Conformationally Constrained 7-Azabicyclo[2.2.1]heptane Amino Acids. Synthesis of a Glutamic Acid Analogue

Barry P. Hart and Henry Rapoport*

Department of Chemistry, University of California, Berkeley, California 94720

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We report the synthesis of 2-substituted 7-azabicyclo[2.2.1]heptane glutamic acid analogue **27** from L-serine. Hemiaminal intermediate **2** can be converted to the 2*S*,3*S*,5*S*-trisubstituted pyrrolidine **3** by a tandem Wittig/Michael reaction or to the 2*S*,3*S*,5*R*-trisubstituted pyrrolidine **4** via an iodosulfonamidation reaction. The key transannular alkylation step to form the [2.2.1] ring system involves a β-elimination of a silyl ether followed by cyclization to afford *tert*-butyl 7-benzyloxycarbonyl-7-azabicyclo[2.2.1]-2-heptene-1-carboxylate (**20**). Selective functionalization at C-2 was accomplished by the direct reduction with SmI_2 of 2-keto-3-silyl ether **23** to the C-2 ketone **24**, which was converted to α,β-unsaturated ester **25**. Stereospecific reduction of the double bond from the exo face leads to a single protected glutamate analogue, *tert*-butyl (1*S*,2*R*,4*R*)-7-benzyloxycarbonyl-2-(methoxycarbonylmethyl)-7-azabicyclo[2.2.1]heptane-1-carboxylate (**27**).

Introduction

The use of conformationally constrained α-amino acid analogues has been actively pursued as a means of overcoming some inherent limitations of natural α-amino acids in biologically active molecules.[1] The strategy of replacing a natural amino acid with a conformationally constrained amino acid has led to enhanced stability of peptide chains to proteolytic enzymes,[2] increased potency of ligand receptor interactions,[3] and the ability to further elucidate receptor-bound ligand conformations.[4]

We now describe the chirospecific synthesis of a 2-substituted 7-azabicyclo[2.2.1]heptane glutamic acid analogue. The synthesis of this 2-substituted 7-azabicyclo-[2.2.1]heptane α-amino acid complements the synthesis of 3-substituted 7-azabicyclo[2.2.1]heptane α-amino acids previously reported from this laboratory.[5] Molecules containing the 7-azabicyclo[2.2.1]heptane ring system have been popular synthetic targets[6] with several methods reported[7] for the synthesis of α-amino acids of this structural type. The strategy we describe affords chirospecific products and versatile intermediates that could lead to the development of a variety of amino acid analogues with substitution at C-2 or disubstitution at the C-2 and C-3 positions.

The route we propose to follow (Figure 1) employs L-serine (**1**) as the starting material that is to be converted to the hemiaminal **2** as previously reported.[8a,b]

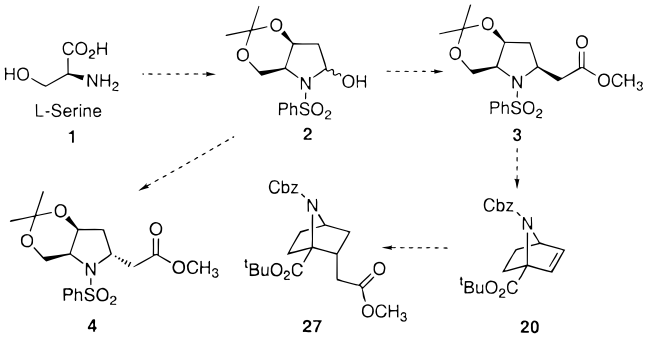

Figure 1. Proposed route to the synthesis of 2-substituted azabicyclo[2.2.1]heptane α-amino acids.

Homologation and cyclization of the hemiaminal **2** to form pyrrolidines **3** and **4** can proceed through a tandem Wittig/Michael sequence, affording only pyrrolidine **3** after crystallization (Scheme 1). Alternatively, the synthesis of (2*S*,3*S*,5*R*)-pyrrolidine **4** can be realized by an iodosulfonamidation cyclization reaction establishing the *R* stereochemistry at the ring-closure site, C-5. A series of functional group transformations will then provide the substrate for the transannular alkylation reaction leading to a β,γ-unsaturated, 7-azabicyclo[2.2.1]heptane α-amino acid **20** and subsequently to the glutamate analogue **27**.

Results and Discussion

The Stereocontrolled Synthesis of Trisubstituted Pyrrolidines 3 and 4. From the hemiaminal intermediate **2**, two strategies for pyrrolidine formation were developed. The first plan involves a tandem Wittig/Michael reaction[9] to afford the 2*S*,3*S*,5*S*, all cis, pyrrolidine **3**. The kinetics and stereochemistry of this reaction sequence are temperature dependent as shown in Table 1. At temperatures between −15 °C and room tempera-

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Scheme 1. Stereoselective Synthesis of 2*S*,3*S*,5*S*-Trisubstituted Pyrrolidine 3 and 2*S*,3*S*,5*R*-Trisubstituted Pyrrolidine 4

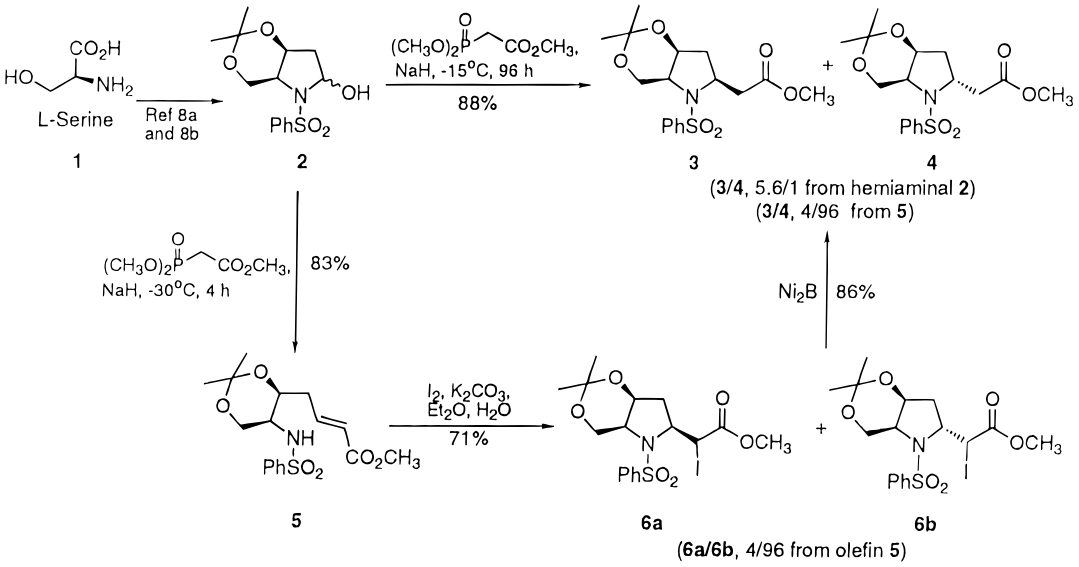
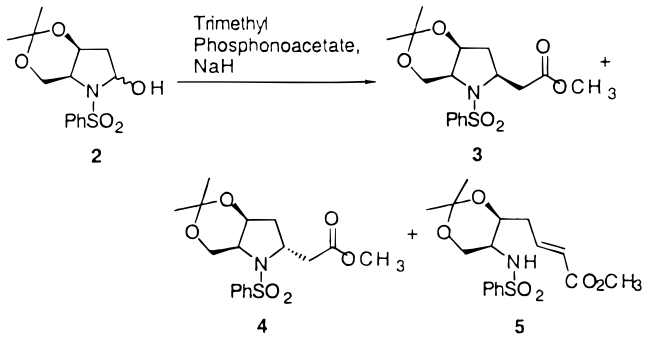


Table 1. Reaction of Hemiaminal 2 with Trimethyl Phosphonoacetate



reaction conditions[a]	*T* °C	time (h)	combined yield (%)	ratio of reaction products (**3**/**4**/**5**)
A	23	2	86	67/33/0
B	0	23	82	80/20/0
C	−15	96	88	85/15/0
D	−30	4	83	0/0/100
E	−30	40	81	7/2/91

[a] Conditions for reactions A−E; trimethyl phosphonoacetate (150 mol%), NaH (150 mol %), THF.

