1058 *J. Org. Chem.* **1994**, *59*, 1058–1066

Conformationally Constrained Analogues of Anatoxin. Chirospecific Synthesis of *s-Trans* Carbonyl Ring-Fused Analogues

Andres Hernandez and Henry Rapoport*

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

Received October 14, 1993[●]

Anatoxin is the most potent agonist known for the nicotinic acetylcholine receptor (nAChR). Although it possesses a semirigid structure, it can adopt four distinctly different conformations. Further conformationally constrained analogues of anatoxin should help to refine and discriminate among the current models for activation of this receptor. This report describes three *s-trans* ring-fused analogues which have been synthesized starting from D-glutamic acid and 3-hydroxyacetophenone. All of them have in common a 3-oxo-13-azatricyclo[8.2.1.0^{2,7}]tridecane structure. They represent the first fully constrained analogues of anatoxin and are designed to serve as probes of the bioactive conformation of anatoxin at the acetylcholine nicotinic receptor site.

Introduction

Determination of the bioactive conformation of acetylcholine at the cholinergic receptor would make the receptor map more precise and could shed considerable light on the poorly understood interactions necessary for inducing ion channel opening.[1] Inspection of various nicotinic acetylcholine agonists prompted the proposal[2] of a model for activation of the nicotinic acetylcholine receptor (nAChR).[3] Subsequently this model has been refined to account for the observed stereodiscrimination at the receptor site.[4]

The design and synthesis of conformationally constrained analogues should help to determine the bioactive conformation at the receptor.[5] Along these lines, important efforts have been made in the nicotine area: three fused nicotines **1**, **2**,[6] **3**[7] and the bridged nicotinoids **4**, **5**[8] have been synthesized.

(±)-Pyrido[3,4-*b*]homotropane (PHT, **4**) is the first bridged nicotinoid with bioactivity equaling or surpassing that of the conformationally free parent nornicotine (**6**).[8a] PHT (**4**) mimics the frozen conformation of nornicotine (**6**) in which the pyrrolidine nitrogen and a hydrogen bond acceptor (pyridine nitrogen lone pair) are in the same spatial orientation as that found in the *s-cis* conformation **8a** of anatoxin. However, for anatoxin (**8**), the H-bond acceptor is the distal lone pair on the carbonyl oxygen of *s-cis*-anatoxin (**8a**).

The semirigid alkaloid anatoxin (**8**) is the most potent agonist known for the nicotinic acetylcholine receptor.[9] It is also one of a very small number of chiral nicotinic agonists.[10] The prototype nicotinic agonist, naturally occurring (*S*)-(−)-nicotine (**7**), is approximately equipotent[11] with its enantiomer. However, this equipotency may be due to the relatively flat structure of nicotine (**7**). The large (>150-fold)[9a] difference between naturally occurring (+)-anatoxin (**8**) and its synthetic (−)-enantiomer provides strong evidence that a high level of stereodiscrimination is exhibited by the nAChR.[4b]

Conformational analysis of (+)-anatoxin based on high-field NMR spectroscopy, X-ray crystallography of **8**·HCl, and force-field calculations have been accomplished.[9b] The *s-trans* conformer **8b** is observed in the solid state, and NMR analysis shows that *s-cis* and *s-trans* conformations are present at room temperature in solution. Molecular mechanics calculations show that an *s-cis* enone-conformer **8a** is the one that has the minimum energy. The conformational energy difference between this conformer and the energetically closest one (an *s-trans* conformer **8b**) is 3.1 kJ mol^{-1}. Also, the conformer **8a** leads to a 6.0 Å distance between the bridging nitrogen atom and the Van der Waals surface of the enone carbonyl oxygen atom, which is in very good agreement with the Beers and Reich model.[2]

The conclusions from these conformational studies and the fact that PHT (**4**) is a potent nicotinic agonist point to the *s-cis*-enone conformation of anatoxin (**8**) as the bioactive one at the receptor site. Contrary to this hypothesis there are at least two observations: (a) 2′-Me-PHT (**5**) is structurally more closely related to the *s-cis* conformer of anatoxin (**8a**) than PHT (**4**), but the incorporation of the methyl group results in a significant loss in activity; (b) the 1,3-diketone **9**, assumed to represent a probe for the *s-cis* conformer of anatoxin (**8a**) since this ligand would be expected to exist predominantly as the

---

[●] Abstract published in *Advance ACS Abstracts*, February 1, 1994.

(1) (a) Chothia, C.; Pauling, P. *Proc. Natl. Sci. U.S.A.* **1970**, *65*, 477. (b) Portoghese, P. S. *Ann. Rev. Pharmacol.* **1970**, *10*, 51. (c) Baker, R. W.; Pauling, P.; Petcher, T. J. *Nature* **1971**, *230*, 439.

(2) Beers, W. H.; Reich, E. *Nature* **1970**, *228*, 917.

(3) AChR activation is reviewed in: (a) Spivak, C. E.; Albuquerque, E. X. *Progress in Cholinergic Biology*: *Model Cholinergic Synapses*; Hanin, I., Goldberg, A. M., Eds.; Raven Press: New York, 1982; p 323 ff. (b) Maelicke, A. *Angew. Chem., Int. Ed. Engl.* **1984**, *32*, 195.

(4) (a) Spivak, C. E.; Waters, J.; Witkop, B.; Albuquerque, E. X. *Mol. Pharmacol.* **1983**, *32*, 337. (b) Witkop, B.; Brossi, A. *Natural Products and Drug Development*; Alfred Benzon Symposium 20; Krogsgaard-Larsen, P., Christiansen, S. B., Eds.; Munksgaard: Copenhagen, 1984; p 283 ff.

(5) (a) Cannon, J. G.; Rege, A. B.; Grunen, J. L. *J. Med. Chem.* **1970**, *15*, 71 and refs therein. (b) Low, S. J.; Morgan, J. M.; Masten, L. W.; Borne, R. F.; Arana, G. W.; Kula, N. S.; Baldessarini, R. J. *J. Med. Chem.* **1982**, *25*, 213. (c) Woodruff, G. N. *Trends Pharmacol. Sci.* **1982**, *3*, 59.

(6) Chavdarian, C. G.; Seeman, J. I.; Wooten, J. B. *J. Org. Chem.* **1983**, *48*, 492.

(7) Catka, T. E.; Leete, E. *J. Org. Chem.* **1978**, *43*, 2125.

(8) (a) Kanne, D. B.; Ashworth, D. J.; Cheng, M. T.; Mutter, L. C.; Abood, L. G. *J. Am. Chem. Soc.* **1986**, *108*, 7864. (b) Kanne, D. B.; Abood, L. G. *J. Med. Chem.* **1988**, *31*, 506.

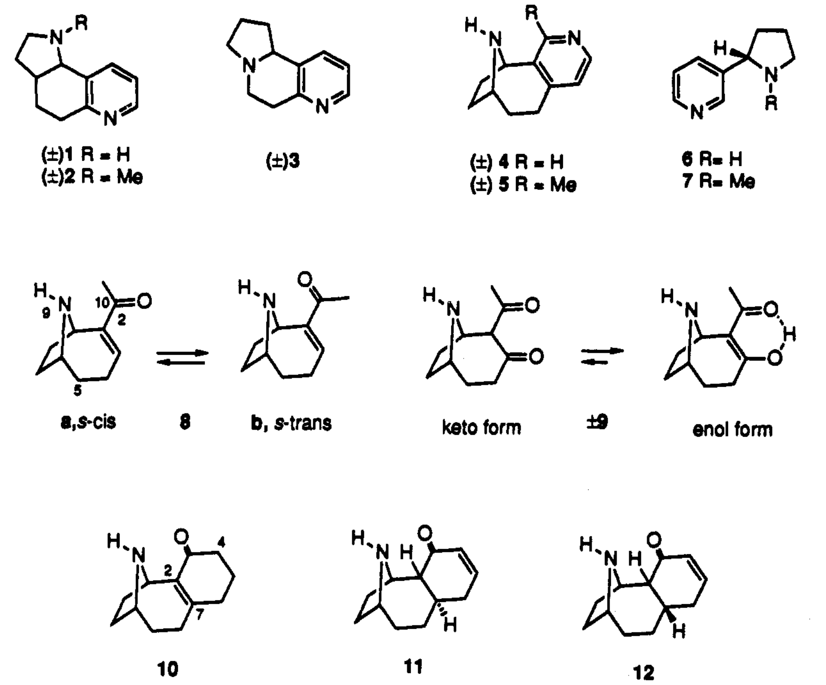
(9) (a) Swanson, K. L.; Allen, C. N.; Aronstam, R. S.; Rapoport, H.; Albuquerque, E. X. *Mol. Pharmacol.* **1986**, *29*, 250. (b) Koskinen, A. M. P.; Rapoport, H. *J. Med. Chem.* **1985**, *28*, 1301.

(10) Witkop, B. *Heterocycles* **1982**, *72*, 431.

(11) Arcava, Y.; Swanson, K. L.; Rozental, R.; Alburquerque, E. X. Structure-Activity Relationships of (+)-Anatoxin Derivates and Enantiomers of Nicotine on The Peripheral and Central Nicotinic Acetyl Receptor Subtypes. In *Neurotox'88*: *Molecular Basis of Drug and Pesticide Action*; Lunt, G. G., Ed.; Elsevier: Amsterdam, 1988; pp 157–184. (b) Swanson, K. L.; Arcava, Y.; Sardina, F. J.; Rapoport, H.; Aronstam, R. S.; Albuquerque, E. X. *Mol. Pharmacol.* **1989**, *35*, 223.

0022-3263/94/1959-1058$04.50/0

Chart 1



corresponding enol tautomer,[12] showed drastically diminished nicotinic potency; however, there are other significant modifications associated with **9**.

Recent computational studies[13] suggest that the *s-trans* chair conformation of **8**·H^+ is more stable (ΔE = 9.4 kJ mol^{-1}) than the corresponding *s-cis* conformer. A similar conclusion is reached by the Hacksell and Mellin model,[14] which uses "the active analogue approach" method and postulates a nicotinic-receptor-excluded volume constructed by superposition of the Van der Waals volumes of the *s-trans* conformation of (+)-anatoxin (**8b**), (−)-cytisine, and isoarecholone methiodide. The receptor-excluded volume map defines that region of the receptor active site available for binding by substrate, substrate analogues, or nonsubstrate analogues. When the *s-trans* conformation was used to model the receptor-excluded volume, a smaller volume was arrived at than the one found by using the *s-cis* conformation; this observation permitted rationalization of the enantioselective activity of anatoxin (**8**).

The design and synthesis of *s-trans* conformationally restricted analogues of anatoxin are the objectives of the present work. Rotation about the exocyclic C2–C10 bond can be restricted and the anatoxin structure can be frozen into the desired *s-trans* enone conformation by insertion of a two-carbon bridge between C-11 of the side chain and C-3 in the seven-membered ring to yield the novel ring-fused analogue **10**. A simple structural change in analogue **10**, that is to shift the enone double bond from the $\Delta^{2,7}$ to the $\Delta^{4,5}$ position in the six-membered ring results in unusual and interesting fused analogues **11** and **12**. The latter analogues are *s-trans* conformationally restricted ones as well, but the two new chirocenters (C-2 and C-7) introduced in their structures modify the distance between the bridging nitrogen and the enone carbonyl oxygen atom, relative to the same structural parameter exhibited by the analogue **10**.

We now report the chirospecific synthesis of these *s-trans* conformationally constrained anatoxin analogues **10**–**12** proceeding from D-glutamic acid and 3′-hydroxyacetophenone.

