(vinyl Me), 25.9 (3 Me of t-Bu), 43.1 (CH_2 of ring), 59.4 (OMe), 63.0 (C-6), 76.0 (C-1 and C-5), 81.5 (C-4), 115.9 (vinyl CH_2), 142.5 (quaternary vinyl C), 206.6 (C=O); MS *m/e* 314, 257, 225, 197, 173, 161, 132, 117, 98, 89 (base); exact mass for $C_{16}H_{30}O_4Si$ calcd 314.1913, found 314.1908.

[2*R*-(2α,3β,6α)]-6-Butyl-2-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]tetrahydro-3-methoxy-4*H*-pyran-4-one (3a). This compound was prepared basically as described below for compound **3b** in 79% yield as a pale yellow liquid which was isolated as a 6.9:1 mixture of α:β isomers. Physical constants for the β isomer (**2a**) are reported separately[9] (^{13}C NMR data are listed above), while those for the α isomer (**3a**) are as follows: IR ($CHCl_3$) 1722 (s), 1460 (m), 1252 (m), 1016 (s), 835 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.08, 0.09 (both s, 3 H each, $SiMe_2$), 0.89 (t, 3 H, J = 10.1 Hz, Me of n-Bu), 0.91 (s, 9 H, *t*-Bu), 1.22–1.66 (m, 6 H, $(CH_2)_3$), 2.34 (dd, 1 H, J_{gem} = 13.5 Hz, $J_{1,2\beta}$ = 2.3 Hz, H-2β), 2.44 (ddd, 1 H, $J_{1,2\alpha}$ = 11.4 Hz, $J_{2\alpha,4}$ = 1.2 Hz, H-2α), 3.39 (ddd, 1 H, $J_{4,5}$ = 9.6 Hz, $J_{5,6a}$ = 3.5 Hz, $J_{5,6b}$ = 1.8 Hz, H-5), 3.50 (s, 3 H, OMe), 3.52–3.58 (m, 1 H, H-1), 3.83–3.90 (m, 3 H, H-4, H-6a, H-6b); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ −5.1 and −5.3 ($Si(Me)_2$), 13.9 (Me of *n*-Bu), 18.3 (quaternary C of *t*-Bu), 22.4 (C-3′ CH_2 of *n*-Bu), 25.8 (3 Me of t-Bu), 27.4 (C-2′, CH_2 of *n*-Bu), 35.6 (C-1′, CH_2 of *n*-Bu), 48.0 (CH_2 of ring), 59.6 (OMe), 62.7 (C-6), 77.6 (C-5), 81.5 (C-1), 81.8 (C-4), 207.1 (C=O); MS *m/e* 307, 273, 241, 185, 161, 131 (base), 117, 89; exact mass for $C_{17}H_{34}O_4Si$ calcd 330.2226, found 330.2214.

[2*R*-(2α,3β,6α)]-2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]tetrahydro-3-methoxy-6-(1-methylethenyl)-4*H*-pyran-4-one (3b). This procedure was adapted from one by House, Latham, and Slater[14] with modifications suggested by the work of Nakamura and Kuwajima et al.[13] Magnesium turnings (956 mg, 39.3 mmol) were broken into small pieces, placed in a dry 500-mL flask, rinsed three times with THF, and covered with THF (12 mL). A small iodine crystal was added, and the flask was flushed with N_2. In a test tube were placed Mg turnings (approximately 100 mg), a few drops of 2-bromopropene, and THF (1 mL). The test tube reaction was initiated by gently breaking some of the turnings with a stirring rod, and then 5–10 drops of the solution were added via syringe to the reaction flask. The mixture was stirred under N_2 without external heating or cooling as a mixture of 2-bromopropene (6.59 g, 0.0545 mol) and THF (3.5 mL) was added over 1 h. The mixture was then stirred at rt until the Mg had completely reacted (approximately 1 h). At this time THF (200 mL) and CuI (369 mg, 1.938 mmol) were quickly added, and the black reaction mixture was cooled to −78 °C with stirring under N_2. A solution of enone **1**[9] (2.529 g, 0.00930 mol), *N,N′*-dimethyl-*N,N′*-propyleneurea[22] (DMPU; 2.5 mL, 2.65 g, 0.0207 mol), and trimethylsilyl chloride (7.08 mL, 6.06 g, 0.0558 mol) in THF (10 mL) was then slowly added. The mixture was stirred at −78 °C under N_2 for 4.5 h, at which time NaOAc solution (10 mL) was added. The flask was removed from the cooling bath, allowed to warm to rt with stirring, and the brown supernatant was decanted. The precipitate was rinsed with ether, combined with the original supernatant, diluted with 1 L of ether, washed with water (6 × 100 mL) and $NaHCO_3$ solution (100 mL), and dried. Removal of solvent in vacuo left the crude product which was purified by flash chromatography[21] (silica gel, 3:1 petroleum ether/ether) to provide the adduct (1.831 g, 63%) as a pale yellow liquid, which was isolated as a 2.9:1 mixture of α:β isomers. Physical constants for the β isomer (**2b**) are reported separately above, while those for the α isomer (**3b**) are as follows: IR ($CHCl_3$) 3070 (w), 1730 (s), 1650 (w), 1460 (m), 1302 (m), 1192 (m), 1125 (s), 836 (s), 777 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.08, 0.09 (both s, 3 H each, $SiMe_2$), 0.92 (s, 9 H, *t*-Bu), 1.76 (dd, 3 H, $J_{Me,vinyl\ H}$ = 1.4 Hz, $J_{Me,vinyl\ H}$ = 0.9 Hz, Me of isopropenyl), 2.52 (dd, 1 H, J_{gem} = 13.5 Hz, $J_{1,2\beta}$ = 2.2 Hz, H-2β), 2.53 (dd, 1 H, $J_{1,2\alpha}$ = 11.9 Hz, $J_{2\alpha,4}$ = 1.1 Hz, H-2α), 3.47 (ddd, 1 H, $J_{4,5}$ = 9.6 Hz, $J_{5,6a}$ = 3.2 Hz, $J_{5,6b}$ = 1.6 Hz, H-5), 3.52 (s, 3 H, OMe), 3.88 (dd, 1 H, J_{gem} = 11.4 Hz, H-6a), 3.91 (dd, 1 H, H-6b), 3.96 (d, 1 H, H-4), 4.01 (dddd, 1 H, $J_{1,vinyl\ H}$ = 0.9 Hz, $J_{1,vinyl\ H}$ = 0.4 Hz, H-1), 4.88 (ddq, 1 H, J_{gem} = 1.4 Hz, one vinyl H), 5.01 (ddq, one vinyl H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ −5.2 and −5.4 ($Si(Me)_2$), 18.1 (vinyl Me), 18.3 (quaternary C of *t*-Bu), 25.8 (3 Me of *t*-Bu), 46.7 (CH_2 of ring), 59.7 (OMe), 62.4 (C-6), 80.4 (C-5), 81.4 (C-4), 81.5 (C-1), 112.0 (vinyl CH_2), 143.3 (quaternary vinyl C), 206.8 (C=O); MS *m/e* (no molecular ion) 257, 225, 197, 161 (base), 117, 95, 89; exact mass for $C_{12}H_{21}O_4Si$ (M^+ − *t*-Bu) calcd 257.1209, found 257.1202.