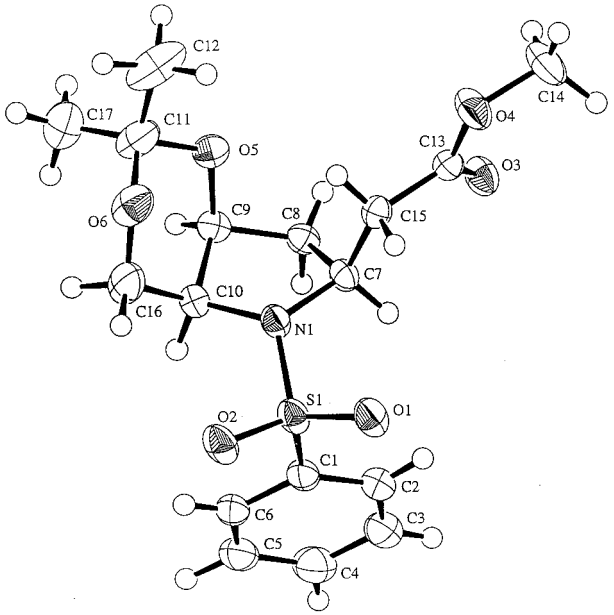


Figure 2. Structure of (2*S*,4*S*,5*S*)-4-hydroxy-5-hydroxymethyl-2-(methoxycarbonyl)methyl-1-(phenylsulfonyl)pyrrolidine isopropylidine ketal (**3**) as determined by X-ray crystallography.

ture, the reaction sequence proceeds in high yields. Thus, at room temperature the products are obtained in 86% combined yield and the ratio of pyrrolidines **3**/**4** is 2/1 after 2 h. On the other hand, at −15 °C the ratio of **3**/**4** is 5.6/1 in 88% combined yield, but 96 h is required. After recrystallization, pyrrolidine **3** was isolated in 64% yield with the stereochemistry shown in Figure 2 as established by X-ray crystallography. When the reaction of **2** is carried out at −30 °C for 4 h, only olefin **5** is isolated in 83% yield.

The second strategy for pyrrolidine formation involves the intramolecular iodosulfonamidation cyclization of olefin **5** to establish stereochemistry at C-5. The olefin **5** was treated with Na_2CO_3 and I_2 under biphasic reaction conditions[10a,b] to afford a mixture of **6a** and **6b** in 71% yield. The mixture of **6a** and **6b** was reduced with H_2 and Pd/C to afford the deiodinated products **4**/**3** in 80% yield with a significant amount (20%) of the byproduct, methyl (5*S*,6*S*)-5,7-dihydroxy-6-phenylsulfonylaminoheptanoate isopropylidine ketal. Byproduct formation was avoided by the use of Ni_2B as a reductant,[11] yielding only pyrrolidines **3** and **4** (4/96, 86% yield). The mixtures **6a**/**6b** or **3**/**4** were not separable by silica gel column chromatography. The iodoamidation sequence from **2** allows for the synthesis of a 2*S*,3*S*,5*R*-trisubstituted pyrrolidine **4** with high level of diastereomeric excess that complements the synthesis of the (2*S*,3*S*,5*S*)-pyrrolidine **3**.

The Synthesis of 7-Azabicyclo[2.2.1]-2-heptene-1-carboxylate 20. The conversion of crystalline **3** to the

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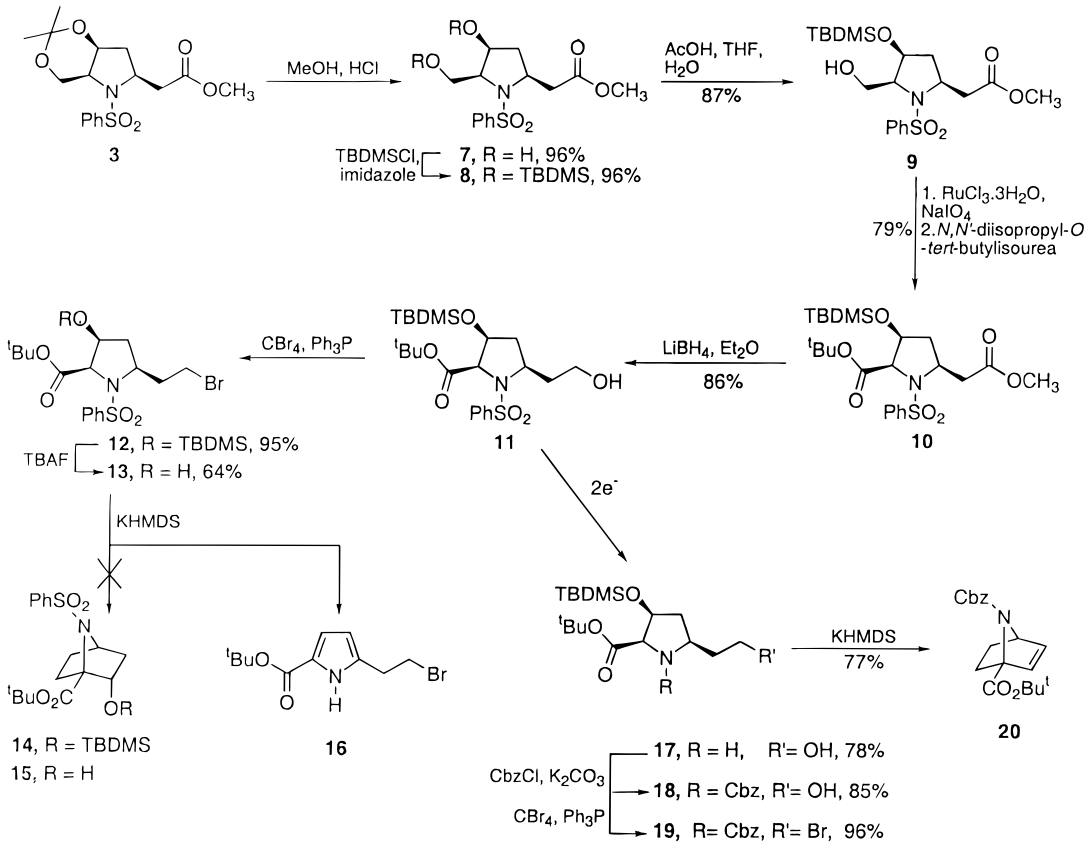
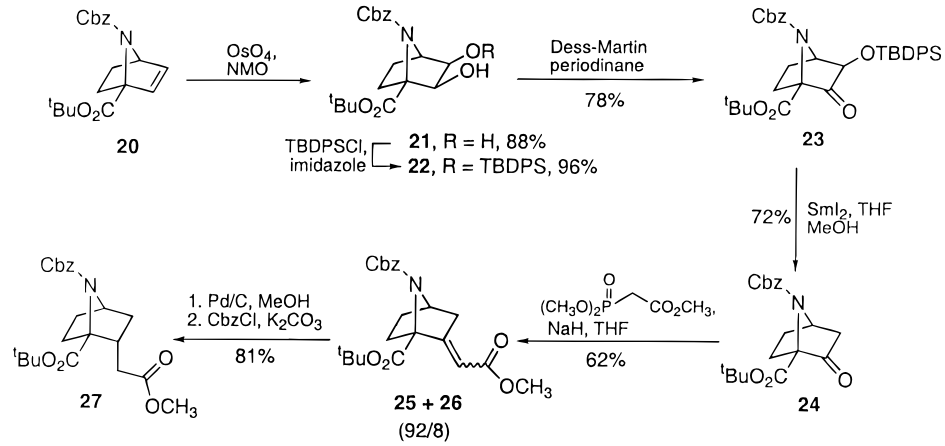
Scheme 2. Synthesis of 7-Azabicyclo[2.2.1]-2-heptene-1-carboxylate 20



