Articles

Chiral Organosilicon Compounds in Asymmetric Synthesis of Chiral 1,3-Diols

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Chiral 1,3-diols can be prepared in high enantiomeric purity (>99% ee) from the reactions of the chiral silylcarbanion 2 with epoxides followed by oxidative cleavage of the carbon–silicon bond with hydrogen peroxide. The absolute configurations of some of the chiral 1,3-diols were determined by circular dichroism (CD).

Introduction

The 1,3-polyhydroxy structure is present in a number of natural products including the polyenemacrolide antibiotics. Much of the recent synthetic chemistry of 1,3-polyols have been directed toward the control of the relative stereochemistries of the polyhydroxy functions.[1] Most preparations of optically pure 1,3-polyols have depended on optical resolution or the use of existing chiral precursors. More recently, asymmetric syntheses of chiral 1,3-diols have been reported by using stereoselective hydrogenation of 1,3-diketones[2,3] or β-hydroxy ketones,[3,4] by asymmetric double hydroboration of 1,3-dienes[5] or allylmetallics,[6] and by catalytic alkylation of β-alkoxy aldehydes.[7]

Recently in our laboratory, we have demonstrated that highly enantioselective synthesis of chiral arylcarbinols[8] and allylic alcohols[9] can be achieved by the use of chiral organosilicon compounds containing the (*S*)-(+)-2-(methoxymethyl)pyrrolidine moiety as the chiral auxiliary. We report here our synthesis of optically pure 1,3-diols based on the reactions of the carbanion 2 derived from the chiral organosilicon compound 1 and various epoxides (Scheme I).

Results

The chiral organosilane 1 was easily prepared[8] from benzylmagnesium chloride and (chloromethyl)dimethylchlorosilane, followed by amination with (*S*)-(+)-2-(methoxymethyl)pyrrolidine. Treatment of 1 with *sec*-butyllithium in ether at −78 °C gave the carbanion 2, which on quenching with ethylene oxide gave compound 3 as a single diastereomer according to ^{1}H NMR. When 3 was treated with H_2O_2 and KF, oxidative cleavage of the carbon–silicon bond occurred[10] to give the 1,3-diol (*S*)-(−)-4. The spectroscopic data of 4 are identical to those of the

Scheme I

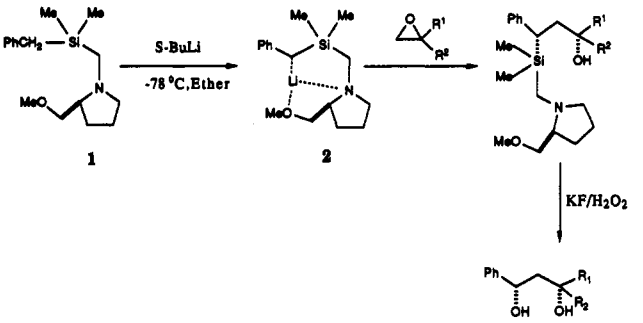

Table I. Oxidation with H_2O_2 and KF To Give 1,3-Diols

1,3-diols[a]	% yield	$[\alpha]^{20}_D$ in $CHCl_3$	% ee[b]
PhCH(OH)CH_2CH_2OH (4)	65	−48.9° (*c* 0.18)	>99
PhCH(OH)CH_2C(OH)C_5H_{10} (8)	69	−18.0° (*c* 0.10)	>99
PhCH(OH)CH_2CH(OH)CH_3 (1*S*,3*S*) (12)	80	−62.7° (*c* 0.15)	>99
PhCH(OH)CH_2CH(OH)CH_3 (1*S*,3*R*) (13)	75	−69.4° (*c* 0.20)[c]	>99
PhCH(OH)CH_2CH(OH)-*n*-C_4H_9 (1*S*,3*S*) (17)	60	−36.5° (*c* 0.15)	>99
PhCH(OH)CH_2CH(OH)-*n*-C_4H_9 (1*S*,3*R*) (18)	53	−43.4° (*c* 0.15)	>99
PhCH(OH)CH_2CH(OH)-*t*-C_4H_9 (1*S*,3*S*) (22)	75	−78.0° (*c* 0.60)	>99
PhCH(OH)CH_2CH(OH)-*t*-C_4H_9 (1*S*,3*R*) (23)	65	−28.0° (*c* 0.40)	>99

[a] Racemic 1,3-diols were prepared by the reduction of corresponding 1,3-diketone, hydroxy ketone, and hydroxy ester. [b] The % ee's were determined by the combination of GC and ^{1}H NMR analysis of the appropriate MTPA esters. [c] Reported values[5] $[\alpha]^{20}_D$ = −32.4° (*c* 0.9, $CHCl_3$) for 1*S*,3*R* and $[\alpha]^{20}_D$ = +50.7° (*c* 0.6, $CHCl_3$) for 1*R*,3*S* diol.

(1) For a recent review, see: Oishi, T.; Tadashi, N. *Synthesis* **1990**, 635–645.
(2) Ito, K.; Harada, T.; Tai, A. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3367–3368.
(3) Katamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629–631.
(4) (a) Narasaka, K.; Pai, F.-C. *Tetrahedron* **1984**, *40*, 2233–2238. (b) Chen, K.; Hardtman, G. E.; Prasad, K.; Repic, O.; Shapiro, J. *Tetrahedron Lett.* **1987**, *28*, 155–158. (c) Evans, D. A.; Hoveyda, A. H. *J. Org. Chem.* **1990**, *55*, 5190–5192.
(5) Matsumoto, Y.; Hayashi, T. *Tetrahedron Lett.* **1991**, *32*, 3387–3390.
(6) (a) Medlik-Balan, A.; Klein, J. *Tetrahedron* **1980**, *36*, 299–304. (b) Klein, J.; Medlik, A. *J. Am. Chem. Soc.* **1971**, *93*, 6313–6314.
(7) Soai, K.; Hatanaka, T.; Yamashita, T. *J. Chem. Soc., Chem. Commun.* **1992**, 927–929.
(8) Chan, T. H.; Pellon, P. *J. Am. Chem. Soc.* **1989**, *111*, 8737–8738.
(9) (a) Chan, T. H.; Horvath, R. *J. Org. Chem.* **1989**, *54*, 317–327. (b) Chan, T. H.; Lamothe, S. *Tetrahedron Lett.* **1991**, *32*, 1847–1850.
(10) (a) Tamao, K.; Takui, T.; Kumada, M. *J. Am. Chem. Soc.* **1978**, *100*, 2268–2269. (b) Tamao, K.; Ishida, N.; Tanaka, T.; Kumada, M. *Organometallics* **1983**, *2*, 1694–1696.

