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SUPPORTING INFORMATION

Title: The Thread & Cut Method: Syntheses of Molecular Knot Precursors
Author(s): Edward E. Fenlon,* Brandon R. Ito
Ref. No.: O200800387

Experimental

General

All reagents were ACS reagent quality, purchased from Aldrich, Alfa-Aesar, or Acros and used without further purification unless otherwise noted. 3,5-dihydroxybenzyl alcohol and 2-methyl-6-nitrobenzoic anhydride (MNBA) were purchased from TCI America. 10-undecyn-1-ol was purchased from GFS Chemicals, Columbus, OH or prepared by a literature method.[1] 10-undecyn-1-methansulfonate (**3**) was prepared according to literature procedures.[2] 11-Bromo-1-undecene was purchased from Oakwood Chemical, West Columbia, SC. 1-azido-4-bromobutane (**8**) was prepared by a literature method.[3] Etherifications were done under Fréchet-like conditions.[4] Click cycloadditions were done under conditions described by Sharpless.[5] All reactions were stirred with a magnetic stir bar and conducted under a dry argon atmosphere unless done in an aqueous solvent system. Analytical thin layer chromatography (TLC) was performed on 0.2 mm silica plastic coated sheets with F_{254} indicator. Preparative TLC was performed on 1.0 mm silica coated glass plates with F_{254} indicator. Flash chromatography was performed on 32-63 μm silica gel.

NMR spectra were obtained at the following frequencies: ^{1}H (500 MHz) and ^{13}C (125 MHz). Spectra were obtained in chloroform-*d* ($CDCl_3$) unless noted otherwise. Chemical shifts are reported in parts per million (ppm) and coupling constants are reported in hertz (Hz). ^{1}H spectra in $CDCl_3$ were referenced to tetramethylsilane (TMS = 0.0 ppm) as an internal standard. ^{13}C NMR spectra in $CDCl_3$ were referenced to the solvent peak at 77.0 ppm. IR spectra were obtained as a thin film (for solid samples) or neat (for liquids) on an ATR instrument and the absorptions are reported in cm^{-1}. Mass spectrometry was performed at F&M or at the University of Illinois School of Chemical Sciences, Urbana, IL and used electrospray ionization (ESI) unless noted otherwise. High resolution mass spectrometry was performed at Illinois. Mass spectral m/z peak data are reported in Daltons with a relative intensity to a base peak (base = 100). Melting points were measured on a Mel–Temp melting point apparatus and are uncorrected. Elemental analysis was performed by Schwarzkopf Microanalytical Laboratory, Woodside, NY.

Abbrevations: ATR (attenuated total reflectance); brine (saturated aqueous sodium chloride); DMAP (4-*N,N*-dimethylaminopyridine), DMF (dimethylformamide); EtOAc (ethyl acetate); Et_2O (diethyl ether); FC (flash column chromatography using silica gel); MNBA (2-methyl-6-nitrobenzoic anhydride); PE (low boiling petroleum ether); water (deionized water).

