Synthesis of Enantiopure 7-[3-Azidopropyl]indolizidin-2-one Amino Acid. A Constrained Mimic of the Peptide Backbone Geometry and Heteroatomic Side-Chain Functionality of the Ala-Lys Dipeptide

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Enantiopure *N*-(BOC)amino-7-[3-azidopropyl]indolizidin-2-one acid **1** has been synthesized by displacement of the methanesulfonate of its 7-hydroxypropyl counterpart **11** with sodium azide and subsequent ester hydrolysis. *N*-(BOC)Amino-7-[3-hydroxypropyl]indolizidin-2-one ester **11** was obtained from a sequence commencing with the alkylation of (2*S*,8*S*)-di-*tert*-butyl 5-oxo-2,8-di-[*N*-(PhF)amino]azelate **5** (PhF = 9-(9-phenylfluorenyl)). Stereoselective allylation of **5**, regioselective olefin hydroboration, selective primary alcohol protection as a silyl ether, and oxidation of the secondary alcohol gave (2*S*,4*R*,8*S*)-di-*tert*-butyl 4-[3-*tert*-butyldimethylsiloxypropyl]-5-oxo-2,8-di-[*N*-(PhF)amino]azelate **9** as a pure diastereomer in 33% overall yield. Linear ketone **9** was then converted into the indolizidinone heterocycle by a route featuring reductive amination, lactam cyclization, and isolation by way of a silyl ether which provided the (6*S*,7*R*)-isomer of **11**.

Introduction

Constrained surrogates of Orn, Lys, and Arg residues are interesting targets because of their potential for probing various recognition events in protein chemistry and biology.[1,2] The orthogonally protected versions of these α,ω-diamino acids are also interesting as inputs for library synthesis in Medicinal Chemistry because they can serve for orchestrating three different pharmacophores in a geometrically defined display.[3] For respective applications as constrained Orn-Pro and Ala-Orn surrogates, 3-*N*-(BOC)amino 5- and 7-azidomethylindolizidin-2-one 9-carboxylates **3** and **4** were synthesized by our methanesulfonate displacement/lactam cyclization sequence.[2] By exploring an alternative sequence, we have now synthesized *N*-(BOC)amino-7-[3-azidopropyl]indolizidin-2-one acid **1**, which may serve as a constrained Ala-Lys mimic.

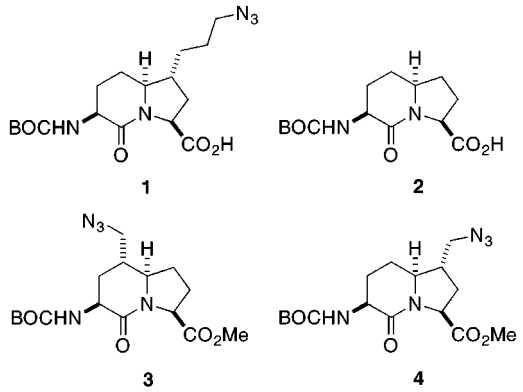

Figure 1. Indolizidin-2-one amino acid **2** and related orthogonally protected indolizidin-2-one diamino carboxylates **1**, **3**, and **4**.

Results and Discussion

Indolizidinone diamino acid **1** was synthesized by a route involving alkylation of (2*S*,8*S*)-di-*tert*-butyl 5-oxo-2,8-di-[*N*-(PhF)amino]azelate **5** (PhF = 9-(9-phenylfluorenyl)) with allyl iodide. δ-Keto azelate **5** was previously alkylated with allyl bromide using potassium bis(trimethylsilyl)amide (KHMDS) in a 2:5 Toluene−THF solution at −78 °C with warming to −20 °C over 1−2 h.[4]