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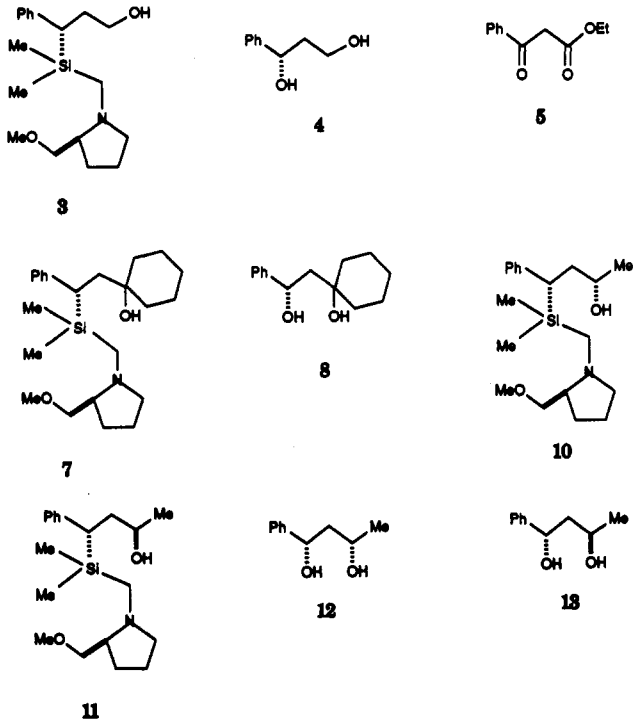
Table II. ^{13}C NMR Analysis of Acetonides of 1,3-Diols

1,3-diols	δ ketal C	δ methyl C	assnt
PhCH(OH)CH_2CH(OH)CH_3 (*S,S*) (12)	99.04	19.64, 30.20	syn
PhCH(OH)CH_2CH(OH)CH_3 (*S,R*) (13)	100.66	24.99, 25.25	anti
PhCH(OH)CH_2CH(OH)-*n*-C_4H_9 (*S,S*) (17)	98.91	19.79, 30.32	syn
PhCH(OH)CH_2CH(OH)-*n*-C_4H_9 (*S,R*) (18)	100.68	24.70, 25.11	anti
PhCH(OH)CH_2CH(OH)-*t*-C_4H_9 (*S,S*) (22)	100.70	24.04, 25.03	anti
PhCH(OH)CH_2CH(OH)-*t*-C_4H_9 (*S,R*) (23)	98.81	19.70, 30.29	syn

racemic compound[6b] prepared from the LAH reduction of **5**. The absolute configuration of **4** is based on literature assignment.[11] The optical purity of **4** was determined by converting both the racemic compound and the (−)-isomer to the corresponding α-methoxy-α-(trifluoromethyl)-phenylacetate (MTPA) esters using (*S*)-(+)-MTPA-Cl.[12] ^1H NMR analyses showed the absence of the other diastereomer in the (*S*)-(−)-**4** MTPA sample. Gas chromatographic analyses of the diastereomeric MTPA esters on a capillary column confirmed that the optical purity of (−)-**4** obtained according to Scheme I was greater than 99% ee (Table I).



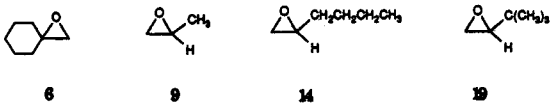
Similar reaction of the carbanion **2** with methylenecyclohexane oxide **6** gave the alcohol **7** regiospecifically. When the reaction was carried out at room temperature, compound **7** was obtained as a mixture of two diastereomers with 67% de. However, by lowering the reaction temperature to −50 °C, **7** could be obtained as one single diastereomer according to ^1H NMR. Oxidative cleavage of **7** gave the corresponding 1,3-diol (−)-**8**. As far as we are aware, the absolute configuration of (−)-**8** had not been previously assigned. The absolute configuration of (−)-**8** was therefore determined by comparing its circular dichroic (CD) spectrum (Table III) with that of (*R*)-(+)-1-phenylethanol and (*S*)-(−)-**4**. It is clear that (−)-**8** has CD similar to that of (*S*)-(−)-**4** but mirror image to that of (*R*)-(+)-1-phenylethanol. Compound (−)-**8** is therefore assigned the same (*S*) configuration as that of (−)-**4**. Its optical purity was determined by the same methods as outlined for **4**. For the diol **8** obtained from the −50 °C reaction, it had >99% ee. The high optical purity of **8** (and **4** as well) could not be due to an artifact of the purification step in the chromatography of **7** (or **3**) because the two diastereomers could be readily distinguished by NMR and no enrichment was observed on chromatography.

Table III. CD Spectra of Various Alcohols in Ethanol[a]

alcohols	λ_{max} (nm)	molecular ellipticity (θ)
PhCH(OH)CH_2CH_2OH (*S*) (4)	255	+456
	211	−1266
PhCH(OH)$CH_2C(OH)C_5H_{10}$ (*S*) (8)	252	+403
	213	−550
PhCH(OH)CH_2CH(OH)CH_3 (*S,S*) (12)	251	+304
	209	−761
PhCH(OH)CH_2CH(OH)-*n*-C_4H_9 (*S,S*) (17)	251	+520
	209	−1976
PhCH(OH)CH_2CH(OH)-*t*-C_4H_9 (*S,S*) (22)	255	+485
	218	−953
PhCH(OH)CH_3 (*R*)	252	−508
	214	+305

[a] Temperature = 20 °C; solvent = ethanol.

When the carbanion **2** was quenched with propylene oxide (**9**), the products obtained were the two diastereomeric alcohols **10** and **11**, formed in nearly equal quantities.



