SYNTHESIS OF DEUTERATED OPTICALLY ACTIVE VERAPAMIL AND GALLOPAMIL, AND OF N-^{13}C-METHYL-VERAPAMIL

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SUMMARY

Deuterated (-)-verapamil, (2S)-(-)-2-(2,5,6-$^{2}H_3$-3,4-dimethoxyphenyl)-2-isopropyl-5-[(2,5,6-$^{2}H_3$-3,4-dimethoxyphenethyl)methylamino]valeronitrile, and its analog (-)-$^{2}H_5$-gallopamil, (2S)-(-)-2-(2,6-$^{2}H_2$-3,4,5-trimethoxyphenyl)-2-isopropyl-5-[(2,5,6-$^{2}H_3$-3,4-dimethoxyphenethyl)methylamino]valeronitrile, were prepared. (-)-Gallopamil readily incorporated five atoms of deuterium into the available positions in the aromatic rings. (-)-$^{2}H_6$-Verapamil was prepared from ring trideuterated 3,4-dimethoxyphenylacetic acid and (2S)-(+)-triphenylmethoxy-2-[(methanesulfonyl)oxy]propane. Three additional atoms of deuterium were incorporated into the aromatic ring of the N-methyl-3,4-dimethoxyphenethylamine moiety incorporated as the the short N-alkyl side chain. N-^{13}C-Methyl-verapamil was prepared from N-^{13}C-methyl-3,4-dimethoxyphenethylamine.

INTRODUCTION

Verapamil (1), 2-(3,4-dimethoxyphenyl)-2-isopropyl-5-[(3,4-dimethoxyphenethyl)methylamino]valeronitrile, is used widely in the treatment of a variety of cardiovascular diseases, including paroxysmal superventricular tachycardia, angina and hypertension.[1-3] Its pharmacologic, metabolic and pharmacokinetic properties have attracted considerable interest.[4-8] Enantiomeric differences in pharmacological effects have been noted,[9-13] and differential metabolism of its enantiomers has been reported.[13-15] We sought heavy isotope labeled enantiomers

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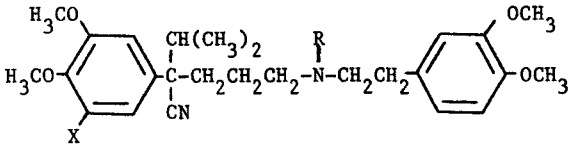
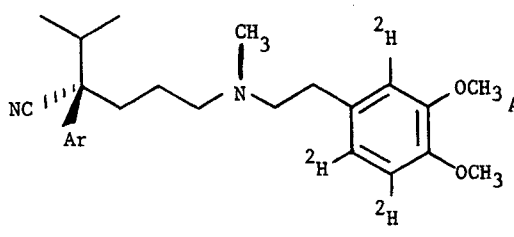
of 1 and of its analog gallopamil (2), 2-(3,4,5-trimethoxyphenyl)-2-isopropyl-5-[(3,4-dimethoxyphenethyl)methylamino]valeronitrile, which would be suitable for analysis of metabolites arising from loss of either the long or short N-alkyl groups of the molecule and for mechanistic work concerning formation of some of the metabolites. Although ^{13}C- and deuterium labeled compounds have been reported previously,[16-19] none afforded labeling of both the long and short N-alkyl groups. In this paper, we report the synthesis of the S-(-)-enantiomers of verapamil and of gallopamil labeled with deuterium in both aromatic rings (3 and 4, respectively). The synthesis of racemic verapamil containing a ^{13}C-atom in the N-methyl group (5) is also reported.



1 X = H R = CH_3 verapamil

2 X = OCH_3 R = CH_3 gallopamil

5 X = H R = $^{13}CH_3$



3 X = ^2H

4 X = OCH_3

RESULTS AND DISCUSSION

Although acid-catalyzed exchange in the phenylacetonitrile aromatic ring of verapamil in $^2H_2$-sulfuric acid-^2H_2O was only partially successful,[20] gallopamil (2) afforded a more activated aromatic ring, and was thus thought to be more amenable to complete exchange. When stirred in $^2H_2$-sulfuric acid-^2H_2O at reflux for 24 hr, (2S)-(-)-gallopamil, synthesized by our previously reported procedure,[21] afforded exchanged (2S)-(-)-gallopamil (4) in 91% yield, with >95% of the molecules containing five deuterium atoms (Figure 1).

