_2Cl_2) 1747, 1703 cm^{-1}; ^{13}C NMR (C_6D_6, 339 K) δ 27.9 (q), 28.7 (t), 39.1 (t), 50.8 (q), 56.0 (t), 61.1 (d), 67.0 (t), 80.8 (s), 127.8 (d), 128.0 (d), 128.25 (d), 132.9 (d), 137.5 (s), 154.1 (s), 171.5 (s), 171.9 (s). Anal. Calcd for $C_{20}H_{27}NO_6$: C, 63.7; H, 7.2; N, 3.7. Found: C, 64.0; H, 7.4; N, 3.6.

(2*S*)-*cis*-1-Benzyl-5-(2-hydroxyethyl)proline *tert*-Butyl Ester (5). A solution of $LiBH_4$ in Et_2O (1 M, 38 mL, 38.0 mmol) was added to a solution of 9.57 g (28.5 mmol) of *cis*-**3** in 68 mL of Et_2O. The mixture was stirred for 4.5 h, poured into 100 mL of 1 M aqueous K_2CO_3, and extracted with Et_2O (5 × 100 mL). The combined organic layers were dried and evaporated. The residue was chromatographed (400 g of silica gel, eluted with 50% EtOAc/hexane) to afford 8.20 g (94%) of alcohol **5** as a colorless oil with properties identical to those reported.[1]

(2*S*)-*cis*-1-(*tert*-Butyloxycarbonyl)-5-(2-hydroxyethyl)-proline *tert*-Butyl Ester (6). A solution of 2.21 g (7.2 mmol) of *N*-benzylamine **5** and 3.64 g (16.7 mmol) of BOC_2O in 80 mL of MeOH was degassed (Ar), and 0.64 g of 10% Pd/C was added. The resulting slurry was hydrogenated (55 psig) over 14 h and filtered through Celite, and the Celite pad was washed with 250 mL of CH_2Cl_2. The filtrate was evaporated and chromatographed (100 g of silica gel, eluted with 40% EtOAc/hexane) to afford 2.26 g (99%) of carbamate **6**: IR (CH_2Cl_2) 3290−3540 (br), 1740, 1675 cm^{-1}; ^1H NMR δ 1.43 (s, 9H), 1.45 (s, 9H), 1.50−1.74 (m, 3H), 1.85−2.05 (m, 2H), 2.25−2.34 (m, 1H), 3.60−3.68 (m, 1H), 3.72−3.80 (m, 1H), 4.13 (dd, J = 9.2, 8.0, 1H), 4.27 (ddd, J = 11.2, 7.2, 3.4, 1H), 4.34 (dd, J = 9.9, 4.5, 1H); ^{13}C NMR δ 27.9 (q), 28.1 (q), 28.9 (t), 30.3 (t), 37.5 (t), 54.6 (d), 58.8 (t), 60.7 (d), 80.5 (s), 80.88 (s), 155.4 (s), 172.1 (s).

(2*S*)-*cis*-1-(Benzyloxycarbonyl)-5-(2-hydroxyethyl)proline *tert*-Butyl Ester (7). A solution of 2.38 g (7.8 mmol) of *N*-benzylamine **5** in 30 mL of MeOH was degassed (Ar), and 0.18 g of 10% Pd−C was added. The resulting slurry was degassed once more and then hydrogenated (60 psig) over 12 h. The slurry was degassed (N_2) and filtered through Celite, and the Celite pad washed with 250 mL of CH_2Cl_2. The filtrate was carefully evaporated at ambient temperature to afford 1.68 g of the crude secondary amine. This mixture was immediately dissolved in 40 mL of 50% EtOAc/H_2O and 3.23 g (23.3 mmol) of calcined K_2CO_3 added, followed by 1.28 mL (9 mmol) of CBZCl dropwise over 5 min. The mixture was stirred 1.5 h, the aqueous layer was extracted with EtOAc (4 × 40 mL), and the combined EtOAc layers were washed with 40 mL of 2 M aqueous HCl, dried, and evaporated. The residue was chromatographed (40 g silica gel, eluted with 50% EtOAc/hexane) to afford 2.67 g (98%) of carbamate **7** as a colorless oil: $[\alpha]^{20}_D$ −56.7° (*c* 1.6, $CHCl_3$); IR (CH_2Cl_2) 3210−3690 (br), 1733, 1682 cm^{-1}; ^1H NMR δ 1.33 (s, 9H), 1.61−1.79 (m, 3H), 1.93−2.08 (m, 2H), 2.28−2.34 (m, 1H), 3 62−3.70 (m, 1H), 3.73−3.81 (tm, J = 11.5, 1H), 4.04 (dd, J = 9.4, 4.3, 1H), 4.22−4.25 (m, 1H), 4.31−4.37 (m, 1H), 5.07 (d, J = 12.4, 1H), 5.18 (d, J = 12.5, 1H), 7.25−7.40 (m, 5H); ^{13}C NMR δ 27.7 (q), 29.0 (t), 30.4 (t), 37.4 (t), 55.5 (d), 58.9 (t), 60.5 (d), 67.4 (t), 81.3 (s), 127.7 (d), 128.0 (d), 128.35 (d), 136.1 (s), 155.9 (s), 171.88 (s). Anal. Calcd for $C_{19}H_{27}NO_5$: C, 65.3; H, 7.8; N, 4.0. Found: C, 65.2; H, 8.0; N, 4.1.

Preparation of *N*-CBZ Alcohol 7 from *N*-CBZ Ester 4. Applying the procedure for preparing *N*-benzyl alcohol **5** from *N*-benzyl ester **3**, 300 mg (0.79 mmol) of *N*-CBZ ester **4** was converted to 226 mg (82%) of *N*-CBZ alcohol **7**.

(2*S*)-*cis*-1-(*tert*-Butyloxycarbonyl)-5-(2-bromoethyl)-proline *tert*-Butyl Ester (8). To a solution of 1.18 g (3.74 mmol) of primary alcohol **6** and 1.74 g (5.24 mmol) of CBr_4 in 17 mL of CH_2Cl_2 at −5 °C was added a solution of PPh_3 (1.18 g, 4.5 mmol) in 9 mL of CH_2Cl_2 dropwise over a 5 min period. The mixture was warmed to 0 °C over 5 min, warmed to rt over 10 min and then stirred for 20 min. The solution was evaporated at rt, and the resulting residue was chromatographed (60 g of silica gel, eluted with 25% EtOAc/hexane) to afford 0.97 g (68%) of bromide **8** as a colorless oil that was used directly in the next reaction. Selected data for **8**: IR (CH_2Cl_2) 1735, 1640 cm^{-1}; ^1H NMR (60/40 rotomers) δ 1.43 (s, 9H), 1.46 (s, minor rotomer, 3.6 H), 1.48 (s, major rotomer, 5.4 H), 1.66−1.75 (m, 1H), 1.87−2.05 (m, 3H), 2.20−2.30 (m, 1H), 2.32−2.46 (m, 1H), 3.38−3.55 (m, 2H), 3.98−4.08 (m, 1H), 4.13 (t, major rotomer, J = 7.8, 0.6H), 4.23 (t, J = 7.6, minor rotomer, 0.4 H); ^{13}C NMR δ (^1H decoupled only, rotomers) 27.9, 28.0, 28.3, 28.4, 28.9, 29.6, 29.7, 30.2, 30.5, 38.0, 38.4, 57.0, 57.4, 60.5, 60.6, 79.9, 80.1, 80.9, 153.9, 172.15, 172.23.

(2*S*)-*cis*-1-(Benzyloxycarbonyl)-5-(2-bromoethyl)proline *tert*-Butyl Ester (9). To a solution of 1.50 g (4.3 mmol) of primary alcohol **7** and 1.99 g (6.0 mmol) of CBr_4 in 17 mL of CH_2Cl_2 at −5 °C was added a solution of 1.99 g (6.0 mmol) of PPh_3 in 11 mL of CH_2Cl_2 dropwise over 18 min. The mixture was warmed to 4 °C over 1.75 h, to rt over 2 h and then stirred 2 h. The solution was evaporated at rt and the residue chromatographed (40 g of silica gel, eluted with hexane then

15% EtOAc/hexane) to afford 1.60 g (90%) of bromide **9** as a colorless oil: $[\alpha]^{20}_D$ −24° (*c* 1.5, $CHCl_3$); IR (CH_2Cl_2) 1735, 1650 cm^{-1}; ^1H NMR (65/35 rotomers) δ 1.30−1.52 (m, 2H), 1.35 (s, 5.85H), 1.45 (s, 3.15H), 1.70−1.78 (m, 1H), 1.90−2.05 (m, 3H), 2.21−2.28 (m, 1H), 2.33−2.43 (m, 0.35H), 2.44−2.53 (m, 65H), 2.34−2.57 (m, 2H), 4.08−4.18 (m, 1H), 4.24 (t, J = 7.4, 0.65H), 4.29 (t, J = 7.6, 0.35 H), 5.10 (dd, J = 12.5, 1.30H), 5.10−5.18 (m, 0.7H), 7.22−7.40 (m, 5H); ^1H NMR (C_6D_6, 298 K, 60/40 rotomers) δ 0.99−1.11 (m, 1H), 1.21 (s, 5.4H), 1.33 (s, 3.6H), 1.12−1.35 (m, 1H), 1.43−1.65 (m, 1.8H), 1.63−1.84 (m, 1.2H), 2.13−2.23 (m, 0.40H), 2.35−2.45 (m, 0.6H), 3.03−3.13 (m, 0.8H), 3.27−3.41 (m, 1.2H), 3.65−3.73 (m, 0.4H), 3.82−3.90 (m, 0.6H), 4.03 (t, J = 7.8, 0.6H), 4.25 (t, J = 7.9, 0.4 H), 4.93−5.08 (m, 2H), 7.00 (t, J = 7.3, 1 H), 7.05−7.12 (m, 2H), 7.20 (d, J = 6.7, 2H); ^{13}C NMR (C_6D_6, 298 K, rotomers) δ 27.8 (q), 27.9 (q), 28.0 (t), 28.03 (t), 29.04 (t), 29.6 (t), 30.1 (t), 30.5 (t), 38.4 (t), 38.7 (t), 57.2 (t), 58.3 (t), 60.6 (t), 61.2 (t), 67.0, 67.2 (t), 80.7 (s), 128.01 (d), 128.05 (d), 128.23 (d), 128.56 (d), 128.66 (d), 137.17 (s), 137.29 (s), 154.35 (s), 154.54 (s), 172.0 (s); ^1H NMR (C_6D_6, 339 K) δ 1.19−1.43 (m, 2H), 1.27 (s, 9H), 1.54−1.72 (m, 2H), 1.79−1.92 (m, 1H), 2.37 (br m_c, 1H), 3.26 (br m_c, 1H), 3.85 (br m_c, 1H), 4.14 (br m_c, 1H), 4.98 (d, J = 12.5, 1H), 5.03 (d, J = 12.5, 1H), 7.01 (t, J = 7.3, 1H), 7.05−7.12 (m, 2H), 7.20 (d, J = 7.3, 2H); ^{13}C NMR (C_6D_6, 339 K) δ 28.0 (q), 28.8 (t), 30.06 (t), 30.24 (t), 38.8 (t), 58.2 (d), 61.0 (d), 67.1 (t), 80.8 (s), 128.07 (d), 128.30 (d), 128.58 (d), 137.4 (s), 154.6 (s), 171.9 (s). Anal. Calcd for $C_{19}H_{26}NO_4Br$: C, 55.4; H, 6.4; N, 3.4. Found: C, 55.2; H, 6.6; N, 3.4.

7-(*tert*-Butyloxycarbonyl)-1-carboxy-7-azabicyclo[2.2.1]-heptane *tert*-Butyl Ester (10). To a solution of KHMDS (5.65 mL of a 0.92 M solution in THF, 5.2 mmol) in 84 mL of THF cooled to −60 °C was added a solution of 960 mg (2.54 mmol) of bromide **8** in 37 mL of THF dropwise, maintaining an internal temperature of −50 °C during the addition (15−20 min). The solution was warmed to −40 °C gradually over 15 min, stirred 60 min, warmed to 0 °C over 30 min, and then warmed to rt over 20 min. The mixture was stirred for an additional 10 min, and then 0.15 mL (2.8 mmol) of glacial AcOH was added. The mixture was evaporated to 15 mL, diluted with 50 mL of 1 M aqueous KH_2PO_4, and extracted with EtOAc (4 × 50 mL). The organic layers were combined, washed with 50 mL of saturated aqueous $NaHCO_3$, dried, and evaporated. The residue was chromatographed (45 g of silica gel, eluted with 15% EtOAc/hexane) to afford 700 mg (93%) of the bicyclic carbamate **10**: mp 63.0−64.3 °C; IR (CH_2Cl_2) 1730, 1703 cm^{-1}; ^1H NMR δ 1.43 (s, 9H), 1.45−1.50 (m, 2H), 1.49 (s, 9H), 1.68 (tm, J = 13.0, 2H), 1.88 (tm, J = 13.0, 2H), 2.14 (tm, J = 13.0, 2H), 4.25 (t, J = 4.8, 1H); ^{13}C NMR δ 27.97 (q), 28.03 (q), 29.5 (t), 32.9 (t), 60.1 (d), 69.2 (s), 80.1 (s), 80.7 (s), 156.5 (s), 170.4 (s). Anal. Calcd for $C_{16}H_{27}NO_4$: C, 64.6; H, 9.2; N, 4.7. Found: C, 64.6; H, 9.5; N, 4.7.

