Electronic Supplementary Material (ESI) for RSC Advances.
This journal is © The Royal Society of Chemistry 2016

Electronic Supplementary Information

A nitrilase-mediated entry to 4-carboxymethyl-β-lactams from chemically prepared 4-(cyanomethyl)azetidin-2-ones

Lena Decuyper,[a] Nicola Piens,[a] Jens Mincke,[a] Jeroen Bomon,[a] Bert De Schrijver,[a] Karen Mollet,[a] Karel De Winter,[b] Tom Desmet[b] and Matthias D'hooghe*[a]

[a]*SynBioC Research Group, Department of Sustainable Organic Chemistry and Technology, Faculty of Bioscience Engineering, Ghent University, Coupure Links 653, B-9000 Ghent, Belgium. E-mail: matthias.dhooghe@UGent.be*

[b]*Department of Biochemical and Microbial Technology, Faculty of Bioscience Engineering, Ghent University, Coupure Links 653, B-9000 Ghent, Belgium*

Contents

Experimental part with procedures and characterization data of compounds **6a,c**, **7a-c**, **8a,b**, **9a-c**, **10a-c**, **11a-c**, **12a-c** 2 – 11

^{1}H NMR and ^{13}C NMR spectra of compounds **6a,c**, **7a-c**, **8a,b**, **9a-c**, **10a-c**, **11a-c**, **12a-c** 12 – 49

Experimental part

General methods

Commercially available solvents and reagents were purchased from common chemical suppliers and used without further purification. Melting points were measured using a Kofler bench, type WME Heizbank of Wagner & Munz. Optical rotations were determined with an JASCO P-2000 series polarimeter. Elemental analyses were obtained by means of a Perkin-Elmer 2400 Series II apparatus. IR spectra were obtained from samples in neat form with an ATR (Attenuated Total Reflectance) accessory with a Perkin-Elmer Spectrum BX FT-IR spectrophotometer. ^{1}H NMR spectra were recorded at 300 MHz (Jeol Eclipse+ 300) or at 400 MHz (Bruker Avance III-400) in deuterated solvents with TMS as internal standard. ^{13}C NMR spectra were recorded at 75 MHz (Jeol Eclipse+ 300) or at 100 MHz (Bruker Avance III-400). Electron spray (ES) mass spectra were obtained with an Agilent 1100 Series MS (ES, 4000V) mass spectrometer. High resolution electron spray (ES-TOF) mass spectra were obtained with an Agilent Technologies 6210 Series Time-of Flight.

Synthesis of 4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidin-2-ones 6a–c

4-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]azetidin-2-ones **6a–c** were prepared according to a literature procedure.[45,47,48]

(3*R*,4*S*)-1-Isopropyl-3-methoxy-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidin-2-one 6a

Yellow oil; yield: 9.00 g (85%); R_f 0.13 (hexane/EtOAc 4/1); $[\alpha]_D$ +37.2 (c 0.33 in $CHCl_3$); IR (ν_{max}/cm^{-1}): 1747 (C=O), 2982, 2936, 1370, 1211, 1064, 1034, 851; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (6H, d, *J* = 6.8 Hz, NCH(C<u>H</u>$_3$)$_2$), 1.35 and 1,45 (2 x 3H, 2 x s, C_{quat}(C<u>H</u>$_3$)$_2$), 3.53 (3H, s, OC<u>H</u>$_3$), 3.59 (1H, d x d, *J* = 7.9, 5.5 Hz, O(<u>H</u>CH)), 3.68 (1H, d x d, *J* = 8.7, 5.2 Hz, OCHC<u>H</u>N), 3.91 (1H, septet, *J* = 6.8 Hz, NC<u>H</u>(CH$_3$)$_2$), 4.13-4.22 (2H, m, O(HC<u>H</u>)C<u>H</u>), 4.35 (1H, d, *J* = 5.2 Hz, CH$_3$OC<u>H</u>); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.4 and 21.3 (NCH(<u>C</u>H$_3$)$_2$), 25.1 and 26.8 (C_{quat}(<u>C</u>H$_3$)$_2$), 44.3 (N<u>C</u>H(CH$_3$)$_2$), 59.1 (OCH$_3$), 59.8 (OCH<u>C</u>HN), 66.9 (OCH$_2$), 77.0 (CH$_2$<u>C</u>HO), 82.0 (CH$_3$O<u>C</u>H), 109.3 (<u>C</u>$_{quat}$(CH$_3$)$_2$), 166.9 (C=O); MS (70 eV): *m*/*z* (%) = 244 (M^+ + H, 100); HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{22}NO_4$: 244.1549, found: 244.1550.

(3*R*,4*S*)-3-Benzyloxy-1-isopropyl-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidin-2-one 6b

Spectral data were in accordance with those reported in the literature.[42]

(3*R*,4*S*)-1-Butyl-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-phenoxyazetidin-2-one 6c

White crystals; yield: 2.84 g (89%); R_f 0.24 (hexane/EtOAc 4/1); mp 52 °C; $[\alpha]_D$ +294.8 (c 0.33 in $CHCl_3$); IR (ν_{max}/cm^{-1}): 1746 (C=O), 2955, 2872, 1599, 1589, 1492, 1418, 1370, 1294, 1227, 1154, 1070,

1061, 940, 856, 756, 697; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (3H, t, *J* = 7.4 Hz, $N(CH_2)_3C\underline{H}_3$), 1.36 (2H, sextet, *J* = 7.4 Hz, $NCH_2CH_2C\underline{H}_2CH_3$), 1.37 and 1.46 (2 x 3H, 2 x s, $C_{quat}(CH_3)_2$), 1.57-1.72 (2H, m, $NCH_2C\underline{H}_2CH_2CH_3$), 3.29 (1H, d x d x d, *J* = 13.8, 7.7, 6.0 Hz, N(<u>H</u>CH)), 3.50 (1H, d x t, *J* = 13.8, 7.4 Hz, N(HC<u>H</u>)), 3.68 (1H, d x d, *J* = 8.9, 6.3 Hz, O(<u>H</u>CH)), 3.82 (1H, d x d, *J* = 9.0, 5.0 Hz, NCH), 4.18 (1H, d x d, *J* = 8.9, 6.3 Hz, O(HC<u>H</u>)), 4.42 (1H, d x t, *J* = 9.0, 6.3 Hz, OC<u>H</u>CH_2), 5.18 (1H, d, *J* = 5.0 Hz, PhOC<u>H</u>), 6.99-7.03 (1H, m, CH_{arom}), 7.06-7.09 (2H, m, CH_{arom}), 7.26-7.31 (2H, m, CH_{arom}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6 ($N(CH_2)_3\underline{C}H_3$), 20.1 ($NCH_2CH_2\underline{C}H_2CH_3$), 25.1 and 26.9 ($C_{quat}(\underline{C}H_3)_2$), 29.4 ($NCH_2\underline{C}H_2CH_2CH_3$), 41.3 ($NCH_2$), 60.4 (NCH), 67.0 ($OCH_2$), 77.2 (O<u>C</u>$HCH_2$), 79.8 (PhO<u>C</u>H), 109.7 ($\underline{C}_{quat}(CH_3)_2$), 115.8 (2 x HC_{arom}), 122.5 (HC_{arom}), 129.7 (2 x HC_{arom}), 157.5 ($C_{quat,arom}$), 165.9 (C=O); MS (70 eV): *m*/*z* (%) = 320 (M^+ + H, 100); HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{26}NO_4$: 320.1862, found: 320.1863; Anal. calcd. (%) for $C_{18}H_{25}NO_4$: C 67.69, H 7.89, N 4.39, found: C 66.53, H 8.48, N 4.25.

Synthesis of 4-(hydroxymethyl)azetidin-2-ones 7a–c

4-(Hydroxymethyl)azetidin-2-ones **7a–c** were prepared in three steps from the corresponding 4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidin-2-ones **6a–c** according to a literature procedure.[47,48]

(3*R*,4*S*)-4-Hydroxymethyl-1-isopropyl-3-methoxyazetidin-2-one 7a

Yellow oil; yield: 0.40 g (82%); R_f 0.32 (hexane/EtOAc 2/1); $[\alpha]_D$ +181.8 (c 0.10 in $CHCl_3$); IR (ν_{max}/cm^{-1}): 3425 (OH), 1726 (C=O), 2934, 1461, 1350, 1213, 1140, 1034, 920, 792, 731, 646; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 and 1.26 (2 x 3H, 2 x d, *J* = 6.8 Hz, $NCH(C\underline{H}_3)_2$), 2.36-2.39 (1H, m, OH), 3.62 (3H, s, OCH_3), 3.80-3.94 (4H, m, $NCHCH_2$ and $NC\underline{H}(CH_3)_2$), 4.47 (1H, d, *J* = 4.7 Hz, OCH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.0 and 21.6 ($NCH(\underline{C}H_3)_2$), 44.1 ($N\underline{C}H(CH_3)_2$), 56.7 ($N\underline{C}HCH_2$), 59.3 (OCH_3), 61.1 ($NCH\underline{C}H_2$), 83.4 (OCH), 166.5 (C=O); MS (70 eV): *m*/*z* (%) = 174 (M^+ + H, 61); HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_8H_{16}NO_3$: 174.1130, found: 174.1130.

(3*R*,4*S*)-3-Benzyloxy-4-hydroxymethyl-1-isopropylazetidin-2-one 7b

Colorless oil; yield: 1.20 g (96%); R_f 0.11 (hexane/EtOAc 2/1); $[\alpha]_D$ +138.7 (c 2.5 in $CHCl_3$); IR (ν_{max}/cm^{-1}): 3417 (OH), 1724 (C=O), 2931, 1402, 1340, 1216, 1037, 1023, 738, 698; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (6H, d, *J* = 6.6 Hz, $NCH(C\underline{H}_3)_2$), 2.48 (1H, br s, OH), 3.74-3.94 (4H, m, $NCHCH_2$ and $NC\underline{H}(CH_3)_2$), 4.65 (1H, d, *J* = 4.9 Hz, CHO), 4.70 and 4.95 (2 x 1H, 2 x d, *J* = 11.6 Hz, O(<u>H</u>C<u>H</u>)Ph), 7.36-7.49 (5H, m, CH_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.1 and 21.7 ($NCH(\underline{C}H_3)_2$), 44.0 ($N\underline{C}H(CH_3)_2$), 56.8 ($N\underline{C}HCH_2$), 61.0 ($NCH\underline{C}H_2$), 73.5 ($O\underline{C}H_2Ph$), 81.0 (CHO), 128.2, 128.4 and 128.7 (5 x HC_{arom}), 136.7 ($C_{arom,quat}$), 166.6 (C=O); MS (70 eV): *m*/*z* (%) = 250 (M^+ + H, 100); HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{20}NO_3$: 250.1443, found: 250.1445.

(3*R*,4*S*)-1-Butyl-4-hydroxymethyl-3-phenoxyazetidin-2-one 7c

Yellow oil; yield: 1.12 g (91%); R_f 0.44 (hexane/EtOAc 1/1); $[\alpha]_D$ +53.3 (c 0.17 in $CHCl_3$); IR (ν_{max}/cm^{-1}): 3424 (OH), 1739 (C=O), 2932, 2874, 1598, 1494, 1415, 1353, 1233, 1174, 1108, 1047, 961, 886, 842, 753, 734, 691; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (3H, t, *J* = 7.4 Hz, $N(CH_2)_3C\underline{H}_3$), 1.38 (2H, sextet, *J* = 7.4 Hz, $NCH_2CH_2C\underline{H}_2CH_3$), 1.51-1.69 (2H, m, $NCH_2C\underline{H}_2CH_2CH_3$), 1.97 (1H, br s, OH), 3.20 and 3.45 (2 x 1H, 2 x (d x d x d), *J* = 14.4, 8.0, 7.8, 6.5, 6.1 Hz, N(HCH)), 3.98-3.99 (3H, m, $NC\underline{H}C\underline{H}_2OH$), 5.28 (1H, d, *J* = 4.5 Hz, OCH), 7.03-7.11 (3H, m, CH_{arom}), 7.29-7.34 (2H, m, CH_{arom}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6 ($N(CH_2)_3\underline{C}H_3$), 20.3 ($NCH_2CH_2\underline{C}H_2CH_3$), 29.8 ($NCH_2\underline{C}H_2CH_2CH_3$), 40.8 ($NCH_2$), 58.3 (NCH), 60.3 ($CH_2OH$), 80.6 (OCH), 115.7 (2 x HC_{arom}), 122.7 (HC_{arom}), 129.7 (2 x HC_{arom}), 157.3 ($C_{quat,arom}$), 165.8 (C=O); MS (70 eV): *m*/*z* (%) = 250 (M^+ + H, 100); HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{20}NO_3$: 250.1443, found: 250.1446.

Synthesis of 4-(mesyloxymethyl)azetidin-2-ones 8a–b

As a representative example, the synthesis of (3*R*,4*S*)-1-isopropyl-4-mesyloxymethyl-3-methoxyazetidin-2-one **8a** is described. A solution of triethylamine (4.05 g, 40 mmol, 4 equiv) in dry THF (16 mL) was added dropwise to a solution of (3*R*,4*S*)-4-hydroxymethyl-1-isopropyl-3-methoxyazetidin-2-one **7a** (1.74 g, 10 mmol, 1 equiv) in dry THF (30 mL) at room temperature. The resulting mixture was cooled to 0 °C and a solution of methanesulfonyl chloride (1.72 g, 15 mmol, 1.5 equiv) in dry THF (7 mL) was added dropwise, after which the mixture was stirred for 1 hour at 0 °C. Afterward, the reaction mixture was washed with brine (2 x 25 mL) and a saturated $NaHCO_3$ solution (2 x 25 mL). The combined aqueous phases were extracted again with EtOAc (40 mL). Drying of the combined organic phases with $MgSO_4$, filtration of the drying agent, and removal of the solvent *in vacuo* afforded crude (3*R*,4*S*)-1-isopropyl-4-mesyloxymethyl-3-methoxyazetidin-2-one **8a**, which was purified in 95% (2.39 g) yield by column chromatography on silica gel (hexane/EtOAc 1/1).

(3*R*,4*S*)-1-Isopropyl-4-mesyloxymethyl-3-methoxyazetidin-2-one 8a

Yellow oil; yield: 2.39 g (95%); R_f 0.11 (hexane/EtOAc 1/1); $[\alpha]_D$ +53.7 (c 0.66 in $CHCl_3$); IR (ν_{max}/cm^{-1}): 1742 (C=O), 1391, 1351, 1216, 1172, 1142, 1032, 961, 824, 798; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 and 1.28 (2 x 3H, 2 x d, *J* = 6.8 Hz, $NCH(C\underline{H}_3)_2$), 3.06 (3H, s, SCH_3), 3.55 (3H, s, OCH_3), 3.89 (1H, septet, *J* = 6.8 Hz, $NC\underline{H}(CH_3)_2$), 4.05 (1H, d x d x d, *J* = 6.4, 5.0, 4.9 Hz, $NC\underline{H}CH_2$), 4.32 and 4.46 (2 x 1H, 2 x (d x d), *J* = 10.9, 6.4, 5.0 Hz, $NCH(\underline{H}C\underline{H})$), 4.50 (1H, d, *J* = 4.9 Hz, OCH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.9 and 21.8 ($NCH(\underline{C}H_3)_2$), 37.4 (SCH_3), 44.4 ($N\underline{C}H(CH_3)_2$), 55.1 ($N\underline{C}HCH_2$), 59.4 (OCH_3), 68.5 ($NCH\underline{C}H_2$), 82.7 (OCH), 166.4 (C=O); MS (70 eV): *m*/*z* (%) = 252 (M^+ + H, 100); HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_{18}NO_5S$: 252.0906, found: 252.0900.

(3*R*,4*S*)-3-Benzyloxy-1-isopropyl-4-(mesyloxymethyl)azetidin-2-one 8b

Light-yellow oil; yield: 1.12 g (84%); R_f 0.10 (hexane/EtOAc 2/1); $[\alpha]_D$ +62.8 (c 1.9 in $CHCl_3$); IR (ν_{max}/cm^{-1}): 1727 (C=O), 2941, 1348, 1168, 1149, 976, 958, 823, 697; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 and 1.27 (2 x 3H, 2 x d, *J* = 6.7 Hz, NCH($C\underline{H}_3$)$_2$), 2.95 (3H, s, SCH_3), 3.90 (1H, septet, *J* = 6.7 Hz, NC$\underline{H}$(CH_3)$_2$), 4.04 (1H, d x d x d, *J* = 6.3, 5.1, 5.0 Hz, NC$\underline{H}CH_2$), 4.32 and 4.41 (2 x 1H, 2 x (d x d), *J* = 10.9, 6.3, 5.0 Hz, NCH($\underline{H}C\underline{H}$), 4.67 (1H, d, *J* = 11.5 Hz, O($\underline{H}$CH)Ph, 4.69 (1H, d, *J* = 5.1 Hz, CHO), 4.86 (1H, d, *J* = 11.5 Hz, O(HC$\underline{H}$)Ph), 7.31-7.38 (5H, m, CH_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.0 and 21.8 (NCH($\underline{C}H_3$)$_2$), 37.3 (SCH_3), 44.5 (N$\underline{C}$H(CH_3)$_2$), 55.1 (N$\underline{C}$HCH_2), 68.7 (NCH$\underline{C}H_2$), 73.5 (O$\underline{C}H_2$Ph), 80.5 (CHO), 128.3, 128.4 and 128.7 (5 x HC_{arom}), 136.7 ($C_{arom,quat}$), 166.6 (C=O); MS (70 eV): *m*/*z* (%) = 328 (M^+ + H, 100); HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{22}NO_5S$: 328.1219, found: 328.1223.

Synthesis of 4-(tosyloxymethyl)azetidin-2-ones 9a–c

A as a representative example, the synthesis of (3*R*,4*S*)-1-butyl-3-phenoxy-4-(tosyloxymethyl)azetidin-2-one **9c** is described. A solution of triethylamine (2.02 g, 20 mmol, 4 equiv) and 4-dimethylaminopyridine (0.06 g, 0.5 mmol, 0.1 equiv) in dry CH_2Cl_2 (20 mL) was added dropwise to an ice-cooled solution of (3*R*,4*S*)-1-butyl-4-hydroxymethyl-3-phenoxyazetidin-2-one **7c** (1.25 g, 5 mmol, 1 equiv) in dry CH_2Cl_2 (15 mL). Subsequently, a solution of *p*-toluenesulfonyl chloride (1.43 g, 7.5 mmol, 1.5 equiv) in dry CH_2Cl_2 (10 mL) was added dropwise, after which the mixture was stirred for 40-48 hours under reflux. Afterward, the reaction mixture was washed with brine (2 x 25 mL) and a saturated $NaHCO_3$ solution (2 x 25 mL). The combined aqueous phases were extracted again with EtOAc (2 x 30 mL). Drying of the combined organic phases with $MgSO_4$, filtration of the drying agent, and removal of the solvent *in vacuo* afforded crude (3*R*,4*S*)-1-butyl-3-phenoxy-4-(tosyloxymethyl)azetidin-2-one **9c**, which was purified in 62% (1.27 g) yield by column chromatography on silica gel (hexane/EtOAc 3/1).

(3*R*,4*S*)-1-Isopropyl-3-methoxy-4-(tosyloxymethyl)azetidin-2-one 9a

Yellow oil; yield: 1.32 g (67%); R_f 0.28 (hexane/EtOAc 1/1); $[\alpha]_D$ +329.5 (c 0.23 in $CHCl_3$); IR (ν_{max}/cm^{-1}): 1748 (C=O), 2936, 1598, 1454, 1360, 1175, 1096, 1032, 974, 815, 767, 731, 666; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17 and 1.22 (2 x 3H, 2 x d, *J* = 6.8 Hz, NCH($C\underline{H}_3$)$_2$), 2.47 (3H, s, PhC$\underline{H}_3$), 3.45 (3H, s, OCH_3), 3.82 (1H, septet, *J* = 6.8 Hz, NC$\underline{H}$(CH_3)$_2$), 3.99 (1H, d x d x d, *J* = 7.2, 4.8, 4.5 Hz, NC$\underline{H}CH_2$), 4.09 and 4,24 (2 x 1H, 2 x (d x d), *J* = 10.7, 7.2, 4.5 Hz, NCH($\underline{H}C\underline{H}$)), 4.43 (1H, d, *J* = 4.8 Hz, OCH), 7.38 (2H, d x d, *J* = 8.5, 0.6 Hz, 2 x CH_{arom}), 7.81 (2H, d, *J* = 8.5 Hz, 2 x CH_{arom}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.8 and 21.6 (NCH($\underline{C}H_3$)$_2$), 21.7 (Ph$\underline{C}H_3$), 44.4 (N$\underline{C}$H(CH_3)$_2$), 55.0 (N$\underline{C}$HCH_2), 59.4 (OCH_3), 69.3 (CH_2O), 82.6 (OCH), 128.0 and 130.0 (4 x HC_{arom}), 132.3 ($CH_3\underline{C}_{quat,arom}$), 145.4 ($SC_{quat,arom}$), 166.3 (C=O); MS (70 eV):

m/z (%) = 328 (M^+ + H, 100); HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{15}H_{22}NO_5S$: 328.1219, found: 328.1217.

(3*R*,4*S*)-3-Benzyloxy-1-isopropyl-4-(tosyloxymethyl)azetidin-2-one 9b

White crystals; yield: 0.96 g (60%); R_f 0.16 (hexane/EtOAc 2/1); mp 86 °C; $[\alpha]_D$ +31.8 (c 2.7 in $CHCl_3$); IR (ν_{max}/cm^{-1}): 1755 (C=O), 2918, 1364, 1350, 1175, 1148, 1015, 972, 850, 763, 749, 702, 663; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.17 and 1.21 (2 x 3H, 2 x d, *J* = 6.7 Hz, NCH($C\underline{H}_3$)$_2$), 2.45 (3H, s, $C_{quat}CH_3$), 3.82 (1H, septet, *J* = 6.7 Hz, NC$\underline{H}$(CH_3)$_2$), 3.97 (1H, d x d x d, *J* = 7.1, 4.7, 4.5 Hz, NC$\underline{H}CH_2$), 4.11 and 4.23 (2 x 1H, 2 x (d x d), *J* = 10.5, 7.1, 4.5 Hz, NCH($\underline{H}C\underline{H}$)), 4.60 (1H, d, *J* = 12.1 Hz, O($\underline{H}$CH)Ph), 4.61 (1H, d, *J* = 4.7 Hz, CHO), 4.75 (1H, d, *J* = 12.1 Hz, O(HC$\underline{H}$)Ph), 7.27-7.33 (7H, m, CH_{arom}), 7.76 (2H, *J* = 8.2 Hz, CH_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.9 ($\underline{C}H_3CHCH_3$), 21.7 and 21.8 ($CH_3CH\underline{C}H_3$ and $C_{quat}\underline{C}H_3$), 44.6 (N$\underline{C}$H(CH_3)$_2$), 55.2 (N$\underline{C}$HCH_2), 69.5 (NCH$\underline{C}H_2$), 73.3 (O$\underline{C}H_2$Ph), 80.4 (CHO), 128.0, 128.1, 128.3, 128.6 and 130.1 (9 x HC_{arom}), 132.5 (S$\underline{C}_{arom,quat}$), 136.7 ($CH_2\underline{C}_{arom,quat}$), 145.4 ($CH_3\underline{C}_{arom,quat}$), 166.5 (C=O); MS (70 eV): *m/z* (%) = 404 (M^+ + H, 100); Anal. calcd. (%) for $C_{21}H_{25}NO_5S$: C 62.51, H 6.25, N 3.47, found: C 62.70, H 6.54, N 3.51.

