# Stereoselective Synthesis of 6-Substituted Decahydroisoquinoline-3-carboxylates: Intermediates for the Preparation of Conformationally Constrained Acidic Amino Acids

Paul L. Ornstein,* Nancy K. Augenstein, and M. Brian Arnold

*Lilly Research Laboratories, A Division of Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana 46285*

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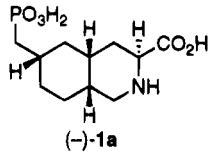
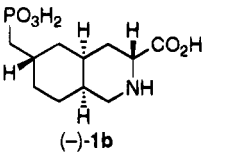
In this article we describe the stereoselective preparation of two 6-(hydroxymethyl) substituted decahydroisoquinoline-3-carboxylates, which are useful in the synthesis of a number of excitatory amino acid antagonists, e.g., (−)-**1a** (LY235959), (−)-**2a** (LY202157) and (−)-**3a** (LY293558). For example, the known ketone **4** was converted to either the (3*SR*,4a*RS*,6*SR*,8a*RS*)-alcohol **18** or the (3*SR*,4a*RS*,6*RS*,8a*RS*)-alcohol **21**, the former via a stereoselective hydroboration reaction, the latter via a stereoselective enol ether hydrolysis followed by reduction. These C-6 epimeric alcohols were easily converted to a number of useful intermediates, e.g., aldehydes, bromides and iodides. If we used resolved ketone **4**, then these intermediates could be obtained in optically active form. In either racemic or non-racemic form, these intermediates provided access to a number of diastereomerically pure amino acids that were difficult to obtain by earlier routes.

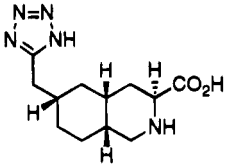
Glutamic acid is the major excitatory neurotransmitter in the central nervous system, acting at a number of subclasses of excitatory amino acid (EAA) receptors.[1] Because of the role that glutamic acid may play in neuronal cell death in certain acute and chronic neurodegenerative diseases,[2] there is significant interest in the development of EAA antagonists as therapeutic agents. Our efforts have focused on the development of competitive EAA antagonists, and we recently described that the 6-substituted decahydroisoquinoline-3-carboxylic acids (−)-**1a** (LY235959) and (−)-**2a** (LY202157) were potent antagonists of neurotransmission mediated through the *N*-methyl-D-aspartic acid (NMDA) subclass of EAA receptors.[3] In the course of our structure activity studies on this class of decahydroisoquinoline amino acids, we also found that amino acid (−)-**3a** (LY293558) was a competitive antagonist of the 2-amino-3-(5-methyl-3-hydroxyisoxazol-4-yl)propanoic acid (AMPA) subclass of EAA receptors.[4] Our structure activity studies directed towards these decahydroisoquinoline EAA antagonists found a clear stereochemical preference for activity. The relative and absolute stereochemistry found in amino acids (−)-**1a**, (−)-**2a** and (−)-**3a** was optimal for high affinity receptor binding and potent in vivo antagonist activity.[3,4] Each was prepared as either the racemate or a single enantiomer from the known ketone **4**.[5] The high degree of stereoselectivity observed for activity in this series necessitated the ability to control relative stereochemistry in the synthesis of these hydroisoquinoline amino acids.



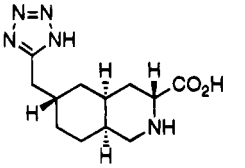
(−)-**1a**



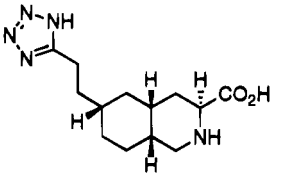
(−)-**1b**



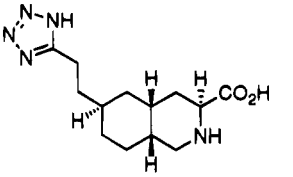
(−)-**2a**



(−)-**2b**



(−)-**3a**



(+)-**3b**

In our original approach to this class of compounds (Scheme 1),[3] stereochemistry at C-3, C-4a and C-8a was set through a stereoselective synthesis of ketone **4** (prepared in five steps from *m*-tyrosine).[5] Introduction of the C-6 stereocenter was then accomplished through catalytic hydrogenation of a suitable olefinic precursor. The chemical yields of these hydrogenations were good, and the epimer that led to the most active antagonists was the major product. A significant limitation of this

* Author to whom correspondence should be addressed. Phone: 317-276-3226. Fax: 317-277-1125.

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(1) Collingridge, G. L.; Lester, R. A. Excitatory amino acid receptors in the vertebrate central nervous system. *Pharmacol. Rev.* **1989**, *41*, 143–210.

(2) Meldrum, B.; Garthwaite, J. Excitatory amino acid neurotoxicity and neurodegenerative disease. *Trends Pharmacol. Sci.* **1990**, *11*, 379–387.

(3) 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. 6-Substituted decahydroisoquinoline-3-carboxylic acids as potent and selective conformationally constrained NMDA receptor antagonists. *J. Med. Chem.* **1992**, *35*, 3547–3560.

(4) Ornstein, P. L.; Arnold, M. B.; Augenstein, N. K.; Lodge, D.; Leander, J. D.; Schoepp, D. D. 3*SR*,4a*RS*,6*RS*,8a*RS*-6-(2-(1H-Tetrazol-5-yl)ethyl)-decahydroisoquinoline-3-carboxylic acid: A structurally novel, systemically active, competitive AMPA receptor antagonist. *J. Med. Chem.* **1993**, *36*, 2046–2048.

(5) Ornstein, P. L.; Arnold, M. B.; Augenstein, N. K.; Paschal, J. W. Syntheses of 6-oxodecahydroisoquinoline-3-carboxylates. Useful intermediates for the preparation of conformationally defined excitatory amino acid antagonists. *J. Org. Chem.* **1991**, *56*, 4388–4392.

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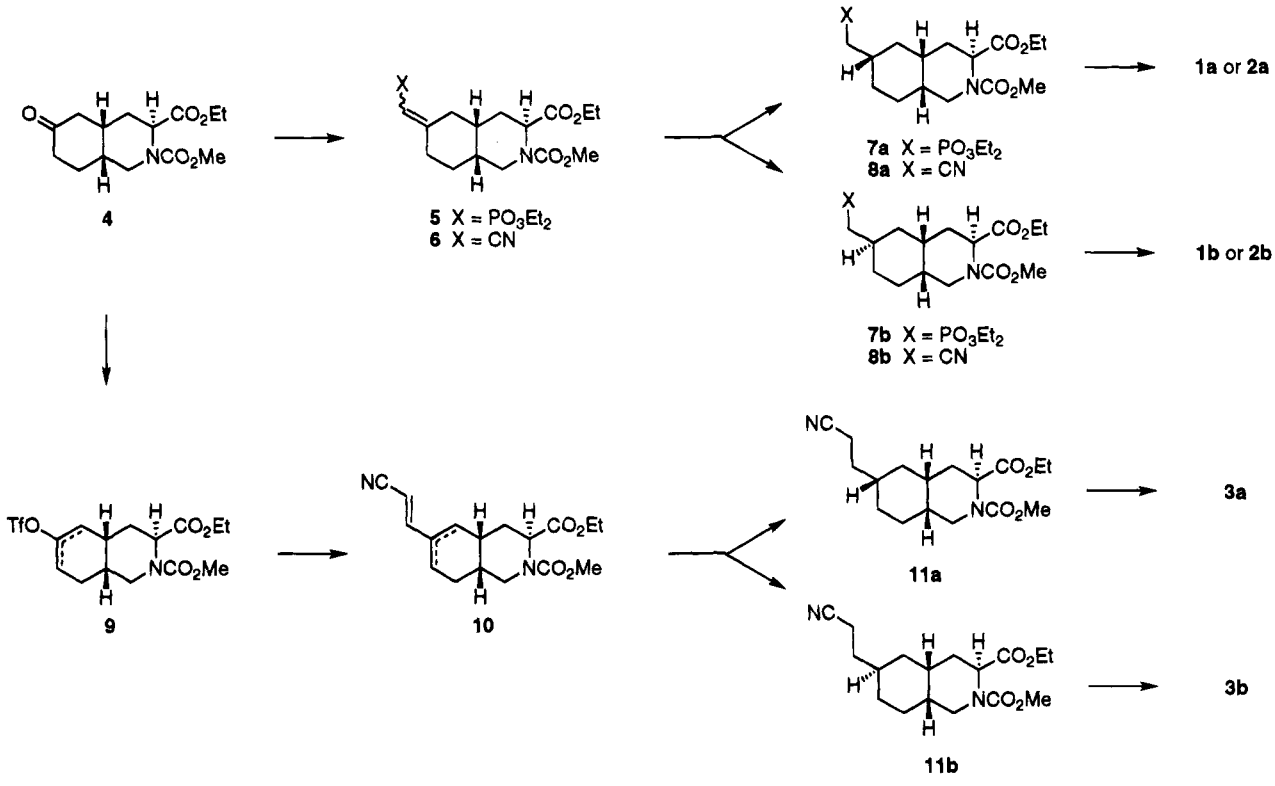
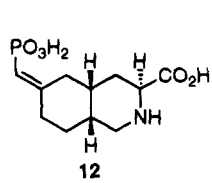
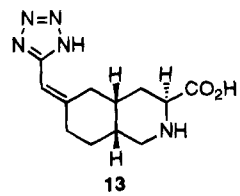
**Scheme 1**




