was irradiated for 10 h (70% conversion of **2**). Workup and chromatographic separation as described above gave 60 mg (29%) of the TMS adduct **20** (as a 1:1 mixture of diastereomers).

20: ^{1}H NMR 0.07 (s, 9 H, $Si(CH_3)_3$), 0.10 (s, 9 H, $Si(CH_3)_3$), 0.88 (s, 6 H, 2 CH_3), 1.04 (s, 3 H, CH_3), 1.06 (s, 3 H, CH_3), 1.51-1.63 (m, 5 H), 1.82 (dd, J = 5.8, 10.8 Hz, 1 H), 2.12-2.55 (m, 6 H), 2.58 (m, 2 H), 2.76 (s, 3 H, NCH_3), 2.94 (s, 3 H, NCH_3), 3.51 (d, J = 8.6, 1 H, CHN), 3.87 (s, 1 H, CHN), 6.55-6.73 (m, 6 H, Ar H), 7.11-7.25 (m, 4 H, Ar H); ^{13}C NMR -0.6 (Si-C), 0.6 (C-Si), 19.6, 20.3, 29.4, 29.5, 34.1, 37.7, 37.9, 40.8, 41.0, 42.0, 43.1, 43.4, 46.7, 49.6, 50.1, 111.2, 113.0, 114.9, 115.8, 129.0, 129.2, 148.9, 151.2, 210.9, 211.4; IR (neat) 2960, 2860, 1713, 1598, 1505, 1250, 860, 840, 750 cm^{-1}; mass spectrum, m/e (rel intensity) 317 (M^+, 1.4), 245 (5.6), 244 (31.6), 192 (19.7), 120 (13.4), 86 (66), 84 (100), 77 (7), high resolution mass spectrum, m/e 317.2176 ($C_{19}H_{31}SiNO$ requires 317.2175).

General Procedure for Determining the Effects of Reaction Conditions on Formation of Adducts 16 and 17 from Irradiation of 4,4-Dimethylcyclohex-2-en-1-one (2) and *N*-Methyl-*N*-[(trimethylsilyl)methyl]aniline (19). Solutions of cyclohexenone **2** (1×10^{-2} M) and aniline **19** (1×10^{-2} M) in the specified solvent and containing the specified additives in 100-mL sealed quartz tubes were simultaneously irradiated in a merry-go-around apparatus. All samples were subjected to an argon purge for 15 min before being sealed and irradiated. The crude photolysates were concentrated in vacuo and then by molecular distillation. The ratios of adducts **16** and **17** were determined by HPLC (on a normal phase column) analysis and are given along with the respective solvent and additive in Table I.

9,10-Dicyanoanthracene SET-Sensitized Photoreaction of 4,4-Dimethylcyclohex-2-en-1-one (2) and (Silylmethyl)aniline 19. Solutions of the cyclohexenone **2** and (silylmethyl)aniline **19** (0.2 M) in 4 mL of 20% MeCN-MeOH containing 9,10-dicyanoanthracene (6×10^{-6} M) were irradiated in a merry-go-round apparatus. The concentrations of **2** used in these simultaneous reactions were varied (0.2, 0.1, and 0.01 M). The photolysates were filtered and concentrated in vacuo and by molecular distillation to yield residues, which were analyzed for adduct **16** and tricyclic adduct **17** by HPLC on a reverse phase column.

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Supplementary Material Available: ^{13}C NMR spectra of **16**, **17**, **18**, **19**, and **20** (5 pages). Ordering information is given on any current masthead page.

Synthesis and Absolute Configuration of LY255582, a Potent Opioid Antagonist

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LY255582 ((+)-**1**) is a potent opioid antagonist recently discovered in our laboratories.[1] As a member of the phenylpiperidine class of opioid antagonists, the compound is structurally distinct from opioid antagonists currently used in clinical practice such as naloxone or naltrexone.[2] While the clinical importance of opioid antagonists in the treatment of narcotic overdose and drug-dependence is well established, recently other possible therapeutic applications for opioid antagonists have emerged, including the treatment of obesity, eating disorders, shock, spinal cord trauma, sexual dysfunction, and psychiatric conditions.[3,4]

Our synthetic strategy for the preparation of LY255582 is based on the coupling of the phenylpiperidine unit (+)-**2** with the cyclohexylpropanol fragment (-)-**3**. Preparation of each component in pure form ensured that the resulting coupled product would be of high enantiomeric purity. The coupling process itself provided a check on the resulting optical purity of the product, as formation of a diastereomeric mixture would result if either or both of the starting components suffered from enantiomeric contamination.

