Structure−Activity Studies of 6-(Tetrazolylalkyl)-Substituted Decahydroisoquinoline-3-carboxylic Acid AMPA Receptor Antagonists. 1. Effects of Stereochemistry, Chain Length, and Chain Substitution

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Received December 12, 1995[⊗]

A series of 6-substituted decahydroisoquinoline-3-carboxylic acids were prepared as excitatory amino acid (EAA) receptor antagonists. These compounds are antagonists at the *N*-methyl-D-aspartate (NMDA) and 2-amino-3-(5-methyl-3-hydroxyisoxazol-4-yl)propanoic acid (AMPA) subclasses of ligand gated ion channel (ionotropic) EAA receptors. (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 (**9**) is a potent, selective and systemically active AMPA antagonist. Other analogs from this series, including (3*S*,4a*R*,6*S*,8a*R*)-6-((1*H*-tetrazol-5-yl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid (**32**) and (3*S*,4a*R*,6*S*,8a*R*)-6-(phosphonomethyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid (**61**) are potent, selective, and systemically active NMDA antagonists. This and the subsequent publication look at the AMPA antagonist aspects of this SAR. Herein we report the effects of varying stereochemistry around the hydroisoquinoline ring; of tetrahydro- versus decahydroisoquinoline; of having the carboxylic acid at C-1 versus C-3; of varying the length of the carbon chain connecting a tetrazole to the bicyclic nucleus; and of holding the connecting chain constant at two atoms, the effect of heteroatom substitution in the position adjacent to the bicyclic nucleus and substitution with methyl or phenyl on the chain. Compounds were evaluated on rat cortical tissue for their ability to inhibit the binding of radioligands selective for AMPA ([^{3}H]AMPA), NMDA ([^{3}H]CGS 19755), and kainic acid ([^{3}H]-kainic acid) receptors and for their ability to inhibit depolarizations induced by AMPA (40 μM), NMDA (40 μM), and kainic acid (10 μM). Our findings revealed that the optimal stereochemical array was the same for both NMDA (**32** and **61**) and AMPA (**9**) antagonists identified in this series and that the tetrahydroisoquinoline (**25**) and the C-1 carboxy (**30**) analogs of **9** are inactive. With a tetrazole in the distal acid position, an ethylene spacer (**9**) is optimal; substitution with oxygen or nitrogen on the chain in the position adjacent to the bicyclic nucleus significantly reduced activity, while substitution with a methyl or phenyl group on the chain was well tolerated.

Introduction

Glutamate is the major excitatory neurotransmitter in the central nervous system (CNS), mediating fast synaptic transmission at the majority of CNS synapses. As an excitatory amino acid (EAA), glutamate acts at a number of receptor subclasses coupled to either ion channels or G-proteins. Ionotropic EAA receptors[1,2] are ligand-gated ion channels which transduce signals through changes in membrane permeability to sodium and calcium ions. They are subdivided into three subclasses, named for the agonist that selectively activates them, and include *N*-methyl-D-aspartate (NMDA), 2-amino-3-(5-methyl-3-hydroxyisoxazol-4-yl)-propanoic acid (AMPA), and kainic acid receptors. Metabotropic EAA receptors[3,4] are coupled via G-proteins to effector systems such as phospholipase C or adenylate cyclase and transduce signals through changes in intracellular concentrations of diacyl glycerol and inositol phosphates or cyclic adenosine monophosphate, respectively.

The development of novel antagonists for these receptor subclasses is a strategy for gaining a greater understanding about the pharmacology of this class of compounds and, ultimately, an understanding of their therapeutic potential. The first reasonably potent compounds described as competitive antagonists of the AMPA subclass of EAA receptors, the quinoxalinediones **1** (DNQX, Chart 1) and **2** (CNQX), helped to identify the potential of these compounds as anticonvulsant and neuroprotective agents.[5] The lack of central activity for **1** and **2** was overcome with the discovery of **3** (NBQX), which showed potent neuroprotectant properties following systemic administration.[6] It is now well understood that AMPA antagonists such as **3** may be useful in the treatment of epilepsy,[7−10] spinal cord trauma,[11] and cerebral ischemia.[12,13] For example, **3** is active in models of both focal[14−16] and global cerebral ischemia;[17−21] activity in the latter distinguishes this class of EAA antagonists from NMDA antagonists, which were not active in models of global ischemia.[22,23]

A significant limitation of **1** and **2** was their lack of potent activity following systemic administration. This has led to subsequent structure−activity studies aimed

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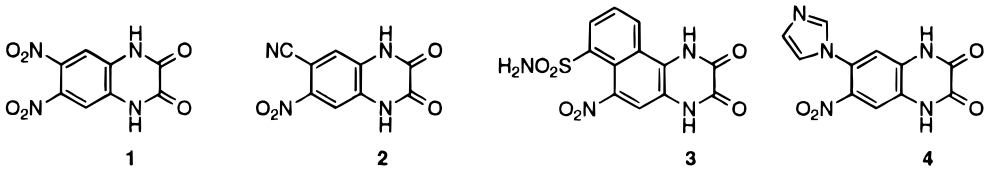
⊗ Abstract published in *Advance ACS Abstracts,* May 1, 1996.

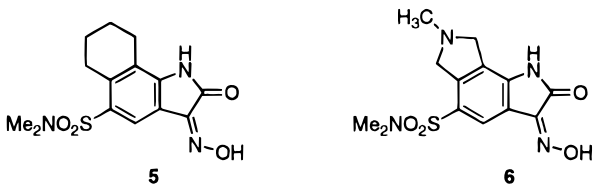
S0022-2623(95)00912-5 CCC: $12.00

Chart 1

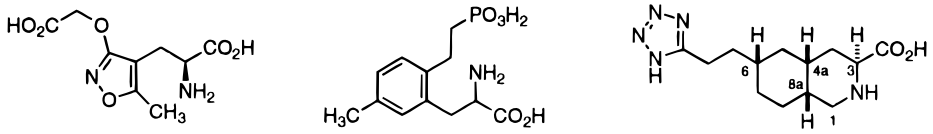
Quinoxalinediones



Isatin Oximes



Acidic Amino Acids

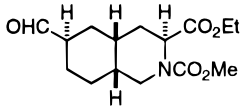


at identifying novel compounds with better pharmacodynamic properties. Three different classes of competitive AMPA antagonists are known. The quinoxalinediones **1**, **2**, **3**, and **4** (YM90K)[24] are among the best known of this class of compounds. Substitution with a nitro group on the aromatic ring portion of these compounds appears requisite for potent activity, and addition of another polar group such as nitro, cyano, sulfamido, or imidazolyl imparts potent antagonist activity. The isatin oximes **5**[25,26] and **6** (NS-257),[27] which can be viewed as structural analogs of the quinoxalinediones, have also been shown to be competitive AMPA receptor antagonists. One unique feature of this class of compounds is that they are active in vivo following oral administration.[25] The acidic amino acids **7** (*S*-AMOA)[28] and **8**[29] are weakly potent competitive AMPA receptor antagonists. Amino acid **8** evolved from a series of compounds that were weakly active as NMDA antagonists; substitution at C-5 on the aromatic ring was critical for enhancing potency of these compounds as AMPA antagonists. We have recently described the tetrazole-substituted amino acid **9** as a potent, systemically active competitive AMPA receptor antagonist.[30,31] This compound evolved from a series of 6-substituted decahydroisoquinoline-3-carboxylic acids that, like **8**, were originally prepared as competitive NMDA antagonists.[32,33] Studies with **9** have shown it to be an effective neuroprotective agent in a model of focal ischemia in cats[34] and rats.[35] Its also been demonstrated that **9** does not increase cerebral glucose utilization in the cingulate cortex[36] and is therefore unlikely to cause the cortical neurotoxicity observed with NMDA antagonists.

In this paper and the one that follows,[37] we report some of the interesting aspects of the structure−activity relationships that we have observed in this series of compounds. This paper looks at optimization of different structural features of this series, including stereochemistry, length of the chain separating the distal acidic moiety and the bicyclic nucleus, and substitutions in and on the connecting chain.

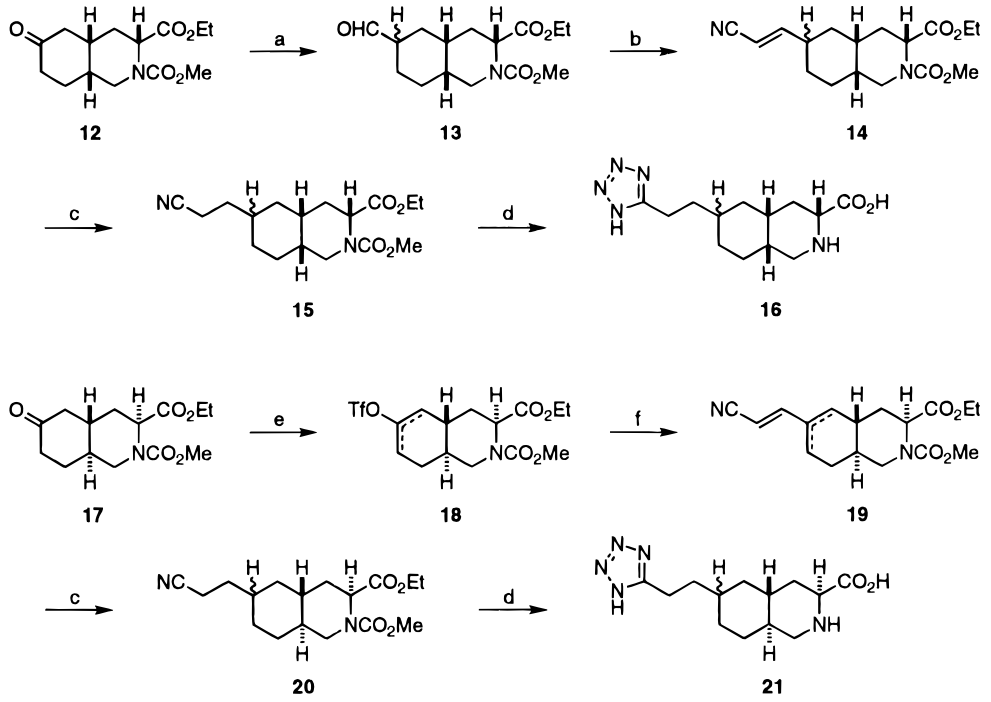
Chemistry

These decahydroisoquinoline amino acids have four stereocenters, and therefore eight different diastereomers are possible. As for our NMDA antagonists, we prepared six of the eight possible diastereomeric pairs in order to determine what stereochemistry is optimal for activity. Amino acid **11** was prepared as previously described for amino acid **9**, starting from the known aldehyde **10**.[38] For the amino acid epimeric at C-3 to