Results and Discussion

Our synthetic route to the ring-fused analogues **10**–**12** is similar to that successfully employed in the chirospecific synthesis[15] of anatoxin **8** and is shown in Scheme 1. We planned to build the bicyclic system by decarbonylation/intramolecular iminium salt cyclization of the corresponding keto acids. The basic skeleton and functionality of these keto acids are present in the alkylation/sulfur-extrusion[16] products produced from thiolactam **17** with a suitable bromo ketone **18** and/or **19**. The syntheses of (*R*)-1-benzyl-5-thioxoproline *tert*-butyl ester (**17**),[15] 2-bromo-1-(3′-methoxyphenyl)ethanone (**18**),[17] and 2-bromo-1-[3′-(benzyloxy)phenyl]ethanone (**19**)[18] have been reported previously; however, the procedure to prepare bromo ketone **19** required significant modification in order to increase the yield and simplify the isolation for multigram scale reactions. From benzyl ether **15**, prepared in quantitative yield from 3′-hydroxyacetophenone (**14**) by treatment with benzyl bromide/K_2CO_3/CH_3CN at rt, direct bromination afforded at best a 70% yield of phenacyl bromide **19**. Enolization of ketone **15** and trapping of the generated enol by refluxing in isopropenyl acetate by addition of p-TsOH as catalyst provided a 24/1 enol acetate **16**/ketone **15** mixture. Bromination of the latter mixture with pyridinium perbromide provided phenacyl bromide

---

[12] Brough, A. P.; Gallagher, T.; Thomas, P.; Wonnacott, S.; Baker, R.; AbdulMalik. K. M.; Hursthouse, M. B. *J. Chem. Soc., Chem. Commun.* **1992**, 1087.

[13] Thompson, P.; Manallach, D. T.; Blaney, F. E.; Gallagher, T. *J. Comput. Aided Mol. Des.* **1992**, 287.

[14] Hacksell, U.; Mellin, C. *Prog. Brain Res.* **1989**, *79*, 95.

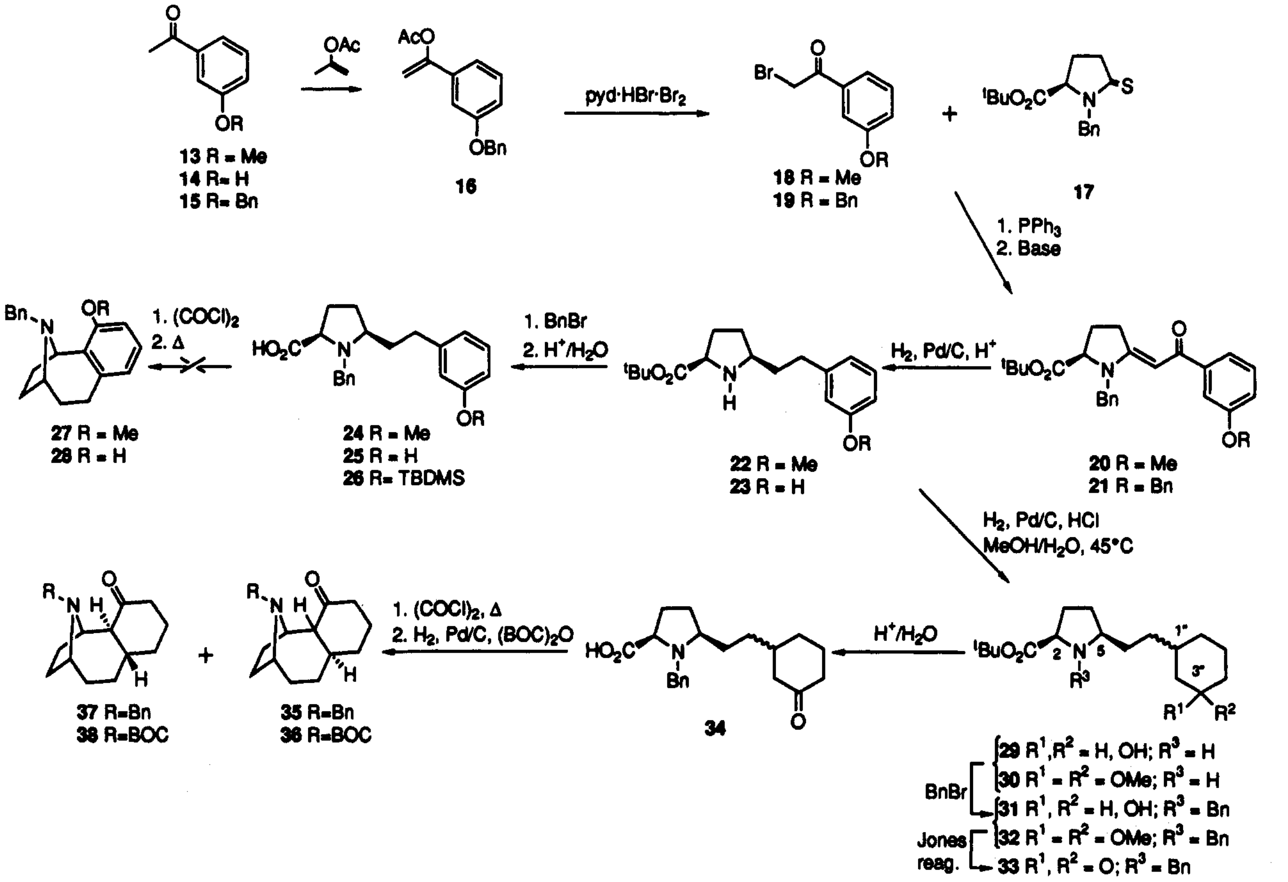
[15] Petersen, J. S.; Fels, G.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 4539, and ref 4a therein.

[16] Shiosaki, K.; Fels, G2., Rapoport, H. *J. Org. Chem.* **1981**, *46*, 3230 and refs. 12–15 therein.

[17] Fuchs, R. *J. Am. Chem. Soc.* **1956**, *78*, 5612.

[18] Fujii, T.; Ohba, M.; Tsuchida, M.; Saito, K.; Hirano, Y.; Sakaguchi, *J. Chem. Pharm. Bull.* **1986**, *34*, 496.

Scheme 1. Route to 3-Oxo-13-azatricyclo[8.2.1.0^{2,7}]tridecanes



19 in an 81% overall yield from the commercially available acetophenone 14. Our two-step procedure avoided overbromination and ether cleavage.

Alkylation of *R*-thiolactam 17 with methyl bromoacetate[15] and α-bromoketones[19] and subsequent sulfide contraction has been developed in detail. Following the same procedure *S*-alkylation of thiolactam 17 with phenacyl bromides 18 and 19 followed by sulfur extrusion provided vinylogous amides 20, 85% yield, and 21, 89% yield.

Hydrogenation of the carbon–carbon double bond, hydrogenolysis of both *N*- and *O*-benzyl protecting groups, and reduction of the aryl ketone to CH_2 was achieved by catalytic hydrogenation in a single reaction. The double-bond reduction is a very highly stereoselective process,[15] only *cis*-pyrrolidines 22 and 23 being formed in an 85% and 91% yield, respectively.[2]

N-Benzylation of crude proline 22 and subsequent acid hydrolysis gave the acid 24. This last acid was shown to smoothly decarbonylate[20] in good yield to the corresponding iminium ion by trapping via reduction with $NaBH_4$ and characterization as the corresponding pyrrolidine. No tricycle 27 was obtained from cyclization attempts of this iminium ion. Decarbonylation of the TBDMS ether 26, synthesized from phenolic acid 25, followed by refluxing in HCl/MeOH and reduction with $NaBH_4$ provided the related [(hydroxyphenyl)ethyl]pyrrolidine in 43% yield, but none of tricycle 28 or its regioisomer.

Hydrogenation of amino phenol 23 (10 or 30% Pd/C, 60 psi, 45 °C) led to complete aromatic ring reduction and formation of cyclohexanols 29 and dimethylketals 30. The *N*-benzylation ($BnBr/K_2CO_3$) of these crude products provided, after chromatography, the diastereomeric mixtures of cyclohexanols 31 (32% from 21) and dimethylketals 32 (5% from 21). Oxidation of cyclohexanols 31 yielded ketones 33 (77%) and acid hydrolysis of dimethylketals 32 afforded ketones 33 (94%) as well.

The synthetic procedure was simplified by performing the oxidation on the benzylation crude, under which conditions the dimethylketals 32 are hydrolyzed to ketones 33, to give a 1/1 diastereomeric mixture of ketones 33 in 34% overall yield from vinylogous amide 21. Hydrolysis (5/5/1, iPrOH/H_2O/AcOH) of the *tert*-butyl ester function provided the desired 1/1 diastereomeric mixture of keto acids 34 in 85% yield.

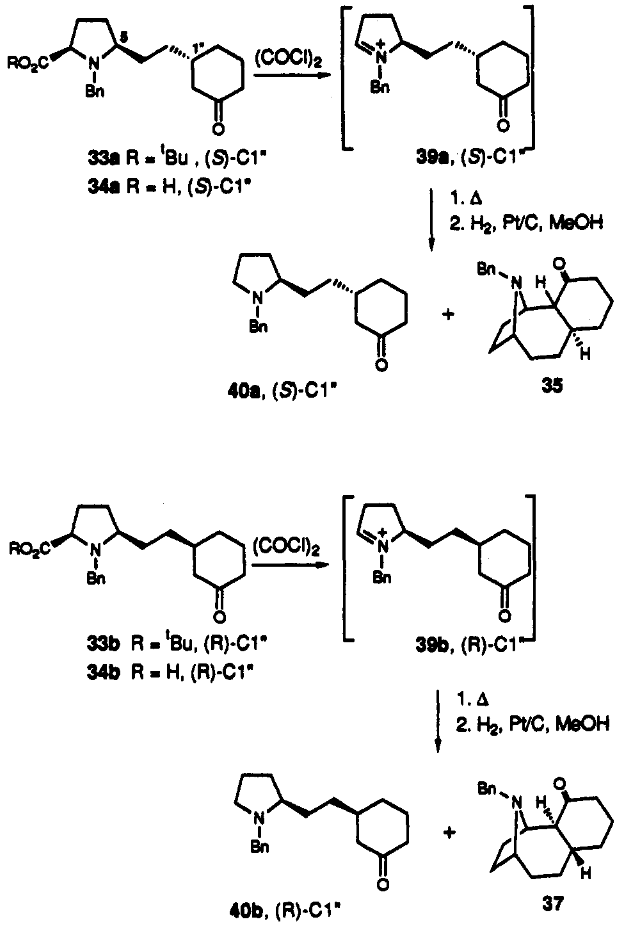
The decarbonylation cyclization of the 1/1 diastereomeric mixture of keto acids 34 using the previously reported conditions[20] afforded an 18% yield of a 1/2 mixture of tricyclic ketones 35 and 37, most of the reaction product being polymer. Other solvents were tried in an attempt to increase the yield by replacing toluene, and the best yield (35% yield, 2/3 diastereomeric mixture) was found when 1,2-dichloroethane (1,2-DCE) was used as diluting solvent. The addition of a nonpolar, protic solvent to 1,2-DCE improved the yield further. Thus by using a 6/1 mixture of 1,2-DCE/*tert*-BuOH, as diluting solvent the yield increased to 40% of a 2/3 mixture of tricyclic ketones 35 and 37. The stereochemistry of these ketones was established by an X-ray crystallographic structure determination, to be described below.

---

[19] Howard, M. H.; Sardina, F. J.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 2829.

[20] Sardina, J. F.; Howard, M. H.; Koskinen, A. M. P.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 4654.