Assembly of the 3,4-dimethylphenylpiperidine nucleus with a high degree of optical purity was accomplished as shown in Scheme I. The aryltetrahydropyridine **4** was metalated with *n*-BuLi in THF at -20 °C, giving a deep red solution of the allylic anion, which was then alkylated with methyl iodide to give enamine **5** in 75% yield.[5,6] Introduction of the methyl group at the 3-position was accomplished with a two-step alkylation-reduction process adopted from Barnett.[7] The initial carbon-carbon bond formation was achieved by the Mannich reaction of enamine **5** with formaldehyde and dimethylamine to give an 86% yield of amino enamine **6**.

Establishment of the correct relative stereochemistry of the 3 and 4 stereocenters was then accomplished through reductive cleavage of the Mannich adduct **6**. Hydrogenolysis with 5% Pt/C afforded (±)-**8** by a stepwise process wherein the allylic amine is first cleaved, followed by reduction of the resulting methyl enamine. The choice of catalyst was crucial for optimizing stereoselectivity in the reduction process. The best degree of selectivity in the hydrogenolytic formation of (±)-**8** and its isomer (**14**—having the 3 and 4 methyl groups in a cis relationship) was obtained with the use of 5% Pt/C in EtOH, affording an 8:1 ratio favoring (±)-**8**. Unfortunately, this ratio of isomers became more nearly 1:1 on larger scale operations of the reaction. However, stereoselectivity could be preserved on scale-up if the reduction was broken up stepwise into its component parts of hydrogenolysis of the carbon-nitrogen bond followed by double-bond hydrogenation. This was readily accomplished due to the substantially slower rate of the second step of the operation. This rate differential could be enhanced through the use of deactivated catalysts such as $Pd/BaSO_4$. The resulting enamine double bond was then reduced with $NaBH_3CN$ in methanol to give a 13:1 ratio of isomers, the desired (±)-**8** predominating. Resolution of (±)-**8** into its optical antipodes was accomplished with dibenzoyl D- and L-tartrates. Evaluation of the enantiomeric purity of (+)-**9** and its antipode was performed by the use of the chiral NMR complexing reagent (*R*)-(-)-2,2,2-trifluoro-1-(9-anthryl)-

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ethanol.[8] This allowed a lower limit of enantiomeric purity of >95% ee to be ascertained for (+)-9, as bounded by the detection limits in the 300-MHz NMR.

For preparation of the now resolved phenylpiperidine fragment for the ultimate coupling process, the nitrogen was unmasked by dealkylation with vinyl chloroformate in refluxing dichloroethylene, followed by hydrolysis of the carbamate with methanolic HCl to give the secondary amine.[9] It was found to be advantageous to also unmask the phenolic functionality at this stage of the synthesis as well. This was carried out by treatment of the aryl methyl ether with HBr in refluxing acetic acid, affording (+)-2 (68% yield from (+)-8) ready for the coupling operation.

Construction of the cyclohexylpropanol fragment is shown in Scheme II. Vinyl alcohol (±)-10 was obtained by the addition of vinylmagnesium bromide to cyclohexanecarboxaldehyde.[10c] Kinetic resolution of (±)-10 under Sharpless conditions was achieved by treatment with titanium(IV) isopropoxide in the presence of L-diisopropyl tartrate and *tert*-butylhydroperoxide, which afforded epoxy alcohol 11 and vinyl alcohol (−)-12.[10] After chromatographic separation of 11 and (−)-12, the enantiomeric purity of (−)-12 was assayed by conversion to its Mosher ester.[11] GC analysis showed this Mosher ester to be greater than 99% in diastereomeric purity, as bounded by the detection limits of the instrument. This confirmed the expected high degree of enantiomeric purity obtained in the Sharpless kinetic resolution. The selection of either the D- or L-tartrate ester employed in the resolution also determined the absolute configuration of the resolved alcohol (−)-12 obtained from this process.[10b] Knowledge of the absolute stereochemistry of the alcohol center, combined with determination of the relative stereochemistry of the three stereocenters by X-ray crystallography, allowed for the unambiguous assignment of the absolute stereochemistry of the final product.