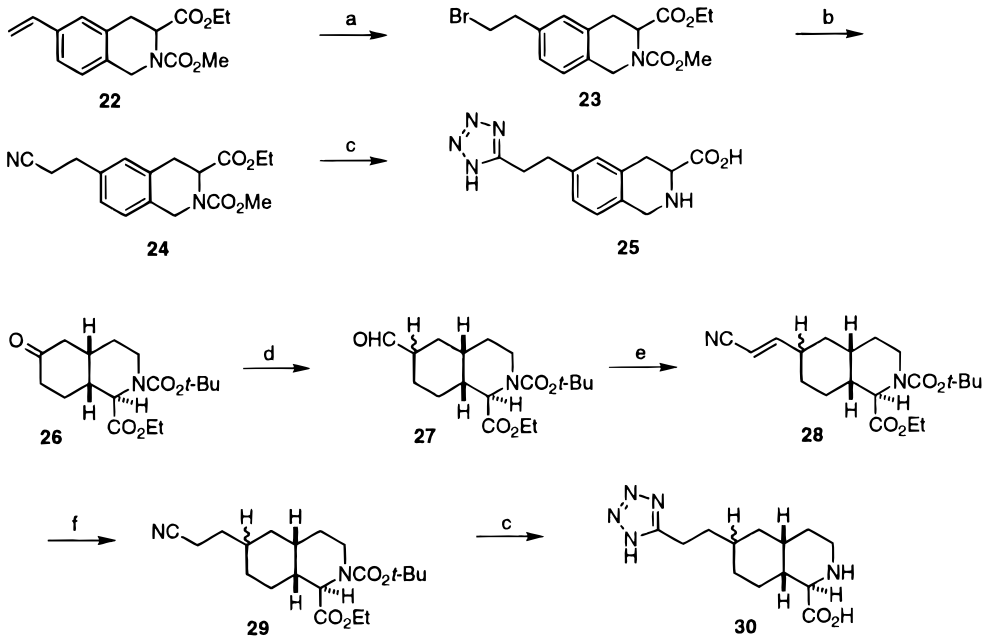
9, *cis*-ketone **12**[39] (Scheme 1) was converted to the homologous enol ether and then hydrolyzed to the aldehyde **13** (mixture of diastereomers at C-6).[38] Condensation of **13** with the sodium salt of diethylphosphonoacetonitrile gave **14**, which was hydrogenated to afford **15**. This was then converted to the tetrazole with azidotri-*n*-butylstannane (Bu_3SnN_3) followed by exhaustive hydrolysis with 6 N hydrochloric acid to afford amino acid **16**. No attempt was made to separate the C-6 epimers of this compound. The *trans*-ketone **17**[39] (Scheme 1) was converted to the enol triflate **18** by treatment with lithium bis(trimethylsilyl)amide (LHMDS) in THF followed by quenching with *N*-phenyltriflamide (preferred over triflic anhydride). Regardless of the base used (e.g., LDA or LHMDS) or the order in which it was added (base to ketone vs ketone to base) we obtained a mixture of double-bond regioisomers. Heck coupling of **18** with acrylonitrile afforded dienes **19**, which were reduced to give the nitrile **20** as a single

Scheme 1[a]



[a] (a) $Ph_3PCH_2OMe^+Cl^-$, $NaN(SiMe_3)_2$, THF, 0 °C; 1 N HCl, CH_3CN, 60 °C; (b) $Et_2O_3PCH_2CN$, NaH, THF, room temperature. (c) H_2, 5% Pd/C, EtOH, 60 psi, room temperature; (d) *n*-Bu_3SnN_3, 80 °C; 6 N HCl, reflux; Dowex 50-X8, 10% pyridine/water; (e) $LiN(SiMe_3)_2$, THF, −78 °C; $PhN(SO_2CF_3)_2$, THF, −78 °C to room temperature; (f) CH_2=CHCN, $(Ph_3P)_2PdCl_2$, Et_3N, DMF, 75 °C.

Scheme 2[a]



[a] (a) BH_3·SMe_2, THF, 0 °C to room temperature; 3 N NaOH, 30% H_2O_2; Ph_3P, Br_2, pyridine, CH_2Cl_2, 0 °C; (b) NaCN, DMSO, 40 °C; (c) *n*-Bu_3SnN_3, 80 °C; 6 N HCl, reflux; Dowex 50-X8, 10% pyridine/water; (d) $Ph_3PCH_2OMe^+Cl^-$, $NaN(SiMe_3)_2$, THF, 0 °C; 1 N HCl, CH_3CN, room temperature; (e) $Et_2O_3PCH_2CN$, NaH, THF, room temperature (f) H_2, 5% Pd/C, EtOH, 60 psi, room temperature.

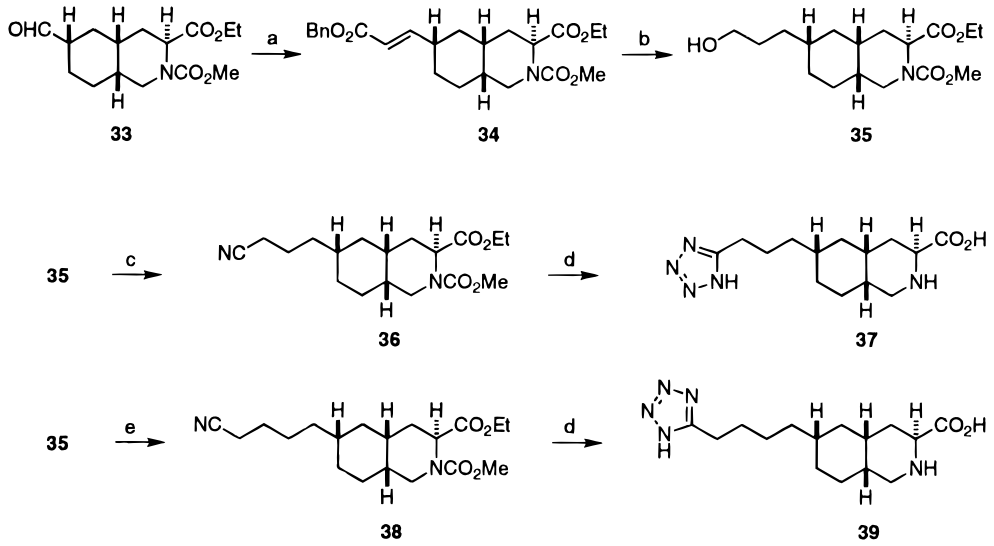
diastereomer whose stereochemistry at C-6 was undefined. Conversion to the tetrazole and hydrolysis afforded amino acid **21**, possessing a *trans* ring juncture.

Using the previously described 6-vinyl compound **22**,[32] (Scheme 2) we prepared the tetrahydroisoquinoline analog of **9**. Hydroboration of **22** followed by bromination of the intermediate alcohol afforded the bromide **23**, which was converted to the nitrile **24**. Tetrazole formation followed by hydrolysis afforded **25**.

To look at the effect of moving the carboxylate group from C-3 to C-1, we prepared amino acid **30** (Scheme 2). Ketone **26**[32] was converted to the enol ether and then hydrolyzed to form aldehyde **27**, which was then transformed to nitrile **29** via ene−nitrile **28**. Formation of the tetrazole followed by hydrolysis afforded the C-1 analog of **9**, amino acid **30** (as a mixture of diastereomers at C-6).

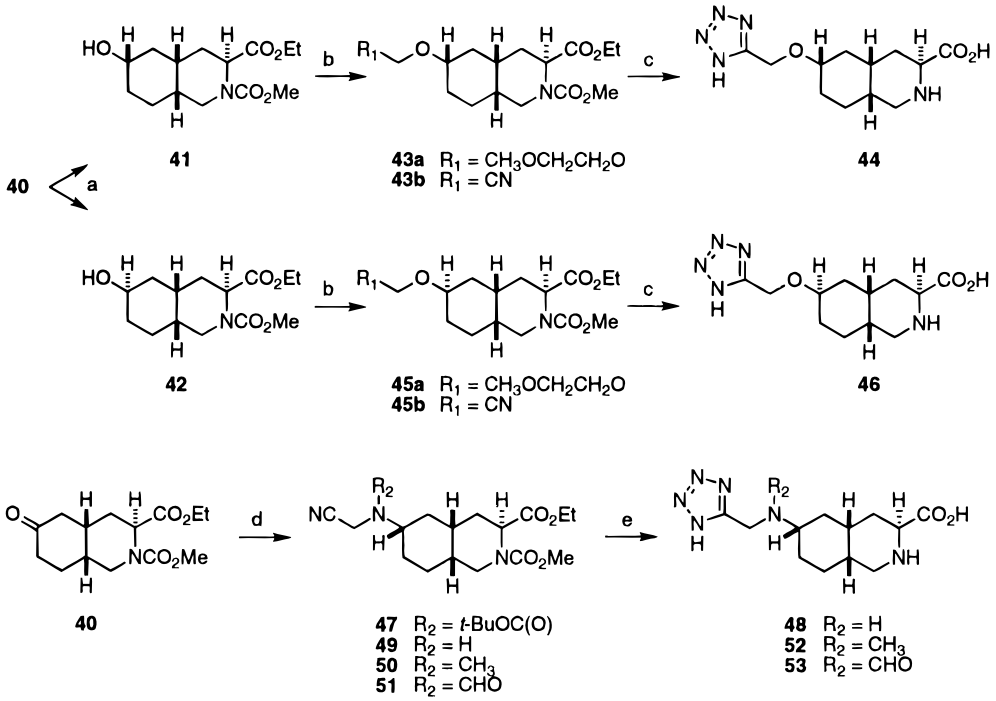
We next turned our attention to preparing compounds in which the length of the carbon chain that connects the tetrazole group to bicyclic nucleus was varied. Synthesis of the amino acids with no carbons (**31**)[40] or one carbon (**32**)[32,33] in the connecting chain has already

Scheme 3[a]



[a] (a) $Bn_2O_3PCH_2CO_2Bn$, NaH, THF, room temperature; (b) H_2, 5% Pd/C, EtOAc, 60 psi, room temperature; $BH_3{\cdot}SMe_2$, THF, 0 °C; (c) Ph_3P, Br_2, pyridine, CH_2Cl_2, 0 °C; NaCN, DMSO, 60 °C; (d) *n*-Bu_3SnN_3, 80 °C; 6 N HCl, reflux; Dowex 50-X8, 10% pyridine/water; (e) DMSO, $(ClCO)_2$, CH_2Cl_2, Et_3N, −78 °C to room temperature; $Et_2O_3PCH_2CN$, NaH, THF, room temperature; Mg, MeOH, room temperature.

