Epimeric *cis*-Decahydroquinoline-5-carboxylic Acids:[1] Effects on γ-Aminobutyric Acid Uptake and Receptor Binding in Vitro

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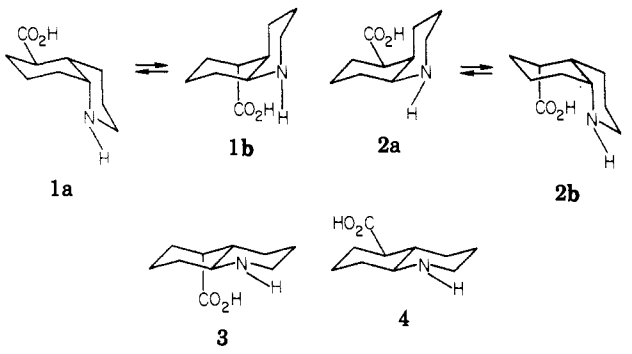
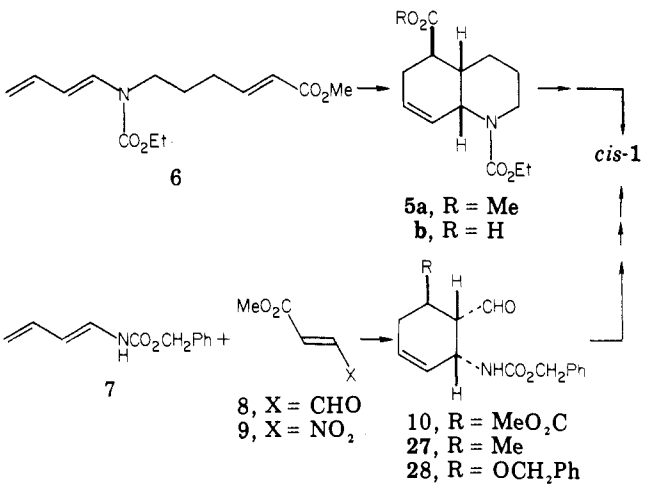
The syntheses for two *cis*-decahydroquinoline-5-carboxylic acid epimers (1 and 2) which contain the $=N(C)_3CO_2H$ (γ-aminobutyric acid; GABA) moiety are described. Both intra- and intermolecular [4 + 2] cycloaddition reactions were employed for the construction of key intermediates. ^1H NMR studies provided evidence for the preferred solution conformations of the two diastereomers. Pharmacological studies revealed that these isomers have little affinity for GABA receptors in vitro relative to GABA agonists. However, expected but weak stereoselective activity was observed when these analogues were assessed for their ability to inhibit high-affinity [^3H]GABA uptake into rat brain synaptosomes. These data are discussed in light of structure–activity studies of other neurotransmitter analogues, and a preliminary hypothesis based upon conformational analysis is presented to explain the results.

The four diastereomers (1–4) of decahydroquinoline-5-

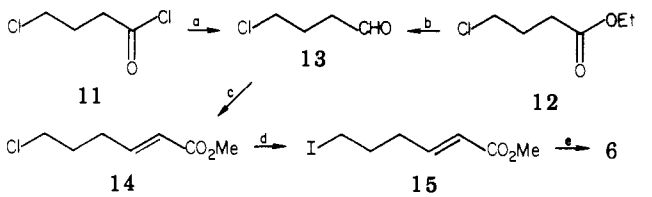


carboxylic acid are zwitterionic species[2] which contain a γ-aminobutyric acid (GABA) moiety [$=N(C)_3CO_2H$]. While it is possible that these stereoisomers may serve as probes to study GABA-mediated neurotransmission, it would not be expected that such structures should have the intrinsic activity of a GABA agonist.[3-6] *cis*-Decahydroquinoline epimers 1 and 2 are conformationally flexible, whereas trans isomers 3 and 4 are rigidly fixed. In the present report the syntheses for *cis*-1 and -2 are described, and evidence for their preferred solution conformations as structures **1a** and **2a** is presented. Additionally, preliminary biochemical data are discussed concerning the effect of these compounds on [^3H]GABA receptor binding[7] and high-affinity [^3H]GABA uptake in rat brain tissue.[8] A preliminary hypothesis is presented to explain the biological properties of 1 and 2, though confirmation must await further studies employing 3 and 4 in these biological systems. Furthermore, a parallelism in stereostructure–activity relationships with small (cyclopropane) vs. larger ring systems in cholinergic vs. GABAergic systems is discussed. This expected correlation and the possibility that indirectly acting anticonvulsants may be obtained through use of large lipophilic moieties pro-

Scheme I



Scheme II[a]



[a] a = H_2/Pd·$BaSO_4$, toluene; b = DIBAL, toluene (−60 °C); c = methyl (triphenylphosphoranylidene)acetate, benzene; d = NaI, DMF; e = CH_2=CHCH=CHNHCO$_2$Et (16), NaH, DMF.

(1) A preliminary account of the chemistry of this series has been presented. See K. Tomita and D. T. Witiak, in "Abstracts of Papers", 179th National Meeting of the American Chemical Society, Houston, TX, Mar 23–28, 1980, American Chemical Society, Washington, DC, 1980, Abstr ORGN 26.

(2) Compounds were studied as their hydrochloride salts. Cyclic compounds are named according to Chemical Abstracts' convention wherein the substituent at the lowest carbon number (i.e., 4a in bicyclic compounds) is arbitrarily assigned the α notation and all other substituents are defined (α or β) relative to this position.

(3) G. A. R. Johnston, R. D. Allan, S. M. E. Kennedy, and B. Twitchin in "Gaba-Neurotransmitters: Pharmacochemical, Biochemical and Pharmacological Aspects", P. Krogsgaard-Larsen, J. Scheel-Krüger, and H. Kofod, Ed., Academic Press, New York, 1979, p 149.

(4) P. Krogsgaard-Larsen and A. V. Christensen, *Annu. Rep. Med. Chem.*, 15, 41 (1980).

(5) P. Krogsgaard-Larsen, T. Honoré, and K. Thyssen, in ref 3, p 201.

(6) J. P. O'Donnell, D. A. Johnson, and A. J. Azzaro, *J. Med. Chem.*, 23, 1142 (1980).

(7) S. J. Enna and S. H. Snyder, *Mol. Pharmacol.*, 13, 442 (1977).

(8) J. P. Bennett, W. J. Logan, and S. H. Snyder, *J. Neurochem.*, 21, 1533 (1973).

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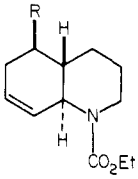
vided the impetus for our effort in this area.

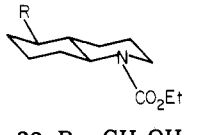
Synthetic Chemistry. Synthesis of target analogue *cis*-1, which may be epimerized to *cis*-2, was carried out using both [4 + 2] intramolecular and intermolecular cycloadditions (Scheme I). Intramolecular reaction affording desired intermediate **5** was modeled after the Oppolzer-Fröstl[9] synthesis wherein the vinylic carbomethoxy group in **6** was replaced by H or Me. Intermolecular reaction of dienamide **7** with dienophile **8** initially affording intermediate **10** and ultimately *cis*-1 was based on Danishefsky and Hershenson's[10] synthesis of isogabaculine, which employed the nitrodienophile **9**. Syntheses for pumiliotoxin-C[11a,b] and (±)-perhydrogephyrotoxin[11c] have been developed by Overman et al., wherein the approach is similar to the preparation of *cis*-1 using the intermolecular Diels–Alder reaction but differs in detail.

Dienamide **6** was synthesized from **16**[15] and methyl 6-iodo-2(*E*)-hexenoate (**15**) in 37% yield[12] using NaH in DMF at room temperature (Scheme II). Hexenoate **14**, which served as precursor to **15**, was prepared using known methodology[13,14] from either 4-chlorobutyryl chloride (**11**) or ethyl 4-chlorobutyrate (**12**) via intermediate chloroaldehyde **13**. Ylide reaction with **13** afforded hexenoate **14** in 47% yield. Reaction with NaI in DMF yielded iodo ester **15** in 78% yield.

