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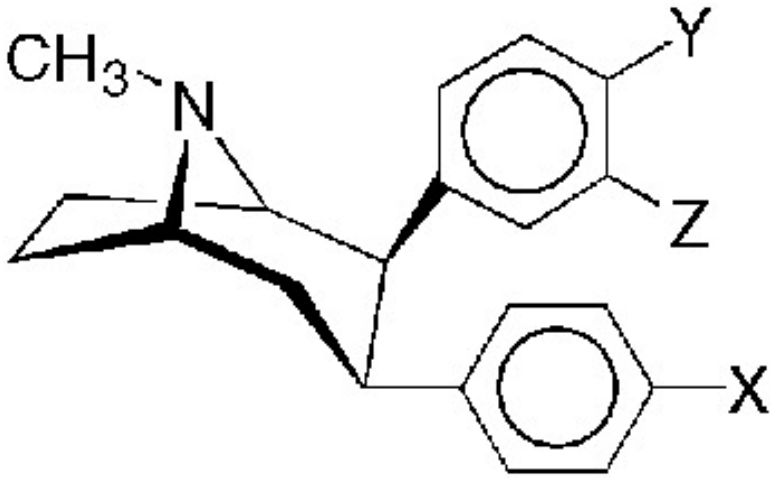

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Synthesis and Monoamine Transporter Binding Properties of 2,3-Diaryltropanes

Sharadsrikar V. Kotturi, Songchun Jiang, An-Chih Chang, Philip Abraham, Hernán A. Navarro, Michael J. Kuhar, and F. Ivy Carroll*

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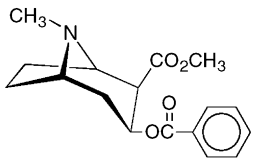
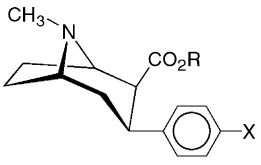
Synthetic procedures were developed for the synthesis of 2β,3β- and 2α,3α-diaryltropanes. These compounds are analogues of the 3-aryltropane-2β-carboxylic acid methyl ester class of monoamine uptake inhibitors, where the 2β-carbomethoxy group has been replaced by an aryl group. The compounds were evaluated for inhibition of radioligand binding at the dopamine, norepinephrine, and serotonin transporters (DAT, NET, and 5-HTT, respectively). The results showed that the replacement of the 2β-carbomethoxy group in the 3-aryltropane class with a 2β-aryl group led to compounds possessing very similar monoamine transporter binding properties. However, the 2β,3β-diaryltropanes tended to be more potent at the DAT and more selective for the DAT relative to the NET and 5-HTT. One of the most interesting compounds was 3β-(4-methylphenyl)-2β-(4-methylphenyl)tropane (**3d**), which showed an IC_{50} of 1.23 nM at the DAT with 289- and 185-fold selectivity for the DAT relative to the NET and 5-HTT. The 2α,3α-diaryltropanes were much less potent at all three transporters than 2β,3β-diaryltropanes.

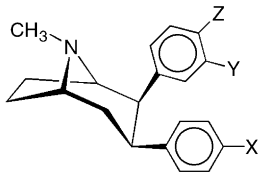
Cocaine (**1**) addiction is a significant socioeconomic problem of our times. Evidence of cocaine addiction being a disease of the brain with specific neurobiological characteristics[1,2] necessitates development of effective therapies to treat cocaine addiction. Cocaine has been shown to block the reuptake of dopamine (DA), serotonin (5-HT), and norepinephrine (NE) as well as to exert effects on the cholinergic, muscarinic, and σ receptors and sodium channels.[3,4] Results from animal studies suggest that the dopamine transporter (DAT) is a key target (receptor) for cocaine regarding the reinforcing effects of the drug.[3,4] Thus, compounds selective for the DAT relative to the norepinephrine transporter (NET) and serotonin transporter (5-HTT) are of particular interest as potential pharmacotherapies to treat cocaine addiction. A number of studies have been directed toward the characterization of the binding site on the DAT with the hope that the information would aid in the discovery of potential pharmacotherapies for treating cocaine addiction.[3,5−8] Many of these studies have been directed toward the 3-phenyltropane class of compounds where 3β-phenyltropane-2β-carboxylic acid methyl ester (**2a**, WIN 35,065-2) served as the lead compound. In this study, we describe the syntheses of 2β,3β- and 2α,3α-diaryltropanes (**3a**−**g** and **4a**−**f**, respectively) and report that some analogues show high potency for the DAT combined with high selectivity relative to the NET and 5-HTT. These compounds can be viewed as structures where the 2β-carbomethoxy group present in **2a** has been replaced by a phenyl or substituted phenyl ring. Preliminary results from some of these studies have been reported.[9]



1, -(-)-Cocaine



2a, X = H
b, X = CH_3



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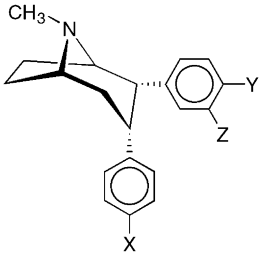

4a, X = Y = Z = H
b, X = CH_3, Y = Z = H
c, X = Z = H, Y = CH_3
d, X = Y = CH_3, Z = H
e, X = CH_3, Y = CH_3O, Z = H
f, X = Y = Z = OCH_3
g, X = CH_3, Y = F, Z = H

Chemistry

The syntheses of compounds **3a**−**g** and **4a**−**f**, starting with the appropriate 2,3-diaryltrop-2-enes (**5a**−**g**), are shown in Scheme 1. Catalytic reduction of **5a** or **5b** in methanol using 5% palladium on carbon gave exclusively the 2α,3α-diaryltropanes **4a** and **4b**, respectively. No reduction conditions were found that would directly convert **5a** or **5b** to the 2β,3β-diaryltropanes **3a** and **3b**, respectively. Fortunately, we found that catalytic reduc-

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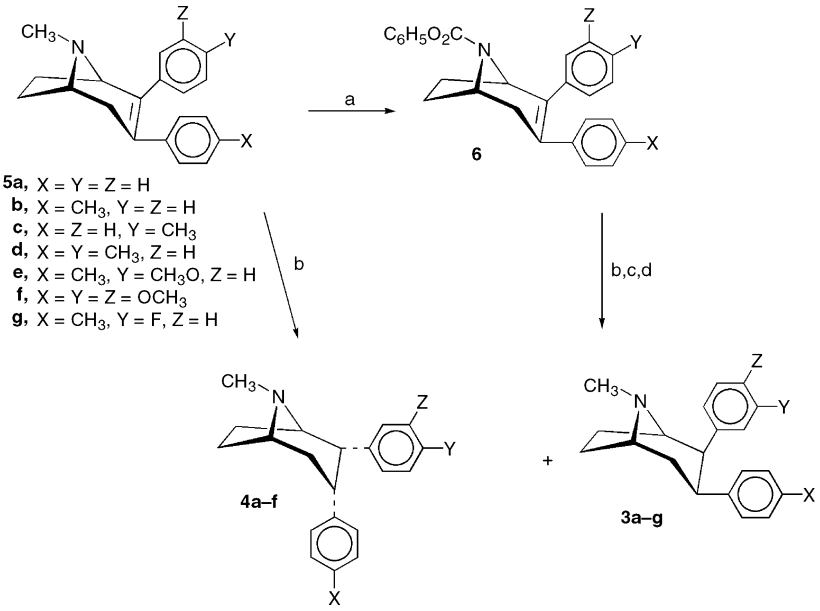
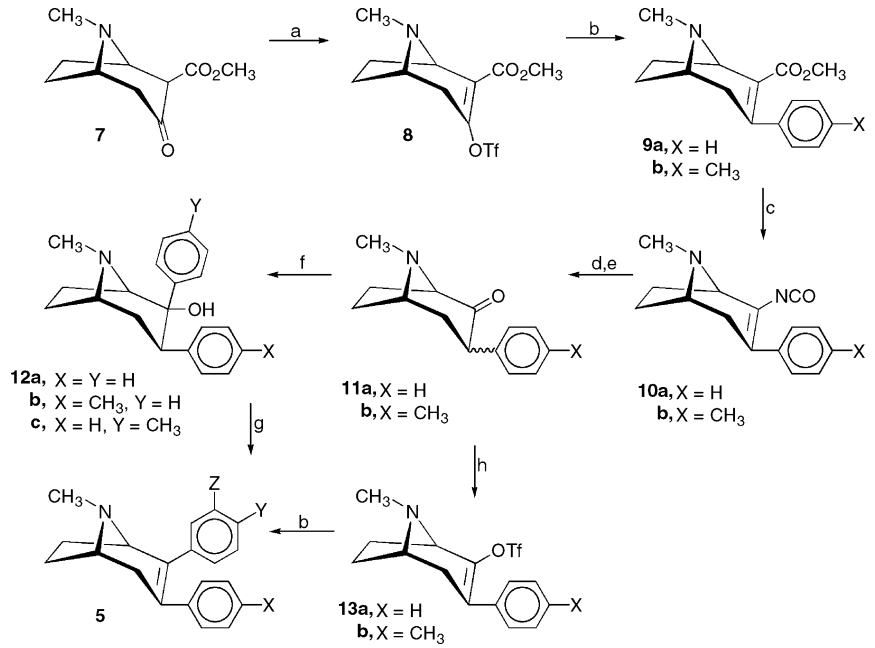
Scheme 1[a]



[a] Reagents: (a) C_6H_5OCOCl, CH_2Cl_2, $NaHCO_3$; (b) H_2, Pd/C, CH_3OH; (c) $LiAlH_4$, $(C_2H_5)_2O$; (d) chromatography separation.