(3*R*,4*S*)-1-Butyl-3-phenoxy-4-(tosyloxymethyl)azetidin-2-one 9c

Yellow crystals; yield: 1.27 g (62%); R_f 0.27 (hexane/EtOAc 3/1); mp 68 °C; $[\alpha]_D$ +23.0 (c 0.33 in $CHCl_3$); IR (ν_{max}/cm^{-1}): 1746 (C=O), 2949, 2873, 1598, 1492, 1418, 1355, 1292, 1238, 1228, 1189, 1171, 968, 896, 850, 829, 812, 764, 735, 699, 656; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (3H, t, *J* = 7.4 Hz, N(CH_2)$_3$C$\underline{H}_3$), 1.31 (2H, sextet, *J* = 7.4 Hz, $NCH_2CH_2C\underline{H}_2CH_3$), 1.47-1.64 (2H, m, $NCH_2C\underline{H}_2CH_2CH_3$), 2.46 (3H, s, Ar$C\underline{H}_3$), 3.11 and 3.40 (2 x 1H, 2 x (d x d x d), *J* = 14.0, 8.1, 8.0, 7.2, 5.9 Hz, N(HCH)), 4.18 (1H, d x d x d, *J* = 7.7, 4.6, 3.5 Hz, NCH), 4.24 and 4.37 (2 x 1H, 2 x (d x d), *J* = 10.4, 7.7, 3.5 Hz, (HCH)O), 5.24 (1H, d, *J* = 4.6 Hz, OCH), 6.91-7.05 (3H, m, CH_{arom}), 7.28-7.34 (4H, m, CH_{arom}), 7.71-7.73 (2H, m, CH_{arom}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.5 (N(CH_2)$_3\underline{C}H_3$), 20.1 ($NCH_2CH_2C\underline{H}_2CH_3$), 21.6 (Ar$\underline{C}H_3$), 29.5 ($NCH_2\underline{C}H_2CH_2CH_3$), 41.2 ($NCH_2$), 56.1 (NCH), 69.0 ($CH_2O$), 80.0 (OCH), 115.5 (2 x HC_{arom}), 122.5 (HC_{arom}), 127.9 (2 x HC_{arom}), 129.6 (2 x HC_{arom}), 130.0 (2 x HC_{arom}), 132.2 ($CH_3\underline{C}_{quat,arom}$), 145.3 and 157.2 ($OC_{quat,arom}$ and $SC_{quat,arom}$), 165.3 (C=O). MS (70 eV): *m/z* (%) = 404 (M^+ + H, 10), 421 (M^+ + NH_4, 100); HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{21}H_{26}NO_5S$: 404.1532, found: 404.1539; Anal. calcd. (%) for $C_{21}H_{25}NO_5S$: C 62.51, H 6.25, N 3.47, found: C 62.85, H 6.46, N 3.37.

Synthesis of 4-(iodomethyl)azetidin-2-ones 10a–c

As a representative example, the synthesis of (3*R*,4*R*)-4-iodomethyl-1-isopropyl-3-methoxyazetidin-2-one **10a** is described. To a solution of (3*R*,4*S*)-1-isopropyl-3-methoxy-4-(tosyloxymethyl)azetidin-2-one **9a** (0.33 g, 1 mmol, 1 equiv) in dry acetone (10 mL), sodium iodide (0.60 g, 4 mmol, 4 equiv) was

added. After a reflux period of 40 hours, the solvent was evaporated, after which water (10 mL) was added and the mixture was extracted with EtOAc (3 × 15 mL). Drying of the combined organic phases with $MgSO_4$, filtration of the drying agent, and removal of the solvent *in vacuo* afforded crude (3*R*,4*R*)-4-iodomethyl-1-isopropyl-3-methoxyazetidin-2-one **10a**, which was purified in 80% (0.23 g) yield by column chromatography on silica gel (hexane/EtOAc 3/1).

(3*R*,4*R*)-4-Iodomethyl-1-isopropyl-3-methoxyazetidin-2-one 10a

Yellow oil; yield: 0.23 g (80%); R_f 0.24 (hexane/EtOAc 3/1); $[\alpha]_D$ +138.1 (c 0.39 in $CHCl_3$); IR (ν_{max}/cm^{-1}): 1740 (C=O), 2971, 2932, 1462, 1389, 1340, 1236, 1212, 1170, 1143, 1033, 861, 730; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27 and 1.30 (2 x 3H, 2 x d, *J* = 6.8 Hz, NCH($C\underline{H}_3$)$_2$), 3.28 and 3.31 (2 x 1H, 2 x (d x d), *J* = 10.0, 8.4, 4.8 Hz, (HCH)I), 3.62 (3H, s, CH_3O), 3.86 (1H, septet, *J* = 6.8 Hz, NC$\underline{H}$(CH_3)$_2$), 4.11 (1H, d x d x d, *J* = 8.4, 4.8, 4.7 Hz, NC$\underline{H}CH_2$), 4.41 (1H, d, *J* = 4.7 Hz, OCH); ^{13}C NMR (100 MHz, $CDCl_3$): δ -1.5 (CH_2I), 18.2 and 20.2 (NCH($\underline{C}H_3$)$_2$), 42.4 (N$\underline{C}$H(CH_3)$_2$), 56.7 (N$\underline{C}HCH_2$), 58.5 (CH_3O), 81.6 (OCH), 164.7 (C=O); MS (70 eV): *m*/*z* (%) = 284 (M^+ + H, 100); HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_8H_{15}NO_2I$: 284.0147, found: 284.0151.

(3*R*,4*R*)-3-Benzyloxy-4-iodomethyl-1-isopropylazetidin-2-one 10b

Light-yellow crystals; yield: 0.31 g (88%); R_f 0.22 (hexane/EtOAc 3/1); mp 60 °C; $[\alpha]_D$ +162.9 (c 1.8 in $CHCl_3$); IR (ν_{max}/cm^{-1}): 1724 (C=O), 2970, 1340, 1227, 1180, 1158, 1049, 735, 696, 641; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 and 1.28 (2 x 3H, 2 x d, *J* = 7.0 Hz, NCH($C\underline{H}_3$)$_2$), 3.32 (2H, d, *J* = 5.8 Hz, CH_2I), 3.87 (1H, septet, *J* = 7.0 Hz, NC$\underline{H}$(CH_3)$_2$), 4.10 (1H, q, *J* = 5.8 Hz, NC$\underline{H}CH_2$), 4.59 (1H, d, *J* = 5.8 Hz, CHO), 4.81 and 4.87 (2 x 1H, 2 x d, *J* = 11.9 Hz, (HCH)O), 7.30-7.44 (5H, m, CH_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): δ 0.9 (CH_2I), 20.3 and 22.2 (NCH($\underline{C}H_3$)$_2$), 44.5 (N$\underline{C}$H(CH_3)$_2$), 58.7 (N$\underline{C}HCH_2$), 73.9 (CH_2O), 81.3 (CHO), 128.0, 128.1 and 128.5 (5 x HC_{arom}), 137.2 ($C_{arom,quat}$), 166.8 (C=O); MS (70 eV): *m*/*z* (%) = 360 (M^+ + H, 100); Anal. calcd. (%) for $C_{14}H_{18}NO_2I$: C 46.81, H 5.05, N 3.90, found: C 47.37, H 5.14, N 3.86.

(3*R*,4*R*)-1-Butyl-4-iodomethyl-3-phenoxyazetidin-2-one 10c

Yellow oil; yield: 0.31 g (69%); R_f 0.21 (hexane/EtOAc 4/1); $[\alpha]_D$ +281.2 (c 0.37 in $CHCl_3$); IR (ν_{max}/cm^{-1}): 1751 (C=O), 2957, 2929, 1597, 1590, 1493, 1402, 1347, 1233, 1171, 1045, 931, 884, 862, 752, 690; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (3H, t, *J* = 7.4 Hz, N(CH_2)$_3C\underline{H}_3$), 1.37 (2H, sextet, *J* = 7.4 Hz, $NCH_2CH_2C\underline{H}_2CH_3$), 1.58-1.73 (2H, m, $NCH_2C\underline{H}_2CH_2CH_3$), 3.32 (1H, d x d x d, *J* = 14.0, 8.1, 5.7 Hz, N($\underline{H}$CH)), 3.35 and 3.39 (2 x 1H, 2 x (d x d), *J* = 10.5, 6.7, 6.5 Hz, (HCH)I), 3.47 (1H, d x d x d, *J* = 14.0, 8.3, 7.2 Hz, N(HC$\underline{H}$)), 4.28 (1H, d x d x d, *J* = 6.7, 6.5, 4.7 Hz, NCH), 5.21 (1H, d, *J* = 4.7 Hz, OCH), 7.01-7.11 (3H, m, CH_{arom}), 7.29-7.34 (2H, m, CH_{arom}); ^{13}C NMR (100 MHz, $CDCl_3$): δ -0.1 (CH_2I), 13.7 (N(CH_2)$_3\underline{C}H_3$), 20.2 ($NCH_2CH_2\underline{C}H_2CH_3$), 29.9 ($NCH_2\underline{C}H_2CH_2CH_3$), 40.6 ($NCH_2$), 59.5 (NCH), 81.1 (OCH),

115.9 (2 x HC_{arom}), 122.5 (HC_{arom}), 129.7 (2 x HC_{arom}), 157.5 ($C_{quat,arom}$), 165.8 (C=O); MS (70 eV): *m/z* (%) = 360 (M^+ + H, 100); HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{19}NO_2I$: 360.0460, found: 360.0467.

Synthesis of 4-(cyanomethyl)azetidin-2-ones 11a–c

As a representative example, the synthesis of (3*R*,4*S*)-4-cyanomethyl-1-isopropyl-3-methoxyazetidin-2-one **11a** is described. To a solution of (3*R*,4*R*)-4-iodomethyl-1-isopropyl-3-methoxyazetidin-2-one **10a** (0.28 g, 1 mmol, 1 equiv) in dry DMF (3 mL), crushed sodium cyanide (0.12 g, 2.5 mmol, 2.5 equiv) was added. After stirring for 72 hours at room temperature, brine was added (30 mL) and the resulting mixture was extracted with Et_2O (2 × 20 mL) and EtOAc (20 mL). Drying of the combined organic phases with $MgSO_4$, filtration of the drying agent, and removal of the solvent *in vacuo* afforded crude (3*R*,4*S*)-4-cyanomethyl-1-isopropyl-3-methoxyazetidin-2-one **11a**, which was purified in 62% (0.11 g) yield by column chromatography on silica gel (hexane/EtOAc 4/1).

(3*R*,4*S*)-4-Cyanomethyl-1-isopropyl-3-methoxyazetidin-2-one 11a

Yellow oil; yield: 0.11 g (62%); R_f 0.12 (hexane/EtOAc 4/1); $[\alpha]_D$ +50.6 (c 0.20 in $CHCl_3$); IR (ν_{max}/cm^{-1}): 2251 (C≡N), 1743 (C=O), 2936, 2840, 1672, 1465, 1394, 1370, 1344, 1250, 1214, 1140, 1089, 1034, 729, 647; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 and 1.31 (2 x 3H, 2 x d, *J* = 6.8 Hz, NCH($C\underline{H}_3$)$_2$), 2.64 and 2.74 (2 x 1H, 2 x (d x d), *J* = 17.1, 6.1, 5.8 Hz, (HCH)CN)), 3.60 (3H, s, CH_3O), 3.88 (1H, septet, *J* = 6.8 Hz, NC$\underline{H}$(CH_3)$_2$), 4.05 (1H, d x d x d, *J* = 6.1, 5.8, 5.3 Hz, NC$\underline{H}CH_2$), 4.48 (1H, d, *J* = 5.3 Hz, OCH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.9 ($\underline{C}H_2CN$), 20.1 and 21.8 (NCH($\underline{C}H_3$)$_2$), 44.5 (N$\underline{C}$H(CH_3)$_2$), 53.1 (N$\underline{C}HCH_2$), 59.6 (CH_3O), 82.7 (OCH), 117.1 (CN), 166.0 (C=O); MS (70 eV): *m/z* (%) = 183 (M^+ + H, 65), 200 ($M^+ + NH_4$, 100); HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_9H_{15}N_2O_2$: 183.1134, found: 183.1134.

(3*R*,4*S*)-3-Benzyloxy-4-cyanomethyl-1-isopropylazetidin-2-one 11b

White crystals; yield: 0.26 g (51%); R_f 0.05 (hexane/EtOAc 9/1); mp <50 °C; $[\alpha]_D$ +110.1 (c 1.42 in $CHCl_3$); IR (ν_{max}/cm^{-1}): 2252 (C≡N), 1744 (C=O), 2928, 1394, 1369, 1339, 1212, 1159, 1023, 739, 698; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 and 1.29 (2 x 3H, 2 x d, *J* = 6.8 Hz, NCH($C\underline{H}_3$)$_2$), 2.62 and 2.70 (2 x 1H, 2 x (d x d), *J* = 17.1, 5.8, 5.8 Hz, CH_2CN), 3.87 (1H, septet, *J* = 6.8 Hz, NC$\underline{H}$(CH_3)$_2$), 4.01 (1H, q, *J* = 5.8 Hz, NC$\underline{H}CH_2$), 4.66 (1H, d, *J* = 5.8 Hz, CHO), 4.71 and 4,87 (2 x 1H, 2 x d, *J* = 11.6 Hz, (HCH)O), 7.27-7.38 (5H, m, CH_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2 ($\underline{C}H_2CN$), 20.1 and 21.8 (NCH($\underline{C}H_3$)$_2$), 44.6 (N$\underline{C}$H(CH_3)$_2$), 53.2 (N$\underline{C}HCH_2$), 73.6 (CH_2O), 80.5 (CHO), 117.3 (CN), 128.2, 128.4 and 128.7 (5 x HC_{arom}), 136.7 ($C_{arom,quat}$), 166.2 (C=O); MS (70 eV): *m/z* (%) = 259 (M^+ + H, 100); HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{19}N_2O_2$: 259.1447, found: 259.1453.

(3*R*,4*S*)-1-Butyl-4-cyanomethyl-3-phenoxyazetidin-2-one 11c

Yellow crystals; yield: 0.12 g (53%); R_f 0.15 (hexane/EtOAc 4/1); mp 55 °C; $[\alpha]_D$ +67.2 (c 0.23 in $CHCl_3$); IR (ν_{max}/cm^{-1}): 2252 (C≡N), 1753 (C=O), 2931, 1591, 1494, 1458, 1407, 1351, 913, 754, 731, 691; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (3H, t, *J* = 7.4 Hz, $N(CH_2)_3C\underline{H}_3$), 1.39 (2H, sextet, *J* = 7.4 Hz, $NCH_2CH_2C\underline{H}_2CH_3$), 1.57-1.71 (2H, m, $NCH_2C\underline{H}_2CH_2CH_3$), 2.75 and 2.81 (2 x 1H, 2 x (d x d), *J* = 17.2, 7.3, 5.2 Hz, (HCH)CN), 3.26 and 3.52 (2 x 1H, 2 x (d x d x d), *J* = 14.1, 8.2, 8.1, 7.1, 5.9 Hz, N(HCH)), 4.23 (1H, d x d x d, *J* = 7.3, 5.2, 4.9 Hz, NCH), 5.30 (1H, d, *J* = 4.9 Hz, CHO), 7.04-7.08 (3H, m, CH_{arom}), 7.30-7.34 (2H, m, CH_{arom}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6 ($N(CH_2)_3\underline{C}H_3$), 18.4 ($\underline{C}H_2CN$), 20.2 ($NCH_2CH_2\underline{C}H_2CH_3$), 29.7 ($NCH_2\underline{C}H_2CH_2CH_3$), 40.9 ($NCH_2$), 54.2 (NCH), 80.3 (CHO), 115.7 (2 x HC_{arom}), 116.8 (CN), 122.9 (HC_{arom}), 129.8 (2 x HC_{arom}), 156.9 ($C_{quat,arom}$), 164.9 (C=O); MS (70 eV): *m*/*z* (%) = 259 (M^+ + H, 12), 276 (M^+ + NH_4, 100); HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{19}N_2O_2$: 259.1447, found: 259.1445.

Synthesis of 4-(carboxymethyl)azetidin-2-ones 12a–c

As a representative example, the synthesis of (3*R*,4*S*)-4-carboxymethyl-1-isopropyl-3-methoxyazetidin-2-one **12a** is described.

Method A: 1 mg/mL nitrilase NIT-P1-121[68] was added to 20 mL of a 20 mM solution of (3*R*,4*S*)-4-cyanomethyl-1-isopropyl-3-methoxyazetidin-2-one **11a** in a K_3PO_4-dithiothreitol-ethylenediaminetetraacetic acid buffer (50 mM/20 mM/1 mM, pH = 7.5) (95%) and MeOH (5%), and the resulting mixture was agitated in a thermomixer (30 °C, 200 rpm). Every 72 h, 1 mg/mL nitrilase NIT-P1-121 was added until a concentration of 4 mg/mL was reached. After four weeks of incubation, 60% conversion toward (3*R*,4*S*)-4-carboxymethyl-1-isopropyl-3-methoxyazetidin-2-one **12a** was attained (ratio determined on the basis of LC-MS analysis). The enzyme was inactivated by heat treatment (95 °C, 10 min – 0 °C, 10 min) and removed by centrifugation (14000 rpm, 10 min), after which the liquid phase was evaporated *in vacuo*. Removal of the buffer salts was achieved by filtration after resolvation in MeOH and EtOAc.

Finally, pure (3*R*,4*S*)-4-carboxymethyl-1-isopropyl-3-methoxyazetidin-2-one **12a** was obtained in 16% (7 mg) yield after separation from the starting material **11a** by preparative HPLC.

Method B: 1 mg/mL nitrilase NIT-P1-121[68] was added to 20 mL of a 20 mM solution of (3*R*,4*S*)-4-cyanomethyl-1-isopropyl-3-methoxyazetidin-2-one **11a** in a K_3PO_4-dithiothreitol-ethylenediaminetetraacetic acid buffer (50 mM/20 mM/1 mM, pH = 7.5) (95%) and MeOH (5%), and the resulting mixture was agitated in a thermomixer (30 °C, 200 rpm). Every 72 h, 1 mg/mL nitrilase NIT-P1-121 was added until a concentration of 4 mg/mL was reached. After four weeks of incubation,

60% conversion toward (3*R*,4*S*)-4-carboxymethyl-1-isopropyl-3-methoxyazetidin-2-one **12a** was attained (ratio determined on the basis of LC-MS analysis). The enzyme was inactivated by heat treatment (95 °C, 10 min – 0 °C, 10 min) and removed by centrifugation (14000 rpm, 10 min). In order to remove the unreacted starting material **11a**, the crude reaction mixture was saturated with sodium chloride and extracted with EtOAc (3 x 30 mL). Subsequently, the mixture was acidified to pH 4 by HCl, saturated with sodium chloride and extracted with EtOAc (3 x 30 mL). Drying of the latter combined organic phases with $MgSO_4$, filtration of the drying agent, and removal of the solvent in vacuo afforded (3*R*,4*S*)-4-carboxymethyl-1-isopropyl-3-methoxyazetidin-2-one **12a** in 43% (19 mg) yield.

(3*R*,4*S*)-4-Carboxymethyl-1-isopropyl-3-methoxyazetidin-2-one 12a

Spectral data based on ^{1}H NMR and ^{13}C NMR analysis of the crude reaction mixture (purity ~85% according to ^{1}H NMR). Yellow oil; yield: 19 mg (43%); R_f 0.18 (hexane/EtOAc 2/1); $[\alpha]_D$ +92.9 (c 0.20 in $CHCl_3$); IR (ν_{max}/cm^{-1}): 3415 (OH), 1732 (NC=O), 1648 (OC=O), 1403, 1369, 1348, 1242, 1209, 1177, 1037; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 and 1.27 (2 x 3H, 2 x d, *J* = 6.7 Hz, NCH($C\underline{H}_3$)$_2$), 2.75 and 2.82 (2 x 1H, 2 x (d x d), *J* = 17.2, 7.7, 5.5 Hz, ($\underline{H}C\underline{H}$)COOH), 3.55 (3H, s, OCH_3), 3.86 (1H, septet, *J* = 6.7 Hz, NC$\underline{H}$(CH_3)$_2$), 4.21 (1H, d x d x d, *J* = 7.7, 5.5, 5.0 Hz, NC$\underline{H}CH_2$), 4.48 (1H, d, *J* = 5.0 Hz, OCH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.1 and 21.6 (NCH($\underline{C}H_3$)$_2$), 34.2 ($\underline{C}H_2$COOH), 44.1 (N$\underline{C}$H(CH_3)$_2$), 52.9 (N$\underline{C}HCH_2$), 59.4 (OCH_3), 82.9 (OCH), 166.8 (NCO), 175.2 (COOH); MS (70 eV): *m*/*z* (%) = 202 (M^+ + H, 72); HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_9H_{16}NO_4$: 202.1079, found: 202.1086.

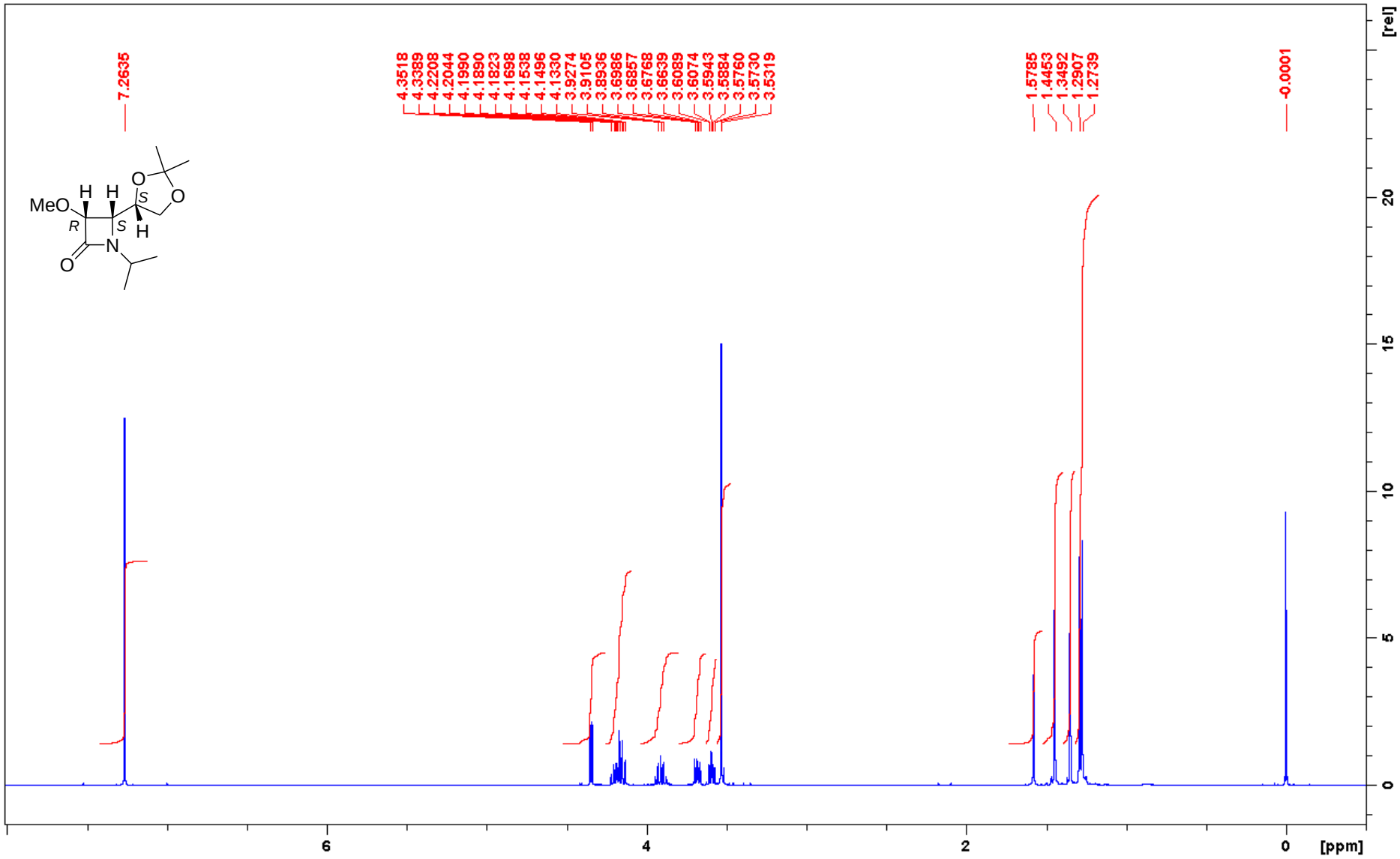
(3*R*,4*S*)-3-Benzyloxy-4-carboxymethyl-1-isopropylazetidin-2-one 12b

White crystals; yield: 40 mg (74%); R_f 0.08 (hexane/EtOAc 2/1); mp 94 °C; $[\alpha]_D$ +60.5 (c 0.23 in $CHCl_3$); IR (ν_{max}/cm^{-1}): 3401 (OH), 1726 (NC=O), 1693 (OC=O), 1242, 1196, 1175, 1140, 1031, 1020, 996, 753, 705; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 and 1.25 (2 x 3H, 2 x d, *J* = 6.7 Hz, NCH($C\underline{H}_3$)$_2$), 2.76 and 2.85 (2 x 1H, 2 x (d x d), *J* = 17.3, 7.7, 5.4 Hz, ($\underline{H}C\underline{H}$)COOH), 3.84 (1H, septet, *J* = 6.7 Hz, NC$\underline{H}$(CH_3)$_2$), 4.19 (1H, d x d x d, *J* = 7.7, 5.4, 4.9 Hz, NC$\underline{H}CH_2$), 4.65 (1H, d, *J* = 4.9 Hz, OCH), 4.66 and 4.83 (2 x 1H, 2 x d, *J* = 12.3 Hz, O($\underline{H}C\underline{H}$)), 7.27-7.35 (5H, m, CH_{arom}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.1 and 21.6 (NCH($\underline{C}H_3$)$_2$), 34.5 ($\underline{C}H_2$COOH), 44.2 (N$\underline{C}$H(CH_3)$_2$), 53.0 (N$\underline{C}HCH_2$), 73.1 (OCH_2), 80.6 (OCH), 127.7, 127.9 and 128.4 (5 x HC_{arom}), 137.0 ($C_{arom,quat}$), 166.9 (NCO), 175.7 (COOH); MS (70 eV): *m*/*z* (%) = 278 (M^+ + H, 100); HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{20}NO_4$: 278.1392, found: 278.1387.