Scheme 4[a]

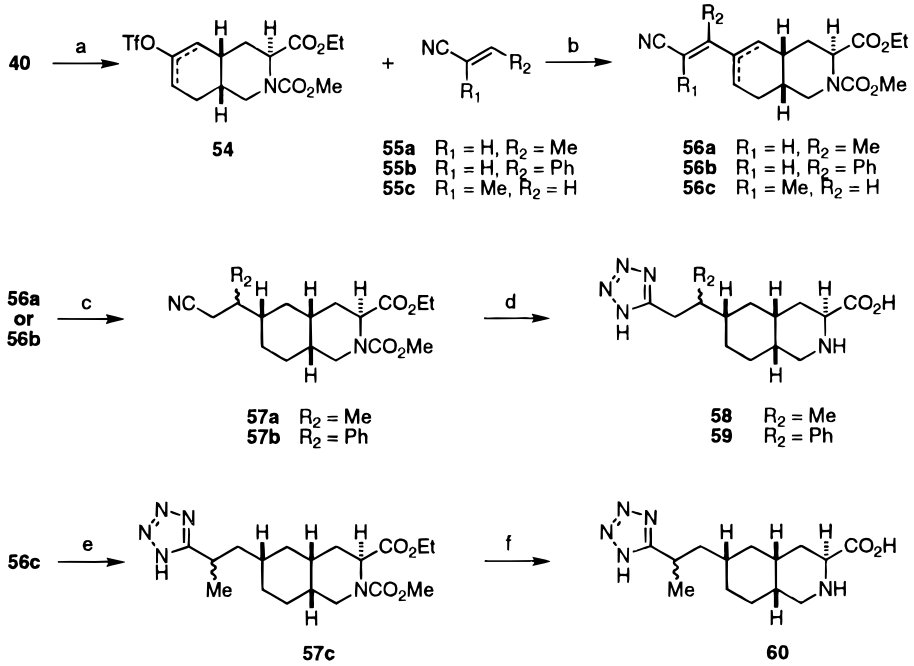


[a] (a) $NaBH_4$, EtOH, 0 °C to room temperature; (b) to **43a** or **45a**: MEMCl, *i*-Pr_2NEt, CH_2Cl_2; to **43b** or **45b**: Me_3SiCN, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C to room temperature; (c) *n*-Bu_3SnN_3, 80 °C; 6 N HCl, reflux; Dowex 50-X8, 10% pyridine/water; (d) **40** to **47**: $HCl{\cdot}H_2NCH_2CN$, EtOH, powdered 4 Å molecular sieves, $NaCNBH_3$, room temperature; $(BOC)_2O$, *i*-Pr_2NEt, EtOAc; **40** to **49**: $HCl{\cdot}H_2NCH_2CN$, EtOH, powdered 4 Å molecular sieves, $NaCNBH_3$, room temperature; **49** to **50**: CH_3I, K_2CO_3, CH_3CN, room temperature. **49** to **51**: HCO_2H, Ac_2O, THF, room temperature; (e) **47** to **48** and **50** to **52**: *n*-Bu_3SnN_3, 80 °C; 6 N HCl, reflux; Dowex 50-X8, 10% pyridine/water; **51** to **53**: *n*-Bu_3SnN_3, 80 °C; HCl (g), ether, room temperature; 1 N NaOH, EtOH, room temperature; Me_3SiI, $CHCl_3$, reflux; Dowex 50-X8, 10% pyridine/water.

been reported. Aldehyde **33**[38] (Scheme 3) was homologated to enoate **34** with the sodium salt of benzyl (diethylphosphono)acetate. The double bond was reduced and the benzyl ester selectively cleaved, allowing for a regioselective borane reduction of the resulting acid to the corresponding alcohol **35**. Conversion of **35** to the corresponding bromide and then displacement with cyanide afforded the nitrile **36**, which as before afforded amino acid **37**. Alternatively, **35** (Scheme 3) was oxidized to the corresponding aldehyde and homologated to the unsaturated nitrile (with the sodium salt of diethylphosphonoacetonitrile) and the double bond reduced with magnesium in methanol to afford **38**, as a mixture of ethyl (**38a**) and methyl esters (**38b**; from transesterification during the reduction). As before, tetrazole formation and hydrolysis afforded **39**.

We prepared compounds having an oxygen or nitrogen in a two-atom connecting chain in the position adjacent to the bicyclic nucleus. For this, ketone **40**[39] (Scheme 4) was reduced with sodium borohydride to afford a mixture of C-6 epimers, 67% of **41** and 31% of **42** (isolated yields). Attempts to introduce the cyanomethyl

Scheme 5[a]



[a] (a) $LiN(SiMe_3)_2$, THF, −78 °C; $PhN(SO_2CF_3)_2$, THF, −78 °C to room temperature; (b) $(Ph_3P)_2PdCl_2$, Et_3N, DMF, 75 °C; (c) H_2, 5% Pd/C, EtOH, 60 psi, room temperature; (d) *n*-Bu_3SnN_3, 80 °C; 6 N HCl, reflux; Dowex 50-X8, 10% pyridine/water; (e) *n*-Bu_3SnN_3, 80 °C; HCl(g), ether, room temperature; H_2, 5% Pd/C, EtOH, 60 psi, room temperature; (f) 6 N HCl, reflux; Dowex 50-X8, 10% pyridine/water.

Table 1. Analytical Data and Melting Points for Novel Compounds

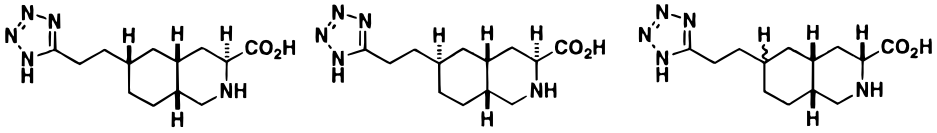
compd	formula	analysis	mp (°C)	compd	formula	analysis	mp (°C)
11	$C_{13}H_{21}N_5O_2 \cdot 0.5H_2O \cdot 0.2C_3H_6O$	C,H,N	255	**47**	$C_{21}H_{32}N_3O_6$	C,H,N	
16	$C_{13}H_{21}N_5O_2 \cdot 1.25H_2O$	C,N; H[a]	191	**48**	$C_{12}H_{20}N_6O_2 \cdot 1.25H_2O$	C,H,N	250−251
21	$C_{13}H_{21}N_5O_2 \cdot 0.7H_2O$	C,H,N	233	**50**	$C_{17}H_{27}N_3O_4$	C,H,N	
25	$C_{13}H_{15}N_5O_2 \cdot 0.75H_2O \cdot 0.1C_3H_6O$	C,N; H[b]		**52**	$C_{13}H_{22}N_6O_2 \cdot 2.5H_2O$	C,H,N	204
30	$C_{13}H_{15}N_5O_2 \cdot H_2O \cdot 0.1C_3H_6O$	C,H,N	245	**51**	$C_{17}H_{25}N_3O_5 \cdot 0.5CHCl_3$	C,H,N	
35	$C_{17}H_{29}NO_5$	C,H,N		**53**	$C_{13}H_{20}N_6O_3 \cdot 1.5H_2O$	C,H; N[d]	117−122
36	$C_{18}H_{28}N_2O_4$	C,H,N		**54**	$C_{15}H_{20}F_3NO_7S$	C,H,N	
37	$C_{14}H_{23}N_5O_2 \cdot 0.75H_2O$	C,H,N	207	**56a**	$C_{18}H_{24}N_2O_4$	C,H,N	
39	$C_{15}H_{25}N_5O_2 \cdot 1.25H_2O$	C,H,N	172−176	**56b**	$C_{23}H_{26}N_2O_4$	C,H,N	
41	$C_{14}H_{23}NO_5$	C,H,N		**56c**	$C_{18}H_{24}N_2O_4$	C,H,N	
42	$C_{14}H_{23}NO_5$	C,H,N		**57a**	$C_{18}H_{28}N_2O_4$	C,H,N	
43a	$C_{18}H_{31}NO_7$	C,H,N		**57b**	$C_{23}H_{30}N_2O_4$	C,H,N	
43b	$C_{16}H_{24}N_2O_5$	C,H,N		**57c**	$C_{18}H_{25}N_5O_4 \cdot 0.25H_2O$	C,H,N	
44	$C_{12}H_{20}N_5O_3 \cdot H_2O \cdot 0.5C_3H_6O$	C,N; H[c]	207	**58**	$C_{14}H_{23}N_5O_2 \cdot H_2O$	C,H,N	215
45a	$C_{18}H_{31}NO_7$	C,H,N		**59**	$C_{19}H_{25}N_5O_2 \cdot 1.8H_2O \cdot 0.25C_3H_6O$	C,N; H[e]	228
45b	$C_{16}H_{24}N_2O_5 \cdot 0.05CHCl_3$	C,H,N		**60**	$C_{14}H_{23}N_5O_2 \cdot 0.9H_2O$	C,N; H[f]	
46	$C_{12}H_{20}N_5O_3 \cdot H_2O \cdot 0.25C_3H_6O$	C,H,N	233				

[a] Anal. C, N; H: calcd, 7.85; found, 7.38 [b] Anal. C, N; H: calcd, 5.89; found, 5.18. [c] Anal. C, N; H: calcd, 7.65; found, 7.04. [d] Anal. C, H; N: calcd, 25.06; found, 25.98. [e] Anal. C, N; H: calcd, 7.63; found, 6.71. [f] Anal. C, N; H: calcd, 8.07; found, 7.54.

