

Electronic Supplementary Information

First Asymmetric Synthesis of a Differentially Silyl-protected Tris(alkynyl)methyl Methyl Ether

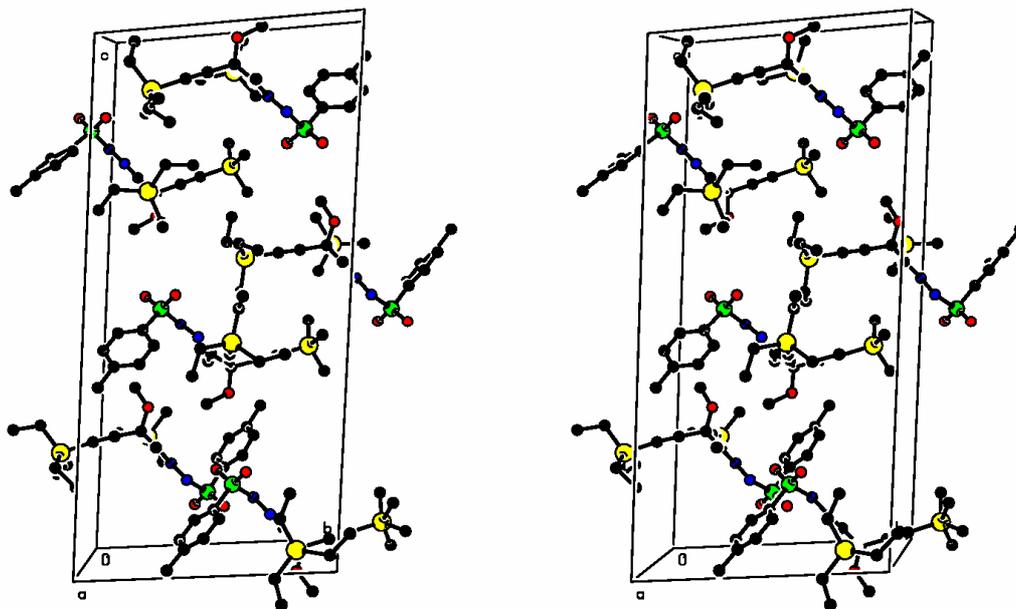
Vito Convertino, Peter Manini, W. Bernd Schweizer and François Diederich*

Laboratorium für Organische Chemie, ETH-Hönggerberg, CH-8093 Zürich, Switzerland.

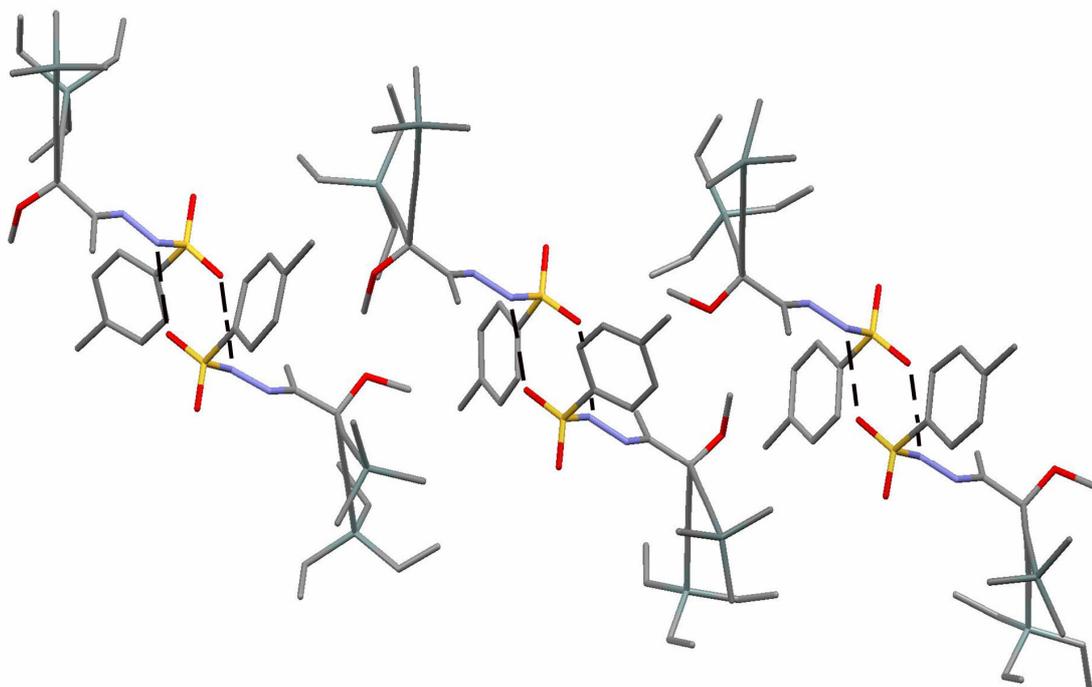
E-mail: diederich@org.chem.ethz.ch

Fig. 1 (ESI). *a)* Stereoview on the crystal packing of (*R*)-**14**. Color codes: C: black, Si: yellow, O: red, S: green, N: blue. *b)* Crystal structure of the six independent molecules of (*R*)-**14** forming the three pairs of H-bonded dimers. Color codes: C: grey, Si: light-green, O: red, S: yellow, N: blue.

a)



b)



Synthesis (ESI)

