236 ($M - C_2H_5$), 208 (236 – CO), 180 (208 – CO); ^1H NMR (CD_2Cl_2) δ 9.72 (br s, 1 H), 8.30–8.14 (m, 2 H), 7.84–7.61 (m, 2 H), 7.56–7.46 (m, 2 H), 7.15–7.01 (m, 1 H), 3.41–3.20 (m, 2 H), 1.91–1.56 (m, 2 H), 1.16–1.00 (t, 3 H); vis max (xylenes) 502 nm (ε 6760).

Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.98; H, 5.66; N, 5.28. Found: C, 76.86; H, 5.72; N, 5.22.

1-Anilinoanthraquinone (7b) was prepared from **6** and aniline in Me_2SO at 180 °C for 2 h. The yield of red solid was 77% with mp 136–138 °C: mass spectrum, *m/e* 299 (M^+); ^1H NMR (CD_2Cl_2) δ 11.32 (br s, 1 H), 8.33–8.16 (m, 2 H), 7.86–7.65 (m, 2 H), 7.61–7.12 (m, 8 H); vis max (xylenes) 501 nm (ε 6200).

Anal. Calcd for $C_{20}H_{13}NO_2$: C, 80.27; H, 4.35; N, 4.68. Found: C, 80.42; H, 4.35; N, 4.69.

Acknowledgment. Thanks are due to David Thomas (SRI International, Menlo Park, CA) for the mass spectra, to Martin Phillippi (Clorox) for the NMR spectra, and to Luann Sylvia (Clorox) for help with the synthesis of hindered aminoanthraquinone compounds.

Stereospecific Synthesis of the Enantiomers of Verapamil and Gallopamil

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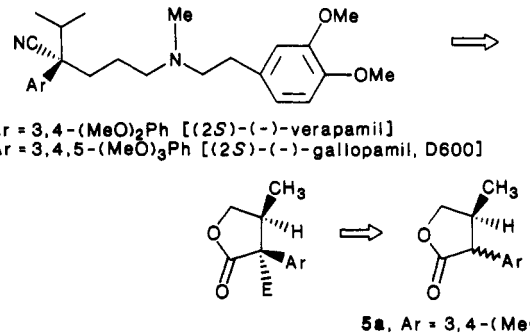
Stereospecific synthesis of the title compounds has been achieved in >95% ee by use of optically active 1,2-propanediols. Nucleophilic displacement of the chiral secondary mesylate **4a**, derived in one step from (2*S*)-(+)-1,2-propanediol (**3a**), with the dianion of 3,4-dimethoxyphenylacetic acid, proceeded with Walden inversion. Subsequent hydrolysis of the trityl protecting group afforded a mixture of (2*R*,3*S*)- and (2*S*,3*S*)-butyrolactones **5a** that, upon alkylation of their sodium enolates with allyl bromide, gave (2*S*,3*S*)-butyrolactone **6a**. Further elaboration afforded (2*S*)-(–)-verapamil (**1a**) in 45% overall yield. Its antipode, **1b**, was synthesized from (2*R*)-(–)-1,2-propanediol (**3b**), and the enantiomers of gallopamil (**2a**, **2b**) were prepared in analogous fashion.

Verapamil and gallopamil are important calcium slow-channel antagonists, useful in the treatment of a variety of cardiovascular disorders. Verapamil, the first calcium channel blocking agent approved in the United States, is used as a racemate orally for the treatment of vasospastic and classical angina pectoris and parenterally for the treatment of superventricular tachycardia. Use in other cardiovascular diseases is under study.

The pharmacological properties of the (–) and (+) enantiomers of verapamil and of gallopamil appear to be quite different. Highly stereoselective effects on the fast sodium ion current and the slow calcium ion current have been noted.[1-6] The (–) enantiomer of each of these agents has greater effects on the slow calcium ion current. In dogs and rabbits, differential pharmacological effects of the enantiomers on the myocardium are noted. Stereoselective metabolism also occurs with substantial "first-pass" metabolism of the more active (–) enantiomer.[7,8] These observations may account for the poor ability to correlate plasma concentration of the racemic drug to cardiovascular measurements and effects.[9-13] Thus, there exists a significant need for methods to obtain the individual enantiomers to allow for further pharmacological and metabolic study.

Scheme I



To date, the only methods available for obtaining the enantiomers of these compounds involve the tedious resolution of diastereomeric salts.[14-16] We herein report the first stereoselective synthesis of the enantiomers of verapamil and gallopamil via a route that should also be applicable to the preparation of analogues containing a quaternary carbon.

In planning a synthetic route toward (2*S*)-(–)-verapamil (**1a**), we chose (3*S*)-methyl-2-(3,4-dimethoxyphenyl)-butyrolactone (**5a**) as our more immediate target (Scheme I). With **5a** in hand, alkylation of its enolate with an

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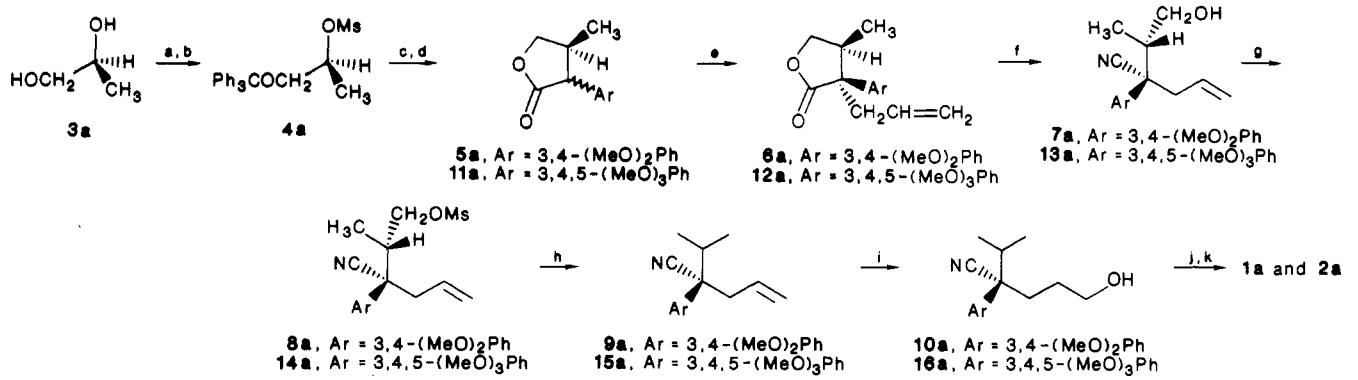
Scheme II[a]



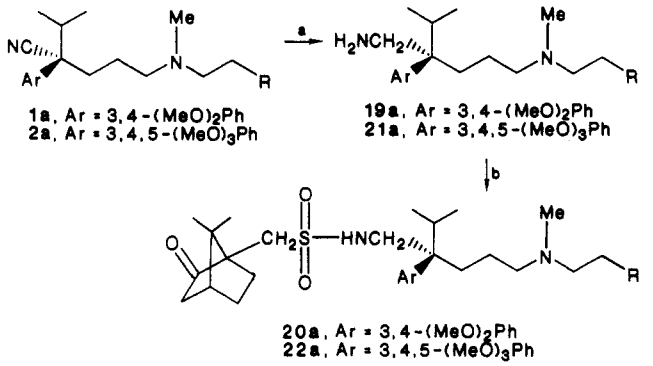
[a] Reagents: (a) Ph_3CCl, Et_3N, DMAP, CH_2Cl_2; (b) MsCl; (c) $ArCH_2COOH$, $LiN(i\text{-}Pr)_2$, THF; (d) MeOH, *p*-TsOH; (e) NaH, $BrCH_2CH{=}CH_2$, THF; (f) Me_2AlNH_2, Cl_2CHCH_2Cl; (g) MsCl, Et_3N, CH_2Cl_2; (h) $NaBH_4$, *t*-BuOH, dimethoxyethane; (i) disiamylborane, THF, then H_2O_2; (j) MsCl, Et_3N, CH_2Cl_2; (k) *N*-methylhomoveratrylamine, Et_3N, THF.

appropriately functionalizable electrophile should proceed anti to the C-3 methyl group, thus establishing the chirality of the quaternary carbon center.