7-(*tert*-Butyloxycarbonyl)-1-carboxy-7-azabicyclo[2.2.1]-heptane Hydrochloride (11). A slurry of 1.00 g (3.36 mmol) of *N*-BOC ester **10** in 38 mL of 2 M aqueous HCl was heated at 85 °C for 25 h, and then the resulting solution was cooled to rt and evaporated. The residue was dissolved in 3.5 mL of MeOH, diluted with 25 mL of Et_2O to form a white flocculent precipitate, and cooled to 0 °C over 12 h. The slurry was filtered and the solid washed with 5 mL of Et_2O and then dried under vacuum (24 h, 55 °C/0.2 Torr then 24 h, 65 °C/0.2 Torr) to afford 590 mg (99%) of HCl salt **11**: mp >210 °C dec; IR (Nujol) 1743 cm^{-1}; ^1H NMR (CD_3OD) δ 1.86−1.97 (m, 2H), 2.04−2.18 (m, 6H), 4.19 (t, J = 3.7, 1H); ^{13}C NMR δ 28.80 (t), 31.82 (t), 60.00 (d), 73.33 (s), 171.09 (s). Anal. Calcd for $C_7H_{12}NO_2Cl$: C, 47.3; H, 6.8; N, 7.9. Found: C, 47.3; H, 7.1; N, 7.5.

1-Carboxy-7-azabicyclo[2.2.1]heptane *tert*-Butyl Ester (12). To a solution of 140 mg (0.471 mmol) of *N*-BOC ester **10** in 2 mL of CH_2Cl_2 at 0 °C was added 0.12 mL (0.53 mmol) of TBDMSOTf and 0.42 mL of 2,6-lutidine. The mixture was stirred 5 min, warmed to rt, stirred 30 min, and then cooled to 0 °C. To this solution was added 0.42 mL (0.18 mmol) of TBDMSOTf, followed by warming of the mixture to rt over 5 min, and stirring 10 min. An additional 0.20 mL (0.17 mmol) portion of 2,6-lutidine was then added and the mixture stirred an additional 10 min. The mixture was cooled to 0 °C and a final 0.42 mL (0.18 mmol) portion of TBDMSOTf added. The mixture was then warmed to rt and stirred for 10 min more. The solution was concentrated to ∼0.5 mL and then chromatographed (15 g of silica gel, eluted with 9% EtOAc/hexane) to afford 140 mg (84%) of the resulting TBDMS carbamate, which was used immediately in the next reaction.

To a solution of 140 mg (0.39 mmol) of the TBDMS carbamate in 7 mL of CH_3CN was added 360 mg (2.37 mmol) of dry CsF. The mixture was heated to reflux for 20 h, cooled to rt, and then partitioned between 100 mL of CH_2Cl_2 and 10 mL of H_2O. The aqueous layer was extracted with two 20 mL portions of CH_2Cl_2. The combined organic layers were dried and evaporated to afford 54 mg (60% from **10**) of amine **12** as an amber oil that was unstable upon prolonged heating under vaccum.

Selected data for TBDMS carbamate: ^1H NMR δ 0.24 (s, 6H), 0.92 (s, 9H), 1.43−1.53 (m with s at d 1.48, 11H), 1.72 (m, 2H), 1.90 (m, 2H), 2.16 (m, 2H), 4.24 (t, J = 4.0, 1H); ^{13}C NMR δ −4.8, −3.0, 17.2, 25.7, 28.0, 29.7, 32.9, 60.1, 69.1, 81.0, 155.7, 170.2.

Selected data for secondary amine **12**: ^1H NMR δ 1.42−1.48 (m with s at d 1.45, 5H), 1.91 (br s, 1H), 3.62 (t, J = 4.0, 1H); ^{13}C NMR δ 27.96 (q), 31.0 (t), 33.7 (t), 56.8 (d), 69.1 (s), 80.7 (s), 173.2 (s).

7-(Benzyloxycarbonyl)-1-carboxy-7-azabicyclo[2.2.1]-heptane *tert*-Butyl Ester (13). Applying the procedure for preparing *N*-BOC bicycle **10**, 1.45 g (3.52 mmol) of *N*-CBZ bromide **9** was converted to 1.05 g (90%) of *N*-CBZ bicycle **13**: mp 74−75 °C; IR (CH_2Cl_2) 1722, 1705 cm^{-1}; ^1H NMR δ 1.47 (s, 9H), 1.43−1.52 (m, 2H), 1.72 (tm, J = 10.3, 2H), 1.83−1.93 (m, 2H), 2.16 (tm, J = 13.1, 2H), 4.38 (t, J = 4.8, 1H), 5.12 (s, 2H), 7.27−7.37 (m, 5H); ^{13}C NMR δ 27.8 (q), 29.4 (t), 33.2 (t), 59.7 (d), 67.0 (s), 69.6 (s), 81.1 (s), 127.85 (d), 127.94 (d), 128.4 (d), 136.4 (s), 156.8 (s), 169.9 (s). Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.9; H, 7.6; N, 4.2. Found: C, 69.1; H, 7.7; N, 4.2.

7-(*tert*-Butyloxycarbonyl)-1-carboxy-7-azabicyclo[2.2.1]-heptane Benzyl Ester (14). A mixture of 732 mg (4.12 mmol) of HCl salt **11**, 980 mg (5.15 mmol) of *p*-TsOH·H_2O, 3.0 mL (28.8 mmol) of BnOH, and 12 mL of benzene was heated at reflux with a Dean−Stark trap for 25 h. The reaction mixture was cooled to rt and evaporated, after which time the residue was dissolved in 40 mL of MeOH containing 2.75 g (12.6 mmol) of $(BOC)_2O$ and 6.0 mL (34.4 mmol) of DIEA. The mixture was stirred for 21 h and evaporated and the residue chromatographed (60 g of silica gel, eluted with 5% then 10% EtOAc/hexane) to afford 1.34 g (96%) of the benzyl ester **14**: mp 58.5−59.5 °C; IR (CH_2Cl_2) 1733, 1695 cm^{-1}; ^1H NMR δ 1.42 (s, 9H), 1.45−1.53 (m, 2H), 1.76 (tm, J = 10.3, 2H), 1.86−1.96 (m, 2H), 2.21(tt, J = 13.1, 3.3, 2H), 4.32 (t, J = 4.7, 1H), 5.24 (s, 2H), 7.30−7.41 (m, 5H); ^{13}C NMR δ 28.0 (q), 29.3 (t), 33.3 (t), 59.7 (d), 66.5 (s), 68.7 (s), 80.6 (s), 127.97 (d), 128.00 (d), 128.4 (d), 136.0 (s), 156.5 (s), 171.2 (s). Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.9; H, 7.6; N, 4.2. Found: C, 68.6; H, 7.8; N, 4.2.

7-(*tert*-Butyloxycarbonyl)-1-formyl-7-azabicyclo[2.2.1]-heptane (15). To a solution of 100 mg (0.30 mmoL) of ester **14** in 0.6 mL of toluene at −78 °C was added dropwise a solution of 0.34 mL (0.51 mmoL) of 1.5 M DibalH in toluene. The mixture was stirred for 2 h, and 0.2 mL (2.9 mmol) of MeOH precooled to −78 °C was added. The solution was stirred for 5 min, warmed to rt, and then diluted with 1 mL of 1 M aqueous HCl solution. The solution was then partitioned between 70 mL of CH_2Cl_2 and 20 mL of 1 N aqueous HCl solution. The CH_2Cl_2 layer was dried and evaporated and the residue chromatographed (15 g of silica gel, eluted with 8% EtOAc/hexane) to afford 57 mg (83%) of the aldehyde **15** (existing presumably as a 83/17 mixture of the aldehyde/hydrate), followed by 10 mg (15%) of alcohol **16**. The aldehyde could be reduced using $Ca(BH_4)_2$ to a single compound **16**. Heating (340 K) did not change the ratio. Selected data for the hydrate form of **15**: ^1H NMR δ 1.44 (s, 1.53H), 2.01 (t, J = 10 Hz, 0.34H), 4.24 (t, J = 4.4 Hz, 0.17H).

Preparation of Aldehyde 15 from Alcohol 16. To a solution of 0.49 mL (5.63 mmol) of oxalyl chloride in 10 mL of CH_2Cl_2 at −78 °C was added dropwise a solution of 0.8 mL (11.3 mmol) of DMSO. The pale yellow solution was stirred for 30 min at −78 °C and a solution of 640 mg (2.8 mmol) of alcohol **16** in 7 mL of CH_2Cl_2 added over a 10 min period. The

mixture was stirred for an additional 1 h to produce a white slurry, and then 3.14 mL (22.5 mmol) of Et_3N was added over 5 min and the mixture warmed to rt over 20 min. The mixture was stirred for an additional 30 min and then partitioned between 150 mL of CH_2Cl_2 and 20 mL of water. The organic layer was washed with 2 M aqueous H_3PO_4 (2 × 20 mL)and 20 mL of brine, dried, and evaporated. The residue was chromatographed (60 g of silica gel, eluted with 10% EtOAc/hexane) to afford 628 mg (99%) of aldehyde **15** (containing <5% of the hydrate) as a colorless oil. For analysis this material was passed through a 2 g plug of anhydrous $MgSO_4$ on top of 5 g of silica gel (eluted with 10% EtOAc/hexane): IR (CH_2Cl_2) 1723, 1683 cm^{-1}; ^1H NMR δ 1.43 (s, 9H), 1.53 (tm, J = 10.0 Hz, 1H), 1.62 (tm, J = 10.0, 2H), 1.88−2.06 (m, 4H), 4.30 (bm, 1H), 9.94 (s, 1H); ^{13}C NMR δ 27.9 (q), 29.3 (t), 30.3 (t), 58.9 (d), 73.4 (s), 81.3 (s), 156.5 (s, very low intensity), 197.3 (s). Anal. Calcd for $C_{12}H_{19}NO_3$: C, 64.0; H, 8.5; N, 6.2. Found: C, 64.0; H, 8.8; N, 6.2.

7-(*tert*-Butyloxycarbonyl)-1-(hydroxymethyl)-7-azabicyclo[2.2.1]heptane (16). To a slurry of 1.00 g (3.0 mmol) of ester **14** and 670 mg (6.0 mmol) of $CaCl_2$ in 10 mL of 60% EtOH/THF at 0 °C was added 457 mg (12.1 mmol) of $NaBH_4$ in one portion. The slurry was stirred for 25 min, warmed to rt over 10 min, stirred 1.5 h, and then poured into 30 mL of 1 M aqueous K_2CO_3. The aqueous layer was extracted with Et_2O (3 × 50 mL), and the combined organic layers were washed with 20 mL of 2 M aqueous HCl and 20 mL of brine, dried, and evaporated. The residue was chromatographed (60 g of silica gel, eluted with 8% EtOAc/hexane) to afford 680 mg (100%) of alcohol **16** as a colorless oil: IR (CH_2Cl_2) 3180−3520 (br), 1648 cm^{-1}; ^1H NMR δ 1.17−1.38 (m, 4H), 1.54−1.75 (m, 4H), 3.70 (d, J = 6.6, 2H), 4.30 (bt, J = 3.8, 1H), 4.71 (bs, 1H); ^{13}C NMR δ 27.9 (q), 28.8 (t), 31.4(t), 57.9 (d), 61.6 (t), 68.6 (s), 79.5 (s), 154.7 (s). Anal. Calcd for $C_{12}H_{21}NO_3$: C, 63.4; H, 9.3; N, 6.2. Found: C, 63.3; H, 9.4; N, 6.4.

7-(Benzyloxycarbonyl)-1-carboxy-7-azabicyclo[2.2.1]-heptane (17). To a solution of 400 mg (2.25 mmol) of **11**·-HCl in 4.5 mL of 1 M aqueous NaOH cooled to 5 °C was added seven equal portions of 0.06 mL (0.4 mmol) of CBZCl in 0.7 mL of dioxane, alternatively with seven portions of 0.32 mL of (0.32 mmol) of 1 M aqueous NaOH over a 1 h period. The mixture was allowed to warm to rt over 3 h, stirred for an additional 15 h, and then basified to pH 12 with NaOH. The mixture was stirred for 1.5 h and extracted with 67% Et_2O/hexane (2 × 25 mL) and the aqueous layer acidified to pH 2 with hydrochloric acid and extracted with CH_2Cl_2 (7 × 25 mL). The combined CH_2Cl_2 layers were dried and evaporated to afford 580 mg (93%) of acid **17**: mp 102−103 °C; IR (CH_2Cl_2) 3000−2200 (br), 1753, 1709 cm^{-1}; ^1H NMR δ 1.49−1.58 (m, 2H), 1.80−2.00 (m, 4H), 2.17−2.30 (m, 2H), 4.44 (bt, J = 4.4, 1H), 5.13 (s, 2H), 7.26−7.40 (m, 5H), 9.63 (s, 1H); ^{13}C NMR δ 29.2 (t), 33.6 (t), 59.7 (d), 67.7 (t), 69.1 (s), 127.97 (s), 128.11 (d), 128.43 (d), 135.8 (s), 157.0 (s), 175.3 (s). Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.4; H, 6.2; N, 5.1. Found: C, 65.2; H, 6.2; N, 5.1.

