Enantiospecific Synthesis of (+)- and (−)-Ferruginine from L-Glutamic Acid. Synthesis of Tropanes *via* Intramolecular Iminium Ion Cyclization

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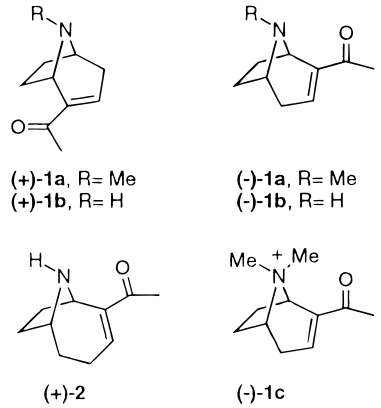
Iminium ions, generated by decarbonylation of *N*-benzyl-5-[1-(methoxycarbonyl)-4-oxopentyl]-prolines, undergo intramolecular cyclization to afford 2,4-disubstituted tropanes in good yields. This transformation is also shown to be a stereospecific reaction. The value of these substituted tropanes has been demonstrated by functional group manipulation, leading to the enantiospecific synthesis of (+)-ferruginine, an alkaloid isolated from *Darlinga ferruginea*, and its unnatural enantiomer, (−)-ferruginine.

Introduction

The alkaloid (+)-ferruginine [**(+)-1a**] has been isolated from *Darlingiana ferruginea*[1] and *D. darlingiana*,[2] and its unnatural enantiomer, (−)-ferruginine [**(−)-1a**], has been prepared from natural (−)-cocaine.[1] (−)-Ferruginine and (−)-norferruginine [**(−)-1b**] are agonists for the nicotinic acetylcholine receptor (nAChR); however, they are only 2.7×10^{-3} and 1.2×10^{-3} as potent, respectively, as (+)-anatoxin (**2**).[3] On the other hand, (−)-*N*-methylferruginine (**1c**) is more active, being 1/30 as potent as (+)-anatoxin (**2**).[3] More relevant than their relative potencies is the contrast in the effect of methylation in the ferruginine and anatoxin series. *N*,*N*-Dimethylation decreases the potency of anatoxin 10^4-fold but increases the potency of (−)-norferruginine [**(−)-1b**] 30-fold.[3] This difference in behavior and structural similarity to anatoxin (Chart 1) suggests that the design and synthesis of ferruginine analogues could contribute to further understanding of the structure/activity relationships at the nAChR.

Chart 1



Results and Discussion

The syntheses of (+)- and (−)-ferruginine (**1a**), 8-azabicyclo[3.2.1]octanes, were projected by a route similar to that applied in previous work related to anatoxin,[4] representative of 9-azabicyclo[4.2.1]nonanes, and epibatidine, 7-azabicyclo[2.2.1]heptane.[5] They were envisioned as proceeding from a 2,4-disubstituted tropane by selective manipulation of the side chains at C-2 and C-4. Formation of the tropane bicyclic system was to be completed *via* decarbonylation/intramolecular iminium ion cyclization from ketoacids **31** (Scheme 2). The skeleton of ketoacids **31** was to be produced from coupling (*S*)-1-benzyl-5-thioxoproline *tert*-butyl ester (**9**),[6] prepared from L-glutamic acid, with an appropiate 2,5-disubstituted hexanoate by the alkylation/*S*-extrusion sequence.[7]

Triflate **6** of α-hydroxy acid **5** was the obvious appropriate candidate hexanoate derivative since it varies by just one carbon in chain length from the related triflates successfully employed in the anatoxin and epibatidine series. The potential parent hydroxy ester of triflate **6** was prepared from readily available methyl vinyl ketone (**3**) which was transformed to bromo ketal **4** as described[8] (Scheme 1). The Grignard reagent from bromo ketal **4** was condensed with dimethyl oxalate, and the resulting 2-oxo ester intermediate (not shown) was hydrogenated (Pt/C, Et_3N) to afford the hydroxy ester **5** in 83% yield. Triflate **6**, however, prepared from 2-hydroxy ester **5** by treatment with Tf_2O and 2,6-di-*tert*-butyl-4-methylpyridine, was highly unstable under the formation conditions; above −20 °C, rapid polymerization took place.

Other derivatives of 2-hydroxy ester **5**, e.g., sulfonate esters and 2-halo esters, were prepared and applied. Only with the iodide **8** was alkylation of the thiolactam **9** obtained, and the subsequent *S*-extrusion reaction (Ph_3P, NMP) gave vinylogous carbamate **10**, as a mixture of geometric isomers, but only in 32% overall yield. Iodide **8** was prepared from 2-hydroxy ester **5** *via* the tosylate **7** (TsCl/Pyd, 83% yield) and nucleophilic displacement of the tosylate group by iodide anion (NaI, 94% yield). The poor results from these *S*-extrusion reactions were

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(1) Bick, I. R. C.; Gillard, J. W.; Leow, H.-M. *Aust. J. Chem.* **1979**, *32*, 2537.

(2) Bick, I. R. C.; Gillard, J. W.; Leow, H.-M. *Aust. J. Chem.* **1979**, *32*, 2523.

(3) Swanson, K. L.; Albuquerque, E. X. *Handbook of Expt. Pharmacology, Vol. 102. Selective Neurotoxicity*; Herken, H., Hucho, F. Eds.; Springer-Verlag: Berlin, Heidelberg, 1992; pp 620−621.

(4) (a) Sardina, F. J.; Howard, M. H.; Morningstar, M.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 5025. (b) Hernández, A.; Rapoport, H. *J. Org. Chem.* **1994**, *59*, 1058.

(5) Hernández, A.; Marcos, M.; Rapoport, H. *J. Org. Chem.* **1995**, *60*, 2683.

(6) Petersen, J. S.: Fels, G.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 4539 and ref 4a therein.

(7) Shiosaki, K.; Fels, G.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 3230 and refs 12−15 therein.

(8) Hsung, R. P. *Synth. Commun.* **1990**, *20*, 1175.

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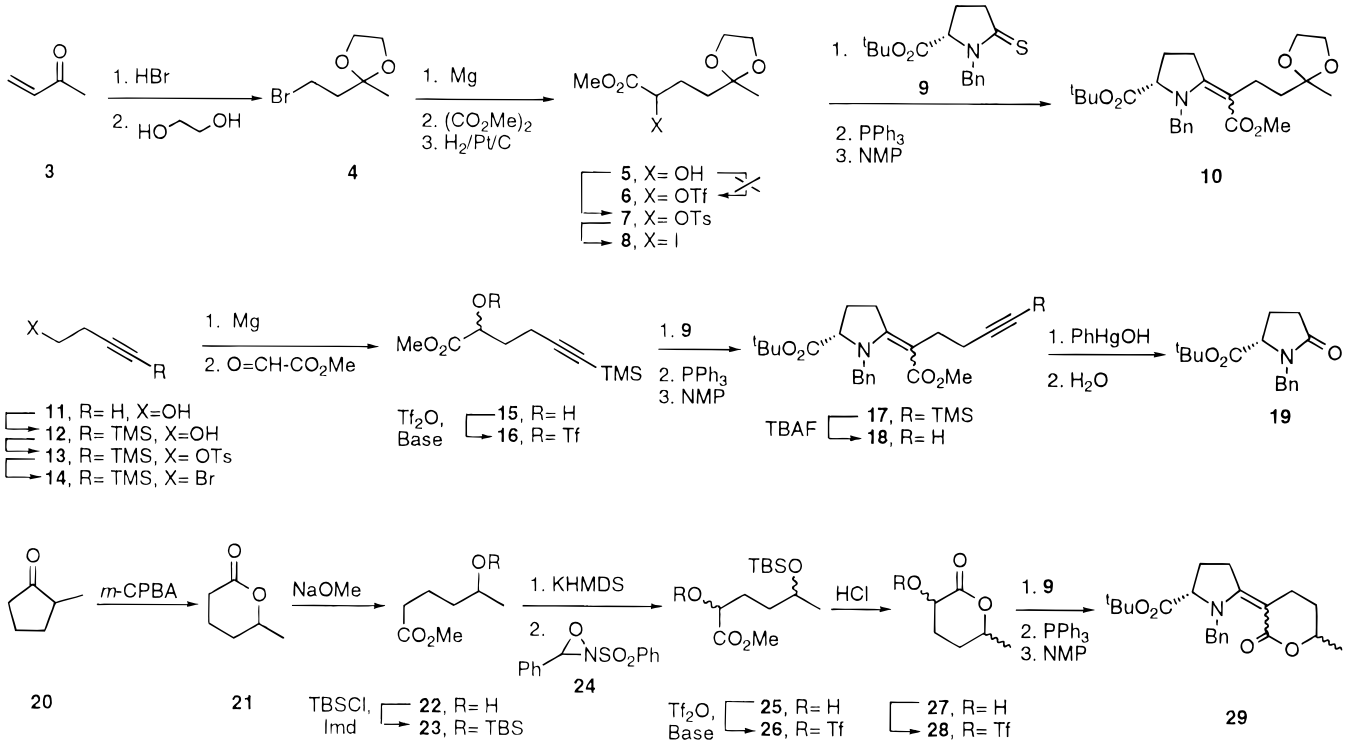
Scheme 1. Preparation of 2,5-Difunctionalized Hexanoates and Their Application in *S*-Extrusion Reactions



not completely unexpected. Our previous studies of the alkylation/*S*-extrusion reaction demonstrated that sulfonate esters, other than triflates, failed due to their poorer leaving group abilities, and halo derivatives are disadvantageous because of the propensity for the nucleophilic halide ion to reverse thioiminium salt formation. The present observations reinforce the use of triflates as the alkylating agent of choice.[7]

Ascribing these poor results to possible interaction with the 1,4-juxtaposed ethylene ketal protecting group, we considered modification or replacement of the protecting group for the function at C-5. The 4,5-dimethyl-1,3-dioxolane and 5,5-dimethyl-1,3-dioxane ketals related to ketal **5** were prepared and submitted to the triflate formation conditions; the resulting triflates were just as unstable as triflate **8**. These results support a hypothesis attributing their unstability to the existing 1,4-relationship of an oxygen to the leaving group. As an alternative, the triflate **16**, where the keto group is masked as an alkyne and no 1,4-interaction of an oxygen with the leaving group is possible, was considered as a candidate side chain for the *S*-extrusion reaction.

The parent 2-hydroxy ester **15** was made by coupling of the Grignard reagent from bromoalkyne **14**, prepared from 3-butyn-1-ol (Scheme 1) as described,[9] and methyl glyoxalate.[10] Triflate **16** was stable under the standard formation conditions. Alkylation of thiolactam **9** by triflate **16** followed by *S*-extrusion provided the vinylogous carbamate **17** in a 73% yield as a 7/3 mixture of geometric isomers. Cleavage of the TMS-protecting group with 1 M TBAF/THF gave the terminal acetylene **18** in 80% yield.

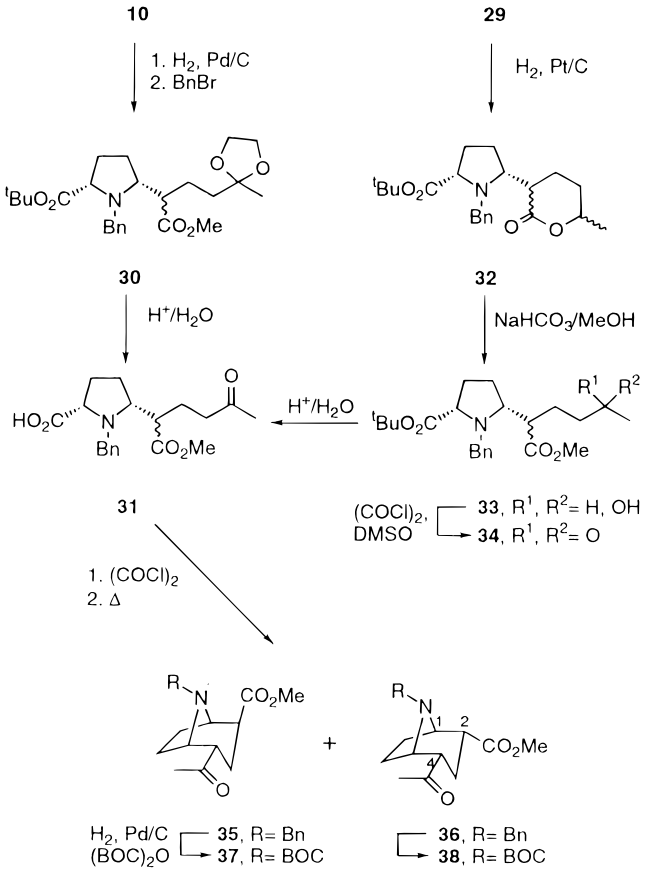
For the selective hydration of a terminal triple bond in the presence of other functional groups, PhHgOH has been indicated as the most effective reagent.[11] This reagent tolerates alkenes, and internal acetylenes afford only unreacted starting material. Unfortunately, the functional groups present in **18** produced a new and unexpected result. When excess of PhHgOH (600 mol %) was used, the lactam **19** was obtained in 78% yield. Furthermore, lactam **19** and intermediates to its formation again were the exclusive products if only 120 mol % of the reagent was used and AcOH was added in an attempt to decrease the nucleophilicity of the double bond by protonating the nitrogen. Thus the internal double bond of the vinylogous carbamate undergoes hydration faster than the terminal triple bond. Hydrogenation experiments, using modified catalysts, also showed no selectivity between either of the unsaturated functions.