Synthesis of **1a** began with commercially available (2*S*)-(+)-1,2-propanediol (**3a**; Scheme II). Selective protection of the primary hydroxyl group with 1.05 equiv of trityl chloride in CH_2Cl_2, followed by reaction with methanesulfonyl chloride, afforded **4a** in 91% yield. Initial attempts at displacement of the chiral mesylate by use of the lithium, sodium, and potassium enolates of methyl 3,4-dimethoxyphenylacetate failed to result in any reaction. However, reaction of **4a** with the dilithium salt of 3,4-dimethoxyphenylacetic acid in THF for 96 h at room temperature resulted in displacement of the methanesulfonate leaving group with a high degree of Walden inversion.[17] Aqueous acidic workup of the reaction mixture, followed by treatment with methanol and catalytic *p*-toluenesulfonic acid, afforded **5a** as a mixture of cis and trans diastereoisomers in 82% overall yield from **4a**. Alkylation of the sodium enolate of **5a** with allyl bromide at 0 °C produced **6a** (84%) in high optical purity.

Having established the chiral quaternary carbon center, lactone **6a** was converted to hydroxy nitrile **7a** by a modification of the procedure of Wood et al.[18] for the conversion of esters to nitriles. Thus, **6a** was allowed to react with dimethylaluminum amide in 1,1,2-trichloroethane at reflux for 60 h to afford **7a** in excellent yield (95%). Reduction of the hydroxymethyl functionality to the needed methyl group was effected via mesylate **8a**, which was prepared in the usual fashion. Initial attempts to reduce **8a** employed the use of sodium borohydride in refluxing 1,2-dimethoxyethane.[19] Unfortunately, extensive side product formation was observed, presumably resulting from reduction of the olefin and/or nitrile by borane, which was generated in situ. This difficulty was overcome by performing the reduction in the presence of excess *tert*-butyl alcohol which proved to be sufficiently inert to sodium borohydride under the reaction conditions to allow smooth reduction of the mesylate to occur, while at the same time serving as an effective agent for the destruction of borane as it was generated. Compound **9a** was formed in 90% overall yield from alcohol **7a**.

Scheme III[a,b]



[a] Reagents: (a) LAH, THF; (b) (1*S*)-(+)-10-camphorsulfonyl chloride, Et_3N, CH_2Cl_2. [b] R = 3,4-$(MeO)_2$Ph.

Final elaboration of olefin **9a** to (2*S*)-(−)-verapamil (**1a**) was performed by modification of the method of Ramuz.[16] Treatment of **9a** with disiamylborane in THF, followed by oxidative workup with hydrogen peroxide, gave the corresponding primary alcohol (**10a**) in 94% yield. Mesylation of **10a**, followed by reaction with *N*-methylhomoveratrylamine in THF at 80 °C for 48 h, afforded (2*S*)-(−)-verapamil (**1a**), the overall yield from **3a** being 45%. Analogously, (2*R*)-(+)-verapamil (**1b**) was produced from (2*R*)-(−)-1,2-propanediol (**3b**).[20] The two enantiomers of gallopamil (**2a, 2b**) were similarly prepared, in overall yields of 40–45%, by use of the dilithium salt of 3,4,5-trimethoxyphenylacetic acid in the displacement step.

As literature rotational values[14,16] for the enantiomers of verapamil were inconsistent (differing by 5%), and those for the enantiomers of gallopamil were unavailable to us, optical purity of the final products (and thus the stereoselectivity of the process) was determined from the 500-MHz ^1H NMR of their diastereomeric (1*S*)-(+)-10-camphorsulfonamide derivatives (**20a, 20b, 22a, 22b**; Scheme III). Thus, reduction of (2*S*)-(−)-verapamil (**1a**) with lithium aluminum hydride in THF afforded the corresponding primary amine (**19a**), which was then allowed to react with excess (1*S*)-(+)-10-camphorsulfonyl chloride, affording **20a**. In Figure 1 is illustrated the ^1H NMR spectra of the camphorsulfonamides formed from racemic verapamil and from (2*S*)-(−)- and (2*R*)-(+)-verapamil (**20a**

(17) The mechanism and degree of inversion in the displacement reaction is inferred from the absolute configuration and optical purity (95–98% ee) of the final products. In the absence of an optical purification, data on the final products infer the minimum specificity of the intermediate processes.

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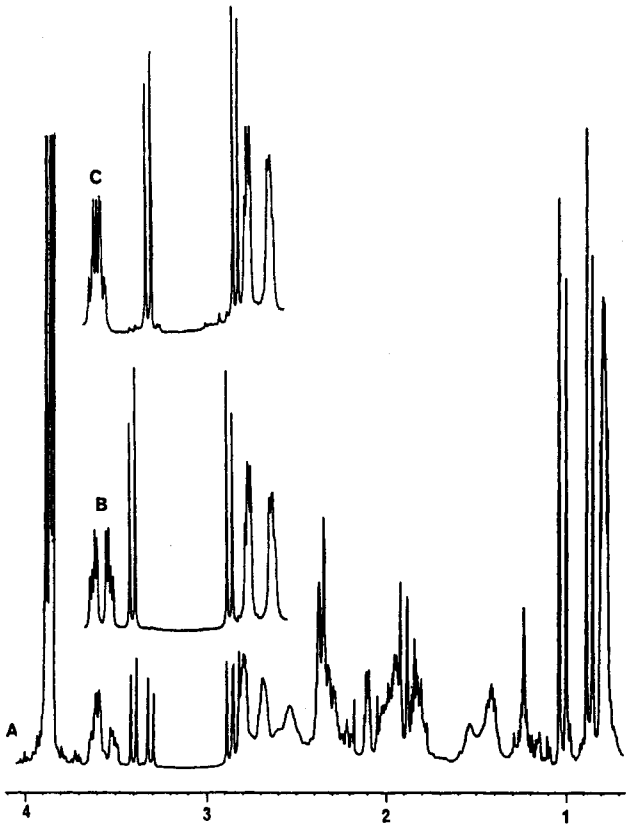

Figure 1. Partial 500-MHz ^1H NMR spectra ($CDCl_3$): A, diastereomeric (1*S*)-10-camphorsulfonamides from racemic verapamil; B, sulfonamide **20a** from **1a**; C, sulfonamide **20b** from **1b**.

and **20b**, respectively). The doublets at δ 3.40 and 2.87 were determined to result from the methylene protons situated between the sulfonamide functionality and the camphor ring system of **20a**, while the doublets at δ 3.33 and 2.84 are from analogous methylene protons of **20b**. Optical purity was determined from the integral ratio of the doublet at δ 3.40 to that at δ 3.33 and was found to be 95–96% ee for the verapamil enantiomers and >98% ee for the gallopamil enantiomers.[21] Recrystallization of the hydrochloride salts of these compounds (**1a**, **1b**, **2a**, **2b**) afforded pure crystalline solids (>99% ee).

In summary, the synthetic route described affords the enantiomers of verapamil and gallopamil in excellent overall yield and optical purity. Also, in addition to providing a route for production of compounds necessary to facilitate study of the pharmacological and metabolic properties of these calcium channel antagonists, the synthetic methodology should be applicable to the elaboration of related structures with a chiral quaternary carbon.

Experimental Section

General Methods. High-field proton NMR spectra were obtained at 500 MHz on a Bruker WM-500 spectrometer. Chemical shifts are expressed in 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 spectra were obtained on a VG-7070 mass spectrometer by direct-insert probe. Infrared spectra were recorded on a Perkin-Elmer 283 infrared spectrophotometer. Elemental combustion analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Optical rotations were measured on a Jasco DIP-4 digital polarimeter at the sodium D line (λ 589 nm). 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 precoated silica gel 60 F-254 TLC plates (2-mm thickness). Merck silica gel 60 (230–400-mesh ASTM) was used for flash-column chromatography.[22] 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 phosphorus pentoxide. Triethylamine and diisopropylamine were distilled under argon from powdered NaH. All solvents used for extraction were reagent grade. Unless otherwise indicated, all other reagents or solvents were purchased from Aldrich Chemical Co. and used without further purification. Prepurified argon was dried by passing through a 2-ft column packed with indicating Drierite and KOH. All glassware was either oven dried for a minimum of 2 h 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.