Scheme 3. Synthesis of a 2-Substituted 7-Azabicyclo[2.2.1]heptane Glutamic Acid Analogue 27



rigid α-amino acid analogue **20** is described in Scheme 2. Thus, pyrrolidine **3** was converted to the bis-silyl ether **7** by treatment with HCl/MeOH followed by bis-silylation in 96% yield for each step. Selective desilylation of **7** was accomplished in 87% yield to give the primary alcohol **9**.[12] Other selective desilylation protocols were examined, including sonication in MeOH/CCl_4,[13] TBAF in THF,[14] and *p*-TsOH in THF/H_2O,[15] but all led to incomplete reaction or poor selectivity. Oxidation of primary alcohol **9** with catalytic $RuCl_3$ and $NaIO_4$ in a biphasic system[16] followed by esterification with *N*,*N*′-diisopropyl-*O*-*tert*-butylisourea[17] afforded the diester **10** in 79% yield. Selective reduction of the methyl ester of **10** provided trisubstituted pyrrolidine alcohol **11** in 86% yield, which was converted to bromide **12** in 95% yield. Attempts to cyclize **12** with KHMDS led to none of the transannular alkylation product **14** under numerous variations of stoichiometry, concentration, and temperature. The loss of the benzenesulfonyl protecting group and the silyl ether were observed in all cases leading to pyrrole formation and other products; pyrrole **16** was isolated

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from the complex reaction mixture. On the assumption that alkoxide formation would prevent β-elimination of the protected alcohol, silyl ether **12** was treated with TBAF, affording the free alcohol **13** in 64% yield. Treatment of **13** with KHMDS, however, again afforded a complex mixture of products and none of the desired [2.2.1]bicyclic amino acid analogue **15**. Also, to prevent the facile elimination of the nitrogen protecting group as benzenesulfinate, the benzenesulfonyl group was removed from **11** by electrolysis[18] in 78% yield. Reprotection of the secondary amine **17** with CbzCl (85% yield) followed by bromide formation from alcohol **18** in 96% yield afforded **19**, the target substrate for transannular cyclization. Treatment of **19** with KHMDS did not cause elimination of the amine protecting group, but elimination of the silyl ether was observed and the 7-azabicyclo-[2.2.1]heptene-1-carboxylate **20** was obtained in 77% yield. Presumably, the cyclization reaction proceeds by elimination of the silyl ether to form the α,β-unsaturated ester, deconjugation of the double bond, and alkylation of the resulting α-anion.

The Synthesis of Glutamic Acid Analogue 27 from Olefin 20. Dihydroxylation[19] of olefin **20** proceeded to exodiol **21** in 88% yield and selective protection of the less hindered C-3 alcohol with TBDPSCl in 96% yield followed to afford monoalcohol **22**. Oxidation of **22** to the ketone **23** proceeded in 78% yield under Dess−Martin conditions.[20] Direct reductive removal of the silyl ether function α to the carbonyl of ketone **23** was effected with SmI_2[21] in 72% yield to give the 2-substituted ketone **24**. Strict stoichiometric control of the SmI_2 is critical for the reduction of **23** to avoid reducing the resulting ketone **24**. The 2-oxo 7-azabicyclo[2.2.1]heptane was clearly differentiated from the possible 3-regioisomer by direct comparison of the spectroscopic data with that of the corresponding 3-oxo-7-azabicyclo[2.2.1]heptane,[5] confirming the regiospecific reaction of diol **21**. Treatment of **24** with a large excess of trimethyl phosphonoacetate and NaH led to a separable mixture of cis and trans olefins **25** and **26** in a ratio of 92/8 and a combined yield of 62%. The major isomer **25** was submitted to hydrogenation (Pd/C) and carbamoylation to afford fully protected glutamate analogue **27** in 88% yield. Selectivity in the reduction was predicted on the basis of the relative accessibility to the exo face of the double bond versus the sterically congested endo face, thus resulting in a single reduction product.

Conclusion

A method for the synthesis of a 2-substituted 7-azabicyclo[2.2.1]heptane glutamic acid analogue **27** from L-serine has been developed. This method could provide an entry into a variety of 2-substituted 7-azabicyclo[2.2.1]-heptane α-amino acid analogues through further functionalization of the ketone **23**.[5] It proceeds via the stereospecific synthesis of (2*S*,3*S*,5*S*)-pyrrolidine **3** or (2*S*,3*S*,5*R*)-pyrrolidine **4**, both of which can be effected from aminal **2**, depending on the mode of cyclization. These trisubstituted pyrrolidines are versatile intermediates for the synthesis of amino acid analogues and may be extrapolated to other biologically active molecules.

Experimental Section

General Procedures. All melting points are uncorrected. All reactions were conducted under an atmosphere of dry nitrogen unless otherwise noted. Final solutions before evaporation were dried over Na_2SO_4. THF and Et_2O were distilled from Na/benzophenone, CH_2Cl_2 was distilled from CaH_2, and CH_3CN was distilled first from P_2O_5 and then CaH. Chromatography was carried out using 230−400 mesh silica gel. ^1H NMR were taken in $CDCl_3$ and referenced to internal TMS unless otherwise noted; coupling constants are reported in hertz. HPLC analyses were conducted with a normal-phase HPLC (Microsorb Si column, 0.46 × 25 cm) using a spectrophotometer set at 254 nm. The mobile phase consisted of a mixture of EtOAc/hexane specific to each compound analyzed, and retention times are reported as t_R in min. Elemental analyses were performed by the Microanalytical Laboratories, University of California, Berkeley.

(2*S*,4*S*,5*S*)-4-Hydroxy-5-hydroxymethyl-2-(methoxycarbonyl)methyl-1-(phenylsulfonyl)pyrrolidine Isopropylidine Ketal (3). To a suspension of THF (500 mL) and NaH (95%, 0.98 g, 40.7 mmol) cooled to −15 °C was added trimethyl phosphonoacetate (6.41 mL, 40.7 mmol). The resulting slurry was mechanically stirred, and a precooled solution of aldehyde **2** (8.50 g, 27.2 mmol), in THF (200 mL), was added, maintaining the temperature at −15 °C. After the mixture was stirred for 96 h between −10 °C and −15 °C, a saturated solution of NaH_2PO_4 (250 mL) was added, and the resulting mixture was evaporated at room temperature to 300 mL. To the suspension was added $CHCl_3$/IPA (4/1, 200 mL). The aqueous and organic layers were separated, and the aqueous layer was extracted with $CHCl_3$/IPA (4/1, 3 × 200 mL). The combined organic layer was dried, filtered, and passed through a plug of silica (hexane/EtOAc, 2/1). The resulting solution, analyzed by HPLC, was determined to be a 5.6/1.0 mixture of **3/4**, 8.83 g, 88% yield (**4**, t_R 10.5 min; **3**, t_R 11.2 min, 7/1 hexane/EtOAc). Crystallization from hexane/EtOAc afforded **3** (6.85 g, 69%) as a pure diastereomer: mp 97−98 °C; $[\alpha]^{23}_D$ +5.8° (*c* 1.0, $CHCl_3$); ^1H NMR δ 1.32 (s, 3H), 1.37 (s, 3H), 1.50−1.59 (m, 1H), 1.81 (d, *J* = 14.2, 1H), 2.95 (m, 2H), 3.52 (m, 1H), 3.66 (s, 3H), 3.97−4.24 (m, 4H), 7.51−7.57 (m, 3H), 7.80−7.83 (m, 2H); ^{13}C NMR δ 172.0, 137.0, 133.1, 129.3, 127.4, 99.0, 70.9, 62.8, 59.7, 58.1, 51.6, 41.6, 36.1, 26.1, 21.3. Anal. Calcd for $C_{17}H_{23}NO_6S$: C, 55.3; H, 6.3; N, 3.8. Found: C, 55.2; H, 6.4; N, 3.8.