Conversion of **6** to *cis*-octahydroquinoline **5a** in approximately 60% yield was carried out by heating (toluene; 200–210 °C) in a sealed tube[9] for 14 h and was accompanied by the formation of a trace amount of *trans*-**17** isomer.



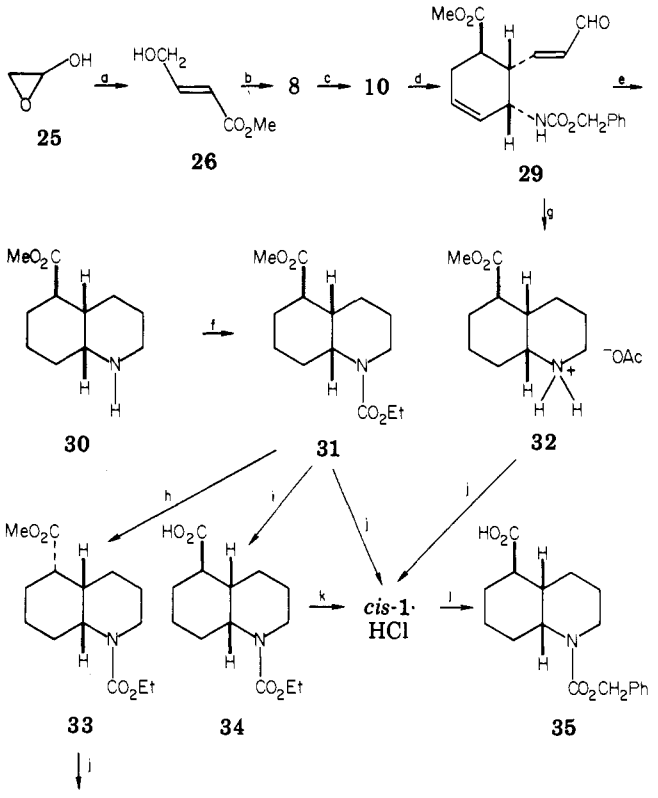
17, R = CO_2Me
18, R = CH_2OH
19, R = $CH_2O_2C[3,5\text{-}(NO_2)_2]Ph$
20, R = CHO
21, R = CO_2H



22, R = CH_2OH
23, R = CHO
24, R = H

Separation of minor adduct *trans*-**17** from *cis*-**5a** was difficult and could only be accomplished by reduction to **18** followed by formation of the 3,5-dinitrobenzoate ester **19**. Pure **18**, derived from hydrolysis of **19**, was converted to **20** with pyridinium chlorochromate[16] and subsequently to **21** using AgO and NaCN.[17] Acid **21**, upon reaction with diazomethane, served as a source of pure *trans*-**17**. Hydrogenation of pure *trans*-**18** afforded **22** whose ^1H NMR spectrum was characteristically similar to the spectrum of authentic *trans*-decahydroquinoline **24**.[18,19] Furthermore,

Scheme III[a]



cis-**2**·HCl

[a] a = methyl (triphenylphosphoranylidene)acetate, $CHCl_3$; b = pyridinium chlorochromate, CH_2Cl_2; c = compound **7**, toluene, Δ; d = formylmethylenetriphenylphosphorane, toluene; e = H_2, 10% Pd/C, MeOH; f = ethyl chloroformate, K_2CO_3; g = H_2, 10% Pd/C, MeOH, HOAc; h = LDA, THF, −70 °C; i = NaOH, H_2O; j = concentrated HCl, Δ; k = concentrated HCl; l = benzyl chloroformate, K_2CO_3.

22 was converted to **24** via oxidation (pyridinium chlorochromate)[16] to **23**, followed by decarbonylation using tris(triphenylphosphine)rhodium(I) chloride.[20]

Alternatively, *cis*-1 was prepared by intermolecular [4 + 2] cycloaddition (Scheme I). Dienamide **7**[15] underwent reaction with methyl 4-oxo-2(*E*)-butenoate (**8**), affording **10** in approximately 65% isolated yield. Aldehyde **8** was prepared by reaction of glycoaldehyde (**25**) with methyl (triphenylphosphoranylidene)acetate, followed by pyridinium chlorochromate[16] oxidation of intermediate methyl 4-hydroxycrotonate (**26**)[23] (Scheme III). Coupound **8** also

(9) W. Oppolzer and W. Fröstl, *Helv. Chim. Acta*, **58**, 590 (1975).
(10) S. Danishefsky and F. M. Hershenson, *J. Org. Chem.*, 44, 1180 (1979).
(11) (a) L. E. Overman and P. J. Jessup, *J. Am. Chem. Soc.*, **100**, 5179 (1978); (b) L. E. Overman and P. J. Jessup, *Tetrahedron Lett.*, 1253 (1977); (c) L. E. Overman and C. Fukaya, *J. Am. Chem. Soc.*, **102**, 1454 (1980).
(12) Reduced yields were attributed to concurrent formation of substantial quantities of methyl β-cyclopropylacrylate.
(13) R. B. Loftfield, *J. Am. Chem. Soc.*, **73**, 1365 (1951).
(14) L. I. Zakharkin and I. M. Khorlina, *Tetrahedron Lett.*, 619 (1962).
(15) L. E. Overman, G. F. Taylor, C. B. Petty, and P. J. Jessup, *J. Org. Chem.*, **43**, 2164 (1978).
(16) E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 2647 (1975).
(17) E. J. Corey, N. W. Gilman, and B. E. Ganem, *J. Am. Chem. Soc.*, **90**, 5616 (1968).
(18) H. Booth and A. H. Bostock, *J. Chem. Soc., Perkin Trans. 2*, 615 (1972).
(19) The 8a proton resonance signal of **22** was found at δ 3.20 in the form of a triplet ($J \approx 12$ Hz) of doublets ($J \approx 4$ Hz). Likewise, a similar 8a proton resonance signal pattern for **24** was observed at δ 3.08, whereas the 8a-proton resonance signal pattern for epimer **16** was found under the methylene proton resonance signal of the ester function as an unresolved doublet ($J \approx 11$ Hz) at approximately δ 4.15. The proton resonance signal for the 5-H proton bonded to the carbon substituted with R in **22** and **23** was masked under the alkyl proton resonance envelope and, thus, the stereochemistry for R (*cis* to the 4a axial proton) was tentatively assigned based on the cyclization mechanism.
(20) J. Tsuji and K. Ohno, *Tetrahedron Lett.*, 3969 (1965).
(21) W. R. Roush, A. I. Ko, and H. R. Gillis, *J. Org. Chem.*, **45**, 4264 (1980).
(22) W. Oppolzer, *Angew. Chem., Int. Ed. Engl.*, **16**, 10 (1977).
(23) R. Rambaud, *Bull. Soc. Chim. Fr.*, 1, 1317 (1934).

Table I. Effect of *cis*-1·HCl and *cis*-2·HCl on [^{3}H]GABA Receptor Binding to Rat Brain Membranes[a]

compd	concn, μM	% displacement of specifically bound [^{3}H]GABA
GABA	0.01	48 ± 5
muscimol	0.01	86 ± 3
cis-1·HCl	100	<5
cis-2·HCl	100	17 ± 3

[a] Each value is the mean plus or minus the SEM of four to six separate determinations. The compounds were analyzed using a previously reported in vitro ligand binding assay for GABA receptors. Specifically (receptor) bound [^{3}H]GABA is defined as the amount of isotope displaced from the brain membrane preparation by a saturating (1 mM) concentration of unlabeled GABA.