Synthesis of (*S*)-4: Trifluoromethanesulfonic acid (0.70 μL , $8.1 \cdot 10^{-4}$ mmol) was added to a solution of ethyl (*S*)-lactate (3.08 mL, 27.0 mmol) and 4-methoxybenzyl trichloroacetimidate (15.26 g, 54.0 mmol) in cyclohexane (45 mL) and CH_2Cl_2 (45 mL) at 0 °C. A white precipitate formed immediately. After 10 min, the mixture was warmed to 20° and stirred for 17 h. Hexane (120 mL) was added, and the resulting white precipitate was removed by filtration and washed again with hexane (60 mL). The organic phase was washed with sat aq. NaHCO_3 solution (120 mL) and sat. aq. NaCl solution (120 mL) and dried (MgSO_4). Evaporation and subsequent column chromatography (SiO_2 , hexane/EtOAc 10:1) afforded 5.52 g (86%) of (–)-(*S*)-4 as a colorless oil; R_f (hexane/EtOAc 10:1) 0.24; $[\alpha]_D^{25} = -78.7$ ($c = 1.08$, CHCl_3); $\nu_{\text{max}}(\text{CHCl}_3)/\text{cm}^{-1}$ 3010, 2984, 2960, 2937, 2904, 2837, 2059, 1887, 1739, 1612, 1586, 1513, 1465, 1456, 1443, 1422, 1395, 1374, 1302, 1249, 1142, 1110, 1062, 1034, 845, 825; $\delta_{\text{H}}(300 \text{ MHz}; \text{CDCl}_3)$ 1.29 (3 H, t, J 7), 1.41 (3 H, d, J 7), 3.80 (3 H, s), 4.02 (1 H, q, J 7), 4.21 (2 H, dq, J 7, J 2), 4.38 (1 H, d, J 11), 4.62 (1 H, d, J 11), 6.87 (2 H, d, J 9); 7.29 (2 H, d, J 9); $\delta_{\text{C}}(75 \text{ MHz}; \text{CDCl}_3)$ 173.18, 159.18, 129.53, 113.71, 73.70, 71.61, 60.81, 55.30, 18.82, 14.35; HR-EI-MS calcd for $\text{C}_{13}\text{H}_{18}\text{O}_4^+$ (M^+): 238.1205; found 238.1210; EA calcd for $\text{C}_{13}\text{H}_{18}\text{O}_4$ (238.28): C 65.53, H 7.61; found: C 65.52, H 7.47%.

Synthesis of (*S*)-5: A 2 M solution of Pr^iMgCl in Et_2O (10.9 mL, 21.8 mmol) was added dropwise over 40 min to a vigorously stirred suspension of $(\text{MeO})\text{MeNH}\cdot\text{HCl}$ (1.07 g, 10.9 mmol) and (–)-(*S*)-4 (1.04 g, 4.37 mmol) in THF (13 mL) at – 30 °C. The mixture was stirred for 1 h, and during that time, the temperature increased to – 5 °C. A sat. aq. NH_4Cl solution (4 mL) was then added dropwise to the mixture. The solution was poured into a mixture of $\text{Et}_2\text{O}/\text{NH}_4\text{Cl}$ (40 mL, 1:4), and the phases were separated. The aqueous phase was extracted with Et_2O (50 mL) and CH_2Cl_2 (40 mL). Evaporation of the combined

organic fractions and subsequent column chromatography (SiO₂; hexane/EtOAc 2:1 to 1:1) afforded 864 mg (78%) of (–)-(S)-**5** as a colorless oil, *R*_f (hexane/EtOAc 1:1) 0.36; $[\alpha]_D^{25} = -78.3$ (*c* = 1.00, CHCl₃); $\nu_{\max}(\text{CHCl}_3)/\text{cm}^{-1}$ 3478, 3003, 2961, 2938, 2909, 2869, 2837, 2641, 2596, 2549, 2462, 2061, 2006, 1888, 1663, 1612, 1585, 1512, 1464, 1442, 1420, 1391, 1368, 1321, 1302, 1172, 1154, 1105, 1058, 1035, 994, 937, 913, 894, 860, 845, 825; $\delta_{\text{H}}(300 \text{ MHz}; \text{CDCl}_3)$ 1.36 (3 H, d, *J* 6), 3.20 (3 H, s), 3.58 (3 H, s), 3.79 (3 H, s), 4.38 (1 H, q, *J* 6), 4.34 (1 H, d, *J* 11), 4.59 (1 H, d, *J* 11), 6.85 (2 H, d, *J* 9), 7.28 (2 H, d, *J* 9); $\delta_{\text{C}}(75 \text{ MHz}; \text{CDCl}_3)$ 173.54, 159.07, 129.75, 129.48, 113.62, 71.08, 70.79, 61.30, 55.25, 32.41, 18.07; ESI-MS 254.1 (*M*H⁺), 276.1 (*[M + Na]*⁺), 292.1 (*[M + K]*⁺); EA calc. for C₁₃H₁₉NO₄ (253.30): C 61.64, H 7.56, N 5.53; found: C 61.86, H 7.40, N 5.31%.

Synthesis of (S)-**6a**: *n*-BuLi (0.45 mL of 1.6 M solution in hexane, 0.72 mmol) was added dropwise to a solution of (triisopropylsilyl)acetylene (162 μL , 0.72 mmol) in THF (1.1 mL) at 0 °C. After stirring for 15 min, the mixture was cooled to – 78 °C and a solution of *Weinreb* amide (–)-(S)-**5** (122 mg, 0.48 mmol) in THF (12 mL) was added dropwise over 75 min. After stirring for 30 min at – 78 °C, the mixture was placed in an ice bath and sat. aq. NH₄Cl solution (0.6 mL) was added. The mixture was partitioned between Et₂O and aqueous NH₄Cl solution (20 mL, 1:1). The phases were separated, and the aqueous layer was extracted with Et₂O (20 mL, 2 x). Evaporation of the combined organic fractions and subsequent column chromatography (SiO₂; hexane/CH₂Cl₂ 1:1) provided ketone (–)-(S)-**6a** (153 mg, 96%) as a colorless oil, *R*_f (hexane/CH₂Cl₂ 1:1) 0.28; $[\alpha]_D^{25} = -58.26$ (*c* = 1.09, CHCl₃); $\nu_{\max}(\text{CHCl}_3)/\text{cm}^{-1}$ 3008, 2944, 2894, 2867, 2839, 2761, 2728, 2719, 2620, 2596, 2549, 2145, 2061, 2007, 1886, 1676, 1612, 1586, 1513, 1464, 1442, 1422, 1389, 1384, 1369, 1319, 1303, 1180, 1174, 1083, 1035, 1019, 997, 976, 935, 919, 906, 882, 846; $\delta_{\text{H}}(300 \text{ MHz}; \text{CDCl}_3)$ 1.11 (21 H, s), 1.43 (3 H, d, *J* 7), 3.80 (3 H, s), 4.03 (1 H, q, *J*

