= 8.2, Ar H), 7.67 (d, 1 H, J = 7.4 Hz, Ar H).

(4*S*,5*R*)-5-Benzyl-4-carboxyimidazolidin-2-one (8b). The urea **37** (30 mg, 0.065 mmol) was deprotected as described for compound **7b** to give 13.7 mg (96%) of **8b**, identical with that described earlier.

(4*S*,5*R*)-5-Benzyl-4-(methoxycarbonyl)imidazolidin-2-one (35). The acid **8b** (22 mg, 0.1 mmol) was stirred in a mixture of methanol (20 mL) and thionyl chloride (5 drops) at room temperature for 12 h. The reaction mixture was concentrated to give the methyl ester **35** in quantitative yield: ^{1}H NMR (CD_3OD) δ 2.91 (d, 2 H, J = 5.8, CH_2Ph), 3.69 (s, 3 H, CO_2CH_3), 4.09–4.15 (m, 2 H, C4-H and C5-H), 7.21–7.34 (m, 5 H, Ar H).

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Enantiodivergent Synthesis of (+)- and (−)-Anatoxin from L-Glutamic Acid

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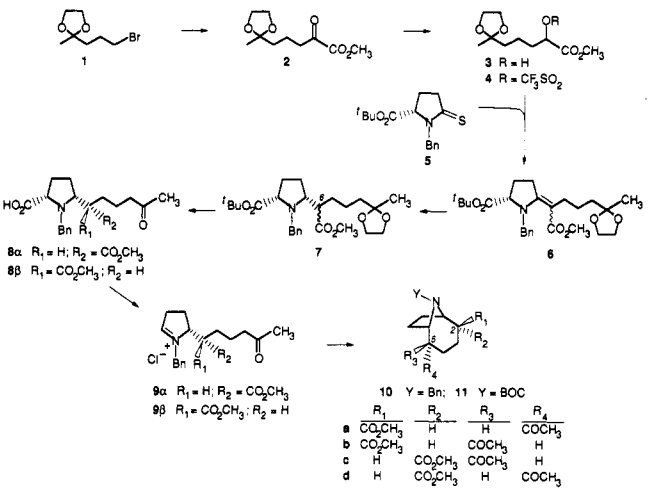
The optically pure 2,5-difunctionalized homotropane **11**, prepared from L-glutamic acid, serves as the common, advanced intermediate for the synthesis of either natural (+)-anatoxin (**30**, 18% overall yield) or unnatural (−)-anatoxin (**33**, 30% overall yield) by selective manipulation of either the C-2 ester or C-5 acetyl functionalities. Side-chain substitution in the decarbonylative iminium ion cyclization of a substituted proline enhanced the yield by 25% as compared to the unsubstituted parent system. The additional substitution at C-5 of the 9-azabicyclo[4.2.1]nonane ring system allows access to analogues of anatoxin not available through other syntheses.

Anatoxin-a, a strong nerve-depolarizing agent isolated from strains of the fresh water blue-green alga *Anabaena flos-aquae* (Lyng.) de Breb,[1] has played a central role in neurotransmission research during the last decade, since it is the most potent agonist known for the nicotinic acetylcholine receptor (nAChR).[2] In our previous publications,[3] we have presented the enantiospecific synthesis of (+)-anatoxin from D-glutamic acid as well as that of a number of its analogues. We have also summarized the synthetic activity of others in this field, all of which led to racemic material.[3f] We now report an enantiodivergent synthesis of either (+)- or (−)-anatoxin proceeding along a common path from L-glutamic acid.

Results and Discussion

Synthesis of 2,5-Difunctionalized Homotropanes 11. The synthesis of our first key intermediate, vinylogous methyl carbamate **6**, follows closely that reported for its benzyl ester analogue[3a] and is presented in Scheme I. The required methyl α-hydroxy ester **3** was prepared from bromo ketal **1**. Thus the Grignard reagent from **1** reacted with dimethyl oxalate to give α-keto ester **2**, which was hydrogenated (Pt/C) to give hydroxy ester **3**. The sulfide-contraction reaction between α-triflate **4** and thiolactam **5** proceeded as previously to give vinylogous carbamate **6** as a 4/1 mixture of double-bond isomers. Strict temperature control during the sulfide-contraction step is critical for the success of this reaction: below −10 °C little or no reaction occurs, while above 0 °C some racemization is observed.[4] Hydrogenation of the carbon–carbon double bond in **6** was achieved over Pd/C in methanol. The initial product contained some N-debenzylated material, and rebenzylation gave proline ester **7** as a 4/1 mixture of epimers at C-6.

Scheme I. Synthesis of 2,5-Difunctionalized Homotropanes



In the previous synthesis,[3] where the vinylogous carbamate was present as its benzyl ester, hydrogenation proceeded by initial O-debenzylation, decarboxylation, and double-bond reduction in a highly stereoselective process.[3a,b,4] The present substitution pattern, in which the ester function is retained at C-6, gave identical results; none of *trans*-pyrrolidine **7** could be detected in the crude product. Acidic hydrolysis then afforded a chromatographically resolvable mixture of keto acids 8α and 8β. Although the stereochemistry at C-6 could not be established at this stage, the stereochemical outcome of the two subsequent steps allowed assignment of 8β (6*R*) to the minor, less polar product and 8α (6*S*) to the major, more polar product.

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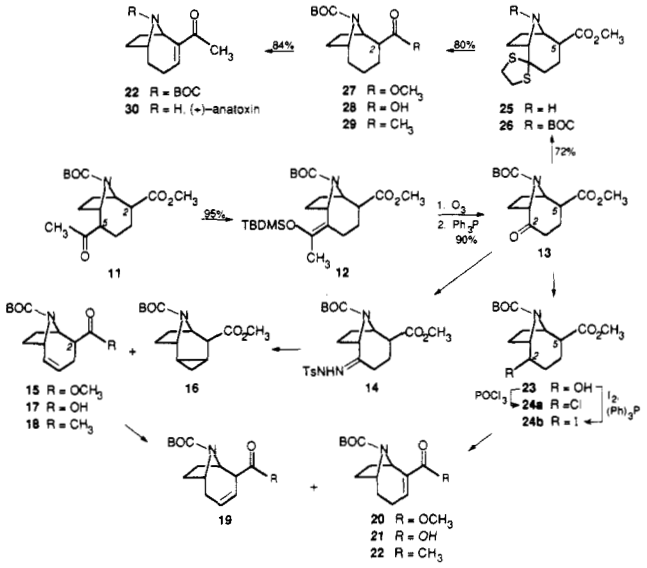
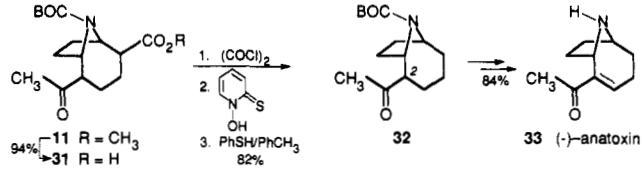
Scheme II. Conversion of Difunctionalized Homotropanes to (+)-Anatoxin and Some Analogues



Scheme III. Synthesis of (-)-Anatoxin from Difunctionalized Homotropanes



In the past, the decarbonylation–iminium ion cyclization to form the 9-azabicyclo[4.2.1]nonane ring system had been effected with an unsubstituted side chain.[3] The first application of this cyclization in the presence of a side-chain substituent was to the 6-methoxycarbonyl derivative **7**. When keto acid **8α** was treated with oxalyl chloride to generate the corresponding iminium salt **9α**, cyclization took place to give a 3/1 mixture of azabicyclononanes **10a** and **10b** in 91% yield.

Analysis of the chemical shifts of H-2 and H-5 in **10a** and **10b** allowed assignment of the stereochemistry of the acetyl and methoxycarbonyl side chains. In the 9-azabicyclo[4.2.1]nonane system, the C-1–N and the C-6–N bonds strongly deshield H-2 and H-5 when these protons possess a β-orientation.[3d] In the less polar, major product, H-5 appears at 2.73 ppm (dt) while H-2 resonates at higher field (<2.50 ppm, not resolved). In the minor product, both protons appear above 2.30 ppm, indicating that the major isomer is **10a** and the minor one is **10b**. When the minor keto acid (**8β**) was submitted to the same cyclization conditions, a mixture of two compounds (different from **10a** and **10b**) was obtained, again in 91% yield. Since the products from this reaction could not be resolved, the stereochemical analysis was postponed until the next step. Debenzylation with simultaneous BOC protection (H_2, Pd/C, $(BOC)_2O$) afforded a 2/1 mixture of isomers which were separated by chromatography. The minor, less polar product showed downfield shifts for both H-2 (2.98 ppm) and H-5 (3.16 ppm); thus, it must be **11d**. The major product showed only a downfield shift for H-2 (two rotamers, 2.83 and 2.99 ppm) while H-5 appeared at 2.40 ppm, corresponding to structure **11c**. Debenzylation–BOC protection of **10a** and **10b** gave **11a** and **11b**, respectively, confirming the previous stereochemical assignments.

This stereochemical analysis answered several questions about the iminium ion cyclization. First, the effect of a C-6 substituent in iminium ion **9** improved the cyclization yield by 25% over the parent system. Second, the stereochemistry at C-6 does not affect the yield of the cyclization. Third, the cyclization conditions do not epimerize the C-6 stereocenter.

Conversion of Difunctionalized Homotropanes 11 to (+)-Anatoxin (30). Due to the formation of all stereoisomers at C-2 and C-5, our synthetic strategy required funnelling all four diastereoisomers **11a–d** into the desired target **29** and is presented in Scheme II. Ketones **13** appeared to be logical intermediates for this purpose since deoxygenation of the ketone carbonyl (C-2) and a one-carbon side-chain extension would lead to *t*-BOC-dihydroanatoxin (**29**), which can be oxidized to enone and quantitatively deprotected to afford (+)-anatoxin (**30**) in 84% yield.[3d] To degrade the C-5 acetyl side chain of **11** to the ring ketone of **13** required regiospecific formation of the thermodynamic enol ether **12** in the presence of an additional enolization site at the ester function. When the reaction conditions developed for regioselective *t*-BOC-dihydroanatoxin TBDMS enol ether formation[3d] (NaH, 300 mol %, cat. CH_3OH, THF, room temperature) were applied to **11**, enol ether **12** was isolated in 60% yield, as a 6/1 mixture of thermodynamic and kinetic silyl enol ethers (each as a mixture of epimers at C-5). Lowering the reaction temperature to −15 °C and decreasing the amount of the base to 200 mol % greatly increased the selectivity of the reaction and resulted in thermodynamic enolate **12** as a >20/1, *Z*/*E* mixture (10/1 mixture of α- and β-epimers at C-5) in 95% yield. The results were identical when the reaction was carried out on a mixture of all four ketones **11**. All the steps from the reduction of vinylogous carbamate **6** to the formation of enol ether **12** can be carried out equally effectively on mixtures of epimers, thus greatly facilitating this synthetic sequence.

Ozonolysis[3e] of **12** proceeded without any complications to give **13α** (less polar) and **13β** (more polar), which were separated by chromatography, in 90% combined yield. The configurational assignment at C-5 in keto ester **13** was made on the basis of the relative downfield chemical shift of H-5 (rotamers: 2.98 and 3.15 ppm) in the less polar isomer, which is virtually identical with the chemical shift (rotamers: 2.97 and 3.12 ppm) for the corresponding proton in the analogous 2-deoxo compound, **27α**.[3e] Conversion of the keto esters **13** to the thioketals **25** proceeded with concomitant loss of the *t*-BOC group. Reprotection of the nitrogen ($(BOC)_2O$, MeOH) gave **26**, and hydrogenolysis of the thioketal with W-2 Raney nickel gave an excellent yield of methyl (1*R*)-*t*-BOC-dihydroanatoxinate (**27**). Ester hydrolysis gave acid **28**, which was converted to (1*R*)-*t*-BOC-dihydroanatoxin (**29**) in 80% overall yield (from **26**) by conversion to the acid chloride followed by reaction with excess lithium dimethylcuprate.[5] The dihydro ketones **29** could be converted to (1*R*)-*t*-BOC-anatoxin (**22**) by selenenylation/oxidation (84% yield).[3d] Acid cleavage of the nitrogen protecting group proceeds quantitatively, thus completing the synthesis of natural (+)-anatoxin (**30**) from L-glutamic acid in 18% overall yield.

