A Highly Enantiocontrolled Strategy for the Synthesis of Benzylic Quaternary Carbon Centers. A Formal Total Synthesis of (−)-Mesembrine

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A remarkable substituent effect by a trimethylsilyl group was observed on the enantioselectivity of the tandem asymmetric epoxidation and enantiospecific ring expansion of 2-cyclopropylidene-2-(4,5-dimethoxy-2-(trimethylsilyl)phenyl)ethanol (**24**), affording (*S*)-(−)-2-(4,5-dimethoxy)-2-(trimethylsilyl)phenyl-2-(hydroxymethyl)cyclobutanone (**25**) in high enantiomeric excess. This feature enabled us to accomplish a concise and highly enantioselective total synthesis of (−)-mesembrine (**1**), providing a new and general strategy for the enantioselective synthesis of benzylic quaternary carbon centers.

Introduction

Control of the enantioselectivity during the creation of quaternary carbon centers is one of the serious challenges in the synthesis of biologically important natural products such as terpenoids, steroids, and alkaloids. Although a number of highly enantioselective methods have been reported recently[1] for the construction of quaternary carbon centers in various molecular frameworks, the isoquinoline alkaloids possessing benzylic quaternary carbon centers, such as mesembrine (**1**),[2] pretazettine (**2**),[3] and morphine (**3**),[4] have remained attractive targets for total synthesis (Figure 1). During the course of our efforts[5] toward the enantioselective construction of cyclobutanones and their application to the synthesis of biologically desirable compounds, we

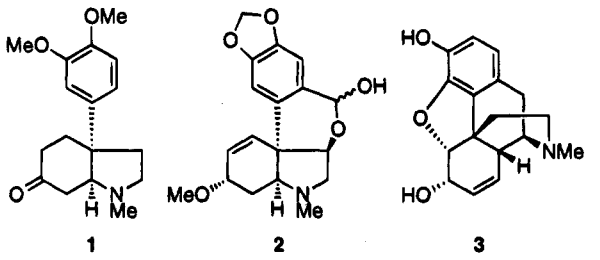
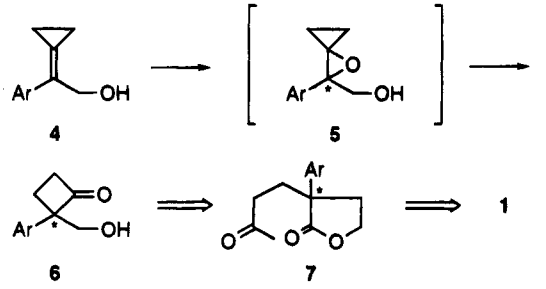


Figure 1.

Scheme 1



developed a new enantiocontrolled approach to (−)-mesembrine (**1**). This synthesis involves the enantiocontrolled creation of geminally-substituted cyclobutanones **6** *via* the tandem Katsuki–Sharpless asymmetric epoxidation of 2-aryl-2-cyclopropylideneethanols **4** and the enantiospecific ring expansion of chiral bicyclooxapentanes **5**. The chiral cyclobutanone **6** was then converted into **1** *via* **7**. In this tandem reaction (**4** → **5** → **6**), a silyl substituent on the aromatic ring had a remarkable effect on the enantioselectivity. This enabled us to develop a highly enantiocontrolled strategy for the construction of benzylic quaternary carbon centers (Scheme 1).

Results and Discussion

The tandem reaction of cyclopropylidene alcohol **11** was examined as follows. Ketone **9**, prepared by a Grignard reaction (100%) of hydroxamate **8**[5k] with (3,4-dimethoxyphenyl)magnesium bromide, was converted into cyclopropylidene ether **10** in 85% yield by a Wittig reaction with cyclopropylidenetriphenylphosphorane. Alcohol **11** was then produced by desilylation of **10** with Bu_4NF in 97% yield. The tandem asymmetric epoxidation and 1,2-rearrangement of cyclopropylidene alcohol **11** was carried out with *tert*-butyl hydroperoxide in the presence of diisopropyl L-(+)-tartrate [(+)-DIPT], titanium tetraiso-

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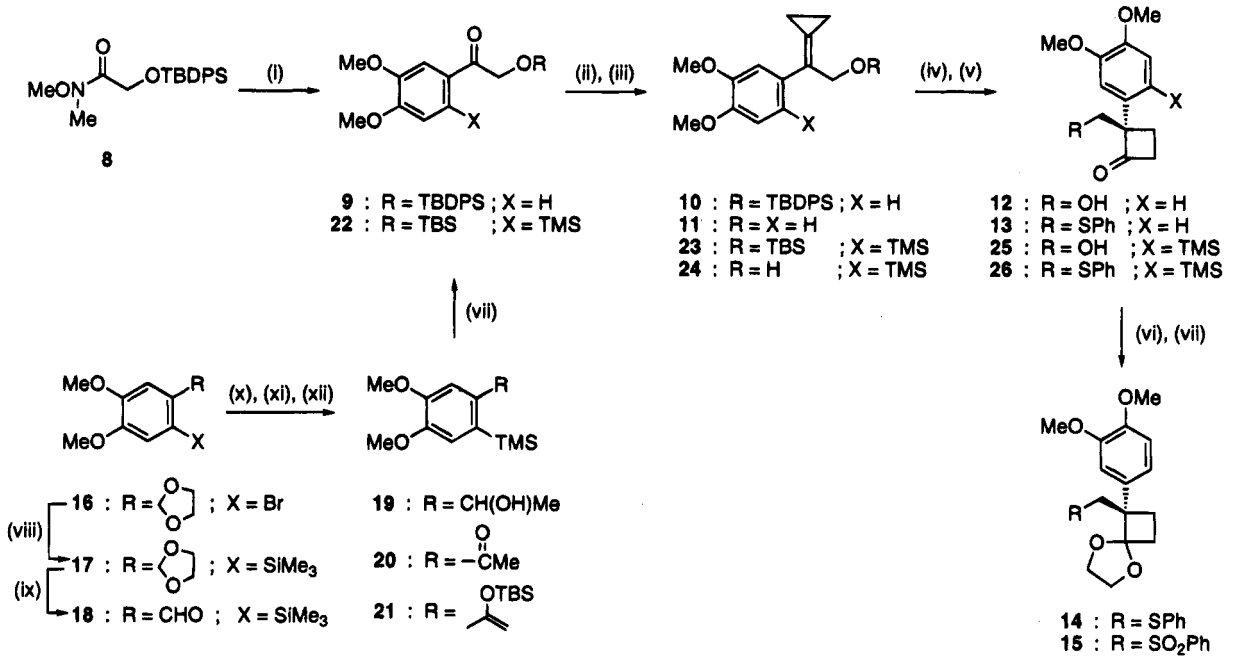
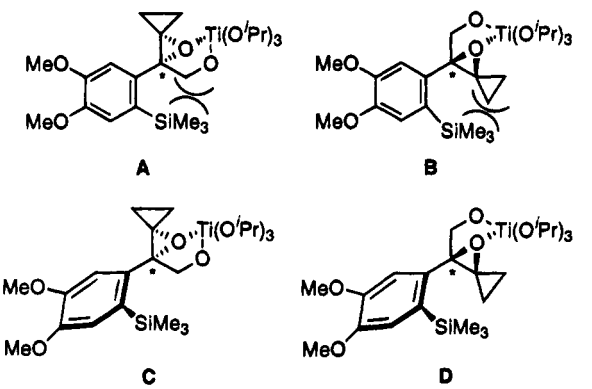
Scheme 2[a]