The alcohol (−)-12 was then protected as its *tert*-butyldimethylsilyl ether, (−)-13 (94% yield), and subjected to hydroboration with a borane–THF complex which gave hydroxy ether (−)-3 in 54% yield.

Reaction of (−)-3 with methanesulfonyl chloride presumably provided an intermediate mesylate, which, without isolation, was coupled with (+)-2 followed by deprotection with HF to give LY255582 ((+)-1) (29% yield based on (+)-2). No diastereomer formation was detected by HPLC, demonstrating the high degree of enantiomeric purity of each of the component parts, as well as of the final product. The relative configuration of the three stereocenters was determined by X-ray crystallography.[12] As the Sharpless kinetic resolution provided the cyclohexylpropanol center with known *S* configuration, it follows that the absolute configuration for the molecule is as shown (3′*S*,3*R*,4*R*).

In the mouse writhing assay, LY255582 was found to have an AD_{50} of 0.015 mg/kg (sc) for antagonizing the analgesic effect of morphine (1.0 mg/kg, sc).[1,13] In comparison, an AD_{50} of 0.13 mg/kg (sc) was found for naloxone, an opioid antagonist with wide clinical usage.

Experimental Section

Melting points were determined with a Melt-temp apparatus and are uncorrected. Proton and carbon magnetic resonance spectra were recorded on a GE QE-300 spectrometer at 300 MHz and 75 MHz, respectively and are reported in ppm on the δ scale from internal tetramethylsilane. Microanalyses, mass spectral measurements and X-ray crystal structures were determined by the Structural and Organic Chemistry Research Department of the Lilly Research Laboratories. Optical rotations were obtained on a Perkin-Elmer Model 241 automatic polarimeter. Gas chromatography was performed on a Hewlett-Packard 5890 instrument with an HP-1 megabore capillary GC column and flame-ionization detection. HPLC analyses were run on a Waters 501 system using a Dupont Zorbax silica column and 280-nM UV detection. Preparative chromatography was performed on a Waters Prep 500 system.

When necessary, solvents and reagents were dried prior to use. Diethyl ether and tetrahydrofuran were distilled from sodium metal/benzophenone ketyl. All other reagents were used as received from Aldrich Chemical Co., Milwaukee. $NaCl/Na_2SO_4$ was used to dry all organic solutions after extractive workups.

1,2,3,4-Tetrahydro-4-(3-methoxyphenyl)-1,4-dimethylpyridine (5). A solution of 320 mL (512 mmol) of *n*-butyllithium (1.6 M) in hexane was added dropwise over 30 min to a −10 °C solution of 15 g (491 mmol) of tetrahydropyridine 4 in 1000 mL in THF.[5] After stirring the resulting deep red solution for 15 min, 72.6 (512 mmol) of MeI in 300 mL of THF was added dropwise over 30 min, with gradual conversion of the color from red to yellow. The cooling bath was removed and 500 mL of brine added. The phases were separated, and the aqueous layer was extracted twice with 500 mL of dichloromethane. The combined organic extracts were dried and evaporated under vacuum. The resulting oil, on bulb-to-bulb distillation (bp 100 °C, 0.04 mmHg), gave 79.5 g (75%) of 5 as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.35–6.60 (m, 4 H), 5.92 (d, 1 H, J = 8 Hz), 4.48 (d, 1 H, J = 8 Hz), 3.76 (s, 3 H), 2.57 (s, 3 H), 1.36 (s, 3 H). Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.07; H, 8.45; N, 6.19.

1,4,5,6-Tetrahydro-4-(3-methoxyphenyl)-*N*,*N*,1,4-tetramethyl-3-pyridinemethanamine (6). To a solution of 7 g (86 mmol) of 37% aqueous formaldehyde and 9 g (80 mmol) of 40% aqueous dimethylamine in 50 mL of water was added sufficient concentrated sulfuric acid to adjust the pH of the mixture to a range of 3–4. A solution of the sulfate of 5 (prepared by the extraction of 10 g (43 mmol) of 5 in 35 mL hexane with 25 mL of 2.5 N H_2SO_4) was added to the mixture of formaldehyde and dimethylamine and the pH adjusted to 3–4 with additional 40% aqueous dimethylamine. The reaction mixture was heated at 70 °C for 2 h, maintaining the pH in the range of 3–4 with additional dimethylamine as needed. Upon cooling to room temperature, the reaction mixture was poured into 50 mL of 25% NaOH. The resulting mixture was extracted three times with 50 mL of hexane. The hexane extracts were washed five times with 50 mL of water, followed by one washing with 50 mL of brine, dried, and evaporated under vacuum. Bulb-to-bulb distillation (bp 160 °C, 0.3 mmHg) gave 10 g (80%) of 6: ^1H NMR ($CDCl_3$) δ 7.2–6.7 (m, 4 H), 6.00 (s, 1 H), 3.80 (s, 3 H), 2.62 (s, 3 H), 2.17 (s, 6 H), 1.56 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 159.28, 151.43, 136.20, 128.65, 119.52, 113.7, 110.48, 110.23, 61.64, 54.83, 46.33, 45.38, 42.87, 41.09, 39.49, 26.85; MS *m*/*z* calcd for $C_{17}H_{26}N_2O$ 274.2045, found 274.2074.