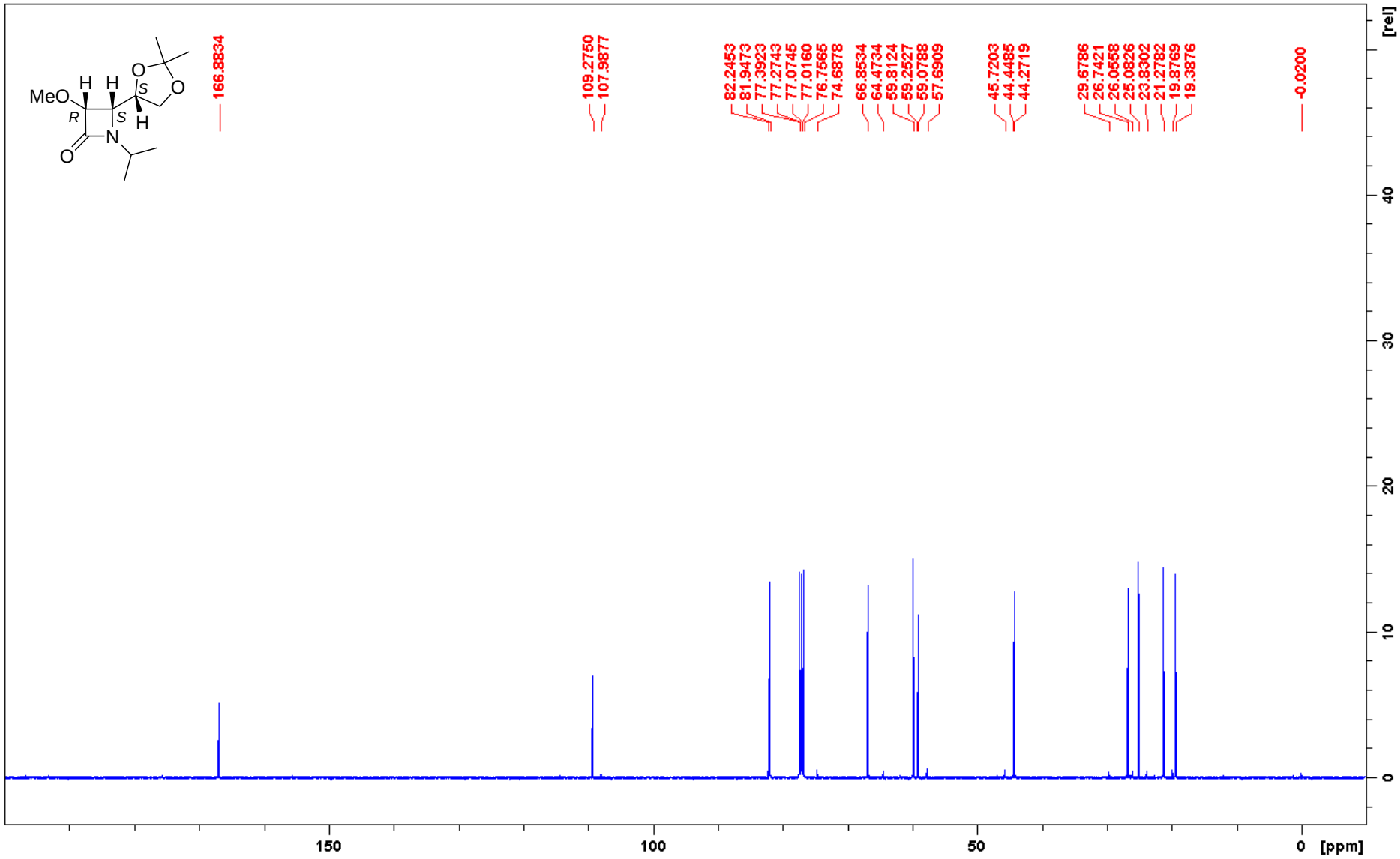
(3*R*,4*S*)-1-Butyl-4-carboxymethyl-3-phenoxyazetidin-2-one 12c

White crystals; yield: 10 mg (12%); R_f 0.13 (hexane/EtOAc 2/1); $[\alpha]_D$ +48.0 (c 0.13 in $CHCl_3$); IR (ν_{max}/cm^{-1}): 3423 (OH), 1731 (NC=O), 1700 (OC=O), 2957, 2871, 1589, 1486, 1433, 1354, 1307, 1212, 1185, 1144, 1111, 1074, 1034, 841, 753, 692, 669; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (3H, t, *J* = 7.3 Hz, $N(CH_2)_3C\underline{H}_3$), 1.34 (2H, sextet, *J* = 7.3 Hz, $NCH_2CH_2C\underline{H}_2CH_3$), 1.49-1.63 (2H, m, $NCH_2C\underline{H}_2CH_2CH_3$), 2.79 and 2.87 (2 x 1H, 2 x (d x d), *J* = 17.5, 6.9, 6.1 Hz, ($\underline{H}C\underline{H}$)COOH), 3.08 and 3.43 (2 x 1H, 2 x (d x d x d), *J* = 14.1, 7.8, 7.5, 7.5, 6.1 Hz, N(HCH), 4.35 (1H, d x d x d, *J* = 6.9, 6.1, 4.8 Hz, NCH), 5.29 (1H, d, *J* = 4.8 Hz, OCH), 6.99-7.05 (3H, m, CH_{arom}), 7.27-7.30 (2H, m, CH_{arom}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6 ($N(CH_2)_3\underline{C}H_3$), 20.1 ($NCH_2CH_2\underline{C}H_2CH_3$), 29.8 ($NCH_2\underline{C}H_2CH_2CH_3$), 33.6 ($\underline{C}H_2COOH$), 40.6 ($NCH_2$), 54.2 (NCH), 80.3 (OCH), 115.6 (2 x HC_{arom}), 122.4 (HC_{arom}), 129.6 (2 x HC_{arom}), 157.4 ($C_{quat,arom}$), 165.7 (NC=O), 175.5 (COOH); MS (70 eV): *m/z* (%) = 278 (M^+ + H, 100); HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{20}NO_4$: 278.1392, found: 278.1397.

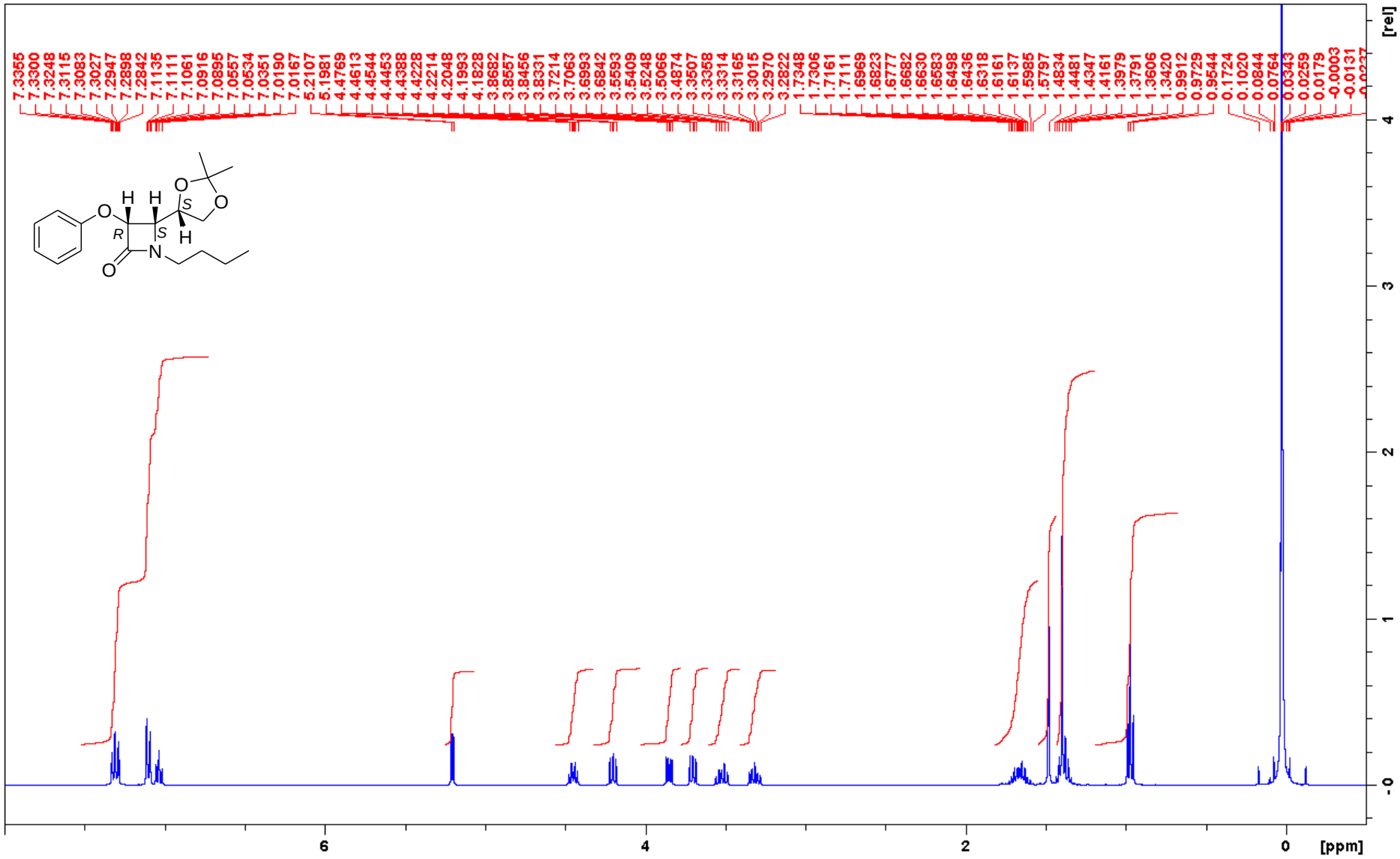
(3*R*,4*S*)-1-Isopropyl-3-methoxy-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidin-2-one 6a



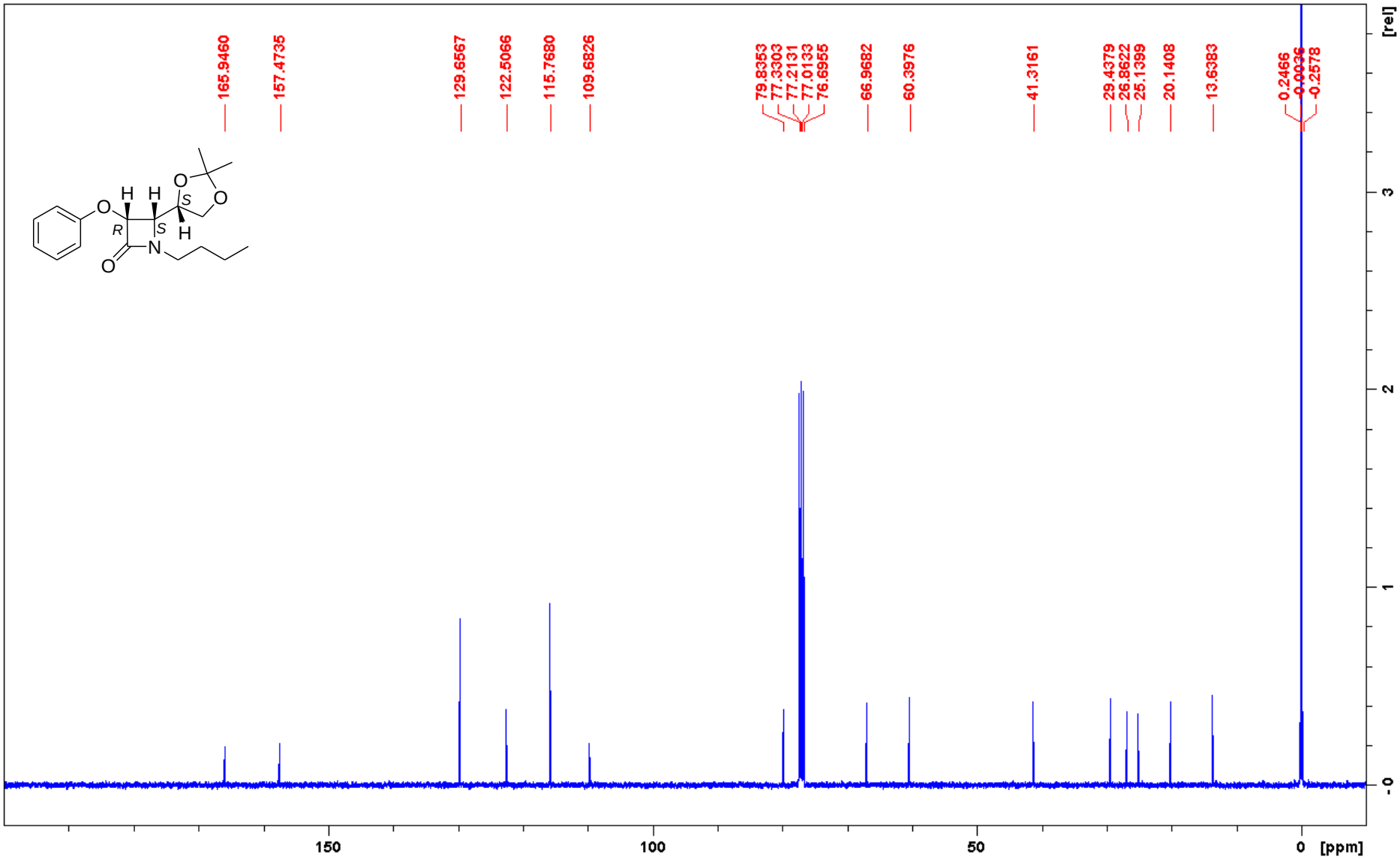
(3*R*,4*S*)-1-Isopropyl-3-methoxy-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidin-2-one 6a



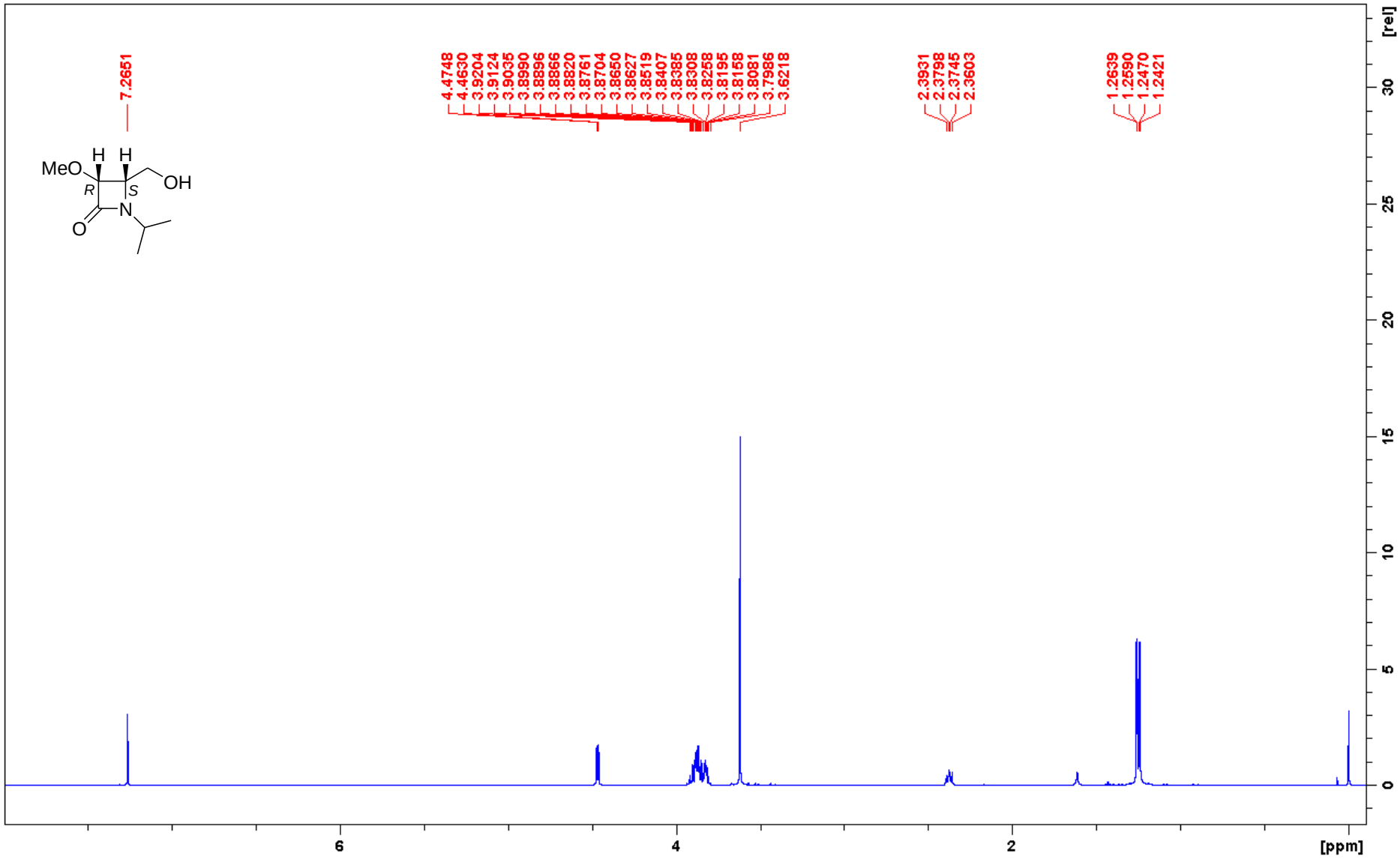
(3*R*,4*S*)-1-Butyl-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-phenoxyazetidin-2-one 6c



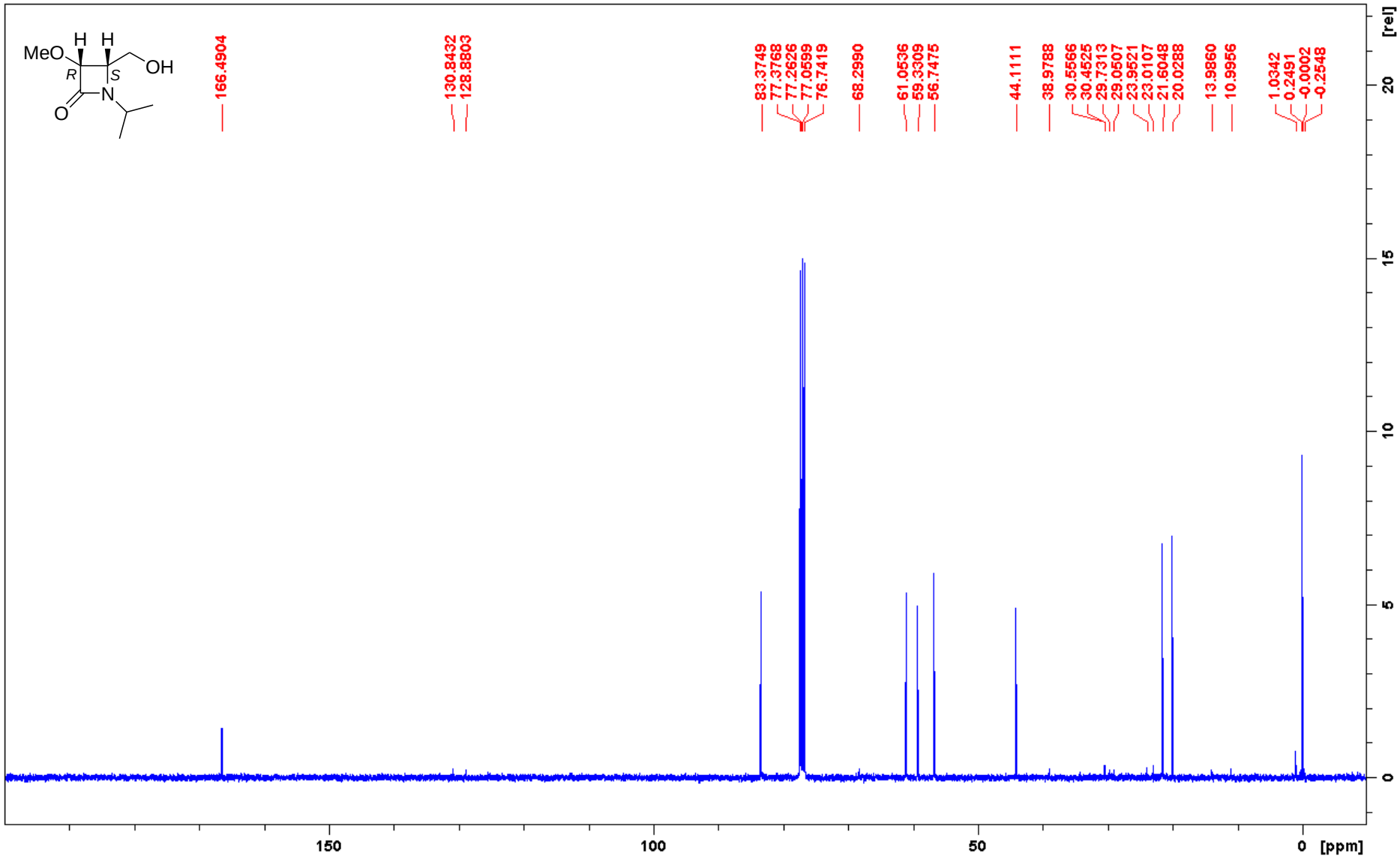
(3*R*,4*S*)-1-Butyl-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-phenoxyazetidin-2-one 6c