Scheme 2[a]

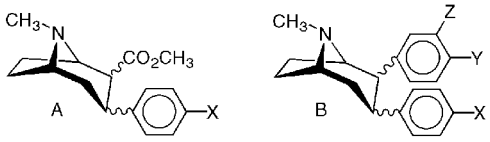


[a] Reagents: (a) $(CF_3SO_2)_2NC_6H_4$, $NaN[Si(CH_3)_3]_2$, THF; (b) *p*-$XC_6H_4B(OH)_2$, $Pd[P(C_6H_5)_3]_4$, CsF, DEM; (c) (i) 0.5 N KOH followed by 1 N HCl, (ii) $(C_6H_5O)_2PON_3$, $(C_2H_5)_3N$, toluene; (d) C_2H_5OH, reflux 8 h; (e) reflux with 19% HCl for 1 h; (f) aryl MgBr, $(C_2H_5)_2O$; (g) concentrated HBr, reflux, 15 min; (h) $(CF_3SO_2)_2NC_6H_4$, $NaN[Si(CH_3)_3]_2$, THF.

tion of the *N*-phenoxycarbonyl-protected analogues **6a**−**g**, followed by lithium aluminum hydride reduction to convert the urethane to the *N*-methyl group, gave a mixture of the 2β,3β- and 2α,3α-isomers **3** and **4**, which could be readily separated by chromatography. The urethanes **6a**−**g** were obtained by N-demethylation of **5a**−**g** with phenyl chloroformate. The relative stereochemistry of each compound was determined by analyses of the ^{1}H NMR spectra.

The 2,3-diaryltrop-2-enes (**5a**−**g**) needed to prepare **3a**−**h** and **4a**−**g** were synthesized starting with 2-carbomethoxy-3-tropinone (**7**) as outlined in Scheme 2.[10,11] The addition of *N*-phenyltrifluoromethanesulfonamide to a tetrahydrofuran solution of **7** containing sodium bis-(trimethylsilyl)amide afforded the triflate **8**. Reaction of **8** with phenyl- or 4-methylphenylboronic acid in refluxing diethoxymethane (DEM) using tetrakis(triphenylphosphine)palladium(0) as catalyst followed by chromatographic purification gave 3-phenyl- or 3-(4-methylphenyl)-2-tropenes **9a** or **9b** in 88% and 89% yields, respectively. Hydrolysis of **9a** and **9b** with 0.5 N potassium hydroxide solution followed by acidification to pH 6 gave the corresponding carboxylic acid, which was treated with diphenylphosphoryl azide in toluene containing triethylamine. The resulting intermediate isocyanate **10a** or **10b** was refluxed in ethanol to afford the corresponding urethane, which was hydrolyzed with 19% hydrochloride acid to give the desired (*R*)-2-

Table 1. Monoamine Transporter Binding Properties of 2,3-Diaryltropanes



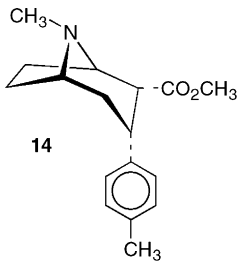
						IC_{50}, nM (K_i, nM)		
compd	X	Y	Z	isomer	structure	DAT [^{3}H]WIN 35,428	NET [^{3}H]Nisoxetine	5-HTT [^{3}H]paroxetine
cocaine						89.1	3300 (1990)	1050 (45)
2a[a]	H			2β,3β	A	23 ± 5	920 ± 70 (550 ± 44)	1960 ± 61 (178 ± 6)
2b[a]	CH_3			2β,3β	A	1.7 ± 0.3	60 ± 1 (36 ± 1)	240 ± 27 (23 ± 3)
14[a]	CH_3	H	H	2α,3α	A	23.4 ± 4.2	3850 ± 1270 (1930 ± 63)	>2000
3a	H	H	H	2β,3β	B	12.6 ± 1.9	920 ± 150 (550 ± 89)	21000 ± 3300 (1900 ± 300)
4a	H	H	H	2α,3α	B	690 ± 37	1040 ± 41 (626 ± 24)	41000 ± 5300 (3700 ± 481)
3b	CH_3	H	H	2β,3β	B	1.96 ± 0.08	480 ± 86 (280 ± 51)	1100 ± 83 (100 ± 7)
4b	CH_3	H	H	2α,3α	B	430 ± 59	4850 ± 72 (2920 ± 43)	16000 ± 3700 (1500 ± 340)
3c	H	CH_3	H	2β,3β	B	22.4 ± 5.5	6100 ± 1100 (3700 ± 640)	45000 ± 9500 (4100 ± 860)
4c	H	CH_3	H	2α,3α	B	540 ± 57	4700 ± 200 (2800 ± 120)	11000 ± 2600 (1000 ± 240)
3d	CH_3	CH_3	H	2β,3β	B	1.35 ± 0.34	780 ± 84 (390 ± 42)	1010 ± 20 (250 ± 5)
4d	CH_3	CH_3	H	2α,3α	B	340 ± 9	13000 ± (7800 ±	10000 ± 1100 (910 ± 100)
3e	CH_3	CH_3O	H	2β,3β	B	1.23 ± 0.13	282 ± 44 (191 ± 22)	1669 ± 167 (410 ± 41)
4e	CH_3	CH_3O	H	2α,3α	B	238 ± 32	NT	1530 ± 255 (376 ± 63)
3f	CH_3	CH_3O	CH_3O	2β,3β	B	23.3 ± 0.8	10000 ± 1400 (6000 ± 840)	13700 ± 7100 (1250 ± 646)
4f	CH_3	CH_3O	CH_3O	2α,3α	B	980 ± 48	78000 ± 2800 (46000 ± 16000)	16200 ± 1700 (1470 ± 154)
3g	CH_3	F	H	2β,3β	B	0.90 ± 0.12	132 ± 25 (61 ± 13)	100 ± 6.0 (25 ± 2)

[a] Taken from ref 12.

tropinone **11a** or **11b** in 62% and 55% yields, respectively, from **7**. Addition of the appropriate arylmagnesium bromide to **11a** or **11b** gives the addition products **12a**−**c**, which were dehydrated with concentrated hydrobromic acid to yield the 2,3-diaryltropenes **5a**−**c**. Tropenes **5d**−**g** as well as **5a** were prepared by converting **11a** and **11b** to triflates **13a** and **13b** using *N*-phenyltrifluoromethanesulfonamide and sodium bis(trimethylsilyl)amide. Reaction of **13a** or **13b** with the appropriate boronic acid in diethoxymethane using tetrakis(triphenylphosphine)palladium(0) gave the desired tropenes **5a** and **5d**−**g**.

Biology

The IC_{50} values for the inhibition of radioligand binding at the dopamine, serotonin, and norepinephrine transporters for **3a**−**g** and **4a**−**f** are listed in Table 1. For comparison, the previously reported IC_{50} values for cocaine (**1**), **2a**, **2b** (RTI-32), and 3α-(4-methylphenyl)-tropane-2α-carboxylic acid methyl ester (**14**) are also listed.[12] The binding affinities at the dopamine, serotonin, and norepinephrine transporters were determined via competitive binding assays using previously reported procedures.[13,14]



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Results and Discussion

Studies from our laboratory as well as from others have shown that replacing the 2β-carbomethoxy group present in **2a** and other 3β-aryl substituted analogues with a carboxamido, heterocyclic, olefinic, keto, or alkyl group has very little effect on binding affinity at the DAT.[5] In the present study, we report the effect of replacing the 2β-carbomethoxy group with various aryl groups. Replacement of the 2β-carbomethoxy group of **2a** with a 3β-phenyl group to give **3a** results in an essential 2-fold increase in binding affinity (12.6 vs 23 nM IC_{50}). In the case of the 3β-(4′-methylphenyl) analogue **2b**, replacing the 2β-carbomethoxy group with a 2β-phenyl ring had almost no effect on binding affinity (1.96 vs 1.7 nM IC_{50}). The addition of a 4-methyl group to **2a** to give **3c** or the addition of 4-methyl, 4-methoxy, or 4-fluoro group to **3b** to give **3d**, **3e**, and **3g**, respectively, had very little effect on binding affinity to the DAT. The most potent compound was the 4-fluoro analogue **3g**, which possessed a 0.9 nM IC_{50} value at the DAT. Results for the 2α,3α analogues were quite different from those of the 2β,3β analogues. For example, replacement of the 2α-carbomethoxy group in the 2α,3α compound **14** with a 3α-phenyl group to give **4b** results in an 18-fold loss in binding affinity at the DAT (430 vs 23.4 nM IC_{50}). The IC_{50} values for the 2α,3α-(4-methylphenyl)tropanes (**4b**−**f**) ranged from 340 to 980 nM. The 2α,3α-diphenyl analogue **4a** possessed an IC_{50} of 690 nM. None of the compounds evaluated have appreciable affinity at the 5-HTT and NET. In fact, compounds **3b**, **3d**, and **3e** with IC_{50} values of 1.96, 1.35, and 1.23 nM, respectively, at the DAT, with K_i values of 280, 390, and 191 nM at the NET and 100, 250, and 410 nM at the 5-HTT, respectively, are selective for the DAT relative to the NET and 5-HTT. Thus, even though the replacement of the carbomethoxy group of the 3-phenyltropanes **2a**,**b** with a 2β-aryl group to give **3a**−**g** had only a small effect on binding to the DAT, the overall effects of binding at the DAT, NET, and 5-HTT resulted in compounds with increased potency at the DAT and selectivity at the DAT relative to the

NET and 5-HTT. The high potency and DAT selectivity of the 2β,3β-aryltropanes increase interest in this class of compounds as potential pharmacotherapies for cocaine addiction.

