

Approach to the Hyacinthacines: First Non-Chiral Pool Synthesis of (+)-Hyacinthacine A₁

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Electronic Supplementary Information

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(2R,3R)-tert-Butyl 2-Allyl-5-oxo-3-[(S)-1-(2,4,6-triisopropylphenyl)ethoxy]-pyrrolidine-1-carboxylate (6): mp 146.9-147.4 °C (pentane); $[\alpha]_D^{21}$ -98.4 (c 0.64, CHCl₃); IR (KBr) 2960, 2928, 2868, 1756, 1726, 1368, 1303, 1204, 1157, 1102, 1058 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.05-1.35 (m, 18 H), 1.49 (s, 9 H), 1.56 (d, *J* = 6.8 Hz, 3 H), 2.35-2.50 (m, 1 H), 2.61 (A of ABX, *J* = 16.7, 10.1 Hz, 1 H), 2.68 (m, 1H), 2.70 (B of ABX, *J* = 16.7, 7.9 Hz, 1 H), 2.85 (sept, *J* = 6.9 Hz, 1 H), 3.02-3.20 (m, 1 H), 3.77-3.95 (m, 1 H), 4.09 (ddd, *J* = 10.1, 7.9, 7.9 Hz, 1 H), 4.24 (ddd, *J* = 7.9, 5.1, 5.1 Hz, 1 H), 4.98-5.15 (m, 3 H), 5.90 (dddd, *J* = 17.5, 10.2, 7.5, 7.5 Hz, 1 H), 6.95 (s, 1 H), 7.05 (s, 1 H); ¹³C NMR (75.5 MHz, CDCl₃) δ 23.1 (CH₃), 23.8 (CH₃), 24.2 (CH₃), 24.9 (CH₃), 27.9 (CH₃), 29.1 (CH), 33.2 (CH₂), 33.9 (CH), 38.8 (CH₂), 59.9 (CH), 69.3 (CH), 71.5 (CH), 82.9 (C), 118.5 (CH₂), 120.6 (CH), 123.4 (CH), 131.8 (C), 134.2 (CH), 145.9 (C), 147.8 (C), 148.7 (C), 149.5 (C), 170.9 (C); MS (ESI) *m/z* 966 (2MNa⁺), 494 (MNa⁺, 100); Anal. calcd for C₂₉H₄₅NO₄: C, 73.85; H, 9.62; N, 2.97. Found: C, 73.67; H, 9.65; N, 3.06.

(2R,3R)-tert-Butyl 2-Allyl-5-methoxy-3-[(S)-1-(2,4,6-triisopropylphenyl)ethoxy]-pyrrolidine-1-carboxylate (7): Minor diastereomer in mixture: ¹H NMR (500 MHz, 85 °C, DMSO) δ 1.16-1.26 (m, 18 H), 1.42 (s, 9 H), 1.51 (d, *J* = 6.8 Hz, 3 H), 1.79-1.90 (m, 1 H), 2.14-2.24 (m, 2 H), 2.45-2.54 (m, 1 H), 2.86 (sept, *J* = 6.8 Hz, 1 H), 3.20 (s, 3 H), 3.05-3.94 (m, 2 H), 3.78-3.87 (m, 1 H), 4.11 (ddd, *J* = 11.2, 6.8, 6.8 Hz, 1 H), 4.85-4.97 (m, 3 H), 5.13 (q, *J* = 6.8 Hz, 1 H), 5.71-5.86 (m, 1 H), 7.02 (s, 2 H). Major diastereomer in mixture: IR (film) 2960, 2929, 2869, 1703, 1389, 1366, 1168, 1079 cm⁻¹; ¹H NMR (500 MHz, 85 °C, DMSO) δ 1.16-1.26 (m, 18 H), 1.40 (s, 9 H), 1.47 (d, *J* = 6.8 Hz, 3 H), 1.79-1.90 (m, 1 H), 2.14-2.24 (m, 1 H), 2.27-2.35 (m, 1 H), 2.58 (ddd, *J* = 13.7, 7.3, 7.3 Hz, 1 H), 2.85 (sept, *J* = 6.8 Hz, 1 H), 3.05-3.94 (m, 2 H), 3.28 (s, 3 H), 3.90 (ddd, *J* = 7.3, 7.3, 7.3 Hz, 1 H), 3.96 (ddd, *J* = 9.3, 7.3, 4.9 Hz, 1 H), 4.85-4.97 (m, 2 H), 5.05 (q, *J* = 6.8 Hz, 1 H), 5.05-5.09 (m, 1 H), 5.71-5.86 (m, 1 H), 7.00 (s, 2 H); MS (ESI) *m/z* 998 (2MNa⁺), 588, 510 (MNa⁺, 100), 231; HRMS calcd for C₃₀H₄₉NO₄Na: 510.3554. Found: 510.3548 (MNa⁺).