Scheme 2. Iminium Ion Generation from Keto Acids 34a and 34b. Cyclization and Trapping of Uncyclized Intermediates



The fact that we obtained a low yield and only two diastereomeric tricycles, **35** and **37**, might suggest that one of the diastereomeric (prolylethyl)cyclohexanones **34** is not reacting to yield cyclization products. In order to test this possibility, separation of the 1/1 mixture of keto esters **33** was undertaken. By conventional chromatography, 9/1 mixtures (ratio determined by ^{1}H NMR) enriched in either one or the other diastereomer, **33a** or **33b**, were obtained and transformed into the corresponding enriched mixtures of keto acids **34a** or **34b**. Both mixtures were exposed to the cyclization conditions and each diastereomer, **34a** or **34b**, generated a different tricyclic ketone, **35** or **37**, respectively, as a single diastereomer (Scheme 2). Hydrogenation of the respective crudes from the cyclization reactions provided, in addition to the corresponding cyclizations products **35** or **37**, the pyrrolidines **40a** or **40b**. These experiments demonstrate that large amounts of uncyclized iminium salts, **39a** and **39b**, remain after the cyclization reaction which is an equilibrium process catalyzed by acid. On protonation of the carbonyl function of **35** or **37** these ketones could revert to the iminium salts, **39a** and **39b**. From these experiments, we conclude that (1) both diastereomers **34a** and **34b** provided cyclization products under decarbonylative-intramolecular iminium ion cyclization conditions; and (2) the cyclization reaction is highly stereoselective because each diastereomer, **34a** and **34b**, produces only one, and distinct tricyclic ketone, **35** and **37**, respectively. In the present example, the cyclizing enol moiety is part of a six-membered ring, while in the previous closely related cases it was in a chain.[20] The current lower yields can be explained by a more sterically demanding nucleophile disfavoring cyclization in the reversible closing/opening process.

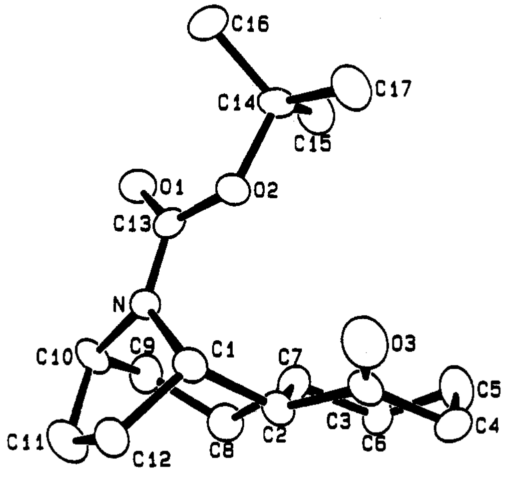


Figure 1. Structure of (1*S*,2*R*,7*S*,10*S*)-3-oxo-13-(*tert*-butoxycarbonyl)-13-azatricyclo[8.2.1.0^{2,7}]tridecane (*L*-38-enantiomer of 38) as determined by X-ray crystallography (arbitrary numbering system).

To establish absolute stereochemistry, we proceeded in one step[20] with removal of the *N*-benzyl group and reprotection as the *tert*-butyl carbamate (BOC) of the 2/3 mixture of tricylcic ketones **35** and **37**, affording the BOC-derivatives **36** (as an oil, 38% yield) and **38** (as a crystalline solid, 44% yield).

By an identical series of reactions starting with L-glutamic acid and proceeding via the (*S*)-thiolactam (*S*)-**17**,[21] the enantiomer of tricyclic ketone **38** was prepared (described in the supplementary material). An X-ray crystallographic structure determination of this enantiomer is shown in Figure 1. This determination establishes the assignment of the *S* and *R* absolute configurations at C-2 and C-7, respectively, of ketone **38**, which is made from D-glutamic acid. Having established that tricyclic ketone **38** has the *R* configuration at C-7, it follows that ketone **36** must have the *S* configuration at C-7 since these ketones were prepared from the diastereomeric uncyclized ketones **34a** and **34b**, differing only in absolute stereochemistry at this center (C-1" in **34a** and **34b**).

When one-pot procedures[23] for selenylation/oxidation were performed, starting with ketone **36** or its kinetic TBDMS-enol ether and using *m*-CPBA as oxidant, α,β-unsaturated ketone **41** was obtained in only 24% yield; the major product was its 4-chloro derivative (Scheme 3). If a two-step procedure is performed with *m*-CPBA as oxidant, a 40% yield of $\Delta^{4,5}$-enone **41** and 19% of its 4-[*m*-(chlorobenzoyloxy)] derivate were found. Isolation of the crude seleno ketone from **36** and then oxidation (NaIO$_4$)/elimination (Na$_2$CO$_3$) afforded a 71% yield of unsaturated ketone **41**. Selenylation (PhSeCl) and subsequently oxidation/elimination[23] applied to ketone **38** provided unsaturated ketone **43** (50% yield) and α-chloro ketone

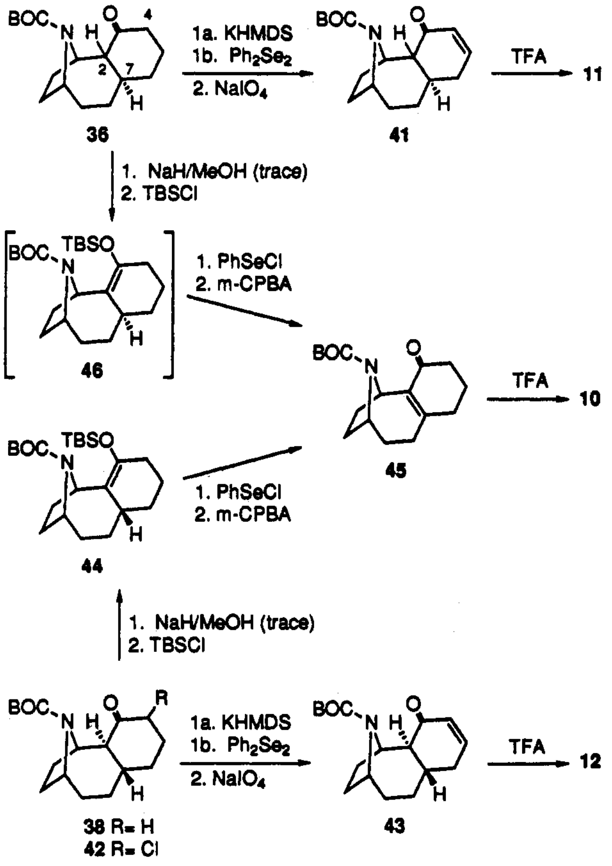
---

(21) Sardina, F. J.; Howard, M. H.; Morningstar, M.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 5025.

(22) The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

(23) (a) Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.* **1973**, *95*, 6137. (b) Zoretic, P. A.; Chambers, R. J.; Marbury, G. D.; Riebero, A. A. *J. Org. Chem.* **1985**, *50*, 2981.

Scheme 3. Synthesis of α,β-Unsaturated Tricyclic Ketones 10–12 from Saturated Precursors



42 (25% yield). Formation of the chloro compound was avoided by selenylation with Ph_2Se_2 of the previously generated kinetic enolate (KHMDS/THF), and a 70% yield of unsaturated ketone 43 was achieved after oxidation ($NaIO_4$) and elimination (Na_2CO_3). Using this selenylation method, a slightly better yield (75%) of unsaturated ketone 41 was obtained.

Treatment of ketone 38 with NaH/THF/MeOH(trace) followed by quenching with TBDMSCl/Et_3N gave the thermodynamic TBDMS-enol ether 44 in 83% yield. Reaction of this TBDMS-enol ether with PhSeCl followed by oxidation (*m*-CPBA) and elimination (Na_2CO_3) of the selenoxide function afforded the $\Delta^{2,7}$-enone 45 in 31% yield. Following the same procedure, ketone 36 afforded the $\Delta^{2,7}$-enone 45 in 32% yield; however, in this case the thermodynamic TBDMS-enol ether 46 was not isolated and was employed directly in the next step.

The *N*-BOC-protected analogues 41, 43, and 45 were deprotected smoothly in anhydrous TFA/CH_2Cl_2 in good yield.[19] For subsequent biological evaluation, to be reported elsewhere, the three amines 10–12 were then converted to water-soluble hydrogen fumarate salts. These tricyclic analogues 10–12, in which ring formation has been used to fix the double bond-carbonyl conformation as *s-trans*, are the first conformationally constrained analogues of anatoxin. They may provide a useful test of the proposed models for the nicotinic acetylcholine receptor (nAChR).

Experimental Section

General. Glassware was oven dried before use and cooled to room temperature under a nitrogen atmosphere. THF was distilled from sodium/benzophenone; CH_3CN, CH_2Cl_2, 1,2-DCE and *tert*-BuOH were distilled from CaH_2; MeOH was distilled from Mg; and *N*-methylpiperidine, oxalyl chloride and TFA were distilled prior to use. Final solutions before evaporation in vacuo were dried over Na_2SO_4. IR spectra were taken in $CHCl_3$ and NMR spectra were taken in $CDCl_3$, unless otherwise noted. ^1H-coupling constants are reported in hertz. In the 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. Column chromatography was carried out using (a) 70-230 or (b) 230-400 mesh SiO_2.

1-[3′-(Benzyloxy)phenyl]ethanone (15).[18] To a stirred mixture of 3′-hydroxyacetophenone (14, 97%, 16.7 g, 0.12 mol) and K_2CO_3 (34.6 g, 0.26 mol) in CH_3CN (175 mL) under Ar was added benzyl bromide (16.0 mL, 23.1 g, 0.14 mol) via syringe. After stirring 24 h at rt, the mixture was diluted with CH_2Cl_2 (300 mL) and washed with water (500 mL). The organic layer was dried and evaporated to give a pale yellow oil (29.2 g). Chromatography (a, Hex/EtOAc, 4/1) afforded pure benzyl ether 15 (26.8 g, quantitative yield): R_f 0.45 (4/1 Hex/EtOAc); IR 1690 cm^{-1}; ^1H NMR δ 7.55 (m, 2H), 7.46–7.25 (m, 6H), 7.17 (ddd, J = 8.1, 2.6, 0.9, 1H), 5.11 (s, 2H), 2.57 (s, 3H); ^{13}C NMR δ 197.8, 158.9 138.4, 136.4, 129.6, 128.6 (2C), 128.1, 127.5 (2C), 121.2, 120.2, 113.4, 70.1, 26.7.

1-Acetoxy-1-[(3′-(benzyloxy)phenyl]ethene (16). A solution of benzyl ether 15 (27.53 g, 0.12 mol) and p-TsOH (2.28 g, 12 mmol) in isopropenyl acetate (226 mL, 205 g, 2.05 mol) was heated for 1 h, distilling 15 mL from the reaction mixture. The oil bath temperature was decreased in order to effect a slower distillation and, after 23 h, 70 mL more had been distilled from the reaction mixture. Fresh isopropenyl acetate (20 mL, 18 g, 0.18 mol) was added and slow distillation was continued for 14 h to collect an additional 35 mL. The last portion of fresh isopropenyl acetate (30 mL, 27 g, 0.27 mol) was added, and the reaction mixture was heated an additional 26 h to distill the final 40 mL. The remaining material was cooled (ice–water bath), and $NaHCO_3$ (1.5 g, 0.18 mmol) was added and the resulting suspension was stirred for 30 min. The excess isopropenyl acetate was evaporated in vacuo and the black residue was dissolved in CH_2Cl_2 (300 mL). This solution was washed with saturated $NaHCO_3$ (100 mL, precooled to 4 °C) and the aqueous wash was back-extracted with CH_2Cl_2 (100 mL). Drying and evaporating the combined organic phase left a brown oil which was chromatographed (4/1 Hex/EtOAc) to give a mixture of enol acetate 16 and ketone 15 (ratio by ^1H NMR, 96/4, 30.33 g, 90% yield of 16, 4% of recovered 15). The first fractions collected were pure enol acetate 16 and this sample was used for spectrometric characterization; R_f 0.46 (4/1, Hex/EtOAc); IR 1760 cm^{-1}; ^1H NMR δ 7.33 (m, 5H), 7.21 (t, J = 8.2, 1H), 7.05 (m, 2H), 6.90 (m, 1H) 5.42 (d, J = 2.2, 1H), 5.00 (s, 2H) 4.99 (d, J = 2.2, 1H), 2.18 (s, 3H); ^{13}C NMR δ 168.8 (0), 158.7 (0), 152.4 (0), 136.6 (0), 135.5 (0), 129.4 (1), 128.4 (1, 2C), 127.8 (1), 127.3 (1, 2C), 117.4 (1), 114.9 (1), 114.1 (1), 111.6 (1), 102.3 (2), 69.9 (2), 20.7 (3). The 96/4 mixture of 16/15 was used directly in the next reaction.