(±)-1,3(*R),4(*R**)-Trimethyl-4-(3-methoxyphenyl)piperidine ((±)-8). Method A.** A solution of 10 g (34.5 mmol) of 6 and 1 g of 5% Pt/C in 90 mL of EtOH was hydrogenated on Parr shaker at 60 psi at room temperature for 18 h. The catalyst was removed by filtration through a pad of Celite and the solvent evaporated under vacuum. The residue was chromatographed on a Waters Prep 500 HPLC, using 1% triethylamine in EtOAc as the elution solvent, affording 3.9 g (48%) of (±)-8 and 1.4 g (17%) of (±)-14 (the isomer with the 3 and 4

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methyl groups in a cis relationship). The stereochemistry of (±)-8 and (±)-14 was assigned on the basis of the chemical shift for the 3-Me group in (±)-8 occurring at lower field than for that (±)-14 (assuming 3-Me equatorial in (±)-8 and axial in (±)-14. This assignment was confirmed by X-ray crystallography. For (±)-14: ^{1}H NMR ($CDCl_3$) δ 7.28–6.64 (m, 4 H), 3.80 (s, 3 H), 2.31 (s, 3 H), 1.28 (s, 3 H), 0.58 (d, 3 H, J = 7 Hz). An analytical sample of (±)-14 was prepared as its HBr salt and recrystallized from 2-propanol/diisopropyl ether: mp 175–177 °C. Anal. Calcd for $C_{15}H_{24}NOBr$: C, 57.33; H, 7.70; N, 4.46. Found: C, 57.57; H, 7.56; N, 4.26. For (±)-8: ^{1}H NMR ($CDCl_3$) δ 7.28–6.64 (m, 4 H), 3.81 (s, 3 H), 2.25 (s, 3 H), 1.33 (s, 3 H), 0.78 (d, 3 H, J = 7 Hz). An analytical sample of (±)-8 was prepared as its HBr salt and recrystallized from 2-propanol/diisopropyl ether: mp 230–232 °C. Anal. Calcd for $C_{15}H_{24}NOBr$: C, 57.33; H, 7.70; N, 4.46. Found: C, 57.43; H, 7.74; N, 4.59.