(2*S*)-(+)-1-(Triphenylmethoxy)-2-[(methylsulfonyl)oxy]propane (4a). To a stirred solution of 11.03 g (144.9 mmol) of (2*S*)-(+)-1,2-propanediol (**3a**) and 41.01 g (147.1 mmol, 1.015 equiv) of triphenylmethyl chloride in 400 mL of dry CH_2Cl_2 was added 200 mg (1.64 mmol) of 4-(dimethylamino)pyridine, followed by 37.0 g (366 mmol, 2.52 equiv) of Et_3N at 0 °C. The solution was stirred at 0 °C to room temperature for 16 h and then cooled to 0 °C. Methanesulfonyl chloride (18.3 g, 160 mmol, 1.10 equiv) was then added via syringe over a 10-min period. After 4 h of stirring at 0 °C, the mixture was washed with 5% v/v aq HCl (3 × 200 mL). The organic phase was dried, filtered, and concentrated. The residue was chromatographed on 225 g of silica gel, eluting first with 10% EtOAc/hexanes and then with 25% EtOAc/hexanes, to afford 52.4 g (132 mmol) of a pale yellow oil that crystallized to an off-white solid: 91%; TLC (25% EtOAc/hexanes) R_f 0.51; mp 82–84 °C; $[\alpha]^{22}_D$ +2.5° (*c* 5.11, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.44–7.23 (15 H, m), 4.84 (1 H, m), 3.30 (1 H, dd, J = 6.9, 10.8 Hz), 3.21 (1 H, dd, J = 3.5, 10.8 Hz), 3.01 (3 H, s), 1.35 (3 H, d, J = 6.8 Hz); IR (neat, as oil) 3065, 3040, 2938, 2858, 1600, 1592, 1551, 1360, 1178, 765, 747, 708 cm^{-1}; HRMS (EI mode) m/z 396.1388 (396.1395 calcd for $C_{23}H_{24}O_4S$).

(2*R*)-(−)-1-(Triphenylmethoxy)-2-[(methylsulfonyl)oxy]propane (4b). (2*R*)-(−)-1,2-Propanediol[20] (**3b**; 12.0 g, 158 mmol) was converted to 50.8 g (128 mmol) of **4b** according to the procedure described for the conversion of **3a** to **4a**: 81%; mp 82–84 °C; $[\alpha]^{22}_D$ −2.5° (*c* 5.03, $CHCl_3$).

(2*RS*,3*S*)-2-(3,4-Dimethoxyphenyl)-3-methylbutyrolactone (5a). To a stirred solution of 52.7 g (521 mmol, 4.13 equiv) of diisopropylamine in 600 mL of dry THF was added 206 mL of 2.45 M *n*-BuLi (505 mmol, 401 equiv) in hexanes at 0 °C over a 15-min period. The mixture was stirred at 0 °C to room temperature for 30 min, and then 49.5 g (252 mmol, 2.00 equiv) of homoveratric acid in 200 mL of dry THF was added via cannula over a 30-min period, the temperature of the reaction mixture being controlled by means of a room-temperature water bath. The mixture was stirred for 1 h after the addition was completed, and then 50.1 g (126 mmol, 1.00 equiv) of mesylate **4a** in 250 mL of dry THF was added via cannula over a 30-min period. The mixture was stirred at room temperature for 96 h and then poured into 800 mL of ice-cold 2 N aqueous H_2SO_4. The mixture was

(21) Purification of the camphorsulfonamide derivatives via silica gel chromatography prior to assessment of diastereomeric purity by NMR afforded the possibility of separation of the diastereomeric sulfonamides and an inaccurate assessment of optical purity. Derivatives **20a** and **20b** were determined to have essentially identical chromatographic behavior (identical R_f values, see the Experimental Section) under the protocols used. Application of the derivatization and chromatographic purification procedures to racemic verapamil resulted in a 50:50 mixture of **20a** and **20b** as assessed by 500-MHz NMR. In addition, prepared mixtures of **20a** and **20b** of known ratios were subjected to the aqueous workup procedure used in the derivatization step and rechromatographed. By NMR, no changes were observed in their diastereomeric composition. We conclude that the cleanup procedure does not result in any changes in the ratio of diastereomeric products.

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stirred for 10 min and the layers were separated. The aqueous phase was extracted with EtOAc (2 × 300 mL). The organic extracts were combined, dried, filtered, and concentrated. The residue (an amber oil) was diluted with 500 mL of methanol and treated with 500 mg of *p*-toluenesulfonic acid (2.63 mmol). The solution was stirred at room temperature for 24 h and then concentrated. The residue was chromatographed on 230 g of silica gel, eluting first with 10% EtOAc/hexanes, then with 25% EtOAc/hexanes, and finally with 40% EtOAc/hexanes, to afford 24.55 g (103.9 mmol) of product **5a**, a mixture of cis (2*S*,3*S*) and trans (2*R*,3*S*) diastereoisomers, as a pale yellow oil that crystallized to a yellow solid on standing: 82%; TLC (25% EtOAc/hexanes) R_f 0.15, (50% EtOAc/hexanes) R_f 0.51; ^{1}H NMR ($CDCl_3$) δ 6.87–6.69 (3 H, m, from cis and trans), 4.51 (0.7 H, t, J = 8.1 Hz, from trans), 4.45 (0.3 H, dd, J = 4.5, 9.0 Hz, from cis), 4.03 (0.3 H, dd, J = 4.2, 9.0 Hz, from cis), 3.92–3.86 (7 H, 2 s on m, from cis and trans), 3.23 (0.7 H, d, J = 11.5 Hz, from trans), 2.86 (0.3 H, m, from cis), 2.66 (0.7 H, m, from trans), 1.16 (2.1 H, d, J = 6.5, from trans), 0.80 (0.9 H, d, J = 7.0 Hz, from cis); IR ($CHCl_3$) 2940, 2842, 1775, 1610, 1597, 1512, 1467, 1016 cm^{-1}; HRMS (EI mode) m/z 236.1041 (236.1048 calcd for $C_{13}H_{16}O_4$).

(2*R*,3*R*)-2-(3,4-Dimethoxyphenyl)-3-methylbutyrolactone (5b). Mesylate **4b** (50.1 g, 126 mmol) was converted to **5b** (24.17 g, 102.3 mmol) according to the procedure desribed for the conversion of **4a** to **5a** (81%).

(2*S*,3*S*)-(−)-2-(2-Propenyl)-2-(3,4-dimethoxyphenyl)-3-methylbutyrolactone (6a). To a stirred solution of 22.01 g (93.2 mmol) of lactone **5a** and 200 mL of dry THF in a 500-mL round-bottom flask was added 3.02 g of NaH (126 mmol, 1.35 equiv). 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 h. After this time, the mixture was cooled to 0 °C, and 14.0 g (116 mmol, 1.24 equiv) of allyl bromide was added over a 10-min period. The mixture was stirred at 0 °C to room temperature for 14 h and then carefully poured into 250 mL of ice-cold 5% v/v aqueous HCl. The layers were separated, and the aqueous phase was extracted with EtOAc (2 × 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 21.56 g (78.03 mmol) of the product (**6a**) as a white crystalline solid: 84%; TLC (25% EtOAC/hexanes) R_f 0.32; mp 88.0–88.5 °C; $[\alpha]^{23}_D$ −51.6° (*c* 3.06, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.84 (1 H, d, J = 8.3 Hz), 6.73 (1 H, dd, J = 2.1, 8.3 Hz), 6.70 (1 H, d, J = 2.1 Hz), 5.82 (1 H, m), 5.79 (1 H, d, J = 17.6 Hz), 5.18 (1 H, d, J = 10.1 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 = 5.9, 13.7 Hz), 2.71 (2 H, m), 0.71 (3 H, d, J = 6.9 Hz); IR ($CHCl_3$) 3085, 2940, 2842, 1772, 1645, 1610, 1593, 1514, 1467, 1258, 1019 cm^{-1}; HRMS (EI mode) m/z 276.1342 (276.1361 calcd for $C_{16}H_{20}O_4$). Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.29. Found: C, 69.43; H, 7.35.

(2*R*,3*R*)-(+)-2-(2-Propenyl)-2-(3,4-dimethoxyphenyl)-3-methylbutyrolactone (6b). Lactone **5b** (24.17 g, 102.3 mmol) was converted to **6b** (23.78 g, 86.06 mmol) according to the procedure described for the conversion of **5a** to **6a**: 84%; mp 88.0–88.5 °C; $[\alpha]^{23}_D$ +51.2° (*c* 3.08, $CHCl_3$).