approach, however, was the inability to engineer in a high degree of stereoselectivity in such hydrogenations. Attempts to control the outcome to favor one or the other diastereomer, i.e., by changing solvent and/or catalyst, were unsuccessful.[3] Hydrogenation of the phosphono- and cyanomethylidine compounds **5** and **6**, for example, gave mixtures of the corresponding C-6 epimeric phosphonomethyl compounds **7a** and **7b**, and the cyanomethyl compounds **8a** and **8b**, respectively (Scheme 1). While the nitriles **8a** and **8b** were separable by chromatography, the phosphonate esters **7a** and **7b** were inseparable, and amino acids **1a** and **1b** were obtained only after hydrolysis and a tedious fractional crystallization.[3] In an early synthesis of the AMPA antagonist **3a** (Scheme 1), ketone **4** was converted to the diene **10** (mixture of regioisomers) via palladium-mediated coupling of acrylonitrile with enol triflate **9** (mixture of regioisomers). Catalytic hydrogenation of **10** then gave the cyanoethyl compounds **11a** and **11b**, and after chromatographic separation of the diastereomers, **11a** was converted to the AMPA antagonist **3a**. The outcome of these hydrogenations appeared to be strongly influenced by the preference for the ester at C-3 to be in an axial orientation, which relieves torsional strain between it and the methyl carbamate at N-2. If we removed the methyl carbamate prior to hydrogenation (as in the dehydro amino acid **12**), the reduction was stereoselective and we



**12**

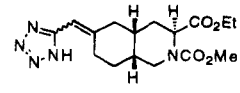


**13**

obtained only the amino acid **1a**.[3] However, hydrogenation of the corresponding unsaturated tetrazole **13** was much less selective, affording a 5:1 mixture of **2a**:**2b**.[6] The synthetic utility of our approach to this class of acidic amino acids was limited by the lack of selectivity in setting the C-6 stereochemistry, and the necessity to chromatographically separate the resultant epimers. We therefore decided to pursue a strategy that obviated a hydrogenation to introduce this center.

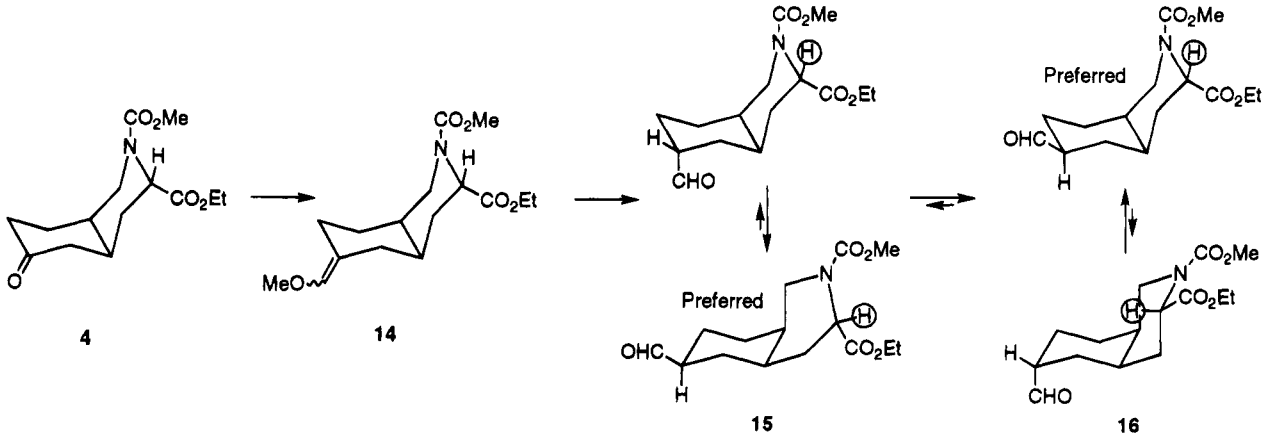
For more extensive structure activity studies in this class of excitatory amino acid antagonists, we desired intermediates that could be prepared with a high degree of selectivity, and that offered synthetic flexibility for the preparation of many different analogs. We felt that the alcohols **18** and **21** (Scheme 3) could serve this role, if they could be prepared with a high degree of stereoselectivity. In this article we describe the stereoselective conversion of **4** to the alcohols **18** and **21**, and their elaboration to the corresponding aldehydes, bromides and iodides.[7] We also exemplify their utility for the synthesis of amino acids **2a**[7] and **3a**, their corresponding C-6 epimers **1b**,[7] **2b**[7] and **3b**, and the individual enantiomers of each of these compounds.[7]

(6) The ratio of **2a**:**2b** was determined by integration of the α-amino acid protons in the $^1$H NMR (taken in $D_2O$). For **2a**, this proton appeared as a doublet of doublets at δ 3.63; for **2b**, this proton appeared as multiplet at δ 3.74. Compound **13** was prepared by treatment of **6** (mixture of olefin isomers) with azido-tri-n-butylstannane at 80 °C for three days, followed by HCl in ether. Chromatography on silica gel with 6% acetic acid/54% ethyl acetate/hexane afforded a 63% yield of the unsaturated tetrazole **i**. This compound was exhaustively hydrolyzed with 6 N aqueous HCl at reflux to afford a 55% yield of the dehydro-amino acid **13** (mixture of olefin isomers). Hydrogenation of **13** in water with 5% Pd/C at room temperature and 60 psi for 2 h gave a 5:1 mixture of **2a**:**2b**.



**i**

**Scheme 2**




We envisioned that for **18**, the hydroxymethyl group at C-6 could be introduced through conversion of **4** to an enol ether followed by hydrolysis to the aldehyde and subsequent reduction (Scheme 2). The condensation of ketone **4** with the ylide derived from methoxymethyl triphenylphosphonium chloride was capricious. When **4** was added to an excess of this ylide, the desired enol ether was formed; however, if the reaction was not carefully monitored, the enol ether was converted to a subsequent compound that in the $^1$H NMR retained many features of the desired product but whose stucture was not fully determined. We found that the reaction proceeded smoothly if the hygroscopic phosphonium salt was washed with THF and dried in vacuo prior to use. Generation of a solution of the ylide in THF at 0 °C with sodium bis(trimethylsilyl)amide followed by dropwise addition of this solution to the ketone **4** in THF at 0 °C until the ylide color just persisted then gave very high yields of enol ether **14**. We attempted the hydrolysis of **14** under a variety of conditions, using mixtures of 1 N aqueous HCl and a co-solvent. With methanol as co-solvent, we obtained mixtures of the aldehydes **15** and **16** and the corresponding dimethyl acetals. With small scale reactions using THF as co-solvent, hydrolysis was complete after 4–5 h and we obtained about a 2:1 ratio of **15**:**16**.[8] When the reaction was performed on a multigram scale, we often observed that even though TLC indicated that the hydrolysis was complete, the starting enol ether was present following work-up. We were able to obviate this difficulty by switching to acetonitrile as the co-solvent. Under these conditions (4:1 $CH_3CN$: 1 N HCl), we were able to reproducibly obtain high yields (90–95%) of a 4:1 ratio of **15**:**16**,[8] independent of the scale of the reaction. We were never able to improve the proportion of the desired aldehyde **15**; shorter reaction times gave incomplete hydrolysis, and longer reaction times gave greater amounts of aldehyde **16**.

While the enol ether **14** was not a good source of the alcohol **18**, this intermediate proved to be useful for the formation of the C-6 epimeric alcohol **21** (Scheme 3). We had observed in earlier experiments that longer exposure of the enol ether to the hydrolytic medium gave a greater proportion of **16**. Thus, it was likely that this epimer was thermodynamically more stable than **15**. When the enol ether hydrolysis was carried out at 60 °C overnight, we obtained a 13:1 mixture of **16**:**15** (Scheme 2).[8] Reduction of aldehyde **16** (sodium borohydride, ethanol, 0 °C) then afforded the desired alcohol **21** (Scheme 3).