(1) Recent examples of α,ω-diamino acids that may be considered as constrained surrogates for Orn, Lys, and Arg residues include (a) 3-aminoproline: Baldwin, J. E.; Adlington, R. M.; Gollins, D. W.; Godfrey, C. R. A. *Tetrahedron* **1995**, *51*, 5169. (b) 4-Aminoproline, 4-aminomethylproline, and their respective guanidino analogues: Webb, T. R.; Eigenbrot, C. *J. Org. Chem.* **1991**, *56*, 3009. (c) β-(2-Aminoethyl)pyroglutamate and γ-(2-aminoethyl)pyroglutamate: Goswami, R.; Moloney, M. G. *Chem. Commun.* **1999**, 2333. (d) 4-(2-Aminoethyl)proline: Wang, Q.; Sasaki, N. A.; Potier, P. *Tetrahedron* **1998**, *54*, 15759. (e) 5-(2-Aminoethyl)pipecolic acid): Murray, P. J.; Starkey, I. D. *Tetrahedron Lett.* **1996**, *37*, 1875. (f) Guanidinomethyl-3,4-cyclopropylproline: Zhang, R.; Mamai, A.; Madalengoitia, J. S. *J. Org. Chem.* **1999**, *64*, 547. (g) 3-Alkyl-4-aminopipecolates: Esch, P. M.; Boska, I. M.; Hiemstra, H.; de Boer, R. F.; Speckamp, W. N. *Tetrahedron* **1991**, *47*, 4039. (h) 4-Aminopipecolic acid: Rutjes, F. P. J. T.; Veerman, J. J. N.; Meester, W. J. N.; Hiemstra, H.; Schoemaker, H. E. *Eur. J. Org. Chem.* **1999**, *1127*, 7. (i) 3-Amino-2-piperidone-6-carboxylic acid: Kemp, D. S.; Sun, E. T. *Tetrahedron Lett.* **1982**, *23*, 3759. Additional examples in which the ω-amine is restricted by a carbocycle in the side-chain or in a heterocycle include the following: (j) Murray, P. J.; Starkey, I. D.; Davies, J. E. *Tetrahedron Lett.* **1998**, *39*, 6721. (k) Adang, A. E. P.; Peters, C. A. M.; Gerritsma, S.; de Zwart, E.; Veeneman, G. *Biorg. Med. Chem. Lett.* **1999**, *9*, 1227 and ref 10 therein. (l) Kent, D. R.; Cody, W. L.; Doherty, A. M. *J. Peptide Res.* **1998**, *52*, 201. A 3,5,5-trisubstituted pyrrolin-4-one designed to mimic lysine in a β-strand conformation is reported: (m) Smith, A. B., III; Benowitz, A. B.; Favor, D. A.; Sprengeler, P. A.; Hirschmann, R. *Tetrahedron Lett.* **1997**, *38*, 3809. 2,5-Diaminocyclohexanecarboxylic acid, a constrained β,ω-diamino acid is reported: (n) Appella, D. H.; LePlae, P. R.; Raguse, T. L.; Gellman, S. H. *J. Org. Chem.* **2000**, *65*, 4766.

(2) Polyak, F.; Lubell, W. D. *J. Org. Chem.* **2001**, *66*, 1171.

(3) For scaffold approaches see the following: Guan, Y.; Green, M. A.; Bergstrom, D. E. *J. Comb. Chem.* **2000**, *2*, 297 and refs 2−9 therein.

(4) Polyak, F.; Lubell, W. D. *J. Org. Chem.* **1998**, *63*, 5937.

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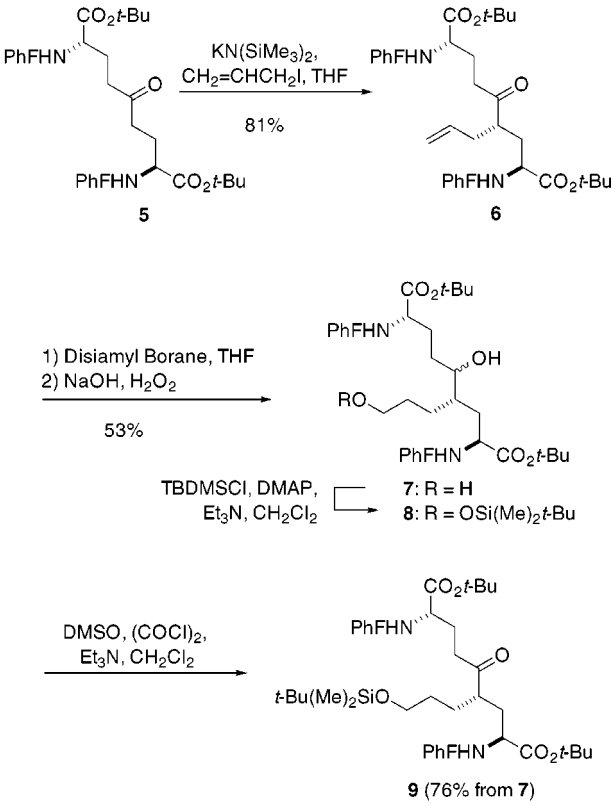
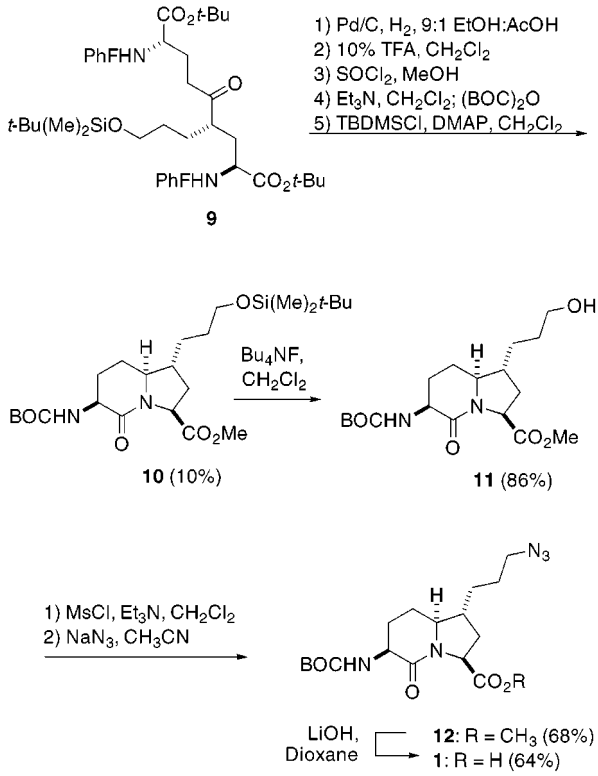
Scheme 1. Synthesis of 5-(3-*tert*-Butyldimethylsiloxpropyl)azelate 9



