Zincate-Mediated Rearrangement Reaction of 2-(1-Hydroxyalkyl)-1-alkylcyclopropanol

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General Information.

All solvents except tetrahydrofuran were used as obtained from commercial suppliers. Tetrahydrofuran was distilled over benzophenone–ketyl. Zinc powder was used after washing with 10% HCl according to the reported procedure.[1] Chromatographic purification of products was accomplished using forced-flow chromatography on Kanto Chemical Co., INC. Silica gel 60 N (spherical, neutral).

^{1}H and ^{13}C NMR spectra were recorded on Varian Gemini-2000 (300 MHz and 75 MHz, respectively) instrument and are internally referenced to residual protio solvent signals. Data for ^{1}H NMR are reported as chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz), integration, and assignment. Data for ^{13}C NMR are reported as chemical shift.

Bis(iodozincio)methane (**1**): A mixture of Zn (25 mmol), diiodomethane (1.0 mmol), and PbCl2 (0.01 mmol) in THF (2.0 mL) was sonicated for 1 h in an ultrasonic cleaner bath under Ar. To the mixture, diiodomethane (10 mmol) in THF (20 ml) was added dropwise over 15 min at 0 ° C with vigorous stirring. The mixture was stirred for 2 h at 0 ° C. After the stirring was stopped, the reaction vessel was stood undisturbed for several hours. Excess zinc was separated by sedimentation. ^{1}H NMR spectra of the obtained supernatant showed a broad singlet at -1.2 ppm at 0 ° C, which corresponded to the methylene proton of **1**. The supernatant was used for the further reaction as a solution of **1** in THF (0.5–0.6 M). Concentration was determined by nmr using 2,2,4,4-tetramethylbutane as an internal standard. Bis(Iodozincio)methane in THF can be kept unchanged at least for a month in the sealed reaction vessel.

General procedure for the preparation of 2-(hydroxyalkyl)-1-alkylcyclopropanol 3:[2] To a solution of α,.β-epoxyketone (**2**, 1 mmol) in THF (4 mL), bis(iodozincio)methane (**1**, 1.2 mmol) was added at room temperature. The mixture was stirred at room temperature for 30 min. Then saturated aqueous solution of NH_4Cl was added to quench the reaction and extracted with ethyl acetate. The combined organic layers were washed with brine, and dried over Na_2SO_4. The

solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography to give the corresponding 2-(hydroxyalkyl)-1-alkylcyclopropanol **3**.

(1*R,2*R**)-2-((*R**)-1-hydroxyethyl)-1-phenylcyclopropanol (3a)**

^{1}HNMR (500MHz, C_6D_6) δ 7.25-7.22 (m, 2H), 7.17-7.14 (m, 2H), 7.07-7.03 (m, 1H), 4.39 (bs, 1H), 3.81-3.75 (m, 1H), 3.44 (bs, 1H), 1.23 (d, *J* = 6.5 Hz, 3H), 1.20-1.14 (m, 1H), 0.89-0.85 (m, 2H); ^{13}CNMR (125MHz, C_6D_6) δ 145.3, 128.3, 126.3, 124.6, 69.0, 59.3, 35.5, 22.7, 21.5; Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.29, H, 8.03.; HRMS (m/z) Found: 178.0992. Calcd for $C_{11}H_{14}O_2$: 178.0994.

(1*R,2*R**)-2-(hydroxymethyl)-1-phenylcyclopropanol (3b)**

^{1}HNMR (500MHz, C_6D_6) δ 7.25-7.22 (m, 2H), 7.17-7.14 (m, 2H), 7.07-7.03 (m, 1H), 4.17 (bs, 1H), 3.86 (dd, *J* = 11.5, 5.0 Hz, 1H), 3.60 (dd, *J* = 11.5, 9.0 Hz, 1H), 3.22 (bs, 1H), 1.35-1.29 (m, 1H), 0.92-0.86 (m, 2H); ^{13}CNMR (125MHz, C_6D_6) δ 145.2, 128.4, 126.3, 124.6, 62.0, 59.2, 29.7, 20.9; HRMS (m/z) Found: 164.0837. Calcd for $C_{10}H_{12}O_2$: 164.0837.