[a] Reagents and conditions: (i) (3,4-dimethoxyphenyl)magnesium bromide, THF, 0 °C, 1.5 h; (ii) cyclopropyltriphenylphosphonium bromide, NaH, THF, 65 °C, 3 h; (iii) Bu_4NF, THF, rt, 3 h; (iv) L-(+)-DIPT, ^tBuOOH, $Ti(OiPr)_4$, 4 Å molecular sieves, CH_2Cl_2, −40 °C, 48 h; (v) PhSSPh, Bu_3P, THF, reflux, 1 h; (vi) $HOCH_2CH_2OH$, *p*-TsOH, benzene, reflux, 4.5 h; (vii) *m*-CPBA, $NaHCO_3$, CH_2Cl_2–H_2O, rt, 1.5 h; (viii) $Me_3SiSiMe_3$, NaOMe, HMPA, rt, 6 h; (ix) *p*-TsOH, acetone–H_2O, reflux, 12 h; (x) MeLi, THF, 0 °C, 1 h; (xi) PDC, CH_2Cl_2, rt, 2 h; (xii) *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf), Et_3N, CH_2Cl_2, rt, 10 min.

propoxide [$Ti(OiPr)_4$], and 4 Å molecular sieves to give cyclobutanone **12** (82%).[6] Sulfide **13**, prepared by following Hata's procedure[7] (93%), was converted into ketal **14** (100%) and then into sulfone **15** by oxidation with *m*-chloroperbenzoic acid (*m*-CPBA) (88% yield). Sulfone **15** so obtained was easily crystallized from ethanol to give the optically pure sample.[8] Although we could obtain the optically pure sulfone **15** (a valuable intermediate for further elaboration), the enantiomeric excess (63% ee) of **12** resulting from the tandem reaction (**11** → **12**) was not sufficiently high to make this procedure efficient. Thus, we chose to examine the tandem reaction of **24** which bears a trimethylsilyl substituent next to the cyclopropylidene group. This choice stemmed from the fact that substituents next to a cyclopropylidene group had been shown to raise the enantiomeric excess of the tandem reaction.[5k] Also the TMS group would lend itself to further manipulation. (Trimethylsilyl)veratraldehyde (**18**), prepared by silylation[9] [$Me_3SiSiMe_3$, NaOMe] (56%) of bromide **16**[10] followed by deprotection (93%) of the resulting acetal **17**, was reacted with methyllithium to give alcohol **19** which was then oxidized to afford ketone **20** (99% from **18**). The silyl enol ether **21** obtained by silylation [*tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf), Et_3N] of **20** was converted into silyloxy ketone **22** (85% from **20**) by oxidation (*m*-CPBA). Following the same procedures described for **9**, compound **22** was converted into cyclopropylidene silyl ether **23** (54%) and then into alcohol **24** (84%). The tandem asymmetric epoxidation and 1,2-rearrangement of cyclopropylidene alcohol **24** was carried out by following the same procedure described for **11** to give cyclobutanone **25** (65%) in 92% enantiomeric excess.[11] The cyclobutanone **25** was converted into sulfide **26** (91%) and then subjected to standard acetalization conditions to give acetal **14** (88%) (Scheme 2).

Chart 1

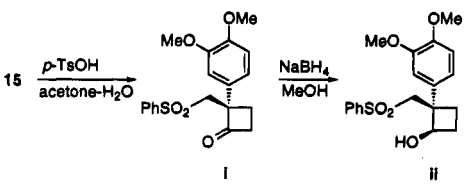


The remarkable substituent effect on the enantioselectivity of tandem asymmetric epoxidation and 1,2-rearrangement of cyclopropylidene alcohol **24** (92% ee) compared with that of **11** (63% ee) may be rationalized partly by steric congestion between the TMS, hydroxymethyl, and cyclopropyl groups in presumed intermediates **A** and **B**. In these intermediates, the developing positive charge at the chiral center is stabilized by overlap with the π-electron system of the phenyl group,

(6) The enantiomeric excess of **12** was estimated to be 63% by ^1H NMR analysis (500 MHz) of the correponding (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetate.

(7) (a) Nakagawa, I.; Hata, T. *Tetrahedron Lett.* **1975**, 1409. (b) Nakagawa, I.; Aki, K.; Hata, T. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1315. (c) Watanabe, Y.; Araki, T.; Ueno, Y.; Endo, T. *Tetrahedron Lett.* **1986**, *27*, 5385.

(8) The optical purity of **15** was determined by ^1H NMR analysis (500 MHz) of the MTPA ester of the alcohol ii which was prepared by deprotection of **15** followed by reduction ($NaBH_4$) of the resulting ketone i.



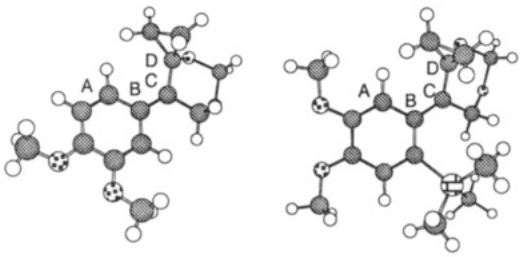
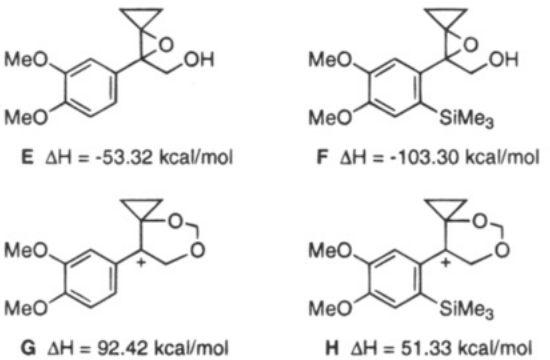


Figure 2.