Synthesis of (−)-Anatoxin (33) from 2,5-Difunctionalized Homotropane 11. Unnatural (−)-anatoxin (**33**) has previously been prepared from L-glutamic acid[3a] using the same sequence of reactions used for the synthesis of (+)-anatoxin from D-glutamic acid. However, the advanced intermediate **11**, derived in 43% yield from L-glutamic acid (Scheme I) and used for the synthesis of (+)-anatoxin (**30**) (Scheme II) might also serve as a precursor to (−)-anatoxin

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(33) if the C-2 carboxyl group could be removed. This has been accomplished in good yield via a reductive radical decarboxylation of an *O*-acyl thiohydroxamate[6] as depicted in Scheme III.

Ester hydrolysis of keto esters 11 and conversion of the corresponding keto acids 31 to acid chlorides followed by treatment with 1-hydroxy-2(1*H*)-pyridinethione gave the *O*-acyl thiohydroxamates, which were reacted directly with thiophenol in refluxing toluene to give 32 (*ent*-29) cleanly in 82% yield. Double-bond introduction by selenenylation/oxidation as recently described,[3d] followed by nitrogen deprotection, gives (−)-anatoxin (33) in 30% overall yield.

Alternative Routes to (+)-Anatoxin (30). Alternatives to the reductive removal of the acetyl side chain of 11 via the thioketal 26 are shown in Scheme II. We sought the exploit the functionality at C-5 by converting the acetyl group of 11 into a group suitable for introduction of a C-4–C-5 double bond. Transition metal catalyzed double-bond migration,[7] one-carbon side-chain extension and nitrogen deprotection would then lead to (+)-anatoxin (30). Our first efforts were directed toward the elimination of a hydroxyl group (or derivative), accessible by a Baeyer–Villiger oxidation of 11.[3d] Thus 11a was treated with trifluoroperacetic acid under buffered conditions followed by hydrolysis to give alcohol 23 in 58% yield. Alternatively, we found that conversion of 11 to keto esters 13 (as described above) followed by sodium borohydride reduction, while necessitating one more step, gave substantially higher yields (>80% overall).

The alcohols 23 were resistant to elimination when treated with $POCl_3$[8] or $SOCl_2$[9] in pyridine, the major products being the chlorides 24a, which did not undergo dehydrohalogenation when treated with DBU or KOtBu. Similarly, the olefin could not be generated from the tosylates or triflates, dehydration with alumina,[10] pyrolysis of the xanthates,[11] from the *o*-nitrophenyl selenides,[12] or via the Burgess reagent.[13]

The mixture of diastereomeric alcohols 23 could be converted to the iodo ester 24b with $I_2/(Ph)_3P$[14] in 82% yield. Elimination did occur with *t*-BuOK, but formation of the corresponding *tert*-butyl ester was a problem. To circumvent this problem the ester was first hydrolyzed to iodo acid then dehydrohalogenation was effected with *t*-BuOK in dimethylacetamide, affording a mixture of unsaturated acids 17 and 19 (R = OH).

A more direct route to these olefins might be through tosylhydrazone elimination, and for this purpose keto esters 13α,β were separately converted to crystalline tosylhydrazones 14α,β in quantitative yield. Base-induced tosylhydrazone elimination[15a,b] has been applied to compounds possessing base (or nucleophile) sensitive groups only rarely.[15c,d] Thus 14β was treated with excess LiH in refluxing toluene to give alkene 15β in 40% yield. Surprisingly, when epimeric 14α was treated in the same way, a mixture (2/1) of 15α and a byproduct to which we have assigned structure 16 was isolated. Cyclopropane 16 would arise from C-3–H bond insertion of a carbene generated from decomposition of tosylhydrazone 14α.[15b,c,e] Why cyclopropane formation results only from the α-ester is not clear. The use of other bases for this elimination reaction led to a large variety of products.

The route to (+)-anatoxin (30) through the olefins would still be synthetically useful if the double bond could be isomerized into the C-2–C-3 position. We first tried isomerizing the double bond of methyl esters 15 by reaction with $RhCl_3 \cdot 3H_2O$[7b,d-h] in a variety of solvents. A 1/1 mixture of the desired α,β-unsaturated ester 20 and its β,γ-isomer 19 (R = OCH_3) resulted; this apparently represents an equilibrium ratio as it did not change on treatment with base. Similarly, γ,δ-unsaturated acids 17 failed to isomerize and were recovered unchanged after treatment with $RhCl_3 \cdot 3H_2O$.

Finally, carboxylic acids 17 and 19 (R = OH) were converted to methyl ketones 18 and 19 (R = CH_3) via the corresponding acid chlorides followed by addition to excess lithium dimethylcuprate.[5]

When these ketones were subjected to the typical $RhCl_3 \cdot 3H_2O$-catalyzed isomerization conditions, an equal distribution of all three ketones 18, 19 (R = CH_3), and 22 was obtained. Attempted base-induced isomerization did not enhance the proportion of the conjugated isomer 22, nor did stoichiometric $RhCl_3 \cdot 3H_2O$ (up to 150 mol %) alter the product distribution. While these olefins do not represent an efficient path to anatoxin, they may be of interest in themselves as double-bond positional analogues.

Summary

An enantiodivergent synthesis of natural (+)- and unnatural (−)-anatoxin (30 and 33) has been accomplished in excellent yield. This now allows the highly potent nicotinic agonist (+)-anatoxin to be prepared from inexpensive L-glutamic acid by a route easily amenable to scale up. While mixtures of stereoisomers are formed at several points, all reactions can be carried out on the mixtures and all diastereomers funnel into a single product, 30 or 33.

The beneficial effect of side-chain branching in the iminium ion cyclization of 9 to 10 to form the azabicyclo[4.2.1]nonane ring system allows entry into functionalized ring derivatives of anatoxin not accessible by any other synthetic routes.

Experimental Section

General Methods. Reactions were conducted under a dry nitrogen atmosphere except when noted otherwise. Solvents were freshly distilled as follows: tetrahydrofuran (THF) from sodium/benzophenone; methylene chloride (CH_2Cl_2), 1,2-dichloroethane (1,2-DCE), toluene, and CH_3CN from CaH_2; CH_3OH from $Mg(OCH_3)_2$; *N*-methylpiperidine from sodium; pyridine and Et_3N were distilled from CaH_2 and stored over KOH pellets. Low-pressure chromatography (LPC) was carried out using columns packed with EM Reagents silica gel 60 (0.040–0.063-mm particle

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size, 230–400 mesh). Column chromatography was carried out using EM Reagent silica gel 60 (0.063–0.200-mm particle size, 70–230 mesh). Melting points (Büchi apparatus, open capillary) are uncorrected. NMR spectra were recorded in $CDCl_3$ or in $CDCl_3/CD_3OD$. Chemical shifts are reported in parts per million downfield from Me_4Si (^1H) or relative to $CDCl_3$ at 77.0 ppm (^{13}C). Significant ^1H NMR data are tabulated in order: multiplicity (s, singlet; d, doublet; t, triplet; dist, distorted; br, broad), number of protons, coupling constant(s) in hertz (Hz), assignment. In cases where DEPT experiments were carried out with ^{13}C NMR acquisitions, the carbon multiplicities are listed as (0) quaternary; (1) methine; (2) methylene; (3) methyl. Both ^1H and ^{13}C NMR spectra of many of the *N*-*t*-BOC-protected intermediates are complicated by doubling up of peaks due to the presence of carbamate rotamers.

Methyl (±)-5-(2-Methyl-1,3-dioxolan-2-yl)-2-hydroxypentanoate (3). Potassium (19.00 g, 0.486 mmol) was added, in small portions, to a suspension of anhydrous $MgCl_2$ (23.40 g, 0.244 mol) in THF (350 mL). The resulting suspension was refluxed for 90 min and then stirred at 0 °C for an hour. A solution of bromo ketal[3a] (1, 42.54 g, 0.203 mol) in THF (100 mL) was added at a rate of 2.1 mL/min. After the addition was completed, the mixture was stirred for 75 min at 0 °C and then transferred via Teflon cannula into a cold (−50 °C) solution of dimethyl oxalate (34.22 g, 0.290 mol) in CH_2Cl_2 (800 mL) over a 20-min period. The resulting suspension was stirred for an additional 90 min while the temperature rose to 0 °C, and then it was transferred via Teflon cannula into a 0.5 M KH_2PO_4 solution. The aqueous layer was extracted with CH_2Cl_2, and the combined organic solution was washed with saturated $NaHCO_3$ and brine (500 mL each), back washing the aqueous phase with CH_2Cl_2 (200 mL). The combined organic extracts were dried, filtered, and evaporated to give α-keto ester **2** as a yellow oil, which was dissolved in deoxygenated EtOAc (230 mL) and Et_3N (7 mL), 5% Pt/C (4.32 g) was added, the resulting suspension was hydrogenated at 50 psig overnight (Parr shaker), the catalyst was filtered off, the filtrate was evaporated, and the residue was purified by column chromatography (1/4 EtOAc/hexanes containing 0.2% Et_3N) to give **3** (26.55 g, 60% yield) as a clear oil: IR (film) 3740 (br), 2960 (s), 1740 (s), 1440 (m) cm^{-1}; ^1H NMR δ 1.30 (s, 3 H, CH_3), 1.4–1.95 (m, 6 H), 2.80 (br s, 1 H, OH), 3.77 (s, 3 H, CH_3O), 3.90 (m, 4 H), 4.15 (m, 1 H, H-2); ^{13}C NMR δ 19.40, 23.72, 34.41, 38.65, 52.44, 64.58, 70.36, 109.84, 175.60.

(2*S*)-1-Benzyl-5-[4-(2-methyl-1,3-dioxolan-2-yl)-1-(methoxycarbonyl)butylidene]proline *tert*-Butyl Ester (6). A solution of hydroxy ester **3** (21.79 g, 100 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (26.65 g, 130 mmol) in CH_2Cl_2 (300 mL) was cooled to −15 °C, and trifluoromethanesulfonic anhydride (Tf_2O) (32.40 g, 19.34 mL, 115 mmol) was added at 1.0 mL/min. The solution was stirred at 0 °C for 4 h, additional 2,6-di-*tert*-butyl-4-methylpyridine (8.20 g, 40.0 mmol) and Tf_2O (5.64 g, 3.36 mL, 20 mmol) were then added, and stirring was continued at 0 °C for an hour. Cold hexanes (250 mL) were added, the resulting suspension was filtered, the filtrate was evaporated (without heating), the residue was triturated with hexanes (100 mL) and filtered again, and the filtrate was evaporated. The residue, triflate **4**, was dried under vacuum (0.1 mmHg, 1 h), cooled to 0 °C, and dissolved in CH_3CN (12 mL). Thiolactam **5**[3a] (22.34 g, 76.77 mmol) was added, the solution was stirred at 0 °C for 30 min and at room temperature (13 h), and then cooled to −7 °C, and CH_2Cl_2 (400 mL) was added, followed by 4-Å molecular sieves and Ph_3P (28.82 g, 110 mmol). The resulting suspension was stirred at −5 °C for 75 min, *N*-methylpiperidine (11.39 g, 13.95 mL, 115 mmol) was then added, and stirring was continued at −5 to −2 °C for 22 h. The solution was washed with 1 M aqueous KH_2PO_4 (2 × 200 mL) and saturated $NaHCO_3$ (200 mL), the combined aqueous phase was extracted with CH_2Cl_2 (200 mL), and the combined organic phase was dried, filtered, and evaporated. The residue was purified by LPC (EtOAc/hexanes, 3/17) to give **6** (as a 4/1 mixture of *E*/*Z* isomers, 24.66 g, 70% yield) as a clear oil: ^1H NMR δ 1.25 and 1.30 (s, 3 H, CH_3), 1.42 and 1.45 (s, 9 H, *t*-BuO), 1.5–2.4 (m, 7 H), 2.72 and 3.15 (m, 2 H), 3.58 and 3.65 (s, 3 H, CH_3O), 3.85 (m, 5 H), 4.26 and 4.33 (d, *J* = 16.4, 1 H, benzylic), 4.65 and 4.87 (d, *J* = 16.4, 1 H, benzylic), 7.25 (m, 5 H); ^{13}C NMR δ 23.73, 24.92, 25.62, 26.72, 27.49, 27.88, 31.51, 32.08, 33.82, 38.69, 38.81, 38.88, 50.43, 50.55, 52.51, 53.99, 57.83, 64.29, 64.43, 64.50, 65.86, 66.16, 81.46, 81.59, 94.52, 96.29, 109.88, 110.08, 126.55, 126.68, 127.21, 127.26, 128.14, 128.26, 128.29, 128.64, 136.89, 137.67, 158.61, 161.59, 168.31, 170.77, 171.26, 171.58, 192.25; IR (film) 2995 (m), 2960 (m), 1740 (s), 1695 (s), 1580 (s) cm^{-1}. Anal. Calcd for $C_{26}H_{37}NO_6$: C, 67.9; H, 8.1; N, 3.0. Found: C, 67.6; H, 8.1; N, 2.8.