(2R,3R)-tert-Butyl 2-Allyl-5-[[dimethyl(phenyl)silyl]methyl]-3-[(S)-1-(2,4,6-triisopropylphenyl)ethoxy]pyrrolidine-1-carboxylate (8): IR (film) 2959, 2927, 2868, 1693, 1458, 1387, 1364, 1249, 1177, 1080, 834 cm⁻¹. Enriched minor diastereomer: ¹H NMR (500 MHz, 85 °C, DMSO) δ 0.31 (s, 3 H), 0.32 (s, 3 H), 0.95 (dd, *J* = 13.7, 11.6 Hz, 1 H), 1.15 (d, *J* = 6.9 Hz, 6 H), 1.20 (d, *J* = 6.9 Hz, 12 H), 1.36 (s, 9 H), 1.43 (d, *J* = 6.9 Hz, 3

H), 1.43-1.50 (m, 1 H), 1.75 (dd, $J = 13.7, 2.6$ Hz, 1 H), 2.05 (ddd, $J = 14.8, 7.4, 7.4$ Hz, 1 H), 2.21 (ddd, $J = 12.1, 6.9, 6.9$ Hz, 1 H), 2.26-2.33 (m, 1 H), 2.84 (sept, $J = 6.9$ Hz, 1 H), 3.10-4.00 (m, 2 H), 3.64-3.73 (m, 1 H), 3.74-3.89 (m, 2 H), 4.84-4.93 (m, 2 H), 4.98 (q, $J = 6.9$ Hz, 1 H), 5.76 (dddd, $J = 17.4, 10.0, 7.4, 7.4$ Hz, 1 H), 6.98 (s, 2 H), 7.35-7.41 (m, 3 H), 7.50-7.58 (m, 2 H). Enriched major diastereomer: ^1H NMR (500 MHz, 85 °C, DMSO) δ 0.31 (s, 6 H), 0.80 (dd, $J = 14.3, 11.6$ Hz, 1 H), 1.16 (d, $J = 6.9$ Hz, 6 H), 1.19-1.24 (m, 12 H), 1.39 (s, 9 H), 1.44 (d, $J = 6.7$ Hz, 3 H), 1.53 (br d, 1 H), 1.77-1.83 (m, 1 H), 1.88-1.99 (m, 1 H), 2.12-2.18 (m, 1 H), 2.44 (ddd, $J = 14.3, 6.9, 6.9$ Hz, 1 H), 2.85 (sept, $J = 6.9$ Hz, 1 H), 3.05-3.75 (m, 2 H), 3.76-3.83 (m, 1 H), 3.83-3.90 (m, 1 H), 4.10 (ddd, $J = 10.6, 6.9, 6.9$ Hz, 1 H), 4.86-4.93 (m, 2 H), 5.02 (q, $J = 6.7$ Hz, 1 H), 5.72-5.83 (m, 1 H), 7.00 (s, 2 H), 7.35-7.41 (m, 3 H), 7.50-7.58 (m, 2 H); ^{13}C NMR (75.5 MHz, CDCl_3) mixture of rotamers δ -2.3 (CH_3), 23.1 (CH_3), 23.9 (CH_3), 24.4 (CH_3), 24.9 (CH_3), 25.2 (CH_3), 28.2 (CH_3), 28.6 (CH_3), 29.2 (CH), 32.4 (CH_2), 34.0 (CH), 35.5 (CH_2), 36.5 (CH_2), 52.4 (CH), 52.8 (CH), 58.7 (CH), 58.9 (CH), 71.4 (CH), 74.0 (CH), 75.0 (CH), 79.0 (C), 116.4 (CH_2), 120.3 (CH), 123.3 (CH), 127.8 (CH), 129.0 (CH), 133.1 (C), 133.6 (CH), 136.6 (CH), 139.1 (C), 145.3 (C), 147.3 (C), 148.9 (C), 153.6 (C). MS (ESI) m/z 1234 (2MNa^+), 628 (MNa^+ , 100); Anal. calcd for $\text{C}_{38}\text{H}_{59}\text{NO}_3\text{Si}$: C, 75.32; H, 9.82; N, 2.32. Found: C, 75.51; H, 10.14; N, 2.58.

(2R,3R)-tert-Butyl 3-((S)-1-(2,4,6-Triisopropylphenyl)ethoxy)-2-(2-(methoxycarbonyl)ethyl)-5-((dimethyl(phenyl)silyl)methyl)pyrrolidine-1-carboxylate (9): Major diastereomer in mixture: IR (film) 2960, 2869, 1740, 1692, 1386, 1365, 1250, 1173, 1080, 834 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 0.33 (s, 6 H), 0.56-0.77 (m, 1 H), 1.10-1.33 (m, 19 H), 1.34-1.57 (m, 12 H), 1.64-1.99 (m, 3 H), 1.99-2.16 (m, 1 H), 2.24-2.53 (m, 2 H), 2.85 (sept, $J = 6.7$ Hz, 1 H), 3.00-3.25 (m, 1 H), 3.63 (s, 3 H), 3.67-4.08 (m, 4 H), 4.85-5.05 (m, 1 H), 6.92 (s, 1 H), 7.03 (s, 1 H), 7.29-7.41 (m, 3 H), 7.41-7.58 (m, 2 H); ^{13}C NMR (75.5 MHz, CDCl_3) δ -2.4 (CH_3), 23.2 (CH_3), 23.9 (CH_3), 24.4 (CH_3), 24.9 (CH_3), 28.2 (CH), 28.5 (CH_3), 29.2 (CH), 31.3 (CH_2), 33.9 (CH), 35.4 (CH_2), 35.9 (CH_2), 51.3 (CH), 52.0 (CH), 57.7 (CH), 71.3 (CH), 74.0 (CH), 74.9 (CH), 79.3 (C), 120.3 (CH), 123.3 (CH), 127.8 (CH), 129.0 (CH), 133.0 (C), 133.5 (CH), 138.9 (C), 145.4 (C), 147.4 (C), 148.8 (C), 153.8 (C), 174.3 (C); MS (ESI) m/z 694 (MK^+), 674 (MNa^+), 652 (MH^+ , 100).

