SYNTHESIS AND DETERMINATION OF THE ABSOLUTE STEREOCHEMISTRY OF THE ENANTIOMERS OF 3-SUBSTITUTED 1,2,3,4-TETRAHYDROISOQUINOLINES RELATED TO THE CALCIUM ANTAGONIST VERAPAMIL[1]

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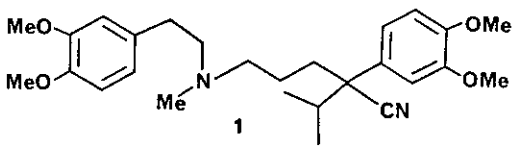
Abstract - The four stereoisomers of 3-[4-cyano-4-(3,4-dimethoxyphenyl)-5-methylhex-1-yl]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (2) were prepared. The stereochemistry of the side chain quaternary carbon was derived from iodide 4 of known absolute configuration. The absolute stereochemistry at the 3-position of the tetrahydroisoquinoline was determined by correlation with L-DOPA. These compounds are related to the calcium antagonist verapamil and the calcium antagonist activity was greatest for the (3S,4S) isomer.

Structure-activity relationship (SAR) studies to date on the Group II calcium antagonist verapamil (1)[2-4] have dealt with substitutions in the aromatic rings[5,6] or modifications at the quaternary carbon atom.[7-9] Our interest in the SAR of verapamil prompted us to prepare and evaluate a number of rigid phenethylamine analogs and preliminary results of these investigations indicated that compound 2 had interesting pharmacological activity. In this structure, the [4-cyano-(3,4-dimethoxyphenyl)-5-methyl]hexan-1-yl component of verapamil is attached to the 3-position of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (THIQ). Additional interest in 2 arose from the fact that remarkably few 3-substituted THIQ derivatives have been reported. This is in contrast to numerous examples of pharmacologically active 1, 2, and 4 substituted THIQ compounds.[10] Since compound 2 contains two asymmetric centers, it was of interest to prepare the four isomers inherent in this structure. Reported herein are the synthesis and establishment of the absolute stereochemistry of these four stereoisomers.



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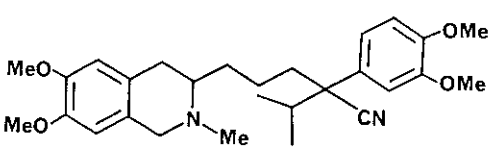
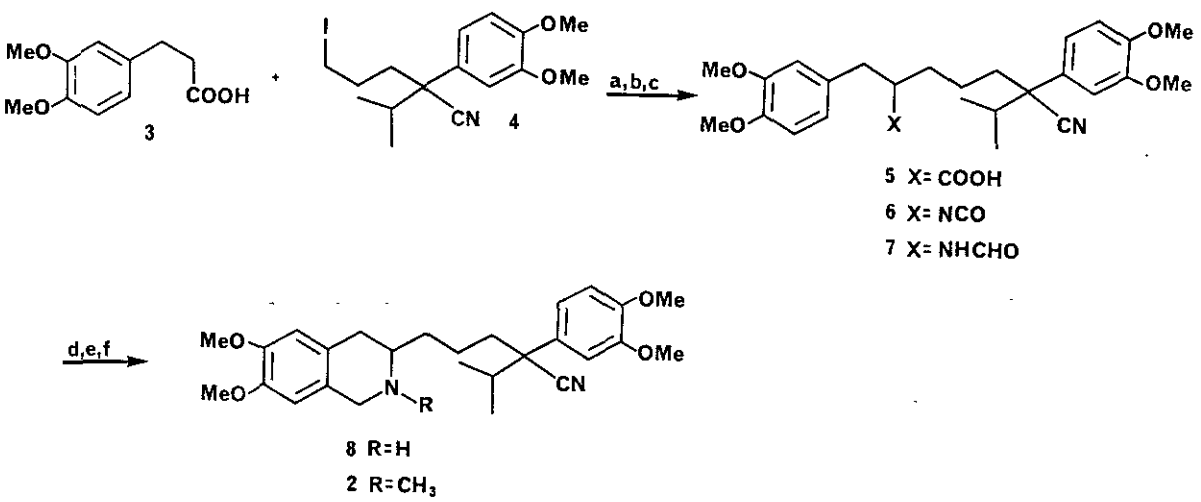


2

The preparation of 2 from 3-(3,4-dimethoxyphenyl)propionic acid (3) is outlined in Scheme I. Alkylation of the dianion of 3 with iodide 4 (prepared from the corresponding chloride[11] with NaI-acetone) gave a mixture of diastereomeric acids 5. Treatment of 5 with diphenylphosphoryl azide (DPPA)[12] gave isocyanate 6 which, without isolation, was reduced with $NaBH_4$ to an

approximately 1:1 mixture of formamides 7 as determined by tlc and ^{1}H NMR analysis. Bischler-Napieralski cyclization of 7 followed by $NaBH_4$ reduction gave THIQ 8 which was subjected to Eschweiler-Clarke methylation to afford 2. Compound 2 thus obtained was an approximately 1:1 mixture of diastereomers as determined by ^{1}H NMR and hplc analysis.