7), 4.39 (1 H, d, J 11), 4.66 (1 H, d, J 11), 6.87 (2 H, d, J 9), 7.29 (2 H, d, J 9); δ_{C} (75 MHz; CDCl_3) 189.10, 159.18, 129.49, 129.43, 113.70, 102.26, 99.3, 80.53, 71.69, 55.29, 18.57, 17.93, 11.09; HR-MALDI (DHB) calcd for $\text{C}_{22}\text{H}_{34}\text{O}_3\text{SiNa}^+$ ($[M + \text{Na}]^+$): 397.2175; found 397.2173; EA calcd for $\text{C}_{22}\text{H}_{34}\text{O}_3\text{Si}$ (374.59): C 70.54, H 9.15; found: C 70.52, H 8.99%.

Synthesis of **7a** (entry 1, Table 1): *n*-BuLi (0.28 mL of 1.6 M solution in hexane, 0.45 mmol) was added dropwise to a solution of (trimethylsilyl)acetylene (64 μL , 0.45 mmol) in Et_2O (0.4 mL) at 0 $^\circ\text{C}$, and the mixture was stirred for 15 min. Then, the mixture was cooled to -78 $^\circ\text{C}$ and a solution of ketone (–)-(*S*)-**6a** (112 mg, 0.30 mmol) in Et_2O (0.8 mL) was added dropwise and stirred for 1.5 h. After that, the mixture was placed in an ice bath and quenched by dropwise addition of sat. aq. NH_4Cl solution (0.5 mL), then extracted with Et_2O (2 x). Evaporation and column chromatography (SiO_2 ; hexane/ EtOAc 96:4) provided the desired alcohol **7a** (colorless oil, 90 mg, 64%) as a mixture of diastereoisomers (d.r. = 91:9, de = 82%); R_f (hexane/ CH_2Cl_2 1:2) 0.38; $\nu_{\text{max}}(\text{CHCl}_3)/\text{cm}^{-1}$ 3534, 3006, 2960, 2944, 2892, 2866, 2840, 2759, 2726, 2716, 2614, 2549, 2174, 2058, 2007, 1947, 1885, 1673, 1612, 1586, 1514, 1463, 1442, 1421, 1409, 1382, 1375, 1367, 1352, 1328, 1302, 1173, 1077, 1034, 1019, 996, 972, 919, 882, 862, 845; δ_{H} (300 MHz, CDCl_3) 0.17 (9 H, s), 1.08 (21 H, s), 1.38 (3 H, d, J 6), 3.15 (0.1 H, s), 3.19 (0.9 H, s), 3.72 (1 H, q, J 6), 3.81 (3 H, s), 4.59 (1 H, d, J 11), 4.67 (1 H, d, J 11), 6.87 (2 H, d, J 8), 7.29 (2 H, d, J 8); δ_{C} (75 MHz, CDCl_3 , resonances of major diastereoisomer only) 159.06, 130.11, 129.19, 113.66, 104.57, 103.80, 88.74, 86.40, 80.41, 71.52, 67.41, 55.30, 18.65, 15.35, 11.31, -0.21 ; HR-MALDI (DHB) calcd for $\text{C}_{27}\text{H}_{44}\text{O}_3\text{Si}_2\text{Na}^+$ ($[M + \text{Na}]^+$): 495.2727; found 495.2734; calcd for $\text{C}_{27}\text{H}_{44}\text{O}_3\text{Si}_2\text{K}^+$ ($[M + \text{K}]^+$): 511.2466; found 511.2461; EA calcd for $\text{C}_{27}\text{H}_{44}\text{O}_3\text{Si}_2$ (472.81): C 68.59, H 9.38; found: C 68.39, H 9.31%.

Synthesis of (*S*)-**6b**: *n*-BuLi (7.12 mL of 1.6 M solution in hexane, 11.4 mmol) was added dropwise to a solution of (triethylsilyl)acetylene (2.04 mL, 11.4 mmol) in THF (18

mL) at 0 °C. After stirring for 30 min, the mixture was cooled to – 78 °C and a solution of *Weinreb* amide (–)-(*S*)-**5** (1.92 mg, 7.6 mmol) in THF (12 mL) was added dropwise over 10 min. After 30 min, the mixture was allowed to warm to 0 °C and stirred for a further 30 min. Then, the mixture was quenched with sat. aq. NH₄Cl solution (4 mL) and extracted with Et₂O (2 x). Evaporation and column chromatography (SiO₂; hexane/CH₂Cl₂ 1:1) provided ketone (–)-(*S*)-**6b** (2.25 g, 89%) as a colorless oil, *R*_f (hexane/EtOAc 98:2) 0.17; $[\alpha]_D^{25} = -60.1$ (*c* = 1.00, CHCl₃); $\nu_{\max}(\text{CHCl}_3)/\text{cm}^{-1}$ 3008, 2958, 2936, 2913, 2876, 2838, 2736, 2146, 2058, 1886, 1675, 1612, 1586, 1513, 1465, 1457, 1442, 1415, 1393, 1370, 1318, 1303, 1180, 1173, 1083, 1035, 1018, 1006, 977, 847; $\delta_{\text{H}}(300 \text{ MHz}; \text{CDCl}_3)$ 0.69 (6 H, q, *J* 8), 1.02 (9 H, t, *J* 8), 1.42 (3 H, d, *J* 7), 3.80 (3 H, s), 4.03 (1 H, q, *J* 7), 4.39 (1 H, d, *J* 11), 4.65 (1 H, d, *J* 11), 6.87 (2 H, d, *J* 9), 7.29 (2 H, d, *J* 9); $\delta_{\text{C}}(75 \text{ MHz}; \text{CDCl}_3)$ 189.20, 159.20, 129.48 (one peak overlaps), 113.70, 101.41, 99.96, 80.45, 71.73, 55.30, 17.89, 7.43, 3.92; HR-MALDI (DHB) calcd for C₁₉H₂₈O₃SiNa⁺ (*[M + Na]*⁺): 355.1705; found 355.1703; EA calcd for C₁₉H₂₈O₃Si (332.51): C 68.63, H 8.49; found: C 68.66, H 8.43%.