In summary, we developed procedures for the synthesis of 2β,3β-diaryltropanes. The compounds can be viewed as analogues of **2a** and **2b** where the 2β-carbomethoxy group has been replaced by a substituted phenyl ring. The compounds having the 2β-aryl group tended to be more potent at the DAT than the corresponding 2β-carbomethoxy analogues and more selective relative to binding at the NET and 5-HTT. The 2β-(4-methylphenyl)-3β-(4-methylphenyl)tropane (**3d**) was the most potent and selective analogue.

Experimental Section

Commercial reagents and solvents were used as received. All reactions were run under dry N_2 in oven-dried glassware. The HCl (1 M), NaOH (6 M), Na_2CO_3 (saturated), NH_4Cl (saturated), and NaCl (saturated) used in various procedures refer to aqueous solutions. All organic solvents used, unless otherwise mentioned, were either distilled before use or were purchased anhydrous and used directly. Reactions were monitored by TLC on silica gel GF plates (0.25 μm film thickness). Preparative separations were performed using flash column chromatography on silica gel (grade 62, 60−200 mesh) and PTLC on 20 cm × 20 cm silica gel GF plates; band elution was monitored using a hand-held UV lamp. Optical rotations were measured on an AutoPol III polarimeter, purchased from Rudolf Research. Elemental analyses were performed by Atlantic Microlab, Norcross, GA. Melting points were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ at 300, 250, 62.5, and 75 MHz, respectively, and were referenced to internal $(CH_3)_4Si$, as the free bases.

(*R*)-2-Carbomethoxy-3-tropinone 3-Triflate (8). To a solution of (*R*)-(+)-2-carbomethoxy-3-tropinone (**7**, 7.08 g, 36 mmol) in dry THF (200 mL) at −78 °C was added dropwise $NaN(TMS)_2$ (1 M solution in THF, 43 mL) in 10 min. The mixture was stirred for 30 min, the mixture was allowed to warm to 0 °C, and *N*-phenyltrifluoromethanesulfonamide (15.4 g, 43 mmol) was added portionwise in 10 min. The reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 4 h. After removal of the solvents, the residue was taken up with water (50 mL) and extracted with EtOAc (4 × 100 mL). The EtOAc extracts were washed with brine (20 mL), dried (Na_2SO_4), and evaporated. The crude product was purified by flash column chromatography on SiO_2, using EtOAc followed by 5% Et_3N in EtOAc as eluent to afford **8** as an amber oil (10.94 g, 92%): $[\alpha]^{23}_D$ +9.86° (*c* 7.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.94 (d, J = 4.9 Hz, 1H), 3.82 (s, 3H), 3.43 (m, 1H), 2.85 (dd, J = 4.6, 18.7 Hz, 1H), 2.40 (s, 3H), 2.25−2.10 (m, 2H), 2.05−1.93 (m, 2H), 1.61 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 163.7, 149.0, 125.2, 118.2 (q, J = 317.8 Hz), 60.0, 57.4, 52.0, 34.8, 34.6, 33.0, 30.0. Anal. ($C_{11}H_{14}F_3NO_5S$) C, H, N.

(*R*)-2-Carbomethoxy-3-phenyl-2-tropene (9a). A mixture of compound **8** (3.29 g, 10 mmol), phenylboronic acid (1.46 g, 12 mmol), $Pd(PPh_3)_4$ (0.035 g, 0.30 mmol), and cesium fluoride (3.34 g, 22 mmol) in DEM (20 mL) was stirred at 60 °C for 2 h. The reaction mixture was diluted with ether (200 mL), and the resulting solid was separated by filtration. The ether extracts were washed with H_2O (10 mL), dried (Na_2SO_4), and evaporated. The resulting dark oil was purified by flash column chromatography (SiO_2, 5% Et_3N in EtOAc) to give **9a** as a light-yellow oil (2.27 g, 88%): $[\alpha]^{26}_D$ −61.4° (*c* 2.87, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.36−7.24 (m, 3H), 7.15−7.11 (m, 2H), 3.87 (d, J = 5.3 Hz, 1H), 3.47 (s, 3H), 3.36 (m, 1H), 2.77 (dd, J = 4.8, 18.9 Hz, 1H), 2.46 (s, 3H), 2.30−2.10 (m, 2H), 2.10−1.94 (m, 2H), 1.66 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 143.6, 141.1, 130.4, 127.9, 127.3, 126.6, 60.2, 57.4, 51.2, 37.4, 35.9, 34.2, 30.1. Anal. ($C_{16}H_{19}NO$) C, H, N.

(*R*)-2-Carbomethoxy-3-(4-methylphenyl)-2-tropene (9b). A mixture of compound **8** (4.95 g, 15 mmol), 4-methylphenylboronic acid (2.30 g, 11 mmol), $Pd(PPh_3)_4$ (0.52 g, 0.045 mmol), and cesium fluoride (3.0 g, 33.0 mmol) in DEM (30 mL) was stirred at 60 °C for 2 h. The solvent was evaporated, and the reaction mixture was diluted with ether (200 mL). The resulting solid was separated by filtration, and the solvent was evaporated. The dark oil was purified by flash column chromatography (SiO_2, 5% Et_3N in EtOAc) to give **9b** as a light-yellow oil (3.61 g, 89%): $[\alpha]^{23}_D$ −72.5° (*c* 3.68, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.13−7.09 (m, 2H), 7.03−7.00 (m, 2H), 3.83 (m, 1H), 3.48 (s, 3H), 3.33 (m, 1H), 2.73 (dd, J = 4.7, 18.8 Hz, 1H), 2.43 (s, 3H), 2.33 (s, 3H), 2.23−2.10 (m, 2H), 2.09−1.90 (m, 2H), 1.63 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 168.4, 143.3, 138.0, 136.9, 130.0, 128.5, 126.5, 60.2, 57.2, 57.1, 37.2, 35.7, 34.1, 30.0, 21.0. Anal. ($C_{17}H_{21}NO_2$) C, H, N.

(*R*)-3-Phenyl-2-tropinone (11a). Methyl ester **9a** (2.06 g, 8.01 mmol) was heated to reflux in KOH solution (0.5 N, 32 mL). After 30 min, the mixture was acidified to pH 6 using HCl solution (1 N). After removal of solvents, the resulting residue was extracted with absolute EtOH (3 × 40 mL). Evaporation of EtOH gave the acid as a white solid. The acid was stirred with diphenylphosphoryl azide (2.64 g, 9.61 mmol) and Et_3N (3.35 mL, 24.03 mmol) in toluene (25 mL) at room temperature. After 30 min, the reaction mixture was maintained at 90 °C for another 30 min and then heated to reflux briefly. Absolute EtOH (10 mL) was added, and the reaction mixture was refluxed for 8 h. The residue obtained after removal of solvents was refluxed in 19% HCl solution (10 mL) for 1 h, basified to pH >9 with 6 N NaOH solution, and extracted with CH_2Cl_2 (4 × 50 mL). The CH_2Cl_2 extracts were washed with H_2O (10 mL) and brine (10 mL) and dried (Na_2SO_4), and the solvents were removed. The resulting dark oil was purified by flash column chromatography (SiO_2, 5−10% MeOH in EtOAc/Et_3N, 90:0.5) to give **11a** as a white solid (1.06 g, 62%): mp 104.0−105.5 °C; $[\alpha]^{24}_D$ +29.8° (*c* 0.63, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.36−7.22 (m, 3H), 7.17−7.13 (m, 2H), 3.59 (dd, J = 8.1, 11.8 Hz, 1H), 3.46 (m, 2H), 2.46 (s, 3H), 2.44−2.20 (m, 3H), 2.12 (m, 1H), 2.00−1.80 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 208.4, 138.3, 129.0, 128.5, 127.0, 71.8, 50.2, 49.3, 40.2, 37.9, 26.6. Anal. ($C_{14}H_{17}NO$) C, H, N.