(5S,7R,7aR)-7-((S)-1-(2,4,6-Triisopropylphenyl)ethoxy)-hexahydro-5-((dimethyl(phenyl)silyl)methyl)pyrrolizin-3-one (10): mp 116.6-117.3 °C (pentane); $[\alpha]_{\text{D}}^{21}$ -82.9 (c

1.4, CHCl₃); IR (film) 2959, 2928, 2869, 1692, 1405, 1247, 1112, 1075, 835, 731 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.33 (s, 3 H), 0.40 (s, 3 H), 0.94 (A of ABX, *J* = 14.3, 10.2 Hz, 1 H), 1.09-1.30 (m, 18 H), 1.37-1.51 (m, 4 H), 1.55 (B of ABX, *J* = 14.3, 4.5 Hz, 1 H), 1.75-1.86 (m, 1 H), 2.17-2.28 (m, 1 H), 2.30-2.42 (m, 2 H), 2.48 (ddd, *J* = 18.8, 16.2, 9.4 Hz, 1 H), 2.78 (sept, *J* = 6.8 Hz, 1 H), 3.04 (sept, *J* = 7.5 Hz, 1 H), 3.58 (t, *J* = 3.4 Hz, 1 H), 3.73-3.90 (m, 2 H), 4.00-4.10 (m, 1 H), 4.97 (q, *J* = 6.4 Hz, 1 H), 6.94 (s, 1 H), 7.03 (s, 1 H), 7.32-7.41 (m, 3 H), 7.53-7.61 (m, 2 H); ¹³C NMR (75.5 MHz, CDCl₃) δ -2.5 (CH₃), -2.3 (CH₃), 18.4 (CH₂), 23.1 (CH₃), 23.3 (CH₂), 23.8 (CH₃), 24.2 (CH₃), 24.8 (CH₃), 24.9 (CH₃), 25.3 (CH₃), 27.8 (CH), 28.9 (CH), 33.8 (CH), 34.4 (CH₂), 41.2 (CH₂), 49.9 (CH), 64.5 (CH), 69.3 (CH), 74.3 (C), 120.53 (CH), 123.0 (CH), 127.7 (CH), 128.9 (CH), 132.1 (C), 133.5 (CH), 138.8 (C), 145.7 (C), 147.4 (C), 148.7 (C), 175.8 (C); MS (ESI) *m/z* 558 (MK⁺), 542 (MNa⁺), 442 (100); Anal. calcd for C₃₃H₄₉NO₂Si: C, 76.25; H, 9.50; N, 2.69. Found: C, 75.85; H, 9.43; N, 2.55; HRMS calcd for C₃₃H₄₉O₂NNaSi: 542.3425. Found: 542.3429.

(5*S*,7*R*,7*aR*)-Hexahydro-7-hydroxy-5-((dimethyl(phenyl)silyl)methyl)pyrrolizin-3-one (11): [α]_D²¹ -73.4 (*c* 1.6, CHCl₃); IR (film) 3369, 2954, 2927, 1666, 1426, 1249, 1112, 834, 730 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.31 (s, 3 H), 0.33 (s, 3 H), 0.95 (A of ABX, *J* = 14.4, 10.2 Hz, 1 H), 1.48 (B of ABX, *J* = 14.4, 4.9 Hz, 1 H), 1.65 (ddd, *J* = 8.7, 4.7, 4.2 Hz, 1 H), 1.82-1.93 (m, 1 H), 2.03-2.15 (m, 1 H), 2.18 (dd, *J* = 14.0, 7.6 Hz, 1 H), 2.31 (ddd, *J* = 16.8, 10.2, 3.6 Hz, 1 H), 2.46-2.64 (m, 2 H), 3.26 (br s, 1 H), 3.81 (ddd, *J* = 8.3, 5.9, 2.8 Hz, 1 H), 3.93 (br s, 1 H), 4.00-4.10 (m, 1 H), 7.32-7.38 (m, 3 H), 7.49-7.55 (m, 2 H); ¹³C NMR (75.5 MHz, CDCl₃) δ -2.1 (CH₃), -2.0 (CH₃), 18.1 (CH₂), 24.1 (CH₂), 34.8 (CH₂), 46.2 (CH₂), 50.0 (CH), 65.6 (CH), 70.8 (CH), 128.0 (CH), 129.3 (CH), 133.8 (CH), 139.2 (C), 176.4 (C); MS (ESI) *m/z* 328 (MK⁺), 312 (MNa⁺), 212 (100); Anal. calcd for C₁₆H₂₃NO₂Si: C, 66.39; H, 8.01; N, 4.84. Found: C, 66.18; H, 8.29; N, 4.64; HRMS calcd for C₁₆H₂₃O₂NNaSi: 312.1390. Found: 312.1394.