Method B. A solution of 9.6 g (33 mmol) of **6** in 65 mL of EtOH was hydrogenolyzed with 1 g of 5% Pd/$BaSO_4$ under 1 atm of hydrogen (inflated balloon) for 11 h. The solution was filtered to remove the catalyst and the solvent was evaporated to give 8.1 g of **7** as an oil: ^{1}H NMR (C_6D_6) δ 7.28–6.74 (m, 4 H), 5.78 (s, 1 H), 3.42 (s, 3 H), 2.37 (s, 3 H), 1.68 (s, 3 H), 1.45 (s, 3 H); ^{13}C NMR (CD_3CN) δ 159.43, 151.36, 134.37, 128.80, 119.45, 113.47, 110.30, 109.52, 54.64, 46.15, 42.13, 40.62, 39.54, 25.98, 16.28 ppm. For **7**: MS m/z calcd for $C_{15}H_{21}NO$ $(M + H)^+$ 232.1701, found 232.1693. Compound **7** was taken up in 150 mL of MeOH and 2.5 g (40 mmol) of sodium cyanoborohydride was added. The reaction mixture was stirred for 16 h at room temperature and then concentrated under vacuum. The residue was taken up in 200 mL of CH_2Cl_2 and washed with 100 mL of saturated aqueous $NaHCO_3$, then dried, and evaporated under vacuum. ^{1}H NMR showed the resulting material to be a 93:7 mixture (±)-8:(±)-14. The HBr salt was prepared and recrystallized from 2-propanol/diisopropyl ether and then converted back to the free base, giving 6.24 g (81%) (±)-8 that was free of (±)-14 and identical with that prepared by method A. **(−)-1,3(*S*),4(*S*)-Trimethyl-4-(3-methoxyphenyl)piperidine ((−)-9).** To 50.7 g of (±)-8 was added 80.7 g of dibenzoyl D-tartrate in 7140 mL of 95% EtOH. The resulting suspension was recrystallized from an additional 5200 mL of 95% EtOH, affording 29.4 g of crystalline material. The crystalline solid was recrystallized from 3500 mL of 95% EtOH and converted to the free base to give 19.6 g of (−)-9 with a rotation of $[\alpha]^{25}_{365}$ = −268° (c = 1.0, MeOH). For (−)-9: ^{1}H NMR ($CDCl_3$) δ 7.28–6.64 (m, 4 H), 3.81 (s, 3 H), 2.25 (s, 3 H), 1.33 (s, 3 H), 0.78 (d, 3 H, J = 7 Hz). An analytical sample of (−)-9 was prepared as its HBr salt and recrystallized from 2-propanol/diisopropyl ether; mp 230–232 °C. Anal. Calcd for $C_{15}H_{24}NOBr$: C, 57.33; H, 7.70; N, 4.46. Found: C, 57.20; H, 7.74; N, 4.42.

(+)-1,3(*R*),4(*R*)-Trimethyl-4-(3-methoxyphenyl)piperidine ((+)-9). The initial filtrate from the preparation of (−)-9 was evaporated and the residue was converted to its free base, giving 34.33 g of material that was combined with 54.76 g of (−)-dibenzoyl L-tartrate in 5800 mL of 95% EtOH. The suspension was recrystallized from an additional 6300 mL of 95% EtOH and converted to its free base to give 20.4 g of (+)-9 with $[\alpha]^{25}_{365}$ = +272° (c = 1.1, MeOH). For (+)-9: ^{1}H NMR ($CDCl_3$) δ 7.28–6.64 (m, 4 H), 3.81 (s, 3 H), 2.25 (s, 3 H), 1.33 (s, 3 H), 0.78 (d, 3 H, J = Hz). An analytical sample of (+)-9 was prepared as its HBr salt and recrystallized from 2-propanol/diisopropyl ether, mp 230–232 °C. Anal. Calcd for $C_{15}H_{24}NOBr$: C, 57.33; H, 7.70; N, 4.46. Found: C, 57.14; H, 7.81; N, 4.29. NMR analysis of (±)-8 with the chiral complexing reagent (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol in C_6D_6 showed doubling of the NMe singlet (d, 2.08 and 2.05 ppm) and the 3-Me doublet (d, 0.94 and 0.92 ppm), as expected for racemic material. NMR analysis of both (+)-9 and (−)-9 with the chiral complexing reagent showed that each was free of its antipode, to the limits of detection in the 300-MHz ^{1}H NMR, indicating enantiomeric purity of greater than 95% for each isomer.