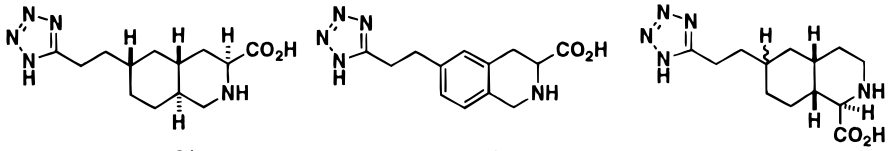
group directly onto the oxygen of **41** by alkylation of the alkoxide consistently failed. Using various bases and solvents (sodium hydride in THF or DMF; sodium bis(trimethylsilyl)amide in THF; *N*,*N*-diisopropyl-*N*-ethylamine in CH_2Cl_2; potassium *tert*-butoxide in THF; DBU in CH_2Cl_2) with bromoacetonitrile gave either starting material or an uncharacterizable mixture of products. However, in no case was any of the desired cyanomethyloxy compound obtained. We were able to circumvent this problem by using a two-step procedure, where the (methoxyethoxy)methyl (MEM) ether group served as an oxonium ion source that could be revealed under Lewis acid catalysis and trapped with cyanotrimethylsilane. The alcohol group of **41** was converted to the MEM ether, **43a**, and then **43a** was treated with an excess of cyanotrimethylsilane and 25 mol % of boron trifluoride etherate in CH_2Cl_2 at 0 °C. Under these reaction conditions, the desired (cyanomethyl)oxy compound **43b** was obtained in 58% (unoptimized) yield for the two steps. Similar reaction of the C-6 epimeric alcohol **42** afforded nitrile **45b** in 58% (unoptimized) yield. Treatment of **43b** and **45b** with Bu_3SnN_3 followed by hydrolysis afforded amino acids **44** and **46**, respectively. Reductive amination of **40**[39] (Scheme 4) with aminoacetonitrile followed by BOC protection of the amine afforded **47**, with a high degree of stereoselectivity. Tetrazole formation and hydrolysis then afforded **48**. If the BOC-protection step was omitted, the corresponding amine **49** could be either methylated or formylated to give **50** or **51**, respectively. Each was then converted to the tetrazole, but in lieu of exhaustive hydrolysis was first treated with base to hydrolyze the ester to the corresponding acid and then treated with excess iodotrimethylsilane to afford amino acids **52** and **53**.

Finally, we prepared analogs of **9** where a methyl or phenyl group was appended to the two-carbon connecting chain. Treatment of the enol triflate **54** (as a mixture of regioisomers; prepared from **40** as described

Table 2. Effects of Hydroisoquinoline Structure on AMPA Antagonist Activity: Stereochemistry, Tetrahydro- versus Decahydroisoquinoline, and C-3 versus C-1 Carboxyl



9 **11** **16**



21 **25** **30**

	IC_{50} (μM) versus radioligand binding at ionotropic excitatory amino acid receptors[a,b]			IC_{50} (μM) versus agonist-induced depolarizations in a cortical slice preparation[c]		
compd	[^{3}H]CGS 19755	[^{3}H]AMPA	[^{3}H]kainic acid	NMDA	AMPA	kainic acid
9[d]	26.4 ± 2.0	4.8 ± 1.2	247 ± 8	61.3 ± 3	6.0 ± 1.0	31.7 ± 4.4
11	60.6 ± 24.8	59.6 ± 4.3	180 ± 22	>100	<100[e]	>100
16	>10	>100	>100	>100	>100	>100
21	>100	>100	>100	>100	>100	>100
25	>10	>100	>10	>100	>100	>100
30	12.8 ± 2.2	>100	>100	100[f]	>100	>100

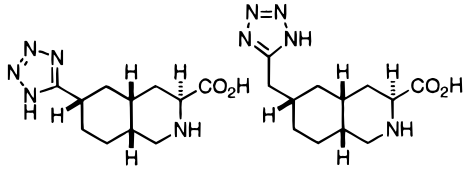
[a] Affinity at NMDA receptors was determined using [^{3}H]CGS 19755; see ref 41. Affinity at AMPA receptors was determined using [^{3}H]AMPA; see ref 42. Affinity at kainic acid receptors was determined using [^{3}H]kainic acid; see ref 43. [b] All assays for affinity were run in triplicate, unless otherwise indicated. [c] See ref 44. [d] Data from ref 30. [e] Tested versus quisqualic acid instead of AMPA. [f] 50% inhibition at 100 μM.

above for **18**) with unsaturated nitriles **55a**−**c** afforded dienes **56a**−**c** (Scheme 5). Hydrogenation of dienes **56a** and **56b** afforded nitriles **57a** and **57b**, which were converted as before to the tetrazole amino acids **58** and **59**, respectively, having a substituent on the carbon of the connecting chain adjacent to the bicyclic ring (**58**, methyl; **59**; phenyl). Alternatively, **56c** was first converted to the tetrazole, and then the double bonds were reduced to form **57c**. This was hydrolyzed to afford **60**, having a methyl group on the carbon of the connecting chain adjacent to the tetrazole ring. Compounds **58**, **59**, and **60** are mixtures of diastereomers at the carbon on the connecting chain to which the methyl or phenyl is attached. Analytical data and melting points for all new compounds are provided in Table 1.

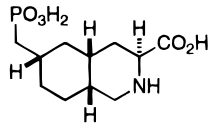
Results and Discussion

The novel amino acids that we prepared were evaluated for affinity at NMDA, AMPA, and kainic acid receptors using [^{3}H]CGS 19755,[41] [^{3}H]AMPA,[42] and [^{3}H]-kainic acid,[43] respectively, in selective radioligand binding assays. All of the compounds were tested for functional activity using a cortical slice preparation (cortical wedge).[44] While the data is not shown, none of the compounds showed significant agonist activity when tested alone in the cortical slice preparation. Antagonist activity and selectivity was determined for NMDA, AMPA, and kainic acid receptors by evaluating the ability of these compounds to inhibit depolarizations induced by 40 μM NMDA, 40 μM AMPA (or in a few cases, 40 μM quisqualic acid (QUIS)), and 10 μM kainic acid, respectively. The data for these novel compounds are shown in Tables 2 and 3, with data for the AMPA/NMDA antagonist **31**[40] and the NMDA antagonist **32**[32] included for comparison.

We originally developed this class of decahydroisoquinoline amino acids in hopes of identifying compounds that were NMDA antagonists. We discovered two potent, systemically active NMDA antagonists, the tetrazole-substituted amino acid **32**[32,33] and phosphonic acid-substituted amino acid **61**.[32,33] In this structure



31 **32**

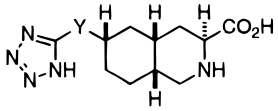


61

activity study (SAR), NMDA antagonist activity was observed for compounds having a one methylene spacer between the distal acidic functionality and the bicyclic nucleus. We found that homologation of **32** to the tetrazolylethyl compound **9** afforded a potent and selective AMPA antagonist. In this paper and the subsequent paper,[37] we have explored the AMPA antagonist SAR.

Holding the basic structure constant (tetrazolylethyl at C-6), we prepared compounds whose stereochemistry differed from that of **9** (Table 2). Amino acid **11**, which is the C-6 epimer of **9**, was about 12-fold less potent in binding to the AMPA receptor, and was much less selective than **9**. In the cortical wedge, **11** was only weakly active as an antagonist. The C-3 epimer of **9**,

Table 3. Effects on AMPA Antagonist Acitivity of Varying Chain Length, Heteroatom Substitution Adjacent to the Nucleus, and Substitution on the Connecting Chain



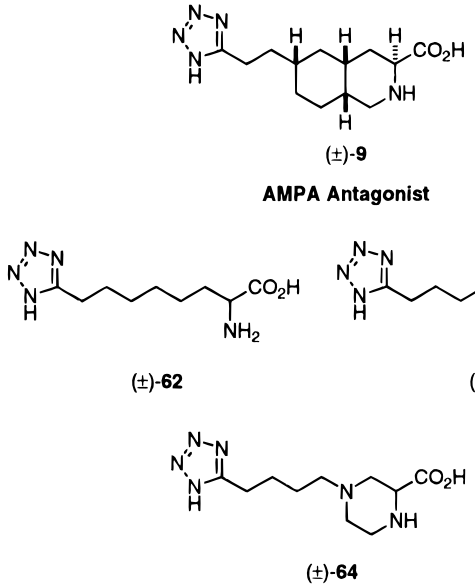
		IC$_{50}$ (μM) versus radioligand binding at ionotropic excitatory amino acid receptors[a,b]			IC$_{50}$ (μM) versus agonist-induced depolarizations in a cortical slice preparation[c]		
compd	linker Y	[^{3}H]CGS 19755	[^{3}H]AMPA	[^{3}H]kainic acid	NMDA	AMPA	kainic acid
			Effects of Chain Length				
31[d]	none	1.6 ± 0.2	12.8 ± 0.3	31.8 ± 2.3	7.5 ± 0.7	40.9 ± 5.2	>100
32[e]	CH_2	0.94 ± 0.20	84.5 ± 1.9	>100	1.4 ± 0.3	>100[f]	>100
9[g]	$(CH_2)_2$	26.4 ± 2.0	4.8 ± 1.2	247 ± 8	61.3 ± 3	6.0 ± 1.0	31.7 ± 4.4
37	$(CH_2)_3$	27.0 ± 9.9	16.8 ± 0.5	18.7 ± 0.3	>100	22.0 ± 3.8[f]	>100
39	$(CH_2)_4$	>100	57.0 ± 8.4	>100	>100	27.6 ± 3.1	<100
			Effects of Heteroatom Substitution Adjacent to the Hydroisoquinoline Nucleus				
44	CH_2O	5.9 ± 2.7	24.0 ± 3.4	55 ± 11	28.3 ± 4.6	29.5 ± 4.9	>100
46	CH_2O	5.3 ± 1.9	>100	>100	13.6 ± 1.7	>100	>100
48	CH_2NH	11.5 ± 1.2	>100	>100	33.4 ± 4.4	69.3 ± 15.4	>100
52	$CH_2N(Me)$	65.8 ± 8.3	>100	>100	>100	>100	>100
53	$CH_2N(CHO)$	>100	23.1 ± 6.3	>100	NT[h]	NT[h]	NT[h]
			Effects of Substitution on the Two-Carbon Connecting Chain				
58	$CH_2CH(Me)$	53.2 ± 6.1	3.0 ± 0.3	35.0 ± 11.3	>100	6.0 ± 1.0	58 ± 13
59	$CH(Me)CH_2$	>100	4.21[i]	27.3[i]	NT[h]	NT[h]	NT[h]
60	$CH_2CH(Ph)$	15.1 ± 0.7	9.8 ± 3.4	>100	100	9.0 ± 2.8	23.6 ± 5.6