(2*S*,5*R*)-1-Benzyl-5-[1-(methoxycarbonyl)-4-(2-methyl-1,3-dioxolan-2-yl)butyl]proline *tert*-Butyl Ester (7). To a solution of vinylogous carbamate **6** (3.87 g, 8.43 mmol) in CH_3OH (40 mL) was added 10% Pd/C (580 mg), and the resulting suspension was hydrogenated at 50 psig for 16 h. The catalyst was filtered off, the filtrate was evaporated, the residue was dissolved in CH_3CN (10 mL), and calcined K_2CO_3 (650 mg, 4.71 mmol) was added, followed by benzyl bromide (504 mg, 0.35 mL, 3.0 mmol). The resulting suspension was stirred at room temperature overnight, H_2O (50 mL) was added, the solution was extracted with CH_2Cl_2 (3 × 50 mL), and the organic extracts were dried, filtered, and evaporated. Purification of the residue by column chromatography (EtOAc/hexanes, 1/4) gave **7** as a 4/1 mixture of epimers at C-6; 3.62 g, 93% yield: ^1H NMR δ 1.28 (major), 1.34 (minor) (s, 9 H, *t*-BuO), 1.20–1.95 (m, 10 H), 2.46 (minor, m, 1 H, H-6), 2.66 (major, q, *J* = 7.0, 1 H, H-6), 3.04 (major, q, *J* = 5.9, 1 H, H-5), 3.22 (major, m, 1 H, H-2), 3.22 (minor, m, 2 H, H-2 and H-5), 3.67 and 4.00 (d, *J* = 14.0) and 3.70 (s) (2 H, benzylic), 3.90 (m, 4 H), 7.28 (m, 5 H); ^{13}C NMR major δ 22.38, 23.60, 27.20, 27.71, 28.58, 29.91, 38.87, 49.41, 51.10, 59.04, 64.42, 66.64, 67.01, 79.58, 109.70, 126.82, 127.89, 129.25, 138.46, 173.36, 174.95; minor δ 22.45, 23.60, 26.72, 27.71, 28.72, 29.91, 38.87, 49.80, 51.18, 59.28, 64.42, 66.87, 67.34, 79.87, 109.75, 126.72, 127.89, 128.79, 139.12, 173.45, 175.34; IR (film) 2980 (s), 2940 (s), 2880 (s), 1735 (s) cm^{-1}. Anal. Calcd for $C_{26}H_{39}NO_6$: C, 67.6; H, 8.5; N, 3.0. Found: C, 67.6; H, 8.6; N, 3.2.

(2*S*,5*R*,6*S*)- and (2*S*,5*R*,6*R*)-1-Benzyl-5-(1-(methoxycarbonyl)-5-oxohex-1-yl)proline (8α and 8β). A solution of ester ketal **7** (3.62 g, 7.85 mmol) in *i*-PrOH (25 mL), H_2O (25 mL), and glacial acetic acid (5 mL) was stirred at 100 °C for 29 h, cooled, poured into 1.5 M aqueous KH_2PO_4 (150 mL), and extracted with $CHCl_3$ (3 × 150 mL). The combined organic phase was dried, filtered, and evaporated. The residue was purified by LPC (*i*-PrOH/CH_2Cl_2, 1/19 to 1/3) to give pure 8β (less polar, 561 mg, 20% yield) and 8α (more polar, 2.246 g, 69% yield) as clear oils.

8β: ^1H NMR δ 1.4–2.1 (m, 8 H), 2.14 (s, 3 H, CH_3), 2.45 (t, *J* = 7.0, 2 H), 2.48 (m, 1 H, H-6), 3.31 (q, *J* = 6.9, 1 H, H-5), 3.57 (t, *J* = 6.4, 1 H, H-6), 3.63 (d, *J* = 13.0, 1 H, benzylic), 3.80 (s, 3 H, CH_3O), 3.97 (d, *J* = 13.0, 1 H, benzylic), 7.33 (m, 5 H); ^{13}C NMR δ 21.22, 28.29, 29.12, 29.61, 42.76, 50.77, 51.72, 59.68, 66.37, 67.56, 77.20, 127.93, 128.57, 129.14, 135.62, 173.76, 174.39, 207.88; IR (film) 3400 (br) 2950 (m), 1715 (s), 1630 (w), 1450 (m), 1360 (m) cm^{-1}.

8α: ^1H NMR δ 1.30–2.05 (m, 8 H), 2.13 (s, 3 H, CH_3), 2.43 (t, *J* = 6.9, 2 H, CH_2), 2.77 (m, 1 H, H-6), 3.16 (m, 1 H, H-5), 3.56 (dd, *J* = 9.0, 3.8, 1 H, H-2), 3.69 (d, *J* = 12.7, 1 H, benzylic), 7.33 (m, 5 H); ^{13}C NMR δ 21.75, 26.42, 28.53, 29.04, 29.84, 42.97, 46.98, 52.04, 57.67, 65.81, 67.52, 128.36, 128.90, 126.55, 135.63, 173.70, 174.78, 208.09; IR (film) 3400 (br), 2950 (m), 1715 (s), 1630 (w), 1450 (m), 1360 (m) cm^{-1}. Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.4; H, 7.5; N, 3.9. Found: C, 66.2; H, 7.5; N, 3.8.

(1*R*,2*R*,5*R*)- and (1*R*,2*R*,5*S*)-5-Acetyl-9-benzyl-2-(methoxycarbonyl)-9-azabicyclo[4.2.1]nonane (10c and 10d). A solution of keto acid 8β (979 mg, 2.712 mmol) in 1,2-DCE (20 mL) was added to a cold (−15 °C) solution of oxalyl chloride (freshly distilled under N_2, 482 mg, 0.33 mL, 3.80 mmol) in 1,2-DCE (65 mL) at 0.24 mL/min. After the addition was completed, the bright yellow solution was stirred for 3 h (−11 °C to 3 °C), toluene (65 mL) was added, and the solution was immersed in a preheated bath (60 °C) and stirred overnight in an Ar atmosphere. The mixture was allowed to cool and then washed with saturated $NaHCO_3$. The aqueous washings were back extracted with CH_2Cl_2 (two times), and the combined organic phase was washed with brine, dried, filtered, and evaporated. The residue was purified by chromatography (EtOAc/hexanes, 3/7) to give a mixture of **10c** and **10d** (1/1 by ^1H NMR, 779 mg, 91% yield) as a clear oil: ^1H NMR δ 1.50–2.05 (m, 6 H), 1.90 and 2.00 (s, 3 H, CH_3), 2.29 (dd, *J* = 11.3, 5.0, 1 H), 2.38 (m, 1 H), 2.68 (dt, *J* = 11.9, 3.7, 1 H), 2.89 (m, 1 H), 3.52 (m, 1 H), 3.60 and 3.62 (s, 3 H, CH_3O), 3.70 (br s, 1 H), 3.74 and 3.85 (s, 2 H, benzylic), 7.32 (m, 5 H);

^{13}C NMR δ 23.33, 24.38, 24.41, 24.78, 25.68, 26.30, 27.05, 27.28, 29.03, 33.89, 49.05, 50.38, 51.43, 57.30, 57.56, 60.95, 61.71, 62.50, 62.94, 63.69, 66.70, 126.94, 126.99, 128.00, 128.19, 128.31, 128.55, 139.98, 140.34, 174.48, 174.87, 210.03, 210.52; IR (film) 3030 (w), 2960 (s), 2880 (m), 1730 (s), 1705 (s) cm^{-1}. Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.3; H, 8.0; N, 4.4. Found: C, 72.2; H, 7.8; N, 4.4.

(1*R*,2*S*,5*S*)- and (1*R*,2*S*,5*R*)-5-acetyl-9-benzyl-2-(methoxycarbonyl)-9-azabicyclo[4.2.1]nonane (10a and 10b) were prepared from 8α as described for **10c,d**. The crude reaction products were separated by LPC (EtOAc/hexanes, 3/17) to give **10a** (less polar, 68% yield) and **10b** (more polar, 23% yield) as clear oils.

10a: ^{1}H NMR δ 1.5–2.5 (m, 9 H), 1.98 (s, 3 H, CH_3), 2.73 (dt, *J* = 11.2, 3.5, 1 H, H-5), 3.49 (s, 3 H, CH_3O), 3.60 (m, 1 H, H-6), 3.71 (br d, *J* = 9.2, 1 H, H-1), 3.77 (d, *J* = 13.0, 1 H, benzylic), 3.79 (d, *J* = 13.0, 1 H, benzylic), 7.35 (m, 5 H); ^{13}C NMR δ 23.34, 24.04, 26.03, 28.98, 33.71, 51.47, 52.60, 58.77, 60.46, 64.28, 64.38, 126.81, 128.07, 128.51, 140.40, 175.72, 210.26; IR (film) 3030 (w), 2960 (s), 2880 (m), 1730 (s), 1705 (s) cm^{-1}.

10b: ^{1}H NMR δ 1.55–2.30 (m, 10 H), 1.79 (s, 3 H, CH_3), 3.45 (s, 3 H, CH_3O), 3.52 (d, *J* = 7.0, 1 H, H-1), 3.65 (s, 2 H, benzylic), 3.85 (br d, *J* = 8.0, 1 H, H-5), 7.26 (m, 5 H); ^{13}C NMR δ 24.42 (2 C), 26.86, 29.18, 32.43, 49.50, 51.38, 60.89, 62.11, 63.69, 65.82, 126.94, 128.11, 129.19, 140.61, 174.58, 210.86; IR (film) 3030 (w), 2960 (s), 2880 (m), 1730 (s), 1705 (s) cm^{-1}. Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.3; H, 8.0; N, 4.4. Found: C, 72.2; H, 7.8; N, 4.4.

(1*R*,2*R*,5*R*)- and (1*R*,2*R*,5*S*)-5-Acetyl-9-(*tert*-butoxycarbonyl)-2-(methoxycarbonyl)-9-azabicyclo[4.2.1]nonane (11c and 11d). Di-*tert*-butyl dicarbonate (1.107 g, 5.08 mmol) was added to a solution of a mixture of **10c** and **10d** (640 mg, 2.03 mmol) in CH_3OH (20 mL) followed by 10% Pd/C (130 mg). The resulting suspension was hydrogenated at 50 psig for 22 h and then filtered, the residue was thoroughly washed with CH_3OH, the combined filtrates were evaporated, and the residue was purified by LPC (EtOAc/hexanes, 1/4) to give pure **11d** (less polar, 223 mg, 34% yield) and **11c** (more polar, 424 mg, 64% yield) as clear oils.