(2*R*,4*S*,5*S*)-4-Hydroxy-5-hydroxymethyl-2-(methoxycarbonyl)methyl-1-(phenylsulfonyl)pyrrolidine Isopropylidine Ketal (4). To a solution of $Ni(OAc)_2 \cdot H_2O$ (10 mg, 0.04 mmol) in MeOH (5 mL), cooled to 0 °C, was added **6a/6b** (96/4, 0.20 g, 0.41 mmol) followed by the addition of $NaBH_4$ (0.16 g, 4.1 mmol) in five portions over 5 min. The reaction mixture turned dark brown upon addition of the $NaBH_4$, and H_2O (20 mL) was added immediately after the final portion of $NaBH_4$. The resulting mixture was extracted with $CHCl_3$/IPA (4/1, 3 × 20 mL), and the combined organic phase was dried, filtered, and evaporated. The residue was chromatographed (hexane/EtOAc,7/1) to afford **4/3** (0.13 g, 86%) as a colorless oil: **4/3** by HPLC, 96/4; $[\alpha]^{23}_D$ +57.5 (*c* 1.0, $CHCl_3$); ^1H NMR δ 1.07 (s, 3H), 1.32 (s, 3H), 1.94 (m, 1H), 2.17 (m, 1H), 2.50 (m, 1H), 3.17 (dd, *J* = 4.3, 16.1, 1H), 3.64 (s, 3H), 3.89 (dd, *J* = 4.9, 5.1, 1H), 4.01 (dd, *J* = 4.9, 12.5, 1H), 4.10 (dd, *J* = 5.9, 12.5, 1H), 4.35−4.40 (m, 2H), 7.48−7.57 (m, 3H), 7.82 (d, *J* = 7.3, 2H); ^{13}C NMR δ 171.2, 140.3, 132.3, 128.8, 126.9, 98.6, 69.1, 59.5, 59.3, 56.6, 51.6, 39.2, 38.2, 26.4, 21.2. Anal. Calcd for $C_{17}H_{23}NO_6S$: C, 55.3; H, 6.3; N, 3.8. Found: C, 55.4; H, 6.2; N, 3.7.

Methyl (2*E*,5*S*,6*S*)-5,7-Dihydroxy-6-phenylsulfonylamino-2-heptenoate Isopropylidine Ketal (5). To a stirred suspension of sodium hydride (95%, 50 mg, 2.10 mmol) in THF (10 mL) at room temperature was added trimethyl phosphonoacetate (0.35 mL, 2.10 mmol) in 5 mL of THF, and the

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mixture was stirred for 30 min. Hemiaminal **2** (0.57 g, 1.80 mmol) was added, and the mixture was stirred for 4 h at −30 °C, saturated NaH_2PO_4 (10 mL) was added, and it was evaporated to 10 mL and extracted with $CHCl_3$/IPA (4 × 15 mL). The combined organic layer was dried, filtered, and evaporated, and the resulting oil was chromatographed (hexane/EtOAc, 2/1) to afford **5** (0.55 g, 83%) as a colorless oil: $[\alpha]^{23}_D$ −47.6 (*c* 0.25, $CHCl_3$); R_f 0.65 (1/1, Hex/EtOAc); ^{1}H NMR δ 1.33 (s, 3H), 1.35 (s, 3H), 1.88−2.26 (m, 1H), 2.36 (m, 1H), 3.12 (dd, J = 10.2, 1.7, 1H), 3.27 (dd, J = 12.2, 1.8, 1H), 3.68 (s, 3H), 3.82 (dd, J = 12.2, 1.6, 1H), 5.49 (d, J = 10.2, 1H, D_2O exchangeable), 5.76 (d, J = 15.7, 1H), 6.74−6.81 (m, 1H), 7.24−7.55 (m, 3H), 7.84−7.86 (m, 2H); ^{13}C NMR δ 166.7, 144.1, 141.1, 132.8, 129.3, 126.8, 123.3, 99.5, 70.4, 64.0, 51.5, 50.0, 34.8, 29.4, 18.4. Anal. Calcd for $C_{17}H_{23}NO_6S$: C, 55.3; H, 6.3; N, 3.8. Found: C, 55.5; H, 6.5; N, 3.7.

Methyl (2*R*,4*S*,5*S*)-4-Hydroxy-5-hydroxymethyl-1-phenylsulfonylpyrrolidine-2-iodoacetate Isopropylidine Ketal (6a/6b). To a solution of unsaturated ester **5** (0.30 g, 0.81 mmol) in Et_2O (20 mL) were added I_2 (1.03 g, 4.1 mmol) and $NaHCO_3$ (1.0 M aqueous, 2.44 mmol) at room temperature. After 48 h, sodium thiosulfate (2 M, 50 mL) was added, the aqueous layer was extracted with $CHCl_3$/IPA (4/1, 3 × 50 mL), and the combined organic layer was dried, filtered, and evaporated. The resulting oil was purified by chromatography (hexane/EtOAc, 3/1) to afford a mixture of **6a** and **6b** (0.29 g, 71%) as a light yellow oil and recovered **5** (50 mg): ^{1}H NMR δ 0.78 (s, 3H), 1.22 (s, 3H),2.08 (m, 1H), 2.27 (m, 1H), 3.75 (s, 3H), 3.80−3.98 (m, 3H), 3.99 (dd, J = 3.8, J = 13.4, 1H), 4.36 (s, 1H), 4.46 (dd, J = 3.4, J = 13.4, 1H), 5.85 (d, J = 3.3, 1H), 7.42−7.57 (m, 3H), 7.82 (d, J = 7.2, 2H); ^{13}C NMR δ 169.8, 141.1, 132.4, 128.7, 127.3, 98.0, 69.5, 61.6, 59.4, 58.1, 52.9, 38.3, 32.9, 27.4, 19.7. Anal. Calcd for $C_{17}H_{23}NO_6S\cdot 0.5H_2O$: C, 40.5; H, 4.6; N, 2.7. Found: C, 40.5; H, 4.8; N, 2.3.

Methyl (2*S*,4*S*,5*S*)-4-Hydroxy-5-hydroxymethyl-1-phenylsulfonylpyrrolidine-2-acetate (7). To a stirred solution of acetonide **3** (1.40 g, 3.79 mmol) in MeOH (30 mL) was added concentrated HCl (0.3 mL) at room temperature. After 24 h, the reaction was evaporated to dryness, and the resulting oil was chromatographed (hexane/EtOAc, 1/1) to afford **7** (1.20 g, 96%) as a colorless oil. Addition of Et_2O followed by evaporation afforded **7** as a white solid: mp 76−78 °C; $[\alpha]^{21}_D$ −12.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 1.80 (m, 2H), 2.86 (dd, J = 8.8, 16.2, 1H), 3.01 (dd, J = 4.7, 16.1, 1H), 3.55 (m, 2H), 3.66 (s, 3H), 4.05 (m, 4H), 7.55 (m, 3H), 7.75 (d, J = 7.8, 2H); ^{13}C NMR δ 172.0, 136.1, 133.3, 129.3, 127.5, 72.1, 64.2, 62.8, 56.5, 51.8, 41.2, 38.3. Anal. Calcd for $C_{14}H_{19}NO_6S$: C, 51.1; H, 5.8; N, 4.3. Found: C, 51.2; H, 5.8; N, 4.3.

Methyl (2*S*,4*S*,5*S*)-4-*tert*-Butyldimethylsilyloxy-5-*tert*-butyldimethylsilyloxy-methyl-1-phenylsulfonylpyrrolidine-2-acetate (8). To a solution of diol **7** (8.0 g, 24.3 mmol) in DMF (10 mL) were added imidazole (10.05 g, 146 mmol) and TBDMSCl (11.0 g, 73.0 mmol) at room temperature. The mixture was stirred for 12 h, extracted with hexane (6 × 50 mL), and evaporated. The resulting oil was chromatographed (hexane/EtOAc, 5/1), affording **8** as a colorless oil (12.96 g, 96%): $[\alpha]^{21}_D$ +20.5 (*c* 1.8, $CHCl_3$); ^{1}H NMR δ −0.089 (s, 3H), −0.058 (s, 3H), 0.067 (s, 6H), 0.80 (s, 9H), 0.88 (s, 9H), 1.76 (m, 2H), 2.87 (dd, J = 10.2, 16.4, 1H), 3.20 (dd, 4.19, 16.4, 1H), 3.33 (m, 1H), 3.63 (s, 3H), 3.82 (m, 2H), 4.01 (m, 2H), 7.54 (m, 3H), 7.82 (d, J = 7.3, 2H); ^{13}C NMR δ 172.1, 137.0, 132.9, 129.1, 127.5, 71.1, 65.3, 61.9, 56.3, 51.4, 41.5, 38.3, 26.0, 25.7, 18.4, 18.0. Anal. Calcd for $C_{26}H_{47}NO_6SSi_2$: C, 56.0; H, 8.5; N, 2.5. Found: C, 56.1; H, 8.4; N, 2.6.