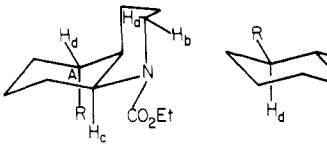
was prepared by the less expensive SeO_2 oxidation of methyl crotonate.[24] Reaction of **7** with dienophile **8** in refluxing toluene for 3 h afforded **10** in a yield similar to the one reported by Overman et al.[11a] for the preparation of **27** under sealed tube conditions. Intermediate **28** also had been prepared in refluxing toluene.[11c] Wittig reaction using **10** and formylmethylenetriphenylphosphorane[25] in toluene afforded **29** in 92% yield. Catalytic hydrogenation of **29** over Pd/C in MeOH afforded **30**. Reaction of crude **30** with ethyl chloroformate yielded **31** in 46% overall yield. Reaction of **31** at −70 °C in THF using LDA afforded a mixture of **31** and **33** in a ratio of approximately 1:2. Epimer **33** was separated as pure colorless crystals, which were hydrolyzed to *cis*-**2**·HCl in 72% yield. Alkaline hydrolysis of **31** afforded **34** in 83% yield. Acid-catalyzed hydrolysis yielded 66% of *cis*-**1**·HCl. Alternatively, hydrogenation of **29** over Pd/C in MeOH containing 1 equiv of HOAc afforded crystalline **32** in 66% yield, which also served as a source of *cis*-**1**·HCl.

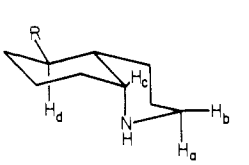
^{1}H NMR Spectroscopy, Characterization and Solution Conformations of Analogues. Cycloadduct **5a** was characterized by analysis of its ^{1}H NMR spectrum and comparison with spectra of reduced analogues **31**, **34**, and *cis*-**1**·HCl. Using standard synthetic reactions, **31** was converted to **38** identical in all respects with the compound prepared from *cis*-decahydroquinoline **39**. Compound **5a** showed the expected vinyl proton resonance signals at δ 5.36 and 5.75 with $J \approx 11$ Hz. The tentatively assigned allylic methine proton resonance signal at δ 4.77 exhibited a half-height width ≈ 12 Hz. Hydrogenation of **5a** over 10% Pd/C afforded decahydroquinoline **31** in 92% yield. The ^{1}H NMR spectrum for **31** was characteristic for the *N*-carbethoxy cis-bicyclic system (i.e., **38**).[18] Resonance signals and splitting patterns for H_a, H_b, and H_c in **31** were virtually identical with those found in **38**. Assuming a preferred equatorial conformation (**31**–**38**) of $EtO_2CN=$ to ring A,[18] the broad singlet at δ 2.50 for **31** with half-height width = 7.0 Hz could readily be assigned to H_d.[26] Acid **34** exhibited a ^{1}H NMR spectrum closely related to ester **31** and could be obtained free of epimer by selective crystallization. Reaction of **34** with diazomethane yielded **31**. Spectral data from benzyl carbamate derivative **35** further served to support structural assignments.

The ^{1}H NMR spectrum of *cis*-**1**·HCl, obtained by acid-catalyzed hydrolysis of **34**, exhibited characteristic proton resonance signals for H_{a-c} similar to those observed in an authentic sample of **39**. Analogues such as *cis*-**1**·HCl and **39** have been shown to exist mainly in that conformation wherein the NH function is axial to ring A[18] (**1a**). In this case, H_d is axial and strongly couples to two adjacent axial protons. Thus, the resonance signal appears as the expected triplet ($J \approx 10$ Hz) of doublets ($J \approx 4$ Hz) at δ 2.56.

Compound **38**, derived from authentic **39** by reaction with ethyl chloroformate, was identical in all respects with **38** prepared from **31** as follows: Reduction (DIBAL) of **31** afforded hydroxymethyl derivative **36** in 85% yield. Oxidation (pyridinium chlorochromate),[16] followed by decarbonylation (Wilkinson's catalyst),[20] afforded **37** (76% yield) and **38** (54% yield), respectively.

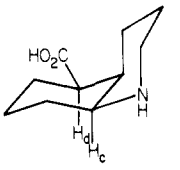
For *cis*-**2**·HCl, the H_d resonance signal appeared as a doublet ($J \approx 13$ Hz) of triplets ($J \approx 4$ Hz) at δ 2.5, but the multiplet is qualitatively different than the H_d resonance signal for *cis*-**1**·HCl, since H_d is coupled to two equatorial and one axial proton rather than two axial and one equatorial proton as for *cis*-**1**·HCl. Clearly, **2b** has no opportunity for 1,2-diaxial coupling with H_d. The H_c resonance signal at δ 3.5 in *cis*-**2**·HCl is also a doublet ($J \approx 12$ Hz) of triplets ($J \approx 4$ Hz) having a qualitatively different multiplet than *cis*-**1**·HCl owing to diaxial rather than diequatorial coupling. Thus, the preferred solution conformation for *cis*-**2**·HCl is **2a**.





31, R = CO_2Me
34, R = CO_2H
36, R = CH_2OH
37, R = CHO
38, R = H

cis-**1**, R = CO_2H
39, R = H



cis-**2**

Pharmacological Results in Vitro. The effects of the HCl salts of *cis*-**1** and *cis*-**2** on [^{3}H]GABA receptor binding to rat brain membranes are compared to GABA and muscimol in Table I. These stereoisomers are virtually inactive relative to the known GABA receptor agonists. However, some stereoselective activity was observed when these analogues were assessed for their ability to inhibit high-affinity [^{3}H]GABA uptake into rat brain synaptosomes (Table II). Whereas *cis*-**1** is inactive, *cis*-**2** inhibited [^{3}H]GABA uptake by approximately 20% at a concentration of 100 μM, making it over 10 times less potent than

Table II. Effect of *cis*-1·HCl and *cis*-2·HCl on High-Affinity [^{3}H]GABA Uptake into Rat Brain Synaptosomes[a]

compd	concn, μM	% inhibn of high-affinity [^{3}H]GABA uptake
GABA	10	61 ± 5
nipecotic acid	10	57 ± 5
cis-1·HCl	100	<1
cis-2·HCl	100	20 ± 4

[a] Each value is the mean plus or minus the SEM of four to six separate determinations. High-affinity transport was analyzed using a previously published procedure.[8]

(24) F. Bohlmann and E. Inhoffen, *Chem. Ber.*, 89, 1276 (1956).
(25) S. Trippett and D. M. Walker, *J. Chem. Soc.*, 1266 (1961).
(26) When the proton (H_d) at position 5 is axial its proton resonance signal appears as a triplet ($J \approx 3$ Hz) of doublets ($J \approx 12$ Hz) centered at δ 2.6. This epimer (at position 5) of **31** was prepared by LDA-catalyzed isomerization of **5** followed by hydrogenation over Pd/C.

GABA and nipecotic acid in this regard.

Discussion

Introduction of six lipophilic methylene groups into the GABA pharmacophore to afforded stereoisomeric decahydroquinoline zwitterions has rendered *cis*-**1** inactive in vitro and epimer *cis*-**2** a weak inhibitor of GABA uptake. Neither *cis*-**1** nor **2** have appreciable affinity for GABA receptors in rat brain membranes. Smissman et al.[27] similarly observed that lipophilic *trans*-decalin analogues incorporating the acetylcholine moiety decreased muscarinic activity, with the 2,3-diaxial isomer being most potent, but 100 times less active than acetylcholine as an agonist on the guinea pig ileum. May and Triggle[28] have suggested that the markedly reduced activity for the trans-decalin analogues may not be due to a "failure to reproduce the geometry of receptor-bound acetylcholine, but to the incorporation of additional potential binding groups, specifically the large hydrocarbon skeleton..." The high muscarinic potency of the *trans*-cyclopropane analogue of acetylcholine supports this proposal.[31] In the GABA series, *trans*-2-(aminomethyl)cyclobutanecarboxylic acid was approximately 15 000 times less potent than GABA for rat brain membrane receptors.[6] Insertion of CH_3 groups into GABA or construction of cyclopentane stereoisomers also markedly reduced the relative affinity of these agents for sodium-independent receptor binding sites,[32,33] whereas the *trans*-(aminomethyl)cyclopropane analogue closely approximated GABA in these assays.[34]

In addition to altering potency, structural modification may markedly alter the mechanism of action of a compound. *cis*-**2**·HCl blocks GABA uptake and it is conceivable that it may also cause a release of GABA from storage sites as certain cholinomimetic analogues release acetylcholine.[28,35] Whereas it is possible that the stereoselective differences in uptake inhibition activity observed between **1** and **2** will provide clues for further drug development, stereoselectivity in itself does not imply biological specificity.[36] Clearly, further pharmacological testing will be necessary to establish this point. Since these species are zwitterionic, future plans are to study all four isomers by direct administration into the nucleus accumbens and substantia nigra (reticulata) using methodology described by Kuruvilla and Uretsky.[37,38]