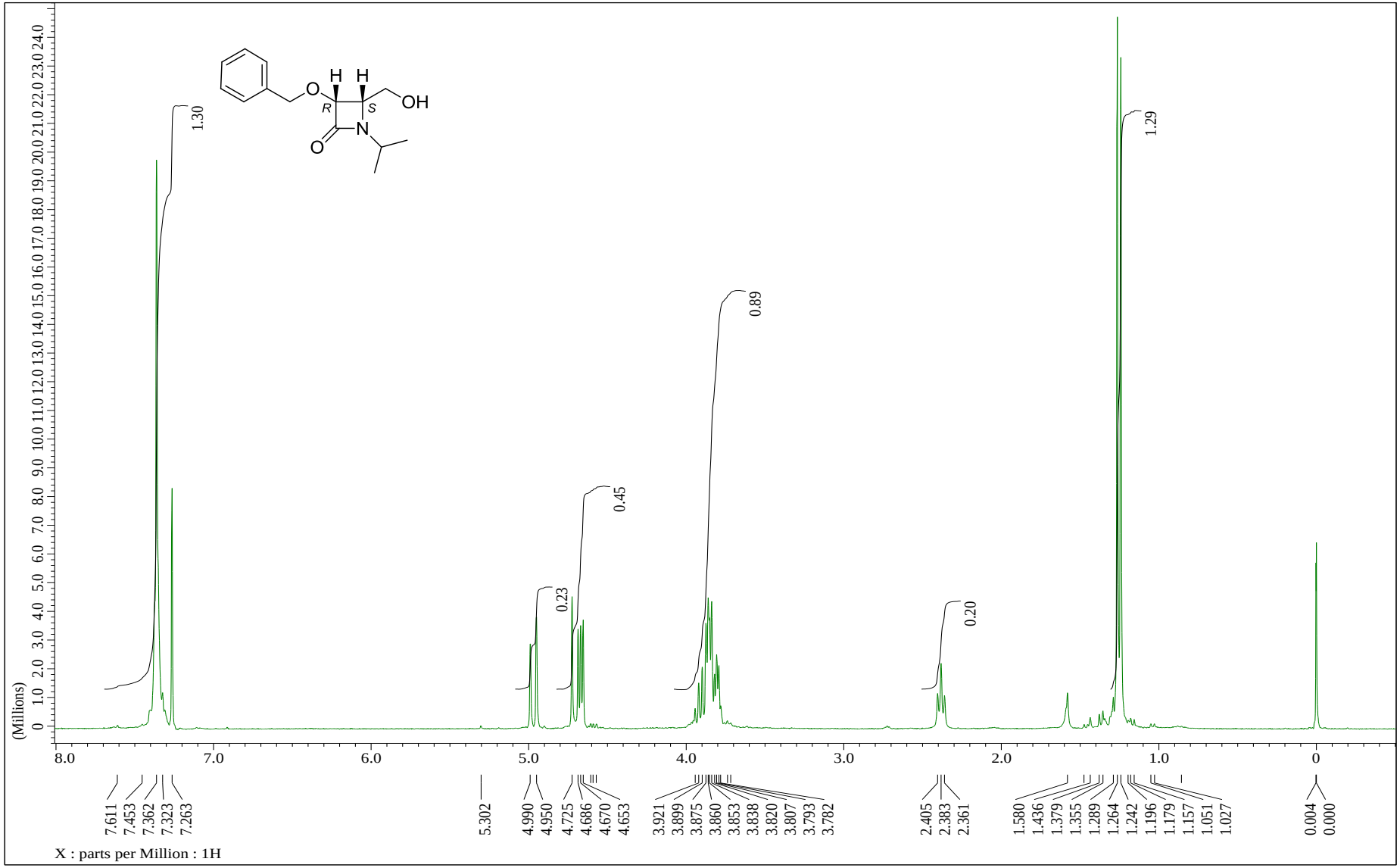
(3*R*,4*S*)-4-Hydroxymethyl-1-isopropyl-3-methoxyazetidin-2-one 7a



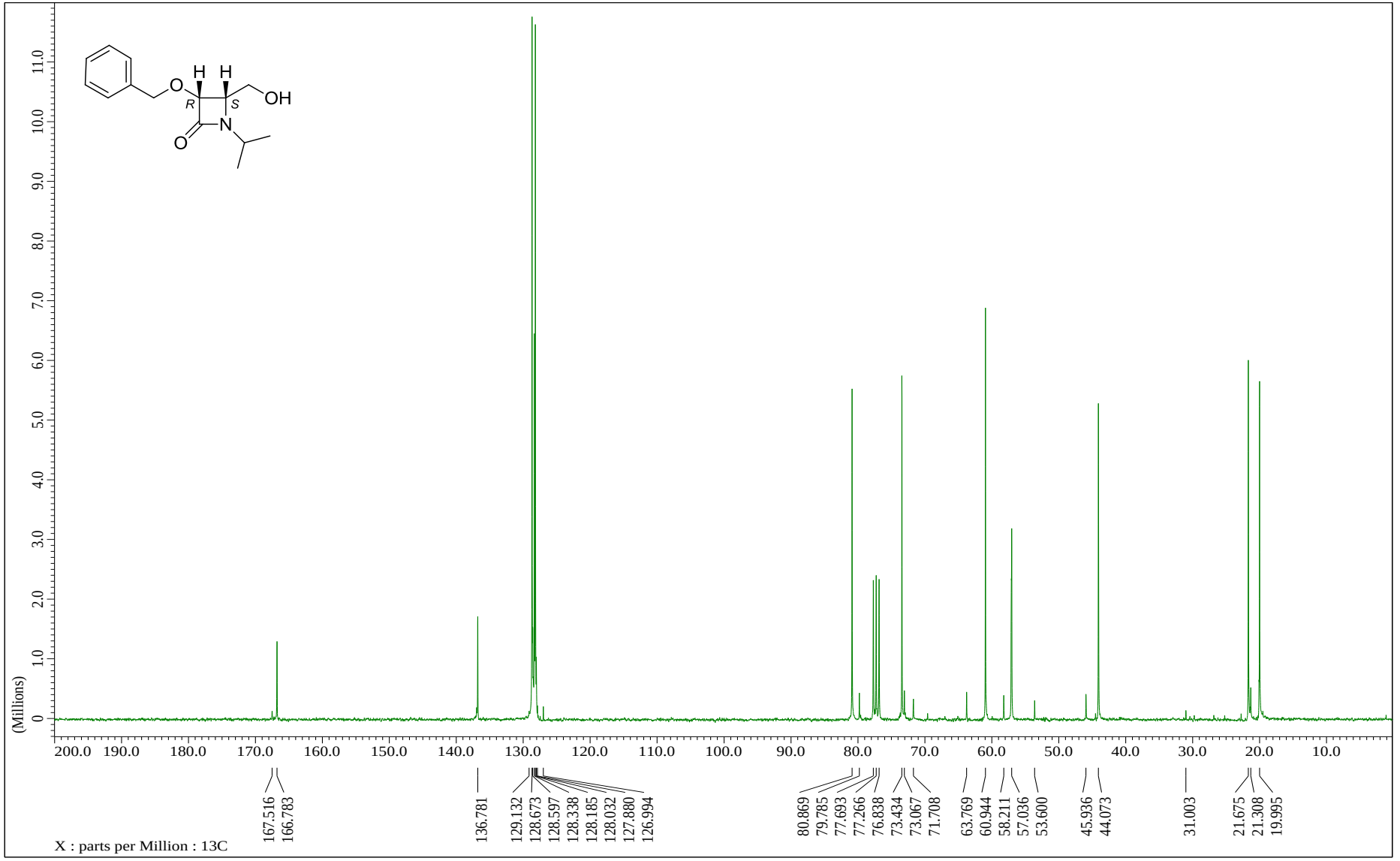
(3*R*,4*S*)-4-Hydroxymethyl-1-isopropyl-3-methoxyazetidin-2-one 7a



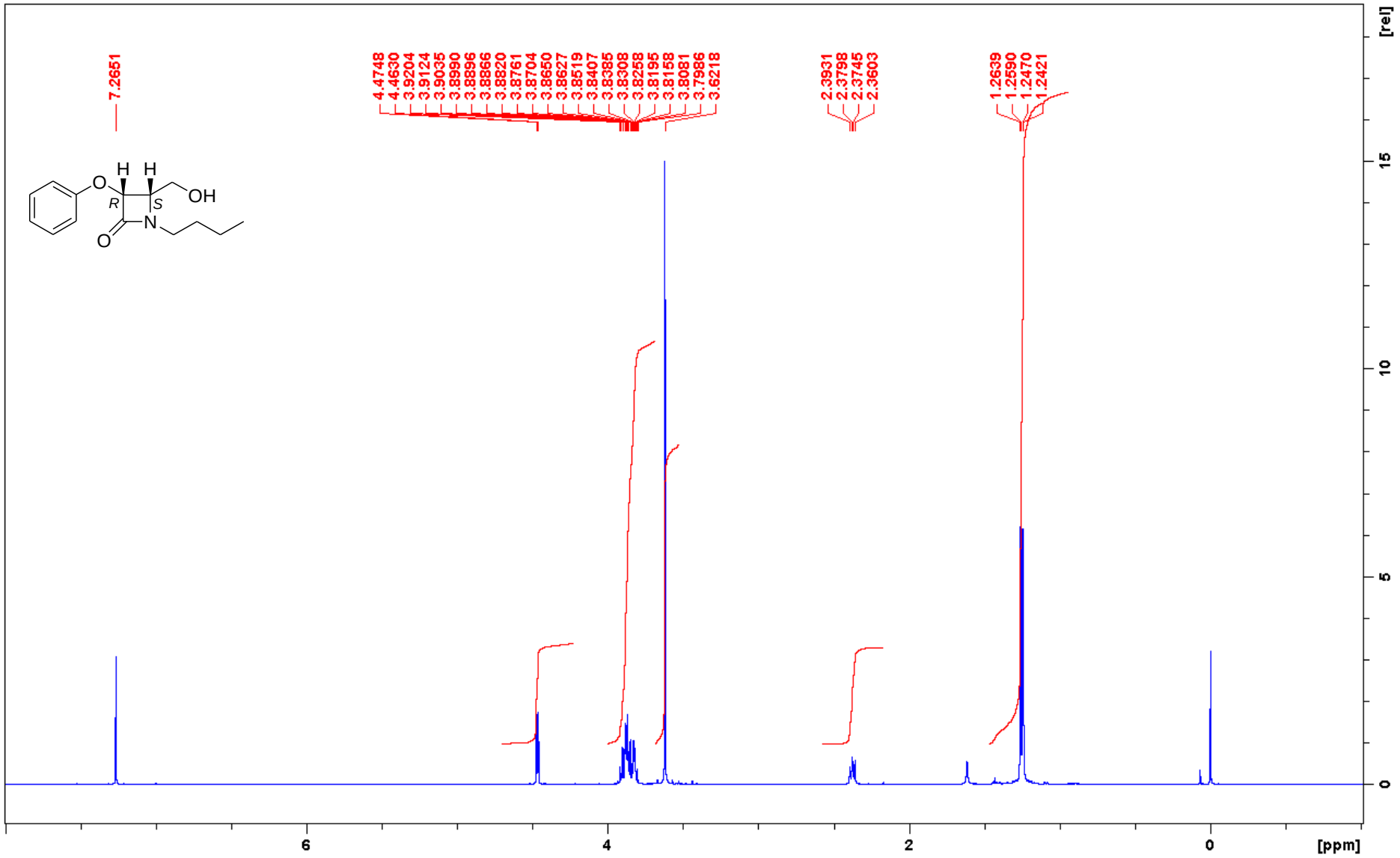
(3*R*,4*S*)-3-Benzyloxy-4-hydroxymethyl-1-isopropylazetidin-2-one 7b



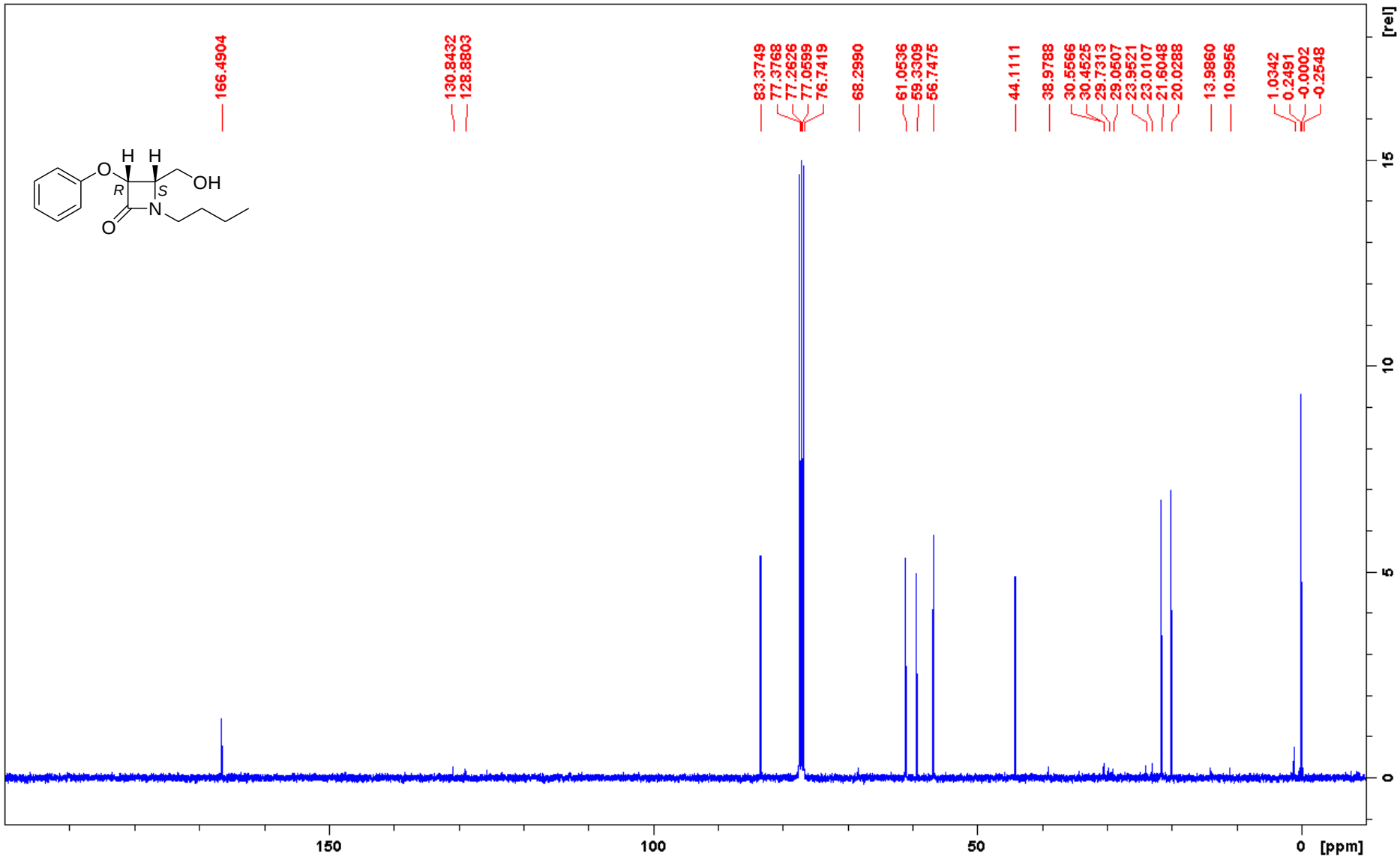
(3*R*,4*S*)-3-Benzyloxy-4-hydroxymethyl-1-isopropylazetidin-2-one 7b



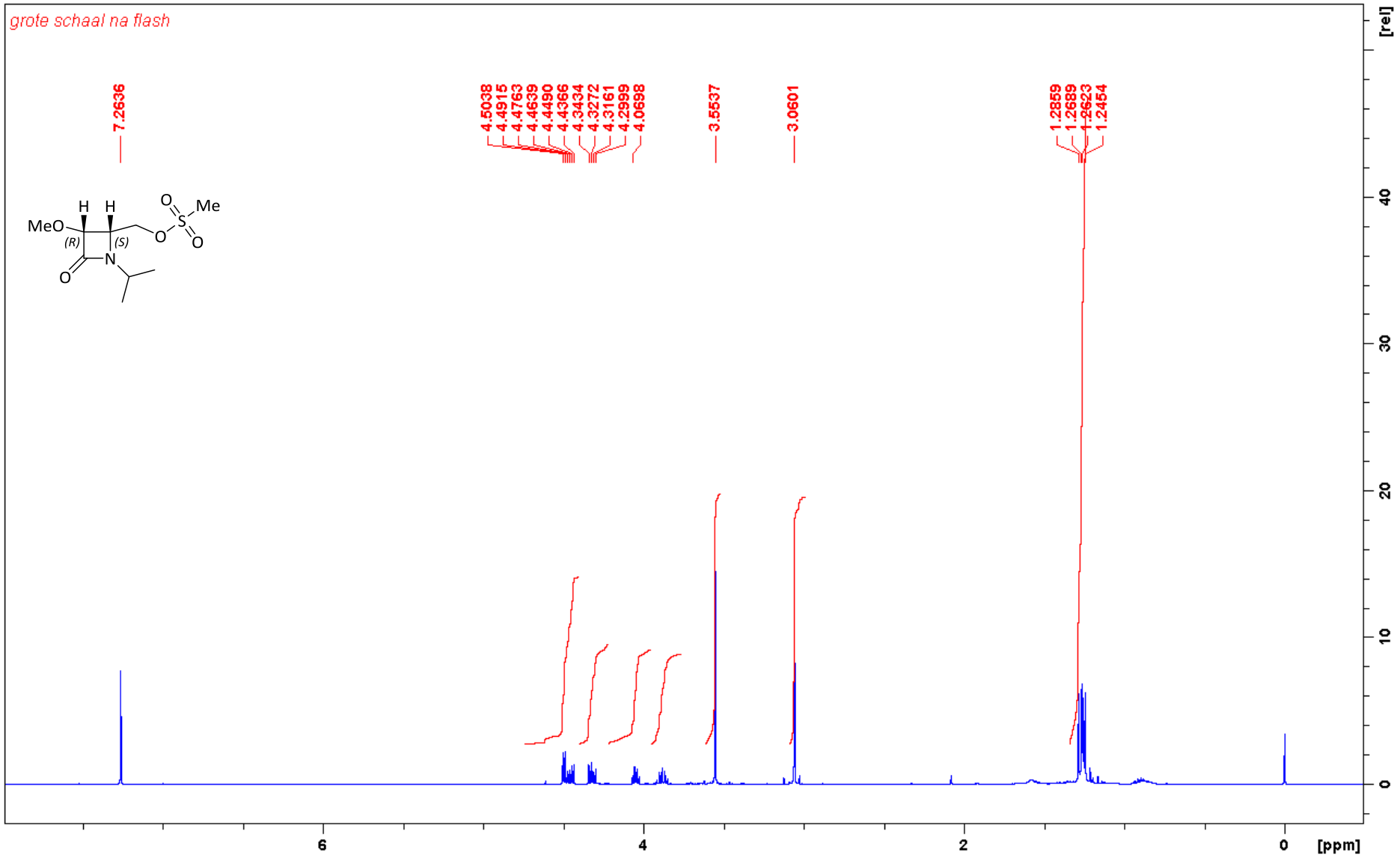
(3*R*,4*S*)-1-Butyl-4-hydroxymethyl-3-phenoxyazetidin-2-one 7c



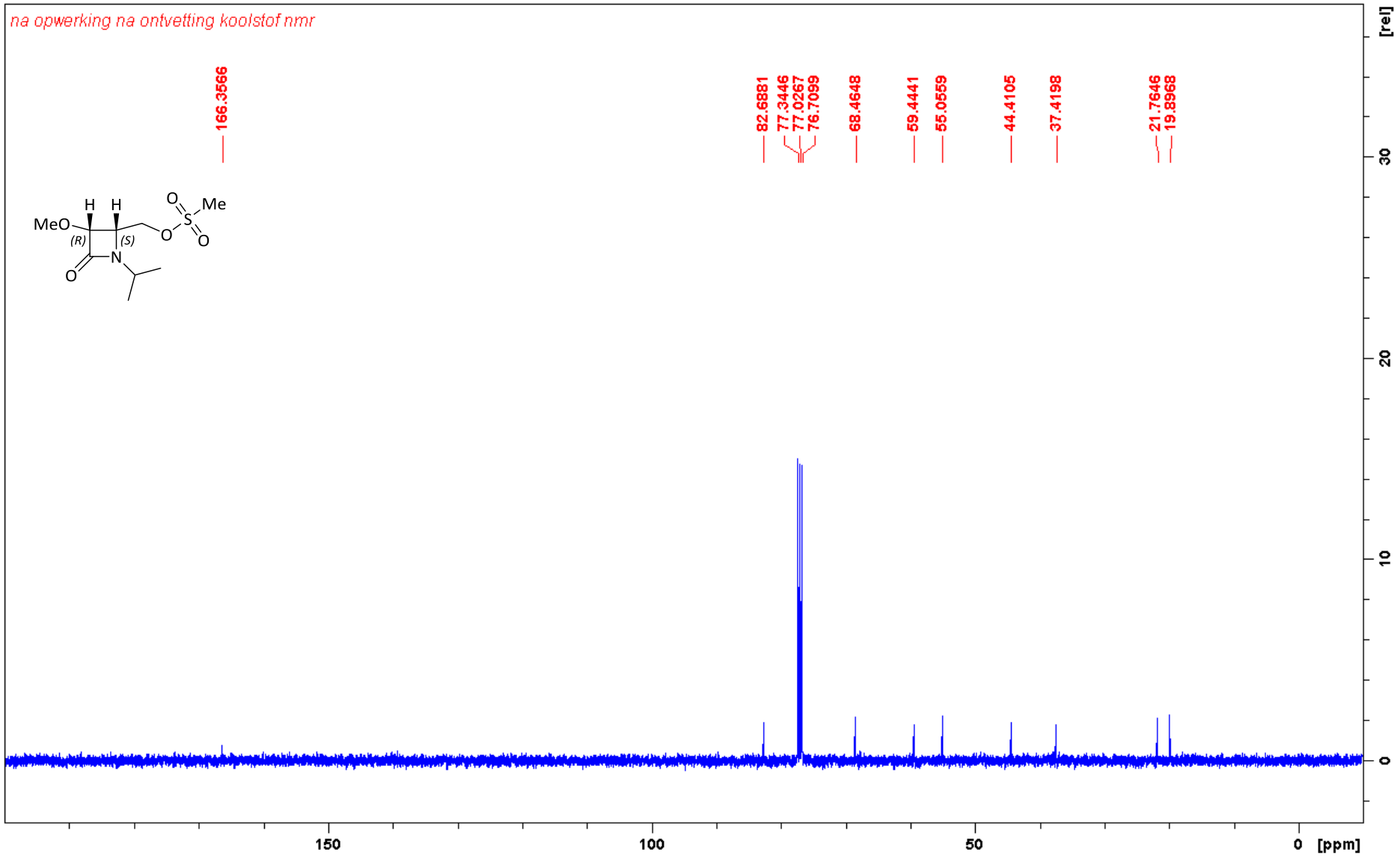
(3*R*,4*S*)-1-Butyl-4-hydroxymethyl-3-phenoxyazetidin-2-one 7c