Scheme 2. Synthesis of 7-(3-Azidopropyl)Indolizidinone Amino Acid 1



Diastereoselectivity was typically low using these conditions which provided a 3:1 mixture of (4*R*)- and (4*S*)-alkyl-branched ketones **6**. Improved diastereoselectivity (6:1) was attained upon switching to allyl iodide as electrophile. After examination of several conditions, a 15:1 ratio of (4*R*)- and (4*S*)-isomers was obtained by treating ketone **5** (100 mol %) in THF at −78 °C with a 0.5 M solution of KHMDS in toluene (80 mol %), stirring for 30 min, and adding allyl iodide followed by a second amount of KHMDS in toluene (60 mol %). After stirring 1h and workup, these conditions delivered (4*R*)-**6** in good yield and high selectivity on a 21 mmol scale.

(2*S*,4*R*,8*S*)-Di-*tert*-butyl 4-allyl-5-oxo-2,8-di-[*N*-(PhF)-amino]azelate (**6**) was hydroborated initially using a borane dimethyl sulfide complex in THF followed by oxidation with an alkaline peroxide solution;[5] however, these conditions were not regioselective and the desired diol **7** was isolated in low yield (35%) after separation from diol possessing two secondary alcohols by chromatography. Selective formation of diol **7** was achieved using 9-BBN in THF at room temperature;[5b,6] however, the cyclooctane diol byproduct, produced in the oxidation step, was difficult to remove from diol **7**. Disiamyl borane proved more effective for producing pure diol **7** albeit in 53% yield after chromatography as a mixture of 5-position diastereomers.[7]

Ketone **9** was synthesized in two steps from diol **7**. First, the primary alcohol was protected selectively as its *tert*-butyldimethylsilyl ether using the respective chlorosilane, triethylamine, and DMAP in dichloromethane.[8] Finally, oxidation of the secondary alcohol with oxalyl chloride and DMSO in dichloromethane gave, after chromatography, ketone **9** in 76% overall yield from **7** (Scheme 1).[9]

7-(3-*tert*-Butyldimethylsiloxypropyl)indolizidinone amino ester **10** was synthesized from ketone **9** using our reductive amination/lactam cyclization protocol[10] as developed previously for the synthesis of its 7-benzylindolizidinone counterpart.[4] Hydrogenation of a solution of ketone **9** in 10:1 EtOH−AcOH with palladium-on-carbon under 10 atm of H_2 caused cleavage of the PhF groups, intramolecular imine formation, and reduction to a 5-alkylproline. Indolizidinone *N*-(BOC)amino ester **11** was then obtained after *tert*-butyl ester and silyl ether removal with TFA in dichloromethane, esterification with thionyl chloride in methanol, lactam cyclization on treatment with triethylamine in dichloromethane, and amine protection with di-*tert*-butyl dicarbonate. (3*S*,6*S*,7*R*,9*R*)-7-(3-*tert*-Butyldimethylsiloxypropyl)indolizidinone *N*-(BOC)amino ester (**10**) was isolated in 10% overall yield after this multiple step sequence concluding with alcohol protection with TBDMSCl, triethylamine, and DMAP in dichloromethane and chromatography on silica gel.

7-(3-Azidopropyl)indolizidinone amino acid **1** was prepared by a sequence commencing with silyl ether **10** which was first deprotected using TBAF in THF to afford alcohol **11**. Activation of alcohol **11** as its methanesulfonate using methanesulfonyl chloride and triethy-

(5) (a) Roemmele, R. C.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 1866. (b) Folmer, J. J.; Acero, C.; Thai, D. L.; Rapoport, H. *J. Org. Chem.* **1998**, *63*, 8170.

(6) Brown, H. C.; Knights, E. F.; Scouten, C. G. *J. Am. Chem. Soc.* **1974**, *96*, 7765.

(7) Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc.* **1961**, *83*, 1241.

(8) Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, 99.

(9) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

(10) (a) Lombart, H.-G.; Lubell, W. D. *J. Org. Chem.* **1994**, *59*, 6147. (b) Lombart, H.-G.; Lubell, W. D. In *Peptides 1994 (Proceedings of the 23rd European Peptide Symposium)*; Maia, H. L. S., Ed.; ESCOM: Leiden, The Netherlands, **1995**, 696. (c) Lombart, H.-G.; Lubell, W. D. *J. Org. Chem.* **1996**, *61*, 9437.

lamine in dichloromethane and subsequent nucleophilic displacement with sodium azide in acetonitrile at room temperature gave azide **12**. Orthogonally protected diamino acid **1** was then isolated in 44% overall yield from **10** after hydrolysis of methyl ester **12** with 1 M aqueous LiOH in dioxane.