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Registry No. 1, 84010-45-7; **2a**, 84010-40-2; **2b**, 139015-69-3; **3a**, 139015-68-2; **3b**, 139015-70-6; **13**, 139015-71-7; **14**, 139163-30-7; 2-bromopropene, 557-93-7.

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Synthesis of Enantiomerically Pure [(Methylenecyclopropyl)acetyl]-CoA: The Causative Agent of Jamaican Vomiting Sickness

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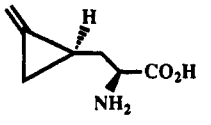
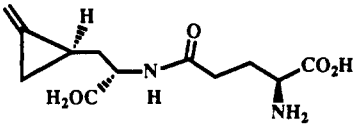
Hypoglycin A (**1**), together with its γ-glutamyl conjugate (hypoglycin B, **2**), was first isolated by Hassal and Reyle from the arillus and seeds of unripe ackee (*Blighia sapida*) in 1955.[1] It is an L-amino acid consisting of only seven carbons, albeit with an unusual methylenecyclopropyl moiety. While ripe ackee fruit serves as a dietary staple in Jamaica, ingestion of hypoglycin from unripe fruit is responsible for the Jamaican vomiting sickness.[2] The



HYPOGLYCIN A (*1*)



HYPOGLYCIN B (*2*)

actual causative agent has been identified as (1*R*)-[(methylenecyclopropyl)acetyl]-CoA (MCPA-CoA, **3**) which is derived in vivo from hypoglycin in three enzymatic steps.[3]

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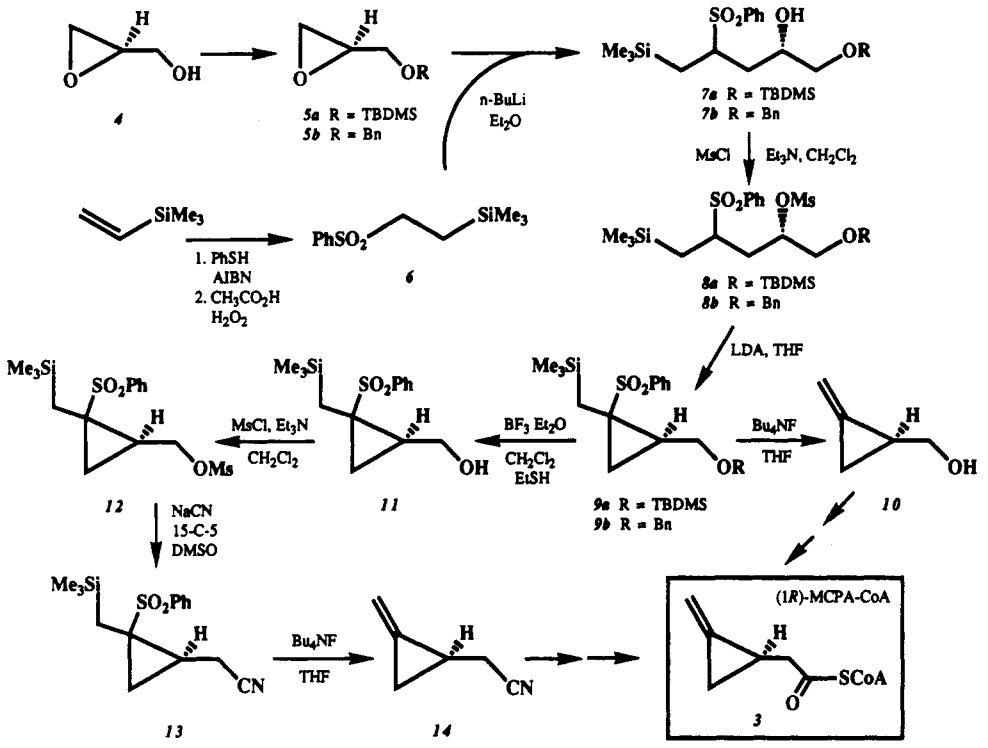
0022-3263/92/1957-2471$03.00/0

Scheme I



The site at which hypoglycin toxicity occurs has been established to be the flavin containing short- and medium-chain acyl-CoA dehydrogenases.[4] Since acyl-CoA dehydrogenases catalyze the first step of β-oxidation, converting a fatty acyl thioester substrate to the corresponding α,β-enolyl-CoA product,[5] inhibition of these enzymes results in mass excretion of medium-chain dicarboxylic acids, ethyl malonate, glutarate, and acylglycines. Thus, Jamaican vomiting sickness is in fact an acquired organic acidemia.[6] The chemical course of this inhibition has been proposed to be initiated by an α-proton abstraction followed by a ring fragmentation, producing a conjugated δ-anion that covalently binds to the flavin coenzyme, thereby irreversibly inactivating the enzyme.[4] Recently, we have found that this inactivation is nonstereospecific, since the partition ratio of the inactivation of GAD caused by racemic MCPA-CoA is identical to that obtained from incubation with naturally derived optically active MCPA-CoA.[7] Because the rearrangement of α-cyclopropyl radicals to ring-opened alkyl radicals is extremely facile,[8] such a lack of stereospecificity for the bond rupture at C_β of MCPA-CoA suggests that the ring-opening step leading to inactivation is likely a radical-initiated process that is too rapid to be confined by the chiral discrimination imposed by the enzyme.[7]

There is no doubt that the methylenecyclopropyl group plays a pivotal role in the actions of hypoglycin. It is also obvious that this unusual structural entity presents a synthetic challenge to prepare MCPA-CoA and its derivatives in enantiomerically pure forms. Although the (1*R*)- and (1*S*)-MCPA-CoA have recently been synthesized by us[7b] and Baldwin's group,[9] both procedures involved chromatographic separation of a diastereomeric mixture of MCPA derivatives that made these preparations ungainly and perplexing. In order to alleviate the painful resolution step, it is necessary to develop an asymmetric synthesis to make the desired enantiomer directly. The ready availability of these enantiomers would certainly facilitate the research using this class of molecules as probes to explore the mechanism of acyl-CoA dehydrogenase, or as inhibitors to control fatty acid metabolism. We report here a facile synthesis of MCPA in enantiomerically pure form which requires no chemical resolution.