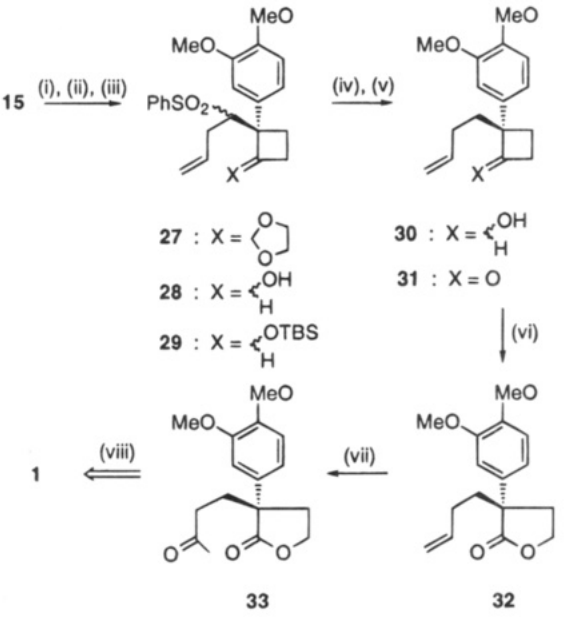
Chart 2



providing an opportunity for epimerization. On the other hand, the developing positive charge at the chiral center of the preferred conformations **C** and **D**, which lack the steric congestion of **A** and **B**, cannot be stabilized by the π-electron system of the phenyl group and thus cannot epimerize, leading to high enantioselectivity (Chart 1). To support these assumptions, semiempirical calculations of the model compounds **E** and **F** as well as the presumed 1,2-rearrangement intermediates **G** and **H** (in which titanium was replaced by methylene for simplicity) were carried out using standard AMI[12] Hamiltonians implemented in MOPAC 6.0.[13] In these calculations, geometries for each substrate were initially optimized using force field calculations (PC MODEL 4.51[14]) and further optimized with respect to all geometrical parameters using Eigenvector following (EF) routine[15] algorithms. All structures were refined using the keyword PRECISE. Thus, the heats of formation (ΔH) of **E**, **F**, **G**, and **H** were calculated to be −53.32, −103.30, 92.42, and 51.33 kcal/mol, respectively. It may be rationalized that the formation of **H** from **F** is more difficult than that of **G** from **E** because of the larger difference in the heats of formation ($\Delta\Delta H = 154.63$ kcal/mol compared to $\Delta\Delta H = 145.74$ kcal/mol) (Chart 2). This may also be explained by the large dihedral angle of **H** (<ABCD = 31.0°) compared with that of **G** ($\angle$ABCD = 18.3°) which would make cation **H** less stable than cation **G** (Figure 2).

The formal total synthesis of (−)-mesembrine (**1**) was completed as follows. The optically pure sulfone **15** was alkylated with allyl bromide to olefin **27** (91%), a diastereomeric mixture, which was deprotected and then

Scheme 3[a]



[a] Reagents and conditions: (i) BuLi, allyl bromide, THF, rt, 5 h; (ii) *p*-TsOH, acetone−H_2O, reflux, 12 h then $NaBH_4$, MeOH, rt, 30 min; (iii) TBSOTf, Et_3N, CH_2Cl_2, rt, 10 min; (iv) Na−Hg, Na_2HPO_4, MeOH, rt, 12 h then Bu_4NF, THF, rt, 3 h; (v) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, 10 min then Et_3N, 0 °C, 5 min; (vi) TESOTf, 2,6-lutidine, CH_2Cl_2, rt, 10 min; O_3, CH_2Cl_2, −78 °C, 20 min then $NaBH_4$; 10% HCl, rt, 10 min; (vii) O_2, $PdCl_2$, CuCl, DMF−H_2O, rt, 48 h; (viii) ref 2a.

reduced to alcohol **28** (100% form **27**). Silylation (TBSOTf, Et_3N) of alcohol **28** gave silyl ether **29** (100%). Reductive elimination (Na−Hg, Na_2HPO_4) followed by deprotection (Bu_4NF) of silyl ether **29** afforded alcohol **30** (94% from **29**), which was then oxidized under Swern conditions to ketone **31** (82%). Successive treatment of **31** with triethylsilyl trifluoromethanesulfonate (TESOTf) in the presence of 2,6-lutidine and ozone followed by $NaBH_4$ and 10% HCl gave olefinic lactone **32** (30% overall yield from **31**). Subjection of **32** to Wacker oxidation furnished ketone **33** (100%) {$[\alpha]^{23}_D$ −43.61° (MeOH); lit.[2a] $[\alpha]^{23}_D$ −42.6° (MeOH)}. Since ketone **33** has been previously transformed into (−)-mesembrine (**1**) in three steps,[2a] this present work constitutes a formal total synthesis of (−)-mesembrine (**1**) (Scheme 3).

Experimental Section

General Procedure. All reactions were carried out under a positive atmosphere of dry N_2 unless indicated otherwise. Solvents were freshly distilled prior to use: THF and Et_2O were distilled from sodium benzophenone and DMSO, DMF, CH_2Cl_2, and Et_3N were distilled from CaH_2 and kept over 4 Å molecular sieves. The phrase "residue upon workup" refers to the residue obtained when the organic layer was separated and dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. Silica gel column chromatography was carried out with Wako gel C-200, while Merck kiesegel 60 Art. 9385 was used for flash chromatography.

***(tert*-Butyldiphenylsiloxy)methyl 3,4-Dimethoxyphenyl Ketone (9).** To a stirred suspension of magnesium (5.0 g, 0.206 mol) in THF (80 mL) was added 4-bromoveratrol (25.0 g, 115 mmol) at rt, and stirring was continued for 3 h at the same temperature. The mixture was poured into a solution of hydroxamate **8** (17.2 g, 48.2 mmol) in THF (100 mL) at −78 °C, stirring was continued for 1.5 h at 0 °C, and then the reaction mixture was treated with 10% HCl solution and extracted with Et_2O. The combined extracts were washed with saturated aqueous $NaHCO_3$ and NaCl. The residue upon workup was chromatographed on silica gel with hexane−

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(10) Charlton, J. L.; Alauddin, M. M. *J. Org. Chem.* **1986**, *51*, 3490.
(11) The enantiomeric excess of **25** was estimated by ^{1}H NMR analysis (500 MHz) of the corresponding (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetate.
(12) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.
(13) Stewart, J. J. P. QCPE No. 455, Indiana University, 1990.
(14) Serena Software, P.O. Box 3076, Bloomington, IN 47402-3076.
(15) Baker, J. *J. Comput. Chem.* **1986**, *7*, 385.

AcOEt (9:1 v/v) as eluant to give the ketone **9** (21.0 g, 100%) as a colorless oil: IR (neat) 1690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.11 (9H, s), 3.89 (3H, s), 3.91 (3H, s), 4.88 (2H, s), 6.78–7.76 (13 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.5 (s), 26.8 (q), 56.0 (q), 56.1 (q), 67.4 (t), 110.0 (d), 110.3 (d), 122.3 (d), 127.8 (d), 128.2 (s), 129.9 (d), 133.0 (s), 135.6 (d), 149.1 (s), 153.1 (s), 195.3 (s); MS *m/z* 377 (M^+ − 57). Anal. Calcd for $C_{26}H_{30}O_4Si$: C, 71.85; H, 6.96. Found: C, 71.83; H, 6.86.