(*R*)-3-(4-Methylphenyl)-2-tropanone (11b). Methyl ester **9b** (1.42 g, 5.24 mmol) was heated to reflux in KOH solution (0.5 N, 21 mL). After 30 min, the mixture was acidified to pH 6 using HCl solution (1 N). After removal of solvents, the resulting residue was extracted with absolute EtOH (3 × 40 mL). The solvent was evaporated to produce the acid as a white solid. The acid was stirred with diphenylphosphoryl azide (1.73 g, 6.29 mmol) and Et_3N (2.2 mL, 15.7 mmol) in toluene (20 mL) at room temperature. After 30 min, the reaction mixture was maintained at 90 °C for another 30 min and then heated to reflux briefly. Absolute EtOH (10 mL) was added, and the reaction mixture was refluxed for 10 h. The residue obtained after removal of solvents was refluxed in 19% HCl solution (10 mL) for 1 h, basified to pH >9 with 6 N NaOH solution, and extracted with CH_2Cl_2 (4 × 50 mL). The CH_2Cl_2 extracts were washed with H_2O (10 mL) and brine (10 mL) and dried (Na_2SO_4), and the solvents were removed. The resulting dark oil was purified by flash column chromatography (SiO_2, 5−10% MeOH in EtOAc/Et_3N, 90:0.5) to give **11b** as a white solid (0.65 g, 55%): mp 100−101.5 °C; $[\alpha]^{24}_D$ +20.2° (*c* 0.59, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.12 (m, 2H), 7.02 (m, 2H), 3.53 (dd, J = 8.1, 11.8 Hz, 1H), 3.42 (m, 2H), 2.47 (s, 3H), 2.40−2.15 (m, 3H), 2.30 (s, 3H), 2.07 (m, 1H), 1.85 (2H); ^{13}C NMR ($CDCl_3$) δ 208.3, 136.3, 135.2, 129.0, 128.7, 71.7, 60.0, 48.7, 40.0, 37.8, 26.4, 20.9. Anal. ($C_{15}H_{19}NO$) C, H, N.

(*R*)-2,3-Diphenyl-2-tropinol (12a). To a solution of ketone **11a** (1.45 g, 6.75 mmol) in ethyl ether (35 mL) was added phenylmagnesium bromide solution (3 M in ether, 6.75 mL) at room temperature. The reaction mixture was stirred at room temperature for 11 h and diluted with ether (100 mL), and the reaction was quenched with H_2O (50 mL). The aqueous layer was extracted with ether (3 × 50 mL). The ether extracts were washed with H_2O (10 mL) and dried (Na_2SO_4), and the solvents were removed. The resulting residue was purified by flash column chromatography (SiO_2, hexane/EtOAc followed

by EtOAc, then 5% MeOH in EtOAc/Et_3N, 99.5:0.5) to give the desired alcohol **12a** as a white solid (0.67 g, 34%) (92% based on recovered ketone) (0.908 g, 63%): mp 92.5−94.0 °C; $[\alpha]^{23}_D$ −137.3° (*c* 0.555, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.75−7.64 (m, 2H), 7.20−7.10 (m, 6H), 6.95−6.90 (m, 2H), 3.43 (m, 1H), 3.27 (m, 1H), 3.15 (dd, J = 5.3, 13.7 Hz, 1H), 2.50 (m, 1H), 2.41 (s, 3H), 2.35−2.00 (m, 3H), 1.89 (s, 1H), 1.82 (m, 1H), 1.67 (ddd, J = 3.1, 5.3, 13.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 144.8, 139.9, 129.6, 128.4, 127.2, 126.7, 126.3, 126.2, 76.2, 72.9, 61.4, 46.2, 41.5, 36.6, 25.2, 22.1.

(*R*)-3-(4-Methylphenyl)-2-phenyl-2-tropinol (12b). To a solution of ketone **11b** (0.84 g, 3.67 mmol) in ethyl ether (25 mL) was added phenylmagnesium bromide solution (3 M in ether, 3.67 mL) at room temperature. The reaction mixture was stirred at room temperature for 11 h and diluted with ether (100 mL), and the reaction was quenched with H_2O (50 mL). The aqueous layer was extracted with ether (3 × 50 mL). The ether extracts were washed with H_2O (10 mL) and dried (Na_2SO_4), and the solvents were removed. The resulting residue was purified by flash column chromatography (SiO_2, hexane/EtOAc followed by EtOAc, then 5% MeOH in EtOAc/Et_3N, 99.5:0.5) to give the desired alcohol **12b** as a white solid (0.47 g, 42%, 89%) based on recovered ketone (0.448 g, 53%): mp 156.0−157.4 °C; $[\alpha]^{23}_D$ −163° (*c* 0.655, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.75−7.71 (m, 2H), 7.14−7.08 (m, 3H), 6.88 (d, $J \cong$ 8.0 Hz, 2H), 6.74 (d, $J \cong$ 8.0 Hz, 2H), 3.36 (m, 1H), 3.22 (m, 1H), 3.03 (dd, J = 5.4, 13.7 Hz, 1H), 2.41 (m, 1H), 2.33 (s, 3H), 2.26−2.00 (m, 3H), 2.22 (s, 3H), 1.77 (s, 1H), 1.74 (m, 1H), 1.58 (ddd, J = 3.1, 5.4, 13.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 145.0, 136.8, 135.8, 129.5, 128.5, 128.1, 126.8, 126.3, 76.3, 73.0, 61.6, 46.1, 41.6, 37.0, 25.4, 22.1, 20.9. Anal. ($C_{21}H_{25}NO$) C, H, N.

(*R*)-3-Phenyl-2-(4′-methylphenyl)-2-tropinol (12c). To a solution of **11a** (860 mg, 4 mmol) in ether (30 mL) at −30 °C was added dropwise a solution of 4-methylphenylmagnesium bromide (1 m, 8 mL) under N_2 in 5 min. The mixture was stirred at −30 °C for 1 h, then warmed to 0 °C. The mixture was diluted with ether (100 mL), and the reaction was quenched with H_2O (50 mL). The aqueous layer was extracted further with ether (50 mL × 3). Ether layers were combined, washed with H_2O (10 mL), dried over Na_2SO_4, and evaporated. The crude residue was purified by flash column chromatography (SiO_2, hexane/EtOAc, 2:1, then EtOAc, then 2% Et_3N in EtOAc) to afford **12c** (0.78 g, 63%) and starting material (0.20 g, 23%): $[\alpha]^{25}_D$ −140.5° (*c* 0.22, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.56 (d, J = 8.4 Hz, 2H), 7.08 (m, 3H), 6.89 (m, 4H), 3.35 (m, 1H), 3.21 (d, J = 6.4 Hz, 1H), 3.07 (dd, J = 5.3, 13.5 Hz, 1H), 2.43 (m, 1H), 2.33 (s, 3H), 2.24 (s, 3H), 2.20−2.00 (m, 2H), 1.79−1.67 (m, 2H), 1.55 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 153.7, 141.8, 140.0, 135.6, 129.6, 129.0, 128.3, 127.4, 127.2, 126.1, 115.1, 73.1, 61.4, 46.1, 41.5, 36.6, 25.2, 22.1, 20.8.

2,3-Diphenyl-2-tropene (5a). Alcohol **12a** (631 mg, 2.15 mmol) was refluxed in concentrated HBr (5 mL) for 15 min. The residue obtained after removal of solvents was taken up in saturated $NaHCO_3$ (10 mL) and extracted with EtOAc (4 × 15 mL). The EtOAc extracts were washed with brine (10 mL), dried (Na_2SO_4), and evaporated to give a yellow oil (580 mg, 98%), which was pure enough for the next step. Purification by flash column chromatography (5% Et_3N in EtOAc) gave **5a** as a clear oil: $[\alpha]^{23}_D$ −277.6° (*c* 0.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.17−7.05 (m, 6H), 7.02−6.96 (m, 4H), 3.75 (d, J = 5.8 Hz, 1H), 3.54 (m, 1H), 2.83 (dd, J = 4.4, 18.2 Hz, 1H), 2.64 (s, 3H), 2.40−2.11 (m, 3H), 2.05 (m, 1H), 1.80 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 140.7, 140.5, 137.7, 130.3, 129.2, 128.7, 128.0, 127.8, 126.4, 65.1, 58.3, 36.0, 35.8, 33.3, 30.0. Anal. ($C_{20}H_{21}NO$) C, H, N.

3-(4-Methylphenyl)-2-phenyl-2-tropene (5b). Alcohol **12b** (331 mg, 1.07 mmol) was refluxed in concentrated HBr (3 mL) for 15 min. The reaction mixture was basified to pH >9 using 6 N NaOH and extracted with CH_2Cl_2 (4 × 15 mL). The CH_2Cl_2 extracts were washed with brine (10 mL), dried (Na_2SO_4), and evaporated. The resulting solid was purified by flash column chromatography (SiO_2, 20% MeOH in EtOAc/Et_3N, 80:0.5) to give **5b** as a colorless oil (251 mg, 81%): $[\alpha]^{23}_D$ −254.1° (*c* 13.84, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.17−7.05 (m, 3H), 7.05−6.99 (m, 2H), 6.89 (m, 4H), 3.64 (d, J = 5.7 Hz, 1H), 3.43 (m, 1H), 2.76 (dd, J = 4.4, 18.0 Hz, 1H), 2.57 (s, 3H), 2.21 (s, 3H), 2.33−1.94 (m, 4H), 1.74 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 141.3, 138.0, 137.9, 135.7, 129.8, 129.2, 128.6; 128.4, 127.8, 126.0, 65.1, 58.1, 35.95, 35.97, 33.4, 30.2, 21.0.