As illustrated in Scheme I, the chiral precursor, (*R*)-(+)-glycidol (**4**), was first derivatized with *tert*-butyldimethylsilyl chloride to yield the protected oxirane **5a**. Meanwhile, the latent exocylic methylene entity, 1-(phenylsulfonyl)-2-(trimethylsilyl)ethane (**6**) was prepared by

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coupling vinyltrimethylsilane and thiophenol in the presence of azobisisobutylnitrile followed by oxidation with hydrogen peroxide.[10] Compound **6**, when treated with *n*-butyllithium at −78 °C, was converted to 1-(phenylsulfonyl)-1-lithio-2-(trimethylsilyl)ethane which upon reaction with oxirane **5a** afforded **7a** in 88% yield.[11] As expected, the nucleophilic ring opening took place at the least hindered side of oxirane **5a** and the nascent product was a mixture of two diastereomers. Although separation of the two diastereomers could be achieved by repeated chromatography on silica gel, such a tedious endeavor was unnecessary since later manipulation rendered the racemic center (C-4) to an sp^2 carbon that would no longer be asymmetric. Thus, resolution of this mixture was attempted only on a small scale to collect samples for analytical purposes with the bulk of the material derivatized directly in the next step by methanesulfonyl chloride and triethylamine to give **8a**. Conversion of **8a** to **9a** was achieved with lithium diisopropylamide at −78 °C, effecting the deprotonation and subsequent cyclization with the expulsion of lithium methanesulfonate.[11] Elimination of (phenylsulfonyl)trimethylsilane to expose the latent exocyclic methylene moiety and removal of the *tert*-butyldimethylsilyl protecting group were accomplished in a single step by treatment of **9a** with a solution of tetra-*n*-butylammonium fluoride in THF.[12] The enantiomeric purity of the product, (1*S*)-(methylenecyclopropane)-methanol (**10**), was assessed to be greater than 94% by NMR analysis of its Mosher ester whose methoxyl signal showed a larger lanthanide-induced shift than that of the *R* isomer.[7,13] Clearly the key cyclopropanation step is highly stereospecific and proceeds with inversion of configuration. As previously described,[7] compound **10** could then be converted by a four-step sequence to MCPA which, upon coupling with coenzyme A, led to the formation of (1*R*)-MCPA-CoA (**3**).[14]

However, the simplicity of such a one-step conversion of **9a** to **10** was derogated by the disappointing yield (35%), which made this preparation less appealing. An alternate approach using benzyl group as the protecting group throughout the synthesis was then developed. The early steps of this route, as depicted in Scheme I, are identical with those employed in the preparation of **9a**, albeit with higher yields for almost all of the reactions. The benzyl protecting group of the key intermediate **9b** was then removed by boron trifluoride etherate and thioethanol. Chain elongation converting **11** to **14** was accomplished in two steps with an overall yield of 81%. Elimination of (phenylsulfonyl)trimethylsilane leading to the formation of the exocyclic methylene moiety was readily achieved by the treatment of **13** with a solution of tetra-*n*-butylammonium fluoride in THF. Since compound **14** had previously been made and converted to **3**,[7] the successful preparation of this intermediate concluded the chemical synthesis of enantiomerically pure MACP-CoA.

In summary, as demonstrated in the preparation of **3**, an efficient pathway has been developed for the synthesis of this important class of inhibitors for acyl-CoA dehydrogenase. Since the overall yield of this synthesis (from **5b** to **14**) is more than 40% and the stereospecificity of the cyclization step is greater than 97%, the procedures described herein should be of general use for the preparation of methylenecyclopropane-containing molecules in enantiomerically pure form.[15]

Experimental Section

Melting points are uncorrected. The NMR spectra were recorded on a 300-MHz spectrometer, except for compound **9a** which was measured with a 500-MHz instrument. The NMR assignments labeled with an asterisk (*) may be interchangable. Flash chromatography was performed in columns of various diameters with J. T. Baker (230–400 mesh) silica gel by elution with the solvents reported. Analytical thin-layer chromatography (TLC) was carried out on Merck silica gel 60 G-254 plates (25 mm). TLC spots were visualized either with UV light or by dipping the plates into the staining solutions of vanillin/ethanol/sulfuric acid (1:98:1) or phosphomolybdic acid (7% ethanolic solution) and then heating them. The drying agent used in the routine workup was anhydrous magnesium sulfate. Solvents, unless otherwise specified, were reagent grade and distilled once prior to use.

(*S*)-Glycidyl *tert*-Butyldimethylsilyl Ether (5a). To a solution of (*R*)-(+)-glycidol (**4**; 2 g, 27.0 mmol, from Aldrich) in methylene chloride (50 mL) was added 4-(dimethylamino)pyridine (DMAP, 3.3 g, 27.0 mmol). After stirring for 10 min, this mixture was treated with *tert*-butyldimethylsilyl chloride (4.17 g, 27.7 mmol), and the resulting solution was allowed to react overnight. The reaction was quenched with water, and the aqueous phase was extracted with methylene chloride. The combined organic extracts were washed with 1 N HCl, saturated $NaHCO_3$, and brine in sequence and then dried and filtered. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography (2% ethyl acetate in hexane) to give 4.51 g of product in 89% yield: ^1H NMR ($CDCl_3$) δ 3.83 (1 H, dd, J = 11.9, 3.2, CHOSi), 3.64 (1 H, dd, J = 11.9, 4.8, CHOSi), 3.06 (1 H, m, CHO), 2.75 (1 H, dd, J = 5.1, 4.1, one of the ring-CH_2O), 2.62 (1 H, dd, J = 5.1, 2.7, one of the ring-CH_2O), 0.89 (9 H, s, C-Me's), 0.06 and 0.07 (3 H each, s, Si-Me's); ^{13}C NMR ($CDCl_3$) δ 63.7 (CH_2OSi), 52.4 (ring-CHO), 44.4 (ring-CH_2O), 25.9 (C-Me), 18.4 (C-Me's), −5.3 and −5.4 (Si-Me's).

(*S*)-Glycidyl Benzyl Ether (5b). To the solution of (*R*)-(+)-glycidol (**4**; 1 g, 13.5 mmol) in dry THF (50 mL) was added sodium hydride (356 mg, 14.8 mmol) at 0 °C. After the resulting solution was stirred for 10 min, the benzyl bromide (1.6 mL, 13.5 mmol) in 10 mL of THF was added dropwise over 10 min and the solution was left stirring overnight. The precipitate was filtered, and the filtrate was concentrated in vacuo. The crude product was purified by flash chromatography (5% ethyl acetate in hexane) to give **5b** in 84% yield: ^1H NMR ($CDCl_3$) δ 7.36–7.28 (5 H, m, Ar H's), 4.61, 4.55 (1 H each, d, J = 12.0, CH_2Ar), 3.76 (1 H, dd, J = 11.4, 2.9, one of side chain-OCH_2), 3.43 (1 H, dd, J = 11.4, 5.8, one of side chain-OCH_2), 3.18 (1 H, m, ring-OCH), 2.78 (1 H, dd, J = 4.6, 4.2, one of ring-OCH_2), 2.60 (1 H, dd, J = 4.6, 2.5, one of ring-OCH_2); ^{13}C NMR ($CDCl_3$) δ 138.0, 128.5, 127.8 (Ar C's), 73.3* (CH_2Ar), 70.9* (side chain-OCH_2), 50.9 (ring-OCH), 44.3 (ring-CH_2O); high-resolution FAB-MS calcd for $C_{10}H_{13}O_2$ $(M + 1)^+$ 165.0916, found 165.0915.

1-(Phenylsulfonyl)-2-(trimethylsilyl)ethane (6). A solution of trimethylvinylsilane (34.6 g, 0.35 mol), thiophenol (50 g, 0.45 mol), and azobisisobutyronitrile (50 mg, 0.3 mmol) was heated under nitrogen to 90 °C to initiate reaction. After the exothermic reaction subsided (ca. 1 h), the mixture was cooled and diluted with ethyl ether. The reaction solution was extracted with 1 N

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(14) Although *syn* elimination of a *o*-nitroselenoxyl group α to a ring structure is a well-known method for generating an exocyclic olefin functionality (Greico, P.; Nishizawa, M. *J. Org. Chem.* **1977**, *42*, 1717; Clive, D. L. J. *Tetrahedron* **1978**, *34*, 1049), attempts to make methylenecyclopropane derivatives by this approach were futile.

