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Enantioselective Synthesis of the Methylenecyclopropane Derivative Related to Hypoglycine, from Malic Acid

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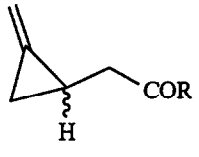
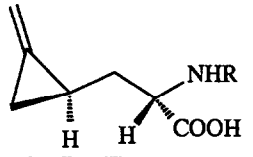
Abstract: Synthesis of (S)-methylenecyclopropaneacetic acid starting from L-(-)-malic acid, *via* (2S)-O-tert-butyldimethylsilyl-1,2-epoxybutan-4-ol and 1-O-tert-butyldiphenylsilyl-5-benzenesulfonyl-6-trimethylsilylhexane-1,3-diols as the key intermediates, is described.

(Methylenecyclopropyl)acetyl-coenzyme A [(R)-**1a**], the causative agent of the Jamaican vomiting sickness, is a mammalian metabolite of amino acids hypoglycine A (**2a**) and hypoglycine B (**2b**), which occur in some unripe tropical fruits.[1] Synthesis of the core of these amino acids, i. e. methylenecyclopropaneacetic acid **1b**, has attracted considerable attention owing to its unusual structure and to the need to provide material required for biochemical studies. Racemic acid **1b** has yielded relatively easily to synthesis utilizing carbene -