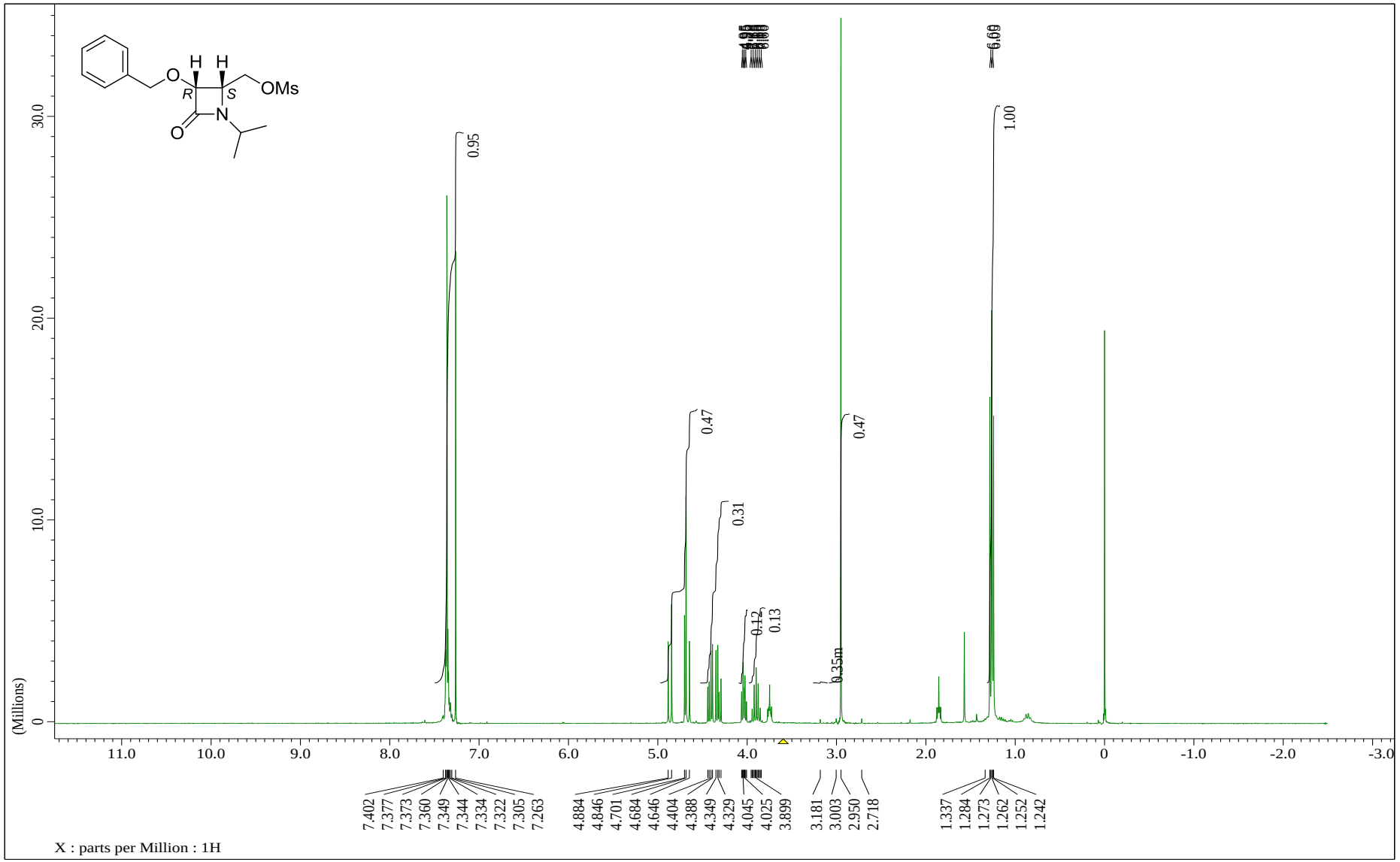
(3*R*,4*S*)-1-Isopropyl-4-mesyloxymethyl-3-methoxyazetidin-2-one 8a



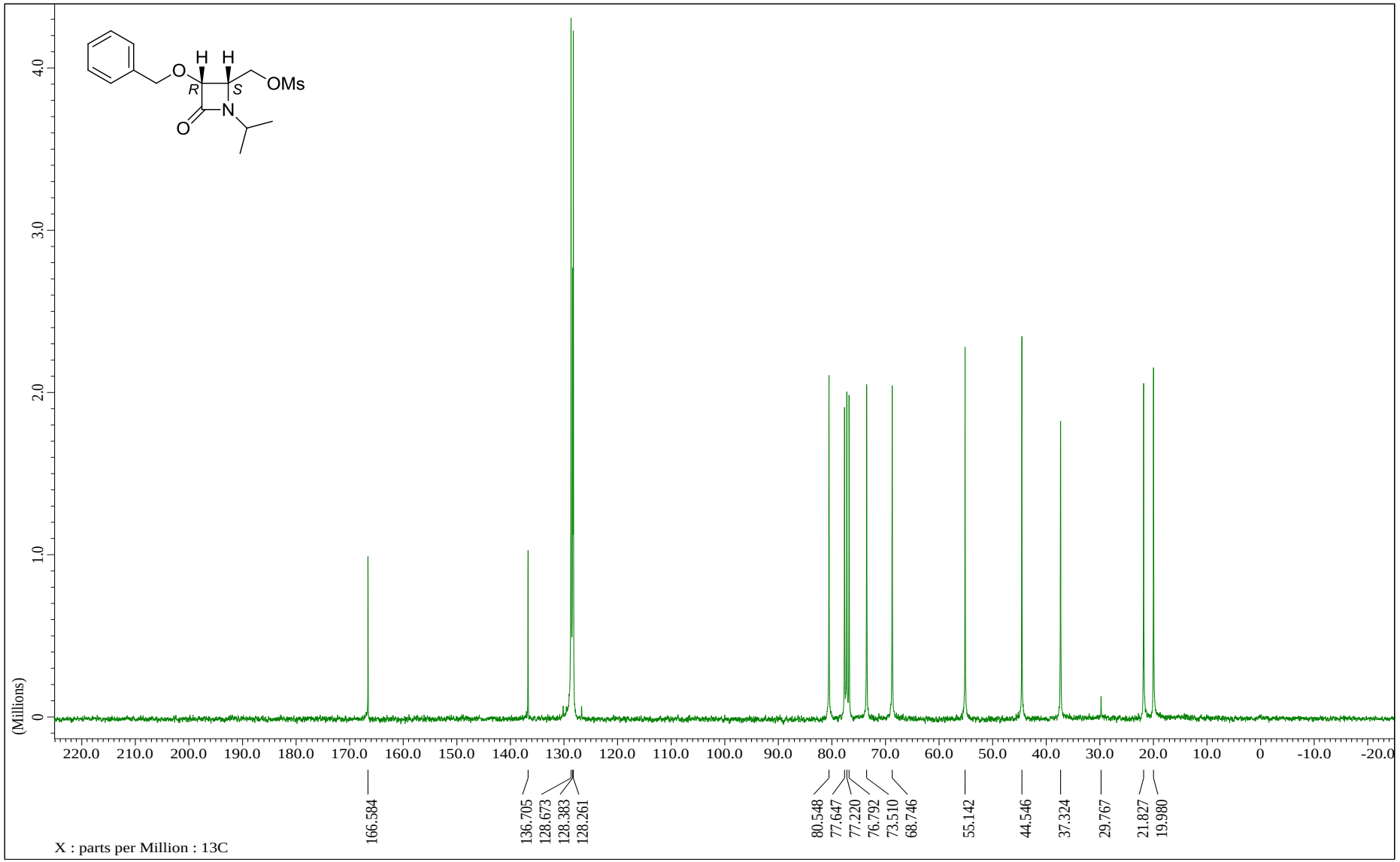
(3*R*,4*S*)-1-Isopropyl-4-mesyloxymethyl-3-methoxyazetidin-2-one 8a



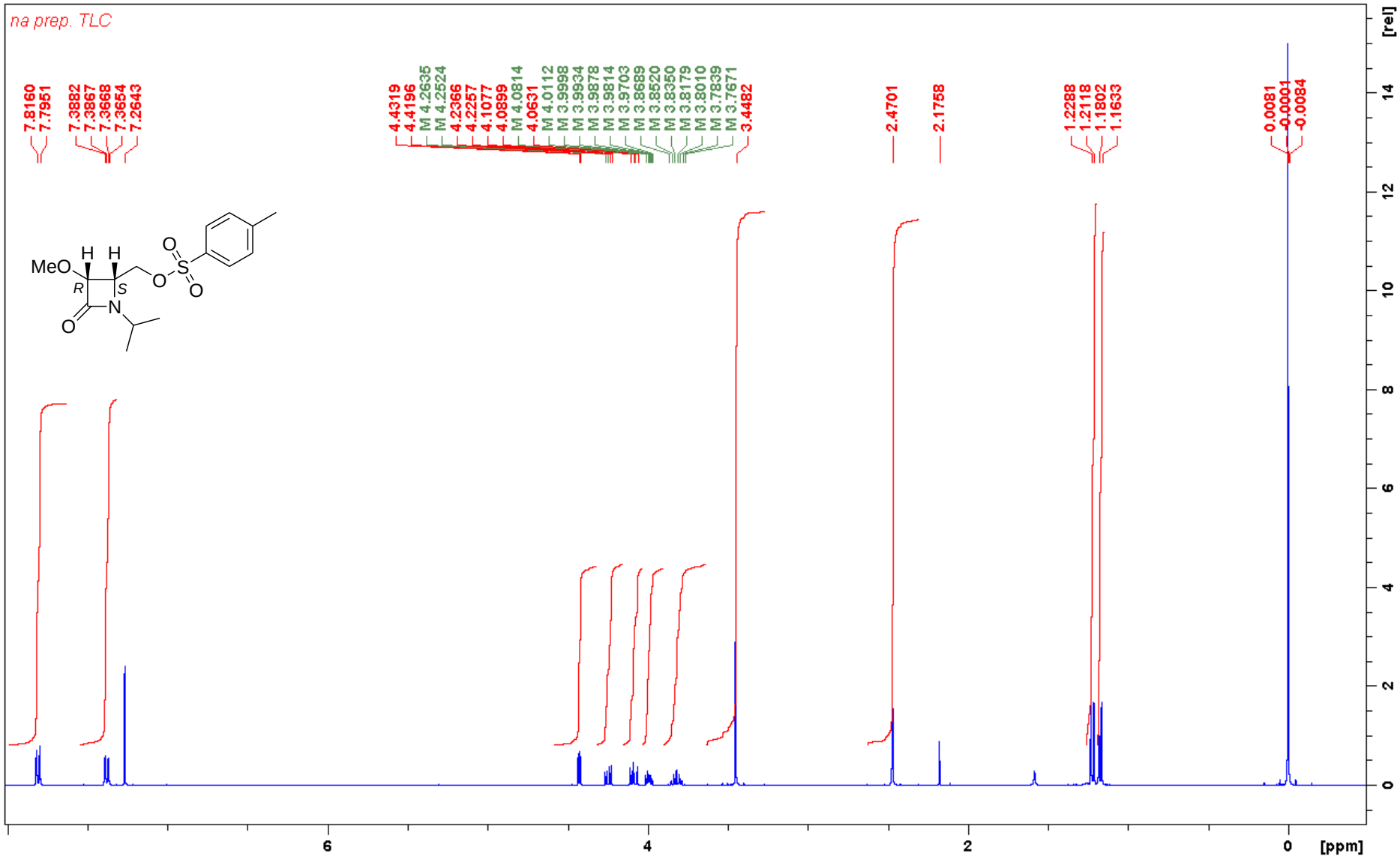
(3*R*,4*S*)-3-Benzyloxy-1-isopropyl-4-(mesyloxymethyl)azetidin-2-one 8b



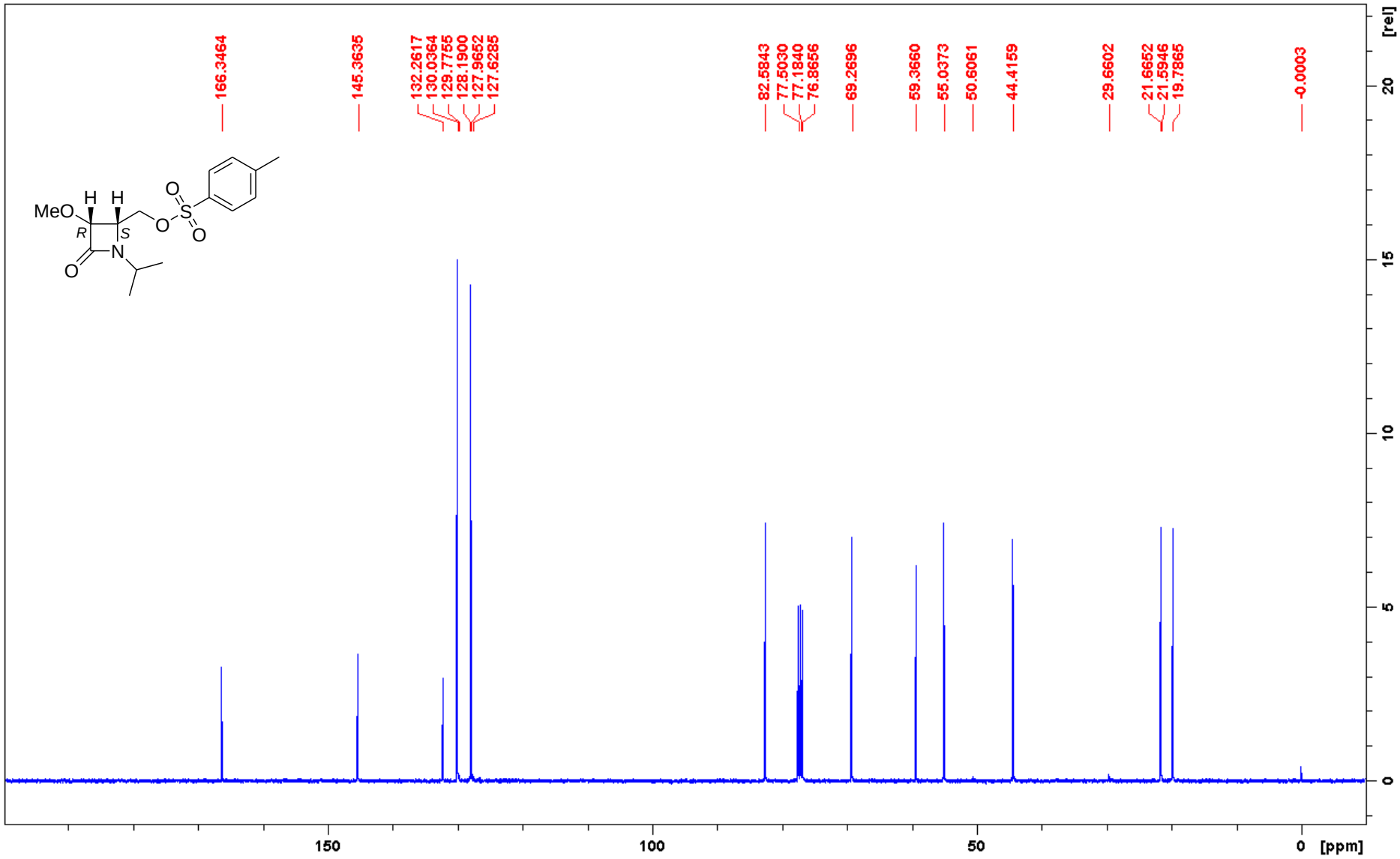
(3*R*,4*S*)-3-Benzyloxy-1-isopropyl-4-(mesyloxymethyl)azetidin-2-one 8b



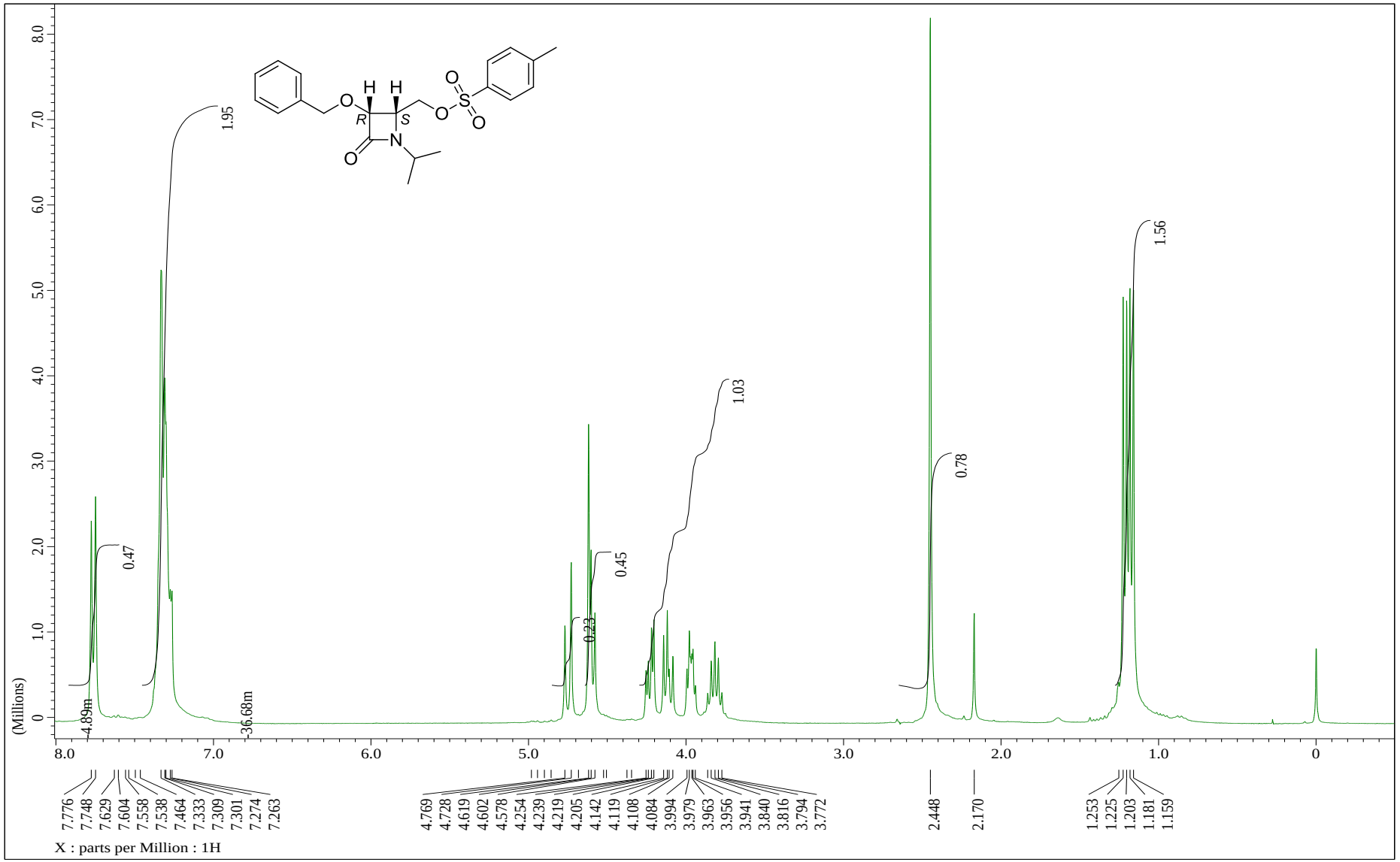
(3*R*,4*S*)-1-Isopropyl-3-methoxy-4-(tosyloxymethyl)azetidin-2-one 9a



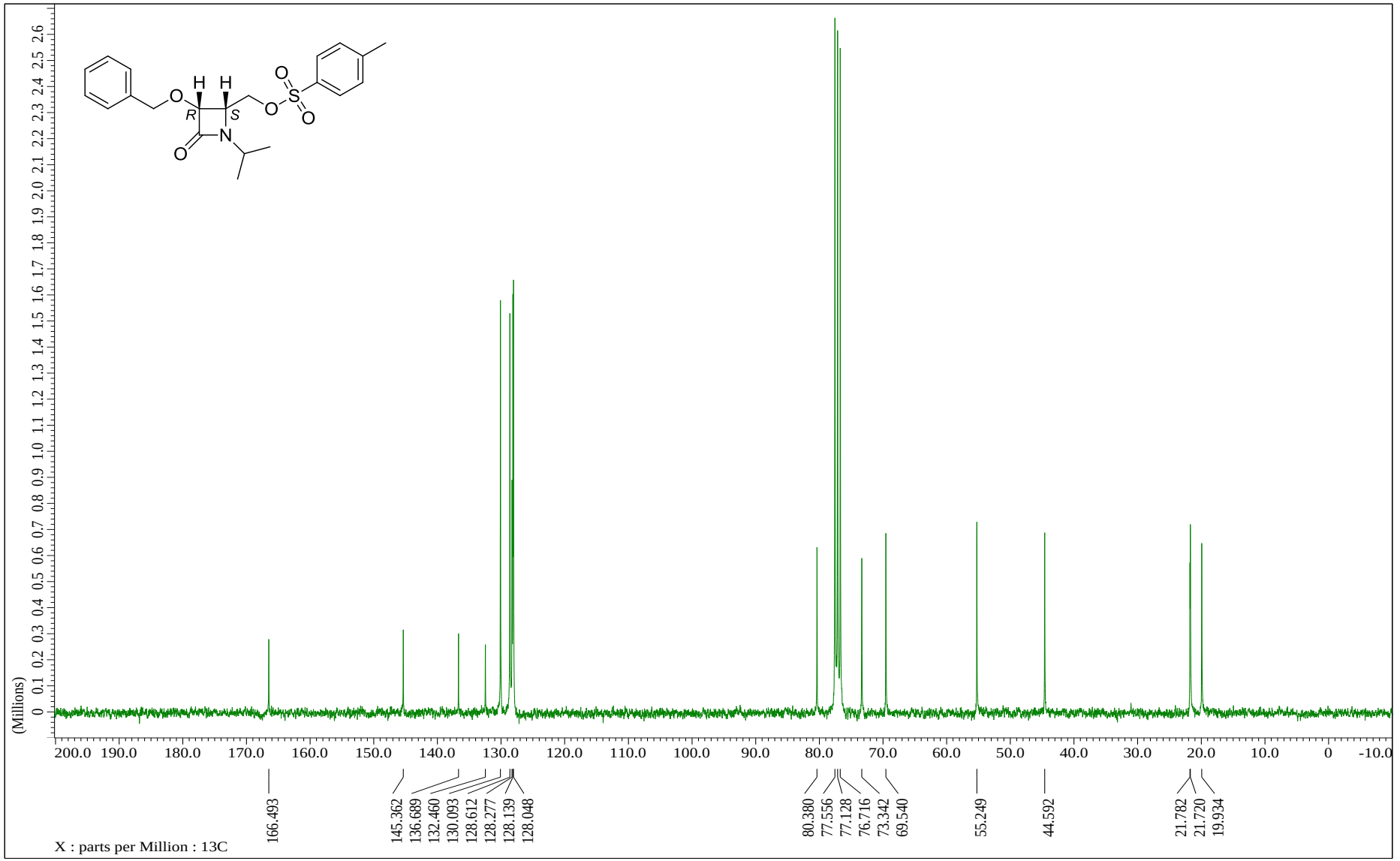
(3*R*,4*S*)-1-Isopropyl-3-methoxy-4-(tosyloxymethyl)azetidin-2-one 9a



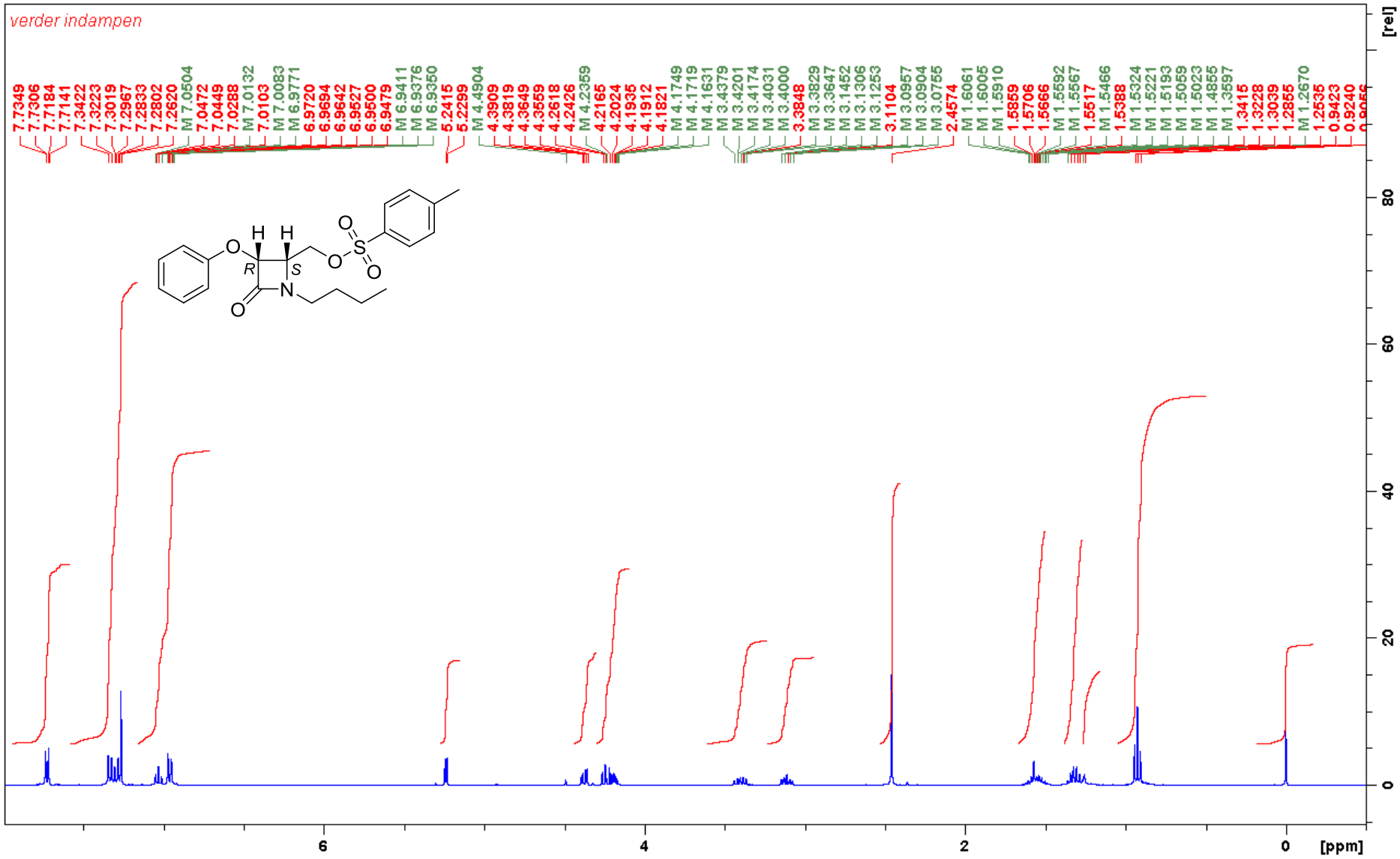
(3*R*,4*S*)-3-Benzyloxy-1-isopropyl-4-(tosyloxymethyl)azetidin-2-one 9b