6 9 14 19

Both **10** and **11** were optically active and could be separated by column chromatography. Oxidative cleavage of **10** and **11** individually by hydrogen peroxide and KF gave (1*S*,3*S*)-(−)- (**12**) and (1*S*,3*R*)-(−)-1-phenyl-1,3-butanediol (**13**), respectively.[3,5] In either case, ^1H NMR and GC analyses of the MTPA esters, in comparison with the corresponding racemic compounds, showed that both the (1*S*,3*S*)-**12** and the (1*S*,3*R*)-**13** were generated in >99% ee. A few comments should be made about the assignment of configurations since optical rotations alone, in comparison with literature values,[5] were insufficient by themselves to confirm the stereochemistry because the literature values were for compounds of lower optical purities. The same reaction of carbanion **2** was carried out with (*S*)-(−)-propylene oxide to give **10** as the sole product, which on oxidative cleavage gave (1*S*,3*S*)-(−)-**12** only. This confirmed the stereochemistry at carbon 3 of **12** as *S*. The stereochemistry at carbon 1 was assigned by converting the diols to the corresponding acetonides. There is an extensive body of literature on the use of ^1H and ^{13}C NMR for the assignment of the relative stereochemistry of syn and anti 1,3-diols via their acetonides.[13] By examination of the NMR data in Table II, it can be concluded that the diol **12** derived from **10** has the syn relative stereochemistry, and thus the 1*S*,3*S* configuration. On the other hand,

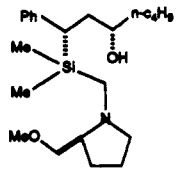
(11) Makaiyama, T.; Tomimori, K.; Oriyama, T. *Chem. Lett.* **1985**, 1359–1362.

(12) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, 95, 512–519. The (*R*)-(+)-MTPA was purchased from Aldrich. The (*S*)-(+)-MTPA-Cl prepared has $[\alpha]^{20}_D$ = +128.6° (*c* 5.10, CCl_4) and % ee = >99. Reported value, $[\alpha]^{24}_D$ = +129.0 ± 0.2° (*c* 5.17, CCl_4).

(13) (a) Evans, D. A.; Rieger, R. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099–7100. (b) Rychnovsky, S. D.; Skalitzky, D. J. *Ibid.* **1990**, *31*, 945–948. (c) Maskens, K.; Mininikin, D. E.; Polgar, N. *J. Chem. Soc. C* **1966**, 2113–2115. (d) Baggett, N.; Buck, K. W.; Foster, A. B.; Randall, M. H.; Webber, M. J. *J. Chem. Soc.* **1965**, 3394–3400.

the diol 13 has the anti stereochemistry and thus the 1S,3R configuration.

Reaction of the carbanion 2 with 1,2-epoxyhexane (14) gave also a mixture of diastereomers 15 and 16 which could be separated by column chromatography. Oxidative



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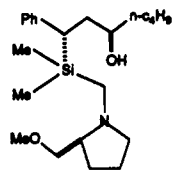

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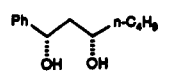

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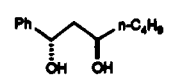

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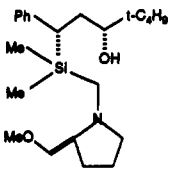

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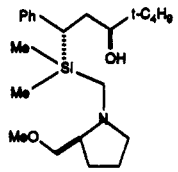

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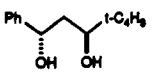

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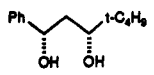

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cleavage of 15 gave the optically active syn diol 17, whereas 16 gave the optically active anti diol 18. Their relative stereochemistries were determined by NMR studies of their acetonides (Table II). The absolute configuration of 17 was then deduced by comparison of its CD curve with that of 12. Compound 17 is therefore assigned the 1S,3S configuration; consequently, compound 18 must have the 1S,3R configuration. The same sequence of reactions was carried out with *tert*-butyloxirane (19) to give first the two diastereomers 20 and 21, which after separation and oxidation gave the syn (1S,3R)-diol 23 and the anti (1S,3S)-diol 22, respectively. In all cases, the optical purities of the diols were determined by the ^{1}H NMR and GC analyses of the MTPA esters of both the racemic and the optically active compounds.

Discussion

It is clear from the present results that highly optically pure 1,3-diols can be prepared from chiral organosilicon compounds employing the strategy outlined in Scheme I. While we have restricted ourselves so far to the synthesis of 1-phenyl-substituted 1,3-diols, carbanions derived from the corresponding allylsilyl precursors[9] would be expected to yield other 1,3-diols. In the case of carbanion 2, using (*S*)-(+)-2-(methoxymethyl)pyrrolidine as the chiral auxiliary, alkylation with aliphatic epoxides have yielded the 1S configuration in the 1,3-diols obtained. This overall stereochemical outcome is the same as that obtained in the alkylation of 2 reported previously.[8] For unsymmetrically substituted epoxides, the alkylation reactions occurred regiospecifically at the less substituted carbon. For epoxides with an existing chiral center, the reaction showed little, if any, diastereoselectivity. The lack of diastereoselectivity did not improve even with a large excess of either the epoxide substrate (e.g., 9) or the carbanion 2 in the reaction. Nevertheless, because the two diastereomers can be separated, the reaction sequence proves to be very effective in generating highly optically pure syn and anti 1,3-diols. The organosilicon methodology is therefore expected to find useful applications in the asymmetric synthesis of various chiral 1,3-diols.

Experimental Section

Melting points were determined on the Gallenkamp melting point apparatus and are uncorrected. Ethylene oxide (84%) was purchased from Andersen Products Inc. Other materials were obtained from commercial suppliers unless mentioned otherwise. Reaction solvents were all dried and distilled. Thin-layer chromatography (TLC) was done on Merck silica gel 60 F_{254}. Column chromatography was done on Merck silica gel 60 (230–240 mesh ASTM). Capillary gas chromatography analysis was performed on a Hewlett-Packard 5890A and 5890 Series II instruments fitted with a (50-m × 0.2-mm) high-performance column (cross-linked methylsilicon, film thickness of 0.33 μm) at the oven temperature range of 150–200 °C. Optical rotations were determined on the JASCO DIP-140 digital polarimeter. Circular dichroism (CD) spectra were recorded on JASCO Model J 500C CD polarimeter. Infrared (IR) spectra were recorded on an Analect FT, AQS-18 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian XL-200 and XL-300 instruments. Low- and high-resolution mass spectra (MS) were obtained with DuPont 21-492B and ZAB 2F HS mass spectrometers, respectively.