(2*S*,3*S*)-(+)-2-Methyl-3-cyano-3-(3,4-dimethoxyphenyl)-hex-5-enol (7a). To 500 mL of dry 1,1,2-trichloroethane in a 1-L round-bottom flask, fitted with a reflux condenser topped with a rubber serum cap and connected to a Drierite-filled drying tube, was bubbled anhydrous NH_3 at 0 °C for 25 min. After this time, 120 mL of 2.0 M $AlMe_3$ (240 mmol, 2.5 equiv) in toluene was added. The mixture was then heated to 80 °C over a 1-h period and stirred at 80 °C for 1 h to bubble off excess NH_3. Then, 26.74 g (96.77 mmol) of lactone **6a** in 100 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 60 h. The mixture was cooled to 0 °C, 300 mL of 10% v/v aqueous 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 × 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 25.40 g (92.25 mmol) of the product (**7a**) as a very pale yellow oil: 95%; TLC (50% EtOAc/hexanes) R_f 0.43; $[\alpha]^{22}_D$ +26.2° (*c* 3.09, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.94 (1 H, dd, J = 2.2, 8.5 Hz), 6.87 (1 H, d, J = 2.2 Hz), 6.85 (1 H, d, J = 8.5 Hz), 5.52 (1 H, m), 5.12 (1 H, d, J = 16.2 Hz), 5.06 (1 H, d, J = 9.6 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 = 7.8, 13.9 Hz), 2.72 (1 H, dd, J = 6.5, 13.9 Hz), 2.20 (1 H, m), 1.48 (1 H, t, J = 5.4 Hz), 0.93 (3 H, d, J = 6.8 Hz); IR (neat) 3520, 3085, 2942, 2842, 2240, 1648, 1610, 1597, 1521, 1470, 1265, 1027, 806, 767 cm^{-1}; HRMS (EI mode) m/z 275.1491 (275.1521 calcd for $C_{16}H_{21}NO_3$).

(2*R*,3*R*)-(−)-2-Methyl-3-cyano-3-(3,4-dimethoxyphenyl)-hex-5-enol (7b). Lactone **6b** (22.38 g, 80.99 mmol) was converted to **7b** (20.93 g, 76.01 mmol) according to the procedure described for the conversion of **6a** to **7a**: 94%; $[\alpha]^{22}_D$ −26.0° (*c* 2.94, $CHCl_3$).

(2*S*,3*S*)-(+)-1-[(Methylsulfonyl)oxy]-2-methyl-3-cyano-3-(3,4-dimethoxyphenyl)hex-5-ene (8a). To a stirred solution of 25.40 g (92.25 mmol) of alcohol **7a** and 11.7 g (115.6 mmol, 1.25 equiv) of Et_3N in 250 mL of dry CH_2Cl_2 was added 11.1 g (96.9 mmol, 1.05 equiv) of methanesulfonyl chloride at 0 °C. The mixture was stirred at 0 °C for 2 h and then washed with 200 mL of 5% v/v aqueous HCl. 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 31.36 g (88.73 mmol) of the product as a pale yellow oil: 96%; TLC (50% EtOAc/hexanes) R_f 0.54; $[\alpha]^{23}_D$ +23.3° (*c* 3.52, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.93 (1 H, dd, J = 2.2, 8.2 Hz), 6.87 (1 H, d, J = 8.2 Hz), 6.85 (1 H, d, J = 2.2 Hz), 5.50 (1 H, m), 5.14 (1 H, d, J = 16.6 Hz), 5.09 (1 H, d, J = 9.6 Hz), 4.50 (1 H, dd, J = 5.1, 10.1 Hz), 4.21 (1 H, dd, J = 6.8, 10.1 Hz), 3.90 (3 H, s), 3.89 (3 H, s), 3.07 (3 H, s), 2.88 (1 H, dd, J = 7.3, 14.2 Hz), 2.74 (1 H, dd, J = 6.4, 14.2 Hz), 2.45 (1 H, m), 0.99 (3 H, d, J = 6.8 Hz); IR (neat) 3085, 2941, 2842, 2239, 1647, 1609, 1595, 1517, 1470, 1357, 1175, 1023, 808, 766 cm^{-1}; HRMS (EI mode) m/z 353.1287 (353.1297 calcd for $C_{17}H_{23}NO_5S$).

(2*R*,3*R*)-(−)-1-[(Methylsulfonyl)oxy]-2-methyl-3-cyano-3-(3,4-dimethoxyphenyl)hex-5-ene (8b). Alcohol **7b** (20.01 g, 72.67 mmol) was converted to **8b** (24.95 g, 70.59 mmol) according to the procedure described for the conversion of **7a** to **8a**: 97%; $[\alpha]^{23}_D$ −23.7° (*c* 2.54, $CHCl_3$).

(4*S*)-(+)-4-Cyano-4-(3,4-dimethoxyphenyl)-4-isopropylbutene (9a). To a stirred solution of 24.25 g (68.61 mmol) of mesylate **8a** and 25.5 g (344 mmol, 5.0 equiv) of *tert*-butyl alcohol in 250 mL of dry 1,2-dimethoxyethane was added 7.80 g (206 mmol, 3.0 equiv) of sodium borohydride at room temperature. The mixture was heated to reflux and stirred for 70 h. 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 200 mL of Et_2O. The filtrates were combined and vigorously stirred with 100 mL of 5% v/v aqueous HCl for 10 min to destroy dissolved sodium borohydride. The layers were separated, and the aqueous phase was extracted with 100 mL of Et_2O. The organic extracts were combined, dried, filtered, and concentrated. The residue, an oil and white solid, was diluted with 200 mL of CH_2Cl_2 and washed with 50 mL of 5% v/v aqueous 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 961 mg (2.72 mmol) of recovered starting material (**8a**; 4%) and 16.55 g (63.82 mmol) of the product (**9a**) as a colorless oil: 93%; TLC (25% EtOAc/hexanes) R_f 0.52; $[\alpha]^{23}_D$ +20.0° (*c* 3.47, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.92 (1 H, dd, J = 2.1, 8.7 Hz), 6.86 (1 H, d, J = 2.1 Hz), 6.85 (1 H, d, J = 8.7 Hz), 5.51 (1 H, m), 5.09 (1 H, d, J = 16.4 Hz), 5.04 (1 H, d, J = 11.0 Hz), 3.89 (3 H, s), 3.88 (3 H, s), 2.83 (1 H, dd, J = 7.3, 13.9 Hz), 2.61 (1 H, dd, J = 6.9, 13.9 Hz), 2.13 (1 H, septet, J = 6.8 Hz), 1.20 (3 H, d, J = 6.8 Hz), 0.83 (3 H, d, J = 6.8 Hz); IR (neat) 3085, 2940, 2840, 2239, 1646, 1610, 1597, 1520, 1470, 1393, 1375, 1255, 1028, 805, 764 cm^{-1}; HRMS (EI mode) m/z 259.1564 (259.1572 calcd for $C_{16}H_{21}NO_2$). Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.97; H, 8.14; N, 5.46.

(4*R*)-(−)-4-Cyano-4-(3,4-dimethoxyphenyl)-4-isopropylbutene (9b). Mesylate **8b** (24.46 g, 69.21 mmol) was converted to **9b** (16.66 g, 64.24 mmol) according to the procedure described for the conversion of **8a** to **9a**: 93%; $[\alpha]^{23}_D$ −20.2° (*c* 3.61, $CHCl_3$).