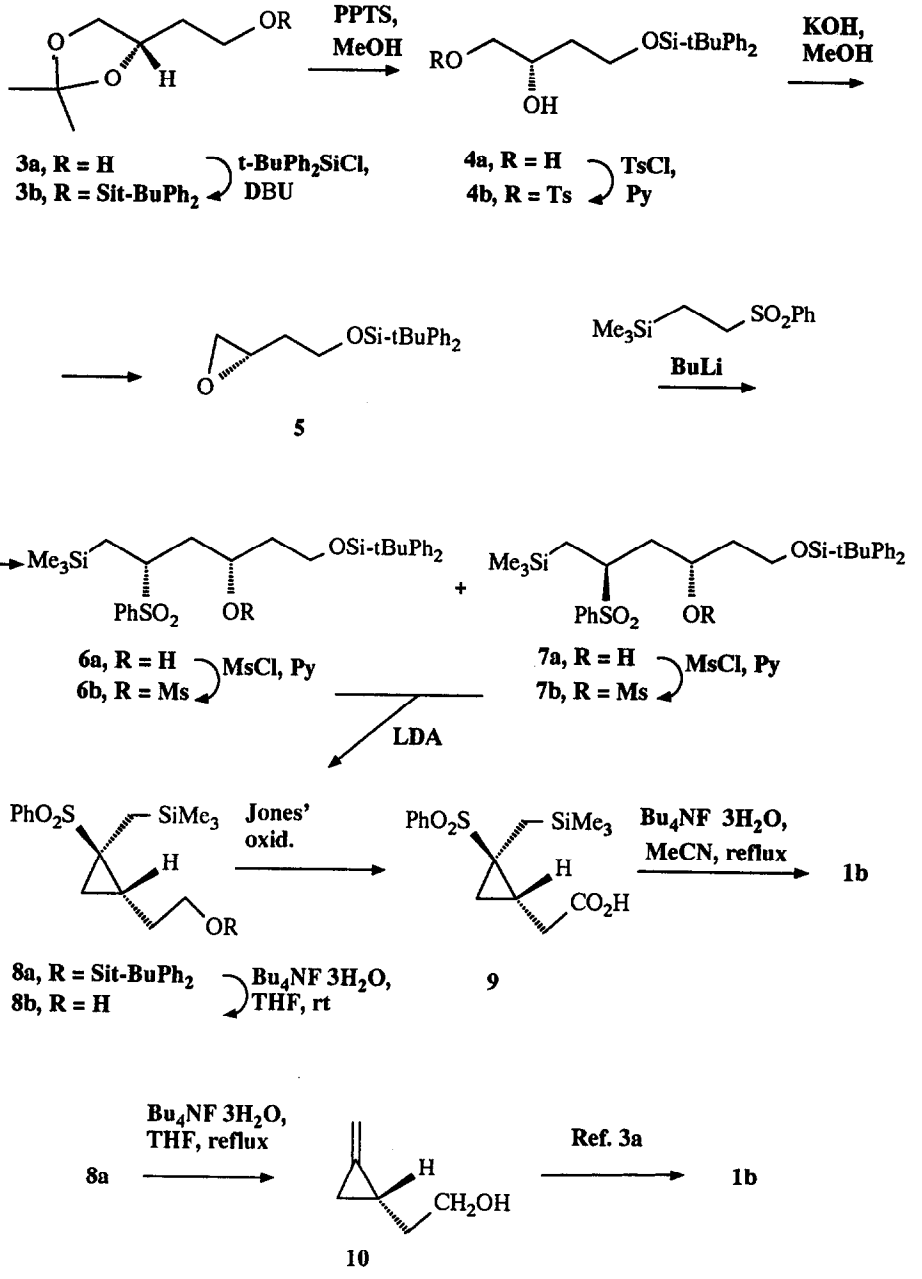
1a, R = SCoA
1b, R = OH



2a, R = H
2b, R = γ- glutaminyl

based cyclopropanation of a suitable allene[2] or ethylene[3] derivative. Optically active forms of acid **1b** have become available, however, only very recently by the racemate resolution[4] or by resolution of a racemic synthetic intermediate[3b]. Now, we present the first enantioselective synthesis of methylenecyclopropaneacetic

Scheme 1


PPTS, MeOH
KOH, MeOH
3a, R = H
3b, R = Sit-BuPh2
t-BuPh2SiCl, DBU
4a, R = H
4b, R = Ts
TsCl, Py
5
BuLi
6a, R = H
6b, R = Ms
MsCl, Py
7a, R = H
7b, R = Ms
MsCl, Py
LDA
Jones' oxid.
Bu4NF 3H2O, MeCN, reflux
1b
8a, R = Sit-BuPh2
8b, R = H
Bu4NF 3H2O, THF, rt
9
Bu4NF 3H2O, THF, reflux
8a
Ref. 3a
1b
10

acid [(S)-**1b**], which allows for a facile approach to both enantiomers of compound **1b**, starting from malic acid.[5]

(S)-1,2-Isopropylidenebutane-1,2,4-triol (**3a**, Scheme 1) prepared from L-(-)-malic acid essentially following the described procedure[6] was transformed in a usual way[7] into the t-butyldiphenylsilyl derivative **3b**. Selective hydrolysis of the isopropylidene protective group with PPTS in methanol containing some water afforded diol **4a** (83% yield) which was transformed into monotosylate **4b** and then into epoxide **5** (71% yield from **4a**).[8,9]

For the construction of the methylene cyclopropane unit a method of Hsiao and Shechter[10] was used. Epoxide **5** was treated with an anion generated from phenyl 2-(trimethylsilyl)ethyl sulfone[11] and butyllithium. Brief chromatography (silica gel) of the reaction product afforded the diastereomeric adducts in a 22 and 65% yield, to which structures **6a** (3S, 5S) and **7a** (3S, 5R), respectively, were tentatively assigned.[12]

Mesyl ester **6b** (obtained from alcohol **6a**) was treated with LDA in THF solution at -78 °C to give a diastereomerically pure cyclopropane derivative in a 89% yield. Under analogous conditions the mesylate **7b** afforded the same cyclopropane derivative (88% yield). Remarkable stereospecifity of cyclization suggested that the less strained diastereomer of the product (**8a**) was formed, with benzenesulfonyl and alkyl substituents in the *trans* configuration. It could be reasoned that the anion generated from the (3S,5S)-diastereomer **6b** undergoes cyclization *via* a relatively unstrained transition state while that generated from the (3S,5R)-diastereomer **7b**, due to nonbonding interactions between the benzenesulfonyl group and the C_1-C_2 fragment, suffers epimerization at the carbanionic center (C_5) prior to its cyclization. Single crystal x-ray analysis[13] showed that, indeed, the cyclization product represents the *trans* diastereomer **8a.**