2-Bromo-1-(3′-methoxyphenyl)ethanone (18). To a stirred solution of 3-methoxyacetophenone (13, 20.0 mL, 21.9 g, 0.15 mol) and AcOH (1.0 mL, 17.4 mmol) in CH_2Cl_2 (200 mL) was added slowly a solution of bromine (9 mL, 27.9 g, 0.17 mmol) in CH_2Cl_2 (100 mL) at rt. After the addition was complete, the solution was washed with saturated $NaHCO_3$ (3 × 200 mL) and saturated NaCl (200 mL) and evaporated to give a yellow solid. Recrystallization from 95% EtOH provided bromo ketone 18 (28.3 g, 85%): mp 57–59 °C (lit.[17] mp 57–59 °C); ^1H NMR δ 7.53 (m, 1H), 7.48 (m, 1H), 7.37 (t, J = 7.9, 1H), 7.13 (ddd, J = 8.0, 2.5, 0.9, 1H), 4.42 (s, 2H), 3.84 (s, 3H).

2-Bromo-1-[3′-(benzyloxy)phenyl]ethanone (19). Nitrogen was bubbled into a stirred solution of a 96/4 mixture of enol acetate 16/ketone 15 (30.33 g, 0.10 mol of 16; 4.60 mmol of 15) in CH_2Cl_2 (1.08 L) at rt. Pyridinium perbromide (46.70 g, 0.15 mol) was added in one portion and N_2 bubbling was continued for 12 min, at which time all the brominating complex had dissolved and the reaction was complete (TLC). The solution was washed with 0.1 M $Na_2S_2O_3$ (700 mL), 0.15 M HCl (500 mL), and saturated $NaHCO_3$ (500 mL), dried, and evaporated in vacuo to give a faintly brown solid (32.7 g, ^1H NMR showed a 94/6 mixture of bromo ketone 19/ketone 15). Chromatography (a, 99/1, CH_2Cl_2/ether) provided pure bromo ketone 19 (30.15 g, 90% yield from the enol acetate fraction) and ketone **15** (1.54 g, 0.50 g from the enol acetate fraction, 2% recovery): R_f 0.50 (4/1 Hex/EtOAc); mp 56–57 °C (lit.[18] mp 58.5–59 °C); IR 1680 cm^{-1}; ^{1}H NMR δ 7.57 (m, 2H), 7.47–7.33 (m, 6H), 7.22 (ddd, *J* = 8.2, 2.6, 0.9, 1H), 5.11 (s, 2H) 4.42 (s, 2H); ^{13}C NMR δ 190.9 (0), 159.0 (0), 136.2 (0), 135.1 (0), 129.8 (1), 128.6 (1, 2C), 128.1 (1), 127.5 (1, 2C), 121.6 (1), 121.1 (1), 114.1 (1), 70.1 (2), 31.1 (2).

(*E*,2*R*)-*N*-Benzyl-5-[2′-(3″-methoxyphenyl)-2′-oxoethylidene]proline *tert*-Butyl Ester (20). Thiolactam **17** (17.8 g, 61.3 mmol)[15] and bromo ketone **18** (16.98 g, 74.15 mmol) were mixed in CH_3CN (30 mL), and the mixture was stirred at rt for 12 h. After dilution with CH_2Cl_2 (180 mL), triphenylphosphine (19.8 g, 75.6 mmol) was added and the mixture was stirred at rt for 1 h. It was cooled in an acetone/dry ice bath (t_b, −30 °C), *N*-methylpiperidine (9.40 mL, 7.9 g, 80.1 mmol) was added via syringe (2.2 mL/min), and stirring was continued for 36 h at −12 °C. The mixture was washed with saturated $NaHCO_3$ (200 mL) and water (100 mL), dried over Na_2SO_4, filtered, and evaporated. Chromatography (4/1 Hex/EtOAc) of the crude reaction gave 22.6 g of a yellow oil. Purification by chromatography (b, 96/4, CH_2Cl_2/Et_2O) afforded vinylogous amide **20** as a faintly yellow oil (21.2 g, 85%): R_f 0.14 (4/1 Hex/EtOAc); ^{1}H NMR δ 7.29 (m, 8H), 6.91 (dd, *J* = 8.0, 2.0, 1H), 5.93 (s, 1H), 4.67 (d, *J* = 15.6, 1H), 4.32 (d, *J* = 15.6, 1H), 4.03 (dd, *J* = 9.0, 3.1, 1H), 3.73 (s, 3H), 3.61 (ddd, *J* = 18.2, 9.0, 2.9, 1H), 3.28 (dt, J_d = 18.2, J_t = 9.1, 1H), 2.24 (m, 1H), 2.10 (m, 1H) and 1.39 (s, 9H); ^{13}C NMR δ 187.24 (0), 170.16 (0), 166.23 (0), 158.93 (0), 142.60 (0), 134.68 (0), 128.41 (1), 128.25 (1, 2C), 127.22 (1), 127.07 (1, 2C), 119.08 (1), 116.38 (1), 111.33 (1), 87.96 (1), 81.61 (0), 64.82 (1), 54.61 (3), 49.33 (2), 31.78 (2), 27.32 (3, 3C) and 25.85 (2). Anal. Calcd for $C_{25}H_{29}NO_4$ C, 73.7; H, 7.2; N, 3.4. Found: C, 73.5; H, 7.2; N, 3.5.

(*E*,2*R*)-*N*-Benzyl-5-[2′-[3″-(benzyloxy)phenyl]-2′-oxoethylidene]proline *tert*-Butyl Ester (21). Thiolactam **17** (27.3 g, 93.7 mmol[15] and bromo ketone **19** (30.2 g, 98.8 mmol) were mixed in CH_3CN (45.0 mL), and the mixture was stirred at rt overnight. After dissolving the white solid which had formed by adding CH_2Cl_2 (355 mL), triphenylphosphine (30.4, 116 mmol) was added and the mixture was stirred at rt for 1 h, followed by cooling in an acetone/dry ice bath (t_b, −30 °C) and stirred for an additional 30 min. *N*-Methylpiperidine (14.4 mL, 11.7 g, 118 mmol) was added via syringe (2.2 mL/min) and stirring was continued for 4.5 days at −14 °C. The mixture was washed with saturated $NaHCO_3$ (400 mL) and water (200 mL), dried, filtered, and evaporated to a red oil. The oil was treated with 3/2 Hex/EtOAc, to precipitate Ph_3P-derivates (white solid), and the red filtrate was concentrated to provide 55.3 g of reaction crude. Chromatography (a, 7/3, then 3/2, Hex/EtOAc) afforded vinylogous amide **21** as a thick faintly yellow oil (40.6 g, 90% yield from **17**): R_f 0.40 (92/8, CH_2Cl_2/ether); $[\alpha]^{21}{}_D$ −174° (*c* 1.1, $CHCl_3$); IR 1730, 1700 cm^{-1}; ^{1}H NMR δ 7.46–7.18 (m, 13H), 6.99 (dd *J* = 8.1, 2.0, 1H), 5.90 (s, 1H), 5.00 (s, 2H), 4.66 (d, *J* = 15.6, 1H), 4.30 (d, *J* = 15.6, 1H), 4.00 (dd, *J* = 9.0, 3.3, 1H), 3.62 (ddd, *J* = 18.5, 9.4, 3.2, 1H), 3.28 (dt, J_d = 18.5, J_t = 9.0, 1H), 2.23 (m, 1H), 2.09 (m, 1H), 1.38 (s, 9H); ^{13}C NMR δ 187.6 (0), 170.4 (0), 166.9 (0), 158.3 (0), 142.8 (0), 136.6 (0), 134.8 (0), 128.7 (1), 128.5 (1, 2C), 128.2 (1, 2C), 127.55 (1), 127.52 (1), 127.3 (1, 2C), 127.2 (1, 2C), 119.7 (1), 117.5 (1), 112.6 (1), 88.2 (1), 81.9 (0), 69.6 (2), 65.0 (1), 49.5 (2), 32.0 (2), 27.6 (3,3 3C), 26.1 (2). Anal. Calcd for $C_{31}H_{33}NO_4$: C, 77.0; H, 6.9; N, 2.9. Found: C, 76.9; H, 7.0; N, 3.0.

(2*R*,5*R*)-[2′-(3″-Methoxyphenyl)ethyl]proline *tert*-Butyl Ester (22). Vinylogous amide **20** (0.80 g, 1.97 mmol) and trifluoroacetic acid (0.30 mL, 0.44 g, 3.86 mmol) were dissolved in MeOH (12 mL). The solution was degassed by bubbling N_2 through it and then 10% Pd/C (0.65 g) was added. The mixture was hydrogenated (60 psi, 32 °C) for 4 days and then it was filtered, and the filter cake was rinsed with MeOH. The methanolic filtrate was adjusted to pH 7 with 2 M NaOH and evaporated, and the residue was digested with CH_2Cl_2 (50 mL). The mixture was washed with saturated $NaHCO_3$ (25 mL), the aqueous phase was extracted with CH_2Cl_2 (2 × 25 mL), and the combined organic layers were dried, filtered, and evaporated to leave 0.57 g of reaction crude. Chromatography (b, 95/5, CH_2Cl_2/MeOH) gave the secondary amine **22** (0.51 g, 85%): R_f 0.49 (9/1 CH_2Cl_2/MeOH); ^{1}H NMR δ 7.17 (t, *J* = 7.7, ^{1}H), 6.79 (d, *J* = 7.7, 1H), 6.74 (s, 1H), 6.71 (d, *J* = 7.8, 1H), 3.79 (s, 3H), 3.63 (dd, *J* = 8.9, 5.3, 1H), 3.03 (m, 1H), 2.67 (m, 2H), 2.11–1.67 (m, 6H) and 1.46 (s, 9H); ^{13}C NMR δ 174.72 (0), 159.53 (0), 143.66 (0), 129.22 (1), 120.69 (1), 113.96 (1), 111.08 (1), 80.98 (0), 60.63 (1), 59.72 (1), 55.13 (1), 37.45 (2), 33.78 (2), 31.74 (2), 30.62 (2) and 28.04 (3, 3C). Anal. Calcd for $C_{18}H_{27}NO_3$: C, 70.6; H, 9.1; N, 4.5. Found: C, 70.8; H, 8.9; N, 4.6.