3-Phenyl-2-(4-methylphenyl)tropene (5c). The **12c** (0.52 g, 1.67 mmol) was refluxed in concentrated HBr (4 mL) for 15 min. HBr was evaporated. The residue was taken up by saturated $NaHCO_3$ and extracted with EtOAc (15 mL × 4). EtOAc was washed with brine (10 mL), dried over Na_2SO_4, and evaporated to give a brownish oil. Purification of crude by flash column chromatography (SiO_2, 5% Et_3N in EtOAc) afforded **5c** as a clear oil: $[\alpha]^{23}_D$ −224.5° (*c* 0.955, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.32−6.86 (m, 9H), 3.61 (d, J = 5.6 Hz, 1H), 3.41 (t, J = 6.3 Hz, 1H), 2.75 (dd, J = 17.3 Hz, 1H), 2.55 (s, 3H), 2.23 (s, 3H), 2.17−1.93 (m, 4H), 1.74 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 141.5, 138.5, 138.3, 135.7, 129.6, 129.1, 128.8, 128.6, 127.7, 126.1, 65.2, 58.2, 36.2, 33.6, 30.4, 21.1.

(*R*)-3-Phenyl-2-tropinone 2-Triflate (13a). A solution of $NaN(TMS)_2$ was added slowly (5 min) to the ketone **11a** in THF (20 mL) at −78 °C. The reaction mixture was stirred at room temperature for 30 min, then warmed to 0 °C. *N*-Phenyltrifluoromethanesulfonamide (0.826 g) was added in one portion. The reaction mixture was stirred for 1 h at 0 °C and then at room temperature for 22 h. The reaction was quenched with H_2O (15 mL) and extracted with EtOAc (3 × 20 mL). The EtOAc extracts were washed with brine (10 mL) and dried ($MgSO_4$). Removal of the solvents gave an amber oil, which was purified by column chromatography (SiO_2, EtOAc then MeOH/EtOAc/Et_3N, 5:94:1) to afford **13a** as a light-yellow oil (250 mg, 34%): $[\alpha]^{23}_D$ +16.7° (*c* 2.43, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.41−7.26 (m, 5H), 3.50 (d, J = 4.8 Hz, 1H), 3.47 (t, J = 5.5 Hz, 1H), 2.96 (dd, J = 4.5, 17.8 Hz, 1H), 2.55 (s, 3H), 2.27−2.17 (m, 3H), 2.10 (d, J = 17.6 Hz, 1H), 1.67 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 144.9, 135.0, 128.2, 128.0, 127.6, 125.8, 118.0 (q, J = 318.2 Hz), 61.4, 56.5, 35.2, 34.6, 33.9, 30.1.

2,3-Diphenyl-2-tropene (5a) from 13a. A mixture of triflate **13a** (95 mg, 0.27 mmol), phenylboronic acid (40 mg, 0.32 mmol), $Pd(PPh_3)_4$ (9 mg), and cesium fluoride (90 mg, 0.59 mmol) in DEM (8 mL) was refluxed for 1 h. The solvent was removed, and the resulting residue was purified by flash column chromatography (SiO_2, 2.5% Et_3N in EtOAc) to give **5a** as a clear oil (55 mg, 74%). The ^{1}H NMR spectrum was identical to the compound prepared from **12a**.

(*R*)-3-(4-Methylphenyl)-2-tropinone 2-Triflate (13b). To a well-stirred hexane-washed suspension of 0.13 g (5.41 mmol) of NaH in THF at −78 °C was added 1.00 g (4.36 mmol) of **8b** in 20 mL of THF over 10 min, and the mixture was stirred for 15 min. The mixture was then warmed to room temperature and stirred for 30 min, and 4.65 g (13.0 mmol) of *N*-phenyltrifluoromethanesulfonamide was added in one portion. The mixture was stirred at room temperature for 2 h. Concentration of the mixture, followed by extraction with ether, resulted in a heavy brown oil, which was purified by column chromatography using hexanes with increasing concentrations of EtOAc and Et_3N to yield 0.93 g (59%) of **6** as a thick red oil that had the following properties: $[\alpha]^{23}_D$ +18.2° (*c* 0.60, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.18 (s, 4H), 3.50 (d, J = 4.8 Hz, 1H), 3.33 (t, J = 5.5 Hz, 1H), 2.96 (dd, J = 17.8, 4.5 Hz, 1H), 2.54 (s, 3H), 2.34 (s, 3H), 2.27−2.17 (m, 3H), 2.10 (d, J = 17.6 Hz, 1H), 1.67 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 144.0, 137.3, 131.4, 128.5, 128.3, 128.1, 126.9, 125.0, 119.5, 115.2, 60.8, 59.4, 56.0, 39.5, 37.2, 34.6, 34.1, 33.3, 29.5, 25.9, 20.4. Anal. ($C_{16}H_{18}F_3NO_3S$) C, H, N.

Synthesis of 5d−g. Compounds **5d−g** were synthesized from triflate **13b** using conditions analogous to that described for the synthesis of **5a** from triflate **13a**.

2,3-Di(4-methylphenyl-2-tropene (5d). Yellow oil, 320 mg (84%); $[\alpha]^{23}_D$ −72.2° (*c* 3.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.90 (m, 8H), 3.60 (d, J = 5.7 Hz, 1H), 3.40 (t, J = 5.8 Hz, 1H), 2.73 (dd, J = 18.7, 4.6 Hz, 1H), 2.55 (s, 3H), 2.26 (s, 3H), 2.24 (s, 3H), 2.20−2.00 (m, 3H), 1.97 (dt, J = 11.6, 2.8 Hz, 1H),

1.74 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 138.5, 138.3, 138.0, 135.6, 129.3, 129.1, 128.6, 128.5, 128.4, 65.2, 58.1, 36.2, 33.5, 30.7, 21.1, 21.0.

3-(4-Methylphenyl)-2-(4-methoxyphenyl)-2-tropene (5e). White semisolid, 380 mg (96%); $[\alpha]^{23}_D$ −234.0° (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.92 (m, 6H), 6.70 (d, J = 8.5 Hz, 2H), 3.74 (s, 3H), 3.60 (d, J = 6.0 Hz, 1H), 3.40 (t, J = 6.0 Hz, 1H), 2.73 (dd, J = 18.0, 4.5 Hz, 1H), 2.25 (s, 3H), 2.20−2.00 (m, 3H), 1.96 (dt, J = 9.5, 3.0 Hz, 1H), 1.73 (m, 1H); ^{13}C NMR δ 157.9, 139.0, 137.8, 135.6, 133.9, 130.3, 129.1, 128.7, 128.5, 113.3, 65.2, 58.2, 55.0, 36.6, 36.3, 33.5, 30.3, 21.0.

3-(Methylphenyl)-2-(2,3-dimethoxyphenyl)-2-tropene (5f). Light-yellow oil, 1.15 g (97%); $[\alpha]^{23}_D$ −189.1° (*c* 2.17, $CHCl_3$); ^{1}H NMR δ ($CDCl_3$) 6.92 (m, 4H), 6.71 (d, J = 8.3 Hz, 1H), 6.65 (dd, J = 8.4, 1.7 Hz, 1H), 6.41 (d, J = 1.7 Hz, 1H), 3.82 (s, 3H), 3.65 (d, J = 5.7 Hz, 1H), 3.54 (s, 3H), 3.42 (t, J = 5.7 Hz, 1H), 2.76 (dd, J = 17.6, 4.3 Hz, 1H), 2.54 (s, 3H), 2.34 (s, 3H), 2.20−2.10 (m, 3H), 1.97 (dt, J = 8.7, 2.5 Hz, 1H), 1.75 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 147.9, 147.3, 138.7, 137.8, 135.6, 133.8, 129.4, 128.5, 128.4, 120.8, 113.4, 110.5, 64.9, 58.2, 55.6, 55.4, 36.5, 33.5, 30.1, 20.9.

3-(4-Methylphenyl)-2-(4-fluorophenyl)-2-tropene (5g). White semisolid, 365 mg (90%); $[\alpha]^{23}_D$ −125.2° (*c* 2.35, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.97−6.92 (m, 4H), 6.88−6.82 (m, 4H), 3.57 (d, J = 6.0 Hz, 1H), 3.41 (t, J = 5.5 Hz, 1H), 2.74 (dd, J = 18.0, 4.0 Hz, 1H), 2.55 (s, 3H), 2.24 (s, 3H), 2.24 (s, 3H), 2.23 (m, 1H), 2.18−2.08 (m, 2H), 1.97 (dt, J = 9.5, 3.0 Hz, 1H), 1.74 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 163.1, 159.2, 137.9, 137.3, 137.2, 137.1, 135.7, 130.6, 130.5, 130.1, 128.5, 128.4, 114.8, 114.5, 65.1, 58.0, 36.1, 33.3, 30.1, 20.9.