11c: ^{1}H NMR (two rotamers) δ 1.2–2.4 (m, 9 H), 1.39 and 1.44 (s, 9 H, *t*-BuO), 2.19 and 2.25 (s, 3 H, CH_3), 2.83 and 2.99 (dt, *J* = 12.2, 3.5, 1 H, H-2), 3.64 and 3.66 (s, 3 H, CH_3O), 4.45 (br d, *J* = 8.8, 1 H), 4.58 (m, 1 H); ^{13}C NMR δ 23.51, 23.97, 24.22, 24.56, 24.87, 27.42, 28.07, 28.34, 33.69, 35.05, 46.63, 47.71, 51.56, 51.70, 55.32, 55.69, 57.55, 60.93, 61.38, 79.78, 80.51, 152.91, 153.21, 173.59, 175.32, 207.77, 208.90; IR (film) 2970 (s), 2950 (s), 1725 (s), 1710 (s), 1685 (s), 1400 (s). Anal. Calcd for $C_{17}H_{27}NO_5$: C, 62.7; H, 8.4; N, 4.3. Found: C, 62.8; H, 8.4; N, 4.2.

11d: ^{1}H NMR (two rotamers) δ 1.40 and 1.41 (s, 9 H, *t*-BuO), 1.4–1.6 (m, 4 H), 1.8–2.0 (m, 4 H), 2.05 and 2.06 (s, 3 H, CH_3), 2.98 (q, *J* = 6.0, 1 H), 3.16 (m, 1 H), 3.56 and 3.58 (s, 3 H, CH_3O), 4.40 and 4.48 (m, 1 H), 4.48 and 4.58 (m, 1 H); ^{13}C NMR 22.56, 22.73, 23.77, 25.29, 26.04, 26.53, 27.35, 28.25, 28.90, 28.98, 46.25, 47.52, 51.33, 51.42, 54.86, 56.31, 56.33, 56.54, 56.58, 79.63, 79.74, 152.54, 152.80, 173.60, 173.82, 208.33, 208.73; IR (film) 2970 (s), 2950 (s), 1725 (s), 1710 (s), 1685 (s), 1400 (s) cm^{-1}. Anal. Calcd for $C_{17}H_{27}NO_5$: C, 62.7; H, 8.4; N, 4.3. Found: C, 62.8; H, 8.3; N, 4.4.

(1*R*,2*S*,5*S*)-5-Acetyl-9-(*tert*-butoxycarbonyl)-2-(methoxycarbonyl)-9-azabicyclo[4.2.1]nonane (11a) was prepared from **10a** as described for **11c** and **11d** as a clear oil, in 98% yield: ^{1}H NMR (two rotamers) δ 1.40 and 1.46 (s, 9 H, *t*-BuO), 1.4–1.7 (m, 4 H), 1.95 (m, 3 H), 2.14 and 2.17 (s, 3 H, CH_3-13), 2.35 (m, 2 H), 2.93 and 3.01 (dt, *J* = 11.6, 3.4, 1 H, H-5), 3.66 and 3.68 (s, 3 H, CH_3O), 4.44 and 4.50 (br d, *J* = 9.0, 1 H), 4.60 and 4.65 (br d, *J* = 9.0, 1 H); ^{13}C NMR δ 22.59, 22.80, 22.98, 23.74, 25.03, 28.16, 28.39, 29.00, 29.14, 33.56, 34.89, 51.60, 51.93, 53.03, 54.54, 56.37, 56.44, 56.97, 153.20, 174.24, 209.10; IR (film) 2970 (s), 2950 (s), 1725 (s), 1710 (s), 1685 (s), 1400 (s). Anal. Calcd for $C_{17}H_{27}NO_5$: C, 62.7; H, 8.4; N, 4.3. Found: C, 63.0; H, 8.4; N, 4.2.

(1*R*,2*S*,5*R*)-5-Acetyl-9-(*tert*-butoxycarbonyl)-5-(methoxycarbonyl)-9-azabicyclo[4.2.1]nonane (11b) was prepared from **10b** as described for **11c** and **11d** as a clear oil, in 98% yield: ^{1}H NMR ($CDCl_3$) (signals are broad due to the coalescence of rotamers) δ 1.2–2.45 (m, 10 H), 1.38 (br s, 9 H, *t*-BuO), 2.35 (br s, 3 H, CH_3), 3.71 (s, 3 H, CH_3O), 4.55 (m, 1 H), 4.61 (m, 1 H); ^{13}C NMR ($CDCl_3$, 55 °C) δ 23.39, 24.08, 28.07, 28.21, 51.63, 56.80, 56.83, 57.86, 80.05, 153.58, 174.09, 208.26; IR (film) 2970 (s), 2950 (s), 1725 (s), 1710 (s), 1685 (s), 1400 (s) cm^{-1}. Anal. Calcd for $C_{17}H_{27}NO_5$: C, 62.7; H, 8.4; N, 4.3. Found: C, 63.0; H, 8.5; N, 4.5.

(1*S*,5*RS*,10*Z*)-9-(*tert*-Butoxycarbonyl)-2-((*Z*)-1-(*tert*-butyldimethylsiloxy)ethylidene)-5-(methoxycarbonyl)-9-azabicyclo[4.2.1]nonane (12). A diastereomeric mixture of keto esters **11a–d** (2.85 g, 8.76 mmol) and CH_3OH (35 μL, 0.88 mmol, 10 mol %) in THF (14 mL) was added to a suspension of sodium hydride (48% dispersion in oil, washed 3 × 10 mL with THF; 876 mg, 17.5 mmol, 200 mol %) in THF (24 mL) at −15 °C. After the dark yellow suspension was stirred at −15 °C to −12 °C for 23 h, it was quenched with a centrifuged solution of TBDMSCl (2.64 g, 17.51 mmol, 200 mol %) and Et_3N (2.04 mL, 14.62 mmol, 167 mol %) in THF (7 mL). The mixture was stirred overnight at 0 °C, poured into cold (4 °C) 1 *M* KH_2PO_4 (75 mL), and extracted with CH_2Cl_2 (3 × 75 mL). The combined organic phase was washed with brine (75 mL), dried, filtered, and evaporated to a yellow oil (4.4 g), which was purified by column chromatography (EtOAc/hexanes, 1/9) to give the thermodynamic enol ether **12** (3.64 g, 95%) as a clear, colorless oil: TLC (EtOAc/hexanes, 1/3) R_f 0.49; IR (film) 2960 (s), 2930 (s), 1735 (s), 1690 (s), 1665 (s), 1400 (s) cm^{-1}; ^{1}H NMR (two rotamers, 2/1) δ 0.10, 0.11, 0.13 (s, 6 H, Me_2Si), 0.89, 0.90 (s, 9 H, *t*-BuSi), 1.39, 1.45 (s, 9 H, *t*-BuO), 1.4–2.2 (m, 7 H), 1.77 (s, 3 H, CH_3-11), 2.30 (dd, 1 H, *J* = 14.8, 6.9, H-3), 2.84, 3.01 (dt, 1 H, *J* = 8.5, 3.8, H-5), 3.60, 3.62 (s, 3 H, CH_3O), 4.47, 4.57 (m, 1 H), 4.81, 4.88 (d, 1 H, *J* = 8.0); ^{13}C NMR (two rotamers, 2/1) δ −3.85, −3.63, −3.36, −3.22, 18.00, 18.80, 18.92, 23.04, 23.77, 25.61, 25.73, 26.20, 26.44, 28.36, 28.42, 28.50, 28.55, 32.71, 33.04, 46.04, 47.27, 51.42, 51.57, 56.19, 56.61, 57.51, 57.73, 79.07, 79.13, 121.37, 122.07, 140.42, 140.97, 152.89, 153.34, 173.98, 174.05. Anal. Calcd for $C_{23}H_{41}NO_5Si$: C, 62.8; H, 9.4; N, 3.2. Found: C, 62.7; H, 9.6; N, 3.1.

(1*S*,5*R*)- and (1*S*,5*S*)-9-(*tert*-Butoxycarbonyl)-5-(methoxycarbonyl)-9-azabicyclo[4.2.1]nonan-2-one (13α and 13β). Ozone (1.8 mL/min) was passed through a solution of **12** (1.10 g, 2.51 mmol) in CH_3OH (90 mL) and pyridine (1 mL) at −78 °C until the colorless solution turned gray, and then the solution was purged with O_2 until the gray color disappeared and then with N_2 for 5 min. Addition of Ph_3P (1.314 g, 5.016 mmol) and stirring at −78 °C for 1 h and at room temperature for 30 min was followed by evaporation. The residue was taken up in CH_2Cl_2 and washed with 5% aqueous HCl and saturated $NaHCO_3$. Drying, filtering, and evaporating afforded a residue, which was purified by LPC (EtOAc/hexanes, 17/83 to 1/3) to give **13α** (less polar, 594 mg, 80%) and **13β** (more polar, 77 mg, 10%; identical with the ketone obtained below by PCC oxidation of alcohol **23** (2α,5β)) as clear oils.

13α: TLC (EtOAc/hexanes, 1/3) R_f 0.21; IR (film) 2990 (s), 1730 (s), 1695 (s), 1400 (s) cm^{-1}; ^{1}H NMR (two rotamers, 2/1) δ 1.33, 1.41 (s, 9 H, *t*-BuO), 1.6–2.4 (m, 8 H), 2.98, 3.15 (br d, 1 H, *J* = 12.5, H-5), 3.58, 3.60 (br s, 3 H, CH_3O), 4.17, 4.26 (d, 1 H, *J* = 10.2), 4.57, 4.66 (br d, 1 H, *J* = 7.8); ^{13}C NMR (two rotamers, 2/1) δ 20.98, 23.88, 24.50, 28.06, 28.19, 29.05, 29.52, 39.78, 46.58, 47.93, 51.58, 51.71, 57.63, 64.13, 64.61, 80.39, 80.51, 152.47, 152.86, 172.46, 172.57, 213.56, 213.89. Anal. Calcd for $C_{15}H_{23}NO_5$: C, 60.6; H, 7.8; N, 4.7. Found: C, 60.6; H, 7.9; N, 4.7.

(1*S*,5*R*)- and (1*S*,5*S*)-2,2-(Ethylenedithio)-5-(methoxycarbonyl)-9-azabicyclo[4.2.1]nonane (25α,β). Boron trifluoride etherate (0.75 mL) was added to a solution of keto esters **13α,β** (302 mg, 1.02 mmol) and ethanedithiol (0.72 mL) in CH_2Cl_2 (1 mL). After the reaction mixture was stirred at room temperature for 24 h it was diluted with 1 N NaOH (15 mL) and extracted with CH_2Cl_2 (4 × 8 mL). The combined organic phase was dried, filtered, and evaporated to an oil (286 mg, after removal of excess ethanedithiol by high vacuum Kugelrohr distillation) that was purified by LPC (EtOAc/hexanes, 2/3) to give amines **25α,β** (1/3, 205 mg, 74% yield).

25α: ^{1}H NMR (partial list) δ 2.85–3.05 (m, 1 H, H-5), 3.67 (s, 3 H), 3.92–4.04 (m, 2 H, H-1, H-6); ^{13}C NMR δ 24.71 (2), 29.01 (2), 30.66 (2), 38.26 (2), 39.23 (2), 39.44 (2), 49.94 (1, C-5), 51.30 (3, C-11), 58.27 (1, C-6), 70.94 (1, C-1), 76.92 (0, C-2), 174.45 (0, C-10).

