Regioselective Alkyl and Alkynyl Substitution Reactions of Epoxy Alcohols by the use of Organoaluminum Ate-Complexes: Regiochemical Reversal of Nucleophilic Substitution Reactions

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Experimental

General. All reactions were carried out under a dry nitrogen atmosphere. Routine flash column chromatography was achieved with Merck silica gel 60 for purification of products.

Material. Anhydrous CH₂Cl₂ was dried by distillation from P₂O₅.

Epoxy alcohols 1¹, 4², and 5² were prepared according to the previously described procedures, respectively. Diols 2a¹, 11³, and 1 3⁴ were also previously reported by other groups.

(2S,3S,4S)-4-(tert-Butyldimethylsiloxyl)-2,3-epoxy-1-pentanol 6: IR (neat) 3450, 1254, 1157, 1103 cm⁻¹;¹H NMR (270 MHz, CDCl₃) δ 0.05 (s, 3 H), 0.06 (s, 3 H), 0.88 (s, 9 H), 1.23 (d, J = 6.3 Hz, 3 H), 1.62 (bt, J = 5.4 Hz, 1 H), 2.91 (dd, J = 2.3, 4.1 Hz, 1 H), 3.13 (dt, J = 2.3, 4.3 Hz, 1 H), 3.64 (ddd, J = 4.3, 7.6, 12.6 Hz, 1 H), 3.83 (dq, J = 4.1, 6.3 Hz, 1 H), 3.94 (ddd, J = 2.5, 5.3, 12.6 Hz, 1 H);¹³C NMR (67.8 MHz, CDCl₃) δ -4.71, -4.60, 18.21, 20.92, 25.82 (3 C), 55.86, 58.97, 61.49, 66.85; HRMS Caled for C₇H₁₅O₃Si (M⁻Bu); 175.0790. Found: 175.0783.

(2S,3S,4S)-5-Benzylxylo-3,4-epoxy-2-pentanol 7: IR (neat) 3430, 1655, 1560, 1113, 895 cm⁻¹;¹H NMR (270 MHz, CDCl₃) δ 1.25 (d, J = 6.4 Hz, 3 H), 1.87 (bs, 1 H), 2.96 (dd, J = 2.5, 3.1 Hz, 1 H), 3.26 (dt, J = 2.3, 5.6 Hz, 1 H), 3.50 (dd, J = 5.6, 11.5 Hz, 1 H), 3.78 (dd, J = 2.8, 11.5 Hz, 1 H), 3.96-4.04 (bm, 1 H), 4.57 (d, J = 12.0 Hz, 1 H), 4.59 (d, J = 12.0 Hz, 1 H), 7.27-7.39 (m, 5 H);¹³C NMR (67.8 MHz, CDCl₃) δ 18.81, 53.53, 58.81, 64.58, 69.71, 73.27, 127.62 (2 C), 127.67, 128.32 (2 C), 137.65; HRMS Caled for C₁₂H₁₆O₃; 208.1099. Found: 208.1094.

(2S,3S,4R)-5-Benzylxylo-2,3-epoxy-4-methyl-1-pentanol 8: IR (neat) 3450, 1497, 1454, 1207, 1099 cm⁻¹;¹H NMR (270 MHz, CDCl₃) δ 1.01 (d, J = 6.9 Hz, 3 H), 1.74-1.86 (m, 2 H), 2.95 (dd, J = 2.5, 6.8 Hz, 1 H), 3.00 (dt, J = 2.5, 4.3 Hz, 1 H), 3.45 (dd, J = 5.6, 9.1 Hz, 1 H), 3.50 (dd, J = 5.6, 9.2 Hz, 1 H), 3.57-3.66 (m, 1 H), 3.86-3.95 (m, 1 H), 4.52 (s, 2 H), 7.20-7.38 (m, 5 H);¹³C NMR (67.8 MHz, CDCl₃) δ 13.43, 35.84, 56.76, 61.83, 72.48, 73.14, 127.44 (3 C), 128.26 (2 C), 138.25; HRMS Caled for C₁₃H₁₈O₃; 222.1256. Found: 222.1219.