The greater stability of **16** versus **15** may reflect the impact of torsional strain between the carbamate at N-2 and the ester at C-3 (Scheme 2). Protonation of enol ether **14** from the sterically-less hindered $\beta$-face is kinetically preferred, and after hydrolysis of the intermediate oxonium ion, affords **15**. Initially we would expect to obtain a conformer where the aldehyde at C-6 and the ester at C-3 are both axial. However, our previous experience with 6-substituted decahydroisoquinoline-3-carboxylates[3,5] would indicate that this conformer is probably less stable than the corresponding conformer (obtained through ring flip) in which the C-6 substituent is equitorial, and the piperidine ring adopts a more boat-like conformation to relieve torsional strain between the ester and carbamate.[9] Aldehyde **15** can equilibrate to **16** via formation of the enol, and subsequent reprotonation from the $\alpha$-face. This affords a more stable compound in which the aldehyde at C-6 is equitorial and the ester at C-3 is axial.

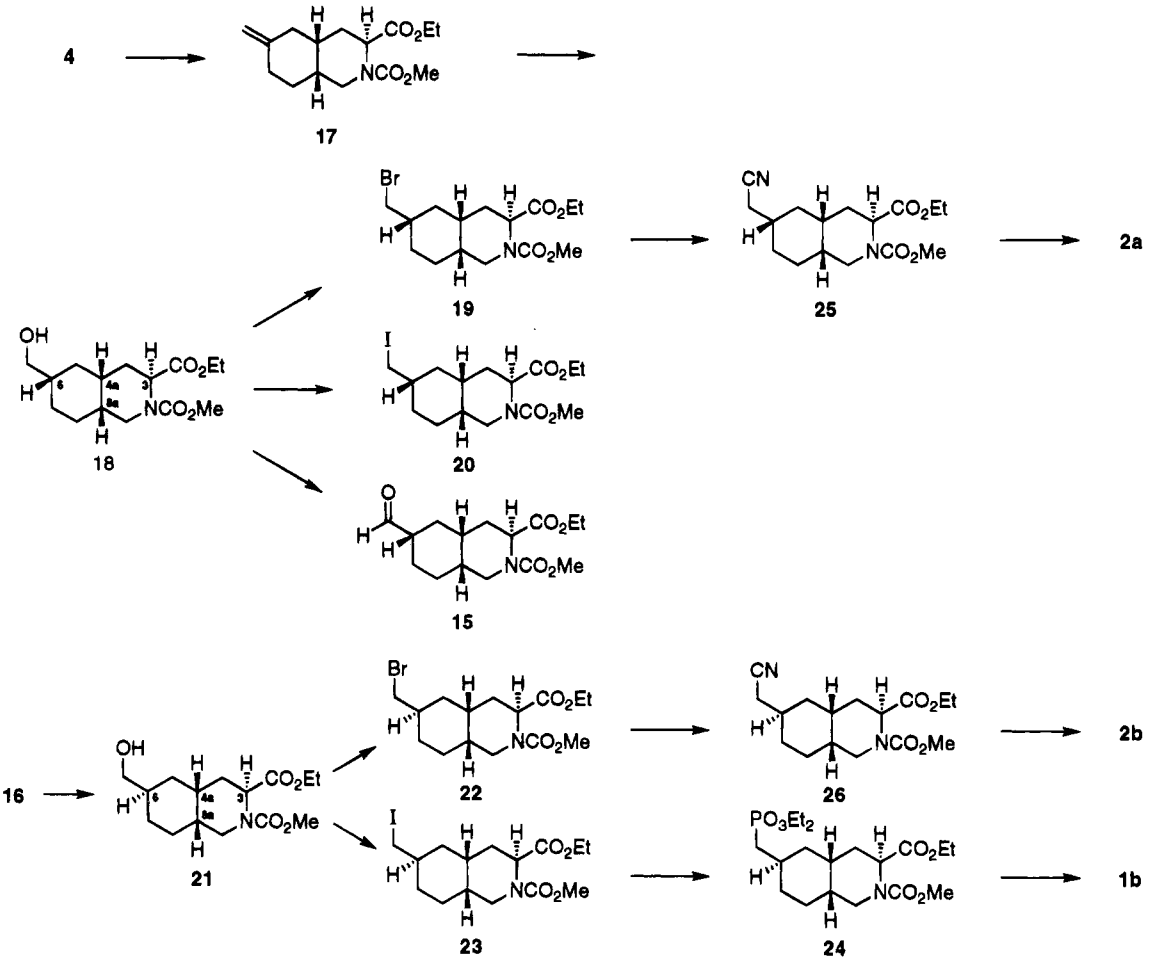
To overcome the limitations of the synthesis of **18** via aldehyde **15**, we examined a different strategy (Scheme 3). Ketone **4** could be cleanly converted in 95% yield to the methylidine compound **17** using methyl triphenylphosphonium bromide and sodium bis(trimethylsilyl)amide in THF. Hydroboration of **17** with borane methyl sulfide in THF at 0 °C, followed by oxidation with basic hydrogen peroxide (3 N aqueous NaOH, then 30% aqueous hydrogen peroxide) gave a 94% yield of the desired alcohol **18**. The diastereoselectivity in this hydroboration was high, providing a $\geq$10:1 ratio of **18**:**21**.[8] Hydroboration with diisoamyl borane offered no improvement in the diastereoselectivity. Aldehyde **15** was obtained without epimer-

(7) Ornstein, P. L.; Arnold, M. B.; Augenstein, N. K.; Deeter, J. B.; Leander, J. D.; Lodge, D.; Calligaro, D. O.; Schoepp, D. D. Unusual stereochemical preferences of decahydroisoquinoline-3-carboxylic acid competitive NMDA antagonists. *BioMed. Chem. Lett.* **1993**, *3*, 2067–2072.

(8) The ratio of **15**:**16** was determined by integration of their respective aldehyde protons in the $^1$H NMR. For **15**, this proton appeared as a singlet at $\delta$ 9.76; for **16**, this proton appeared as a singlet at $\delta$ 9.56. The ratio of **18**:**21** was determined by integration of the $\alpha$-amino ester protons. For **18**, this proton appeared as a triplet at $\delta$ 4.37; for **21**, this proton appeared as two doublets at $\delta$ 4.99 and 4.82 (amide rotamers).

(9) The boat-like conformation for the piperidine ring in this epimer is implied from analysis of the splitting pattern for the C-3 proton ($\alpha$ to the amino ester). In epimers such as **7a**, **8a** or **11a**, this proton appears as a triplet. Examination of Dreiding models indicates that when the piperidine ring adopts a boat-like conformation, the dihedral angles between the C-3 proton and the C-4 protons are approximately equal. We expect similar coupling constants, and consequently this proton appears as a triplet. We only observe a single amide rotamer for this epimer.

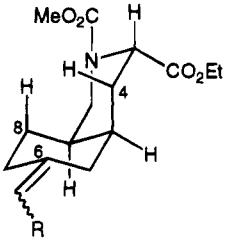
**Scheme 3**



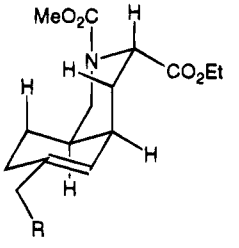

ization by oxidation of alcohol **18** using oxalyl chloride and dimethylsulfoxide.

Endo-face addition to the olefin of **17** (top-face with respect to the conformer shown below) is hindered by the axial proton at C-4 (and to a lesser extent by the axial proton at C-8). We therefore expect that addition of borane to the double bond of **17** should occur preferentially from the sterically less-hindered exo-face (bottom-face with respect to the conformer shown below), delivering alcohol **18** after oxidation. We would also predict the same facial bias for hydrogenation of olefins **5** or **6**, however this reaction is much less selective. This corruption of selectivity may result from double bond isomerization to the corresponding $\Delta_{5,6}$ or $\Delta_{6,7}$ olefins (**5a** or **5b**, respectively) prior to reduction. We would expect that exo-face addition would still be preferred for **5b**, however, the facial bias imparted by the C-4 axial hydrogen may be diminished for additions to the double bond in **5a**, and this may lead to the less selective hydrogenations of these compounds.