1-(*tert*-Butyldiphenylsiloxy)-2-cyclopropylidene-2-(3,4-dimethoxyphenyl)ethane (10). To a stirred suspension of NaH (6.0 g, 152 mmol) in THF (150 mL) was added cyclopropyltriphenylphosphonium bromide (60.8 g, 159 mmol) at rt. After the mixture had been stirred for 10 h at 65 °C, a solution of the ketone **9** (29.0 g, 66.7 mmol) in THF (30 mL) was added in 10 min, and stirring was continued for 3 h at the same temperature. The reaction mixture was diluted with water and extracted with Et_2O. The combined extracts were washed with saturated aqueous NaCl. The residue upon workup was chromatographed on silica gel with hexane–benzene (1:1 v/v) as eluant to give the cyclopropylideneethyl silyl ether **10** (26.0 g, 85%) as colorless leaflets: mp 52–53 °C (from Et_2O): ^1H NMR (300 MHz, $CDCl_3$) δ 0.77–0.87 (2H, m), 1.27–1.36 (2H, m), 1.01 (9H, s), 3.90 (3H, s), 3.91 (3H, s), 4.73 (2H, s), 6.83–7.76 (13H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 0.7 (t), 4.8 (t), 19.4 (s), 26.9 (q), 55.8 (q), 56.0 (q), 66.7 (t), 109.9 (d), 110.9 (d), 119.0 (d), 122.4 (s), 125.7 (s), 127.6 (d), 129.6 (d), 132.0 (s), 133.9 (s), 135.8 (d), 148.0 (s), 148.6 (s); MS *m/z* 458 (M^+). Anal. Calcd for $C_{29}H_{34}O_3Si$: C, 75.94; H, 7.47. Found: C, 76.02; H, 7.50.

2-Cyclopropylidene-2-(3,4-dimethoxyphenyl)ethanol (11). To a stirred solution of the silyl ether **10** (209 mg, 0.456 mmol) in THF (10 mL) was added a 1 M solution of Bu_4NF in THF (0.912 mL, 0.912 mmol) at rt, and stirring was continued for 3 h at the same temperature. The reaction mixture was diluted with water and extracted with Et_2O. The combined extracts were washed with saturated aqueous NaCl. The residue upon workup was chromatographed on silica gel with hexane–AcOEt (2:1 v/v) as eluant to give the cyclopropylidene alcohol **11** (97.5 mg, 97%) as colorless leaflets: mp 115 °C (from Et_2O); IR ($CHCl_3$) 3400 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.23–1.30 (2H, m), 1.42–1.50 (2H, m), 1.60–1.71 (1H, bs), 3.90 (3H, s), 3.91 (3H, s), 4.70 (2H, s), 6.88 (1H, d, J = 8.8 Hz), 7.22 (1H, dd, J = 8.8, 2.2 Hz), 7.31 (1H, d, J = 2.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.8 (t), 4.3 (t), 55.9 (q), 55.9 (q), 65.0 (t), 109.5 (d), 111.0 (d), 118.3 (d), 122.1 (s), 126.4 (s), 130.9 (s), 148.3 (s), 148.8 (s); MS *m/z* 220 (M^+). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.75; H, 7.54.

(*S*)-(−)-2-(Hydroxymethyl)-2-(3,4-dimethoxyphenyl)cyclobutanone (12). To a stirred solution of the cyclopropylidene alcohol **11** (1.68 g, 7.63 mmol) and L-(+)-DIPT (1.93 mL, 9.16 mmol) in CH_2Cl_2 (10 mL) was added 4 Å molecular sieves (400 mg) at −20 °C. After the solution was stirred for 30 min at −20 °C, $Ti(OiPr)_4$ (2.28 mL, 7.63 mmol) was added, and stirring was continued for 30 min at the same temperature. To this reaction mixture was added a 3.5 M solution of ^{t}BuOOH in CH_2Cl_2 (5.45 mL, 19.1 mmol) at −78 °C, and stirring was continued for an additional 48 h at −55 °C. The reaction mixture was treated with a solution of citric acid monohydrate (3.50 g, 16.7 mmol) in Et_2O–acetone (9:1 v/v) (40 mL), stirred for 30 min, and filtered through Celite. The residue upon evaporation of the solvent was chromatographed on silica gel with hexane–AcOEt (3:1 v/v) as eluant to give the cyclobutanone **12** (1.48 g, 82%) as a colorless oil: $[\alpha]^{23}_D$ −33.9° (*c* 1.00, $CHCl_3$); IR (neat) 1770, 3500 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.62–1.72 (1H, bs), 2.37–2.57 (2H, m), 3.02–3.18 (2H, m), 3.70 (1H, s), 3.73 (1H, s), 3.87 (3H, s), 3.90 (3H, s), 6.84–6.95 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.4 (t), 43.2 (t), 55.5 (q), 67.5 (t), 73.6 (s), 109.4 (d), 110.9 (d), 118.2 (d), 130.6 (s), 147.7 (s), 148.5 (s), 211.7 (s); MS *m/z* 236 (M^+). Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 65.64; H, 6.66.

(*R*)-(+)-2-((Phenylthio)methyl)-2-(3,4-dimethoxyphenyl)cyclobutanone (13). After a solution of the cyclobutanone **12** (624 mg, 2.64 mmol), diphenyl disulfide (1.73 g, 7.93 mmol), and tri-*n*-butylphosphine (2.63 mL, 10.6 mmol) in THF (10 mL) was refluxed for 1 h under stirring, the reaction mixture was diluted with Et_2O and washed with aqueous 10% NaOH and saturated aqueous NaCl. The residue upon workup was chromatographed on silica gel with hexane–AcOEt (95:5 v/v) as eluant to give the sulfide **13** (805 mg, 93%) as a colorless oil: $[\alpha]^{23}_D$ +9.46 ° (*c* 1.53, $CHCl_3$); IR (neat) 1770 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.41–2.58 (2H, m), 3.03–3.21 (2H, m), 3.33 (1H, d, J = 13.0 Hz), 3.38 (1H, d, J = 13.0 Hz), 3.86 (3H,s), 3.88 (3H, s), 6.80–7.31 (8H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.8 (t), 43.1 (t), 43.5 (t), 55.9 (q), 56.0 (q), 71.5 (s), 109.7 (d), 111.1 (d), 118.7 (d), 126.4 (d), 128.9 (d), 129.7 (d), 131.8 (s), 136.4 (s), 148.4 (s), 149.0 (s), 209.7 (s); MS *m/z* 328 (M^+). Anal. Calcd for $C_{19}H_{20}O_3S$: C, 69.49; H, 6.14; S, 9.76. Found: C, 69.49; H, 6.17; S, 9.84.