7-(Benzyloxycarbonyl)-1-(chlorocarbonyl)-7-azabicyclo-[2.2.1]heptane (18). To a solution of 578 mg (2.09 mmol) of acid **17** and 0.02 mL (0.22 mmol) of DMF in 4.5 mL of 1,2-DCE was added 0.38 mL (4.4 mmol) of oxalyl chloride. The mixture was stirred 24 h and was concentrated in vacuo until the theoretical mass (616.5 mg) was achieved. This material was taken directly into the next reaction without further purification: IR (CH_2Cl_2) 1777, 1708 cm^{-1}.

7-(Benzyloxycarbonyl)-1-(*tert*-butylaminocarbonyl)-7-azabicyclo[2.2.1]heptane (19). To a solution of 616 mg (2.1 mmol) of acid chloride **18** and 25 mg (0.20 mmol) of 4-DMAP in 8 mL of 1,2-DCE at 0 °C was added 2.2 mL (20.9 mmol) of *tert*-$BuNH_2$ dropwise over a 5 min period. The reaction mixture was stirred for 30 min and 0.58 mL (4.2 mmol) of Et_3N added. The mixture was warmed to rt, stirred for 24 h, heated to reflux for 15 min, and then diluted with 125 mL of CH_2Cl_2. The organic layer was washed with 2 M aqueous HCl (2 × 25 mL) and 30 mL of 1 M aqueous K_2CO_3, dried, and evaporated. The residue was chromatographed (60 g of silica gel, eluted with 15% EtOAc/hexane) to afford 671 mg (97%) of amide **19**: mp 115−116 °C; IR (CH_2Cl_2) 3425, 1709, 1678 cm^{-1}; ^1H NMR δ 1.32 (s, 9H), 1.42−1.51 (m, 2H), 1.78−1.91 (m, 4H), 1.97−2.07 (m, 2H), 4.39 (t, J = 4.5, 1H), 5.11 (s, 2H), 5.84 (s, 1H), 7.27−7.38 (m, 5H) ^{13}C NMR δ 28.5 (q), 29.1 (t), 34.1 (t), 50.9 (s), 60.7 (d), 67.2 (t), 71.3 (s), 128.05 (s), 128.11 (d), 128.42 (d), 136.2 (s), 157.5 (s), 170.4 (s). Anal. Calcd for $C_{19}H_{26}N_2O_3$: C, 69.1; H, 7.9; N, 8.5. Found: C, 68.9; H, 8.1; N, 8.4.

(2*S*)-*cis*-1-(Benzyloxycarbonyl)-5-[2-[(methanesulfonyl)oxy]ethyl]proline *tert*-Butyl Ester (20). To a solution of 8.87 g (25.4 mmol) of alcohol **7** in 140 mL of CH_2Cl_2 at 0 °C was added 8.8 mL (63.5 mmol) of Et_3N, followed by 2.50 mL (31.8 mmol) of MsCl. The reaction mixture was stirred for 5 min, warmed to rt over 5 min, washed with 20 mL of 1 M aqueous H_3PO_4 and 30 mL of 50% (v/v) aqueous 2 M NaOH/$NaHCO_3$ (saturated), dried, and evaporated to afford the crude mesylate **20**. The oil was dried at 0.3 Torr, and the residual pale yellow oil, 10.85 g (100%), was used in the next reaction without further purification.

(2*S*)-*cis*-1-(Benzyloxycarbonyl)-5-[2-(phenylselenyl)-ethyl]proline *tert*-Butyl Ester (21). To a stirred solution of 20.6 g (66.0 mmol) of $(PhSe)_2$ in 90 mL of absolute EtOH at 0 °C was added 2.50 g (66.0 mmol) of $NaBH_4$ slowly over 8 min, followed by stirring of the mixture for an additional 5 min and then heating to reflux for 1 h and cooling to 0 °C. To this orange slurry was added a solution of 10.85 g (25.4 mmol) of mesylate **20** in 44 mL of EtOH over a 5 min period. The mixture was gradually heated to reflux over 10 min, stirred 20 min, and then allowed to cool to rt over 35 min. It was diluted with 750 mL of EtOAc and washed with 75 mL of saturated aqueous $NaHCO_3$. The aqueous layer was back-extracted with EtOAc (3 × 75 mL), and the combined organic layers were dried, evaporated, and chromatographed (300 g of silica gel, eluted with 5% CH_2Cl_2/hexane to remove selenide byproducts then 15% EtOAc/hexane) to afford 11.79 g (95% overall from alcohol **7**) of selenide **21**: $[\alpha]^{20}_D$ −8.7° (*c* 1.3, $CHCl_3$); IR (CH_2Cl_2) 1738, 1700 cm^{-1}; ^1H NMR (rotomers, C_6D_6, 298 K) δ 1.15−1.21 (m, 1H), 1.31 (s, 6.13H), 1.44 (s, 3.87H), 1.63−1.77 (m, 2H), 1.78−1.92 (m, 1H), 2.22−2.32 (m, 0.43H), 2.41−2.51 (m, 0.57H), 2.80−2.90 (m, 0.86H), 3 02−3.17 (m, 1.14H), 3.79−3.84 (m, 0.43H), 4.07−4.13 (m, 0.57H), 4.17 (t, J = 7.8, 0.57H), 4.39 (t, J = 7.9, 0.43H), 5.02−5.35 (m, 2H), 7.00−7.12 (m, 4H), 7.17 (t, J = 7.4, 2H), 7.31 (m, 2H), 7.50 (d, J = 6.5, 0.86H), 7.59 (d, J = 7.2, 1.14H); ^{13}C NMR (rotomers, C_6D_6, 298 K, three obscured signals between δ 127.75−128.24) δ 24.3, 24.4, 27.79, 27.95, 28.1, 29.1, 29.6, 30.1, 35.6, 58.4, 59.3, 60.6, 61.2, 66.9, 67.1, 77.7, 80.6, 126.6, 128.53, 128.60, 128.92, 129.06, 131.29, 131.46, 132.51, 132.58, 137.34, 137.42, 154.44, 154.73, 172.1; ^1H NMR (C_6D_6, 339 K) δ 1.15−1.40 (m, 11H), 1.57−1.71 (m, 2H), 1.77−1.87 (m, 1H), 2.22−2.43 (bm, 1H), 2.77−3.00 (bm, 1H), 3.83−4.00 (bm, 1H), 4.06−4.23 (bm, 1H), 4.99 (d, J = 12.5, 1H), 5.07 (d, J = 12.5, 1H), 6.90−7.02 (m, 4H), 7.03−7.10 (m, 2H), 7.20 (d, J = 7.4, 2H), 7.45 (bd, J = 6.6, 2H); ^{13}C NMR (C_6D_6, 339 K) δ 24.6 (t), 28.0 (q), 28.7 (t), 30.0 (t), 35.8 (t), 59.2 (d), 61.1 (d), 67.1 (t), 80.6 (s), 126.7 (d), 127.98 (d), 128.29 (d), 128.56 (d), 129.2 (d), 131.5 (s), 132.9 (d), 137.6 (s), 154.7 (s), 171.9 (s). Anal. Calcd for $C_{25}H_{31}NO_4$-Se: C, 61.5; H, 6.4; N, 2.9. Found: C, 61.4; H, 6.4; N, 3.0.

(2*S*)-*cis*-1-(Benzyloxycarbonyl)-5-vinylproline *tert*-Butyl Ester (22). To a solution of 11.68 g (23.9 mmol) of selenide **21** in 176 mL of THF was added a solution of $NaIO_4$ (15.34, 71.7 mmol) in 176 mL of water. The mixture was stirred for 45 min, heated to 55 °C, and stirred for 2.5 h more. To this mixture was added 6.6 mL of 30% H_2O_2, the mixture was stirred 30 min, and then three portions of 6.6 mL of 30% H_2O_2 at 1 h intervals were added. During the second 1 h, a single portion of 1.33 mL (12.1 mmol) of NMM was also added. The mixture was heated for an addition 3 h, cooled to rt over 1 h, and diluted with 750 mL of EtOAc, which was washed with saturated aqueous $NaHCO_3$ (2 × 200 mL), 200 mL of 1 M aqueous H_3PO_4, dried, and evaporated. The residue was chromatographed (400 g of silica gel, eluted with 25% EtOAc/hexane) to afford 7.85 g (99%) of olefin **22** as a pale yellow oil: $[\alpha]^{20}_D$ −51.7° (*c* 1.5, $CHCl_3$); IR (CH_2Cl_2) 1740, 1706 cm^{-1}; ^1H NMR (rotomers, C_6D_6, 298 K) δ 1.21 (s, 4.3H), 1.34 (s, 4.7H) 1.26−1.43 (m, 2H), 1.57−1.73 (m, 2H), 4.03−4.11 (m, 1H), 4.24−4.31 (m, 0.52H), 4.33−4.42 (m, 0.48H), 4.93−5.12 (m, 3H), 5.34 (d, J = 7.0, 0.52H), 5.49 (d, J = 7.1, 0.48H), 5.78−5.96 (m, 1H), 7.00 (d, J = 7.3, 1H), 7.03−7.12 (m, 2H), 7.17−

7.23 (m, 2H); ^{13}C NMR (rotomers, C_6D_6, 298 K) δ 27.85 (q), 27.96 (q), 28.13 (t), 29.2 (t), 30.6 (t), 31.6 (t), 60.6 (d), 60.9 (d), 61.2 (d), 61.6 (d), 66.87 (t), 66.89 (t), 80.6 (s), 114.9 (t), 115.3 (t), 127.9 (d), 129.2 (d), 132.5 (d), 137.5 (s), 138.7 (d), 139.4 (d), 153.9 (s), 154.8 (s), 171.7 (s), 171.8 (s); ^{1}H NMR (C_6D_6, 339 K) δ 1.29 (s, 9H), 1.40−1.56 (m, 2H), 1.65−1.78 (m, 2H), 4.12−4.32 (m, 2H), 4.98 (d, J = 10.2, 1H), 5.02 (d, J = 13.2, 1H), 5.06 (d, J = 12.6, 1H), 5.32 (d, J = 16.7, 1H), 5.89 (ddd, J = 17.0, 10.4, 6.4, 1H), 6.99−7.03 (m, 1H), 7.06−7.11 (m, 2H), 7.20 (d, J = 7.3, 2H); ^{13}C NMR (C_6D_6, 339 K) δ 28.0 (q), 28.8 (t), 31.3 (t), 61.0 (d), 61.4 (d), 67.0 (t), 80.6 (s), 115.8 (t), 127.3 (d), 129.2 (d), 132.9 (d), 137.7 (s), 139.4 (d), 154.47 (s), 154.79 (s), 171.7 (s). Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.9; H, 7.3; N, 4.0. Found: C, 68.6; H, 7.6; N, 4.1.

(2*S*)-*cis*-1-(Benzyloxycarbonyl)-5-(*S*)-oxiranylproline *tert*-Butyl Ester (23*β*) and (2*S*)-*cis*-1-(Benzyloxycarbonyl)-5-(*R*)-oxiranylproline *tert*-Butyl Ester (23α). To a solution of 15.74 g (63.8 mmol) of *m*-CPBA (prewashed with pH 8 aqueous 0.1 M K_2HPO_4 (2 × 70 mL) in 295 mL of CH_2Cl_2 at −10 °C) was added a solution of 7.60 g (22.9 mmol) of olefin **22** in 35 mL of CH_2Cl_2 over 5 min. The mixture was allowed to warm to 4 °C over 6 h and then was stirred for an additional 41 h at 4 °C. The resulting slurry was filtered at 0 °C, and the filtrate was added over 5 min to a rapidly stirred ice-cold solution of 700 mL of 10% aqueous Na_2SO_3. The aqueous layer was back-extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with 10% aqueous Na_2SO_3 (2 × 200 mL), pH 8 aqueous 0.1 M K_2HPO_4 (2 × 200 mL), and saturated aqueous $NaHCO_3$ (200 mL), dried, evaporated, and chromatographed (200 g of silica gel, eluted with 15% EtOAc/hexane) to afford 230 mg (3%) of recovered olefin **22**, followed by 7.06 g (89%) of epoxide **23** as a 2.2/1 mixture of easily separable **23***β*/**23**α epoxide diastereomers. Chromatography of 3.19 g of this mixture (300 g of silica gel, eluted with 13% and then 25% EtOAc/hexane) gave 2.19 g of **23***β*, followed by 1.00 g of **23**α.