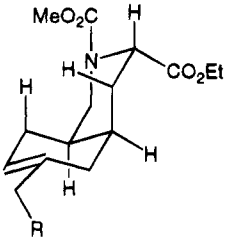
With the alcohols **18** and **21** in hand, we turned our attention to the formation of other useful intermediates (Scheme 3).[7] Alcohol **18** was readily converted to either the corresponding bromide **19** or iodide **20** with triphenylphosphine dibromide or diiodide, respectively. Similar conversion of alcohol **21** then afforded the corresponding epimeric bromide **22** and iodide **23**. All of the chemistry that was described for the racemic compounds **14-23** could also be performed using resolved ketone **4**, providing access to the corresponding nonracemic intermediates. The (+)-isomer of iodide **23**,



**5** X = $PO_3Et_2$
**6** X = CN
**17** X = H



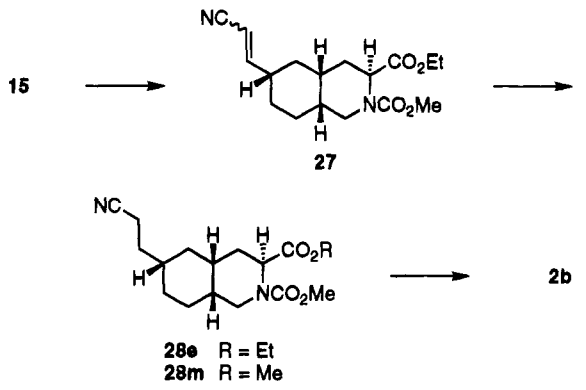
**5a** X = $PO_3Et_2$
**6a** X = CN



**5b** X = $PO_3Et_2$
**6b** X = CN

derived from the (+)-isomer of ketone **4**, was crystalline, and we were able to obtain a single-crystal suitable for X-ray crystallographic analysis. The observation that this compound possessed the 3*R*,4a*S*,6*R*,8a*S* stereochemistry provided unambiguous confirmation that the absolute stereochemistry of (−)-**4** is 3*S*,4a*R*,8a*R* and (+)-**4** is 3*R*,4a*S*,8a*S*, and allowed assignment of the relative and

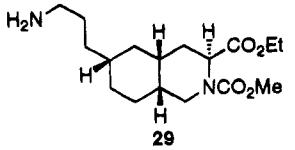
**Scheme 4**




absolute configuration of all of these hydroisoquinoline intermediates and the derived amino acids, e.g. **1a**, **2a** and **3a**.

In order to study the stereochemical preferences for NMDA receptor antagonist activity in this series of amino acids, we required pure samples of each of the enantiomers of **1a**, **1b**, **2a** and **2b**.[7] Our early routes allowed only for the preparation of (−)-**1a** and (+)-**1a**.[3] The availability of both racemic and non-racemic **18** and **21** allowed for the straightforward preparation of the racemic and non-racemic versions of these amino acids (Scheme 3). Refluxing a solution of the iodide **23** in triethylphosphite afforded a 75% yield of the desired phosphonate **24**, along with 9% of the olefin **17**. Hydrolysis of **24** in refluxing 6 N hydrochloric acid followed by anion exchange chromatography afforded a diastereomerically pure sample of amino acid **1b** in 55% yield. Treatment of the bromides **19** and **22** with sodium cyanide in DMSO afforded the corresponding nitriles **25** and **26**, respectively. Conversion to the tetrazole was effected by treatment with two equivalents of azido-tri-n-butylstannane (neat), and exhaustive hydrolysis with refluxing 6 N aqueous hydrochloric acid then afforded the desired amino acids **2a** and **2b**, respectively.

This technology was also applied to a diastereoselective (and enantioselective) synthesis of **3a**. Horner–Emmons condensation of the sodium salt of diethylphosphonoacetonitrile with **15** gave the desired unsaturated nitrile **27** as a mixture of E- and Z-isomers. On a small scale, we had reasonably good success using catalytic hydrogenation to reduce **27** to the cyanoethyl compound **28a**, with little to no reduction of the nitrile to the amine **29**. However, as the reaction scale was increased (e.g., from 1–3 g to 10–20 g of **27**), **29** was formed in significant quantities. To overcome this problem, we performed the reduction using magnesium in methanol. Yields of the desired nitrile **28** were high with this reaction, and no amine was formed. We did observe transesterification of ethyl ester **28e** to the methyl ester **28m** (Scheme 4), however, this was of no concern, because following conversion to the tetrazole, the ester was to be hydrolyzed. Treatment of **28em** with azido-tri-n-butylstannane and exhaustive hydrolysis then afforded amino acid **3a**.




In conclusion, we devised stereoselective routes to a number of useful intermediates that allowed for the preparation of many different hydroisoquinoline amino acids. The approach detailed in this paper allowed us to obviate hydrogenations for the introduction of stereochemistry, and the utility of this chemistry is exemplified by the synthesis of some NMDA and AMPA receptor antagonists. Subsequent applications of this chemistry to our AMPA antagonist structure activity studies will be reported elsewhere.

## Experimental Section

All experiments were run under a positive pressure of dry nitrogen. Tetrahydrofuran (THF) was distilled from sodium prior to use. Methyl triphenylphosphonium bromide and methoxymethyl triphenylphosphonium chloride were suspended in THF and stirred 15 min at room temperature, then filtered, washed with THF and pentane and dried in vacuo at 50 °C for 30 min (on a rotary evaporator). All other solvents and reagents were used as obtained. "Workup" refers to addition to the reaction mixture of a neutral or acidic aqueous solution, separation of the organic layer and then extraction of the aqueous layer n-times (X) with the indicated solvent(s). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuo, then purified as indicated. The aqueous solution and organic solvent(s) used are provided parenthetically in the text. "Chromatography" refers to flash chromatography on 230–400 mesh Silica Gel 60, using the amount of silica gel and solvent of elution referred to parenthetically in the text. "Preparative HPLC" refers to chromatographic separation on a preparative HPLC instrument, using a linear gradient of hexane to the solvent indicated in parentheses in the text. The enantiomers of each compound were prepared using the same procedure as is shown below for the racemate. Each enantiomer gave an identical $^1H$ NMR spectrum as for the corresponding racemate.

**Ethyl (3*SR*,4a*RS*,8a*RS*)-6-Methylidine-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (17).** To a 0 °C suspension of 76.3 g (213 mmol) of methyl triphenylphosphonium bromide in 220 mL of THF was added 213 mL (213 mmol, 1 M in THF) of sodium bis(trimethylsilyl)amide. After 15 min, the resulting solution/suspension was added via teflon cannula to a 0 °C solution of 43.2 g (153 mmol) of **4** in 320 mL of THF until a pale yellow color persisted. Workup (water/ether 3X) afforded a residue that was suspended in 25% ethyl acetate/hexane, stirred at room temperature for one hr, then filtered and the filtrate concentrated in vacuo. Chromatography of the residue (400 g, 25% ethyl acetate/hexane) gave 40.7 g (95%) of **17**. $^1H$ NMR ($CDCl_3$, doubling due to amide rotamers) $\delta$: 4.93 and 4.76 (m, 1H), 4.68 (s, 1H), 4.57 (s, 1H), 4.15 (m, 2H), 3.91 and 3.76 (d, $J$ = 12.0 Hz, 1H), 3.67 and 3.65 (s, 3H), 3.21 and 3.16 (dd, $J$ = 12.0, 3.0 Hz, 1H), 2.28 (m, 2H), 2.10–1.40 (m, 8H), 1.24 (t, $J$ = 7.1 Hz, 3H). Anal. Calcd for $C_{15}H_{23}NO_4$: C, 64.04; H, 8.24; N, 4.98. Found: C, 63.96; H, 8.22; N, 4.84.

**Ethyl (3*S*,4a*R*,8a*R*)-6-methylidine-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate ((−)-17)**: 94% yield. $[\alpha]_D = -39.2°$ (c = 1, $CH_2Cl_2$). Anal. Calcd for $C_{15}H_{23}NO_4$: C, 64.04; H, 8.24; N, 4.98. Found: C, 63.85; H, 8.19; N, 4.70.

**Ethyl (3*R*,4a*S*,8a*S*)-6-methylidine-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate ((+)-17)**: 86% yield. $[\alpha]_D = +38.6°$ (c = 1, $CH_2Cl_2$). Anal. Calcd for $C_{15}H_{23}NO_4$: C, 64.04; H, 8.24; N, 4.98. Found: C, 63.90; H, 8.25; N, 4.90.