(4*S*)-(−)-4-Cyano-4-(3,4-dimethoxyphenyl)-4-isopropylbutanol (10a). To 148 mL of 1 M borane in THF (148 mmol,

2.0 equiv) was added 21.0 g (299 mmol, 4.0 equiv) of 2-methyl-2-butene at 0 °C over a 10-min period. The mixture was stirred at 0 °C for 2 h and then transferred via cannula, over a 10-min period, to a stirred solution of 19.23 g (74.15 mmol) of olefin **9a** in 100 mL of dry THF. The mixture was stirred at 0 °C for 1 h, and the excess disiamylborane was then destroyed by careful addition of 25 mL of 5% aqueous NaOH. Then, 50 mL of 30% aqueous H_2O_2 was added over a 30-min period. The mixture was stirred for 30 min after the addition was complete, and then 75 mL of H_2O was added, followed by careful addition of 15.4 g (148 mmol) of powdered 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 × 100 mL). The organic extracts were combined, dried, filtered, and concentrated. The residue was chromatographed on 200 g of silica gel, eluting first with 40% EtOAc/hexanes and then with 70% EtOAc/hexanes, to afford 19.24 g (69.37 mmol) of the product (**10a**) as a colorless oil: 94%; TLC (50% EtOAc/hexanes) R_f 0.34; $[\alpha]^{22}_D$ −12.6° (*c* 3.84, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 6.93 (1 H, dd, *J* = 2.0, 8.2 Hz), 6.87 (1 H, d, *J* = 2.0 Hz), 6.85 (1 H, d, *J* = 8.2 Hz), 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* = 6.7 Hz), 1.93 (1 H, m), 1.62 (1 H, m), 1.27 (1 H, m), 1.20 (3 H, d, *J* = 6.7 Hz), 1.15 (1 H, t, *J* = 5.4 Hz), 0.81 (3 H, d, *J* = 6.7 Hz); IR (neat) 3460, 2940, 2840, 2238, 1610, 1595, 1519, 1468, 1393, 1375, 1260, 1025, 803, 764 cm^{-1}; HRMS (EI mode) 277.1663 (277.1678 calcd for $C_{16}H_{23}NO_3$).

(4*R*)-(+)-4-Cyano-4-(3,4-dimethoxyphenyl)-4-isopropylbutanol (10b). Olefin **9b** (15.61 g, 60.19 mmol) was converted to **10b** (15.12 g, 54.52 mmol) according to the procedure described for the conversion of **9a** to **10a**: 91%; $[\alpha]^{22}_D$ +12.7° (*c* 3.23, $CHCl_3$).

(3,4-Dimethoxyphenethyl)trifluoroacetamide (17). To a stirred solution of 50.0 g (0.276 mol) of homoveratrylamine in 400 mL of dry CH_2Cl_2 was slowly added 87.0 g (0.414 mol, 1.50 equiv) of trifluoroacetic anhydride at 0 °C. The mixture was stirred at 0 °C for 1 h. Then, 300 mL of H_2O was added, followed by the slow addition of 50 g (0.60 mol, 2.2 equiv) of powdered sodium bicarbonate. The mixture was stirred for 15 min after the addition was complete, and the layers were then separated. The organic phase was washed with 150 mL of saturated aqueous sodium bicarbonate and then dried, filtered, and concentrated to afford 75.5 g (0.272 mol) of **17** as a pale yellow solid: 99%; mp 82.0–83.0 °C; ^1H NMR ($CDCl_3$) δ 6.83 (1 H, d, *J* = 8.1 Hz), 6.73 (1 H, dd, *J* = 1.7, 8.1 Hz), 6.69 (1 H, d, *J* = 1.7 Hz), 6.27 (1 H, br s), 3.87 (6 H, s), 3.60 (2 H, q, *J* = 6.7 Hz), 2.83 (2 H, t, *J* = 6.7 Hz); IR ($CHCl_3$) 3445, 2945, 2845, 1730, 1611, 1598 cm^{-1}.

(3,4-Dimethoxyphenethyl)methylamine (18, *N*-Methylhomoveratrylamine). To a stirred solution of 75.0 g (0.271 mol) of **17** in 400 mL of dry THF was added 58.0 g (0.409 mol, 1.50 equiv) of iodomethane. The mixture was cooled to 0 °C, and 9.80 g (0.408 mol, 1.50 equiv) of NaH was added in 1-g portions over a 45-min period. The mixture was stirred at room temperature for 4 h and then filtered through a layer of Celite. The filtrate was concentrated, and the residue was diluted with 300 mL of EtOAc and washed with 200 mL of 10% aqueous sodium thiosulfate followed by 100 mL of 5% aqueous HCl. The organic phase was dried, filtered, and concentrated. The residue was treated with 250 mL of 20% v/v aqueous H_2SO_4 and stirred at reflux for 30 h. The mixture was then cooled to 0 °C, diluted with 200 mL of H_2O, and treated with 100 g (2.50 mol) of NaOH. The mixture was then extracted with methylene chloride (3 × 200 mL). The organic extracts were then combined, dried, filtered, and concentrated. The residue was distilled to afford 44.1 g (22.58 mmol) of the product (**18**) as a colorless oil: 82%; bp 124–128 °C (0.5 mmHg); ^1H NMR ($CDCl_3$) δ 6.80 (1 H, d, *J* = 7.8 Hz), 6.75 (1 H, dd, *J* = 1.7, 7.8 Hz), 6.74 (1 H, d, *J* = 1.7 Hz), 3.87 and 3.85 (6 H, 2 s), 2.82 (2 H, t, *J* = 6.6 Hz), 2.75 (2 H, t, *J* = 6.6 Hz), 2.44 (3 H, s), 1.29 (1 H, br s); IR (neat) 3340, 2840, 1610, 1592 cm^{-1}.

(2*S*)-(−)-2-(3,4-Dimethoxyphenyl)-2-isopropyl-5-[(3,4-dimethoxyphenethyl)methylamino]valeronitrile [1a, (2*S*)-(−)-Verapamil]. To a stirred solution of 17.41 g (62.77 mmol) of alcohol **10a** and 7.95 g (78.57 mmol, 1.25 equiv) of Et_3N in 200 mL of dry CH_2Cl_2 was slowly added 7.41 g (64.7 mmol, 1.03 equiv) of methanesulfonyl chloride at 0 °C. The mixture was stirred at 0 °C for 2 h and then washed with 5% v/v aqueous HCl (2 × 100 mL). The organic phase was dried, filtered, and concentrated. The residue was diluted with 75 mL of dry THF and then treated with 15.35 g (78.61 mmol, 1.25 equiv) of *N*-methylhomoveratrylamine (**18**) and 7.95 g (78.57 mmol, 1.25 equiv) of Et_3N. The mixture was stirred at 80 °C for 48 h, cooled to 0 °C, and then treated with 19.8 g (94.27 mmol, 1.50 equiv) of trifluoroacetic anhydride. The mixture was stirred at room temperature for 8 h and then concentrated. The residue was diluted with 100 mL of Et_2O and 200 mL of H_2O and then treated with 16.8 g (200 mmol) of sodium bicarbonate. The mixture was stirred at room temperature for 1 h, and the phases were then separated. The aqueous phase was extracted with Et_2O (3 × 100 mL). The organic extracts were combined, dried, filtered, and concentrated. The residue was chromatographed on 235 g of silica gel, eluting first with EtOAc and then with 20% MeOH/EtOAc, to afford 25.73 g (56.60 mmol) of (2*S*)-(−)-verapamil (**1a**) as a very pale yellow oil: 90%; TLC (5:5:90 Et_3N/MeOH/EtOAc) R_f 0.55; ^1H NMR ($CDCl_3$) δ 6.91 (1 H, dd, *J* = 1.9, 8.4 Hz), 6.86 (1 H, d, *J* = 1.9 Hz), 6.83 (1 H, d, *J* = 8.4 Hz), 6.78 (1 H, d, *J* = 8.6 Hz), 6.70 (1 H, d, *J* = 1.9 Hz), 6.69 (1 H, dd, *J* = 1.9, 8.6 Hz), 3.88–3.85 (12 H, 4 s), 2.66 (2 H, m), 2.50 (2 H, m), 2.34 (2 H, m), 2.18 (3 H, s), 2.11 (1 H, m), 2.05 (1 H, septet, *J* = 6.6 Hz), 1.83 (1 H, m), 1.55 (1 H, m), 1.18 (4 H, d on m, *J* = 6.6 Hz), 0.79 (3 H, d, *J* = 6.6 Hz); IR (neat) 2962, 2942, 2840, 2798, 2232, 1609, 1593, 1518, 1467, 1391, 1374, 1262, 1028, 803, 763 cm^{-1}; HRMS (EI mode) *m/z* 454.2831 (454.2831 calcd for $C_{27}H_{38}N_2O_4$).

The HCl salt of **1a** was prepared as follows: To 20.10 g (44.21 mmol) of amine **1a** in 150 mL of dry THF was added 22.2 g (66.37 mmol) of a 10.9 wt % ethereal HCl solution at 0 °C. The mixture was stirred for 1 min and then concentrated. The residue was crystallized from 250 mL of 1:1 2-propanol/cyclohexane. A second recrystallization afforded 19.98 g (40.69 mmol) of **1a**·HCl as a white crystalline solid: 92%; mp 131–133 °C; $[\alpha]^{24}_D$ −8.9° (*c* 5.03, ethanol) [lit.[16] mp 134–136 °C (2-propanol); $[\alpha]^{25}_D$ −8.9° (*c* 5.00, ethanol)].