23*β*: $[\alpha]^{20}_D$ −45.5° (*c* 1.9, $CHCl_3$) IR (CH_2Cl_2) 1740, 1705 cm^{-1}; ^{1}H NMR (rotomers, C_6D_6, 298 K) δ 1.21 (s, 5.1H), 1.33 (s, 4.9H), 1.33−1.49 (m, 1H), 1.58−1.82 (m, 3H), 2.32−2.42 (m, 0.86 H), 2.57 (t, J = 4.6, 0.57H) 2.75 (dd J = 4.8, 2.1, 0.57H) 3.03−3.10 (m, 0.43H), 3.11−3.18 (m, 0.57H), 3.26 (t, J = 7.1, 0.43H), 3.56 (td, J = 5.6, 2.2 Hz, 0.57H), 4.04 (t, J = 7.2, 0.57H), 4.23−4.30 (m, 0.43H), 4.90−5.13 (m, 2H), 7.00−7.32 (m, 5H); ^{13}C NMR (rotomers, C_6D_6, 298 K, two =*C*H obscured) δ 27.23, 27.75, 27.9, 28.24, 28.48, 29.3, 47.66, 47.86, 52.64, 52.99, 60.15, 60.62, 61.06, 61.38, 67.00, 67.26, 80.73, 80.79, 126.92, 127.20, 128.55, 128.57, 137.05, 137.20, 154.23, 154.52, 171.9; ^{1}H NMR (C_6D_6, 339 K) δ 1.27 (s, 9H), 1.42−1.58 (m, 1H), 1.65−1.83 (m, 3H), 2.38−2.68 (bm, 2H), 3.04−3.14 (bm, 1H) 3.38−3.58 (bm, 1H), 4.08−4.24 (bm, 1H) 4.92−5.08 (m, 2H), 6.97−7.15 (m, 3H), 7.17 (d, J = 7.3, 2H); ^{13}C NMR (C_6D_6, 339 K) δ 27.56 (t), 27.96 (q), 29.0 (t), 47.6 (t), 52.9 (d), 60.9 (d), 61.2 (d), 67.2 (t), 80.8 (s), 126.97 (d), 127.76 (d), 128.6 (d), 137.4 (s), 154.5 (s), 171.8 (s). Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.7; H, 7.3; N, 4.0. Found: C, 65.6; H, 7.3; N, 3.8.

23α: $[\alpha]^{20}_D$ −9.0° (*c* 1.1, $CHCl_3$); IR (CH_2Cl_2) 1737, 1702 cm^{-1}; ^{1}H NMR (rotomers, C_6D_6, 298 K) δ 1.22 (s, 5.04H), 1.32 (s, 3.96H), 1.32−1.59 (m, 2H), 1.63−2.03 (m, three overlapping signals, 2H), 2.27−2.36 (m, 0.44H), 2.36−2.45 (m, 0.56H) 2.48−2.58 (m, 0.44H), 2.76−2.82 (m, 0.56H) 2.87−3.03 (m, two overlapping signals, 1H), 3.66−3.75 (m, 0.44H), 3.99 (t, J = 7.5, 0.56H) 4.07−4.16 (m, 0.56H) 4.17−4.27 (m, 0.44H) 4.95−5.18 (m, 2H) 6.98−7.18 (m, 3H), 7.18−7.30 (m, 2H); ^{13}C NMR (rotomers, C_6D_6, 298 K, two =*C*H obscured) δ 27.1, 27.82, 27.90, 28.64, 29.7, 44.0, 44.3, 53.5, 53.9, 58.15, 58.22, 60.6, 61.3, 67.1, 80.6, 128.5, 137.23, 137.38, 154.7, 171.15, 171.27; ^{1}H NMR (C_6D_6, 339 K) δ 1.28 (s, 9H), 1.20−1.48 (m, 1H), 1.48−1.58 (m, 1H), 1.67−1.77 (m, 1H) 1.80−1.92 (bm, 1H), 2.36 (t, J = 4.3, 1H), 2.62 (bm, 1H), 2.97−3.03 (bm, 1H), 3.83−4.08 (bm, 1H), 4.09−4.22 (bm, 1H), 5.00−5.14 (m, 2H) 7.02 (t, J = 7.2, 1H) 7.09 (t J = 7.6, 2H) 7.24 (d, J = 7.3, 2H); ^{13}C NMR (C_6D_6, 339 K) δ 27.4 (t), 28.0 (q), 29.3 (t), 44.2 (t), 53.6 (d), 58.5 (d), 61.2 (d), 67.2 (t), 80.6 (s), 128.0 (d), 128.2 (d), 128.5 (d), 137.5 (s), 154.8 (s), 171.2 (s). Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.7; H, 7.3; N, 4.0. Found: C, 65.5; H, 7.2; N, 4.1.

(2*S*)-*cis*-1-(Benzyloxycarbonyl)-5-[(1′*R*)-2′-bromo-1′-[(triethylsilyl)oxy]ethyl]proline *tert*-Butyl Ester (24*β*) and (2*S*)-*cis*-1-(Benzyloxycarbonyl)-5-[(1′*S*)-2′-bromo-1′-[(triethylsilyl)oxy]ethyl]proline *tert*-Butyl Ester (24α). To a solution of 670 mg (2.55 mmol) of PPh_3 in 4 mL of CH_2Cl_2 was added 0.97 mL (2.55 mmol) of freshly prepared 2.63 M Br_2 in CH_2Cl_2 to form a slurry that was stirred for 10 min. To this mixture was added a solution of 785 mg (2.25 mmol) of epoxide **23**, as a 2.2/1 mixture of *β*/α epoxide diastereomers, in 7 mL of CH_2Cl_2 over a 5 min period. The mixture was stirred for 50 min, transferred into 25 mL of rapidly stirring ice-cold saturated aqueous $NaHCO_3$, stirred for 3 min, and diluted with 25 mL of CH_2Cl_2. The aqueous layer was extracted with 25 mL of CH_2Cl_2, and the combined organic extract was dried, evaporated at rt, and chromatographed (15 g of silica gel, eluted with 13% EtOAc/hexane) to afford 895 mg (92%) of the mixed bromohydrins. To a solution of the mixture of bromohydrins in 20 mL of CH_2Cl_2 at 0 °C was added 786 mg (11.5 mmol) of imidazole, followed by 780 mL (4.65 mmol) of TESCl dropwise over 3 min. The mixture was warmed to rt after 10 min, stirred for 35 min, and evaporated. The residue was chromatographed (15 g of silica gel, eluted with 10% EtOAc/hexane) to afford a mixture of the silyl ethers (**24***β*/**24**α) and unreacted TESCl. Heating at 60 °C/0.1 Torr for 15 min and then for 36 h at rt afforded 1.10 g (98%, 90% overall from epoxides **23***β*/**23**α) of pure silyl ethers **24** as a colorless oil, existing as a 2/1 mixture of diastereomers (**24***β*/**24**α). The yield range of this two-step procedure, 87−92%, was identical when using the α- or *β*-epoxide diastereomer of **23** to afford, respectively, the individual bromo silyl ether diastereomers of **24**.

24*β*: $[\alpha]^{20}_D$ −4.6° (*c* 1.6, $CHCl_3$); IR (CH_2Cl_2) 1740, 1703 cm^{-1}; ^{1}H NMR (rotomers, C_6D_6, 298 K) δ 0.50−0.76 (br m, 6H), 0.80−1.07 (br m, 9H), 1.24 (s, 5.6H), 1.10−1.27 (m, 1H), 1.34 (s, 4.4H), 1.76 (t, J = 8.1, 2H) 1.80−1.93 (m, 1H), 3.47−3.60 (m, 0.76H), 3.62−3.80 (m, 1.24 H) 3.93−4.32 (m, 3H) 4.97 (d, J = 12.5, 1H) 4.98−5.16 (bm, 1H), 7.01 (t, J = 7.2, 1H), 7.03−7.14 (m, 2H), 7.15−7.30 (bm, 2H); ^{13}C NMR (rotomers, C_6D_6, 298 K, two =*C*H obscured) δ 5.7, 7.2, 26.3, 26.7, 27.9, 29.1, 37.4, 37.7, 60.9, 61.5, 61.7, 63.0, 67.3, 73.2, 74.1, 80.7, 128.6, 129.0, 137.1, 155.1, 171.7; ^{1}H NMR (C_6D_6, 339 K) δ 0.66 (q, J = 7.9, 6H), 0.96 (t, J = 8.0, 9H), 1.29 (s, 9H), 1.26−1.37 (m, 2H) 1.76−1.82 (m, 2H), 1.87−1.97 (bm, 1H), 3.50−3.57 (bm, 1H), 3.58−3.67 (bm, 1H) 4.08 (t, J = 6.6, 1H), 4.12−4.22 (bm, 2H), 5.03 (d, J = 12.4, 1H) 5.06 (d, J = 12.4, 1H), 7.02 (t, J = 7.3, 2H), 7.08 (t, J = 7.6, 2H), 7.22 (d, J = 7.3, 2H); ^{13}C NMR (C_6D_6, 339 K) δ 5.9 (t), 7.1 (q), 26.6 (t), 28.0 (q), 28.8 (t), 37.4 (t), 61.4 (d), 62.9 (d), 67.4 (t), 74.0 (d), 80.8 (s), 128.15 (d), 128.50 (d), 128.58 (d), 137.2 (s), 155.2 (s), 171.6 (s). Anal. Calcd for $C_{25}H_{40}NO_5SiBr$: C, 55.3; H, 7.4; N, 2.6. Found: C, 55.6; H, 7.6; N, 2.3.

24α: mp 90−91.5 °C; $[\alpha]^{20}_D$ −18.8° (*c* 1.1, $CHCl_3$); IR (CH_2Cl_2) 1736, 1703 cm^{-1}; ^{1}H NMR (rotomers, C_6D_6, 298 K) δ 0.48−0.67 (m, 2.88H), 0.73−0.83 (m, 3H), 1.19 (s, 4.32H), 1.36 (s, 4.68H), 1.20−1.48 (m, 2H), 1.53−1.62 (m, 1H), 1.64−1.77 (m, 1H), 3.10 (t, J = 10.0, 0.48H), 3.10 (t, J = 10.0, 0.48H), 3.21 (t, J = 9.9, 0.52H), 3.63−3.68 (m, 0.48H), 3.87−3.97 (m, 1.04H), 4.13 (t, J = 8.5, 0.52H), 4.27 (t, J = 10.1, 0.52H), 4.36 (t, J = 10.1, 0.48H), 4.46−4.51 (m, 0.48H), 4.83−5.05 (m, 2H), 6.99−7.18 (m, 5H); ^{13}C NMR (rotomers, C_6D_6, 298 K, one =*C*H obscured) δ 5.3, 5.5, 7.2, 23.9, 24.7, 27.78, 27.96, 28.9, 30.0, 35.7, 61.6, 62.5, 62.8, 64.1, 67.3, 67.8, 73.4, 74.2, 81.03, 81.11, 128.58, 128.65, 129.1, 136.6, 136.9, 154.8, 171.6; ^{1}H NMR (C_6D_6, 339 K) δ 0.57−0.80 (bm, 6H), 0.93−1.08 (bm, 9H), 1.28 (s, 9H), 1.31−1.45 (m, 1H), 1.50−1.58 (m, 1H), 1.60−1.71 (m, 1H) 1.77−1.85 (bm, 1H), 3.21 (t, J = 9.6, 1H), 3.77−3.95 (bm, 1H), 4.00−4.12 (bm, 1H) 4.21 (dd, J = 10.3, 1.3, 1H) 4.58−4.85 (bm, 1H) 4.95 (d, J = 12.3, 1H) 5.00 (d, J = 12.3, 1H) 7.01 (t, J = 7.3, 1H), 7.08 (t, J = 7.6, 2H), 7.17 (d, J = 7.2, 2H); ^{13}C NMR (C_6D_6, 339 K) δ 5.7 (t), 7.0 (q), 24.5 (t), 28.0 (q), 29.5 (t), 35.5 (t), 62.2 (d), 63.8 (d), 67.6 (t) 73.8 (d), 81.1 (s), 128.2 (d), 128.6 (d), 137.0 (s), 155.0 (s), 171.5 (s). Anal. Calcd for $C_{25}H_{40}NO_5SiBr$: C, 55.3; H, 7.4; N, 2.6. Found: C, 55.6; H, 7.7; N, 2.3.

(1*S*,3*S*,4*R*)-7-(Benzyloxycarbonyl)-1-carboxy-3-hydroxy-7-azabicyclo[2.2.1]heptane *tert*-Butyl Ester (25*β*) and (1*S*,3*R*,4*R*)-7-(Benzyloxycarbonyl)-1-carboxy-3-hydroxy-7-azabicyclo[2.2.1]heptane *tert*-Butyl Ester (25α). Cyclization of a Diastereomeric Mixture of 24α/24*β* or 24α.