Preparation of Amino Benzylsilane 1. Compound 1 was prepared according to the literature procedure.[8]

General Procedure for the Reaction of 2 with Different Epoxides. A typical example for the preparation of 3 is as follows. *sec*-Butyllithium (2 mL, 1.3 M in cyclohexane, 2.6 mmol) was added dropwise to a solution of amino benzylsilane 1 (277 mg, 1 mmol) in anhydrous ether (20 mL) at −78 °C, under argon. The reaction mixture was stirred for 1 h, and 84% ethylene oxide (8 mL, ~1 M in ether, 8 mmol) was added dropwise. The mixture was stirred for 4 h at −78 °C, quenched with saturated NH_4Cl solution at −78 °C, and warmed to room temperature. The mixture was extracted with ether, and the organic layer was washed with brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded the crude mixture which was purified by column chromatography [50% ethyl acetate (EtOAc) in hexanes] to give 160 mg (50% yield) of 3: ^{1}H NMR ($CDCl_3$) δ 7.00–7.30 (m, 5 H), 3.50–3.70 (m, 2 H), 3.36 (s, 3 H), 3.20–3.50 (m, 2 H), 3.00–3.20 (m, 1 H), 2.53 and 1.77 (d, J = 14.3 Hz, 2 H), 2.30–2.45 (m, 3 H), 1.50–2.20 (m, 7 H), 0.12 (s, 3 H), −0.24 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 143.91, 128.17, 127.86, 124.61, 75.87, 67.46, 61.97, 59.09, 57.54, 45.49, 33.90, 32.06, 28.10, 23.12, −3.32, −4.21; IR ($CHCl_3$ cm^{-1}) 3400, 2959, 2881, 1454, 1253, 1131; MS (EI) m/z (rel intensity) 276 (73, $M^+ - CH_2OCH_3$), 128 (39), 117 (25), 84 (100), 75 (60); HRMS(CI) calcd for $C_{18}H_{31}SiNO_2$ $(MH)^+$ 322.2203, found 322.2203; $[\alpha]^{20}_D$ = −58.1° (*c* 0.5, $CHCl_3$).

The other compounds were prepared as follows. A solution of the epoxide (2 mmol) in 10 mL of ether was added dropwise after the generation of carbanion 2 and stirred at −78 °C for 4 h. However, in the case of methylenecyclohexane oxide and *tert*-butyloxirane it was stirred at −50 °C (12 h) and −25 °C (12 h) respectively. In all the cases, the corresponding product and 10–20% of 1 were obtained after separation by column chromatography (50% EtOAc in hexanes).

General Procedure for Oxidation with H_2O_2 and KF. A typical example for the preparation of 4 is as follows. A mixture of 3 (32 mg, 0.1 mmol), KF (18 mg, 0.3 mmol), $KHCO_3$ (30 mg, 0.3 mmol), 30% H_2O_2 (0.1 mL, 0.9 mmol), THF (2 mL), and MeOH (2 mL) was stirred at room temperature for 17 h. The reaction mixture was washed with 10% $NaHSO_3$ and aqueous Na_2CO_3 solutions and extracted with ether. After evaporation of the solvent, the crude mixture was separated by column chromatography (50% EtOAc in hexanes) to give 9.8 mg (65% yield) of 4. ^{1}H NMR ($CDCl_3$) δ 7.20–7.40 (m, 5 H), 4.96 (dd, J = 4.2, 8.0 Hz, 1 H), 3.86 (t, J = 6 Hz, 2 H), 2.50 (s, br, 2 H), 1.80–2.20 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 144.26, 128.51, 127.59, 125.61, 74.43, 61.51, 40.44; IR ($CHCl_3$, cm^{-1}) 3400, 2929, 1422, 1054; $[\alpha]^{20}_D$ = −48.89° (*c* 0.18, $CHCl_3$).[11]

In the cases of the other 1,3-diols, 20% EtOAc in hexanes was used as eluting solvent for column chromatography.

Preparation of Racemic 1-Phenyl-1,3-propanediol (4). To a solution of ethyl benzoylacetate 5 (200 mg, 1 mmol) in 20 mL of anhydrous ether under argon was added dropwise a solution

of $LiAlH_4$ (40 mg, 1 mmol) in 10 mL of ether. After the addition, the reaction mixture was refluxed for 5 h. It was cooled in an ice bath, and 10 mL of MeOH was added dropwise, followed by aqueous $NaHCO_3$ solution. The gelatinous precipitate was filtered, and the filtrate was extracted with ether. The organic layer was dried ($MgSO_4$) and the solvent removed to give 70 mg of the crude mixture. Separation by column chromatography (50% EtOAc in hexanes) afforded 74 mg (49% yield) of racemic **4**.[6b]

Preparation of 7. Compound **7** was prepared in a similar way from methylenecyclohexane oxide, which was prepared according to the literature procedure.[14] After purification by column chromatography (50% EtOAc in hexanes), 156 mg (40% yield) of **7** was obtained. ^1H NMR ($CDCl_3$) δ 7.00–7.30 (m, 5 H), 3.50–3.70 (m, 1 H), 3.36 (s, 3 H), 3.20–3.36 (m, 1 H), 3.00–3.20 (m, 1 H), 2.60 and 1.73 (d, J = 14.3 Hz, 2 H), 2.30–2.50 (m, 1 H), 2.10–2.30 (m, 2 H), 1.70–2.10 (m, 7 H), 1.10–1.70 (m, 10 H), 0.09 (s, 3 H), –0.30 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 145.94, 128.15, 127.85, 124.21, 75.44, 71.62, 67.89, 59.13, 57.28, 45.97, 42.60, 40.39, 35.94, 29.25, 28.38, 25.98, 22.89, 22.66, 22.28, –3.57, –4.52; IR ($CHCl_3$, cm^{-1}) 3400, 2935, 2858, 1450, 1255, 1126; MS (EI) m/z (rel intensity) 344 (2, $M^+ - CH_2OCH_3$), 260 (52), 217 (57), 156 (32), 75 (100); HRMS(CI) calcd for $C_{23}H_{39}SiNO_2$ $(MH)^+$ 390.2828, found 390.2827; $[\alpha]^{20}_D$ = –11.69° (*c* 0.65, $CHCl_3$).

