Cyclopropanation Reactions of Pyroglutamic Acid-Derived Synthons with Akylidene Transfer Reagents

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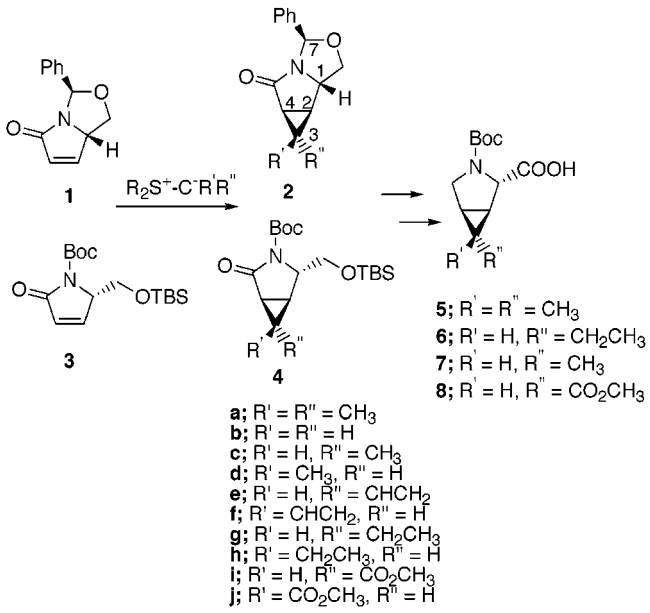
The cyclopropanation of unsaturated lactams **1** and **3** derived from pyroglutamic acid with nucleophilic alkylidene transfer reagents is investigated. Good-to-modest yields of cyclopropanes were obtained with most sulfur ylides explored. *Syn*/*anti* selectivity was found to be dependent on the synthon as well as the sulfur ylide. This cyclopropanation methodology is used in the synthesis of arginine and glutamic acid analogues.

As part of our program aimed at the development of mimics of the poly-L-proline type II (PPII) secondary structure by the synthesis of oligopeptides composed of proline templated amino acids (PTAAs), we are involved in developing methods for the synthesis of substituted proline analogues.[1] Of special interest to us is the synthesis of PTAAs based on the 3-aza-bicyclo[3.1.0]-hexane ring system (**5**−**8**, Scheme 1) because molecular modeling studies show that these will enforce a $\chi 1$ angle $\sim -60°$ (*gauche* relative to the amine) and a $\chi 2$ angle $\sim -155°$ ($\sim$ *trans*). These PTAAs are critical for our studies because several NMR and X-ray crystal structures of receptor-bound PPII helices show that a $\chi 1$ angle $\sim -60°$ and a $\chi 2$ angle $\sim 180°$ are common in the nonprolyl amino acids in the PPII helices. There are limited examples of this class of amino acids in the literature. Witkop reported the synthesis of *trans*-3,4-methylene-L-proline, a naturally occurring amino acid isolated from *Aesculus parviflora*, and Nagasaka details the cyclopropanation of a pyroglutamic acid derived α,β-unsaturated lactam which could be further transformed into *trans*-3,4-methylene-L-proline.[2−4] For our purposes, we sought to explore methodology which (1) could introduce additional substitution into the cyclopropane ring, (2) was selective for the anti isomer, and (3) was amenable to scale-up (appropriate for the multigram synthesis of PTAAs). To introduce additional substitution into the cyclopropane ring, we envisioned that reaction of an appropriately substituted nucleophilic alkylidene transfer reagent with an unsaturated pyroglutamic acid derived synthon could potentially afford entry to the target structures.[5] Because comprehensive studies of the stereochemistry of the cyclopropanation reaction of cyclic Michael acceptors with sulfur ylides are few and there are contrasts in the

Scheme 1



stereochemical outcome of this transformation, we first sought to investigate this issue.[5b,6] This paper reports the scope and limitations of this transformation with two synthons derived from pyroglutamic acid (*O,N*-acetal **1** and *N*-Boc-pyrrolinone **3** (Scheme 1)) and the synthesis of arginine and glutamic acid PTAA analogues from a cyclopropanated intermediate.[7,8]

The synthesis of the unsaturated *O,N*-acetal **1** from (5*S*,8*R*)-1-aza-7-oxa-8-phenylbicyclo[3.3.0]octan-2-one has been reported through an enolization, selenylation, oxidation, and elimination sequence in 56% overall yield.[7] We have found that trapping of the enolate with TMSCl followed by treatment with PhSeCl and oxidation of the resultant selenide with H_2O_2 affords the unsaturated *O,N*-acetal **1** in 72% yield from the saturated lactam, improving the efficiency of the process. Among the PTAAs of interest to us is the leucine analogue **5**, which should be accessible from the product obtained by reaction of

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(1) (a) Zhang, R.; Brownewell, F.; Madalengoitia, J. S. *J. Am. Chem. Soc.* **1998**, *120*, 3894. (b) Zhang, R.; Madalengoitia, J. S. *Tetrahedron Lett.* **1996**, *37*, 6235.

(2) Fujimoto, Y.; Irreverre, F.; Karle, J. M.; Karle, I. L.; Witkop, B. *J. Am. Chem. Soc.* **1971**, *93*, 3471.

(3) Nagasaka, T.; Imai, T. *Chem. Pharm. Bull.* **1997**, *45*, 36.

(4) (a) For a review of cyclopropane amino acids, see: Stammer, C. H. *Tetrahedron* **1990**, *46*, 2231. (b) For a construction of 2,3- and 4,5-methanoproline, see: Hanessian, S.; Reinhold: U.; Gentile, G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1881 and references therein.

(5) (a) For a comprehensive review, see: Trost, B. M.; Melvin, L. S., Jr. *Sulfur Ylides: Emerging Synthetic Intermediates*; Academic Press: New York, 1975. (b) Romo, D.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 6265. (c) Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503 and references therein.

(6) (a) Pyne, S. G.; Dong, Z.; Skelton, B. W.; White, A. H. *J. Org. Chem.* **1997**, *62*, 2337. (b) Jung, M. E.; Rayle, H. L. *J. Org. Chem.* **1997**, *62*, 4601.

(7) Baldwin, J. E.; Moloney, M. G.; Shim, S. B. *Tetrahedron Lett.* **1991**, *32*, 1379.

(8) Ohfune, Y.; Tomita, M. *J. Am. Chem. Soc.* **1982**, *104*, 3511.

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Table 1. Results of Cyclopropanation of Synthon 1 and Synthon 3 with Sulfur Ylides

sulfur ylide	product	*anti*/*syn* ratio of **2** (yield %)	*anti*/*syn* ratio of **4** (yield %)
$Ph_2S^+-CMe_2^-$	**a**: R′ = R″ = Me	(89)	(79)
$Me_2S^+(O)-CH_2^-$	**b**: R′ = R″ = H	(76)	(trace)
$PhS^+(O)(NMe_2)-CH_2^-$	**b**: R′ = R″ = H	(60)	(19)
$Ph_2S^+-CH^-CH_3$	**c**: R′ = H; R″ = CH_3	2.5:1 (84)	4:1 (54)
	d: R′ = CH_3; R″ = H		
$Ph_2S^+-CH^-CH{=}CH_2$	**e**: R′ = H; R″ = $CH{=}CH_2$	1:5 (60)	1:1 (68)
	f: R′ = $CH{=}CH_2$; R′ = H		
$Ph_2S^+-CH^-C_2H_5$	**g**: R′ = H, R″= C_2H_5	1.3:1 (82)	3:1 (62)
	h: R′ = C_2H_5, R″ = H		
$Me_2S^+-CH^-CO_2Me$	**i**: R′ = H; R″ = CO_2Me	1:1 (78)	1:1 (82)
	j: R′ = CO_2Me; R″ = H		

diphenylsulfonium isopropylide with either **1** or **3**.[9] Cyclopropanation of **1** and **3** with diphenylsulfonium isopropylide in THF at −78 °C smoothly afforded the products **2a** and **4a** in 89% and 79% yields, respectively (Table 1). The products **2a** and **4a** arise from cyclopropanation of the less hindered "*exo*" face. The stereochemical assignments were confirmed by single-crystal X-ray diffraction of **2a** or from coupling constants.[10]

Examples of the efficient use of norleucine as a methionine isostere also make the PTAA norleucine analogue **6** a potential target for us.[11] It was expected that access to this molecule would be possible through cyclopropanation of either **1** or **3** with diphenylsulfonium allylide followed by hydrogenation of the resultant vinyl cyclopropane.[12] Treatment of **1** with diphenylsulfonium allylide in THF at −40 °C for 4 h afforded the *exo*-*anti* product **2e** and *exo*-*syn* product **2f** in 60% yield, in a 1:5 ratio, respectively, (Table 1) thus favoring the undesired isomer.[13] Reaction of the other synthon **3** with diphenylsulfonium allylide in THF at −78 °C increased the proportion of *anti* isomer, affording a 1:1 mixture of isomers in 68% yield. Stereochemistry for these products was assigned from either NOEs or coupling constants.[14]

We next investigated an alternative approach to **6** involving reaction of synthons **1** and **3** with diphenylsulfonium *n*-propylide. The synthesis of the sulfonium salt *n*-propyldiphenylsulfonium triflate has been reported, but in 1.6% yield from *n*-propanol.[15] A modified procedure which accomplishes this transformation in 34% overall yield is reported in the Experimental Section. Reaction of **1** with diphenylsulfonium *n*-propylide resulted in a reversal of selectivity in comparison with the vinyl cyclopropane series, affording a 1.3:1 ratio of *anti*-**2g** to *syn*-**2h** in 82% yield. Reaction of **3** with diphenylsulfonium *n*-propylide further improved the *anti* selectivity affording a 3:1 mixture of *anti*-**4g** and *syn*-**4h** products, respectively, in 62% yield. Although the diastereomers **4g** and **4h** were inseparable, assignments of these products in the inseparable mixture were accomplished by comparison with pure **4g** and **4h** obtained by catalytic hydrogenation of pure *anti* vinyl cyclopropane **4e** and *syn* vinyl cyclopropane **4f**, respectively. Interestingly, the stereochemical outcome of these reactions is in contrast to results observed by Meyers for reaction of sulfur ylides with a related bicyclic lactam for which the *syn* isomers are favored.[5b]

To access the norvaline PTAA **7**, we next investigated the introduction of the two-carbon fragment with diphenylsulfonium ethylide. Interestingly, reaction of the bicyclic lactam **1** with diphenylsulfonium ethylide in THF at −78 °C was also *anti* selective, affording the isomers *anti*-**2c** and *syn*-**2d** in 84% yield and 2.5:1 ratio, respectively. Furthermore, reaction of diphenylsulfonium ethylide with **3** resulted in an increase of the *anti*/*syn* ratio to 4:1.