25β: ^{1}H NMR δ 1.57–2.35 (m, 9 H), 2.45–2.55 (m, 1 H), 3.21–3.36 (m, 4 H, $-SCH_2CH_2S-$), 3.68 (s, 3 H, CH_3O), 3.73–3.85

(m, 2 H); ^{13}C NMR δ 26.76 (2), 28.55 (2), 34.61 (2), 37.92 (2), 39.07 (2), 39.26 (2), 51.59 (3, C-11), 52.98 (1, C-5), 57.77 (1, C-6), 70.21 (1, C-1), 76.92 (0, C-2), 175.84 (0, C-10). Anal. Calcd for $C_{12}H_{19}NO_2S_2$: C, 52.7; H, 7.0; N, 5.1. Found: C, 52.6; H, 6.9; N, 4.9.

(1*S*,5*R*)- and (1*S*,5*S*)-9-(*tert*-Butoxycarbonyl)-2,2-(ethylenedithio)-5-(methoxycarbonyl)-9-azabicyclo[4.2.1]nonane (26α,β). Di-*tert*-butyl dicarbonate (245 mg, 1.12 mmol, 150 mol %) was added to a solution of secondary amines **25** (205 mg, 0.75 mmol) in CH_3OH (3 mL). After being stirred at room temperature for 1 h, the solution was diluted with CH_2Cl_2 (25 mL) and washed with 10% Na_2CO_3 (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic phase was dried, filtered, and evaporated, and the residue (clear oil, 390 mg) was purified by column chromatography (EtOAc/hexanes, 1/9) to give thioketals **26**α,β, 272 mg, 97% yield.

26α: TLC (EtOAc/hexanes, 1/3) R_f 0.37; ^1H NMR δ 1.50 (s, 9 H, *t*-BuO), 1.57–1.70 (m, 1 H), 1.78–2.20 (m, 7 H), 2.25–2.37 (m, 1 H), 3.05–3.40 (m, 5 H, H-5 and $-SCH_2CH_2S-$), 3.67 (s, 3 H, CH_3O), 4.50–4.78 (m, 2 H); ^{13}C NMR δ 24.91 (2), 26.94 (2), 28.43 (3, 3 C, C-16), 29.69 (2), 30.35 (2), 37.86 (2), 39.19 (2), 46.44 (1, C-5), 51.62 (3, C-11), 56.82 (1), 66.94 (1), 80.30 (0, C-15), 153.54 (0, C-14), 174.23 (0, C-10), C-2 carbon not located.

26β: TLC (EtOAc/hexanes, 1/3) R_f 0.29; ^1H NMR δ 1.44 (s, 9 H, *t*-BuO), 1.65–1.80 (m, 1 H), 1.82–1.98 (m, 2 H), 2.02–2.30 (m, 4 H), 2.33–2.56 (m, 2 H), 3.18–3.43 (m, 4 H, $-SCH_2CH_2S-$), 3.71 (s, 3 H, CH_3O), 4.45–4.85 (m, 2 H); ^{13}C NMR δ 25.95 (2), 28.24 (3, 3 C, C-16), 29.22 (2), 34.84 (2), 38.04 (2), 38.71 (2), 39.41 (2), 51.66 (3, C-11), 52.44 (1, C-5), 57.80 (1), 66.40 (1), 75.81 (0, C-2), 79.92 (0, C-15), 153.96 (0, C-14), 174.02 (0, C-10). Anal. Calcd for $C_{17}H_{27}NO_4S_2$: C, 54.7; H, 7.3; N, 3.7. Found: C, 54.3; H, 7.3; N, 3.7.

Raney Nickel Desulfurization. (1*R*,2*R*)- and (1*R*,2*S*)-9-(*tert*-Butoxycarbonyl)-2-(methoxycarbonyl)-9-azabicyclo[4.2.1]nonane (27α,β). A solution of thioketals **26** (272 mg, 0.73 mmol) in EtOH (10 mL) was added to a suspension of W-2 Raney Ni[16] (2.0 g) in EtOH, heated at reflux for 30 min, cooled to room temperature, and filtered through a short plug of Celite. The catalyst was digested three times by suspending it in EtOH (3 × 10 mL), heating at reflux for 5 min, and filtering. The combined filtrates were evaporated to an oil, which was purified by column chromatography (1/4, EtOAc/hexanes) to give **27**α,β as a clear oil (196 mg, 95%), identical (TLC, NMR) with the dihydro esters prepared previously.[3e]

Conversion of Dihydro Esters 27 to (1*R*)-*t*-BOC-Dihydroanatoxin (29). Potassium hydroxide (388 mg, 6.92 mmol, 1000 mol %) in H_2O (4 mL) was added to a solution of dihydro esters **27** (196 mg, 0.69 mmol) in CH_3OH (8 mL), and the resulting mixture was stirred at room temperature for 20 h and then evaporated to remove most of the methanol. The residue was diluted with H_2O (15 mL) and extracted with Et_2O (2 × 10 mL), the combined organic layer was washed with 1 N NaOH (5 mL) and chilled (0 °C), and the combined aqueous phase was acidified to pH 3.2 with 7 M H_3PO_4 and then extracted with $CHCl_3$ (3 × 8 mL), and the combined $CHCl_3$ layers were dried, filtered, and evaporated to afford *t*-BOC-dihydroanatoxinic acid **28** (181 mg, 98% yield). Oxalyl chloride (148 μL, 1.69 mmol, 250 mol %) was added dropwise to a solution of acids **28** (181 mg, 0.68 mmol) and catalytic DMF (1 drop) in benzene (2 mL), and the resulting solution was stirred for 90 min and then evaporated to dryness. The mixture of crude acid chlorides in THF (2 mL) was added dropwise to a −78 °C solution of 300 mol % of Me_2CuLi [prepared by addition of 2.28 M CH_3Li in Et_2O (1.78 mL, 4.07 mmol, 600 mol %) to a slurry of cuprous iodide (CuI, 387 mg, 2.03 mmol, 300 mol %) in THF (3 mL) at 0 °C, stirring for 10 min, then cooling to −78 °C, and using directly] in Et_2O/THF. After stirring at −78 °C for 15 min the reaction mixture was quenched by addition of methanol (2 mL) and allowed to warm to room temperature. It was poured into 1 N NaOH (20 mL) and extracted with $CHCl_3$ (3 × 20 mL), the combined organic phase was dried, filtered, and evaporated, and the yellow oily residue (200 mg) was purified by column chromatography (1/4 EtOAc/hexanes) to give pure (1*R*)-*t*-BOC-dihydroanatoxin (**29**α,β, 156 mg, 86% from acid **28**), identical with material previously prepared.[3a,d]

(+)-Anatoxin (33). Via the reported procedure,[3d] (1*R*)-*t*-BOC-dihydroanatoxin (**29**) was converted to BOC-anatoxin (**22**) and then to (+)-anatoxin (**30**) in 84% overall yield.

(1*R*,2*R*,5*R*)- and (1*R*,2*R*,5*S*)-5-Acetyl-9-(*tert*-butoxycarbonyl)-2-carboxy-9-azabicyclo[4.2.1]nonane (31). Potassium hydroxide (517 mg, 9.22 mmol, 1000 mol %) in H_2O (5 mL) was added to a solution of keto esters **11c** and **11d** (2/1, 300 mg, 0.92 mmol) in CH_3OH (15 mL), and the mixture was stirred at room temperature for 3 h. Most of the methanol was evaporated, H_2O (15 mL) was added, and the mixture was washed with Et_2O (2 × 10 mL). The aqueous phase, cooled to 0 °C and adjusted to pH 3.5, was extracted with $CHCl_3$ (3 × 15 mL), the combined organic phase was dried, filtered, and evaporated, and the residue (300 mg) was purified by column chromatography (1/1 EtOAc/hexanes to 100% EtOAc) to give keto acids **31** (270 mg, 94% yield): mp 120–121 °C; IR (film) 3600–2700 (br s), 1680, 1400 cm^{-1}; ^1H NMR δ 1.25–1.73 (m, 5 H), 1.37 (major) and 1.46 (minor) (s, 9 H, *t*-BuO), 1.82–2.40 (m, 6 H), 2.12 (minor) and 2.14 (major) (s, 3 H, CH_3CO), 2.52 (br d, J = 11.6, minor, H-5β), 2.84 (br d, J = 12.1, minor, H-2), 3.07 (br d, 1 H, J = 10.7, major, H-2), 4.49 (dist d, 1 H, J = 8.8), 4.57 (dist t, 1 H, J = 8.8); ^{13}C NMR (major isomer) δ 22.68 (2), 22.75 (2), 24.77 (2), 27.96 (3, 3 C), 28.26 (3), 34.66 (2), 52.59 (1), 54.69 (1), 56.41 (1), 56.93 (1), 80.46 (0), 153.18 (0), 179.17 (0), 209.31 (0); (minor isomer) δ 23.11 (2), 23.37 (2), 26.67 (2), 28.93 (3), 29.07 (3, 3 C), 33.45 (2), 55.3 (1), 55.73 (1), 55.77 (1), 57.29 (1), 81.49 (0), 154.77 (0), 176.78 (0), 208.10 (0). Anal. Calcd for $C_{16}H_{25}NO_5$: C, 61.7; H, 8.1; N, 4.5. Found: C, 61.8; H, 8.1; N, 4.5.

(1*S*)-*t*-BOC-Dihydroanatoxin (32). Keto acids **31** (55 mg, 0.18 mmol) in benzene (1 mL) containing DMF (1 drop) were treated with oxalyl chloride (39 μL, 56 mg, 0.44 mmol, 250 mol %) at room temperature for 3 h. The reaction mixture was evaporated to dryness, benzene (2 mL) was added, and the evaporation was repeated. The residual acid chloride was dissolved in toluene (1 mL) and added to a solution of 2-mercapto-*N*-hydroxypyridine[6] (24.7 mg, 0.19 mmol, 110 mol %) and pyridine (3 drops) in toluene (2 mL). The resulting yellow solution was stirred in the dark for 1 h at room temperature and then added at 0.17 mL/min to a solution of thiophenol (81.6 μL, 87.6 mg, 0.79 mmol, 450 mol %) in toluene (4 mL) at reflux. Reflux was continued for 45 min after addition was complete, the reaction mixture was cooled to room temperature and washed with 1 N NaOH (15 mL), and the aqueous layer was extracted with benzene (8 mL). The combined organic phase was washed with brine (10 mL), dried, filtered, and evaporated to a pale oil (70 mg) that was purified by column chromatography (1/9 EtOAc/hexanes) to give (1*S*)-*t*-BOC-dihydroanatoxin (**32**, 39 mg, 82% yield) as a mixture of epimers at C-2.

(−)-Anatoxin (33). Via the previous procedure,[3d] **32** was converted to (−)-anatoxin (**33**)[3a] in 84% overall yield.

(1*S*,2*S*,5*S*)-9-(*tert*-Butoxycarbonyl)-2-hydroxy-5-(methoxycarbonyl)-9-azabicyclo[4.2.1]nonane (23, 2α,5β): Baeyer–Villiger Oxidation/Hydrolysis Route. To a cold (0 °C) suspension of H_2O_2 (70%, 352 mg, 7.237 mmol) in CH_2Cl_2 (9 mL) was added $(CF_3CO)_2O$ (2.279 g, 1.53 mL, 10.8 mmol). The solution was stirred for 5 min, and then solid Na_2HPO_4 (3.082 g, 21.7 mmol) was added followed by a solution of **11a** (784 mg, 2.4 mmol) in CH_2Cl_2 (10 mL). The resulting suspension was stirred at 0 °C for 1 h and at room temperature overnight, poured into saturated $NaHCO_3$, and extracted with CH_2Cl_2 (three times). The organic extracts were dried, filtered, and evaporated to a clear oil, which was dissolved in CH_3OH (1 mL) and H_2O (1 drop), calcined K_2CO_3 (500 mg, 3.6 mmol) was added, and the mixture was stirred at room temperature overnight, poured into 1.5 M aqueous KH_2PO_4, and extracted with CH_2Cl_2 (three times). The organic extracts were dried, filtered, and evaporated, and the residue was purified by column chromatography (EtOAc/hexanes, 1/1) to give pure **23** (2α,5β) (418 mg, 58% yield) as a white solid, identical with the more polar alcohol product from the reduction of keto ester **13**β.

