An Enantioselective Synthesis of Cis Perhydroisoquinoline LY235959

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A novel synthesis of NMDA receptor antagonist LY235959 (**1**) has been achieved in 13% overall yield and 17 steps from (*R*)-pantolactone (**7**). Highlights of the synthesis include (a) use of a chiral auxiliary controlled asymmetric Diels−Alder reaction to provide the desired absolute and relative stereochemistry at C-4a, C-6, and C-8a, (b) an efficient alkylation of hindered iodide **13** using a novel amide benzophenone imine, (c) oxidative ring opening of the [2.2.2] bicyclic system to simultaneously functionalize the molecule for intramolecular cyclization and phosphonate introduction, and (d) an increased understanding of how the C-3 stereochemistry may be controlled by thermodynamic equilibration. Synthesis of epimer **20** in high overall yield makes this synthetic route attractive for future development efforts.

LY235959 (**1**) is a potent NMDA receptor antagonist previously under development for the treatment of neurodegenerative disorders such as Alzheimer's disease.[1] The synthesis of material for toxicology and clinical studies provided a number of strategic challenges. Construction of the cis-fused perhydroisoquinoline core, stereoselective installation of the amino acid center at C-3 and introduction of the axial substituent at C-6 are obvious hurdles. An initial synthesis of LY235959 (**1**), which suffered from a late stage resolution and less than 1% overall yield, has been reported.[1]

We envisioned a stereoselective approach to LY235959 (**1**) which utilized a [2.2.2] bicyclic framework to generate three of the required stereocenters (Scheme 1). Disconnection of **1** via an Arbuzov reaction leads to the precursor halide **2**. Halide **2** should be available from cyclization of a bis-functionalized intermediate **3**, wherein regiocontrolled closure should favor the desired fused ring system. Recognition that bis-activated intermediate **3** could be derived from ring opening of a [2.2.2] bicyclic system such as amino ester **4** was a key element of the synthetic strategy. It was anticipated that an asymmetric Diels−Alder reaction of cyclohexadiene with an appropriate acrylate followed by alkylation of intermediate **5** would provide an expeditious route to amino ester **4**. This retrosynthesis did not explicitly account for stereocontrol at C-3; however, we anticipated that this center could be controlled by equilibration after closure to the perhydroisoquinoline ring system.

After surveying the extensive Diels−Alder literature employing either chiral acrylates[2] or chiral Lewis acid catalysts,[3] and performing some initial experiments, (*R*)-pantolactone (**7**)-derived acrylate **8** was chosen as a suitable dienophile (Scheme 2). As described by Helmchen and co-workers, Diels−Alder reaction of acrylate **8** with cyclohexadiene provided adduct **9** in 75% yield.[4] Diels−Alder adduct **9** was converted to bicyclic iodide **13** in 80% overall yield using the four-step process shown. Ester hydrolysis using lithium hydroxide in aqueous tetrahydrofuran afforded acid **10**. After extraction of acid **10**, (*R*)-pantolactone (**7**) could be recovered in >90% yield by evaporation of the acidic aqueous layer and heating the residual solid in toluene to reclose the hydroxy-acid. Acid **10** was reduced to alcohol **11** with Red-Al and the alcohol was converted to iodide **13** via mesylate **12** under Finkelstein conditions.[5]

A variety of methods for attachment of a glycine unit to scalemic iodide **13** could be considered.[6] As the C-3 stereochemistry was to be addressed by equilibration after closure to the perhydroisoquinoline, a classical acetamido malonate alkylation was investigated first.[7] Iodide **13** reacted with diethyl acetamidomalonate sluggishly or not at all under typical reaction conditions (e.g.

(1) (a) Ornstein, P. L.; Arnold, M. B.; Augenstein, N. K.; Paschal, J. W. *J. Org. Chem.* **1991**, *56*, 4388−4392. (b) Ornstein, P. L.; Schoepp, D. D.; Arnold, M. B.; Augenstein, N. K.; Lodge, D.; Millar, J. D.; Chambers, J.; Campbell, J.; Paschal, J. W.; Zimmerman, D. M.; Leander, J. D. *J. Med. Chem.* **1992**, *35*, 3547−3560. (c) Ornstein, P. L.; Arnold, M. B.; Augenstein, N. K.; Deeter, J. B.; Leander, J. D.; Lodge, D.; Calligaro, D. O.; Schoepp, D. D. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2067−2072.

(2) For reviews, see: (a) Nogradi, M. *Stereoselective Synthesis*; VCH: Weinheim, FRG, 1987; pp 266−274. (b) Helmchen, G.; Karge, R.; Weetman, J. In *Modern Synthetic Methods 1986*; Sheffold, R., Ed.; Springer-Verlag: New York, 1986; Vol. 4, pp 262−306. For recent work, see: (c) Busacca, C. A.; Meyers, A. I. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2299−2316 and ref 1 therein. (d) Maruoka, K.; Akakura, M.; Saito, S.; Ooi, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 6153−6158.

(3) For reviews, see: (a) Kagan, H. B.; Riant, O. *Chem. Rev. (Washington, D.C.)* **1992**, *92*, 1007−1019. (b) Deloux, L.; Srebnik, M. *Chem. Rev. (Washington, D.C.)* **1993**, *93*, 763−784. (c) Togni, A.; Venanzi, L. M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 497−526. For recent work, see: (d) Evans, D. A.; Barnes, D. M. *Tetrahedron Lett.* **1997**, *38*, 57−58. (e) Corey, E. J.; Letavic, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 9616−9617.

(4) Poll, T.; Abdel Hady, A. F.; Karge, R.; Linz, G.; Weetman, J.; Helmchen, G. *Tetrahedron Lett.* **1989**, *30*, 5595−5598. See Supporting Information for a detailed procedure.

(5) Finkelstein, H. *Ber.* **1910**, *43*, 1528.

(6) (a) Greenstein, J. P.; Winitz, M. *Chemistry of the Amino Acids*; Wiley: New York, 1961; Volume 2, pp 697−714. (b) For a review of asymmetric methods, see: Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539−1650.

(7) (a) See ref 6a, pp 709−712. (b) Albertson, N. F. *J. Am. Chem. Soc.* **1946**, *68*, 450−453.

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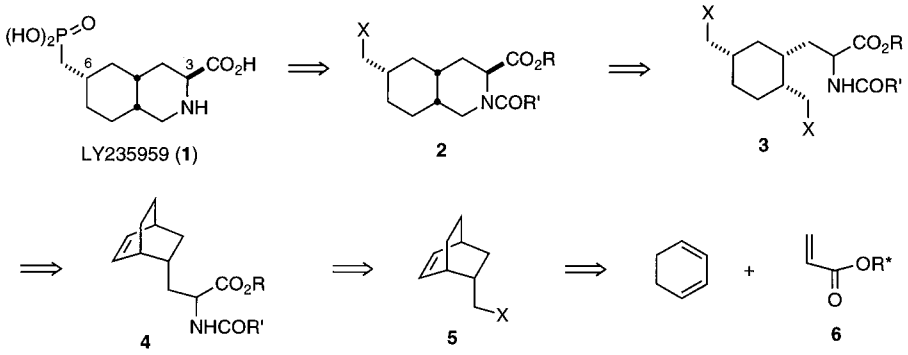
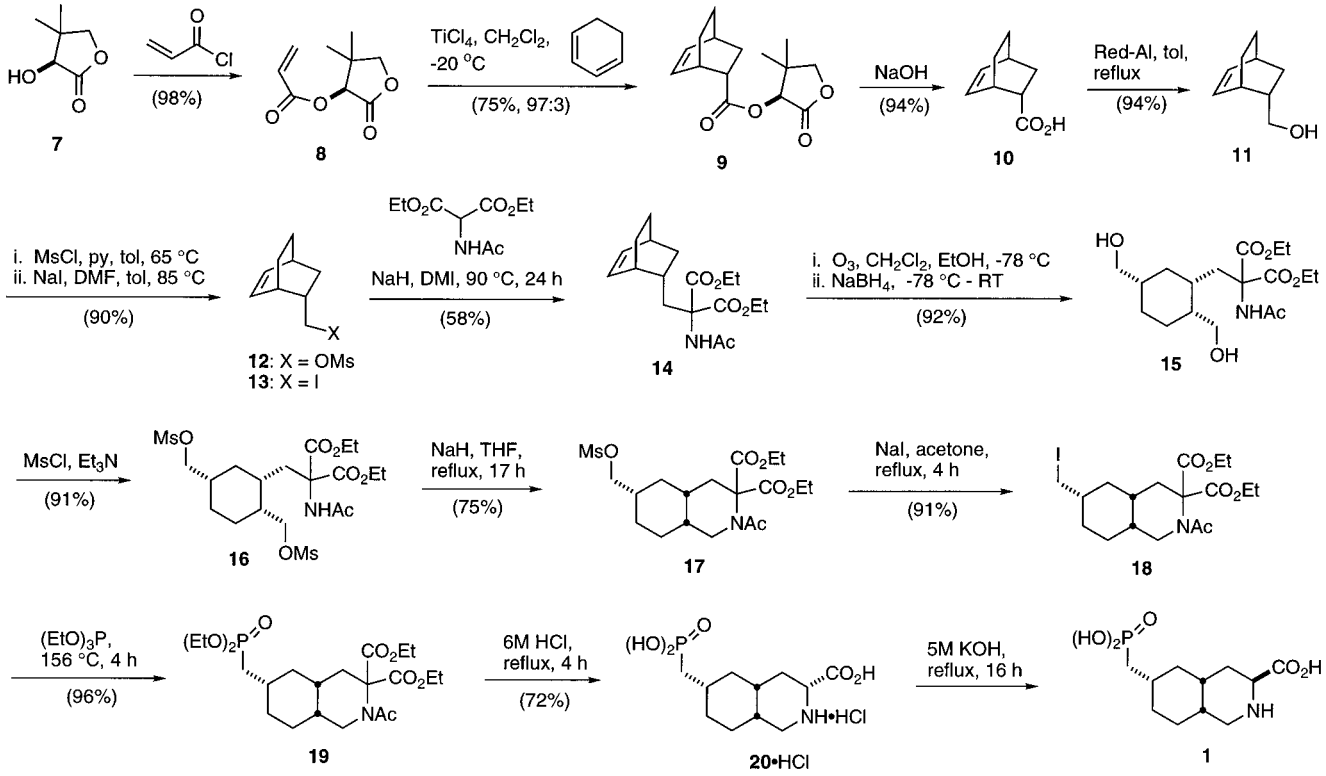
Scheme 1. Retrosynthesis



Scheme 2. Synthesis of LY235959 via Acetamidomalonate Alkylation



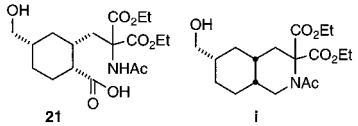
NaOEt/EtOH, reflux; NaH, toluene, reflux; KOH/K_2CO_3, DMF, 55 °C). Successful alkylation was ultimately achieved in 58% yield using a concentrated solution of 2 equiv of the sodium malonate in dimethylimidazolidinone (DMI)[8] at 90 °C for 21 h. All the iodide **13** was consumed in the reaction, suggesting that iodide elimination to the alkene was a competing reaction.