**Ethyl (3*SR*,4a*RS*,6*SR*,8a*RS*)-6-(Hydroxymethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (18).** A 0 °C solution of 40.7 g (144 mmol) of **17** in 285 mL of THF was treated dropwise with 9.7 mL (97 mmol) of borane methyl sulfide (10 M). After two hr at 0 °C, the reaction was warmed to room temperature and stirred for an additional 2.5 h. The reaction mixture was cooled to 0 °C and treated with 25 mL of ethanol, then 200

mL of 3 N sodium hydroxide, and finally 200 mL of 30% hydrogen peroxide. After 30 min at 0 °C, the reaction mixture was warmed to room temperature and stirred an additional two hr. Workup (ether 3X) and preparative HPLC of the residue (hexane to 60% ethyl acetate/hexane) gave 40.4 g of (94%) of **18**. $^1$H NMR ($CDCl_3$) $\delta$: 4.37 (t, $J$ = 5.9 Hz, 1H), 4.16 (q, $J$ = 7.1 Hz, 2H), 3.68 (s, 3H), 3.47 (m, 2H), 3.37 (m, 2H), 2.14 (m, 1H), 1.95−1.40 (m, 9H), 1.23 (t, $J$ = 7.1 Hz, 3H), 1.18 (m, 2H). Anal. Calcd for $C_{15}H_{25}NO_5$: C, 60.18; H, 8.42; N, 4.68. Found: C, 59.90; H, 8.62; N, 4.68.

**Ethyl (3*S*,4a*R*,6*S*,8a*R*)-6-(hydroxymethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate ((−)-18)**: 98% yield. $[\alpha]_D$ = −36.4° (c = 1, $CH_2Cl_2$). Anal. Calcd for $C_{15}H_{25}NO_5$: C, 60.18; H, 8.42; N, 4.68. Found: C, 60.15; H, 8.30; N, 4.71.

**Ethyl (3*R*,4a*S*,6*R*,8a*S*)-6-(hydroxymethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate ((+)-18)**: 95% yield. $[\alpha]_D$ = +37.3° (c = 1, $CH_2Cl_2$). Anal. Calcd for $C_{15}H_{25}NO_5$: C, 60.18; H, 8.42; N, 4.68. Found: C, 59.90; H, 8.62; N, 4.68.

**Ethyl (3*SR*,4a*RS*,6*SR*,8a*RS*)-6-(Bromomethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (19).** To a 0 °C suspension of triphenylphosphine dibromide [prepared from 23.8 g (90.8 mmol) of triphenylphosphine and 4.65 mL (14.5 g, 90.8 mmol) of bromine] in 185 mL of dichloromethane was added a solution of 20.0 g (66.8 mmol) of **18** and 14.5 mL (14.3 g, 180 mmoL) of pyridine in 70 mL of dichloromethane. The reaction mixture was stirred at 0 °C for 15 min and room temperature for one hr. Workup (10% sodium bisulfate/dichloromethane 2X; ether 1X) afforded a residue that was suspended in 50% ether/hexane, stirred at room temperature for one hr, then filtered and the filtrate concentrated in vacuo. Chromatography of the residue (400 g, 25% ethyl acetate/hexane) gave 21.7 g (90%) of **19**. $^1$H NMR ($CDCl_3$) $\delta$: 4.37 (t, $J$ = 6.0 Hz, 1H), 4.17 (q, $J$ = 7.1 Hz, 2H), 3.68 (s, 3H), 3.43 (m, 1H), 3.30 (m, 3H), 2.18 (m, 1H), 1.95−1.40 (m, 8H), 1.25 (m, 2H), 1.24 (t, $J$ = 7.1 Hz, 3H). Anal. Calcd for $C_{15}H_{24}BrNO_4$: C, 49.73; H, 6.68; N, 3.87. Found: C, 49.85; H, 6.53; N, 3.61.

**Ethyl (3*S*,4a*R*,6*S*,8a*R*)-6-(bromomethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate ((−)-19)**: 87% yield. $[\alpha]_D$ = −37.1° (c = 1, $CH_2Cl_2$). Anal. Calcd for $C_{15}H_{24}BrNO_4$: C, 49.73; H, 6.68; N, 3.87. Found: C, 49.87; H, 6.81; N, 3.73.

**Ethyl (3*R*,4a*S*,6*R*,8a*S*)-6-(bromomethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate ((+)-19)**: 95% yield. $[\alpha]_D$ = +39.1° (c = 1, $CH_2Cl_2$). Anal. Calcd for $C_{15}H_{24}BrNO_4$: C, 49.73; H, 6.68; N, 3.87. Found: C, 50.40; H, 6.88; N, 3.40.

**Ethyl (3*SR*,4a*RS*,6*SR*,8a*RS*)-6-(Cyanomethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (25).** A solution of 1.8 g (5.0 mmol) of **19** and 0.5 g (9.9 mmol) of sodium cyanide was heated to 75 °C for 1.5 h, then cooled to room temperature. Workup (1:1 water: brine/dichloromethane 3X; ether 1X) and chromatography (80 g, 40% ethyl acetate/hexane) afforded 1.1 g (71%) of **25**. Anal. Calcd for $C_{16}H_{24}N_2O_4$: C, 62.32; H, 7.85; N, 9.08. Found: C, 62.49; H, 7.72; N, 9.17.

**Ethyl (3*S*,4a*R*,6*S*,8a*R*)-6-(Cyanomethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate ((−)-25)**: 75% yield. $[\alpha]_D$ = −43.2° (c = 1, $CH_2Cl_2$). Anal. Calcd for $C_{16}H_{24}N_2O_4$: C, 62.32; H, 7.85; N, 9.08. Found: C, 62.05; H, 7.65; N, 9.08.

**Ethyl (3*R*,4a*S*,6*R*,8a*S*)-6-(cyanomethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate ((+)-25)**: 50% yield. $[\alpha]_D$ = +42.8° (c = 1, $CH_2Cl_2$). Anal. Calcd for $C_{16}H_{24}N_2O_4 \cdot 0.15CHCl_3$: C, 59.45; H, 7.46; N, 8.59. Found: C, 59.67; H, 7.58; N, 8.67.

**(3*S*,4a*R*,6*S*,8a*R*)-6-(1*H*-Tetrazol-5-ylmethyl)-1,2,3,4,-4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid ((−)-2a)**: 54% yield. m.p. 224−225 °C (dec.). $[\alpha]_D$ = −36.0° (c = 1, 1 N HCl). Anal. Calcd for $C_{12}H_{19}N_5O_2 \cdot 1.0H_2O$: C, 50.87 H, 7.47 N, 24.72 Found: C, 50.53; H, 7.57; N, 24.56.

**(3*R*,4a*S*,6*R*,8a*S*)-6-(1*H*-Tetrazol-5-ylmethyl)-1,2,3,4,-4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid ((+)-2a)**: 64% yield. m.p. 226−228 °C (dec.). $[\alpha]_D$ = +34.8° (c = 1, 1 N HCl). Anal. Calcd for $C_{12}H_{19}N_5O_2 \cdot 1.5H_2O \cdot 0.1C_3H_6O$: C, 49.55; H, 7.64 N, 23.49. Found: C, 49.74; H, 7.44; N, 23.29.

**Ethyl (3*SR*,4a*RS*,6*SR*,8a*RS*)-6-(Iodomomethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (20).** To a room temperature solution of 1.7 g (6.3 mmol) of triphenylphosphine, 1.6 g (6.3 mmol) of iodine and 0.7 g (10.5 mmol) of imidazole in 25 mL of dichloromethane was added a solution of 1.3 g (4.2 mmol) of **18** in 5 mL of dichloromethane and the mixture was stirred 45 min at room temperature. Workup (10% sodium bisulfate/ether 1X) and chromatography (60 g, 25% ethyl acetate/hexane) gave 1.3 g (73%) of **20**. $^1$H NMR ($CDCl_3$) $\delta$: 4.37 (t, $J$ = 6.0 Hz, 1H), 4.19 (q, $J$ = 7.1 Hz, 2H), 3.70 (s, 3H), 3.45 (dd, $J$ = 12.9, 5.1 Hz, 1H), 3.33 (m, 1H), 3.16 (dd, $J$ = 9.8, 6.8 Hz, 1H), 3.11 (dd, $J$ = 9.8, 6.6 Hz, 1H), 2.20 (dt, $J$ = 13.8, 6.0 Hz, 1H), 1.87 (m, 2H), 1.80−1.40 (m, 6H), 1.26 (t, $J$ = 7.1 Hz, 3H), 1.22 (m, 2H). Anal. Calcd for $C_{15}H_{24}INO_4$: C, 44.02; H, 5.91; N, 3.42. Found: C, 43.91; H, 5.92; N, 3.42.