Entry into the PTAA glutamic acid analogue **8** was envisioned by the use of a stabilized sulfur ylide.[16] Treatment of **1** with 3 equiv of methyl dimethylsulfonium acetylide (MDSA) in THF at room temperature for 30 h gave the diastereomers **2i** and **2j** in 78% yield in a 1:1 ratio. The reaction could also be carried out in DMSO in comparable yields and selectivity but with considerably shorter reaction times (11 h). To ascertain whether this ratio of isomers represents a true kinetic distribution or whether there may be some epimerization occurring under the reaction conditions, the *syn* isomer was isolated and treated with MDSA under the reaction conditions. This experiment returned only the *syn* isomer. An analogous experiment with the *anti* isomer also returned only the *anti* isomer. These results indicate that the 1:1 distribution of products does not result from equilibration or partial equilibration of the *syn*/*anti* isomers under the reaction conditions. Thermodynamic equilibration of the two products is possible, however, with 20 mol % $CH_3SOCH_2^-$ affording a 98:2 mixture of *anti*/*syn* products in 85% yield (Scheme 2).[17] Efforts to effect the epimerization with weaker bases, including DBU, MeONa, and *t*-BuOK, were unsuccessful. The *syn* isomer may also be obtained preferentially. Treatment of a mixture of both isomers **2i** and **2j** with KHMDS at −78 °C in THF followed by kinetic protonation of the resultant enolate with water affords a 9.3:1 mixture of *syn*/*anti* products, respectively (31% yield). Thus, although the cyclopropanation reaction is not stereoselective, either diastereomer may be obtained from the diastereomeric mixture. Reaction of the other pyroglutamic acid derived synthon **3**

(9) Corey, E. J.; Jautelat, M.; Oppolzer, W. *Tetrahedron Lett.* **1967**, 2325.

(10) The stereochemistry of **2a** was confirmed by single-crystal X-ray defraction. The stereochemistry of **4a** was assigned from the H1−H2 coupling pattern. Witkop notes that the α-hydrogen in *trans* methylene proline is a singlet indicative of a small αH−βH coupling constant, whereas $J_{\alpha H-\beta H}$ = 4.5 Hz for *cis* methylene proline. The H1 and H2 splitting patterns of **4a** are consistent with a small J_{H1-H2}. See ref 2.

(11) Piccione, E.; Case, R. D.; Domcheck, S. M.; Hu, P.; Chaudhuri, M.; Backer, J. M.; Schlessinger, J.; Shoelson, S. E. *Biochemistry* **1993**, *32*, 3197.

(12) LaRochelle, R. W.; Trost, B. M.; Krepski, L. *J. Org. Chem.* **1971**, *36*, 1126.

(13) *Exo* denotes addition to the *exo* face of the bicyclic lactam, whereas *anti* and *syn* denote the cyclopropane stereochemistry.

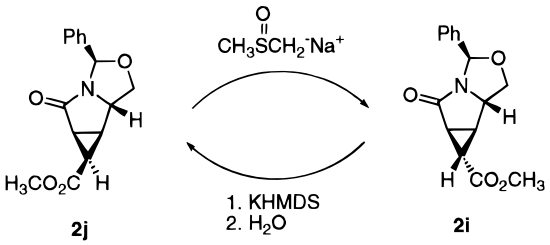
(14) The stereochemistry of the vinyl group was assigned by the presence of a positive NOE between H1 and H3 for the *anti* isomer and the absence of a positive NOE between H1 and H3 for the *syn* isomer (see Scheme 1 for numbering) or by coupling constants as described in ref 5b. All additional stereochemical assignments were accomplished in an analogous manner.

(15) Tang, C. S. F.; Rapoport, H. *J. Org. Chem.* **1973**, *38*, 2806.

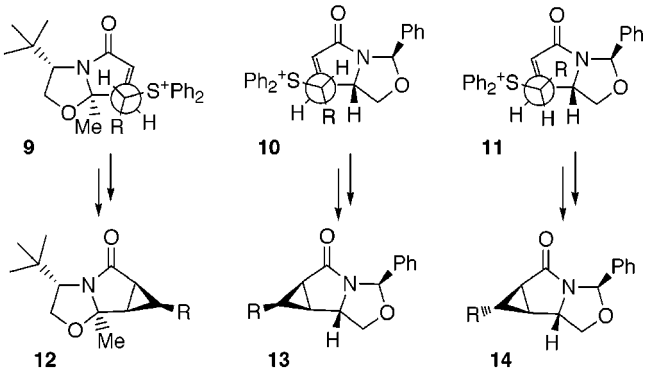
(16) Payne, G. B. *J. Org. Chem.* **1967**, *32*, 3351.

(17) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 866.

Scheme 2



Scheme 3



with MDSA also afforded a 1:1 mixture of diastereomers in 82% yield.

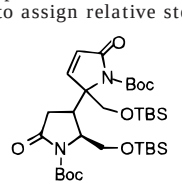
Cyclopropanation of **1** with dimethylsulfoxonium methylide afforded the cyclopropane **2b** in 75% yield.[3,18] However, reaction of **3** with $(CH_3)_2SO^+CH_2^-$ afforded only trace amounts of product and a dimerization product.[19,20] We attempted the reaction with the less basic ylide, $PhS^+ONMe_2CH_2^-$; however, this also resulted in a low yield of cyclopropane (19%). Interestingly, the acidity of the methine proton was not a problem in the reaction of **3** with the other sulfur ylides used in this study.

An analysis of the transition-state geometry is useful in rationalizing the stereochemical outcome of these reactions. Meyers proposes a *synclinal*-like transition state for the conjugate addition of the sulfur ylide to the unsaturated lactam in which the group R is *anti* to the π acceptor (see transition state **9**, Scheme 3).[5b,21] Bond rotation, followed by nucleophilic displacement of the sulfonium group, affords the *syn* cyclopropane **12**. The *anti* isomer, formed as the minor product, would result from the transition state in which the R group would be over the sterically hindered concave face of the lactam. This model is also consistent with our results. With the lactams **1** and **3**, a *synclinal*-like transition state should also be favored by steric and electrostatic factors. However, it is the orientation of the group R which may now vary. Because the conjugate addition with **1** and **3** takes place from the less hindered *exo* face, the orientation of the group R *anti* to the π acceptor is less rigorously enforced than in the transition state leading to **12**. Consequently, when R is small (i.e., R = Me, Et), the transition state **11** is favored over transition state **10**. As the size of R increases (R = $CHCH_2$), however, the steric repulsion between R and the pyrrolidine ring disfavors transition state **11** (Scheme 3).[22] The reversal of diastereoselectivity may alternatively be explained by a later transition state for the addition of diphenylsulfonium allylide, which would make it more sensitive to sterics. The absence of selectivity observed for the reaction of MDSA with both **1** and **3** is less clear.[23]

Some general statements may be made regarding the reactivity and utility of the two synthons studied. Generally, *N*-Boc pyrrolinone **3** is more reactive than **1** toward cyclopropanation, which should not be surprising because examples of increased reactivity of α,β-unsaturated amides bearing an electron-withdrawing group on nitrogen toward 1,4-additions have been reported.[24] Chemical yields are comparable for both synthons. For reactions involving diphenylsulfonium allylide, diphenylsulfonium ethylide, and diphenylsulfonium *n*-propylide, there is a higher proportion of the *anti* isomers formed from reaction with **3** versus **1**; however, when executing multigram reactions it must also be considered that the *syn*/*anti* isomers derived from **1** are more easily separable by flash chromatography than those derived from **3**.

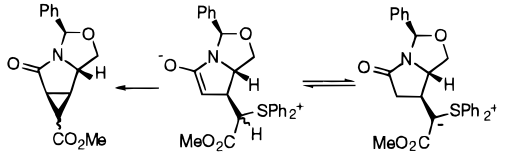
We have used this cyclopropanation methodology in the synthesis of two PTAAs, an arginine PTAA analogue and a glutamic acid PTAA analogue. The synthesis of the arginine PTAA analogue **19** (Scheme 4) begins with the ester **21**. Amonolysis of ester **21** in MeOH smoothly gave the amide **15** in 85% yield. Reduction of the two amides and oxazolidine functions with LAH in refluxing THF gave the *N*-benzyl amino-alcohol **16**, which was used without further purification. The amine **16** was guanylated with 1*H*-pyrazole-1-carboxamidine hydrochloride and diisopropylethylamine (DIEA) in DMF, and the guanidine group was subsequently protected with 2-mesitylenesulfonyl chloride (MtsCl) to afford the alcohol **17** in 50% yield from **15**.[25,26] *N*-Debenzylation failed to proceed to completion under standard conditions (H_2, Pd−C) even at high pressures; however, the benzyl group was easily removed with Pd−C and HCO_2NH_4 in refluxing MeOH.[27] Protection of the resultant amine with di-

(18) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.
(19) Johnson, C. R.; Haake, M.; Schroeck, C. W. *J. Am. Chem. Soc.* **1970**, *92*, 6594.
(20) The dimerization product is formed as a single diastereomer. We have not attempted to assign relative stereochemistry.