Scheme I

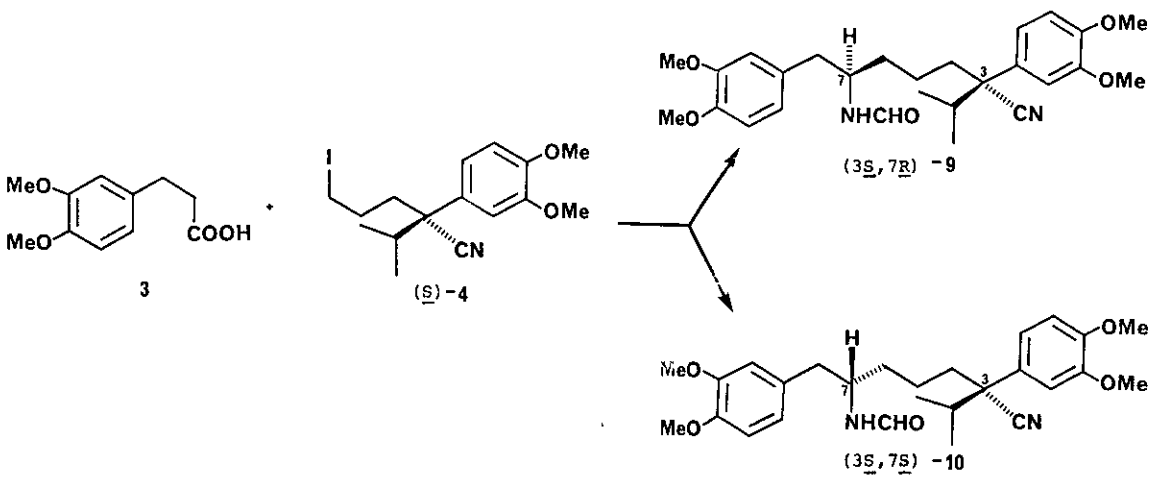


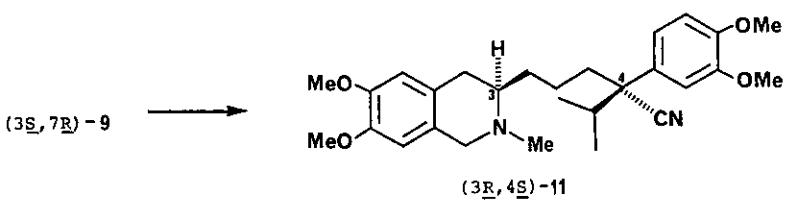
a) LDA, THF; b) $(PhO)_2PON_3$, TEA, toluene; c) $NaBH_4$, DME;
d) $POCl_3$, AcN; e) $NaBH_4$, EtOH; f) CH_2O, HCO_2H.

The four isomers of 2 were obtained by the same basic route as was used for the parent compound (Schemes II and III). The (S)-iodide 4 was obtained from the known optically active chloride which had been used to prepare the enantiomers of verapamil.[11] Aklylation of 3 with (S)-4 followed by DPPA treatment and $NaBH_4$ reduction as before gave diastereomeric formamides (-)-9 and (-)-10 which were separated by chromatography on silica gel. The pure diastereomers thus obtained were converted to the THIQ final products as previously described to afford (-)-(3R,4S)-11 and (+)-(3S,4S)-12. The stereochemical assignments for position 3 of the THIQ are made in a following section.

The other two isomers, (+)-(3S,4R)-11 and (-)-(3R,4R)-12, were obtained by an analogous series of reactions (and chromatographic separation) from (R)-4 which was obtained from the corresponding known (R)-chloride[11] (Scheme III). The physical data obtained for these four isomers (Table I) is in accord with the assignment of 11 and 12 as enantiomeric pairs. Compounds (-)-11 and (+)-12, both of which were derived from (S)-4, are assigned enantiomer excesses (ee) of >88% based on the optical purity (>88% ee) of (S)-4 (experimental section). Compounds (+)-11 and (-)-12 are assigned ee of >96% based on the purity of (R)-4 (>96% ee).