(2R*,3R*)-2,3-Epoxy-5-phenyl-1-pentanol 9: IR (neat) 3410, 1603, 1541, 1093, 1030, 880, 700 cm⁻¹;¹H NMR (270 MHz, CDCl₃) δ 1.53 (b, 1 H), 1.82-1.98 (m, 2 H), 2.68-2.89 (m, 3 H), 2.99 (dt, J = 2.3, 5.8 Hz, 1 H), 3.57 (ddd, J = 4.3, 7.4, 12.5 Hz, 1 H), 3.84 (ddd, J = 2.6, 5.3, 12.5 Hz, 1 H).
7.18-7.33 (m, 5 H); $^{13}$C NMR (67.8 MHz, CDCl$_3$) $\delta$ 32.24, 33.38, 55.35, 58.63, 61.60, 126.00, 128.26 (2 C), 128.36 (2 C), 140.90; HRMS Calcd for C$_{11}$H$_{12}$O ($\text{[M-H$_2$O]}$); 160.0888. Found: 160.0913.

(2R*,3R*)-2,3-Epoxy-5-phenylsulfonyl-1-pentanol 10: IR (neat) 3500, 1655, 1560, 1448, 1308, 1146, 1086, 1026, 881, 689 cm$^{-1}$; $^1$H NMR (270 MHz, CDCl$_3$) $\delta$ 1.81 (b, 1 H), 1.86-2.00 (m, 1 H), 2.10-2.22 (m, 1 H), 2.94-2.98 (bm, 1 H), 3.07 (ddd, J = 2.1, 4.6, 6.6 Hz, 1 H), 3.23 (dd, J = 6.9, 8.1 Hz, 2 H), 3.62-3.70 (b, 1 H), 3.82-3.87 (b, 1 H), 7.55-7.94 (m, 5 H); $^{13}$C NMR (67.8 MHz, CDCl$_3$) $\delta$ 25.14, 52.77, 53.58, 58.56, 61.20, 127.91 (2 C), 129.33 (2 C), 133.85, 138.69; HRMS Calcd for C$_{11}$H$_{12}$O$_3$S ($\text{[M-H$_2$O]}$); 224.0507. Found: 224.0470.

Typical Procedure for the Alkyl Substitution Reaction of 2,3-Epoxy Alcohols.

(2R*,3R*)-4-Benzylxy-2-methyl-1,3-butanediol 11: To a solution of epoxy alcohol 4 (97 mg, 0.5 mmol) in CH$_2$Cl$_2$ (10 mL) was added a 1.50 M hexane solution of n-BuLi (0.37 mL, 0.55 mmol) at 0 °C. After being stirred for 30 min, a 1.0 M hexane solution of Me$_3$Al (1.5 mL, 1.5 mmol) was added at 0 °C, and the mixture was stirred for 30 min. Water followed by aqueous 3 N HCl was added, and the mixture was separated. The aqueous layer was extracted with ethyl acetate, and the combined organic layer was washed with brine, and dried over MgSO$_4$. Concentration under reduced pressure followed by flash column chromatography afforded 101 mg (96%) of the known diol 11 as a 97:3 mixture of regio isomers.

(2R*,3R*)-4-(tert-Butyldimethylsiloxy)-2-ethyl-1,3-butanediol 2b: IR (neat) 3400, 1460, 1256, 1111 cm$^{-1}$; $^1$H NMR (270 MHz, CDCl$_3$) $\delta$ 0.09 (b, 6 H), 0.91 (s, 9 H), 0.95 (t, J = 3.6 Hz, 3 H), 1.35-1.50 (m, 3 H), 2.84 (bd, J = 2.8 Hz, 1 H), 3.06 (b, 1 H), 3.57 (dd, J = 8.6, 10.7 Hz, 1 H), 3.65-3.84 (m, 4 H); $^{13}$C NMR (67.8 MHz, CDCl$_3$) $\delta$ -5.28, -5.23, 11.77, 18.35, 21.33, 25.92 (3C), 43.67, 63.71, 65.84, 75.27; HRMS Calcd for C$_8$H$_{19}$O$_3$Si ($\text{[M-4Bu]}$); 191.1103. Found: 191.1104.