(*R*)-(+)-2-((Phenylthio)methyl)-2-(3,4-dimethoxyphenyl)-cyclobutanone Ethylene Acetal (14). Sufide **13** (10.7 mg, 0.0326 mmol) was dissolved in benzene (5 mL). A catalytic amount of *p*-TsOH and ethylene glycol (0.007 mL, 0.129 mmol) were added to this solution which was then refluxed for 4.5 h using a Dean–Stark trap to remove water. The reaction mixture was diluted with Et_2O and washed with aqueous saturated $NaHCO_3$ and saturated aqueous NaCl. The residue upon workup was chromatographed on silica gel with hexane–AcOEt (82:18 v/v) as eluant to give the ketal **14** (12.2 mg, 100%) as a colorless oil: $[\alpha]^{23}_D$ +82.19° (*c* 1.02, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 2.06–2.53 (4H, m), 3.50–4.02 (6H, m), 3.84 (3H, s), 3.86 (3H, s), 6.69–6.84 (3H, m), 7.08–7.25 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.5 (t), 32.6 (t), 43.0 (t), 55.8 (q), 55.9 (q), 58.5 (s), 64.3 (t), 65.0 (t), 76.3 (s), 110.7 (d), 111.1 (d), 119.4 (d), 125.6 (d), 128.7 (d), 129.2 (d), 133.3 (s), 137.8 (s), 147.7 (s), 148.4 (s); MS *m/z* 372 (M^+). Anal. Calcd for $C_{21}H_{24}O_4S$: C, 67.72; H, 6.49; S, 8.61. Found: C, 67.59; H, 6.47; S, 8.47.

(*R*)-(+)-2-(3,4-Dimethoxyphenyl)-2-((phenylsulfonyl)-methyl)cyclobutanone Ethylene Acetal (15). To a stirred solution of the ketal **14** (11.0 mg, 0.0295 mmol) in CH_2Cl_2 (2 mL) was added an aqueous saturated $NaHCO_3$ (3 mL) and *m*-CPBA (80%, 15.9 mg, 0.0738 mmol) at rt, and stirring was continued for 1.5 h. The reaction mixture was treated with 10% $Na_2S_2O_3$ aqueous solution and extracted with CH_2Cl_2. The combined extracts were washed with saturated aqueous NaCl. The residue upon workup was chromatographed on silica gel with hexane–AcOEt (1:1 v/v) as eluant to give the sulfone **15** (10.5 mg, 88%) as colorless needles: mp 97–98 °C (from EtOH); $[\alpha]^{23}_D$ +24.40° (*c* 1.79, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 2.18–2.62 (4H, m), 3.64–3.98 (6H, m), 3.65 (3H, s), 3.81 (3H, s), 6.32 (1H, s), 6.60 (2H, s), 7.20–7.43 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.8 (t), 32.9 (t), 55.7 (q), 55.8 (q), 56.2 (s), 62.8 (t), 64.5 (t), 64.9 (t), 110.8 (s), 110.9 (d), 111.1 (d), 120.0 (d), 127.5 (d), 128.3 (d), 130.4 (d), 132.4 (s), 141.0 (s), 147.9 (s), 148.3 (s); MS *m/z* 263 (M^+ − 141). Anal. Calcd for $C_{21}H_{24}O_6S$: C, 62.36; H, 5.98; S, 7.93. Found: C, 62.27; H, 5.95; S, 7.74.

6-(Trimethylsilyl)veratraldehyde Ethylene Acetal (17). To a stirred solution of the bromo acetal **16** (3.50 g, 12.1 mmol) in HMPA (100 mL) were added NaOMe (3.06 g, 56.7 mmol) and hexamethyldisilane (6.94 mL, 33.9 mmol) at rt, and stirring was continued for 6 h at the same temperature. The reaction mixture was diluted with water and extracted with Et_2O. The combined extracts were washed with saturated aqueous NaCl. The residue upon workup was chromatographed on silica gel with hexane–AcOEt (85:15 v/v) as eluant to give starting material **16** (1.54 g, 44%) and the TMS acetal **17** (1.05 g, 56%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 0.28 (9H, s), 3.85 (3H, s), 3.88 (3H, s), 4.02–4.19 (4H, m), 5.74 (1H, s), 7.05 (1H, d, J = 1.0 Hz), 7.07 (1H, d, J = 1.0 Hz); MS *m/z* 282 (M^+); HRMS calcd for $C_{14}H_{22}O_4Si$ 282.1286 (M^+), found 282.1301.

6-(Trimethylsilyl)veratraldehyde (18). To a stirred solution of the TMS acetal **17** (970 mg, 3.43 mmol) in acetone–H_2O (3:1 v/v) (60 mL) was added a catalytic amount of *p*-TsOH at rt, and stirring was continued for 12 h under reflux. The reaction mixture was treated with saturated aqueous $NaHCO_3$ solution and extracted with Et_2O. The combined extracts were washed with 10% HCl solution and saturated aqueous NaCl. The residue upon workup was chromatographed on silica gel with hexane–AcOEt (9:1 v/v) as eluant to give the aldehyde **18** (761 mg, 93%) as a colorless oil: IR (neat) 1695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.32 (9H, s), 3.92 (3H, s), 3.95 (3H,

s), 7.47 (2H, s), 9.90 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.7 (q), 55.7 (q), 60.7 (q), 112.0 (d), 131.5 (d), 132.5 (s), 133.7 (s), 152.3 (s), 159.1 (s), 191.6 (d); MS m/z 238 (M^+). Anal. Calcd for $C_{12}H_{18}O_3Si$: C, 60.47; H, 7.61. Found: C, 60.22; H, 7.50.

4-Acetyl-5-(trimethylsilyl)veratrole (20). To a stirred solution of the aldehyde **18** (911 mg, 3.82 mmol) in THF (60 mL) was added a 1.4 M hexane solution of methyllithium (3.00 mL, 4.21 mmol) at 0 °C, and stirring was continued for 1 h at the same temperature. The reaction mixture was diluted with water and extracted with Et_2O. The combined extracts were washed with saturated aqueous NaCl. The residue upon workup was dissolved in CH_2Cl_2 (50 mL), and to this solution were added PDC (4.31 g, 11.5 mmol) and 4 Å molecular sieves (2.00 g) at rt. After stirring for 2 h at the same temperature, the reaction mixture was chromatographed on silica gel with hexane−AcOEt (9:1 v/v) as eluant to give the methyl ketone **20** (921 mg, 99%) as a colorless oil: IR (neat) 1680 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.31 (9H, s), 2.58 (3H, s), 3.91 (3H, s), 3.93 (3H, s), 7.57 (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.7 (q), 26.4 (q), 55.7 (q), 60.6 (q), 113.1 (d), 127.8 (d), 133.0 (s), 133.1 (s), 151.7 (s), 158.0 (s), 197.3 (s); MS m/z 252 (M^+). Anal. Calcd for $C_{13}H_{20}O_3Si$: C, 61.87; H, 7.99. Found: C, 61.99; H, 7.92.