Procedures

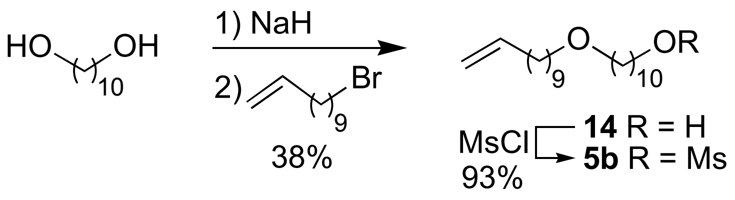
3-(undec-10-yn-1-oxy)-5-hydroxybenzyl alcohol (4). A mixture of 3,5-dihydroxybenzyl alcohol (**2**)(2.49 g, 17.8 mmol, 1 eq), 10-undecyn-1-methansulfonate (**3**)(4.36 g, 17.8 mmol, 1 eq), powdered potassium carbonate (3.17 g, 23.0 mmol, 1.3 eq), 18-crown-6 (0.24 g, 0.89 mmol, 0.05 eq), THF (150 mL), and acetonitrile (20 mL) was heated at 90 °C in an oil bath with vigorous stirring for 14 h. The mixture was then partitioned between water and ethyl acetate and the organic layer was washed with water, brine, and dried (Na_2SO_4). The product was concentrated to give a yellow oil. Purification by FC (30→40% EtOAc/PE) yielded 2.15 g (42%) of **4** as a white solid: mp 69-71 °C; IR 3294.5, 2926.8, 2854.3, 2116.3, 1598.5, 1503.3, 1452.9, 1333.89, 1300.7, 1218.1, 1152.2, 1020.3, 996.1, 968.4, 835.5, 705.4, 629.0; ^{1}H NMR δ 6.46 (s, 1H), 6.42 (s, 1H), 6.32 (m, 1H), 5.69 (s, 1H) 4.58 (s, 2H), 3.90 (t, *J* =6.6, 2H), 2.18 (dt, *J* = 7.3, *J* = 2.7, 2H), 1.94 (t, *J* = 2.7, 1H), 1.75 (m, 2H), 1.52 (m, 2H), 1.41 (m, 2H), 1.32 (m, 7H); ^{13}C NMR δ 160.48, 157.13, 142.89, 106.26, 105.47, 101.28, 84.79, 68.11, 65.03, 29.37, 29.28, 29.15, 28.99, 28.43, 25.94, 18.35; MS 291.2 (M+1, 100); HRMS calcd for $C_{18}H_{27}O_3$: 291.1960. Found: 291.1966 (2.1 ppm difference).

13-Bromo-1-tridecene (5a).[7]

12-tridecen-1-ol (**12**):[6] To a mixture of ethylene oxide (**CAUTION:** toxic, carcinogen, mutagen) (7.568 g, 172 mmol) and copper (I) iodide (1.0637 g, 5.6 mmol) in THF (25 mL) at -5 °C was added a solution of 10-undecenyl Grignard [derived from 12.63 g (51 mmol) of 95% 11-bromo-1-undecene and 1.311 g (54 mmol) of magnesium in 100 mL of THF] over a period of 20 minutes with the temperature staying below 0 °C. The resulting mixture was stirred at low temperature for an additional 75 min and then quenched by addition of saturated aqueous ammonium chloride. The reaction was then diluted with Et$_2$O. The aqueous layer was collected and extracted with additional Et$_2$O. The combined organic layers were washed with brine, dried (Na$_2$SO$_4$), and concentrated under reduced pressure. The crude alcohol (13.966 g) was a colorless liquid that was purified by FC (PE→10% EtOAc/PE) followed by Kugelrohr distillation (185 °C, 1 mm Hg) to yield 8.203 g (80%) of 12-tridecen-1-ol as a slightly yellow liquid. The product is known,[6] although spectral data have not been reported: IR 3330.6, 3076.5 2922.3, 2852.5, 1640.8, 1464.7, 1369.3, 1053.7, 992.7, 907.9, 720.9, 634.0; ^{1}H NMR δ 5.81 (m, 1H), 4.99 (m, 1H), 4.93 (m, 1H), 3.64 (t, *J* = 6.6, 2H), 2.04 (m, 2H), 1.57 (m, 2H), 1.36 (m, 2H), 1.27 (m, 14H).

12-tridecen-1-methansulfonate (**13**):[7] To a 0 °C solution of **12** (8.0 g, 40 mmol), triethyl amine (7.0 mL, 50 mmol) in CH$_2$Cl$_2$ (45 mL) was added methanesulfonyl chloride (3.8 mL, 48 mmol) over a 5 min period. The resulting mixture was allowed to warm to ambient temperature and was stirred for 23 h. The reaction was quenched by the addition of water (80 mL) and the organic layer was separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 50 mL) and the combined organic layers were washed with brine, dried (Na$_2$SO$_4$), and concentrated under reduced pressure to give the crude mesylate as a yellow-orange oil. The spectral data of the product matched the literature values:[7] IR 2923.9, 2853.4, 1640.1, 1465.8, 1350.9, 1171.1, 971.5, 933.2, 908.9, 818.8, 747.8, 721.9, 638.6.