(2*R*)-(+)-2-(3,4-Dimethoxyphenyl)-2-isopropyl-5-[(3,4-dimethoxyphenethyl)methylamino]valeronitrile [1b, (2*R*)-(+)-Verapamil]. Alcohol **10b** (14.20 g, 51.20 mmol) was converted to **1b** (21.00 g, 46.20 mmol) according to the procedure described for the conversion of **10a** to **1a** (90%).

Amine **1b** (16.03 g, 35.26 mmol) was converted to **1b**·HCl (15.59 g, 31.75 mmol) according to the procedure described for the conversion of **1a** to **1b**·HCl: 90%; mp 131–133 °C; $[\alpha]^{25}_D$ +8.9° (*c* 5.01, ethanol) [lit.[16] mp 134–136 °C (2-propanol); $[\alpha]^{25}_D$ +8.8° (*c* 5.00, ethanol)].

(2*RS*,3*S*)-2-(3,4,5-Trimethoxyphenyl)-3-methylbutyrolactone (11a). Following the experimental procedure used for the conversion of **4a** to **5a**, mesylate **4a** (45.0 g, 113 mmol) was allowed to react with 168 mmol (1.48 equiv) of the dianion of 3,4,5-trimethoxyphenylacetic acid to afford 25.05 g (94.07 mmol) of product **11a**, a mixture of cis (2*R*,3*S*) and trans (2*S*,3*S*) diastereomers, as a pale yellow oil that crystallized to a yellow solid on standing: 83%; TLC (25% EtOAc/hexanes) R_f 0.15, (50% EtOAc/hexanes) R_f 0.51; ^1H NMR ($CDCl_3$) δ 6.41 and 6.40 (2 H, 2 s, from cis and trans), 4.52 (0.45 H, dd, *J* = 8.0, 8.2 Hz, from trans), 4.46 (0.55 H, dd, *J* = 6.4, 9.0 Hz, from cis), 4.04 (0.55 H, dd, *J* = 4.6, 9.0 Hz), 3.91–3.84 (10 H, 3 s on m, from cis and trans), 3.22 (0.45 H, d, *J* = 11.3 Hz, from trans), 2.87 (0.55 H, m, from cis), 2.67 (0.45 H, m, from trans), 1.19 (1.35 H, d, *J* = 6.8 Hz, from trans), 0.83 (1.65 h, d, *J* = 7.3 Hz, from cis); IR (neat) 2945, 2845, 1781, 1773, 1592, 1513, 1464, 1248, 1129, 1011, 796, 760, 730 cm^{-1}; HRMS (EI mode) 266.1132 (266.1154 calcd for $C_{14}H_{18}O_5$).

(2*RS*,3*R*)-2-(3,4,5-Trimethoxyphenyl)-3-methylbutyrolactone (11b). Mesylate **4b** (50.0 g, 126 mmol) was converted to **11b** (25.65 g, 93.33 mmol) according to the procedure described for the conversion of **4a** to **11a** (77%).

(2*S*,3*S*)-(−)-2-(2-Propenyl)-2-(3,4,5-trimethoxyphenyl)-3-methylbutyrolactone (12a). Lactone **11a** (24.06 g, 90.36 mmol) was converted to **12a** (22.33 g, 72.89 mmol; a white crystalline solid) according to the procedure described for the conversion of **5a** to **6a**: 81%; TLC (25% EtOAc/hexanes) R_f 0.34; mp 61.0–62.0 °C; $[\alpha]^{22}_D$ −43.3° (*c* 3.03, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 6.39 (2 H, s), 5.83 (1 H, m), 5.20 (1 H, d, *J* = 16.8 Hz), 5.19 (1 H, d, *J* = 11.0 Hz), 4.36 (1 H, dd, *J* = 7.6, 9.0 Hz), 3.85 (6 H, s), 3.84 (3 H, s), 3.74 (1 H, t, *J* = 9.0 Hz), 2.84 (1 H, dd *J* = 5.8, 14.1 Hz), 2.72 (2 H m), 0.74 (3 H, d, *J* = 6.9 Hz); IR ($CHCl_3$) 2940, 2840, 1772, 1645,

1591, 1464, 1255, 1128 cm^{-1}; HRMS (EI mode) m/z 306.1462 (306.1467 calcd for $C_{17}H_{22}O_5$). Anal. Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.34; H, 7.38.

(2*R*,3*R*)-(+)-2-(2-Propenyl)-2-(3,4,5-trimethoxyphenyl)-3-methylbutyrolactone (12b). Lactone **11b** (23.00 g, 86.38 mmol) was converted to **12b** (21.18 g, 69.14 mmol) according to the procedure described for the conversion of **5a** to **6a**: 80%; mp 61.0–62.0 °C; $[\alpha]^{22}_D$ +43.1° (*c* 3.08, $CHCl_3$).

(2*S*,3*S*)-(+)-2-Methyl-3-cyano-3-(3,4,5-trimethoxyphenyl)hex-5-enol (13a). Lactone **12a** (22.01 g, 71.85 mmol) was converted to **13a** (20.74 g, 67.92 mmol; a nearly colorless oil that slowly crystallized to an off-white solid) according to the procedure described for the conversion of **6a** to **7a**: 95%; TLC (50% EtOAc/hexanes) R_f 0.42; mp 82.0–83.0 °C; $[\alpha]^{22}_D$ +30.8° (*c* 3.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.59 (2 H, s), 5.53 (1 H, m), 5.14 (1 H, d, J = 17.3 Hz), 5.08 (1 H, d, J = 10.3 Hz), 4.01 (1 H, m), 3.87 (6 H, s), 3.86 (3 H, s), 3.70 (1 H, m), 2.94 (1 H, dd, J = 7.7, 14.0 Hz), 2.72 (1 H, dd, J = 6.4, 14.0 Hz), 1.52 (1 H, t, J = 5.4 Hz); IR (neat) 3520, 3083, 2943, 2842, 2239, 1647, 1594, 1515, 1467, 1253, 1130, 769, 740 cm^{-1}; HRMS (EI mode) m/z 305.1621 (305.1627 calcd for $C_{17}H_{23}NO_4$).

(2*R*,3*R*)-(−)-2-Methyl-3-cyano-3-(3,4,5-trimethoxyphenyl)hex-5-enol (13b). Lactone **12b** (20.02 g, 65.35 mmol) was converted to **13b** (18.76 g, 61.43 mmol) according to the procedure described for the conversion of **6a** to **7a**: 94%; mp 82.0–83.0 °C; $[\alpha]^{21}_D$ −31.1° (*c* 3.01, $CHCl_3$).

(2*S*,3*S*)-(+)-1-[(Methylsulfonyl)oxy]-2-methyl-3-cyano-3-(3,4,5-trimethoxyphenyl)hex-5-ene (14a). Alcohol **13a** (20.28 g, 66.41 mmol) was converted to **14a** (24.70 g, 64.41 mmol; a pale yellow oil) according to the procedure described for the conversion of **7a** to **8a**: 97%; TLC (50% EtOAc/hexanes) R_f 0.54; $[\alpha]^{23}_D$ +24.4° (*c* 4.62, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.57 (2 H, s), 5.51 (1 H, m), 5.17 (1 H, d, J = 17.0 Hz), 5.11 (1 H, d, J = 10.1 Hz), 4.51 (1 H, dd, J = 5.2, 10.3 Hz), 4.23 (1 H, dd, J = 6.9, 10.3 Hz), 3.88 (6 H, s), 3.86 (3 H, s), 3.08, (3 H, s), 2.88 (1 H, dd, J = 8.0, 14.0 Hz), 2.74 (1 H, dd, J = 6.4, 14.0 Hz), 2.46 (1 H, m), 1.00 (3 H, d, J = 6.8 Hz); IR (neat) 3085, 2950, 2845, 2240, 1648, 1594, 1515, 1465, 1360, 1255, 1175, 1130, 768, 740 cm^{-1}; HRMS (EI mode) m/z 383.1406 (383.1402 calcd for $C_{18}H_{25}NO_6S$).