(1*S,2*R**)-2-(hydroxymethyl)-2-methyl-1-phenylcyclopropanol (3c)**

^{1}HNMR (300MHz, $CDCl_3$) δ 7.39-7.23 (m, 5H), 3.91 (d, *J* = 11.7 Hz, 1H), 3.80 (d, *J* = 11.7 Hz, 1H), 3.06 (bs, 2H), 1.05 (s, 2H), 0.81 (s, 3H); ^{13}CNMR (75MHz, C_6D_6) δ 140.6, 128.7, 128.6, 127.8, 67.7, 65.6, 29.5, 22.7, 19.0; HRMS (m/z) Found: 178.0990. Calcd for $C_{11}H_{14}O_2$: 178.0994.

(1*R,2*R**)-2-(hydroxymethyl)-1-pentylcyclopropanol (3d)**

^{1}HNMR (300MHz, $CDCl_3$) δ 3.99 (dd, *J* = 11.4, 5.1 Hz, 1H), 3.59 (dd, *J* = 11.4, 9.0 Hz, 1H), 2.39 (bs, 2H), 1.56-1.46 (m, 4H), 1.35-1.26 (m, 4H), 1.07-0.97 (m, 1H), 0.89 (t, J = 7.2 Hz, 3H), 0.67-0.57 (m, 2H); ^{13}CNMR (125MHz, C_6D_6) δ 62.6, 59.0, 39.1, 31.8, 25.5, 25.4, 22.7, 17.4, 14.0; HRMS (m/z) Found: 158.1309. Calcd for $C_9H_{18}O_2$: 158.1307.

(1*R,2*R**)-2-((*R**)-1-hydroxyethyl)-2-methyl-1-pentylcyclopropanol (3e)**

^{1}HNMR (500MHz, C_6D_6) δ 7.29-7.26 (m, 2H), 7.18-7.14 (m, 2H), 7.10-7.07 (m, 1H), 4.03 (q, *J* = 7.0 Hz, 1H), 2.73 (bs, 1H), 2.62 (bs, 1H), 1.29 (d, *J* = 7.0 Hz, 3H), 0.83 (d, *J* = 5.5 Hz, 1H), 0.80 (d, *J* = 5.5 Hz, 1H), 0.70 (s, 3H); ^{13}CNMR (125MHz, C_6D_6) δ 141.2, 128.7, 128.3, 127.4, 70.6, 65.6, 32.0, 22.3, 19.6, 14.9; HRMS (m/z) Found: 192.1146. Calcd for $C_{12}H_{16}O_2$: 192.1150.

(1*R,2*R**)-2-((*S**)-hydroxy(phenyl)methyl)-1-methylcyclopropanol (3f)**

^{1}HNMR (500MHz, C_6D_6) δ; 7.47-7.45 (m, 2H), 7.24-7-20 (m, 2H), 7.14-7.10 (m, 1H), 4.63 (d, *J* = 9.0 Hz, 1H), 3.33 (bs, 2H), 1.27 (s, 3H), 0.95 (ddd, *J* = 9.5, 9.0, 6.0 Hz, 1H), 0.70 (dd, *J* = 6.0, 6.0

Hz, 1H), 0.36 (dd, *J* = 9.5, 6.0 Hz, 1H); ^{13}CNMR (125MHz, C_6D_6) δ 143.9, 127.6, 126.5, 125.5, 74.2, 54.9, 31.7, 24.6, 18.0; IR (neat) 3345, 3335 cm^{-1}; Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.07, H, 7.90.

(1*R,2*R**)-2-(2-hydroxypropan-2-yl)-1-phenylcyclopropanol (3g)**

^{1}HNMR (300MHz, C_6D_6) δ 7.22-7.19 (m, 2H), 7.16-7.12 (m, 2H), 7.05-7.00 (m, 1H), 4.19 (bs, 1H), 3.55 (bs, 1H), 1.37-1.33 (m, 1H), 1.31 (s, 3H), 1.20 (s, 3H), 1.03-0.95 (m, 1H), 0.89-0.79 (m, 1H); ^{13}CNMR (75MHz, C_6D_6) δ 144.8, 128.4, 126.4, 124.7, 70.4, 60.6, 37.1, 31.0, 30.3, 17.1; Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.13; H, 8.19.