Procedure A. To a solution of 8.5 mL (7.83 mmol) of KHMDS in 150 mL of THF at −70 °C was added a solution of 3.08 g (5.68 mmol) of silyl ether **24**, existing as a 2/1 mixture **24***β*/**24**α, over a 10 min period via cannula. The mixture was stirred for 10 min, warmed to −40 °C, stirred for 1 h, warmed to −10 °C, stirred for 30 min, warmed to 0 °C, and stirred for 20 min. The mixture was warmed to rt over 10 min and stirred 20 min, and 0.3 mL of AcOH (5.68 mmol) was added. The mixture was concentrated at ambient temperature to 10 mL and diluted with 400 mL of EtOAc, the EtOAc layer was washed with 1 M H_3PO_4 (2 × 100 mL) and saturated aqueous $NaHCO_3$ (2 × 50 mL), dried, and evaporated, and the residue was immediately dissolved in 50 mL of THF. The aqueous washes from the extraction were then combined. To the organic residue was added 6.9 mL of 1 M TBAF in THF, the mixture was stirred for 20 min, and then 0.42 mL (7.41 mmol) of AcOH was added. The solution was evaporated at rt, and the residue was chromatographed (100 g of silica gel, eluted with 25% EtOAc/hexane then 1% MeOH/35% EtOAc/hexane) to afford 1.65 g (84%) of alcohol **25**, existing as 3/1 mixture of *β*/α stereoisomers that was used immediately in the preparation of ketone **26**. The *β*/α stereoisomers were completely separated (the α-stereoisomer eluted first) during the chromatography but were recombined for the preparation of ketone **26**. Alcohol **25***β* was labile to mild heating under reduced pressure but could be stored indefinitely at 0 °C.

(1*S*,3*S*,4*R*)-7-(Benzyloxycarbonyl)-1-carboxy-3-[(triethylsilyl)oxy]-7-azabicyclo[2.2.1]heptane *tert*-Butyl Ester, TES Ether of 25*β*. Cyclization of 24*β*. Procedure B. Following the procedure described for the preparation of **10** and **13**, except that the mixture, rather than being stirred for 30 min at 0 °C, was stirred for 30 min at −10 °C and then 20 min at 0 °C, 131 mg of **24***β* was converted to 104 mg (93%) of the triethylsilyl ether of **25***β*. Following the TBAF treatment described in procedure A, 150 mg (0.325 mmol) of the TES ether of **24***β* was converted to 112 mg (99%) of alcohol **25***β*.

TES ether of 25*β*: IR (CH_2Cl_2) 1728, 1703 cm^{-1}; ^1H NMR δ 0.53 (q, J = 8.1, 6H), 0.89 (t, J = 8.0, 9H), 1.22−1.30 (m, 1H), 1.40−1.54 (m, 1H), 1.45 (s, 9H), 1.78−1.88 (m, 1H), 1.98−2.12 (m, 3H), 3.93 (dd, J = 5.6, 3.3, 1H), 4.19 (d, J = 5.4, 1H), 4.93 (d, J = 12.5, 1H), 5.18 (d, J = 12.5, 1H), 7.23−7.35 (m, 5H); ^{13}C NMR δ 4.6 (t), 6.6 (q), 23.9 (t), 27.8 (q), 33.2 (t), 44.4 (t), 66.63 (d), 66.84 (t), 68.5 (s), 74.9 (d), 81.2 (s), 127.73 (d), 127.78 (d), 128.2 (d), 136.5 (s), 157.2 (s), 169.2 (s).

25*β*: mp 101−102 °C; $[\alpha]^{20}_D$ −38.4° (*c* 1.4, $CHCl_3$); IR (CH_2Cl_2) 3600−3300, 1733, 1710 cm^{-1}; ^1H NMR δ 1.27−1.37 (m, 1H) 1.46 (s, 9H), 1.50−1.58 (m, 1H), 1.76−1.87 (m, 1H), 1.96−2.06 (m, 1H), 2.11 (dd, J = 12.9, 6.8, 1H) 2.48 (bs, 1H), 3.92 (dm, J = 6.3, 1H), 4.26 (d, J = 5.5, 1H) 5.08 (d, J = 12.4, 1H), 5.12 (d, J = 12.3, 1H) 7.26−7.35 (m, 5H); ^{13}C NMR δ 24.0 (t), 27.8 (q), 31.2 (t), 45.7 (t), 66.3 (d), 67.2 (t), 68.8 (s), 73.5 (d), 81.5 (s), 127.92 (d), 127.98 (d), 128.3 (d), 136.2 (s), 157.4 (s), 169.0 (s). Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.7; H, 7.3; N, 4.0. Found: C, 65.8; H, 7.3; N, 3.8.

25α: mp 94−96 °C; $[\alpha]^{20}_D$ −10.5° (*c* 1.1, $CHCl_3$); IR (CH_2Cl_2) 3630−3400, 1733, 1713 cm^{-1}; ^1H NMR δ 1.38 (dd, J = 12.8, 3.2, 1H) 1.45 (s, 9H), 1.68−1.83 (m, 1H), 2.13−2.24 (m, 1H) 2.55 (t, J = 10.1, 1H), 4.28 (t, J = 4.4, 1H), 4.33−4.38 (m, 1H), 5.10 (s, 1H), 7.30−7.40 (m, 5H); ^{13}C NMR δ 20.9 (t), 27.8 (q), 32.9 (t), 42.6 (t), 63.2 (d), 67.2 (t), 69.6 (s), 70.3 (d), 81.4 (s), 127.9 (d), 128.07 (d), 128.43 (d), 136.2 (s), 156.6 (s), 169.3 (s). Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.7; H, 7.3; N, 4.0. Found: C, 66.0; H, 7.6; N, 3.9.

(1*S*,4*R*)-7-(Benzyloxycarbonyl)-1-carboxy-7-azabicyclo-[2.2.1]-3-heptanone *tert*-Butyl Ester (26). To a solution of 0.79 mL (9.04 mmol) of oxalyl chloride in 17 mL of CH_2Cl_2 at −78 °C was added dropwise 1.28 mL (18.1 mmol) of DMSO. The pale yellow solution was stirred for 45 min at −78 °C, and a solution of 1.495 g (4.30 mmol) of a mixture of alcohols **25***β*/**25**α, prepared according to cyclization procedure A, was added in 35 mL of CH_2Cl_2 added over a 10 min period. The mixture was stirred for an additional 1 h to produce a white slurry, and then 4.8 mL (34.4 mmol) of Et_3N was added over 5 min and the mixture stirred for 30 min and then warmed to rt. The mixture was stirred for an additional 1 h and then partitioned between 250 mL of CH_2Cl_2 and 30 mL of water. The organic layer was washed with 1 M aqueous H_3PO_4 (2 × 5 mL) and 25 mL of saturated aqueous $NaHCO_3$, dried, and evaporated. The residue was chromatographed (125 g of silica gel, eluted with 10% EtOAc/hexane) to afford 1.38 g (93%) of ketone **26**: mp 68−69 °C; $[\alpha]^{20}_D$ −40.7° (*c* 1.3, $CHCl_3$); IR (CH_2Cl_2) 3630−3400, 1733, 1713 cm^{-1}; ^1H NMR δ 1.49 (s, 9H), 1.64 (ddd, J = 13.2, 9.0, 4.5, 1H) 1.85 (ddd, J = 12.5, 9.0, 4.4, 1H) 2.11 (ddd, J = 15.3, 12.8, 5.3, 1H), 2.28 (d, J = 17.7, 1H), 2.36 (ddd, J = 12.2, 4.3, 3.4, 1H), 2.84 (dd, J = 17.7, 2.6H), 4.41 (d, J = 5.6, 1H) 5.10 (d, J = 12.3, 1H) 5.14 (d, J = 12.3, 1H), 7.27−7.37 (m, 5H); ^{13}C NMR δ 23.9 (t), 27.7 (q), 31.5 (t), 47.3 (t), 66.9 (d), 67.7 (t), 69.4 (s), 82.3 (s), 127.9 (d), 128.25 (d), 128.45 (d), 135.6 (s), 155.9 (s), 167.2 (s), 207.0 (s). Anal. Calcd for $C_{19}H_{23}NO_5$: C, 66.1; H, 6.7; N, 4.1. Found: C, 65.9; H, 6.9; N, 3.7.

(1*S*,3*R*,4*R*)-7-(Benzyloxycarbonyl)-1-carboxy-3-hydroxy-7-azabicyclo[2.2.1]heptane *tert*-Butyl Ester (25α). To a solution of 66 mg (0.19 mmol) of ketone **26** in 3 mL of THF cooled to −55 °C was added dropwise 0.22 mL of a 1 M L-Selectride (Aldrich) solution in THF. The mixture was allowed to warm to −40 °C over 15 min, stirred for 30 min, warmed to rt, stirred for 20 min, and then quenched with 1 mL of 50% (v/v) EtOH/saturated aqueous NH_4Cl and partitioned between 70 mL of CH_2Cl_2 and 10 mL of water. The organic layer was washed with 20 mL of 2 M NaOH containing 1 mL of 30% H_2O_2, dried, evaporated, and chromatographed (15 g of silica gel, eluted with 40% EtOAc/hexane) to afford 57 mg (87%) of alcohol **25**α, identical spectroscopically to that isolated from the transannular alkylation sequence.

(1*S*,3*R*,4*R*)-7-(Benzyloxycarbonyl)-1-carboxy-3-fluoro-7-azabicyclo[2.2.1]heptane *tert*-Butyl Ester (27α) and (1*S*,3*S*,4*R*)-7-(Benzyloxycarbonyl)-1-carboxy-3-fluoro-7-azabicyclo[2.2.1]heptane *tert*-Butyl Ester (27*β*). To a solution of 0.11 mL (0.86 mmol) of DAST in 1.38 mL of pyridine at 0 °C was added a solution of 300 mg (0.86 mmol) of alcohol **25**α in 5 mL of CH_2Cl_2. The mixture was warmed to rt over 5 min, stirred for 6 h, cooled to 0 °C, and quenched by the dropwise addition of 1 mL of H_2O and then partitioned between 75 mL of CH_2Cl_2 and 20 mL of aqueous $NaHCO_3$. The aqueous layer was washed with CH_2Cl_2 (2 × 40 mL), and the combined organic extracts were washed with 10 mL of 2 M aqueous HCl and 10 mL of brine, dried, and evaporated. The residue was chromatographed (70 g of silica gel, eluted with 15% EtOAc/hexane) to afford 44 mg (18%) of fluoro analogue **27**α, 35 mg (14%) of **27***β*, and 50 mg (17%) of recovered **25**α.

27α: $[\alpha]^{20}_D$ −5.8° (*c* 1.2, $CHCl_3$); IR (CH_2Cl_2) 1725, 1715 cm^{-1}; ^1H NMR δ 1.47 (s, 9H), 1.62−1.73 (m, 1H), 1.75−1.86 (m, 2H), 2.08−2.17 (m, 1H), 2.18−2.27 (m, 1H), 2.52−2.65 (m, 1H), 4.50 (t, J = 4.1, 1H), 5.07 (dm, J_{HF} = 53, 1H), 5.11 (s, 2H), 7.26−7.38 (m, 5H); ^{19}F NMR δ −42.55 (ddd, J_{FH} = 53.4, 34.8, 18.7, 1F); ^{13}C NMR δ 20.2 (t, J_{CF} = 7.0), 27.8 (q), 32.0 (t), 40.8 (t, J_{CF} = 23.1), 61.5 (d, J_{CF} = 23.3), 67.4 (t), 69.9 (s), 81.6 (s), 89.1 (d, J_{CF} = 190.7), 127.96 (d), 128.18 (d), 128.46 (d), 136.0 (s), 156.2 (s), 168.5 (s). Anal. Calcd for $C_{19}H_{24}NO_4F$: C, 65.3; H, 6.9; N, 4.0. Found: C, 65.5; H, 7.1; N, 3.9.

27*β*: $[\alpha]^{20}_D$ −20.7° (*c* 1.5, $CHCl_3$); IR (CH_2Cl_2) 1740, 1715 cm^{-1}; ^1H NMR δ 1.24−1.33 (m, 2H), 1.49 (s, 9H), 1.45−1.62 (m, 1H), 1.85−1.97 (m, 1H), 2.03−2.20 (m, 2H), 2.35 (dd, J = 38.8, 14.5, 1H), 4.53 (dd, J = 7.8, 6.4, 1H), 4.80 (dd, J_{HF} = 54.5, 5.5, 1H), 5.09 (d, J = 12.3, 1H), 5.14 (d, J = 12.3, 1H), 7.26−7.40 (m, 5H); ^{19}F NMR δ −17.93 (ddm, J_{FH} = 54.5, 38.8, 1F); ^{13}C NMR δ 22.3 (t, J_{CF} = 7.3), 27.8 (q), 32.3 (t), 41.9 (t, J_{CF} = 22.7), 63.9 (d, J_{CF} = 20.0), 67.2 (t), 68.4 (s), 81.7 (s), 93.8 (d, J_{CF} = 188.5), 127.9 (d), 128.3 (d), 136.1 (s), 156.7 (s), 168.8 (s). Anal. Calcd for $C_{19}H_{24}NO_4F$: C, 65.3; H, 6.9; N, 4.0. Found: C, 65.4; H, 7.0; N, 3.9.