When compound **8a** was treated with tetrabutylammonium fluoride trihydrate (TBAF) in boiling THF known[3a] methylenecyclopropanethanol **10** was obtained (41% yield, volatile liquid). On the other hand, on reaction of **8a** with TBAF in THF at rt a clean selective removal of the *t*-butyldiphenylsilyl protective group occurred to give alcohol **8b** (97% yield after chromatography). Oxidation of alcohol **8b** with an excess of the Jones' reagent in acetone at 0 °C afforded acid **9** (86% yield) which was then treated with TBAF in boiling acetonitrile to give the target compound, (S)-methylenecyclopropaneacetic acid [(S)-**1b**], in a 74% yield.[14]

Experimental Section

Melting points were determined on a hot-stage apparatus. NMR spectra were recorded in $CDCl_3$. Mass spectra were obtained at 70 eV. Column chromatography was performed on Merck silica gel 60, 230-400 mesh, and TLC on Merck slica gel G. A standard workup consists of partitioning the reaction mixture between the solvent of choice and water, separating and washing aqueous layer with solvent, combining the organic layers, washing them with water and with brine, and then drying them with anhyd. $MgSO_4$. The solvents were evaporated on a rotary evaporator.

(2S)-1,2-O-Isopropylidene-4-(*tert*-butyldiphenylsilyl)butane-1,2,4-triol (3b). A solution of hydroxy acetonide **3a**[6] (2.44 g, 16.7 mmol), *tert*-butyldiphenylsilyl chloride (5.13 mL, 20.0 mmol), DBU (3 mL, 20.0 mmol) in CH_2Cl_2 (15 mL) was stirred at 0 °C for 15 h and then at rt for 16 h. The mixture was concentrated *in vacuo* to a half of its volume and the residue was chromatographed (SiO_2, pentane-ether, 98:2). Silyl ether **3b** was obtained (5.76 g, 86% yield) as a colorless oil: $[\alpha]_D^{23}$ + 3.0° ($CHCl_3$, c 2.8).

(2S) 4-O-(tert-Butyldiphenylsilyl)butane-1,2,4-triol (4a). A solution of acetonide **3b** (5.10 g, 13.3 mmol) in methanol (30 mL), containing PPTS (2 mg) and a drop of water was stirred at rt for 24 h whereupon the solvent was evaporated *in vacuo* and the residue (4.7 g) was crystallized from hexane. Diol **4a** (3.8 g, 83% yield) was obtained: mp 73°C; $[\alpha]_D^{18}$ + 5.4° ($CHCl_3$, c 1.58). Anal. Calcd for $C_{20}H_{28}O_3Si$ (344.51): C, 69.72; H, 8.19. Found: C, 69.67; H, 8.13.

(2S)-O-tert-Butyldiphenylsilyl-1,2-epoxybutan-4-ol[8] **(5).** Diol **4a** (3.9 g, 12 mmol) was dissolved in pyridine (20 mL) and tosyl chloride (2.54 g, 13.3 mmol) was added. The mixture was stirred at rt for 24 h. Workup (ether) gave crude tosylate **4b**. To this product 10% methanolic KOH (30 mL) was added and the mixture was stirred at rt for 30 min. Workup and chromatography of the crude product (SiO_2, hexane - ether, 97:3) gave epoxide **5** (2.61 g, 71% yield from **4a**): mp 38-40 °C; $[\alpha]_D^{18}$ - 6.00° ($CHCl_3$, c 8.49) {lit.[8] $[\alpha]^{24}$ - 3.60° ($CHCl_3$)}. Anal. Calcd for $C_{20}H_{26}O_2Si$ (326.50): C, 73.57; H, 8.03. Found: C, 73.54; H, 8.09.