Preparation of (*S*)-(–)-8. Compound **7** was treated with H_2O_2 and KF as described in the previous procedure. The reaction mixture was separated by column chromatography (20% EtOAc in hexanes) to give 15.4 mg (69% yield) of **8** as white solid: mp 107–109 °C; ^1H NMR ($CDCl_3$) δ 7.20–7.50 (m, 5 H), 5.08 (dd, J = 4, 8 Hz, 1 H), 3.70 (s, br, 1 H), 2.70 (s, br, 1 H), 1.80–2.00 (m, 2 H), 1.20–1.80 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 144.92, 128.44, 127.39, 125.63, 72.64, 71.41, 49.03, 40.20, 35.70, 25.72, 22.36, 22.08; IR ($CHCl_3$) cm^{-1} 3400, 2930, 1420, 1045; $[\alpha]^{20}_D$ = –18.0° (*c* 0.10, $CHCl_3$); MS(EI) m/z (rel intensity) 202 (39, $M^+ - H_2O$), 203 (38), 185 (100), 117 (32); HRMS(EI) calcd for $C_{14}H_{18}O$ ($M^+ - H_2O$) 202.1357, found 202.1342.

Preparation of 10 and 11. Compounds **10** and **11** were prepared in a similar way from propylene oxide. Column chromatography (50% EtOAc in hexanes) of the crude mixture gave 119 mg (36% yield) each of **10** and **11**.

10: ^1H NMR ($CDCl_3$) δ 7.00–7.30 (m, 5 H), 3.50–3.70 (m, 1 H), 3.37–3.50 (m, 1 H), 3.36 (s, 3 H), 3.20–3.35 (m, 1 H), 3.00–3.15 (m, 1 H), 2.25 and 1.75 (d, J = 14.3 Hz, 2 H), 2.30–2.50 (m, 1 H), 2.10–2.30 (m, 2 H), 1.50–2.00 (m, 7 H), 1.12 (d, J = 6 Hz, 3 H), 0.10 (s, 3 H), –0.21 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 144.28, 128.22, 128.06, 124.58, 75.87, 67.48, 66.25, 58.96, 57.31, 45.09, 40.24, 32.03, 28.00, 24.34, 22.88, –3.80, –4.54; IR ($CHCl_3$, cm^{-1}) 3400, 2930, 2850, 1450, 1252, 1120; MS(EI) m/z (rel intensity) 290 (26, $M^+ - CH_2OCH_3$), 206 (14), 162 (18), 128 (34), 117 (17), 91 (10), 84 (91), 75 (100); HRMS(CI) calcd for $C_{19}H_{33}SiNO_2$ $(MH)^+$ 336.2358, found 336.2358; $[\alpha]^{20}_D$ = –41.9° (*c* 0.5, $CHCl_3$).

11: ^1H NMR ($CDCl_3$) δ 7.00–7.30 (m, 5 H), 3.70–3.90 (m, 1 H), 3.30–3.50 (m, 1 H), 3.36 (s, 3 H), 3.20–3.35 (m, 1 H), 2.90–3.10 (m, 1 H), 2.50 and 1.80 (d, J = 14.3 Hz, 2 H), 2.30–2.45 (m, 1 H), 2.10–2.30 (m, 2 H), 1.50–2.00 (m, 7 H), 1.15 (d, J = 6 Hz, 3 H), 0.10 (s, 3 H), –0.24 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 144.28, 128.22, 128.06, 124.58, 75.56, 66.35, 66.24, 58.97, 57.31, 45.09, 40.24, 31.86, 28.01, 22.97, 22.88, –2.72, –4.55; IR ($CHCl_3$, cm^{-1}) 3400, 2928, 2876, 1450, 1232, 1131; MS(EI) m/z (rel intensity) 290 (27), 206 (24), 162 (31), 128 (39), 117 (26), 91 (15), 84 (89), 75 (100); HRMS(CI) calcd for $C_{19}H_{33}SiNO_2$ $(MH)^+$ 336.2358, found 336.2358; $[\alpha]^{20}_D$ = –57.5° (*c* 0.7, $CHCl_3$).

Preparation of 10 from (*S*)-(–)-Propylene Oxide. Compound **10** was prepared as described in the previous procedure except that (*S*)-(–)-propylene oxide was used. Column chromatography of the crude mixture gave 201 mg (60% yield) of **10**: $[\alpha]^{20}_D$ = –40.2° (*c* 0.25, $CHCl_3$).

Preparation of (1*S*,3*S*)-(–)-1-Phenyl-1,3-butanediol (12). Oxidation of **10** with H_2O_2 and KF gave 13.3 mg (80% yield) of **12** as a white solid, after separation by column chromatography (20% EtOAc in hexanes): mp 50–51 °C; ^1H NMR ($CDCl_3$)[3] δ 7.20–7.50 (m, 5 H), 4.90 (dd, J = 3.5, 9.4 Hz, 1 H), 4.00–4.30 (m, 1 H), 2.60 (s br, 2 H), 1.60–2.00 (m, 2 H), 1.21 (d, J = 6.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 144.40, 128.53, 127.64, 125.61, 75.42, 68.90, 47.06, 24.14; IR ($CHCl_3$, cm^{-1}) 3400, 2930, 1400, 1063; $[\alpha]^{20}_D$ = –62.7° (*c* 0.15, $CHCl_3$).[5]

Preparation of (1*S*,3*R*)-(–)-1-Phenyl-1,3-butanediol (13). Compound **13** was similarly prepared from **11** to give 12.5 mg (75% yield): ^1H NMR ($CDCl_3$) δ 7.20–7.40 (m, 5 H), 5.06 (dd, J = 4.0, 7.6 Hz, 1 H), 3.90–4.20 (m, 1 H), 2.30 (s br, 2 H), 1.80–2.00 (m, 2 H), 1.23 (d, J = 6.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 144.40, 128.42, 127.32, 125.54, 71.79, 65.40, 46.05, 23.52; IR ($CHCl_3$, cm^{-1}) 3400, 2930, 1420, 1050; $[\alpha]^{20}_D$ = –69.4° (*c* 0.2, $CHCl_3$).[5]

Preparation of 15 and 16. Compounds **15** and **16** were prepared in a similar way from 1,2-epoxyhexane. After purification by column chromatography, the reaction afforded 150.3 mg (40% yield) of **15** and 75 mg (20% yield) of **16**, respectively.