**Ethyl (3*S*,4a*R*,6*S*,8a*R*)-6-(iodomomethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate ((−)-20)**: 81% yield. $[\alpha]_D$ = −36.8° (c = 1, $CH_2Cl_2$). Anal. Calcd for $C_{15}H_{24}INO_4$: C, 44.02; H, 5.91; N, 3.42. Found: C, 43.95; H, 5.95; N, 3.37.

**Ethyl (3*R*,4a*S*,6*R*,8a*S*)-6-(iodomomethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate ((+)-20)**: 85% yield. $[\alpha]_D$ = +38.6° (c = 1, $CH_2Cl_2$). Anal. Calcd for $C_{15}H_{24}INO_4$: C, 44.02; H, 5.91; N, 3.42. Found: C, 44.20; H, 6.15; N, 3.45.

**Ethyl (3*SR*,4a*RS*,6*SR*,8a*RS*)-6-Formyl-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (15).** To a −78 °C solution of 22.1 mL of DMSO (24.3 g, 311 mmol) in 250 mL of dichloromethane was added 13.1 mL (19.0 g, 150 mmol) of oxalyl chloride. After five min at −78 °C, a solution of 37.3 g (125 mmol) of **18** in 150 mL of dichloromethane was added, followed in 15 min by 87 mL (63.1 g, 623 mmol) of triethylamine. After an additional 45 min at −78 °C, the reaction mixture was allowed to warm to room temperature. Workup (10% sodium bisulfate/ether 2X) afforded 36.1 g (97%) of **15**, used without further purification. $^1$H NMR ($CDCl_3$) $\delta$: 9.76 (s, 1H), 4.79 (m, 1H), 4.18 (m, 2H), 3.73 (m, 1H), 3.67 (s, 3H), 3.18 (m, 1H), 2.30 (m, 2H), 2.11 (m, 1H), 2.00−1.20 (m, 8H), 1.25 (t, 3H).

**Ethyl (3*SR*,4a*RS*,6*SR*,8a*RS*)-6-(2-Cyanoethenyl)-2-carbomethoxy-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (27).** To a room temperature suspension of 7.0 g (174.6 mmol) of 60% sodium hydride (washed three times with hexane) in 185 mL of THF was added dropwise 30.9 g (174.6 mmol) of diethylphosphonoacetonitrile. After 30 min at room temperature, the mixture was cooled to 0 °C, a solution of 37.1 g (124.7 mmol) of **15** in 185 mL of THF was added, and the mixture stirred another 45 min at 0 °C. Workup (10% aq sodium bisulfate/3X ether) and chromatography (300 g, 35% ethyl acetate/hexane) afforded 37.8 g (95%) of **27**, as an E,Z-mixture of olefins.

**Ethyl and Methyl (3*SR*,4a*RS*,6*RS*,8a*RS*)-6-(2-Cyanoethyl)-2-carbomethoxy-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (28e and 28m).** To a solution of 37.8 g (118.0 mmol) of **27** in 1150 mL of methanol was added 57.4 g of magnesium turnings. Vigorous hydrogen efflux was observed, and the reaction was placed in an ice water bath and stirred 1.5 h until TLC (10% ethyl/acetate/toluene) indicates the reaction is complete. To the reaction mixture was added 1.5 L of dichloromethane, the mixture was decanted to remove most of the remaining magnesium, and then filtered thru celite. The filtrate was divided into two portions, and each was washed with 2 L of 10% aqueous sodium bisulfate. The organic layer was separated and the aqueous layer extracted three times with dichloromethane and once with ether. The combined organics from both extractions were dried ($MgSO_4$), filtered and concentrated in vacuo. Prepartive HPLC (hexane to 60% ethyl acetate/hexane) afforded 28.0 g (74%) of **28em**, as a mixture of ethyl (**28e**) and methyl (**28m**) esters. An analytical sample of **28e** was prepared by flash chromatography on silica gel, eluting with 50% ethyl acetate/hexane. **28e** $^1$H NMR ($CDCl_3$) $\delta$: 4.39 (t, $J$ = 5.9 Hz, 1H), 4.18 (q, $J$ = 7.1 Hz, 2H), 3.69 (s, 3H), 3.39 (m, 2H), 2.36 (t, $J$ = 7.0 Hz,

2H), 2.18 (dt, $J$ = 13.8, 5.9 Hz, 1H), 1.88 (m, 2H), 1.74 (m, 1H), 1.56 (m, 7H), 1.25 (t, $J$ = 7.1 Hz, 3H), 1.12 (m, 2H). Anal. Calcd for $C_{17}H_{26}N_2O_4$: C, 63.33; H, 8.13; N, 8.69. Found: C, 63.04; H, 8.35; N, 8.75.

**(3*SR*,4a*RS*,6*RS*,8a*RS*)-6-(2-(1*H*-Tetrazol-5-yl)ethyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic Acid (3a).** A mixture of 28.0 g (86.7 mmol) of **28em** and 57.6 g (173 mmol) of azidotri-*n*-butylstannane was heated to 80 °C for 48 h, then 200 mL of 6 N aqueous HCl was added, and the mixture stirred overnight at 90 °C. The mixture was cooled to room temperature, extracted three times with ether, and the aqueous phase concentrated in vacuo. Water was added to the residue, the pH adjusted to 5 with 3 N sodium hydroxide, and after concentration in vacuo to a small volume (~50 mL), a white precipitate was formed that was filtered, washed with water, acetone and ether, and dried in vacuo at 60 °C to afford 13.4 g (55%) of **3a**, m.p. 223 °C (dec.). $^1$H NMR ($D_2O$/KOD) $\delta$: 3.22 (m, 1H), 2.83 (m, 3H), 2.55 (m, 1H), 1.10–1.95 (m, 12H), 0.96 (m, 1H). Analysis calculated for $C_{13}H_{21}N_5O_2 \cdot 0.45\ H_2O$: C, 54.32; H, 7.68; N, 24.36. Found: C, 53.89; H, 7.81; N, 24.78.

**(3*S*,4a*R*,6*R*,8a*R*)-6-(2-(1*H*-Tetrazol-5-yl)ethyl)-1,2,3,4,-4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic Acid ((−)-3a).** This compound was prepared by the same route outlined above; however, following hydrolysis, extraction of the tin byproducts with ether and concentration in vacuo, the amino acid was isolated in 62% yield after cation exchange chromatography on Dowex 50-X8 (100–200 mesh), eluting with 10% pyridine/water, m.p. 250–257 °C (dec.). $[\alpha]_D$ = −30.0° (c = 1, 1 N HCl). Anal. Calcd for $C_{13}H_{21}N_5O_2 \cdot 0.6H_2O \cdot 0.1C_3H_6O$: C, 53.98; H, 7.77; N, 23.66. Found: C, 53.62; H, 7.38; N, 23.32.

**(3*R*,4a*S*,6*S*,8a*S*)-6-(2-(1*H*-Tetrazol-5-yl)ethyl)-1,2,3,4,-4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic Acid ((+)-3a).** This compound was prepared by the same route outlined above; however, following hydrolysis, extraction of the tin byproducts with ether and concentration in vacuo, the amino acid was isolated in 55% yield after cation exchange chromatography on Dowex 50-X8 (100–200 mesh), eluting with 10% pyridine/water, m.p. 282–284 °C (dec.). $[\alpha]_D$ = +35.0° (c = 1, 1 N HCl). Anal. Calcd for $C_{13}H_{21}N_5O_2 \cdot 0.5H_2O$: C, 54.15; H, 7.69; N, 24.28. Found: C, 54.02; H, 7.49; N, 23.94.

**Ethyl (3*SR*,4a*RS*,8a*RS*)-2-(Methoxycarbonyl)-6-(methoxymethylidene)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (14).** To a 0 °C suspension of 20.6 g (60 mmol) of methoxymethyl triphenylphosphonium chloride in 60 mL of THF was added 60 mL (60 mmol, 1 M in THF) of sodium bis(trimethylsilyl)amide. After 15 min, the resulting solution/suspension was added via funnel to a 0 °C solution of 11.4 g (40 mmol) of **4** in 80 mL of THF until a pale yellow color persisted. Workup (water/ether 3X) and chromatography (300 g, 35% ethyl acetate/hexane) afforded 11.7 g (94%) of **14**. $^1$H NMR ($CDCl_3$, doubling due to amide rotamers) $\delta$: 5.84 and 5.65 (s, 1H), 4.93 and 4.75 (m, 1H), 4.16 (m, 2H), 3.89 and 3.74 (dd, $J$ = 13.6, 5.1 Hz, 1H), 3.67 and 3.65 (s, 3H), 3.51 and 3.48 (s, 3H), 3.17 (m, 1H), 2.75 and 2.57 (d, $J$ = 12.3 Hz, 1H), 2.18 and 2.02 (m, 1H), 2.00–1.30 (m, 8H), 1.24 (t, $J$ = 7.1 Hz, 3H). Anal. Calcd for $C_{16}H_{25}NO_5$: C, 61.72; H, 8.09; N, 4.50. Found: C, 61.81; H, 8.22; N, 4.52.