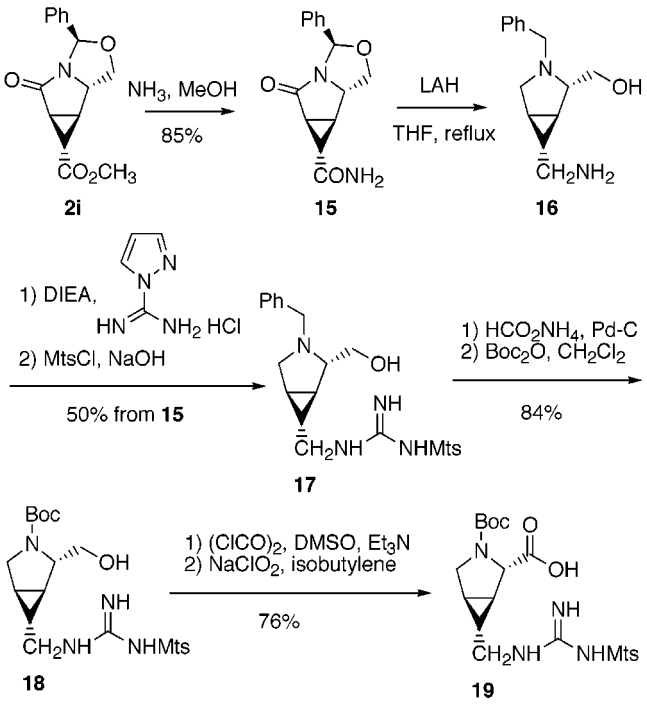
(21) For a discussion of *synclinal* transition states, see: Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, *64*, 1413.

(22) Although it is unusual to think of an ethyl group as smaller than a vinyl group, in this instance, a vinyl group may be considered more sterically demanding because it is coplanar with the sulfur and anionic carbon, whereas with the ethyl group, the terminal methyl may rotate away from the pyrrolidine ring.
(23) A possible explanation for the lack of selectivity is that following conjugate addition disproportionation scrambles the stereochemistry at the newly formed stereocenter. Products which arise from this alternate mechanistic pathway have been reported: (a) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1963**, *86*, 1640. (b) Tamura, Y.; Taniguchi, H.; Miyamoto, T.; Tsunekawa, M.; Ikeda, M. *J. Org. Chem.* **1974**, *39*, 3519.

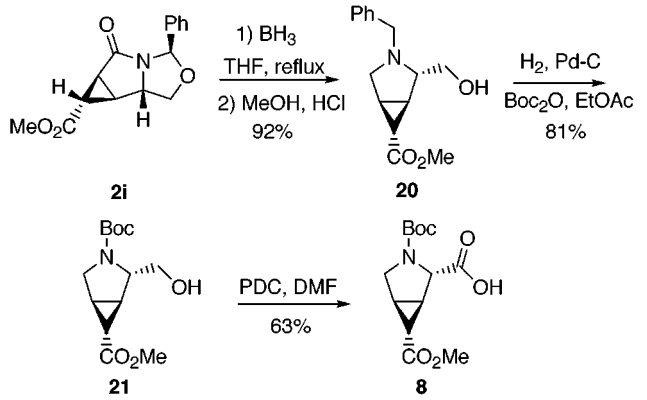


(24) Nagashima, H.; Ozaki, N.; Washiyama, M.; Itoh, K. *Tetrahedron Lett.* **1985**, *26*, 657.
(25) Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R. *J. Org. Chem.* **1992**, *57*, 2497.
(26) Yajima, H.; Takeyama, M.; Kanaki, J.; Nishimura, O.; Fujino, M. *Chem. Pharm. Bull.* **1978**, *26*, 3752.
(27) Ram, S.; Spicer, L. D. *Tetrahedron Lett.* **1987**, *28*, 515.

Scheme 4



Scheme 5



tert-butyl dicarbonate yielded the *N*-Boc prolinol **18** (84% yield for two steps). Attempted oxidation of the alcohol to the carboxylic acid under a variety of conditions ($RuCl_3$/$NaIO_4$, PDC/DMF, Jones reagent) resulted in low yields of the PTAA.[28,29] To optimize the yield of the PTAA, we opted for a two-step conversion involving first Swern oxidation of the alcohol followed by $NaClO_2$ oxidation of the resultant aldehyde to give the PTAA **19** (76% yield for two steps) protected for Boc−solid-phase peptide synthesis.[30]

The glutamic acid PTAA analogue is also synthesized from cyclopropane **2i** (Scheme 5). Selective reduction of the amide and oxazolidine groups is accomplished with BH_3 in refluxing THF, yielding the amino-ester **20** (92%).[31] The *N*-Boc protected prolinol **21** was obtained by hydrogenolysis of **20** with H_2/Pd−C in the presence of di-*tert*-butyl dicarbonate (81%). Finally, PDC oxidation of **21** gave the PTAA **8** in 63% yield.

We are currently studying the conformational properties of peptides composed of 3,4-cyclopropyl-substituted PTAAs and also pursuing the synthesis of bioactive peptides derived from these novel amino acids.

Experimental Section

General. Unless otherwise specified, all reagents were purchased from commercial sources and were used without further purification. THF was distilled from sodium/benzophenone ketyl, and CH_2Cl_2 was distilled from CaH_2. All reactions were carried out under a N_2 atmosphere. Flash chromatography was carried out on Selecto silica gel (230−400 mesh). 1D and 2D NMR spectra were collected in $CDCl_3$ using standard pulse sequences provided by Bruker.

(5*R*,7*S*)-5-Phenyl-5,6,7,7a-tetrahydro-6-oxapyrrolizin-3-one (1). (5*S*,8*R*)-1-Aza-7-oxa-8-phenylbicyclo[3.3.0]octan-2-one (48.3 g, 0.238 mol) in THF (100 mL) was added dropwise to a 0.5 M solution of KHMDS in toluene (475 mL, 0.238 mol) (diluted with THF (350 mL)) at −78 °C. After the addition was finished, the resulting mixture was maintained at −78 °C for 30 min, and TMSCl (40 mL, 0.31 mol) in THF (60 mL) was added dropwise. The solution was allowed to warm to 0 °C over 1 h and was then maintained at 0 °C for 3 h. PhSeCl (52.0 g, 0.266 mol) in THF (80 mL) was added at 0 °C, and the resulting mixture was maintained at room temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ (250 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 250 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. Purification by flash chromatography with 3:1 hexanes−EtOAc gave a mixture of *cis* and *trans* products (71.6 g, 84%).

The mixture was dissolved in EtOAc (600 mL) and cooled to 0 °C, and 30% H_2O_2 (90 mL) was added. After 20 min at 0 °C, the organic layer was separated, washed with water (2 × 400 mL) and brine (400 mL), dried over Na_2SO_4, and concentrated. Flash chromatography with 3:1 hexanes−EtOAc afforded **1** (34.6 g, 86%): mp 86−87 °C; $[\alpha]^{25}_D$ = +225.1° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.3 Hz, 2H), 7.30−7.37 (m, 3H), 7.18 (dd, *J* = 1.8, 5.7 Hz, 1H), 6.13 (s, 1H), 6.07 (dd, *J* = 1.2, 5.7 Hz, 1H), 4.52 (dd, *J* = 7.1, 8.3 Hz, 1H), 4.18 (dd, apparent t, *J* = 7.4 Hz, 1H), 3.34 (dd, apparent t, *J* = 7.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 176.7, 147.9, 138.5, 128.6, 128.3, 128.1, 125.9, 87.1, 67.8, 64.8 ppm; IR (film) 1684 cm^{-1}; MS (CI) *m*/*z* 202 (MH). Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.50; H, 5.52; N, 6.99.

(1*S*,2*S*,4*S*,7*R*) 6-Aza-3,3-dimethyl-8-oxa-7-phenyltricyclo-[4.3.0.0]nonan-5-one (2a). Diphenylethylsulfonium tetrafluoroborate (740 mg, 2.45 mmol) in DME (20 mL) was cooled to −70 °C. CH_2Cl_2 (0.17 mL, 2.6 mmol) was added, followed by cold LDA (2.6 mmol, prepared freshly by the addition of 1.65 mL of 1.6 M *n*-BuLi in hexane to 370 μL of diisopropylamine in 5 mL DME at −70 °C). A yellow-green solution resulted immediately and became cloudy after several minutes. After 30 min, MeI (0.16 mL, 2.5 mmol) was added, and the reaction mixture was slowly warmed to −50 to −60 °C and maintained at that temperature with good stirring for 2 h. LDA (2.64 mmol) as above was then added at −70 °C, and an orange color was produced immediately. After 1 h at −70 °C, the *O*,*N*-acetal **1** (201 mg, 0.990 mmol) was added, as a solution in DME (2 mL). The mixture was maintained at −70 °C for 1 h, quenched with saturated aqueous $NaHCO_3$ (20 mL), and warmed to room temperature. The aqueous layer was separated and extracted with Et_2O (3 × 30 mL). The combined organic fractions were dried over Na_2SO_4 and concentrated. Flash chromatography with 2.5:1 hexanes−EtOAc afforded **2a** (215 mg, 89%) as a colorless solid: mp 127−128 °C; $[\alpha]^{25}_D$ = +272.6° (*c* = 0.52, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27−7.39 (m, 5H), 6.30 (s, 1H), 4.19 (dd, *J* = 6.3, 7.7 Hz, 1H), 3.71 (dd, *J* = 6.3, 9.1 Hz, 1H), 3.51 (dd, *J* = 7.7, 9.1 Hz, 1H), 1.91 (dd, *J* = 0.9, 6.0 Hz, 1H), 1.89 (d, *J* = 6.0 Hz, 1H), 1.32 (s, 3H), 1.18 (s, 3H);

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^{13}C NMR (125 MHz, $CDCl_3$) 177.8, 139.5, 128.4, 128.3, 125.8, 88.2, 69.4, 57.5, 34.6, 32.8, 26.2, 25.6, 15.2 ppm; FTIR (film) 1700 cm^{-1}; MS (CI) *m*/*z* 244 (MH). Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.89; H, 7.06; N, 5.67.

(1*S*,2*S*,4*R*,7*R*)-6-Aza-8-oxa-7-phenyltricyclo[4.3.0.0]-nonan-5-one (2b). Method 1. DMSO (5 mL) was added to a mixture of 60% NaH dispersion in mineral oil (96 mg, 2.4 mmol) and trimethylsulfoxonium iodide (594 mg, 2.74 mmol). After 30 min of stirring at room temperature, the reaction mixture was maintained at 50−60 °C for another 30 min. Then, a solution of **1** (201 mg, 0.990 mmol) in DMSO (2 mL) was added dropwise, and the resulting mixture was kept at that temperature for 1.5 h and then cooled to room temperature. Water (20 mL) was added, and the mixture was extracted with Et_2O (3 × 30 mL). The combined organic fractions were dried over Na_2SO_4, concentrated, and purified by flash chromatography (2:1 hexanes−EtOAc) to give **2b** (163 mg, 76%) as a pale oil.