15: ^1H NMR ($CDCl_3$) δ 7.00–7.30 (m, 5 H), 3.35–3.50 (m, 2 H), 3.35 (s, 3 H), 3.20–3.30 (m, 1 H), 3.00–3.20 (m, 1 H), 2.55 and 1.75 (d, J = 14.3 Hz, 2 H), 2.30–2.50 (m, 1 H), 2.00–2.20 (m, 2 H), 1.50–2.00 (m, 7 H), 1.10–1.50 (m, 6 H), 0.85 (t, J = 6 Hz, 3 H), 0.09 (s, 3 H), –0.23 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 144.02, 128.13, 128.05, 127.92, 127.79, 124.51, 75.52, 70.00, 67.57, 58.89, 57.34, 45.24, 38.42, 38.22, 32.06, 28.16, 27.89, 23.02, 22.74, 13.99, –3.53, –4.29; IR ($CHCl_3$, cm^{-1}) 3400, 2930, 2858, 1451, 1232, 1126; MS(EI) m/z (rel intensity) 332 (7, $M^+ - CH_2OCH_3$), 248 (39), 191 (100), 162 (37), 128 (36), 117 (57), 91 (34), 75 (87), 57 (52); HRMS(CI) calcd for $C_{22}H_{39}SiNO_2$ $(MH)^+$ 378.2828, found 378.2829; $[\alpha]^{20}_D$ = –58.4° (*c* 0.75, $CHCl_3$).

16: ^1H NMR ($CDCl_3$) δ 7.00–7.30 (m, 5 H), 3.55–3.70 (m, 1 H), 3.40–3.55 (m, 1 H), 3.36 (s, 3 H), 3.20–3.30 (m, 1 H), 2.95–3.10 (m, 1 H), 2.50 and 1.80 (d, J = 14.3 Hz, 2 H), 2.30–2.60 (m, 1 H), 2.10–2.35 (m, 2 H), 1.50–2.00 (m, 7 H), 1.00–1.50 (m, 6 H), 0.85 (t, J = 6 Hz, 3 H), 0.12 (s, 3 H), –0.29 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 144.70, 128.30, 128.23, 128.08, 127.94, 124.67, 75.42, 70.52, 67.14, 59.03, 57.49, 45.73, 39.03, 36.36, 31.20, 27.87, 27.75, 22.87, 22.54, 13.83, –3.30, –4.55; IR ($CHCl_3$) cm^{-1} 3400, 2930, 2860, 1450, 1252, 1100; MS(EI) m/z (rel intensity) 332 (18, $M^+ - CH_2OCH_3$), 248 (14), 191 (14), 128 (32), 117 (13), 91 (11), 84 (81), 75 (100), 57 (8); HRMS(CI) calcd for $C_{22}H_{39}SiNO_2$ $(MH)^+$ 378.2828, found 378.2829; $[\alpha]^{20}_D$ = –67.3° (*c* 1.0, $CHCl_3$).

Preparation of (1*S*,3*S*)-(–)-1-Phenyl-1,3-heptanediol (17). Compound **17** was prepared from **15** in 60% yield (12.5 mg): mp 65–66 °C; ^1H NMR ($CDCl_3$) δ 7.20–7.45 (m, 5 H), 4.95 (dd, J = 6, 8 Hz, 1 H), 3.85–4.05 (m, 1 H), 2.90 (s br, 1 H), 3.30 (s br, 1 H), 1.70–2.00 (m, 2 H), 1.20–1.70 (m, 6 H), 0.85 (t, 3 H); ^{13}C NMR ($CDCl_3$) δ 144.51, 128.46, 128.40, 127.55, 125.64, 75.44, 72.85, 45.30, 37.79, 27.44, 22.65, 14.02; IR ($CHCl_3$, cm^{-1}) 3400, 2930, 1420, 1045; $[\alpha]^{20}_D$ = –36.5° (*c* 0.15, $CHCl_3$).

Preparation of (1*S*,3*R*)-(–)-1-Phenyl-1,3-heptanediol (18). Compound **18** was prepared from **16** in 53% yield (10.6 mg): ^1H NMR ($CDCl_3$) δ 7.20–7.40 (m, 5 H), 5.05 (dd, J = 4.0, 8.0 Hz, 1 H), 3.70–3.90 (m, 1 H), 3.00 (s br, 2 H), 1.70–2.00 (m, 2 H), 1.10–1.70 (m, 6 H), 0.85 (t, 3 H); ^{13}C NMR ($CDCl_3$) δ 144.54, 128.42, 128.30, 127.29, 127.23, 125.51, 71.80, 64.38, 44.51, 37.15, 27.81, 22.67, 14.03; IR ($CHCl_3$, cm^{-1}) 3400, 2930, 1423, 1045; $[\alpha]^{20}_D$ = –43.4° (*c* 0.15, $CHCl_3$).

Preparation of 20 and 21. Compounds **20** and **21** were prepared as described above from *tert*-butyloxirane, which was prepared according to the literature procedure.[15] Column chromatography (50% EtOAc in hexanes) gave 94 mg (25% yield) each of **20** and **21**.