Synthesis of (+)-**7b**: *n*-BuLi (8.25 mL of 1.6 M solution in hexane, 13.2 mmol) was added dropwise over 40 min to a solution of (trimethylsilyl)acetylene (1.85 mL, 13.2 mmol) in Et₂O (9 mL) at 0 °C, and the mixture was stirred for 15 min. The mixture was cooled to – 78 °C, and a solution of ketone (–)-(*S*)-**6b** (2.20 g, 6.6 mmol) in Et₂O (18 mL) was added dropwise. After stirring for 1.5 h, the mixture was placed in an ice bath, quenched by the dropwise addition of sat. aq. NH₄Cl solution (0.5 mL), extracted with Et₂O (2 x), dried (MgSO₄) and concentrated *in vacuo*. ¹H NMR (500 MHz, (CD₃)₂CO) analysis of the residue showed that two diastereoisomers were formed in the ratio 95:5 (d.e. = 90%), as obtained by integrating the HO signals (δ = 5.16 (*S,S*) and 5.13 (*R,S*); see Fig. 2 (ESI)). Purification of the residue by column chromatography (SiO₂; hexane/EtOAc 96:4) provided the desired alcohol (+)-(*R,S*)-**7b** with a small amount of diastereoisomer (*S,S*)-**7b** (colorless

oil, 2.26 g, 83%), (d.r. = 95:5, d.e. = 90%; see Fig. 2 (ESI)); R_f (hexane/EtOAc 4:1) 0.52; $[\alpha]_D^{25} = + 1.4$ ($c = 0.96$, CHCl_3); $\nu_{\text{max}}(\text{CHCl}_3)/\text{cm}^{-1}$ 3534, 3007, 2957, 2936, 2912, 2875, 2837, 2734, 2687, 2641, 2598, 2547, 2173, 2057, 2005, 1949, 1885, 1612, 1586, 1513, 1464, 1457, 1442, 1414, 1375, 1352, 1328, 1302, 1180, 1173, 1164, 1123, 1110, 1079, 1034, 1018, 972, 860, 842; $\delta_{\text{H}}(500 \text{ MHz}, \text{CDCl}_3)$ 0.18 (9 H, s), 0.62 (6 H, q, J 8), 1.00 (9 H, t, J 8), 1.36 (3 H, d, J 6), 3.13 (0.1 H, s), 3.15 (0.9 H, s), 3.72 (1 H, q, J 6), 3.81 (3 H, s), 4.61 (1 H, d, J 11), 4.67 (1 H, d, J 11), 6.88 (2 H, m), 7.29 (2 H, m); $\delta_{\text{C}}(75 \text{ MHz}, \text{CDCl}_3)$ 159.12, 130.09, 129.29, 113.72, 103.86, 103.81, 88.78, 87.48, 80.30, 72.00, 67.38, 55.33, 15.32, 7.56, 4.40, -0.18; HR-MALDI (DHB): calcd for $\text{C}_{24}\text{H}_{38}\text{O}_3\text{Si}_2\text{Na}^+$ ($[M + \text{Na}]^+$): 453.2257; found 453.2257; EA calcd for $\text{C}_{24}\text{H}_{38}\text{O}_3\text{Si}_2$ (430.73): C 66.92, H 8.89; found: C 66.78, H 8.76%.

Synthesis of (–)-**8**: *n*-BuLi (3.4 mL of a 1.6 M solution in hexane, 5.49 mmol) was added dropwise to a solution of (*R,S*)-**7b**/*(S,S)*-**7b** (2.06 g, 4.99 mmol) (d.r. = 95:5, d.e. = 90%) in THF (20 mL) cooled to -78 °C. After 20 min, iodomethane (2.5 mL, 40 mmol) was added. The temperature was slowly raised to -20 °C and was then allowed to warm to 20 °C over 16 h. The mixture was poured into sat. aq. NH_4Cl solution (50 mL) and extracted with Et_2O (2 x). Evaporation and column chromatography (SiO_2 ; hexane/EtOAc 30:1) provided (–)-**8** (2.02 g, 91%) as a pale yellow oil, R_f (hexane/EtOAc 30:1) 0.21; $[\alpha]_D^{25} = - 35.8$ ($c = 0.96$, CHCl_3); $\nu_{\text{max}}(\text{CHCl}_3)/\text{cm}^{-1}$ 3006, 2956, 2936, 2911, 2874, 2837, 2827, 2167, 1611, 1585, 1513, 1464, 1456, 1441, 1415, 1372, 1303, 1250, 1173, 1143, 1081, 1035, 1019, 976, 952; $\delta_{\text{H}}(300 \text{ MHz}; \text{CDCl}_3)$ 0.19 (9 H, s), 0.63 (6 H, q, J 8), 1.00 (9 H, t, J 8), 1.29 (3 H, d, J 6), 3.51 (3 H, s), 3.71 (1 H, q, J 6), 3.80 (3 H, s), 4.64 (1 H, d, J 12), 4.79 (1 H, d, J 12), 6.85 (2 H, d, J 9), 7.32 (2 H, d, J 9); $\delta_{\text{C}}(75 \text{ MHz}; \text{CDCl}_3)$ 158.77, 130.77, 129.12, 113.37, 102.64, 101.48, 90.69, 88.54, 79.61, 74.82, 72.52, 55.15, 52.86, 15.93, 7.49, 4.38, -0.18; HR-MALDI (DHB) calcd for $\text{C}_{25}\text{H}_{40}\text{O}_3\text{Si}_2\text{Na}^+$ ($[M + \text{Na}]^+$): 467.2414; found

467.2403; calcd for $C_{25}H_{40}O_3Si_2K^+$ ($[M + K]^+$): 483.2153; found 483.2143; EA calcd for $C_{25}H_{40}O_3Si_2$ (444.76): C 67.51, H 9.07; found: C 67.37, H 9.09%.