At this point, other functionalities at C-5, such as a protected hydroxyl group, were considered. As protecting group, a TBDMS was chosen because its steric demand might avoid electronic interactions between the functions at C-2 and C-5. 2-Hydroxy ester **25** was prepared from 2-methylcyclopentanone (**20**) in four straightforward steps. Baeyer−Villiger oxidation (*m*-CPBA) of **20** provided δ-caprolactone (**21**) in 98% yield. Basic methanolysis (NaOMe) produced, in 93% yield, 5-hydroxy ester **22** which was converted, in 95% yield, to its TBDMS ether **23** (TBDMSCl/imidazole). The potassium enolate (KHMDS) of methyl ester **23** was α-hydroxylated (oxaziridine **24**)[12] to provide the 2-hydroxy ester **25** in 90% yield along with a small amount of adducts (four diastereomers), the nature of which is similar to that reported.[5]

2-Hydroxy ester **25** led to a stable triflate **26**, but alkylation of thiolactam **9** with triflate **26** and subsequent

(9) Negishi, E.; Boardman, L. D.; Sawada, H.; Bagheri, V.; Stoll, A. T.; Tour, J. M.; Rand, C. L. *J. Am. Chem. Soc.* **1988**, *110* , 5383.
(10) Kelly, T. R.; Schmidt, T. E.; Haggerty, J. G. *Synthesis* **1972**, 544.
(11) Janout, V.; Regen, S. L. *J. Org. Chem.* **1982**, *47*, 3331.
(12) (a) Davis, F. A; Vishwakarma, L. C.; Billmers J. M.; Finn, J. *J. Org. Chem.* **1984**, *49*, 3241. (b) Vishwakarma, L. C.; Stringer, O. D.; Davis, F. A. *Org. Synth.* **1988**, *66*, 203. (c) Davis, F. A.; Chattopadhyay, S.; Towson, J. C.; Lal, S.; Reddy T. *J. Org. Chem.* **1988**, *53*, 2087.

Scheme 2. Synthesis of 2,4-Disubstituted Tropanes from Vinylogous Carbamates 10 and 29



S-extrusion gave poor yields of the related vinylogous carbamate. The major product observed is L-lactam **19**, and the 2-thiol corresponding to ester **25** also was isolated in 45% yield. These data suggest that alkylation is occurring, but *S*-extrusion is not proceeding. Replacement of the trialkyl silyl by a MOM group led to the related MOM-triflate which was unstable due to the formation of tetrahydrofuran derivatives, the same kind of instability observed by the 1,4-interactions in the ketal examples.

To eliminate this type of interaction, we turned to internal protection of the 5-hydroxy function as its δ-lactone, 2-hydroxy δ-lactone **27**, as a synthetic target. 2-Hydroxy lactone **27** was obtained in 73% yield from 2-hydroxy ester **25** by a combined TBDMS cleavage and acid-catalyzed lactonization process (HCl/CH_2Cl_2/MeOH). The alternative α-hydroxylation of lactone **21** (KHMDS, oxaziridine **24**) or TMS-ketene acetal formation followed by oxidation with **24** failed to provide 2-hydroxy lactone **27**.

Triflate **28** was stable under formation conditions and alkylated L-thiolactam **9** to generate an α-thioiminium ion. The latter underwent *S*-extrusion to produce the vinylogous carbamate **29** as two pairs of diastereomers (9/1 ratio of geometric isomers, 1/1 ratio of epimers at C-6′, 68% yield).[13] Vinylogous carbamate **29** was contaminated with L-lactam **19** (15% yield),[13] and a further purification allowed pure **29** to be obtained. For the continuing synthesis, however, the mixture **29**/**19** was submitted to the next step after which the lactam **19** was easily removed.

(13) The yield was calculated on the basis of the weight of the mixture and the observed ratios in the ^{1}H NMR spectrum.

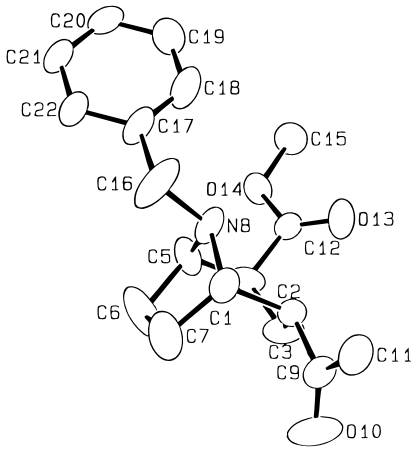


Figure 1. Structure of (1*R*,2*S*,4*S*,5*S*,)-4-Acetyl-8-benzyl-2-(methoxycarbonyl)-8-azabicyclo[3.2.1]octane (**35**) as determined by X-ray crystallography (arbitrary numbering system).

Before the synthesis of lactonic vinylogous carbamate **29**, vinylogous carbamate **10** was our exclusive and limiting source of ketoacids **31** (Scheme 2). Hydrogenation (Pd/C, MeOH) of **10** and *N*-rebenzylation ($BnBr/K_2CO_3$) afforded the *cis*-pyrrolidines **30** in 82% yield. Acidic hydrolysis of pyrrolidines **30** provided the keto acids **31** in 95% yield as a 7/3 diasteromeric mixture, the same composition as the mixture **30**.

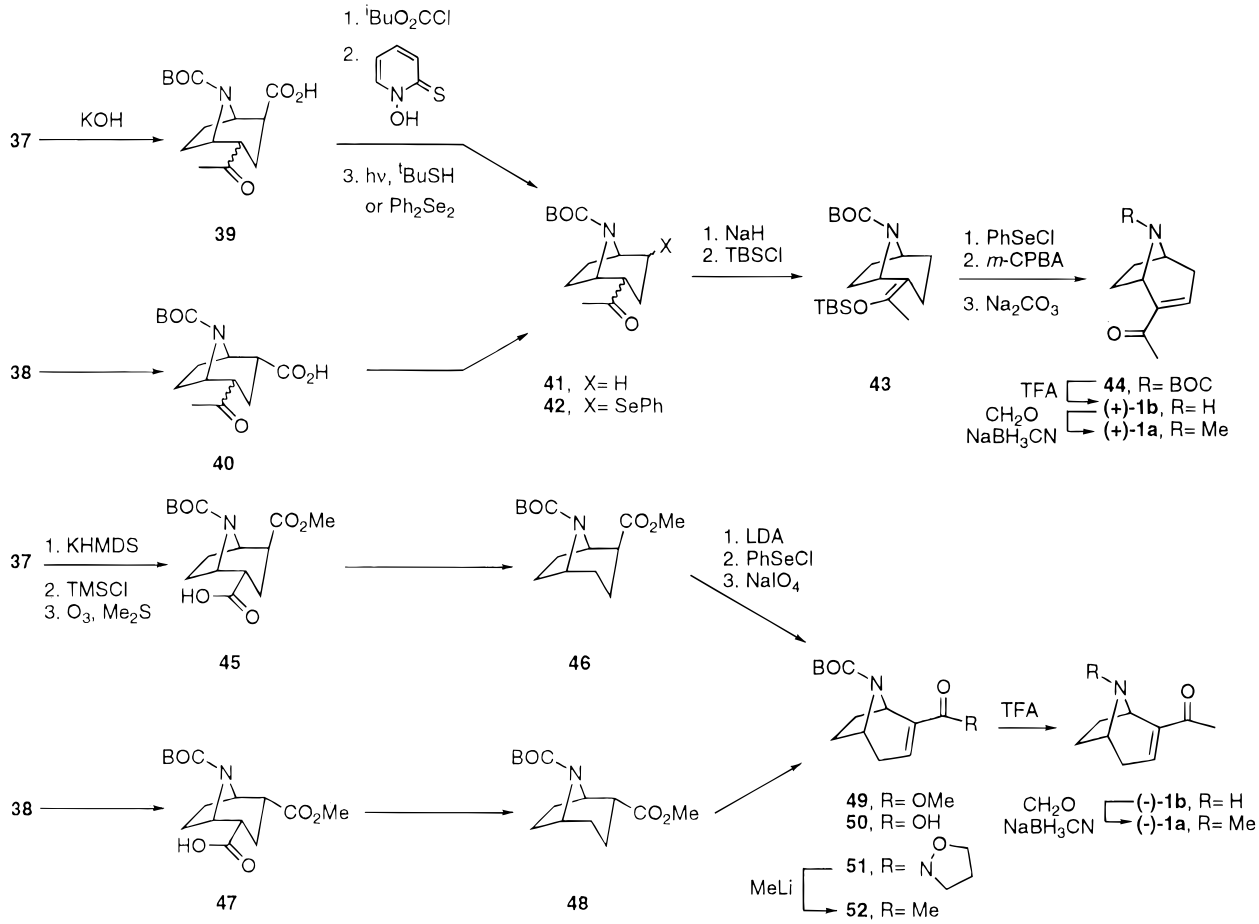
Proceeding with the lactonic variation, hydrogenation (Pt/C, EtOAc) of the vinylogous carbamate **29**/L-lactam **19** mixture afforded the *cis*-pyrrolidines **32** in 64% overall yield from L-thiolactam **9**, and at this stage L-lactam **19** was easily removed. *cis*-Pyrrolidines **32** were found as a 9/1 mixture of epimers at C-3′ of two pairs of diastereomers. Basic methanolysis ($NaHCO_3$) provided the hydroxy esters **33** in 90% yield, but the C-2′-epimeric ratio of the two diasteromeric mixtures had changed to 7/3. Oxidation of the two diasteromeric mixtures of alcohols **33** gave ketoesters **34** in 85% yield, as the expected 7/3 mixture as epimers at C-2′. Acid hydrolysis of keto esters **34** resulted in keto acids **31** (85% yield, 7/3 mixture), which were subjected to decarbonylation $(COCl)_2$/iminium ion cyclization (Δ, 1,2-DCE/toluene) to give the 2,4-disubstituted tropanes **35** and **36** in 62 and 27% yield, respectively.

We assigned the stereochemistry of bicycles **35** and **36** on the basis of ^{1}H NMR data for both bicycles in conjunction with an X-ray crystallographic structure determination of bicycle **35**. The ^{1}H NMR spectrum of bicycle **35** shows a double-double doublet and a multiplet at 3.16 and 2.44 ppm, β- and α-H, respectively,[4a,14] which can be assigned to either one H-2 or H-4 and therefore pointing to a *trans*-spatial relationships of the side chains. An X-ray crystalographic structure determination[15] of **35** (Figure 1) confirms the NMR data and also allows assignment of the *S* absolute configurations at C-2 and C-4 of bicycle **35**. The ^{1}H NMR spectrum of bicycle **36** presents a multiplet at 2.85 ppm, two β-H's, which are assigned to H-2 and H-4.[4a,14] These NMR data indicate a *cis* relationship of the side chains and the

(14) Sardina, F. J.; Howard, M. H.; Koskinen, A. M. P.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 4654.

(15) 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.

Scheme 3. Synthesis of (+)- and (−)-Ferruginine from 2,4-Disubstituted Tropanes 37 and 38



assignment of the *R* and *S* absolute configurations at C-2 and C-4, respectively, in bicycle **36**. Since the cyclization conditions do not epimerize the C-2′ stereocenter,[4b,5] each diastereomer of **31** gives only one diastereomer, **35** or **36**. Thus, intramolecular cyclization of the iminium ions generated from keto acids **31** is highly stereoselective, producing 2,4-disubstituted tropanes **35** and **36** in which the acetyl group occupies an equatorial position in the six-membered ring, an effect that probably originates from the thermodynamic nature of the iminium ion cyclization.[6]

Thus, with an 89% combined yield in the bicyclization step, we have accomplished the asymmetric synthesis of 2,4-difunctionalized tropanes which can lead to the obtention of a wide range of tropane derivatives. As a probe of the versatility of these chiro intermediates, we present the enantiospecific synthesis of (+)- and (−)-ferruginine (**1a**). Selective removal of the side chain at C-2 or C-4 and manipulation of the remaining functionality at C-4 or C-2, to introduce the double bond, could generate (+)-**1a** and (−)-**1a**, respectively.

Selective removal of either side chain was carried out by its transformation to a carboxyl group and subsequent reductive decarboxylation. Conversion of the side chain at C-2 to a carboxyl group requires simply hydrolysis of the methyl ester. Removal of the *N*-benzyl group and reprotection as the *tert*-butyl carbamate (BOC) of each bicycle **35** and **36** provided the *N*-BOC bicycles **37**, 93% yield, and **38**, 97% yield, respectively. Basic hydrolysis ($KOH/H_2O/^{i}PrOH$) of keto ester **37** gave keto acids **39** in quantitative yield, as a mixture of epimers at C-4, in a *S*/*R* ratio greater than 7/1 (Scheme 3). When keto ester **38** was submitted to the same hydrolysis conditions, keto acids **40** were obtained quantitatively, as an epimeric mixture at C-4 also, but in a *S*/*R* ratio of 3/2.