The mass spectrum (CI-methane) of 4 showed ions at m/z 489, 490, 491 and 492 (8:68:22:4) vs. gallopamil 484, 485, 486 and 487 [4:70:22(^{13}C):4($^{13}C_2$)] (Figure 1). In addition, protonated M-2 ions at m/z 488 and 483, respectively,

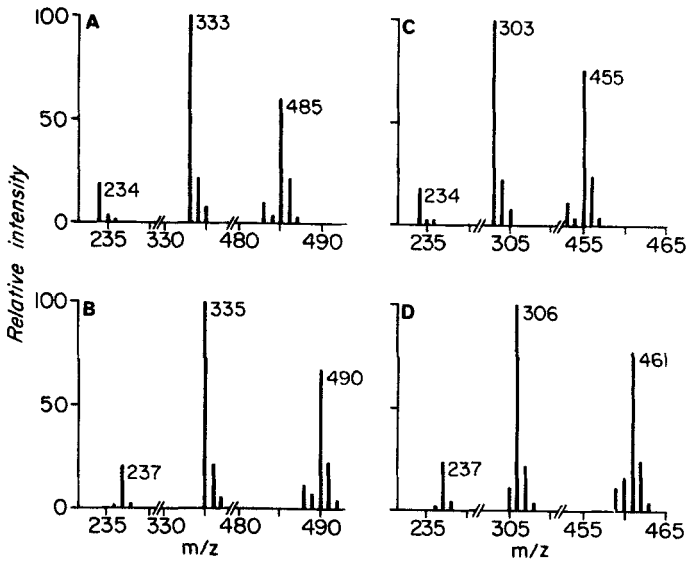


Figure 1. Partial CI-methane mass spectra of A., gallopamil; B. compound 4; C., verapamil; D., compound 3.

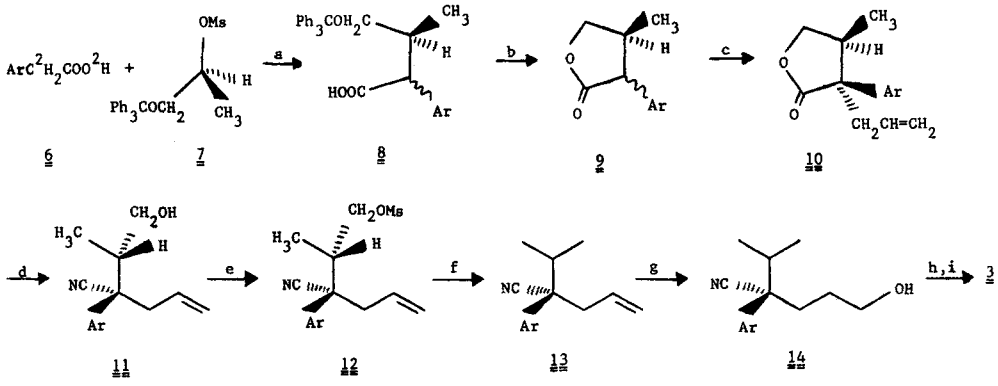
were observed in both spectra. Significant EI fragmentation also occurred as shown by ions at m/z 334, 335 and 336 (2:100:21) and at 236, 237 and 238 (1.6:20:4) for 4. The m/z 335 ion is accounted for by loss of the 3,4-dimethoxybenzyl group. The m/z 334-336 ions arise from incorporation of two atoms of deuterium in >97% into the 3,4,5-trimethoxyphenylacetonitrile portion of 4. The ions at m/z 236-238 are thought to arise from a fragment which has lost the elements of 2-isopropyl-2-(3,4-dimethoxyphenyl)acetonitrile and are thus consistent with >90% incorporation of three atoms of deuterium into the 3,4-dimethoxyphenyl group.

Because the direct deuterium exchange on verapamil was incomplete,[20] we chose to introduce the needed deuterium atoms via exchange on aryl intermediates in the synthetic process previously used for preparation of the enantiomers of verapamil.[21] 3,4-Dimethoxyphenylacetic acid was exchanged in 25% (w/w) ^2H-sulfuric acid-^2H_2O at 105°C for 48 hr. Cooling the reaction mixture to room temperature followed by extraction with CH_2Cl_2 afforded the partially exchanged acid in nearly quantitative yield. As ^1H NMR spectroscopy indicated that these

conditions are sufficient to attain aromatic ^{1}H-^{2}H equilibrium, the process was repeated two additional times to afford almost isotopically pure $^{2}H_{6}$-dimethoxyphenylacetic acid 6 in 88% overall yield.

As illustrated in Scheme 1, the dilithium salt of 6 was allowed to react with chiral mesylate 7 in THF at room temperature for 126 hr. Aqueous acidic work-up afforded hydroxy acid 8 (a mixture of 2R,3S and 2S,3S diastereomers), which was then deprotected and cyclized to lactone 9 (also a mixture of 2R,3S and 2S,3S diastereomers) by stirring in methanol, in the presence of catalytic p-toluenesulfonic acid at room temperature for 12 hr. The overall yield of 9 from 7 was 71%. Alkylation of the sodium salt of 9 with allyl bromide at 0°C for 4 hr gave lactone 10 as a single diastereomer (2S,3S) in 85% yield.

Further elaboration of 10 to alcohol 14 was carried out according to our previously described procedure[21] in 72% overall yield. Displacement of the mesylate of 14 with (2,5,6-$^{2}H_{3}$-3,4-dimethoxyphenethyl)methylamine (15), made by deuteration of (3,4-dimethoxyphenethyl)methylamine according to the procedure used for deuteration of acid 6, afforded (2S)-(-)-$^{2}H_{6}$-verapamil (3) in 82% yield.