(3S,5S)- and (3S,5R)-1-O-tert-Butyldiphenylsilyl-5-benzenesulfonyl--6-(trimethylsilyl)-hexane-1,3-diols (6a and 7a). To a solution of phenyl 2-(trimethylsilyl)ethyl sulfone[11] (1.13 g, 4.67 mmol) in THF (10 mL),

stirred under Ar at -78 °C, BuLi (1.5 M in hexane, 3.11 mL, 4.67 mmol) was added. After 30 min epoxide **5** (0.435 g, 1.33 mmol) in THF (5 mL) was added during 5 min. The mixture was allowed to warm to rt (within ca. 2 h). Workup and chromatography of the crude product on SiO_2 gave:

1. on elution with hexane-ether, 95:5, unreacted sulfone (0.6 g),

2. on elution with hexane-ether, 88:12, adduct **6a**[12] (0.165 g, 22% yield): IR (film) 3540 (OH) cm^{-1}; δ_H (500 MHz) 7.89, 7.60 and 7.41 (3m, 15, aromat. H), 4.12 (m, 1, C_3 H), 3.80 (dt, 2, J = 5.8, 2.7 Hz, C_1 H), 3.53 (ddt, 1, J = 9.0, 6.9, 2.0 Hz, C_5 H), 3.26 (d, 1, J = 2.9 Hz, OH), 1.93 (ddd, 1,J = 15.2, 9.0, 2.7 Hz, C_2 Ha), 1.65 (ddd, 1, J = 15.3, 10.6, 2.7 Hz, C_2 Hb), 1.05 (m, 1, C_6 Ha) overlapping 1.05 (s, 9, t-Bu H), 0.73 (dd, 1, J = 14.5, 12.2 Hz, C_6 Hb), 0.025 (s, 9, SiCH); δ_C (125 MHz) -0.99 (SiC), 17.65, 19.05, 26.86 (t-Bu), 38.70, 39.24, 58.63, 62.66, 68.23, 127.79, 128.98, 129.09, 129.81, 129.83, 133.12, 133.16, 133.41, 135.55, 135.58, 137.77;

3. on elution with hexane-ether, 85:15, adduct **7a**[12] (less mobile diastereomer) (0.495 g, 65% yield): IR (film) 3540 (OH) cm^{-1}; δ_H (500 MHz) 7.90, 7.65, 7.56, and 7.41 (4m, 15, aromat. H), 4.01 (m, 1, C_3 H), 3.83 (m, 2, C_1 H), 3.37 (m, 1, C_5 H) overlapping 3.33 (d, 1, J = 3.5 Hz, OH), 2.04 (ddd, 1, J = 14.5, 9.7, 4.8 Hz, C_2 Ha), 1.65 (dd, 2, J = 11.2, 5.9 Hz, C_4 H), 1.58 (ddd, 1, J = 14.5, 7.1, 3.4 Hz, C_2 Hb), 1.22 (dd, 1, J = 15.0, 3.8 Hz, C_6 Ha), 1.03 (s, 9, t-Bu), 0.80 (dd, 1, J = 15.1, 9.2 Hz, C_6 Hb), 0.04 (s, 9, SiCH); δ_C (125 MHz) -0.89 (SiC), 16.41, 19.06, 26.85 (t-Bu), 38.51, 39.24, 59.50, 62.58, 68.97, 127.81, 129.05, 129.24, 129.86, 129.87, 133.02, 133.10, 133.50, 135.55, 135.57, 137.42. HRMS. Calcd for $C_{27}H_{35}O_4SSi$ (M^+): 511.1795. Found: 511.1808.

(3S,5S)-1-O-tert-Butyldiphenylsilyl-3-O-methanesulfonyl-5-benzenesulfonyl--6-(trimethylsilyl)hexane-1,3-diol (6b). To a solution of alcohol **6a** (0.449 g, 0.79 mmol) in pyridine (3 mL), stirred at 0 °C, mesyl chloride