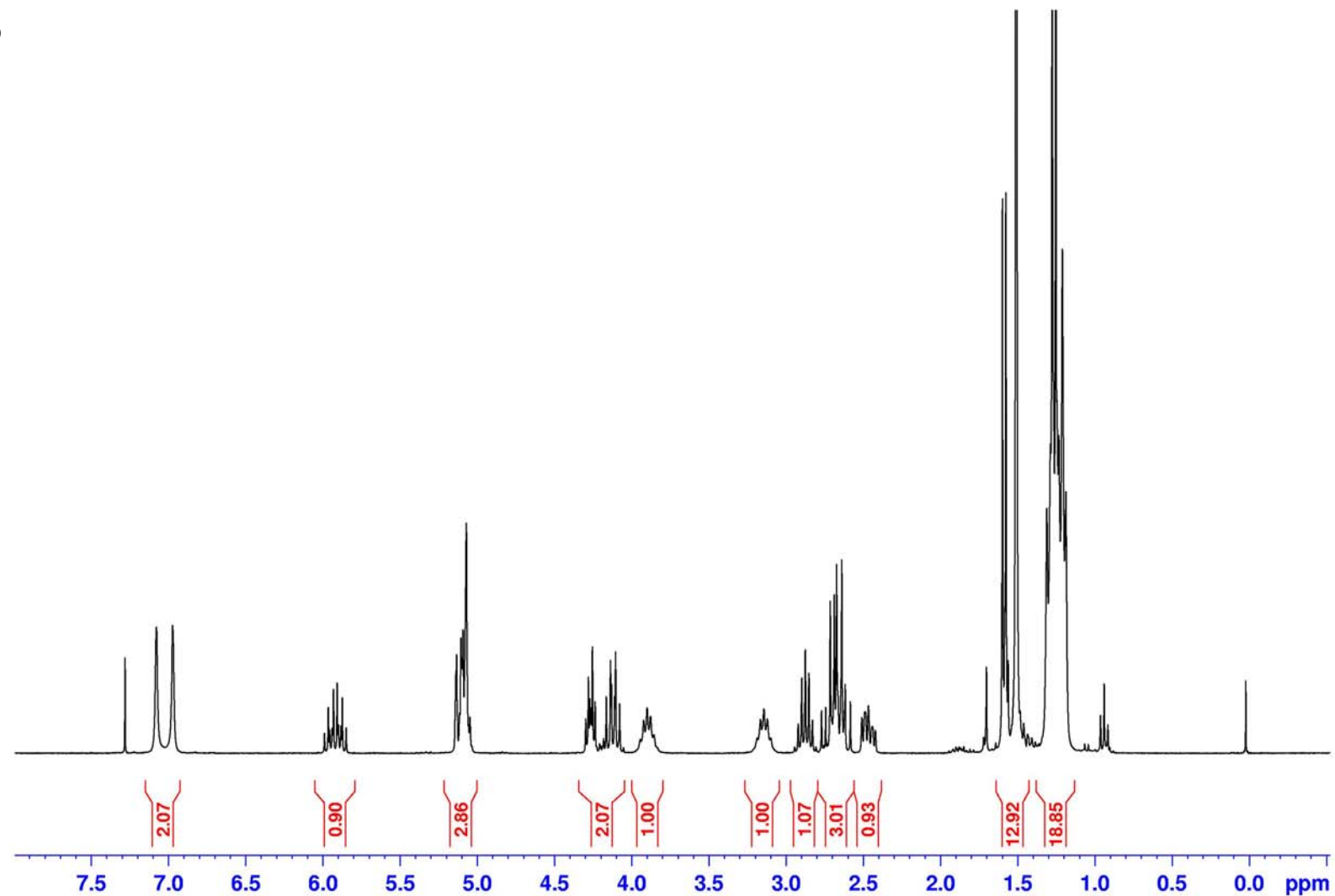
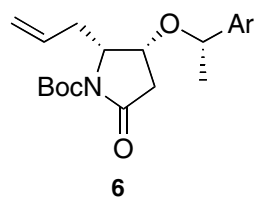
(5*S*,7*aR*)-1,2-Dihydro-5-((dimethyl(phenyl)silyl)methyl)-5*H*-pyrrolizin-3(7*aH*)-one (12): [α]_D²¹ -177.2 (*c* 0.66, CHCl₃); IR (film) 2959, 2928, 2869, 1692, 1405, 1247, 1112, 1075, 835, 731 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.34 (s, 3 H), 0.38 (s, 3 H), 1.05 (A of ABX, *J* = 14.5, 7.8 Hz, 1 H), 1.19 (B of ABX, *J* = 14.6, 6.9 Hz, 1 H), 1.62-1.76 (m, 1 H), 2.20-2.34 (m, 2 H), 2.57 (dddd, *J* = 16.2, 12.8, 8.3, 8.3, Hz, 1 H), 4.47-4.54 (m, 1 H), 4.70-4.76 (m, 1 H), 5.69-5.73 (m, 2 H), 7.31-7.36 (m, 3 H), 7.48-7.56 (m, 2 H); ¹³C NMR (75.5