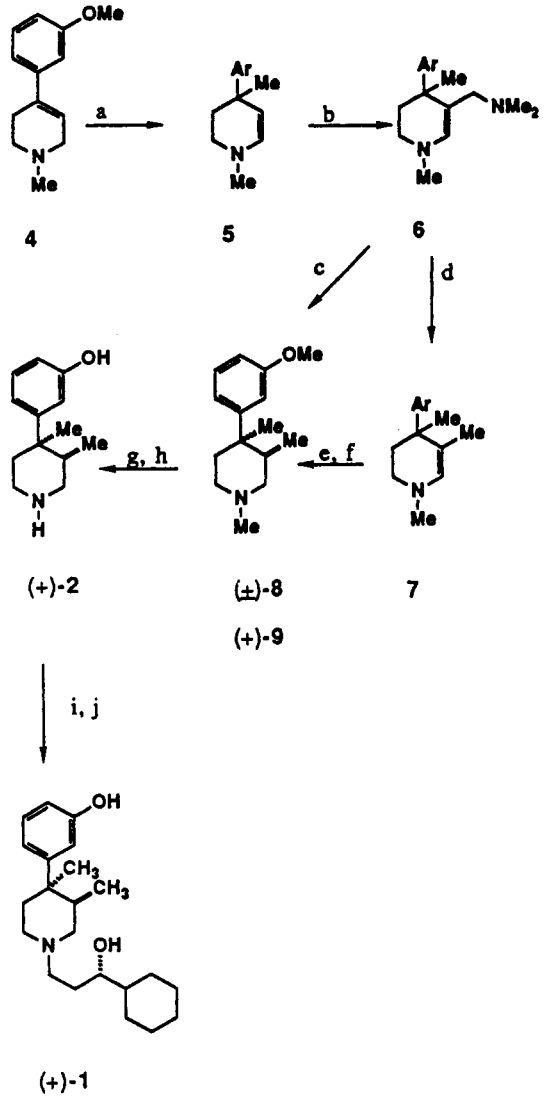
(+)-3(*R*),4(*R*)-Dimethyl-4-(3-hydroxyphenyl)piperidine ((+)-2). To a solution of 10.2 g (43 mmol) of *N*-methylpiperidine (+)-9 and 17.8 g (86 mmol) of Proton sponge [1,8-bis(dimethylamino)naphthalene] in 600 mL of 1,2-dichloroethane was added 11 mL (130 mmol) of vinyl chloroformate. After refluxing for 5 h, the solvent was evaporated under vacuum, and the residue taken up in 500 mL of Et_2O. This solution was washed three times with 250 mL of 1 N HCl, followed by 250 mL of saturated aqueous $NaHCO_3$ and 250 mL of brine. The solution was dried and evaporated under vacuum. The resulting urethane was taken up in 250 mL of absolute EtOH, a solution of 100 mL of absolute EtOH saturated with HCl gas was added, and the solution was refluxed for 3 h. After evaporation under vacuum, the residue was partitioned between 500 mL of Et_2O and 250 mL of 1 N NaOH. The ether extracts were washed with brine, dried, and evaporated under vacuum. The resulting amine was then refluxed for 18 h in a solution of 100 mL of glacial AcOH and 100 mL of 48% HBr. The reaction mixture was cooled in an ice bath and the pH adjusted to approximately 9.8 by slow addition of 50% NaOH. The resulting suspension was extracted four times with 250 mL of a 1:3 solution of toluene and 1-butanol. The combined extracts were washed with brine, dried, and evaporated under vacuum. The residue was triturated with hexane and dried under vacuum to give 6 g (68%) of (+)-2 as a white solid (mp 174–175 °C), with a rotation of $[\alpha]^{25}_{365}$ = +361° (c = 1.1, MeOH): ^{1}H NMR ($CDCl_3$) δ 7.12–6.52 (m, 5 H), 1.27 (s, 3 H), 0.64 (d, 3 H, J = 7 Hz). Anal. Calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Found: C, 75.85; H, 9.24; N, 6.96.

(−)-(1*R*)-1-Hydroxy-1-cyclohexyl-2-propene ((−)-12). Diisopropyl L-tartrate (71 g, 303 mmol) was added to a −78 °C solution of 74.5 mL (252 mmol) of titanium(IV) isopropoxide in 1000 mL of CH_2Cl_2, followed by addition of a solution of 35.5 g (252 mmol) of (±)-10 in 200 mL of CH_2Cl_2.[10] Then 51.3 mL (151 mmol) of 2.95 M *tert*-butyl hydroperoxide in toluene was added, and the solution allowed to warm to −10 °C and stirred for 48 h while being maintaining that temperature in a refrigerated cooling bath. For workup of the reaction, a solution of 71 g of ferrous sulfate and 27 g of tartaric acid in 270 mL of water was added, the cooling bath, was removed and the solution was stirred for 30 min. The aqueous layer was separated and extracted twice with 500 mL of Et_2O. The combined organic extracts were washed with brine, dried, and evaporated under vacuum. The residue was taken up in 500 mL of Et_2O and stirred with 11 g of NaOH in 270 mL of brine for 4 h. The aqueous layer was extracted twice with 250 mL of Et_2O and the combined organic extracts were washed with brine, dried, and evaporated under vacuum. The residue was chromatographed on silica gel with a Waters Prep 500 HPLC, using 10% EtOAc in hexane as the eluent. Distillation (bp 60 °C, 0.35 mmHg) afforded 15 g of (−)-12 with a rotation $[\alpha]^{25}_{365}$ = −92° (c = 1.0, MeOH): ^{1}H NMR ($CDCl_3$) δ 5.82 (m, 1 H), 5.18 (m, 2 H), 3.85 (m, 1 H). Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.31, 11.64.