Method 2. A mixture of (dimethylamino)phenyloxosulfonium methylide (195 mg, 0.72 mmol) in DMSO (1 mL) was added slowly to 60% NaH dispersion in mineral oil (24 mg, 0.60 mmol) with stirring at room temperature. The mixture was stirred for 1 h, then **1** (100.6 mg, 0.492 mmol) in DMSO (1 mL) was added, and the mixture was stirred overnight. Water (10 mL) was added, and the mixture was extracted with Et_2O (4 × 10 mL); the combined organic fractions were dried (Na_2SO_4) and concentrated. Flash chromatography with 2% acetone in CH_2Cl_2 gave **2b** (64.6 mg, 60%) as a pale oil: $[\alpha]^{25}_D$ = +263.4° (*c* = 0.35, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27−7.38 (m, 5H), 6.31 (s, 1H), 4.20 (dd, *J* = 6.2, 7.9 Hz, 1H), 3.88 (dd, *J* = 6.2, 9.3 Hz, 1H), 3.45 (dd, *J* = 7.9, 9.3 Hz, 1H), 2.12 (ddd, *J* = 4.6, 5.5, 8.1 Hz, 1H), 2.03 (m, 1H), 1.31 (ddd, apparent dt, *J* = 4.8, 8.4 Hz, 1H), 1.13 (ddd, apparent dd, *J* = 4.4, 7.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 180.6, 139.5, 128.3, 125.8, 87.6, 69.4, 60.2, 20.8, 19.9, 14.8 ppm; FTIR (film) 1712 cm^{-1}; MS (CI) *m*/*z* 216 (MH). Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.42; H, 6.12; N, 6.57.

Reaction of 1 with Diphenylsulfonium Ethylide. A 1.7 M solution of *t*-BuLi in pentane (3.10 mL, 5.25 mmol) was added dropwise to a suspension of diphenylethylsulfonium fluoroborate (1.54 g, 5.09 mmol) in THF (40 mL) at −78 °C. After 30 min, *O*,*N*-acetal **1** (402 mg, 2.00 mmol) was added as a solution in THF (2 mL). The resulting mixture was maintained at −78 °C for 2 h, quenched with saturated aqueous $NaHCO_3$ (30 mL), and allowed to warm to room temperature. The aqueous layer was separated and extracted with Et_2O (3 × 30 mL). The combined organic fractions were dried (Na_2SO_4) and concentrated. Purification by flash chromatography with 3:1 hexanes−EtOAc gave *anti* product **2c** as a colorless powder (275 mg, 60%) and *syn* product **2d** as a pale oil (110 mg, 24%). **2c**: mp 91−92 °C; $[\alpha]^{25}_D$ = +268.9° (*c* = 0.71, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27−7.37 (m, 5H), 6.29 (s, 1H), 4.16 (dd, *J* = 6.2, 7.8 Hz, 1H), 3.88 (dd, *J* = 6.2, 9.2 Hz, 1H), 3.41 (dd, *J* = 7.8, 9.2 Hz, 1H), 1.88 (dd, *J* = 3.8, 5.6 Hz, 1H), 1.80 (ddd, *J* = 1.0, 2.6, 5.6 Hz, 1H), 1.51 (m, 1H), 1.15 (d, *J* = 5.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 180.0, 139.5, 128.2, 125.8, 87.5, 69.2, 60.1, 28.8, 27.4, 23.4, 16.6 ppm; FTIR (film) 1710 cm^{-1}; MS (CI) *m*/*z* 230 (MH). Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.14. Found: C, 73.23; H, 6.57; N, 6.06. **2d**: $[\alpha]^{25}_D$ = +192.1° (*c* = 0.78, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27−7.39 (m, 5H), 6.33 (s, 1H), 4.21 (dd, *J* = 6.5, 7.4 Hz, 1H), 3.69 (dd, *J* = 6.5, 9.0 Hz, 1H), 3.55 (dd, *J* = 7.4, 9.0 Hz, 1H), 2.10 (m, 2H), 1.60 (m, 1H), 1.27 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 177.8, 139.5, 128.3, 128.2, 125.7, 88.1, 69.4, 56.6, 26.4, 25.0, 18.8, 8.2 ppm; FTIR (film) 1707 cm^{-1}; MS (CI) *m*/*z* 230 (MH). Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.14. Found: C, 73.11; H, 6.68; N, 6.08.

Reaction of 1 with Diphenylsulfonium Allylide. A 1.7 M solution of *t*-BuLi in pentane (1.5 mL, 2.6 mmol) was added dropwise to a suspension of diphenylallylsulfonium tetrafluoroborate (944 mg, 3.00 mmol) in THF (12 mL) at −78 °C. After 1 h, *O*,*N*-acetal **1** (254 mg, 1.26 mmol) in THF (2 mL) was added, and the resulting mixture was warmed to −40 to −50 °C. The solution was maintained between −40 and −50 °C for 4 h. The reaction was then quenched with saturated aqueous $NaHCO_3$ (15 mL) and allowed to warm to room temperature. The aqueous layer was separated and extracted with Et_2O (3 × 20 mL). The combined organic fractions were dried (Na_2SO_4) and concentrated. Flash chromatography of the residue on silica gel with 3:1 hexanes−EtOAc gave the *anti* product **2e** as a colorless solid (30.9 mg, 10%) and the *syn* product **2f** as a pale yellow oil (153 mg, 50%). An analytical sample of **2e** was obtained by recrystallyzation from CH_2Cl_2−hexanes: mp 87−88 °C; $[\alpha]^{25}_D$ = +256.2° (*c* = 0.26, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27−7.38 (m, 5H), 6.30 (s, 1H), 5.40 (ddd, *J* = 8.2, 10.7, 17.0 Hz, 1H), 5.18 (d, *J* = 17.0 Hz, 1H), 5.05 (d, *J* = 10.7 Hz, 1H), 4.20 (dd, *J* = 6.4, 8.2 Hz, 1H), 3.94 (dd, *J* = 6.4, 9.4 Hz, 1H), 3.44 (dd, *J* = 8.2, 9.4 Hz, 1H), 2.15 (dd, *J* = 3.8, 5.6 Hz, 1H), 2.12 (ddd, *J* = 3.0, 3.8, 8.2 Hz, 1H), 2.08 (ddd, *J* = 1.1, 3.0, 5.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 179.0, 139.3, 135.2, 128.3, 125.8, 115.8, 87.7, 69.2, 60.1, 31.4, 28.8, 26.8 ppm; FTIR (film) 1711 cm^{-1}; MS (CI) *m*/*z* 242 (MH). Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.80. Found: C, 74.41; H, 6.35; N, 5.63. **2f**: $[\alpha]^{25}_D$ = +288.5° (*c* = 0.85, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28−7.38 (m, 5H), 6.33 (s, 1H), 5.77 (ddd, *J* = 8.4, 10.2, 17.0 Hz, 1H), 5.44 (d, *J* = 17.0 Hz, 1H), 5.26 (d, *J* = 10.2 Hz, 1H), 4.22 (dd, *J* = 6.4, 7.6 Hz, 1H), 3.77 (dd, *J* = 6.4, 9.1 Hz, 1H), 3.55 (dd, *J* = 8.0, 9.1 Hz, 1H), 2.32 (dd, apparent d, *J* = 8.4 Hz, 2H), 2.23 (ddd, apparent q, *J* = 8.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 177.2, 139.3, 130.7, 128.3, 125.8, 120.1, 88.2, 69.3, 57.3, 28.0, 27.6, 26.6 ppm; FTIR (film) 1708 cm^{-1}; MS (CI) *m*/*z* 242 (MH). Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.80. Found: C, 74.52; H, 6.30; N, 5.80.

Synthesis of *n*-Propyldiphenylsulfonium Triflate. A solution of *n*-propanol (1.02 mL, 13.7 mmol) in CH_2Cl_2 (25 mL) was cooled to −15 °C, and dry pyridine (1.33 mL, 16.4 mmol) was added followed by trifluoromethanesulfonic anhydride (2.30 mL, 13.7 mmol) in CH_2Cl_2 (5 mL) with vigorous stirring. The reaction mixture was allowed to warm to 0 °C over 1 h, pentane (40 mL) was added, and the resulting mixture was shaken and filtered. The filtrate was concentrated to within 4 mL of volume under reduced pressure at room temperature. The solution was cooled to −35 °C, and then diphenylsulfide (10 mL, 60 mmol) was added. The mixture was allowed to warm to room temperature, maintained at room temperature for 20 h, warmed to 45 °C for 30 min, and cooled to room temperature. Pentane (100 mL) was added, the mixture was shaken to induce solidification, and then the solid was collected by filtration. The solid was dissolved in CH_2Cl_2, triturated with pentane, and filtered to yield *n*-propyldiphenylsulfonium triflate (1.8 g, 34% for two steps). ^{1}H NMR spectrum was consistent with that reported.[15]