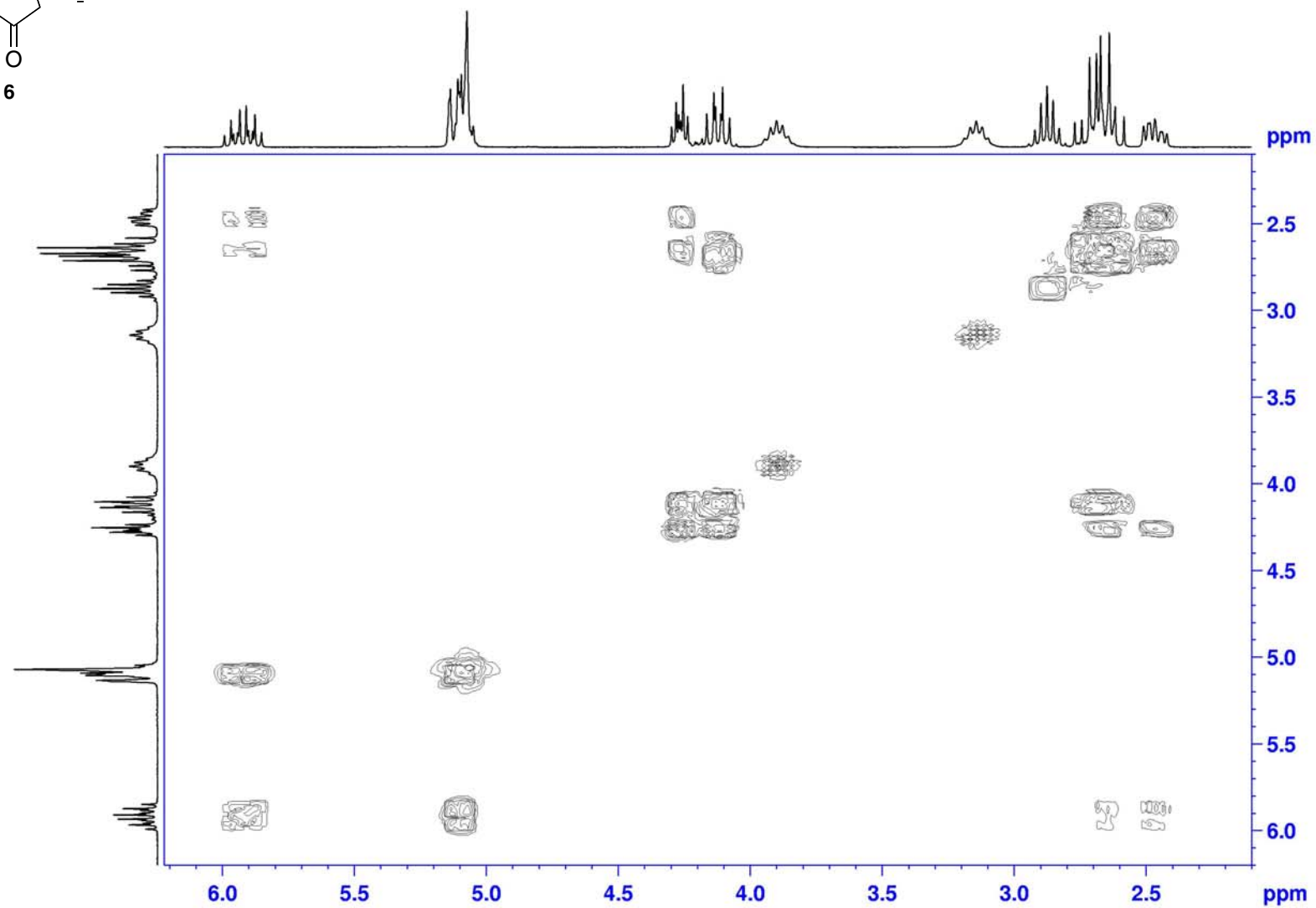
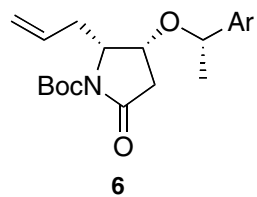
MHz, CDCl₃) δ -2.6 (CH₃), -2.5 (CH₃), 22.9 (CH₂), 29.1 (CH₂), 34.2 (CH₂), 58.5 (CH), 66.0 (CH), 127.7 (CH), 128.87 (CH), 128.91 (CH), 133.6 (CH), 134.2 (CH), 138.9 (C), 177.1 (C); MS (ESI) m/z 294 (MNa⁺, 100); HRMS calcd for C₁₆H₂₁ONNaSi: 294.1285. Found: 294.1288.