[a] Affinity at NMDA receptors was determined using [^{3}H]CGS 19755; see ref 41. Affinity at AMPA receptors was determined using [^{3}H]AMPA; see ref 42. Affinity at kainic acid receptors was determined using [^{3}H]kainic acid; see ref 43. [b] All assays for affinity were run in triplicate, unless otherwise indicated. [c] See ref 44. [d] Data from ref 40. [e] Data from ref 31. [f] Tested versus quisqualic acid instead of AMPA. [g] Data from ref 30. [h] NT = not tested. [i] IC$_{50}$ was the result of a single assay.

amino acid **16** (as a mixture of isomers at C-6), was inactive in both binding and the cortical wedge. Also inactive were the trans ring juncture isomer **21** and the tetrahydroisoquinoline analog **25**. Moving the carboxy group from C-3 to C-1, as in **30**, abolished AMPA receptor affinity but slightly increased affinity for the NMDA receptor. This compound showed very weak NMDA antagonist activity in the cortical wedge. Overall, the stereochemical and gross structural preferences for AMPA antagonist activity are identical to those of the NMDA antagonist SAR.[32]

One of the most striking features of this SAR became evident when we examined the effects of varying chain length, with a tetrazole as the distal acid moiety. Our original discovery was that a compound with a methylene spacer, e.g., **32**, was a selective NMDA antagonist (90-fold selective for NMDA over AMPA in receptor binding; >16-fold for cortical wedge antagonist activity). We recently reported that amino acid **31**, where the tetrazole ring is bound directly to the bicyclic nucleus, showed affinity for both NMDA and AMPA receptors.[40] Its AMPA affinity is about 2.5-fold less than **9**, and its NMDA affinity is about 1.6-fold less than **32**. Nonetheless, this dual antagonist activity is evident functionally in vitro in the cortical wedge and in vivo in mice and pigeons.[40] As we have already described, the ethylene-spaced compound **9** is a selective AMPA antagonist.[30,31] Homologation to the propylene- and butylene-spaced compounds, **37** and **39**, respectively, diminished affinity, activity, and selectivity for AMPA over NMDA receptors. At best, the compounds in this series are only weakly active at the kainic acid receptor.

We have previously reported the synthesis and structure−activity studies of three other series of amino acids substituted with a tetrazole ring as the distal acid bioisostere. These compounds were prepared as potential NMDA antagonists. One is an acyclic series of amino acids (e.g., **62**);[45] the others are 4-substituted piperidine- (e.g., **63**)[46] and piperazine-2-carboxylic acids (e.g, **64**).[45] In all cases one of the key components of the SAR was to look at the effect of varying the distance between the two acidic moieties. Figure 1 shows a structural comparison of **9** with **62** (acyclic), **63** (piperidine), and **64** (piperazine), which all have in common the critical amino acid substructure found in **9**. No affinity or antagonist activity at AMPA receptors is observed for **62**, **63**, or **64**, nor any of the close congeners in these series. Thus, AMPA antagonist activity is unique for the 6-substituted decahydroisoquinoline-3-carboxylic acids. This may reflect unique conformational preferences for **9** that result from the more rigid



(±)-**9**

AMPA Antagonist

(±)-**62** (±)-**63**

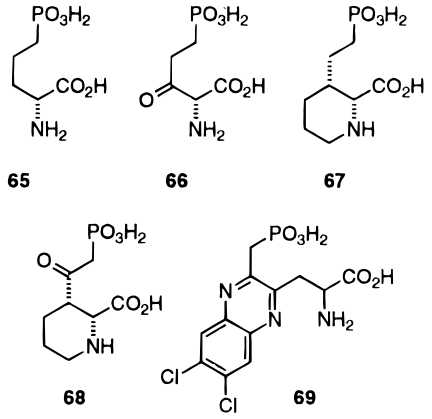
(±)-**64**

Figure 1. Is the hydroisoquinoline nucleus unique? No AMPA antagonist activity observed for acyclic (**66**), piperidine (**67**), and piperazine (**68**) tetrazoles.

cis-decahyroisoquinoline when compared to the conformatoinally more mobile acyclic or monocyclic compounds **62**, **63**, and **64**. However, the exact reason for these striking differences is still unknown.

Holding the stereochemistry in the bicyclic nucleus constant, with a two-atom spacer between the acid and ring, and having a tetrazole in the distal acid position, we next looked at the effect of heteroatom substitution in the spacer at the position adjacent to the bicyclic nucleus. Oxygen substitution, as in **44** and its C-6 epimer **46**, gave a 5-fold or greater decrease in AMPA receptor affinity and a corresponding 5-fold decrease in AMPA antagonist activity for **44** in the cortical wedge. However, **44** and **46** showed a 4.5- and 11-fold increase in affinity at the NMDA receptor, and a 2- and >7-fold increase in NMDA antagonist activity in the cortical wedge, respectively. At doses up to 320 mg/kg, ip, in mice, **9** was ineffective in blocking NMDA-induced lethality, an assay that is particularly sensitive and specific for NMDA antagonists. However, both **44** and **46** were active in this assay, blocking lethality in mice induced by a 200 mg/kg ip dose of NMDA with minimum effective doses of 80 mg/kg, ip, each. Introduction of a nitrogen, as in **48**, abolished AMPA affinity and antagonist activity, and like oxygen, gave a 2-fold increase in NMDA affinity and antagonist potency. *N*-Methylation of the nitrogen of **48** provided **52**, which was inactive, and *N*-formylation provided **53**, which was inactive at the NMDA receptor and had weak affinity at the AMPA receptor.

The improvement in NMDA receptor antagonist affinity and potency from appropriately placed heteroatom substitution is known. The keto-substituted amino acids **66**[47] and **68**[48,49] are significantly more potent than their unsubstituted counterparts, **65**[50] and **67**,[48,49] respectively. And the quinoxaline-substituted amino acid **69** is significantly more potent than structurally related compounds which lack the heteroatom-containing quinoxaline ring.[51] The exact nature of this increase in



potency is unknown, although previous investigators have ascribed this effect to a conformational bias toward a receptor-active conformation that is imparted through an intramolecular hydrogen bond between the amino and keto functionalities. However, in the case of **44** or **46**, it would be impossible for such an interaction to occur. Therefore one may speculate that this increase in potency may arise from a favorable hydrogen bond acceptor interaction between this heteroatom functionality (e.g., ether or ketone) on the ligand and the NMDA receptor protein.

Using optimized stereochemistry, distal acid, and spacing, we investigated the effect of incorporating alkyl or aryl substitution on the spacer. Compounds with a methyl group on either carbon of the ethylene spacer (**58** and **60**, each as a mixture of diastereomers) were comparable to **9** in both AMPA receptor affinity and antagonist potency and were somewhat more selective. Amino acid **59**, with a phenyl on the carbon adjacent to the bicyclic nucleus, was slightly lower in affinity and antagonist potency than **9** and gained slightly in affinity at the NMDA receptor.

Conclusions

From a series of 6-(tetrazolylalkyl)-substituted decahydroisoquinoline-3-carboxylic acids we have realized potent and selective AMPA receptor antagonists. The optimal stereochemical array for AMPA antagonists is exemplified by **9**, which is the same diastereomer that was optimal for NMDA antagonist activity. Varying the length of the carbon chain that connects the tetrazole to the bicyclic nucleus gave compounds with different selectivity between AMPA and NMDA receptors. **31**, in which the tetrazole is bound directly to the bicyclic ring, is an antagonist at both AMPA and NMDA receptors; with a methylene spacer, **32** is a selective NMDA antagonist; and **9**, with an ethylene spacer, is a selective AMPA antagonist. Substitution of one of the carbon atoms of the ethylene spacer in the position adjacent to the bicyclic ring with a heteroatom (O or N) reduced potency at AMPA receptors, while substitution on the ethylene chain with a methyl or phenyl had minimal effect on activity. In the following paper, we explore other aspects of this SAR.[37] These include varying the distal acid bioisostere, looking at the absolute stereochemical preferences for AMPA antagonist activity, and describing the activity of some of these analogs in mice.

Experimental Section

General Experimental. All experiments were run under a positive pressure of dry nitrogen. Tetrahydrofuran (THF) was distilled from sodium prior to use. Sodium hydride refers to 60% by weight sodium hydride (Aldrich) that was washed three times with hexane prior to use. 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 (×) with the indicated solvent(s). The combined organic extracts were dried over $MgSO_4$, filtered, concentrated in vacuo, and 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 Waters Prep 500 HPLC or a Waters Prep 2000 HPLC, using a linear gradient of hexane to the solvent indicated in parentheses in the text. "Cation exchange chromatography" refers to ion exchange with Dowex 50X-8 (100−200) resin (H^+ form). The resin was prepared by washing (in a coarse porosity sintered glass funnel) with water, methanol, water, 3 N ammonium hydroxide (pH ≥ 12), water, 1 N HCl (pH ≤ 1), and then water until the pH is neutral. The resin was packed into a glass column in water, the compound (at pH ≤ 2) was slowly eluted on with water, and then the column was washed with water, 50% aqueous THF, and then water until the pH was neutral. The compound was eluted off of the column with 10% aqueous pyridine, and product-containing fractions (which are detected with ninhy-

drin stain on a TLC plate) were combined and concentrated in vacuo. Water was added and the mixture concentrated in vacuo. This procedure was repeated two more times to ensure complete removal of pyridine. The residue was then typically suspended in water, filtered, washed with water, acetone, and ether, and dried in vacuo overnight at 60 °C. ^{1}H NMR spectra were obtained on a GE QE-300 spectrometer at 300.15 MHz. Where indicated, a small amount of 40% aqueous KOD was added to aid solution of NMR samples run in D_2O. The reactions were generally monitored for completion using thin layer chromatography (TLC). Thin layer chromatography was performed using E. Merck Kieselgel 60 F_{254} plates, 5 × 10 cm, 0.25 mm thickness. Spots were detected using a combination of UV and chemical detection [plates dipped in a ceric ammonium molybdate solution (75 g of ammonium molybdate and 4 g of cerium (IV) sulfate in 500 mL of 10% aqueous sulfuric acid) and then heated on a hot plate]. Elemental analyses for carbon, hydrogen, and nitrogen were determined on a Control Equipment Corporation 440 elemental analyzer. Melting points were determined in open glass capillaries on a Gallenkamp hot air bath melting point apparatus and are uncorrected.