(2R*,3R*)-4-Benzylxy-2-ethyl-1,3-butanediol 12: IR (neat) 3400, 1655, 1560, 1099, 1028, 910, 737 cm$^{-1}$; $^1$H NMR (270 MHz, CDCl$_3$) $\delta$ 0.93 (t, J = 7.3 Hz, 3 H), 1.29-1.56 (m, 3 H), 2.78 (bd, J = 3.1 Hz, 1 H), 2.85 (bt, J = 5.9 Hz, 1 H), 3.51 (dd, J = 7.7, 9.4 Hz, 1 H), 3.61 (dd, J = 3.5, 9.4 Hz, 1 H), 3.69 (dt, J = 5.6, 11.4 Hz, 1 H), 3.81 (dddt, J = 3.0, 6.1, 11.4 Hz, 1 H), 3.86-3.93 (m, 1 H), 4.57 (s, 2 H), 7.27-7.64 (m, 5 H); $^{13}$C NMR (67.8 MHz, CDCl$_3$) $\delta$ 11.76, 21.36, 43.81, 63.63, 73.21, 73.45, 73.84, 127.68 (2 C), 127.81, 128.41 (2 C), 137.58; HRMS Calcd for C$_{13}$H$_{20}$O$_3$; 224.1412. Found: 224.1383.

(2R*,3S*)-4-Benzylxy-2-ethyl-1,3-butanediol 14: IR (neat) 3400, 1655, 1560, 1497, 1101, 698 cm$^{-1}$; $^1$H NMR (270 MHz, CDCl$_3$) $\delta$ 0.94 (t, J = 7.4 Hz, 3 H), 1.29-1.47 (m, 2 H), 1.63-1.73 (m, 1 H), 2.65 (b, 1 H), 2.77 (bd, J = 3.1 Hz, 1 H), 3.53-3.61 (m, 2 H), 3.72 (bt, J = 4.4 Hz, 2 H), 4.00-4.07 (m, 1 H), 4.56 (d, J = 12.3 Hz, 1 H), 4.57 (d, J = 12.3 Hz, 1 H), 7.26-7.39 (m, 5 H); $^{13}$C NMR (67.8 MHz, CDCl$_3$) $\delta$ 12.23, 19.03, 44.44, 63.37, 71.88, 73.23, 73.54, 127.67 (2 C), 127.80, 128.41 (2 C), 137.58; HRMS Calcd for C$_{13}$H$_{20}$O$_3$; 224.1412. Found: 224.1395.

(2R,3S,4S*)-4-(tert-Butyldimethylsiloxy)-2-methyl-1,3-pentanediol 15: IR (neat) 3400, 1385, 1256, 937, 810 cm$^{-1}$; $^1$H NMR (270 MHz, CDCl$_3$) $\delta$ 0.09 (s, 3 H), 0.09 (s, 3 H), 0.82 (d, J = 6.9 Hz, 3 H), 0.90 (s, 9 H), 1.11 (d, J = 6.3 Hz, 3 H), 1.73-1.83 (m, 1 H), 2.75 (bd, J = 1.6 Hz, 1 H), 3.35-3.43 (b, 1 H), 3.48 (bd, J = 8.7 Hz, 1 H), 3.54-3.70 (bm, 2 H), 3.92 (dq, J = 3.3, 6.3 Hz, 1 H); $^{13}$C
NMR (67.8 MHz, CDCl$_3$) $\delta$ -4.80, -4.40, 13.20, 15.90, 18.12, 25.85 (3 C), 36.53, 68.03, 69.37, 80.19; HRMS Calcd for C$_9$H$_{19}$O$_3$Si (M$^+$/Bu); 191.1103. Found: 191.1115.