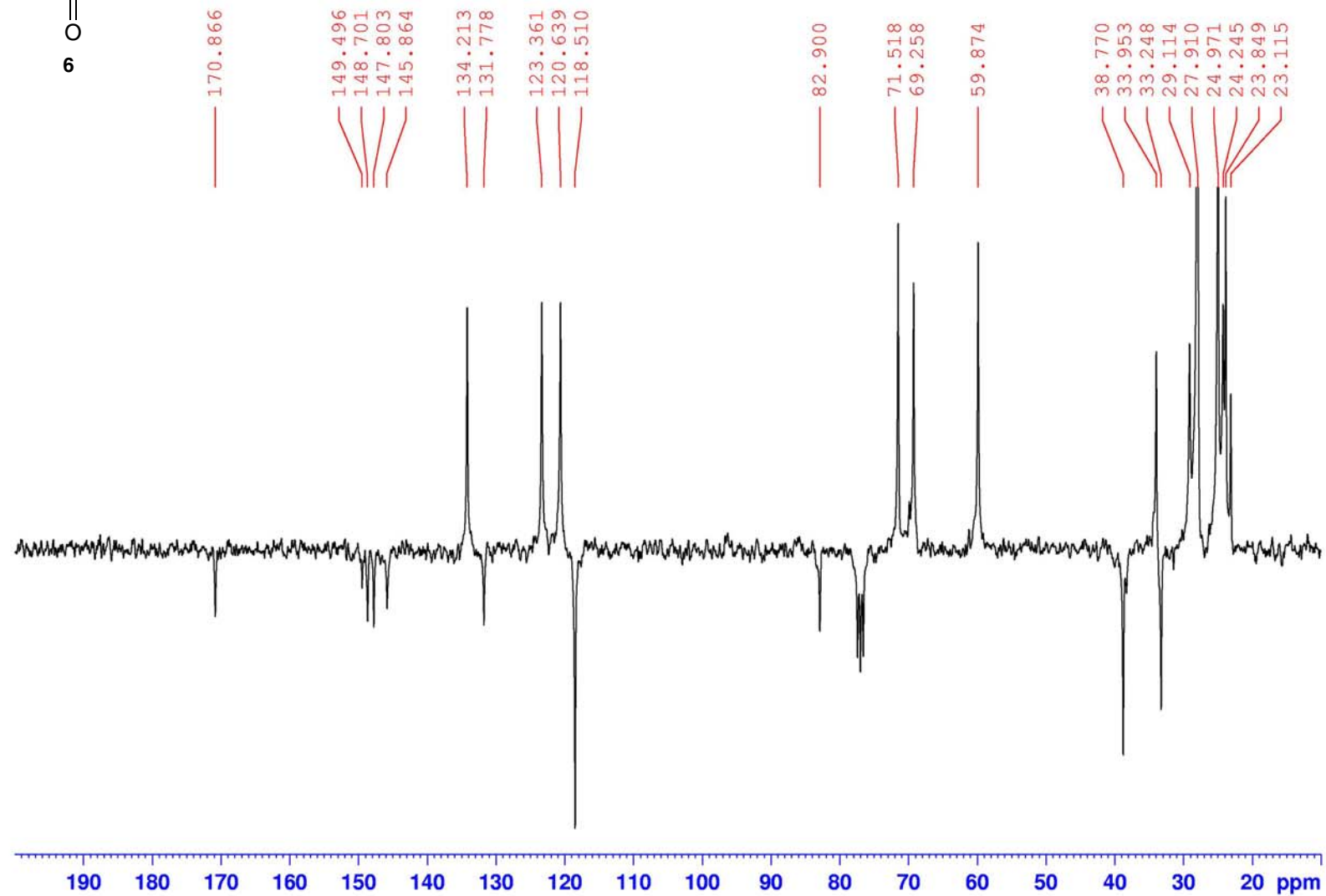
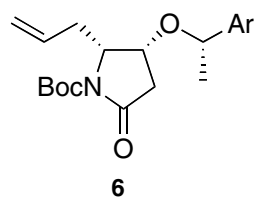
(5S,6R,7S,7aR)-Hexahydro-6,7-dihydroxy-5-((dimethyl(phenyl)silyl)methyl)-pyrrolizin-3-one (15): mp 93.2-93.9 °C (pentane); $[\alpha]_D^{21}$ -58.7 (*c* 1.1, CHCl₃); IR (film) 3385, 2955, 2922, 1659, 1426, 1113, 840 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.35 (s, 3 H), 0.40 (s, 3 H), 1.10 (A of ABX, *J* = 14.5, 8.8 Hz, 1 H), 1.35 (B of ABX, *J* = 14.5, 5.8 Hz, 1 H), 1.84-1.93 (m, 1 H), 2.11-2.20 (m, 1 H), 2.23-2.31 (m, 1 H), 2.37-2.46 (m, 1 H), 3.00 (br s, 2 H), 3.66-3.71 (m, 1 H), 3.75-3.79 (m, 1 H), 3.82 (t, *J* = 3.8 Hz, 1 H), 3.84-3.88 (m, 1 H), 7.33-7.35 (m, 3 H), 7.53-7.56 (m, 2 H); ¹³C NMR (100.6 MHz, CDCl₃) δ -2.7 (CH₃), -2.5 (CH₃), 18.1 (CH₂), 21.1 (CH₂), 33.0 (CH₂), 57.1 (CH), 62.3 (CH), 71.4 (CH), 81.9 (CH), 127.8 (CH), 129.0 (CH), 133.6 (CH), 139.0 (C), 176.8 (C); MS (ESI) m/z 344 (MK⁺), 328 (MNa⁺, 100); HRMS calcd for C₁₆H₂₃O₃NNaSi: 328.1339. Found: 328.1343.