Procedure for the preparation of 2,3-dihydroxy-3-phenyl-4-pentene (5a)

To the solution of (3-methyloxiran-2-yl)(phenyl)methanone (**2a**, 0.5 mmol) and THF (2 mL), bis(iodozincio)methane (**1**, 0.55 mmol, 0.5 M in THF) was added at room temperature, and stirred for 30 min. Then the reaction mixture was heated to reflux for additional 2 h. The resulting mixture was poured into sat. NH_4Claq and extracted with ethyl acetate. The combined organic layers were washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography to give **5a** in 68% yield. ^{1}HNMR (300MHz, $CDCl_3$) δ 7.52-7.23 (m, 5H), 6.34 (dd, *J* = 17.1, 10.5 Hz, 0.28H), 6.27 (dd, *J* = 17.1, 10.5 Hz, 0.72H), 5.47 (dd, *J* = 17.1, 1.5 Hz, 0.28H), 5.46 (dd, *J* = 17.1, 1.5 Hz, 0.72H), 5.30 (dd, *J* = 10.5, 1.5 Hz, 0.28H), 5.29 (dd, *J* = 10.5, 1.5 Hz, 0.72H), 4.14 (q, *J* = 6.3 Hz, 0.72H), 4.10 (q, *J* = 6.3 Hz, 0.28H), 1.18 (d, *J* = 6.3 Hz, 2.16H), 0.97 (d, *J* = 6.3 Hz, 0.84H); ^{13}CNMR (75MHz, $CDCld_3$) δ 143.8, 142.5, 139.3, 129.0, 128.8, 128.6, 127.7, 127.3, 126.3, 125.6, 115.7, 115.2, 79.7, 79.3, 73.9, 73.1, 17.4, 16.7; IR (neat) 3383 cm^{-1}; Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.84, H, 8.03.; HRMS (m/z) Found: 178.0993. Calcd for $C_{11}H_{14}O_2$: 178.0994.

General procedure of the rearrangement with catalytic *t*-Bu$_3$ZnLi: *t*-Bu_3ZnLi was prepared by liberated procedure.[3] To a solution of 2-(1-hydroxyalkyl)-1-alkylcyclopropanol (**3**, 1 mmol) in THF (8 mL), *t*-BuLi (1.6 M in pentane, 3 mmol) was added at 0 °C, and stirred for 10 min. To the solution, prepared ^{t}Bu_3ZnLi (THF solution, 0.2 mmol) was added at 0 °C. The mixture was heated to reflux. Then saturated aqueous solution of NH_4Cl was added to quench the reaction and extracted with ethyl acetate. The combined organic layers were washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography to give the corresponding *vic*-diol.

1,2-Dihydroxy-2-phenyl-3-butene (5b)

^{1}HNMR (300MHz, $CDCl_3$) δ 7.48-7.43 (m, 2H), 7.39-7.33 (m, 2H), 7.30-7.25 (m, 1H), 6.15 (dd, *J*

= 17.4, 10.5 Hz, 1H), 5.39 (dd, *J* = 17.4, 1.2 Hz, 1H), 5.29 (dd, *J* = 10.5, 1.2 Hz, 1H), 3.78 (d, *J* = 1.5 Hz, 2H), 2.64 (bs, 2H); ^{13}CNMR (75MHz, $CDCld_3$) δ 142.7, 140.8, 128.7, 127.7, 125.9, 115.8, 77.8, 69.8; HRMS (m/z) Found:164.0833. Calcd for $C_{10}H_{12}O_2$:164.0837.

1,2-Dihydroxy-3-methyl-2-phenyl-3-butene (5c)

^{1}HNMR (300MHz, $CDCl_3$) δ 7.47-7.25 (m, 5H), 5.16 (dq, *J* = 0.9, 0.9 Hz, 1H), 5.08 (dq, *J* = 1.2, 0.9 Hz, 1H), 4.05 (d, *J* = 11.1 Hz, 1H), 3.89 (d, *J* = 11.1 Hz, 1H), 1.64 (dd, *J* = 1.2, 0.9 Hz, 3H); ^{13}CNMR (75MHz, $CDCld_3$) δ 147.1, 142.2, 128.6, 127.8, 126.0, 112.2, 79.5, 68.4, 19.8; IR (neat) 3546, 3278 cm^{-1}; mp 30.0 – 30.5 ˚C; Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.41, H, 7.94.; HRMS (m/z) Found: 178.0993. Calcd for $C_{11}H_{14}O_2$:178.0994.