***(tert*-Butyldimethylsiloxy)methyl 4,5-Dimethoxy-2-(trimethylsilyl)phenyl Ketone (22).** To a stirred solution of methyl ketone **20** (880 mg, 3.49 mmol) in CH_2Cl_2 (30 mL) were added Et_3N (2.43 mL, 17.5 mmol) and TBSOTf (2.00 mL, 8.73 mmol) at 0 °C, and stirring was continued for 10 min at rt. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined extracts were washed with saturated aqueous NaCl. The residue upon workup was dissolved in CH_2Cl_2 (30 mL), and to this solution was added saturated aqueous $NaHCO_3$ (20 mL). After addition of *m*-CPBA (80%, 1.51 g, 6.98 mmol) in 30 min at 0 °C, stirring was continued for 1.5 h at rt. The reaction mixture was treated with 10% $Na_2S_2O_3$ aqueous solution and extracted with CH_2Cl_2. The combined extracts were washed with saturated aqueous NaCl. The residue upon workup was chromatographed on silica gel with hexane−AcOEt (95:5 v/v) as eluant to give the TBS ether **22** (1.13 g, 85%) as a colorless oil: IR (neat) 1700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.13 (6H, s), 0.30 (9H, s), 0.94 (9H, s), 3.90 (3H, s), 3.93 (3H, s), 4.88 (2H, s), 7.53 (1H, s, J = 1.8 Hz), 7.57 (1H, s, J = 1.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.1 (q), −0.6 (q), 18.6 (s), 26.0 (q), 55.8 (q), 60.7 (q), 67.5 (t), 113.3 (d), 127.0 (d), 130.8 (s), 133.2 (s), 151.8 (s), 158.1 (s), 196.8 (s); MS m/z 325 (M^+ − 57). Anal. Calcd for $C_{19}H_{34}O_4Si_2$: C, 59.64; H, 8.96. Found: C, 59.29; H, 8.91.

1-(*tert*-Butyldimethylsiloxy)-2-cyclopropylidene-2-(4,5-dimethoxy-2-(trimethylsilyl)phenyl)ethane (23). To a stirred suspension of NaH (261 mg, 6.51 mmol) in THF (30 mL) was added cyclopropyltriphenylphosphonium bromide (2.50 g, 6.51 mmol) at rt. After the mixture had been stirred for 10 h at 65 °C, a solution of the TBS ether **22** (1.08 g, 2.83 mmol) in THF (10 mL) was added in 10 min, and stirring was continued for 3 h at the same temperature. The reaction mixture was diluted with water and extracted with Et_2O. The combined extracts were washed with saturated aqueous NaCl. The residue upon workup was chromatographed on silica gel with hexane−benzene (1:1 v/v) as eluant to give the cyclopropylidene silyl ether **23** (616 mg, 54%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 (6H, s), 0.30 (9H, s), 0.90 (9H, s), 1.18−1.28 (2H, m), 1.40−1.46 (2H, m), 3.87 (3H, s), 3.88 (3H, s), 4.68 (2H, s), 7.38 (1H, d, J = 2.2 Hz), 7.40 (1H, d, J = 2.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.0 (q), −0.4 (q), 1.0 (t), 4.8 (t), 18.4 (s), 26.0 (q), 55.5 (q), 60.6 (q), 65.9 (t), 112.5 (d), 122.4 (s), 124.4 (d), 126.6 (s), 132.3 (s), 134.7 (s), 151.4 (s), 152.7 (s); MS m/z 406 (M^+); HRMS calcd for $C_{22}H_{38}O_3Si_2$ 406.2357 (M^+), found 406.2380.

2-Cyclopropylidene-2-(4,5-dimethoxy-2-(trimethylsilyl)-phenyl)ethanol (24). To a stirred solution of the cyclopropylidene silyl ether **23** (506 mg, 1.24 mmol) in THF (15 mL) was added 1 M solution of Bu_4NF in THF (3.73 mL, 3.73 mmol) at rt, and stirring was continued for 3 h at the same temperature. The reaction mixture was diluted with water and extracted with Et_2O. The combined extracts were washed with saturated aqueous NaCl. The residue upon workup was chromatographed on silica gel with hexane−AcOEt (8:2 v/v) as eluant to give the cyclopropylidene alcohol **24** (304 mg, 84%) as colorless needles: mp 71−72 °C (from hexane); IR ($CHCl_3$) 3450 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.30 (9H, s), 1.23−1.29 (2H, m), 1.41−1.48 (2H, m), 1.60 (1H, bs), 3.87 (3H, s), 3.88 (3H, s), 4.70 (2H, s), 7.30 (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.0 (q), −0.4 (q), 1.0 (t), 4.8 (t), 18.4 (s), 26.0 (q), 55.5 (q), 60.6 (q), 65.9 (t), 112.5 (d), 122.4 (s), 124.4 (d), 126.6 (s), 132.3 (s), 134.7 (s), 151.4 (s), 152.7 (s); MS m/z 292 (M^+); HRMS calcd for $C_{16}H_{24}O_3Si$ 292.1494 (M^+), found 292.1476.

***(S)*-(−)-2-(4,5-Dimethoxy-2-(trimethylsilyl)phenyl)-2-(hydroxymethyl)cyclobutanone (25).** To a stirred solution of the cyclopropylidene alcohol **24** (299 mg, 1.02 mmol) and L-(+)-DIPT (381 mg, 1.63 mmol) in CH_2Cl_2 (20 mL) was added 4 Å molecular sieves (300 mg) at −20 °C. After the solution was stirred for 30 min at −20 °C, $Ti(OiPr)_4$ (0.410 mL, 1.37 mmol) was added, and stirring was continued for 30 min at the same temperature. To this reaction mixture was added a 3.5 M solution of ^{t}BuOOH in CH_2Cl_2 (1.07 mL, 3.75 mmol) at −78 °C, and stirring was continued for an additional 48 h at −40 °C. The reaction mixture was treated with a solution of citric acid monohydrate (650 mg, 3.10 mmol) in Et_2O−acetone (9:1 v/v) (8 mL), stirred for 30 min, and filtered through Celite. The residue upon evaporation of the solvent was chromatographed on silica gel with hexane−AcOEt (8:2 v/v) as eluant to give the cyclobutanone **25** (205 mg, 65%) as colorless needles: mp 119−120 °C (from hexane); $[\alpha]^{23}_D$ −57.6° (*c* 0.98, $CHCl_3$); IR ($CHCl_3$) 1790, 3500 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.63−1.71 (1H, m), 2.37−2.60 (2H, m), 2.97−3.17 (2H, m), 3.85 (3H, s), 3.87 (3H, s), 3.68−3.96 (2H, m), 6.88 (1H, d, J = 2.2 Hz), 7.02 (1H, d, J = 2.2 Hz); MS m/z 308 (M^+). Anal. Calcd for $C_{16}H_{24}O_4Si$: C, 62.30; H, 7.84. Found: C, 62.55; H, 7.59.