Methyl (2*S*,4*S*,5*S*)-4-*tert*-Butyldimethylsilyloxy-5-hydroxymethyl-1-phenylsulfonylpyrrolidine-2-acetate (9). A solution of bis-silyl ether **8** (11.42 g, 20.5 mmol) in AcOH/H_2O/THF (13/7/3, 500 mL) was stirred for 22 h at room temperature, the volatiles were evaporated at room temperature, and to the residue was added EtOAc (200 mL) followed by saturated $NaHCO_3$. The resulting aqueous layer was extracted with EtOAc (4 × 200 mL), the combined organic layer was washed with saturated NaCl, dried, and evaporated, and the resulting oil was chromatographed (hexane/EtOAc, 3/1) to afford **9** (6.54 g, 72%), recovered **8** (2.44 g, 21%), and a trace of diol **7**. A single resubjection of the recovered **8** to the above conditions afforded additional **9** (1.4 g): total yield of **9**, 87%; $[\alpha]^{20}_D$ −13.9 (*c* 3.6, $CHCl_3$); ^{1}H NMR δ −0.11 (s, 3H), −0.083 (s, 3H), 0.77 (s, 9H), 1.66 (m, 1H), 1.83 (m, 1H), 2.76 (dd, J = 10.1, 16.4, 1H), 2.88 (dd, J = 5.2, 8.1, 1H), 3.08 (dd, J = 4.2, 16.4 1H), 3.52 (dd, J = 5.6, 11.5, 1H), 3.62 (s, 3H), 3.84 (m, 2H), 4.00 (m, 1H), 7.54 (m, 3H), 7.81 (d, J = 7.1, 2H); ^{13}C NMR δ 171.6, 136.5, 133.2, 129.3, 127.5, 72.2, 64.9, 63.1, 56.2, 51.5, 41.9, 38.3, 25.5, 17.8. Anal. Calcd for $C_{20}H_{33}NO_6SSi$: C, 54.2; H, 7.5; N, 3.2. Found: C, 54.5; H, 7.7; N, 3.2.

(2*R*,3*S*,5*S*)-3-*tert*-Butyldimethylsilyloxy-5-methoxycarbonylmethyl-1-phenylsulfonylproline *tert*-Butyl Ester (10). To a solution of alcohol **9** (1.18 g, 2.67 mmol) in CH_3CN (12 mL) and CCl_4 (12 mL) was added a mixture of H_2O (9 mL), $NaIO_4$ (1.71 g, 8.0 mmol), and $RuCl_3\cdot 3H_2O$ (50 mg). The biphasic mixture was vigorously stirred (magnetic) for 3 h, the phases were separated, and the aqueous phase was extracted with $CHCl_3$/IPA (4/1, 4 × 50 mL). The combined organic phase was dried, filtered, and evaporated, and the resulting oil was passed through a plug of silica gel (EtOAc/hexane, 2/1) to afford crude carboxylic acid (1.04 g) as a yellow foam. To the crude carboxylic acid dissolved in CH_2Cl_2 (10 mL) and *t*-BuOH (40 mL) was added *N*,*N*′-diisopropyl-*O*-*tert*-butylisourea (0.48 g, 2.40 mmol) and the mixture stirred at room temperature for 105 min. The mixture was evaporated at room temperature, and to the residue was added H_2O (100 mL) followed by $CHCl_3$/IPA (4/1, 50 mL). The aqueous phase was extracted with additional $CHCl_3$/IPA (4/1, 3 × 50 mL), the combined organic phase was dried, filtered, and evaporated, the resulting solid was digested in hexane/EtOAc (5/1, 10 mL) and filtered, and the filtrate was evaporated and chromatographed (hexane/EtOAc, 5/1) to afford the *tert*-butyl ester **10** (1.02 g, 79% from **9**) as a colorless oil: $[\alpha]^{23}_D$ −5.28 (*c* 2.5, $CHCl_3$); ^{1}H NMR δ −0.076 (s, 3H), −0.053 (s, 3H), 0.76 (s, 9H), 1.38 (s, 9H), 2.17 (m, 1H), 2.91 (dd, J = 10.1, 16.6, 1H), 3.45 (dd, J = 4.1, 16.6, 1H), 3.63 (s, 3H), 3.89 (dd, J = 8.4, 7.1, 1H), 4.04 (m, 1H), 4.10 (d, J = 7.6, 1H), 7.56 (m, 3H), 7.81 (d, J = 7.4, 2H); ^{13}C NMR δ 171.9, 168.1, 138.2, 133.0, 129.2, 127.2, 81.9, 71.5, 65.4, 55.2, 51.5, 41.0, 38.7, 28.0, 25.6, 18.0. Anal. Calcd for $C_{24}H_{39}NO_7SSi$: C, 56.1; H, 7.7; N, 2.7. Found: C, 56.3; H, 7.7; N, 2.8.

(2*R*,3*S*,5*S*)-3-*tert*-Butyldimethylsilyloxy-5-*β*-hydroxyethyl-1-phenylsulfonylproline *tert*-Butyl Ester (11). To a solution of diester **10** (0.96 g, 1.87 mmol) in Et_2O was added $LiBH_4$ (2M in THF, 1.3 mL). After 8 h, K_2CO_3 (1M, 30 mL) was added, and the mixture was concentrated at room temperature and extracted with $CHCl_3$/IPA (4/1, 4 × 50 mL). The combined organic layer was dried, filtered, and evaporated, and the resulting oil was chromatographed (hexane/EtOAc, 2/1) to afford **11** (0.78 g, 86%) as a colorless oil: $[\alpha]^{22}_D$ +44.2 (*c* 1.15, $CHCl_3$); ^{1}H NMR δ −0.064 (s, 3H), −0.049 (s, 3H), 0.77 (s, 9H), 1.40 (s, 9H), 1.70−1.99 (m, 3H), 2.24 (m, 1H), 2.87 (dd, J = 5.7, 6.5, 1H), 3.70 (m, 1H), 3.92−4.14 (m, 4H), 7.54 (m, 3H), 7.86 (d, J = 7.7); ^{13}C NMR δ 168.4, 137.8, 133.1, 129.3, 127.4, 82.1, 72.5, 66.7, 59.3, 57.3, 39.2, 38.3, 28.1, 25.8, 18.1. Anal. Calcd for $C_{23}H_{39}NO_6SSi$: C, 56.9; H, 8.1; N, 2.9. Found: C, 56.7; H, 8.0; N, 2.9.

(2*R*,3*S*,5*S*)-3-*tert*-Butyldimethylsilyloxy-5-*β*-bromoethyl-1-phenylsulfonylproline *tert*-Butyl Ester (12). To a solution of alcohol **11** (0.78 g, 1.72 mmol) in CH_2Cl_2 (20 mL) were added CBr_4 (0.80 g, 2.40 mmol) and Ph_3P (0.54 g, 2.06 mmol) at room temperature. The reaction mixture was stirred for 2 h, H_2O (20 mL) was added, and the aqueous phase was extracted with $CHCl_3$/IPA (4/1, 4 × 50 mL). The combined organic phase was dried, filtered, and evaporated, and the resulting oil was chromatographed (hexane/EtOAc, 5/1) to afford **12** (0.85 g, 95%) as a colorless oil that crystallized from $CHCl_3$: mp 98−99 °C; $[\alpha]^{21}_D$ +3.4 (*c* 2.4, $CHCl_3$); ^{1}H NMR δ −0.051 (s, 3H), −0.034 (s, 3H), 0.78 (s, 9H), 1.40 (s, 9H), 1.75 (m, 1H), 1.88 (m, 1H), 2.20 (m, 1H), 2.68 (m, 1H), 3.40 (dd, J = 9.8, 7.4, 1H), 3.54 (m, 1H), 3.90 (m, 1H), 3.99 (dd, J = 13.8, 7.0, 1H), 4.17 (d, J = 7.4, 1H), 7.55 (m, 3H), 7.81 (d, J = 7.5, 2H); ^{13}C NMR δ 168.2, 138.2, 132.9, 129.2, 127.3, 81.9, 71.9,

66.1, 58.0, 38.8, 38.3, 30.5, 28.0, 25.7, 18.1. Anal. Calcd for $C_{23}H_{38}NO_5SSiBr$: C, 50.4; H, 7.0; N, 2.6. Found: C, 50.5; H, 7.2; N, 2.5.