(15) It is worth mentioning that attempts to substitute the oxirane **5a**/**5b** with the corresponding vicinal diol cyclic sulfate derivative (Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538. Kim, M.; Sharpless, K. B. *Tetrahedron Lett.* **1989**, *30*, 655), which was prepared from (*R*)-(+)-malic acid according to a procedure of Collum et al. (Collum, D. B.; McDonald, J. H., III; Still, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2118) and Saito et al. (Saito, S.; Hasegawa, T.; Inaba, M.; Nishida, R.; Fugii, T.; Nomizu, S.; Moriwake, T. *Chem. Lett.* **1984**, 1389), failed. However, coupling of **6** with the cyclic sulfate of 1,2-butanediol proceeded swiftly giving the cyclic product, 1-(phenylsulfonyl)-2-ethyl-1-[(trimethylsilyl)methyl]cyclopropane, in moderate yield.

KOH to remove excess thiophenol, and the organic layer was then washed with brine. The combined organic layers were dried, filtered, and concentrated. Vacuum distillation of the crude product afforded 62 g of 1-(trimethylsilyl)-2-thiophenoxyethane in 86% yield: ^{1}H NMR ($CDCl_3$) δ 7.36–7.15 (5 H, m, Ar H's), 2.99 (2 H, m, 2-H's), 0.97 (2 H, m, 1-H's), 0.07 (9 H, s, Si-Me's); ^{13}C NMR ($CDCl_3$) δ 137.3, 129.0, 128.9, 125.7 (Ar C's), 29.6 (C-2), 16.9 (C-1), -1.7 (Si-Me's). The purified 1-(trimethylsilyl)-2-thiophenoxyethane (62 g, 0.3 mol) was dissolved in glacial acetic acid (135 mL) and treated with 30% hydrogen peroxide (60 mL, 0.5 mol). The mixture was heated to initiate the oxidation. A second portion of 30% hydrogen peroxide solution (90 mL, 0.75 mol) was then added dropwise, and the resulting solution was kept at 100 °C for 2 h. After cooling to room temperature, the solution was evaporated under reduced pressure to remove most of the water and acetic acid. The residue was then diluted with ether, washed with saturated $NaHCO_3$ and brine, dried, and then evaporated in vacuo. The desired product crystallized during the concentration. The yield was nearly quantitative; mp 52 °C;[10] ^{1}H NMR ($CDCl_3$) δ 7.85 (2 H, d, J = 8.4, Ar H's), 7.62 (1 H, d, J = 7.3, Ar H), 7.53 (2 H, dd, J = 8.4, 7.3, Ar H's), 2.96 (2 H, m, 1-H's), 0.88 (2 H, m, 2-H's), -0.04 (9 H, s, Si-Me's); ^{13}C NMR ($CDCl_3$) δ 138.7, 133.6, 129.2, 128.2 (Ar C's), 52.7 (C-1), 9.1 (C-2), -2.0 (Si-Me's).

(2*S*)-1-(*tert*-Butyldimethylsiloxy)-4-(phenylsulfonyl)-5-(trimethylsilyl)-2-pentanol (7a) and (2*S*)-1-(Phenylmethoxy)-4-(phenylsulfonyl)-5-(trimethylsilyl)-2-pentanol (7b). *n*-Butyllithium (9.76 mL of 2.5 M solution, 24.4 mmol) was added dropwise to a solution of **6** (5.8 g, 24.0 mmol) in 150 mL of anhydrous ether at -78 °C. After the solution was stirred for 20 min, 24.0 mmol of oxirane **5a** (4.51 g) in 10 mL of ether was added. The resulting mixture was gradually brought to room temperature and allowed to react overnight. The reaction was quenched by adding saturated ammonium chloride solution, and the aqueous phase was then extracted with ether. The organic fractions were combined, dried, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (10% ethyl acetate in hexane) to give **7a** in 88% yield as a mixture of two diastereomers (9.06 g). Small amount of each diastereomer was obtained by repeated chromatography on silica gel and subjected to spectral analysis. Diastereomer I: ^{1}H NMR ($CDCl_3$) δ 7.81 (2 H, d, J = 7.3, Ar H's), 7.57 (1 H, d, J = 7.8, Ar H), 7.50 (2 H, dd, J = 7.8, 7.3, Ar H's), 3.81 (1 H, m, 2-H), 3.47 (1 H, m, 4-H), 3.46 (1 H, dd, J = 10.0, 4.0, 1-H), 3.30 (1 H, dd, J = 10.0, 5.8, 1-H), 2.56 (1 H, d, J = 4.8, OH), 1.85 (1 H, m, 3-H), 1.58 (1 H, m, 3-H), 1.02 (1 H, dd, J = 14.3, 2.0, 5-H), 0.67 (1 H, dd, J = 14.3, 12.3, 5-H), 0.79 (9 H, s, C-Me's), -0.06 (15 H, s, Si-Me's); ^{13}C NMR ($CDCl_3$) δ 137.5, 133.6, 129.2, 129.0 (Ar C's), 69.2 (C-1), 67.1 (C-2), 58.4 (C-4), 34.2 (C-3), 25.9 (C-Me's), 17.6 (C-Me's), 16.3 (C-5), -1.0 (Si-Me's), -5.4 (Si-Me's). Diastereomer II: ^{1}H NMR ($CDCl_3$) δ 7.85 (2 H, d, J = 8.4, Ar H's), 7.62 (1 H, d, J = 7.3, Ar H), 7.53 (2 H, dd, J = 8.4, 7.3, Ar H's), 3.72 (1 H, m, 2-H), 3.53 (1 H, dd, J = 10.0, 4.7, 1-H), 3.45 (1 H, dd, J = 10.0, 5.4, 1-H), 3.31 (1 H, m, 4-H), 2.74 (1 H, d, J = 5.1, OH), 1.91 (1 H, ddd, J = 14.8, 9.7, 5.1, 3-H), 1.63 (1 H, ddd, J = 14.8, 6.5, 3.1, 3-H), 1.17 (1 H, dd, J = 14.8, 3.7, 5-H), 0.84 (9 H, s, C-Me's), 0.76 (1 H, dd, J = 14.8, 9.7, 5-H), -0.03 (15 H, s, Si-Me's); ^{13}C NMR ($CDCl_3$) δ 137.1, 133.6, 129.2, 129.1 (Ar C's), 69.1 (C-1), 66.9 (C-2), 59.7 (C-4), 34.4 (C-3), 25.9 (C-Me's), 18.3 (C-Me's), 16.4 (C-5), -0.9 (Si-Me's), -5.4 (Si-Me's); high-resolution FAB-MS calcd for $C_{20}H_{39}SO_4Si_2$ $(M + 1)^+$ 431.2107, found 431.2115. When **5b** (2.0 g, 12.2 mmol) was used as the reactant, the same procedure led to the formation of **7b** as a mixture of two diastereomeric forms in 95% yield. These two diastereomers could be isolated in pure form by flash chromatography (5% ethyl acetate in hexane). Diastereomer I: ^{1}H NMR ($CDCl_3$) δ 7.88–7.25 (10 H, m, Ar H's), 4.55, 4.47 (1 H each, d, J = 13.5, CH_2Ar), 3.94 (1 H, m, 2-H), 3.44 (1 H, dd, J = 9.5, 4.5, 1-H), 3.39 (1 H, dd, J = 9.5, 5.8, 1-H), 3.32 (1 H, m, 4-H), 2.89 (1 H, d, J = 4.6, OH), 1.98 (1 H, ddd, J = 15.0, 9.4, 5.7, 3-H), 1.69 (1 H, ddd, J = 15.0, 6.2, 3.6, 3-H), 1.15 (1 H, dd, J = 15.0, 3.6, 5-H), 0.75 (1 H, dd, J = 15.0, 9.7, 5-H), -0.01 (9 H, s, Si-Me's); ^{13}C NMR ($CDCl_3$) δ 137.8–127.8 (Ar C's), 73.9 (CH_2Ar)*, 73.4 (C-1)*, 68.0 (C-2), 59.8 (C-4), 34.7 (C-3), 16.7 (C-5), -1.0 (Si-Me's). Diastereomer II: ^{1}H NMR ($CDCl_3$) δ 7.86–7.21 (10 H, m, Ar H's), 4.51, 4.48 (1 H each, d, J = 12.2, CH_2Ar), 4.10 (1 H, m, 2-H), 3.51 (1 H, m, 4-H), 3.41 (1 H, dd, J = 9.5, 3.9, 1-H), 3.28 (1 H, dd, J = 9.5, 6.5, 1-H), 2.76 (1 H, d, J = 4.3, OH), 1.94 (1 H, m, 3-H), 1.65 (1 H, m, 3-H), 1.06 (1 H, dd, J = 14.4, 2.0, 5-H), 0.69 (1 H, dd, J = 14.4, 12.3, 5-H), -0.01 (9 H, s, Si-Me's); ^{13}C NMR ($CDCl_3$) δ 138.0–127.7 (Ar C's), 74.3 (CH_2Ar)*, 73.3 (C-1)*, 67.9 (C-2), 58.5 (C-4), 34.4 (C-3), 17.7 (C-5), -1.0 (Si-Me's); high-resolution FAB-MS calcd for $C_{21}H_{31}SO_4Si$ $(M + 1)^+$ 407.1712, found 407.1708.