Conformation **2a** may be preferred for GABA uptake inhibition activity. Whereas the solution conformation for *cis*-**1** favors **1a** in D_2O, interaction of the axial NH with a receptor protein function may favor conformation **1b**. Acylation of N in **39** favors such a conformational flip.[18] (Also, note the preferred conformations of **31**–**37** wherein N is substituted with functions larger than H.) Investigations using *trans*-**3** and *trans*-**4** having topographies of pharmacophores related to conformations **1b** and **2a**, respectively, are desired to further correlate stereostructure–activity relationships with inhibition of GABA uptake. Depending upon the results, resolved isomers and nonzwitterionic prodrugs will be investigated. Since nipecotic acid is over ten times more effective than *cis*-**2** when assessed for its ability to block neuronal GABA uptake, more lipophilic decahydroquinoline analogues incorporating the nipecotic acid structure are also of interest. However, even minor structural alterations of the potent uptake inhibitors, guvacine or *cis*-4-hydroxynipecotic acid, result in markedly decreased activities in this regard.[39]

Experimental Section

All melting points are uncorrected and were determined on a Thomas-Hoover capillary melting point apparatus. Infrared spectra were recorded on a Beckman IR 4230 instrument. ^1H NMR spectra were determined on a Bruker 90-MHz instrument. Mass spectra were determined using a DuPont 491 mass spectrometer. Analyses were obtained from Galbraith Laboratories Inc., Knoxville, TN.

4-Chlorobutyraldehyde (13) was prepared according to the reported procedure[13] using 28 g (0.20 mol) of 4-chlorobutyryl chloride (**11**), 2.7 g of Pd–$BaSO_4$ catalyst, and 0.2 mL of poison (prepared by refluxing 0.5 g of sulfur in 3 g of quinoline and then diluting with 300 mL of xylene) in 200 mL of toluene. Reaction workup afforded 8.0 g (38%) of **13**, bp 74–75 °C (35 mm) [lit.[13] bp 69–70 °C (35 mm)].

Alternatively, to a solution of ethyl 4-chlorobutyrate (**12**; Aldrich; 30 g, 0.20 mol) in toluene (300 mL) was added 130 mL of DIBAL (25% solution in toluene, 0.20 mol) at −60 °C. After 1 h, the mixture was decomposed with excess saturated ammonium chloride solution and poured into ice–HCl–H_2O and extracted with Et_2O. The Et_2O extract was washed with H_2O and dried (Na_2SO_4). Removal of the solvent gave 16 g (75%) of **13**: NMR (CCl_4) δ 2.07 (quint, 2 H, $J \approx 7$ Hz, 3-CH_2), 2.63 (t, 2 H, $J \approx 7$ Hz, 2-CH_2), 3.58 (t, 2 H, $J \approx 7$ Hz, $ClCH_2$), 9.45 (s, 1 H, CHO).

Methyl 6-Chloro-2(*E*)-hexenoate (14). To a solution of **13** (8.0 g, 0.075 mol) in benzene 200 mL) was added methyl (triphenylphosphoranylidene)acetate (Aldrich; 25.1 g, 0.075 mol). The mixture was stirred overnight at room temperature and concentrated under reduced pressure. The resulting crystals were filtered and washed with Et_2O. The filtrate and combined washings were concentrated under reduced pressure and the residue was distilled, yielding 5.7 g (47%) of **14**: bp 64–65 °C (1 mm); IR (neat) 1720, 1650 cm^{-1}; NMR (CCl_4) δ 1.90 (quint, 2 H, $J \approx 6$ Hz, 5-CH_2), 2.29 (q, d, 2 H, $J \approx 6$ and 1.5 Hz, 4-CH_2), 3.50, (t, 1 H, $J \approx 6$ Hz, 6-CH_2), 3.62 (s, 3 H, CO_2CH_3), 5.73 (d, t, 1 H, $J \approx 15$ and 1.5 Hz, 2-H), 6.72 (d, t, 1 H, $J \approx 15$ and 6 Hz, 3-H); MS (70 eV), m/e 162 (M^+).

Methyl 6-Iodo-2(*E*)-hexenoate (15). A solution of **14** (5.7 g, 0.035 mol) in DMF (100 mL) was added to NaI (20 g) and the mixture stirred at 70–80 °C overnight. The reaction mixture was poured into ice–H_2O and extracted with Et_2O. The Et_2O extract was washed with H_2O and dried (Na_2SO_4). The solvent was evaporated to yield 6.9 g (78%) of **15**, which was used immediately in the subsequent reaction owing to decomposition upon standing: NMR (CCl_4) δ 1.7–2.6 (m, 4 H, 4-CH_2, 5-CH_2), 3.20 (t, 2 H, $J \approx$ 6 Hz, 6-CH_2), 3.68 (s, 3 H, CO_2CH_3), 5.85 (d, t, 1 H, $J \approx 15$ and 1.5 Hz, 2-H), 6.73 (d, t, 1 H, $J \approx 15$ and 6 Hz, 3-H).

Methyl 6-[1,3-Butadienyl(ethoxycarbonyl)amino]-2(*E*)-hexenoate (6). To a suspension of NaH (50% dispersion in mineral oil; 0.50 g) in DMF (50 mL) was added 1(*E*)-[(ethoxycarbonyl)amino]-1,3-butadiene (**16**;[15] 1.41 g, 0.01 mol) at room temperature. After the mixture stirred for 0.5 h, **15** (2.54 g, 0.01 mol) was added dropwise at room temperature. Stirring was continued for an additional 1.5 h. The reaction mixture was poured into ice–H_2O and extracted with Et_2O. The Et_2O extract was washed with H_2O and dried (Na_2SO_4). After the solvent was removed, the residual oil was chromatographed on silica gel

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(column) by elution with EtOAc–benzene (1:1). After the solvent was removed, the yellow oil was distilled [oil bath temperature bp 150–160 °C (0.5 mm)] and immediately utilized for cycloaddition owing to its instability: IR (neat) 1710, 1650 cm^{-1}; NMR (CCl_4) δ 1.30 (t, 3 H, $J \approx 7$ Hz, CH_2CH_3), 1.60–2.5 (m, 4 H, 4-CH_2, 5-CH_2), 3.58 (t, 2 H, $J \approx 7$ Hz, 6-CH_2), 3.69 (s, 3 H, CO_2CH_3), 4.20 (q, 2 H, $J \approx 7$ Hz, CH_2CH_3), 4.7–7.2 (m, 7 H, olefinic protons); MS (70 eV), m/e 267 (M^+).

Methyl (4aα,5α,8aα)-1-(Ethoxycarbonyl)-1,2,3,4,4a,5,6,8a-octahydroquinoline-5-carboxylate (5a). Method A. A solution of dienamide **6** (0.30 g, 1.12 mmol), 4-*tert*-butylcatechol (trace), and bis(trimethylsilyl)acetamide (trace) in 50 mL of toluene was heated at 200–210 °C in a sealed tube for 14 h.[29] Following concentration under reduced pressure, the residue was chromatographed over silica gel using EtOAc–benzene (1:1) as the eluting solvent. Concentration under reduced pressure and distillation afforded 0.21 g (70%) of **5a** (containing a trace of 4aα,8aβ isomer **17**) as a light yellow oil [oil bath temperature 150 °C (0.2 mm)].

Method B. A solution of dienamide **6** (0.20 g, 0.75 mmol), bis(trimethylsilyl)acetamide (0.5 mL), and 4-*tert*-butylcatechol (trace) in 10 mL of *o*-dichlorobenzene was heated at reflux for 3 days. Concentration under reduced pressure afforded an oil which upon treatment as described above afforded 0.12 g (60%) of cycloadduct **5a**. For both methods A and B an approximate 93:7 ratio of **5a**/**17** was observed by NMR and gas chromatographic (GLPC) analysis. GLPC analyses (carried out on a 6-ft glass column of 0.25 in. o.d. packed with 3% OV-17 on W.H.P. (80–100 mesh), column temperature 180 °C, injection port temperature 250 °C, detector temperature 250 °C, and carrier gas He) showed two peaks at 9 and 10 min in a 7:93 ratio.