The diastereoisomeric ratio could not be determined because only one set of signals was present in the 1H NMR spectrum (300 MHz; $CDCl_3$); however, when the same reaction was performed using a diastereoisomeric mixture of **7b** with d.r. = 80 : 20 (d.e. = 60%), a new quartet was visible at around 3.70 ppm, proving that the two isomers have very similar spectra (see Fig. 3 (ESI)).

Synthesis of (–)-**9**: A solution of (–)-**8** (1.50 g, 3.37 mmol) in MeOH/THF 1:1 (500 mL), 1 N aq. NaOH solution (15 drops) was added, followed by a further addition of 8 drops 30 min later. After stirring for 1 h, the reaction mixture was quenched with sat. aq. NH_4Cl solution, extracted with Et_2O , dried ($MgSO_4$), and the solvents were evaporated in *vacuo*. Purification of the residue by column chromatography (SiO_2 , hexane/ $EtOAc$ 15:1) provided (–)-**9** (colorless oil, 1.12 g, 89%) as a mixture of diastereoisomers (*R,S*)-**9** and (*S,S*)-**9**; R_f (hexane/ $EtOAc$ 15:1) 0.21; $[\alpha]_D^{25} = -51.7$ ($c = 1.14$, $CHCl_3$). Analytical HPLC analysis (LiChroCART[®] 250-4, LiChrospher[®] Si 60, 10 μm , Hexane/ Pr^iOH 99.88:0.12, 1 mL/min) showed a 96:4 ratio for the mixture of diastereoisomers. Isolation of isomers on the preparative scale was successful with Hibar[®] 250-25, LiChrospher[®] Si 60, 5 μm (hexane/ Pr^iOH 99.85:0.15, 10 mL/min), as shown in Fig. 4 (ESI). (*R,S*)-**9**: $[\alpha]_D^{25} = -54.1$ ($c = 0.87$, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3283, 2955, 2875, 1613, 1514, 1463, 1372, 1302, 1247, 1117, 1079, 1037, 973, 821, 728, 631; $\delta_H(300\text{ MHz}; CDCl_3)$ 0.64 (6 H, q, J 8), 1.01 (9 H, t, J 8), 1.29 (3 H, d, J 6), 2.54 (1 H, s), 3.52 (3 H, s), 3.72 (1 H, q, J 6), 3.80 (3 H, s), 4.65 (1 H, d, J 12), 4.77 (1 H, d, J 12), 6.85 (2 H, m), 7.32 (2 H, m); $\delta_C(75\text{ MHz}; CDCl_3)$ 158.87, 130.60, 129.31, 113.47, 102.41, 88.58, 80.01, 79.58, 74.29, 73.89, 72.68, 55.28, 52.99, 15.82, 7.59, 4.39; HR-EI-MS calcd for $C_{22}H_{32}O_3Si^+$ (M^+): 372.2121; found 372.2120; calcd for $C_{12}H_{19}OSi^+$ ($[M - C_{10}H_{13}O_2]^+$): 207.1205; found 207.1203; calcd for $C_8H_9O^+$ ($[M -$

$C_{14}H_{23}O_2Si^+$): 121.0653; found 121.0634; EA calc. for $C_{22}H_{32}O_3Si$ (372.58): C 70.92, H 8.66; found: C 71.16, H 8.81%. (*S,S*)-**9**: $[\alpha]_D^{25} = -25.5$ ($c = 1.02$, $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 0.63 (6 H, q, J 8), 1.00 (9 H, t, J 8), 1.33 (3 H, d, J 6), 2.55 (1 H, s), 3.54 (3 H, s), 3.73 (1 H, q, J 6), 3.80 (1 H, s), 4.65 (1 H, d, J 12), 4.79 (1 H, d, J 12), 6.86 (2 H, m), 7.31 (2 H, m); δ_C (75 MHz; $CDCl_3$) 158.85, 130.72, 129.26, 113.49, 102.30, 89.02, 79.89, 79.56, 75.14, 74.01, 72.78, 55.28, 53.12, 16.51, 7.58, 4.37; HR-EI-MS calcd for $C_{12}H_{19}OSi^+$ ($[M - C_{10}H_{13}O_2]^+$): 207.1205; found 207.1207; calcd for $C_8H_9O^+$ ($[M - C_{14}H_{23}O_2Si]^+$): 121.0653; found 121.0650.

Synthesis of (*R,S*)-**8**: NaHMDS (1.5 mL of a 1 M solution in THF, 1.53 mmol) was added dropwise to a solution of (*R,S*)-**9** (438 mg, 1.18 mmol) in THF (16 mL) cooled to $-78^\circ C$. After 30 min, trimethylchlorosilane (208 μL , 1.65 mmol) was added. After stirring for 2 h, the mixture was poured into sat. aq. NH_4Cl solution (2 mL) and extracted with Et_2O (2 x). Evaporation and column chromatography (SiO_2 ; hexane/ $EtOAc$ 30:1) provided (*R,S*)-**8** (450 mg, 86%) as a pale yellow oil, R_f (hexane/ $EtOAc$ 30:1) 0.21; $[\alpha]_D^{25} = -35.3$ ($c = 1.11$, $CHCl_3$).