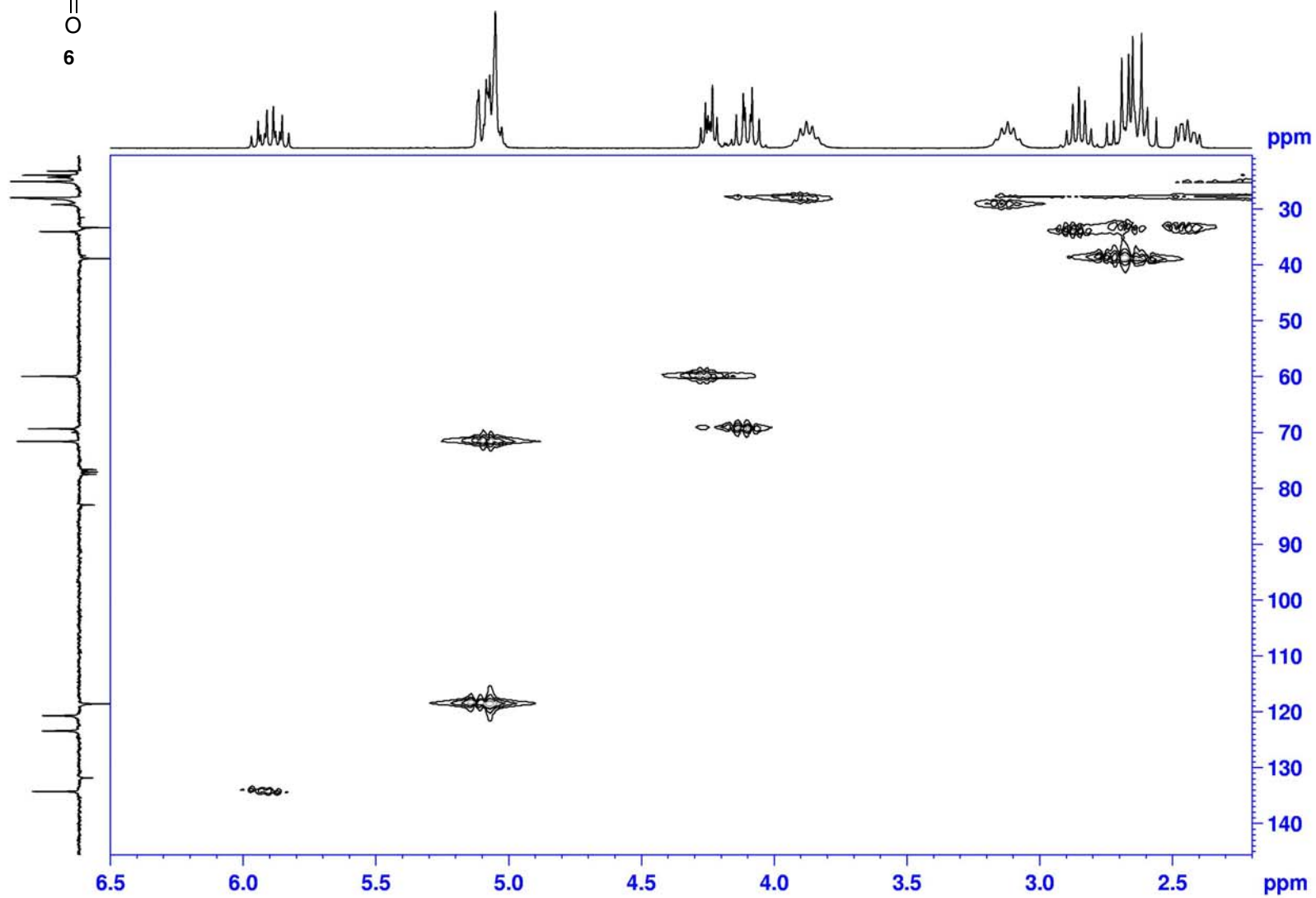
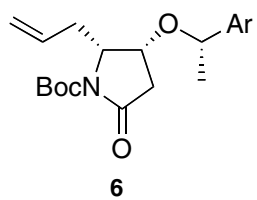
(5R,6R,7S,7aR)-Hexahydro-6,7-dihydroxy-5-(hydroxymethyl)pyrrolizin-3-one (16): $[\alpha]_D^{21}$ -49.9 (*c* 0.67, MeOH); IR (film) 3363, 2924, 1659, 1650, 1419, 1380, 1289, 1120, 833 cm⁻¹; ¹H NMR (300 MHz, CD₃OD) δ 2.01-2.20 (m, 1 H), 2.23-2.42 (m, 2 H), 2.59-2.74 (m, 1 H), 3.54-3.58 (m, 1 H), 3.68 (dd, *J* = 11.3, 4.1 Hz, 1 H), 3.88 (t, *J* = 3.2 Hz, 1 H), 3.93 (dd, *J* = 11.3, 3.4 Hz, 1 H), 4.02 (ddd, *J* = 9.8, 7.3, 3.2 Hz, 1 H), 4.38 (dd, *J* = 7.9, 3.2 Hz, 1 H); ¹³C NMR (75.5 MHz, CD₃OD) δ 20.1 (CH₂), 34.6 (CH₂), 62.6 (CH₂), 62.7 (CH), 66.0 (CH), 72.7 (CH), 77.4 (CH), 180.0 (C); MS (DCI) m/z 188 (MH⁺); HRMS calcd for C₈H₁₃O₄NNa: 210.0737. Found: 210.0739.