(*R*)-*N*-Phenoxycarbonyl-2,3-diphenyl-2-tropene (6a). A mixture of diphenyltropene **5a** (220 mg, 0.80 mmol), phenyl chloroformate (0.40 mL, 0.32 mmol), and $NaHCO_3$ (402 mg, 4.8 mmol) in dry CH_2Cl_2 was stirred at room temperature. After 16 h, the reaction was quenched with saturated $NaHCO_3$ (10 mL). The aqueous layer was separated and extracted further with EtOAc (3 × 20 mL). The EtOAc extracts were washed with H_2O (10 mL) and dried (Na_2SO_4). The residue obtained after removal of solvents was purified by flash column chromatography (SiO_2, 20% ether in hexane) to give **6a** as a white solid (286 mg, 94%): $[\alpha]^{23}_D$ −337.8° (*c* 0.97, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.39−6.97 (m, 15H), 4.89 (d, J = 13.1 Hz, 1H), 4.62 (m, 1H), 3.13 (t, J = 13.6 Hz, 1H), 2.55−2.37 (m, 2H), 2.17−1.97 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 152.8, 151.3, 141.6, 141.1, 140.6, 139.6, 139.4, 131.4, 130.3, 129.7, 129.34, 129.26, 128.9, 128.1, 128.0, 127.8, 126.7, 126.5, 125.2, 121.7, 121.6, 119.9, 115.3, 59.2, 59.0, 53.6, 53.4, 39.9, 38.8, 34.3, 30.6, 29.8.

(*R*)-*N*-Phenoxycarbonyl-2-phenyl-3-(4-methylphenyl)-2-tropene (6b). Compound **6b** was prepared using a procedure similar to that described for **6a**. The compound was obtained as a white semisolid: 296 mg (95%); $[\alpha]^{23}_D$ −279.0° (*c* 0.935, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.40−7.30 (m, 2H), 7.32−7.10 (m, 7H), 7.00−6.70 (m, 5H), 4.90 (m,1H), 4.70 (m, 1H), 3.09 (m, 1H), 2.50−2.30 (m, 2H), 2.23 (s, 3H), 2.10−1.90 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 152.7, 151.2, 141.2, 140.6, 139.8, 139.6, 137.5, 136.0, 131.1, 130.0, 129.7, 129.3, 129.2, 128.7, 128.5, 128.0, 127.9, 126.6, 125.2, 121.7, 121.6, 59.2, 58.9, 53.6, 53.3, 39.9, 38.7, 34.2, 33.3, 30.6, 29.7, 20.6.

(*R*)-*N*-Phenoxycarbonyl-2-(4-methylphenyl)-3-phenyl-2-tropene (6c). Compound **6c** was prepared using a procedure similar to that described for **6a**. The compound was obtained as a white semisolid: 495 mg (75%); $[\alpha]^{23}_D$ −327.9° (*c* 1.06, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.40−7.30 (m, 2H), 7.25−7.00 (m, 6H), 7.04−6.90 (m, 6H), 4.90 (m, 1H), 4.70 (m, 1H), 3.10 (m, 1H), 2.53−2.30 (m, 2H), 2.23 (s, 3H), 2.15−1.80 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 152.8, 151.3, 141.5, 141.0, 140.8, 136.4, 130.9, 129.3, 128.9, 127.8, 126.4, 125.2, 121.8, 59.3, 58.9, 53.7, 53.4, 40.0, 38.8, 34.3, 33.4, 30.7, 29.8, 21.1.

(*R*)-*N*-Phenoxycarbonyl-2,3-di-(4-methylphenyl)-2-tropene (6d). Compound **6d** was prepared using a procedure similar to that described for **6a**. The compound was obtained as a colorless heavy oil; $[\alpha]^{23}_D$ −310.0° (*c* 2.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.35 (m, 2H), 7.17 (m, 3H), 6.92 (m, 8H), 4.87 (d, J = 14.7 Hz, 1H), 4.64 (d, J = 18.5 Hz, 1H), 3.08 (t, J = 17.2, 1H), 2.50−2.30 (m, 2H), 2.25 (s, 3H), 2.24 (s, 3H), 2.20−1.80 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 152.7, 151.3, 141.0, 140.5, 137.8, 136.8, 136.6, 136.2, 136.0, 129.6, 129.2, 128.7, 128.5, 125.2, 121.8, 121.7, 59.3, 58.9, 53.7, 53.4, 40.0, 38.8, 34.2, 33.3, 30.5, 29.8, 21.1, 21.0.

(*R*)-*N*-Phenoxycarbonyl-2-(4-methoxyphenyl)-3-(4-methylphenyl)-2-tropene (6e). Compound **6e** was prepared using a procedure similar to that described for **6a**. The compound was obtained as a white semisolid: 380 mg (85%); $[\alpha]^{23}_D$ −330.0° (*c* 0.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.40 (m, 2H), 7.30−7.15 (m, 4H), 7.09 (m, 2H), 6.96 (m, 4H), 6.80−6.70 (m, 3H), 4.92 (dd, J = 16.0, 4.3 Hz, 1H), 4.70 (m, 1H), 3.75 (s, 3H), 3.12 (dt, J = 16.5, 3.5 Hz, 1H), 2.60−2.40 (m, 2H), 2.29 (s, 3H), 2.20−1.90 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 158.2, 156.2, 152.7, 151.3, 140.5, 140.0, 137.7, 136.0, 132.0, 131.8, 130.8, 130.5, 130.3, 129.3, 129.2, 128.7, 128.6, 125.2, 121.8, 121.6, 119.8, 115.5, 113.5, 113.4, 59.3, 58.9, 55.0, 53.6, 53.4, 39.9, 38.8, 34.2, 33.3, 30.5, 29.8, 21.0.

(*R*)-*N*-Phenoxycarbonyl-2-(2,3-dimethoxyphenyl-3)-4-methylphenyl-2-tropene (6f). Compound **6f** was prepared using a procedure similar to that described for **6a**. The compound was obtained as a white semisolid: 1.34 g (90%); $[\alpha]^{23}_D$ −270.7° (*c* 1.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.34 (m, 2H), 7.16 (m, 3H), 6.92 (m, 4H), 6.72 (m, 2H), 6.54 (d, J = 19.3 Hz, 1H), 4.91 (dd, J = 17.2, 4.2 Hz, 1H), 4.65 (m, 1H), 3.80 (s, 3H), 3.58 (s, 3H), 3.49 (s, 3H), 3.09 (t, J = 17.2 Hz, 1H), 2.53−2.30 (m, 2H), 2.24 (s, 3H), 2.20−1.90 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 152.7, 151.2, 148.1, 147.7, 140.6, 140.3, 137.9, 136.0, 132.1, 131.9, 130.5, 129.4, 129.2, 128.5, 125.1, 121.7, 121.6, 121.0, 113.2, 110.5, 59.0, 58.6, 55.6, 55.4, 53.5, 53.4, 39.9, 38.8, 34.3, 33.4, 30.5, 29.8, 20.9.

(*R*)-*N*-Phenoxycarbonyl-2-(4-fluorophenyl)-3-(4-methylphenyl)-2-tropene (6g). Compound **6g** was prepared using a procedure similar to that described for **6a**. The compound was obtained as a thick colorless oil: 320 mg (95%); $[\alpha]^{23}_D$ −298° (*c* 0.20, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 7.38 (m, 2H), 7.20−7.10 (m, 3H), 7.08 (m, 2 H), 6.98−6.70 (m, 6 H), 4.90 (dd, J = 16.0, 4.3 Hz, 1 H), 4.70 (m, 1 H), 3.20 (dt, J = 16.0, 4.0 Hz, 1 H), 2.60−2.30 (m, 2 H), 2.20 (s, 3 H), 2.19−1.90 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ: 163.1, 159.2, 152.8, 152.0, 147.9, 147.3, 140.5, 140.0, 138.5, 137.7, 136.0, 132.0, 131.8, 129.4, 128.7, 128.2, 120.9, 114.8, 114.0, 113.5, 113.0, 65.0, 57.5, 35.5, 33.3, 30.0, 20.9.

2*β*,3*β*- and 2α,3α-Diphenyltropanes (3a and 4a). A mixture of carbamate alkene **6a** (216 mg, 0.56 mmol) and 5% Pd/C (215 mg) in MeOH (5 mL) was hydrogenated at room temperature under 50 psi. After 4 days, the solvent was evaporated to give the reduced carbamate as a clear oil (221 mg). The carbamate (156 mg, 0.407 mmol) and LAH (77 mg, 2.03 mmol) were refluxed in ether (15 mL) under N_2 for 3 h, and the reaction mixture was diluted with ether (50 mL). The reaction was quenched with H_2O (0.5 mL). The reaction mixture was stirred with Celite (1 g) and Na_2SO_4 (2.0 g) and filtered. Removal of the solvent produced a clear oil (130 mg). Purification by flash column chromatography (SiO_2, MeOH/CH_2Cl_2/Et_3N, 5:95:0.5) afforded **3a** as a white solid (39 mg, 35%) and **4a** (46 mg, 41%) as a clear oil. The free bases were converted to the HCl salt using HCl/ether (1 M).

2*β*,3*β*-3a·HCl: mp 240 °C (dec); $[\alpha]^{24}_D$ −21.8° (*c* 0.17, CH_3OH); ^{1}H NMR (free base, $CDCl_3$) δ 7.26−6.95 (m, 9H), 3.99 (m, 1H), 3.82 (m, 1H), 3.54 (m, 1H), 3.31 (m, 1H), 2.64 (m, 1H), 2.37 (s, 3H), 2.14−1.91 (m, 2H), 1.90−1.78 (m, 2H), 1.46 (m, 1H); ^{13}C NMR (free base, $CDCl_3$) δ 144.0, 142.7, 128.4, 128.3, 127.9, 127.2, 125.5, 124.8, 64.3, 60.4, 49.4, 40.7, 37.1, 36.9, 27.3, 22.6. Anal. ($C_{20}H_{24}ClN\cdot0.25H_2O$) C, H, N.