***(R)*-(−)-2-(4,5-Dimethoxy-2-(trimethylsilyl)phenyl)-2-((phenylthio)methyl)cyclobutanone (26).** After a solution of the cyclobutanone **25** (60.3 mg, 0.195 mmol), diphenyl disulfide (149 mg, 0.681 mmol), and tri-*n*-butylphosphine (0.226 mL, 0.907 mmol) in THF (10 mL) was refluxed for 1 h under stirring, the reaction mixture was diluted with Et_2O and washed with aqueous 10% NaOH and saturated aqueous NaCl. The residue upon workup was chromatographed on silica gel with hexane−AcOEt (95:5 v/v) as eluant to give the sulfide **26** (70.8 mg, 91%) as a colorless oil: $[\alpha]^{23}_D$ −2.0° (*c* 2.30, $CHCl_3$); IR (neat) 1780 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.28 (9H, s), 2.42−2.57 (2H, m), 3.00−3.19 (2H, m), 3.33 (1H, d, J = 12.0 Hz), 3.39 (1H, d, J = 12.0 Hz), 3.82 (3H, s), 3.83 (3H, s), 6.91−7.27 (7H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.4 (q), 22.9 (t), 43.1 (t), 43.5 (t), 55.7 (q), 60.6 (q), 71.9 (s), 112.4 (d), 124.0 (d), 126.3 (d), 128.9 (d), 129.6 (d), 133.2 (s), 134.8 (s), 136.4 (s), 151.6 (s), 153.0 (s), 209.8 (s); MS m/z 400 (M^+); HRMS calcd for $C_{22}H_{28}O_3SSi$ 400.1527 (M^+), found 400.1522.

***(R)*-(+)-2-(3,4-Dimethoxyphenyl)-2-((phenylthio)methyl)cyclobutanone Ethylene Acetal (14) from 26.** Sulfide **26** (26.0 mg,0.0649 mmol) was dissolved in benzene (8 mL). A catalytic amount of *p*-TsOH and ethylene glycol (0.0230 mL, 0.412 mmol) were added to the solution which was then refluxed for 4.5 h using a Dean−Stark trap to remove water. The reaction mixture was diluted with Et_2O and washed with aqueous saturated $NaHCO_3$ and saturated aqueous NaCl. The residue upon workup was chromatographed on silica gel with hexane−AcOEt (82:18 v/v) as eluant to give the ketal **14** (21.2 mg, 88%) as a colorless oil: $[\alpha]^{23}_D$ +96.01° (*c* 1.02, $CHCl_3$).

(2*R*)-2-(3,4-Dimethoxyphenyl)-2-(1-(phenylsulfonyl)-3-buten-1-yl)cyclobutanone Ethylene Acetal (27). To a stirred solution of the sulfone **15** (236 mg, 0.584 mmol) in THF (10 mL) was added a 1.56 M hexane solution of ^{n}BuLi (0.449 mL, 0.700 mmol) in 5 min at 0 °C, and stirring was continued for 1 h. To this mixture was added allyl bromide (0.100 mL, 1.16 mmol) at the same temperature, and stirring was continued for an additional 5 h. The reaction mixture was diluted with water and extracted with Et_2O. The combined extracts were washed with saturated aqueous NaCl. The residue upon workup was chromatographed on silica gel with hexane−benzene (1:1 v/v) as eluant to give the allyl sulfone **27** which was a 1:1 mixture of diastereomers (235 mg, 91%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.79−1.91 (0.5H, m), 2.02−2.16 (2H, m), 2.32−2.50 (2.5H, m), 2.57−2.70

(0.5H, m), 2.82–2.93 (0.5H, m), 3.87 (1.5H, s), 3.89 (3H, s), 3.90 (1.5H, s), 3.91–4.10 (3H, m), 4.08 (0.5H, dd, J = 2.6 Hz, 9.2 Hz), 4.19 (0.5H, t, J = 6.2 Hz), 4.32–4.44 (1H, m), 4.69–4.98 (2H, m), 5.29–5.49 (1H, m), 6.82–7.77 (8H, m); MS m/z 444 (M^+); HRMS calcd for $C_{24}H_{28}O_6S$ 444.1606 (M^+), found 444.1618.

(2*R*)-2-(3,4-Dimethoxyphenyl)-2-(1-(phenylsulfonyl)-3-buten-1-yl)cyclobutanol (28). To a stirred solution of the allyl sulfone **27** (2.11 g, 4.75 mmol) in acetone–H_2O (3:1 v/v) (8 mL) was added a catalytic amount of *p*-TsOH at rt, and stirring was continued for 12 h under reflux. The reaction mixture was treated with saturated aqueous $NaHCO_3$ solution and extracted with Et_2O. The combined extracts were washed with a 10% HCl solution and NaCl. The residue upon workup was dissolved in CH_2Cl_2–MeOH (2:1 v/v) (8 mL). To this solution was added $NaBH_4$ (368 mg, 4.75 mmol) at rt, and the solution was stirred at the same temperature for 30 min. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined extracts were washed with saturated aqueous NaCl. The residue upon workup was chromatographed on silica gel with hexane–AcOEt (1:1 v/v) as eluant to give the alcohol **28** (1.91 g, 100%) as a colorless oil: IR (neat) 3500 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.60–2.50 (6.5H, m), 3.14–3.17 (0.5H, m), 3.43–3.53 (1H, m), 3.86 (1.5H, s), 3.90 (4.5H, s), 4.51–4.72(1H, m), 4.83–4.99 (2H, m), 5.44–5.99 (1H, m), 6.82–7.82 (8H, m); MS m/z 261 (M^+ – 141); HRMS calcd for $C_{16}H_{21}O_3$ 261.1489 (M^+ – 141), found 261.1494.

(2*R*)-1-(*tert*-Butyldimethylsiloxy)-2-(3,4-dimethoxyphenyl)-2-(1-(phenylsulfonyl)-3-buten-1-yl)cyclobutane (29). To a solution of the alcohol **28** (3.5 mg, 0.00870 mmol) in CH_2Cl_2 (0.5 mL) were added Et_3N (0.007 mL, 0.052 mmol) and TBSOTf (0.006 mL, 0.026 mmol) at 0 °C, and stirring was continued at the same temperature for 10 min. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined extracts were washed with saturated aqueous NaCl. The residue upon workup was chromatographed on silica gel with hexane–AcOEt (8:2 v/v) as eluant to give the TBS ether **29** (4.5 mg, 100%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ –0.07 (1.5H, s), –0.05 (1.5H, s), 0.05 (1.5H, s), 0.06 (1.5H, s), 0.82 (4.5H, s), 0.83 (4.5H, s), 1.60–1.77 (1H,m), 1.98–2.20 (2H, m), 2.24–2.41 (1H, m), 2.62–2.79 (2H, m), 3.42–3.49 (0.5H, m), 3.55–3.61 (0.5H, m), 3.78 (1.5H, s), 3.79 (1.5H, s), 3.83 (1.5H, s), 3.87 (1.5H, s), 4.38–4.45 (0.5H, m), 4.62–4.69 (0.5H, m), 4.73–4.97 (2H, m), 5.48–5.70 (1H, m), 6.64–7.59 (8H, m); MS m/z 375 (M^+ – 141); HRMS calcd for $C_{22}H_{35}O_3Si$ 375.2354 (M^+ – 141), found 375.2352.