Reductive decarboxylation was effected by photolysis of the corresponding thioxamate esters[16] of each keto acid in the presence of 2-methylpropanethiol, leading to methyl ketones **41** in 79% and 81% yields as mixtures of epimers at C-2. The epimeric ratio for methyl ketones **41**, proceeding from keto acids **39**, is 9/1 and, when proceeding from keto acids **40**, is 2/1.

Introduction of the double bond was planned by selective α-selenation of the carbonyl function, followed by oxidation/elimination. Enolization (500 mol % of NaH, 10 mol % of MeOH)[4b] of ketones **41** and trapping (TBSCl) of the resulting thermodynamic enolates gave 1-(silyloxy)-alkene **43** and recovered starting ketones. *Z*-Geometry was assigned to the double bond on the basis of the configuration found for similar compounds.[14] Addition of PhSeCl to 1-(silyloxy)alkene **43** followed by oxidation (*m*-CPBA) and elimination (Na_2CO_3) of the selenoxide function provided α,β-unsaturated ketone **44**. Replacement of the carboxy function in keto acids **39** and **40** by a phenylseleno group was undertaken in order to avoid the poor enolization step and in anticipation of isomerizing the generated double bond into conjugation. When radical decarboxylation of keto acids **39** was performed in the presence of Ph_2Se_2,[17] phenylseleno ketone **42** was

(16) (a) Barton, D. H. R.; Hervé, Y.; Potier, P.; Thierry, J. *Tetrahedron* **1988**, *44*, 5479. (b) Barton, D. H. R.; Bridon, D.; Fernandez-Picot, I; Zard, S. Z. *Tetrahedron* **1987**, *43*, 2733.

(17) Barton, D. H. R.; Bridon, D; Zard, S. Z. *Heterocycles* **1987**, *25*, 449.

obtained in 73% yield as a 4/1 mixture of diastereomers. Oxidation ($NaIO_4$) of **42** occurred readily, but the resulting selenoxide did not undergo facile elimination. Treatment of the selenoxide reaction mixture with inorganic bases at rt provided low yields (≤15%) of the α,β-unsaturated ketone **44**, while various organic and inorganic bases and/or higher temperatures[18] produced complex mixtures. The selenoxide in refluxing toluene provided a 79% yield of the mixture of β,γ-unsaturated ketones which were isomerized (10% Na_2CO_3) to the α,β-unsaturated ketone **44**. Thus, the route to α,β-unsaturated ketone **44** from saturated ketones **41**, via the 4-phenylseleno ketone **42** instead of the 2-phenylseleno derivative, was longer and did not give a better overall yield.

Transformation of the side chain at C-4 to a carboxyl group occurs by kinetic enolization of the acetyl group and oxidative cleavage of the trapped enol ether. Selective enolization (KHMDS) of the acetyl groups of bicycles **37** and **38**, trapping (TMSCl) of the generated kinetic enolates, and ozonolysis[5,19] of the crude 1-(silyloxy)alkenes led to the formation of the methyl ester acids **45**, 79% yield, and **47**, 84% yield, respectively. Radical decarboxylation[16] of each acid, **45** and **47**, using 2-methylpropanethiol as radical quencher, supplied the methyl esters, **46** and **48**, in 66% and 70% yield, respectively. Both methyl esters **46** and **48** were obtained as single isomers.

Related previous work in the anatoxin field[4a] suggested the conversion of saturated esters **46** and **48** into α,β-unsaturated ketone **52** *via* the enantiomers of ketones **21**. This approach was not followed because of the poor results obtained in the thermodynamic enolization of ketones **21**, and the reverse sequence of events was considered. This last route requires producing α,β-unsaturated ketone **52** from a suitable derivative of α,β-unsaturated ester **49** by nonconjugative addition of MeMgBr or MeLi to the enone system. α,β-Unsaturated methyl ester **49** was obtained by selenation (PhSeCl) of the kinetic enolates (LDA) generated from each saturated ester **46** and **48**, in 84% and 88% yield, respectively. Basic hydrolysis ($KOH/^iPrOH/H_2O$) of α,β-unsaturated methyl ester **49** provided, quantitatively, the α,β-unsaturated acid **50** which was condensed with isoxazolidine *via* its isobutyl mixed carbonic anhydride to afford the α,β-unsaturated isoxazolidide **51** in 87% yield. Addition of MeLi to the α,β-unsaturated isoxazolidine **51** was regiospecific, producing exclusively α,β-unsaturated ketone **52** in 92% yield.

Acidic cleavage (TFA) of the nitrogen protecting group provided (+)- and (−)-norferruginine (**1b**) from the *N*-BOC unsaturated ketones **44** and **52**, respectively, in 93% yield for each. Methylation (CH_2O, $NaCNBH_3$) of the nitrogen in (+)- and (−)-norferruginine to afford (+)- and (−)-ferruginine (**1a**), respectively, was done as described for its racemic mixture.[20]

Conclusion

We report the stereospecific formation of 2,4-disubstituted 8-azabicyclo[3.2.1]octanes from L-glutamic acid and 2-methylcyclopentanone via 1-benzyl-5-[1-(methoxycarbonyl)-4-oxopentyl]proline followed by decarbonylation/iminium ion cyclization. These bicycles in turn have been converted enantiospecifically into (+)- and (−)-ferruginine (**1a**). In addition, the synthetic route produces (+)- and (−)-norferruginine, avoiding a demethylation step.[21] Other synthetic intermediates, such as esters **46** and **48**, can serve as key compounds en route to tropene and the unnatural (+)-cocaine.

Experimental Section

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

Methyl (±)-2-Hydroxy-4-(2-methyl-1,3-dioxolan-2-yl)-butanoate (5). To Mg turnings (8.06 g, 0.34 mol) suspended in THF (170 mL) was added a solution of bromo ketal **4** (27.3 g, 0.14 mol) in THF (20 mL) in one portion. After the mixture was heated to 35 °C, the formation of the Grignard reagent started and the mixture was stirred for 2 h, keeping the temperature between 30−35 °C. With stirring, the solution was cannulated into a −50 °C solution of dimethyl oxalate (24.81 g, 0.21 mol) in CH_2Cl_2 (500 mL) over a period of 30 min. The reaction mixture was allowed to reach 0 °C over an additional period of 2.5 h, and then it was cannulated into 0.5 M KH_2PO_4 (550 mL) and diluted with CH_2Cl_2 (450 mL). The aqueous layer was extracted with CH_2Cl_2 (250 mL) and the combined organic phase was washed with saturated $NaHCO_3$ (330 mL) and saturated NaCl (330 mL), the aqueous layers were back-extracted with CH_2Cl_2 (100 mL), and the combined organic phase was dried, filtered, and evaporated to give a yellow oil. To a degassed solution of this crude and Et_3N (5 mL, 3.63 g, 0.36 mol) in EtOAc (250 mL) was added 5% Pt/C (2.70 g), and the resulting suspension was hydrogenated (50 psi) overnight at rt. The solution was filtered (Celite), evaporated, and chromatographed (b, 50/50/0.2 Hex/EtOAc/Et_3N) to give 2-hydroxy methyl ester **5** (23.7 g, 83%) which was further purified by distillation (110−115 °C, 0.4 mm Hg) to give pure **5** (22.9g, 80%) as a colorless oil: IR (neat) 3460, 1730 cm^{-1}; ^{1}H NMR δ 4.25 (m, 1H), 3.95 (m, 4H), 3.79 (s, 3H), 3.15 (m, 1H), 2.00−1.70 (m, 4H), 1.33 (s, 3H); ^{13}C NMR δ 175.0 (0), 109.3 (0), 70.1 (1), 64.4 (2), 64.3 (2), 52.1 (3), 33.9 (2), 28.6 (2), 23.6 (3). Anal. Calcd for $C_9H_{16}O_5$: C, 52.9; H, 7.9. Found: C, 52.8; H, 8.1.

Methyl (±)-4-(2-methyl-1,3-dioxolan-2-yl)-2-[(*p*-toluenesulfonyl)oxy]butanoate (7). The 2-hydroxy methyl ester **5** (2.04 g, 10.0 mmol) was dissolved in pyridine (3.5 mL), and *p*-TsOH·H_2O (2.29 g, 12.0 mmol) was added. Afterthe mixture was stirred for 5 h at rt, CH_2Cl_2 (150 mL) was added and the the resulting solution was washed with saturated $NaHCO_3$ (100 mL) and saturated NaCl (100 mL). The aqueous layers were extracted with CH_2Cl_2 (50 mL each), the combined organic phase was dried, filtered, and evaporated, and the residue was chromatographed (b, 65/35 Hex/EtOAc) to provide the tosylate **7** (2.99 g, 83%), as a colorless oil: ^{1}H NMR δ 7.4 (d, *J* = 8, 2H), 7.8 (d, *J* = 8, 2H), 4.90 (m, 1H), 3.90 (m, 4H), 3.65 (s, 3H), 2.45 (s, 3H), 2.05−1.60 (m, 4H), 1.25 (s, 3H).

Methyl (±)-2-Iodo-4-(2-methyl-1,3-dioxolan-2-yl)butanoate (8). Tosylate **7** (49.1 g, 137 mmol) was added to a solution of LiI (19.1 g, 143 mmol) in THF (600 mL) at 0 °C. The reaction mixture was stirred and allowed to reach rt over a period of 3.5 h. After the THF volume was reduced by 2/3,

(18) (a) Raederstorff, D.; Shu, A. Y. L.; Thompson, J. E.; Djerassi, C. *J. Org. Chem*. **1987**, *52*, 2337. (b) Zoretic, P. A.; Chambers, R. J.; Marbury, G. D.; Riebiro, A. A. *J. Org. Chem*. **1985**, *50*, 2981.

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

(20) Davies, H. M. L.; Saikali, E.; Young, W. B. *J. Org. Chem*. **1991**, *56*, 5696.

(21) Campbell, H. F.; Edwards, O. E.; Kolt, R. *Can. J. Chem*. **1977**, *55*, 1372.

the solution was diluted with ether (1.00 L) and washed with saturated $NaHCO_3$ (450 mL), 0.4 M $Na_2S_2O_3$ (2 × 450 mL), and saturated NaCl (2 × 450 mL). The organic phase was dried, filtered, and evaporated to leave 41.0 g of crude as an orange-red oil. Chromatography (b, 85/15 Hex/EtOAc) afforded 2-iodo methyl ester **8** (40.3 g, 94%) as a colorless oil: ^{1}H NMR δ 4.35 (t, J = 7.6, 1H), 3.87 (m, 4H), 3.72 (s, 3H), 2.20−1.55 (m, 4H), 1.29 (s, 3H). Anal. Calcd for $C_9H_{15}O_4I$: C, 34.4; H, 4.8. Found: C, 34.8; H, 5.1.

(*E*/*Z*,2*S*)-1-Benzyl-5-[1-(methoxycarbonyl)-3-(2-methyl-1,3-dioxolan-2-yl)propylidene]proline *tert*-Butyl Ester (10). A solution of 2-iodo ester **8** (7.09 g, 22.6 mmol) and L-thiolactam **9** (5.92 g, 20.3 mmol) in CH_3CN (9.00 mL), containing 4 Å molecular sieves, was stirred for 25 h at 45 °C. The reaction mixture was cooled at −10 °C and diluted with CH_2Cl_2 (80 mL), additional 4 Å molecular sieves and PPh_3 (6.51 g, 24.8 mmol) were added, and the resulting suspension was stirred for 1.25 h at −5 °C. After the mixture was cooled to −25 °C, *N*-methylpiperidine (2.57 g, 26.0 mmol) was added and the mixture was stirred at −25 °C for 0.5 h and at −18 °C for 44 h. The reaction mixture was filtered, diluted with CH_2Cl_2 (300 mL), and washed with 1 M KH_2PO_4 (2 × 200 mL) and saturated $NaHCO_3$ (200 mL). The aqueous washes were extracted separately with CH_2Cl_2 (200 mL each), and the combined organic solution was dried, filtered, evaporated, and chromatographed (0−30%, Et_2O/CH_2Cl_2) to afford vinylogous carbamate **10** (2.89 g, 32%), as a mixture of two diastereomers: IR (neat) 1700, 1655 cm^{-1}; ^{1}H NMR δ (major diastereomer) 7.40−7.15 (m, 5H), 4.94 (d, J = 16.6, 1H), 4.39 (d, J = 16.6, 1H), 3.91 (m, 5H), 3.70 (s, 3H), 3.35−3.05 (m, 2H), 2.55−1.65 (m, 6H), 1.45 (s, 9H), 1.20 (s, 3H); ^{13}C NMR δ (major diastereomer) 171.7, 170.7, 161.7, 137.7, 128.6, 127.2, 126.7, 109.8, 94.9, 81.6, 66.2, 64.6, 52.2, 50.6, 39.8, 33.9, 27.9, 26.7, 24.0, 21.7. Anal. Calcd for $C_{25}H_{35}NO_6$: C, 67.4; H, 7.9; N, 3.1. Found: C, 67.0; H, 8.2; N, 2.9.