(2*R*,3*S*,5*S*)-5-*β*-Bromoethyl-3-hydroxy-1-phenylsulfonylproline *tert*-Butyl Ester (13). A solution of **12** (100 mg, 0.20 mmol) in THF (5 mL) was cooled to 0 °C, and TBAF (1 M in THF, 0.21 mL, 0.21 mmol) was added dropwise. The solution was stirred for 30 min at 0 °C, phosphate buffer, pH 7 (1 M, 25 mL), was added, and the mixture was concentrated under reduced pressure and extracted with $CHCl_3$/IPA (4/1, 3 × 25 mL). The combined organic phase was dried, filtered, and evaporated, and the resulting oil was chromatographed (hexane/EtOAc, 2/1) to afford **13** (50 mg, 64%) as a colorless oil: $[\alpha]^{22}_D$ +20.3 (*c* 0.3, $CHCl_3$); ^{1}H NMR *δ* 1.43 (s, 9H), 1.69−1.76 (m, 2H), 2.10 (m, 1H), 2.56 (m, 1H), 2.79 (bs, 1H), 3.42 (m, 1H), 3.53 (m, 1H), 3.91 (m, 1H), 4.26 (m, 2H), 7.48−7.61 (m, 3H), 7.81 (d, 2H); ^{13}C NMR *δ* 169.1, 137.2, 128.5, 128.0, 127.8, 82.8, 72.2, 68.1, 66.3, 57.7, 57.0, 38.5, 31.8, 28.0; HRMS calcd for C_{17} H_{24} NO_5 SBr 433.0559, found 433.0524.

***tert*-Butyl 5-*β*-Bromoethylpyrrole-2-carboxylate (16).** To a solution of bromide **12** (0.10 g, 0.19 mmol) in THF (3 mL) at −78 °C was added KHMDS (0.92 M, 0.2 mL) dropwise. After 45 min, KH_2PO_4 (1M, 20 mL) was added, and the mixture was concentrated at room temperature and extracted with $CHCl_3$/IPA (4/1, 4 × 50 mL). The combined organic phase was dried, filtered, and evaporated, and the resulting oil was purified by preparative thin-layer chromatography (hexane/EtOAc, 5/1) to afford **16** (8 mg, 22%) as a white solid: mp 118−119 °C; ^{1}H NMR *δ* 1.54 (s, 9H), 3.19 (t, *J* = 7.17, 2H), 3.56 (t, *J* = 7.15, 2H), 6.01 (t, *J* = 3.06, 1H), 6.75 (t, *J* = 2.61, 1H); ^{13}C NMR *δ* 160.6, 133.8, 123.7, 115.1, 108.7, 80.7, 31.4, 30.9, 28.3; HRMS calcd for $C_{11}H_{16}NO_2Br$ 273.0364, found 273.0401.

(2*R*,3*S*,5*S*)-3-*tert*-Butyldimethylsilyloxy-5-*β*-hydroxyethylproline *tert*-Butyl Ester (17). A solution of Et_4NBr dissolved in CH_3CN (0.1 M) was used to fill the electrolysis cell, and argon was bubbled through the solution for 15 min. The current was set at 1.73 eV, and pre-electrolysis of the Hg resulted in a stable background reading of 1.7 mA after 2 h. 4-Phenylphenol (6.6 mmol) was added to the cathode solution, and argon was bubbled through the solution for 15 min. Pre-electrolysis of the solution resulted in a background reading of 1.9 mA in 15 h. The protected amine **11** (1.00 g, 2.2 mmol) dissolved in CH_3CN was added, and the initial current reading was 13 mA. After 6 h the current was 1.4 mA. The reaction mixture was decanted into a round-bottom flask, 100 mL of H_2O was added, the mixture was evaporated at room temperature to remove the acetonitrile, and the resulting mixture was extracted with $CHCl_3$/IPA (4/1, 4 × 50 mL). The combined organic phase was dried, filtered, and evaporated, and the resulting oil was chromatographed (hexane/EtOAc, 1/2) to afford **17** (0.49 g, 78%) as a colorless oil: $[\alpha]^{22}_D$ +21.2 (*c* 0.7, $CHCl_3$); ^{1}H NMR *δ* 0.06 (s, 3H), 0.07 (s, 3H), 0.88 (s, 9H), 1.47 (s, 9H), 1.47−1.49 (m, 1H), 1.91−1.74 (m, 2H), 2.2 (m, 1H), 2.35 (bs, 1H), 3.21 (m, 1H), 3.55 (d, *J* = 5.3, 1H), 3.88−3.69 (m, 2H), 4.48 (dd, *J* = 9.5, 5.5); ^{13}C NMR *δ* 169.5, 81.2, 74.3, 67.6, 60.6, 55.2, 41.9, 38.2, 28.1, 25.8, 18.0, −4.8, −4.6. Anal. Calcd for $C_{17}H_{35}NO_4Si$: C, 59.0; H, 10.2; N, 4.0. Found: C, 58.6; H, 10.4; N, 4.0.

(2*R*,3*S*,5*S*)-3-*tert*-Butyldimethylsilyloxy-1-benzyloxycarbonyl-5-*β*-hydroxyethylproline *tert*-Butyl Ester (18). To a suspension of **17** (0.49 g, 1.56 mmol) dissolved in EtOAc (10 mL) were added H_2O (10 mL), K_2CO_3 (0.52 g, 3.12 mmol), and CbzCl (0.45 mL, 3.12 mmol) at 0 °C. The cooling bath was removed, and after 1.5 h, KH_2PO_4 (1 M, 50 mL) was added to the mixture, the aqueous phase was extracted with EtOAc (3 × 50 mL), and the combined organic layer was dried, filtered, and evaporated. The resulting oil was chromatographed (hexane/EtOAc, 1/1) to afford **18** (0.60 g, 85%) as a colorless oil: $[\alpha]^{22}_D$ +49.4 (*c* 0.95, $CHCl_3$); ^{1}H NMR 0.024 (s, 3H), 0.027 (s, 3H), 0.82 (s, 9H), 1.32 (s, 7.8H major rotomer), 1.44 (s, 1.2H, minor rotomer), 1.73 (m, 2H), 2.05−2.20 (m, 2H), 3.61 (m, 1H), 3.70−3.90 (m, 2H), 4.23 (m, 1H), 4.47 (d, 1H), 4.56 (m, 1H), 5.00−5.22 (m, 2H). 7.18−7.39 (m, 5H); ^{13}C NMR (rotomers) *δ* 168.4, 155.8, 136.1, 128.5, 128.2, 128.1, 127.9, 81.6, 73.0, 67.4, 66.5, 60.4, 59.2, 54.9, 40.0, 37.8, 28.1, 25.9,18.1; ^{1}H NMR (C_6D_6, 60 °C) *δ* 0.037 (s, 3H), 0.087 (s, 3H), 0.94 (s, 9H), 1.39 (s, 9H), 2.10−1.71 (m, 3H),2.45 (m, 1H), 3.38 (m, 1H), 3.76 (m, 1H), 3.92 (m, 1H),, 4.22 (m, 2H), 4.41 (m, 1H), 5.00−5.22 (m, 2H), 7.10−7.37 (m, 5H); ^{13}C NMR (C_6D_6 at 333K) *δ* 168.3, 155.0, 136.8, 128.2, 127.1, 127.8, 127.6, 127.3, 80.7, 72.5, 66.9, 65.9, 59.3, 54.8, 39.5, 38.1, 27.9, 25.6,17.9, −5.0, −5.4. Anal. Calcd for $C_{25}H_{42}NO_6Si$: C, 62.5; H, 8.8; N, 2.9. Found: C, 62.5; H, 8.7; N, 2.9.