20: ^1H NMR ($CDCl_3$) δ 7.00–7.30 (m, 5 H), 3.40–3.60 (m, 1 H), 3.36 (s, 3 H), 3.20–3.40 (m, 2 H), 2.95–3.15 (m, 1 H), 2.55 and 1.80 (d, J = 14.3 Hz, 2 H), 2.30–2.50 (m, 1 H), 1.95–2.20 (m, 2 H), 1.50–1.95 (m, 7 H), 0.84 (s, 9 H), 0.09 (s, 3 H), –0.24 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 144.23, 128.07, 124.44, 77.84, 75.88, 67.79, 59.11, 57.35, 45.77, 34.89, 32.47, 32.28, 28.35, 25.77, 23.00, –3.46, –4.27; IR ($CHCl_3$, cm^{-1}) 3400, 2960, 1455, 1240, 1121; MS m/z (rel intensity) 377 M^+ (100), 186 (41), 129 (24); HRMS(EI) calcd for $C_{20}H_{34}SiNO$ ($M^+ - CH_2OCH_3$) 332.2410, found 332.2372; $[\alpha]^{20}_D$ = –28.7° (*c* 1.0, $CHCl_3$).

21: ^1H NMR ($CDCl_3$) δ 7.00–7.30 (m, 5 H), 3.45–3.60 (m, 1 H), 3.36 (s, 3 H), 3.25–3.40 (m, 2 H), 3.00–3.20 (m, 1 H), 2.50 and 1.85 (d, J = 14.3 Hz, 2 H), 2.20–2.40 (m, 1 H), 1.95–2.20 (m, 2 H), 1.50–1.95 (m, 7 H), 0.90 (s, 9 H), 0.15 (s, 3 H), –0.39 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 145.51, 128.28, 127.99, 124.68, 78.22, 75.28, 67.19,

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59.13, 57.80, 47.01, 35.16, 34.29, 32.47, 28.07, 26.05, 22.99, -2.52, -4.16; IR ($CHCl_3$, cm^{-1}) 3400, 2963, 1456, 1240, 1130; MS m/z (rel intensity) 377 (M^+ (100), 186 (60), 128 (26); HRMS(EI) calcd for $C_{20}H_{34}SiNO$ ($M^+ - CH_2OCH_3$) 332.2410, found 332.2458; $[\alpha]^{20}_D$ = -50.7° (c 0.58, $CHCl_3$).

Preparation of (1*S*,3*S*)-(-)-1-Phenyl-4,4-dimethyl-1,3-pentanediol (22). Compound **22** was prepared from **21** in 75% yield (15.6 mg): mp 96–98 °C; ^1H NMR ($CDCl_3$) δ 7.20–7.40 (m, 5 H), 5.07 (dd, J = 3.8, 6.6 Hz, 1 H), 3.50 (dd, J = 2.6, 10.2 Hz, 1 H), 2.10 (s br, 2 H), 1.70–2.00 (m, 2 H), 0.86 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 144.78, 128.42, 127.19, 125.72, 76.24, 71.92, 39.35, 34.66, 25.51; IR ($CHCl_3$, cm^{-1}) 3400, 2963, 1422, 1060; $[\alpha]^{20}_D$ = -78.0° (c 0.6, $CHCl_3$).

Preparation of (1*S*,3*R*)-(-)-1-Phenyl-4,4-dimethyl-1,3-pentanediol (23). Compound **23** was prepared from **20** in 65% yield (13.5 mg): mp 105–108 °C; ^1H NMR ($CDCl_3$) δ 7.20–7.40 (m, 5 H), 4.90 (dd, J = 2.2, 6.4 Hz, 1 H), 3.60 (dd, J = 1.4, 6.8 Hz, 1 H), 2.90 (s br, 2 H), 1.70–1.90 (m, 2 H), 0.90 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 144.73, 128.50, 127.59, 125.74, 80.91, 75.83, 40.02, 34.95, 25.49; IR ($CDCl_3$, cm^{-1}) 3400, 2964, 1421, 1070; $[\alpha]^{20}_D$ = -28.0° (c 0.4, $CHCl_3$).

General Method of Preparation of Acetonides of 1,3-Diols. A mixture of 1,3-diol (10 mg), 2,2-dimethoxypropane (1 mL), a catalytic amount of *p*-toluenesulfonic acid, and acetone (3 mL) was stirred at room temperature overnight. The reaction mixture was diluted with 10 mL of ether and eluted through the column containing basic alumina. Quantitative yield of acetonide was obtained after evaporation of the solvent.

Acetonide of (1*S*,3*S*)-1-phenyl-1,3-butanediol (12): ^1H NMR ($CDCl_3$) δ 7.20–7.40 (m, 5 H), 4.90 (dd, J = 2.6, 10.6 Hz, 1 H), 4.00–4.30 (m, 1 H), 1.73 (m, 1 H), 1.57 (s, 3 H), 1.51 (s, 3 H), 1.40 (m, 1 H), 1.21 (d, J = 6.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 142.40, 128.57, 127.69, 126.06, 99.04, 71.51, 65.27, 40.87, 30.20, 21.97, 19.64.

Acetonide of (1*S*,3*R*)-1-phenyl-1,3-butanediol (13): ^1H NMR ($CDCl_3$) δ 7.20–7.40 (m, 5 H), 4.89 (dd, J = 6.3, 9.5 Hz, 1 H), 4.13 (m, 1 H), 1.80–2.10 (m, 2 H), 1.45 (s, 3 H), 1.46 (s, 3 H), 1.26 (d, J = 6.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 142.75, 128.43, 127.34, 126.01, 100.66, 68.50, 63.02, 41.44, 25.25, 24.99, 21.76.

Acetonide of 17: ^1H NMR ($CDCl_3$) δ 7.20–7.40 (m, 5 H), 4.85 (dd, J = 1.8, 8.0 Hz, 1 H), 3.95–4.05 (m, 1 H), 1.60–1.80 (m, 2 H), 1.56 (s, 3 H), 1.50 (s, 3 H), 1.20–1.48 (m, 6 H), 0.85 (t, J = 6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 142.56, 128.39, 127.52, 125.93, 98.91, 71.66, 69.19, 39.39, 36.06, 30.32, 27.11, 22.65, 19.79, 14.05.