Methyl (±)-2-Hydroxy-6-(trimethylsilyl)-5-hexynoate (15). To Mg turnings (0.61 g, 25.0 mmol) suspended in THF (5 mL) was added 1 mL of a solution of bromoacetylene **14** (2.05 g, 10 mol) in THF (5 mL). When the mixture was heated to 40 °C, the formation of the Grignard reagent started and the remaining bromoacetylene **14**/THF solution was added dropwise, keeping the temperature between 30−35 °C. The mixture was stirred for 3 h at rt then cannulated into a freshly distilled (from P_2O_5) solution of methyl glyoxylate[10] (1.3 mL) in CH_2Cl_2 (35 mL) at −60 °C over 30 min. After the stirred reaction mixture was allowed to reach 0 °C over an an additional period of 2.5 h, it was cannulated into 0.5 M KH_2PO_4 (150 mL) and diluted with CH_2Cl_2 (100 mL). The aqueous layer was extracted with CH_2Cl_2 (100 mL), and the combined organic phase was washed with saturated $NaHCO_3$ (100 mL) and saturated NaCl (100 mL). The aqueous layers were back-extracted with CH_2Cl_2 (50 mL), the combined organic phase was dried, filtered, and evaporated, and the residue was chromatographed (b, 20−25% Hex/EtOAc) to give 2-hydroxy methyl ester **15** (680 mg, 32%), as a colorless liquid: ^{1}H NMR δ 4.25 (m, 1H), 3.74 (s, 3H), 2.92 (m, 1H), 2.35 (m, 2H), 1.97 and 1.75 (2m, 2H), 0.08 (s, 9H).

(*E*/*Z*,2*S*)-1-Benzyl-5-[1-(methoxycarbonyl)-3-[(trimethylsilyl)ethynyl]propylidene]proline *tert*-Butyl Ester (17). 2-Hydroxy ester **15** (240 mg, 1.12 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (345 mg, 1.68 mmol) were dissolved in CH_2Cl_2 (190 mL), and the solution was cooled at −15 °C. Freshly distilled (from P_2O_5) Tf_2O (411 mg, 1.46 mmol) was added dropwise, and the resulting white suspension was stirred, keeping the temperature below 0 °C, for 4 h. Cold hexanes (6 mL) were added, the reaction mixture was filtered, the white solid was washed with additional hexanes, and the combined filtrates were evaporated at rt. The residue was diluted with hexanes (4 mL), filtered, evaporated, and dried. The resulting crude triflate **16** (420 mg) was dissolved in CH_3CN (0.5 mL) at 0 °C, L-thiolactam **9** (261 mg, 0.90 mmol) was added, and the solution was stirred overnight at rt. The reaction mixture was cooled to −10 °C, diluted with CH_2Cl_2 (5 mL), 4 Å molecular sieves and PPh_3 (320 mg, 1.32 mmol) were added, and the resulting solution was stirred for 1.5 h. After mixture was cooled at −20 °C, *N*-methylpiperidine (128 mg, 1.29 mmol) was added dropwise and the mixture was allowed to warm to −12 °C and stirred for 24 h. The reaction mixture was poured into 0.5 M KH_2PO_4 (25 mL) and extracted with CH_2Cl_2 (2 × 25 mL). The combined organic phase was washed with saturated $NaHCO_3$ (40 mL), and the aqueous layer was back-extracted with CH_2Cl_2 (40 mL). The combined organic solution was dried, filtered, evaporated, and chromatographed (b, 0−5% Et_2O/CH_2Cl_2) to afford vinylogous carbamate **17** (300 mg, 73%), as a 7/3 mixture of diastereomers (^{1}H NMR ratio): ^{1}H NMR δ 7.40−7.15 (m, 5H), 4.94 and 4.39 (2d, J = 16.6, 2H), 3.91 (d,d J = 13.0, 3.9, 1H), 3.65 (s, 3H), 3.20, 2.85, 2.50, 2.17, 1.97 (5m, 8H), 1.43 (2s, 9H), 0.10 (s, 9H).

(*E*/*Z*,2*S*)-1-Benzyl-5-[1-(methoxycarbonyl)-3-ethynylpropylidene]proline *tert*-Butyl Ester (18). Vinylogous carbamate **17** (120 mg, 0.26 mmol) was dissolved in a 1 M solution of n-$Bu_4N^+F^-$/THF (0.7 mL), and the mixture was stirred at rt overnight. Then it was poured into water and extracted with CH_2Cl_2 (3 × 15 mL). The combined extracts were washed with brine, dried, and evaporated to provide 140 mg of residue which was chromatographed (b, 4/1 Hex/EtOAc), yielding pure terminal acetylene **18** (80 mg, 0.21 mmol, 81%) as a 7/3 mixture of geometric isomers: ^{1}H NMR δ 7.49−7.25 (m; 3H), 7.17 (m, 2H), 4.98 (d, J = 16.4, 0.70 H), 4.68 (d, J = 15.0, 0.30 H), 4.37 (d, J = 16.4, 0.70 H), 4.31 (d, J = 15.1, 0.30 H), 3.90 (m, 1 H), 3.65 (s, 3 × 0.7H), 3.59 (s, 3 × 0.3 H), 3.38−2.06 (m, 7H), 2.02−1.86 (m, 2H), 1.45 and 1.43 (2s, 9H); ^{13}C NMR δ (major diastereomer) 171.5, (0), 170.3 (0), 162.4 (0), 137.0 (0), 128.7 (1), 126.9 (1), 94.1 (0), 84.3 (1), 81.8 (0), 68.6 (0), 66.2 (1), 52.7 (2), 50.7 (3), 34.0 (2), 27.9 (3, 3C), 26.6 (2), 26.4 (2), 19.5 (2). Anal. Calcd for $C_{23}H_{29}O_4N$: C, 72.0; H, 7.6; N, 3.7. Found: C, 71.7; H, 7.8; N, 3.4.

(±)-5-Hydroxyhexanoic Acid, δ-Lactone (21)[22] was prepared from (±)-2-methylcyclopentanone (**20**) using an improved general procedure.[23] Final purification was accomplished by column chromatography (a, 7/3 Hex/EtOAc) to afford a 98% yield of the title compound: bp 110−114 °C, 15 Torr; ^{1}H NMR δ 4.44 (m, 1H), 2.58 (m, 1H), 2.44 (m, 1H), 1.89 (m, 3H), 1.52 (m, 1H), 1.38 (d, J = 6.3, 3H); ^{13}C NMR δ 171.5 (0), 76.5 (1), 29.0 (2), 28.7 (2), 21.1(3), 18.0 (2).

Methyl (±)-5-Hydroxyhexanoate (22).[24] A MeONa/MeOH solution, prepared from sodium (185 mg, 8.04 mmol) and MeOH (11 mL) and cooled at −78 °C, was cannulated into a solution of the lactone **21** (5.86 g, 51.4 mmol) in MeOH (40 mL), also cooled at −78 °C. The reaction mixture was warmed to 0 °C and stirred at this temperature for 6 h, AcOH (580 mg, 9.65 mmol) was added, and stirring was continued for an additional 15 min. Evaporation left a residue which was taken up in CH_2Cl_2 (200 mL). Washing with saturated $NaHCO_3$ (2 × 100 mL), back-extracting with CH_2Cl_2 (3 × 100 mL), drying, and evaporating provided the 5-hydroxy methyl ester **23** (6.98 g, 93% yield) as a clear liquid: bp 44 °C, 0.01 Torr; IR 3610, 3580, 1730 cm^{-1}; ^{1}H NMR δ 3.79 (m, 1H), 3.68 (s, 3H), 2.57 (s, 1H), 2.35 (t, J = 7.4, 2H), 1.71 (m, 2H), 1.47 (m, 2H), 1.38 (d, J = 6.3, 3H); ^{13}C NMR δ 174.2 (0), 67.3 (1), 51.4 (3), 38.4 (2), 33.7 (2), 23.3 (3), 20.9 (2).

Methyl (±)-5-(*tert*-Butyldimethylsilyl)oxyhexanoate (23).[25] To a solution of 5-hydroxy methyl ester **21** (6.98 g, 47.8 mmol) and imidazole (8.5 g, 1.24 mol) in CH_2Cl_2 (100 mL) was added a solution of TBDMSCl (9.74 g, 62.1 mmol) in CH_2Cl_2 (50 mL) dropwise, and the resulting suspension was stirred at rt overnight. The reaction mixture was washed with saturated $NaHCO_3$ (2 × 100 mL) and saturated NaCl (50 mL), dried, filtered, and evaporated to give 13.81 g of crude. Chromatography (a, 95/5, Hex/EtOAc) provided the TBDMS ether **23** (11.68 g, 95%) as a clear liquid: ^{13}C NMR δ 174.0 (0), 68.1 (1), 51.4 (3), 38.9 (2), 34.0 (2), 25.8 (3, 3C), 23.7 (3) 21.2 (2), 18.1 (0), −4.7 and −5.0 (3, 2C).

Methyl (2*R*/*S*,5*R*/*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-2-hydroxyhexanoate (25). A solution of methyl ester **23** (11.65

(22) Lukes, R.; Dolezal, S.; Capek, K. *Collect. Czech. Chem. Commun.* **1962**, *27*, 2408.
(23) Magnusson, G. *Tetrahedron* **1978**, *34*, 1385.
(24) Machleidt, H. v.; Cohnen, E.; Tschesche, R. *Liebigs Ann. Chem.* **1962**, *655*, 70.
(25) Solladié, G; Maestro, M. C.; Rubio, A; Pedregal C.; Carreño, M. C.; Ruano, J. L. G. *J. Org. Chem.* **1991**, *56*, 2317.

g, 44.8 mmol) in THF (45 mL) was added to 0.93 M KHMDS/THF (72.3 mL, 67.2 mmol) and diluted with additional THF (108 mL) at −78 °C over a period of 20 min, stirring the resulting solution for an additional 35 min. A suspension of oxaziridine **24** (17.55 g, 67.2 mmol) in THF (80 mL) at −78 °C was cannulated into the enolate solution over 5 min, and after being stirred for 10 min the resulting reaction mixture was quenched with saturated NH_4Cl (80 mL). The mixture was allowed to warm to rt for 25 min, most of the THF was evaporated, ether (100 mL) was added, and the aqueous layer was separated and extracted with additional ether (50 mL). The combined organic phase was washed with saturated NaCl (30 mL), dried, and evaporated to leave a solid which was taken up in 4/1 Hex/EtOAc (150 mL). The suspension was filtered, and the filtrate was evaporated to a residue which was treated with additional 4/1 Hex/EtOAc (50 mL). The resulting suspension was filtered, the filtrate evaporated to dryness, and the residue chromatographed (b, 97/3 to 4/1 CH_2Cl_2/ether) to give 2-hydroxy ester **25** (12.81 g), contaminated with an expected byproduct.[5] Further purification by chromatography (b, 4/1 to 7/3, Hex/EtOAc) afforded pure 2-hydroxy ester **25** (11.13 g, 90%): IR 3520, 1740 cm^{-1}; ^1H NMR δ 4.21 (m, 1H), 3.86 (m, 1H), 3.79 (s, 3H), 3.08 (d, J = 5.1, 0.5H), 3.01 (d, J = 6.0, 0.5H), 2.00−1.40 (m, 4H), 1.14 and 1.13 (2d, J = 6.1, 3H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR δ 175.6 and 175.5 (0, 1C), 70.7 and 70.2 (1, 1C), 68.1 and 67.8 (1, 1C), 52.3 (3), 34.6 and 34.1 (2, 1C), 30.3 and 30.1 (2, 1C), 25.7 (3, 3C), 23.4 and 23.2 (3, 1C), 18.0 (0), −4.7, −4.8 and −5.2 (3, 2C). Anal. Calcd for $C_{13}H_{28}O_4Si$: C, 56.5; H, 10.6. Found: C, 56.4; H, 10.4.