With malonate **14** in hand, we were prepared to investigate the oxidative opening of the bicyclic ring system. Ozonolysis under standard conditions, followed by addition of solid sodium borohydride and warming to room temperature, afforded diol **15** in 92% yield. The yield for this process was somewhat variable, and a significant byproduct was characterized as acid **21**.[9] Acid **21** was isolated in 5−15% yield but could be easily removed by a base wash during the workup. Formation of acid **21** may be explained by cleavage of the intermediate alkoxy hydroperoxide to the carboxylic acid or ester.[10]

Initial experiments with diol **15** showed that the bis-iodide could be prepared, albeit in low yield, using triphenylphosphine, iodine, and imidazole. Bis-mesylate **16** proved to be more robust and was isolated in 91% yield after treatment with methanesulfonyl chloride and triethylamine in dichloromethane at 0 °C. Cyclization to perhydroisoquinoline **17** was best accomplished using sodium hydride in tetrahydrofuran at reflux. The isolated yield was moderate and somewhat variable, possibly due to partial ester hydrolysis or mesylate decomposition by adventitious water. Other cyclization conditions (e.g. sodium or potassium hexamethyldisilazide or potassium *tert*-butoxide in tetrahydrofuran) afforded

(8) DMI is a less toxic substitute for HMPA, see: Sakurai, H.; Kondo, F. *J. Organomet. Chem.* **1976**, *117*, 149−155. We thank Dr. Tom Britton for recommending this solvent.

(9) A 20:1 mixture of regioisomeric acids was isolated, and the major regioisomer was assigned as acid **21**. The regiochemical assignment is based on comparison of the ^1H NMR spectra of acid **21**, diol **15**, and alcohol **i**.



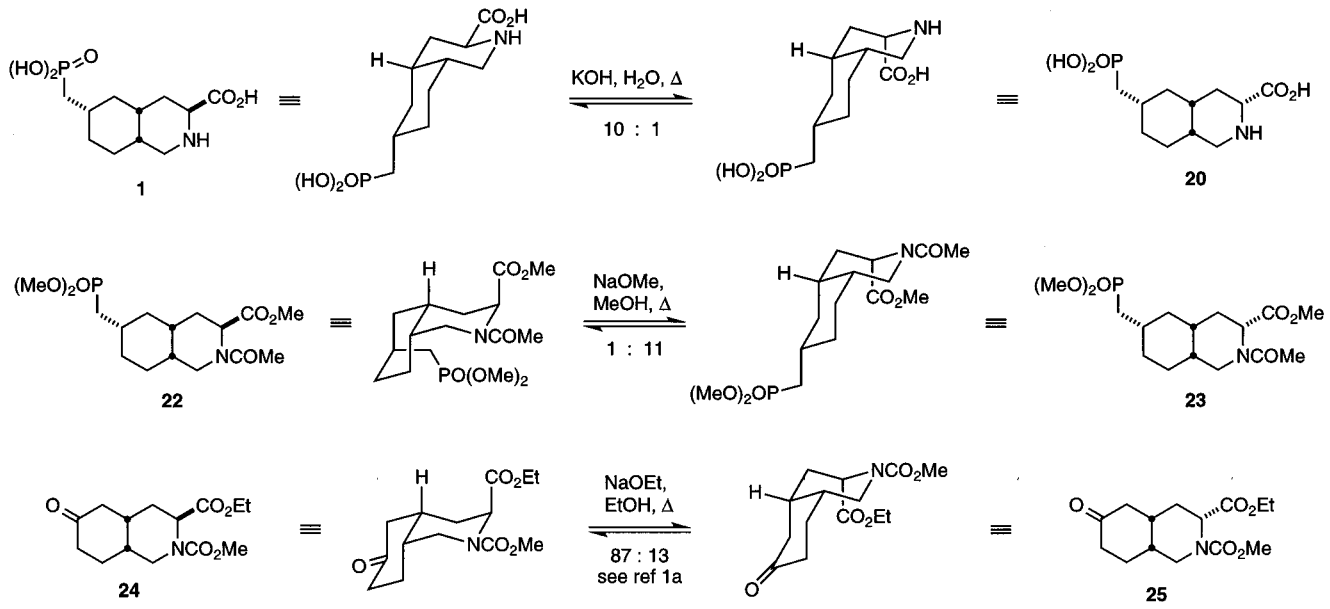


Figure 1. Base Catalyzed Epimerization of C-3 Stereocenter

cyclized material at 25 °C, but multiple byproducts were formed.

In preparation for introduction of the phosphonate group, mesylate **17** was converted to iodide **18** using the Finkelstein reaction.[5] In the Arbuzov reaction, an alkyl phosphite is used to convert reactive alkyl halides to the corresponding alkyl phosphonate.[11] Iodide **18** was anticipated to undergo an S_N2 reaction with alkyl phosphites slowly, so triethyl phosphite was employed as the reaction solvent.[12] When iodide **18** was heated at reflux (156 °C) in 73 volumes of triethyl phosphite for 4 h, phosphonate **19** was obtained in 96% yield after chromatography. A slow stream of nitrogen was passed through a sparge tube into the hot reaction mixture, and the triethyl phosphite was slowly distilled to aid in removal of ethyl iodide as the reaction progressed. Formation of ethyl iodide is problematic as it is more reactive than iodide **18** and serves to convert triethyl phosphite to triethyl phosphonate. Residual triethyl phosphonate was removed with some difficulty by chromatography. Trimethyl phosphite also reacted with iodide **18** at reflux (111 °C); however, 60 h was required for complete conversion and competing elimination and partial exchange to the malonate methyl esters was observed.

With phosphonate **19** in hand, we were ready to investigate protecting group removal and decarboxylation to create the C-3 stereocenter. Treatment of phosphonate **19** with 6 M HCl at reflux for 16 h followed by solvent removal afforded an inseparable 5:1 mixture of amino acids **20**·HCl and **1**·HCl in high yield. An analytical sample was prepared in 72% yield by ion exchange chromatography. The stereochemistry was assigned by spectral comparison with authentic LY235959 (**1**) and its epimer **20**.[13] The observed 5:1 preference for formation of the incorrect stereochemistry at C-3 can be understood as arising from protonation of the intermediate enol on the convex face of the cis-fused ring system.

The most direct method for epimerizing **20**·HCl to **1** was treatment with 5 M KOH at reflux for 16 h. Similar treatment with NaOH resulted in no epimerization.[14] After acidifying the mixture with HCl, analysis of the product in deuterium oxide without removal of potassium chloride indicated that a 10:1 mixture of LY235959 (**1**) to amino acid **20** was produced. Equilibration to **1** under thermodynamic conditions can be understood by looking at the first equation in Figure 1.[15] If one assumes a chair−chair conformation, amino acid **20** must have one substituent in an axial position while amino acid **1** can assume a conformation with all substituents in equatorial positions.

An optional method of achieving C-3 stereocenter epimerization is shown in Scheme 3. Treatment of a 5:1 mixture favoring epimer **20**·HCl with trimethyl orthoacetate in acetic acid at reflux resulted in esterification[16] of all three acid groups and amine acetylation. The resulting 5:1 product isomer ratio was similar to the starting material ratio, and it was assumed that no C-3 epimerization had occurred. However, exposure of the opposite epimer **1**[17] to the same reaction conditions afforded the same major product **22** with <5% of C-3 epimer **23**. The stereochemistry of **22** was assigned by hydrolysis of the 5:1 mixture of **22** and **23** with 6 M HCl at reflux to afford a 5:1 mixture of LY235959 (**1**) and C-3 epimer **20**.[18] Preferential formation of isomer **22** under the orthoacetate reaction conditions might be explained by the equilibrium shown in Scheme 3. If acetylation precedes carboxyl methylation, the *N*-acetyl group might

(10) For activation of the intermediate alkoxy hydroperoxide by Ac_2O and elimination to the ester using Et_3N, see: Schreiber, S. L.; Claus, R. E.; Reagan, J. *Tetrahedron Lett.* **1982**, *23*, 3867−3870.

(11) Bhattacharya, A. K.; Thyagarajan, G. *Chem. Rev. (Washington, D.C.)* **1981**, *81*, 415−430.

(12) For the Arbuzov reaction on a similar substrate, see ref 1c and Ornstein, P. L.; Augenstein, N. K.; Arnold, M. B. *J. Org. Chem.* **1994**, *59*, 7862−7869.

(13) ^1H and ^{13}C NMR spectra were comparable to those reported in ref 1b.

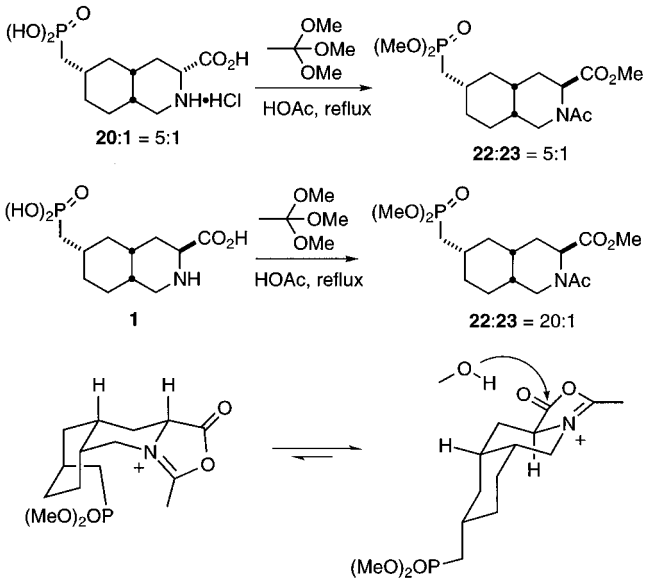
(14) Heating in aqueous barium hydroxide at 180 °C is frequently used to racemize the natural amino acids, see: Greenstein, J. P.; Winitz, M. *Chemistry of the Amino Acids*; Wiley: New York, 1961; Volume 3.

(15) Conformations shown in Figure 1 have not been minimized but are useful in rationalizing the observed results.

(16) Zeiss, H. *J. Org. Chem.* **1991**, *56*, 1783−1788.

(17) LY235959 (**1**) containing <1% epimer **20** which was prepared using a modification of the reported procedure. See ref 1.

Scheme 3. Epimerization by Trimethyl Orthoformate



intercept an activated carboxyl intermediate to afford the oxazolidinium species shown.[19] Equilibration of the oxazolidinium ions through C-3 proton loss should be facile. Attack of methanol on the more stable isomer would result in formation of the major product observed. Higher than predicted retention of stereochemistry when starting from **1** suggests that attack by methanol occurs prior to complete equilibration to a thermodynamic mixture of oxazolidinium intermediates.

The isomer ratios shown in Scheme 3 may result from a thermodynamically controlled equilibration of an intermediate, but they do not represent a thermodynamic product ratio. When the 5:1 mixture of **22** and **23** was subjected to base-catalyzed epimerization using sodium methoxide in methanol at reflux, an 11:1 mixture of products favoring isomer **23** was produced. The stereochemistry of isomer **23** was confirmed by treatment with 6 M HCl at reflux to afford a 10:1 mixture of amino acids **20** and **1**.[18] Preferential formation of **23** under basic conditions can be explained by the equilibria shown in Figure 1.[15] Ornstein and co-workers have shown that the ester group in ketones **24** and **25** prefer an axial disposition to avoid $A^{1,3}$ strain with the carbamate. Base-catalyzed equilibration favors ketone **24** due to a 1,3-diaxial interaction between the ester group and C-5 in ketone **25**. We believe that the same axial ester preference will be present in esters **22** and **23**. Isomer **23** should be favored over **22** as the former isomer has the C-6 substituent in an equatorial position.

The synthesis of LY235959 (**1**) shown in Scheme 2 demonstrates the utility of such a Diels−Alder approach as epimer **20** was prepared in 12 steps and 13.4% overall yield; however, a number of issues remained to be addressed. Alkylation of the glycine unit to provide malonate **14** proceeded in low yield under rather harsh conditions. The cyclization to mesylate **17** was sensitive to adventitious moisture or other impurities. Control of the C-3 stereocenter was delayed until a final base-catalyzed equilibration step and complete epimerization to the desired epimer was not achieved. Our efforts to address these deficiencies are described below.