Ar = 2,5,6-$^{2}H_{3}$-3,4-$(MeO)_{2}$-Ph

Reagents: (a) $LiN(iPr)_{2}$, THF; (b) MeOH, p-TsOH; (c) NaH, $BrCH_{2}$-CH=CH_{2}, THF; (d) $Me_{2}AlNH_{2}$, $Cl_{2}CHCH_{2}Cl$; (e) MsCl, $Et_{3}N$, $CH_{2}Cl_{2}$; (f) $NaBH_{4}$, t-BuOH, DME; (g) disiamylborane, THF, then $H_{2}O_{2}$; (h) MsCl, $Et_{3}N$, $CH_{2}Cl_{2}$; (i) 15, $Et_{3}N$, THF.

SCHEME 1.

The mass spectrum (CI-methane) of 3 indicated incorporation of three deuterium atoms in the aromatic ring of the short N-alkyl group was 95-96% while incorporation of three deuterium atoms in the aromatic ring of the long N-alkyl group was 90% (Figure 1). The slightly diminished isotopic purity of the latter aromatic ring is presumed to be a result of slow exchange in methanol during lactonization of acid 8 to 9. Greater enrichment could obviously be achieved by performing this step in ^{2}H-methanol. At any rate, the extent of deuterium incorporation is still substantial, and is adequate for our metabolic studies and a great improvement over the previously published procedure.[20]

Racemic N-^{13}C-methyl-verapamil (5) was prepared by displacement of the mesylate of racemic alcohol 16 with (3,4-dimethoxyphenethyl)-^{13}C-methylamine (17). The labeled amine was prepared via a variation of the procedure of Johnstone.[22] Treatment of (3,4-dimethoxyphenethyl)trifluoroacetamide with NaH in THF at room temperature for 30 min was followed by addition of ^{13}C-iodomethane and stirring for 3 hr to afford N-(3,4-dimethoxyphenethyl)-N-(^{13}C-methyl)trifluoroacetamide. Hydrolysis of the trifluoroacetyl group was performed by stirring in 6:1 EtOH/4N aq KOH at room temperature for 2 hr affording amine 17 in 84% overall yield.

Metabolic studies on verapamil and gallopamil utilizing these chiral deuterated and racemic C^{13}-labeled compounds are currently in progress.

EXPERIMENTAL

High field proton NMR spectra were obtained at 500 MHz on a Brucker WM-500 spectrometer. Chemical shifts are expressed in parts per million (δ) downfield from internal tetramethylsilane (δ 0.0). Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. High resolution mass sepctra were obtained on a VG-7070 mass spectrometer by direct insert probe. Infrared spectra were recorded on a Perkin-Elmer 283 infrared spectrometer. Optical rotations were measured on a Jasco DIP-4 digital polarimeter at the sodium D-line. Analytical thin-layer chromatography (TLC) was carried out on Analtech silica gel HLF TLC plates (0.25 mm thickness) and the spots were detected by a UV lamp (254 nm). Preparative TLC was carried out on Merck pre-coated silica gel 60 F-254 PLC plates (2 mm thickness). Merck Silica Gel 60 (230-400 mesh ASTM) was used for flash column chromatography.[23] Melting points were determined with a Thomas Hoover capillary melting point apparatus

and are uncorrected. Unless otherwise specified, concentration of reaction mixtures or extracts was carried out (after drying with $MgSO_4$) on a Buchi rotary evaporator at aspirator pressure.

Tetrahydrofuran (THF) was distilled under argon from sodium metal with benzophenone as an indicator. Methylene chloride and 1,1,2-trichloroethane were distilled from phosphorous pentoxide. Triethylamine and diisopropylamine were distilled under argon from powedered NaH. All solvents used for extraction were reagent grade. Unless otherwise indicated, all other reagents or solvents were used without further purification. Prepurified argon was dried by passing through a two foot column packed with indicating Drierite™ and KOH. All glassware was either oven dried for a minimum of 2 hr at 140°C and then purged with argon or flame dried under a continuous flow of argon. All reactions were carried out under an argon atmosphere.