Synthesis of (*R,S*)-**10**: A solution of ($-$)-(*R,S*)-**8** (400 mg, 0.9 mmol) and CAN (1.1 g, 2.0 mmol) in $MeCN/H_2O$ 9:1 (5 mL) was stirred for 2 h. The mixture was poured into CH_2Cl_2 (4 mL) and washed with sat. aq. $NaHCO_3$. The aqueous phase was further extracted with CH_2Cl_2 (2 mL, 2 x). Evaporation of the combined organic fractions and subsequent column chromatography (SiO_2 ; hexane/ CH_2Cl_2 1:2) afforded 263 mg (90%) of ($-$)-(*R,S*)-**10** as a yellow oil, R_f (hexane/ CH_2Cl_2 1:2) 0.38; $[\alpha]_D^{25} = -11.5$ ($c = 1.14$, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3572, 2988, 2957, 2936, 2911, 2875, 2828, 2734, 2170, 1463, 1414, 1398, 1379, 1361, 1339, 1270, 1251, 1151, 1120, 1077, 1017, 983, 956, 897, 861, 845; δ_H (300 MHz; $CDCl_3$) 0.18 (9 H, s), 0.63 (6 H, q, J 8), 1.00 (9 H, t, J 8), 1.36 (3 H, d, J 2), 2.53 (1 H,

d, J 3), 3.51 (3 H, s), 3.81 – 3.91 (1 H, m); δ_{C} (75 MHz; CDCl_3) 100.94, 100.76, 91.40, 89.65, 75.48, 73.39, 53.27, 17.40, 7.54, 4.42, -0.18; EI-MS 324 (M^+), 279 ($[M - \text{C}_2\text{H}_5\text{O}]^+$); EA calc. for $\text{C}_{17}\text{H}_{32}\text{O}_2\text{Si}_2$ (324.61): C 62.90, H 9.94; found: C 63.11, H 9.85%.

Synthesis of (*R*)-**11**: DMP (2.2 mL of a 15 wt% solution in CH_2Cl_2 , 1.02 mmol) was added to a solution of (-)-(*R,S*)-**10** (220 mg, 0.68 mmol) in CH_2Cl_2 (7 mL) at 0 °C. After 10 min, the mixture was allowed to warm to 20 °C and stirred for 22 h. Then, MeOH (0.3 mL) was added. Evaporation of the combined organic fractions and column chromatography (SiO_2 ; hexane/ CH_2Cl_2 1:1) afforded 210 mg (96%) of (+)-(*R*)-**11** as a colorless oil, R_f (hexane/ CH_2Cl_2 1:1) 0.47; $[\alpha]_D^{25} = +2.3$ ($c = 1.02$, CHCl_3); $\nu_{\text{max}}(\text{CHCl}_3)/\text{cm}^{-1}$ 2958, 2935, 2911, 2875, 2829, 2734, 2165, 1740, 1601, 1463, 1458, 1437, 1414, 1379, 1355, 1263, 1252, 1176, 1128, 1092, 1053, 1018, 1003, 975, 949, 916, 859, 847; δ_{H} (300 MHz; CDCl_3) 0.19 (9 H, s), 0.63 (6 H, q, J 8), 1.00 (9 H, t, J 8), 2.41 (3 H, s), 3.52 (3 H, s); δ_{C} (75 MHz; CDCl_3) 196.55, 99.43, 98.22, 93.29, 91.34, 75.90, 53.33, 24.12, 7.48, 4.25, -0.36; HR-EI-MS calcd for $\text{C}_{17}\text{H}_{30}\text{O}_2\text{Si}_2^+$ (M^+): 322.1784; found 322.1785; calcd for $\text{C}_{15}\text{H}_{27}\text{OSi}_2^+$ ($[M - \text{C}_2\text{H}_3\text{O}]^+$): 279.1600; found 279.1628; EA calc. for $\text{C}_{17}\text{H}_{30}\text{O}_2\text{Si}_2$ (322.59): C 63.30, H 9.37; found: C 63.46, H 9.20%.

Synthesis of (*R*)-**12**: A solution of ketone (+)-(*R*)-**11** (124 mg, 0.38 mmol) in THF (0.7 mL) was cooled to -78 °C, treated with NaHMDS (1.0 M in THF, 0.96 mL, 0.96 mmol) and stirred for 1 h. A solution of 2-[*N,N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine (377 mg, 0.96 mmol) in THF (0.7 mL) was then added. The mixture was warmed gradually to -40 °C over a period of 3 h, diluted with Et_2O (10 mL), washed with H_2O and sat. aq. NaCl solution (10 mL each), dried over MgSO_4 , filtered and concentrated *in vacuo*. Flash chromatography (SiO_2 ; hexane/ CH_2Cl_2 10:1) afforded 79 mg (45%) of (-)-(*R*)-**12** as a colorless oil, R_f (hexane/ CH_2Cl_2 10:1) 0.24; $[\alpha]_D^{25} = -1.3$ ($c = 1.04$, CHCl_3); $\nu_{\text{max}}(\text{CHCl}_3)/\text{cm}^{-1}$ 2958, 2878, 2156, 1427, 1252, 1212, 1144, 971, 937, 845, 728; δ_{H} (300

MHz; CDCl₃) 0.20 (9 H, s), 0.64 (6 H, q, *J* 8), 1.00 (9 H, t, *J* 8), 3.48 (3 H, s), 5.36 (1 H, d, *J* 4), 5.83 (1 H, d, *J* 4); δ_{C} (75 MHz; CDCl₃) 150.88, 116.21, 106.54, 98.77, 97.62, 93.12, 91.33, 70.05, 52.88, 7.43, 4.20, -0.48; δ_{F} (282 MHz, CDCl₃) -74.65; HR-EI-MS calcd for C₁₆H₂₄F₃O₄SSi₂⁺ (*[M* - C₂H₅]⁺): 425.0886; found 425.0882.