(2*R*,3*S*,5*S*)-3-*tert*-Butyldimethylsilyloxy-1-benzyloxycarbonyl-5-*β*-bromoethylproline *tert*-Butyl Ester (19). To a solution of alcohol **18** (0.52 g, 1.00 mmol) in CH_2Cl_2 (20 mL) at 0 °C were added triphenylphosphine (0.82 g, 2 mmol) and CBr_4 (0.46 g, 1.4 mmol). The cooling bath was removed, the reaction mixture was stirred for 2 h at room temperature, and H_2O (50 mL) was added. The aqueous phase was extracted with $CHCl_3$/IPA (4/1, 3 × 20 mL), the combined organic phase was dried, filtered, and evaporated, and the resulting oil was chromatographed (hexane/EtOAc/$CHCl_3$, 4/1/1) to afford **19** (0.49 g, 96%) as a colorless oil: $[\alpha]^{22}_D$ −10.1 (*c* 1.3, $CHCl_3$); ^{1}H NMR 0.028 (s, 3H), 0.034 (s, 3H), 0.92 (s, 9H), 1.38 (s, 6.4H, major rotomer), 1.43 (s, 2.6H, minor rotomer), 1.81 (m, 1H), 2.20 (m, 2H), 2.63 (m, 0.3H), 2.82 (m, 0.7H), 3.32−3.58 (m, 2H), 4.06 (m, 1H), 4.35−4.57 (m, 2H), 5.02−5.09 (m, 2H), 7.25−7.42 (m, 5H); ^{1}H NMR (C_6D_6, 60 °C) *δ* 0.028 (s, 3H), 0.078 (s, 3H), 0.94 (s, 9H), 1.42 (s, 9H), 1.72 (m, 1H), 1.85 (m, 1H), 2.25 (m, 1H), 2.63−2.95 (m, 1H), 3.21−3.50 (m, 2H), 3.94 (m, 1H), 4.16 (m, 1H), 4.38 (m, 1H) 5.07−5.10 (m, 2H). 7.09−7.69 (m, 5H); ^{13}C NMR (C_6D_6, 60 °C) *δ* 169.2, 154.8, 137.7, 129.0, 128.6, 128.4, 128.1, 81.5, 72.5, 67.6, 65.9, 56.8, 39.6, 39.0, 30.9, 28.7, 26.5, 18.7, −4.3, −4.6. Anal. Calcd for $C_{25}H_{40}NO_5BrSi$: C, 55.2; H, 7.6; N, 2.6. Found: C, 55.4; H, 7.6; N, 2.6.

***tert*-Butyl 7-Benzyloxycarbonyl-7-azabicyclo[2.2.1]-2-heptene-1-carboxylate (20).** To a solution of bromide **19** (0.10 g, 0.20 mmol) in THF (5 mL) at −78 °C was added KHMDS (0.92 M in toluene, 0.40 mmol). The mixture stirred at −78 °C for 1 h, −40 °C for 2 h, and 0 °C for 1 h, and then KH_2PO_4 (1 M, 15 mL) was added. After evaporation to remove the THF, the aqueous residue was extracted with $CHCl_3$/IPA (4/1, 3 × 20 mL). The combined organic layer was dried, filtered, and evaporated, and the resulting oil was chromatographed (hexane/EtOAc, 7/1) to afford **20** (51 mg, 77%) as a colorless oil: $[\alpha]^{22}_D$ +9.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR *δ* 1.17 (ddd, *J* = 11.3, 8.8, 3.5, 1H), 1.44 (m, 1H), 1.49 (s, 9H), 2.05 (m, 1H), 2.23 (m, 1H), 4.83 (dd, *J* = 4.1, 2.2, 1H), 5.07 (S, 3H), 6.28 (dd, *J* = 5.8, 2.1, 1H), 6.46 (d, *J* = 5.8, 1H), 7.33 (m, 5H); ^{13}C NMR *δ* 168.4, 156.5, 136.1, 135.2, 134.6, 128.3, 127.9, 127.8, 81.6, 73.3, 67.1, 62.7, 29.2, 27.8, 24.8. Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.3; H, 7.0; N, 4.3. Found: C, 68.9; H, 7.0; N, 4.5.

***tert*-Butyl (1*S*,2*S*,3*R*,4*R*)-7-Benzyloxycarbonyl-2,3-dihydroxy-7-azabicyclo[2.2.1]heptane-1-carboxylate (21).** To a solution of olefin **20** (0.22 g, 0.67 mmol) in acetone (18 mL) and H_2O (2 mL) were added NMMO (0.13 g, 1.10 mmol) and OsO_4 (2% solution in H_2O, 0.45 mL). The solution was stirred for 12 h at room temperature, saturated aqueous $NaHSO_3$ (50 mL) was added, the mixture was extracted with $CHCl_3$/IPA (4/1, 3 × 20 mL), and the combined organic layer was dried, filtered, and evaporated. The resulting oil was chromatographed (hexane/EtOAc, 3/1) to afford **21** (0.21 g, 88%) as a colorless oil: $[\alpha]^{24}_D$ −13.8 (*c* 2.1, $CHCl_3$); ^{1}H NMR *δ* 1.13 (m 1H), 1.48 (s, 9H), 1.72 (m, 1H), 2.05 (dt, *J* = 4.3, 12.5, 1H), 3.81 (m, 2H), 3.96 (dd, *J* = 3.5, 5.1, 1H), 4.24 (d, *J* = 5.2, 1H), 4.50 (d, *J* = 3.3, 1H), 5.08 (m, 2H), 7.33 (m, 5H); ^{13}C NMR *δ* 168.7, 157.3, 136.2, 128.2, 127.8, 83.1, 75.2, 74.0, 70.0, 67.1, 64.8, 29.3, 27.8, 23.9. Anal. Calcd for $C_{19}H_{25}NO_6$: C, 62.8; H, 6.9; N, 3.9. Found: C, 62.4; H, 7.2; N, 3.9.

***tert*-Butyl (1*S*,2*S*,3*R*,4*R*,)-7-Benzyloxycarbonyl-3-*tert*-butyldiphenylsilyloxy-2-hydroxy-7-azabicyclo[2.2.1]heptane-1-carboxylate (22).** To a solution of diol **21** (0.40 g, 1.10 mmol) in CH_2Cl_2 (50 mL) were added imidazole (0.23 g, 3.3 mmol) and TBDPSCI (0.61 mL, 2.22 mmol). The mixture was stirred at room temperature for 48 h, extracted with hexane (6 × 50 mL), dried, filtered, and evaporated. The resulting oil was chromatographed (hexane/EtOAc, 10/1), affording **22** as a colorless oil (0.64 g, 96%): HPLC, t_R 6.6 min (hexane/EtOAc,

9/1, 3 mL/min); ^{1}H NMR δ 0.98 (m, 1H), 1.11 (s, 9H), 1.46−1.51 (m, 12H), 1.95 (m, 1H), 3.49 (d, J = 3.6, 1H), 3.88−3.91 (m, 2H), 4.99 (d, J = 4.6, 1H), 5.15 (m, 2H), 7.76−7.33 (m, 15 H); ^{13}C NMR δ 166.8, 157.7, 136.5, 135.7, 135.6, 133.0, 132.6, 129.9, 129.8, 128.2, 127.8, 127.7, 127.6, 81.2, 77.6, 74.9, 72.5, 67.1, 64.6, 28.3, 27.9, 26.8, 24.1, 19.2. Anal. Calcd for $C_{35}H_{43}NO_6Si$: 69.8; H, 7.2; N, 2.3. Found: C, 68.9; H, 7.4; N, 2.3.