(2*R*,5*R*)-5-[2′-(3″-Hydroxyphenyl)ethyl]proline *tert*-Butyl Ester (23). Vinylogous amide **21** (11.0 g, 22.7 mmol) was dissolved in 4/1, MeOH/H_2O (288 mL). The solution was degassed by bubbling N_2 through it and then hydrochloric acid (2.84 mL, 12.1 M, 34.4 mmol) and 10% Pd/C (4.38 g, 40 w/w%) were added. The mixture was hydrogenated (60 psi, rt) for 48 h and then filtered, and the filter cake was rinsed with MeOH. Saturated $NaHCO_3$ solution (2.49 g, 34.4 mmol, dissolved in 6 mL of H_2O) was added to the combined methanolic solution, the solvents were evaporated, and the residue was digested with CH_2Cl_2 (200 mL). The mixture was washed with 5% $NaHCO_3$ (50 mL) and the aqueous phase was extracted with 4/1 $CHCl_3$/iPrOH (2 × 50 mL). The combined organic layers were dried, filtered, and evaporated to leave a faintly yellow solid. Based on the ^{1}H NMR of this reaction crude, amino phenol **23** was identified as the major component (6.19 g, 93% based on crude); other components are products from aromatic ring reduction. A 280-mg sample of this crude was purified by chromatography (b, 95/5, EtOAc/MeOH) followed by crystallization (EtOAc/Hex) to afford pure amino phenol **23** (225 mg, 74% yield) as a white solid: R_f 0.41 (9/1, CH_2Cl_2/MeOH); mp 127–128 °C; $[\alpha]^{20}{}_D$ +23.8° (*c* 0.9, $CHCl_3$); IR 1720 cm^{-1}; ^{1}H NMR δ 7.08 (dd, *J* = 8.6, 7.6, 1H), 6.63 (m, 3H), 3.68 (dd, *J* = 9.1, 4.6, 1H), 3.10 (m, 1H), 2.63 (t, *J* = 7.9, 2H), 2.10–1.89 (m, 4H), 1.79 (m, 1H), 1.46 (s, 9H), 1.30 (m, 1H); ^{13}C NMR δ 173.91 (0), 157.3 (0), 142.9 (0), 129.4 (1), 119.3 (1), 115.3 (1), 113.3 (1), 81.6 (0), 60.0 (1), 59.5 (1), 36.9 (2), 33.4 (2), 31.4 (2), 30.7 (2) and 27.94 (3, 3C). Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.1; H, 8.6; N, 4.8. Found: C, 69.7; H, 8.7; N, 4.8.

(2*R*,5*R*)-*N*-Benzyl-5-[2′-(3″-methoxyphenyl)ethyl]proline (24). To a stirred mixture of secondary amine **22** (0.79 g, 2.58 mmol) and K_2CO_3 (1.21 g, 8.96 mmol) in CH_3CN (9 mL) under N_2 was added benzyl bromide (0.35 mL, 0.50 g, 2.94 mmol) via syringe. After stirring overnight at rt, the mixture was diluted with CH_2Cl_2 and washed with water. The organic layer was dried, filtered, and evaporated to afford a pale yellow oil. Chromatography (85/15, Hex/EtOAc) provided the corresponding benzylamine (0.81 g, 2.05 mmol, 80%) as a clear oil of which 0.41 g (1.04 mmol) was dissolved in *i*-PrOH/H_2O/AcOH (13 mL, 5/5/1) and the solution refluxed for 10 h. After cooling, the solution was diluted with CH_2Cl_2 (23 mL) and washed with 1.5 M KH_2PO_4 (20 mL). The organic layer was dried, filtered, and evaporated to give an oil from which HOAc was removed by azeotropic distillation with toluene leaving crude acid **24**. Chromatography (b, very short path, 9/1 CH_2Cl_2/MeOH) provided pure **24** (0.31 g, 87% from the benzylamine) as a clear oil: R_f 0.37 (9/1 CH_2Cl_2/MeOH); ^{1}H NMR δ 7.55–7.38 (s, 1H, CO_2H), 7.36–7.17 (m, 6H), 6.75 (dd, J_1 = 8.2, 2.3, 1H), 6.68 (d, *J* = 7.7, 1H), 6.65 (d, *J* = 2.2, 1H), 4.20 (d, *J* = 13.3, 1H), 4.11 (d, *J* = 13.3, 1H), 3.78 (s, 3H), 3.78 (overlap), 3.07 (m, 1H), 2.72 (m, 1H), 2.44 (m, 1H), 2.26–1.93 (m, 5H) and 1.69 (m, 1H); ^{13}C NMR δ 171.7 (0), 159.4 (0), 141.5 (0), 131.1 (0), 130.3 (1, 2C), 129.3 (1), 128.8 (1), 128.7 (1,2C), 120.3 (1), 113.8 (1), 111.2 (1), 67.4 (1), 64.9 (1), 56.1 (2), 54.9 (3), 33.6 (2), 32.0 (2), 29.3 (2) and 27.5 (2). Anal. Calcd for $C_{21}H_{25}O_3N$: C, 74.3; H, 7.4; N, 4.1. Found: C, 74.3; H, 7.5; N, 4.0.

(2*R*,5*R*)-*N*-Benzyl-5-[2′-(3″-hydroxyphenyl)ethyl]proline (25). A solution of the benzylamine of **22** (1.78 g, 4.50 mmol) in acetic acid (27.5 mL) and hydrobromic acid (13.5 mL, 48%) was boiled under refluxed for 15 h. The mixture was poured onto water/ice (pH 1.5) and extracted with CH_2Cl_2 (100 mL). The combined organic extracts were dried, filtered, and evaporated to give a brown solid (0.67 g). Four consecutive digestions with CH_2Cl_2 (4 × 100 mL) provided a combined solution, which was dried, filtered, and evaporated to give a white solid (0.39 g). Chromatography (b, 8/2, CH_2Cl_2/MeOH) of the combined solids afforded acid phenol **25** (0.98 g, 67%) as a white solid: R_f 0.18 (streak, 9/1 CH_2Cl_2/MeOH); mp 184–190 °C decomposed; $[\alpha]^{22}{}_D$ −2.1° (*c* 1.0, MeOH); ^{1}H NMR δ (CD_3OD) 7.40 (m, 5H), 7.10 (t, *J* = 7.6, 1H), 6.65 (m, 3H), 4.45 (d, *J* = 14.0, 1H), 4.33 (d, *J* = 14.0, 1H), 3.92 (dd, *J* = 7.4, 5.4, 1H), 3.47 (m, 1H), 2.65 (m, 1H), 2.48 (m, 1H), 2.37–2.01 (m, 4H), 1.90 (m, 1H) and 1.70 (m, 1H); ^{13}C NMR δ [$(CD_3)_2SO$] 173.3, 157.2, 143.1, 136.1, 129.5 (2C), 129.2, 128.2 (2C), 127.5, 118.8, 115.1, 112.7, 66.1, 64.4, 56.2, 35.1, 31.7, 29.5, 27.7.

(2*R*,5*R*)-*N*-Benzyl-5-[2′-[3″-[(*tert*-butyldimethylsilyl)oxy]phenyl]ethyl]proline (26). A solution of TBDMSCl (1.52 g, 10.1 mmol) in CH_2Cl_2 (7 mL) was added to a solution of phenol **25** (0.39 g, 1.2 mmol) and imidazole (1.8 g, 26.5 mmol) in CH_2Cl_2 (30 mL). The solution was stirred overnight at rt and then the reaction mixture was diluted with CH_2Cl_2 (40 mL) and washed with 5% $NaHCO_3$ (40 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic phases were dried and evaporated to give 1.98 g of reaction crude. Chromatography (a, 95/5, CH_2Cl_2/MeOH) afforded aryl silyl ether **26** (0.44 g, 84%) as a clear oil: R_f 0.37 (streak, 9/1 CH_2Cl_2/MeOH); ^{1}H NMR δ 7.34–7.19 (m, 5H), 7.16 (t, *J* = 7.8, 1H), 6.71 (dd, *J* = 7.8, 1.6, 1H), 6.58 (d, *J* = 1.6, 1H), 4.16 (d, *J* = 13.3, 1H), 4.03 (d, *J* = 13.3, 1H), 3.72 (dd, *J* = 5.3, 4.1, 1H), 3.04 (m, 1H), 2.62 (m, 1H), 2.45 (m, 1H), 2.25–1.9 (m, 5H) and 1.65 (m, 1H); ^{13}C NMR δ 172.0 (0), 155.6 (0), 141.7 (0), 131.7 (0), 130.3 (1, 2C), 129.3 (1), 128.8 (1, 3C), 121.1 (1), 120.0 (1), 117.7 (1), 67.1 (1), 64.7 (1), 56.2 (2), 34.0 (2), 32.1 (2), 29.5 (2), 27.7 (2), 25.5 (3, 3C), −4.5 (3, 2C).

(2*R*,5*R*,1″*R* and *S*,3″*R* and S)-5-[2′-(3″-Hydroxycyclohexyl)ethyl]proline *tert*-Butyl Ester (29) and (2*R*,5*R*,1″*R* and *S*)-5-[2′-(3″,3″-Dimethoxycyclohexyl)ethyl]proline *tert*-Butyl Ester (30). Crude amino phenol **23** (16.1 g, ~57 mmol) was dissolved in 4/1 MeOH/H_2O (460 mL). The solution was degassed with N_2, and concd HCl (8.22 mL, 12 M, 99 mmol) and 30% Pd/C (8.03 g) were added. The mixture was hydrogenated (60 psi, 45 °C) for 72 h and then filtered, and the filter cake was rinsed with MeOH. Sodium bicarbonate (8.35 g, 99 mmol, dissolved in the minimum volume of H_2O) was added to the combined methanolic solution. The solvents were evaporated, and the residue was mixed with CH_2Cl_2 (250 mL). The mixture was washed with 5% $NaHCO_3$ (75 mL) and the aqueous phase was extracted twice with 4/1, $CHCl_3$/iPrOH (2 × 75 mL). The combined organic layers were dried, filtered, and evaporated to afford 12.3 g of a faintly yellow oil. On the basis of the ^{1}H NMR spectrum of the crude, amino cyclohexanols **29** (four diastereomers) were the major components, and amino dimethylketals **30** (two diastereomers) were the minor components. Chromatography (a, 95/5, CH_2Cl_2/MeOH) allowed isolation of fractions of amino cyclohexanols **29** as a faintly yellow oil, free of ketals **30**: R_f 0.35 (9/1, CH_2Cl_2/MeOH; ^{1}H NMR δ 4.10* (m, 0.25H), 3.64 (dd, *J* = 9.0, 5.1, 1H), 3.54 (m, 0.75H), 2.98 (m, 1H), 2.70 (m, 2H, NH and OH), 2.12–0.75 (m, 17H) and 1.46 (s, 9H); ^{13}C NMR δ 174.3, (0), 81.2 (0), 70.58, 70.55 and 66.60* (1), 60.4 (1, 2C), 42.6 and 39.7* (2), 36.5 and 36.5 (1), 35.7 (2), 34.55 and 34.0* (2), 33.2* and 33.0 (2), 32.0 (2), 31.2 and 31.6* (2), 30.7 (2), 28.0 (3, 3C), 24.0 (2) (*indicates exclusive peak of two minor diastereomers).

(2*R*,5*R*,1″R or *S*, 3″*S* or *R*)-*N*-Benzyl-5-[2′-(3″-hydroxycyclohexyl)ethyl]proline *tert*-Butyl Ester (31, axial-OH); (2*R*,1″*R* or *S*, 3″*R* or *S*)-*N*-Benzyl-5-[2′-(3″-hydroxycyclohexyl)ethyl]proline *tert*-Butyl Ester (31, equatorial-OH), and (2*R*,5*R*,1″*R* and *S*)-*N*-Benzyl-5-[2′-(3″,3″-dimethoxycyclohexyl)ethyl]proline *tert*-Butyl Ester (32). To a stirred suspension of the crude mixture of **29** and **30** (12.3 g, ~41.3 mmol) and K_2CO_3 (16.7 g, 124 mmol) in CH_3CN (143 mL) under N_2 was added benzyl bromide (6.12 mL, 88.4 g, 51.7 mmol) via syringe. After stirring overnight at rt, the mixture was diluted with CH_2Cl_2 (250 mL) and washed with H_2O (100 mL). The organic layer was dried, filtered, and evaporated to give a yellow oil (17.5 g). Chromatography (a, 3/2, Hex/EtOAc) led to isolation of dimethylketals **32** (5% yield from **21**), cyclohexanols **31** (axial-OH, 9% yield from **21**), and the cyclohexanols **31** (equatorial-OH, 23% yield from **21**).