2α,3α-4a·HCl: mp 233.4−235 °C; $[\alpha]^{23}_D$ +8.33° (*c* 0.12, CH_3OH); ^{1}H NMR (free base, $CDCl_3$) δ 7.40−7.36 (m, 2H), 7.08−6.98 (m, 6H), 6.89−6.86 (m, 2H), 3.45−3.29 (m, 3H), 2.92 (m, 1H), 2.45 (t, J = 12.7 Hz, 1H), 2.27 (s, 3H), 2.27−2.21 (m, 2H), 1.82 (m, 2H), 1.69 (m, 1H); ^{13}C NMR (free base, $CDCl_3$) δ 142.9, 142.4, 130.6, 127.9, 127.6, 127.1, 125.5, 125.4, 67.8, 62.0, 53.1, 41.9, 37.2, 35.0, 27.3, 25.0. Anal. ($C_{20}H_{24}ClN\cdot0.5H_2O$) C, H, N.

(*R*)-3*β*-(Methylphenyl)-2*β*-phenyltropane (3b) and (*R*)-3α-(Methylphenyl)-2α-phenyltropane (4b). A mixture of carbamate alkene **6b** (296 mg, 0.75 mmol) and 10% Pd/C (150 mg) in MeOH (10 mL) was hydrogenated at room temperature under 50 psi. After 3 days, more catalyst (500 mg) was added, and the reduction was continued for an additional 4 days. The catalyst was separated by filtration and washed with ether (100 mL). The solvent was evaporated to give the carbamates, which were separated by flash column chromatography (SiO_2, 30% EtOAc in hexane) to give the 2α,3α-isomer **4b** (86 mg, 30%) and the 2*β*,3*β*-isomer **3b** (88 mg, 30%).

2α,3α-Isomer: ^{1}H NMR ($CDCl_3$) *δ* 7.40−6.76 (m, 14H), 4.84−4.50 (m, 2H), 4.20 (m, 1H′), 3.64 (m, 1H), 2.80 (m, 1H), 2.19 (s, 3H), 2.20−1.50 (m, 5H).

2*β*,3*β*-Isomer: ^{1}H NMR ($CDCl_3$) *δ* 7.30−7.00 (m, 8H), 6.95−6.85 (m, 4H), 6.65 (m, 2H), 4.82 (m, 1H), 4.70 (m, 1H), 3.64 (m, 1H), 3.26 (m, 1H), 2.70 (m, 1H), 2.11 (s, 3H), 2.26−2.00 (m, 3H), 1.93 (m, 2H).

The 2α,3α-carbamate (86 mg, 0.22 mmol) and LAH (42 mg, 1.10 mmol) were refluxed in ether (20 mL) under N_2 for 3 h, the reaction mixture was diluted with ether (50 mL), and the reaction was quenched with H_2O (0.5 mL). The reaction mixture was stirred with Celite (1 g) and Na_2SO_4 (2.0 g), filtered, and washed with ether. Removal of the solvent and purification of the residue by flash column chromatography (SiO_2, 5% Et_3N in EtOAc) afforded **4b** (50 mg, 79%) as a clear oil. The amine was converted to the HCl salt as a white solid using HCl/ether: mp 226.0−227.5 °C; $[\alpha]^{24}_D$ +5.24° (*c* 0.21, CH_3OH); ^{1}H NMR (free base, $CDCl_3$) *δ* 7.20−7.06 (m, 5H), 6.86 (dd, *J* = 8.2, 19.9 Hz, 4H), 3.93 (m, 1H), 3.79 (m, 1H), 3.54 (m, 1H), 3.29 (m, 1H), 2.61 (m, 1H), 2.36 (m, 3H), 2.17 (s, 3H), 2.10 (m, 1H), 2.05−1.75 (m, 3H), 1.44 (m, 1H); ^{13}C NMR (free base, $CDCl_3$) *δ* 142.9, 140.9, 134.0, 128.3, 128.1, 127.9, 125.4, 64.2, 60.5, 49.2, 40.7, 37.3, 36.6, 26.9, 22.7, 20.7. Anal. ($C_{21}H_{26}ClN\cdot0.25H_2O$) C, H, N.

The 2*β*,3*β*-carbamate (88 mg, 0.221 mmol) and LAH (42 mg, 1.10 mmol) were refluxed in ether (20 mL) under N_2 for 3 h, the reaction mixture was diluted with ether (50 mL), and the reaction was quenched with H_2O (0.5 mL). The reaction mixture was stirred with Celite (1 g) and Na_2SO_4 (2.0 g) and filtered. Removal of the solvent and purification of the residue by flash column chromatography (SiO_2, MeOH:CH_2Cl_2/Et_3N, 3:97:0.5) afforded **3b** as a white solid (39 mg, 35%). The amine was converted to the HCl salt as a white solid using HCl/ether (1 M): mp 228 °C (dec); $[\alpha]^{23}_D$ −17.1° (*c* 0.21, CH_3OH); ^{1}H NMR (free base, $CDCl_3$) *δ* 7.41−7.37 (m, 2H), 7.10−7.00 (m, 3H), 6.80 (dd, *J* = 8.0, 17.9 Hz, 4H), 3.41−3.24 (m, 3H), 2.90 (m, 1H), 2.38 (m, 1H), 2.24 (s, 3H), 2.18 (s, 3H), 2.30−2.00 (m, 2H), 1.80 (m, 2H), 1.64 (m, 2H); ^{13}C NMR (free base, $CDCl_3$) *δ* 143.0, 140.0, 134.8, 130.7, 128.3, 127.8, 127.0, 125.4, 67.8, 62.0, 53.2, 42.0, 37.0, 35.5, 27.3, 25.1, 20.9. Anal. ($C_{21}H_{26}ClN\cdot1.5H_2O$) C, H, N.

3*β*-Phenyl-2*β*-(4-methylphenyl)tropane (3c) and 3α-Phenyl-2α-(4-methylphenyl)tropane (4c). Compounds **3c** and **4c** were prepared using a procedure similar to that described for **3a** and **4a**. From 305 mg (0.77 mmol) of **6c**, 76 (34%) and 82 mg (36%) of the 2α,3α- and 2*β*,3*β*-isomers were obtained.

2*β*,3*β*-3c·HCl: mp 230−232 °C (dec); $[\alpha]^{24}_D$ −25.0° (*c* 0.28, CH_3OH); ^{1}H NMR (free base $CDCl_3$) *δ* 7.26 (m, 2H), 7.08−6.95 (m, 3H), 6.90−6.80 (m, 4H), 3.40−3.24 (m, 3H), 2.86 (dd, *J* = 2.2, 6.6, Hz, 1H), 2.36 (dt, *J* = 2.7, 1.29 Hz, 1H), 2.23 (s, 3H), 2.19 (s, 3H), 2.10−2.00 (m, 2H), 1.84−1.70 (m, 2H), 1.64 (dt, *J* = 4.1, 12.6 Hz, 1H); ^{13}C NMR (free base, $CDCl_3$) *δ* 143.3, 139.8, 134.7, 130.4, 128.0, 127.8, 127.5, 125.4, 67.9, 61.93, 52.9, 42.0, 37.4, 35.2, 27.3, 25.1, 20.9. Anal. ($C_{21}H_{26}ClN\cdot1.25H_2O$): C, H, N.

2α,3α·4c·HCl: mp 224−225 °C (dec); $[\alpha]^{24}_D$ −6.84° (*c* 0.19, CH_3OH); ^{1}H NMR (free base $CDCl_3$) *δ* 7.03−6.85 (m, 9H), 3.96 (dd, *J* = 8.0, 5.1 Hz, 1H), 3.79 (dd, *J* = 7.7, 14.0 Hz, 1H), 3.50 (m, 1H), 3.28 (m, 1H), 2.62 (m, 1H), 2.35 (s, 3H), 2.22 (s, 3H), 2.21−1.90 (m, 2H), 1.89−1.77 (m, 2H), 1.43 (m, 1H); ^{13}C NMR (free base, $CDCl_3$) *δ* 144.1, 139.5, 134.7, 128.6, 128.4, 128.1, 127.2, 124.7, 64.4, 60.4, 49.0, 40.7, 37.1, 36.8, 27.3, 22.5, 20.9. Anal. ($C_{21}H_{26}ClN\cdot1.0H_2O$) C, H, N.

2*β*,3*β*- and 2α,3α-Di(4-methylphenyl)tropane (3d and 4d). Compounds **3d** and **4d** were prepared by a procedure similar to that described for **3a** and **4a**. From 158 mg (0.39 mmol) of **6d**, 33 mg (28%) and 44 mg (38%) of **3d** and **4d** were obtained.