(320 μL, 4 mmol) was added. The mixture was stirred at rt for 24 h. Workup and chromatography of the product (SiO_2, toluene - ethyl acetate, 98:2) gave mesylate **6b** (0.488g, 95% yield): mp 136-138 °C (*i*-PrOH); δ_H (200 MHz) 7.65 (m, 15, arom. H), 5.50-5,35 (m, 1, C_3 H), 3.75 (t, 2, J = 6.1 Hz, C_1 H), 3.57 (br.t, 1, J = ca. 10 Hz, C_5 H), 3.01 (s, 3, SO_2CH_3), 2.34 (ddd, 1, J = 16.4, 10.3, 1.5 Hz, C_2 Ha), 2.00-1.85 (m, 3, C_2 Hb and C_4 H), 1.06 (s, 9, *t*-Bu H), 0.90 (dd, 1,, J = 14.5, 1.9 Hz, C_6 Ha), 0.67 (dd, 1, J = 14.5, 11.8 Hz, C_6 Hb), 0.05 (s, 9, $SiCH_3$). Anal. Calcd for $C_{32}H_{46}O_6S_2Si_2$ (647.01): C, 59.40; H, 7.17. Found: C, 59.07; H, 7.18.

(3S,5R)-1-O-tert-Butyldiphenylsilyl-3-O-methanesulfonyl-5-benzenesulfonyl--6-(trimethylsilyl)hexane-1,3-diol (7b). In a similar way as described above, from alcohol **7a** (0.63 g, 0.97 mmol), mesylate **7b** was obtained (0.673 g, 94% yield); δ_H (200 MHz) 7.65 (m, 15, aromat.H), 5.25 (m, 1, C_3 H), 3.72 (m, 2, C_1 H), 3.25 (m, 1, C_5 H), 2.92 (s, 3, SO_2CH_3), 2.24 (m, 1, C_2 Ha), 1.90 (m, 1, C_2 Hb), 1.72 (m, 2, C_4 H), 1.13 (dd, 1, J = 15.0, 4.5 Hz, C_6 Ha), 1.04 (s, 9, t-Bu H), 0.69 (dd, 1, J = 14,8, 9.0, Hz, C_6 Hb), 0.05 (s, 9, Si-CH_3); MS m/z 613 (M^+-CH_3) 589 (M^+-Bu), 492, 421, 322, 259, 214, 199, 135, 125, 81, 73. HRMS. Calcd for $C_{28}H_{37}O_6S_2Si_2$ (M^+-C_4H_9): 589.1370. Found: 589.1370.

(1'R,2'R)-1-O-tert-Butyldiphenylsilyl-2-[2'-benzenesulfonyl-2'-(trimethyl--silyl)-methylcyclopropyl]ethan-1-ol (8a).

a. From mesylate **6b**. To a solution of LDA [prepared from diisopropylamine (175 μL, 1.23 mmol) and BuLi (1.6 M in hexane, 0.82 mL, 1.23 mmol)] in THF (8 mL), stirred under Ar at -78 °C, mesylate **6b** (0.530 g, 0.82 mmol) in THF (3 mL) was slowly added. Stirring at -78 °C was continued for 1h whereupon the mixture was allowed to warm to rt (within ca. 2 h). Workup and chromatography of the product (SiO_2, hexane - ether, 94:6) gave the cyclopropane derivative **8a** (0.402 g, 89% yield): mp 70-71 °C; $[\alpha]_D^{18}$ + 8.77° ($CHCl_3$, c 2.37,); δ_H (500 MHz) 7.57 (3m, 15, aromat. H), 3.62-3.40

(m, 2, C_1, H), 1.85-1.75 (m, 2, C_2 H), 1.52-1.40 (m, 2, C_1, H and C_3, Ha), 1.04 (s, 9, t-Bu H), 0.93 (d, 1, J = 16.2 Hz, CHa-$SiMe_3$), 0.51 (d, 1, J = 16.2 Hz, CHb-$SiMe_3$) overlapping 0.54-0.51 (m, 1, C_3, Hb), 0.05 (s, 9, Si-CH_3); δ_C(50 MHz) -0.07 (Si-C), 13.23, 17.59 (C_3, and C-$SiMe_3$), 19.13 (t-Bu quaternary C), 20.67 (C_1,), 26.86 (t-Bu primary C), 31.33 (C_2), 42.65 (C_2,), 63.04 (C_1), 127.69, 128.75, 128.85, 129.67, 129.69, 133.02, 133.62, 133.71, 135.52, 135.54, 138.85 (arom, C); MS, m/z, 550 (M^+), 535 (M^+-15), 493 ($M^+-C_4H_9$), 323, 259, 199, 135, 73. HRMS. Calcd for $C_{27}H_{33}O_3SSi_2$ ($M^+-C_4H_9$): 493.1689. Found: 493.1703. Anal. Calcd for $C_{31}H_{42}O_3SSi_2$ (550.896): C, 67.58; H, 7.68. Found: C, 67.56; H, 8.09.