(2S, 3R, 4S)-1-Benzylxoxy-3-methyl-2, 4-pentanediol 16: IR (neat) 3400, 1655, 1560, 1105, 905 cm$^{-1}$; $^1$H NMR (270 MHz, CDCl$_3$) $\delta$ 0.89 (d, J = 7.1 Hz, 3 H), 1.18 (d, J = 6.6 Hz, 3 H), 1.74 (d, quint, J = 2.3, 7.1 Hz, 1 H), 2.89-2.98 (b, 2 H), 3.47 (dd, J = 7.7, 9.4 Hz, 1 H), 3.59 (dd, J = 3.3, 9.4 Hz, 1 H), 3.86 (dt, J = 3.3, 7.4 Hz, 1 H), 3.99-4.08 (b, 1 H), 4.57 (s, 2 H), 7.30-7.36 (m, 5 H); $^{13}$C NMR (67.8 MHz, CDCl$_3$) $\delta$ 11.57, 19.34, 40.19, 69.29, 72.98, 73.44, 73.70, 127.67 (2 C), 127.79, 128.41 (2 C), 137.66; HRMS Calcd for C$_{13}$H$_{20}$O$_3$; 224.1418. Found: 191.1412.

(2R, 3S, 4R)-5-Benzylxoxy-2, 4-dimethyl-1, 3-pentanediol 17: IR (neat) 3450, 1456, 1096, 1076, 986, 698 cm$^{-1}$; $^1$H NMR (270 MHz, CDCl$_3$) $\delta$ 0.97 (d, J = 6.9 Hz, 3 H), 1.01 (d, J = 6.9 Hz, 3 H), 1.85 (d, s, 3.3, 6.9 Hz, 1 H), 1.98-2.13 (m, 1 H), 3.43-3.54 (m, 3 H involving a dd at 3.50, J = 5.9, 9.2 Hz), 3.58-3.67 (m, 1 H), 3.73 (dd, J = 3.8, 9.2 Hz, 1 H), 3.77-3.85 (m, 1 H), 4.52 (d, J = 11.9 Hz, 1 H), 4.53 (d, J = 11.9 Hz, 1 H), 7.20-7.40 (m, 5 H); $^{13}$C NMR (67.8 MHz, CDCl$_3$) $\delta$ 14.58, 14.76, 35.53, 37.24, 66.98, 73.73, 74.36, 82.69, 127.61 (2 C), 127.83, 128.43 (2 C), 137.28; HRMS Calcd for C$_{14}$H$_{23}$O$_3$ (M+H$^+$); 239.1647. Found: 239.1681.

(2R*, 3R*)-3-Methyl-5-phenyl-1,2-pentanediol 18: IR (neat) 3380, 1560, 1497, 1070, 1030, 908, 698 cm$^{-1}$; $^1$H NMR (270 MHz, CDCl$_3$) $\delta$ 0.97 (d, J = 6.6 Hz, 3 H), 1.40-1.70 (m, 2 H), 1.80-1.97 (m, 2 H), 2.08 (bd, J = 3.0 Hz, 1 H), 2.55 (ddd, J = 6.6, 10.1, 13.7 Hz, 1 H), 2.76 (ddd, J = 5.1, 10.4, 13.7 Hz, 1 H), 3.45-3.58 (m, 2 H), 3.64-3.76 (m, 1 H), 7.15-7.30 (m, 5 H); $^{13}$C NMR (67.8 MHz, CDCl$_3$) $\delta$ 15.28, 33.26, 34.32, 35.75, 64.57, 76.07, 125.62, 128.21 (4 C), 142.32; HRMS Calcd for C$_{12}$H$_{18}$O$_2$; 194.1307. Found: 194.1314.

(2R*, 3R*)-2-Methyl-5-(phenylsulfonyl)-1,3-pentanediol 19: IR (neat) 3450, 1447, 1304, 1146, 1086, 1026, 689 cm$^{-1}$; $^1$H NMR (270 MHz, CDCl$_3$) $\delta$ 0.86 (d, J = 6.9 Hz, 3 H), 1.64-2.17 (m, 3 H), 2.37 (bs, 1 H), 3.23 (ddd, J = 5.9, 9.9, 14.2 Hz, 1 H), 3.35 (ddd, J = 5.4, 10.1, 14.2 Hz, 1 H), 3.48 (b, 1 H), 3.58-3.82 (bm, 3 H), 7.54-7.70 (m, 3 H), 7.90-7.95 (m, 2 H); $^{13}$C NMR (67.8 MHz, CDCl$_3$) $\delta$ 13.61, 28.09, 39.95, 52.97, 67.70, 75.00, 127.86 (2 C), 129.23 (2 C), 133.65, 139.06; HRMS Calcd for C$_{12}$H$_{19}$O$_4$S; 259.1004. Found: 259.0978.