Scheme II


MeO
MeO
COOH
3
OMe
OMe
CN
(S)-4
H
NHCHO
(3S,7R) -9
(3S,7S) -10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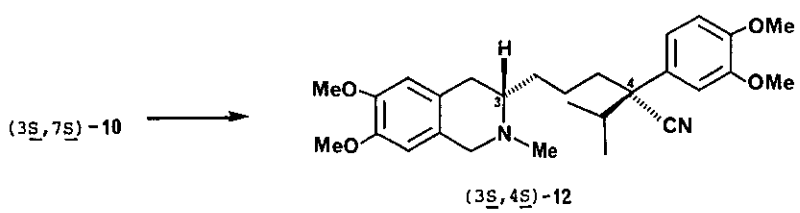
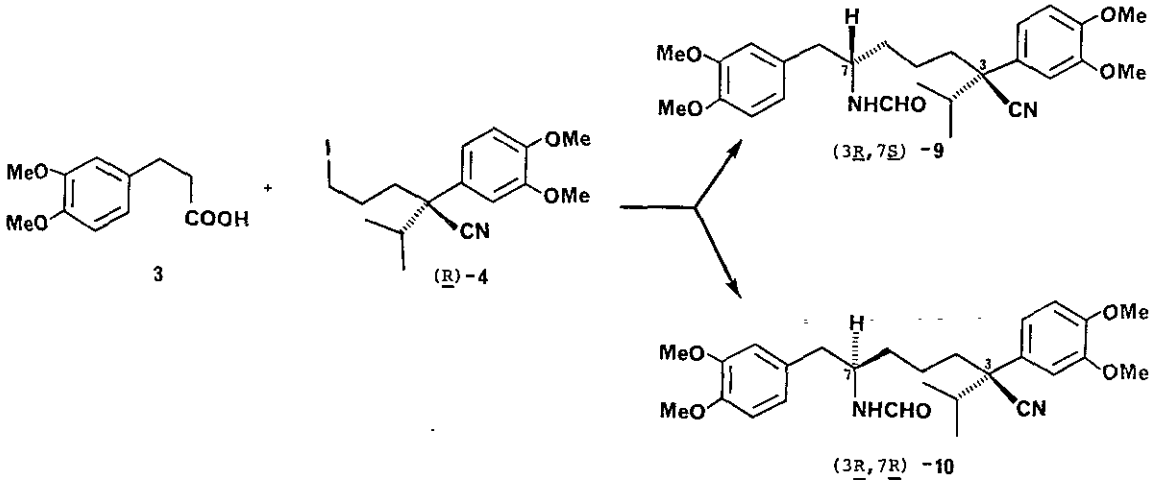
MeO
N
Me
OMe
OMe
CN
(3R,4S) -11


(3S,7S) -10
MeO
MeO
N
Me
OMe
OMe
CN
(3S,4S) -12

Scheme III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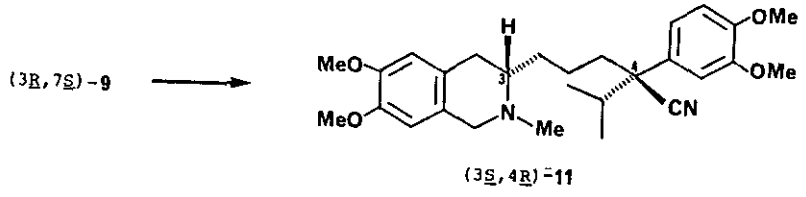
MeO
COOH
3
OMe
OMe
CN
(R)-4
H
NHCHO
(3R,7S) -9
(3R,7R) -10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MeO
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N
Me
OMe
OMe
CN
(3S,4R)-11