31, axial-OH: R_f 0.32 (7/3 Hex/EtOAc); ^{1}H NMR δ 7.24 (m, 5H), 4.03 (m, width = 7.5 Hz, 1H), 3.88 (d, *J* = 14.0, 1H), 3.72 (d, *J* = 14.0, 1H), 3.18 (dd, *J* = 8.3, 5.8, 1H), 2.63 (m, 1H), 1.95–1.09 (m, 16H), 1.33 (s, 9H) and 0.90 (m, 1H); ^{13}C NMR δ 173.9, 138.8, 129.3 (2C), 127.9 (2C), 126.7, 80.0, 66.9 and 66.7 (1C), 64.8 and 64.7 (1C), 57.3 and 57.2 (1C), 39.9 and 39.6 (1C), 33.35 and 33.28 (1C), 32.76 and 32.35 (1C), 31.9, 31.83, 31.77, 31.7, 30.0, 28.3, 27.9 (3C), 20.02 and 19.98 (1C).

31, equatorial-OH: R_f 0.28 (7/3, Hex/EtOAc); ^{1}H NMR δ 7.25 (m, 5H), 3.87 (d, *J* = 14.0, 1H), 3.71 (d, *J* = 14.0, 1H), 3.52 (m, width = 25 Hz, 1H), 3.18 (dd, *J* = 8.3, 5.6, 1H), 2.63 (m, 1H), 1.95–1.04 (m, 15H), 1.33 (s, 9H), 0.78 (m, 2H); ^{13}C NMR δ 173.9 (0), 138.8 (0), 129.2 (1, 2C), 127.9 (1, 2C), 126.7 (1), 79.9 (0), 70.7 (1), 66.7 and 66.6 (1, 1C), 64.78 and 64.72 (1, 1C), 57.3 and 57.2 (2, 1C), 42.8 and 42.5 (2, 1C), 36.70 and 36.66 (1, 1C), 35.73 and 35.69 (2, 1C), 33.34 and 33.29 (2, 1C), 32.17 and 31.91 (2, 1C), 31.85 and 31.82 (2, 1C), 30.00 (2), 28.21 (2), 7.79 (3, 3C), 24.06 (2).

32: R_f 0.69 (7/3, Hex/EtOAc); ^{1}H NMR δ 7.24 (m, 5H), 3.88 and 3.86 (2d, *J* = 14.0, 1H), 3.71 and 3.70 (2d, *J* = 14, 1H), 3.20 and 3.19 (2s, 3H), 3.14 (overlap, 1H), 3.11 (s, 3H), 2.61 (m, 1H), 2.10–0.7 (m, 18H) and 1.33 (s, 9H); ^{13}C NMR δ 173.8, 138.78 and 138.73 (1C), 129.2 (2C), 127.9 (2C), 126.7, 100.4, 79.9, 66.66 and 66.58 (1C), 64.85 and 64.77 (1C), 57.22 and 57.16 (1C), 47.35 (2C), 39.36 and 39.06 (1C), 34.55 and 34.48 (1C), 33.3 and 33.2 (1C), 32.52 and 32.47 (1C), 32.47 and 32.17 (1C), 31.88, 30.05 and 30.01 (1C), 28.19 and 28.17 (1C), 27.89 (3C) and 22.28.

(2*R*,5*R*,1″*R* and *S*)-*N*-Benzyl-5-[2′-(3″-oxocyclohexyl)ethyl]proline *tert*-Butyl Ester (33). To a stirred solution of cyclohexanols **32** (3.50 g, 9.04 mmol) in acetone (105 mL) was added dropwise Jones reagent, until the red color was no longer discharged (TLC monitored as well). Sodium thiosulfate was added to decolorize the reaction mixture and it was diluted with acetone (145 mL) and stirred overnight at rt. After filtration through Celite, the yellow filtrate was treated with 2 M NaOH to pH 7. The solvents were evaporated in vacuo and the residue was dissolved in CH_2Cl_2 (100 mL). This solution was washed with saturated $NaHCO_3$ (50 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 × 75 mL). The combined organic phase was dried and evaporated to give 3.31 g of crude which on chromatography (a, 3/1, Hex/EtOAc) afforded pure keto esters **33** (2.69 g, 77%, 1/1 mixture of diastereomers at C-1″) as a pale yellow oil.

On a larger scale, a mixture of crude cyclohexanols **31** and dimethylketals **32** [17.54 g from vinylogous amide **21** (26.2 g, 54.2 mmol)] was treated with Jones reagent (9 mL/500 mL acetone) and after filtering through Celite, saturated Na_2CO_3 (4.00 g, 37.7 mmol, dissolved in 10 mL H_2O) was added and the reaction mixture stirred for an additional 4 h and filtered through Celite again. Isolation and chromatography as described above provided keto esters **33** (7.17 g, 34% yield from vinylogous amide **21**): R_f 0.51 (7/3, Hex/EtOAc); IR (neat) 1735, 1710 cm^{-1}. Anal. Calcd for $C_{24}H_{35}NO_3$: C, 74.8; H, 9.2; N, 3.6. Found: C, 74.6; H, 9.4; N, 3.6.

By two consecutive chromatographies (b, 9/1 $CHCl_3$/EtOAc) a portion of the 1/1 diastereomeric mixture of keto esters **33** was separated into a 9/1 mixture enriched in **33a** (15%), a 1/1 mixture of **33a**/**33b** (31%), and a 9/1 mixture enriched in **33b** (20%); 34% of the starting mixture was lost in the separation process. The diastereomeric ratios were determined by ^{1}H NMR. The only distinctly different absorptions are 3.84 ppm (d, *J* = 13.9 Hz, ^{1}H, benzylic hydrogen of **33a**) and 3.82 ppm (d, *J* = 13.8 Hz, 1H, benzylic hydrogen of **33b**):

(2*R*,5*R*,1″*S*)-Keto ester 33a: ^{1}H NMR δ 7.26 (m, 5H), 3.84 (d, *J* = 13.9, 1H), 3.73 (d, *J* = 13.9, 1H), 3.20 (dd, *J* = 8.4, 5.8, 1H), 2.67 (m, 1H), 2.49–2.13 (m, 3H), 2.11–1.74 (m, 6H), 1.74–1.48 (m, 4H), 1.36 (s, 9H), 1.48–0.99 (m, 4H); ^{13}C NMR δ 211.7 (0), 173.6 (0), 138.7 (0), 129.0 (1, 2C), 127.8 (1, 2C), 126.6 (1), 79.8 (0), 66.7 (1), 64.5 (1), 57.4 (2), 48.2 (2), 41.3 (2), 39.1 (1), 32.5 (2), 31.5 (2), 30.8 (2), 29.78 (2), 28.1 (2), 27.7 (3, 3C), 25.0 (2).

(2*R*,5*R*,1″*R*)-Keto ester 33b: ^{1}H NMR δ 7.26 (m, 5H), 3.82 (d, *J* = 13.8, 1H), 3.73 (d, *J* = 13.8, 1H), 3.20 (dd, *J* = 8.2, 5.9, 1H), 2.68 (m, 1H), 2.47–2.14 (m, 3H), 2.12–1.77 (m, 6H), 1.74–1.08 (m, 8H), 1.36 (s, 9H); ^{13}C NMR δ 211.4 (0), 173.4 (0), 138.6 (0), 128.8 (1, 2C), 127.6 (1, 2C), 126.5 (1), 79.6 (0), 66.6 (1), 64.5 (1), 57.4 (2), 47.7 (2), 41.1 (2), 39.0 (1), 32.3 (2), 31.2 (2), 31.0 (2), 29.7 (2), 28.1 (2), 27.9 (3, 3C), 24.9 (2).

(2*R*,5*R*,1″*R* and *S*)-*N*-Benzyl-5-[2′-(3″-oxocyclohexyl)ethyl]proline (34). *tert*-Butyl Ester **33** (9.25 g, 24.02 mmol) was dissolved in iPrOH/H_2O/AcOH (396 mL, 5/5/1) and the solution refluxed for 3.5 h. After being cooled, the solution was diluted with CH_2Cl_2 (720 mL) and washed with 1.5 M KH_2PO_4 (300 mL), and the aqueous was was extracted with 4/1 $CHCl_3$/iPrOH (3 × 150 mL). The combined organic layer was dried, filtered, and evaporated in vacuo to give an oil from which HOAc was removed by an azeotropic distillation with toluene leaving crude acid **34** as a mixture of diastereomers at C-1″ (6.68 g, 85%).

Using the procedure above for preparing the 1/1 diastereomeric mixture of keto acids **34**, the 9/1 mixture enriched in keto ester **33a** was converted to an enriched mixture of (2*R*,5*R*,1″*S*)-keto acid **34a**: R_f 0.35 (streak, 9/1 CH_2Cl_2/MeOH); ^{1}H NMR δ 8.86 (s, 1H, CO_2H), 7.36 (s, 5H), 4.24 (d, *J* = 13.3, 1H), 4.09 (d, *J* = 13.2, 1H), 3.79 (dd, *J* = 8.4, 4.0, 1H), 3.09 (m, 1H), 2.35–1.26 (m, 17H); ^{13}C NMR δ 210.9 (0), 172.1 (0), 132.5 (0), 129.9 (1, 2C), 129.0 (1, 3C), 67.8 (1), 66.5 (1), 57.4 (2), 47.8 (2), 41.1 (2), 38.6 (1), 32.7 (2), 30.6 (2), 30.2 (2), 30.0 (2), 27.9 (2), 24.8 (2).

Using the procedure described above for preparing the 1/1 diastereomeric mixture of keto acids **34**, the 9/1 mixture enriched in keto ester **33b** was converted to an enriched mixture of (2*R*,5*R*,1″*R*)-keto acid **34b**: R_f 0.35 (streak, 9/1 CH_2Cl_2/MeOH); ^{1}H NMR δ 8.06 (s, 1H, CO_2H), 7.36 (s, 5H), 4.19 (d, *J* = 13.2, 1H), 4.12 (d, *J* = 13.2, 1H), 3.78 (dd, *J* = 9.5, 3.9, 1H), 3.10 (m, 1H), 2.44–0.98 (m, 17H); ^{13}C NMR δ 210.8 (0), 171.9 (0), 132.3 (0), 129.9 (1, 2C), 128.8 (1, 3C), 67.9 (1), 66.5 (1), 57.4 (2), 47.4 (2), 41.0 (2), 38.4 (1), 32.5 (2), 30.6 (2), 29.9 (2), 29.8 (2), 27.7 (2), 24.7 (2).