The cycloadduct **5a** (60 mg, 0.22 mmol) was refluxed in 4% aqueous NaOH solution for 2 h, and the reaction mixture was poured into ice–H_2O. After extraction with Et_2O, the H_2O layer was made acidic (dilute HCl) and extracted with Et_2O. The Et_2O layer was washed (H_2O), dried (Na_2SO_4), and concentrated under reduced pressure to afford 30 mg (53%) of colorless crystals of **(4aα,5α,8aα)-1-(ethoxycarbonyl)-1,2,3,4,4a,5,6,8a-octahydroquinoline-5-carboxylic acid (5b)**: mp 116–118 °C (Et_2O–petroleum ether); NMR ($CDCl_3$) δ 1.24 (t, 3 H, $J \approx 7$ Hz, CH_2CH_3), 1.3–2.9 (m, 9 H, 2β-, 3β-, 3α-, 4β-, 4α-, 4aα-, 5β-, 6β-, 6α-H), 3.95 (d, partially obscured half peak, 1 H, 2α-H), 4.14 (q, 2 H, $J \approx 7$ Hz, CH_2CH_3), 4.88 (br s, half-height width $\approx$ 12 Hz, 8aα-H), 5.40 (d, 1 H, $J \approx 10$ Hz, 8-H), 5.73 (d, m, 1 H, $J \approx 10$ Hz, 7-H), 8.1 (br s, 1 H, CO_2H); MS (70 eV), m/e 253 (M^+). Anal. ($C_{13}H_{19}NO_4$) C, H, N.

Pure **5a** (free of isomer **17**) was obtained in quantitative yield by addition of a diazomethane-Et_2O solution to **5b**, followed by distillation of the isolated oil. Octahydroquinoline **5a** exhibited MS (70 eV), m/e 267 (M^+); IR 1720 and 1680 cm^{-1}; NMR ($CDCl_3$) δ 1.24 (t, 3 H, $J \approx 7$ Hz, CH_2CH_3), 1.3–2.9 (m, 9 H, 2β-, 3β-, 3α-, 4β-, 4α-, 4aα-, 5β-, 6β-, 6α-H), 3.71 (s, 3 H, CO_2CH_3), 3.94 (d, 1 H, 2α-H), 4.13 (q, 2 H, $J \approx 7$ Hz, CH_2CH_3), 4.77 (br s, half-height width $\approx$ 12 Hz, 8aα-H), 5.38 (d, 1 H, $J \approx 11$ Hz, 8-H), 5.74 (d, m, 1 H, $J \approx 11$ Hz, 7-H). Anal. ($C_{14}H_{21}NO_4$) C, H, N.

Isolation of Minor Isomer (17), via Synthetic 19 and Intermediates 18, 20, and 21, from the Cycloadduct Mixture. To a solution of 110 mg of cycloadduct mixture **5a** and **17** (prepared as above) in 10 mL of toluene was added 2 mL of DIBAL (25% solution in toluene) at –60 °C. After 0.5 h, saturated NH_4Cl solution was added, and the organic layer was separated, washed with H_2O, and dried (Na_2SO_4). Evaporation under reduced pressure afforded 75 mg of oily products containing hydroxymethyl derivatives and **18 [(4aα,5α,8aβ)-1-(ethoxycarbonyl)-5-(hydroxymethyl)-1,2,3,4,4a,5,6,8a-octahydroquinoline]** and its cis 4aα,8aα isomer. To 180 mg of the isomeric mixture and 0.3 g of K_2CO_3 in 10 mL of acetone was added 0.4 g of 3,5-dinitrobenzoyl chloride. After stirring overnight at room temperature, the reaction mixture was poured into ice-H_2O and extracted with Et_2O. The Et_2O solution was washed with H_2O and dried (Na_2SO_4). Concentration under reduced pressure afforded an oily mixture of two benzoates: TLC (silica gel; benzene–EtOAc, 5:1) R_f 0.50 (main), 0.45 (minor). The minor ester **19 [(4aα,5α,8aβ)-1-(ethoxycarbonyl)-5-[[(3,5-dinitrobenzoyl)oxy]methyl]-1,2,3,4,4a,5,6,8a-octahydroquinoline]** (14 mg) was isolated by preparative TLC: NMR ($CDCl_3$) δ 1.24 (t, 3 H, $J \approx 7$ Hz, CH_2CH_3), 1.2–2.3 (m, 8 H), 2.7–3.1 (m, 1 H, 2β-H), 3.4–3.75 (m, 1 H, 2α-H), 4.11 (q, 2 H, $J \approx 7$ Hz, CH_2CH_3), 4.3–4.7 (m, 2 H, CH_2O), 5.63 (d, t, 1 H, $J \approx 11$ and 2 Hz, 7-H), 5.92 (d, 1 H, $J \approx 11$ Hz, 8-H), 9.12 (d, 2 H, $J \approx 2$ Hz, 2′-, 6′-H), 9.23 (t, 1 H, $J \approx 2$ Hz, 4′-H).

The benzoate **19** (14 mg) was heated at 70 °C in 15 mL of EtOH containing 2 mL of 10% aqueous NaOH solution. The reaction mixture was concentrated under reduced pressure, poured into ice-H_2O, and extracted with Et_2O. The Et_2O layer was washed with H_2O and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded 7 mg (91%) of **18** which was not further purified but used as such in the conversion to **20** and **22**: NMR ($CDCl_3$) δ 1.23 (t, 3 H, $J \approx 7$ Hz, CH_2CH_3), 1.3–2.3 (m, 8 H), 2.75–3.1 (m, 1 H, 2β-H), 3.4–3.75 (m, 3 H, 2α-H, CH_2O), 4.09 (q, 2 H, $J \approx 7$ Hz, CH_2CH_3), 5.60 (d, t, 1 H, $J \approx 12$ and 3 Hz, 7-H), 5.88 (d, d, 1 H, $J \approx 12$ and 2 Hz, 8-H).

A solution of **18** (7.0 mg, 0.03 mmol) in 10 mL of EtOH was hydrogenated over 3 mg of 10% Pd/C for 2 h at 40 psi. After removal of the catalyst by filtration, the reaction mixture was concentrated under reduced pressure and the residual oil was purified by TLC (silica gel), affording 7 mg (98%) of **22 [(4aα,5α,8aβ)-1-(ethoxycarbonyl)-5-(hydroxymethyl)decahydroquinoline]**: NMR ($CDCl_3$) δ 1.25 (t, 3 H, $J \approx 7$ Hz, CH_2CH_3), 1.2–2.2 (m, 12 H), 3.0–3.4 (m, 2 H, 2a-, 8aβ-H), 3.5–3.8 (m, 3 H, 2α-H, CH_2O), 4.12 (q, 2 H, $J \approx 7$ Hz, CH_2CH_3); MS (70 eV), m/e 241 (M^+).

Seven milligrams (0.029 mmol) of **18** was treated with 10 mg of pyridinium chlorochromate[16] (procedure similar to the preparation of **37**) to yield 4 mg (58%) of **(4aα,5α,8aβ)-1-(ethoxycarbonyl)-1,2,3,4,4a,5,6,8a-octahydroquinoline-5-carboxaldehyde (20)** as a colorless oil: NMR ($CDCl_3$) δ 1.24 (t, 3 H, $J \approx 7$ Hz, CH_2CH_3), 1.3–2.5 (m, 8 H), 2.7–3.1 (m, 1 H, 2β-H), 3.3–3.6 (m, 1 H, 2α-H), 4.12 (q, 2 H, $J \approx 7$ Hz, CH_2CH_3), 5.62 (d, m, 1 H, $J \approx 13$ Hz, 7-H), 5.95 (d, 1 H, $J \approx 13$ Hz, 8-H), 9.57 (d, 1 H, $J \approx 3$ Hz, CHO).