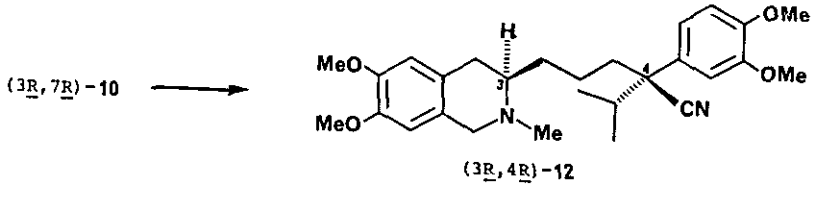

(3R,7R)-10
MeO
MeO
N
Me
OMe
OMe
CN
(3R,4R)-12

TABLE I

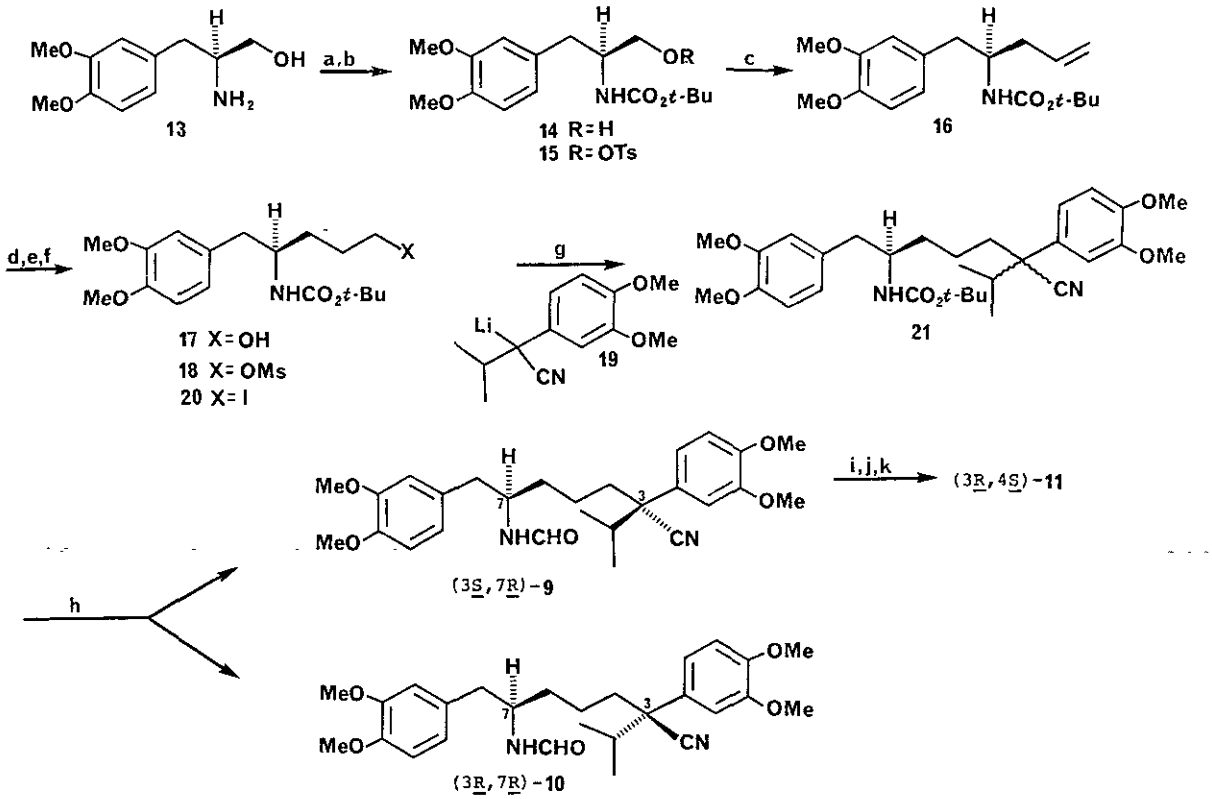
PHYSICAL DATA FOR THIQ DERIVATIVES

Compound	Absolute Stereochem	Scheme	mp,°C	Solvent	$[\alpha]_D^{25}$ (c, MeoH)
2		I	109-111	EtOH-Et_2O	
(+)-11	3S,4R	II	108-110	MeOH-Et_2O	+25.8°(0.28)
(-)-11	3R,4S	II	108-110	EtOH-Et_2O	-24.0°(0.34)
		IV	108-110	EtOH-Et_2O	-24.4°(0.40)
(+)-12	3S,4S	III	155-157	IPA-Et_2O	+43.7°(0.32)
(-)-12	3R,4R	III	155-157	IPA-Et_2O	-42.5°(0.28)

The assignment of the absolute stereochemistry of the 3 position of the THIQ was made by synthesis of (-)-(3R,4S)-11 from (S)-13 which was prepared from (-)-(S)-3,4-dihydroxyphenylalanine (L-DOPA)[13] (Scheme IV). Amino alcohol 13 was converted to the BOC derivative 14 and then to tosylate 15. Treatment of 15 with vinylmagnesium bromide and cuprous iodide afforded 16. Precedent for this useful conversion comes from the reported reaction of BOC-serine derivatives with organocuprates.[14] Conversion of 16 to alcohol 17 and mesylate 18 proceeded without incident. However, attempted alkylation of 18 with the lithium salt of 2-(3,4-dimethoxyphenyl)-3-methylbutyronitrile (19) gave none of the desired product (21). The major side reaction which occurred under these conditions was intramolecular alkylation of the BOC nitrogen to form a BOC protected pyrollidine. Fortunately, use of freshly prepared iodide 20, while an unstable material, did afford a modest yield of 21 as a mixture of two diastereomers. Deprotection of 21 followed by formylation gave the diastereomeric formamides which were separated by chromatography as before to afford (-)-(3S,7R)-9 and (+)-(3R,7R)-10.

The major formamide thus obtained, (-)-9, was cyclized, reduced, and N-methylated to afford (-)-11 identical in all respects to material obtained by the previous route (Scheme II). This sequence established the 3R configuration of the THIQ (-)-11 and, coupled with the known 4S configuration, established the complete absolute stereochemistry of (-)-11 as 3R,4S). The complete absolute stereochemistries of the other three isomers follow from the enantiomeric and diastereomeric relationships already established.

Scheme IV



a) (t-BuOCO)$_2$O, THF; b) TsCl, pyridine; c) (CH_2=CH)MgBr, CuI, THF; d) (Disiamyl)$_2$BH, THF; NaOH, H_2O_2; e) MsCl, TEA, CH_2Cl_2; f) NaI, acetone; g) 19, THF; h) HCO_2H, HCO_2Ac; i) $POCl_3$, AcN; j) $NaBH_4$, EtOH; k) CH_2O, HCO_2H.