(1*R*,2*R* or *S*,7*S*,10*R*)-3-Oxo-13-benzyl-13-azatricyclo[8.2.1.$0^{2,7}$]tridecane (35), (1*R*,2*S*,7*R*,10*R*)-3-Oxo-13-benzyl-13-azatricyclo[8.2.1.$0^{2,7}$]tridecane (37), (2*R*,1″*S*)-*N*-Benzyl-2-[2′-(3″-oxocyclohexyl)ethyl]pyrrolidine (40a), and (2*S*,1″*R*)-*N*-Benzyl-2-[2′-(3″-oxocyclohexyl)ethyl]pyrrolidine (40b). A solution of keto acids **34** (1.53 g, 4.65 mmol) in 1,2-DCE (16 mL) was added to a cold (−15 °C) solution of oxalyl chloride (0.56 mL, 815 mg, 6.42 mmol) in 1,2-DCE (32 mL), at 1.5 mL/min. After the addition was complete, the solution was stirred for 3 h (−10 °C to −5 °C), the cooling bath was removed, and the reaction mixture was stirred for an additional 45 min. *tert*-BuOH (15.0 mL) and then 1,2-DCE (90 mL) were added, and the solution was immersed in a preheated bath (70 °C) and stirred for 22 h under an Ar atmosphere. The mixture was allowed to cool and then it was washed with saturated $NaHCO_3$ (150 mL), and the aqueous washing was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phase was dried, filtered, and evaporated to give a brown oil (1.18 g) which was chromatographed (a, 9/1 CH_2Cl_2/ether) to afford a 2/3 mixture of tricyclic ketones **35** and **37** (530 mg, 40% yield): R_f 0.43 (streak, 7/3 Hex/EtOAc). Anal. Calcd for $C_{19}H_{25}NO \cdot {}^1/_3H_2O$; C, 78.9; H, 8.9; N, 4.8. Found: C, 79.2; H, 8.6; N, 4.8.

A mixture enriched in keto acid **34a** (0.23 g, 0.73 mmol) undergoes decarbonylation/iminium ion cyclization, under the conditions described above (using only 1,2-DCE as diluent), to provide a crude reaction mixture from which solvent was removed and the residue was dissolved in MeOH. The new solution was degassed by with N_2, and concd HCl (0.4 mL, 12 M, 4.84 mmol) and 5% Pt/C (30 mg) were added. The mixture was hydrogenated (20 psi, rt) for 45 min and then filtered, and the filter cake was rinsed with MeOH. After the addition of 2 M NaOH to pH 7, the solvent were removed and the residue was mixed with CH_2Cl_2 (40 mL). This solution was washed with saturated $NaHCO_3$ (20 mL) and the aqueous wash extracted three times with CH_2Cl_2 (3 × 25 mL). The combined organic phase was dried and evaporated to give a brown oil (0.22 g). Chromatography with 7/3 Hex/EtOAc gave a diastereomeric mixture enriched in tricyclic ketone **35** (50 mg, 25%); further elution with 9/1 EtOAc/MeOH gave a diastereomeric mixture enriched in the dimethylketal of pyrrolidine **40a** (80 mg, 35%).

This mixture enriched in the dimethylketal of pyrrolidine **40a** (80 mg, 0.24 mmol) was dissolved in acetone (2.0 mL), and *p*-TsOH·H_2O (110 mg, 0.58 mmol) and water (0.05 mL) were added. The reaction mixture was stirred at rt for 2 h, the solution was evaporated, and CH_2Cl_2 (20 mL) was added to the residue. The mixture was washed with saturated $NaHCO_3$ (10 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried, filtered, and evaporated to afford a diastereomeric mixture enriched in pyrrolidine **40a** (60 mg, 87%). Chromatography (b, 9/1, CH_2Cl_2/MeOH) did not provide further purification and only 29 mg, 43%, of pyrrolidine **40a** was recovered.

Tricyclic ketone 35: ^{1}H NMR δ 7.22 (m, 5H), 3.70 (s, 2H), 3.66 (overlap, 1H), 3.23 (m, 1H), 2.40–1.00 (m, 16H); ^{13}C NMR δ 212.5 (0), 141.3 (0), 128.0 (1, 4C), 126.5 (1), 64.2 (1), 62.5 (1), 61.2 (2), 60.9 (1), 41.6 (2), 40.8 (1), 35.1 (2), 34.5 (2), 33.6 (2), 33.1 (2), 26.1 (2), 25.6 (2).

(2*R*,1″*S*)-pyrrolidine 40a: ^{1}H NMR δ 7.31 (m, 5H), 4.04 (d, *J* = 12.9, 1H), 3.36 (d, *J* = 12.9, 1H), 3.06 (m, 1H), 2.60–1.01 (m, 19H); ^{13}C NMR δ 211.7 (0), 129.3 (1), 128.3 (1), 64.6 (1), 58.2 (2), 54.0 (2), 48.3 (2), 41.4 (2), 39.2 (1), 33.0 (2), 30.9 (2), 30.1 (2), 25.1 (2), 21.8 (2).

A mixture enriched in keto acid **34b** (0.23 g, 0.73 mmol) undergoes decarbonylation/iminium ion cyclization/hydrogenation under the same conditions described for its C-1″ epimer, to provide a diastereomeric mixture enriched in tricyclic ketone **37** (25% yield), the dimethylketal of tricycle **37** (13% yield), and a diastereomeric mixture enriched in the dimethylketal of pyrrolidine **40b** (13% yield). Using the procedure describe above to hydrolyze its C-1″ epimer, the dimethylketal of **40b** provided crude pyrrolidine **40b** (93% yield). Chromatography (9/1, CH_2Cl_2/MeOH) did not result in further purification and only a 75% yield of pyrrolidine **40b** was recovered.

Tricyclic ketone 37: ^{1}H NMR δ 7.26 (m, 5H), 4.15 (d, *J* = 9.6, 1H), 3.90 (d, *J* = 13.5, 1H), 3.62 (d, *J* = 13.5, 1H), 3.16 (m, 1H), 2.50–1.07 (m, 16H); ^{13}C NMR δ 211.5 (0), 141.8 (0), 128.4 (1, 2C), 127.8 (1, 2C), 126.3 (1), 66.6 (1), 62.3 (1), 60.9 (2), 60.8 (1), 43.5 (1), 41.1 (2), 35.7 (2), 35.0 (2), 34.5 (2), 32.3 (2), 26.8 (2), 26.1 (2).

(2*S*,1″*R*)-pyrrolidine (40b): ^{1}H NMR δ 7.24 (m, 5H), 3.96 (d, *J* = 12.8, 1H), 3.18 (d, *J* = 12.8, 1H), 2.91 (m, 1H), 2.50–1.10 (m, 19H); ^{13}C NMR δ 211.8 (0), 129.0 (1), 128.2 (1), 64.3 (1), 58.6 (2), 54.2 (2), 48.1 (2), 41.5 (2), 39.4 (1), 33.0 (2), 31.4 (2), 30.2 (2), 25.3 (2), 21.9 (2).

(1*R*,2*R* or *S*,7*S*,10*R*)-3-Oxo-13-(*tert*-butoxycarbonyl)-13-azatricyclo[8.2.1.$0^{2,7}$]tridecane (36) and (1*R*,2*S*,7*R*,10*R*)-3-Oxo-13-(*tert*-butoxycarbonyl)-13-azatricyclo[8.2.1.$0^{2,7}$]tridecane (38). Di-*tert*-butyl dicarbonate (1.23 g, 5.64 mmol) was added to a solution of the mixture of tricycles **35** and **37** (530 mg, 1.87 mmol) in dry MeOH (22 mL) followed by 10% Pd/C (160 mg), and the resulting suspension was hydrogenated (55 psi, rt) for 3 h. The reaction mixture was filtered, the insoluble material was thoroughly washed with MeOH, and the combined filtrates were evaporated. The residue was diluted with ether, washed with saturated $NaHCO_3$ and brine (25 mL of each), dried, and evaporated, leaving an oil (1.38 g) which was chromatographed (b, 7/3, Hex/EtOAc) to provide *N*-BOC-tricyclic ketone **36** (210 mg, 38%) as a clear oil, and *N*-BOC-tricyclic ketone **38** (240 mg, 44%) as a crystalline solid.

36: R_f 0.47 (7/3, Hex/EtOAc): $[\alpha]^{21}_D$ + 21.1° (*c* 1.4, $CHCl_3$); IR 1705, 1680 cm^{-1}; ^{1}H NMR δ (rotamers, ratio 3/2): 4.60 (dd, *J* = 5.5, 2.7, 0.6H), 4.52 (dd, *J* = 5.7, 2.7, 0.4H), 4.27 (t, *J* = 8.3, 0.4H), 4.15 (t, *J* = 8.2, 0.6H), 2.59 (dd, *J* = 11.1, 3.0, 0.6H), 2.52–1.21 (m, 15H) and 1.45 and 1.46 (2s, 9H); ^{13}C NMR δ (two rotamers) 211.29 and 211.22 (0, 1C), 156.4 and 153.3 (0, 1C), 78.94 and 78.86 (0, 1C), 59.9 and 58.2 (1, 1C), 55.81 and 55.66 (1, 1C), 53.5 and 53.0 (1, 1C), 41.4 (2, 2C), 40.5 (1), 34.46, 34.02, 33.63, 33.27, 33.04 (2, 4C) 28.5 (3, 3C), 26.18, 25.59, 25.47 and 25.40 (2, 2C). Anal. Calcd for $C_{17}H_{27}NO_3$: C, 69.6; H, 9.3; N, 4.8. Found: C, 69.6; H, 9.4; N, 5.0.

38: R_f 0.39 (7/3, Hex/EtOAc); mp 104–105 °C; $[\alpha]^{22}_D$ −111° (*c* 1.1, $CHCl_3$); IR 1710, 1680 cm^{-1}; ^{1}H NMR δ (two rotamers, ratio 7/3) 5.10 (m, 1H), 4.30 (m, 0.7H), 4.17 (m, 0.3H), 2.45 (m, 1H), 2.25–1.41 (m, 15H) and 1.40 (s, 9H); ^{13}C NMR δ (two rotamers, peaks of the major one) 207.4 (0), 153.1 (0), 79.9 (0), 65.0 (1), 55.2 (1), 51.4 (1), 40.6 (1), 40.1 (2), 34.5 (2) 34.0 (2) 32.2 (2), 30.7 (2), 28.3 (3, 3C), 25.3 (2), 24.3 (2). Anal. Calcd for $C_{17}H_{25}NO_3$: C, 69.6; H, 9.3; N, 4.8. Found: C, 69.7; H, 9.1; N, 4.6.

(1*R*,2*R* or *S*,7*S*,10*R*)-3-Oxo-13-(*tert*-butoxycarbonyl)-13-azatricyclo[8.2.1.$0^{2,7}$]-4-tridecene (41). A −78 °C solution of BOC-tricycle **36** (330 mg, 1.13 mmol) in THF (2.90 mL) was added to a 1.0 M solution of KHMDS/THF (3.40 mL) at −78 °C at 0.25 mL/min. The mixture was stirred at this temperature for 45 min, and then a solution of Ph_2Se_2 (700 mg, 2.25 mmol) in THF (3.40 mL) was added at 0.84 mL/min. The reaction mixture was stirred for 15 min at −78 °C and at 0 °C for 10 min. The reaction mixture was poured onto a 1 M KH_2PO_4 (20 mL) solution and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phase was dried, filtered, and evaporated to give 780 mg of crude α-phenylseleno ketone which was dissolved in THF (6.0 mL), and a solution of $NaIO_4$ (1.45 g, 6.78 mmol) in H_2O (3.0 mL) was added dropwise. After stirring the resulting suspension at rt for 2 h, the mixture was poured onto 10% Na_2CO_3 (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic phase was dried, filtered, and evaporated to give 500 mg of crude residue which was chromatographed (b, 7/3, Hex/EtOAc) to provide unsaturated ketone **41** (246 mg, 75%): mp 86–87 °C; $[\alpha]^{22}_D$ −12.6° (*c* 1.0, $CHCl_3$); IR 1675 cm^{-1}; ^1H NMR δ (two rotamers, ratio 1/1) 6.90 (m, 1H), 5.96 (m, 1H), 4.88 (m, 0.5H), 4.81 (m, 0.5H), 4.29 (t, *J* = 8.1, 0.5H), 4.17 (t, *J* = 8.4, 0.5H), 2.72 (dd, *J* = 12.5, 0.5H), 2.46 (dd, *J* = 12.5, 3.8, 0.5H), 2.42–1.23 (m, 11H), 1.46 (s, 9H); ^{13}C NMR δ (2 rotamers) 200.37 and 200.23 (0, 1C), 153.4 (0), 149.9 and 148.86 (1, 1C), 129.81 and 129.77 (1, 1C), 79.16 and 78.97 (0, 1C), 56.4, 56.0, 55.8, 54.7, 53.52 and 53.05 (1, 3C), 37.33 and 37.30 (1, 1C), 35.00 and 34.89 (2, 1C), 34.03 and 34.84 (2, 1C), 33.27 (2), 32.14 (2), 28.55 (3, 3C), 25.92 and 25.19 (2, 1C). Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.1; H, 8.6; N, 4.8. Found: C, 69.6; H, 8.5; N, 4.7.