(2*S*)-1-(*tert*-Butyldimethylsiloxy)-4-(phenylsulfonyl)-5-(trimethylsilyl)-2-pentyl Methanesulfonate (8a) and (2*S*)-1-(Phenylmethoxy)-4-(phenylsulfonyl)-5-(trimethylsilyl)-2-pentyl Methanesulfonate (8b). To a solution of **7a** (9.06 g, 21.1 mmol) in methylene chloride (150 mL) at 0 °C was added triethylamine (4 mL, 21.5 mmol). After the solution was stirred for 20 min, methanesulfonyl chloride (3.24 mL, 42.1 mmol) was added dropwise. The resulting mixture was stirred at room temperature overnight. The reaction was quenched with water and then extracted with methylene chloride. The combined organic extracts were washed with 1 N HCl, saturated $NaHCO_3$, and brine in sequence, dried, filtered, and concentrated. The desired product **8a** was isolated as a mixture of two diastereomers in 98% yield by flash chromatography (5% ethyl acetate in hexane). Small amount of each diastereomer in pure form was obtained by collecting the early and tail fractions separately during the purification. Diastereomer I: ^{1}H NMR ($CDCl_3$) δ 7.89 (2 H, m, Ar H's), 7.66 (1 H, m, Ar H), 7.61 (2 H, m, Ar H's), 5.08 (1 H, m, 2-H), 3.89 and 3.83 (1 H each, d, J = 11.3, 1-H's), 3.24 (1 H, m, 4-H), 3.02 (3 H, s, OMs), 2.00 (2 H, m, 3-H's), 1.14 (1 H, dd, J = 14.7, 4.1, 5-H), 0.88 (9 H, s, C-Me's), 0.69 (1 H, dd, J = 14.7, 9.9, 5-H), 0.07 (6 H, s, Si-Me's), -0.04 (9 H, s, Si-Me's); ^{13}C NMR ($CDCl_3$) δ 136.1, 133.8, 129.5, 129.2, 129.1 (Ar C's), 79.8 (C-2), 64.2 (C-1), 59.1 (C-4), 38.4 (OMs), 32.8 (C-3), 25.9 (C-Me's), 18.5 (C-Me's), 17.2 (C-5), -0.8 (Si-Me's), -5.3 (Si-Me's). Diastereomer II: ^{1}H NMR ($CDCl_3$) δ 7.92 (2 H, d, J = 7.6, Ar H's), 7.64 (1 H, m, Ar H), 7.56 (2 H, dd, J = 7.6, 7.2, Ar H's), 5.19 (1 H, m, 2-H), 3.81 (1 H, dd, J = 11.4, 3.3, 1-H), 3.70 (1 H, dd, J = 11.4, 5.3, 1-H), 3.52 (1 H, t, J = 11.0, 4-H), 3.10 (3 H, s, OMs), 2.21 (1 H, dd, J = 16.5, 10.1, 3-H), 1.92 (1 H, dd, J = 16.5, 11.1, 3-H), 0.89 (9 H, s, C-Me's), 0.86 (1 H, burried under C-Me's, m, 5-H), 0.72 (1 H, dd, J = 14.4, 12.2, 5-H), 0.08 (6 H, s, Si-Me's), -0.04 (9 H, s, Si-Me's); ^{13}C NMR ($CDCl_3$) δ 136.6, 133.8, 129.2, 129.1 (Ar C's), 82.2 (C-2), 65.2 (C-1), 56.9 (C-4), 38.4 (OMs), 31.9 (C-3), 25.9 (C-Me's), 18.2 (C-Me's), 17.8 (C-5), -1.2 (Si-Me's), -5.4 (Si-Me's); high-resolution FAB-MS calcd for $C_{21}H_{41}S_2O_6Si_2$ $(M + 1)^+$ 509.1883, found 509.1886. Following an identical procedure, compound **7b** (3.6 g, 8.9 mmol) was converted to **8b** in quantitative yield. The two diastereomers derived from enantiomerically pure **7b** gave the following spectral data. Diastereomer I: ^{1}H NMR ($CDCl_3$) δ 7.83 (2 H, d, J = 7.6, Ar H's), 7.63 (1 H, dd, J = 7.6, 7.2, Ar H), 7.56 (2 H, t, J = 7.2, Ar H's), 7.28 (5 H, m, Ar H's), 5.21 (1 H, m, 2-H), 4.54, 4.50 (1 H each, d, J = 12.5, CH_2Ar), 3.73 (1 H, dd, J = 11.3, 5.2, 1-H), 3.66 (1 H, dd, J = 11.3, 3.0, 1-H), 3.20 (1 H, m, 4-H), 2.95 (3 H, s, OMs), 1.97 (2 H, m, 3-H's), 1.06 (1 H, dd, J = 14.7, 4.0, 5-H), 0.65 (1 H, dd, J = 14.7, 9.9, 5-H), -0.01 (9 H, s, Si-Me's); ^{13}C NMR ($CDCl_3$) δ 137.2–128.0 (Ar C's), 78.6 (C-2), 73.5 (CH_2Ar)*, 70.5 (C-1)*, 59.0 (C-4), 38.5 (OMs), 33.2 (C-3), 17.1 (C-5), -0.9 (Si-Me's). Diastereomer II: ^{1}H NMR ($CDCl_3$) δ 7.91 (2 H, d, J = 7.6, Ar H's), 7.67 (1 H, dd, J = 7.8, 7.6, Ar H), 7.56 (2 H, t, J = 7.8, Ar H's), 7.35 (5 H, m, Ar H's), 5.36 (1 H, m, 2-H), 4.56 (2 H, s, CH_2Ar), 3.58 (2 H, d, J = 5.4, 1-H's), 3.52 (1 H, dd, J = 11.8, 10.4, 4-H), 3.07 (3 H, s, OMs), 2.23 (1 H, ddd, J = 16.5, 10.5, 1.7, 3-H), 1.92 (1 H, dd, J = 16.5, 10.5, 3-H), 0.93 (1 H, dd, J = 14.6, 1.9, 5-H), 0.70 (1 H, dd, J = 14.6, 12.1, 5-H), -0.01 (9 H, s, Si-Me's); ^{13}C NMR ($CDCl_3$) δ 138.0–128.2 (Ar C's), 80.9 (C-2), 73.7 (CH_2Ar)*, 72.0 (C-1)*, 57.2 (C-4), 38.8 (OMs), 32.7 (C-3), 18.1 (C-5), -1.2 (Si-Me's). High-resolution FAB-MS calcd for $C_{22}H_{33}S_2O_6Si$ $(M + 1)^+$ 485.1488, found 485.1476.