**Ethyl (3*S*,4a*R*,8a*R*)-2-(methoxycarbonyl)-6-(methoxymethylidene)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate ((−)-14)**: 95% yield. $[\alpha]_D$ = −26.0° (c = 1, $CH_2Cl_2$). Anal. Calcd for $C_{16}H_{25}NO_5$: C, 61.72; H, 8.09; N, 4.50. Found: C, 61.49; H, 8.03; N, 4.38.

**Ethyl (3*R*,4a*S*,8a*S*)-2-(methoxycarbonyl)-6-(methoxymethylidene)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate ((+)-14)**: 93% yield. $[\alpha]_D$ = +27.6° (c = 1, $CH_2Cl_2$). Anal. Calcd for $C_{16}H_{25}NO_5$: C, 61.72; H, 8.09; N, 4.50. Found: C, 62.00; H, 8.18; N, 4.40.

**Ethyl (3*SR*,4a*RS*,6*RS*,8a*RS*)-6-Formyl-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (16).** A solution of 4.8 g (15.4 mmol) of **14** in 135 mL of acetonitrile and 35 mL of 1 N HCl was heated to 60 °C overnight, then cooled to room temperature. Workup (saturated sodium bicarbonate/ether 5X) and chromatography (140 g, 35% ethyl acetate/hexane) gave 3.9 g (85%) of **16**. $^1$H NMR ($CDCl_3$, doubling due to amide rotamers) $\delta$: 9.56 (s, 1H), 5.01 and 4.83 (d, $J$ = 4.0 Hz, 1H), 4.18 (m, 2H), 3.87 and 3.74 (d, $J$ = 13.7 Hz, 1H), 3.70 and 3.69 (s, 3H), 3.21 and 3.11 (d, $J$ = 13.7 Hz, 1H), 2.33 (m, 1H), 1.97 (m, 4H), 1.80 (m, 1H), 1.57 (m, 4H), 1.28 (m, 1H), 1.26 (t, $J$ = 7.1 Hz, 3H). Anal. Calcd for $C_{15}H_{23}NO_5$: C, 60.59; H, 7.80; N, 4.71. Found: C, 60.49; H, 8.02; N, 4.76.

**Ethyl (3*SR*,4a*RS*,6*RS*,8a*RS*)-6-(Hydroxymethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (21).** A solution of 3.8 g (12.6 mmol) of **16** and 0.5 g (12.6 mmol) of sodium borohydride in 40 mL of ethanol was stirred 30 min at room temperature, then concentrated in vacuo. Workup (1:1 brine:water/3:2 ether: dichloromethane 3X) and chromatography (140 g, 60% ethyl acetate/hexane) gave 3.3 g (86%) of **21**. $^1$H NMR ($CDCl_3$, doubling due to amide rotamers) $\delta$: 4.99 and 4.82 (d, $J$ = 5.7 Hz, 1H), 4.18 (m, 2H), 3.92 and 3.78 (d, $J$ = 13.5 Hz, 1H), 3.70 and 3.68 (s, 3H), 3.41 (d, $J$ = 5.6 Hz, 2H), 3.21 and 3.11 (dd, $J$ = 13.5, 2.7 Hz, 1H), 2.00 (m, 1H), 1.84 (m, 3H), 1.70–1.30 (m, 6H), 1.25 (t, $J$ = 7.1 Hz, 3H), 1.23 (m, 1H), 0.96 (m, 1H). Anal. Calcd for $C_{15}H_{25}NO_5$: C, 60.18; H, 8.42; N, 4.68. Found: C, 59.95; H, 8.72; N, 4.71.

**Ethyl (3*S*,4a*R*,6*R*,8a*R*)-6-(hydroxymethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate ((−)-21)**: 89% yield (two steps). $[\alpha]_D$ = −15.9° (c = 1, $CH_2Cl_2$). Anal. Calcd for $C_{15}H_{25}NO_5$: C, 60.18; H, 8.42; N, 4.68. Found: C, 59.97; H, 8.41; N, 4.66.

**Ethyl (3*R*,4a*S*,6*S*,8a*S*)-6-(hydroxymethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate ((+)-21)**: 82% yield (two steps). $[\alpha]_D$ = +15.8° (c = 1, $CH_2Cl_2$). Anal. Calcd for $C_{15}H_{25}NO_5$: C, 60.18; H, 8.42; N, 4.68. Found: C, 59.97; H, 8.24; N, 4.90.

**Ethyl (3*SR*,4a*RS*,6*RS*,8a*RS*)-6-(Bromomethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (22).** As for **19**, 4.0 g (15.3 mmol) of triphenylphosphine, 0.78 mL (2.4 g, 15.3 mmol) of bromine, 1.7 mL (1.6 g, 20.4 mmoL) of pyridine and 3.1 g (10.2 mmol) of **21** in 60 mL of dichloromethane gave 3.3 g (90%) of **22**. Recrystallization from ether afforded 2.7 g (73%) of **22**, m.p. 112–114 °C. $^1$H NMR ($CDCl_3$, doubling due to amide rotamers) $\delta$: 4.98 and 4.80 (d, $J$ = 5.0 Hz, 1H), 4.17 (m, 2H), 3.92 and 3.78 (d, $J$ = 13.6 Hz, 1H), 3.69 and 3.67 (s, 3H), 3.22 (d, $J$ = 5.7 Hz, 2H), 3.15 (m, 1H), 2.10–1.40 (m, 9H), 1.30 (m, 1H), 1.25 (t, $J$ = 7.1 Hz, 3H), 1.01 (m, 1H). Anal. Calcd for $C_{15}H_{24}BrNO_4$: C, 49.73; H, 6.68; N, 3.87. Found: C, 50.03; H, 6.74; N, 3.89.

**Ethyl (3*S*,4a*R*,6*R*,8a*R*)-6-(bromomethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate ((−)-22)**: 79% yield after chromatography; 53% yield after recrystallization from ethyl acetate and hexane, m.p. 114–115 °C. $[\alpha]_D$ = −12.9° (c = 1, $CH_2Cl_2$). Anal. Calcd for $C_{15}H_{24}BrNO_4$: C, 49.73; H, 6.68; N, 3.87. Found: C, 49.92; H, 6.62; N, 3.88.

**Ethyl (3*R*,4a*S*,6*S*,8a*S*)-6-(bromomethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate ((+)-22)**: 84% yield after chromatography; 38% yield after recrystallization from ethyl acetate and hexane, m.p. 115–117 °C. $[\alpha]_D$ = +12.2° (c = 1, $CH_2Cl_2$). Anal. Calcd for $C_{15}H_{24}BrNO_4$: C, 49.73; H, 6.68; N, 3.87. Found: C, 50.00; H, 6.88; N, 3.94.

**Ethyl (3*SR*,4a*RS*,6*RS*,8a*RS*)-6-(Cyanomethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (26).** A solution of 2.1 g (5.7 mmol) of **22** and 0.6 g (11.3 mmol) of sodium cyanide was heated to 75 °C for 1.5 h, then cooled to room temperature. Workup (1:1 water: brine/dichloromethane 3X; ether 1X) and chromatography (80 g, 40% ethyl acetate/hexane) afforded 1.5 g (87%) of **26**. Anal. Calcd for $C_{16}H_{24}N_2O_4$: C, 62.32; H, 7.85; N, 9.08. Found: C, 62.12; H, 7.63; N, 9.19.

**Ethyl (3*S*,4a*R*,6*R*,8a*R*)-6-(cyanomethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate ((−)-26)**: 67% yield. $[\alpha]_D$ = −17.0° (c = 1, $CH_2Cl_2$). Anal. Calcd for $C_{16}H_{24}N_2O_4$: C, 62.32; H, 7.85; N, 9.08. Found: C, 62.40; H, 7.69; N, 9.20.

**Ethyl (3*R*,4a*S*,6*S*,8a*S*)-6-(cyanomethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate ((+)-26)**: 62% yield. $[\alpha]_D$ = +20.8° (c = 1, $CH_2Cl_2$).

Anal. Calcd for $C_{16}H_{24}N_2O_4$: C, 62.32; H, 7.85; N, 9.08. Found: C, 62.31; H, 7.89; N, 9.10.