The approach shown in Scheme 4 presented the opportunity to replace the difficult glycine alkylation step with a condensation reaction. In addition, the opportunity to control the C-3 stereochemistry through stereoselective reduction of an enamide was appealing. Ozonolysis of protected alcohol **26**[20] followed by borohydride reduction of the intermediate dialdehyde gave diol **27** in a 93% yield. Tosylation of **27** followed by removal of the CBZ group, Swern oxidation and condensation of the aldehyde[21] with *N*-(benzyloxycarbonyl)-α-phosphonoglycine trimethyl ester[22] provided acylenamide **29** in 55% overall yield from **27**. Reduction of the double bond and cyclization with NaH gave a 1.7:1 mixture of C-3 epimeric decahydroisoquinolines.[23] The major isomer **30** was isolated by chromatography and converted to iodide **31**. Treatment of **31** with triethyl phosphite provided phosphonate ester **32** and deprotection with 6 M HCl gave the undesired epimer **20**·HCl in 12% overall yield from **26**. This material was identical by ^{1}H NMR to product previously obtained and could be converted to LY235959 (**1**) by base-promoted equilibration (Scheme 2). Attempts to invert the diastereoselectivity in the hydrogenation of **29** were unsuccessful since the acylenamide was unreactive toward hydrogenation in the presence of homogeneous catalysts other than $(Ph_3P)_3RhCl$[24] and use of heterogeneous catalysts led to cleavage of the CBZ group. However, the mixture of diastereomers could be carried through the synthesis to provide a 2.9:1 mixture of **20**:**1**[25] in an improved 22% overall yield from **26**. This mixture could be converted to LY235959 (**1**) by equilibration as described above.

The enamide approach shown in Scheme 4 provided an improved method for attachment of the glycine unit, but did not solve the C-3 stereocontrol issues and did not increase the overall yield. An alternate solution to the poor alkylation yield of iodide **13** was provided by employment of a benzophenone imine glycine enolate. O'Donnell pioneered use of ester analogue **33** for glycine ester alkylation under remarkably mild conditions.[26] Subsequently, other workers have employed related glycine amide benzophenone imines[27] or bis(methylthio)-

(18) Such acidic hydrolysis conditions do not epimerize the C-3 stereocenter, see ref 1. Close correspondence of the ^{1}H NMR spectral data of isomers **27** and **28** with analogous C-3 epimers reported by Ornstein also supports the stereochemical assignment: **27**, C-3 proton a triplet at 4.70 ppm, $J = 5$ Hz; **28**, C-3 proton a doublet at 5.21 ppm, $J = 7$ Hz. Compare with compounds **31a** and **40** in ref 1b.

(19) Such intermediates are presumably involved in the racemization of L-proline by treatment with acetic anhydride in refluxing acetic acid, see ref 14, p 2195.

(20) Prepared from corresponding alcohol in 93% yield.

(21) The aldehyde is sensitive to epimerization and should be kept cold and used without delay.

(22) Schmidt U.; Griesser, H.; Leitenberger, V.; Lieberknecht, A.; Mangold, R.; Meyer, R.; Riedl, B. *Synthesis* **1992**, 487.

(23) Product ratio was determined by the ratio of integral areas of the C-3 protons in the ^{1}H NMR spectrum of the crude product mixture.

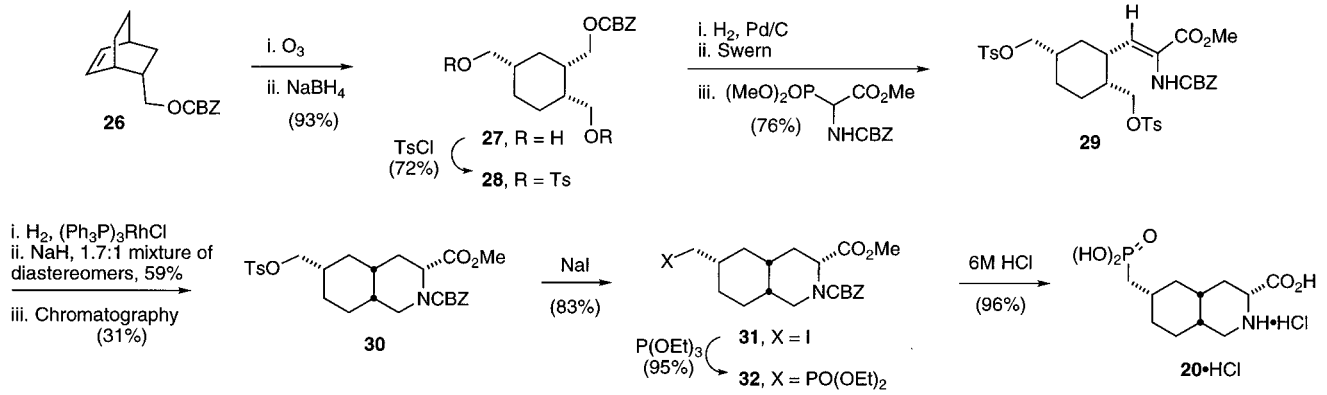
(24) For a recent review on the use of homogeneous catalysts in hydrogenation, see: Burk, M. J.; Gross, M. F.; Harper, T. G. P.; Kalberg, C. S.; Lee, J. R.; Martinez, J. P. *Pure Appl. Chem.* **1996**, *68 (1)*, 37. See also: Scott, J. W.; Keith, D. D.; Nix, Jr., G.; Parrish, D. R.; Remington, S.; Roth, G. P.; Townsend, J. M.; Valentine, Jr., D., Yang, R. *J. Org. Chem.* **1981**, *46*, 5086.

(25) Product was identical with material previously prepared by ^{1}H NMR. Ratio was determined by integral areas of the C-3 protons.

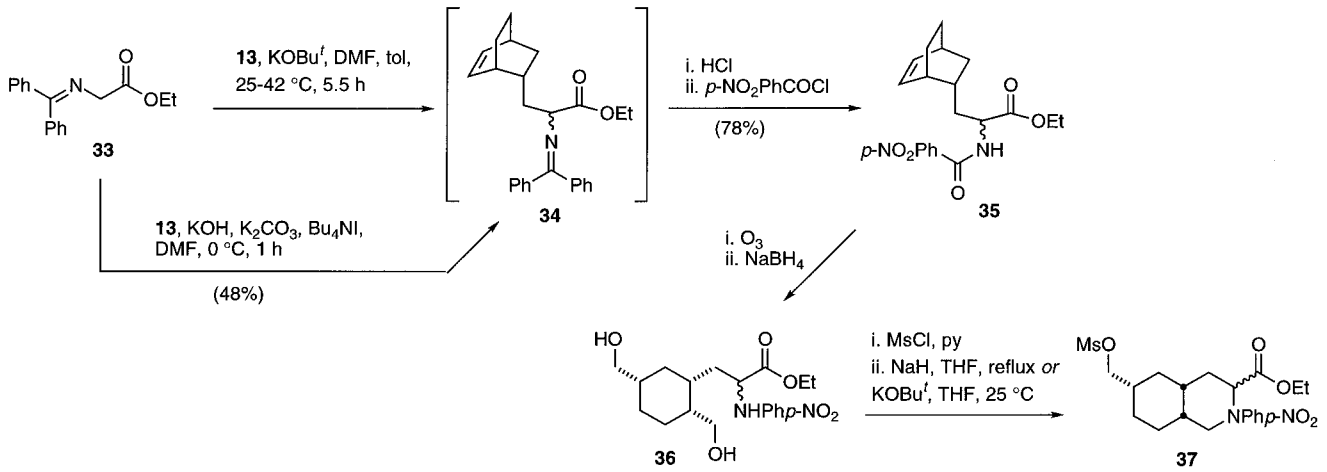
(26) O'Donnell, M. J.; Boniece, J. M.; Earp, S. E. *Tetrahedron Lett.* **1978**, 2641−2644. (b) O'Donnell, M. J.; Eckrich, T. M. *Tetrahedron Lett.* **1978**, 4625−4628. (c) O'Donnell, M. J.; Wu, S. *Tetrahedron: Asymmetry* **1992**, *3*, 591−594.

(27) Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett.* **1989**, *30*, 6009−6010.

Scheme 4. Enamide Hydrogenation Approach



Scheme 5. O'Donnell Ester Alkylation



methylene imines[28] for similar alkylations. We found that iodide **13** was smoothly alkylated by the potassium enolate of ester **33** under a variety of conditions (Scheme 5). The conditions are much milder than those employed with acetamido malonate (Scheme 2), and only a 10% excess of enolate was required. The crude product was susceptible to hydrolysis but could be directly converted to amide **35** in 78% overall yield by hydrolysis and acylation with *p*-nitrobenzoyl chloride under Schotten–Bauman conditions. Imine **34** could be isolated in 48% yield by alkylation under the conditions reported by O'Donnell.[29]

The resulting 1:1 mixture of isomeric amides **35** was treated with ozone followed by sodium borohydride under similar conditions to those discussed above. Poor yields of diol **36** were realized in this reaction due to formation of byproducts tentatively identified as the triol resulting from reduction of the α-amido ester group[30] and the amino acid corresponding to **36**. Diol **36** was converted to the bismesylate and cyclization to mesylate **37** was achieved in marginal yield using either sodium hydride in tetrahydrofuran at reflux or potassium *tert*-butoxide in tetrahydrofuran at room temperature. We concluded from these experiments that the ester functionality in these intermediates is too susceptible to nucleophilic attack by hydride or hydroxide derived from adventitious moisture. These side reactions were observed to a lesser extent even with the more hindered ester groups in the corresponding malonate intermediates discussed above.

We anticipated that the ester hydrolysis and reduction problems described above could be avoided by use of the known pyrrolidine amide **39**.[31] The successful synthesis of LY235959 (**1**) using amide **39** is shown in Scheme 6. Treatment of iodide **13** with the potassium enolate of amide **39** afforded the alkylation product **41** after 3 h at room temperature. Intermediate **40** was not isolated, but was hydrolyzed to the amine and then acylated with benzoyl chloride under Schotten–Baumann conditions to afford amide **41** in 77% yield for two steps. Ozonolysis of amide **41** and reduction of the intermediate ozonide with sodium borohydride afforded the ring-opened diol. The diol was converted to the bis-mesylate **42** in 90% overall yield for three steps. Cyclization of bis-mesylate **42** to assemble the perhydroisoquinoline ring occurred in high yield using excess potassium *tert*-butoxide in tetrahydrofuran. The inconsistent reaction rates and

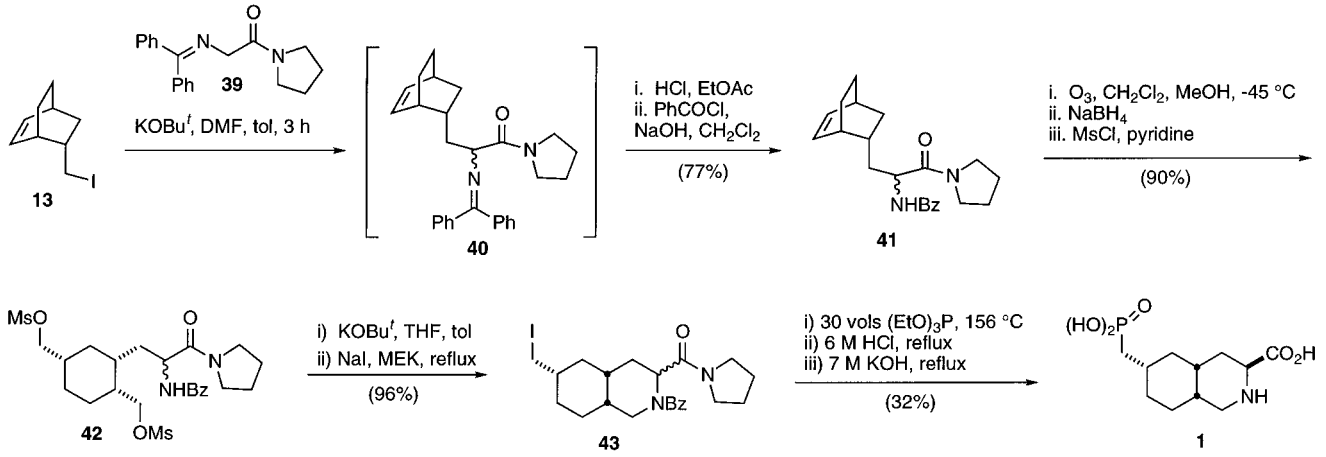
(28) Ikegami, S.; Uchiyama, H.; Hayama, T.; Katsuki, T.; Yamaguchi, M. *Tetrahedron* **1988**, *44*, 5333–5342.