Reaction of 1 with Diphenylsulfonium *n*-Propylide. A 1.7 M solution of *t*-BuLi in pentane (2.54 mL, 4.31 mmol) was added dropwise to a suspension of *n*-propyldiphenylsulfonium triflate (1.70 g, 4.53 mmol) in THF (30 mL) at −78 °C. After 30 min, *O*,*N*-acetal **1** (403 mg, 2.00 mmol) in THF (3 mL) was added, and the resulting mixture was maintained at −78 °C for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (30 mL) and warmed to room temperature. The aqueous layer was separated and extracted with Et_2O (3 × 30 mL). The combined organic fractions were dried (Na_2SO_4) and concentrated. Flash chromatography of the residue with 2:1 hexanes−EtOAc gave the *anti* product **2g** as a pale oil (229 mg, 47%) and the *syn* product **2h** as a pale oil (170 mg, 35%). **2g**: $[\alpha]^{25}_D$ = +215.7° (*c* = 0.74, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26−7.37 (m, 5H), 6.28 (s, 1H), 4.14 (dd, *J* = 6.2, 7.9 Hz, 1H), 3.84 (dd, *J* = 6.2, 9.3 Hz, 1H), 3.39 (dd, *J* = 7.9, 9.3 Hz, 1H), 1.89 (dd, *J* = 3.7, 5.6 Hz, 1H), 1.80 (ddd, *J* = 1.0, 2.4, 5.6 Hz, 1H), 1.43 (m, 1H), 1.35 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 Hz, $CDCl_3$) 180.0, 139.4, 128.1, 125.6, 87.4, 69.1, 60.0, 30.5, 27.4, 26.0, 24.8, 12.7 ppm; FTIR (film) 1710 cm^{-1}; MS (CI) *m*/*z* 244 (MH). Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.79; H, 6.99; N, 5.82. **2h**: $[\alpha]^{25}_D$ = +224.6° (*c* = 0.48, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26−7.38 (m, 5H), 6.31 (s, 1H), 4.20 (dd, *J* = 6.3, 7.7 Hz, 1H), 3.69 (dd, *J* = 6.3, 9.2 Hz, 1H), 3.52 (dd, *J* = 7.7, 9.2 Hz, 1H), 2.12 (m, apparent d, *J* = 8.5 Hz, 2H), 1.58 (m,

2H), 1.48 (m, 1H), 1.06 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 177.9, 139.4, 128.3, 128.2, 125.7, 88.1, 69.4, 56.7, 26.6, 26.0, 25.2, 16.6, 13.5 ppm; FTIR (film) 1705 cm^{-1}; MS (CI) *m/z* 244 (MH). Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.85; H, 7.02; N, 5.72.

Reaction of 1 with Methyl Dimethylsulfonium Acetylide. A solution of **1** (24.0 g, 0.119 mol) and methyl (dimethylsulfuranylidene)acetate (48.0 g, 0.357 mol) in DMSO (50 mL) was stirred at room temperature for 30 h. Water (100 mL) was added, and the resulting mixture was extracted with Et_2O (4 × 150 mL). The combined organic fractions were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel (2:1 to 1:2 hexanes−EtOAc) to give the *anti* product **2i** as a glassy oil (13.0 g, 40%) and the *syn* product **2j** as a colorless solid (12.4 g, 38%). **2i**: $[\alpha]^{25}_D = +256.9°$ ($c = 0.5$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27−7.49 (m, 5H), 6.29 (s, 1H), 4.22 (dd, $J = 6.2$, 8.1 Hz, 1H), 3.95 (dd, $J = 6.2$, 9.2 Hz, 1H), 3.72 (s, 3H), 3.48 (dd, $J = 8.1$, 9.2 Hz, 1H), 2.62 (dd, $J = 3.3$, 6.2 Hz, 1H), 2.51 (ddd, $J = 1.0$, 2.4, 6.2 Hz, 1H), 2.25 (dd, apparent t, $J = 2.9$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 177.2, 170.2, 138.8, 128.5, 128.4, 125.7, 87.7, 69.0, 59.8, 52.4, 28.9, 27.8, 27.2 ppm; FTIR (film) 1722 cm^{-1}; MS (CI) *m/z* 274 (MH). Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.93; H, 5.53; N, 5.12. Found: C, 65.71; H, 5.57; N, 5.05. **2j**: mp 98−100 °C; $[\alpha]^{25}_D = +180.5°$ ($c = 0.32$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27−7.34 (m, 5H), 6.32 (s, 1H), 4.21 (dd, $J = 6.3$, 7.7 Hz, 1H), 4.09 (dd, $J = 6.3$, 9.4 Hz, 1H), 3.63 (s, 3H), 3.49 (dd, $J = 7.7$, 9.4 Hz, 1H), 2.41−2.47 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 175.8, 167.5, 138.9, 128.4, 128.3, 125.8, 87.8, 69.1, 57.6, 52.3, 27.0, 26.3, 24.8 ppm; FTIR (film) 1734, 1717 cm^{-1}; MS (CI) *m/z* 274 (MH). Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.93; H, 5.53; N, 5.12. Found: C, 65.85; H, 5.52; N, 5.16.

(1*S*,2*S*,5*S*)-*tert*-Butyl 3-Aza-6,6-dimethyl-4-oxo-2-[(1,1,2,2-tetramethyl-1-silapropoxy)methyl]bicyclo[3.1.0]hexane-3-carboxylate (4a). 4a was synthesized as described for **2a** except that synthon **3** (328 mg, 1.09 mmol) was used instead of **1**. Purification by flash chromatography with 8:1 hexanes−EtOAc gave **4a** (292 mg, 79%) as a pale oil: $[\alpha]^{25}_D = -33.5°$ ($c = 1.05$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.90 (m, 1H), 3.85 (dd, $J = 2.8$, 10.1 Hz, 1H), 3.80 (dd, $J = 5.6$, 10.1 Hz, 1H), 1.81 (dd, $J = 1.3$, 6.3 Hz, 1H), 1.69 (d, $J = 6.3$ Hz, 1H), 1.50 (s, 9H), 1.14 (s, 3H), 1.11 (s, 3H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 172.1, 149.7, 82.5, 63.7, 57.6, 33.5, 28.0, 27.1, 25.9, 25.7, 22.5, 18.1, 14.4, −5.5 ppm; FTIR (film) 1786, 1750, 1711 cm^{-1}; MS (CI) *m/z* 370 (MH); 270. Anal. Calcd for $C_{19}H_{35}NO_4Si$: C, 61.75; H, 9.54; N, 3.79. Found: C, 61.79; H, 9.58; N, 3.83.

(1*S*,2*S*,5*R*)-*tert*-Butyl 3-Aza-4-oxo-2-[(1,1,2,2-tetramethyl-1-silapropoxy)methyl]bicyclo[3.1.0]hexane-3-carboxylate (4b). 4b was produced as described in method 2 for the synthesis of **2b** except that synthon **3** (328 mg, 1.09 mmol) was used instead of **1**. Flash chromatography with 5:1 hexanes−EtOAc afforded **4b** (64 mg, 19%) as a colorless powder, as well as a dimer of **3** (92 mg, 14%) as a colorless solid. **4b**: mp 68−70 °C; $[\alpha]^{25}_D = -52.4°$ ($c = 0.25$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.02 (m, 1H), 3.85 (dd, $J = 2.7$, 10.1 Hz, 1H), 3.76 (dd, $J = 5.5$, 10.1 Hz, 1H), 1.93 (m, 2H), 1.50 (s, 9H), 1.12 (ddd, apparent dt, $J = 5.0$, 8.1 Hz, 1H), 0.89 (s, 9H), 0.72 (ddd, apparent dd, $J = 4.5$, 8.1 Hz, 1H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 173.9, 150.5, 82.6, 63.9, 60.1, 28.1, 25.8, 20.8, 18.2, 14.6, 11.3, −5.5 ppm; FTIR (film) 1789, 1755, 1711 cm^{-1}; MS (CI) *m/z* 342 (MH), 242. Anal. Calcd for $C_{17}H_{31}NO_4Si$: C, 59.79; H, 9.15; N, 4.10. Found: C, 59.92; H, 9.14; N, 4.03. Dimer of **3**: fine needles from EtOAc−hexanes, mp 181−182 °C; $[\alpha]^{25}_D = -11.6°$ ($c = 0.62$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91 (d, $J = 6.2$ Hz, 1H), 6.20 (d, $J = 6.2$ Hz, 1H), 4.34 (m, 1H), 4.11 (d, $J = 10.0$ Hz, 1H), 4.07 (d, $J = 10.0$ Hz, 1H), 3.89 (dd, $J = 4.3$, 10.2 Hz, 1H), 3.72 (dd, $J = 2.2$, 10.2 Hz, 1H), 3.31 (d, $J = 9.5$ Hz, 1H), 2.64 (dd, $J = 9.9$, 18.4 Hz, 1H), 1.96 (dd, $J = 1.3$, 18.4 Hz, 1H), 1.54 (s, 9H), 1.53 (s, 9H), 0.89 (s, 9H), 0.84 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 172.3, 168.6, 149.8, 149.5, 148.7, 129.2, 83.5, 83.3, 73.2, 64.9, 64.2, 60.0, 36.5, 33.4, 28.1, 25.8, 25.6, 18.1, 18.0, −5.6, −5.7 ppm; FTIR (film) 1767, 1712, 1688 cm^{-1}; MS (CI) *m/z* 555, 455. Anal. Calcd for $C_{32}H_{58}N_2O_8Si_2$: C, 58.68; H, 8.93; N, 4.28. Found: C, 58.79; H, 8.95; N, 4.22.

Reaction of 3 with Diphenylsulfonium Ethylide. 4c and **4d** were synthesized by the same procedure used for the synthesis of **2c/2d** except that synthon **3** (589 mg, 1.99 mmol) was used instead of **1**. Purification by flash chromatography with 6:1 hexanes−EtOAc afforded an inseparable mixture of 4:1 **4c**/**4d** (345 mg, 54% and 70% based on recovered starting material). The residue (0.34 g, 0.96 mmol) containing both isomers was dissolved in THF (3 mL) and treated with AcOH (9 mL) in water (3 mL), and the resulting mixture was stirred at room temperature for 24 h. $NaHCO_3$ powder was then added slowly until gas evolution ceased. The mixture was extracted with EtOAc (3 × 15 mL), and the combined organic fractions were dried over Na_2SO_4 and concentrated. Repeated flash chromatography with 2:3 hexanes−EtOAc gave the alcohols of **4c** (152 mg, 66%) and **4d** (23 mg, 10%) as colorless solids. Alcohol of **4c**: colorless cubic crystalline solid from Et_2O−hexanes, mp 85−86 °C; $[\alpha]^{25}_D = -24.6°$ ($c = 0.37$, $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6) δ 3.89 (dd, $J = 4.3$, 4.7 Hz, 1H), 3.65 (m, 2H), 2.62 (br s, 1H), 1.44 (s, 9H), 1.41 (ddd, apparent td, $J = 1.1$, 6.0 Hz, 1H), 1.14 (dd, $J = 3.6$, 6.0 Hz, 1H), 0.56 (d, $J = 5.7$ Hz, 3H), 0.49 (m, 1H); ^{13}C NMR (125 MHz, C_6D_6) 172.0, 152.2, 82.4, 64.8, 60.7, 28.8, 28.1, 22.2, 19.7, 16.5 ppm; FTIR (film) 3483 (br), 1774, 1732, 1714 cm^{-1}; MS (CI) *m/z* 242 (MH), 142. Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.80. Found: C, 59.81; H, 8.01; N, 5.80. Alcohol of **4d**: colorless needles from Et_2O−hexanes, mp 107−109 °C; $[\alpha]^{25}_D = -47.5°$ ($c = 0.1$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.00 (dd, $J = 3.8$, 4.1 Hz, 1H), 3.88 (m, 2H), 2.30 (t, $J = 6.0$ Hz, 1H, disappeared upon addition of D_2O), 2.08 (ddd, $J = 1.2$, 6.3, 8.8 Hz, 1H), 1.83 (dd, $J = 6.3$, 7.7 Hz, 1H), 1.51 (s, 9H), 1.44 (m, 1H), 1.08 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 172.0, 150.5, 83.4, 65.1, 57.2, 28.1, 25.9, 19.4, 16.2, 7.5 ppm; FTIR (film) 1766, 1717 cm^{-1}; MS (CI) *m/z* 242 (MH), 142. Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.80. Found: C, 59.80; H, 8.00; N, 5.88.