(2*R*)-2-[(*tert*-Butyldimethylsiloxy)methyl]-1-(phenylsulfonyl)-1-[(trimethylsilyl)methyl]cyclopropane (9a) and (2*R*)-1-(Phenylsulfonyl)-1-[(trimethylsilyl)methyl]-2-[(phenylmethoxy)methyl]cyclopropane (9b). Lithium diisopropylamide (22.7 mmol) was generated at -78 °C by the addition of 22.7 equiv of 2.5 M solution of *n*-butyllithium in hexane to a THF solution of 24 equiv of diisopropylamine. After the solution was stirred for 10 min, 20.6 mmol of **8a** (10.5 g) in dry THF (150 mL) was added dropwise. The resulting mixture was gradually brought up to room temperature, stirred at room temperature for 3 h, and quenched with ice-cold saturated ammonium

chloride solution. After stirring for an additional 10 min, the mixture was extracted with ether and the combined organic extracts were dried, filtered, and concentrated. The crude product was purified by flash chromatography (5% ethyl acetate in hexane) to afford **9a** in 79% yield (6.71 g). Although TLC of **9a** gave only one spot, 500-MHz ^{1}H NMR analysis clearly revealed the presence of two diastereomers in a 1.5:1 ratio. It should be noted that these two isomers were not discernible by 300-MHz ^{1}H NMR. Diastereomer I: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (2 H, m, Ar H's), 7.55 (1 H, m, Ar H), 7.47 (2 H, m, Ar H's), 3.81 (1 H, dd, J = 11.1, 4.8, one of CH_2OSi), 3.42 (1 H, dd, J = 11.1, 9.1, one of CH_2OSi), 2.05 (1 H, m, 3-H), 1.80 (1 H, dd, J = 10.3, 5.8, 3-H), 1.10 (1 H, d, J = 16.3, one of CH_2Si), 0.77 (9 H, s, C-Me's), 0.72 (1 H, d, J = 16.3, one of CH_2Si), 0.07 (9 H, s, Si-Me's), −0.02 and −0.05 (3 H each, s, Si-Me); ^{13}C NMR ($CDCl_3$) δ 138.8, 133.0, 128.9, 128.7 (Ar C's), 61.0 (CH_2Si), 42.4 (C-1), 25.8 (C-Me's), 18.1 (C-Me's), 14.2 (C-2), 13.1 (CH_2Si), −0.06 (Si-Me's), −5.4 and −5.6 (Si-Me's). Diastereomer II: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (2 H, m, Ar H's), 7.52 (1 H, m, Ar H), 7.44 (2 H, m, Ar H's), 3.91 (1 H, dd, J = 11.1, 4.6, one of CH_2OSi), 3.35 (1 H, dd, J = 11.1, 9.3, one of CH_2OSi), 2.05 (1 H, m, 3-H), 1.80 (1 H, dd, J = 10.3, 5.8, 3-H), 1.06 (1 H, d, J = 16.3, one of CH_2Si), 0.77 (9 H, s, C-Me's), 0.72 (1 H, d, J = 16.3, one of CH_2Si), 0.07 (9 H, s, Si-Me's), −0.02 and −0.05 (3 H each, s, Si-Me); both isomers gave identical ^{13}C NMR (75 MHz, $CDCl_3$) spectra, δ 138.8, 133.0, 128.9, 128.7 (Ar C's), 61.0 (CH_2Si), 42.4 (C-1), 25.8 (C-Me's), 18.1 (C-Me's), 14.2 (C-2), 13.1 (CH_2Si), −0.06 (Si-Me's), −5.4 and −5.6 (Si-Me's); high-resolution FAB-MS calcd for $C_{20}H_{37}SO_3Si_2$ $(M + 1)^+$ 413.2002, found 413.2009. When **8b** (4.0 g, 8.3 mmol) was used as the reactant, the same procedure led to the formation of **9b** in nearly quantitative yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (2 H, d, J = 7.9, Ar H's), 7.59 (1 H, m, Ar H), 7.49 (2 H, dd, J = 7.9, 7.4, Ar H's), 4.48, 4.36 (1 H each, d, J = 11.9, CH_2Ar), 3.68 (1 H, dd, J = 10.6, 5.1, one of side chain-CH_2O), 3.23 (1 H, dd, J = 10.6, 9.0, one of side chain-CH_2O), 2.19 (1 H, m, 3-H), 1.88 (1 H, dd, J = 10.3, 5.8, 3-H), 1.06 (1 H, d, J = 16.3, one of CH_2Si), 0.74 (1 H, m, 2-H), 0.67 (1 H, d, J = 16.3, one of CH_2Si), 0.04 (9 H, s, Si-Me's); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7–127.5 (Ar C's), 72.6 (CH_2Ar), 67.9 (side chain CH_2O), 42.6 (C-1), 23.2 (C-3), 14.9 (C-2), 13.2 (CH_2Si), −0.11 (Si-Me's); high-resolution FAB-MS calcd for $C_{21}H_{29}SO_3Si$ $(M + 1)^+$ 389.1607, found 389.1602.