The enantiomeric purity of (−)-12 was evaluated by conversion of the alcohol to its Mosher ester followed by analysis of diastereomers by HPLC. To a 0 °C solution of 20 mg (0.14 mmol) of (−)-12, 17 mg (0.14 mmol) of 4-(dimethylamino)pyridine, and 15 mg (0.14 mmol) of triethylamine in CH_2Cl_2 was added 63 mg (0.28 mmol) of (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid chloride (prepared from the acid and oxalyl chloride in CH_2Cl_2 with DMF catalysis). After 16 h, the reaction mixture was poured into 30 mL of Et_2O and washed with 20 mL of 1 N HCl, 20 mL of saturated aqueous $NaHCO_3$, and 20 mL of brine, dried, and evaporated under vacuum. Analysis by HPLC (1% EtOAc/hexane as eluent) of this unpurified material showed that the Mosher ester of (−)-12 was free to the limits of detection (>99%) of the diastereomer that would result from (+)-12. Similar analysis of (±)-10 demonstrated the resulting diasteriomeric Mosher esters to have a difference in retention times of 0.63 min, easily separable on our HPLC system. Preparative chromatography (2% EtOAc/hexane) provided an analytical sample of the Mosher ester of (−)-12. Anal. Calcd for $C_{19}H_{23}O_3F_3$: C, 64.04; H, 6.51. Found: C, 63.81; H, 6.70.

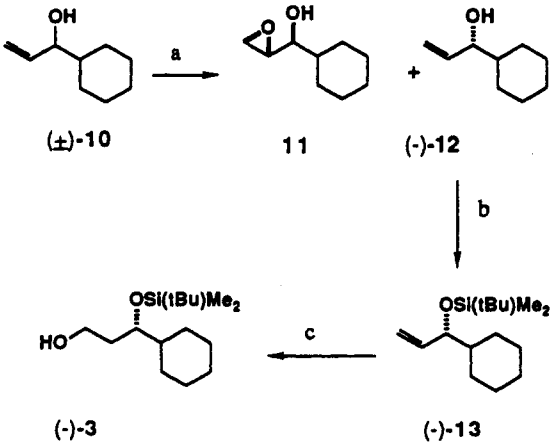
(−)-(1*R*)-1-(*tert*-Butyldimethylsiloxy)-1-cyclohexyl-2-propene ((−)-13). To a 0 °C solution of 10 g (70 mmol) of (−)-12, 9 g (88.9 mmol) of triethylamine, and 3 g (24.6 mmol) of 4-(dimethylamino)pyridine in 100 mL of CH_2Cl_2 was added 12 g (79.6 mmol) of *tert*-butyldimethylsilyl chloride, and the resulting mixture was stirred for 18 h with gradual warming to room temperature. The reaction mixture was then concentrated under vacuum to remove dichloromethane followed by addition of 500 mL of Et_2O. This solution was extracted with 300 mL of 1 N HCl, 300 mL of saturated aqueous $NaHCO_3$, and 300 mL of brine. It was dried and evaporated under vacuum. Distillation (bp 90 °C,

Scheme I[a]



[a] (a) *n*-BuLi, MeI; (b) CH_2O, $HNMe_2$; (c) H_2/Pt–C; (d) H_2/$BaSO_4$; (e) $NaBH_3CN$; (f) dibenzoyl L-tartrate; (g) vinyl chloroformate; HCl, MeOH; (h) HBr, AcOH; (i) (–)-3 + MsCl; (j) HF.

Scheme II[a]



[a] (a) Ti(O-*i*-Pr)$_4$, diisopropyl L-tartrate; (b) ClSi(*t*-Bu)Me_2; (c) BH_3–THF.

1 mmHg) afforded 16.7 g (94%) of (–)-13 having a rotation of $[\alpha]^{25}_{365}$ = –37° (*c* = 1.0, MeOH): ^{1}H NMR ($CDCl_3$) δ 5.74 (m, 1 H), 5.12 (m, 2 H), 4.81 (m, 1 H), 0.92 (s, 9 H), 0.05 (s, 3 H), 0.00 (s, 3 H). Anal. Calcd for $C_{15}H_{30}OSi$: C, 70.80; H, 11.88. Found: C, 70.59; H, 11.68.