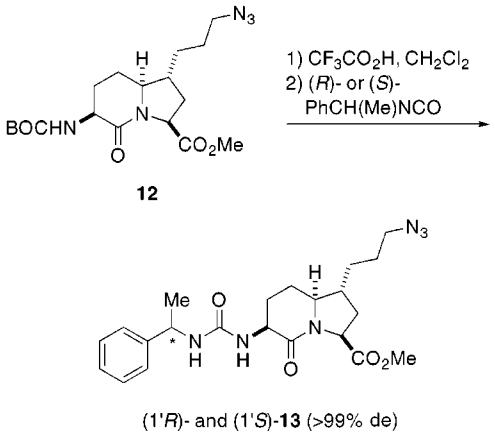
Relative Stereochemistry and Enantiomeric Purity of Diamino Indolizidinone Carboxylate 12. Stereochemical assignments at the indolizidinone ring-fusion and alkyl-branched centers were made based on a series of two-dimensional NMR experiments on siloxypropyl analogue **10**. Initially, COSY spectroscopy was used to locate the alkyl branch at the 7-position. The downfield chemical shifts for the proton signals of the three amine-bearing carbons appeared in the same order (C-9 > C-3 > C-6) as in the parent (3*S*,6*S*,9*S*)-indolizidinone *N*-(BOC)amino methyl ester **2**.[10c] The C-3 proton (4.02 ppm) was identified by its coupling to the carbamate proton. The C-9 proton (4.41 ppm) was observed as an apparent doublet indicating a ~90° dihedral angle with its neighboring C-8$_\beta$ proton. The ring-fusion C-6 proton (3.18 ppm) showed scalar couplings with the C-5 protons (~1.6 and 1.98 ppm), which were correlated back to the C-3 proton, and with the C-7 proton (1.88 ppm), which was related to both the C-9 and side-chain protons.

In a subsequent NOESY experiment, a transfer of magnetization was observed between the ring-fusion C-6 proton and the protons of the peptide backbone at C-3 and C-9 that confirmed the concave indolizidinone geometry. Furthermore, through-space magnetization transfer was observed between the C-6 and C-8$_\alpha$ protons. The 7*R* stereochemical assignment was made based on observation of a greater nuclear Overhauser effect between the side-chain methylene protons (1.24 and 1.35 ppm) with the C-8$_\alpha$ proton (1.73 ppm) relative to the C-8$_\beta$ proton (2.08 ppm). In addition, the C-7 proton exhibited a nuclear Overhauser effect with the C-5$_\beta$ proton. Additional support for the stereochemical assignment came from the strong nuclear Overhauser effects between the side-chain methylene and C-6 protons. The COSY and NOESY spectra used to make the stereochemical assignments for **10** are provided in the Supporting Information.

A predominance of the (6*S*,7*R*)-stereoisomer had previously been observed in the 7-benzylindolizidinone products obtained from the reductive amination/lactam cyclization sequence using either the (4*S*)- or (4*R*)-isomer of the related 4-benzyl-5-oxo-2,8-di-[*N*-(PhF)amino]azelate and was ascribed earlier to an imine−enamine tautomerization during the hydrogenation step.[4] Although the stereochemistry at the alkyl branch may arise from a retention of configuration, a similar tautomeric equilibrium may play a role in the production of the (7*R*)-siloxypropylindolizidinone isomer **10** (Scheme 2).

The enantiomeric purity of diamino indolizidinone carboxylate **12** was ascertained after conversion to diastereomeric ureas (1′*R*)- and (1′*S*)-**13**.[4,10] Cleavage of carbamate **12** with TFA in dichloromethane followed by treatment with triethylamine and acylation respectively with (*R*)- and (*S*)-α-methylbenzylisocyanate in THF at room temperature gave α-methylbenzyl ureas **13** that were directly examined by 400 MHz NMR spectroscopy in $CDCl_3$. Measurement of the diastereomeric methyl ester singlets at 3.72 and 3.73 ppm demonstrated the ureas to be of >99% diastereomeric excess. Hence, 7-(3-hydroxpropyl)indolizidinone **11** and diamino indolizidinone carboxylates **12** and **1** are all presumed to be of >99% enantiomeric excess.

Scheme 3. Enantiomeric Purity of 7-(3-Azidopropyl)Indolizidinone Amino Ester 12



Conclusion

Toward the design of conformationally rigid dipeptide surrogates possessing heteroatomic side-chains, we have synthesized 7-(3-hydroxypropyl)indolizidinone amino ester **11** from azelate **5** by a strategy featuring selective allylation, hydroboration, reductive amination, and lactam cyclization. The alcohol of **11** can be converted to other heteroatomic side chains, as demonstrated by the preparation of enantiopure 7-(3-azidopropyl)indolizidinone amino acid **1** via displacement of its respective methanesulfonate with sodium azide. Complementing the related recently synthesized 5- and 7-azidomethylindolizidinones **3** and **4**,[2] orthogonally protected diamino indolizidinone acid **1** expands a unique series of constrained dipeptide surrogates for exploring recognition events in peptide science involving α,ω-diamino acid residues.