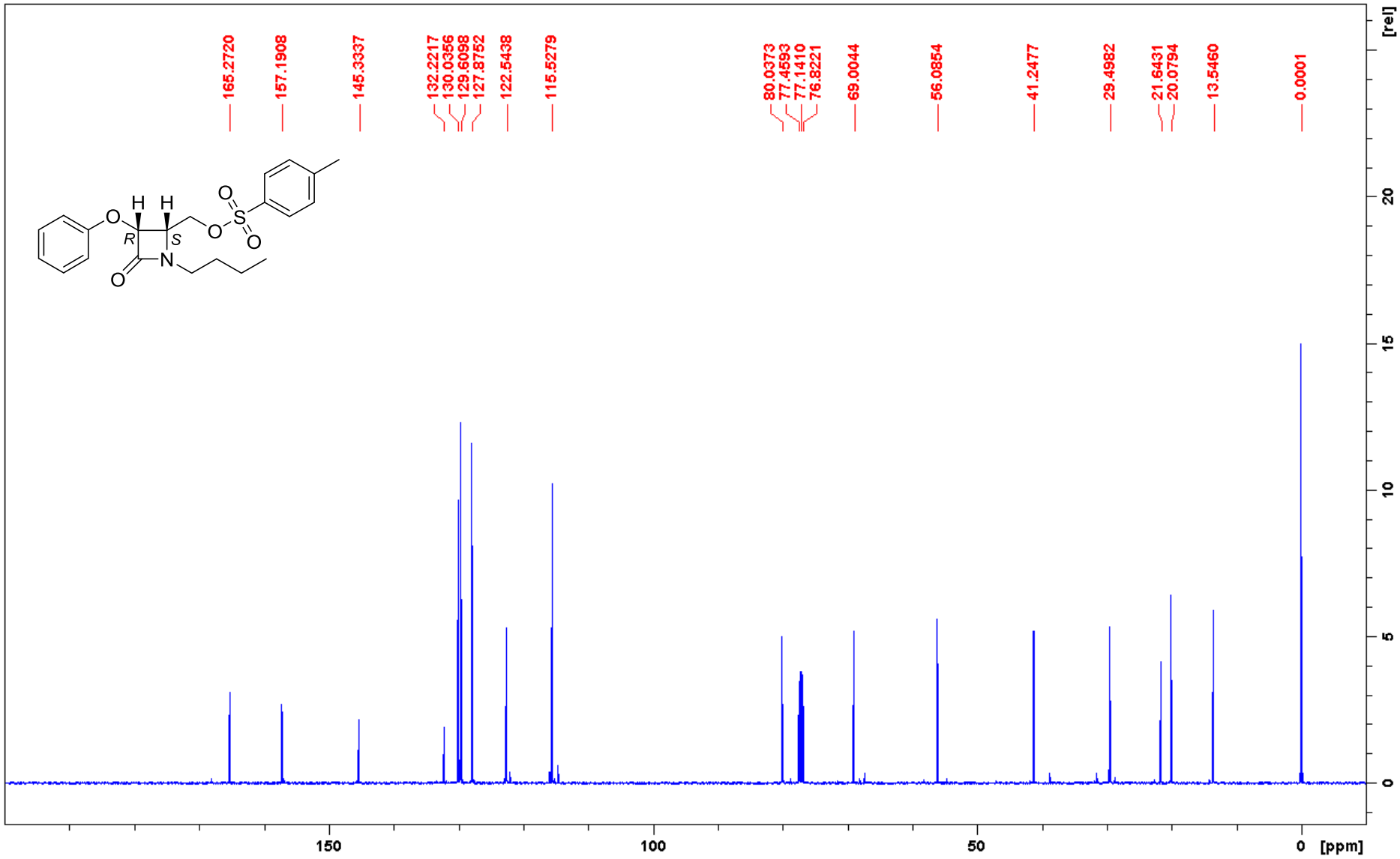
(3*R*,4*S*)-3-Benzyloxy-1-isopropyl-4-(tosyloxymethyl)azetidin-2-one 9b



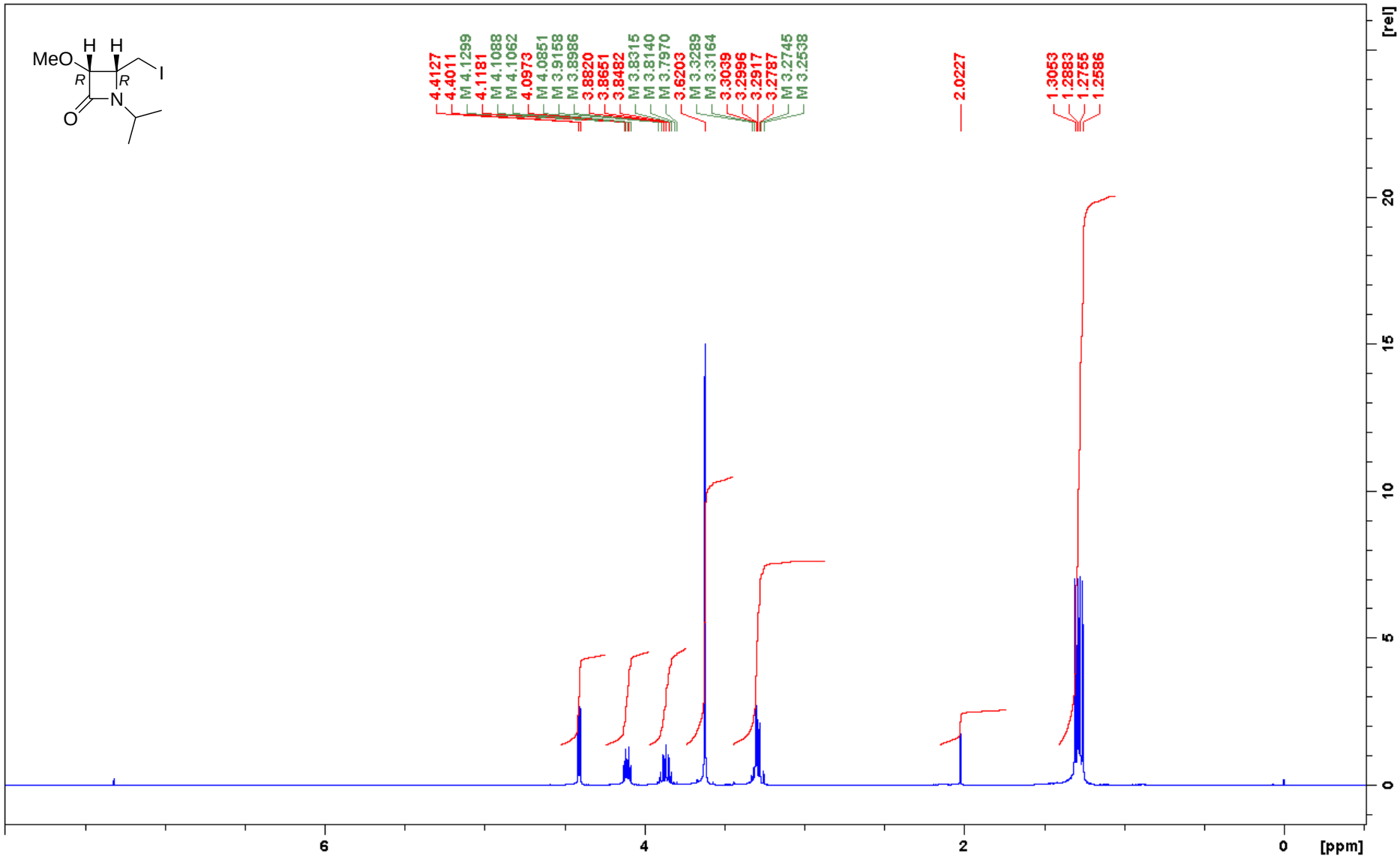
(3*R*,4*S*)-1-Butyl-3-phenoxy-4-(tosyloxymethyl)azetidin-2-one 9c



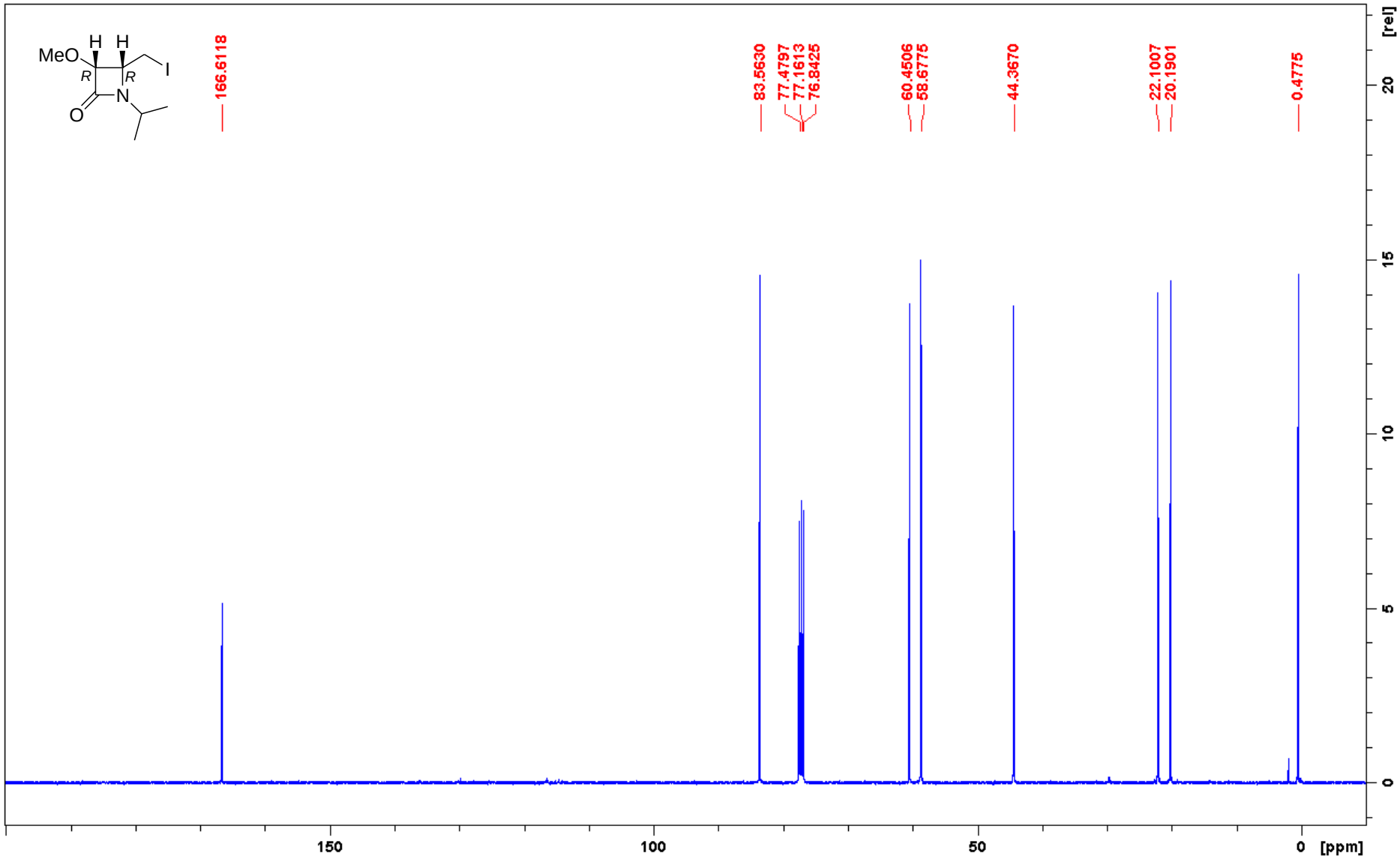
(3*R*,4*S*)-1-Butyl-3-phenoxy-4-(tosyloxymethyl)azetidin-2-one 9c



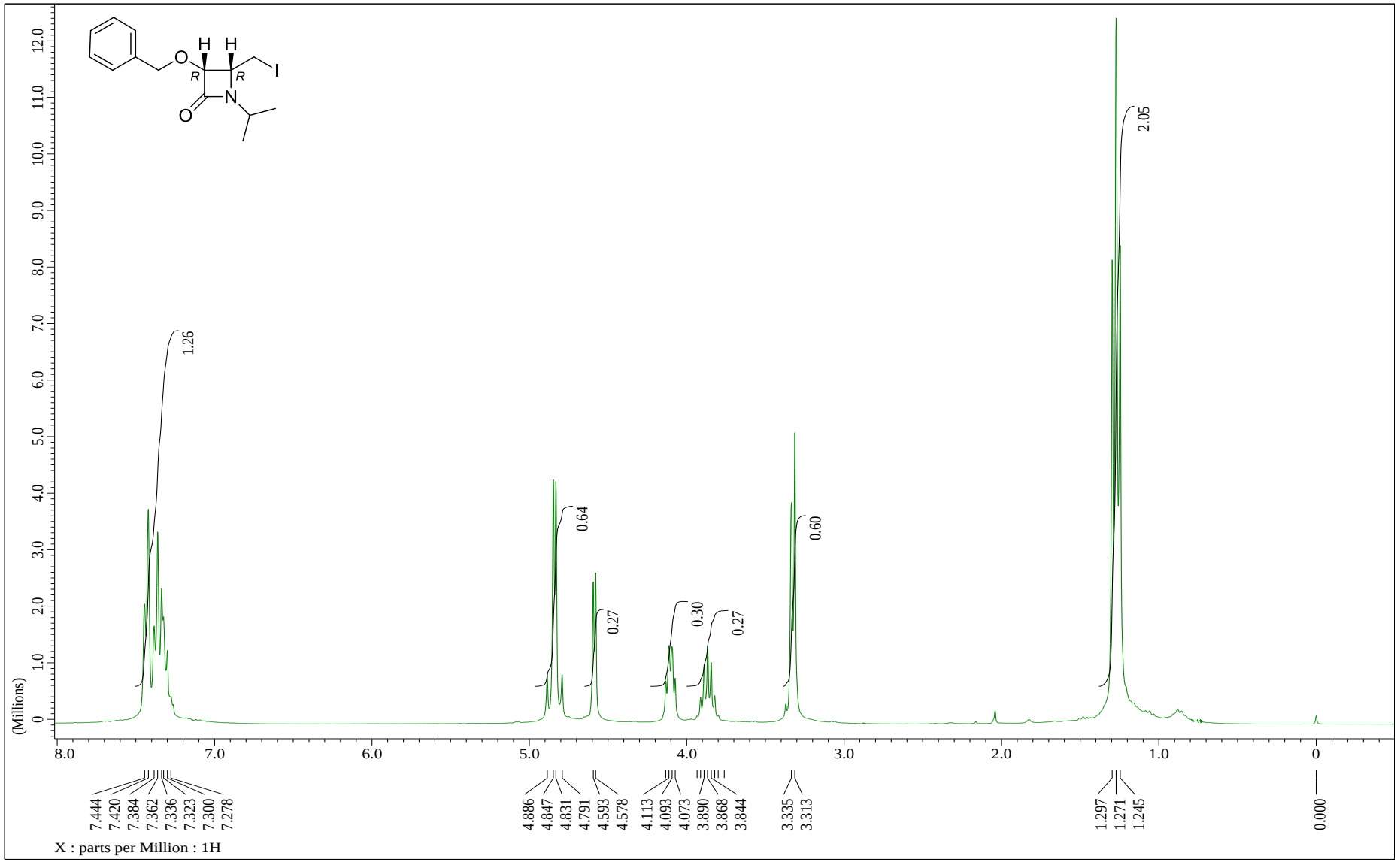
(3*R*,4*R*)-4-Iodomethyl-1-isopropyl-3-methoxyazetidin-2-one 10a



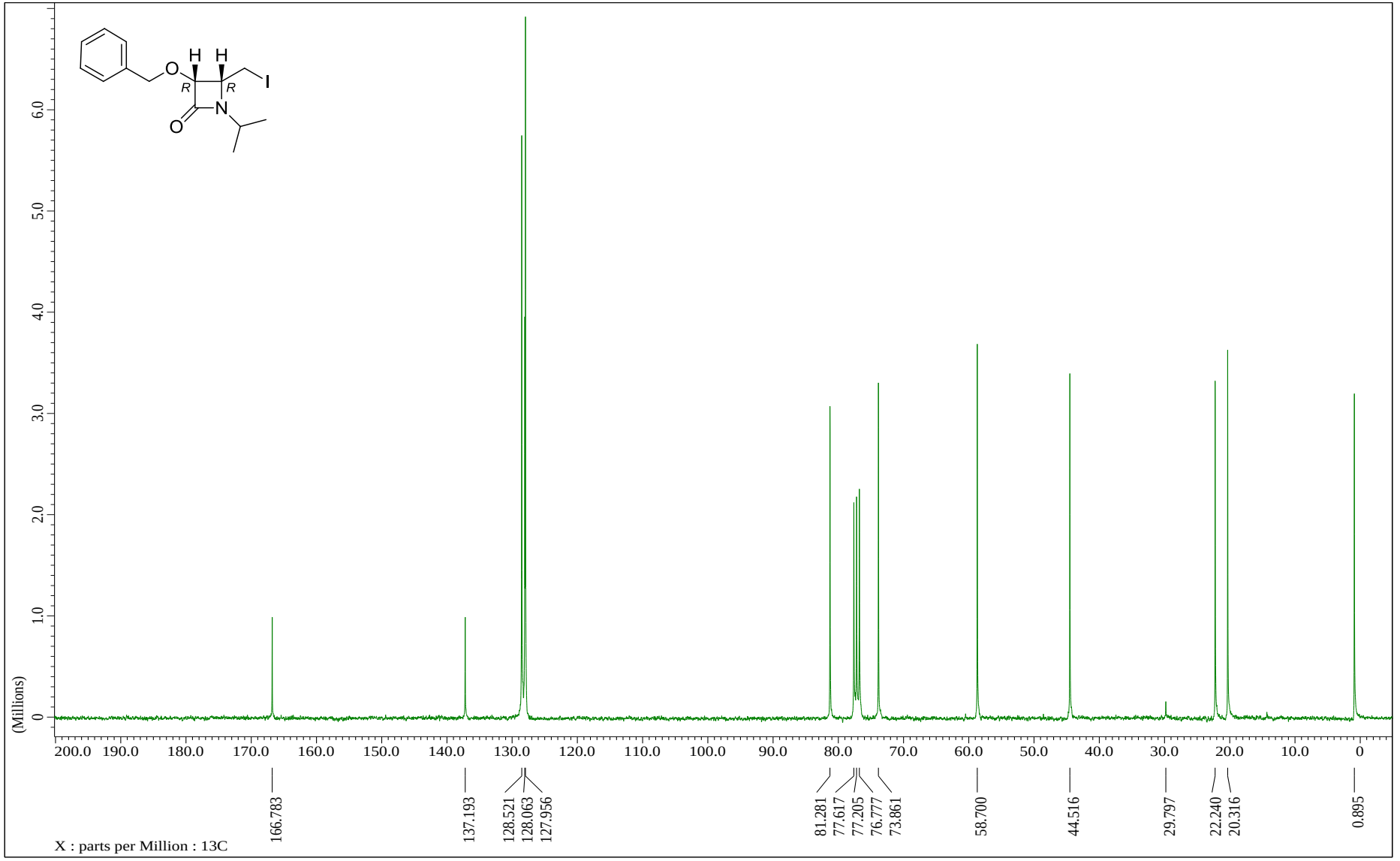
(3*R*,4*R*)-4-Iodomethyl-1-isopropyl-3-methoxyazetidin-2-one 10a



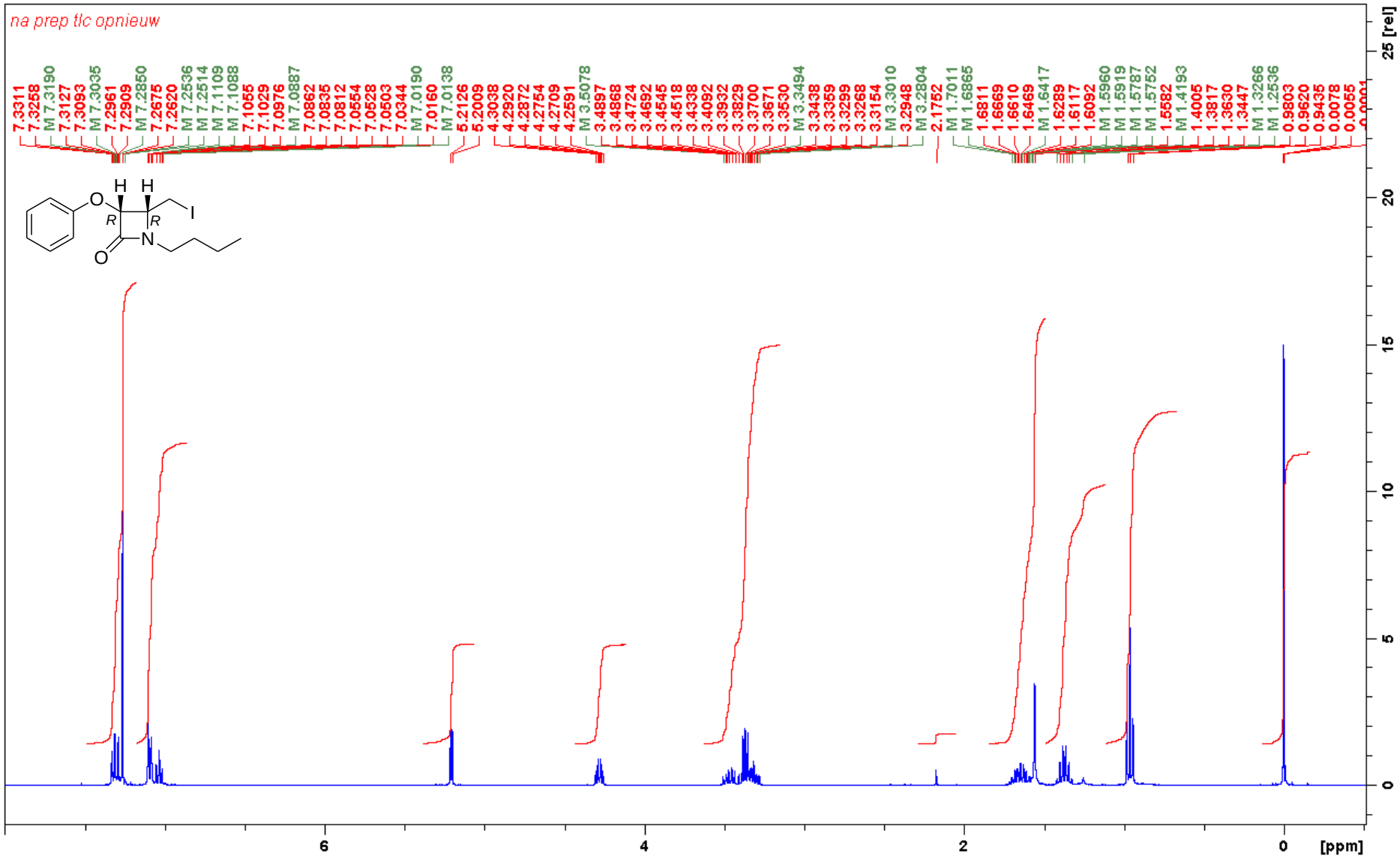
(3*R*,4*R*)-3-Benzyloxy-4-iodomethyl-1-isopropylazetidin-2-one 10b