These isomers were tested for calcium antagonist activity as determined by their ability to relax the barium chloride contracted rat aortic strip (Table II). It was found that the majority of the calcium antagonist activity of the parent compound 2 resided in the (3S,4S)-12 enantiomer. This is consistent with the finding that the S enantiomer of verapamil is responsible for most of the parent compounds activity.[15] In the THIQ derivatives, constraining the phenylethylamine moiety in the THIQ framework apparently introduces an additional stereochemical requirement in the binding of these compounds to the receptor which mediates the calcium antagonism in this series.[16]

TABLE II
CALCIUM ANTAGONIST PROPERTIES OF THIQ DERIVATIVES[a]

Compound	ED_{50} (mM)	Relative Potency
(+)-(3S,4R)-11	4.0	0.08
(-)-(3R,4S)-11	0.7	0.4
(+)-(3S,4S)-12	0.1	3
(-)-(3R,4R)-12	2.0	0.15
2	0.3	1
Verapamil (1)	0.2	

[a]Determined by measuring the relaxation of $BaCl_2$ contracted rat aortic strips.

EXPERIMENTAL

^1H NMR spectra were recorded with a Bruker WM 300 instrument and are reported in ppm δ downfield from an internal standard of TMS. Medium pressure (flash) chromatography was performed using 230-400 mesh Merck Kieselgel. Melting points are uncorrected. Elemental analyses were done by the Syntex analytical department.

(S) and (R)-3-Cyano-3-(3,4-dimethoxyphenyl)-6-iodo-2-methylhexane ((S)-4 and (R)-4)

Resolution of 4-(3,4-dimethoxyphenyl)-4-(2-propyl)-4-pentenoic acid using (-)-cinchonidine was carried out as described in the literature.[11] The optical purities of the (S)-(-)-acid and (R)-(+)-acid thus obtained were determined by ^1H NMR analysis of the diastereomeric amides derived from the acid chlorides (oxalyl chloride, benzene) and (S)-(-)-α-methylbenzylamine. In the ^1H NMR spectrum of the amide from the (S)-(-)-acid, resonances for the methoxy groups were at δ 3.63 and δ 3.87 while in the amide from the (R)-(-)-acid, resonances at δ 3.74 and δ 3.86 were observed. In the amide from the racemic acid, these four resonances appeared with equal intensities (thus ruling out any differences in the rates of formation of the diastereomeric amides). The amide from the (S)-(-)-acid was determined to have a diastereomeric ratio of >94:<6 by integration of the methoxy resonances at δ 3.63 and δ 3.74 respectively. Thus, an ee of >88% was assigned to the (S)-(-)-acid. The amide from the (R)-(+)-acid was pure (>98%) by ^1H NMR analysis and the (R)-(+)-acid was therefore assigned an ee of >96%.

These acids were converted into the (S)-iodide 4 and (R)-iodide 4 by conversion to the corresponding chlorides as described,[11] followed by treatment with NaI in acetone. They were obtained as thick oils which were used without purification in the next step.

(3S,7R) and (3S,7S)-7-Formamido-3,8-di-(3,4-dimethoxyphenyl)-2-methyl-3-octanenitrile ((-)-9 and (-)-10)

To a solution of 21 ml (0.15 mol) of diisopropylamine in 480 ml of THF at -50°C was added 91.8 ml (0.147 mol) of 1.6M n-butyllithium in hexane. HMPA (56 ml) was added followed by a solution of 15.1 g (0.072 mol) of 3-(3,4-dimethoxyphenyl)propionic acid (3) in 75 ml of THF. The