1,2-Dihydroxy-2-vinylheptane (5d)

^{1}HNMR (300MHz, $CDCl_3$) δ 5.80 (ddd, *J* = 17.4, 10.8, 0.6 Hz, 1H), 5.34 (ddd, *J* = 17.4, 1.5, 0.6 Hz, 1H), 5.25 (ddd, *J* = 10.8, 1.5, 0.6 Hz, 1H), 3.49 (s, 2H), 2.28 (bs, 1H), 1.97 (bs, 1H), 1.58-1.42 (m, 2H), 1.36-1.24 (m, 6H), 0.87 (t, 3H, *J* = 6.6 Hz); ^{13}CNMR (125MHz, $CDCld_3$) δ 140.8, 115.0, 76.0, 68.7, 37.0, 32.2, 22.8, 22.5, 14.0; IR (neat) 3382 cm^{-1}; Calcd for $C_9H_{18}O_2$: C, 68.31; H, 11.47. Found: C, 68.04, H, 11.54.; HRMS (m/z) Found: 157.1233. Calcd for $C_9H_{17}O_2$:157.1229.

2,3-Dihydroxy-4-methyl-3-phenyl-4-pentene (5e)

^{1}HNMR (500MHz, $CDCl_3$) δ 7.57-7.20 (m, 5H), 5.28 (dq, *J* = 1.0, 1.0 Hz, 0.72H), 5.24 (dq, *J* = 1.0, 1.0 Hz, 0.28H), 5.07 (dq, *J* = 1.5, 1.0 Hz, 0.28H), 4.89 (dq, *J* = 1.5, 1.0 Hz, 0.72H), 4.61 (q, *J* = 6.0 Hz, 0.72H), 4.49 (q, *J* = 6.0 Hz, 0.28H), 1.65 (dd, *J* = 1.5, 1.0 Hz, 0.84H), 1.56 (dd, *J* = 1.5, 1.0 Hz, 2.16H), 1.24 (d, *J* = 6.0 Hz, 2.16H), 0.93 (d, *J* = 6.0 Hz, 0.84H); ^{13}CNMR (125MHz, $CDCld_3$) δ 149.1, 146.5, 143.7, 141.4, 128.3, 127.9, 127.2, 126.9, 126.1, 125.3, 110.8, 110.7, 80.9, 80.8, 70.0, 69.2, 19.4, 19.3, 16.5, 16.4; IR (neat) 3458 cm^{-1}; Calcd for $C_9H_{18}O_2$: C, 74.97; H, 8.39. Found: C, 74.91, H, 8.56.

1,2-Dihydroxy-2-methyl-1-phenyl-3-butene (5f)

^{1}HNMR (300MHz, $CDCl_3$) δ 7.35-7.25 (m, 5H), 5.86 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.25 (dd, *J* = 17.4, 1.5 Hz, 1H), 5.16 (dd, *J* = 10.8, 1.5 Hz, 1H), 2.17 (s, 1H), 1.27 (s, 3H); ^{13}CNMR (75MHz, $CDCl_3$) δ 140.4, 128.22, 128.17, 128.0, 127.8, 114.9, 80.9, 76.1, 24.8; IR (neat) 3406 cm^{-1}; Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.00, H, 8.11.