2*β*,3*β*·4d·HCl: mp 233−244 °C (dec); $[\alpha]^{24}_D$ -9.3° (*c*, 0.22, CH_3OH); ^{1}H NMR (free base $CDCl_3$) *δ* 7.26 (d, *J* = 8.1 Hz, 2H), 6.86 (m, 4H), 6.75 (d, *J* = 8.1 Hz, 2H), 3.38 (m, 1H), 3.25 (m, 2H), 2.85 (dd, *J* = 2.5, 6.5 Hz, 1H), 2.31 (m 3H), 2.22 (s, 3H), 2.21 (s, 3H), 2.19 (s, 3H), 1.76 (m, 2H), 1.62 (m, 1H); ^{13}C NMR (free base, $CDCl_3$) *δ* 141.1, 139.8, 134.8, 134.0, 128.7, 128.4, 128.3, 64.4, 60.6, 49.9, 40.7, 37.3, 36.6, 27.0, 22.7, 20.9, 20.8. Anal. ($C_{22}H_{28}ClN\cdot0.5H_2O$) C, H, N.

2α,3α·4d·HCl: mp 218 °C (dec); $[\alpha]^{23}_D$ −10.5° (*c*, 0.19, CH_3OH); ^{1}H NMR (free base $CDCl_3$) *δ* 6.96 (m, 4H), 6.94−6.82 (m, 4H), 3.90 (dd, *J* = 5.0, 7.9 Hz, 1H), 3.76 (dd, *J* = 7.2, 13.5 Hz, 1H), 3.51 (m, 1H), 3.27 (m, 1H), 2.59 (pent. *J* = 6.8 Hz, 1H), 2.35 (s, 3H), 2.25 (s, 3H), 2.18 (s, 3H), 2.10 (m, 1H), 1.97 (m, 1H), 1.84 (m, 2H), 1.43 (m, 1H); ^{13}C NMR (free base, $CDCl_3$) *δ* 140.3, 140.0, 134.7, 134.6, 130.5, 128.3, 127.9, 127.8, 68.1, 62.0, 52.8, 42.0, 37.0, 36.0, 27.3, 25.1, 21.0, 20.8. Anal. ($C_{22}H_{28}ClN\cdot0.75H_2O$) C, H, N.

3*β*-(4-Methoxyphenyl)-2*β*-(4-methylphenyl)tropane (3e) and 3α-(4-Methoxyphenyl)-2α-(4-methylphenyl)tropane (4e). Compounds **3e** and **4e** were prepared using a procedure similar to that described for **3a** and **4a**. From 239 mg (0.56 mmol) of **6e**, 32 mg (18%) and 35 mg (19%) of the **3**α and **4e** were obtained.

2*β*,3*β*·3e·HCl: mp 218−220 °C; $[\alpha]^{23}_D$ −20.6° (*c* 1.00, CH_3OH); ^{1}H NMR (free base, $CDCl_3$) *δ* 7.32 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.0 Hz, 2H), 6.73 (d, *J* = 8.0 Hz, 2H), 6.60 (d, *J* = 8.0 Hz, 2H), 3.71 (s, 3H), 3.37−3.19 (m, 3H), 2.83 (m, 1H), 2.27 (s, 3H), 2.19 (s, 3H), 2.18−2.10 (m, 3H), 1.74 (m, 2H), 1.60 (m, 1H); ^{13}C NMR *δ* 157.4, 140.3, 135.3, 134.8, 131.6, 128.3, 127.9, 112.3, 68.0, 62.0, 55.0, 52.4, 42.0, 37.2, 35.5, 27.3, 25.0, 20.9. Anal. ($C_{22}H_{28}ClN\cdot0.25H_2O$) C, H, N.

2α,3α·4e·HCl: mp 151−153 °C; $[\alpha]^{23}_D$ −13.0° (*c* 0.13, CH_3OH); ^{1}H NMR (free base, $CDCl_3$) *δ* 6.97 (d, *J* = 8.3 Hz, 2H), 6.91 (m, 4H), 6.71 (d, *J* = 8.3 Hz, 2H), 3.89 (m, 1H), 3.73 (m, 4H), 3.48 (m, 1H), 3.28 (m, 1H), 2.59 (m, 1H), 2.35 (s, 3H), 2.19 (s, 3H), 2.11−1.96 (m, 2H), 1.82 (m, 2H), 1.46 (m, 1H); ^{13}C NMR ($CDCl_3$) *δ* 157.3, 141.0, 135.0, 134.0, 129.1, 128.3, 128.0, 113.3, 64.5, 60.5, 55.0, 48.6, 40.7, 37.0, 36.6, 27.1, 22.5, 20.7. Anal. ($C_{22}H_{28}ClNO\cdot0.2H_2O$) C, H, N.

3*β*-(4′-Methylphenyl)-2*β*-(3,4-dimethoxyphenyl)tropane (3f) and 3α-(4-Methylphenyl)-2*β*-(3,4-dimethoxyphenyl)tropane (4f). Compounds **3f** and **4f** were prepared using a procedure similar to that described for **3a** and **4a**. From 312 mg (0.69 mmol) of **6f**, 73 mg (31%) and 83 mg (35%) of **3f** and **4f** were obtained.

2*β*,3*β*-3f·HCl: mp 144−146 °C (dec); $[\alpha]^{23}_D$ −1.6 ° (*c* 0.19, CH_3OH); ^{1}H NMR (free base, $CDCl_3$) *δ* 7.06 (dd, *J* = 1.9, 83 Hz, 1H), 6.97 (d, *J* = 1.9 Hz, 1H), 6.86 (d, *J* = 7.9 Hz, 2H), 6.71 (d, *J* = 7.9 Hz, 2H), 6.58 (d, *J* = 8.3 Hz, 1H), 3.79 (s, 3H), 3.63 (s, 3H), 3.37 (m, 2H), 3.25 (m, 1H), 2.76 (dd, *J* = 2.4, 6.6 Hz, 1H), 2.35−2.05 (m, 3H), 2.27 (s, 3H), 2.19 (s, 3H), 1.77 (m, 2H), 1.57 (m, 1H); ^{13}C NMR (free base, $CDCl_3$) *δ* 147.2, 146.6, 140.2, 135.6, 134.8, 128.2, 128.0, 122.5, 114.5, 109.7, 67.6, 61.9, 55.5, 55.4, 52.3, 41.8, 37.5, 35.4, 27.3, 24.9, 20.8. Anal. ($C_{23}H_{30}ClNO\cdot0.25H_2O$) C, H, N.

2α,3α-4f·HCl: mp 132−134 °C (dec); $[\alpha]^{23}_D$ −20.0° (*c* 0.13, CH_3OH); ^{1}H NMR (free base, $CDCl_3$) *δ* 6.94−6.84 (m, 4H), 6.69 (d, *J* = 8.3 Hz, 1H), 6.61 (dd, *J* = 1.7, 8.3 Hz, 1H), 6.48 (d, *J* = 1.7 Hz, 1H), 3.91 (m, 1H), 3.81 (s, 3H), 3.73 (m, 1H), 3.67 (s, 3H), 3.46 (t, *J* = 5.5 Hz, 1H), 3.30 (t, *J* = 6.0 Hz, 1H), 2.61 (m, 1H) 2.36 (s, 3H), 2.19 (s, 3H), 2.05 (dd, *J* = 5.8, 11.7 Hz, 2H), 1.08 (m, 2H), 1.53 (m, 1H); ^{13}C NMR (free base, $CDCl_3$) *δ* 148.1, 146.7, 141.0, 135.4, 134.1, 128.6, 128.5, 128.2, 128.0, 120.4, 112.1, 110.6, 64.7, 60.4, 55.6, 55.4, 49.0, 40.7, 36.7, 36.5, 27.5, 22.3, 20.7. Anal. ($C_{23}H_{30}ClNO_2\cdot H_2O$) C, H, N.

2*β*-(4-Fluorophenyl)-3*β*-(4-methylphenyl)tropane (3g). Compound **3g** was prepared by a procedure similar to that

described for **3a**. In this case, it was necessary to prepare the tartarate salt 2β,3β-**4f**·$CH_3C_6H_4SO_3$: mp 174−177 °C; $[\alpha]^{23}_D$ −17.0° (*c* 0.13, CH_3OH); ^{1}H NMR (free base, $CDCl_3$) δ 7.37 (dd, J = 5.8, 2.1 Hz, 2H), 6.85 (d, J = 7.9 Hz, 2H), 6.71 (d, J = 8.3 Hz, 6H), 6.85 (d, J = 7.9 Hz, 2H), 6.71 (d, J = 8.3 Hz, 4H), 3.38−3.23 (m, 3H), 2.83 (m, 2H), 2.23 (s, 3H), 2.19 (s, 3H), 2.35−2.06 (m, 4H), 1.79 (m, 3H), 1.60 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 162.8, 159.5, 139.9, 138.6, 135.0, 132.0, 131.9, 128.4, 127.9, 120.9, 113.8, 113.5, 67.7, 62.0, 52.4, 42.0, 37.0, 35.2, 27.3, 25.0, 20.9. Anal. ($C_{28}H_{32}FNO_3S$·1.75H_2O) C, H, N.

(*R*)-2α,3α-Diphenyltropane (4a). A mixture of alkene **6a** (61 mg, 0.21 mmol) and Pd/C (5%) in CH_3OH (3 mL) was hydrogenated under H_2 (50 psi). After 8 days, the catalyst was removed by filtration. The residue obtained after removal of solvent was purified by flash column chromatography (SiO_2, 10% CH_3OH in CH_2Cl_2/Et_3N (99.5/0.5) to give the starting material (22 mg, 36%) and the 2α,3α-isomer **4a** as a clear oil (19 mg, 31%).

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Supporting Information Available: Results from elemental analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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