Acetonide of 18: ^1H NMR ($CDCl_3$) δ 7.20–7.40 (m, 5 H), 4.83 (dd, J = 6.4, 9.6 Hz, 1 H), 3.80–4.00 (m, 1 H), 1.80–2.10 (m, 2 H), 1.65–1.20 (m, 6 H), 1.45 (s, 3 H), 1.44 (s, 3 H), 0.85 (t, J = 6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 142.74, 128.40, 127.29, 125.99, 100.68, 68.61, 66.90, 40.31, 35.70, 27.54, 25.11, 24.70, 22.64, 14.06.

Acetonide of 22: ^1H NMR ($CDCl_3$) δ 7.20–7.40 (m, 5 H), 4.76 (dd, J = 3, 10 Hz, 1 H), 3.65 (dd, J = 6, 8 Hz, 1 H), 1.70–2.10 (m, 2 H), 1.41 (s, 6 H), 0.89 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 143.01, 128.41, 127.27, 126.06, 100.70, 73.73, 69.18, 35.69, 33.51, 25.25, 25.04, 24.03.

Acetonide of 23: ^1H NMR ($CDCl_3$) δ 7.20–7.40 (m, 5 H), 4.85 (dd, J = 2.6, 8.4 Hz, 1 H), 3.58 (dd, J = 2.4, 9.0 Hz, 1 H), 1.40–1.70 (m, 2 H), 1.52 (s, 3 H), 1.48 (s, 3 H), 0.88 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 143.02, 128.39, 127.45, 125.94, 98.81, 76.45, 71.94, 34.00, 33.68, 30.29, 25.50, 19.70.

Preparation of 1-Phenylheptane-1,3-dione. 1-Phenylheptane-1,3-dione was prepared according to the literature procedure.[16]

General Procedure for Reduction of β-Diketones to 1,3-Diols. A solution of $NaBH_4$ (2.0 mmol) in 15 mL of absolute ethanol was added dropwise to a stirred solution of the β-diketone (0.5 mmol) in 25 mL of ethanol, cooled in an ice bath. After the addition, the reaction mixture was refluxed for 2 h. It was cooled, and 10 mL of H_2O was added and extracted with ether. After drying ($MgSO_4$) and removing the solvent, the crude mixture was purified by column chromatography (20% ethyl acetate in hexanes) to give the corresponding 1,3-diol.

Preparation of Racemic Diol 8. To a solution of cyclohexanone (100 mg, 1 mmol) in 5 mL of dried CH_2Cl_2 under argon at 0 °C was added 1 mL of $TiCl_4$ (1 M in CH_2Cl_2), and the reaction mixture was stirred for 15 min. Then, a solution of 1-phenyl-1-[(trimethylsilyl)oxy]ethylene (192 mg, 1 mmol) in 5 mL of CH_2Cl_2 was added dropwise and stirred for 15 min. The reaction mixture was stirred at room temperature for another 3 h, and it was poured into 10 mL of $NaHCO_3$ solution and extracted with ether. The organic layer was dried ($MgSO_4$) and evaporated. Column chromatography (20% ethyl acetate in hexanes) afforded 129 mg (60% yield) of β-hydroxy ketone: ^1H NMR ($CDCl_3$) δ 7.80–8.00 (m, 2 H), 7.40–7.60 (m, 3 H), 3.95 (s, 1 H), 3.09 (s, 2 H), 1.10–1.80 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 201.88, 137.47, 133.47, 128.62, 128.05, 70.92, 47.65, 37.75, 25.73, 21.92; IR ($CHCl_3$, cm^{-1}) 3490, 2938, 2859, 1700, 1450, 1060.

Reduction of β-hydroxy ketone was carried out as follows. A solution of $NaBH_4$ (40 mg, 1 mmol) in 10 mL of absolute ethanol was added dropwise to a solution of β-hydroxy ketone (80 mg, 0.4 mmol), cooled in an ice bath. After the addition, the reaction mixture was refluxed for 3 h. 15 mL of water was added after cooling, and the mixture was extracted with ether. The organic layer was dried ($MgSO_4$) and the solvent evaporated. Purification by column chromatography (20% ethyl acetate in hexanes) gave 42 mg (50% yield) of racemic alcohol 8.

Preparation of Racemic Diols 22 and 23. To a solution of trimethylacetyl chloride (121 mg, 1 mmol) in 5 mL of dried CH_2Cl_2 under argon at -78 °C was added 1 mL of $TiCl_4$ (1 M in CH_2Cl_2), and the solution was stirred for 15 min. Then a solution of 1-phenyl-1-[(trimethylsilyl)oxy]ethylene (192 mg, 1 mmol) in 5 mL of CH_2Cl_2 was added dropwise and stirred for 3 h at -78 °C. It was warmed to room temperature, poured into 10 mL of $NaHCO_3$ solution, and extracted with ether. The organic layer was dried ($MgSO_4$) and the solvent removed. Column chromatography (1% ethyl acetate in hexanes) gave 62 mg (30% yield) of β-diketone: ^1H NMR ($CDCl_3$) enol form δ 7.80–8.00 (m, 2 H), 7.40–7.60 (m, 3 H), 6.40 (s, 1 H), 1.30 (s, 9 H); IR ($CHCl_3$, cm^{-1}) 2967, 1602, 1460, 1216.

Reduction with $NaBH_4$ was carried out as mentioned in the previous procedure. After purification by column chromatography (15% ethyl acetate in hexanes), a 25% yield of racemic **22** and a 30% yield of racemic **23** were obtained, respectively.

General Procedure for Preparation of MTPA Esters of 1,3-Diols. A mixture of 8 mg of 1,3-diol, 45 mg of (*S*)-(+)-MTPA-Cl,[12] 26 mg of DMAP, and 3 mL of CH_2Cl_2 was stirred at 30 °C overnight. Then H_2O (1 mL) and ether (2 mL) were added and stirred for 15 min. The mixture was diluted with ether, washed with 1 N HCl (3 mL), 1 N NaOH (3 mL), and brine (3 mL). After drying ($MgSO_4$) and removing of solvent a quantitative yield of the di-MTPA ester of the corresponding 1,3-diol was obtained.

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Supplementary Material Available: Proton NMR spectra for all new compounds (40 pages). This material is contained in many 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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