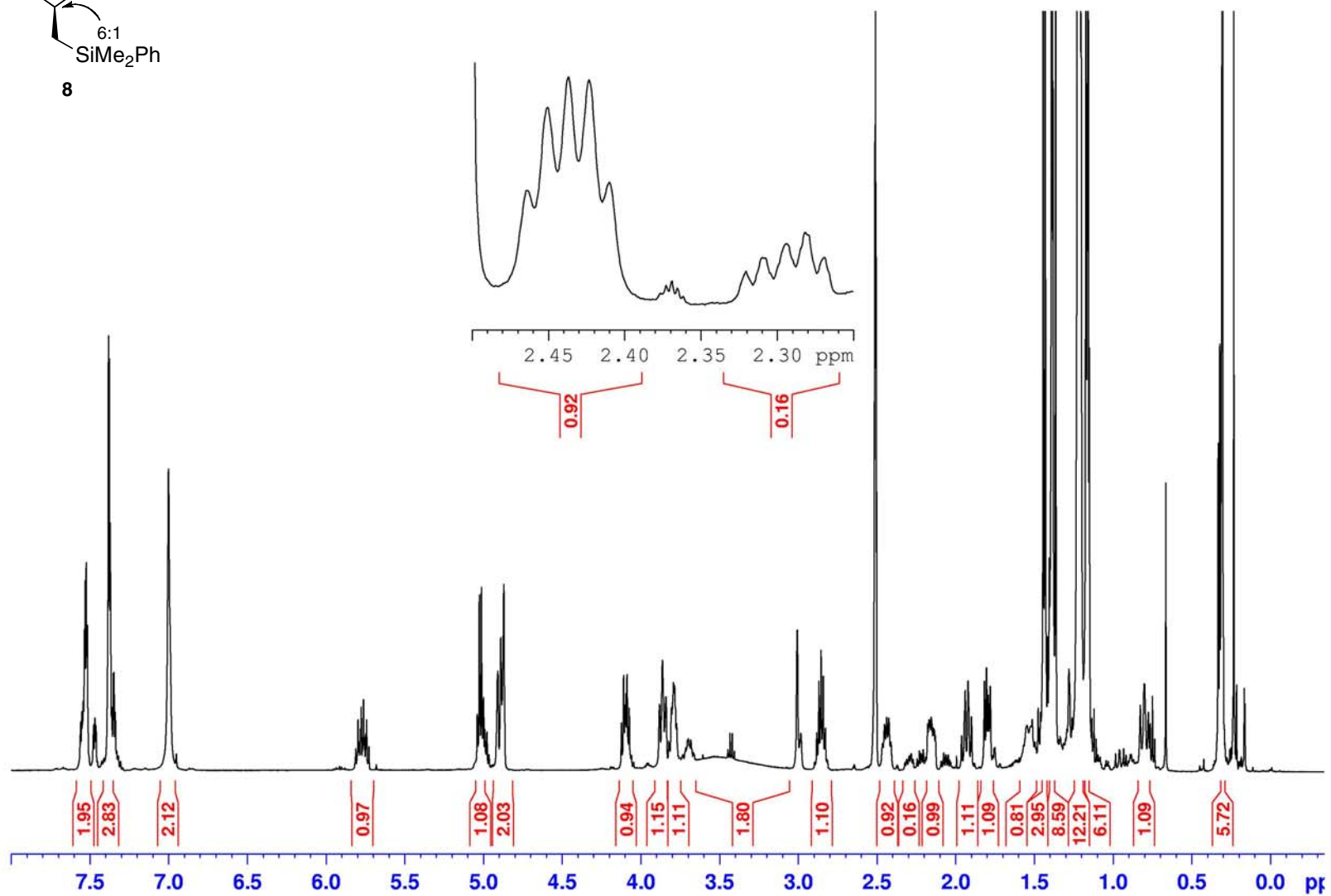
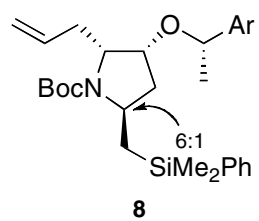
(+)-Hyacinthacine A₁ (1): $[\alpha]_D^{21}$ +43.9 (*c* 0.29, H₂O); ¹H NMR (400 MHz, CD₃OD) δ 1.66-1.74 (m, 1 H), 1.75-1.84 (m, 1 H), 1.92-2.00 (m, 1 H), 2.06-2.15 (m, 1 H), 2.63-2.69 (m, 1 H), 2.75-2.81 (m, 1 H), 3.05-3.10 (m, 1 H), 3.45-3.52 (m, 1 H), 3.60 (dd, *J* = 11.0, 6.5 Hz, 1 H), 3.81 (dd, *J* = 11.0, 3.4 Hz, 1 H), 3.88-3.91 (m, 2 H); ¹³C NMR (75.5 MHz, CD₃OD) δ 25.9 (CH₂), 28.8 (CH₂), 57.5 (CH₂), 65.4 (CH₂), 67.7 (CH), 71.8 (CH), 73.7 (CH), 77.5 (CH); MS (ESI) m/z 174 (MH⁺, 100).

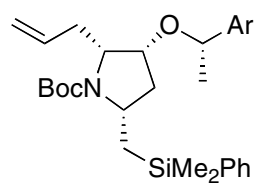












8 : minor diastereomer