Typical Procedure for the Alkynyl Substitution Reaction of 2,3-Epoxy Alcohols.

(2R*, 3R*)-4-Benzylxoxy-2-[(trimethylsilyl)ethylxyl]-1,3-butanediol 20: To a solution of (trimethylsilyl)acetylene (0.17 mL, 1.2 mmol) in CH$_2$Cl$_2$ (4 mL) was added a 1.5 M hexane solution of n-BuLi (0.80 mL, 1.2 mmol) at 0 °C. After being stirred for 30 min, a 1.0 M hexane solution of Me$_2$AlCl (1.2 ml, 1.2 mmol) was added at 0 °C. After being stirred for 30 min, the mixture was cooled to -78 °C. To this was added a solution of lithium alkoxide, which was prepared from epoxy alcohol 4 (58 mg, 0.3 mmol) in CH$_2$Cl$_2$ (2 ml) and a 1.5 M hexane solution of n-BuLi (0.22 mL, 0.33 mmol) at 0 °C for 30 min. After being stirred for 30 min, the mixture was allowed to warm to 0 °C and stirring was continued for 1 h. Water followed by aqueous 3 N HCl was added, and the mixture was separated. The aqueous layer was extracted with ethyl acetate, and the combined organic layer was washed with brine, and dried over MgSO$_4$. Concentration under reduced pressure followed by flash column chromatography afforded 82 mg (94%) of
diol 20 as a 91:9 mixture of regioisomers: IR (neat) 3450, 1454, 1250, 1074, 1030, 900, 698 cm\(^{-1}\); \(^1\)H NMR (270 MHz, CDCl\(_3\)) \(\delta\) 0.13 (s, 9 H), 2.51-2.61 (brm, 1 H), 2.69 (bd, \(J = 4.6\) Hz, 1 H), 2.77 (dt, \(J = 5.6, 9.2\) Hz, 1 H), 3.59 (dd, \(J = 6.3, 9.6\) Hz, 1 H), 3.77 (dd, \(J = 3.1, 9.6\) Hz, 1 H), 3.80-3.88 (brm, 2 H), 3.89-3.98 (brm, 1 H), 4.58 (d, \(J = 12.0\) Hz, 1 H), 4.62 (d, \(J = 12.0\) Hz, 1 H), 7.25-7.40 (m, 5 H); \(^13\)C NMR (67.8 MHz, CDCl\(_3\)) \(\delta\) 0.09 (3 C), 38.79, 63.97, 72.13, 72.48, 73.46, 89.49, 102.93, 127.67 (2 C), 127.77, 128.37 (2 C), 137.56; HRMS Calcd for C\(_{16}\)H\(_{24}\)O\(_3\)Si: 292.1495. Found: 292.1538.

\((2S*,3R*)\)-4-Benzylloxy-2-[2-((trimethylsilyl)ethynyl)-1,3-butanediol 21: IR (neat) 3460, 2341, 1686, 1250, 1094, 1047, 843, 698 cm\(^{-1}\); \(^1\)H NMR (270 MHz, CDCl\(_3\)) \(\delta\) 0.15 (s, 9 H), 2.22 (t, \(J = 6.4\) Hz 1 H), 2.48 (d, \(J = 5.3\) Hz, 1 H), 2.91 (dt, \(J = 3.8, 5.9\) Hz, 1 H), 3.59 (dd, \(J = 5.4, 9.6\) Hz, 1 H), 3.64 (dd, \(J = 6.3, 9.6\) Hz, 1 H), 3.75-3.85 (m, 2 H), 3.96-4.05 (m, 1 H), 4.58 (s, 2 H), 7.26-7.39 (m, 5 H); \(^13\)C NMR (67.8 MHz, CDCl\(_3\)) \(\delta\) 0.16 (3 C), 39.13, 63.01, 69.79, 72.11, 73.43, 89.98, 102.28, 127.65 (2 C), 127.72, 128.34 (2 C), 137.61; HRMS Calcd for C\(_{16}\)H\(_{24}\)O\(_3\)Si: 292.1495. Found: 292.1477.