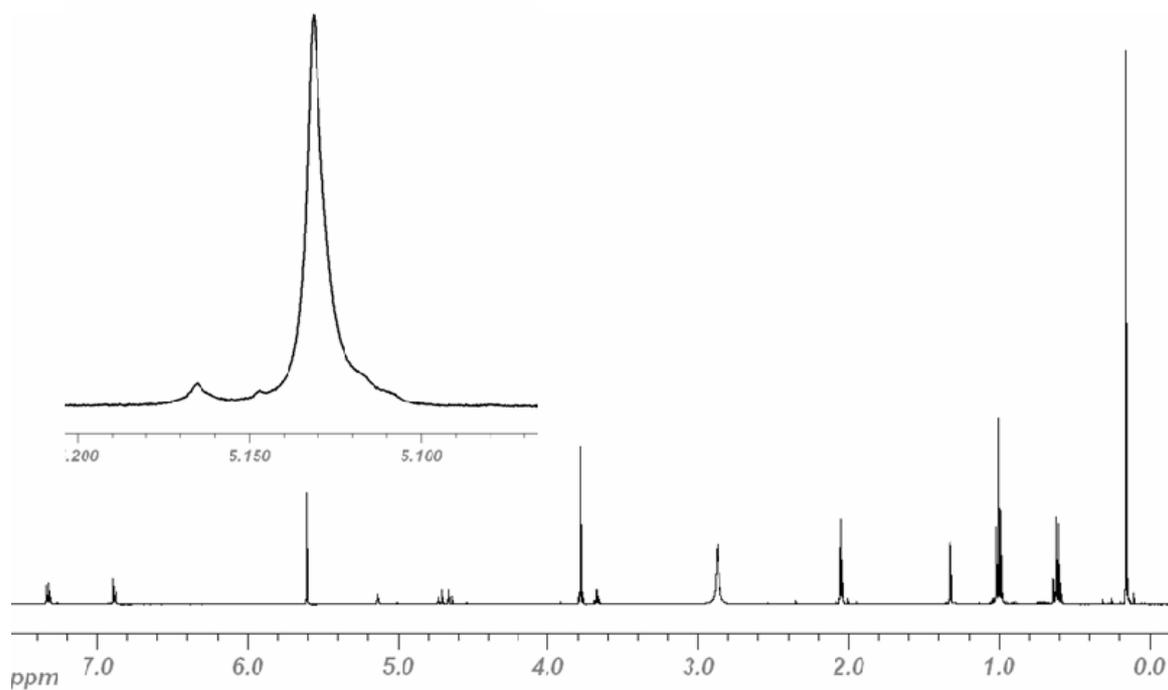
Synthesis of (*R*)-**2**: To a stirred solution of Pr₂^tNH (48 μ L, 0.37 mmol) in THF (0.4 mL) cooled to -78 °C, *n*-BuLi (215 μ L of a 1.6 M solution in hexane, 0.34 mmol) was added. The mixture was stirred for 30 min at -78 °C and then for 30 min at 20 °C. The mixture was again cooled to -78 °C, and a solution of (-)-(*R*)-**12** (78 mg, 0.17 mmol) in THF (0.6 mL) was added dropwise. After stirring for 40 min, the mixture was allowed to warm up to -40 °C over 30 min and stirred for further 90 min; then it was diluted with Et₂O (10 mL), washed with H₂O (10 mL each), dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂; hexane/CH₂Cl₂ 9:1) afforded 42 mg (82 %) of the desired product (+)-(*R*)-**2** as colorless oil, *R*_f (hexane/CH₂Cl₂ 9:1) 0.13; $[\alpha]_{\text{D}}^{25} = +2.4$ (*c* = 0.76, CHCl₃); ν_{max} (CHCl₃)/cm⁻¹ 3302, 2961, 2939, 2917, 2866, 2844, 2735, 2183, 2125, 1733, 1457, 1406, 1370, 1123, 1086, 1050, 1006, 948; δ_{H} (300 MHz; CDCl₃) 0.20 (9 H, s), 0.64 (6 H q, *J* 8), 1.01 (9 H t, *J* 8), 2.63 (1 H, s), 3.49 (3 H, s); δ_{C} (75 MHz; CDCl₃) 100.42, 99.22, 89.21, 87.46, 79.21, 72.03, 60.76, 52.49, 7.45, 4.25, -0.38; HR-EI-MS calcd for C₁₆H₂₅OSi₂⁺ (*[M* - CH₃]⁺): 289.1444; found 289.1455; EA calc. for C₁₇H₂₈OSi₂ (304.57): C 67.04, H 9.27; found: C 67.21, H 9.28%.

Synthesis of (*R*)-**13**: To a solution of the ketone (+)-(*R*)-**11** (100 mg, 0.31 mmol) in EtOH (0.1 mL), *p*-toluenesulfonyl hydrazide (64 mg, 0.34 mmol) was added. The resulting suspension was stirred and heated up to 40 °C until all solid had dissolved (about 5 min). Then, the solution was allowed to reach 20 °C and stirred vigorously overnight. Evaporation and column chromatography (SiO₂; hexane/EtOAc 6:1) provided (+)-(*R*)-**13**

(145 mg, 95%) as a white solid, mp 94 °C; R_f (hexane/EtOAc 6:1) 0.22; $[\alpha]_D^{25} = +12.0$ ($c = 0.99$, CHCl_3); $\nu_{\text{max}}(\text{CHCl}_3)/\text{cm}^{-1}$ 3198, 2956, 2874, 2358, 2340, 1957, 1463, 1398, 1346, 1250, 1166, 1137, 1078, 1048, 934, 907, 858, 843, 809, 761, 724; $\delta_{\text{H}}(300 \text{ MHz}; \text{CDCl}_3)$ 0.20 (9 H, s), 0.62 (6 H, q, J 8), 0.99 (9 H, t, J 8), 1.88 (3 H, s), 2.41 (3 H, s), 3.28 (3 H, s), 7.26 (2 H, m), 7.89 (2 H, m), 8.03 (1 H, bs); $\delta_{\text{C}}(75 \text{ MHz}; \text{CDCl}_3)$ 151.69, 143.82, 135.20, 129.25, 127.98, 100.41, 99.16, 92.47, 90.36, 73.70, 52.31, 21.68, 11.60, 7.53, 4.33, -0.22; ESI-MS: 513.2 ($[M + \text{Na}]^+$); EA calc. for $\text{C}_{24}\text{H}_{38}\text{N}_2\text{O}_3\text{SSi}_2$ (490.81): C 58.73, H 7.80, N 5.71; found: C 58.88, H 7.74, N 5.79%.