(2*R*/*S*,5*R*/*S*)-2,5-Dihydroxyhexanoic Acid, δ-Lactone (27). A saturated HCl_g/CH_2Cl_2 solution (230 mL) and then MeOH (1.23 mL, 0.97 g, 3.03 mmol) were added to a solution of 2-hydroxy ester ester **25** (11.5 g, 40.0 mmol) in CH_2Cl_2 (690 mL), and the resulting solution was stirred at rt for 1.75 h. The volume of the solution was reduced to 75 mL by a N_2 sweep over a period of 2.5 h. The remaining mixture was evaporated and chromatographed (a, 1/1 Et_2O/CH_2Cl_2) to afford 2-hydroxy lactone **27** (3.81 g, 73% yield): IR 3520, 1740 cm^{-1}; ^1H NMR δ 4.51 (m, 1H), 4.37 (m, 0.5H), 4.11 (ddd, J = 11.8, 6.5, 1.5, 0.5H), 3.44 and 3.43 (2d, J = 1.5, 3.2, 1H), 2.42 (m, 0.5H), 2.30 (m, 0.5H), 2.00 (m, 1H), 1.86 (m, 0.5H), 1.72 (m, 1.5H), 1.38 and 1.37 (2d, J = 6.3, 6.2, 3H); ^{13}C NMR δ 175.9 and 174.2 (0, 1C), 79.0, 73.9, 67.3 and 64.9 (1, 2C), 29.7, 27.7, 27.5 and 25.2 (2, 2C), 21.4 and 20.7 (3, 1C). Anal. Calcd for $C_6H_{10}O_3$: C, 55.4; H, 7.7. Found: C, 55.4; H, 8.0.

(*E*/*Z*)-(2*S*,6′*R*/*S*)-1-Benzyl-5-(6′-methyl-2′-oxotetrahydropyran-3′-ylidene)proline *tert*-Butyl Ester (29). To 2-hydroxy ester **27** (820 mg, 6.3 mmol) and 2,6-di-*tert*-butyl-4−methylpyridine (1.42 g, 6.9 mmol) dissolved in CH_2Cl_2 (19 mL) and cooled at −15 °C was added dropwise freshly distilled (from P_2O_5) Tf_2O (1.64 g, 6.27 mmol), and the resulting white suspension was stirred for 2 h, keeping the temperature below −5 °C. Cold hexanes (27 mL) were added, the reaction mixture was filtered, the white solid was washed with additional hexanes (15 mL), and the combined filtrate was evaporated and dried (in vacuo, 5 min). The resulting crude triflate **28** was dissolved in CH_3CN (1.5 mL), L-thiolactam **9** (1.47 g, 5.05 mmol) was added, and the solution was stirred for 24 h at rt. The reaction mixture was cooled at 0 °C and diluted with CH_2Cl_2 (27 mL), PPh_3 (2.48 g, 9.45 mmol) was added, and the resulting solution was allowed to warm to rt during 1 h. After the solution was cooled to −15 °C, *N*-methylpiperidine (0.94 g, 9.46 mmol) was added at 0.57 mL/min, and the mixture was allowed to warm to −3 °C and stirred for 36 h. The reaction mixture was washed with 0.5 M KH_2PO_4 (2 × 50 mL) and saturated $NaHCO_3$ (50 mL), the aqueous washes were extracted separately with CH_2Cl_2 (30 mL each), and the combined organic solution was dried, filtered, and evaporated. The yellow solid residue was triturated with 7/3 Hex/EtOAc (30 mL), the mixture filtered, and the filter cake rinsed with additional 4/1 Hex/EtOAc. Evaporation and chromatography (a, 7/3 Hex/EtOAc) of the combined filtrates afforded a mixture of vinylogous carbamate **29** and L-lactam **19** (1.45 g, 68% and 15%, respectively, as determined by ^1H NMR). The ^1H NMR spectrum also showed that vinylogous carbamate **29** is a 9/1 mixture of two pairs of diastereomers. For characterization purposes, a portion of the mixture was further chromatographed (b, 6/4 pentane/EtOAc) to isolate pure vinylogous carbamate **29**: IR 1735, 1670 cm^{-1}; ^1H NMR δ (major pair of diastereomers) 7.25 (m, 3H), 7.14 (t, J = 8.5, 2H), 5.13 (d, J = 16.8, 0.5H), 5.02 (d, J = 15.9, 0.5H), 4.33 (d, J = 15.9, 0.5 H), 4.25 (d, J = 16.9, 0.5H), 4.24 (m, 1H, overlap) 3.94 (dd, J = 9.3, 5.2, 0.5H), 3.85 (dd, J = 7.9, 6.8, 0.5H), 3.32 (m, 1H), 3.14 (m, 1H), 2.66 (m, 2H), 2.19 (m, 1H), 1.87 (m, 2H), 1.49 (m, 1H, overlap), 1.42 and 1.41 (2s, 9H), 1.31 and 1.28 (2d, J = 6.3, 3H); ^{13}C NMR δ (major pair of diastereomers) 171.4 (0, 1C), 168.9 and 168.5 (0, 1C), 165.6 and 164.5 (0, 1C),137.2 and 136.9 (0, 1C), 128.8 (1, 2C), 127.7 and 127.5 (1, 1C), 127.3 and 126.6 (1, 2C), 89.2 and 89.0 (0, 1C), 81.9 and 81.7 (0, 1C), 74.1 and 73.5 (1, 1C), 66.2 and 65.4 (1, 1C), 52.5 and 51.8 (2, 1C), 34.6 and 34.3 (2, 1C) 30.3 and 29.8 (2, 1C), 27.8 (3, 3C), 26.7 and 26.3 (2, 1C), 25.4 and 23.8 (3, 1C). Anal. Calcd for $C_{22}H_{29}NO_4$: C, 71.1; H, 7.9; N, 3.8. Found: C, 70.7; H, 8.1; N, 3.7.

(2*S*,5*R*,3′*R*/*S*,6′*R*/*S*)-1-Benzyl-5-(6′-methyl-2′-oxotetrahydropyran-3′-yl)proline *tert*-Butyl Ester (32). To a degassed solution of vinylogous carbamate **29** contaminated with L-lactam **19** (1.45 g) in dry EtOAc (19 mL) was added 5% Pt/C (191 mg), and the resulting suspension was hydrogenated (50 psi) for 13 h. The solution was filtered (Celite), the filter cake was rinsed with MeOH and CH_2Cl_2, and the combined filtrate was evaporated and chromatographed (b, 7/3 and 1/1 Hex/EtOAc) to give L-lactam **19** (170 mg, 12%) and pyrrolidines **32** (1.21 g, 64% from **9**), as a 9/1 mixture of two pairs of diastereomers: IR 1725 cm^{-1}; ^1H NMR δ (major pair of diastereomers) 7.20 (m, 5H), 4.45 (m, 0.5H), 4.24 (m, 0.5H), 3.96 (d, J = 13.8, 0.5H), 3.90 (m, 0.5H, overlap), 3.92 (d, J = 13.1, 0.5H), 3.70 (d, J = 13.1, 0.5 H), 3.64 (d, J = 13.8, 0.5H), 3.59 (m, 0.5H), 3.32 (q, J = 5.8, 1H), 2.52 (m, 1H), 2.30 (m, 1H), 1.98 (m, 4 + 0.5H), 1.81 (m, 2+ 0.5H), 1.54 (m, 1H), 1.34 and 1.31 (2d, J = 6.2, 3H, overlap), 1.32 and 1.29 (2s, 9H); ^{13}C NMR δ (major pair of diastereomers) 175.1, 174.1, 173.9 and 173.6 (0, 2C), 138.8 and 138.6 (0, 1C), 129.2 and 129.1 (1, 2C), 128.0 and 127.9 (1, 2C), 126.8 and 126.7 (1, 1C), 79.8 (0), 77.4 and 74.3 (1, 1C), 67.8 and 67.4 (1, 1C), 65.0 and 64.9 (1, 1C), 60.4 and 59.3 (2, 1C), 44.7 and 44.4 (1, 1C) 30.4, 29.7, 29.1 and 28.5 (2, 3C), 27.7 (3, 3C), 21.8 and 20.9 (3, 1C), 19.6 and 19.5.(2, 1C). Anal. Calcd for $C_{22}H_{31}NO_4$: C, 70.8; H, 8.4; N, 3.8. Found: C, 70.8; H, 8.5; N, 3.9.

(2*S*,5*R*,1′*R*/*S*,4′*R*/*S*)-1-Benzyl-5-[4′-hydroxy-1′-(methoxycarbonyl)pentyl]proline *tert*-Butyl Ester (33). To a solution of lactone **32** (1.43 g, 3.83 mmol) in MeOH (30 mL) was added $NaHCO_3$ (1.61 g, 19.9 mmol), and the suspension was stirred for 20 min at rt and 36 h at 5 °C. Chloroform (60 mL) was added, the mixture was filtered, and the solid was washed with additional $CHCl_3$ (60 mL). The solvents were removed, and the residue was dissolved in CH_2Cl_2 (100 mL), washing the solution with 0.27 M phosphate buffer (pH 7). The aqueous wash was back-extracted with CH_2Cl_2 and the combined organic phase was dried, filtered, and evaporated to leave 1.64 g of crude. Chromatography (b, 6/4 Hex/EtOAc) gave starting lactone **32** (70 mg, 5%) and hydroxy methyl ester **33** (1.39 g, 90%) as a 7/3 mixture of two pairs of diastereomers (^1H NMR ratio): IR 3510, 1725 cm^{-1}; ^1H NMR δ (major pair of diastereomers) 7.25 (m, 5H), 3.99 and 3.98 (2d, J = 13.4 and 13.5, 1H), 3.78 (m, 1H, overlap), 3.71 and 3.69 (2s, 3H), 3.68 (d, 1H, overlap), 3.23 (m, 1H), 3.07 (m, 1H), 2.63 (m, 1H), 2.00 −1.77-(m, 5H), 1.66 (m, 1H), 1.39 (m, 2H), 1.29 and 1.27 (2s, 9H), 1.17 and 1.15 (2d, J = 6.2 and 6.3, 3H); ^{13}C NMR δ (major pair of diastereomers) 175.3 (0), 174.1 and 173.6 (0, 1C), 138.6 and 138.5 (0, 1C), 129.3 (1, 2C), 128.0 (1, 2C), 126.9 (1), 80.0 and 79.8 (0, 1C), 67.6, 67.1, 67.0, 66.8 and 66.4 (1, 3C), 60.0 and 59.2 (2, 1C), 51.2 (3), 49.5 and 49.3 (1, 1C) 37.3 and 36.9 (2, 1C), 29.0 and 28.6 (2, 1C), 27.7 (3, 3C), 27.8 and 27.3 (2, 1C), 26.0 and 25.5 (2, 1C), 23.3 and 22.2.(3, 1C). Anal. Calcd for $C_{23}H_{35}NO_5$: C, 68.1; H, 8.7; N, 3.5. Found: C, 68.2; H, 8.8; N, 3.6.

(2*S*,5*R*,1′*R*/*S*)-1-Benzyl-5-[1′-(methoxycarbonyl)-4′-oxopentyl]proline *tert*-Butyl Ester (34). To a −78 °C solution of $(COCl)_2$ (0.97 g, 7.62 mmol) in CH_2Cl_2 (9.4 mL) was added DMSO (1.25 g, 16.0 mmol), and the mixture was stirred for

15 min at −78 °C, at which time a solution of hydroxy ester **33** (1.47 g, 3.63 mmol) in CH_2Cl_2 (9.4 mL) was added at 0.84 mL/min. The reaction mixture was stirred for 1.25 h, keeping the temperature at −78 °C, Et_3N (1.47 g, 14.5 mmol) was added dropwise, and stirring was continued for 10 min at −78 °C and for 1.5 h while allowing it to reach rt. The reaction mixture was washed with cold 1 M KH_2PO_4 (100 mL), the aqueous layer was extracted (3 × 100 mL) with CH_2Cl_2, the combined organic phase was washed with saturated $NaHCO_3$, dried, filtered, and evaporated, and the 1.57 g of crude residue was chromatographed (b, 7/3 to 1/1 Hex/EtOAc) to afford keto ester **34** (1.24 g, 85%) as a 7/3 mixture of diastereomers: IR 1720 cm^{-1}; ^1H NMR δ 7.27 (m, 5H), 3.98 (d, J = 13.7, 0.7 H), 3.85 and 3.75 (2d, J = 13.8, 2 × 0.3H), 3.70 (s, 3 × 0.7H), 3.69 (d, 0.7H, overlap) 3.64 (s, 3 × 0.3H), 3.24 (m, 0.7 and 2 × 0.3H), 3.09 (m, 0.7H), 2.61 (m, 0.7H), 2.40 (m, 2 and 0.3H), 2.11 (s, 3H), 2.20−1.77(m, 6H), 1.35 (s, 9 × 0.3H), 1.29 (s, 9 × 0.7H); ^{13}C NMR δ 208.1 and 207.8 (0, 1C), 175.0 and 174.7 (0, 1C), 173.4 (0), 139.1 and 138.4 (0, 1C), 129.4 and 129.0 (1, 2C), 128.0 (1, 2C), 127.0 and 126.8 (1, 1C), 80.1 and 79.7 (0, 1C), 67.3, 67.0, and 66.5 (1, 2C), 59.2 and 59.1 (2, 1C), 51.4 and 51.3 (3, 1C), 48.7 and 48.5 (1, 1C) 41.8 and 41.6 (2, 1C), 29.8 and 28.0 (3, 1C), 28.7 and 28.6 (2, 1C), 27.8 (3, 3C), 27.4 and 27.0 (2, 1C), 23.5 and 20.4.(2, 1C). Anal. Calcd for $C_{23}H_{33}NO_5$: C, 68.5; H, 8.2; N, 3.5. Found: C, 68.5; H, 8.4; N, 3.8.