(1*S*,5*S*)-9-(*tert*-Butoxycarbonyl)-5-(methoxycarbonyl)-9-azabicyclo[4.2.1]nonan-2-one (13β): By Oxidation of Alcohol 23 (2α,5β). Pyridinium chlorochromate (244 mg, 1.13 mmol) was added to a solution of **23** (2α,5β) (232 mg, 0.8 mmol) in CH_2Cl_2.

(16) Mozingo, R. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. 3, p 181.

The solution was stirred at room temperature for 19 h, Et_2O (10 mL) was added, the suspension was filtered through a pad of Celite and silica gel, the residue was washed with Et_2O, and the combined filtrates were evaporated. The residue was purified by column chromatography (EtOAc/hexanes, 3/7) to give **13β** (212 mg, 92% yield) as a clear oil: TLC (EtOAc/hexanes, 1/3) R_f 0.15; ^1H NMR δ 1.38 (s, 9 H, *t*-BuO), 1.70 (m, 2 H), 1.87 (m, 1 H), 2.03 (m, 1 H), 2.23 (m, 3 H), 2.60 (br s, 1 H), 3.42 (br t, J = 14.0, 1 H, H-3), 3.71 (s, 3 H, CH_3O), 4.28 (br s, 1 H), 4.94 (br s, 1 H); ^{13}C NMR δ 20.60, 28.15, 28.34, 29.20, 38.37, 46.96, 52.04, 58.16, 65.12, 80.53, 152.85, 173.73, 215.01; IR (film) 2990 (s), 1730 (s), 1695 (s), 1400 (s) cm^{-1}. Anal. Calcd for $C_{15}H_{23}NO_5$: C, 60.6; H, 7.8; N, 4.7. Found: C, 60.7; H, 8.0; N, 5.1.

(1*S*,5*S*)-9-(*tert*-Butoxycarbonyl)-5-(methoxycarbonyl)-9-azabicyclo[4.2.1]nonan-2-one (4-Tolylsulfonyl)hydrazone (14α). (*p*-Tolylsulfonyl)hydrazine (667 mg, 3.51 mmol), pyridinium tosylate (60 mg, 0.24 mmol), and molecular sieves (3 Å) were added to a solution of **13α** (710 mg, 2.39 mmol) in CH_2Cl_2 (12 mL). The resulting suspension was stirred at room temperature for 9 h, and then pyridine (1 mL) was added, followed by succinic anhydride (717 mg, 7.173 mmol) and DMAP (15 mg). After being stirred overnight, the reaction mixture was poured into saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3×). The combined organic extracts were washed with H_2O, 1 M H_3PO_4, and brine, dried, filtered, and evaporated to give pure **14α** (1.110 g, 100% yield): mp 152–155 °C (Et_2O/hexanes); ^1H NMR (mixture of two rotamers and *E*/*Z* isomers) δ 1.05, 1.17 and 1.32 (s, 9 H, *t*-BuO), 1.4–2.4 (m, 7 H), 2.28 (s, 3 H, CH_3Ar), 2.63–2.90 (m, 2 H), 3.54 (s, 3 H, CH_3O), 4.3–4.5 (m, 2 H), 7.17 (m, 3 H, aromatic + NH), 7.67 (m, 2 H, aromatic); ^{13}C NMR δ 21.10, 21.69, 23.15, 23.27, 23.56, 24.07, 24.14, 25.31, 27.59, 27.72, 27.96, 28.32, 29.01, 30.84, 33.24, 46.08, 47.11, 47.15, 47.91, 51.52, 51.57, 51.66, 55.21, 57.42, 57.69, 57.75, 61.17, 80.13, 80.55, 80.93, 127.42, 127.66, 129.14, 129.21, 135.23, 135.33, 135.39, 143.56, 143.68, 152.47, 152.97, 162.87, 164.60, 165.33, 172.90, 173.08; IR ($CDCl_3$) 3700 (w), 3040 (m), 1735 (s), 1695 (s), 1410 (s) cm^{-1}. Anal. Calcd for $C_{22}H_{31}N_3O_6S$: C, 56.7; H, 6.7; N, 9.0. Found: C, 56.7; H, 6.7; N, 8.9.

(1*S*,5*R*)-9-(*tert*-Butoxycarbonyl)-5-(methoxycarbonyl)-9-azabicyclo[4.2.1]nonan-2-one (4-Tolylsulfonyl)hydrazone (14β) was prepared from **13β** in the same way as **14α** above, in quantitative yield: mp 134–136 °C (Et_2O/hexanes); ^1H NMR mixture of two rotamers and *E*/*Z* isomers) δ 1.14, 1.25 and 1.32 (s, 9 H, *t*-BuO), 1.15–2.5 (m, 8 H), 2.40 and 2.41 (s, 3 H, CH_3Ar), 2.83 and 2.98 (m, 1 H, H-3), 3.65 and 3.66 (s, 3 H, CH_3O), 4.45–5.00 (m, 2 H), 7.27 (m, 2 H, aromatic), 7.58 and 8.82 (br s, 1 H, NH), 7.82 (m, 2 H, aromatic); ^{13}C NMR δ 20.22, 20.62, 21.08, 21.14, 22.44, 23.37, 23.70, 27.10, 27.51, 27.67, 27.81, 27.89, 28.55, 28.76, 30.19, 30.96, 31.25, 33.87, 46.50, 47.01, 51.41, 51.70, 54.58, 55.61, 57.47, 57.71, 58.03, 60.11, 60.31, 61.66, 79.72, 80.22, 81.07, 127.48, 127.69, 127.86, 129.12, 129.58, 135.16, 135.43, 143.42, 152.59, 153.06, 153.79, 163.44, 164.63, 165.70, 165.76, 173.78, 174.10; IR ($CHCl_3$) 3700 (w), 3040 (m), 1735 (s), 1695 (s), 1410 (s) cm^{-1}. Anal. Calcd for $C_{22}H_{31}N_3O_6S$: C, 56.7; H, 6.7; N, 9.0. Found: C, 56.8; H, 6.8; N, 8.6.

(1*R*,2*R*)-9-(*tert*-Butoxycarbonyl)-2-(methoxycarbonyl)-9-azabicyclo[4.2.1]non-4-ene (15β). To a solution of **14β** (226 mg, 0.486 mmol) in toluene (20 mL) was added LiH (226 mg, 28.25 mmol). The resulting suspension was immersed in a preheated oil bath (120 °C), refluxed for 5 h, allowed to cool to room temperature, and slowly added to a cold (0 °C), vigorously stirred mixture of 1 M aqueous KH_2PO_4/CH_2Cl_2 (1/1, 50 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2×). The combined organic extracts were dried, filtered, and evaporated, and the residue was column chromatographed to give pure **15β** (56 mg, 41% yield) as a clear oil: ^1H NMR δ 1.42 (s, 9 H, *t*-BuO), 1.4–2.8 (m, 7 H), 3.70 (s, 3 H, CH_3O), 4.54 (m, 1 H, H-1), 4.71 (br s, 1 H, H-6), 5.60 (m, 2 H, H-4 and H-5); ^{13}C NMR δ 24.51, 28.25, 29.37, 33.98, 51.69, 54.33, 55.74, 57.90, 79.81, 124.95, 132.32, 153.48, 173.96; IR (film) 2990 (m), 1740 (s), 1700 (s), 1420 (s) cm^{-1}. Anal. Calcd for $C_{15}H_{23}NO_4$: C, 64.0; H, 8.3; N, 5.0. Found: C, 63.7; H, 8.2; N, 4.7.

In a similar experiment using NaH as the base and starting with hydrazone **14α**, **15α** was obtained in 40% yield along with **15β** and **16**.

15α: ^1H NMR (two rotamers) δ 1.41 and 1.45 (9 H, s, *t*-BuO), 1.6–2.6 (m, 6 H), 3.00 and 3.12 (m, 1 H, H-2), 3.64 and 3.66 (s, 3 H, CH_3O), 4.25–4.62 (m, 2 H, H-1 and H-6), 5.58 (m, 1 H, H-4), 5.96 (m, 1 H, H-5); ^{13}C NMR δ 24.92, 25.81, 25.86, 25.93, 28.42, 28.50, 30.89, 31.51, 44.41, 46.28, 51.69, 51.76, 54.76, 55.02, 57.09, 57.15, 79.45, 79.63, 126.70, 126.94, 135.72, 136.07, 152.80, 152.96, 173.37, 174.11; IR (film) 2990 (m), 1740 (s), 1700 (s), 1420 (s) cm^{-1}. Anal. Calcd for $C_{15}H_{23}NO_4$: C, 64.0; H, 8.3; N, 5.0. Found: C, 63.7; H, 8.2; N, 4.7.

(1*S*,2*R*,5*R*)- and (1*S*,2*S*,5*R*)-9-(*tert*-Butoxycarbonyl)-2-hydroxy-5-(methoxycarbonyl)-9-azabicyclo[4.2.1]nonane (23). Sodium borohydride (98%, 38 mg, 0.98 mmol, 54 mol %) was added to a −15 °C solution of keto ester **13α** (539 mg, 1.81 mmol) in CH_3OH (10 mL). After 30 min, acetone (2 mL) was added, the cooling bath was removed, the mixture was allowed to come to room temperature, saturated $NaHCO_3$ (15 mL) was added, and most of the CH_3OH was evaporated. The resulting aqueous solution was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic phase was washed with brine, dried, filtered, and evaporated, and the residue was purified by LPC (1/3 to 1/1 EtOAc/hexanes) to give the less polar epimer (1*S*,2*R*,5*R*)-**23** (143 mg) followed by the more polar epimer (1*S*,2*S*,5*R*)-**23** (396 mg, 99% combined yield) as clear, foamy oils.

(1*S*,2*R*,5*R*)-23: TLC (EtOAc/hexanes, 1/1) R_f 0.38; $[\alpha]^{23}_D$ −57.9° (*c* 0.9, $CHCl_3$); IR (film) 3440, 2930, 1720, 1660 cm^{-1}; ^1H NMR (two rotamers, 4/1) δ 1.24–1.55 (m, 1 H), 1.51 (s, 9 H, *t*-BuO), 1.57–1.74 (m, 3 H), 1.85–2.18 (m, 3 H), 2.25–2.38 (m, 1 H), 2.65 (br d, 0.2 H, J = 8.7, OH), 2.89 (dt, 0.8 H, J = 4.4, 5.2, H-5β), 3.06 (dt, 0.2 H, J = 4.9, 5.1, H-5β), 3.62–3.78 (m, 1 H, H-2α), 3.67 (s, 0.6 H, OCH_3), 3.69 (s, 2.4 H, OCH_3), 4.14 (d, 0.8 H, J = 9.2, OH), 4.26 (br d, 0.2 H, J = 9.8, H-1), 4.38 (dd, 0.8 H, J = 2.7, 10.9, H-1), 4.51 (dd, 0.8 H, J = 4.5, 8.4, H-6), 4.68 (dd, 0.2 H, H-6); ^{13}C NMR major rotamer δ 20.68 (2), 25.63 (2), 28.32 (3 C, *t*-BuO), 28.86 (2), 32.42 (2), 48.41 (1, C-5), 51.67 (3, C-11), 57.66 (1, C-6 or C-1), 62.81 (1, C-1 or C-6), 77.85 (1, C-2), 80.53 (0, C-13), 156.00 (0, C-12), 173.39 (0, C-10); minor rotamer δ 20.48 (2), 24.60 (2), 28.38 (3 C, *t*-BuO), 30.12 (2), 32.39 (2), 46.99 (1, C-5), 51.54 (3, C-11), 57.34 (1, C-6 or C-1), 62.98 (1, C-1 or C-6), 78.09 (1, C-2), 80.95 (0, C-13), 152.99 (0, C-11), 173.56 (0, C-10). Anal. Calcd for $C_{15}H_{25}NO_5$: C, 60.2; H, 8.4; N, 4.7. Found: C, 60.0; H, 8.7; N, 4.8.