(29) O'Donnell, M. J.; Wojciechowski, K. *Synthesis* **1984**, 313–315.

(30) Esters with electron-withdrawing substituents at the α-position can be reduced using $NaBH_4$, see: (a) Sasaki, N. A.; Hashimoto, C.; Potier, P. *Tetrahedron Lett.* **1987**, *28*, 6069–6072. (b) Levai, L.; Ritvay-Emandity, K. *Ber. Dutsch. Chem. Ges.* **1959**, *92*, 2775.

(31) Amide **39** has been used in aldol addition reactions but has not been previously employed in glycine enolate alkylations, see: Kanemasa, S.; Mori, T.; Wada, E.; Tatsukawa, A. *Tetrahedron Lett.* **1993**, *34*, 677–680. Amide **39** could be prepared by reaction of ester **33** with pyrrolidine using the Weinreb procedure (Lipton, M. F.; Basha, A.; Weinreb, S. M. *Organic Syntheses*; *Vol. VI*; Wiley: New York, 1988; Coll. Vol. VI, pp 492–495) or by treatment of *N*-(aminoacetyl)-pyrrolidine (**38**) with benzophenone imine using the O'Donnell procedure.[26] Both methods provided amide **39** which contained minor amounts of benzophenone; however, benzophenone did not interfere with the subsequent alkylation reaction and was removed at a later stage (see Supporting Information).

Scheme 6. Synthesis via Glycine Amide



ester hydrolysis observed previously were completely circumvented with this amide substrate. The cyclized mesylate was converted to iodide **43** in 96% overall yield for two steps. The phosphonate moiety was introduced as described above using the Arbuzov reaction. The crude phosphonate was taken directly into an acidic hydrolysis which removed all the protecting groups to afford a 1:2 mixture of **1**·HCl to the undesired epimer **20**·HCl. Base-catalyzed epimerization using KOH as described above (Figure 1) afforded a 10:1 mixture favoring the desired isomer **1**. Crystallization of crude LY235959 (**1**) from an aqueous solution at pH 2.6 was achieved in 32% overall yield for three steps.[32] LY235959 (**1**) was obtained in 94% ee and contained 4.7% of epimer **20**.[33] Other physical data was in accord with that reported by Ornstein.[34]

In summary, a novel synthesis of NMDA receptor antagonist LY235959 (**1**) has been achieved in 13% overall yield and 17 steps from (*R*)-pantolactone (**7**). Highlights of the synthesis include (a) use of a chiral auxiliary controlled asymmetric Diels−Alder reaction to provide the desired absolute and relative stereochemistry at C-4a, C-6, and C-8a, (b) an efficient alkylation of hindered iodide **13** using a novel amide benzophenone imine, (c) oxidative ring opening of the [2.2.2] bicyclic system to simultaneously functionalize the molecule for intramolecular cyclization and phosphonate introduction, and (d) an increased understanding of how the C-3 stereochemistry may be controlled by thermodynamic equilibration. Further development of this synthetic route is needed to address stereocontrol at C-3. Synthesis of epimer **20** in high overall yield makes this synthetic route attractive for future development efforts.

Experimental Section

General. Reactions involving air or moisture sensitive reagents were carried out under nitrogen. Tetrahydrofuran (THF) was distilled from benzophenone ketyl and dimethylformamide (DMF) was dried over 3 Å molecular sieves. Unless otherwise noted, other reagents and solvents were used as received from commercial suppliers. Flash chromatography was performed using Merck silica gel 60 (230−400 mesh). Ozonolysis was performed using a PCI generator operated at 20 psi air @ 6 SCFH and 80% output. Melting points were obtained using a Mettler FP62 automatic melting point apparatus. ^{1}H and ^{13}C NMR spectra were obtained at 300 and 75 MHz, respectively, in $CDCl_3$ unless otherwise noted. Chemical shifts are in ppm downfield from internal tetramethylsilane. ^{1}H NMR data are tabulated in order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons, coupling constant(s) in hertz. Mass spectral analysis and combustion analysis was performed by the Eli Lilly and Company Physical Chemistry Department.

(1*S*,2*S*,4*S*)-Bicyclo[2.2.2]oct-5-en-2-ylmethyl Methanesulfonate (12). To alcohol **11** (0.16 mol) in toluene (125 mL) were added pyridine (30 mL, 0.37 mol) and CH_3SO_2Cl (16 mL, 0.21 mol), each washed in with 3 × 5 mL of toluene. The solution was heated at 65 °C for 16 h and cooled to rt, and 5% aqueous $NaHCO_3$ (150 mL) was added. The mixture was stirred for 15 min, and the phases were separated. The aqueous layer was washed with toluene (2 × 100 mL). The combined organic layers were washed in turn with H_2O (150 mL) and 1 M HCl (2 × 100 mL). The combined organic layers were concentrated to 125 mL in vacuo, and the mesylate solution was carried on to the next reaction. In a separate experiment, the solution was concentrated to afford mesylate **12** as an analytically pure oil in 96% yield. IR: 3100−2860 cm^{-1}; ^{1}H NMR: δ 0.75 (m, 1), 1.18−1.38 (m, 2), 1.43−1.59 (m, 2), 1.73 (m, 1), 2.17 (m, 1), 2.55 (m, 1), 2.64 (m, 1), 2.99 (s, 3), 3.81 (d, 2, J = 8), 6.12 (t, 1, J = 7), 6.32 (t, 1, J = 7). ^{13}C NMR: δ 24.47, 25.29, 29.40, 29.48, 30.92, 37.23 (2C), 73.47, 131.10, 135.49. MS (FD) m/z 216 (M^+). Anal. Calcd for $C_{10}H_{16}O_3S$: C, 55.53; H, 7.46; S, 14.82. Found: C, 55.79; H, 7.50; S, 14.66.

(1*S*,2*S*,4*S*)-Bicyclo[2.2.2]oct-5-en-2-ylmethyl Iodide (13). A solution of mesylate **12** (0.16 mol) in toluene (125 mL) was added to a slurry of NaI (60 g, 0.4 mol) in dry DMF (100 mL) and washed in with toluene (4 × 5 mL). The mixture was heated at 85 °C for 21 h. The mixture was partitioned between hexane (50 mL) and water (80 mL). The lower aqueous/salt/DMF layer was washed with hexane (2 × 150 mL). The organic layers were washed in turn with dilute $Na_2S_2O_3$ solution (1 g in 150 mL H_2O) and H_2O (2 × 150 mL). The organic solution was filtered through a pad of silica gel (15 g, 60−200 mesh), concentrated to an oil, and distilled in vacuo. The fraction distilling at 100−105 °C at ~8 mm amounted to 35.58 g (90% from alcohol **11**) of iodide **13**. IR: 3048−2868 cm^{-1}; ^{1}H NMR: δ 0.81 (m, 1), 1.20 (m, 1), 1.28 (m, 1), 1.48 (m, 2), 1.80 (m, 1), 2.10 (m, 1), 2.55 (m, 1), 2.69 (m, 1), 2.85 (t, 1, J = 7), 2.95 (t, 1, J = 7), 6.12 (t, 1, J = 7), 6.31 (t, 1, J = 7); ^{13}C NMR: δ 15.61, 23.97, 25.94, 30.73, 35.34, 35.75, 41.28, 130.89, 135.46; MS (FD) m/z 248 (M^+). Anal. Calcd for $C_9H_{13}I$: C, 43.57; H, 5.28; I, 51.15. Found: C, 43.28; H, 5.28; N, 51.40. $[\alpha]_D$ = −24.78 (CH_2Cl_2, c = 1.0).

Diethyl 2-Acetamido-2-[(1*R*,2*R*,4*S*)-bicyclo[2.2.2]oct-5-en-2-ylmethyl]malonate (14). Diethyl acetamidomalonate (15.7 g, 72.5 mmol) was dissolved in 40 mL of DMI (stored

(32) The low isolated yield of **1** is due to an inefficient crystallization.
(33) The enantiomeric excess of **1** correlates to the diastereomer ratio of Diels−Alder adduct **9**. The enantiomeric excess and diastereomeric purity were assigned by HPLC.

over 3 Å molecular sieves). The solution was placed in a rt H_2O bath and 2.90 g (72.5 mmol) of NaH (60% in mineral oil) was added slowly. After 15 min, 8.80 g (35.5 mmol) of iodide **13** was added. The mixture was heated at 90 °C for 21 h. The brown solution was allowed to cool to rt and was diluted with 120 mL of 3:1 ether/hexanes followed by 60 mL of H_2O. The aqueous layer was adjusted to pH = 5−7 with 1 M HCl. Layers were separated, and the aqueous layer was extracted with 3:1 ether/hexanes (2 × 100 mL). The combined organic layers were washed with 100 mL of brine and dried (Na_2SO_4). The solvent was removed in vacuo to afford 18.18 g of an orange oil which contained DMI. The crude material was dissolved in 180 mL of 3:1 ether/hexanes and washed with H_2O (2 × 50 mL) followed by 25 mL of brine. The organic layer was dried (Na_2SO_4), and the solvent was removed in vacuo to leave 12.14 g of yellow solids. The solids were dissolved in 10 mL of EtOAc and 60 mL of hexanes at reflux. The solution was allowed to cool to rt, and the resulting slurry was stirred for 2 h in an ice bath. The solid was collected by filtration, washed with hexanes, and dried to afford 6.98 g (58%) of diester **14** as white solids. IR: 3416, 3029−2868, 1734, 1679 cm^{-1}; ^1H NMR: δ 0.74 (m, 1), 1.20 (m, 8), 1.28−1.75 (m, 4), 2.02 (s, 3), 2.08 (dd, 1, J = 15, 8), 2.29 (m, 2), 2.40 br s, 1), 4.20 (m, 4), 6.05 (t, 1, J = 8), 6.23 (t, 1, J = 8), 6.80 (br s, 1); ^{13}C NMR: δ 13.95, 13.98, 23.10, 24.18, 26.44, 30.02, 33.56, 35.24, 35.63, 40.31, 62.39, 62.44, 66.14, 103.94, 131.65, 135.01, 168.67, 168.79. MS (FD) m/z 338 (M^+). Anal. Calcd for $C_{18}H_{27}N_1O_5$: C, 64.08; H, 8.07; N, 4.15. Found: C, 63.90; H, 8.01; N, 4.18.