(2*S*,5*R*,1′*R*/*S*)-1-Benzyl-5-[1′-(methoxycarbonyl)-3′-(2″-methyl-1″,3″-dioxolan-2″-yl)propyl]proline *tert*-Butyl Ester (30). To a degassed solution of vinylogous carbamate **10** (6.49 g, 14.6 mmol) in MeOH (200 mL) was added 10% Pd/C (1.33 g), and the resulting suspension was hydrogenated (50 psi) for 20 h. The solution was filtered (Celite), the filter cake was washed with warm MeOH (200 mL) and CH_2Cl_2 (200 mL), and the combined filtrate was evaporated to leave a residue which was dissolved in CH_3CN (50 mL). To this solution, were added calcined K_2CO_3 (6.01 g, 43.5 mmol) and BnBr (1.99 mL, 2.86 g, 16.7 mmol), and the resulting suspension was stirred at rt overnight. The reaction mixture was poured onto H_2O (250 mL) and extracted with CH_2Cl_2 (3 × 250 mL), and the combined organic solution was dried, filtered, evaporated, and chromatographed (b, 85/15 Hex/EtOAc) to give the ketal esters **31** (5.36 g, 7/3 mixture of diastereomers by ^1H NMR ratio, 82%) as a a clear oil: IR (neat) 1705 cm^{-1}; ^1H NMR δ 7.40−7.20 (m, 5H), 4.06 (d, J = 13, 1H), 3.89 (m, 4H), 3.72 (s, 3 × 0.7H), 3.68 (d, J = 13, 1H), 3.64 (s, 3 × 0.3H), 3.24 (m, 1H), 3.08 (m, 1H) 2.67 and 2.45 (2m, 1H) 2.05−1.40 (m, 8H), 1.35 (s, 3H), 1.24 (s, 9H); ^{13}C NMR δ 174.9, 173.5, 139.3, 138.6, 129.4, 128.9, 128.0, 126.9, 126.8, 109.8, 109.7, 79.8, 67.6, 67.2, 67.0, 66.7, 64.6, 64.5, 59.5, 59.2 51.4, 51.3, 49.9, 49.5, 37.1, 37.0, 28.8, 28.7, 27.9, 27.4, 27.3, 24.4, 23.8, 23.6, 21.5. Anal. Calcd for $C_{25}H_{37}NO_6$: C, 67.1; H, 8.3; N, 3.1. Found: C, 67.4; H, 8.5; N, 2.7.

(2*S*,5*R*,1′*R*/*S*)-1-Benzyl-5-[1′-(methoxycarbonyl)-4′-oxopentyl]proline (31). From 30. A solution of ester ketals **30** (5.3 g, 11.8 mmol) in *i*-PrOH (50 mL), H_2O (50 mL) and glacial acetic acid (10 mL) was refluxed for 7.5 h, cooled to rt, poured into 1.5 M KH_2PO_4 (300 mL), and extracted with $CHCl_3$ (3 × 300 mL). The combined organic phase was dried, filtered, evaporated, and chromatographed (b, 15−35% ^{i}PrOH/CH_2Cl_2) to give keto acids **31** (3.94 g, 96%).

From **34**: Using the procedure described above, keto esters **34** (1.95 g, 4.84 mmol) provided keto acids **31** (1.42 g, 85%): IR 3200, 1760, 1725 cm^{-1}; ^1H NMR δ 7.31 (m, 5H), 4.05 (d, J = 12.9, 0.7H), 3.97 (2d, J = 13.0, 0.3H), 3.78 (s, 3 × 0.3H), 3.75 (s, 3 × 0.7H), 3.69 (d, J = 12.9, 0.7H, overlap), 3.64 (d, J = 13.0, 0.3H), 3.56 (dd, J = 9.4, 3.5, 1H), 3.32 (q, J = 7.3, 0.3H), 3.17 (m, 0.7H), 2.82 (m, 0.7H), 2.49 (m, 2 and 0.3H), 2.14 (s, 3H), 2.14−1.80 (m, 4H), 1.71 (m, 2H); ^{13}C NMR δ 207.4 (0), 174.4, 174.0 and 173.2 (0, 1C), 135.7 and 135.5 (0, 1C), 129.5, 129.4, 128.7, 128.1 (1, 5C), 67.6 and 67.5 (1, 1C), 66.2 and 65.6 (1, 1C), 59.5 and 57.8 (2, 1C), 52.0 and 51.9 (3, 1C), 46.2 and 46.1 (1, 1C) 41.1 and 40.7 (2, 1C), 29.8 (3), 28.8, 28.5, 26.5, 23.3, and 22.3 (2, 3C). Anal. Calcd for $C_{19}H_{25}NO_5 \cdot 1/3H_2O$: C, 64.6; H, 7.3; N, 4.0. Found: C, 64.8; H, 7.3; N, 3.8.

(1*R*,2*S*,4*S*,5*S*)- and (1*R*,2*R*,4*S*,5*S*)-4-Acetyl-8-benzyl-2-(methoxycarbonyl)-8-azabicyclo[3.2.1]octane (35) and (36). A solution of keto acids **31** (580 mg, 1.67 mmol) in 1,2-DCE (5.0 mL) was added at 0.39 mL/min to a solution of oxalyl chloride (291 mg, 2.29 mmol) in 1,2-DCE (9.0 mL) cooled at −12 °C. The solution was stirred for 3 h, allowing it to reach 0 °C, 1,2-DCE (20 mL) was added, and the solution was warmed to rt over a period of 5 min. Toluene (11 mL) was added, the solution was immersed in a preheated bath (60 °C) and stirred for 17 h under an Ar atmosphere, the mixture was allowed to cool to rt and then washed with saturated $NaHCO_3$ (93 mL), and the aqueous washing was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phase was washed with saturated NaCl (50 mL), dried, filtered, and evaporated to give a light brown oil (620 mg) which was chromatographed (b, 7/3 Hex/EtOAc) to afford bicyclic ketones **35** (310 mg, 62%)- and **36** (140 mg, 27%).

35: mp 69 °C; $[\alpha]^{21}_D$ +29.2° (*c* 1.15, $CHCl_3$); IR 1730, 1705 cm^{-1}; ^1H NMR δ 7.26 (m, 5H), 3.55 (m, 1H, overlap), 3.54 (s, 3H), 3.51 (d, J = 13.4, 1H), 3.49 (m, 1H, overlap), 3.37 (d, J = 13.4, 1H), 3.16 (ddd, J = 12.3, 4.8, 2.6, 1H), 2.44 (m, 1H), 2.10 (s, 3H), 2.06 (m, 2H), 1.93 (m, 1H), 1.66 (m, 1H), 1.54 (m, 2H); ^{13}C NMR δ 209.3 (0), 173.7 (0), 139.4 (0), 128.5 (1, 2C), 127.9 (1, 2C), 126.8 (1), 62.1 (1), 61.1 (1), 58.0 (2), 52.6 (1), 51.3 (3), 45.8 (1), 28.4 (3), 25.7 (2), 22.9 (2), 19.3 (2). Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.7; H, 7.7; N, 4.7. Found: C, 71.5; H, 7.8; N, 4.5.

36: mp 113 °C, $[\alpha]^{21}_D$ +34.6° (*c* 1.00, $CHCl_3$); IR 1730, 1705 cm^{-1}; ^1H NMR δ 7.31 (m, 5H), 3.64 (s, 3H) 3.63 (s, 2H), 3.48 (m, 2H), 2.85 (m, 2H), 2.07 (s, 3H), 1.97−1.78 (m, 4H), 1.61−1.45 (2m, 2H); ^{13}C NMR 8,9 δ 286.8 (0), 173.8 (0), 139.2 (0), 128.4 (1, 2C), 128.3 (1, 2C), 127.0 (1), 60.7 (1), 59.9 (1), 56.2 (1), 52.4 (1), 51.6 (3), 44.4 (1), 28.4 (3), 24.1 (2), 23.7 (2), 20.9 (2). Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.7; H, 7.7; N, 4.7. Found: C, 71.7; H, 7.8; N, 4.8.

(1*R*,2*S*,4*S*,5*S*)-4-Acetyl-8-(*tert*-butoxycarbonyl)-2-(methoxycarbonyl)-8-azabicyclo[3.2.1] octane (37). To a solution of **35** (330 mg, 1.10 mmol) in MeOH (13 mL) was added $(BOC)_2O$ (960 mg, 4.40 mmol) followed by 10% Pd/C (70 mg), and the resulting suspension was hydrogenated (50 psi, rt) for 3.5 h. The reaction mixture was filtered, the insoluble material was thoroughly washed with MeOH and CH_2Cl_2, and the combined filtrates were evaporated. The residue was diluted with ether, washed with saturated $NaHCO_3$ and saturated NaCl, dried, and evaporated, leaving an oil which was chromatographed (b, 7/3 Hex/EtOAc) to afford *N*-BOC carbamates **37** (310 mg, 91%) as a clear oil: $[\alpha]^{22}_D$ +107.2° (*c* 1.00, $CHCl_3$); IR 1725, 1685 cm^{-1}; ^1H NMR δ (rotamers) 4.63 and 4.42 (2m, 2H), 3.70 (s, 3H), 3.32 (m, 1H), 2.55 (m, 1H), 2.19 (s, 3H), 1.92−1.82 (m, 4H), 1.63 (m, 2H), 1.46 (s, 9H); ^{13}C NMR δ (rotamers) 208.2 (0), 173.5 and 173.0 (0, 1C), 152.2 (0), 79.4 (0), 54.7, 53.5, 53.3, 50.0, 44.5 and 44.1 (1, 4C), 51.7 (3), 28.7 and 28.0 (2, 1C), 28.3 (3), 28.1 (3, 3C), 24.1 and 23.4 (2, 1C), 19.5 (2). Anal. Calcd for $C_{16}H_{25}NO_5$: C, 61.7; H, 8.1; N, 4.1. Found: C, 61.4; H, 8.1; N, 4.4.

(1*R*,2*R*,4*S*,5*S*)-4-Acetyl-8-(*tert*-butoxycarbonyl)-2-(methoxycarbonyl)-8-azabicyclo[3.2.1] octane (38). Using the procedure described above, *N*-Bn bicycle **36** (330 mg, 1.10 mmol) gave the related *N*-BOC carbamate **38** (330 mg, 97%): $[\alpha]^{22}_D$ +44.0° (*c* 1.01, $CHCl_3$); IR 1730, 1690 cm^{-1}; ^1H NMR δ (rotamers) 4.48 and 4.39 (2m, 2H), 3.70 (s, 3H), 2.82 (m, 2H), 2.18 (s, 3H), 2.00 (m, 4H), 1.68 (m, 1H), 1.50 (m, 1H), 1.50 (s, 9H); ^{13}C NMR δ (rotamers) 207.3 (0), 172.6 (0), 152.8 (0), 79.9 (0), 55.0, 54.5, 54.0, 52.2, 51.2, 44.2 and 43.4 (1, 4C), 51.6 (3), 28.4, 28.3, 28.2 and 28.1 (3, 4C), 25.6, 25.0, 24.2 and 20.8 (2, 3C). Anal. Calcd for $C_{16}H_{25}NO_5$: C, 61.7; H, 8.1; N, 4.1. Found: C, 61.9; H, 8.1; N, 4.4.

(1*R*,2*S*,4*S*/*R*,5*S*)-4-Acetyl-8-(*tert*-butoxycarbonyl)-2-carboxy-8-azabicyclo[3.2.1]octane (39). To 1.8 M KOH/H_2O (4.90 mL, 8.82 mmol) was added a solution of keto esters **37** (270 mg, 0.87 mmol) in *i*-PrOH (14.0 mL) at 0 °C, and the mixture was stirred for 40 min at 0 °C and 3.6 h at rt. Most of the *i*-PrOH was evaporated, H_2O (4.5 mL) was added, and the solution was cooled at 0 °C and adjusted to pH 3.2 with 1 M H_3PO_4. The aqueous solution was extracted with $CHCl_3$ (5 × 20 mL), and the combined organic phase was dried, filtered, and evaporated to provide keto acids **39** (256 mg, 99%) as a mixture of epimers at C-4 in an *S*/*R* ratio ≥ 7/1: ^1H NMR δ

(*S*-epimer, rotamers) 11.0 (s, 1H) 4.56 (m, 2H), 3.23 (m, 1H), 2.53 (m, 1H), 2.14 (2s, 3H), 2.06−1.53 (m, 6H), 1.46 (s, 9H); ^{13}C NMR δ (rotamers) 208.5 (0), 178.2(0), 152.5 (0), 80.1 (0), 54.8, 53.6, 53.3, 50.1 and 44.5 (1, 4C), 28.9 (2), 28.5, 28.3 and 28.1 (3, 4C), 23.5 (2), 19.4 (2). Anal. Calcd for $C_{15}H_{23}NO_5 \cdot 1/3H_2O$: C, 59.4; H, 7.9; N, 4.6. Found: C, 59.2; H, 8.02; N, 4.4.