Ethyl (3*SR*,4a*SR*,6*RS*,8a*SR*)- and (3*SR*,4a*SR*,6*SR*,8a*SR*)-6-(2-Cyanoethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,-8a-decahydroisoquinoline-3-carboxylate (15). To a suspension of 0.9 g (21.8 mmol) of sodium hydride in 26 mL of THF was added 3.9 g (21.8 mmol) of (diethylphosphono)-acetonitrile. After 30 min at room temperature, this mixture was treated with 4.6 g (15.5 mmol) of **13** in 32 mL of THF (5 mL rinse). After stirring overnight at room temperature, workup (water/3× ether) afforded 5.5 g of **14**. This mixture was hydrogenated with 1.0 g of 5% Pd/C in 95 mL of ethanol at room temperature and 60 psi for 4 h, then filtered through diatomaceous earth, and concentrated in vacuo. Chromatography (500 g silica gel, 35% ethyl acetate/hexane) afforded 3.7 g (67%) of **15** (as a 1/1 mixture of C-6 epimers).

(3*SR*,4a*SR*,6*RS*,8a*SR*)- and (3*SR*,4a*SR*,6*SR*,8a*SR*)-6-(2-(1*H*-Tetrazol-5-yl)ethyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic Acid (16). one gram (3.1 mmol) of **15** and 2.1 g (6.3 mmol) of azidotri-*n*-butylstannane were heated to 80 °C for 4 days, then 15 mL of 6 N hydrochloric acid was added, and the mixture was heated to 100 °C overnight. The mixture was cooled to room temperature and extracted four times with ether, and then the aqueous layer was concentrated in vacuo. Cation exchange chromatography gave a solid that was suspended in acetone, refluxed for 1 h, then filtered, washed with acetone and ether, and dried in vacuo at 60 °C to afford 0.7 g (68%) of **16**.

Ethyl Δ^5- and Δ^6-(3*SR*,4a*RS*,8a*SR*)-6-(((Trifluoromethyl)sulfonyl)oxy)-2-(methoxycarbonyl)octahydroisoquinoline-3-carboxylate (18). To a −78 °C solution of 6.0 mL of lithium bis(trimethylsilyl)amide (6.0 mmol, 1 M in THF) in 6 mL of THF was added 1.5 g (5.4 mmol) of **17**[3] in 2 mL of THF. After 1 h, a solution of 1.9 g (5.4 mmol) of *N*-phenyltrifluoromethanesulfonimide in 6 mL of THF was added, and then the mixture warmed to room temperature and stirred for 3 h. Workup (10% sodium bisulfate/3× ether) gave 1.8 g (84%) of **18**, used without purification.

Ethyl (3*SR*,4a*RS*,6*RS*,8a*SR*)-6-(2-Cyanoethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (20). A solution of 1.8 g (4.6 mmol) of **18**, 0.8 mL (0.6 g, 11.4 mmol) of acrylonitrile, 2.2 mL (1.6 g, 16.0 mmol) of triethylamine, and 0.07 g (0.1 mmol) of bis(triphenylphosphine)palladium(II) chloride in 15 mL of degassed dimethylformamide was heated to 75 °C for 3 h and then cooled to room temperature. Workup (water/3× 1/1 ether/hexane) afforded 1.4 g (98%) of **19**. A solution of 1.4 g (4.5 mmol) of **19** and 0.4 g of 5% Pd/C in 50 mL of ethanol was hydrogenated at room temperature and 60 psi for 5 h and then filtered through diatomaceous earth and the filtrate concentrated in vacuo. Chromatography (60 g silica gel, 35% ethyl acetate/hexane) gave 1.0 g (72%) of **20**.

(3*SR*,4a*RS*,6*RS*,8a*SR*)-6-(2-(1*H*-Tetrazol-5-yl)ethyl)-1,-2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic Acid (21). One gram (3.2 mmol) of **20** and 2.1 g (6.5 mmol) of azido tri-*n*-butylstannane were heated to 80 °C for 3 days, then treated with 15 mL of 6 N hydrochloric acid, heated to 90 °C overnight, and cooled to room temperature. The mixture was extracted five times with ether, and the aqueous phase was concentrated in vacuo. Cation exchange chromatography gave a solid that was suspended in acetone, refluxed for 1 h, then filtered, washed with acetone and ether, and dried in vacuo at 80 °C to afford 0.2 g (19%) of **21**.

Ethyl (3*SR*)-6-(2-Bromoethyl)-2-(methoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (23). A solution of 3.8 g (13.3 mmol) of **22** and 5.3 mL (10.6 mmol, 2.0 M in THF) of borane methyl sulfide in 40 mL of THF was stirred 3 h at 0 °C and 0.5 h at room temperature and then quenched by the sequential addition of 4.4 mL of 3 N sodium hydroxide and 4.4 mL of 30% hydrogen peroxide. After 1.5 h at room temperature, workup (3× ether) afforded an oil. This was dissolved in 25 mL of dichloromethane and 1.5 mL (1.5 g, 18.6 mmol) of pyridine and added to a 0 °C suspension of triphenylphosphine dibromide [prepared from 4.9 g (18.6 mmol) of triphenylphosphine and 1.0 mL (3.0 g, 18.6 mmol) of bromine] in 75 mL of dichloromethane. After 2 h at 0 °C, workup (10% sodium bisulfate/3× dichloromethane, 1× ether) and chromatography (260 g silica gel, 25% ethyl acetate/hexane) afforded 1.4 g (29%) of **23**.

Ethyl (3*SR*)-6-(2-Cyanoethyl)-2-(methoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (24). A solution of 1.4 g (3.9 mmol) of **23** and 0.4 g (7.8 mmol) of sodium cyanide in 10 mL of dimethyl sulfoxide was heated to 40 °C for 2 h and then cooled to room temperature. Workup (brine/3× dichloromethane, 1× ether) and chromatography (70 g silica gel, 40% ethyl acetate/hexane) afforded 0.9 g (76%) of **24**.

(3*SR*)-6-(2-(1*H*-Tetrazol-5-yl)ethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (25). A 0.9 g (3.0 mmol) portion of **24** and 1.9 g (6.0 mmol) of azido tri-*n*-butylstannane were heated to 80°C for 3 days, treated with 25 mL of 6 N hydrochloric acid, heated to 100 °C overnight, and then cooled to room temperature. The mixture was extracted four times with ether, and the aqueous phase was concentrated in vacuo. Cation exchange chromatography afforded 0.3 g (42%) of **25**.

Ethyl (1*SR*,4a*SR*,6*SR*,8a*SR*)- and (1*SR*,4a*SR*,6*RS*,8a*SR*)-6-Formyl-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-1-carboxylate (27). A solution of 0.9 g (2.6 mmol) of ethyl (1*SR*,4a*SR*,8a*SR*)-6-(methoxymethyene)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-1-carboxylate (prepared from **26** and methoxymethyl triphenylphosphonium chloride as described in ref 38) in 4.8 mL of acetonitrile and 1.2 mL of 1 N HCl was stirred for 6 h at room temperature, and then workup (saturated sodium bicarbonate/4× ether) afforded 0.9 g (100%) of **27** (as a 2/1 mixture of 6*SR*/6*RS* epimers at C-6), used without purification.

Ethyl (1*SR*,4a*SR*,6*SR*,8a*SR*)- and (1*SR*,4a*SR*,6*RS*,8a*SR*)-6-(2-Cyanoethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,-8a-decahydroisoquinoline-1-carboxylate (29). To a suspension of 0.14 g (3.6 mmol) of sodium hydride in 5 mL of THF was added 0.6 g (3.6 mmol) of (diethylphosphono)acetonitrile. After 30 min at room temperature, this mixture was cooled to 0 °C and treated with 0.9 g (2.6 mmol) of **27** in 4 mL of THF (1 mL rinse). After stirring for 1 h at room temperature, workup (water/3× ether) and chromatography (50 g silica gel, 35% ethyl acetate/hexane) afforded 0.6 g (61%) of **28** (mixture of epimers at C-6). This mixture was hydrogenated with 0.1 g of 5% Pd/C in 50 mL of ethanol at room temperature and 60 psi for 4 h, then filtered through diatomaceous earth, and concentrated in vacuo. Chromatography (50 g silica gel, 30% ethyl acetate/hexane) afforded 0.3 g (53%) of **29** (as a 1/1 mixture of C-6 epimers).

(1*SR*,4a*SR*,6*SR*,8a*SR*)- and (1*SR*,4a*SR*,6*RS*,8a*SR*)-6-(2-(1*H*-Tetrazol-5-yl)ethyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-1-carboxylic Acid (30). A 0.3 g (0.8 mmol) portion of **29** and 0.6 g (1.7 mmol) of azidotri-*n*-butylstannane were heated to 80 °C for 3 days, then 3 mL of 6 N hydrochloric acid was added, and the mixture was heated to 90 °C overnight. The mixture was cooled to room temperature and extracted six times with ether, and then the aqueous layer was concentrated in vacuo. Cation exchange chromatography

gave a solid that was suspended in acetone, refluxed for 1 h, then filtered, washed with acetone and ether, and dried in vacuo at 60 °C to afford 0.2 g (63%) of **30**.

Ethyl (3*SR*,4a*RS*,6*SR*,8a*RS*)-6-(2-(Benzyloxycarbonyl)-ethen-1-yl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (34). To a suspension of 1.1 g (28.3 mmol) of sodium hydride in 50 mL of THF was added 8.1 g (28.3 mmol) of benzyl (diethylphosphono)acetate. After 30 min, the resulting clear solution was treated with 5.6 g (18.8 mmol) of **33** in 25 mL of THF and then stirred 5 h at room temperature. Workup (water/3× ether) and chromatography (35% ethyl acetate/hexane) gave 7.4 g (91%) of **34**.

Ethyl (3*SR*,4a*RS*,6*RS*,8a*RS*)-6-(2-Carboxyethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate. A solution of 7.2 g (16.8 mmol) of **34** in 90 mL of ethyl acetate was hydrogenated with 2.5 g of 5% Pd/C at 60 psi and room temperature for 4 h. Filtration through diatomaceous earth and concentration in vacuo afforded 5.7 g (100%) of ethyl (3*SR*,4a*RS*,6*RS*,8a*RS*)-6-(2-carboxyethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate.

Ethyl (3*SR*,4a*RS*,6*RS*,8a*RS*)-6-(3-Hydroxyprop-1-yl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (35). A 5.7 g (16.8 mmol) sample of ethyl (3*SR*,4a*RS*,6*RS*,8a*RS*)-6-(2-carboxyethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate was dissolved in 40 mL of THF, cooled to 0 °C, and treated with 17 mL (34.0 mmol) of a 2 M solution of borane−methyl sulfide in THF. After 3 h, workup (saturated aqueous sodium bicarbonate/3× ether) and chromatography (250 g of silica gel, 50% ethyl acetate/hexane) gave 3.7 g (68%) of **35**.