resulting solution was allowed to warm to 10°C over 1 h and was then cooled to -50°C. A solution of 28.0 g (0.072 mol) of (S)-iodide 4 in 75 ml of THF was added and the mixture was stirred and allowed to warm to room temperature. After 12 h the mixture was poured into water and washed with Et_2O. The aqueous layer was acidified with HCl, extracted with Et_2O, and the Et_2O extract was washed with aqueous $NaHSO_3$ and brine, dried (Na_2SO_4), and evaporated to 31.0 g (91%) of crude acid. This material (30.5 g, 0.066 mol) was dissolved in a mixture of 200 ml of toluene and 11.7 ml (0.084 mol) of triethylamine and 15 ml (19.3 g, 0.07 mol) of diphenylphosphoryl azide was added. The mixture was gradually heated to 100°C over 1 h at which time IR analysis showed conversion to the isocyanate. The mixture was concentrated under reduced pressure and the residue was dissolved in 300 ml of DME. The solution was cooled in an ice bath and 4.0 g (0.11 mol) of $NaBH_4$ was added in small portions over a 2 h period. The mixture was added to water and extracted with EtOAc. The extract was washed with brine, dried (Na_2SO_4), and evaporated to afford a mixture of formamides (-)-9 and (-)-10 which were separated by medium pressure chromatography (10% hexane-EtOAc). The first component eluted was (-)-9:(oil) 5.8 g (19% overall yield); ^1H NMR ($CDCl_3$) δ 0.76 (d, 3H), 1.00 (m, 1H), 1.16 (d, 3H), 1.35-1.60(m, 3H), 1.90-2.10 (m, 3H), 2.68 (dd, 2H, H-7ab), 3.85 (s, 6H), 3.87 (s, 3H), 3.90 (s, 3H), 4.20 (m, 1H, H-6), 6.58-6.90 (m, 6H), 8.03 (s, 1H, CHO); $[\alpha]_D^{25}$ -6.84° (c 0.2, MeOH). Anal. Calcd for $C_{27}H_{36}N_2O_5$: C,69.20; H, 7.74; N, 5.98. Found: C, 68.89; H, 7.80; N, 5.81.

The second component eluted was (-)-10:(oil) 8.7 g (28% overall yield); ^1H NMR ($CDCl_3$) δ 0.78 (d, 3H), 1.10 (m, 1H), 1.16 (d, 3H), 1.30-1.55 (m, 3H), 1.75 (m, 1H), 2.00-2.20 (m, 2H), 2.65 (d, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 3.89 (s, 6H), 6.60-6.92 (m, 6H), 8.07 (s, 1H, CHO); $[\delta]_D^{25}$ -2.98°(c 0.2, MeOH). Anal. Calcd for $C_{27}H_{36}N_2O_5$: C, 69.20; H, 7.74; N, 5.98. Found: C, 68.81; H, 7.85; N, 5.84.

(S)-3-[(S)-4-Cyano-4-(3,4-dimethoxyphenyl)-5-methylhex-1-yl]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline hydrochloride ((3S,4S)-12)

To a solution of 5.67 g (0.012 mol) of (-)-10 in 100 ml of MeCN was added 2.8 ml (0.03 mol) of $POCl_3$. The resulting solution was stirred 3 h at room temperature, concentrated at reduced pressure, and partitioned between Et_2O and aqueous NH_4OH. The Et_2O was evaporated and the residue was dissolved in 100 ml of EtOH, cooled in an ice bath, and treated with 1.0 g of $NaBH_4$. The mixture was stirred for 30 min and then added to water and acidified with HCl. The solution was washed with Et_2O and the aqueous layer was basified with NH_4OH and extracted with Et_2O. The Et_2O extract was evaporated and the residue was dissolved in 30 ml of formic acid and 30 ml of 37% aqueous formaldehyde. This solution was stirred at 100°C for 1 h and then added to ice-water which was subsequently basified with NH_4OH. Et_2O extraction followed by drying (Na_2SO_4) and evaporation afforded the crude free base as an oil. This was dissolved in a small amount of EtOH-HCl and crystallization was induced by adding Et_2O. The yield of (3S,4S)-12 was 4.5 g (74%): ^1H NMR (Me_2SO-d_6) 0.71 (d, 3H), 1.13 (d, 3H), 2.65 and 2.70 (broad s, 3H, pseudo axial, equitorial NCH3), 3.73 (s, 6H), 3.78 (s, 6H), 6.74 (s, 2H), 6.91 (s, 1H), 6.96 (s, 2H). Anal. Calcd for $C_{28}H_{38}N_2O_4 \cdot HCl$: C, 66.85; H, 7.81; N, 5.57. Found: C, 66.79; H, 7.85; N, 5.57.

(R)-3-[(S)-4-Cyano-4-(3,4-dimethoxyphenyl)-5-methylhex-1-yl]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline hydrochloride ((3R,4S)-11)

This compound was prepared from (-)-9 in 67% yield using procedures analogous to those used for

(3S,4S)-12: ^{1}H NMR (Me_2SO-d_6) δ 0.72 (d, 3H), 1.14 (d, 3H), 2.64 and 2.78 (broad s, 3H, NCH3), 3.73 (s, 3H), 3.74 (s, 3H), 3.78 (s, 6H), 6.74 (s, 2H), 6.93 (s, 1H), 6.96 (s, 2H). Anal. Calcd for $C_{28}H_{38}N_2O_4 \cdot HCl \cdot H_2O$: C, 65.54; H, 7.93; N, 5.38. Found: C, 64.10; H, 7.98; N, 5.30.

(3R,7S) and (3R,7R)-7-Formamido-3,8-di-(3,4-dimethoxyphenyl)-2-methyl-3-octanenitrile ((+)-9 and (+)-10)).