(1*S*,4*R*)-7-(Benzyloxycarbonyl)-1-carboxy-3,3-difluoro-7-azabicyclo[2.2.1]-heptane *tert*-Butyl Ester (28). To a solution of 180 mg (0.52 mmol) of ketone **26** in 5 mL of CH_2Cl_2 at −78 °C was added 0.35 mL (2.61 mmol) of DAST. The mixture warmed to rt over 5 min, stirred for 38 h, and cooled to 0 °C, and an additional 0.14 mL (1.04 mmol) of DAST was added. The mixture was then warmed to rt, stirred for 17 h, cooled to 0 °C, and quenched by the dropwise addition of 1 mL of H_2O. The solution was partitioned between 70 mL of CH_2Cl_2 and 20 mL of aqueous $NaHCO_3$, the aqueous layer was washed with CH_2Cl_2 (2 × 40 mL), and the combined organic extracts were washed with 20 mL of brine, dried, and

evaporated. The residue was chromatographed (90 g of silica gel, eluted with 10% EtOAc/hexanes) to afford 50 mg (26%) of difluoro analogue **28** and 81 mg (45%) of recovered **26**: IR (CH_2Cl_2) 1710 cm^{-1}; ^1H NMR δ 1.50 (s, 9H), 1.77−1.83 (m, 1H), 1.92−1.98 (m, 1H), 2.10 (td, J = 9.1, 13.9, 1H), 2.20−2.28 (m, 1H), 2.67−2.79 (m, 1H), 4.42−4.45 (m, 1H), 5.11 (d, J = 12.2, 1H), 5.15 (d, J = 12.2, 1H), 7.26−7.42 (m, 5H); ^{19}F NMR δ 53.52 (dd, $J_{FF/FH}$ = 26.1, 6.1, 1F), 54.11 (dd, $J_{FF/FH}$ = 26.1, 7.3, 1F); ^{13}C NMR δ 27.5 (t, J_{CF} = 4.3), 27.8 (q), 32.0 (t), 44.7 (t, J_{CF} = 25.2), 64.5 (d, J_{CF} = 25.2), 67.6 (s, J_{CF} = 4.6, 1.5), 82.2 (s), 126.9 (s, m from J_{CF}), 127.9 (d), 128.47 (d), 128.51 (d), 135.8 (s), 155.9 (s), 167.4 (s); HRMS (FAB) calcd for $C_{19}H_{24}NO_4F_2$ (M^+ + 1) 368.1673, found 368.1675.

(1*S*,3*R*,4*R*)-7-(Benzyloxycarbonyl)-1-carboxy-3-[(methoxycarbonyl)methyl]-7-azabicyclo[2.2.1]-heptane *tert*-Butyl Ester (29*β*) and (1*S*,3*S*,4*R*)-7-(Benzyloxycarbonyl)-1-carboxy-3-[(methoxycarbonyl)methyl]-7-azabicyclo[2.2.1]heptane *tert*-Butyl Ester (29α). To a solution of 0.63 mL (3.91 mmol) of trimethyl phosphonoacetate in 18 mL of THF at 0 °C was added 4.20 mL (3.86 mmol) of 0.92 M KHMDS in THF. The mixture was stirred for 10 min, warmed to rt, and stirred for an additional 15 min, producing a white slurry. The mixture was cooled to 4 °C, a solution of 900 mg (2.61 mmol) of ketone **26** was added in 18 mL of THF, and the mixture was stirred for 15 h and then for 2 h at rt. A solution of 0.22 mL (3.90 mmol) of AcOH was added, the mixture was stirred for 5 min, and then the slurry was chromatographed (15 g of silica gel, eluted with 20% EtOAc/hexane) to afford 1.05 g of the α,*β*-unsaturated ester. Applying the procedure for preparing *N*-CBZ alcohol **7**, except that 110 mL of MeOH and 350 mg of 10% Pd/C were used, 966 mg (2.41 mmol) of the *N*-CBZ unsaturated ester was converted to 963 mg (99%) of *N*-CBZ bicycle **29** as a 3.7/1 mixture of **29***β* and **29**α. Chromatography (150 g of silica gel, eluted with 10% EtOAc/hexane and then 20% EtOAc/hexane) afforded 208 mg (21%) of **29***β*, 16 mg (1.6%) of mixed fractions, and 749 mg (77%) of **29**α.

29*β*: $[\alpha]^{20}_D$ −27.2° (*c* 1.2, $CHCl_3$); IR (CH_2Cl_2) 1732, 1710 cm^{-1}; ^1H NMR δ 1.45 (s, 9H), 1.46−1.57 (m, 1H), 1.64−1.77 (m, 2H), 1.79−1.89 (m, 1H), 1.99 (dd, J = 12.2, 8.4, 1H), 2.06−2.16 (m, 1H), 2.17−2.26 (m, 1H), 2.28 (dd, J = 16.3, 7.0, 1H), 2.46 (dd, J = 16.3, 7.9, 1H), 3.63 (s, 3H), 4.16 (d, J = 4.2, 1H), 5.08 (d, J = 12.5, 1H), 5.12 (d, J = 12.4, 1H), 7.26−7.38 (m, 5H); ^{13}C NMR δ 27.8 (q), 29.3 (t), 31.3 (t), 38.6 (d), 39.2 (t), 41.6 (t), 51.5 (q), 63.4 (d), 67.0 (t), 69.7 (s), 81.2 (s), 127.89 (d), 127.96 (d), 128.3 (d), 136.2 (s), 156.7 (s), 169.2 (s), 172.6 (s). Anal. Calcd for $C_{22}H_{29}NO_6$: C, 65.5; H, 7.2; N, 3.5. Found: C, 65.4; H, 7.3; N, 3.6.

29α: $[\alpha]^{20}_D$ −11.8° (*c* 1.7, $CHCl_3$); IR (CH_2Cl_2) 1732, 1712 cm^{-1}; ^1H NMR δ 1.20 (dd, J = 12.1, 5.1, 1H), 1.42 (s, 9H), 1.55−1.83 (m, 3H), 2.08−2.18 (m, 1H), 2.31 (dd, J = 15.8, 7.5, 1H), 2.37 (dd, J = 15.8, 8.1, 1H), 2.47 (dd, J = 11.7, 3.2, 1H), 3.63 (s, 3H), 4.31 (t, J = 4.2, 1H), 5.05−5.15 (m, 2H), 7.25−7.40 (m, 5H); ^{13}C NMR δ 23.1 (t), 27.6 (q), 33.1 (t), 36.02 (t), 36.21 (d), 39.9 (t), 51.5 (q), 62.3 (d), 66.9 (t), 69.9 (s), 81.0 (s), 127.73 (d), 127.85 (d), 128.25 (d), 136.1 (s), 156.4 (s), 169.2 (s), 172.1 (s). Anal. Calcd for $C_{22}H_{29}NO_6$: C, 65.5; H, 7.2; N, 3.5. Found: C, 65.6; H, 7.4; N, 3.3.

(1*S*,3*S*,4*R*)-7-(Benzyloxycarbonyl)-1-carboxy-3-[[*N*-[[[2-(trimethylsilyl)ethyl]oxy]carbonyl]amino]methyl]-7-azabicyclo[2.2.1]heptane *tert*-Butyl Ester (30α). To a solution of 400 mg (0.991 mmol) of ester **29**α in 4.89 mL of 50% THF/MeOH was added a solution of 250 mg (5.95 mmol) of $LiOH\cdot H_2O$ in 0.96 mL of H_2O. The mixture was stirred for 24 h, acidified to pH 3 using 1 M H_3PO_4, and extracted with EtOAc (4 × 45 mL). The EtOAc layers were combined, dried, and evaporated to afford 386 mg (100%) of the corresponding carboxylic acid, which was used without further purification: IR (CH_2Cl_2) 3300−2700 (br), 1732, 1718 cm^{-1}; ^1H NMR δ 1.25 (dd, J = 11.9, 5.1, 1H), 1.45 (s, 9H), 1.60−1.85 (m, 3H), 2.18 (tt, J = 12.1, 3.6, 1H), 2.38 (dd, J = 16.1, 7.6, 1H), 2.45 (dd, J = 16.2, 7.9, 1H), 2.50−2.58 (m, 1H), 2.59−2.69 (m, 1H), 4.37 (t, J = 4.3, 1H), 5.09−5.16 (m, 2H), 7.26−7.38 (m, 5H); ^{13}C NMR δ 23.2 (t), 27.8 (q), 33.3 (t), 36.1 (t), 39.99 (d), 39.89 (t), 62.4 (d), 67.2 (t), 70.1 (s), 81.4 (s), 127.9 (d), 128.0 (d), 128.4 (d), 136.2 (s), 156.6 (s), 169.4 (s), 177.5 (s); FABMS calcd for $C_{21}H_{28}NO_6$ $(M + H)^+$ 390.1919, found 390.1917.

To a solution of 373 mg (0.96 mmol) of this acid in 5 mL of dry toluene containing 4 Å molecular sieves was added 0.16 mL (1.15 mmol) of Et_3N, followed by 0.24 mL (1.11 mmol) of DPPA. The mixture was heated at 85 °C for 2 h and cooled to rt, 0.16 mL (1.15 mmol) of 2-(trimethylsilyl)ethanol added, and the mixture heated to 85 °C for an additional 12 h. The mixture was cooled to rt, concentrated to 1/4 volume, and filtered, washing with 120 mL of EtOAc. The filtrate was evaporated and the residue chromatographed (100 g of silica gel, eluted with 17% EtOAc/hexane then 25% EtOAc/hexane) to afford 450 mg (93%) of *N*-TEOC carbamate **30**α as a colorless oil: $[\alpha]^{20}_D$ −12.1° (*c* 1.2, $CHCl_3$); IR (CH_2Cl_2) 3450, 1710 cm^{-1}; ^1H NMR δ 0.04 (s, 9H), 0.96 (t, J = 8.4, 2H), 1.18−1.28 (m, 1H), 1.45 (s, 9H), 1.60−1.70 (m, 2H), 1.73−1.84 (m, 1H), 2.10−2.20 (m, 1H), 2.33−2.43 (m, 2H), 3.08−3.20 (m, 1H), 3.22−3.31 (m, 1H), 4.14 (t, J = 8.4, 2H), 4.30 (m, 1H), 4.53−4.60 (bm, 1H), 5.09 (d, J = 12.4, 1H), 5.13 (d, J = 12.4, 1H), 7.26−7.38 (m, 5H); ^{13}C NMR δ −1.5 (q), 17.7 (t), 23.2 (t), 27.8 (q), 33.3 (t), 38.2 (t), 40.8 (d), 42.2 (t), 61.6 (d), 63.1 (t), 67.2 (t), 70.0 (s), 81.3 (s), 127.9 (d), 128.0 (d), 128.4 (s), 136.2 (s), 156.5 (s), 169.3 (s). Anal. Calcd for $C_{26}H_{40}SiN_2O_6$: C, 61.9; H, 8.0; N, 5.6. Found: C, 62.0; H, 8.1; N, 5.7.

(1*S*,3*R*,4*R*)-7-(Benzyloxycarbonyl)-1-carboxy-3-[[*N*-[[[2-(trimethylsilyl)ethyl]oxy]carbonyl]amino]methyl]-7-azabicyclo[2.2.1]heptane *tert*-Butyl Ester (30*β*). Applying the hydrolysis procedure used in the preparation of carbamate **30**α from ester **29**α, 279 mg (0.69 mmol) of ester **29***β* was converted to 270 mg (100%) of the resulting carboxylic acid **30***β*, which was used without further purification: IR (CH_2Cl_2) 3300−2800 (br), 1730, 1710 cm^{-1}; ^1H NMR δ 1.46 (s, 9H), 1.48−1.58 (m, 1H), 1.65−1.79 (m, 2H), 1.80−1.90 (m, 1H), 2.02 (d, J = 12.3, 8.5, 1H), 2.07−2.23 (m, 2H), 2.35 (dd, J = 16.9, 7.1, 1H), 2.52 (dd, J = 16.9, 8.0, 1H), 4.20 (d, J = 4.9, 1H), 5.09 (d, J = 12.4, 1H), 5.14 (d, J = 12.4, 1H), 7.26−7.38 (m, 5H); ^{13}C NMR δ 27.8 (q), 29.3 (t), 31.2 (t), 38.3 (d), 39.2 (t), 41.8 (t), 63.4 (d), 67.1 (t), 69.7 (s), 81.4 (s), 127.98 (d), 128.05 (d), 128.4 (d), 136.2 (s), 156.8 (s), 169.2 (s), 177.9 (s).