Reaction of 3 with Diphenylsulfonium Allylide. The procedure was as used in the synthesis of **2e**/**2f** except that synthon **3** (478 mg, 1.59 mmol) was used instead of **1** and the reaction was finished at −78 °C for 1 h. Repeated flash chromatography with 96:4 hexanes−EtOAc afforded **4e** (187 mg, 35%) as a colorless solid and **4f** (180 mg, 33%) as a colorless oil. **4e**: mp 71−73 °C; $[\alpha]^{25}_D = -7.2°$ ($c = 0.65$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.37 (ddd, $J = 8.5$, 10.4, 17.0 Hz, 1H), 5.17 (d, $J = 17.0$ Hz, 1H), 5.03 (d, $J = 10.4$ Hz, 1H), 4.10 (m, 1H), 3.83 (dd, $J = 2.6$, 10.2 Hz, 1H), 3.79 (dd, $J = 5.2$, 10.2 Hz, 1H), 2.01 (m, 1H), 1.95 (dd, $J = 3.8$, 6.2 Hz, 1H), 1.73 (ddd, apparent td, $J = 3.0$, 8.5 Hz, 1H), 1.51 (s, 9H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 172.3, 150.2, 135.1, 115.6, 82.8, 63.6, 60.2, 28.8, 28.1, 28.0, 25.7, 21.9, 18.1, −5.5 ppm; FTIR (film) 1787, 1754, 1712 cm^{-1}; MS (CI) *m/z* 368 (MH), 268. Anal. Calcd for $C_{19}H_{33}NO_4Si$: C, 62.09; H, 9.05; N, 3.81. Found: C, 62.34; H, 9.15; N, 3.71. **4f**: $[\alpha]^{25}_D = -29.8°$ ($c = 0.52$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.51 (ddd, $J = 7.0$, 10.2, 17.0 Hz, 1H), 5.40 (d, $J = 17.0$ Hz, 1H), 5.25 (d, $J = 10.2$ Hz, 1H), 3.98 (m, 1H), 3.86 (dd, $J = 2.9$, 10.2 Hz, 1H), 3.83 (dd, $J = 5.3$, 10.2 Hz, 1H), 2.25 (ddd, $J = 1.0$, 6.6, 9.2 Hz, 1H), 2.10 (dd, $J = 6.6$, 7.7 Hz, 1H), 2.03 (m, 1H), 1.50 (s, 9H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 171.6, 149.5, 129.8, 120.4, 82.7, 63.7, 57.3, 29.7, 28.1, 27.5, 25.8, 24.4, 21.2, 18.1, −5.5 ppm; FTIR (film) 1787, 1752, 1712 cm^{-1}; MS (CI) *m/z* 368 (MH), 268. Anal. Calcd for $C_{19}H_{33}NO_4Si$: C, 62.09; H, 9.05; N, 3.81. Found: C, 62.34; H, 9.15; N, 3.71.

Reaction of 3 with Diphenylsulfonium *n*-Propylide. The procedure was as described for the synthesis of **2g**/**2h** except that synthon **3** (196 mg, 0.580 mmol) was used instead of **1**. Flash chromatography with 10:1 hexanes−EtOAc gave an inseparable mixture of *anti* and *syn* products **4g** and **4h** as a pale yellow oil (136 mg, 62%). The pure *anti* product was obtained by Pd−C (2 mol %) hydrogenation of **4e** followed by purification on silica gel (15:1 hexanes−EtOAc) to give **4g** as a pale oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.02 (m, 1H), 3.83 (dd, $J = 2.8$, 10.1 Hz, 1H), 3.73 (dd, $J = 5.6$, 10.1 Hz, 1H),

1.73 (ddd, J = 1.1, 2.3, 5.7 Hz, 1H), 1.70 (dd, J = 3.9, 5.7 Hz, 1H), 1.50 (s, 9H), 1.36 (m, 2H), 1.05 (m, 1H), 1.00 (t, J = 7.4 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 173.5, 150.5, 82.5, 63.9, 60.3, 28.1, 27.5, 27.2, 25.8, 24.4, 21.0, 18.2, 13.1, −5.4 ppm; FTIR (film) 1786, 1754, 1711 cm^{-1}; MS (CI) m/z 370 (MH), 270. The pure *syn* product was obtained by Pd−C (2 mol %) hydrogenation of **4f** followed by purification on silica gel (15:1 hexanes−EtOAc) to give **4f** as a pale oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.90 (m, 1H), 3.86 (dd, J = 2.8, 10.0 Hz, 1H), 3.79 (dd, J = 5.8, 10.0 Hz, 1H), 2.05 (m, 1H), 1.92 (dd, J = 6.6, 7.2 Hz, 1H), 1.50 (s, 9H), 1.35 (m, 2H), 1.27 (m, 1H), 1.05 (t, J = 7.2 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR 172.3, 149.7, 82.7, 63.9, 57.0, 28.1, 25.8, 25.7, 24.0, 19.6, 18.2, 16.4, 13.6, −5.4 ppm; FTIR (film) 1786, 1750, 1710 cm^{-1}; MS (CI) m/z 370 (MH), 270. Anal. Calcd for $C_{19}H_{35}NO_4Si$: C, 61.75; H, 9.54; N, 3.79. Found: C, 61.78; H, 9.67; N, 3.84.

Reaction of 3 with Methyl Dimethylsulfonium Acetylide. The procedure was as described for the synthesis of **2i**/**2j** except that synthon **3** (426 mg, 1.42 mmol) was used instead of **1**. Purification by flash chromatography with 5:1 hexanes−EtOAc afforded **4i** (201 mg, 39%) as a colorless solid and **4j** (222 mg, 43%) as a colorless oil. **4i**: cottony solid from 1% EtOAc−hexanes, mp 139−140 °C; $[\alpha]^{25}_D$ = +2.8° (c = 0.58, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.11 (m, 1H), 3.85 (dd, J = 4.3, 10.4 Hz, 1H), 3.83 (dd, J = 3.0, 10.4 Hz, 1H), 3.72 (s, 3H), 2.46 (ddd, J = 1.1, 2.3, 6.2 Hz, 1H), 2.38 (dd, J = 3.3, 6.5 Hz, 1H), 1.85 (dd, apparent t, J = 2.9 Hz, 1H), 1.50 (s, 9H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 170.5, 170.4, 149.9, 83.2, 63.4, 60.0, 52.4, 29.4, 28.1, 25.8, 24.5, 22.9, 18.1, −5.5 ppm; FTIR (film) 1803, 1758, 1720 cm^{-1}; MS (CI) m/z 400 (MH), 299. Anal. Calcd for $C_{19}H_{33}NO_6Si$: C, 57.12; H, 8.32; N, 3.51. Found: C, 57.26; H, 8.38; N, 3.52. **4j**: $[\alpha]^{25}_D$ = −44.2° (c = 0.65, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.25 (m, 1H), 3.89 (dd, J = 2.9, 10.3 Hz, 1H), 3.84 (dd, J = 5.2, 10.3 Hz, 1H), 3.67 (s, 3H), 2.41 (ddd, J = 1.0, 6.3, 8.5 Hz, 1H), 2.26 (dd, J = 6.3, 7.9 Hz, 1H), 2.15 (dd, apparent t, J = 8.3 Hz, 1H), 1.51 (s, 9H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 169.7, 168.6, 149.8, 82.6, 63.7, 57.6, 52.2, 28.0, 25.8, 23.4, 22.0, 18.1, −5.5 ppm; FTIR (film) 1789, 1752, 1739, 1715 cm^{-1}; MS (CI) m/z 400 (MH), 299. Anal. Calcd for $C_{19}H_{33}NO_6Si$: C, 57.12; H, 8.32; N, 3.51. Found: C, 57.24; H, 8.24; N, 3.54.

Epimerization of *syn* Product 2j. A 2.0 M solution of methylsulfinylcarbanion in DMSO (3.17 mL, 6.34 mmol) was added to a solution of *syn* product **2j** (8.67 g, 31.7 mmol) in THF (25 mL) at 0 °C, and then the ice bath was removed. The resulting mixture was maintained at room temperature for 30 min, quenched with H_2O (30 mL), and extracted with Et_2O (3 × 30 mL). The combined organic fractions were dried (Na_2SO_4) and concentrated. Purification by flash chromatography with 2:1 hexanes−EtOAc gave only *anti* product **2i** (7.37 g, 85%).

Epimerization of *anti* Product 2i. A solution of *anti* product **2i** (269 mg, 0.990 mmol) in THF (1.5 mL) was added dropwise to a 0.50 M solution of KHMDS in toluene (2.4 mL, 1.8 mmol) which was diluted with THF (1 mL) at −78 °C. The resulting mixture was maintained at −78 °C for 30 min and quenched with H_2O (5 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic fractions were dried (Na_2SO_4) and concentrated. Flash chromatography with 1.5:1 hexanes−EtOAc afforded *syn* product **2j** (75.8 mg, 28%) and *anti* product **2i** (7.6 mg, 3%).