A mixture of (+)-9 and (+)-10 was obtained in 78% overall yield from acid 3. The pure compounds were obtained by medium pressure chromatography (10% hexane-EtOAc). The first component eluted was (+)-9:(oil) ^{1}H NMR identical to (-)-9: $[\alpha]_D^{25}$ +8.07° (c 0.33, MeOH). Anal. Calcd for $C_{27}H_{36}N_2O_5$: C,69.20; H, 7.74; N, 5.98. Found: C, 69.09; H, 7.76; N, 5.93. The second component eluted was (+)-10:(oil) ^{1}H NMR identical to (-)-10; $[\alpha]_D^{25}$ +3.84° (c 0.37, MeOH). Anal. Calcd for $C_{27}H_{36}N_2O_5$: C, 69.20; H, 7.74; N, 5.98. Found : C, 69.00; H, 7.95; N, 5.74.

(R)-3-[(R)-4-Cyano-4-(3,4-dimethoxyphenyl)-5-methylhex-1-yl]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline hydrochloride ((3R,4R)-12)

This compound was prepared from (+)-10 in 76% yield and was spectrally identical to (3S,4S)-12. Anal. Calcd for $C_{28}H_{38}N_2O_4 \cdot HCl$: C, 66.85; H, 7.81; N, 5.57. Found: C, 66.77; H, 7.86; N, 5.54.

(S)-3-[(R)-4-Cyano-4-(3,4-dimethoxyphenyl)-5-methylhex-1-yl]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline hydrochloride ((3S,4R)-11)

This compound was prepared from (+)-9 in 66% yield and was spectrally identical to (3R,4S)-11. Anal. Calcd for $C_{28}H_{38}N_2O_4 \cdot HCl \cdot 0.5\ H_2O$: C, 65.57; H, 7.87; N, 5.47. Found: C, 65.59; H, 7.89; N, 5.46.

(RS)-3-[(RS)-4-Cyano-4-(3,4-dimethoxyphenyl)-5-methylhex-1-yl]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline hydrochloride (2)

This was prepared according to the procedures described for the synthesis of the isomers except that (±)-4 was used and the diastereomeric formamides were not separated. The final product was analyzed by HPLC using a Spherisorb 5 C8 column with a mobile phase of 0.1 M triethylamine adjusted to pH 5.0:MeOH:AcN, 60:35:10. The two diastereomers were cleanly separated with the (R,S)/(S,R) pair eluting as the first peak followed by the (R,R)/(S,S) pair as the second. The diastereomer ratio was determined to be ~50:50. Anal. Calcd for $C_{28}H_{38}N_2O_4 \cdot HCl$: C, 66.85; H, 7.81; N, 5.57. Found: C, 66.92; H, 7.58; N, 5.60.

(S)-2-(tert-Butoxycarbonylamino)-3-(3,4-dimethoxyphenyl) propanol (14)

To a solution of 23.3 g (0.11 mol) of 13[13] in 400 ml of THF was added 24.0 g (0.11 mol) of di-tert-butyldicarbonate and the resulting solution was heated at reflux for 1 h. The mixture was concentrated at reduced pressure and the residue was filtered through silica gel (EtOAc). Evaporation afforded 32.4 g (95%) of (S)-14: mp 92-93°C; $[\alpha]_D^{25}$ -19.6° (c 0.3, MeOH). Anal. Calcd for $C_{16}H_{25}NO_5$: C, 61.72; H, 8.09; N, 4.50. Found: C, 61.62; H, 8.13; N, 4.57.

(S)-2-(tert-Butoxycarbonylamino)-3-(3,4-di-methoxyphenyl)-1-(4-methylbenzenesulfonyloxy)-propane (15)

A solution of 32.4 g (0.10 mol) of 14, 29.8 g (0.16 mol) of p-toluenesulfonyl chloride, and 0.63 g of DMAP in 100 ml of pyridine was stirred at room temperature for 48 h. The mixture was diluted with ether and washed with aqueous cupric sulfate and water. The ether was dried ($MgSO_4$) and evaporated to a residue that was purified by medium pressure chromatography (30% EtOAc-hexane) to afford 43.5 g (90%) of 15: mp 146-148°C; $[\alpha]_D^{25}$ -15.4° (c 0.36, $CHCl_3$). Anal. Calcd for $C_{23}H_{31}NO_7S$: C, 59.34; H, 6.71; N, 3.01. Found: C, 59.37; H, 6.73; N, 2.98.