Ethyl (3*SR*,4a*RS*,6*RS*,8a*RS*)-6-(3-Cyanoprop-1-yl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (36). A solution of 2.0 g (6.0 mmol) of **35** in 10 mL of dichloromethane and 1.5 mL (1.4 g, 18.0 mmol) of pyridine was added to a 0 °C suspension of triphenylphosphine dibromide [prepared from 3.2 g (12.0 mmol) of triphenylphosphine and 0.6 mL (1.9 g, 12.0 mmol) of bromine] in 10 mL of dichloromethane. After 2 h at 0 °C, workup (2× 10% aqueous sodium bisulfate/2× dichloromethane, 1× ether) afforded the corresponding bromide. This was dissolved in 10 mL of dimethyl sulfoxide and heated for 2 h at 60 °C with 0.6 g (12.0 mmol) of sodium cyanide. Workup (1/1 brine/water/5× dichloromethane, 1× ether) and chromatography (50% ethyl acetate/hexane) gave 1.7 g (85%) of **36**.

(3*SR*,4a*RS*,6*SR*,8a*RS*)-6-(3-(1*H*-Tetrazol-5-yl)prop-1-yl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic Acid (37). A mixture of 1.6 g of **36** and 4.1 g (12.4 mmol) of azidotri-*n*-butylstannane was heated to 90 °C for 3 days and then treated with 50 mL of 6 N hydrochloric acid, and the resulting mixture was heated at 100 °C overnight. The reaction mixture was cooled and extracted twice with dichloromethane and once with ether, and then the aqueous phase was concentrated in vacuo. Cation exchange chromatography of the residue afforded 0.4 g (28%) of **37**.

Ethyl and Methyl (3*SR*,4a*RS*,6*RS*,8a*RS*)-6-(4-Cyanobut-1-yl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (38). To a −78 °C solution of 0.9 mL (1.0 g, 12.6 mmol) of dimethyl sulfoxide in 10 mL of dichloromethane was added 0.5 mL (0.8 g, 6.1 mmol) of oxalyl chloride, and then after 2 min, a solution of 1.7 g of **35** in 6 mL of dichloromethane was added. After an additional 15 min, the reaction mixture was treated with 3.5 mL (2.6 g, 25.2 mmol) of triethylamine and the resulting mixture allowed to warm to room temperature over 45 min. Workup (10% sodium bisulfite/3× ether) afforded 1.7 g (99%) of the corresponding aldehyde as an oil. To a 0 °C suspension of 0.3 g (7.1 mmol) of sodium hydride in 7.5 mL of THF was added 1.3 g (7.1 mmol) of diethyl (cyanomethyl)phosphonate, and after 30 min this mixture was treated with a solution of 1.7 g of the above aldehyde in 5 mL of THF, and the resulting mixture was allowed to warm to room temperature. After 30 min, workup (water/3× ether) afforded an oil. This was dissolved in 50 mL of methanol and added to 2.5 g (101.0 mol) of magnesium; after 10 min, a rapid hydrogen efflux ensued, requiring water-bath cooling as necessary. After 4 h, workup (1 N HCl/3× ether) and chromatography (100 g of silica gel, 35% ethyl acetate/hexane) afforded 0.6 g (34%) of the ethyl ester **38a** and 0.4 g (24%) of the methyl ester **38b**, which were combined for use in the next step.

(3*SR*,4a*RS*,6*RS*,8a*RS*)-6-((1*H*-Tetrazol-5-yl)but-1-yl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic Acid (39). A mixture of 1.0 g (2.8 mmol) of **38ab** and 1.8 g of azidotri-*n*-butylstannane was heated to 80 °C for 3 days, treated with 60 mL of 6 N hydrochloric acid, and heated to 100 °C overnight. The mixture was cooled to room temperature and extracted six times with ether and the aqueous phase concentrated in vacuo. Cation exchange chromatography afforded a solid, which was suspended in 1/1 water/acetone and filtered, washing with acetone and ether, and then dried in vacuo at 60 °C to yield 0.7 g (86%) of **39**.

Ethyl (3*SR*,4a*SR*,6*SR*,8a*RS*)-6-Hydroxy-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (41) and Ethyl (3*SR*,4a*SR*,6*RS*,8a*RS*)-6-Hydroxy-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (42). To a 0 °C solution of 10.0 g (35.3 mmol) of × in 100 mL of ethanol was added 1.3 g (35.3 mmol) of sodium borohydride. After 5 min at 0 °C and 30 min at room temperature, the mixture was concentrated in vacuo. Workup (water/2× 2/1 ether/dichloromethane) and chromatography (450 g of silica gel, step gradient of 35% ethyl acetate/hexane (3000 mL), then 50% ethyl acetate/hexane (3500 mL), and then 60% ethyl acetate/hexane (2500 mL)) gave 6.7 g (67%) of **41** and 3.1 g (31%) of **42**.

Ethyl (3*SR*,4a*SR*,6*SR*,8a*RS*)-6-((Methoxyethoxy)methoxy)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (43a). A solution of 1.6 g (5.8 mmol) of **41**, 1.3 mL (1.4 g, 11.5 mmol) of (methoxyethoxy)-methoxy chloride (MEMCl), and 2.0 mL (1.5 g, 11.5 mmol) of diisopropyl-*N*-ethylamine in 18 mL of dichloromethane was stirred 4 h at room temperature. Workup (saturated sodium bicarbonate/4× dichloromethane) and chromatography (115 g of silica gel, 40% ethyl acetate/hexane) afforded 1.5 g (68%) of **43a**.

Ethyl (3*SR*,4a*SR*,6*SR*,8a*RS*)-6-((Cyanomethyl)oxy)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (43b). To a 0 °C solution of 1.5 g (3.9 mmol) of **43a** and 2.3 mL (1.7 g, 17.5 mmol) of cyanotrimethylsilane in 12 mL of dichloromethane was added 1.4 mL (1.7 g, 11.7 mmol) of boron trifluoride etherate. The mixture was stirred 30 min while warming to room temperature and then carefully quenched with 50 mL of 10% potassium carbonate. Workup (3× 1/1 chloroform/ethyl acetate) and chromatography (75 g of silica gel, 35% ethyl acetate/hexane) gave 1.1 g (85%) of **43b**.

(3*SR*,4a*SR*,6*SR*,8a*RS*)-6-((1H-tetrazol-5-ylmethyl)oxy)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic Acid (44). A 1.1 g (3.3 mmol) portion of **43b** and 2.2 g (6.6 mmol) of azidotri-*n*-butylstannane were heated to 80 °C for 3 days, then 25 mL of 6 N hydrochloric acid was added, and the mixture was heated to reflux overnight. The mixture was cooled to room temperature and extracted six times with ether, and then the aqueous layer was concentrated in vacuo. Cation exchange chromatography gave a solid that was suspended in acetone, refluxed for 1 h, then filtered, washed with acetone and ether, and dried in vacuo at 60 °C to afford 0.6 g (68%) of **44**.

Ethyl (3*SR*,4a*SR*,6*RS*,8a*RS*)-6-((methoxyethoxy)methoxy)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (45a). As for **43a**, 1.3 g (4.6 mmol) of **42**, 1.3 mL (1.4 g, 11.5 mmol) of MEMCl, and 2.0 mL (1.5 g, 11.5 mmol) of diisopropyl-*N*-ethylamine in 14 mL of dichloromethane afforded 1.4 g (80%) of **45a**.

Ethyl (3*SR*,4a*SR*,6*RS*,8a*RS*)-6-((Cyanomethyl)oxy)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (45b). As for **43b**, 1.4 g (3.7 mmol) of **45a**, 2.2 mL (1.6 g, 16.5 mmol) of cyanotrimethylsilane, and 1.4 mL (1.6 g, 11.0 mmol) of borontrifluoride etherate in 11 mL of dichloromethane gave 0.8 g (66%) of **45b**.

(3*SR*,4a*SR*,6*RS*,8a*RS*)-6-((1*H*-tetrazol-5-ylmethyl)oxy)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic Acid (46). As for **44**, 0.7 g (2.2 mmol) of **45b** and 1.5 g

(4.4 mmol) of azidotri-*n*-butylstannane afforded 0.5 g (82%) of **46**.

Ethyl (3*SR*,4a*RS*,6*SR*,8a*RS*)-6-(*N*-(cyanomethyl)-*N*-(*tert*-butoxycarbonyl)amino)-2-(methoxycarbonyl)-1,2,3,4,4a,-5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (47). A solution of 1.0 g (3.5 mmol) of **40**, 3.3 g (35.3 mmol) of aminoacetonitrile hydrochloride, and 1.0 g of powered 4 Å molecular sieves in 12 mL of ethanol was stirred 20 min at room temperature, and then the mixture was treated with 0.2 g (3.5 mmol) of sodium cyanoborohydride and stirred overnight at room temperature. The reaction mixture was filtered through diatomaceous earth and then concentrated *in vacuo*. Workup (15% sodium hydroxide/2× CH_2Cl_2; 2× ether) afforded **49**, which was dissolved in 10 mL of ethyl acetate and treated at room temperature with 1.2 mL (1.2 g, 7.1 mmol) of *N*,*N*-diisopropylethylamine and 1.6 mL (1.5 g, 7.1 mmol) of di-*tert*-butyl dicarbonate. After 5 h, workup (water/3× ethyl acetate) and chromatography (120 g silica gel, 50% ethyl acetate/hexane) afforded 0.9 g (62%) of **47**.

(3*SR*,4a*RS*,6*SR*,8a*RS*)-6-(*N*-(1*H*-Tetrazol-5-ylmethyl)-amino)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic Acid (48). A solution of 0.9 g (2.0 mmol) of **47** and 2.4 g (7.2 mmol) of azidotri-*n*-butylstannane was heated to 80 °C for 4 days, then 25 mL of 6 N hydrochloric acid was added, and the mixture was heated to reflux overnight. The reaction mixture was cooled, extracted twice with dichloromethane and once with ether, and then the aqueous phase was concentrated in vacuo. Cation exchange chromatography afforded a foam which crystallized upon addition of 7 mL of water. The resultant solid was isolated as above to afford 0.3 g (47%) of **48**.