Applying the rearrangement procedure used in the preparation of **30**α from **29**α, 260 mg (0.67 mmol) of the above acid was converted to 273 mg (81% yield from **29***β*) of carbamate **30***β* as a colorless oil: $[\alpha]^{20}_D$ −36.4° (*c* 1.1, $CHCl_3$); IR (CH_2Cl_2) 3445, 1710 cm^{-1}; ^1H NMR δ 0.03 (s, 9H), 0.96 (t, J = 8.4, 2H), 1.40−1.53 (m, 2H), 1.45 (s, 9H), 1.63−1.73 (m, 1H), 1.80−1.89 (m, 1H), 2.05−2.18 (m, 1H), 2.87−2.95 (m, 2H), 2.98−3.07 (m, 1H), 4.12 (t, J = 8.4, 2H), 4.18 (d, J = 4.7, 1H), 4.85−4.93 (bm, 1H), 5.08−5.13 (m, 2H), 7.28−7.37 (m, 5H); ^{13}C NMR δ −1.5 (q), 17.7 (t), 27.8 (q), 29.2 (t), 31.8 (t), 39.0 (t), 42.2 (d), 44.4 (t), 61.6 (d), 62.9 (t), 67.1 (t), 69.6 (s), 81.3 (s), 128.03 (d), 128.13 (d), 128.5 (s), 136.2 (s), 156.7 (s), 169.2 (s). Anal. Calcd for $C_{26}H_{40}SiN_2O_6$: C, 61.9; H, 8.0; N, 5.6. Found: C, 61.9; H, 8.2; N, 5.6.

(1*S*,3*S*,4*R*)-7-(Benzyloxycarbonyl)-1-carboxy-3-[[*N*′,*N*″-bis(*tert*-butyloxycarbonyl)guanidino]methyl]-7-azabicyclo[2.2.1]heptane *tert*-Butyl Ester (31α). To a solution of 92 mg (0.18 mmol) of *N*-TEOC carbamate **30**α in 1 mL of THF was added 0.2 mL (0.2 mmol) of 1 M TBAF in THF. The mixture was heated at 50 °C for 24 h and cooled to rt and then 12.4 μL (0.22 mmol) of glacial AcOH added. The mixture was stirred for 10 min, 100 μL of water at pH 7 and 76 mg of *N*,*N*′-bis(*tert*-butyloxycarbonyl)-*S*-methylisothiourea were added, the mixture was heated to 50 °C for 24 h and then cooled to rt and evaporated. The residue was chromatographed (15 g of silica gel, eluted with 15% EtOAc/hexane) to afford 98 mg (89%) of arginine analogue **31**α as a foam: $[\alpha]^{20}_D$ −10.7° (*c* 1.0, $CHCl_3$); IR (CH_2Cl_2) 3321, 3270, 1721,1636, 1616 cm^{-1}; ^1H NMR δ 1.27 (dd, J = 10.1, 3.0, 1H), 1.46 (s, 9H), 1.50 (s, 9H), 1.51 (s, 9H), 1.57−1.68 (m, 1H), 1.80−1.87 (m, 2H), 2.12−2.20 (m, 1H), 2.38−2.48 (m, 2H), 3.34−3.40 (m, 1H), 3.42−3.48 (m, 1H), 4.33−4.35 (m, 1H), 4.30 (m, 1H), 5.13 (s, 2H), 7.26−7.39 (m, 5H), 8.34 (t, J = 3.5, 1H), 11.46 (s, 1H); ^{13}C NMR δ 23.3 (t), 27.8 (q), 28.02 (q), 28.22 (q), 33.4 (t), 38.2 (t), 39.8 (d), 42.1 (t), 61.6 (d), 67.2 (t), 70.0 (s), 79.3 (s), 81.3 (s), 83.3 (s), 127.88 (d), 128.03 (d), 128.4 (s), 136.3 (s), 153.2 (s), 156.1 (s), 156.5 (s), 163.4 (s), 169.3 (s). Anal. Calcd for $C_{31}H_{46}N_4O_8$: C, 61.8; H, 7.7; N, 9.3. Found: C, 61.5; H, 7.7; N, 9.2.

(1*S*,3*R*,4*R*)-7-(Benzyloxycarbonyl)-1-carboxy-3-[[*N*′,*N*″-bis(*tert*-butyloxycarbonyl)guanidino]methyl]-7-azabicyclo[2.2.1]heptane *tert*-Butyl Ester (31*β*). Applying the procedure used for the preparation of **31**α, 200 mg (0.40 mmol) of **30***β* was converted to 173 mg (73%) of arginine analogue **31***β* as a foam: $[\alpha]^{20}_D$ −26.7° (*c* 1.4, $CHCl_3$); IR (CH_2Cl_2) 3320, 3280, 1720, 1638, 1620 cm^{-1}; ^1H NMR *δ* 1.46 (s, 9H), 1.49 (s, 18H), 1.61−1.73 (m, 1H), 1.77−1.95 (m, 2H), 2.04−2.20 (m, 2H), 3.21−3.28 (m, 1H), 3.33−3.40 (m, 1H), 4.22 (d, *J* = 4.7, 1H), 5.09 (d, *J* = 12.4, 1H), 5.13 (d, *J* = 12.3, 1H), 7.26−7.40 (m, 5H), 8.52 (t, *J* = 3.5, 1H), 11.47 (s, 1H); ^{13}C NMR *δ* 27.8 (q), 28.04 (q), 28.26 (q), 29.3 (t), 31.5 (t), 39.4 (t), 41.6 (t), 44.3 (t), 61.6 (d), 67.1 (t), 69.6 (s), 79.2 (s), 81.3 (s), 83.0 (s), 128.0 (d), (d), 128.4 (d), 153.1 (s), 156.27 (s), 156.51 (s), 163.5 (s), 169.1 (s). Anal. Calcd for $C_{31}H_{46}N_4O_8$: C, 61.8; H, 7.7; N, 9.3. Found: C, 61.4; H, 7.6; N, 9.1.

(1*S*,3*S*,4*R*)-7-(Benzyloxycarbonyl)-1-carboxy-3-(2-hydroxyethyl)-7-azabicyclo[2.2.1]heptane *tert*-Butyl Ester (32). Applying the procedure used for the preparation of alcohol **5** from ester **3**, 480 mg (1.19 mmol) of ester **29**α was converted to 332 mg (74%) of alcohol **32** as a colorless oil: $[\alpha]^{20}_D$ −17.8° (*c* 1.2, $CHCl_3$); IR (CH_2Cl_2) 3618, 1728, 1708 cm^{-1}; ^1H NMR *δ* 1.21 (dd, *J* = 11.9, 5.3, 1H), 1.44 (s, 9H), 1.56−1.66 (m, 3H), 1.68−1.80 (m, 2H), 2.06 (bs, 1H), 2.10−2.18 (m, 1H), 2.22−2.32 (m, 1H), 2.41 (td, *J* = 11.8, 3.4, 1H), 3.52−3.63 (m, 2H), 4.24 (t, *J* = 3.8, 1H), 5.08 (d, *J* = 12.4, 1H), 5.12 (d, *J* = 12.5, 1H), 7.25−7.37 (m, 5H); ^{13}C NMR *δ* 23.1 (t), 27.8 (q), 33.4 (t), 34.6 (t), 37.1 (d), 40.3 (t), 61.5 (t), 62.9 (d), 67.0 (t), 70.0 (s), 81.1 (s), 127.8 (d), 127.96 (d), 128.35 (d), 136.3 (s), 156.7 (s), 169.7 (s). Anal. Calcd for $C_{21}H_{29}NO_5$: C, 67.2; H, 7.8; N, 3.7. Found: C, 67.2; H, 8.0; N, 3.6.

(1*S*,3*S*,4*R*)-7-(Benzyloxycarbonyl)-1-carboxy-3-[2-[*N*-(*tert*-butyloxycarbonyl)-*N*-[[2-(trimethylsilyl)ethyl]sulfonyl]amino]ethyl]-7-azabicyclo[2.2.1]heptane *tert*-Butyl Ester (33). To a solution of 627 mg (2.39 mmol) of PPh_3, 448 mg (1.59 mmol) of *tert*-butyl *N*-[2-(trimethylsilylethyl)sulfonyl]-carbamate, and 299 mg (0.96 mmol) of alcohol **32** in 9 mL of THF at 0 °C was added 0.30 mL (1.91 mmol) of DEAD over a 5 min period. The solution was stirred for 4 h and concentrated in vacuo, and 500 mg of the Ph_3PO and diethyl hydrazinedicarboxylate was removed by recrystallization from 7.5 mL of 20% EtOAc/hexane at 0 °C. The residue was chromatographed (100 g of activity grade II basic alumina, eluted with 10% EtOAc/hexane) to afford 485 mg (95%) of lysine analogue **33** as a colorless oil: $[\alpha]^{20}_D$ −8.8° (*c* 1.2, $CHCl_3$); IR (CH_2Cl_2) 1725 cm^{-1}; ^1H NMR *δ* 0.06 (s, 9H), 0.90−0.96 (m, 2H), 1.24 (dd, *J* = 11.9, 5.0, 1H), 1.44 (s, 9H), 1.52 (s, 9H), 1.57−1.87 (m, 5H), 2.10−2.20 (m, 2H), 2.42 (td, *J* = 11.8, 2.8, 1H), 3.33−3.39 (m, 1H), 3.47−3.60 (m, 2H), 4.24 (t, *J* = 4.2, 1H), 5.07 (d, *J* = 12.4, 1H), 5.13 (d, *J* = 12.4, 1H), 7.26−7.37 (m, 5H); ^{13}C NMR *δ* −2.1 (q), 10.4 (t), 23.1 (t), 27.81 (q), 27.97 (q), 32.7 (t), 33.3 (t), 37.7 (d), 40.2 (t), 45.9 (t), 50.8 (t), 62.5 (d), 67.1 (t), 70.0 (s), 81.1 (s), 84.4 (s), 127.9 (d), 127.99 (d), 128.39 (d), 136.3 (s), 151.4 (s), 156.6 (s), 169.5 (s). Anal. Calcd for $C_{31}H_{50}N_2O_8SiS$: C, 58.3; H, 7.9; N, 4.4. Found: C, 58.0; H, 8.1; N, 4.3.

(1*S*,3*S*,4*R*)-7-(Benzyloxycarbonyl)-1-carboxy-3-[2-[*N*-[[2-(trimethylsilyl)ethyl]sulfonyl]amino]ethyl]-7-azabicyclo[2.2.1]heptane (34). To a solution of 213 mg (0.334 mmol) of *tert*-butyl ester **33** in 1.3 mL of CH_2Cl_2 was added 2.60 mL (33.8 mmol) of TFA. The mixture was stirred for 42 h and evaporated to afford 161 mg of slightly impure crude acid **34** as a brownish oil that was used without further purification: IR (CH_2Cl_2) 2100−3400 cm^{-1}; selected data for ^1H NMR (rotomers) *δ* 0.06 (s, 9H), 0.89−0.99 (m, 2H), 1.35−3.15 (several br m, 17H), 4.43 (m, 1H), 5.12 (m, 2H), 7.25−7.43 (m, 5H); ^{13}C NMR (rotomers) *δ* −2.2, 10.2, 10.3, 14.0, 17.5, 21.7, 22.5, 23.0, 29.6, 31.1, 31.5, 32.5, 33.7, 35.8, 36.8, 37.6, 40.2, 41.4, 42.0, 48.6, 48.8, 53.4, 62.7, 68.0, 69.5, 127.9, 128.3, 128.5, 128.8, 129.2, 130.3, 133.2, 135.4, 157.1, 161.3, 174.5; HRMS (FAB) calcd for $C_{22}H_{35}N_2O_6SiS$ ($M^+ + 1$) 483.1985, found 483.1989.

(1*S*,3*S*,4*R*)-7-(Benzyloxycarbonyl)-1-carboxy-3-[2-[*N*-[[2-(trimethylsilyl)ethyl]sulfonyl]amino]ethyl]-7-azabicyclo[2.2.1]heptane Methyl Ester (35). To a solution of crude acid 34 (161 mg, 0.334 mmol) in 12 mL of 30% THF/Et_2O was added an ethereal solution of 1.2 M CH_2N_2 dropwise until a yellow color persisted and bubbling had ceased. The mixture was stirred 30 min, 0.2 mL of AcOH was added, and the mixture was stirred overnight. The solution was dissolved in 100 mL of CH_2Cl_2, washed with 20 mL of saturated aqueous $NaHCO_3$, dried, and evaporated, and the residue was chromatographed (15 g of silica gel, eluted with 25% EtOAc/hexane) to afford 128 mg (77%) of the methyl ester **35** as a colorless oil: $[\alpha]^{20}_D$ −12.3° (*c* 1.0, $CHCl_3$); IR (CH_2Cl_2) 410, 1753, 1718 cm^{-1}; ^1H NMR *δ* 0.05 (s, 9H), 0.93−1.02 (m, 2H), 1.16−1.30 (m, 1H), 1.55−1.72 (m, 4H), 1.75−1.88 (m, 2H), 2.13−2.29 (m, 2H), 2.44 (td, *J* = 11.8, 2.3, 1H), 2.85−2.93 (m, 2H), 2.95−3.08 (m, 2H), 3.61 (br s, 3H), 4.27 (m, 1H), 4.68 (t, *J* = 4.2, 1H), 5.00−5.10 (m, 2H), 7.28−7.37 (m, 5H); ^{13}C NMR *δ* −2.1 (q), 10.5 (t), 23.1 (t), 33.0 (t), 33.3 (t), 37.7 (d), 40.0 (t), 42.2 (t), 52.1 (t), 62.2 (d), 67.5 (t), 69.2 (s), 128.1 (d), 128.2 (d), 128.5 (d), 135.8 (s), 156.4 (s), 170.9 (s). Anal. Calcd for $C_{23}H_{36}N_2O_6SiS$: C, 55.6; H, 7.3; N, 5.6. Found: C, 55.8; H, 7.5; N, 5.3.