Experimental Section

General. Unless otherwise noted, all reactions were run under nitrogen atmosphere and distilled solvents were transferred by syringe. Tetrahydrofuran (THF) and ether were distilled from sodium/benzophenone immediately before use; CH_2Cl_2 was distilled from CaH_2; $CHCl_3$ from P_2O_5; triethylamine (Et_3N) was distilled from BaO. Final reaction mixture solutions were dried over Na_2SO_4. Melting points are uncorrected. Mass spectral data, HRMS and MS (EI and FAB), were obtained by the Université de Montréal Mass Spec. facility. Unless otherwise noted, ^{1}H NMR (300/400 MHz) and ^{13}C NMR (75/100 MHz) spectra were recorded in $CDCl_3$. Chemical shifts are reported in ppm (δ units) downfield of internal tetramethylsilane ($(CH_3)_4Si$), $CHCl_3$, and C_6H_6; coupling constants are reported in hertz. Chemical shifts of PhF aromatic carbons are not reported for the ^{13}C NMR spectra. Analytical thin-layer chromatography (TLC) was performed by using aluminum-backed silica plates coated with a 0.2 mm thickness of silica gel 60 F_{254} (Merck). Chromatography was performed using Kieselgel 60 (230−400 mesh).

(2*S*,4*R*,8*S*)-Di-*tert*-butyl 4-Allyl-5-oxo-2,8-di-[*N*-(PhF)-amino]azelate (6). A −78 °C solution of ketone **5** (18 g, 21.8 mmol, 100 mol %) in THF (44 mL) was treated with a 0.5 M solution of KHMDS in toluene (35 mL, 17.5 mmol, 80 mol %), stirred for 30 min, and treated with allyl iodide (2.0 mL, 22.9 mmol, 105 mol %). After it was stirred for 0.5 h at −78 °C, the reaction mixture was treated with a second 0.5 M solution of

KHMDS in toluene (26.2 mL, 13.1 mmol, 60 mol %), stirred for an additional 2 h at −78 °C, and then partitioned with agitation between 1 M KH_2PO_4 (400 mL) and EtOAc (400 mL). The aqueous layer was extracted with EtOAc (2 × 400 mL). The combined organic layers were washed with brine, dried, and evaporated to a residue that was analyzed by proton NMR spectroscopy which showed a 15:1 ratio of diastereomeric *tert*-butyl ester signals. Chromatography of the residue on silica gel using an eluant of hexane to 95:5 hexane−EtOAc gave first a 1:1 mixture of (4*S*)- and (4*R*)-**6** (1.3 g, 7%), followed by pure (4*R*)-**6** (15.3 g, 81%): mp 131−133 °C; $[\alpha]^{20}_D$ −175.1° (*c* 0.74, $CHCl_3$), lit.[4] $[\alpha]^{20}_D$ −74.0° (*c* 1.5, $CHCl_3$); the spectral data for **6** were identical with values reported in ref 4.

(2*S*,4*R*,8*S*)-Di-*tert*-butyl 4-(3-*tert*-Butyldimethylsiloxypropyl)-5-oxo-2,8-di-[*N*-(PhF)amino]azelate (9). A 0 °C solution of olefin **6** (3.2 g, 3.7 mmol, 100 mol %) in THF (200 mL) was treated dropwise with a 0.5 M solution of disiamyl borane in THF (28 mL, 380 mol %) over 20 min. The reaction mixture was warmed to room temperature and stirred for 8 h, cooled to 0 °C, and quenched with 5 mL of ethanol. The reaction mixture was treated with 3 M NaOH (5.5 mL, 450 mol %) and aqueous H_2O_2 (5.5 mL, 30 wt %), heated at a reflux for 90 min, cooled to room temperature, and concentrated to ∼40% of its original volume. The mixture was extracted with ether (200 mL). The aqueous phase was diluted with water (150 mL), adjusted to ∼pH 7 with 3 M H_3PO_4, and extracted with EtOAc (3 × 200 mL). The combined organic phase was dried and evaporated. The residue was chromatographed using 10 g of silica gel for each gram of residue with an eluant of hexane to EtOAc−hexane (1:9) to remove the higher R_f products. The column was then washed with pure hexane. The desired alcohols were eluted using a gradient of CH_2Cl_2 to CH_2Cl_2−EtOAc (6:4) in order to afford **7** as a mixture of diastereomeric diols 1.7 g (53%). To obtain analytical samples of pure diastereomeric diols **7**, 100 mg of the mixture was chromatographed on silica gel using a gradient of CH_2Cl_2 to CH_2Cl_2−EtOAc (6:4). The first diastereomer to elute gave the following: $[\alpha]^{20}_D$ −119.0 (*c* 0.42, $CHCl_3$); ^{1}H NMR δ 1.18 (s, 9H), 1.19 (s, 9H), 1.21−1.41 (m, 7H), 1.50−1.65 (m, 5H), 2.35 (m, 1H), 2.49 (m, 1H), 3.40 (t, 2H), 3.48 (m, 1H), 7.13−7.68 (m, 26H); ^{13}C NMR δ 27.2, 28.08, 28.11, 29.0, 32.7, 35.7, 40.4, 55.6, 56.7, 63.1, 72.9, 73.2, 73.3, 80.8, 80.9, 175.3, 175.8. The second diastereomer to elute gave the following: $[\alpha]^{20}_D$ −132.1 (*c* 0.84, $CHCl_3$); ^{1}H NMR δ 1.17 (s, 9H), 1.22 (s, 9H), 1.25−1.38 (m, 7H), 1.46−1.64 (m, 5H), 2.33 (m, 1H), 2.57 (m, 1H), 3.39 (t, 2H), 7.13−7.68 (m, 26H); ^{13}C NMR δ 27.0, 27.9, 29.5, 30.1, 37.0, 40.0, 55.3, 56.0, 62.8, 72.9, 73.1, 73.3, 80.8, 175.2, 175.6.