(2*S*)-2-(3-Buten-1-yl)-2-(3,4-dimethoxyphenyl)cyclobutanol (30). To a solution of the TBS ether **29** (28.3 mg, 0.0547 mmol) in MeOH (5 mL) were added Na_2HPO_4 (35.0 mg, 0.247 mmol) and 5% Na(Hg) (500 mg) at rt, and stirring was continued at the same temprature for 12 h. After the reaction mixture had been filtered through Celite, the solvent was diluted with H_2O and extracted with Et_2O. The combined extracts were washed with saturated aqueous NaCl. The residue upon workup was dissolved in THF (5 mL), and a 1 M solution of $^nBu_4NF$ in THF (0.106 mL, 0.106 mmol) was added to this solution at rt. After 3 h of stirring at the same temperature, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined extracts were washed with saturated aqueous NaCl. The residue upon workup was chromatographed on silica gel with hexane–AcOEt (1:1 v/v) as eluant to give the alcohol **30** (13.1 mg, 94%) as a colorless oil: IR (neat) 3450 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.55–2.64 (6H, m), 2.97–3.04 (1H, m), 3.58–3.67 (1H, m), 3.87–4.14 (1H, m), 3.88 (1.5H, s), 3.90 (3H, s), 3.91 (1.5H, s), 4.86–5.17 (2H, m), 5.64–5.99 (2H, m), 6.80–6.96 (3H, m); MS m/z 262 (M^+). Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.05; H, 8.46.

(2*S*)-(–)-2-(3-Buten-1-yl)-2-(3,4-dimethoxyphenyl)cyclobutanone (31). To a solution of dimethyl sulfoxide (0.026 mL, 0.361 mmol) in CH_2Cl_2 (1 mL) was added oxalyl chloride (0.026 mL, 0.301 mmol) at –78 °C, and stirring was continued for 10 min. A solution of the alcohol **30** (15.1 mg, 0.058 mmol) in CH_2Cl_2 (1 mL) was added to this solution, and the reaction mixture was stirred for 30 min at the same temperature and then treated with Et_3N (0.0840 mL, 0.602 mmol). After further stirring for 5 min at 0 °C, the reaction mixture was treated with 10% HCl solution and extracted with Et_2O. The combined extracts were washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The residue upon workup was chromatographed on silica gel with hexane–AcOEt (9:1 v/v) as eluant to give the cyclobutanone **31** (12.3 mg, 82%) as a colorless oil: $[\alpha]^{23}_D$ –14.51° (*c* 3.58, $CHCl_3$); IR (neat) 1765 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.86–2.04 (4H, m), 2.18–2.26 (1H, m), 2.42–2.51 (1H, m), 2.96–3.17 (2H, m), 3.87 (3H, s), 3.90 (3H, s), 4.88–4.99 (2H, m), 5.68–5.77 (1H, m), 6.82–6.94 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.8 (t), 29.0 (t), 38.6 (t), 42.6 (t), 56.0 (q), 56.1 (q), 71.7 (s), 109.9 (d), 111.3 (d), 114.8 (t), 118.5 (d), 133.1 (s), 137.8 (d), 148.0 (s), 149.0 (s), 211.7 (s); MS m/z 260 (M^+); Anal. Calcd for $C_{16}H_{20}O_3 \cdot 0.1H_2O$: C, 73.77; H, 7.82. Found: C, 73.41; H, 8.17.

(3*S*)-(–)-3-(3-Buten-1-yl)-3-(3,4-dimethoxyphenyl)tetrahydro-2-furanone (32). To a stirred solution of the cyclobutanone **31** (40.7 mg, 0.156 mmol) in CH_2Cl_2 (5 mL) were added 2,6-lutidine (0.215 mL, 1.85 mmol) and TESOTf (0.209 mL, 0.924 mmol) at 0 °C, and stirring was continued for 10 min at rt. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined extracts were washed with saturated aqueous NaCl. The residue upon workup was dissolved in MeOH and treated with ozone at –78 °C until the starting material disappeared (20 min). The resulting ozonide was reduced by addition of $NaBH_4$ (40.0 mg, 1.06 mmol), and the reaction mixture was stirred for 20 min at the same temperature. After the solvent had been evaporated, the residue was mixed with 10% HCl solution and stirred for an additional 1 h at rt. The reaction mixture was extracted with CH_2Cl_2. The combined extracts were washed with saturated aqueous NaCl. The residue upon workup was chromatographed on silica gel with hexane–AcOEt (2:1 v/v) as eluant to give the lactone **32** (12.7 mg, 30%) as a colorless oil: $[\alpha]^{23}_D$ –67.34° (*c* 0.94, $CHCl_3$); IR (neat) 1750 cm^{-1};^1H NMR (300 MHz, $CDCl_3$) δ 1.83–2.17 (4H, m), 2.38–2.77 (2H, m), 3.88 (3H, s), 3.89 (3H, s), 4.08–4.38 (2H, m), 4.91–5.04 (2H, m), 5.68–5.82 (1H, m), 6.84 (1H, d, J = 8.4 Hz), 6.94 (1H, dd, J = 1.8, 8.4 Hz), 7.04 (1H, d, J = 1.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.1 (t), 34.5 (t), 38.6 (t), 50.4 (s), 56.0 (q), 56.1 (q), 65.2 (t), 110.3 (d), 111.2 (d), 115.1 (t), 118.6 (d), 130.8 (s), 137.7 (d), 148.6 (s), 149.4 (s), 179.1 (s); MS m/z 276 (M^+); HRMS calcd for $C_{16}H_{20}O_4$ 276.1360 (M^+), found 276.1372.

(3*S*)-(–)-3-(3,4-Dimethoxyphenyl)-3-(3-oxobutyl)tetrahydro-2-furanone (33). Cupper(I) chloride (8.0 mg, 0.081 mmol) and palladium(II) chloride (4.0 mg, 0.0226 mmol) were suspended in DMF–H_2O (4:1 v/v) (2 mL), and the mixture was stirred for 24 h at rt under an O_2 (1 atm) atmosphere. The lactone **32** (9.4 mg, 0.034 mmol) was added, and stirring was continued for an additional 48 h at the same temperature. The reaction mixture was diluted with water and extracted with Et_2O. The combined extracts were washed with saturated aqueous NaCl. The residue upon workup was chromatographed on silica gel with hexane–AcOEt (1:1 v/v) as eluant to give the keto lactone **33** (9.9 mg, 100%) as a colorless oil: $[\alpha]^{23}_D$ –43.61° (*c* 0.21, MeOH); IR (neat) 1710, 1760 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.06 (3H, s), 2.18–2.49 (4H, m), 2.58–2.71 (2H, m), 3.89 (6H, s), 4.05–4.19 (2H, m), 6.81–6.98 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.0 (q), 32.3 (t), 36.5 (t), 38.9 (t), 50.0 (s), 56.0 (q), 56.2 (q), 65.2 (t), 110.1 (d), 111.4 (d), 118.7 (d), 130.8 (s), 148.7 (s), 149.5 (s), 178.9 (s), 207.6 (s); MS m/z 292 (M^+); HRMS calcd for $C_{16}H_{20}O_5$ 292.1310 (M^+), found 292.1310.

Supporting Information Available: ^1H NMR spectra of **17**, **23**, **24**, **26–29**, and **31–33** (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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