**(3*S*,4a*R*,6*R*,8a*R*)-6-(1*H*-Tetrazol-5-ylmethyl)-1,2,3,4,-4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid ((+)-2b)**: 76% yield. $[\alpha]_D$ = +25.2° (c = 1, 1 N HCl). Anal. Calcd for $C_{12}H_{19}N_5O_2 \cdot 0.3H_2O$: C, 53.24; H, 7.30; N, 25.87. Found: C, 53.14; H, 7.31; N, 25.55.

**(3*R*,4a*S*,6*S*,8a*S*)-6-(1*H*-Tetrazol-5-ylmethyl)-1,2,3,4,-4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid ((−)-2b)**: 46% yield. m.p. 287−290 °C (dec.). $[\alpha]_D$ = −27.6° (c = 1, 1 N HCl). Anal. Calcd for $C_{12}H_{19}N_5O_2 \cdot 1.2H_2O$: C, 50.23; H, 7.52 N, 24.41 Found: C, 50.53; H, 7.02; N, 24.03.

**Ethyl (3*SR*,4a*RS*,6*RS*,8a*RS*)-6-(Iodomethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (23).** To a room temperature solution of 8.6 g (32.8 mmol) of triphenylphosphine, 8.3 g (32.8 mmol) of iodine and 3.7 g (54.6 mmol) of imidazole in 75 mL of dichloromethane was added a solution of 6.5 g (21.8 mmol) of **21** in 20 mL of dichloromethane and the mixture was stirred 45 min at room temperature. Workup (10% sodium bisulfate/ether 1X) and chromatography (250 g, 25% ethyl acetate/hexane) gave 6.4 g (72%) of **23**. Recrystallization from ethyl acetate and hexane afforded 5.3 g (60%) of **23**, m.p. 129−131 °C. $^1$H NMR ($CDCl_3$, doubling due to amide rotamers) $\delta$: 4.98 and 4.80 (d, $J$ = 5.0 Hz, 1H), 4.18 (m, 2H), 3.93 and 3.79 (d, $J$ = 13.6 Hz, 1H), 3.70 and 3.67 (s, 3H), 3.21 (dd, $J$ = 13.6, 2.8 Hz, 1H), 3.04 (d, $J$ = 6 Hz, 2H), 2.00−1.40 (m, 9H), 1.25 (t, $J$ = 7.1 Hz, 3H), 1.20 (m, 1H), 0.96 (m, 1H). Anal. Calcd for $C_{15}H_{24}INO_4$: C, 44.02; H, 5.91; N, 3.42. Found: C, 44.32; H, 6.21; N, 3.34.

**Ethyl (3*S*,4a*R*,6*R*,8a*R*)-6-(iodomethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate ((−)-23)**: 83% yield after chromatography; 55% yield after recrystallization from ethyl acetate and hexane, m.p. 112.5−115.5 °C. $[\alpha]_D$ = −11.0° (c = 1, $CH_2Cl_2$). Anal. Calcd for $C_{15}H_{24}INO_4$: C, 44.02; H, 5.91; N, 3.42. Found: C, 44.25; H, 5.83; N, 3.41.

**Ethyl (3*R*,4a*S*,6*S*,8a*S*)-6-(iodomethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate ((+)-23)**: 71% yield after chromatography; 55% yield after recrystallization from ethyl acetate and hexane, m.p. 116−118 °C. Recrystallization from 2-propanol afforded crystals suitable for X-ray crystallography. $[\alpha]_D$ = +8.0° (c = 1, $CH_2Cl_2$). Anal. Calcd for $C_{15}H_{24}INO_4$: C, 44.02; H, 5.91; N, 3.42. Found: C, 44.12; H, 6.03; N, 3.39.

**Ethyl (3*SR*,4a*RS*,6*RS*,8a*RS*)-6-(Phosphonomethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (24).** A solution of 3.1 g (7.6 mmol) of **23** and 35 mL (33.9 g, 204.1 mmol) of triethylphosphite was heated to 120 °C for two hr, then cooled and the excess triethylphosphite was removed by vacuum distillation at 1 torr. The residue was dissolved in ether, washed twice with 3 N aq sodium hydroxide, and the ether layer was dried ($MgSO_4$), filtered and concentrated in vacuo. Chromatography (150 g, ethyl acetate) gave 2.4 g (75%) of **24** and 0.2 g (9%) of **17**. $^1$H NMR ($CDCl_3$, doubling due to amide rotamers) $\delta$: 5.00 and 4.82 (d, $J$ = 5.8 Hz, 1H), 4.19 (m, 2H), 4.07 (m, 4H), 3.92 and 3.77 (d, $J$ = 13.6 Hz, 1H), 3.71 and 3.69 (s, 3H), 3.20 and 3.15 (dd, $J$ = 13.6, 2.7 Hz, 1H), 2.15−1.00 (m, 13H), 1.32 (t, $J$ = 7.0 Hz, 6H), 1.26 (t, $J$ = 7.1 Hz, 3H). Anal. Calcd for $C_{19}H_{34}NO_7 \cdot 0.25H_2O$: C, 53.83; H, 8.20; N, 3.30. Found: C, 53.65; H, 8.00; N, 3.62.

**Ethyl (3*S*,4a*R*,6*R*,8a*R*)-6-(phosphonomethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate ((−)-24)**: 59% yield. $[\alpha]_D$ = −7.0° (c = 1, $CH_2Cl_2$). Anal. Calcd for $C_{19}H_{34}NO_7P$: C, 54.41; H, 8.17; N, 3.34. Found: C, 54.71; H, 8.39; N, 3.54.

**Ethyl (3*R*,4a*S*,6*S*,8a*S*)-6-(phosphonomethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate ((+)-24)**: 52% yield. $[\alpha]_D$ = +7.5° (c = 1, $CH_2Cl_2$). Anal. Calcd for $C_{19}H_{34}NO_7P$: C, 54.41; H, 8.17; N, 3.34. Found: C, 54.68; H, 8.36; N, 3.44.

**(3*SR*,4a*RS*,6*RS*,8a*RS*)-6-(Phosphonomethyl)-1,2,3,4,-4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic Acid (1b).** A solution of 2.3 g (5.4 mmol) of **24** in 75 mL of 6 N aq hydorchloric acid was heated to reflux overnight, then cooled and concentrated in vacuo. The material was redissolved in water, the pH adjusted to 9 with 3 N aq sodium hydroxide, then applied to a 3 × 19 cm column of Bio-Rad AG1-X8 anion exchange resin (hydroxide form). The column was eluted slowly with water until the pH of the effluent was 7, then the product was eluted with 3 N aq acetic acid. Product containing fractions (detected by spotting on a TLC plate and staining with ninhydrin) were combined and concentrated in vacuo. The residue was dissolved in 8 mL of water, and heated to 110 °C (bath temperature) to induce crystallization. The mixture was cooled, and the resulting solid was filtered, washed with water, acetone and ether, and dried overnight in vacuo at 60 °C to afford 0.85 g (55%) of **1b** as the hemihydrate, m.p. 257−262 °C (dec.). $^1$H NMR ($D_2O$/KOD) $\delta$: 3.70 (s, 1H), 3.16 (m, 2H), 2.20−1.00 (m, 13H). Anal. Calcd for $C_{11}H_{20}NO_5P \cdot 0.5H_2O$: C, 46.15; H, 7.39; N, 4.89. Found: C, 45.99; H, 7.46; N, 4.78.

**(3*S*,4a*R*,6*R*,8a*R*)-6-(Phosphonomethyl)-1,2,3,4,4a,5,6,7,8,-8a-decahydroisoquinoline-3-carboxylic acid ((+)-1b)**: 27% yield. m.p. 299−300 °C (dec.). $[\alpha]_D$ = +20.2° (c = 1, 6 N HCl). Anal. Calcd for $C_{11}H_{20}NO_5P \cdot 0.1C_4H_{10}O$: C, 48.10; H, 7.44; N, 4.92. Found: C, 48.41 H, 7.54; N, 4.72.

**(3*R*,4a*S*,6*S*,8a*S*)-6-(Phosphonomethyl)-1,2,3,4,4a,5,6,7,8,-8a-decahydroisoquinoline-3-carboxylic acid ((−)-1b)**: 38% yield. m.p. 303−304 °C (dec.). $[\alpha]_D$ = −22.4° (c = 1, 6 N HCl). Anal. Calcd for $C_{11}H_{20}NO_5P$: C, 47.65; H, 7.27; N, 5.05. Found: C, 47.67; H, 7.33; N, 4.90.

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**Supplementary Material Available:** $^1$H NMR spectra of **15**, **16**, **18**, and **21** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.