A solution of diastereomeric diols **7** (1.5 g 1.5 mmol, 100 mol %) in 200 mL of CH_2Cl_2 at room temperature was treated with TBDMSCl (270 mg, 1.8 mmol, 105 mol %), DMAP (8 mg, 0.06 mmol, 4 mol %), and triethylamine (255 μL, 105 mol %) and stirred for 18 h and evaporated. The residue was dissolved in EtOAc (200 mL) and washed with 1M KH_2PO_4 (50 mL). The aqueous phase was extracted with EtOAc (2 × 30 mL). The combined organic phase was dried and evaporated to a crude residue containing alcohol **8** which was used without further purification.

A −78 °C solution of oxalyl chloride (220 μL, 2.6 mmol, 150 mol %) in CH_2Cl_2 (20 mL) was treated with DMSO (322 μL, 2.4 mmol, 200 mol %), stirred for 30 min, warmed to −30 °C, cooled to −78 °C, and then treated dropwise with a solution of the protected alcohol **8** (1.7 g, 1.7 mmol, 100%) in CH_2Cl_2 (20 mL) followed by triethylamine (360 μL, 5.1 mmol, 300 mol %). The reaction mixture was stirred at −78 °C for 1h, warmed to room temperature over 1h, and quenched with a solution of 1M aqueous NaH_2PO_4 (200 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 200 mL). The combined organic phase was dried and evaporated. Chromatography of the residue on silica gel (0−10% EtOAc in hexane) gave ketone **9** (1.3 g, 76%): $[\alpha]^{20}_D$ −137.4 (c 0.39, $CHCl_3$); ^{1}H NMR δ 0.01 (s, 6H), 0.91 (s, 9H), 1.18 (s, 9H), 1.23 (s, 9H), 1.26−1.38 (m, 5H), 1.69−1.74 (m, 3H), 2.45−2.53 (m, 3H), 2.71−2.80 (m, 2H), 3.01−3.10 (br, 2H), 3.39 (t, 2H), 7.27−7.73 (m, 26H); ^{13}C NMR δ −5.1, 18.5, 27.4, 28.0, 28.1, 29.5, 30.4, 37.0, 38.6, 48.1, 54.5, 55.5, 63.2, 73.1, 73.2, 80.7, 175.3, 175.5, 213.5; FAB *m*/*z* 997.5 (M + 1, 17%), 241.0 (100%).

(3*S*,6*S*,7*R*,9*S*)-Methyl 2-Oxo-3-*N*-(BOC)amino-7-(3-*tert*-butyldimethylsiloxypropyl)-1-azabicyclo[4.3.0]nonane-9-carboxylate (10). A hydrogenation vessel containing a solution of ketone **9** (1.57 g, 1.57 mmol, 100 mol %) in anhydrous EtOH (100 mL) and AcOH (10 mL) was charged with 0.16 g of palladium-on-carbon (10 wt %), then filled, vented, and refilled three times with hydrogen. After stirring for 24 h under 10 atm of hydrogen, the reaction mixture was filtered through Celite and washed with EtOAc (100 mL). The combined organic solution was evaporated to dryness and the residue was digested in 85:15 EtOH−H_2O (50 mL), then filtered. The filter cake was washed with 85:15 EtOH−H_2O (50 mL). The combined filtered solution was evaporated to dryness. The crude product was dissolved in a solution of 10% TFA in CH_2Cl_2 (15 mL) and stirred overnight. Evaporation of the volatiles gave a residue which was dissolved in methanol (30 mL), cooled to 0 °C, treated with $SOCl_2$ (300 mol %), stirred at 0 °C for 2h, at room-temperature overnight, and then evaporated. The residue was dissolved in CH_2Cl_2 (60 mL) treated with Et_3N (500 mol %), stirred at room temperature for 36 h, treated with di-*tert*-butyl dicarbonate (500 mol %), and stirred at room temperature for 4 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL), washed with a 1 M solution of NaH_2PO_4 (10 mL) and brine (10 mL), dried and evaporated. The residue was dissolved in EtOAc (5 mL), filtered through a plug of silica gel, washed first with 1:1 hexane−EtOAc to remove higher R_f products, and washed next with EtOAc−methanol (10:1) to obtain the alcohol product. The collected fractions were evaporated. The residue was dissolved in CH_2Cl_2 (20 mL), treated with TBDMSCl (0.25 g, 1.65 mmol, 105 mol %), DMAP (6.4 mg, 4 mol %) and Et_3N (100 mol %), stirred at room-temperature overnight, diluted with CH_2Cl_2 (20 mL), and then washed with 1M NaH_2PO_4 (10 mL) and brine (10 mL), dried and evaporated. The residue was chromatographed with 3:7 hexane−EtOAc as eluant. Evaporation of the collected fractions gave **10** (60 mg, 10% from **9**): $[\alpha]_D^{20}$ −18.0 (*c* 0.15, CH_2Cl_2); ^{1}H NMR δ −0.06 (s, 6H), 1.18 (s, 9H), 1.20−1.24 (m, 1H), 1.34 (s, 9H), 1.34−1.38 (m, 3H), 1.42−1.50 (m, 2H), 1.58−1.65 (m, 2H), 1.88 (m, 1H), 1.98 (m, 1H), 2.08 (dd, 1H, J = 6, 10), 2.34 (m, 1H), 3.18 (m, 1H), 3.51 (t, 2H, J = 6), 3.64 (s, 3H), 4.02 (m, 1H), 4.41 (d, 1H, J = 6), 5.40 (bs, 1H); ^{13}C NMR δ −5.1, 18.5, 21.8, 26.1, 26.2, 27.3, 28.6, 31.2, 35.4, 45.2, 50.3, 52.6, 58.0, 61.8, 63.0, 79.7, 156.0, 169.4, 172.4; HRMS cacld for $C_{24}H_{45}SiO_6N_2$ (MH^+) 485.3047 found 485.3080.