Fig. 2 (ESI). ^1H NMR spectra (500 MHz, CD_3COCD_3) of diastereoisomeric mixture of (*R,S*)-**7b** (major) and (*S,S*)-**7b** (minor): *a*) Before purification by chromatography. *b*) After purification by chromatography.

a)



b)

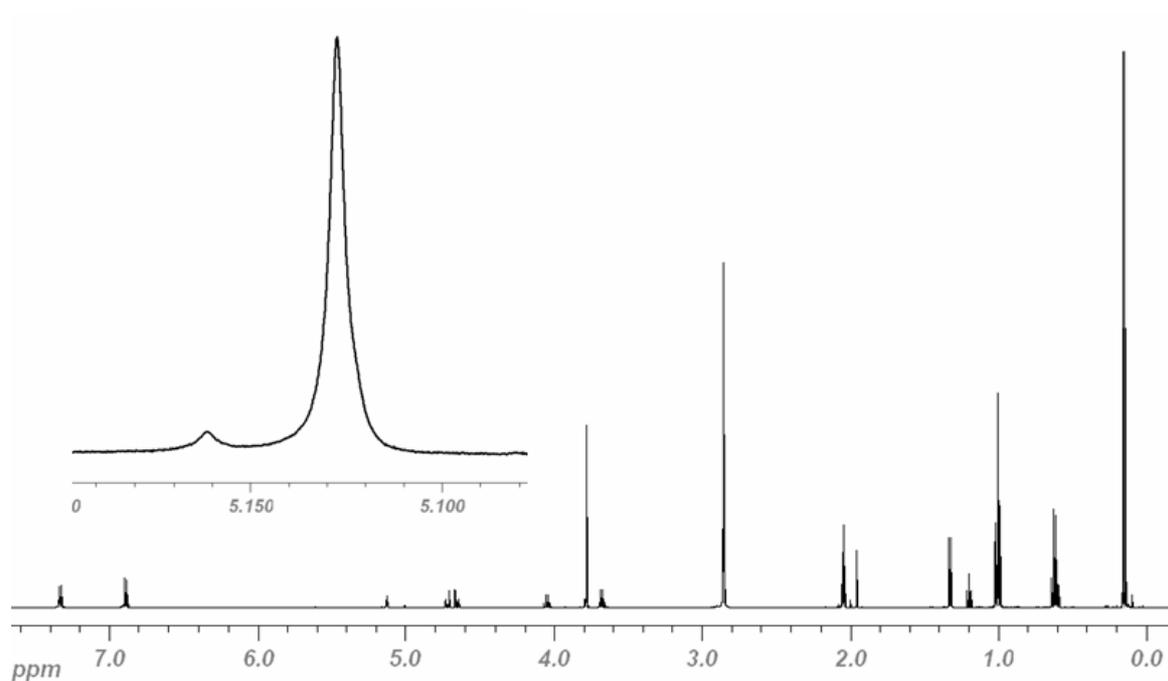


Fig. 3 (ESI). ^1H NMR spectra (300 MHz, CDCl_3) of diastereoisomeric mixture of (*R,S*)-**8** (major) and (*S,S*)-**8** (minor), deriving from **7b** (d.r. = 80/20, d.e. = 60%).

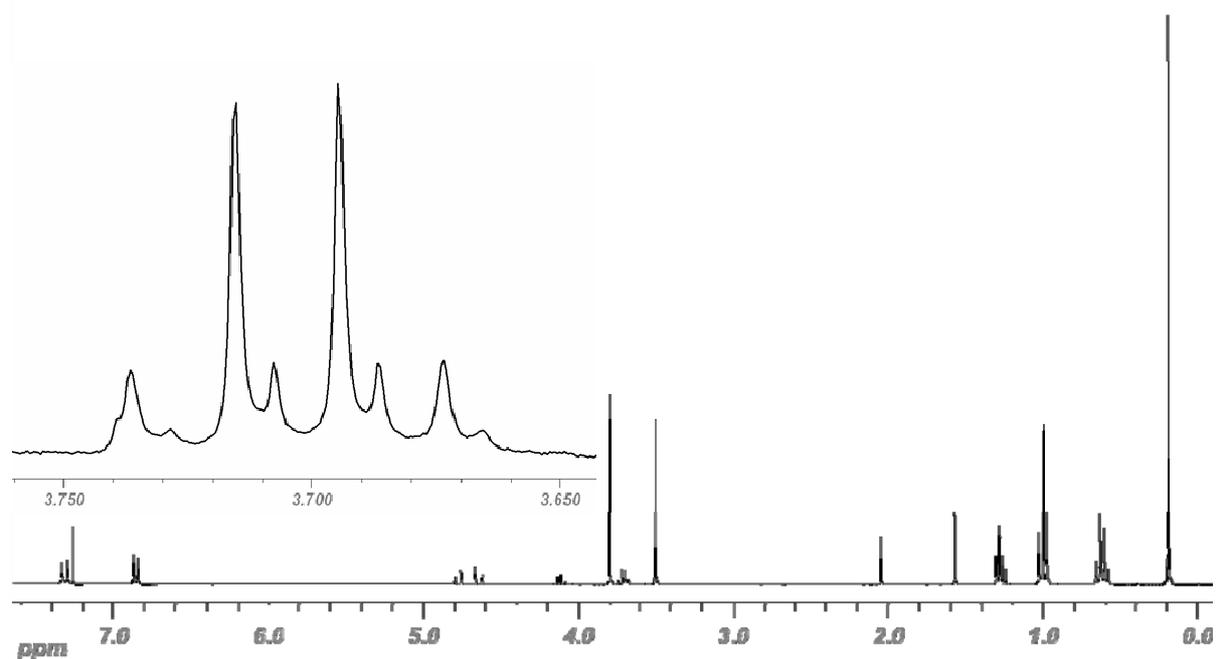


Fig. 4 (ESI). Preparative HPL chromatogram of (*R,S*)-**9** and (*S,S*)-**9**, d.r. = 96 : 4 (d.e. = 92%). Hibar[®] 250-25, LiChrospher[®] Si 60, 5 μm , hexane: *Pr*^{*i*}OH = 99.85:0.15, 10 mL/min.