(1*S*,3*R*/*S*,4*R*)-7-(Benzyloxycarbonyl)-1-carboxy-3-phenyl-3-hydroxy-7-azabicyclo[2.2.1]heptane *tert*-Butyl Ester (36α/36*β*). To 4 mL of Et_2O at −85 °C was added 0.41 mL (0.69 mmol) of 1.67 M PhLi in Et_2O/pentane, followed by 207 mg (0.60 mmol) of ketone **26** in 4 mL of THF over 30 min. The mixture was warmed to −78 °C and stirred 45 min and 0.40 mL (0.69 mmol) of glacial AcOH added. After partitioning between 75 mL of CH_2Cl_2 and 20 mL of aqueous $NaHCO_3$, the aqueous layer was washed with CH_2Cl_2 (2 × 40 mL), and the combined organic extracts were washed with 20 mL of brine, dried, and evaporated. The residue was chromatographed (90 g of silica gel, eluted with 8% EtOAc/hexane) to afford 98 mg (47%) of recovered ketone **26**, as well as 120 mg (47%) of the carbinol as a 8/1 mixture of **36***β*/**36**α, respectively, 90% yield, based on recovered ketone **26**. This mixture was used without further purification as a 1/8, **36**α/**36***β* mixture: IR (CH_2Cl_2) 3580−3570, 1733, 1711 cm^{-1}; major isomer **36***β* only ^1H NMR *δ* 1.49 (s, 9H), 1.68−1.78 (m, 1H), 1.84−2.00 (m, 2H), 1.17−2.27 (m, 1H), 2.33−2.57 (m, 2H), 2.96 (dd *J* = 12.7, 2.7, 1H), 4.32 (d, *J* = 4.5, 1H), 4.80−4.96 (br m, 1H), 5.02 (d, *J* = 12.4, 1H), 7.08−7.20 (m, 2H), 7.22−7.43 (m, 6H), 7.63 (d, *J* = 7.5, 1H); ^{13}C NMR *δ* 23.4 (t), 27.8 (q), 31.0 (t), 51.1 (t), 66.9 (t), 68.8 (d), 78.7 (s), 81.4 (s), 125.6 (d), 127.3 (d), 127.5 (d), 127.9 (d), 128.24 (d), 128.29 (d), 136.2 (s), 146.7 (s), 156.0 (s), 169.0 (s). Anal. Calcd for $C_{25}H_{29}NO_5$: C, 70.9; H, 6.9; N, 3.3. Found: C, 70.8; H, 7.2; N, 3.2.

(1*S*,4*R*)-7-(Benzyloxycarbonyl)-1-carboxy-3-phenyl-7-azabicyclo[2.2.1]-2-heptene *tert*-Butyl Ester (37), (1*S*,3*S*,4*R*)-7-(Benzyloxycarbonyl)-1-carboxy-3-phenyl-7-azabicyclo[2.2.1]heptane *tert*-Butyl Ester (38α), and (1*S*,3*R*,4*R*)-7-(Benzyloxycarbonyl)-1-carboxy-3-phenyl-7-azabicyclo[2.2.1]heptane *tert*-Butyl Ester (38*β*). To a solution of 120 mg (0.28 mmol) of the carbinol mixture **36**α/**36***β* in 2.5 mL of pyridine at 0 °C was added 231 mg (0.71 mmol) of Ts_2O. The mixture was warmed to rt over 1 h, stirred for 21 h, heated for 3 h at 95 °C, stirred for 12 h at rt, and partitioned between 75 mL of CH_2Cl_2 and 40 mL of aqueous 2 M HCl solution. The aqueous layer was washed with CH_2Cl_2 (2 × 40 mL), and the combined organic extracts were washed with 20 mL of brine, dried, and evaporated. The residue was chromatographed (15 g of silica gel, eluted with 15% EtOAc-hexane) to afford 94 mg (82%) of pure styrene **37** as an oil that crystallized upon standing. Applying the hydrogenation−CBZ acylation procedure described for the preparation of **4** from **2**, 131.5 mg (0.32 mmol) of styrene **37** gave 97 mg (74%) of **38**α and 27 mg (20%) of **38***β* as colorless oils. Selected data for styrene **37**: mp 103−104 °C; IR (CH_2Cl_2) 1743, 1750 cm^{-1}; ^1H NMR *δ* 1.35 (ddd, *J* = 11.8, 9.3, 3.4, 1H), 1.54 (s, 9H), 1.67 (ddd, *J* = 11.8, 8.5, 3.6, 1H), 2.13−2.23 (m, 1H), 2.41 (ddd, *J* = 11.8, 9.3, 3.4, 1H), 5.06 (d, *J* = 12.5, 1H), 5.12 (d, *J* = 12.5, 1H), 5.27 (d, *J* = 4.2, 1H), 6.71 (s, 1H), 7.26−7.42 (m, 10H); ^{13}C NMR *δ* 25.2 (t), 27.9 (q), 29.6 (t), 31.7 (t), 63.9 (d), 67.2 (t), 74.8 (s), 81.8 (s), 125.4 (d), 127.7 (d), 127.9 (d), 128.09 (d), 128.18 (d), 128.32 (d), 128.66 (d), 132.4 (s), 136.1 (s), 147.5 (s), 156.7 (s), 16.4 (s); HRMS (FAB) calcd for $C_{25}H_{28}NO_4$ ($M^+ + 1$) 406.2018, found 406.2015.

38α: $[\alpha]^{20}_D$ +8.0° (*c* 1.0, $CHCl_3$); IR (CH_2Cl_2) 1737, 1718 cm^{-1}; ^1H NMR *δ* 1.45−1.58 (m, 1H), 1.52 (s, 9H), 1.63−1.78 (m, 2H), 2.02 (dd, *J* = 12.6, 5.8, 1H), 2.18−2.27 (m, 1H), 2.64 (td, *J* =

12.2, 3.1, 1H), 3.61 (td, J = 5.6, 3.8, 1H), 4.52 (t, J = 4.5, 1H), 5.19 (s, 2H), 7.17−7.40 (m, 10H); ^{13}C NMR δ 23.3 (t), 27.8 (q), 33.8 (t), 37.3 (t), 46.0 (d), 64.2 (d), 67.2 (t), 70.5 (s), 81.3 (s), 126.3 (d), 127.82 (d), 127.93 (d), 128.04 (d), 128.42 (d), 128.45 (d), 136.3 (s), 139.3 (s), 156.7 (s), 169.6 (s). Anal. Calcd for $C_{25}H_{29}NO_4$: C, 73.7; H, 7.2; N, 3.4. Found: C, 73.5; H, 7.3; N, 3.3.

38*β*: IR (CH_2Cl_2) 1730, 1710 cm^{-1}; ^{1}H NMR δ 1.51 (s, 9H), 1.65−1.70 (m, 1H), 1.78−1.93 (m, 2H), 2.17−2.25 (m, 1H), 2.27 (dd, J = 12.4, 9.2, 1H), 2.42 (td, J = 12.4, 4.1, 1H), 2.97 (dd, J = 9.1, 4.9, 1H), 4.32 (d, J = 4.5, 1H), 5.02 (bd, J = 12.0, 1H), 5.10 (d, J = 12.4, 1H), 7.20−7.38.(m, 10H); ^{13}C NMR δ 27.9 (q), 30.2 (t), 30.9 (t), 47.6 (d), 65.9 (d), 67.0 (t), 69.6 (s), 81.3 (s), 126.5 (d), 127.36 (d), 127.80 (d), 127.93 (d), 128.36 (d), 128.43 (d), 136.4 (s), 144.8 (s), 156.6 (s), 169.4 (s); HRMS (FAB) calcd for $C_{25}H_{30}NO_4$ ($M^+ + 1$) 408.2175, found 408.2169.

(1*S*,4*R*)-7-(Benzyloxycarbonyl)-1-carboxy-7-azabicyclo-[2.2.1]-3-heptanone (40) and (1*R*,4*S*)-7-(Benzyloxycarbonyl)-7-azabicyclo[2.2.1]-2-heptanone (41). To a solution of 350 mg (1.01 mmol) of ketone **26** in 1.50 mL of CH_2Cl_2 was added 1.82 mL (23.6 mmol) of TFA. The mixture was stirred for 48 h and then evaporated to afford 305.3 mg (100%) of the acid **40** as a brown oil that was used without further purification: IR (CH_2Cl_2) 3300−2800 (br), 1725, 1770 cm^{-1}; ^{1}H NMR δ 1.68−1.74 (m, 1H), 1.92−1.98 (m, 1H), 2.11−2.20 (m, 1H), 2.38 (d, J = 17.7, 1H), 2.37−2.45 (m, 1H), 2.91 (dd, J = 17.7, 2.6, 1H), 4.48 (d, J = 5.5, 1H), 5.11 (d, J = 12.2, 1H), 5.16 (d, J = 12.2, 1H), 7.27−7.37 (m, 5H), 10.14 (br s, 1H); ^{13}C NMR δ 24.0 (t), 31.6 (t), 47.2 (t), 66.8 (d), 68.3 (t), 68.6 (s), 128.1 (d), 128.46 (d), 128.58 (d), 135.2 (s), 156.2 (s), 173.2 (s), 206.3 (s); HRMS (FAB) calcd for $C_{15}H_{15}NO_5$ ($M^+ + 1$) 290.1036, found 290.1036.

To a solution of 300 mg (1.0 mmol) of acid **40** in 6 mL of 1,2-DCE was added 0.01 mL (0.129 mmol) of DMF, followed by 0.22 mL (2.50 mmol) of oxalyl chloride. The mixture was stirred for 3 h and evaporated, and proceeding in the dark, the residue was dissolved in 1 mL of THF and cooled to 0 °C, and a solution of 268 mg (2.10 mmol) of *N*-hydroxy-2-thiopyridone and 0.31 mL (2.20 mmol) of Et_3N in 5 mL of THF added over 5 min. The mixture was warmed to rt over 10 min, stirred for 1 h, and filtered, washing the filter cake with 5 mL of THF and diluting the filtrate with 0.7 mL of *tert*-butyl thiol. The filtrate solution was irradiated for 2 h using two tungsten lamps (100 W each), with external cooling to maintain the reaction mixture at rt. Addition of 90 mg (0.34 mmol) of PPh_3 was followed by partition between 75 mL of CH_2Cl_2 and 40 mL of saturated aqueous $NaHCO_3$. The aqueous layer was washed with CH_2Cl_2 (2 × 40 mL), and the combined organic extracts were washed with 40 mL of aqueous 1 M H_3PO_4 and 20 mL of brine, dried, and evaporated. The residue was chromatographed (15 g of silica gel, eluted with 12% EtOAc/hexane) to afford 206 mg (81%) of bicyclic ketone **41** as a colorless oil: $[\alpha]^{20}_D$ −64.6° (*c* 1.9, $CHCl_3$); IR (CH_2Cl_2) 3630−3400, 1763, 1708 cm^{-1}; ^{1}H NMR δ 1.57−1.67 (m, 2H), 1.94−2.03 (m, 2H), 2.01 (d, J = 17.5, 1H), 2.47 (dd, J = 17.4, 5.2, 1H), 4.35 (d, J = 5.2, 1H), 4.64 (t, J = 4.6, 1H), 5.11 (d, J = 12.3, 1H), 5.14 (d, J = 12.3, 1H), 7.25−7.37 (m, 5H); ^{13}C NMR δ 24.4 (t), 27.5 (t), 45.1 (t), 56.0 (d), 63.6 (d), 67.2 (t), 127.8 (d), 128.13 (d), 128.44 (d), 136.0 (s), 155.1 (s), 208.6 (s). Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.6; H, 6.2; N, 5.7. Found: C, 68.8; H, 6.2; N, 5.8.

(1*R*,4*S*)-7-(*tert*-Butyloxycarbonyl)-7-azabicyclo[2.2.1]-2-heptanone (39). To a solution of 115 mg (0.45 mmol) of ketone **41** in 10 mL of degassed MeOH under Ar was added 1 drop of DIEA, 293 mg (1.34 mmol) of BOC_2O, and 40 mg of 10% Pd/C. The resulting slurry was degassed and stirred under a balloon of H_2 for 5 h and then filtered through Celite, and the Celite pad was washed with 15 mL of CH_2Cl_2. The filtrate was evaporated and the residue chromatographed (15 g of silica gel, eluted with 10% EtOAc/hexane then 25% EtOAc/hexane) to afford 97.5 mg (98%) of the *N*-BOC ketone **39**: $[\alpha]^{20}_D$ −75.5° (*c* 1.0, $CHCl_3$) [lit.[23] $[\alpha]^{20}_D$ −73.6° (*c* 1.1, $CHCl_3$)]; spectral data were identical to those reported.[23]

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