(1*S*,2*S*,5*R*)-23: TLC (EtOAc/hexanes, 1/1) R_f 0.31; $[\alpha]^{23}_D$ −4.0° (*c* 0.9, $CHCl_3$): IR (film) 3420, 2940, 1720, 1665 cm^{-1}; ^1H NMR (two rotamers, 5/4) δ 1.40–1.92 (m, 5 H), 1.47 (s, 9 H, *t*-BuO), 2.02–2.25 (m, 3 H), 2.37–2.43, 2.87–2.96 (br s, 1 H, OH), 3.14 (dt, 0.56 H, J = 4.0, 6.4, H-5β), 3.29 (0, 0.44 H, J = 6.0, 11.2, H-5β), 3.67, 3.69 (s, 3 H, OCH_3), 3.98–4.11 (m, 1 H, H-2β), 4.22 (dd, 0.44 H, J = 5.8, 7.9, H-1), 4.32 (dd, 0.56 H, J = 5.2, 8.2, H-1), 4.49 (ddd, 0.56 H, J = 3.0, 6.6, 9.4, H-6), 4.60 (ddd, 0.44 H, J = 2.7, 6.4, 9.9, H-6); ^{13}C NMR major rotamer δ 21.22 (2), 21.79 (2), 28.17 (2), 28.38 (3 C, *t*-BuO), 29.93 (2), 46.59 (1, C-5), 51.54 (3, C-11), 55.75 (1, C-6 or C-1), 60.02 (1, C-1 or C-6), 70.26 (1, C-2), 79.82 (0, C-13), 153.18 (0, C-12), 174.43 (0, C-10); minor rotamer δ 20.95 (2), 22.59 (2), 27.01 (2), 28.38 (3 C, *t*-BuO), 30.74 (2), 45.71 (1, C-5), 51.49 (3, C-11), 55.75 (1, C-6 or C-1), 59.91 (1, C-1 or C-6), 71.19 (1, C-2), 79.55 (0, C-13), 153.08 (0, C-12), 174.18 (0, C-10). Anal. Calcd for $C_{15}H_{25}NO_5$: C, 60.2; H, 8.4; N, 4.7. Found: C, 59.8; H, 8.5; N, 4.8.

(1*S*,2*R*,5*S*)- and (1*S*,2*S*,5*S*)-9-(*tert*-Butoxycarbonyl)-2-hydroxy-5-(methoxycarbonyl)-9-azabicyclo[4.2.1]nonane (23). The 5β-keto ester **13β** (378 mg) was reduced with $NaBH_4$ (27 mg) in MeOH (10 mL) in the same manner as described above for **13α** to give, after LPC (1/4 to 1/1 EtOAc/hexanes), the hydroxy esters (1*S*,2*R*,5*S*)-**23** (161 mg) and (1*S*,2*S*,5*S*)-**23** (197 mg, 94% combined yield) as white solids.

(1*S*,2*R*,5*S*)-23: mp 75–76 °C; TLC (EtOAc/hexanes, 1/1) R_f 0.29; $[\alpha]^{24}_D$ −44° (*c* 0.5, CH_2Cl_2); IR (CH_2Cl_2) 3440, 2960, 1730, 1670 cm^{-1}; ^1H NMR δ 1.4–1.6 (m, 2 H), 1.44 (s, 9 H, *t*-BuO), 1.62–1.80 (m, 2 H), 1.91–2.21 (m, 3 H), 2.30–2.50 (m, 2 H), 3.72 (s, 3 H, CH_3O), 3.78–3.88 (m, 1 H, H-2), 4.31 (br d, 1 H, J = 4.5, OH), 4.50 (br d, 1 H, J = 8.7, H-1), 4.62 (br d, 1 H, J = 9.1, H-6); ^{13}C NMR δ 19.97 (2), 25.62 (2), 28.00 (3, 3 C, C-14), 29.48 (2), 34.00 (2), 51.56 (3, C-11), 52.73 (1), 56.80 (1), 61.41 (1), 73.80 (1, C-2), 80.77 (0, C-13), 156.45 (0, C-12), 174.23 (0, C-10). Anal. Calcd for $C_{15}H_{25}NO_5$: C, 60.2; H, 8.4; N, 4.7. Found: C, 60.0; H, 8.5; N, 4.5.

(1*S*,2*S*,5*S*)-23: mp 105–106 °C; TLC (EtOAc/hexanes, 1/1) R_f 0.20; $[\alpha]^{24}_D$ −24.1° (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2) 3450, 2990, 1735,

1685 cm^{-1}; ^1H NMR (two rotamers, 6/1) δ 1.24–1.58 (m, 5 H), 1.40, 1.45 (s, 9 H, *t*-BuO), 1.66–1.80 (m, 1 H), 1.82–2.08 (m, 3 H), 2.32–2.50 (m, 2 H), 3.69, 3.72 (s, 3 H, CH_3O), 3.87–3.95, 3.98–4.05 (m, 1 H), 4.15–4.22, 4.30–4.38 (m, 1 H), 4.53, 4.68 (br d, 1 H, J = 9.2); ^{13}C NMR (major rotamer) δ 20.67 (2), 21.94 (2), 28.11 (3, 3 C, C-14), 29.61 (2), 34.94 (2), 51.51 (3, C-11), 52.58 (1), 55.94 (1), 60.24 (1), 69.43 (1, C-2), 80.02 (0, C-13), 153.49 (0, C-12), 174.35 (0, C-10); (minor rotamer, partial list) δ 21.69 (2), 21.83 (2), 28.27 (3, 3 C), 51.75 (3, C-11), 56.03 (1), 60.13 (1), 71.03 (1), 79.5 (0, C-13). Anal. Calcd for $C_{15}H_{25}NO_5$: C, 60.2; H, 8.4; N, 4.7. Found: C, 60.0; H, 8.4; N, 5.0.

(1*S*,2*R*,5*R*)- and (1*S*,2*R*,5*S*)-9-(*tert*-Butoxycarbonyl)-2-chloro-5-(methoxycarbonyl)-9-azabicyclo[4.2.1]nonane (24a). Phosphorus oxychloride (0.22 mL, 2.32 mmol, 500 mol %) was added to a 0 °C solution of hydroxy ester (1*S*,2*S*,5*R*)-**23** (139 mg, 0.464 mmol) in pyridine (2 mL). The mixture was stirred at 0 °C for 40 min and then at room temperature overnight. After cooling to 0 °C, ice (2 g) was added, and the mixture was poured into cold 1 M HCl (10 mL) and extracted with CH_2Cl_2 (3 × 8 mL). The combined organic phase was washed with saturated $NaHCO_3$ (10 mL), dried, filtered, and evaporated to a yellow oil that was purified by column chromatography (1/9 to 1/4 EtOAc/hexanes) to give pure chloride (1*S*,2*R*,5*R*)-**24a** (106 mg, 72%) as a clear oil: TLC (EtOAc/hexanes, 1/3) R_f 0.39; ^1H NMR (two rotamers, 6/5) δ 1.47 (s, 9 H, *t*-BuO), 1.60–1.90 (m, 4 H), 2.07–2.27 (m, 3 H), 2.36 (br d, 1 H, J = 17.6), 2.77–2.88 (m, 1 H, H-5β), 3.69, 3.72 (s, 3 H, H-11), 4.09–4.17 (m, 1 H, H-2α), 4.18–4.22, 4.33–4.37, 4.39–4.42, 4.53–4.58 (m, 2 H, H-1 and H-6); ^{13}C NMR major rotamer δ 21.95 (2), 22.34 (2), 26.49 (2), 28.35 (3, 3 C, C-14), 31.40 (2), 44.12 (1), 45.46 (1), 51.22 (1), 51.73 (3, C-11), 58.51 (1), 80.41 (0, C-13), 153.59 (0, C-12), 173.35 (0, C-10); minor rotamer δ 21.95 (2), 22.11 (2), 26.97 (2), 28.35 (3, 3C, C-14), 31.40 (2), 44.65 (1), 47.09 (1), 49.47 (1), 51.73 (3, C-11), 58.01 (1), 80.3 (0, C-13), 153.59 (0, C-12), 173.35 (0, C-10). Anal. Calcd for $C_{15}H_{24}NO_4Cl$: C, 56.7; H, 7.6; N, 4.4. Found: C, 56.9; H, 7.9; N, 4.3.

In the same manner as described above, treatment of (1*S*,2*S*,5*S*)-**23** with $POCl_3$ gave the chloro ester (1*S*,2*R*,5*S*)-**24a** in 89% yield: ^1H NMR (two rotamers, 3/2 ratio) δ 1.45 (s, 9 H, *t*-BuO), 1.6–2.3 (m, 8 H), 2.45–2.60 (m, 1 H), 3.68, 3.70 (s, 3 H, CH_3O), 4.05–4.15 (m, 1 H), 4.25–4.35, 4.4–4.5 (m, 1 H), 4.6–4.75 (m, 1 H).

(1*S*,2*S*,5*R*)-, (1*S*,2*R*,5*R*)-, (1*S*,2*S*,5*S*)-, and (1*S*,2*R*,5*S*)-9-(*tert*-Butoxycarbonyl)-2-iodo-5-(methoxycarbonyl)-9-azabicyclo[4.2.1]nonane (24b). A solution of hydroxy esters **23** (567 mg, 1.89 mmol) in toluene (4 mL) was added to a mixture of triphenylphosphine (621 mg, 2.37 mmol, 125 mol %), imidazole (516 mg, 7.57 mmol, 400 mol %), and iodine (625 mg, 2.46 mmol, 130 mol %) in toluene (15 mL). The resulting mixture was heated at reflux for 20 min, cooled to room temperature, diluted with EtOAc (15 mL), and washed with 10% Na_2CO_3, 1/1 saturated Na_2SO_3/1 N, NaOH, and brine (30 mL each). The separate aqueous layers were back-extracted with EtOAc (2 × 15 mL). The combined organic phase was dried, filtered, and evaporated to a white solid that was purified by LPC (1/9 EtOAc/hexanes) to give a mixture of iodo esters **24b** (636 mg, 82% yield).

In separate experiments, the individual diastereomeric alcohols **23** were converted to the iodo esters **24b** as described above.

(1*S*,2*S*,5*R*)-24b: 82% yield; mp 119–120 °C; ^1H NMR (two rotamers, 1/1) δ 1.30–1.57 (m, 2 H), 1.48 (s, 9 H, *t*-BuO), 1.58–1.73 (m, 1 H), 1.94–2.13, 2.14–2.35 (m, 5 H), 3.24 (ddd, 0.5 H, J = 2.4, 7.2, 9.3, H-5β), 3.42 (ddd, 0.5 H, J = 2.7, 7.1, 9.6, H-5β), 3.68, 3.70 (s, 3 H, H-11), 4.32–4.40, 4.41–4.51, 4.53–4.62, 4.64–4.73 (m, 3 H, H-1, H-2β, H-6); ^{13}C NMR (two rotamers, 1/1) δ 26.35 (2), 27.07 (2), 27.11 (2), 27.28 (2), 27.96 (2), 28.41 (3, 3 C, C-14), 28.93 (2), 33.94 (1, C-2), 34.23 (2), 34.62 (1, C-2), 45.21 (1, C-5), 46.36 (1, C-5), 51.61 (3, C-11), 51.66 (3, C-11), 56.31 (1, C-6 or C-1), 56.41 (1, C-6 or C-1), 62.67 (1, C-1 or C-6), 63.02 (1, C-1 or C-6), 80.20 (0, C-13), 152.73 (0, C-12), 152.81 (0, C-12), 173.95 (0, C-10), 174.22 (0, C-10). Anal. Calcd for $C_{15}H_{24}INO_4$: C, 44.0; H, 5.9; N, 3.4. Found: C, 44.3; H, 6.0; N, 3.3.