(1*S*)-(Methylenecyclopropyl)methanol (10). Tetra-*n*-butylammonium fluoride in THF (50 mL of 1.0 M solution) was added into a solution of **9a** (6.71 g, 16.3 mmol) in 100 mL of THF. After refluxing for 30 min, the solution was cooled to room temperature and concentrated in vacuo. The residue was diluted with water and then extracted with ether several times. The combined organic extracts were dried, filtered, and evaporated under reduced pressure. The crude product was purified by flash chromatography (15% ether in petroleum ether) to give **10** in 35% yield: ^{1}H NMR ($CDCl_3$) δ 5.40, 5.34 (1 H each, d, J = 1.2, $=CH_2$), 3.55, 3.38 (1 H each, m, CH_2O), 2.90 (1 H, br s, OH), 1.70 (1 H, m, 1-H), 1.24, 0.89 (1 H each, m, 3-H's); ^{13}C NMR ($CDCl_3$) δ 132.2 (C-2), 103.0 ($=CH_2$), 64.2 (CH_2O), 16.9 (C-1), 7.2 (C-3); high-resolution FAB-MS: calcd for C_5H_9O $(M + 1)^+$ 85.0653, found 85.0668. In order to confirm the stereochemical assignment, the Mosher ester of **10** was prepared and analyzed by NMR. Specifically, to a methylene chloride (5 mL) solution of α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA, 47 mg, 0.2 mmol), DMAP (24.7 mg, 0.2 mmol), and compound **10** (17 mg, 0.2 mmol) was added 1,3-dicyclohexylcarbodiimide (DCC, 43.6 mg, 0.21 mmol) at 0 °C under argon. The resulting cloudy mixture was stirred at room temperature for 5 h. The precipitate was filtered, and the filtrate was concentrated in vacuo. After purification by flash chromatography (0.5% ethyl acetate in hexane), the desired Mosher ester was isolated in 83% yield: ^{1}H NMR ($CDCl_3$) δ 7.55 (2 H, m, Ar H's), 7.43–7.39 (3 H, m, Ar H's), 5.43, 5.41 (1 H each, d, J = 1.1, $=CH_2$), 4.23 (2 H, d, J = 7.5, CH_2O), 3.58 (3 H, s, OMe), 1.89 (1 H, m, 1-H), 1.24, 1.07 (1 H each, m, 3-H's); ^{13}C NMR ($CDCl_3$) δ 166.6 (C=O), 132.4 (C-2), 131.4, 129.6, 128.4, 127.4 (Ar C's), 105.3 ($=CH_2$), 77.2 (OCF_3), 69.0 (CC=O), 55.5 (OMe), 13.9 (C-1), 8.8 (C-3). The magnitudue of Eu(fod)$_3$ induced downfield shift for the methoxyl signal of the MTPA ester of **10** is larger than that of the (1*R*)-(methylenecyclopropyl)methanol.[7]

(1*R*)-[2-(Phenylsulfonyl)-2-[(trimethylsilyl)methyl]cyclopropyl]methanol (11). To a solution of **9b** (3.0 g, 7.7 mmol) in dry methylene chloride (10 mL) was added boron trifluoride etherate (8.4 mL, 68 mmol) and thioethanol (17 mL) in sequence. The reaction was stirred at room temperature overnight. The resulting mixture was poured into water and extracted with ether. The organic layer was washed with brine, dried, filtered, and evaporated. The crude material was purified by flash chromatography (30% ethyl acetate in hexane) to give pure alcohol in 83% yield: ^{1}H NMR ($CDCl_3$) δ 7.88 (2 H, d, J = 8.0, Ar H's), 7.58 (3 H, m, Ar H's), 3.80 (1 H, dd, J = 11.6, 5.2, one of side chain CH_2O), 3.42 (1 H, dd, J = 11.6, 8.8, one of side chain CH_2O), 2.12 (1 H, m, 3-H), 1.84 (1 H, dd, J = 10.2, 5.7, 3-H), 1.10 (1 H, d, J = 16.2, one of CH_2Si), 0.76 (1 H, d, J = 16.2, one of CH_2Si), 0.77 (1 H, m, 1-H), 0.04 (9 H, s, Si-Me's); ^{13}C NMR ($CDCl_3$) δ 138.5, 133.4, 129.1, 128.9 (Ar C's), 61.0 (side chain CH_2O), 43.0 (C-2), 25.3 (C-3), 15.4 (C-1), 13.2 (CH_2Si), −0.13 (Si-Me's); high-resolution FAB-MS calcd for $C_{14}H_{23}SO_3Si$ $(M + 1)^+$ 299.1137, found 299.1142.

(1*R*)-[2-(Phenylsulfonyl)-2-[(trimethylsilyl)methyl]cyclopropyl]methyl Methanesulfonate (12). To a solution of alcohol **11** (1.9 g, 6.3 mmol) in methylene chloride (50 mL) at 0 °C was added triethylamine (1.7 mL, 12.0 mmol). After the solution was stirred for 10 min, methanesulfonyl chloride (924 μL, 12.0 mmol) was added dropwise. The resulting mixture was allowed to react at room temperature for 1 h. The reaction was then quenched with water and extracted with methylene chloride. The combined organic extracts were washed with 1 N HCl, saturated $NaHCO_3$, and brine in sequence, dried, and filtered. The solvent was evaporated under reduced pressure to give **12** in 95% yield: ^{1}H NMR ($CDCl_3$) δ 7.85 (2 H, d, J = 7.0, Ar H's), 7.66–7.52 (3 H, m, Ar H's), 4.44 (1 H, dd, J = 11.2, 5.9, one of side chain-CH_2O), 3.92 (1 H, dd, J = 11.2, 9.5, one of side chain-CH_2O), 2.88 (3 H, s, OMs), 2.24 (1 H, m, 3-H), 1.97 (1 H, ddd, J = 10.2, 6.1, 1.0, 3-H), 1.12 (1 H, d, J = 16.3, one of CH_2Si), 0.85 (1 H, t, J = 6.3, 1-H), 0.66 (1 H, d, J = 16.3, one of CH_2Si), 0.08 (9 H, s, Si-Me's); ^{13}C NMR ($CDCl_3$) δ 138.0, 133.6, 129.1, 129.0 (Ar C's), 67.4 (CH_2OMs), 43.6 (C-2), 37.8 (OMs), 22.0 (C-3), 15.8 (C-1), 13.3 (CH_2Si), −0.15 (Si-Me's); high-resolution FAB-MS calcd for $C_{15}H_{25}S_2O_5Si$ $(M + 1)^+$ 377.0913, found 377.0920.

(1*S*)-[2-(Phenylsulfonyl)-2-[(trimethylsilyl)methyl]cyclopropyl]acetonitrile (13). To a mixture of 15-crown-5 (290 mg, 0.11 mmol) and sodium cyanide (660 mg, 13.5 mmol) in anhydrous dimethyl sulfoxide (10 mL) was added dropwise a solution of **12** (2.2 g, 5.9 mmol) in 3 mL of DMSO. The reaction mixture was maintained at room temperature overnight. The solution was then mixed with water and extracted with methylene chloride. The combined organic extracts were washed with 1 N HCl, saturated $NaHCO_3$, and brine in sequence, dried, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (10% ethyl acetate in hexane) to afford **13** in 85% yield: ^{1}H NMR ($CDCl_3$) δ 7.82 (2 H, d, J = 7.1, Ar H's), 7.65–7.52 (3 H, m, Ar H's), 2.52 (1 H, dd, J = 17.3, 5.7, one of side chain-CH_2CN), 2.19 (1 H, dd, J = 17.3, 8.5, one of side chain-CH_2CN), 2.06 (1 H, m, 3-H), 1.95 (1 H, dd, J = 9.7, 5.9, 3-H), 1.11 (1 H, d, J = 16.2, one of CH_2Si), 0.72 (1 H, t, J = 6.2, 1-H), 0.52 (1 H, d, J = 16.2, one of CH_2Si), 0.08 (9 H, s, Si-Me's); ^{13}C NMR ($CDCl_3$) δ 137.9, 133.9, 129.4, 128.9 (Ar C's), 117.5 (CN), 43.3 (C-2), 17.0* (CH_2CN), 16.7* (C-3), 14.3 (C-1), 13.4 (CH_2Si), −0.01 (Si-Me's); high-resolution FAB-MS calcd for $C_{15}H_{22}NSO_2Si$ $(M + 1)^+$ 308.1140, found 308.1138.