(2*R*,3*R*)-(−)-1-[(Methylsulfonyl)oxy]-2-methyl-3-cyano-3-(3,4,5-trimethoxyphenyl)hex-5-ene (14b). Alcohol **13b** (18.40 g, 60.25 mmol) was converted to **14b** (22.17 g, 57.82 mmol) according to the procedure described for the conversion of **7a** to **8a**: 96%; $[\alpha]^{21}_D$ −24.5° (*c* 3.68, $CHCl_3$).

(4*S*)-(+)-4-Cyano-4-isopropyl-4-(3,4,5-trimethoxyphenyl)butene (15a). Mesylate **14a** (24.15 g, 62.98 mmol) was converted to **15a** (17.10 g, 59.09 mmol; a white crystalline solid) according to the procedure described for the conversion of **8a** to **9a**: 94%; TLC (25% EtOAc/hexanes) R_f 0.52; mp 51.0–52.0 °C; $[\alpha]^{24}_D$ +26.1° (*c* 3.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.57 (2 H, s), 5.52 (1 H, m), 5.11 (1 H, d, J = 17.0 Hz), 5.06 (1 H, d, J = 10.2 Hz), 3.87 (6 H, s), 3.85 (3 H, s), 2.82 (1 H, dd, J = 7.8, 13.9 Hz), 2.60 (1 H, dd, J = 6.6, 13.9 Hz), 2.13 (1 H, septet, J = 6.8 Hz), 1.21 (3 H, d, J = 6.8 Hz), 0.85 (3 H, d, J = 6.8 Hz); IR ($CHCl_3$) 3090, 2942, 2842, 2240, 1648, 1594, 1505, 1464, 1396, 1377, 1249, 1128 cm^{-1}; HRMS (EI mode) m/z 289.1669 (289.1678 calcd for $C_{17}H_{23}NO_3$). Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.27; H, 8.01; N, 4.84.

(4*R*)-(−)-4-Cyano-4-isopropyl-4-(3,4,5-trimethoxyphenyl)butene (15b). Mesylate **14b** (21.10 g, 55.03 mmol) was converted to **15b** (14.67 g, 50.70 mmol; a white crystalline solid) according to the procedure described for the conversion of **8a** to **9a**: 92%; mp 51.0–52.0 °C; $[\alpha]^{24}_D$ −26.2° (*c* 3.01, $CHCl_3$).

(4*S*)-(−)-4-Cyano-4-isopropyl-4-(3,4,5-trimethoxyphenyl)-butanol (16a). Olefin **15a** (16.27 g, 56.23 mmol) was converted to **16a** (16.34 g, 53.16 mmol; a colorless oil) according to the procedure described for the conversion of **9a** to **10a**: 95%; TLC (50% EtOAc/hexanes) R_f 0.31; $[\alpha]^{22}_D$ −11.5° (*c* 4.24, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.59 (2 H, s), 3.87 (6 H, s), 3.85 (3 H, s), 3.62 (2 H, m), 2.22 (1 H, m), 2.09 (1 H, septet, J = 6.7 Hz), 1.92 (1 H, m), 1.63 (1 H, m), 1.29 (1 H, m), 1.21 (3 H, d, J = 6.7 Hz), 1.11 (1 H, t, J = 5.3 Hz), 0.83 (3 H, d, J = 6.7 Hz); IR (neat) 3500, 2945, 2840, 2239, 1593, 1513, 1465, 1394, 1375, 1252, 1128, 769, 733 cm^{-1}; HRMS (EI mode) m/z 307.1780 (307.1777 calcd for $C_{17}H_{25}NO_4$).

(4*R*)-(+)-4-Cyano-4-isopropyl-4-(3,4,5-trimethoxyphenyl)butanol (16b). Olefin **15b** (14.17 g, 48.97 mmol) was converted to **16b** (14.24 g, 46.33 mmol) according to the procedure described for the conversion of **9a** to **10a**: 95%; $[\alpha]^{21}_D$ +11.6° (*c* 3.91, $CHCl_3$).

(2*S*)-(−)-2-(3,4,5-Trimethoxyphenyl)-2-isopropyl-5-[(3,4-dimethoxyphenethyl)methylamino]valeronitrile [2a, (2*S*)-(−)-Gallopamil]. Alcohol **16a** (14.95 g, 48.64 mmol) was converted to **2a** (21.41 g, 44.18 mmol; a very pale yellow oil) according to the procedure described for the conversion of **10a** to **1a**: 91%; TLC (5:5:90 Et_3N/MeOH/EtOAc) R_f 0.55; ^{1}H NMR (CD_3OD) δ 6.83 (1 H, d, J = 8.0 Hz), 6.76 (1 H, d, J = 1.5 Hz), 6.70 (2 H, s), 6.67 (1 H, dd, J = 1.5, 8.0 Hz), 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, s on m), 2.21 (4 H, m), 2.13 (1 H, m), 1.94 (1 H, m), 1.53 (1 H, m), 1.19 (4 H, d on m, J = 6.6 Hz), 0.78 (3 H, d, J = 6.6 Hz); IR (neat) 2970, 2942, 2840, 2798, 2235, 1592, 1516, 1465, 1391, 1373, 1126, 805, 763 cm^{-1}; HRMS (EI mode) m/z 484.2939 (484.2937 calcd for $C_{28}H_{40}N_2O_5$).

Amine **2a** (18.41 g, 37.99 mmol) was converted to **2a**·HCl (17.41 g, 33.41 mmol; a white crystalline solid) according to the procedure described for the conversion of **1a** to **1a**·HCl: 88%; mp 160.5–161.5 °C; $[\alpha]^{23}_D$ −11.7° (*c* 5.04, ethanol).

(2*R*)-(+)-2-(3,4,5-Trimethoxyphenyl)-2-isopropyl-5-[(3,4-dimethoxyphenethyl)methylamino]valeronitrile [2b, (2*R*)-(+)-Gallopamil]. Alcohol **16b** (13.85 g, 45.06 mmol) was converted to **2b** (19.89 g, 41.04 mmol) according to the procedure described for the conversion of **10a** to **1a** (91%).

Amine **2b** (18.87 g, 38.94 mmol) was converted to **2b**·HCl (16.95 g, 32.53 mmol) according to the procedure described for the conversion of **1a** to **1a**·HCl: 84%; mp 160.5–161.5 °C; $[\alpha]^{25}_D$ +11.7° (*c* 5.02, ethanol).

***N*-[(2*S*)-2-(3,4-Dimethoxyphenyl)-2-isopropyl-5-[(3,4-dimethoxyphenethyl)methylamino]pentyl]-(1*S*)-10-camphorsulfonamide (20a).** To a stirred solution of 100 mg (0.220 mmol) of (2*S*)-(−)-verapamil (**1a**) in 10 mL of dry THF was added 202 mg (5.32 mmol) of lithium aluminum hydride. The mixture was stirred at reflux for 8 h, cooled to 0 °C, and diluted with 70 mL of Et_2O. The excess lithium aluminum hydride was then destroyed by slow addition of 2 mL of 2 N aqueous KOH. The mixture was stirred for 30 min and then dried, filtered, and concentrated. The residual crude primary amine **19a** was diluted with 15 mL of dry CH_2Cl_2, cooled to 0 °C, and then sequentially treated with 500 mg (4.94 mmol) of triethylamine and 235 mg (0.937 mmol) of (1*S*)-(+)-10-camphorsulfonyl chloride. The mixture was stirred at room temperature for 12 h and then diluted with 50 mL of CH_2Cl_2. The mixture was then washed with 50 mL of 5% aqueous NaOH. The organic phase was dried, filtered, and concentrated. The residue was chromatographed on a preparative TLC plate (two elutions with 40% methanol/EtOAc) to afford 121 mg (0.180 mmol) of the camphorsulfonamide derivative (**20a**) as a pale yellow oil and 9 mg (0.02 mmol) of unreacted **1a**: 90% based on reduced verapamil; TLC (5:5:90 Et_3N/MeOH/EtOAc) R_f 0.53; ^{1}H NMR ($CDCl_3$) δ 6.85–6.72 (6 H, m), 5.78 (1 H, br s), 3.88 (3 H, s), 3.86 (6 H s), 3.84 (3 H, s), 3.61 (1 H, d, J = 12.7 Hz), 3.52 (1 H, d, J = 12.7 Hz), 3.40 (1 H, d, J = 14.8 Hz), 2.87 (1 H, d, J = 14.8 Hz), 2.79–1.39 (21 H, m), 2.33 (3 H, s), 1.05 (3 H, s), 0.89 (3 H, s), 0.82 (3 H, d, J = 6.8 Hz), 0.81 (3 H, d, J = 6.8 Hz); IR (neat) 3295, 2970, 2841, 1746, 1609, 1594, 1518, 1468, 1395, 1376, 1332, 1262, 1029, 805, 758 cm^{-1}.