(2S)-(-)-2(2,6-$^2H_2$-3,4,5-Trimethoxyphenyl)-2-isopropyl-5-[(2,5,6-$^2H_3$-3,4-dimethoxyphenethyl)methylamino]valeronitrile [4, (-)-$^2H_5$-gallopamil]. To 1.31 g (2.51 mmol) of (-)-gallopamil·HCl[21] in 47.6 g (2.38 mol) of ^2H_2O, was added 11.8 g (0.118 mol) of $^2H_2$-sulfuric acid. The mixture was heated to reflux and stirred for 24 hr. The mixture was then cooled to 0°C, neutralized by addition of 20 g of solid NaOH (0.25 mol) and extracted with ether (3 x 75 mL). The organic extracts were combined, filtered and concentrated to afford 1.12 g (2.29 mmol) of the product (4) as a colorless oil (91%): TLC (5:5:90 Et_3N/MeOH/EtOAc) R_f 0.55; NMR (CD_3OD) 3.83 (6 H, s), 3.80 (3 H, s), 3.78 (3 H, s), 3.76 (3 H, s), 2.64 (2 H, m), 2.51 (2 H, m), 2.40 (2 H, m), 2.21 (4 H, singlet on multiplet), 2.13 (1 H, m), 1.94 (1 H, m), 1.53 (1 H, m), 1.19 (4 H, doublet on multiplet, J = 6.6 Hz) and 0.78 ppm (3 H, d, J = 6.6 Hz); IR (neat) 2970, 2945, 2850, 2800, 2235, 1582, 1473 and 1127 cm^{-1}; MS (CI-methane) m/z 492, 491, 490 489, 488 (4, 22, 68, 7.8, 11), 337, 336, 335, 334 (5, 21, 100), 238, 237, 236 (4, 20, 1.6). The oil was dissolved in 30 mL of THF and 2.33 g of 8.4% etheral HCl (5.37 mmol) was added at 0°C. The mixture was stirred for 1 min and then concentrated. The resulting amorphous HCl salt was recrystallized from 25 mL of 2:3 2-propanol/cyclohexane to afford 621 mg of the HCl salt of 4 as a white crystalline solid (52%): mp 158-159.5°C; $[\alpha]_D$ -11.6°(c 5.00, ethanol). Lit.[21] (non-deuterated): mp 160.5-161.5°C; $[\alpha]_D^{23}$ -11.7° (c 5.04, ethanol).

2,5,6-$^2H_3$-3,4-Dimethoxyphenyl-$^2H_3$-acetic acid (6). To a mixture of 35.0 g (0.178 mmol) of 3,4-dimethoxyphenylacetic acid and 45.0 g (2.25 mol) of deuterium oxide, was added 15.0 g (0.150 mol) of $^2H_2$-sulfuric acid. The mixture was stirred at 105°C for 48 hr and then cooled to room temperature and extracted with CH_2Cl_2 (3 x 150 mL). The organic extracts were combined, dried, filtered and concentrated. The residue was subjected to the above reaction two more times to afford 31.8 g (157 mmol) of 6 as a beige solid (88%).

(2RS,3S)-2-(2,5,6-$^2H_3$-3,4-Dimethoxyphenyl)-2,3-methylbutyrolactone (9). To a stirred solution of 31.6 g (312.3 mmol, 2.30 equiv) of diisopropylamine in 500 mL of THF was added 113 mL of 2.67M n-BuLi (302 mmol, 2.22 equiv) in hexane at 0°C over a 15 minute period. The mixture was stirred at 0°C to room temperature for 30 min and then 30.5 g (151 mmol, 1.11 equiv) of 6 in 150 mL of THF was added via cannula over a 30 minute period, the temperature of the reaction mixture being controlled by means of a room temperature water bath. The mixture was stirred for 1 hr after the addition was completed, and then 54.0 g (136 mmol, 1.00 equiv) of (2S)-(+)-triphenylmethoxy-2-[(methanesulfonyl)oxy]propane (7)[21] in 250 mL of dry THF was added via cannula over a 30 min period. The mixture was stirred at room temperature for 126 hr and then poured into 500 mL of ice cold 2N aq H_2SO_4. The mixture was stirred for 10 minutes and the layers separated. The aqueous phase was extracted with EtOAc (2 x 200 mL). The organic extracts were combined, dried, filtered and concentrated. The residue, acid 8 (an amber oil), was diluted with 300 mL of methanol and treated with 500 mg (2.63 mmol) of p-toluenesulfonic acid. The solution was stirred at room temperature for 12 hr and then concentrated. The residue was chromatographed on 220 g of silica gel, eluting first with 5% EtOAc/hexanes, then with 25% EtOAc/hexanes and finally with 40% EtOAc/hexanes, to afford 23.03 g (95.85 mmol) of the product [9, a mixture of cis (2R,3S) and trans (2S,3S) diastereomers] as a pale yellow oil which crystallized to a yellow solid on standing (71%): TLC (25% EtOAc/hexanes) R_f 0.15, (50% EtOAc/hexanes) R_f 0.51; ^1H NMR ($CDCl_3$) 4.51 (0.65 H, dd, J = 7.5, 8.9 Hz, from trans), 4.45 (0.35 H, dd, J = 6.4, 8.9 Hz, from cis), 4.03 (0.35 H, dd, J = 4.4, 8.9 Hz, from cis), 3.90-3.87 (7 H, 2 singlets on multiplets, from cis and trans), 3.23 (0.65 H, d, J = 11.2 Hz, from trans), 2.86 (0.35 H, m, from cis), 2.66 (0.65 H, m, from trans), 1.17 (1.95 H, d, J = 6.4 Hz, from trans) and 0.81 ppm (1.05 H, d, J = 7.0 Hz, from cis); IR ($CHCl_3$) 2940, 2840, 1778, 1593, 1578, 1471 and 1017 cm^{-1}.