(1*R*,2*R*,4*S*/*R*,5*S*)-4-Acetyl-8-(*tert*-butoxycarbonyl)-2-carboxy-8-azabicyclo[3.2.1] octane (40). Using the procedure described above, keto ester **38** (160 mg, 0.51 mmol) gave the corresponding keto acids **40** (150 mg, 93%) as a mixture of epimers at C-4 in an *S*/*R* ratio of 3/2: ^{1}H NMR δ (epimers, rotamers) 4.85−4.4 (m, 2H), 3.20 (m, 0.4H), 2.85 (m, 2 × 0.6H), 2.62 (m, 0.4H), 2.30 (s, 3 × 0.4H), 2.20 (s, 3 × 0.6H), 2.20−1.55 (m, 6H), 1.50 and 1.42 (2s, 9H); ^{13}C NMR δ (epimers, rotamers) 209.0 and 207.7 (0, 1C), 178.0 and 177.1 (0, 1C), 153.0 (0), 80.4 (0), 55.0, 54.0, 52.6, 51.2, 44.1 and 42.2 (1, 4C), 28.3, 28.3 and 28.1 (3, 4C), 25.1, 24.9, 24.3, 20.5 and 19.4 (2, 3C).

(1*S*,2*S*/*R*,5*S*)-2-Acetyl-8-(*tert*-butoxycarbonyl)-8-azabicyclo[3.2.1]octane (41). To a solution of keto acids **39** (256 mg, 0.86 mmol) in THF (6.00 mL) at −10 °C was added Et_3N (139 mg, 1.37 mmol) and isobutyl chloroformate (179 mg, 1.31 mmol). After 20 min, a solution of *N*-hydroxy-2-thiopyridone (234 mg, 1.84 mmol) and Et_3N (190 mg, 1.87 mmol) in THF (6 mL) was added, and the resulting mixture was allowed to warm to rt during 2.6 h, sheltered from the light. The precipitate of $Et_3NH^+Cl^-$ was filtered off and washed with dry THF (15 mL). The yellow filtrate and washing were irradiated for 2 h in the presence of 2-methylpropanethiol (854 mg, 9.47 mmol) with two tungsten lamps (100 w each) at rt (water bath). The solution was reduced to ∼8 mL, diluted with ether (50 mL), and then washed with saturated $NaHCO_3$ (50 mL) and saturated NaCl (20 mL). Drying and evaporation gave a residue which was chromatographed (b, 4/1 Hex/EtOAc) to provide ketones **41** (172 mg, 79% yield) as a 9/1 mixture of epimers at C-2. A further chromatography (b, 4/1 Hex/EtOAc) allowed isolation of pure *S*-epimer **41**, which solidified upon standing: mp 60−61 °C; $[\alpha]^{22}_D$ +112.1° (*c* 1.00, $CHCl_3$); IR 1695, 1680 cm^{-1}; ^{1}H NMR δ (rotamers) 4.45 and 4.37 (2m, 1H) 4.23 and 4.14 (m, 1H), 2.89 and 2.77 (2m, 1H), 2.16 (s, 3H), 1.90 (m, 3H), 1.70−1.49 (m, 5H), 1.49 (s, 9H); ^{13}C NMR δ (rotamers) 208.5 (0), 153.2 and 152.8 (0, 1C), 79.2 (0), 54.7, 54.2, 53.7, 53.0 and 51.9 (1, 3C), 29.8 and 29.1 (2, 1C), 28.3 and 28.1 (3, 3 + 1C), 27.9 and 27.2 (2, 1C), 25.2 and 24.4 (2, 1C), 18.1 (2). Anal. Calcd for $C_{14}H_{23}NO_3$: C, 66.4; H, 9.2; N, 5.5. Found: C, 66.3; H, 9.3; N, 5.4.

Using the same procedure, the keto acid **40** (150 mg, 0.51 mmol) gave the ketones **41** (103 mg, 81%) as a 2/1 mixture of epimers at C-2. Chromatography (b, 7/3 Hex/ EtOAc) gave a 93% mixture enriched in the *R*-epimer **41**: ^{1}H NMR δ (*R*-epimer, rotamers) 4.79 and 4.64 (2m, 1H) 4.35 and 4.18 (2m, 1H), 2.47 (d, J = 4.4, 1H), 2.31 (bs, 3H), 2.12−1.88 (m, 3H), 1.75 (m, 1H), 1.61 (m, 2H), 1.42 (s, 9H), 1.36 (m, 2H overlap). Anal. Calcd for $C_{14}H_{23}NO_3$: C, 66.4; H, 9.2; N, 5.5. Found: C, 66.6; H, 9.2; N, 5.6.

(1*R*,2*R*/*S*,4*R*/*S*,5*S*)-4-Acetyl-8-(*tert*-butoxycarbonyl)-2-(phenylseleno)-8-azabicyclo[3.2.1]octane (42). To a solution of keto acids **41** (60 mg, 0.20 mmol) in THF (1.00 mL) at 0 °C were added Et_3N (29 mg, 0.29 mmol) and isobutyl chloroformate (42 mg, 0.31 mmol). After 15 min, a solution of *N*-hydroxy-2-thiopyridone (45 mg, 0.35 mmol) and Et_3N (36 mg, 0.36 mmol) in THF (0.60 mL) was added dropwise, and the mixture was allowed to warm to rt for 2 h, sheltered from the light. The precipitate of $Et_3NH^+Cl^-$ was filtered off and washed with dry THF. The combined filtrate and washing were evaporated, and the residue was dissolved in CH_2Cl_2 (2.00 mL). A solution of Ph_2Se_2 (218 mg, 0.69 mmol) in CH_2Cl_2 (4 mL) was added, and the mixture was irradiated for 2 h with two tungsten lamps (100 W each) at rt (water bath). The reaction mixture was taken to dryness and chromatographed (b, 4/1 Hex/EtOAc) to provide 4-phenylseleno ketones **42** (60 mg, 73% yield): ^{1}H NMR δ (major diastereomer, rotamers) 7.53 (m, 2H), 7.27 (m, 3H), 4.66 and 4.55 (2m, 1H) 4.48 and 4.08 (2m, 1H), 3.45 (m, 1H), 3.25 and 3.02 (2m, 1H), 2.15 (s, 3H), 2.15−1.82.90 (m, 5H), 1.60 (m, 1H), 1.52 (s, 9H); ^{13}C NMR δ (rotamers) 208.3 and 207.1 (0, 1C), 152.8 and 152.7 (0, 1C), 133.9 and 133.4 (1, 1C), 129.8 and 128.8 (0, 2C), 129.1 (1, 2C), 79.9 (0), 57.4, 53.8, 53.1, 49.6, 46.2 and 43.7 (1, 4C), 29.7 (3), 28.3 (3, 3C), 25.0, 24.6 and 24.3 (2, 3C).

(*Z*,1*S*,5*S*)-2-[[1-(*tert*-Butyldimethylsilyl)oxy]ethylidene]-8-(*tert*-butoxycarbonyl)-8-azabicyclo[2.2.1]octane (43). A suspension of NaH (69 mg, 80% oil dispersion, 2.30 mmol) was washed with THF (2 × 1.0 mL). A solution of ketone **41** (110 mg, 0.43 mmol) and MeOH (8 mg, 0.12 mmol) in THF (2.60 mL) was added to a suspension of the washed NaH in THF (3.25 mL) at 0 °C, and the mixture was stirred for 14 h at this temperature. After the mixture was cooled to −12 °C, a centrifugated solution of TBDMSCl (330 mg, 2.20 mmol) and Et_3N (48 mg, 0.43 mmol) in THF (0.42 mL) was added and stirring was continued for 9 h at rt. The reaction mixture was poured into 1 M KH_2PO_4 (15 mL) and extracted with CH_2Cl_2 (4 × 20 mL). The combined organic phase was washed with 5% $NaHCO_3$ (15 mL), dried, filtered, and evaporated to give 170 mg of crude enol ether. Purification by chromatography (b, 4/1 Hex/EtOAc) provided 1-(silyloxy)alkene **43** (56 mg, 35%) as a single diastereomer and starting material **41** (50 mg, 45%). **43**: ^{1}H NMR δ (rotamers) 5.13 (m, 1H) 4.24 (m, 1H), 2.17(m, 2H), 1.96 (m, 2H), 1.84 (m, 1H), 1.71 (s, 3H), 1.63−1.42 (m, 3H), 1.42 (s, 9H), 0.93(s, 9H), 0.11 and 0.90 (2s, 6H); ^{13}C NMR δ (rotamers) 138.6, 116.5, 78.9, 53.2, 30.6, 30.0, 28.6 (3C), 28.4, 27.0, 25.9 (3C), 25.8, 25.7, 25.6, 20.1, 18.2, −3.8 and −3.9 (2C).

(1*S*,5*R*)-2-Acetyl-8-(*tert*-butoxycarbonyl)-8-azabicyclo-[3.2.1]-2-octene (44). A solution of PhSeCl (55 mg, 0.29 mmol) in THF (0.80 mL) was slowly added to a cold (−78 °C) solution of silyl enol ether **43** (56 mg, 0.15 mmol) in THF (2.00 mL). The solution was stirred at −78 °C for 2 h, and then it was warmed to 0 °C and *m*-CPBA (112 mg, 70−75%, ∼0.45 mmol) was added in portions over 2 min. The resulting solution was stirred at 0 °C for 30 min, and then it was poured onto 10% Na_2CO_3 (20 mL) and extracted with CH_2Cl_2 (4 × 20 mL). The organic phase was dried, filtered, and evaporated to give 60 mg of crude which was chromatographed (b, 7/3 Hex/EtOAc) to give α,β-unsaturated ketone **44** (28 mg, 74%).

Enolization/trapping (5.3 and 3.5 h reaction times, respectively) and selenation/oxidation as described above, with no chromatography of the 1-(silyloxy)alkene **43**, from ketones **41** (173 mg, 0.68 mmol) gave a better overall yield of α,β-unsaturated ketones **44** (82 mg, 48%): mp 64−65 °C; $[\alpha]^{24}_D$ +129.1° (*c* 1.00, $CHCl_3$); IR 1685, 1665 cm^{-1}; ^{1}H NMR δ (rotamers) 6.66 (m, 1H), 4.92 (d, J = 5.7, 1H) 4.36 (m, 1H), 2.93 (m, 1H), 2.27 (s, 3H), 2.15 (m, 1H), 2.04 (m, 2H), 1.79 (dt, J = 2.4, 11.8, 1H), 1.55 (m, 1H), 1.43 (s, 9H); ^{13}C NMR δ (rotamers) 196.4 (0), 153.9 (0), 145.5 (0), 137.1 (1), 79.5 (0), 52.0 (1), 51.2 (1), 34.9 (2), 34.6 (2), 29.7 (2), 28.3 (3, 3C), 24.8 (3). Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.9; H, 8.4; N, 5.6. Found: C, 66.7; H, 8.5; N, 5.4.

(1*S*,5*R*)-2-Acetyl-8-azabicyclo[3.2.1]-2-octene, (+)-Norferruginine [(+)-1b]. TFA (562 mg, 4.93) was added to a solution of *N*-BOC bicycle **44** (34 mg, 0.14 mmol) in CH_2Cl_2 (2.26 mL). After 3 h at rt, the solvents and excess TFA were evaporated and the crude TFA salt was dissolved in brine (4 mL). The aqueous solution was adjusted to pH 10 with 1 M K_2CO_3 and extracted with 3/1 $CHCl_3$/^{i}PrOH (3 × 10 mL). The combined organic phase was dried, filtered, and evaporated to give the free amine (+)-**1b** (19 mg, 93%): $[\alpha]^{22}_D$ +69.4° (*c* 0.96, $CHCl_3$); ^{1}H NMR spectrum identical to that reported for the racemic mixture (±)-**1b**.[20]

(1*S*,5*R*)-2-Acetyl-8-methyl-8-azabicyclo[3.2.1]-2-octene, (+)-ferruginine [(+)-1a].[1] Methylation (CH_2O, $NaCNBH_3$) of the nitrogen in (+)-norferruginine [(+)-**1b**] to afford (+)-ferruginine [(+)-**1a**] was done as described[20] for its racemic mixture. The ^{1}H NMR spectrum is identical to that of its racemic mixture (±)-**1a**.[20]

(1*R*,2*S*,4*S*,5*S*)-8-(*tert*-Butoxycarbonyl)-4-carboxy-2-(methoxycarbonyl)-8-azabicyclo[3.2.1]octane (45). A 0.94 M KHMDS/THF solution (0.65 mL, 0.61 mmol) was cooled to −78 °C and cannulated into a solution of keto esters **37** (100 mg, 0.32 mmol) in THF (2 mL), also cooled at −78 °C. The resulting solution was stirred at −78 °C for 45 min, and TMSCl (163 mg, 1.50 mmol) was added. The mixture was stirred at

−78 °C for 10 min and then allowed to warm to 0 °C for 30 min. It was diluted with hexanes (9 mL) and washed with 0.01 M phosphate buffer (pH 7, 2 × 10 mL). The aqueous layer was extracted with hexanes (2 × 10 mL), and the combined organic phase was dried, filtered, and evaporated to provide a crude which was dissolved in CH_2Cl_2 (6.6 mL). Methanol (8.4 mL) was added, and the resulting solution was treated with excess O_3 at −78 °C. After O_2 and N_2 purges, the −78 °C solution was treated with Me_2S (93.1 mg, 1.50 mmol), stirred at this temperature for 15 min, and allowed to warm to rt during 4 h. Evaporation gave a residue which was dissolved in 20% $KHCO_3$ (9 mL), washed with $CHCl_3$ (3 × 10 mL), and adjusted to pH 3.2 with 1 M H_3PO_4. The acidic aqueous phase was extracted with $CHCl_3$ (4 × 20 mL) to provide keto acid **45** (80 mg, 79%): ^{1}H NMR δ (7/2 rotamers) 9.69 (bs, 1H), 4.64 and 4.49 (2m, 2H), 3.79 (s, 3 × 0.23H), 3.69 (s, 3 × 0.77H), 3.26 (m, 1H), 2.56 (d, J = 5.3, 1H), 2.24−1.55 (m, 6H), 1.49, 1.44 (2s, 9H); ^{13}C NMR δ (rotamers) 177.0, 173.5, 172.6 and 171.7, (0, 2C), 153.0 and 152.5 (0, 1C), 80.0 and 79.9 (0, 1C), 55.1 (1), 54.6 (1), 51.9 (3), 44.2 and 44.0 (1, 1C), 42.1 (1), 28.3 (3), 28.2 (3, 3C), 28.0 (2), 25.0 (2), 20.3 (2).