(R)-2-(tert-Butoxycarbonylamino)-1-(3,4-dimethoxyphenyl)-4-pentene (16)

Vinylmagnesium bromide (37.3 ml, 0.06 mol, 1.6M in THF) was added to a -5°C suspension of 5.8 g (0.03 mol) of cuprous iodide in 75 ml of THF. The mixture was cooled to -70°C and a solution of 4.6 g (0.01 mol) of 15 in 80 ml of THF was added slowly. The resulting mixture was stirred at -70°C for 0.5 h and then allowed to warm to room temperature. The mixture was poured into aqueous NH_4Cl and extracted with Et_2O. The Et_2O was dried ($MgSO_4$) and evaporated. Purification of the residue by medium pressure chromatography (30% EtOAc-hexane) gave 2.0 g (63%) of 16: mp 91-92°C; ^1H NMR ($CDCl_3$) δ 1.41 (s, 9H), 2.05-2.30 (m, 2H), 2.70 (m, 2H), 3.86 (s, 3H), 3.86 (m, 1H, CHN), 3.87 (s, 3H), 5.10 (m, 2H), 5.80 (m, 1H), 6.70-6.82 (m, 3H); $[\delta]_D^{25}$ -20.9° (c 0.26, MeOH). Anal. Calcd for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47; N, 4.36. Found: C, 67.33; H, 8.49; N, 4.36.

(S)-4-(tert-Butoxycarbonylamino)-5-(3,4-dimethoxyphenyl)-1-pentanol (17)

A solution of 1.6 g (0.005 mol) of 16 was added to a 0°C solution of disiamylborane (0.0075 mol, from 1.6 ml of 2-methyl-2-butene and 7.5 ml of 1.0M BH_3) in 25 ml of THF. The mixture was stirred at room temperature for 1 h, cooled to 0°C, and treated with 1.7 ml of 3N NaOH and 1.7 ml of 30% H_2O_2. The resulting solution was stirred 0.5 h at room temperature, diluted with ether, and washed with water and brine. Evaporation of the ether and crystallization of the residue from Et_2O-hexane gave 1.2 g (70%) of 17: mp 73-75°C; $[\alpha]_D^{25}$ +0.89° (c 0.2, MeOH). Anal. Calcd for $C_{18}H_{29}NO_5$: C, 63.69; H, 8.61; N, 4.13. Found: C, 63.58; H, 8.64; N, 4.06.

(-)-9 and (+)-10 from 17, Scheme IV

A solution of 1.0 g (0.003 mol) of 17 in 15 ml of CH_2Cl_2 and 1.3 ml of triethylamine was cooled to 0°C and 0.26 ml (0.003 mol) of methanesulfonyl chloride was added. After 10 min the mixture was added to water and the CH_2Cl_2 was separated, dried ($MgSO_4$), and evaporated. The crude mesylate (18) was dissolved in 25 ml of acetone and 3.0 g of NaI were added. The mixture was heated under reflux of 0.5 h, poured into water, and extracted with Et_2O. The Et_2O extract was washed with aqueous $NaHSO_3$, water, and brine, dried ($MgSO_4$), and evaporated to crude 20 which was used at once in the next reaction.

A solution of 1.3 g (0.006 mol) of nitrile 19 in 5 ml of THF was added to a -70°C solution of LDA (0.006 mol) in 20 ml of THF. After 20 min at -70°C, the mixture was treated with a solution of crude 20 (from above) in 5 ml of THF and the resulting solution was allowed to warm to 0°C. Aqueous HCl was added and the mixture was extracted with Et_2O. The Et_2O extract was washed with water and brine, dried ($MgSO_4$), and evaporated to a residue which was

purified by medium pressure chromatography (30% EtOAc-hexane) to afford 0.6 g (38%) of the diastereomeric mixture 21. This material was dissolved in 5 ml of formic acid and the resulting solution was heated at reflux for 15 min. The mixture was concentrated under reduced pressure and the residue was treated with 2 ml of formic-acetic anhydride. Et_2O was added and the mixture was washed with water, aqueous $NaHCO_3$, and brine. After drying (Na_2SO_4) the ether was evaporated and the residue was purified by medium pressure chromatography (EtOAc). The first component eluted was (-)-9, (0.18 g), identical by tlc and nmr analysis with material from the other route: $[\alpha]_D^{25}$ -4.3° (c 0.28, MeOH). The second component eluted was (+)-10 (0.04 g) identical by tlc and nmr analysis with material from the other route: $[\alpha]_D^{25}$ +2.3° (c 0.3, MeOH).

(-)-(3R,4S)-11 from Scheme IV

This was prepared from formamide (-)-9, derived from 13 in Scheme IV, in 68% yield according to the previously described procedure. Anal. Calcd for $C_{28}H_{38}N_2O_4 \cdot HCl \cdot 0.5\ H_2O$: C, 65.57; H, 7.87; N, 5.47. Found: C, 65.59; H, 7.89; N, 5.46.

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10. Examples would include such compounds as the β-agonists trimetoquinol and higenamine (1-substituted THIQ), the antidepressant nomifensin (2,4-disubstituted), and the tranquilizer butaclamol (1,2,4-trisubstituted) among others.

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16. It is interesting to note that attaching the verapamil side chain to the 2-position of 6,7-dimethoxy-THIQ gave a compound with minimal calcium antagonist activity (ED_{50} = 1 mM) (D. Repke, unpublished results).

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