(3*S*,6*S*,7*R*,9*S*)-Methyl 2-Oxo-3-*N*-(BOC)amino-7-(3-hydroxypropyl)-1-azabicyclo [4.3.0]nonane-9-carboxylate (11). Methyl ester **10** (60 mg, 0.15 mmol) in 10 mL of CH_2Cl_2 was treated with TBAF (80 mg, 0.3 mmol, 200 mol %) stirred overnight at room temperature. The reaction mixture was diluted with 10 mL of CH_2Cl_2 and washed with 1M NaH_2PO_4 (5 mL) and brine (5 mL), dried, and evaporated. The residue was chromatographed using a gradient of EtOAc to 1:20 ethanol−EtOAc as eluant. Evaporation of the collected fractions gave the alcohol **11** (48 mg, 86%): $[\alpha]_D^{20}$ −18.3 (*c* 0.11, CH_2Cl_2); ^{1}H NMR δ 1.21−1.24 (m, 1H), 1.33 (s, 9H), 1.34−1.40 (m, 3H), 1.45−1.61 (m, 2H), 1.63−1.65 (m, 2H), 1.72−1.93 (m, 1H), 1.96−2.01 (m, 1H), 2.11 (dd, 1H, J = 6), 2.37 (m, 1H), 3.35 (t, 2H, J = 6), 3.64 (s, 3H), 4.02 (m, 1H), 4.41 (d, 1H, J = 6), 5.40 (bs, 1H); ^{13}C NMR δ, 25.1, 26.2, 27.3, 31.2, 35.4, 39.8, 45.2, 50.3, 52.6, 58.0, 62.8, 64.2, 79.7, 156.0, 169.4, 172.4; HRMS cacld for $C_{18}H_{31}O_6N_2$ (MH^+) 371.2182, found 371.2169.

(3*S*,6*S*,7*R*,9*S*)-Methyl 2-Oxo-3-*N*-(BOC)amino-7-(3-azidopropyl)-1-azabicyclo [4.3.0]nonane-9-carboxylate (12). Alcohol **11** (35 mg, 0.07 mmol) in 15 mL of CH_2Cl_2 was treated with methanesulfonyl chloride (11 μL, 200 mol %) and Et_3N (24 μL, 250 mol %) and stirred at 0 °C for 1h. The ice bath was removed, and the reaction mixture was stirred an additional 1h at room temperature. The solution was diluted with CH_2Cl_2 (15 mL) and washed with 1M NaH_2PO_4 (10 mL) and brine (10 mL), dried, and evaporated. The crude residue was dissolved in acetonitrile (10 mL), treated with NaN_3 (30 mg, 300 mol %), stirred at room temperature for 18 h, and evaporated. The crude residue was dissolved in EtOAc (10 mL),

washed with 1M NaH_2PO_4 (5 mL) and brine (5 mL), dried, and evaporated. The crude product was chromatographed using a gradient of 20−50% EtOAc in hexane. Evaporation of the collected fractions gave **12** (19.2 mg, 68% yield): $[\alpha]_D^{20}$ −18.3 (*c* 0.19, CH_2Cl_2); IR (KBr), 2093 cm^{-1}; ^1H NMR δ 1.36−1.39 (m, 1H), 1.44 (s, 9H), 1.57−1.59 (m, 3H), 1.70−1.75 (m, 3H), 1.82−1.86 (m, 1H), 1.90−2.10 (m, 1H), 2.10−2.16 (m, 1H), 2.18 (dd, 1H, J = 6), 2.35−2.46 (m, 1H), 3.29 (t, 2H, J = 6), 3.75 (s, 3H), 4.13−4.19 (m, 1H), 4.53 (d, 1H), 5.50 (br, 1H); ^{13}C NMR δ 26.2, 27.3, 27.5, 28.6, 29.3, 35.2, 45.3, 50.3, 51.5, 52.7, 58.0, 61.6, 79.8, 155.9, 169.4, 172.3; HRMS cacld for $C_{18}H_{30}O_6N_5$ (MH^+) 396.2247, found 396.2255.