A mixture of 4 mg (0.017 mmol) of **20**, 6 mg (0.12 mmol) of NaCN, and 20 mg (0.16 mmol) of AgO in 20 mL of THF–H_2O (9:1) was stirred for 5 h at room temperature. The reaction mixture was poured into aqueous $NaHCO_3$ solution and extracted with Et_2O. The aqueous layer was made acidic with dilute HCl solution and extracted with Et_2O. The Et_2O layer was washed with H_2O, dried (Na_2SO_4), and concentrated under reduced pressure to afford 2 mg (47%) of oil **21 [(4aα,5α,8aβ)-1-(ethoxycarbonyl)-1,2,3,4,4a,5,6,8a-octahydroquinoline-5-carboxylic acid]**. Addition of an Et_2O solution of CH_2N_2 to 2 mg (0.008 mmol) of **23** in Et_2O afforded 2 mg (95%) of **17** as a colorless oil: NMR ($CDCl_3$) δ 1.2 (t, 3 H, $J \approx 7$ Hz, CH_2CH_3), 1.2–2.4 (m, 8 H), 2.6–3.1 (m, 1 H, 2β-H), 3.4–3.7 (m, 1 H, 2α-H), 3.66 (s, 3 H, CO_2CH_3), 4.12 (q, 2 H, $J \approx 7$ Hz, CH_2CH_3), 6.1 (d, m, 1 H, $J \approx 13$ Hz, 7-H), 6.4 (d, 1 H, $J \approx 13$ Hz, 8-H).

Seven milligrams (0.029 mmol) of **22** was added to a solution of 10 mg of pyridinium chlorochromate[16] in 2 mL of CH_2Cl_2. After the mixture stirred for 1 h at room temperature, reaction workup (according to the preparation of **37**) afforded colorless oil **23 [(4aα,5α,8aβ)-1-(ethoxycarbonyl)decahydroquinoline-5-carboxaldehyde]** (6 mg, 86%). Oil **23** was sufficiently pure to be used in the conversion to **24**: NMR ($CDCl_3$) δ 1.25 (t, 3 H, $J \approx 7$ Hz, CH_2CH_3), 1.2–2.3 (m, 12 H), 3.16 (t, d, 1 H, $J \approx 11$ and 4 Hz, 8aβ-H), 3.3–3.8 (m, 2 H, 2α- and 2β-H), 4.12 (q, 2 H, $J \approx 7$ Hz, CH_2CH_3), 9.56 (d, 1 H, $J \approx 3$ Hz, CHO).

A mixture of **23** (6 mg, 0.025 mmol) and tris(triphenylphosphine)rhodium(I) chloride[26] (50 mg) in 1.0 mL of benzonitrile was heated at 175 °C for 1 h. The reaction mixture was concentrated under reduced pressure, and the residual oil was purified by TLC (silica gel) by developing with benzene–EtOAc (15:1) to afford 2 mg (38%) of oily **24 [(4aα,8aβ)-1-(ethoxycarbonyl)-decahydroquinoline]** identical with the compound prepared from authentic *trans*-decahydroquinoline. Thus, 0.1 g (0.57 mmol) of *trans*-decahydroquinoline hydrochloride[30] was stirred with 0.1 g (1.0 mmol) of ethyl chloroformate and 0.2 g of K_2CO_3 in 5 mL of acetone. Reaction workup afforded 0.9 g (75%) of **24** [oil bath temperature 130 °C (1 mm)]: IR 1690 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (t, 3 H, $J \approx 7$ Hz, CH_2CH_3), 0.6–2.2 (m, 13-H), 3.05 (t, d, $J \approx 12$ and 4 Hz, 8aβ-H), 3.1-3.4 (m, 1 H), 3.6 (d, m, 1 H, $J \approx 13$ Hz, 2α-H), 4.12 (q, 2 H, $J \approx 7$ Hz, CH_2CH_3); MS (70 eV), m/e 211 (M^+).

Methyl (4aα,5α,8aα)-1-(Ethoxycarbonyl)decahydroquinoline-5-carboxylate (31). Method A. A solution of **5a** (0.35

g, 1.31 mmol) in 100 mL of EtOH was hydrogenated over 0.30 g of 10% Pd/C at room temperature and 40 psi for 3 h. After the solution was filtered and concentrated under reduced pressure, the residue was chromatographed on silica gel (column) and eluted with EtOAc–benzene (1:1). After concentration under reduced pressure, 0.32 g (91%) of **31** was obtained as a colorless oil [oil bath temperature 160 °C (1.5 mm)].

Method B. Hydrogenation of **29** (2.6 g, 10.5 mmol) in 100 mL of MeOH was carried out over 0.9 g of 10% Pd/C for 3 h at 40 psi. After filtration, the solvent was removed under reduced pressure and the residual oil **30** was dissolved in 20 mL of acetone. To this solution was added 2.0 g (18.0 mmol) of ethyl chloroformate and 5.0 g of K_2CO_3. Stirring was continued for 1 h at room temperature. The reaction mixture was poured into ice–H_2O and extracted with Et_2O. The Et_2O layer was washed with H_2O and dried (Na_2SO_4). After the solvent was removed under reduced pressure, the residual oil was distilled to afford 1.3 g (46%) of **31** [oil bath temperature 170 °C (2.0 mm)]: IR (neat) 1690, 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.23 (t, 3 H, $J \approx 7$ Hz, CH_2CH_3), 1.2–2.1 (m, 10 H), 2.25 (d, m, 1 H, $J \approx 12$ Hz, 8α-H), 2.50 (s, 1 H, half-height width ≈ 7 Hz, 5α-H), 2.85 (t, m, 1 H, $J \approx 13$ Hz, 2β-H), 3.70 (s, 3 H, CO_2CH_3), 3.9 (d, m, 1 H, $J \approx 11$ Hz, 2α-H), 4.12 (q, 2 H, $J \approx 7$ Hz, CH_2CH_3), 4.23 (d, m, 1 H, $J \approx 12$ Hz, 8aα-H); MS (70 eV), m/e 269 (M^+). Anal. ($C_{14}H_{23}NO_4$) C, H, N.

Methyl (4aα,5α,8aα)-Decahydroquinoline-5-carboxylate Hydroacetate (32). Hydrogenation of **29** (500 mg, 1.46 mmol) in 75 mL of MeOH containing 0.1 mL of glacial HOAc was carried out over 0.125 g of 10% Pd/C for 2.5 h at 40 psi. After filtration, the solvent was removed under reduced pressure to afford a solid, which when washed with acetone yielded 0.25 g (66%) of pure crystalline **32**, mp 144–145 °C. Anal. ($C_{13}H_{23}NO_4$) C, H, N.

(4aα,5α,8aα)-1-(Ethoxycarbonyl)decahydroquinoline-5-carboxylic Acid (34). Ester **31** (0.14 g, 0.52 mmol) was refluxed in 5.0 mL of 4% NaOH solution for 1.5 h and, after cooling, was washed with Et_2O. The aqueous layer was made acidic with dilute HCl and extracted with Et_2O. The Et_2O extract was dried (Na_2SO_4) and concentrated under reduced pressure to yield 0.11 g (83%) of **34**: mp 124–125 °C (Et_2O–petroleum ether); IR (Nujol) 1720, 1650 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (t, 3 H, $J \approx 7$ Hz, CH_2CH_3), 1.2–2.1 (m, 9 H), 2.32 (d, m, 1 H, $J \approx 12$ Hz, 8α-H), 2.51 (br s, 1 H, half-height width ≈ 7 Hz, 5α-H), 2.83 (t, m, 1 H, $J \approx 11$ Hz, 2β-H), 3.9 (d, m, 1 H, $J \approx 11$ Hz, 2α-H), 4.12 (q, 2 H, CH_2CH_3), 4.3 (d, d, 1 H, $J \approx 12$ and 4 Hz, 8aα-H); MS (70 eV), m/e 225 (M^+).