(–)-(1*S*)-1-Cyclohexyl-1,3-dihydroxypropane ((–)-3). To a 0 °C solution of 10.8 g (42.4 mmol) of (–)-13 in 100 mL of THF was slowly added 64 mL (64 mmol) of 1 M BH_3·THF complex. After 2 h, the reaction mixture was carefully quenched by slow addition of 50 mL of water. Seventy milliliters of 3 N NaOH was added followed by 70 mL of 30% hydrogen peroxide. The mixture was stirred vigorously for 3 h and then extracted three times with 250 mL of Et_2O. The combined extracts were washed with brine, dried, and evaporated under vacuum. Purification on a Waters Prep 500 apparatus using 10% EtOAc/hexane as eluent afforded 6.2 g (54%) of (–)-3: $[\alpha]^{25}_{365}$ = –67° (*c* = 1.0, MeOH): ^{1}H NMR ($CDCl_3$) δ 3.74 (m, 1 H), 0.91 (s, 9 H), 0.09 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 74.97, 59.91, 43.35, 35.04, 28.87, 28.04, 26.63, 26.44, 26.35, 25.81, 17.93, –4.54, –4.58; MS *m/z* calcd for $C_{15}H_{32}O_2Si$ $(M + H)^+$ 273.2250, found 273.2251.

(+)-1-[(3*S*)-3-Hydroxy-3-cyclohexylpropyl]-(3*R*,4*R*)-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine ((+)-1). To a 0 °C solution of 2.73 g (10 mmol) of (–)-3 and 2.1 mL (15 mmol) of triethylamine in 50 mL of CH_2Cl_2 was added 0.85 mL (11 mmol) of methanesulfonyl chloride. After 30 min the solution was concentrated under vacuum. The residue was taken up in 50 mL of DMF, 2.05 g (10 mmol) of (+)-2 and 8.4 g of $NaHCO_3$ were added, and the mixture was heated at reflux for 1 h. After cooling to room temperature, 500 mL of EtOAc was added and the solution was extracted three times with 200 mL of brine. The organic phase was then dried and evaporated under vacuum. The residue was taken up in 100 mL of acetonitrile and 5 mL of 48% aqueous HF was added. After being stirred for 2 h at room temperature, an additional 5 mL of 48% HF was added. After a total reaction time of 4 h, the solution was basified to approximately pH 10 with 50% NaOH. The mixture was concentrated under vacuum and diluted with 100 mL of water. The solution was extracted with three 250-mL portions of EtOAc, and the combined extracts were washed with brine, dried, and evaporated under vacuum. HPLC analysis (eluent: 800 mL of hexane, 400 mL of EtOAc, 6 mL of MeOH, 2 mL of water, and 1 mL of triethylamine; silica gel column) showed that the unpurified material was free of possible diastereomers to the limits of detection (>99%). Preparative chromatography (1:1 EtOAc/hexane, 1% triethylamine as eluent) followed by recrystallization from EtOAc/hexane gave 1.0 g (29%) of (+)-1 as needles: mp 154–155 °C and $[\alpha]^{25}_{365}$ = +229° (*c* = 1.0, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.18 (m, 5 H), 3.55 (m, 1 H), 1.24 (s, 3 H), 0.58 (d, 3 H, *J* = 7 Hz). Anal. Calcd for $C_{22}H_{35}NO_2$: C, 76.48; H, 10.21; N, 4.05. Found: C, 76.64; H, 10.48; N, 4.17.

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Supplementary Material Available: ^{1}H NMR and ^{13}C NMR data for compounds 6, 7, and (–)-3 and details of the crystal structure determination for compound (+)-1, including tables of atomic coordinates, bond lengths and angles, anisotropic displacement parameters, H-atom coordinates, isotropic displacement parameters, and an ORTEP drawing of the structure showing the numbering scheme used in the tables (12 pages). Ordering information is given on any current masthead page.

Single Atom, *peri*-Bridged Arenes: 1-Alkylidene-1*H*-cyclobuta[*de*]naphthalenes and $\Delta^{1,1}$-Bi-1*H*-cyclobuta[*de*]naphthalene

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The abilities of naphthalenes to adjust to enormous strain are impressively illustrated upon preparing stable *peri* derivatives (1 and 2) in which bridging by single atoms

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