b. From mesylate **7b**. Mesylate **7b** (0.93 g, 1.44 mmol) was treated with LDA in an analogous way as described for **6b**. The cyclopropane derivative **8a** was obtained (0.70 g, 88% yield) identical in all respects with the product described above.

An X-ray crystallographic analysis of compound **8a** was carried out.[13] **Crystal data**: $C_{31}H_{42}O_3SSi_2$, M_r = 550.97, orthorombic, space group $P2_12_12_1$, α = 10.098 (2), b = 15.048(3), c = 20.880(4) Å, V = 3175.1(3) Å^3, Z = 4, F(000), D_x = 1.15 g cm^{-3}, μ(MoKα) = 1.67 mm^{-1}.

(1'R)-2-(Methylenecyclopropyl)ethanol (10). A mixture of compound **8a** (0.11 g, 0.2 mmol), anhyd. Bu_4NF (0.13 g, 0.5 mmol) and THF (5 mL) was refluxed for 5 h. Workup and chromatography (SiO_2) of the crude product gave:

1. on elution with hexane-ether, 95:5, (t-butyl)(fluoro)diphenylsilane (0.048 g, 93% yield)

2. on elution with hexane-ether, 85:15, compound **10**, (volatile liquid , 8 mg, 41% yield): δ_H (500 MHz) 5.45-5.43 (m, 10 lines, 1) and 5.40-5.38 (m, 1, vinylic H), 3.75 (t, 2, J = 6.5 Hz, C_1 H), 1.69 (dt, 1, J = 13.8, 7.2 Hz, C_2 Ha), 1.58 (dt, 1, J = 13.6, 6.7 Hz, C_2- Hb), 1.48 (qt, 1, J = 7, 2 Hz, C_3, Ha), 1.29 (tt, 1, J = 8.8, 2.2 Hz, C_3, Hb) and 0.82 (m, 1, C_1, H); δ_C (125 MHz) 9.22, 12.54, 36.00, 62.85 (C_1), 103.21 and 135.94 (ethylenic C) [lit.[3a] δ_H ($CDCl_3$) 5.41 (d, 2), 3.75 (t, 2), 1.8-1.3 (m, 4), 1.28 (t,

1), 0.91 (m, 1); δ_C 9, 13, 36, 62, 103 and 136].

(1'R,2'R)-2-[2'-Benzenesulfonyl-2'-(trimethylsilyl)methylcyclopropyl)--ethanol (8b). A mixture of silyl ether **8a** (0.40 g, 0.73 mmol), Bu_4NF 3 H_2O (0.234 g, 0.73 mmol) and THF (5 mL) was stirred at rt for 30 min. Workup and chromatography (SiO_2) of the crude product gave:

1. on elution with hexane-ether, 9:1, (t-butyl)(fluoro)diphenylsilane,

2. on elution with hexane-ether, 1:1, alcohol **8b** (0.22 g, 97% yield): IR (film) 3500 cm^{-1}; δ_H (200 MHz) 7.70 (m, 5, aromatic H), 3.55 (t, 2, J = 6.5 Hz, C_1 H), 1.82 (m, 2, C_2 H), 1.60-1.45 (m, 2, C_1, H and C_3, Ha), 1.06 (d, 1, J = 16.3 Hz, CHa-$SiMe_3$), 0.69 (d, 1, J = 16.3 Hz, CHb-$SiMe_3$), 0.62 (m, 1, C_3, Hb) 0.06 (s, 9, SiCH); MS, m/z, 297 (M^+-15), 215, 199, 166, 135 125, 73. HRMS. Calcd for $C_{14}H_{21}O_3SSi$ (M^+-CH_3): 297.0981. Found: 297.0981. 3,5-Dinitrobenzoate of **8b**, mp 134-137 °C (hexane-ether). Anal. Calcd for $C_{22}H_{26}O_8N_2SSi$ (507.2): C, 52.16; H, 5.17; N, 5.53. Found: C, 51.62; H, 5.08; N, 5.23.