(2S,3S)-(-)-2-(2-Propenyl)-2-(2,5,6-$^2H_3$-3,4-dimethoxyphenyl)-3-methylbutyrolactone (10). To a stirred solution of 22.01 g (91.56 mmol) of lactone 9 in 200 mL of dry THF in a 500 mL round bottom flask was added 3.30 g (138 mmol, 1.50 equiv) of NaH. The flask was fitted with a rubber serum cap and connected to a bubbler via a 14 gauge syringe needle. The heterogeneous mixture was warmed to 45°C and stirred for 4 hr. After this time, the mixture was cooled to 0°C and 13.85 g (114.5 mmol, 1.25 equiv) of allyl bromide was added over a 10 minute period. The mixture was stirred at 0°C for 4 hr and then carefully poured into 250 mL of ice cold 5% v/v aq HCl. The layers were separated and the aqueous phase was extracted with EtOAc (2 x 100 mL). The organic extracts were combined, dried, filtered and concentrated. The residue was chromatographed on 220 g of silica gel, eluting first with 20% EtOAc/hexanes and then with 30% EtOAc/hexanes, to afford 21.70 g (77.68 mmol) of the product (10) as a white

crystalline solid (85%): TLC (25% EtOAc/hexanes) R_f 0.32; mp 86.0-87.5°C; $[\alpha]_D^{22}$ -48.5° (c 3.80, $CHCl_3$); ^1H NMR ($CDCl_3$) 5.83 (1 H, m), 5.19 (1 H, d, J = 17.6 Hz), 5.18 (1 H, d, J = 10.3 Hz), 4.34 (1 H, t, J = 8.8 Hz), 3.87 (3 H, s), 3.86 (3 H, s), 3.70 (1 H, t, J = 8.8 Hz), 2.84 (1 H, dd, J = 6.0, 13.8 Hz), 2.71 (2 H, m) and 0.71 ppm (3 H, d, J = 6.9 Hz); IR ($CHCl_3$) 2940, 2840, 1771, 1643, 1590, 1574, 1470, 1247 and 1018 cm^{-1}.

(2S,3S)-(+)-2-Methyl-3-cyano-3-(2,5,6-$^2H_3$-3,4-dimethoxyphenyl)hex-5-enol (11). To 500 mL of dry 1,1,2-trichloroethane in a 1 liter round botom flask, fitted with a reflux condenser topped with a rubber serum cap and connected to a Drierite™ drying tube, was bubbled anhydrous ammonia at 0°C for 25 min. After this time, 115 mL of 2.0M $AlMe_3$ (230 mmol, 3.03 equiv) in toluene was added. The mixture was then heated to 80°C over a 1 hr period and stirred at 80°C for 1 hr to bubble off excess ammonia. Then, 21.19 g (75.86 mmol) of lactone 10 in 150 mL of dry 1,1,2-trichloroethane was added via cannula over a 15 min period and the mixture was stirred at reflux (oil bath temperature of 125°C) for 44 hr. The mixture was cooled to 0°C, 300 mL of 10% v/v aq HCl was added (very cautiously at first) and the resulting mixture was stirred for 30 min. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 150 mL). The organic extracts were combined, dried, filtered and concentrated. The residue was chromatographed on 200 g of silica gel, eluting first with 30% EtOAc/hexanes and then with 50% EtOAc/hexanes, to afford 19.43 g (69.80 mmol) of 11 as a very pale yellow oil (92%): TLC (50% EtOAc/hexanes) R_f 0.43; $[\alpha]_D^{22}$ +26.8° (c 3.40, $CHCl_3$); ^1H NMR ($CDCl_3$) 5.53 (1 H, m), 5.12 (1 H, d, J = 16.5 Hz), 5.06 (1 H, d, J = 10.3 Hz), 4.00 (1 H, m), 3.89 (3 H, s), 3.88 (3 H, s), 3.69 (1 H, m), 2.94 (1 H, dd, J = 7.6, 14.2 Hz), 2.72 (1 H, dd, J = 6.5, 14.2 Hz), 2.19 (1 H, m), 1.48 (1 H, t, J = 4.9 Hz) and 0.93 ppm (3 H, d, J = 6.8 Hz); IR (neat) 3520, 3090, 2950, 2885, 2840, 2240, 1648, 1591, 1578 and 1475 cm^{-1}.