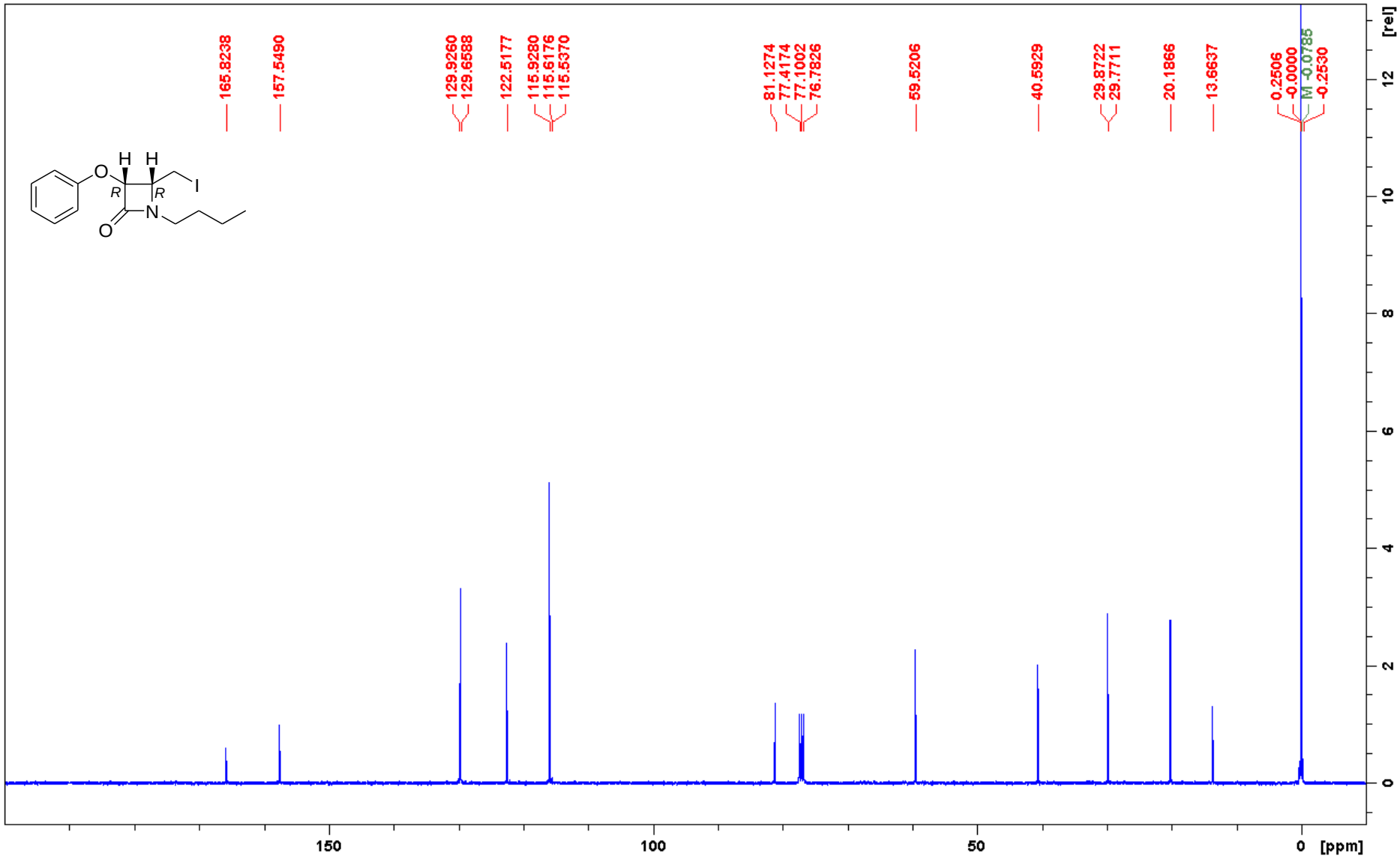
(3*R*,4*R*)-3-Benzyloxy-4-iodomethyl-1-isopropylazetidin-2-one 10b



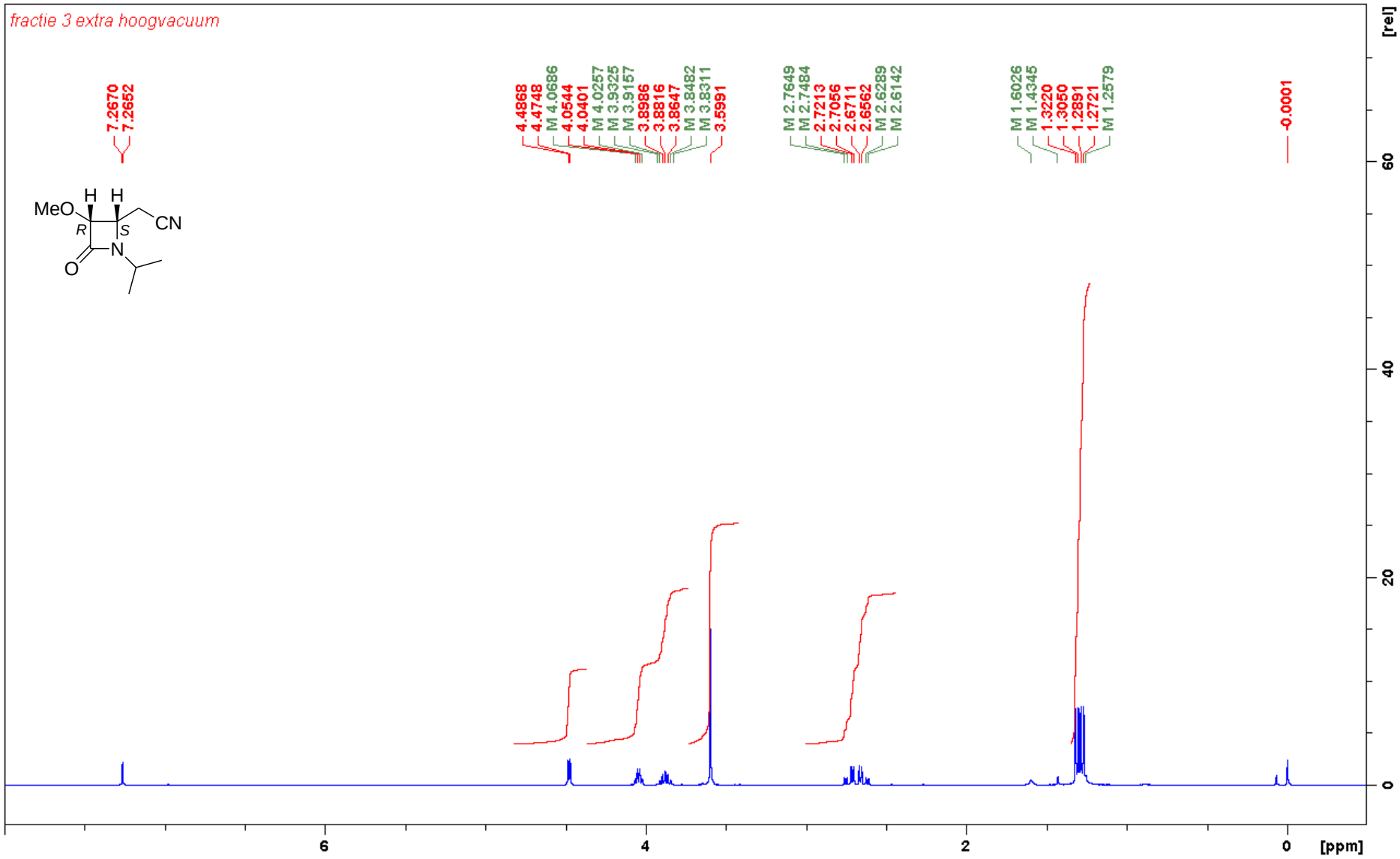
(3*R*,4*R*)-1-Butyl-4-iodomethyl-3-phenoxyazetidin-2-one 10c



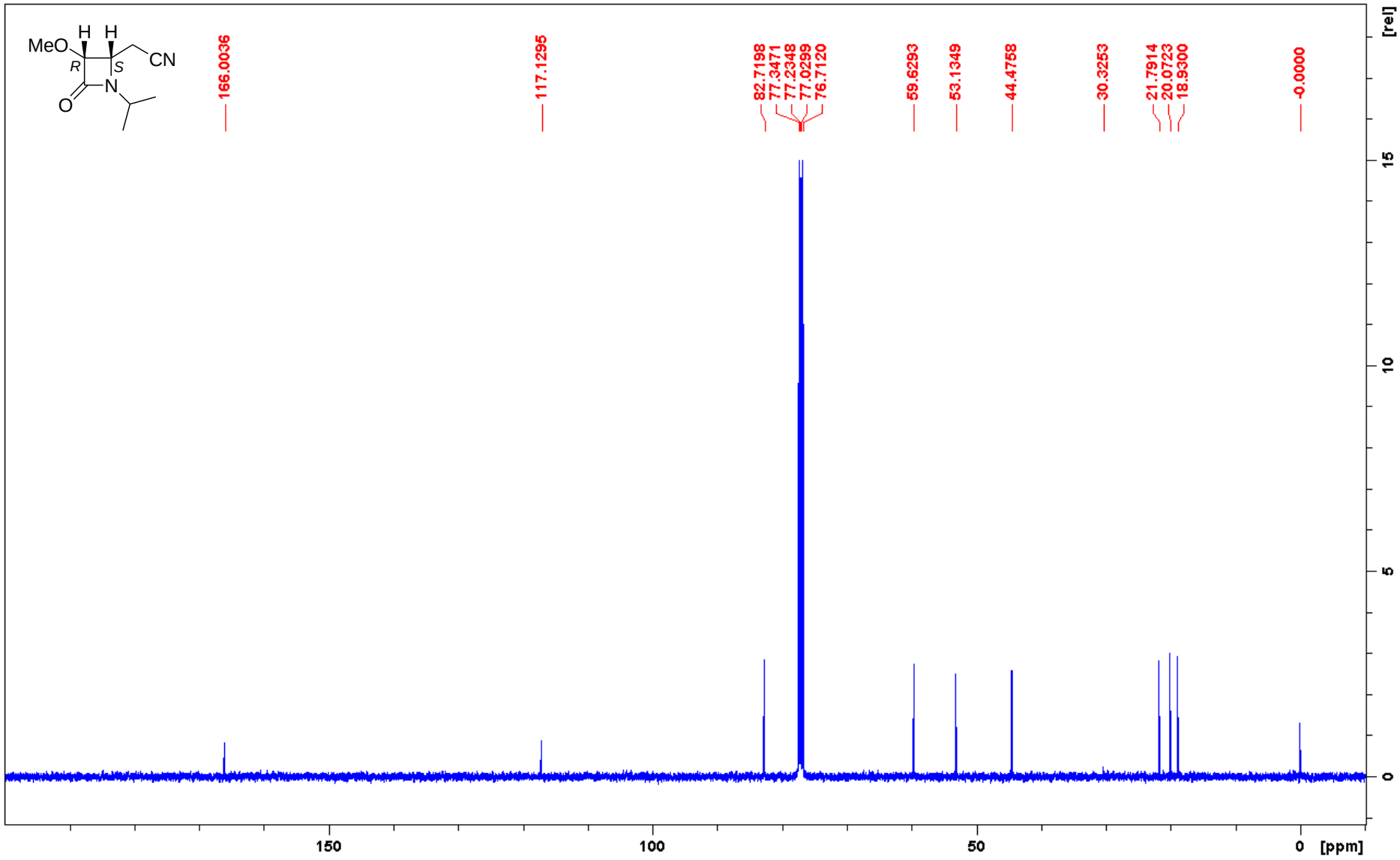
(3*R*,4*R*)-1-Butyl-4-iodomethyl-3-phenoxyazetidin-2-one 10c



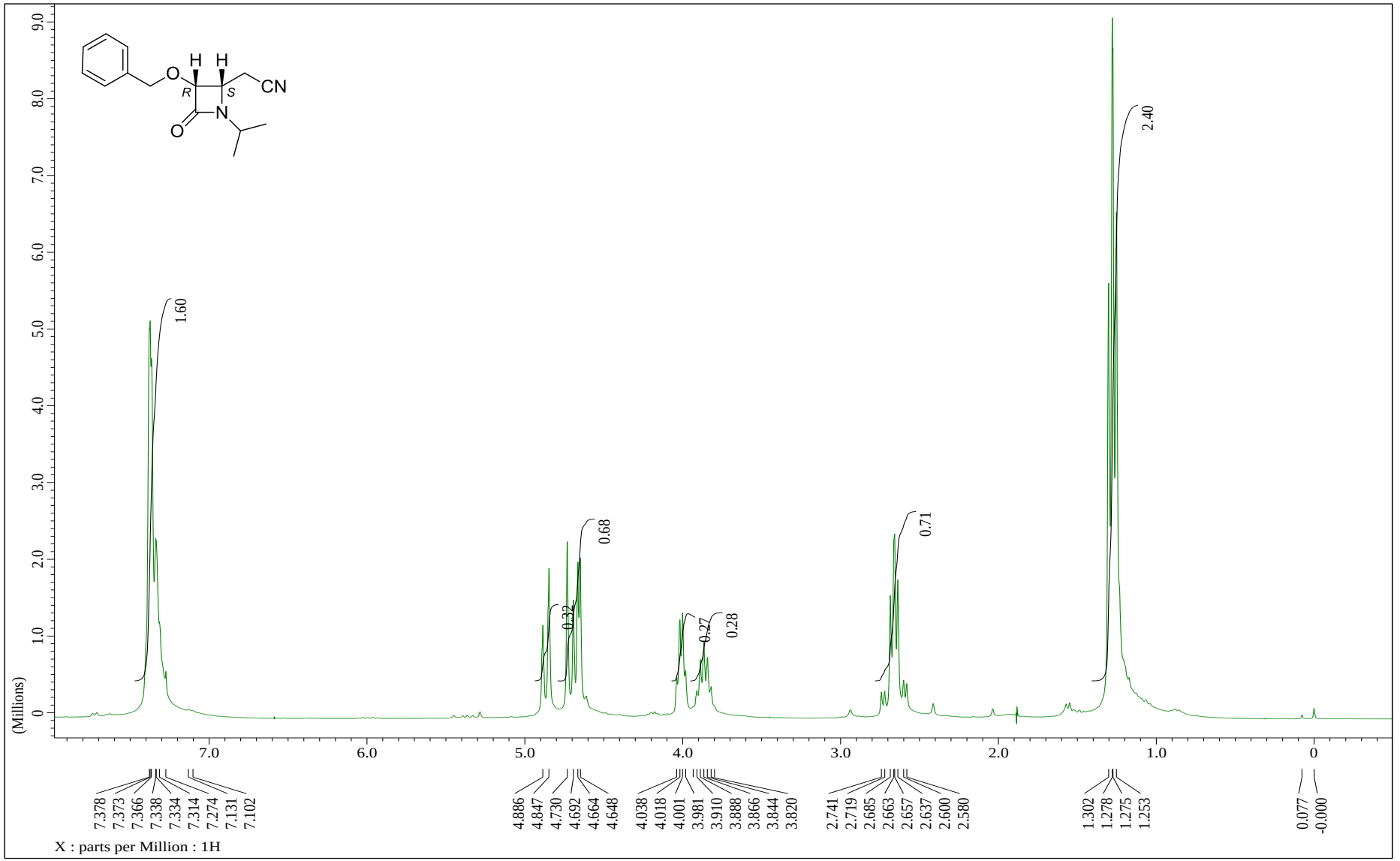
(3*R*,4*S*)-4-Cyanomethyl-1-isopropyl-3-methoxyazetidin-2-one 11a



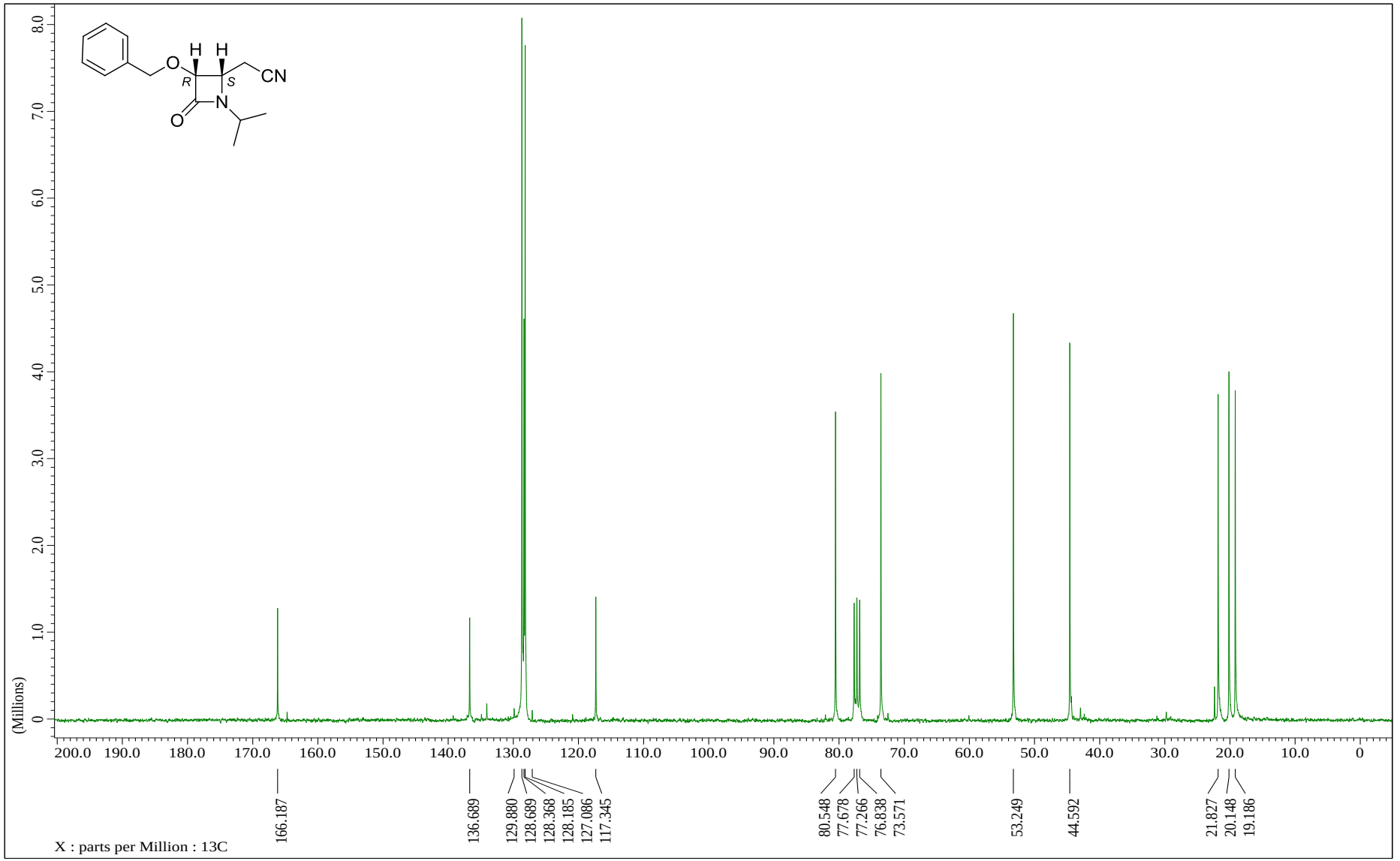
(3*R*,4*S*)-4-Cyanomethyl-1-isopropyl-3-methoxyazetidin-2-one 11a



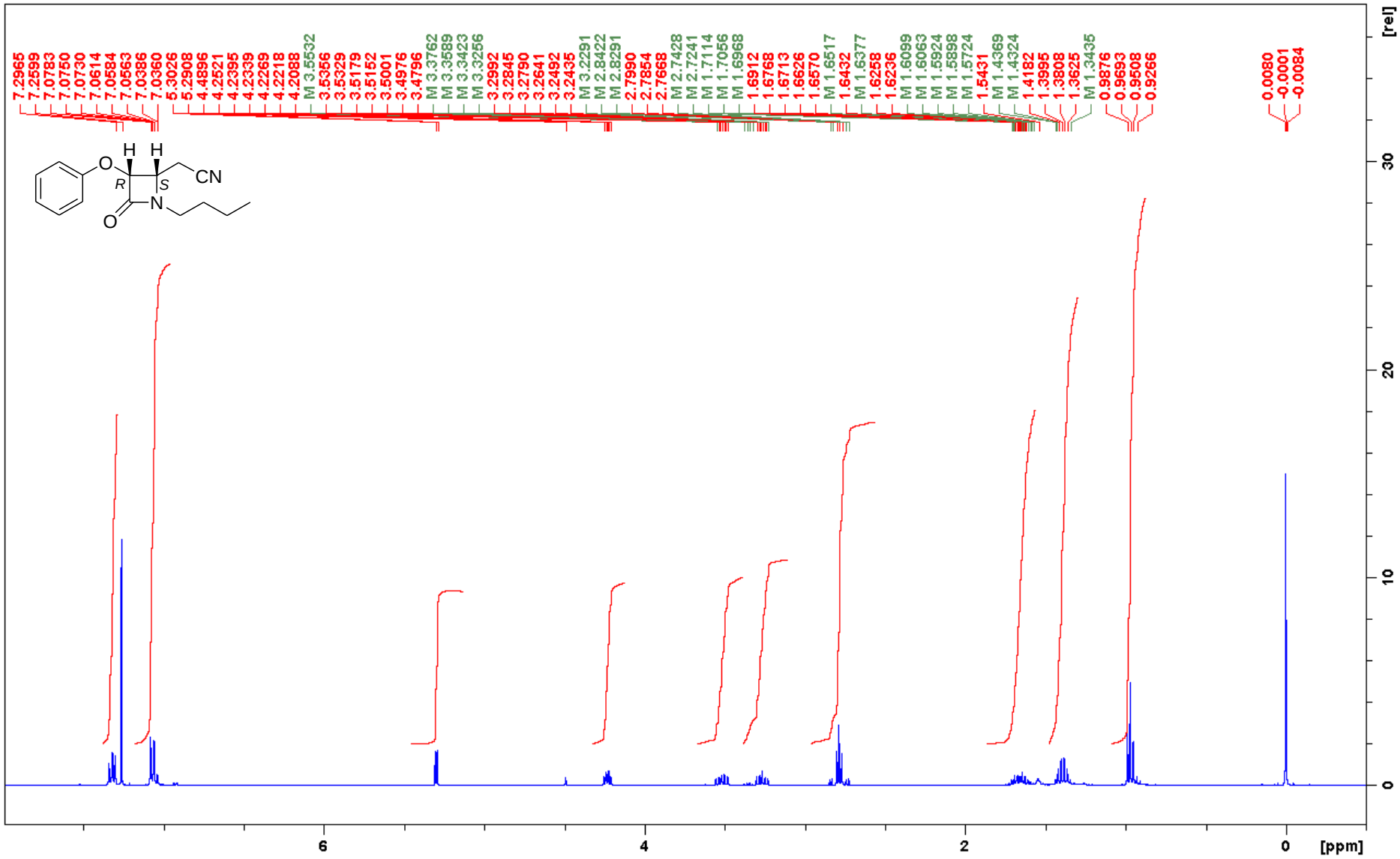
(3*R*,4*S*)-3-Benzyloxy-4-cyanomethyl-1-isopropylazetidin-2-one 11b