(1'R,2'R)-[2'-Benzenesulfonyl-2'-(trimethylsilyl)methylcyclopropyl]acetic Acid (9). To a solution of alcohol **8b** (0.505 g, 1.6 mmol) in acetone (16 mL), stirred at 0 °C, Jones' reagent was added dropwise until the yellow color persisted. Stirring at 0 °C was continued for additional 30 min. The reagent excess was decomposed with *i*-PrOH. Workup gave the crude product which was purified by chromatography (SiO_2, toluene - ethyl acetate, 85:15) to give acid **9** (amorphous solid, 0.451 g, 86% yield): IR ($CHCl_3$): 3480-3040 (OH), 1740 (CO) cm^{-1}, δ_H (200 MHz): 7.8 (m, 2) and 7.5 (m, 3, arom. H), 2.44 (dd, 1, J = 16.0, 6.2 Hz, C_2 Ha), 2.23 (dd, 1, J = 16.0, 7.6, Hz, C_2 Hb), 2.12 (m, 1, C_1, H), 1.9 (dd, 1, J = 9.6, 6.0 Hz, C_3, Ha), 1.08 (d, 1, J = 16.0 Hz, CHa-$SiMe_3$), 0.65 (t, 1, J = 6.0 Hz, C_3, Hb), 0.57 (d, 1, J = 16.0 Hz, CHb-$SiMe_3$), 0.05 (s, 9, Si-CH); δ_C(50 MHz): 0.12 (Si-C), 13.48, 16.95 (C_3, and CH_2-Si), 19.11 (C_2), 33.14, 42.93 (C_1,),

128.89; 129.14; 133.34; 138.24 (arom.), 177.03 (CO_2H); MS, m/z, 325 (M^+-1), 311 (M^+-15), 281 (M^+-CO_2H), 267 (M^+-CH_2CO_2H), 253, 214, 199, 166, 135, 125, 91, 73. HRMS. Calcd for $C_{14}H_{19}O_4SSi$ (M^+-CH_3): 311.0773. Found: 311.0772.

(1'S)-(2'-Methylenecyclopropyl)acetic Acid [(S)-1b]. A solution of acid **9** (0.326 g, 1 mmol) in acetonitrile (20 mL) containing Bu_4NF $3H_2O$ (0.63 g, 2 mmol) was refluxed for 6 h. After cooling, ice water was added and the mixture was adjusted to pH 8-9 with saturated aq. $NaHCO_3$. The mixture was washed with ether. The aq. layer was acidified to pH 1-2 with conc. HCl and extracted with ether. The ethereal extract was washed with brine, dried and evaporated. The residue (150 mg) was chromatographed (SiO_2, $CHCl_3$-toluene-hexane-i-PrOH, 10:5:25:0.5) to give the title compound as colorless liquid (83 mg, 74% yield): $[\alpha]_D^{18}$ + 11.5° (c 0.7, $CHCl_3$) [lit.[4] $[\alpha]_D$ + 9 (c 0.5, $CHCl_3$)]; IR ($CHCl_3$) 3600-3060, 3020, 2955, 2880, 1735, 1342, 1220, 1165 cm^{-1}; δ_H (200 MHz) 13.14 (s, CO_2H), 5.53 (m, 1) and 5.44 (m, 1, vinylic H), 2.40 (d, 2, J = 7.2 Hz, C_2 H), 1.73 (m, 1, C_1, H), 1.40 (m, 1, C_3, Ha), 0.90 (m, 1, C_3, Hb); MS, m/z, 111 (M^+ H), 83 (M^+-CO), 67 (M^+-CO_2H), 53 (M^+- CH_2CO_2H). HRMS. Calcd for $C_6H_7O_2$ (M^+-H): 111.0446. Found: 111.0446.

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