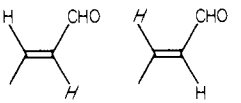
(4aα,5α,8aα)-Decahydroquinoline-5-carboxylic Acid (*cis*-1) Hydrochloride. A solution of **34** (52 mg, 0.20 mmol) in concentrated HCl (50 mL) was refluxed for 5 h and concentrated to give crystalline *cis*-1. Recrystallization from MeOH afforded a colorless powder (36 mg, 80%): mp 305–307 °C dec; IR (Nujol) 2580, 2540, 2490, 2470, 1700 cm^{-1}; NMR (D_2O) δ 1.2–2.0 (m, 10 H), 2.1 (d, d, 1 H, $J \approx 10$ and 4 Hz, 8β-H), 2.56 (t, m, 1 H, $J \approx 10$ Hz, 5β-H), 2.86 (d, d, $J \approx 15$ and 9 Hz, 2α-H), 3.20 (d, t, 1 H, $J \approx 15$ and 3 Hz, 2β-H), 3.41 (d, d, 1 H, $J \approx 5$ and 3 Hz, 8aα-H). [Preparation of *cis*-1 (0.7 g, 66%) was also carried out by hydrolysis of ester **31** (1.30 g, 4.8 mmol) in concentrated HCl (50 mL) by refluxing for 4 h.] Anal. ($C_{10}H_{18}ClNO_2$) C, H, N, Cl.

Methyl 4-Hydroxycrotonate (26). A mixture of 4.4 g (0.073 mol) of glycoaldehyde (**25**) and 24.5 g (0.073 mol) of methyl (triphenylphosphoranylidene)acetate in 300 mL of chloroform was stirred for 24 h at room temperature. After the solvent was removed, the crystalline triphenylphosphine oxide was filtered and the residual oil was distilled to afford 8.0 g (94%) of **26**: bp 86–89 °C (1.0 mm) [lit.[22] bp 98–105 °C (5.0 mm)]; NMR ($CDCl_3$) δ 2.70 (br s, 1 H, OH), 3.70 (s, 3 H, CO_2CH_3), 4.25 (br s, 2 H, CH_2), 6.0 (d, t, 1 H, $J \approx 16$ and 2 Hz, 2-H), 6.9 (d, t, $J \approx 16$ and 3 Hz, 3-H).

Methyl 4-Oxo-2(*E*)-butenoate (8). To a solution of 12.5 g (0.058 mol) of pyridinium chlorochromate[16] in 300 mL of CH_2Cl_2 was added 6.2 g (0.053 mol) of **26**. After the solution stirred for 3 h at room temperature, excess Et_2O was added and the precipitate was filtered. The filtrate was concentrated under reduced pressure and the residual oil was chromatographed on silica gel by elution with benzene. Concentration of the eluate under reduced pressure afforded 4.4 g (73%) of 8 as colorless crystals: mp 38–40 °C (lit.[23] mp 41 °C; bp 80–90 °C (12 mm). Compound 8 was also prepared as described in ref 23, wherein starting materials are less expensive: NMR ($CDCl_3$) δ 3.81 (s, 3 H, CH_3), 6.73 (m, 2 H, CH=CH), 9.66 (d, d, 1 H, CHO, $J \approx 6$ and 1 Hz).

Methyl 2β-Formyl-3β-[(benzyloxycarbonyl)amino]-4-cyclohexene-α-carboxylate (10). A mixture of 1(*E*)-[(benzyloxycarbonyl)amino]-1,3-butadiene (7;[15] 10.0 g, 0.049 mol) and 8 (5.5 g, 0.048 mol) in 300 mL of toluene was refluxed for 3 h, and the reaction mixture was concentrated under reduced pressure to afford a crystalline mass. Addition of Et_2O, followed by filtration, afforded 10.1 g (65%) of pure **10**: mp 95–97 °C (CH_2Cl_2–*n*-hexane); IR (Nujol) 3300, 1745, 1720, 1685 cm^{-1}; NMR ($CDCl_3$) δ 2.0–2.4 (m, 2 H, 6-CH_2), 2.5–2.95 (m, 1 H, 1β-H), 3.2 (d, d, 1 H, $J \approx 13$ and 4 Hz, 2α-H), 3.71 (s, 3 H, CO_2CH_3), 4.6–5.0 (m, 2 H, 3α-H, NH), 5.05 (s, 2 H, OCH_2), 5.7–6.0 (m, 2 H, olefinic), 7.32 (s, 5 H, phenyl), 9.81 (s, 1 H, CHO). Analysis of the NMR spectrum of the reaction mixture showed regio- and stereoselective formation of **10** (approximately 90% of the reaction mixture): MS (70 eV), m/e 317 (M^+). Anal. ($C_{17}H_{19}NO_5$) C, H, N.

Methyl 2β-[3-Oxo-2(*E*)-propenyl]-3β-[(benzyloxycarbonyl)amino]-4-cyclohexene-α-carboxylate (29). A mixture of **10** (9.9 g, 0.031 mol) and (formylmethylene)triphenylphosphorane[24] (9.9 g, 0.033 mol) was refulxed for 2 h in 200 mL of toluene. After solvent removal, the residual oil was chromatographed on silica gel by elution with EtOAc–benzene (1:10). After solvent removal under reduced pressure, 9.9 g (92%) of crystalline **29** was obtained: mp 90–91 °C; IR (Nujol) 3370, 1720, 1700, 1675 cm^{-1}; NMR ($CDCl_3$) δ 2.25–3.2 (m, 4 H, 1α-H, 2β-H, 6-CH_2), 3.63 (s, 3 H, CO_2CH_3), 4.3–4.5 (m, 1 H, 3β-H), 4.7 (d, 1 H, $J \approx 11$ Hz, NH), 5.06 (s, 2 H, OCH_2), 5.7–6.0 (m, 2 H, olefinic), 6.12 (d, d, 1 H, $J \approx 16$ and 8 Hz, i), 6.75 (d, d, 1 H, $J \approx 15$ and 8 Hz, ii), 9.38 (d, 1 H, $J \approx 8$ Hz, CHO); MS (70 eV), m/e 343 (M^+). Anal. ($C_{19}H_{21}NO_5$) C, H, N.



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Methyl (4aα,5α,8aα)-1-(Ethoxycarbonyl)decahydroquinoline-5-carboxylate (33). One gram (3.7 mmol) of **31** was treated at −70 °C for 0.5 h with LDA in 10 mL of THF, prepared from 2 mL of isopropylamine and 6 mL of *n*-BuLi (1.6 M solution in hexane). The reaction was quenched by the addition of aqueous saturated NaCl solution and poured into ice–H_2O. The H_2O solution was extracted with Et_2O, and the Et_2O extract was washed with H_2O and dried (Na_2SO_4). Concentration under reduced pressure afforded a nearly 1:2 mixture of **31** and **33** by NMR analysis. From the reaction mixture, **33** (0.1 g, 10%) separated as pure colorless crystals upon standing in the refrigerator. Crystals (mp 80–82 °C) were washed with cold petroleum ether and utilized as such in the conversion to *cis*-**2**. Separation of isomers **31** and **33** from the oil was not possible by TLC. NMR ($CDCl_3$) δ 1.25 (t, 3 H, $J \approx 7$ Hz, CH_2CH_3), 1.2–2.4 (m, 11 H), 2.6 [d, t, 1 H, $J \approx 12$ and 3 Hz, 5α_{ax}-H], 2.7 [d, t, 1 H, $J \approx 13$ and 3 Hz, 2β_{ax}-H], 3.66 (s, 3 H, CO_2CH_3), 3.95 (d, 1 H, 2$_{eq}$-H), 4.13 (q, 2 H, $J \approx 7$ Hz, CH_2CH_3); 8aα_{ax} proton is hidden under the CH_2CH_3 signals; MS (70 eV), m/e 269 (M^+).

(4aα,5β,8aα)-Decahydroquinoline-5-carboxylic Acid (*cis*-2) Hydrochloride. One-tenth gram (0.37 mmol) of **33** was refluxed in 10 mL of concentrated HCl. The solvent was removed under reduced pressure, affording 59 mg (72%) of crystalline *cis*-**2**: mp 250–255 °C dec (MeOH–Me_2CO); NMR (D_2O) δ 1.0–2.0 (m, 11 H), 2.3 (m, 1 H, 2β_{ax}-H), 2.50 (d, t, 1 H, $J \approx 13$ and 4 Hz, 5α_{ax}-H), 3.0 (d, 1 H, $J \approx 7$ Hz, 2α_{eq}-H) 3.5 (d, t, 1 H, $J \approx 12$ and 4 Hz, 8aα_{ax}-H). Anal. ($C_{10}H_{18}ClNO_2$) C, H, N, Cl.