13-Bromo-1-tridecene (**5a**):[7] Crude mesylate **13** was diluted with THF (35 mL) and LiBr (5.3 g, 61 mmol) was added. The resulting mixture was heated at reflux for 18 h. The reaction was diluted with saturated aqueous NaHCO$_3$ and Et$_2$O. The organic layer was separated and the aqueous layer was extracted with Et$_2$O (3 x 25 mL), dried (Na$_2$SO$_4$), and concentrated under reduced pressure to give the crude bromide. Purification by FC (PE) yielded 7.26 g (65% from the alcohol) **5a** as a colorless liquid. The spectral data of the product matched the literature values:[7] IR 3075.7, 2922.8, 2852.8, 1640.5, 1463.9, 1438.5, 1250.2, 992.6, 908.5, 721.6, 645.6.



10-(undec-10-en-1-oxy)-decan-1-ol (14). To a solution of powdered 1,10-decanediol (10.67 g, 61 mmol) in THF (400 mL, stabilized with BHT) was added sodium hydride (5.20 g of a 60% dispersion in mineral oil, 130 mmol). The heterogeneous solution was heated to reflux for 30 min, cooled in an ice-water bath, and then 11-bromo-1-undecene (14.0 mL of 95% purity, 61 mmol) was added over 3 h. The mixture was then stirred at ambient temperature for 2.5 days, then DMF (140 mL) was added and mixture was heated at 50 °C for 46 h. The reaction was concentrated and then partitioned between saturated aqueous sodium bicarbonate and Et_2O. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with water, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting orange oil was purified by FC (compound loaded onto column as a $CHCl_3$ solution: 10→15% EtOAc/PE) to afford 7.35 g (37%) of **14** as an off-white waxy solid: mp 38.5-40 °C; IR 3320.1, 3080.0, 2976.0, 2925.7, 2850.5, 2802.6, 1642.3, 1463.9, 1120.6, 1065.0, 911.7, 720.4, 635.1; ^{1}H NMR δ 5.81 (m, 1H), 4.99 (m, 1H), 4.93 (m, 1H), 3.63 (t, *J* = 6.6, 2H), 3.39 (t, *J* = 6.7, 4H), 2.06 (m, 2H), 1.56 (m, 8H), 1.29 (m, 22H); ^{13}C NMR δ (accidental equivalence observed) 139.18, 114.05, 70.91, 62.95, 33.76, 32.75, 29.71, 29.50, 29.48, 29.43, 29.39, 29.27, 29.08, 28.88, 26.14, 25.69; MS (EI) 326.3 (M^+, 3), 83.1 (90), 54.9 (100); HRMS calcd for $C_{21}H_{42}O_2$: 326.3185. Found: 326.3182 (0.9 ppm difference).

10-(undec-10-en-1-oxy)-decan-1-methansulfonate (5b). A solution of **14** (4.01 g, 12.3 mmol) in dry CH_2Cl_2 (25 mL) and triethyl amine (2.9 mL, 21 mmol) was cooled in an ice-water bath and then methanesulfonyl chloride (1.3 mL, 16.7 mmol) was added over 10 minutes. The resulting mixture was stirred for 15 min at low temperature and then for 2 h at ambient temperature. The excess methansulfonyl chloride was quenched by the addition of some ice and water and then the organic layer was collected. The aqueous layer was extracted with Et_2O (50 mL) and the combined organic layers were washed with sat. aq. $NaHCO_3$ (2x), 0.5 M HCl (1x), water (1x), and brine (1x), dried (Na_2SO_4), and concentrated under reduced pressure to give 4.63 g (93%) of **5b** as a pale yellow solid. The product was used directly in the next step. IR 3035.2, 2978.2, 2915.5, 2851.5, 2799.2, 1641.5, 1470.1, 1341.2, 1327.3, 1166.1, 1116.3, 983.3, 944.8, 909.2, 852.8, 751.8, 719.1; ^{1}H NMR δ 5.81 (m, 1H), 4.99 (m, 1H), 4.93 (m, 1H), 4.22 (t, *J* = 6.7, 2H), 3.39 (t, *J* = 6.7, 4H), 3.00 (s, 3H), 2.04 (m, 2H), 1.75 (m, 2H), 1.56 (m, 4H), 1.34 (m, 2H), 1.29 (m, 22H); MS (CI, CH_4) 405.3 (M+1, 34), 97.1 (77), 83.1 (100); HRMS calcd for $C_{22}H_{45}O_4S$: 405.3039. Found: 405.3037 (0.5 ppm difference).