2,3-Dihydroxy-2-methyl-3-phenyl-4-pentene (5g)

^{1}HNMR (300MHz, $CDCl_3$) δ 7.57-7.53 (m, 2H), 7.37-7.23 (m, 3H), 6.74 (dd, *J* = 17.1, 10.8 Hz, 1H), 5.47 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.34 (dd, *J* = 10.8, 1.5 Hz, 1H), 1.27 (d, *J* = 0.3 Hz, 3H), 1.10

(d, J = 0.3 Hz, 3H); ^{13}CNMR (75MHz, $CDCl_3$) δ 142.7, 140.5, 128.0, 127.4, 127.3, 115.8, 80.9, 75.9, 25.8, 25.0; IR (neat) 3462, 3326 cm^{-1}; mp 45.3 - 46.0 ˚C; Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.70, H, 8.38.;

Stereospecificity of the rearrangement (Scheme 3)

The enantiomeric purity of (*S*)-**5b** was determined by ^{1}HNMR after converting into the corresponding Mosher ester: To the solution of **5b** (0.1 mmol), dichloromethane (0.5 mL) and pyridine (0.24 mmol), (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (0.12 mmol) was added at 0 ˚C and stirred for 1 h. Then the solution was poured into sat. Na_2CO_3aq, and the organic layer was extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified with silica gel column chromatography to give the corresponding ester. The enantiomeric excess of the product was determined by ^{1}HNMR based on methoxy group (3.40 ppm for (*S*)-isomer and 3.44 ppm for (*R*)-isomer).

(1*R,14*R**,15*S*)-bicyclo[13.1.0]hexadecane-1,14-diol (10)**

^{1}HNMR (500MHz,$CDCl_3$) δ 4.05 (dt, J = 6.0, 3.0 Hz, 1H), 2.41 (bs, 2H), 2.12-2.05 (m, 1H), 1.75-1.71 (m, 2H), 1.58-1.25 (m, 20H), 1.02-0.88 (m, 3H), 0.62 (dd, J = 10.0, 5.5 Hz, 1H); ^{13}CNMR (125MHz, $CDCl_3$) δ 71.2, 61.0, 39.2, 38.8, 28.1, 27.8, 27.2, 26.92, 26.85, 26.44, 26.42, 26.3, 25.9, 25.4, 24.2, 15.7; Calcd for $C_{16}H_{30}O_2$: C, 75.54; H, 11.89. Found: C, 75.37, H, 12.03.; HRMS (m/z) Found: 255.2320. Calcd for C16H31O2: 255.2324.

1,2-Dihydroxy-1-vinylcyclotetradecane (11)

^{1}HNMR (500MHz, $CDCl_3$) δ 5.92 (dd, J = 17.5, 10.5 Hz, 1H), 5.37 (dd, J = 17.5, 1.5 Hz, 1H), 5.23 (dd, J = 10.5, 1.5 Hz, 1H), 3.72 (d, J = 10.0 Hz, 1H), 1.71-1.04 (m, 24H); ^{13}CNMR (125MHz, $CDCl_3$) δ 140.5, 115.0, 77.5, 74.4, 36.9, 28.6, 26.43, 26.35, 25.8, 24.5, 23.7, 23.6, 23.5, 23.4, 19.2; IR (neat) 3325 cm^{-1}; mp 107.5 – 108.5 ˚C; Calcd for $C_{16}H_{30}O_2$: C, 75.54; H, 11.89. Found: C, 75.26, H, 11.98.; HRMS (m/z) Found: 254.2247. Calcd for $C_{16}H_{30}O_2$: 254.2246.

(*E*)-Cyclohexadec-3-enone (12):[4] To a solution of **10** (1 mmol) in CH_2Cl_2 (4 mL), trifluoroacetic acid (5 mmol) was added at 0 ˚C, and stirred for 30 min. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography to give (*E*)-Cyclohexadec-3-enone (**12**, >99%).

^{1}HNMR (500MHz, $CDCl_3$) δ 5.58-5.47 (m, 2H), 3.03 (d, J = 6.5 Hz, 2H), 2.49 (t, J = 7.0 Hz, 2H), 2.09 (dt, J = 6.5, 6.0 Hz, 2H), 1.59 (tt, J = 7.0, 7.0 Hz), 1.42-1.21 (m, 18H). ^{13}CNMR (125MHz, $CDCl_3$) δ 210.4, 135.6, 123.2, 47.7, 40.9, 32.1, 28.2, 27.4, 27.2, 27.1, 26.9, 26.5, 26.2, 26.1, 25.6, 22.3.; HRMS (m/z) Found: 236.2136. Calcd for $C_{16}H_{28}O$: 236.2140.

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