Diethyl 2-Acetamido-2-[(1*R*,2*R*,5*S*)-[1-[2,5-Bis(hydroxymethyl)cyclohexyl]methyl]malonate (15). In 35 mL of 3:1 CH_2Cl_2/EtOH was dissolved 2.53 g (7.51 mmol) of diester **14**. The solution was purged with N_2 while stirring in an acetone/dry ice bath. With an N_2 blanket over the solution, O_3 was bubbled into the solution through a fritted glass sparger until the reaction was complete as indicated by Sudan III indicator (orange-red to colorless). To the solution was added 1.40 g (37.04 mmol) of $NaBH_4$ in one portion. The cooling bath was removed after 5 min and after 50 min the solution was diluted with 10 mL of CH_2Cl_2 and cooled in an ice bath. The mixture was treated with 10 mL of saturated aq. NH_4Cl slowly over 12 min. After stirring for 1 h, 5 mL of H_2O was added. Layers were separated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). Solvent was removed in vacuo to afford 2.57 g (92%) of diol **15** as a slightly yellow foam. IR: 3600, 3400, 3050−2800, 1734, 1682 cm^{-1}; ^1H NMR: δ 0.74 (m, 1), 1.10 (m, 1), 1.20−1.56 (m, 5), 1.43 (t, 6, J = 7), 1.72 (br s, 1), 1.90 (br s, 2), 1.97 (br s, 1), 2.03 (s, 3), 2.21 (dd, 1, J = 15, 6), 2.52 (dd, 1, J = 15, 5), 3.38 (m, 2), 3.58 (dd, 1, J = 10, 10), 3.67 (dd, 1, J = 10, 4), 4.42 (q, 4, J = 7), 6.95 (br s, 1); ^{13}C NMR: δ 13.91, 22.94, 22.99, 26.94, 31.76, 35.17, 35.66, 40.48, 40.58, 59.28, 62.59, 66.15, 68.02, 168.32. 168.43, 169.52. MS (FD) m/z 374 (M^+). Anal. Calcd for $C_{18}H_{31}NO_7$: C, 57.89; H, 8.37; N, 3.75. Found: C, 57.79; H, 8.51; N, 3.75.

Diethyl 2-Acetamido-2-[(1*R*,2*R*,5*S*)-[1-[[2,5-bis[(methylsulfonyl)oxy]methyl]cyclohexyl]methyl]malonate (16). Diol **15** (4.02 g, 10.78 mmol) was dissolved in 45 mL of CH_2Cl_2. The solution was cooled in an ice bath, and 3.06 mL (22.1 mmol) of Et_3N was added followed by dropwise addition of 1.72 mL (22.2 mmol) of CH_3SO_2Cl. After 20 min, 20 mL of H_2O was added, and the aqueous layer was adjusted to pH = 1 with 1 M HCl. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were washed with 15 mL of saturated aqueous $NaHCO_3$ followed by 15 mL of brine and dried (Na_2SO_4). The solvent was removed in vacuo to leave 5.51 g of a viscous oil. Chromatography on 400 g of flash silica gel using EtOAc afforded 5.18 g (91%) of **16** as a white foam/oil. IR: 3400, 3050−2800, 1736, 1681 cm^{-1}; ^1H NMR: δ 0.89 (q, 1, J = 12), 1.15 (m, 1), 1.25 (m, 6), 1.35−170 (m, 4), 1.81 (m, 1), 1.92−2.10 (m, 2), 2.07 (s, 3), 2.25 (dd, 1, J = 15, 6), 2.53 (dd, 1, J = 15, 5), 3.02 (s, 3), 3.06 (s, 3), 3.95 (dd, 1, J = 9, 8), 4.04 (dd, 1, J = 9, 6), 4.25 (m, 6), 5.87 (br s, 1); ^{13}C NMR: δ 13.97, 22.46, 23.13, 26.67, 31.04, 34.57, 35.57, 37.20, 37.38, 37.62, 62.81, 62.97, 66.03, 67.44, 73.85, 168.02, 168.41, 169.57. MS (FD) m/z 530 (M^+ for $C_{20}H_{35}NO_{11}S_2$).

Diethyl (4a*R*,6*S*,8a*R*)-6-[(Methanesulfonyl)methyl]-2-acetyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3,3-dicarboxylate (17). NaH (0.78 g, 60% dispersion in mineral oil, 19.5 mmol) was slurried with 16 mL of dry THF. The solvent was decanted by syringe, and 25 mL of dry THF, followed by a solution of 5.15 g (9.72 mmol) of dimesylate **16** in 17 mL of dry THF, was added. The tan suspension was heated at reflux for 17 h. After cooling to rt, excess NaH was quenched with 10 mL of EtOH. The mixture was diluted with 20 mL of CH_2Cl_2 and 20 mL of H_2O. The aqueous layer was adjusted to pH = 1 with HCl, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). The solvent was removed in vacuo to afford 4.24 g of an oil. Flash chromatography on 400 g of silica gel using EtOAc afforded 3.15 g (75%) of **17** as a viscous yellow oil. IR: 3050−2800, 1727, 1662 cm^{-1}; ^1H NMR: δ 0.95 (m, 1), 1.08 (m, 1), 1.27 (t, 3), 1.32 (t, 3), 1.50−1.83 (m, 5), 1.95 (m, 1), 2.15 (m, 1), 2.18 (s, 3), 2.32 (dd, 1, J = 14, 6), 2.47 (dd, 1, J = 14, 3), 3.00 (s, 3), 3.28 (dd, 1, J = 13, 13), 3.41 (dd, 1, J = 13, 5), 3.99 (m, 2), 4.15−4.38 (m, 4). MS (FD) m/z 433 (M^+). Anal. Calcd for $C_{19}H_{31}NO_8S$: C, 52.64; H, 7.21; N, 3.23. Found: C, 52.40; H, 7.31; N, 3.50.

Diethyl (4a*R*,6*S*,8a*R*)-6-(Iodomethyl)-2-acetyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3,3-dicarboxylate (18). Mesylate **17** (2.30 g, 5.31 mmol) was dissolved in 13 mL of acetone, and 2.39 g of NaI (15.93 mmol) was added. The solution was heated at reflux for 4 h. After cooling to rt, 20 mL of H_2O and 20 mL of CH_2Cl_2 were added. Layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with 20 mL of brine and dried (Na_2SO_4). The solvent was removed in vacuo to afford 2.24 g (91%) of iodide **18** as a viscous yellow oil. IR: 3050−2800, 1727, 1661 cm^{-1}; ^1H NMR: δ 0.83−1.12 (m, 2), 1.27 (t, 3, J = 7), 1.34 (t, 3, J = 7), 1.40 (m, 1), 1.54−1.75 (m, 4), 1.87−2.10 (m, 2), 2.17 (s, 3), 2.31 (dd, 1, J = 14, 5), 2.49 (dd, 1, J = 14, 3), 3.04 (dd, 1, J = 10, 6), 3.12 (dd, 1, J = 10, 5), 3.26 (dd, 1, J = 13, 13), 3.40 (dd, 1, J = 13, 5), 4.17−4.35 (m, 4); ^{13}C NMR: δ 13.78, 14.02, 15.03, 22.29, 27.72, 28.19, 32.32, 32.37, 32.49, 37.00, 39.37, 44.02, 61.75, 62.00, 65.65, 168.58, 169.20, 172.82. MS (FD+) m/z 465 (M^+). Anal. Calcd for $C_{18}H_{28}NO_5$: C, 46.46; H, 6.06; N, 3.01. Found: C, 46.21; H, 6.07; N, 2.89.

Diethyl (4a*R*,6*S*,8a*R*)-6-[(Diethylphosphono)methyl]-2-acetyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3,3-dicarboxylate (19). In a flask fitted with a short path condenser was dissolved 1.50 g (3.19 mmol) of iodide **18** in 110 mL (643 mmol) of $(EtO)_3P$. The solution was sparged with N_2 and heated at a mild reflux for 4 h during which time a few milliliters of EtI and $(EtO)_3P$ was distilled off. The heat was increased to distill off 100 mL of $(EtO)_3P$, and the remaining solvent was removed in vacuo followed by 5 days under high vacuum (0.1 mmHg) to afford 2.56 g of a viscous oil. Flash chromatography on 170 g of silica gel using 5% EtOH in EtOAc afforded 1.46 g (96%) of phosphonate **19** as a viscous, colorless oil. IR: 3050−2800, 1727, 1650 cm^{-1}; ^1H NMR: δ 0.88−1.10 (m, 2), 1.23−1.42 (m, 12 H), 1.55−1.80 (m, 7), 1.89−2.00 (m, 1), 2.00−2.13 (m, 1), 2.17 (s, 3), 2.28 (dd, 1, J = 14, 6), 2.45 (dd, 1, J = 14, 3), 3.28 (dd, 1, J = 12, 12), 3.39 (dd, 1, J = 12, 5), 3.98−4.38 (m, 8); ^{13}C NMR: δ 13.58, 13.71, 15.84, 16.12, 16.20, 22.09, 28.20, 28.42, 28.56, 31.79, 31.94, 32.20, 32.45, 32.50, 33.25, 33.39, 33.63, 36.85, 43.90, 61.02, 61.10, 61.49, 61.61, 62.30, 65.47, 168.52, 169.01, 172.60. MS (FD) m/z 475 (M^+ for $C_{22}H_{38}NO_8$).

(3*R*,4a*R*,6*S*,8a*R*)-6-(Phosphonomethyl)-1,2,3,4,4a,5,6,7,8,8a-decahydro-isoquinoline-3-carboxylic Acid (20). To 694 mg (1.46 mmol) of phosphonate **19** was added 18 mL of 6 M HCl. The solution was heated at reflux for 16 h. The solvent was removed in vacuo, and H_2O was removed twice to provide 514 mg (112%) of tacky, white solids. Analysis by ^1H NMR indicated that a ratio of 5:1 of amino acids **20**:**1** as HCl

salts was obtained. **20·HCl:** ^{1}H NMR (D_2O): δ 0.95−1.20 (m, 3), 1.50−2.40 (m, 10), 3.04 (dd, 1, J = 4, 12), 3.40 (dd, 1, J = 12, 12), 4.19 (d, 1, J = 6). Ion exchange chromatography on 7.5 g of BioRad AX1−8, 50−100 mesh, chloride form ion-exchange resin (load in aqueous NaOH, elute with aqueous AcOH) afforded 384 mg of a slightly yellow foam. A 198 mg portion was reslurried twice in 10 mL of boiling acetone to afford 177 mg (72%) of offwhite solids characterized as a 5:1 ratio of **20**:**1**. The major isomer was identified by ^{1}H NMR and ^{13}C NMR comparison with the data reported previously.[34] **20:** ^{1}H NMR (D_2O, KOD): δ 0.86−1.15 (m, 3), 1.43−2.25 (m, 10), 2.94 (dd, 1, J = 3, 12), 3.36 (dd, 1, J = 12, 12), 4.00 (d, 1, J = 5). MS (FAB+) m/z 278.2 (MH+ for $C_{11}H_{21}NO_5P$).