(3*S*,6*S*,7*R*,9*S*)-2-Oxo-3-*N*-(BOC)amino-7-(3-azidopropyl)-1-azabicyclo[4,3,0]nonane-9-carboxylic Acid (1). Methyl ester **12** (5.6 mg, 0.014 mmol) in 2 mL of dioxane was treated with 1M aqueous LiOH (0.03 mL, 200 mol %), stirred at room temperature for 1.5 h, and treated with 1 M NaH_2PO_4 (5 mL). The pH was adjusted to ∼pH 2 using H_3PO_4, and the mixture was extracted with EtOAc (3 × 15 mL). The organic solutions were combined, dried, and evaporated to a residue that was chromatographed using a gradient of 0−5% AcOH in EtOAc to give **1** (3.4 mg, 0.009 mmol, 64%): $[\alpha]_D^{20}$ −17.1 (*c* 0.032, CH_2Cl_2); ^1H NMR δ 1.46 (s, 9H), 1.52−1.57 (m, 3H), 1.61−1.69 (m, 3H), 1.80−1.85 (m, 1H), 1.91−2.36 (m, 3H), 2.35−2.46 (m, 1H), 3.29−3.36 (m, 2H), 3.72−3.75 (m, 1H), 4.28−4.30 (m, 1H), 4.58 (d, 1H, J = 7.7), 5.50 (br, 1H); ^{13}C NMR δ 25.9, 27.2, 27.6, 28.4, 29.1, 35.0, 45.8, 51.4, 52.7, 58.0, 61.5, 79.7, 154.7, 169.4, 174.8; FAB *m*/*z* 404.1 (M + Na 10%), 382.2 (M + 1, 17%), 154.0 (90%).

Enantiomeric Purity of (3*S*,6*S*,7*R*,9*S*)-Methyl 2-Oxo-3-*N*-(BOC)amino-7-(3-azidopropyl)-1-azabicyclo[4,3,0]-nonane-9-carboxylate (12). A solution of (3*S*,6*S*,7*R*,9*S*)-**12** (7.8 mg, 0.025 mmol) in CH_2Cl_2 (1 mL) was treated with TFA (0.3 mL) and stirred for 5h at room temperature and the volatiles were removed under vacuum to provide a residue: ^1H NMR δ 1.28−1.37 (m, 1H), 1.56−1.66 (m, 3H), 1.71−1.77 (m, 1H), 1.88−2.05 (m, 3H), 2.13−2.20 (m, 2H) 2.40−2.43 (m, 1H), 3.30 (t, 2H, J = 6.3), 3.71 (s, 3H), 4.01 (m, 1H), 4.49 (d, 1H, J = 8.5). Without further purification, the residue was dissolved in CH_2Cl_2 (2 mL), treated with either (*R*)- or (*S*)-1-phenylethylisocyanate (7.5 mg, 0.05 mmol, 200 mol %) and Et_3N (7 μL, 0.05 mmol, 200 mol %), and stirred at room temperature for 5 h. The volatiles were removed under vacuum, and the residue was directly examined by proton NMR spectroscopy. The limits of detection were determined by measuring the diastereomeric methyl ester singlets at 3.73 and 3.72 ppm in $CDCl_3$ in the 400 MHz ^1H NMR spectra.

Urea (1′*R*)-13. ^1H NMR δ 1.28−1.37 (m, 1H), 1.56−1.78 (m, 6H), 1.71−1.77 (m, 1H), 1.88−2.05 (m, 3H), 2.13−2.20 (m, 2H), 2.40−2.43 (m, 1H), 3.30 (m, 3H), 3.73 (s, 3H), 4.15−4.26 (m, 1H), 4.44 (d, 1H, J = 8.9), 4.83 (t, 1H, J = 7.2), 5.09−5.14 (br, 1H), 5.47 (br, 1H), 7.26−7.40 (m, 5H).

Urea (1′*S*)-13. ^1H NMR δ 1.28−1.37 (m, 1H), 1.56−1.78 (m, 6H), 1.71−1.77 (m, 1H), 1.88−2.05 (m, 3H), 2.13−2.20 (m, 2H), 2.40−2.43 (m, 1H), 3.30 (m, 3H), 3.72 (s, 3H), 4.15−4.26 (m, 1H), 4.44 (d, 1H, J = 8.9), 4.84 (t, 1H, J = 7.2), 5.09−5.14 (br, 1H), 5.47 (br, 1H), 7.26−7.40 (m, 5H).

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Supporting Information Available: ^1H and ^{13}C NMR spectra of **1**, **7**, and **9**−**3** and COSY and NOESY spectra of **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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