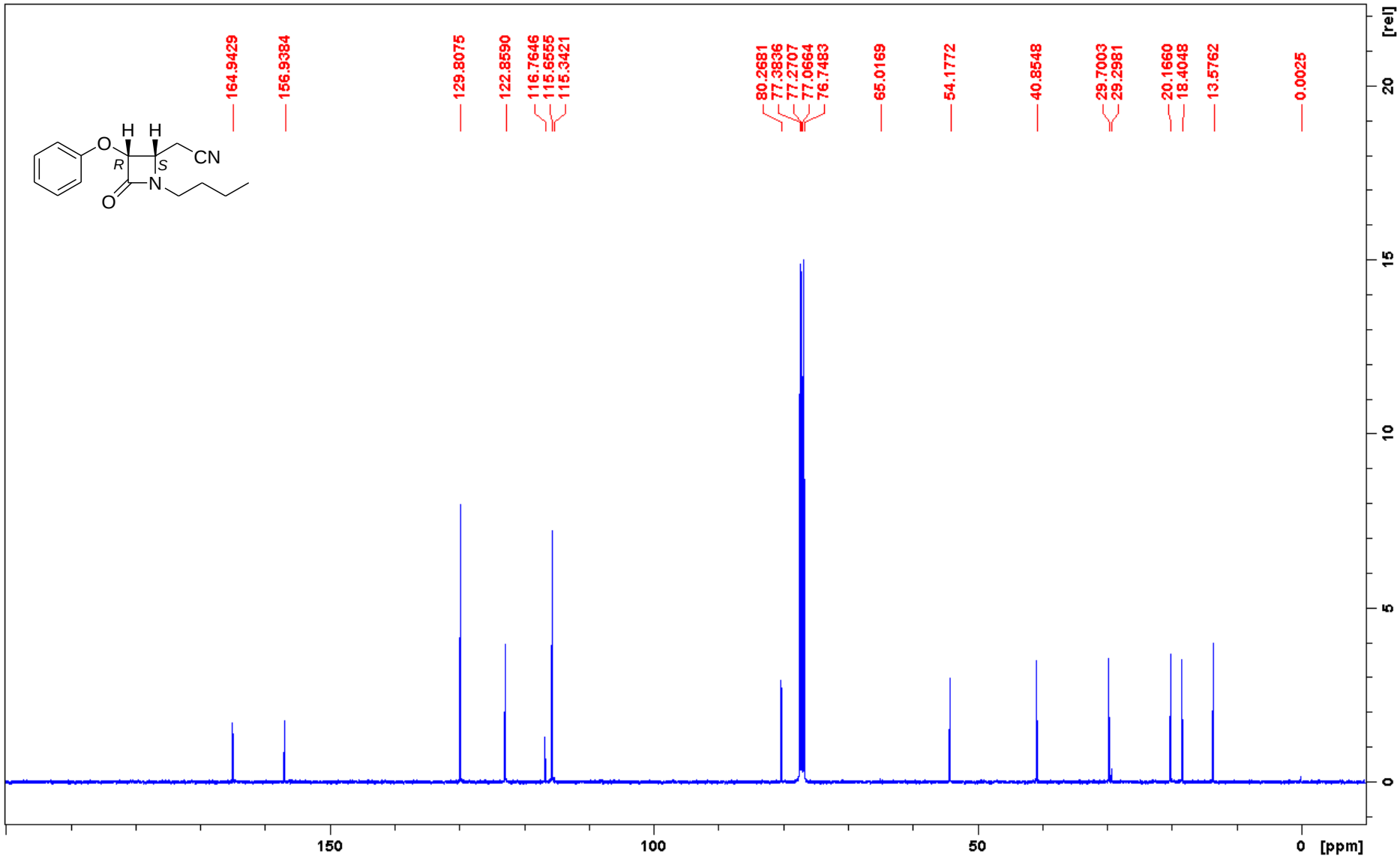
(3*R*,4*S*)-3-Benzyloxy-4-cyanomethyl-1-isopropylazetidin-2-one 11b



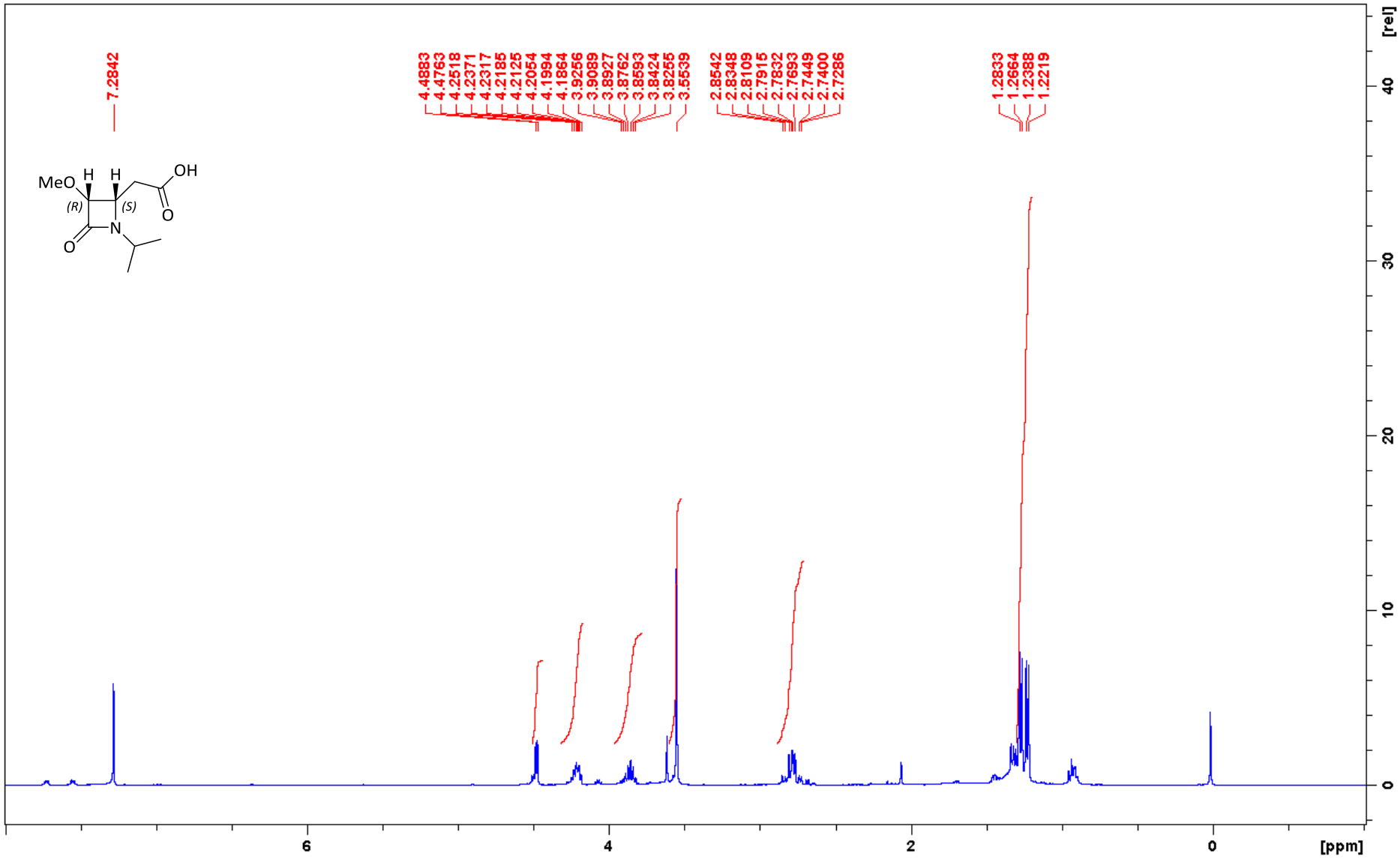
(3*R*,4*S*)-1-Butyl-4-cyanomethyl-3-phenoxyazetidin-2-one 11c



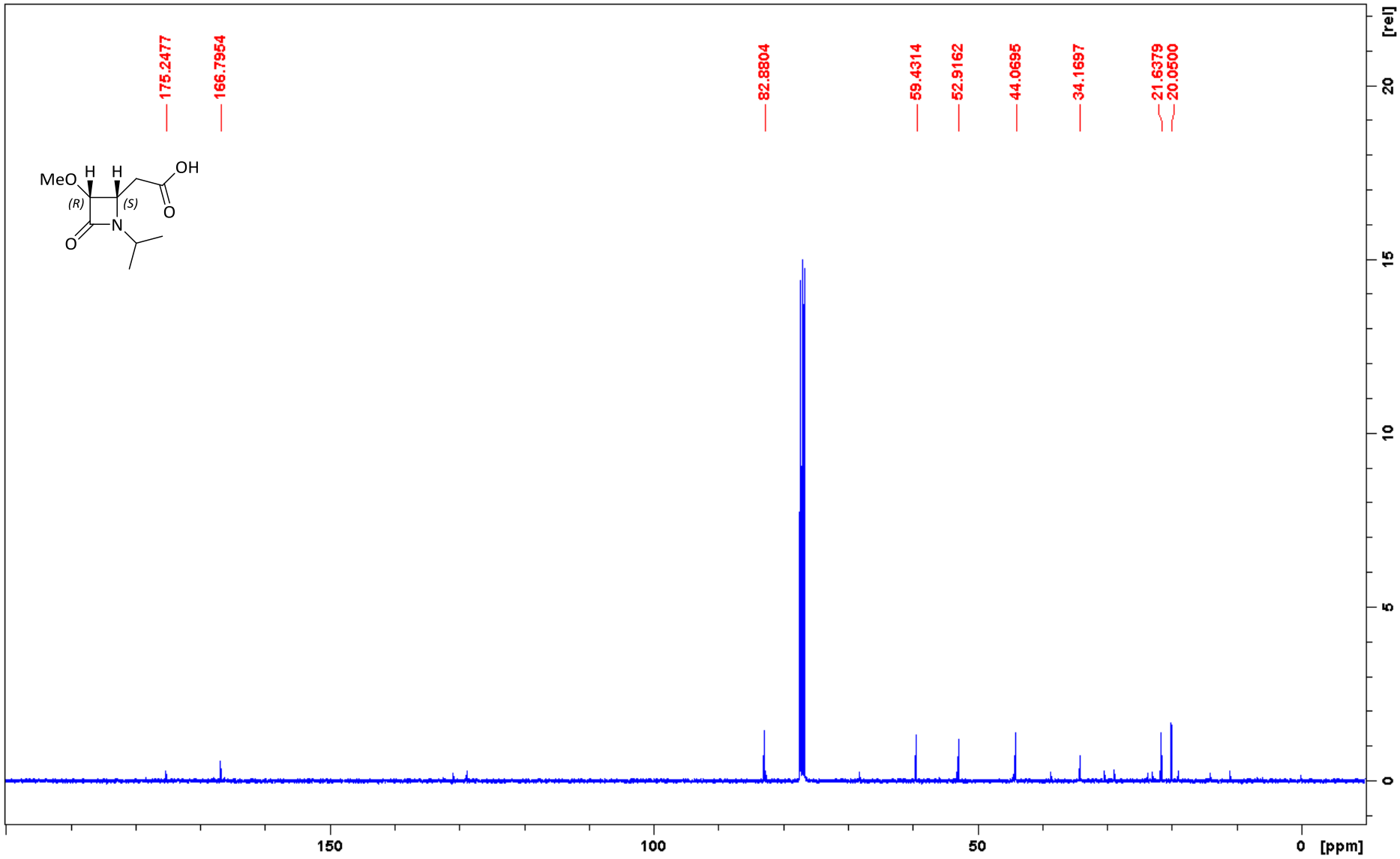
(3*R*,4*S*)-1-Butyl-4-cyanomethyl-3-phenoxyazetidin-2-one 11c



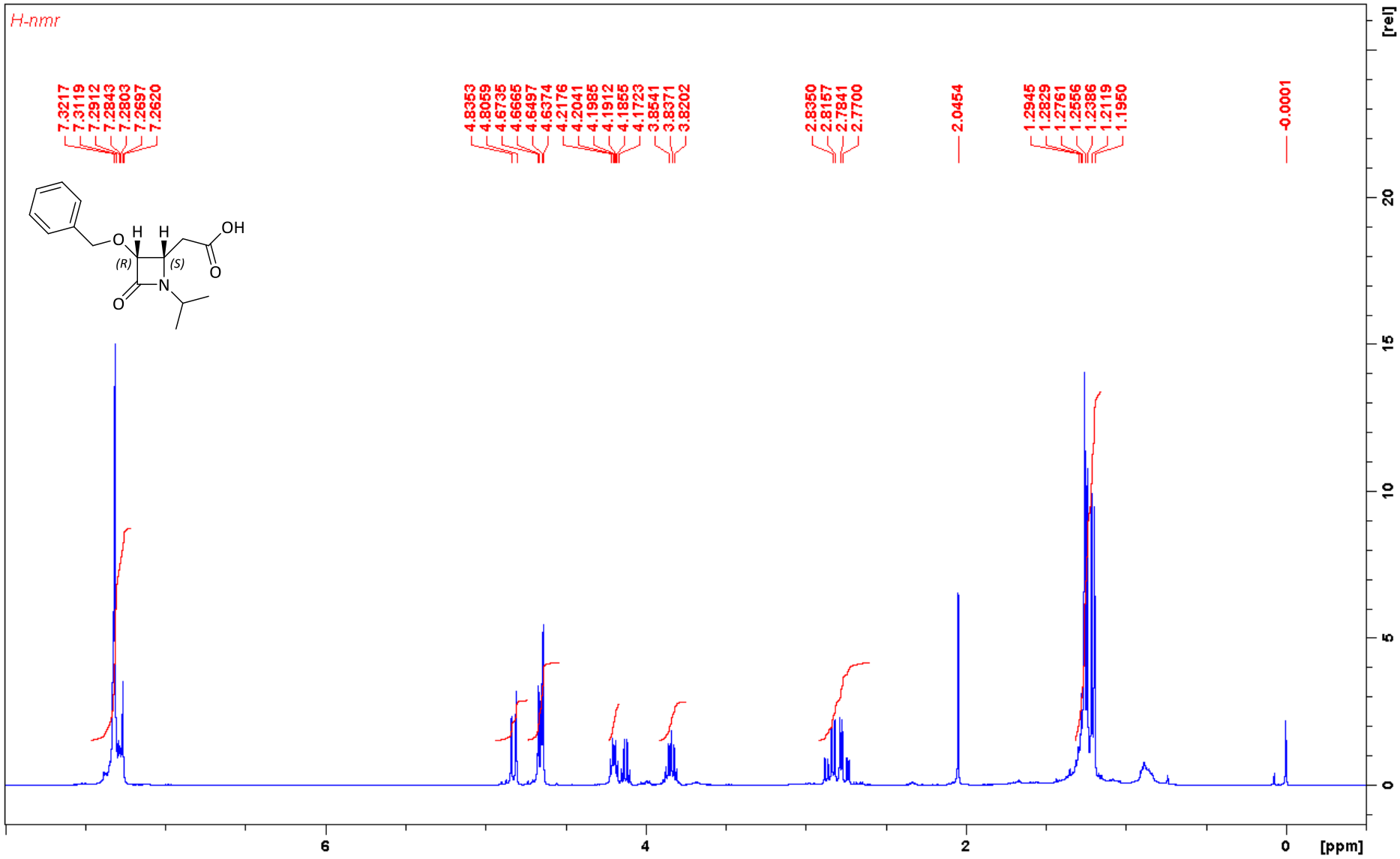
(3*R*,4*S*)-4-Carboxymethyl-1-isopropyl-3-methoxyazetidin-2-one 12a



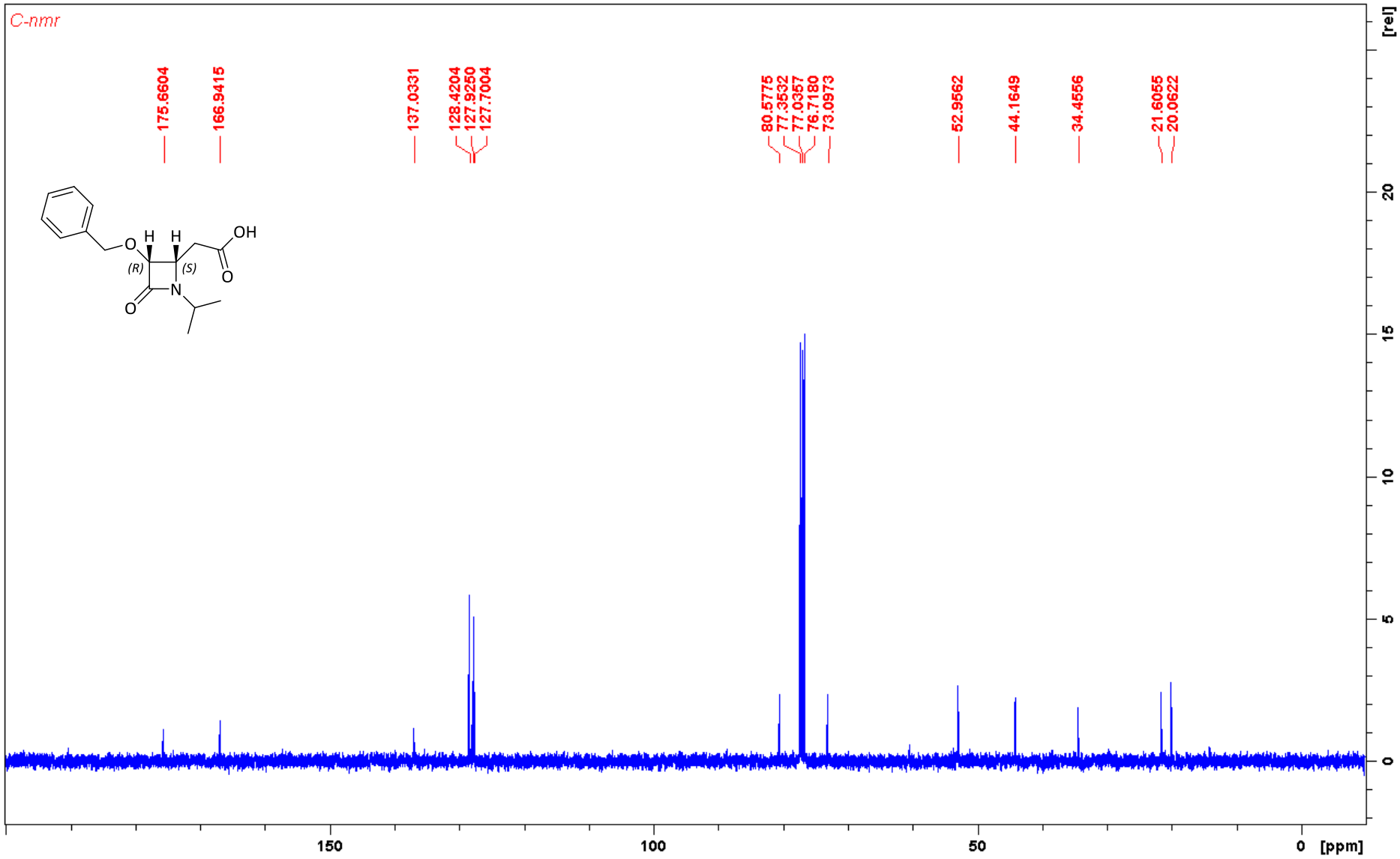
(3*R*,4*S*)-4-Carboxymethyl-1-isopropyl-3-methoxyazetidin-2-one 12a



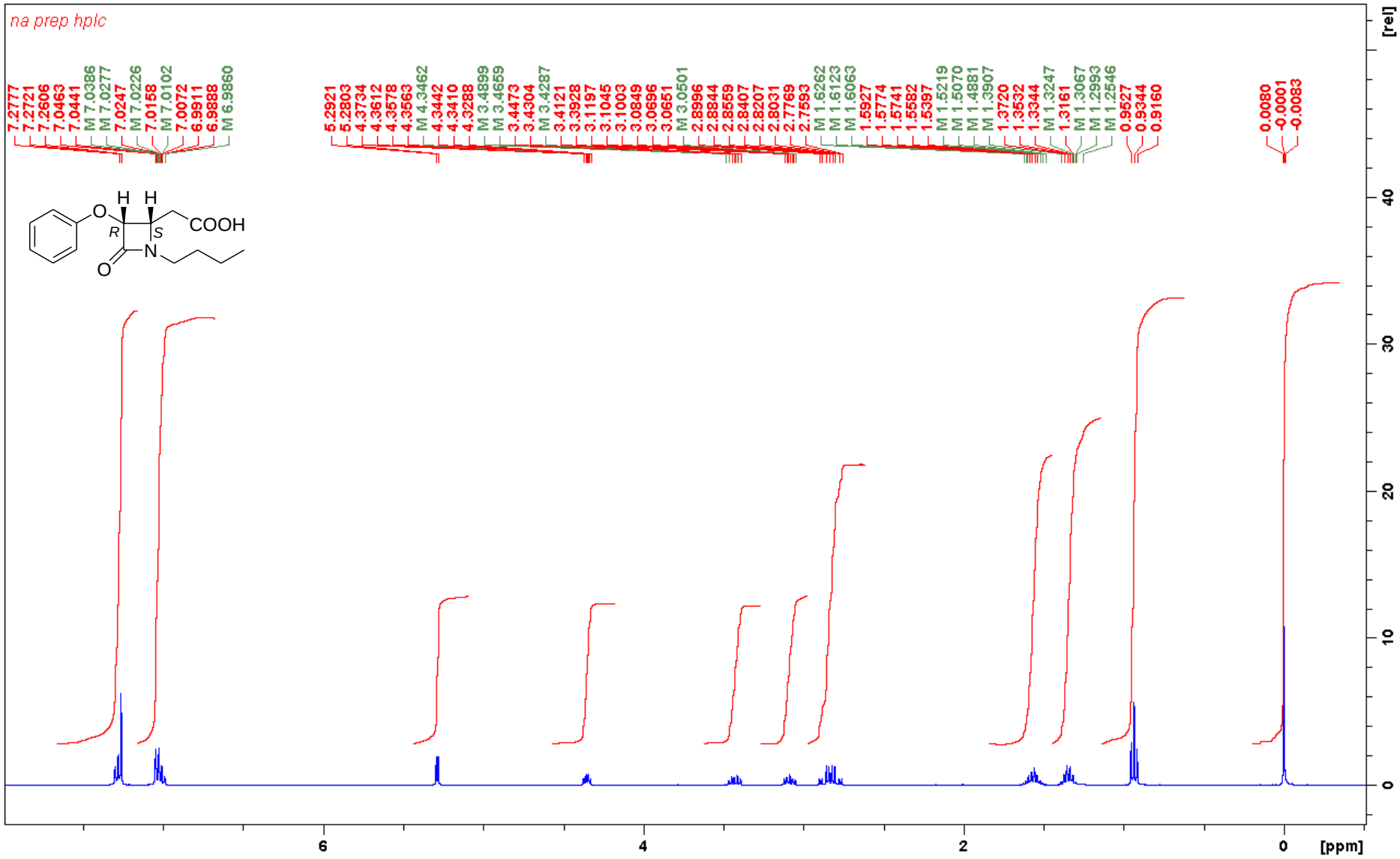
(3*R*,4*S*)-3-Benzyloxy-4-carboxymethyl-1-isopropylazetidin-2-one 12b



(3*R*,4*S*)-3-Benzyloxy-4-carboxymethyl-1-isopropylazetidin-2-one 12b



(3*R*,4*S*)-1-Butyl-4-carboxymethyl-3-phenoxyazetidin-2-one 12c



(3*R*,4*S*)-1-Butyl-4-carboxymethyl-3-phenoxyazetidin-2-one 12c