Diethyl 2-Acetamido-2-[(1*R*,2*R*,5*S*)-[1-[2-carboxy-5-(hydroxymethyl)cyclohexyl]methyl]malonate (21). The procedure above for diol **15** was followed starting from 0.99 g of diester **14**. After extraction of the diol from the basic aqueous layer, addition of HCl (pH 1) and extraction afforded 190 mg (17%) of acid **21** as a foamy oil. IR: 3650−2500, 3400, 1735, 1681 cm^{-1}; ^{1}H NMR: δ 1.00−1.25 (m, 1), 1.25 (m, 6), 1.35−1.68 (m, 6), 2.05 (s, 3), 2.12 (s, 1), 2.42 (br dd, 1, J = 15, 3), 2.61 (m, 2), 3.43 (br d, 2, J = 4), 4.22 (m, 4), 5.8−6.4 (br s, 2), 7.15 (s, 1); ^{13}C NMR: δ 13.88, 22.88, 24.45, 29.12, 31.60, 34.61, 36.49, 40.34, 43.36, 62.56, 62.60, 66.17, 67.83, 168.29, 168.47, 169.84. High-resolution MS (FAB), exact mass calcd for MH^+ $C_{18}H_{30}NO_8$: 388.1998. Found: 388.1971.

Methyl (3*S*,4a*R*,6*S*,8a*R*)-6-[(Dimethylphosphono)methyl]-2-acetyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (22) from 1. To 2.0 g (7.2 mmol) of amino acid **1** prepared independently[34] were added 110 mL of AcOH and 230 mL of trimethyl orthoacetate. The mixture was heated at reflux for 2 h, and the solvent was removed in vacuo to afford ester **22** (<5% **23**). The residue was chromatographed on 400 g of silica gel using 10:1 EtOAc/MeOH to afford 2.26 g (87%) of ester **22** as a viscous oil. IR: 1738, 1640 cm^{-1}; ^{1}H NMR: δ 1.25 (m, 2), 1.45−2.30 (m, 11), 2.12 (s, 3), 3.40 (m, 2), 3.71 (s, 3), 3.72 (s, 3), 3.74 (s, 3), 4.70 (br t, 1, J = 5). ^{13}C NMR: δ 21.56, 25.78, 28.81, 28.94, 30.18, 30.23, 30.55, 30.64, 30.95, 32.16, 32.39, 35.16, 35.30, 46.38, 51.33, 52.02, 52.11, 171.19, 172.30. MS (FD) m/z 361 (M^+).

Ester 22 from 20. To 1.17 g (3.73 mmol) of **20**·HCl were added 12 mL of AcOH and 24 mL of trimethyl orthoacetate. The mixture was heated at reflux for 3 h. The solvent was removed in vacuo, and $CHCl_3$ was removed three times to afford 1.45 g (95%) of a viscous golden oil. Analysis by ^{1}H NMR indicated a 5:1 ratio of methyl esters **22** and **23**.

Methyl (3*R*,4a*R*,6*S*,8a*R*)-6-[(Dimethylphosphono)methyl]-2-acetyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (23). To 1.17 g (3.23 mmol) of ester **22** were added 25 mL of MeOH and 0.33 mL (1.6 mmol) of a 28% solution of NaOMe in MeOH. The mixture was heated at reflux for 20 h and then partitioned between 150 mL of CH_2Cl_2, 150 mL of water, and 5 mL of 1 M HCl. The layers were agitated and separated, and the aqueous layer was washed with 20 mL of CH_2Cl_2. The organic layers were dried, and the solvent was removed in vacuo to afford an 11:1 mixture of esters **23** and **22**. The residue was chromatographed on 150 g of silica gel using 6:1 EtOAc/MeOH to afford 0.96 g (82%) of ester **23** (**23**:**22** = 16:1) as mixture of rotomers. ^{1}H NMR data is for the major rotomer only and ^{13}C NMR data is for both rotomers. IR: 1732, 1638 cm^{-1}; ^{1}H NMR: δ 0.90−1.15 (m, 2), 1.50−2.35 (m, 11), 2.16 (s, 3), 3.35 (dd, 1, J = 4.3, 13), 3.51 (dd, 1, J = 13, 13), 3.70 (s, 3), 3.72 (s, 3), 3.74 (s, 3), 5.23 (d, 1, J = 7.0). ^{13}C NMR: δ 21.39, 21.51, 28.56, 28.70, 28.79, 30.81, 31.44, 32.44, 32.57, 32.65, 32.74, 32.79, 32.89, 33.04, 33.15, 33.28, 33.51, 37.64, 43.06, 48.45, 52.01, 52.38, 53.79, 170.56, 170.64, 172.45, 172.90. MS (FD) m/z 361 (M^+). Anal. Calcd for $C_{16}H_{28}NO_6P$: C, 53.18; H, 7.81; N, 3.88. Found: C, 53.44; H, 7.66; N, 3.97.

(1*S*,2*R*,5*S*)-[2,5-Bis(hydroxymethyl)cyclohexyl]methyl Phenylmethyl Carbonate (27). A solution of **26** (18.8 g, 69.0 mmol, 1.0 equiv) in 3:1 CH_2Cl_2:MeOH (380 mL) was treated with Sudan III (a dilute solution in EtOAc), and the pink solution was cooled to −78 °C. O_3 was passed through the solution until the pink color disappeared (∼1.5 h at 25% output and 2.5% O_2 flow). The clear solution was sparged with N_2 for 10 min and then treated with $NaBH_4$ (11.5 g, 305.0 mmol, 5 equiv). The reaction was allowed to warm to 0 °C and was stirred for 20 min. The mixture was treated with saturated NH_4Cl (600 mL) in a slow stream and stirred at 0 °C for 50 min. The layers were separated, and the organic phase was dried (Na_2SO_4) and concentrated in vacuo to provide **27** as a yellow oil which crystallized upon standing (19.7 g, 93%), mp 75.7 °C: IR ($CHCl_3$): 3626, 3453, 3018, 2927, 2869, 1715, 1456, 1401, 1268, 1052, 943 cm^{-1}; ^{1}H NMR: δ 7.30−7.50 (5, m,), 5.15 (2, s,), 4.00−4.20 (2, m), 3.55−3.80 (2, m), 3.45 (2, d, J = 7.3), 1.90−2.10 (3, m), 1.35−1.70 (6, m), 0.80−1.15 (2, m); ^{13}C NMR: δ 155.1, 135.0, 128.4, 128.2, 71.0, 69.5, 69.4, 67.7, 60.0, 39.8, 38.5, 37.0, 27.1, 27.0, 23.6. MS (FD) m/z 309 (M + 1). Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85. Found: C, 66.44; H, 7.77.

(1*S*,2*R*,5*S*)-[2,5-Bis[[[(4-methylphenyl)sulfonyl]oxy]methyl]cyclohexyl]methyl Phenylmethyl Carbonate (28). A solution of **27** (2.00 g, 6.49 mmol, 1.0 equiv) in pyridine (15 mL) was treated with *p*-toluenesulfonyl chloride (2.97 g, 15.56 mmol, 2.4 equiv) and stirred at rt overnight. The mixture was concentrated in vacuo and the residue was dissolved in EtOAc (40 mL) and washed with 1 M HCl (2 × 15 mL), dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography (gradient of 12.5% to 50% EtOAc in hexane, 30 g of silica) to provide **28** as a colorless oil (3.02 g of 95 wt %,[35] corrected yield 2.86 g, 72%): IR ($CHCl_3$): 3028, 2931, 1744, 1711, 1362, 1267, 1189, 1176, 946 cm^{-1}; ^{1}H NMR: δ 7.70−7.80 (4, m), 7.25−7.45 (9, m), 5.15 (2, s), 3.70−4.05 (6, m), 2.40−2.45 (6, 2s), 1.30−2.20 (7, m), 0.70−0.95 (2, m); ^{13}C NMR: δ 154.8, 144.8, 132.6, 129.9, 128.5, 128.3, 127.8, 74.2, 69.7, 37.8, 36.6, 33.6, 26.6, 26.5, 23.0, 21.6, 21.5. MS (FD) m/z 616 (M + 1). Anal. Calcd for $C_{31}H_{36}O_9S_2$: C, 60.37; H, 5.88. Found: C, 60.58; H, 6.05.

(1*S*(*Z*),2*R*,5*S*)-3-[2,5-Bis[[[(4-methylphenyl)sulfonyl]oxy]methyl]cyclohexyl]-2-[[(phenylmethoxy)carbonyl]amino]-2-propenoic Acid Methyl Ester (29). A solution of **28** (9.60 g, 15.6 mmol, 1.0 equiv) in CH_2Cl_2 (40 mL) was treated with 10% Pd/C (1.50 g) and stirred at rt under an atmosphere of H_2 for 5 h. The mixture was filtered through Hyflo, and the filtrate was used directly in the next step. A solution of oxalyl chloride (1.63 mL, 18.7 mmol, 1.2 equiv) in CH_2Cl_2 (35 mL) was cooled to −78 °C and treated dropwise with DMSO (2.65 mL, 37.4 mmol, 2.4 equiv). After 15 min at −78 °C, the solution prepared above was added by cannulation, and the mixture was stirred at −78 °C for 10 min and at −20 °C for 30 min. The mixture was treated with diisopropylethylamine (13.0 mL, 74.7 mmol, 4.8 equiv) and washed with 1 M HCl (2 × 90 mL) and dried (Na_2SO_4) and the solution was used directly in the next step. A solution of *N*-(benzyloxycarbonyl)-α-phosphinoglycine trimethyl ester (5.42 g, 16.3 mmol, 1.05 equiv) in CH_2Cl_2 (70 mL) was cooled to −78 °C and treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (2.44 mL, 16.3 mmol, 1.05 equiv). The reaction was stirred at −78 °C for 15 min and then treated with the solution prepared above. The mixture was stirred at −78 °C for 1 h and at −30 °C for 30 min. The mixture was warmed to 0 °C and washed with 1 M HCl (2 × 50 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography (gradient of 12.5% to 50% EtOAc in hexane, 75 g of silica) and further purified by flash chromatography (gradient of 2.5% to 5% EtOAc in CH_2Cl_2, 75 g of silica) to provide **29** as a white foam (8.10 g, 76%): ^{1}H NMR: δ 7.70−7.80 (4, m), 7.30−7.40 (9, m), 6.35 (1, d, J = 9.7), 6.20 (1, br s), 5.10 (2, s), 4.05 (2, d, J = 7.3), 3.70−3.80 (5, m), 2.65−2.80 (1, m), 2.40−2.45 (6, 2s), 2.10−2.25 (1, m), 1.25−1.85 (5, m), 0.80−1.05 (2, m); ^{13}C NMR: δ 164.6, 154.1, 144.9, 144.8, 144.7, 137.2, 135.7, 132.7, 132.6, 132.5, 129.8, 128.4, 128.2, 128.0, 127.8,

(34) See ref 1b.

(35) Yield correction was based on residual EtOAc on sample as determined by integral area in the ^{1}H NMR. An analytical sample was prepared by drying at 60 °C under high vacuum.

125.3, 74.0, 68.2, 67.3, 52.4, 37.2, 36.2, 35.2, 29.0, 25.9, 22.3, 21.5. MS (FD) *m/z* 685 (M^+). Anal. Calcd for $C_{34}H_{39}NO_{10}S_2$: C, 59.55; H, 5.73; N, 2.04. Found: C, 59.62; H, 5.76; N, 1.84.