(1*S*,2*S*,3*S*,4*S*,7*R*)-6-Aza-8-oxa-5-oxo-7-phenyltricyclo-[4.3.0.0⟨2,4⟩]nonane-3-carboxamide (15). Compound **2i** (12.2 g, 44.6 mmol) was dissolved in dry MeOH (250 mL), ammonia gas was bubbled through the solution for 30 min, and the solution was maintained at room temperature for 40 h. The solvent was evaporated, and the residue was purified on silica gel eluting with 5% MeOH in EtOAc to give amide **15** (9.80 g, 85%) as a white solid: mp 160−162 °C; $[\alpha]^{25}_D$ = +220.7° (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30−7.36 (m, 5H), 6.39 (br s, 1H), 6.20 (s, 1H), 5.94 (br s, 1H), 4.16 (dd, J = 5.8, 7.4 Hz, 1H), 3.46 (dd, J = 5.8, 9.5 Hz, 1H), 3.40 (dd, J = 7.4, 9.5 Hz, 1H), 2.54 (dd, J = 3.3, 6.0 Hz, 1H), 2.39 (dd, J = 2.2, 6.0 Hz, 1H), 1.80 (dd, apparent t, J = 2.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 178.6, 170.5, 138.9, 128.6, 128.4, 125.8, 87.8, 69.1, 59.5, 29.0, 28.7, 26.4 ppm; FTIR (film) 3413 (br), 3345 (br), 3203 (br), 1705, 1682 cm^{-1}; MS (CI) m/z 259 (MH). Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.70. Found: C, 65.03; H, 5.62; N, 10.70.

(1*S*,2*S*,5*S*,6*R*)-6-(Aminomethyl)-3-aza-3-benzylbicyclo-[3.1.0]hexyl-2-methanol (16). A solution of the amide **15** (9.70 g, 37.6 mmol) in THF (80 mL) was added dropwise to a suspension of lithium aluminum hydride (5.71 g, 150 mmol) in THF (120 mL) at room temperature. After the addition was complete, the reaction mixture was heated at reflux for 15 h and then cooled to 0 °C. Saturated aqueous Na_2SO_4 solution was added slowly until a white precipitate formed. The mixture was diluted with EtOAc (150 mL) and filtered through Celite. The filtrate was dried (Na_2SO_4) and concentrated to give the amine **16** (8.74 g) as a pale oil which was used without further purification: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21−7.32 (m, 5H), 3.80 (d, J = 13.6 Hz, 1H), 3.67 (d, J = 13.6 Hz, 1H), 3.57 (dd, J = 4.6, 10.6 Hz, 1H), 3.52 (dd, J = 4.5, 10.6 Hz, 1H), 3.19 (dd, J = 4.7, 10.0 Hz, 1H), 2.99 (dd, apparent t, J = 4.4 Hz, 1H), 2.61 (d, J = 10.1 Hz, 1H), 2.57 (d, J = 6.9, 2H), 2.04 (br s, 3H), 1.33 (m, 1H), 1.29 (dd, J = 3.1, 7.2 Hz, 1H), 0.93 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 140.1, 128.3, 128.1, 126.8, 67.3, 62.9, 58.2, 55.6, 44.5, 29.3, 26.8, 23.2 ppm; FTIR (film) 3359 (br), 3288 (br), 3189 (br) cm^{-1}; MS (CI) m/z 233 (MH).

(1*S*,2*S*,5*R*,6*R*)-3-Aza-3-benzyl-6-(((imino(((2,4,6-trimethylphenyl)sulfonyl)amino)methyl)amino)methyl)bicyclo-[3.1.0]hexyl-2-methanol (17). The amine **16** (8.74 g), 1*H*-pyrazole-1-carboxamidine hydrochloride (5.57 g, 36.7 mmol), and diisopropylethylamine (DIEA) (6.6 mL, 38 mmol) in DMF (10 mL) were maintained at room temperature overnight. Ether (150 mL) was added to induce precipitation, and the solvent was decanted. The precipitate was dissolved in MeOH (10 mL), and the precipitation procedure was repeated twice as above to give the guanylated amine hydrochloride as a pale foam (11.5 g) which was used without further purification: ^{1}H NMR (500 MHz, CD_3OD) δ 7.23−7.27 (m, 5H), 3.86 (d, J = 13.5 Hz, 1H), 3.79 (d, J = 13.5 Hz, 1H), 3.65 (dd, J = 4.3, 11.0 Hz, 1H), 3.54 (dd, J = 6.2, 11.0 Hz, 1H), 3.28 (m, 1H), 3.06 (d, J = 7.2 Hz, 2H), 3.00 (dd, J = 3.8, 9.3 Hz, 1H), 2.74 (d, J = 9.3 Hz, 1H), 1.47 (m, 2H), 1.29 (m, 1H); ^{13}C NMR (125 MHz, CD_3OD) 158.5, 139.3, 130.1, 129.6, 129.2, 67.3, 62.7, 56.9, 55.4, 44.7, 27.1, 24.3, 23.6 ppm; FTIR (KBr) 3335 (br), 3172 (br), 1662 cm^{-1}; MS (CI) m/z 275 (MH − HCl). The foam (11.4 g) from above was dissolved in a solution of 4 N NaOH (19.3 mL, 77.0 mmol) and acetone (150 mL), and the solution was then cooled to 0 °C. A solution of 2-mesitylenesulfonyl chloride (MtsCl) (8.10 g, 36.7 mmol) in acetone (35 mL) was added dropwise, and the resulting mixture was stirred at 0 °C for 1.5 h. The solution was concentrated to a volume of about 20 mL at room temperature, water (80 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), and concentrated. The resulting residue was purified on silica gel eluting with 10% MeOH in CH_2Cl_2 to afford compound **17** (8.32 g, 50% for three steps) as a white foam: $[\alpha]^{25}_D$ = −14.6° (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24−7.27 (m, 2H), 7.18−7.21 (m, 3H), 6.85 (s, 2H), 6.35 (br s, 2H), 6.28 (t, J = 4.6 Hz, 1H), 3.69 (d, J = 13.6 Hz, 1H), 3.59 (d, J = 13.6 Hz, 1H), 3.44 (d, J = 4.6 Hz, 2H), 3.10 (m, 1H), 3.02 (dd, J = 3.2, 10.0 Hz, 1H), 2.94 (m, 1H), 2.89 (t, J = 4.6 Hz, 1H), 2.73 (br s, 1H), 2.63 (s, 6H), 2.51 (d, J = 10.0 Hz, 1H), 2.22 (s, 3H), 1.28 (m, 2H), 0.94 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 156.3, 140.8, 139.7, 137.9, 137.8, 131.5, 128.3, 128.2, 127.0, 67.0, 62.8, 58.0, 55.3, 43.4, 26.7, 24.8, 23.2, 22.9, 20.8 ppm; FTIR (film) 3443 (br), 3342 (br), 1619, 1552 cm^{-1}; MS (CI) m/z 457 (MH). Anal. Calcd for $C_{24}H_{32}N_4O_3S$: C, 63.13; H, 7.06; N, 12.27; S, 7.02. Found: C, 63.06: H, 7.00; N, 12.27; S, 6.87.

(1*S*,2*S*,5*R*,6*R*)-3-Aza-3-[(*tert*-butyl)oxycarbonyl]-6-(((imino(((2,4,6-trimethylphenyl)sulfonyl)amino)methyl)-amino)methyl)bicyclo[3.1.0]hexyl-2-methanol (18). A solution of *N*-benzylamine **17** (3.62 mg, 7.93 mmol), 10% Pd−C

(0.85 g, 0.80 mmol), and ammonium formate (3.10 g, 47.7 mmol) in MeOH (50 mL) was heated at reflux for 30 min. After cooling, the mixture was filtered through Celite, and the Celite plug was washed with MeOH (100 mL) and CH_2Cl_2 (100 mL). The filtrate was concentrated to yield the secondary amino alcohol as a white foam (2.57 g) which was used without purification: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.88 (s, 2H), 6.51 (br s, 1H), 6.43 (br s, 2H), 3.50 (d, J = 7.4 Hz, 1H), 3.28 (m, 2H), 3.16 (m, 3H), 2.98 (m, 3H), 2.62 (s, 6H), 2.26 (s, 3H), 1.37 (m, 1H), 1.23 (m, 1H), 0.89 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 156.4, 140.9, 137.9, 137.7, 131.5, 62.9, 62.0, 46.4, 42.7, 24.6, 22.9, 22.5, 20.8, 19.3 ppm; FTIR (film) 3436 (br), 3332 (br), 3143 (br), 1620, 1551 cm^{-1}; MS (CI) m/z 367 (MH). The secondary amino alcohol (2.56 g) from above in CH_2Cl_2 (60 mL) and di-*tert*-butyl dicarbonate (1.53 g, 7.00 mmol) were maintained at room temperature for 30 min. The solvent was removed under reduced pressure, and the residue was purified on silica gel eluting with 5% MeOH in CH_2Cl_2 to give the alcohol **18** (3.11 g, 84% for two steps) as a colorless foam: $[\alpha]^{25}_D$ = −29.2 (c = 0.96, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.89 (s, 2H), 6.36 (br s, 2H), 6.26 (br s, 1H), 3.96 (t, J = 5.5 Hz, 0.6H), 3.83 (t, J = 4.4 Hz, 0.4H), 3.49−03.60 (m, 3H), 3.29−3.33 (m, 1.6H), 3.18 (m, 0.4H), 3.06 (m, 0.4H), 2.91 (m, 0.6H), 2.64 (s, 6H), 2.26 (s, 3H), 1.41 (s, 9H), 1.33−1.39 (m, 2.4H), 1.29 (m, 0.6H), 0.73 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 156.2, 155.7, 154.3, 140.6, 137.7, 137.5, 131.3, 80.0, 79.8, 64.9, 63.8, 61.0, 60.7, 47.8, 42.3, 28.3, 28.2, 24.2, 23.4, 22.7, 21.3, 21.0, 20.9, 20.6, 20.3 ppm; FTIR (film) 3441 (br), 3342 (br), 1670, 1622, 1551 cm^{-1}; MS (CI) m/z 467 (MH). Anal. Calcd for $C_{22}H_{34}N_4O_5S$: C, 56.63; H, 7.34; N, 12.01; S, 6.87. Found: C, 56.77; H, 7.40; N, 11.89; S, 6.73.