(1*R*)-(Methylenecyclopropyl)acetonitrile (14). Compound **13** (1.5 g, 4.9 mmol) in 50 mL of THF was treated with tetra-*n*-butylammonium fluoride (1.0 M, 30 mL). After refluxing for 30 min, the solution was cooled to room temperature and concentrated in vacuo. The residue was mixed with water and extracted with ether several times. The combined organic extracts were dried, filtered, and evaporated. The crude product was purified by flash chromatography (5% ethyl ether in petroleum ether) to give **14** in 86% yield: ^{1}H NMR ($CDCl_3$) δ 5.53, 5.44 (1 H each, d, J = 1.2, $=CH_2$), 2.40 (2 H, d, J = 6.5, CH_2CN), 1.67 (1 H, m, 1-H), 1.40 (1 H, br t, J = 9.0, 3-H), 0.96 (1 H, m, 3-H); ^{13}C NMR ($CDCl_3$) δ 132.0 (C-2), 118.4 (CN), 105.5 ($=CH_2$), 20.6 (CH_2CN), 10.6 (C-1), 9.4 (C-3); high-resolution CI-MS (CH_4) calcd for C_6H_8N $(M + 1)^+$ 94.0657, found 94.0660.

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Registry No. 3, 125827-35-2; 4, 57044-25-4; 5a, 12327-62-7; 5b, 16495-13-9; 6, 73476-18-3; 7a (diastereomer-1), 139242-75-4; 7a (diastereomer-2), 139344-59-5; 7b (diastereomer-1), 139242-76-5; 7b (diastereomer-2), 139344-60-8; 8a (diastereomer-1), 139242-77-6; 8a (diastereomer-2), 139344-61-9; 8b (diastereomer-1), 139242-78-7; 8b (diastereomer-2), 139344-62-0; 9a (diastereomer-1), 139242-79-8; 9a (diastereomer-2), 139344-63-1; 9b (diastereomer-1), 139242-80-1; 9b (diastereomer-2), 139242-81-2; 10, 139242-82-3; 10 (MTPA ester), 136060-96-3; 11 (diastereomer-1), 139242-83-4; 11 (diastereomer-2), 139344-64-2; 12 (diastereomer-1), 139242-84-5; 12 (diastereomer-2), 139344-65-3; 13 (diastereomer-1), 139242-85-6; 13 (diastereomer-2), 139344-66-4; 14, 139242-86-7; MTPA, 56135-03-6; TBDMS-Cl, 18162-48-6; $PhCH_2Br$, 100-39-0; CH_2=$CHSiMe_3$, 754-05-2; PhSH, 108-98-5; $Me_3SiCH_2CH_2SPh$, 17988-59-9.

Supplementary Material Available: Spectra of 5-14 (38 pages). Ordering information is given on any current masthead page.

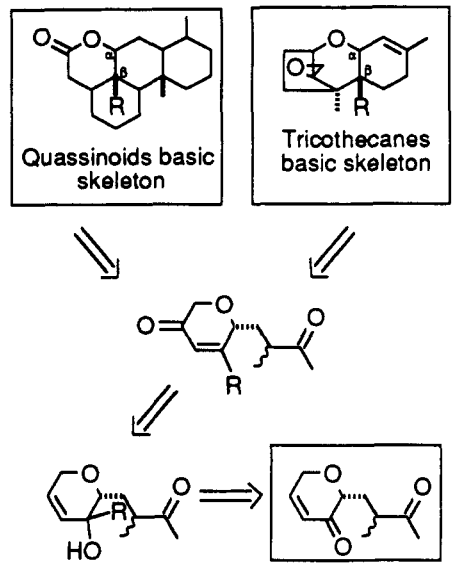

Figure 1.

Lewis Acid Induced Homoallylic C-Alkylation. 2.[1] Application to the Synthesis of Unsaturated Diketo *C*-Glycosides. Mechanistic Aspect of the Reaction

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Keto unsaturated glycosides play a pivotal role as building blocks in organic synthesis.[2] Moreover, these molecules have attracted an increasing interest recently with the discovery of the antitumor properties of keto unsaturated *N*- and *C*-glycosides.[3,4] We are currently engaged in studies directed toward the synthesis of complex unsaturated *C*-glycosides[1,5,6] and their use as building blocks in the synthesis of naturally occurring antitumoral compounds.[7] Among these molecules β-substituted keto unsaturated *C*-glycosides are of special interest because they are potent key intermediates for the synthesis of important synthetic targets with a framework of β-substituted tetrahydropyran like quasinoids and tricothecanes (Figure 1). This type of *C*-glycoside should be readily available by a Cr(IV) oxidative rearrangement of a tertiary allylic alcohol prepared from dioxo unsaturated *C*-glycosides.

The syntheses of *C*-glycosides by way of CC bond formation between a peracetylated glycal and a nucleophilic reagent draw considerable attention in recent years.[8-10] However, only our olefin-based methodologies[1,5,6] allow the direct generation of 2-keto unsaturated C-glycosides.[6] Herein we report the first preparation of keto and aldehydo 2*H*-pyran-3-ones by the reaction of peracetylated 2-hydroxy glycals with silyloxy allylic ethers. This process avoids the deprotection of enol esters that requires multistep reactions[11] or processes not always compatible with the stability of the glycosides.[12]

Our results are summarized in Table I. The coupling of tri-*O*-acetyl-2-hydroxy-L-fucal (1) and [(thexyldimethylsilyl)oxy]-3-methyl-3-buten-2-ol (2) was chosen as a model system. After examining the effect of a variety of catalytic systems ($ZnBr_2$, $SnCl_4$, $SnBr_4$, $TiCl_4$, $FeCl_3/SiO_2$, $BF_3{\cdot}Et_2O$, $SnBr_4/SnCl_4$ 4-Å molecular sieves, $ZnBr_2$ ultrasound) we arrived at the following optimal procedure. Glycal 1 (5-10 mmol) and thexyldimethylsiloxy ether 2 (1.2 equiv) was added dropwise to a stirred suspension of 4-Å molecular sieves and dry zinc bromide (1 equiv) in dichloroethane under ultrasound at 15 °C. After 5 h the *C*-glycoside 3 was isolated in 72% yield (Table I, entry 1). The enone structure of 3 was dictated by the conjugated olefinic resonances at δ_H 6 and 6.9 ppm and by the carbonyl signal at δ_C 212.06 ppm.

With a good catalytic system at hand we extended the reaction to various glycals. Table I shows clearly that the reaction was dependent on the substitution at C-6. Thus,

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