(2S,3S)-(+)-1-[(Methanesulfonyl)oxy]-2-methyl-3-cyano-3-(2,5,6-$^2H_3$-3,4-dimethoxyphenyl)hex-5-ene (12). To a stirred solution of 18.90 g (67.90 mmol) of alcohol 11 and 8.60 g (85.0 mmol, 1.25 equiv) of Et_3N in 200 mL of CH_2Cl_2 was added 8.20 g (71.58 mmol, 1.05 equiv) of methanesulfonyl chloride at 0°C. The mixture was stirred at 0°C for 1 hr and then washed with 5% (v/v) aq HCl (2 x 150 mL). The organic phase was dried filtered and concentrated. The residue was chromatographed on 200 g of silica gel, eluting with 50% EtOAc/hexanes, to afford 23.01 g (64.56 mmol) of 12 as a pale yellow oil (95%): TLC (50% EtOAc/hexanes) R_f 0.54; $[\alpha]_D^{22}$ +22.5° (c 5.20, $CHCl_3$); ^1H NMR ($CDCl_3$) 5.50 (1 H, m), 5.15 (1 H, d, J = 16.7 Hz), 5.09 (1 H, d, J = 9.8 Hz), 4.50 (1 H, dd, J = 5.1, 10.3 Hz), 4.21 (1 H, dd, J = 6.9, 10.3 Hz), 3.90 (3 H, s), 3.89 (3 H, s), 3.07 (3 H, s), 2.88 (1 H, dd, J = 7.7, 13.9 Hz), 2.74 (1 H, dd, J = 6.3, 13.9 Hz), 2.45 (1 H, m) and 0.99 ppm (3 H, d, J = 6.9 Hz); IR (neat) 3085, 2980, 2945, 2885, 2840, 2240, 1647, 1590, 1576, 1476, 1359 and 1178 cm^{-1}.

(4S)-(+)-4-Cyano-4-(2,5,6-$^2H_3$-3,4-dimethoxyphenyl)-4-isopropylbutene (13). To a stirred solution of 22.47 g (63.04 mmol) of mesylate 12 and 23.4 g (316 mmol, 5.0 equiv) of t-butanol in 200 mL of dry DME was added 7.15 g (189 mmol, 3.0 equiv) of sodium borohydride at room temperature. The mixture was heated to reflux and stirred for 48 hr. The mixture was then cooled to room temperature, diluted with 200 mL of Et_2O and vacuum filtered through a layer of celite. The solids were washed with 100 mL of Et_2O. The filtrates were combined and vigorously stirred with 50 mL of H_2O to destroy dissolved sodium borohydride. The mixture was then concentrated. The residue was diluted with 250 mL of CH_2Cl_2 and washed with 150 mL of 5% (v/v) aq HCl. The organic phase was dried, filtered and concentrated. The residue was chromatographed on 200 g of silica gel, eluting with 25% EtOAc/hexanes, to afford 14.89 g (56.76 mmol) of 13 as a colorless oil (90%): TLC (25% EtOAc/hexanes) R_f 0.52; $[\alpha]_D^{22}$ +19.8° (c 3.63, $CHCl_3$); ^1H NMR ($CDCl_3$) 5.51 (1 H, m), 5.09 (1 H, d, J = 17.3 Hz), 5.04 (1 H, d, J = 9.8 Hz), 3.89 (3 H, s), 3.88 (3 H, s), 2.83 (1 H, dd, J = 7.7, 14.0 Hz), 2.61 (1 H, dd, J = 6.4, 14.0 Hz), 2.13 (1 H, septet, J = 6.6 Hz), 1.20 (3 H, d, J = 6.6 Hz) and 0.83 ppm (3 H, d, J = 6.6 Hz); IR (neat) 3085, 2980, 2945, 2880, 2840, 2240, 1647, 1590, 1576, 1478 and 1260 cm^{-1}.

(4S)-(-)-4-Cyano-4-(2,5,6-$^2H_3$-3,4-dimethoxyphenyl)-4-isopropylbutanol (14). To 110 mL of 1M borane in THF (110 mmol, 2.0 equiv) was added 15.4 g (220 mmol, 4.0 equiv) of 2-methyl-2-butene at 0°C over a 10 minute period. The mixture was stirred at 0°C for 2 hr and then transferred via cannula, over a 10 min period, to a stirred solution of 14.45 g (55.08 mmol) of olefin 13 in 100 mL of dry THF. The mixture was stirred at 0°C for 1 hr and the excess disiamylborane was destroyed by careful addition of 30 mL of 5% aq NaOH. Then, 40 mL of 30% aq H_2O_2 was added over a 30 min period. The mixture was stirred for an additional 15 min after the addition was complete, and then 75 mL of H_2O was added followed by careful addition of 15 g (144 mmol) of solid sodium hydrogen sulfite. The mixture was stirred for 10 min after the addition was complete and the organic phase was separated. The aqueous phase was extracted with EtOAc (2 x 100 mL). The organic extracts were combined, dried, filtered and concentrated. The residue was chromatographed on 200 g of silica gel, eluting first with 30% EtOAc/hexanes and then with 75% EtOAc/hexanes, to afford 14.13 g (50.40 mmol) of 14 as a colorless oil (92%): TLC (50% EtOAc/hexanes) R_f 0.34; $[\alpha]_D^{22}$ -12.9° (c 5.29, $CHCl_3$); ^1H NMR ($CDCl_3$) 3.89 (3 H, s), 3.88 (3 H, s), 3.60 (2 H, m), 2.22 (1 H, m), 2.09 (1 H, septet, J = 6.5 Hz), 1.93 (1 H, m), 1.62 (1 H, m), 1.26 (1 H, m), 1.20 (3 H, d, J = 6.5 Hz), 1.15 (1 H, m) and 0.81 ppm (3 H, d, J = 6.5 Hz); IR (neat) 3520, 2980, 2945, 2885, 2840, 2240, 1590, 1575 and 1476 cm^{-1}.