(1*R*,2*S*,7*R*,10*R*)-3-Oxo-13-(*tert*-butoxycarbonyl)-13-azatricyclo[8.2.1.$0^{2,7}$]-4-tridecene (43). Applying the procedure described above for preparing diastereomer **41**, the saturated ketone **38** (55 mg, 0.19 mmol) provided unsaturated ketone **43** (38 mg, 70%): R_f 0.31 (7/3, Hex/EtOAc); mp 98–99 °C; $[\alpha]^{22}_D$ −86.6° (*c* 1.3, $CHCl_3$); IR 1680 cm^{-1}; ^1H NMR δ (mostly one rotamer) 6.92 (m, 1H), 6.06 (m, 1H), 5.07 (m, 1H), 4.34 (m, 1H), 2.48–1.36 (m, 12H), 1.36 (s, 9H); ^{13}C NMR δ (major rotamer) 197.6 (0), 148.9 (1), 129.2 (1), 79.6 (0), 62.7 (1), 55.9 (1), 52.8 (1), 38.0 (1), 35.1 (2), 35.0 (2), 31.6 (2), 30.9 (2), 28.5 (3, 3C, of the minor rotamer) 28.4 (3, 3C), 26.3 (2). Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.1; H, 8.6; N, 4.8. Found: C, 69.8; H, 8.6; N, 4.6.

(1*R*,7*R*,10*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-13-(*tert*-butoxycarbonyl)-13-azatricyclo[8.2.1.$0^{2,7}$]-2(3)-tridecene (44). A suspension of NaH (66 mg, 80% oil dispersion, 2.2 mmol) was washed with THF (2 × 2 mL) and the washed NaH was suspended in THF (3.25 mL). A solution of ketone **38** (130 mg, 0.44 mmol) in THF (2.0 mL + 2 × 0.3 mL rinses) containing a trace of MeOH (5 μL) was added. The suspension was stirred for 16 h, then it was cooled to −15 °C and a centrifuged solution of TBDMSCl (330 mg, 2.2 mmol) and Et_3N (0.06 mL, 48 mg, 0.43 mmol) in THF (0.42 mL) was added. The reaction mixture was stirred at rt for 21 h, poured into 1 M KH_2PO_4 (15 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phase was washed with 5% $NaHCO_3$ (20 mL), dried, filtered, and evaporated to give 110 mg of residue. Purification by column chromatography (a, 92/8, Hex/EtOAc) afforded the thermodynamic silyl enol ether **44** as a clear oil (150 mg, 83%): ^1H NMR (two rotamers, ratio 3/2): 4.99 (m, 1H), 4.29 (m, 0.6H), 4.23 (m, 0.4H), 2.33 (m, 1H), 2.01 (m, 4H), 1.78–1.54 (m, 5H), 1.53–1.37 (m, 4H), 1.46 and 1.41 (2s, 9H), 1.17 (m, 2H), 0.94 (s, 9H), 0.14 and 0.12 (2s, 6H); ^{13}C NMR δ (major rotamer) 153.6 (0), 143.2 (0), 123.4 (0), 78.4 (0), 55.9 (1), 55.6 (1), 36.6 (1), 33.5 (2), 33.1 (2), 32.6 (2), 32.0 (2), 30.5 (2), 28.6 (3, 3C), 26.6 (2), 25.8 (3, 3C), 22.2 (2), 18.1 (0), −3.4 (3, 2C).

(1*R*,10*R*)-3-Oxo-13-(*tert*-butoxycarbonyl)-13-azatricyclo-[8.2.1.$0^{2,7}$]-2-tridecene (45). A solution of PhSeCl (54 mg, 0.28 mmol) in THF (0.40 mL) was slowly added to a cold (−78 °C) solution of silyl enol ether **44** (90 mg, 0.22 mmol) in THF (1.00 mL). The solution was stirred at −78 °C for 2 h, it was warmed to 0 °C, and *m*-CPBA (70%, 136 mg, 0.55 mmol) was added in portions over 2 min. The resulting solution was stirred at 0 °C for 30 min, and then it was poured into 10% Na_2CO_3 (15 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic phase was dried, filtered, and evaporated to give 70 mg of crude which upon chromatography (b, 4/1, Hex/EtOAc) gave ketone **38** (10 mg, 0.03 mmol, 16%) and $\Delta^{2,7}$-unsaturated ketone **45** (20 mg, 31%) as an oil: R_f 0.22 (7/1 Hex/EtOAc); $[\alpha]^{22}_D$ −67.6° (*c* 0.9, $CHCl_3$); IR 1680 cm^{-1}; ^1H NMR (major rotamer) δ 5.29 (d, *J* = 9.3, 1H), 4.37 (m, 1H), 2.59 (m, 1H), 2.41–1.25 (m, 13H) and 1.37 (s, 9H); ^{13}C NMR δ 197.0 (0), 153.3 (0), 142.1 (0), 79.1 (0), 55.5 (1), 51.2 (1), 37.0 (2), 34.5 (2), 31.9 (2), 31.0 (2), 30.1 (2), 29.0 (2), 28.3 (3, 3C), 22.5 (2); HRMS, *m/z* calcd for $C_{17}H_{25}NO_3H^+$ 292.1914, found 292.1917. As described above for preparing silyl enol ether **44** from ketone **38**, ketone **36** (160 mg, 0.55 mmol) provided 260 mg of crude silyl enol ether **46** which was converted directly to $\Delta^{2,7}$-unsaturated ketone **45** by the same procedure as used with pure **44**. The yield from ketone **36** was 38 mg, 32%.

(1*R*,2*R* or *S*,7*S*,10*R*)-3-Oxo-13-azatricyclo[8.2.1.$0^{2,7}$]-4-tridecene (11). Hydrogen Fumarate. TFA (2.58 mL, 3.84 g 33.72 mmol) was added to a solution of **41** (280 mg, 0.96 mmol) in CH_2Cl, (15.5 mL). After 2.5 h, the solvent and excess TFA were evaporated and the crude TFA salt was dissolved in brine (10 mL). The aqueous solution was adjusted to pH 10 with 1 M K_2CO_3 and extracted with 3/1 $CHCl_3$/iPrOH (3 × 20 mL)). Drying and evaporating the organic layers gave the free amine **11** (170 mg, 92%). This amine in iPrOH was added to a solution of fumaric acid (113 mg, 0.97 mmol) in iPrOH (3.7 mL) at 65 °C. The resulting suspension was allowed to cool to rt and then evaporated in vacuo to give 270 mg of crude salt. Crystallization from MeOH/iPrOH/ether afforded the pure hydrogen fumarate salt of **11** (235 mg, 80% from *N*-BOC tricycle **41**): mp 204–205 °C dec; $[\alpha]^{20}_D$ −27.4° (*c* 0.5, MeOH); ^1H NMR δ (CD_3OD) 7.06 (m, 1H), 6.67 (s, 2H), 6.00 (d, *J* = 9.8, 1H), 4.63 (m, 1H), 4.09 (m, 1H), 2.72 (d, *J* = 9.7, 1H), 2.48 (m, 1H), 2.39–2.04 (m, 5H) and 1.96–1.50 (m, 5H); ^{13}C NMR (CD_3OD) 198.8 (0), 171.4 (0, 2C), 152.4 (1), 136.2 (1, 2C), 129.5 (1), 59.2 (1), 57.2 (1), 55.6 (1), 37.5 (1), 37.0 (2), 33.5 (2), 31.4 (2), 31.3 (2), 25.5 (2). Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.5; H, 6.9; N, 4.6. Found: C, 62.6; H, 7.0; N, 4.6.

(1*R*,2*S*,7*R*,10*R*)-3-Oxo-13-azatricyclo[8.2.1.$0^{2,7}$]-4-tridecene (12). Hydrogen Fumarate. Using the procedure described above for making its diastereomer **11**, the *N*-BOC tricycle **43** (64 mg, 0.22 mmol) was converted to crude free amine **12** (37 mg, 0.19 mmol, 88%). As described above for preparing the hydrogen fumarate salt of diastereomer **11**, the crude free amine **12** (37 mg, 0.19 mmol) was converted to its hydrogen fumarate (51 mg, 76% from *N*-BOC tricycle **43**): mp 109–112 °C (softens), 139–142 °C dec; $[\alpha]^{20}_D$ +81.4° (*c* 0.9, MeOH); ^1H NMR δ (CD_3OD) 7.07 (m, 1H), 6.66 (s, 2H), 6.02 (d, *J* = 10.1, 1H), 4.87 (d, *J* = 8.1, 1H), 4.10 (d, *J* = 7.23, 1H), 2.61 (d, *J* = 12.8, 1H), 2.52 (m, 2H), 2.29–1.61 (m, 8H); ^{13}C NMR δ (CD_3OD) 198.9 (0), 171.4 (0, 2C) 151.8 (1), 136.3 (1, 2C), 129.1 (1), 60.1 (1), 58.9 (1), 54.1 (1), 40.8 (1), 37.1 (2), 32.8 (2), 32.1 (2), 29.6 (2), and 27.7 (2). Anal. Calcd for $C_{16}H_{21}NO_5 \cdot CH_3OH$: C, 60.2; H, 7.4; N, 4.1. Found: C, 60.0; H, 7.2; N, 4.5.

(1*R*,10*R*)-3-Oxo-13-azatricyclo[8.2.1.$0^{2,7}$]-2-tridecene (10). Using the procedure described above for the preparation of isomer **11**, the *N*-BOC tricycle **45** provided amine **10** (12 mg, 85%): ^1H NMR δ 4.88 (dd, *J* = 9.4, 2.2, 1H), 3.72 (m, 1H), 2.97 (br s, 1H), 2.62 (m, 1H), 2.54–1.49 (m, 13H); ^{13}C NMR δ 197.7 (0), 160.9 (0), 143.3 (0), 57.8 (1), 52.2 (1), 36.9 (2), 34.3 (2), 32.5 (2), 32.4 (2), 31.9 (2), 31.0 (2), 21.1 (2). The fumarate salt was obtained as an oil and could not be crystallized.

Acknowledgment. A. Hernandez is grateful to the Ministerio de Educacion y Ciencia of Spain for a fellowship. This work was supported in part by the U.S. Army, ERDEC, under Contract No. DAAD0592W0330.

Supplementary Material Available: Copies of ^1H and ^{13}C NMR spectra of **10**, **16**, **25**, **26**, **29**, **31** (axial-OH), **31** (equatorial-OH), **32**, **34a**, **34b**, **35**, **37**, **40a**, **40b**, **44**, **45**, and pyrrolidines from **L-24** and **L-26**; experimental details for preparation of the compounds which proceeded from L-glutamic acid (45 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.