***N*-[(2*R*)-2-(3,4-Dimethoxyphenyl)-2-isopropyl-5-[(3,4-dimethoxyphenethyl)methylamino]pentyl]-(1*S*)-10-camphorsulfonamide (20b).** (2*R*)-(+)-Verapamil (**1b**; 102 mg, 0.224 mmol) was converted to 119 mg (0.177 mmol) of camphorsulfonamide derivative **20b** (a pale yellow oil) according to the procedure described for the conversion of **1a** to **20a**: 79%; TLC (5:5:90 Et_3N/MeOH/EtOAc) R_f 0.53; ^{1}H NMR ($CDCl_3$) δ 6.86–6.73 (6 H, m), 5.66 (1 H, br s), 3.88 (3 H, s), 3.86 (6 H, s), 3.84 (3 H, s), 3.59 (2 H, m), 3.33 (1 H, d, J = 14.9 Hz), 2.84 (1 H, d, J = 14.9 Hz), 2.79–1.38 (21 H, m), 2.34 (3 H, s), 1.02 (3 H, s), 0.86 (3 H, s), 0.81 (3 H, d, J = 6.7 Hz), 0.80 (3 H, d, J = 6.7 Hz); IR (neat) 3300, 2965, 2841, 1745, 1610, 1592, 1519, 1469, 1395, 1376, 1362, 1334, 1029, 806, 760 cm^{-1}.

***N*-[(2*S*)-2-(3,4,5-Trimethoxyphenyl)-2-isopropyl-5-[(3,4-dimethoxyphenethyl)methylamino]pentyl]-(1*S*)-10-camphorsulfonamide (22a).** (2*S*)-(−)-Gallopamil (**2a**; 135 mg, 0.279 mmol) was converted to 149 mg (0.212 mmol) of camphor-

sulfonamide derivative **22a** (a pale yellow oil) according to the procedure described for the conversion of **1a** to **20a**: 74%; TLC (5:5:90 Et_3N/MeOH/EtOAc) R_f 0.53; ^1H NMR ($CDCl_3$) δ 6.78 (1 H, d, J = 8.2 Hz), 6.74 (1 H, d, J = 1.6 Hz), 6.73 (1 H, dd, J = 1.6, 8.2 Hz), 6.52 (2 H, s), 5.79 (1 H, br s), 3.86 (9 H, s), 3.85 (3 H, s), 3.84 (3 H, s), 3.56 (2 H, br s), 3.41 (1 H, d, J = 14.9 Hz), 2.89 (1 H, d, J = 14.9 Hz), 2.82–1.38 (21 H, m), 2.34 (3 H, s), 1.05 (3 H, s), 0.89 (3 H, s), 0.85 (3 H, d, J = 6.8 Hz), 0.84 (3 H, d, J = 6.8 Hz); IR (neat) 3295, 2970, 2845, 2800, 1748, 1591, 1518, 1469, 1397, 1378, 1335, 1130, 807, 761 cm^{-1}.

***N*-[(2*R*)-2-(3,4,5-Trimethoxyphenyl)-2-isopropyl-5-[(3,4-dimethoxyphenethyl)methylamino]pentyl]-(1*S*)-10-camphorsulfonamide (22b).** (2*R*)-(+)-Gallopamil (**2b**; 130 mg, 0.268 mmol) was converted to 129 mg (0.184 mmol) of camphorsulfonamide derivative **22b** (a pale yellow oil) according to the procedure described for the conversion of **1a** to **20a**: 69%; TLC (5:5:90 Et_3N/MeOH/EtOAc) R_f 0.53; ^1H NMR ($CDCl_3$) δ 6.78 (1 H, d, J = 8.0 Hz), 6.75 (1 H, d, J = 1.6 Hz), 6.73 (1 H, dd, J = 1.6, 8.0 Hz), 6.53 (2 H, s), 5.61 (1 H, br s), 3.86 (9 H, s), 3.85 (3 H, s), 3.84 (3 H, s), 3.59 (2 H, br s), 3.33 (1 H, d, J = 14.9 Hz), 2.86 (1 H, d, J = 14.9 Hz), 2.79–1.37 (21 H, m), 2.33 (3 H, s), 1.02 (3 H, s), 0.87 (3 H, s), 0.83 (3 H, d, J = 6.5 Hz), 0.82 (3 H, d, J = 6.5 Hz); IR (neat) 3290, 2972, 2842, 2700, 1748, 1590, 1518, 1468, 1396, 1380, 1334, 1130, 807, 761 cm^{-1}.

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Alkynylcyanoketenes

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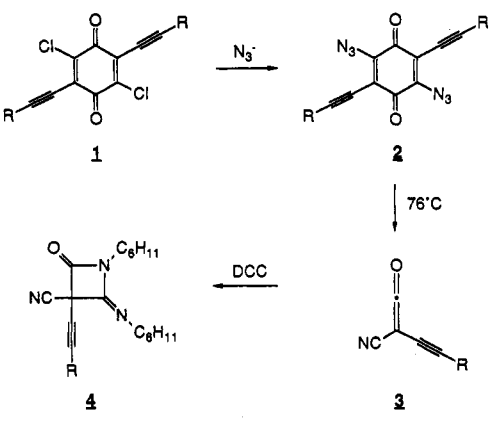
Alkynylcyanoketenes are now available from the thermolysis of 2,5-dialkynyl-3,6-diazido-1,4-benzoquinones. The scope of this reaction is discussed as well as some chemical properties of the resulting ketenes. Specifically, the cycloaddition of hexynylcyanoketene to a series of alkenes and its reaction with alcohols are reported here. The former reaction results in synthetically useful cyclobutanones and the latter in unexpected alkenyl esters (2:1 adducts) arising from intermediate cyanoallenes.

We have previously reported that cyanoketenes can be generated from the thermolysis of 2,5-diazido-1,4-benzoquinones.[1] This reaction has received detailed study for the syntheses of alkyl- and arylcyanoketenes and has been particularly useful as a route to the extensively studied *tert*-butylcyanoketene (TBCK).[2] Reported here is an extension of this reaction which now allows the generation of alkynylcyanoketenes.[3] In addition to the synthesis of a series of alkynylcyanoketenes, some selected reactions of this class will also be reported in this paper. To our knowledge, the ketenes described here are the only examples to appear in which an alkyne group is in direct conjugation with the ketene moiety (alkynylketenes). This is a surprising observation in view of the extensive knowledge gathered on alkenylketenes.[4]

The diazidoquinone precursors **2a–g** of the ketenes **3a–g** are readily obtained from 2,5-dialkynyl-3,6-dichloro-1,4-benzoquinones **1a–g** upon treatment with azide ion (Scheme I). The alkynylquinones **1a–g**, in turn, come from chloranilic acid as reported previously.[5,6] The ketenes **3a–g** were generated in situ from the thermolysis of **2a–g** in refluxing carbon tetrachloride in the presence of dicyclohexylcarbodiimide (DCC). Thus, the ketenes were trapped via their cycloadditions to DCC to give the respective adducts **4a–g** in 42–86% yield.

Scheme I



	R	%4
a)	$-nC_4H_9$	86%
b)	$-C_6H_5$	78%
c)	$-C_6H_4$-o-OCH_3	47%
d)	$-C_6H_4$-o-CH_3	56%
e)	$-CH_2$-O-THP	80%
f)	$-CH_2CH_2C_6H_5$	56%
g)	$-C(CH_3)=CH_2$	42%

Hexynylcyanoketene (HCK) **3a** was chosen as a representative member of the alkynylcyanoketene class and utilized to explore selected reactions. Of particular interest was an investigation to establish the facility of the cycloaddition of the alkynylcyanoketenes to alkenes. This study resulted in a number of important observation (Scheme II).[5] First, HCK expresses significant reactivity with di-,

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