N-(2,5,6-$^2H_3$-3,4-Dimethoxyphenethyl)-N-methylamine (15). To a mixture of 30.1 g (0.154 mol) of (3,4-dimethoxyphenethyl)methylamine and 50 g (2.50 mol) of

^2H_2O, was added 20 g (0.20 mol) of $^2H_2$-sulfuric acid. The mixture was heated to 100°C and stirred for 48 hr. The mixture was cooled to 0°C and neutralized by addition of 17 g (0.425 mol) of solid NaOH. The mixture was extracted with CH_2Cl_2 (3 x 100 mL). The organic extracts were combined, dried, filtered and concentrated. The residue was subjected to the above reaction sequence a second time and then distilled under reduced pressure to afford 22.4 g (112.4 mmol) of 15 as a colorless oil (73%): bp 127-131°C (0.5 mm Hg); ^1H NMR ($CDCl_3$) 3.87 (3 H, s), 3.85 (3 H, s), 2.82 (2 H, t, J = 6.6 Hz), 2.75 (2 H, t, J = 6.6 Hz) and 2.44 (3 H, s).

(2S)-(-)-2-(2,5,6-$^2H_3$-3,4-Dimethoxyphenyl)-2-isopropyl-5-[(2,5,6-$^2H_3$-3,4-dimethoxyphenethyl)methylamino]valeronitrile [3, (-)-$^2H_6$-verapamil]. To a stirred solution of 13.40 g (47.79 mmol) of alcohol 14 and 6.04 g (59.7 mmol, 1.25 equiv) of Et_3N in 200 mL of dry CH_2Cl_2 was slowly added 5.75 g (50.2 mmol, 1.05 equiv) of methanesulfonyl chloride at 0°C. The mixture was stirred at 0°C for 2 hr and then washed with 5% (v/v) aq HCl (2 x 100 mL). The organic phase was dried, filtered and concentrated. The residue was diluted with 75 mL of dry THF and then treated with 11.2 g (56.2 mmol, 1.10 equiv) of 15 and 6.45 g (63.7 mmol, 1.25 equiv) of Et_3N. The mixture was stirred at 80°C for 24 hr, cooled to 0°C and then treated with 5.36 g (25.5 mmol, 0.53 equiv) of trifluoroacetic anhydride. The mixture was stirred at room temperature for 1 hr and then concentrated. The residue was diluted with 100 mL of Et_2O, 200 mL of H_2O and then treated with 21 g (250 mmol) of sodium bicarbonate. The mixture was stirred at room temperature for 1 hr and the phases were then separated. The aqueous phase was extracted with Et_2O (3 x 100 mL). The organic extracts were combined, dried, filtered and concentrated. The residue was chromatographed on 220 g of silica gel, eluting first with EtOAc and then with 20% MeOH/EtOAc, to afford 18.03 g (39.14 mmol) of 3 as a very pale yellow oil (82%): TLC (5:5:90 Et_3N/MeOH/EtOAc) R_f 0.55; ^1H NMR (CD_3OD) δ 3.83 (3 H, s), 3.82 (3 H, s), 3.80 (3 H, s), 3.79 (3 H, s), 2.64 (2 H, m), 2.53 (2 H, m), 2.43 (1 H, m), 2.22 (3 H, s), 2.17 (1 H, septet), J = 6.8 Hz), 2.12 (1 H, m), 1.92 (1 H, m), 1.53 (1 H, m, 1.18 (4 H, d on a multiplet), J = 6.8 Hz) and 0.77 ppm (3 H, d, J = 6.8 Hz); IR (neat) 2965, 2940, 2880, 2850, 2800, 2235, 1590, 1577, 1465 and 1248 cm^{-1}; MS (CI-methane) m/e 463, 462, 461,460, 459 (4, 23, 78, 17, 11.7), 308, 307, 306, 305 (5, 1, 100, 11), 238, 237, 236 (4.4, 24, 2.7). The oil was dissolved in 150 mL of THF and 25.8 g of 8.3% etheral HCl (58.7 mmol, 1.50 equiv) was added at 0°C. The mixture was stirred for 1 minute and then concentrated. The resulting amorphous HCl salt was recrystallized from 250 mL of 1:1 2-propanol/cyclohexane to afford 17.31 g (34.82 mmol) of the HCl salt of 3 as a white crystalline solid (89%): mp 130-134°C; $[\alpha]_D^{23}$ -8.8° (c 5.00, ethanol). Lit.[21] (non-deuterated): mp 131-133°C; $[\alpha]_D^{23}$ -8.9° (c 5.00, ethanol).