\((2R*,3R*)\)-4-(tert-Butyldimethylsiloxy)-2-[2-((trimethylsilyl)ethynyl)1,3-butanediol 22: IR (neat) 3460, 2363, 1420, 1252 cm\(^{-1}\); \(^1\)H NMR (270 MHz, CDCl\(_3\)) \(\delta\) 0.10 (s, 3 H), 0.11 (s, 3 H), 0.15 (s, 9 H), 0.92 (s, 9 H), 2.65-2.76 (m, 3 H), 3.70-3.93 (m, 5 H); \(^13\)C NMR (67.8 MHz, CDCl\(_3\)) \(\delta\) -5.31, -5.24, 0.10 (3 C), 18.44, 25.96 (3 C) 38.54, 64.12, 65.24, 73.40, 89.42, 103.11; HRMS Calcd for C\(_{15}\)H\(_{33}\)O\(_2\)Si\(_2\) ([M]+H): 317.168. Found: 317.1959.

\((2R,3S,4R*)\)-5-Benzylloxy-4-methyl-2-[2-((trimethylsilyl)ethynyl)1,3-pentanediol 23: IR (neat) 3460, 1686, 1560, 1250, 1078, 1030, 843, 698 cm\(^{-1}\); \(^1\)H NMR (270 MHz, CDCl\(_3\)) \(\delta\) 0.13 (s, 9 H), 1.18 (d, \(J = 7.3\) Hz, 3 H), 2.15-2.25 (m, 1 H), 2.71-2.79 (m, 1 H), 3.12 (bt, \(J = 6.2\) Hz, 1 H), 3.54 (dd, \(J = 3.6, 9.4\) Hz, 1 H), 3.65-3.72 (m, 2 H), 3.83-3.91 (m, 3 H), 4.49 (d, \(J = 11.9\) Hz, 1 H), 4.54 (d, \(J = 11.9\) Hz, 1 H), 7.25-7.40 (m, 5 H); \(^13\)C NMR (67.8 MHz, CDCl\(_3\)) \(\delta\) 0.15 (3 C), 15.56, 35.64, 40.50, 65.22, 72.94, 73.73, 78.93, 89.13, 103.90, 127.56 (2 C), 127.85, 128.44 (2 C), 137.32; HRMS Calcd for C\(_{18}\)H\(_{26}\)O\(_2\)Si ([M-H\(_2\)O]): 302.1702. Found: 302.1739.

\((2R*,3R*)\)-5-phenylsulfonfonyl-2-[2-((trimethylsilyl)ethynyl)1,3-pentanediol 24: IR (neat) 3500, 1717, 1558, 1306, 1250, 1148, 1086, 843, 689 cm\(^{-1}\); \(^1\)H NMR (270 MHz, CDCl\(_3\)) \(\delta\) 0.12 (s, 9 H), 1.85-2.05 (m, 1 H), 2.18-2.34 (m, 1 H), 2.40 (bs, 1 H), 2.61 (dd, \(J = 4.6, 6.8, 8.2\) Hz, 1 H), 3.17 (bd, \(J = 4.1\) Hz, 1 H), 3.22-3.43 (m, 2 H), 3.70-3.95 (m, 3 H), 7.53-7.95 (m, 5 H); \(^13\)C NMR (67.8 MHz, CDCl\(_3\)) \(\delta\) 0.08 (3 C), 28.57, 41.81, 52.88, 64.05, 71.40, 90.26, 102.32, 127.94 (2 C), 129.25 (2 C), 133.67, 138.83; HRMS Calcd for C\(_{16}\)H\(_{25}\)O\(_4\)SSi ([M]+H): 341.1243. Found: 341.1241.

References