(4aα,5α,8α)-1-(Benzyloxycarbonyl)decahydroquinoline-5-carboxylic Acid (35). To a solution of *cis*-1 (5 mg, 0.023 mmol) in acetone (1.0 mL) was added 7.0 mg of K_2CO_3 and 5.0 mg of benzyl chloroformate at room temperature. The mixture was stirred for 4 h, poured into ice–H_2O, and extracted with Et_2O. The H_2O layer was made acidic with dilute HCl and extracted with Et_2O. The Et_2O extract was washed with H_2O and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded 6.0 mg (82%) of **35** as colorless crystals: mp 145–147 °C (CH_2Cl_2–petroleum ether); IR (Nujol) 1660, 1725 cm^{-1}; NMR ($CDCl_3$) δ 1.3–2.5 (m, 12 H), 2.55 (s, 1 H, half-height width ≈ 9 Hz, 5β_{eq}-H], 2.85 (t, m, 1 H, $J \approx 13$ Hz, 2β_{ax}-H), 4.05 (d, m, 1 H,

$J \approx 13$ Hz, $2\alpha_{eq}$-H), 4.45 (d, m, 1 H, $J \approx 12$ Hz, $8a\alpha_{ax}$-H); MS (70 eV), m/e 317 (M^+).

(4aα,5α,8aα)-1-(Ethoxycarbonyl)-5-(hydroxymethyl)decahydroquinoline (36). To a solution of **31** (190 mg, 0.71 mmol) in toluene (10 mL) was added 1 mL of DIBAL (25% solution in toluene) at −60 °C. After 0.5 h, the mixture was decomposed with excess saturated ammonium chloride solution and poured into ice–H_2O. The H_2O layer was extracted with Et_2O and the Et_2O layer was washed with H_2O and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded 145 mg (85%) of a colorless oil (**36**) which was not further purified but used as such in subsequent reactions: IR (neat) 3400, 1660 cm^{-1}; NMR ($CDCl_3$) δ 1.23 (t, 3 H, $J \approx 7$ Hz, CH_2CH_3), 1.2–2.0 (m, 12 H), 2.4 (s, 1 H, OH), 2.80 (t, m, 1 H, $J \approx 11$ Hz, 2β-H), 3.65 (d, 2 H, $J \approx 7$ Hz, CH_2O), 3.9 (d, 1 H, 2α-H), 4.17 (q, 2 H, $J \approx 7$ Hz, CH_2CH_3); 8aα-H is hidden under the CH_2CH_3 resonance signals.

(4aα,5α,8aα)-1-(Ethoxycarbonyl)decahydroquinoline-5-carboxaldehyde (37). A mixture of **36** (140 mg, 0.58 mmol) and pyridinium chlorochromate[16] (150 mg, 0.70 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 1 h and excess Et_2O was added. The solvent was removed from the precipitate by decanting. Et_2O was added several times to the residue. Following decantation, the combined solutions were concentrated under reduced pressure and the residual oil was chromatographed on silica gel using EtOAc–benzene (1:10) as the eluent. After solvent removal, **37** (105 mg, 76%) was obtained as a colorless oil, which was used without further purification in the next reaction: IR (neat) 1725, 1690 cm^{-1}; NMR ($CDCl_3$) δ 1.23 (t, 3 H, $J \approx 7$ Hz, CH_2CH_3), 1.3–2.0 (m, 11 H), 2.26 (s, 1 H, half-height width ≈ 6 Hz, 5β-H), 2.78 (t, m, 1 H, $J \approx 11$ Hz, 2β-H), 3.9 (d, 1 H, 2α-H), 4.05 (q, 2 H, $J \approx 7$ Hz, CH_2CH_3), 8.95 (s, 1 H, CHO); 8aα-H is hidden under the CH_2CH_3 signals. Upon standing at room temperature, the aldehyde **37** [MS (70 eV), m/e 239 (M^+)] air oxidizes to carboxylic acid **34** [m/e 225 (M^+)].

(4aα,8aα)-1-(Ethoxycarbonyl)decahydroquinoline (38). A solution of **37** (38 mg, 0.16 mmol) and tris(triphenylphosphine)rhodium(I) chloride[26] (190 mg) in benzonitrile (10 mL) was heated at 170 °C for 40 min. The reaction mixture was chromatographed over silica gel using EtOAc–benzene (1:10) as eluent. Following removal of the solvent under reduced pressure, **38** (18 mg, 54%) was obtained as a colorless oil [oil bath temperature 130 °C (1.0 mm)]. This compound was identical in all respects with **38** prepared as follows: to a solution of *cis*-decahydroquinoline (**39**) (from 68 mg of *cis*-decahydroquinoline HCl salt[30]) in acetone (10 mL) was added K_2CO_3 (0.2 g) and ethyl chloroformate (0.1 g) at room temperature. The mixture was stirred for 3 h, poured into ice–H_2O, and extracted with Et_2O. The Et_2O extract was washed with dilute HCl, aqueous Na_2CO_3, and H_2O and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded 60 mg (73%) of **38** as a colorless oil [oil bath temperature 130 °C (1.0 mm)]: IR (neat) 1690 cm^{-1}; NMR ($CDCl_3$) δ 1.16 (t, 3 H, $J \approx 7$ Hz, CH_2CH_3), 1.1–2.2 (m, 13 H), 2.77 (t, m, 1 H, $J \approx 12$ Hz, 2β-H), 3.9 (d, m, 1 H, $J \approx 12$ Hz, 2α-H), 4.07 (q, 2 H, $J \approx 7$ Hz, CH_2CH_3); 8aα-H is hidden under the CH_2CH_3 signals; MS (70 eV), m/e 211 (M^+). Anal. ($C_{12}H_{21}NO_2$) C, H, N.

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Potential Pancreatic Imaging Agents. Tellurium-123m Labeled DL-α-Amino-γ-(phenyltelluro)butyric Acid

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This report describes the first successful preparation of a ^{123m}Te-labeled α-amino acid as a potential pancreatic imaging agent. Tellurium-123m labeled DL-α-amino-γ-(phenyltelluro)butyric acid was prepared by basic hydrolysis of the radiolabeled 5-[β-(phenyltelluro)ethyl]hydantoin. The hydantoin was prepared by the reaciton of ^{123m}Te-labeled phenyltellurol, generated by sodium borohydride reduction of diphenyl ditelluride, with 5-(β-bromoethyl)hydantoin. Tissue distribution studies in rats with the ^{123m}Te-labeled amino acid for periods varying from 30 min to 24 h demonstrated only marginal pancreatic accumulation of radioactivity. The significant result of these studies is that a general synthetic method has been developed for the preparation of ^{123m}Te-labeled amino acids.

The 159-keV γ photon (84% abundance) emitted from ^{123m}Te is within the optimal energy range for detection with the sodium iodide detectors presently used clinically for nuclear medicine imaging procedures. The potential use of tissue-specific ^{123m}Te-labeled radiopharmaceuticals has been recognized for several years,[1] and we have recently described the pronounced adrenal uptake of two ^{123m}Te-labeled steroids in several animal species.[2-4] Prior to these studies, however, there were no reported attempts to chemically incorporate ^{123m}Te into tissue-specific imaging agents. Tellurium succeeds selenium in group 4A of the periodic table and in some respects these two elements exhibit similar properties, although their specific chemical properties quite often differ dramatically.[5] Despite several major disadvantages, ^{75}Se-labeled selenomethionine[6,7] is still used for the clinical detection and diagnosis of pancreatic disease.[8] The more efficient collimation and detection of the single 159-keV γ photon from ^{123m}Te suggested that ^{123m}Te-labeled telluromethionine would be an attractive alternative to ^{75}Se-labeled selenomethionine for pancreatic imaging.[1] Although selenomethionine has been prepared by a variety of microbiological and chemical methods,[9,10] attempts to prepare telluromethionine by microbiological methods have been unsuccessful.[11] The

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