(1*R*,2*R*,4*S*,5*S*)-8-(*tert*-Butoxycarbonyl)-4-carboxy-2-(methoxycarbonyl)-8-azabicyclo[3.2.1]octane (47). Using the procedure described, but performing reverse addition of the keto ester **38** (336 mg, 1.08 mmol) in THF (3.4 mL) to the 0.94 M KHMDS solution,[4] 283 mg, 84% yield, of keto acid **47** was obtained from ketoester **38**: ^{1}H NMR δ (rotamers) 4.47 (m, 2H), 3.69 (s, 3H), 2.76 (m, 2H), 2.13 (m, 1H), 2.00 (m, 3H), 1.74 (m, 2H), 1.48 (s, 9H); ^{13}C NMR δ (rotamers) 175.5 (0), 172.6 (0), 152.9 (0), 80.0 (0), 54.9 (1), 54.3 (1), 51.7 (3), 44.2 (1), 43.4 (1), 28.3 (3, 3C), 25.6 (2), 24.8 (2), 21.5 (2).

(1*R*,2*S*,5*R*)-8-(*tert*-Butoxycarbonyl)-2-(methoxycarbonyl)-8-azabicyclo[3.2.1]octane (46). Using the procedure described for making ketones **41**, the acid methyl ester **45** (193 mg, 0.62 mmol) gave the methyl ester **46** (109 mg, 81%) as an oil: $[\alpha]^{22}_D$ +15.2° (*c* 1.20, $CHCl_3$); ^{1}H NMR δ (rotamers) 4.62 (d, J= 6.3, 1H), 4.37 and 4.18 (2m, 1H), 3.69 (s, 3H), 2.45 (d, J = 5.6, 1H), 2.18−1.89 (m, 4H), 1.80−1.58 (m, 4H), 1.43 (s, 9H); ^{13}C NMR δ (rotamers) 173.9 (0), 152.8 (0), 79.0 (0), 55.3 and 54.8 (1, 1C), 53.9 and 52.7 (1, 1C), 51.7 (3), 45.3 and 44.9 (1, 1C), 28.9 and 28.4 (2, 2C), 28.4 (3, 3C), 27.5 and 26.8 (2, 1C), 18.1 (2). Anal. Calcd for $C_{14}H_{23}NO_4$: C, 66.4; H, 8.6; N, 5.2. Found: C, 66.2; H, 8.6; N, 5.4.

(1*R*,2*R*,5*R*)-2-(Methoxycarbonyl)-8-(*tert*-butoxycarbonyl)-8-azabicyclo[3.2.1]octane (48). Using the procedure described for making the ketones **41**, the methyl ester acid **47** (283 mg, 0.90 mmol) gave the methyl ester **48** (170 mg, 70%) which solidified upon standing: mp 37−38 °C; $[\alpha]^{22}_D$ −49.8° (*c* 1.00, $CHCl_3$); ^{1}H NMR δ (rotamers) 4.44 and 4.36 (2m, 1H) 4.24 and 4.13 (2m, 1H), 3.67 (s, 3H), 2.80 and 2.70 (2m, 1H), 2.04−1.63 (m, 6H), 1.60 (m, 1H), 1.50 (m, 1H), 1.48 (s, 9H); ^{13}C NMR δ (rotamers) 173.5 (0), 153.1 (0), 79.3 (0), 55.2 and 54.6 (1, 1C), 53.7 and 52.8 (1, 1C), 51.5 (3), 44.9 and 44.0 (1, 1C), 29.8 and 29.7 (2, 1C), 28.4 (3, 3C), 27.9 and 27.3 (2, 1C), 25.7 and 25.0 (2, 1C), 19.3 (2). Anal. Calcd for $C_{14}H_{23}NO_4$: C, 62.4; H, 8.6; N, 5.2. Found: C, 62.7; H, 8.5; N, 5.2.

(1*R*,5*S*)-2-(Methoxycarbonyl)-8-(*tert*-butoxycarbonyl)-8-azabicyclo[3.2.1]-2-octene (49). From 46. A solution of LDA/THF was prepared at 0 °C from diisopropylamine (229 mg, 2.28 mmol), 2.16 M BuLi (0.86 mL, 1.86 mmol), and THF (3.16 mL) by stirring for 20 min. This solution was cooled at −78 °C, and a solution of methyl ester **46** (166 mg, 0.62 mmol) in THF (1.90 mL) was added at 0.25 mL/min. The mixture was stirred at this temperature for 1 h, and then a solution of PhSeCl (437 mg, 2.28 mmol) in THF (1.00 mL) was added at 0.37 mL/min. After addition, the reaction mixture was stirred for 5 min at rt and for 1 h while warming to 0 °C. The reaction mixture was poured into 1 M KH_2PO_4 (25 mL) and extracted with CH_2Cl_2 (4 × 20 mL). The combined organic phase was dried, filtered, and evaporated to give 0.78 g of crude which was dissolved in THF (3.00 mL), and a solution of $NaIO_4$ (800 mg, 3.74 mmol) in H_2O (4.5 mL) was added dropwise to produce a suspension. After the suspension was stirred at rt for 7 h, 10% Na_2CO_3 (23 mL) was added, and the aqueous solution was stirred for an additional 15 min and then extracted with CH_2Cl_2 (4 × 20 mL). The organic phase was dried, filtered, and evaporated to give 197 mg of crude residue which was chromatograped (b, 7/3 Hex/EtOAc) to provide unsaturated methyl ester **49** (165 mg, 84%) as an oil that solidified upon standing.

From 48. Using the procedure described, methyl ester **48** (131 mg, 0.49 mmol) afforded the α,β-unsaturated ester **49** (115 mg, 88%): mp 57−58 °C; $[\alpha]^{21}_D$ −52.4° (*c* 1.00, $CHCl_3$); IR 1710, 1685 cm^{-1}; ^{1}H NMR δ (rotamers) 6.76 (t, J = 2.8, 1H), 4.81 (m, 1H) 4.34 (m, 1H), 3.76 (s, 3H), 2.86 (m, 1H), 2.18 (m, 1H), 2.11−1.88 (m, 3H), 1.58 (m, 1H), 1.44 (s, 9H); ^{13}C NMR δ (rotamers) 165.5 (0), 153.8 (0), 136.6 (1), 79.6 (0), 53.3 and 52.7 (1, 1C), 52.1 (1), 51.6 (3), 35.1, 34.8 and 34.2 (2, 2C), 30.1 and 29.6 (2, 1C), 28.3 (3, 3C). Anal. Calcd for $C_{14}H_{21}NO_4$: C, 62.9; H, 7.9; N, 5.2. Found: C, 62.8; H, 8.0; N, 5.1.

(1*R*,5*S*)-2-Carboxy-8-(*tert*-butoxycarbonyl)-8-azabicyclo[3.2.1]-2-octene (50). Using the procedure described for making the keto acids **39**, the methyl ester **49** (105 mg, 0.39 mmol) gave the acid **50** (101 mg, quantitative): ^{1}H NMR δ (rotamers) 10.4 (bs, 1H), 6.88 (m, 1H), 4.82 (m, 1H) 4.36 (m, 1H), 2.89 (m, 1H), 2.20 (m, 1H), 2.12−1.91 (m, 3H), 1.60 (m, 1H), 1.45 (s, 9H); ^{13}C NMR δ (rotamers) 169.7 (0), 153.8 (0), 139.0 and 137.7 (1, 1C), 136.1 (0), 79.4 (0), 52.9 and 52.4 (1, 1C), 51.7 and 51.0 (1, 1C), 35.0, 34.7 and 34.3 (2, 2C), 29.9 and 29.6 (2, 1C), 28.3 (3, 3C).

(1*R*,5*S*)-8-(*tert*-Butoxycarbonyl)-8-azabicyclo[3.2.1]-2-octene-2-carboxylic Acid Isoxazolidide (51). To a solution of keto acid **50** (90 mg, 0.36 mmol) in THF (1.1 mL) at −10 °C was added Et_3N (66 mg, 0.65 mmol) and isobutyl chloroformate (84 mg, 0.62 mmol). After 20 min, a suspension of isoxazolidine hydrochloride (86 mg, 0.79 mmol) and Et_3N (160 mg, 1.58 mmol) in CH_2Cl_2 (0.90 mL), previously stirred for 20 min at rt, was added *via* cannula, and the resulting mixture was allowed to warm to rt during 4.5 h. The precipitate of $Et_3NH^+Cl^-$ was filtered off and washed with THF (10 mL), and the combined filtrate and washing were evaporated and chromatographed (b, 1/1 CH_2Cl_2/EtOAc) to afford the isoxazolidide **51** (96 mg, 88%): ^{1}H NMR δ (rotamers) 6.44 (m, 1H), 4.68 (m, 1H) 4.30 (m, 1H), 3.93 (m, 3H), 3.70 (m, 1H), 2.89 (m, 1H), 2.30 (m, 2H), 2.11 (m, 3H), 1.98 (dd, J = 18.9, 4.3, 1H), 1.64 (m, 1H), 1.44 (s, 9H); ^{13}C NMR δ (rotamers) 168.1 (0), 153.9 (0), 138.3 (0), 133.2 and 132.2 (1, 1C), 79.3 (0), 69.2 (2), 54.3 and 53.7 (1, 1C), 52.2 and 51.3 (1, 1C), 44.7 (2), 35.7 (2), 33.9 (2) 30.3 and 29.6 (2, 1C), 28.3 (3, 3C), 27.1 (2).

(1*R*,5*S*)-2-Acetyl-8-(*tert*-butoxycarbonyl)-8-azabicyclo-[3.2.1]-2-octene (52). To a solution of isoxazolidide **51** (64 mg, 0.20 mmol) in THF (1.4 mL), cooled at −78 °C, was added 1.4 M MeLi/Et_2O solution (0.19 mL, 0.27 mmol) over a period of 2 min. The solution was stirred for 5 min at −78 °C and for 1 h while warming to 0 °C. The mixture was poured onto 1 M KH_2PO_4 (15 mL) and extracted with CH_2Cl_2 (4 × 20 mL). The combined organic phase was dried, filtered, and evaporated to give 55 mg of crude which was chromatographed (b, 3/1 Hex/EtOAc) to provide unsaturated ketone **52** (48 mg, 92%): mp 63−64 °C; $[\alpha]^{22}_D$ −126.8° (*c* 1.00, $CHCl_3$); ^{1}H NMR spectrum is identical to that of its enantiomer **44**.

(1*R*,5*S*)-2-Acetyl-8-azabicyclo[3.2.1]-2-octene, (−)-Norferruginine [(−)-1b]. Using the procedure described for making its enantiomer (+)-norferruginine [(+)-**1b**], the *N*-BOC bicycle **52** was converted to the amine (−)-**1b**: $[\alpha]^{22}_D$ −70.3° (*c* 1.00, $CHCl_3$); the ^{1}H NMR spectrum is identical to that of its racemic mixture (±)-**1b**.[20]

(1*R*,5*S*)-2-Acetyl-8-methyl-8-azabicyclo[3.2.1]-2-octene, (−)-Ferruginine [(−)-1a].[1] Methylation (CH_2O, $NaCNBH_3$) of the nitrogen in (−)-norferruginine [(−)-(**1b**] to afford (−)-ferruginine [(−)-(**1a**] was done as described[20] for its racemic mixture. The ^{1}H NMR spectrum is identical to that of its racemic mixture (±)-**1a**.[20]

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