***tert*-Butyl (1*S*,3*R*,4*R*)-7-Benzyloxycarbonyl-3-*tert*-butyldiphenylsilyloxy-2-oxo-7-azabicyclo[2.2.1]heptane-1-carboxylate (23).** To a suspension of periodinane[20] (0.22 g, 0.53 mmol) in CH_2Cl_2 (10 mL) was added alcohol **22** (0.21 g, 0.35 mmol) in CH_2Cl_2 (3 mL). The suspension was stirred at room temperature for 36 h, $Na_2S_2O_3\cdot5H_2O$ (1.0 g, 4.0 mmol) and H_2O (20 mL) were added, and the aqueous layer was extracted with $CHCl_3$/IPA (4/1, 3 × 20 mL). The combined organic layer was dried, filtered, and evaporated, and the residual oil was chromatographed (hexane/EtOAc, 3/1) to afford ketone **23** (0.164 g, 78%): mp 103−104 °C; HPLC, t_R 11.4 min (hexane/EtOAc, 9/1 mL/min); $[\alpha]^{23}_D$ −28.7 (*c* 0.7, $CHCl_3$); ^{1}H NMR δ 1.11 (s, 9H), 1.21 (m, 1H), 1.53 (s, 9H), 1.66−1.81 (m, 3H), 2.18 (dt, J = 4.3, 12.6, 1H), 3.69 (s, 1H), 4.35 (dt, J = 3.7, 1H), 5.2 (m, 2H), 7.78−7.33 (m, 15H); ^{13}C NMR δ 201.7, 164.3, 156.3, 136.1, 135.8, 135.7, 133.2, 132.4, 129.9, 128.4, 128.1, 127.8, 127.7, 82.2, 75.7, 74.3, 67.4, 63.6, 27.3, 26.6, 26.0, 24.0, 19.2. Anal. Calcd for $C_{35}H_{41}NO_6Si$: C, 70.1; H, 6.9; N, 2.3. Found: C, 69.7; H, 6.9; N, 2.3.

***tert*-Butyl (1*S*,4*R*)-7-Benzyloxycarbonyl-2-oxo-7-azabicyclo[2.2.1]heptane-1-carboxylate (24).** A solution of **23** (0.59 g, 1.0 mmol) in THF (30 mL) was degassed by bubbling N_2 through the solution for 30 min; degassed MeOH (10 mL) was added, and the solution was cooled to −78 °C. To this solution was added a solution of SmI_2 in THF (10 mL, 0.22 M, 0.22 mmol) over 10 min, maintaining the temperature at −78 °C, and then the reaction mixture was stirred for 5 min at −78 °C and saturated aqueous $NaHCO_3$ (50 mL) was added. The mixture was concentrated to 60 mL and was extracted with $CHCl_3$/IPA (4/1, 3 × 20 mL). The combined organic layer was dried, filtered, and evaporated, and the resulting oil was chromatographed (hexane/EtOAc, 3/1) to afford **24** (0.25 g, 72%): mp 97−98 °C; $[\alpha]^{22}_D$ −27.0 (*c* 1.4, $CHCl_3$); ^{1}H NMR δ 1.45 (s, 9H), 1.64 (m, 1H), 1.78 (m, 1H), 1.84 (m, 1H), 2.11 (d, J = 17.5, 1H), 2.28 (m, 1H), 2.65 (d, J = 14.3, 1H), 5.16 (s, 2H), 7.38−7.35 (m, 5H); ^{13}C NMR δ 204.5, 165.0, 156.4, 135.7, 128.5, 128.4, 128.1, 82.5, 76.3, 67.7, 57.1, 44.7, 31.6, 28.4, 27.8, 25.7, 22.6, 14.1. Anal. Calcd for $C_{19}H_{23}NO_5$: C, 66.1; H, 6.7; N, 4.1. Found: C, 66.0; H, 6.5; N, 4.0.

***tert*-Butyl (1*S*,4*R*)-7-Benzyloxycarbonyl-2-*E*-[(methoxycarbonyl)methylene]-7-azabicyclo[2.2.1]heptane-1-carboxylate (25) and *tert*-Butyl (1*S*,4*R*)-7-Benzyloxycarbonyl-2-*Z*-[(methoxy-carbonyl)methylene]-7-azabicyclo-[2.2.1]-heptane-1-carboxylate (26).** To a suspension of NaH (88 mg, 3.7 mmol) in THF (10 mL) was added trimethyl phosphonoacetate (0.60 mL, 3.7 mmol) at 0 °C, and the suspension was warmed to room temperature and stirred for 1 h. To the mixture was added a solution of ketone **24** (0.14 g, 0.41 mmol) in THF (5 mL), the mixture was stirred for 72 h at room temperature, saturated $NaHCO_3$ (20 mL) was added, and the mixture was concentrated to 60 mL and extracted with $CHCl_3$/IPA (4/1, 3 × 20 mL). The combined organic layer was dried, filtered, and evaporated, leaving an oil that was chromatographed (hexane/EtOAc, 15/1) to afford a separable mixture of **25** (92 mg, 57%) and **26** (8 mg, 5%) as a colorless oils. **25**: $[\alpha]^{23}_D$ −32.4 (*c* 1.6, $CHCl_3$); ^{1}H NMR δ 1.49 (s, 9H), 1.73 (m, 1H), 1.87 (m, 1H), 2.32 (m, 1H), 2.75−2.96 (m, 2H), 3.71 (s, 1H), 4.51 (t, J = 4.5, 1H), 5.14 (s, 2H), 5.86 (s, 1H), 7.78−7.33 (m, 15H); ^{13}C NMR δ 167.2, 166.8, 162.2, 156.6, 136.0, 128.5, 128.2, 128.0, 110.5, 82.2, 74.4, 67.4, 58.7, 51.2, 39.7, 31.4, 29.7, 28.8, 27.8. Anal. Calcd for $C_{22}H_{27}NO_6$: C, 65.8; H, 6.8; N, 3.5. Found: C, 66.1; H, 7.0; N, 3.2. **26**: $[\alpha]^{23}_D$ −34.8 (*c* 1.7, $CHCl_3$); ^{1}H NMR δ 1.43 (s, 9H), 1.90 (m, 2H), 2.22 (d, 1H), 2.24 (m, 1H), 2.81 (d, 1H), 3.63 (s, 1H), 4.48 (t, J = 4.5, 1H), 5.14 (m, 2H), 5.84 (s, 1H), 7.40−7.33 (m, 5H); ^{13}C NMR δ 165.3, 158.8, 154.5, 136.3, 128.4, 127.9, 127.8, 112.2, 81.8, 81.2, 74.7, 67.0, 56.6, 51.4, 51.2, 41.7, 31.2, 27.8, 27.7. Anal. Calcd for $C_{22}H_{27}NO_6$: C, 65.8; H, 6.8; N, 3.5. Found: C, 66.1; H, 7.0; N, 3.2.

***tert*-Butyl (1*S*,2*R*,4*R*)-7-Benzyloxycarbonyl-2-(methoxycarbonylmethyl)-7-azabicyclo[2.2.1]heptane-1-carboxylate (27).** To a solution of **25** (50 mg, 0.12 mmol) dissolved in MeOH (5 mL) was added 10%Pd/C (10 mg). The reaction was shaken under H_2 (50 psi) for 20 h at room temperature, and then the mixture was filtered through Celite. The filtrate was evaporated, and the residue was dissolved in EtOAc. To this solution were added CbzCl (7 μL, 0.47 mmol) and K_2CO_3 (80 mg, 0.47 mmol) at 0 °C, the ice bath was removed, and the biphasic mixture was stirred for 12 h at room temperature. The aqueous phase was extracted with $CHCl_3$/IPA (4/1, 3 × 20 mL); the combined organic phase was dried, filtered, and evaporated; and the resulting oil was chromatographed (hexane/EtOAc, 10/1) to afford **27** (44 mg, 88%) as a colorless oil: $[\alpha]^{23}_D$ −54.0 (*c* 0.45, $CHCl_3$); ^{1}H NMR δ 1.47 (s, 9h), 1.67−1.87 (m, 3H), 2.13−2.30 (m, 2H), 2.44−2.50 (m, 1H), 2.78 (dd, J = 5.4, 16.4, 1H), 3.71 (s, 1H), 4.51 (t, J = 4.5, 1H), 5.14 (s, 2H), 5.86 (s, 1H), 7.78−7.33 (m, 15H); ^{13}C NMR δ 172.9, 168.4, 158.2, 136.2, 128.4, 127.9, 81.6, 71.1, 67.1, 59.4, 51.4, 42.6, 38.2, 37.5, 32.9, 29.5, 27.8. Anal. Calcd for $C_{22}H_{29}NO_6$: C, 65.5; H, 7.2; N, 3.5. Found: C, 65.8; H, 7.6; N, 3.3.

Supporting Information Available: Tables of X-ray crystallographic data, bond lengths and angles, atomic coordinates, and anisotropic thermal parameters are available for compound **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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