Methyl(3*R*,4a*R*,6*S*,8a*R*)-6-[[[(4-Methylphenyl)sulfonyl]-oxy]methyl]-2-(carbobenzyloxy)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (30). A solution of **29** (1.90 g, 2.77 mmol, 1.0 equiv) in 2.5:1 MeOH:toluene (40 mL) was treated with $(Ph_3P)_3RhCl$ (769 mg, 0.83 mmol, 0.3 equiv) and shaken on a Parr apparatus at 50 psi H_2 for 22 h. The mixture was concentrated in vacuo, and the residue was treated with silica gel (3.5 g) and 50:50 EtOAc:hexane (100 mL). The mixture was stirred at rt for 15 min and then filtered, and the filter-cake was washed with 50:50 EtOAc: hexane. The filtrate was concentrated in vacuo, and the residue was dissolved in toluene (35 mL) and treated with NaH (166 mg of 60% in mineral oil, 4.16 mmol, 1.5 equiv). The mixture was heated at 95 °C for 1 h, cooled, washed with 50% saturated NaCl solution (15 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash chromatography (gradient of 12.5% to 25% EtOAc in hexane, 60 g of silica) to provide **30** as a colorless film (472 mg of 95 wt %[36] or 447 mg corrected, 31%): ^{1}H NMR (500 MHz): δ 7.78−7.81 (2, m), 7.28−7.39 (7, m), 5.11−5.22 (2, m), 4.70 and 4.81 (1, d, J = 6.9), 3.67−3.81 (6, m), 3.14 and 3.24 (1, t, 13.7), 2.47 (3, s), 2.00−2.25 (2, m), 1.35−1.92 (7, m), 0.88−1.05 (2, m); ^{13}C NMR (125.7 MHz): δ 173.5, 156.9, 156.5, 145.1, 137.0, 133.5, 130.3, 128.9, 128.8, 128.6, 128.5, 128.4, 128.3, 128.2, 75.0, 67.8, 67.7, 51.9, 51.6, 41.0, 40.7, 38.2, 38.1, 33.7, 33.4, 33.3, 33.1, 32.4, 32.1, 28.6, 28.5, 28.3, 24.1, 24.0, 22.0. MS (FD) *m/z* 515 (M^+). Anal. Calcd for $C_{27}H_{33}NO_7S$: C, 62.89; H, 6.45; N, 2.72. Found: C, 62.82; H, 6.53; N, 2.66. Further elution of the column provided a mixture of **30** (116 mg, 8% and the other C-3 epimer (288 mg, 20%) (total yield of 851 mg, 59%).[37]

Methyl (3*S*,4a*R*,6*S*,8a*R*)-6-(Iodomethyl)-2-(carbobenzyloxy)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (31). A solution of **30** (1.15 g, 2.23 mmol, 1.0 equiv) in 2-butanone (20 mL) was treated with NaI (6.7 g, 44.6 mmol, 20 equiv) and stirred at 60 °C for 1.5 h. The mixture was cooled, concentrated to ∼10 mL, and partitioned between EtOAc and H_2O. The organic phase was washed with 50% brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash chromatography (gradient of 10% to 20% EtOAc in hexane, 20 g of silica) to provide **31** as a light tan oil (910 mg of 96 wt %[37] or 876 mg corrected, 83%): IR ($CHCl_3$): 3013, 2928, 1739, 1693, 1426, 1142, 1020 cm^{-1}; ^{1}H NMR: δ 7.25−7.40 (5, m), 5.10−5.30 (2, m), 4.70−4.90 (1, m), 3.70−3.90 (4, m), 3.00−3.35 (3, m), 2.20−2.30 (1, m), 2.00−2.10 (1, m), 0.95−1.95 (9, m); ^{13}C NMR: δ 173.0, 172.9, 156.4, 155.9, 136.5, 128.3, 128.2, 127.8, 127.7, 67.2, 67.1, 52.3, 51.4, 51.0, 40.4, 40.2, 39.5, 39.4, 33.0, 32.8, 32.7, 32.1, 32.0, 31.9, 31.6, 28.4, 28.3, 27.7, 27.6, 15.9, 15.7. MS (FD) *m/z* 471 (M^+). Anal. Calcd for $C_{20}H_{26}INO_4$: C, 50.95; H, 5.56; N, 2.97. Found: C, 51.09; H, 5.62; N, 2.97.

Methyl (3*S*,4a*R*,6*S*,8a*R*)-6-[(Diethylphosphono)methyl]-2-(carbobenzyloxy)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (32). A solution of **31** (143 mg, 0.303 mmol) in 5.0 mL of $(EtO)_3P$ was heated at 148 °C with a gentle stream of N_2 passing through the solution for 28 h. The mixture was cooled, and solvent was removed by evaporation under a stream of N_2. The residue was purified by flash chromatography (gradient of 2.5% to 5% EtOH in EtOAc, 4.5 g of silica) to provide **32** as a colorless film (143 mg of 97 wt %[37] or 139 mg corrected, 95%): ^{1}H NMR (500 MHz): δ 7.28−7.38 (5, m), 5.13−5.19 (2, m), 4.69 and 4.81 (1, d, J = 7.0), 4.05−4.12 (4, m), 3.65−3.88 (4, m), 3.19 and 3.30 (1, t, J = 13.7), 2.12−2.25 (1, m), 1.96−2.07 (1, m), 1.80−1.95 (2, m), 1.48−1.79 (7, m), 1.25−1.40 (6, m), 0.95−1.03 (2, m); ^{13}C NMR (125.7 MHz): δ 173.7, 157.0, 156.5, 137.1, 128.9, 128.8, 128.4, 128.2, 128.1, 67.7, 67.6, 61.8, 61.7, 61.6, 52.0, 51.7, 41.0, 40.8, 34.1, 33.8, 33.7, 33.6, 33.4, 33.2, 33.0, 32.4, 32.2, 29.4, 29.3, 29.2, 16.9, 16.8. MS (FD) *m/z* 481 (M^+). Anal. Calcd for $C_{24}H_{36}NO_7P$: C, 59.87; H, 7.54; N, 2.91. Found: C, 59.73; H, 7.46; N, 3.18.

Compound 20·HCl from 32. A solution of **32** (49 mg, 0.10 mmol) in CH_2Cl_2 (0.1 mL) was treated with 6 M HCl (1.5 mL), and the mixture was heated at reflux (110 °C) for 22 h. The mixture was cooled and washed several times with CH_2Cl_2. The aqueous portion was concentrated in vacuo to provide **20·HCl** as a colorless foam (30 mg, 96%): ^{1}H NMR (500 MHz, D_2O): δ 4.18 (1, d, J = 6.0), 3.40 (1, t, J = 13.0), 3.03 (1, dd, J = 13, 3.7), 2.11−2.29 (2, m), 2.00−2.10 (1, m), 1.89−1.99 (1, m), 1.53−1.80 (7, m), 0.96−1.15 (2, m); ^{13}C NMR (125.7 MHz, D_2O): δ 172.8, 51.8, 41.2, 34.4, 33.6, 33.5, 33.4, 32.8, 32.1, 31.2, 29.6, 28.3, 28.2, 27.7. MS (FD) *m/z* 278 (M + 1). Anal. Calcd for $C_{11}H_{21}ClNO_5P\cdot1.25\ H_2O$: C, 39.29; H, 7.04; N, 4.17. Found: C, 39.42; H, 7.02; N, 3.99.

***N*-[1-[(1*R*(*RS**),2*R*,4*S*)-Bicyclo[2.2.2]oct-5-en-2-ylmethyl]-2-oxo-2-(1-pyrrolidinyl)ethyl]benzamide (41).** Imine **39** (37.3 g, assumed 85% pure, 0.11 mol) was dissolved in a mixture of dry DMF (100 mL) and dry toluene (50 mL). Solid KOBu^t (14.7 g, 95%, 0.12 mol) was added to the reaction mixture, and the addition funnel was washed down with DMF−toluene (25 mL each). The solution became dark, and an orange precipitate began to form after 10 min. After 15 min, a solution of iodide **13** (20.0 g, 0.081 mol) in DMF−toluene (25 mL each) was added over 1.6 h. After 18 h (reaction complete in 2−3 h), the mixture was partitioned between toluene (150 mL) and H_2O (100 mL). The layers were separated, and the aqueous layer was extracted with toluene (2 × 150 mL). The combined toluene layers were washed with 100 mL each of H_2O, 0.2 M HCl, and 1% $NaHCO_3$ and brine (25 mL). The solvent was removed in vacuo to afford 42.8 g of an oil which was dissolved in 75 mL of EtOAc and stirred with 330 mL of 1 M HCl for 2 h. The mixture was extracted with toluene (3 × 100 mL), and the organic layers were washed with 0.2 M HCl (2 × 25 mL). The combined aqueous layers were cooled in an ice bath, and 100 mL of CH_2Cl_2, followed by 92 mL of 5 M NaOH, was added (pH 10). The aqueous layer was washed with CH_2Cl_2 (3 × 50 mL). The combined organic layers were layered with H_2O (50 mL), and 9.4 mL (0.081 mol) of PhCOCl followed by 14.5 mL of 5 M NaOH was added. The addition of NaOH was stopped when the pH was stable at 9−10. After stirring for 1 h, the layers were separated, and the aqueous layer was washed with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried (Na_2SO_4 and Darco) and concentrated. Recrystallization from EtOAc afforded 21.9 g (2 crops, 77%) of amide **41** as a 1:1 mixture of diastereomers. IR: 1633 cm^{-1}. ^{1}H NMR: δ 0.74−0.98 (m, 1), 1.10−2.06 (m, 12), 2.33 (m, 0.5), 2.48 (m, 1), 2.67 (m, 0.5), 3.34−3.57 (m, 3), 3.66−3.83 (m, 1), 4.88−5.08 (m, 1) 6.07−6.18 (m, 1), 6.23−6.34 (m, 1), 7.10−7.21 (m, 1), 7.36−7.53 (m, 3), 7.79−7.88 (m, 2). ^{13}C NMR: δ 24.15, 24.17, 24.52, 26.05, 26.33, 30.05, 30.18, 33.62, 34.08, 34.35, 34.66, 35.63, 40.81, 41.29, 46.02, 46.09, 46.44, 49.05, 49.45, 127.19, 128.47, 131.52, 131.59, 132.02, 134.19, 134.21, 134.85, 135.20, 166.91, 170.93, 171.15. MS (FAB) *m/z* 353 (MH+). Anal. Calcd for $C_{22}H_{28}N_2O_2$: C, 74.97; H, 8.01; N, 7.95. Found: C, 74.75; H, 7.94; N, 8.16. $[\alpha]_D$ = −6.32 (CH_2Cl_2, c = 1.0).

***N*-[1-[(1*R*(*RS**),2*R*,5*S*)-[1-[[2,5-Bis[[(methylsulfonyl)-oxy]methyl]cyclohexyl]methyl]-2-oxo-2-(1-pyrrolidinyl)-ethyl]]]benzamide (42).** A solution of amide **41** (20.7 g, 0.059 mol) in a mixture of CH_2Cl_2 (150 mL) and EtOH (100 mL) was stirred under N_2 at −45 °C. Sudan III (20 drops of a 0.1% solution in EtOAc) was added as an indicator, and O_3 was added through a subsurface glass frit until the indicator color faded (25 min). The mixture was purged with N_2. A $NaBH_4$ (4.44 g, 0.118 mol) solution was prepared in ice cold H_2O (55 mL). The $NaBH_4$ solution was stirred vigorously at −5 °C while the cold (−45 °C) ozonolysis mixture was added over 20 min. When the exotherm subsided (10 min), the mixture was allowed to warm to rt. After ∼3 h, the mixture was cooled in

(36) Product was concentrated in vacuo from dichloromethane, and yield correction was based on residual solvent as determined by integral area in the ^{1}H NMR. An analytical sample was prepared by drying at 60 °C under high vacuum.