(1*S*,2*R*,5*R*)-24b: 87% yield; clear oil; ^1H NMR (two rotamers, 1/1) δ 1.48 (s, 9 H, H-14), 1.53–1.93 (m, 3 H), 1.95–2.35 (m, 3 H), 2.54–2.67 (m, 2 H), 2.75–2.93 (m, 1 H, H-5β), 3.69, 3.72 (s, 3 H, H-11), 4.19–4.30, 4.33–4.52, 4.60–4.70 (m, 3 H, H-1, H-2α, H-6); ^{13}C NMR (two rotamers, 1/1) δ 21.81 (2), 21.96 (2), 24.76 (2), 25.04 (2), 28.30 (3, C-14), 28.35 (3, C-14), 28.70 (2), 29.15 (2), 29.76 (1, C-2), 30.20 (1, C-2), 34.36 (2), 44.11 (1, C-5?), 44.63 (1, C-5?), 45.48 (1, C-6 or C-1), 47.13 (1, C-6 or C-1), 50.23 (1, C-1 or C-6), 51.70 (3, C-11), 51.82 (3, C-11), 52.11 (1, C-1 or C-6), 80.31 (0, C-13), 80.36 (0, C-13), 153.25 (0, C-12), 173.21 (0, C-10). Anal. Calcd for $C_{15}H_{24}INO_4$: C, 44.0; H, 5.9; N, 3.4. Found: C, 44.0; H, 6.0; N, 3.4.

(1*S*,2*S*,5*S*)-24b: 67% yield; clear oil; ^1H NMR δ 1.41 (s, 9 H, *t*-BuO), 1.4–2.65 (m, 9 H), 3.70 (s, 3 H, CH_3O), 4.28–4.45 (m, 1 H), 4.48, 4.50 (t, 1 H, J = 4.0), 4.64 (br d, 1 H, J = 8); ^{13}C NMR δ 24.15 (2), 28.13 (3, 3 C, C-14), 28.43 (2), 32.53 (1, C-2), 34.84 (2), 35.28 (2), 51.76 (3, C-11), 52.76 (1, C-5), 57.04 (1), 62.38 (1), 80.38 (0, C-13), 153.06 (0, C-12), 173.96 (0, C-10). Anal. Calcd for $C_{15}H_{24}INO_4$: C, 44.0; H, 5.9; N, 3.4. Found: C, 44.0; H, 5.9; N, 3.2.

(1*S*,2*R*,5*S*)-24b: 87% yield; clear oil; ^1H NMR (two rotamers, 2/1) δ 1.39 (s, 9 H, *t*-BuO), 1.55–2.58 (m, 9 H), 3.62, 3.65 (s, 3 H, CH_3O), 4.21–4.49 (m, 2 H), 4.64–4.68, 4.70–4.76 (m, 1 H); ^{13}C NMR (major rotamer) δ 21.08 (2), 22.18 (2), 28.17 (3, 3 C, C-14), 30.17 (1, C-2), 31.77 (2), 32.87 (2), 43.24 (1), 47.44 (1), 49.78 (1, C-5), 51.66 (3, C-11), 79.91 (0, C-13), 153.54 (0, C-12), 174.10 (0, C-10); (minor rotamer) δ 20.97 (2), 22.18 (2), 28.17 (3, 3 C, C-14), 30.75 (1, C-2), 32.35 (2), 32.43 (2), 42.76 (1), 46.01 (1), 51.76 (1, C-5), 51.85 (3, C-11), 80.05 (0, C-13), 153.42 (0, C-12), 173.83 (0, C-10). Anal. Calcd for $C_{15}H_{24}INO_4$: C, 44.0; H, 5.9; N, 3.4. Found: C, 43.8; H, 6.0; N, 3.4.

Hydrolysis of the Iodo Esters. (1*S*,2*S*,5*R*)-, (1*S*,2*R*,5*R*)-, (1*S*,2*S*,5*S*)-, and (1*S*,2*R*,5*S*)-9-(*tert*-Butoxycarbonyl)-5-carboxy-2-iodo-9-azabicyclo[4.2.1]nonane. A solution of KOH (872 mg, 15.5 mmol, 1000 mol %) in H_2O (5 mL) was added to a solution of iodo esters **24b** (636 mg, 1.55 mmol) in methanol (15 mL). After the mixture was stirred at room temperature overnight (14 h), most of the solvent was evaporated, and the residue was diluted with brine (30 mL) and extracted with Et_2O (2 × 15 mL). The aqueous layer was diluted with CH_2Cl_2 (20 mL), chilled in an ice bath (4 °C), and adjusted to pH 3.2 with 7 M H_3PO_4. The aqueous layer was extracted with $CHCl_3$ (3 × 10 mL), and the combined organic phase was dried, filtered, and evaporated to give the iodo acids (all four isomers; 610 mg, 99%) as a foamy white solid. An analytical sample of this epimeric mixture was prepared by column chromatography (EtOAc/hexanes). Anal. Calcd for $C_{14}H_{21}NO_4I$: C, 42.6; H, 5.6; N, 3.5. Found: C, 43.0; H, 5.6; N, 3.5.

Dehydrohalogenation of the Iodo Acids. (1*R*,2*R*)- and (1*R*,2*S*)-9-(*tert*-Butoxycarbonyl)-2-carboxy-9-azabicyclo-[4.2.1]non-4-ene (17) and (1*R*,2*R*)- and (1*R*,2*S*)-9-(*tert*-Butoxycarbonyl)-2-carboxy-9-azabicyclo[4.2.1]non-3-ene (19, R = OH). Solid potassium *tert*-butoxide (sublimed; 298 mg, 2.66 mmol, 350 mol %) was added to a solution of the iodo acids (300 mg, 0.76 mmol) in *N*,*N*-dimethylacetamide (DMA, 7.5 mL). The resulting solution was heated at 125 °C for 3 h, cooled to room temperature, diluted with Et_2O (10 mL), and extracted with 1 N NaOH (10 mL). The aqueous layer was extracted with Et_2O (10 mL), and the combined organic layer was washed with 1 N NaOH (10 mL). To the combined basic aqueous layers was added $CHCl_3$ (10 mL), and the resulting mixture was chilled in an ice bath and adjusted to pH 3.5 with 7 M H_3PO_4. The aqueous layer was again extracted with $CHCl_3$ (4 × 10 mL), the combined organic phase was dried, filtered, and evaporated, and residual DMA was removed by heating at 50 °C in a Kugelrohr apparatus for 2 h to give a yellow oil (202 mg) that was purified by column chromatography (1/3 to 1/1 EtOAc/hexanes) to give a mixture of olefinic acids **17** and **19** (R = OH) (148 mg, 73%) as a clear oil: ^1H NMR (mixture of double bond isomers, both epimers at C-2) δ 1.2–2.2 (m, 5 H), 1.43 and 1.45 and 1.47 (s, 9 H, *t*-BuO), 2.41–2.58 (m, 1 H), 2.62–2.76 (m, ca. 1 H), 2.98–3.04 and 3.11–3.18 (m, H-2β), 4.55 and 4.68 (br s, 1 H), 4.81 (dist t) and 4.91 (br d) (1 H total), 5.56–5.74 (m, 1 H, H-4), 5.92 (dist t) and 5.96–6.08 (m) (1 H total, H-5); ^{13}C NMR (mixture of double bond isomers, both epimers at C-2) δ 17.27 (2), 17.89 (2), 18.93 (2), 19.72 (2), 24.10 (2), 25.13 (2), 25.61 (2), 25.75 (2), 26.23 (2), 26.48 (2), 27.48 (2), 27.94 (2), 28.19 (3, 3 C), 28.34 (3, 3 C), 28.44 (3, 3 C), 30.87 (2), 31.33 (2), 45.57 (1), 45.82 (1), 45.96 (1), 46.37 (1), 47.41 (1), 54.61 (1), 55.15 (1), 56.82 (1), 57.11 (1), 79.78 (0), 79.95 (0), 126.42 (1), 126.53 (1), 126.63 (1), 127.13 (1), 127.23 (1), 127.72 (1), 135.83 (1), 153.92 (0), 177.86 (0), 178.18 (0). Anal. Calcd for $C_{14}H_{21}NO_4$: C, 62.9; H,

7.9; N, 5.2. Found: C, 62.7; H, 7.9; N, 5.1.

(1*R*,2*R*)- and (1*R*,2*S*)-9-(*tert*-butoxycarbonyl)-2-(methoxycarbonyl)-9-azabicyclo[4.2.1]non-3-ene (19, R = OCH_3) were obtained (along with their respective γ,δ-unsaturated isomers) by treatment of the iodo acids with excess potassium *tert*-butoxide (300 mol %) in DMA (0.1 M) at 125 °C according to the dehydrohalogenation procedure described above. After 3 h the reaction mixtures were cooled to 0 °C, calcined K_2CO_3 (500 mol %) and iodomethane (300 mol %) were added, and stirring was continued at room temperature for 90 min. Aqueous workup followed by LPC (3/17 EtOAc/hexanes) gave **18** and **19** (R = OCH_3) in a combined 72% yield.

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Vinylphosphonium Salts: Stereoselective Palladium-Catalyzed Vinylation of Triphenylphosphine with Vinyl Triflates

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The reaction of vinyl triflates with a slight excess of triphenylphosphine and 1–3 mol % $Pd(PPh_3)_4$ in refluxing THF results in the formation of the corresponding vinyltriphenylphosphonium triflate salts in good yield. A wide variety of salts, including cyclic ones, can be prepared. Unlike past syntheses of these compounds, pure stereoisomeric starting triflates stereoselectively yield stereoisomeric products. The current synthesis is especially useful for the preparation of *Z* isomers.

Vinylphosphonium salts[1–3] are useful for cycloadditions,[4–8] for Michael additions, for the synthesis of heterocyclic compounds,[9–12] and as reagents in a variety of other transformations.[13,14] Unfortunately, the syntheses of vinylphosphonium salts have been limited to mixtures of isomers, or at best the *E* isomers, exclusively.[15] As a result, studies of the Michael additions and, more importantly, [2 + 4] cycloaddition[4] reactions have only been carried out to a very limited degree and most extensively with the parent salt (vinyltriphenylphosphonium bromide), available commercially as Schweizer's reagent.[16]

Previously used syntheses include additions of triphenylphosphine to allyl bromide followed by base-catalyzed prototropic rearrangement,[9] additions to alkynylphosphonium salts,[11] and, most recently, the oxidative elimination of phenyl selenoxide from cyclic alkyl phenyl selenides.[5] As we recently reported in preliminary form, a wide variety of vinylphosphonium salts can now be synthesized stereoselectively by the palladium-catalyzed coupling of vinyl triflates with triphenylphosphine.[17] The most beneficial aspect of this synthesis is that the previously unavailable *Z* isomers of the salts can be obtained in good yield. Herein we report the full details of this novel, new synthesis of vinylphosphonium species.

Results and Discussion

Attempts to synthesize stable (σ-vinyl)palladium(II) species using vinyl triflates and tetrakis(triphenylphosphine)palladium(0) resulted in the formation of the vinylphosphonium salts as the only isolable organic species. It was then established that this reaction could be carried out with catalytic quantities of palladium(0).

Interaction of vinyl triflates[18] **1–5** with a slight excess of triphenylphosphine and 1–3 mol % of tetrakis(triphenylphosphine)palladium(0) in refluxing THF resulted in the corresponding vinylphosphonium salts **6–10** in 62–90% isolated yields (eq 1). Reaction of triflate **1** with 1.05 equiv of PPh_3 and 3 mol % $Pd(PPh_3)_4$ at 66 °C for 6 h gave **6** in 89% isolated yield. Crystallization of salts **6**, **8**, and **9** is rapid upon addition of hexanes or pentane, whereas compounds **7** and **10** crystallized only after extended periods of time at low temperatures. Passing the crude solutions through a plug of unactivated florisil before adding the alkanes facilitates crystallization. Alternatively,

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