N-(3,4-Dimethoxyphenethyl)-N-(^{13}C-methyl)amine (17). To a stirred solution of 1.81 g (6.53 mmol) of (3,4-dimethoxyphenethyl)trifluoroacetamide[22] in 50 mL of THF was added 265 mg (11.04 mmol, 1.50 equiv) of NaH. The mixture was stirred at room temperature for 30 min and then 1.34 g (9.38 mmol, 1.43 equiv) of ^{13}C-iodomethane (99% ^{13}C) was added. The mixture was stirred for 3 hr and then filtered. The filtrate was then concentrated and the residue was chromatographed on silica gel, eluting with CH_2Cl_2, to afford 1.71 g (5.85 mmol) of N-(3,4-dimethoxyphenethyl)-N-(^{13}C-methyl)trifluoroacetamide, as a white solid. The solid was dissolved in 30 mL of EtOH and treated with 5 mL of 4N aq KOH. The mixture was stirred at room temperature for 2 hr and then concentrated. The residue was diluted with 50 mL of CH_2Cl_2 and washed with 20 mL of saturated aq $NaHCO_3$. The organic phase was dried, filtered and concentrated to afford 1.08 g (5.50 mmol) of 17 as a pale yellow oil (84%): NMR ($CDCl_3$) 6.80 (1H, d, J = 7.9 Hz), 6.75 (1 H, dd, 1.7, 7.9 Hz), 6.74 (1 H, d, J = 1.7 Hz), 3.87 and 3.85 (6 H, 2s), 2.82 (2 H, t, J = 6.6 Hz), 2.75 (2 H, t, J = 6.6 Hz), 2.45 (3 H, d, J = 134.7 Hz) and 1.28 ppm (1 H, broad s).

2-(3,4-Dimethoxyphenyl)-2-isopropyl-5-[(3,4-dimethoxyphenethyl)-^{13}C-methyl-amino]valeronitrile (5, N-^{13}C-methyl-verapamil). To a stirred solution of 1.21 g (4.36 mmol) of alcohol 16[24] and 0.56 g (5.53 mmol, 1.25 equiv)) of Et_3N in 25 mL of dry CH_2Cl_2 was slowly added 0.53 g (4.63 mmol, 1.05 equiv) of methanesulfonyl chloride at 0°C. The mixture was stirred at 0°C for 2 hr and then washed with 25 mL of 5% v/v aq HCl. The organic phase was dried, filtered and concentrated. The residue was diluted with 10 mL of dry THF and then treated with 1.04 g (5.30 mmol, 1.20 equiv) of 17 and 1.00 g (9.88 mmol, 2.27 equiv) of Et_3N. The mixture was stirred at reflux for 40 hr and then cooled and concentrated. The residue was diluted with 100 mL of EtOAc and then washed with 25 mL of 1N aq NaOH. The organic phase was dried, filtered and concentrated. The residue was chromatographed on silica gel, eluting first with 5:95 Et_3N/CH_2Cl_2 and then with 5:5:90 Et_3N/MeOH/CH_2Cl_2, to afford 1.41 (3.09 mmol) of as a very pale yellow oil (71%): TLC (5:5:90 Et_3N/MeOH/EtOAc) R_f 0.55; ^{1}H NMR (CD_3OD) δ 6.99 (1 H, dd, J = 1.8, 8.4 Hz), 6.96 (1 H, d, J = 8.4 Hz), 6.94 (1 H, d, J = 1.8 Hz), 6.84 (1 H, d, J = 8.0 Hz), 6.75 (1 H, d, J = 1.6 Hz), 6.66 (1 H, dd, J = 1.6, 8.0 Hz), 3.83 (3 H, s), 3.82 (3 H, s), 3.80 (3 H, s), 3.79 (3 H, s), 2.65 (2 H, m), 2.52 (2 H, m), 2.42 (1 H, m), 2.22 (1 H, d, J = 133.9 Hz), 2.17 (1 H, septet, J = 6.8 Hz), 2.12 (1 H, m), 1.92 (1 H, m), 1.53 (1 H, m), 1.18 (4 H, d on a multiplet; J = 6.8 Hz) and 0.77 ppm (3 H, d, J = 6.8 Hz); IR (neat) 2960, 2940, 2840, 2240, 1610, 1596, 1511, 1467, 1393, 1377, 1262 and 1021 cm^{-1}; MS (CI-methane) m/e 458, 457, 456 (6, 31, 77), 306, 305, 304 (5, 20, 100), 236, 235 (4, 22). The oil was dissolved in 50 mL of THF and 1.85 g of 9.8% ethereal HCl (4.97 mmol) was added at 0°C. The mixture was stirred for 1 min and then concentrated. The resulting amorphous HCl salt was recrystallized from 25 mL of

2:3 2-propanol/cyclohexane to afford 1.10 g (2.24 mmol) of the HCl salt of 5 as a white crystalline solid (73%): mp 142.5-143.5°C (unlabeled verapamil HCl: mp 143.5-146°C).

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