(1*S*,2*S*,5*R*,6*R*)-3-Aza-3-[(*tert*-butyl)oxycarbonyl]-6-(((imino(((2,4,6-trimethylphenyl)sulfonyl)amino)methyl)-amino)methyl)bicyclo[3.1.0]hexane-2-carboxylic acid (19). A solution of oxalyl chloride (440 μL, 5.04 mmol) in CH_2Cl_2 (25 mL) was cooled to −78 °C, and DMSO (730 μL, 10.3 mmol) was added dropwise. After 15 min, a solution of compound **12** (2.29 g, 4.91 mmol) in CH_2Cl_2 (8 mL) was added dropwise over 15 min, and the resulting mixture was maintained at −78 °C for another 30 min. Triethylamine (4.1 mL, 29.4 mmol) was added, and the reaction mixture was allowed to warm to −30 °C over 40 min; water (30 mL) was then added to quenched the reaction. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated. Flash chromatography of the residue with 2% MeOH in EtOAc yielded the aldehyde (1.83 g, 80%) as a white foam: $[\alpha]^{25}_D$ = −33.2° (c = 0.75, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.45 (s, 0.4H), 9.41 (s, 0.6H), 6.89 (s, 2H), 6.30−6.41 (m, 3H), 4.30 (s, 0.4H), 4.19 (s, 0.6H), 3.53 (m, 1H), 3.41 (m, 1H), 3.25 (m, 0.4H), 3.14 (m, 1.2H), 3.02 (m, 0.4H), 2.64 (s, 6H), 2.26 (s, 3H), 1.40−1.55 (m, 5.6H), 1.38 (s, 5.4H), 0.89 (m, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) 199.3, 198.7, 156.2, 154.8, 154.2, 140.9, 137.8, 137.6, 131.5, 80.6, 80.5, 67.2, 66.9, 48.5, 48.2, 42.2, 28.3, 28.2, 22.8, 22.4, 22.1, 22.0, 21.5, 21.3, 20.7, 20.6 ppm; FTIR 3442 (br), 3340 (br), 1735, 1695, 1619, 1551 cm^{-1}; MS (CI) m/z 465 (MH). The aldehyde from above (1.92 g, 4.13 mmol) and sodium dihydrogenphosphate monohydrate (873 mg, 6.20 mmol) were dissolved in a 4:1 *tert*-butyl alcohol−H_2O solution (50 mL), and isobutylene (10.3 mL, 20.6 mmol) was added as a 2 M solution in THF. Sodium chlorite (1.12 g, 12.40 mmol) was added, and the resulting mixture was maintained at room temperature for another 2 h. Water (20 mL) was added, and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), and concentrated to yield compound **13** (1.89 g, 95%) as a white foam: $[\alpha]^{25}_D$ = −23.6 (c = 0.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.43 (br s, 1H), 6.87 (s, 2H), 6.45 (br s, 3H), 4.35 (s, 0.4H), 4.30 (s, 0.6H), 3.46−3.52 (m, 2.4H), 3.19 (m, 0.6H), 3.05 (m, 0.6H), 2.90 (m, 0.4H), 2.62 (s, 6H), 2.25 (s, 3H), 1.63 (m, 1H), 1.41 (s, 3.6H), 1.37 (s, 5.4H), 1.26 (m, 1H), 0.9 (m, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) 175.3, 174.6, 156.4, 155.5, 154.8, 140.9, 137.9, 137.6, 131.5, 81.1, 80.7, 61.2, 61.0, 48.4, 48.2, 42.3, 28.3, 28.2, 25.3, 24.4, 22.8, 21.6, 21.2, 20.8, 20.5 ppm; FTIR (film) 3443 (br), 3342 (br), 3224 (br), 3160 (br), 1702, 1625, 1551 cm^{-1}; HRMS (electrospray) m/z 481.2130 (481.2121 calcd for $C_{22}H_{33}N_4O_6S$, MH).

(1*R*,2*S*,5*S*,6*R*)-3-Aza-3-benzyl-6-methoxycarbonylbicyclo[3.1.0]hexyl-2-methanol (20). BH_3 (92 mmol, 92 mL) was added dropwise as a 1 M solution in THF to the amide **2i** (15.4 g, 56.4 mmol) in THF (120 mL), and the resultant solution was heated at reflux for 1 h. After the solution cooled to room temperature, the solvent was removed under reduced pressure, and the residue was dissolved in methanolic hydrogen chloride (150 mL). The solution was heated at reflux for 2 h, and the methanol was removed under reduced pressure. The resulting oil was dissolved in CH_2Cl_2 (60 mL) and washed with a 20% aqueous solution of potassium carbonate (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated. Flash chromatography of the residue on silica gel eluting with 1:1 hexanes−EtOAc afforded the amino ester **20** (13.5 g, 92%) as a pale yellow oil: $[\alpha]^{25}_D$ = −13.5° (c = 0.22, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18−7.28 (m, 5H), 3.77 (s, 2H), 3.63 (s, 3H), 3.58 (dd, J = 4.9, 10.9 Hz, 1H), 3.55 (dd, J = 4.7, 10.9 Hz, 1H), 3.14 (dd, app t, J = 3.9 Hz, 1H), 3.12 (dd, J = 2.3, 4.7 Hz, 1H), 2.77 (d, J = 10.2 Hz, 1H), 2.33−2.43 (br s, 1H), 2.00−2.05 (m, 1H), 1.98 (dd, app t, J = 3.0 Hz, 1H), 1.70 (dd, app t, J = 3.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 173.3, 139.7, 128.3, 128.0, 126.9, 65.9, 62.3, 57.1, 54.2, 51.6, 30.6, 27.6, 25.2 ppm; FTIR (film) 3442, 1730, 1437, 1298 cm^{-1}; HRMS (CI) m/z 262.1443 (262.1443 calcd for $C_{15}H_{20}NO_3$, MH).

(1*R*,2*S*,5*S*,6*R*)-3-Aza-3-[(*tert*-butyl)oxycarbonyl]-6-methoxycarbonylbicyclo[3.1.0]hexyl-2-methanol (21). Pd−C (1.8 g) was added to a solution of the alcohol **20** (12.2 g, 46.7 mmol) and di-*tert*-butyl dicarbonate (11.7 g, 53.7 mmol) in EtOAc (50 mL). The mixture was stirred overnight under H_2 (200 psi), and the catalyst was filtered off over a Celite pad. The filtrate was concentrated, and the resulting thick oil was purified by flash chromatography on silica gel (1:1 hexanes−EtOAc) to give the compound **21** as a colorless oil (10.3 g, 81%): $[\alpha]^{25}_D$ = −67.9° (c = 0.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.02 (dd, app t, J = 5.1 Hz, 1H), 3.87 (dd, app t, J = 4.5 Hz, 1H), 3.74−3.82 (m, 1H), 3.62 (s, 3H), 3.53−3.58 (m, 1H), 3.39−3.42 (m, 1H), 2.78−2.84 (m, 1H), 2.04 (dd, J = 2.4, 7.0 Hz, 1H), 1.95−2.01 (m, 1H), 1.94 (dd, J = 2.8, 7.0 Hz, 1H), 1.40 (s, 9H); ^{13}C (125 MHz, $CDCl_3$) 172.7, 172.5, 155.0, 154.0, 80.2, 79.9, 64.2, 63.5, 60.8, 60.7, 51.6, 47.9, 47.6, 28.9, 28.2, 28.0, 25.7, 25.1, 23.6, 23.4 ppm; FTIR (film) 3450, 1765, 1757, 1735 cm^{-1}; HRMS (CI) m/z 272.1501 (272.1498 calcd for $C_{13}H_{22}NO_5$, MH).

(1*R*,2*S*,5*S*,6*R*)-3-Aza-3-[(*tert*-butyl)oxycarbonyl]-6-methoxycarbonylbicyclo[3.1.0]hexane-2-carboxylic acid (8). PDC (16.6 g, 44.2 mmol) was added to a solution of the compound **21** (3 g, 11.0 mmol) in dry DMF (30 mL). The reaction mixture was maintained at room temperature for 2 days, and the DMF was removed under reduced pressure. The resulting brown residue was diluted with water (50 mL) and extracted with EtOAc (4 × 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. Flash chromatography on silica gel (EtOAc) afforded the acid **8** as a white foam (2.0 g, 63%): mp 53−55 °C; $[\alpha]^{25}_D$ = −81.8 (c = 0.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.51−10.69 (br s, 1H), 4.43 (s, 0.4H), 4.31 (s, 0.6H), 3.61 (s, 3H), 3.55−3.59 (m, 2H), 2.24 (dd, J = 7.1, J = 3.0 Hz, 0.4H), 2.21 (dd, J = 3.0, J = 7.1 Hz, 0.6H), 2.07 (dd, J = 3.4, J = 7.1 Hz, 0.6H), 2.04 (dd, J = 3.4, J = 7.1 Hz, 0.4H), 1.57 (dd, app t, J = 3.0 Hz, 0.6H), 1.53 (dd, app t, J = 3.0 Hz, 0.4H), 1.41 (s, 3.6H), 1.34 (s, 5.4H); ^{13}C NMR (125 MHz, $CDCl_3$) 174.4, 174.0, 172.0, 154.8, 154.2, 80.9, 60.8, 60.4, 51.9, 48.0, 47.8, 29.0, 28.1, 28.0, 25.4, 24.7, 23.8, 23.6 ppm; FTIR (KBr) 3203, 1735, 1727, 1705 cm^{-1}; HRMS (CI) m/z 286.1284 (286.1290 calcd for $C_{13}H_{20}NO_6$, MH).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of **1**, **2a**−**j**, **4a**−**j**, **8**, and **15**−**31**, NOESY spectra of **2c**−**j** and **4c**−**j**, and crystal data, bond lengths and angles, atomic coordinates, and anisotropic parameters for **2a** (83 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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