(37) Yields were determined by integral areas of the C-3 protons in the ^{1}H NMR after subtracting for residual solvent.

ice and quenched by cautious addition of 2 M HCl. The mixture was acidified to pH 2 and stripped in vacuo to remove the organic solvents. The residual aqueous solution was extracted with EtOAc (3 × 200 mL) and 1:1 toluene/EtOAc (3 × 200 mL). The organic extracts were washed with a mixture of brine and 10% aqueous $NaHCO_3$ (50 mL each). The organic solution was dried (Na_2SO_4) and concentrated in vacuo to afford 23.9 g of the diol corresponding to dimesylate **42**. Spectral data was obtained on this crude material before carrying it directly into the next reaction IR: 1631 cm^{-1}. ^1H NMR: δ 0.80−1.13 (m, 2), 1.21−2.16 (m, 14), 3.30−3.65 (m, 7), 3.68−3.88 (m, 2), 4.95 and 5.18 (m,1), 7.30−7.55 (m, 4), 7.78−7.92 (m, 2). ^{13}C NMR: δ 23.80, 23.93, 24.16, 26.02, 28.08, 28.15, 30.81, 31.82, 35.80, 36.41, 36.66, 37.40, 38.44, 40.37, 40.43, 40.51, 40.77, 46.26, 46.75, 46.84, 49.36, 50.16, 60.41, 60.69, 68.06, 68.08, 125.32, 127.35, 127.39, 128.24, 128.45, 128.50, 129.05, 131.62, 131.69, 133.79, 133.84, 167.25, 167.39, 171.42, 171.47. MS (FD+) *m/z* 389 (MH^+). The crude diol was dissolved in 150 mL of toluene and 100 mL of THF, and 22 mL of pyridine (0.27 mol) and 15 mL of CH_3SO_2Cl (0.19 mol) were added. The mixture was heated at 70 °C for 5 h and stirred for 70 h at rt. Aqueous $NaHCO_3$ (100 mL, 10%) was added with stirring (to pH 6). The pH was brought to 7.5 by addition of saturated aqueous Na_2CO_3 (70 mL) and held for 20 min to allow hydrolysis of excess CH_3SO_2Cl. The mixture was extracted with EtOAc (3 × 200 mL), and the combined organic layers were washed in turn with 10% $NaHCO_3$ (200 mL), 1 M HCl (2 × 150 mL), and brine (100 mL). The organic layer was dried ($MgSO_4$ and Darco) and concentrated in vacuo to afford 28.9 g (90.1%) of dimesylate **42** as a 1:1 mixture of diastereomers. IR: 1634 cm^{-1}. ^1H NMR: δ 0.83−1.31 (m, 2), 1.40−2.08 (m, 12), 2.13 and 2.45 (m, 1), 2.97 and 3.04 and 3.05 (s, 6), 3.35−3.65 (m, 3), 3.69−3.86 (m, 1), 3.94−4.14 (m, 2), 4.16−4.40 (m, 2), 4.96−5.19 (m, 1), 7.33−7.56 (m, 4), 7.77−7.88 (m, 2). ^{13}C NMR: δ 23.04, 24.14, 26.01, 26.78, 27.22, 29.63, 31.09, 34.96, 35.08, 35.24, 36.32, 37.21, 37.24, 37.28, 37.39, 37.53, 37.59, 46.34, 46.48, 46.69, 47.00, 49.08, 49.12, 67.53, 67.91, 73.90, 74.07, 127.25, 128.54, 128.59, 131.76, 131.83, 133.70, 167.10, 167.37, 170.46, 170.57. MS (FAB+) *m/z* 545 (MH^+). $[\alpha]_D = -16.06$ (CH_2Cl_2, $c = 1.0$).

(3*R*,4a*R*,6*S*,8a*R*)- and (3*S*,4a*R*,6*S*,8a*R*)-6-(iodomethyl)-2-benzoyl-3-(*N*-pyrrolidinylcarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline (43). The 28.9 g (0.053 mol) of dimesylate **42** was dissolved in toluene (200 mL), and the volume was reduced in vacuo to 150 mL. The solution was diluted with dry THF (100 mL), and a 1 M solution of $KOBu^t$ in $HOBu^t$ (133 mL, 0.133 mol) was added over 3 h. After 21 h, a solution of AcOH (14.3 mL, 0.25 mol) in toluene (25 mL) was added, and the mixture was concentrated in vacuo to a thick slurry (150 mL). The mixture was transferred to a separatory funnel with EtOAc (150 mL) and washed with 125 mL of 10% $NaHCO_3$. The aqueous layer was washed with EtOAc (2 × 150 mL). The organic layers were washed in turn with 10% $NaHCO_3$ (50 mL), 0.2 M HCl (50 mL), and brine (25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to 22.7 g of the mesylate corresponding to iodide **43**. Spectral data was obtained on this crude material (5−10:1 mixture of isomers) before carrying it on directly to the iodide. ^1H NMR: δ 0.90−1.10 (m, 1), 1.30−2.07 (m, 13), 2.08−2.22 and 2.38−2.49 (m, 1), 2.99, 3.00 (s, 3), 3.26−3.86 (m, 5), 3.91−4.12 (m, 3), 4.18, 4.42, 4.78 (m, 3), 5.32 and 5.56 (d, 1, $J \sim 8$), 7.31−7.51 (m, 5). ^{13}C NMR: δ 23.65, 23.83, 23.91, 24.12, 26.24, 26.43, 28.11, 28.16, 31.05, 33.21, 33.57, 34.16, 37.20, 37.88, 45.37, 46.09, 46.19, 46.29, 46.73, 48.73, 74.37, 125.89, 127.80, 128.23, 128.40, 128.48, 129.51, 136.24, 171.74, 171.86. MS (FD) *m/z* 448 (M^+). The mesylate (22.3 g) was dissolved in methyl ethyl ketone (255 mL), and 22.5 g of NaI (0.15 mol) was added. After heating for 5 h at reflux, the mixture was concentrated in vacuo to a thick slurry. EtOAc (200 mL) and dilute aqueous $Na_2S_2O_3$ (100 mL) were added, and the layers were separated. The aqueous layer was washed with EtOAc (3 × 150 mL). The organic layers were washed with brine (2 × 75 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to a yellow foam (22.9 g, 95.9%). Iodide **43** thus obtained was a 5−10:1 mixture of isomers and was suitable for use in the next reaction. IR: 1623, 1650 cm^{-1}. ^1H NMR: δ 0.84−1.06 (m, 1), 1.33−2.06 (m, 13), 2.06−2.21 and 2.39−2.49 (m, 1), 3.06 (d, 2, $J = 7$), 3.22−3.81 (m, 5), 4.01 (t, 1, $J = 13$), 4.19 and 4.41 and 4.76 (m, 3), 5.32 and 5.56 (d, 1, $J = 8$), 7.30−7.50 (m, 5). ^{13}C NMR: δ 14.69, 23.93, 26.45, 28.05, 28.69, 30.97, 32.56, 33.82, 34.12, 40.80, 45.44, 46.31, 46.73, 48.80, 125.90, 128.38, 128.46, 129.47, 136.29, 171.62, 171.85. MS (FD) *m/z* 480 (M^+). $[\alpha]_D = -79.05$ (CH_2Cl_2, $c = 1.0$).

(3*S*,4a*R*,6*S*,8a*R*)-6-(Phosphonomethyl)-1,2,3,4,4a,5,6,7,8,8a-decahydro-isoquinoline-3-carboxylic Acid (1). Iodide **43** (22.7 g, 0.047 mol) was dissolved in $(EtO)_3P$ (690 mL, 4 mol) in a flask equipped with a subsurface frit for nitrogen purging and a 25 in. Vigreaux distillation column. The solution was heated with heating rate and an N_2 flow balanced to keep the pot temperature at 138−146 °C and the distillation head temperature at 40−60 °C with slow distillation to remove EtI. After 22 h (115 mL distillate collected), the solution was cooled to <60 °C, tetraethylene glycol dimethyl ether (100 mL) was added as a scavenger solvent (bp 275 °C), and the excess $(EtO)_3P$ was removed by distillation in vacuo. When the pot temperature reached 155 °C, the heat was removed. The pot residue was taken up in toluene (250 mL) and washed with H_2O (3 × 200 mL). The aqueous layers were back-washed with toluene (3 × 200 mL). The combined toluene layers were concentrated in vacuo to 200 mL and passed through a short column of silica gel (340 g, EM Grade 62, 60−200 mesh), eluting initially with toluene and then EtOH in EtOAc (15%, then 30%) to afford 19.3 g of the diethyl phosphonate. Spectral data was obtained on the mixture of diethyl phosphonate isomers before carrying it on directly into the next reaction. IR: 1623, 1650 cm^{-1}. ^1H NMR: δ 0.94−1.12 (m, 1), 1.31 (t, 6, $J = 8$), 1.31−2.07 (m, 13), 2.07−2.21 (m, 1), 3.25−3.86 (m, 5), 3.96−4.14 (m, 7), 5.24−5.36 (m, 1), 7.31−7.49 (m, 5). ^{13}C NMR: δ 16.41, 16.49, 23.93, 26.45, 28.86, 29.02, 31.07, 31.85, 32.93, 32.98, 33.41, 33.55, 33.68, 33.83, 33.87, 45.52, 46.26, 46.72, 48.80, 61.24, 61.32, 125.90, 127.02, 128.37, 128.45, 129.43, 136.37, 171.78, 171.88. MS (FD) *m/z* 490 (M^+). $[\alpha]_D = -77.23$ (CH_2Cl_2, $c = 1.0$). To a solution of the diethyl phosphonate (18.9 g, 0.039 mol) in CH_2Cl_2 was added 6 M HCl (220 mL, 1.32 mol). The mixture was heated at reflux for 16 h and then cooled and extracted with CH_2Cl_2 (3 × 200 mL) to remove benzoic acid. The organic extract was back-washed with 1 M HCl (40 mL). The aqueous layers were concentrated in vacuo to afford 16.7 g of amine hydrochloride salts. The mixture of pyrrolidine and product HCl salts was dissolved in H_2O (100 mL) and cooled while KOH pellets (89.9 g, 1.36 mol) were added slowly, with stirring (washed in with 85 mL of H_2O). The solution was heated at reflux with a nitrogen purge to sweep out pyrrolidine). After 23 h, the solution was cooled, 135 mL of 12 M HCl was added, and the solvent was removed in vacuo. The solid was extracted repeatedly with 1:1 MeOH/CH_2Cl_2, and the organic extracts were stripped in vacuo to yield 12.6 g of a glassy foam. ^1H NMR and FAB-MS showed this material to be a mixture consisting of ∼40% of the methyl esters. The material was taken up in H_2O (50 mL), heated at reflux 1 h, and then distilled until the volume was reduced to about half. The solution was cooled to rt and the pH adjusted from 0.7 to 2.6 by addition of 5 M NaOH (8 mL). The solution was seeded with an authentic sample of **1**.[34] After standing at rt overnight and in an ice bath for 4 h, the resulting precipitate was filtered, washed with cold H_2O (4 × 4 mL) and acetone, and air-dried, yielding 4.18 g (33%) of a white solid. LY235959 (**1**) was obtained in 94% ee and contained 4.7% of epimer **20** as determined by HPLC. This material was characterized by MS, ^1H NMR, IR, and by HPLC comparison with authentic material prepared independently.[34] IR (KBr): cm^{-1}, 1736. ^1H NMR (D_2O/DCl): δ 0.98−1.22 (1, m), 1.35−1.58 (1, m), 1.58−1.95 (7, m), 1.95−2.26 (4, m), 3.09−3.40 (2, m), 4.11 (1, dd, $J \sim 14$, 4). MS (FD+) *m/z* 278 (MH^+).

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Supporting Information Available: Experimental procedures for the synthesis of compounds **8**, **9**, **10**, **11**, **34**, **35**, **38**, and **39**; ^{1}H NMR spectra for compounds **16**, **19**, **21**, **22**, **42**, and **43** (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and may be ordered from the ACS; see any current masthead page for ordering information.

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