Ethyl (3*SR*,4a*RS*,6*SR*,8a*RS*)-6-(*N*-(Cyanomethyl)amino)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (49). A solution of 2.5 g (28.2 mmol) of **40**, 25.2 g (276.0 mmol) of aminoacetonitrile hydrochloride and 8.0 g of powered 4 Å molecular sieves in 100 mL of ethanol was stirred for 20 min at room temperature, and then the mixture was treated with 1.7 g (28.2 mmol) of sodium cyanoborohydride and stirred overnight at room temperature. The reaction mixture was filtered through diatomaceous earth and then concentrated in vacuo. Workup (15% sodium hydroxide/2× CH_2Cl_2; 2× ether) and chromatography (600 g of silica gel; 50/49/1 ethyl acetate/hexane/methanol) (50/49/1) afforded 5.4 g (59%) of **49**.

Ethyl (3*SR*,4a*RS*,6*SR*,8a*RS*)-6-(*N*-(Cyanomethyl)-*N*-methylamino)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (50). To a solution of 2.5 g (7.7 mmol) of **49** and 2.7 g (19.2 mmol) of potassium carbonate in 250 mL of acetonitrile was added dropwise 1.1 g (7.7 mmol) of iodomethane in 10 mL of acetonitrile. The mixture was stirred overnight at room temperature, then treated with 1.1 g (7.7 mmol) of iodomethane, and heated to 55 °C overnight. The mixture was cooled and concentrated in vacuo. Workup (water/2× ethyl acetate) and chromatography (210 g of silica gel, 40% ethyl acetate/hexane) gave 0.6 g (23%) of **50**.

(3*SR*,4a*RS*,6*SR*,8a*RS*)-6-(*N*-(1*H*-tetrazol-5-ylmethyl)-*N*-methylamino)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic Acid (52). As for **48**, 0.5 g (1.5 mmol) of **50** and 11 mL of azidotri-*n*-butylstannane gave 0.4 g (78%) of **52**.

Ethyl (3*SR*,4a*RS*,6*SR*,8a*RS*)-6-(*N*-(Cyanomethyl)-*N*-formylamino)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (51). A solution of 1.5 g (4.6 mmol) of **49** in 100 mL of THF was treated with 1.3 g (14.6 mmol) of formic acetic anhydride, and after 1 h at room temperature, the mixture was concentrated in vacuo. Workup (water/ethyl acetate) and chromatography (200 g of silica gel; 2/23/75 methanol/hexane/ethyl acetate) afforded 1.0 g (62%) of **51**.

(3*SR*,4a*RS*,6*SR*,8a*RS*)-6-(*N*-(1*H*-Tetrazol-5-ylmethyl)-*N*-formylamino)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic Acid (53). A mixture of 1.0 g (2.8 mmol) of **51** and 13 mL of azidotri-*n*-butylstannane was heated to 80 °C for 7 days, then cooled to room temperature, diluted with 100 mL of ether, treated with HCl(g), and concentrated in vacuo. The mixture was dissolved in 100 mL of acetonitrile and extracted five times with 100 mL each of hexane, and then the acetonitrile phase was concentrated in vacuo. The residue was dissolved in 50 mL of ethanol, treated with 2.8 mL (2.8 mmol) of 1 N sodium hydroxide, and then stirred overnight at room temperature. The mixture was concentrated in vacuo, and ^{1}H NMR indicated the presence of ester, so the residue was dissolved in 20 mL of ethanol and stirred overnight at room temperature with 5.5 mL (5.5 mmol) of 1 N sodium hydroxide. The mixture was adjusted to pH 4 with 3 N hydrochloric acid and then extracted four times with ethyl acetate. The aqueous layer was concentrated in vacuo to afford an oil. This was dissolved in 10 mL of chloroform, treated with 1.1 mL (1.5 g, 7.5 mmol) of iodotrimethylsilane, and heated to reflux for 2 h. The mixture was dissolved in water and extracted four times with ether, and then the aqueous layer was concentrated in vacuo. Cation exchange chromatography afforded 0.1 g (12%) of **53**.

Ethyl Δ^5- and Δ^6-(3*SR*,4a*RS*,8a*RS*)-6-(((trifluoromethyl)sulfonyl)oxy)-2-(methoxycarbonyl)octahydroisoquinoline-3-carboxylate (54). To a −78 °C solution of 38.8 mL of lithium bis(trimethylsilyl)amide (38.8 mmol, 1 M in THF) in 100 mL of THF was added 10.0 g (35.3 mmol) of **40** in 10 mL of THF. After 1 h, a solution of 12.6 g (35.5 mmol) of *N*-phenyltrifluoromethanesulfonimide in 10 mL of THF was added, and then the mixture was warmed to room temperature and stirred for 3 h. Workup (10% sodium bisulfate/3× ether) and preparative HPLC (hexane to 35% ethyl acetate/hexane) gave 10.4 g (71%) of **54**.

Ethyl Δ^5- and Δ^6-(3*SR*,4a*RS*,8a*RS*)-6-(2-cyano-1-methylethenyl)-2-(methoxycarbonyl)octahydroisoquinoline-3-carboxylate (56a). A solution of 2.5 g (6.0 mmol) of **54**, 1.2 mL (1.0 g, 15.0 mmol) of crotononitrile (**55a**), 2.9 mL (2.1 g, 21 mmol) of triethylamine, and 0.1 g (0.1 mmol) of bis(triphenylphosphine)palladium(II) chloride in 21 mL of degassed dimethylformamide was heated to 75 °C overnight, then filtered, treated with another 0.1 g (0.1 mmol) of bis(triphenylphosphine)palladium(II) chloride, heated again at 75 °C overnight, and then cooled to room temperature. Workup (water/3× 1/1 ether/hexane) and chromatography (200 g of silica gel; 25% ethyl acetate/hexane) afforded 1.2 g (59%) of **56a**.

Ethyl (3*SR*,4a*RS*,6*RS*,8a*RS*)-6-(2-Cyano-1-methylethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (57a). A solution of 1.1 g (3.3 mmol) of **56a** and 0.5 g of 5% Pd/C in 80 mL of ethanol was hydrogenated at room temperature and 60 psi for 6 h and then filtered through diatomaceous earth, and the filtrate was concentrated in vacuo. Chromatography (100 g silica gel, linear gradient of 25% ethyl acetate/hexane to 30% ethyl acetate/hexane) gave 0.7 g (59%) of **57a** (mixture of diastereomers at the methyl-substituted carbon).

(3*SR*,4a*RS*,6*RS*,8a*RS*)-6-(2-(1*H*-Tetrazol-5-yl)-1-methylethyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic Acid (58). A 0.6 g (1.8 mmol) portion of **57a** and 1.2 g (3.6 mmol) of azidotri-*n*-butylstannane were heated 80 °C for 4 days, then treated with 5 mL of 6 N hydrochloric acid, heated to reflux overnight, and cooled to room temperature. The mixture was extracted three times with ether, and the aqueous phase was concentrated in vacuo. Cation exchange chromatography gave 0.4 g (71%) of **58**.

Ethyl Δ^5- and Δ^6-(3*SR*,4a*RS*,8a*RS*)-6-(2-Cyano-1-phenylethenyl)-2-(methoxycarbonyl)octahydroisoquinoline-3-carboxylate (56b). As for **56a**, 2.5 g (6.0 mmol) of **54**, 1.9 mL (1.9 g, 15.0 mmol) of cinnamonitrile (**55b**), 2.9 mL (2.1 g, 21.0 mmol) of triethylamine, and 0.1 g (0.1 mmol) of bis(triphenylphosphine)palladium(II) chloride in 21 mL of degassed dimethylformamide gave 1.5 g (61%) of **56b**.

Ethyl (3*SR*,4a*RS*,6*RS*,8a*RS*)-6-(2-Cyano-1-phenylethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (X). As for **57a**, 1.4 g (3.4 mmol) of **56b** and 0.3 g of 5% Pd/C in 85 mL of ethanol was hydrogenated to afford 0.6 g (45%) of **57b** (mixture of diastereomers at the phenyl-substituted carbon).

(3*SR*,4a*RS*,6*RS*,8a*RS*)-6-(2-(1*H*-Tetrazol-5-yl)-1-phenylethyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic Acid (59). As for **58**, 0.6 g (1.5 mmol) of **57b** and 1.0 g (3.0 mmol) of azidotri-*n*-butylstannane gave 0.4 g (72%) of **59**.

Ethyl Δ^5- and Δ^6-(3*SR*,4a*RS*,8a*RS*)-6-(2-Cyano-2-methylethenyl)-2-(methoxycarbonyl)octahydroisoquinoline-3-carboxylate (56c). As for **56a**, 8.0 g (20.0 mmol) of **54**, 4.1 mL (3.3 g, 50.0 mmol) of α-methyl acrylonitrile (**55c**), 9.8 mL (7.1 g, 70.0 mmol) of triethylamine, and 0.3 g (0.4 mmol) of bis(triphenylphosphine)palladium(II) chloride in 60 mL of degassed dimethylformamide gave 6.3 g (94%) of **56c**.

Ethyl (3*SR*,4a*RS*,6*RS*,8a*RS*)-6-(2-(1*H*-tetrazol-5-yl)-2-methylethyl)-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (57c). A solution of 6.2 g (18.6 mmol) of **56c** and 12.4 g (37.3 mmol) of azidotri-*n*-butylstannane was heated to 80 °C for 3 days, then cooled, dissolved in ether, treated with HCl(g), and concentrated in vacuo. The residue was dissolved in acetonitrile, extracted six times with hexane, and then concentrated in vacuo. Chromatography (350 g of silica gel; 2% acetic acid/50% ethyl acetate/48% hexane) afforded 6.2 g (88%) of the corresponding tetrazole diene. This was hydrogenated as for **57a**, with 1.5 g of 5% Pd/C in 190 mL of ethanol to afford 3.5 g (56%) of **57c** (mixture of diastereomers at the methyl-substituted carbon).

(3*SR*,4a*RS*,6*RS*,8a*RS*)-6-(2-(1*H*-Tetrazol-5-yl)-2-methylethyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic Acid (60). A 2.8 g (7.4 mmol) portion of **57c** was heated to 100 °C overnight with 50 mL of 6 N hydrochloric acid, then cooled, and concentrated in vacuo. Cation exchange chromatography gave a solid that was refluxed in acetone for 1 h, then filtered, washed with acetone and ether, and dried in vacuo at 60 °C to afford 1.7 g (76%) of **60**.

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JM950912P