3-(undec-10-yn-1-oxy)-5-(tridec-12-en-1-oxy)benzyl alcohol (6a). A mixture of **4** (1.79 g, 6.17 mmol, 1 eq), **5a** (1.78 g, 6.81 mmol, 1.1 eq), powdered potassium carbonate (1.24 g, 8.99 mmol, 1.45 eq), and 18-crown-6 (0.084 g, 0.32 mmol, 0.05 eq) THF (55 mL), and acetonitrile (15 mL) was heated to reflux for 19 h. The reaction mixture was concentrated under reduced pressure and the residue was partitioned between ether and water. The organic layer was washed with brine and dried (Na_2SO_4). Purification by a silica gel plug (2→20% EtOAc/Hexane) gave 2.13 g (73%) of **6a** as a yellow oil: IR 3310.8, 2922.8, 2852.7, 2118.0, 1639.7, 1595.8, 1452.4, 1386.0, 1345.9, 1321.5, 1292.6, 1159.6, 1054.1, 994.9, 938.2, 908.7, 830.4, 721.2, 706.8, 675.3, 626.6; ^{1}H NMR δ (alcohol proton not observed) 6.49 (d, *J* = 2.2, 2H), 6.36 (t, *J* = 2.2, 1H), 5.83 (m, 1H), 4.95 (m, 2H), 4.60 (s, 2H), 3.92 (t, *J* = 6.6, 4H), 2.17 (dt, *J* = 7.1, *J* = 2.7, 2H), 1.94 (t, *J* = 2.7, 1H), 1.77 (m, 4H), 1.53 (m, 2H), 1.40 (m, 4H), 1.26 (m, 24H); ^{13}C NMR δ 160.54, 160.52, 143.20, 139.26, 114.10, 105.05, 100.55, 84.78, 68.09, 68.07, 68.03, 65.45, 33.82, 29.60, 29.57, 29.50, 29.39, 29.30, 29.27, 29.24, 29.16, 29.02, 28.95, 28.72, 28.47, 26.05, 26.02; MS 471.3 (M+1, 100), 282.0 (40), 238.0 (26); HRMS calcd for $C_{31}H_{51}O_3$: 471.3838. Found: 471.3833 (1.1 ppm difference).

3-(undec-10-yn-1-oxy)-5-(10-(undec-10-en-1-oxy)-decan-1-oxy)benzyl alcohol (6b). A mixture of **4** (0.800 g, 2.75 mmol), **5b** (1.174 g, 2.9 mmol), potassium carbonate (0.77 g, 5.6 mmol), 18-crown-6 (36 mg, 0.14 mmol), dry THF (100 mL), and dry acetonitrile (15 mL) was heated at reflux for 4 days. The reaction mixture concentrated under reduced pressure and then partitioned between Et_2O and water. The aqueous layer was extracted with

Et_2O and the combined organic layers were washed with brine (1x), dried (Na_2SO_4), and concentrated under reduced pressure. The resulting orange oil was purified by FC (6→8% EtOAc/PE) to afford 0.762 g (46%) of **6b** as a yellow oil that solidified upon standing, to give a waxy solid: mp 26-28 °C; IR 33.10.7, 2923.7, 2853.0, 2118.1, 1640.6, 1596.1, 1455.7, 1358.3, 1349.9, 1323.2, 1292.4, 1160.7, 1112.6, 1054.9, 994.6, 908.9, 830.6, 721.7, 626.9; ^1H NMR δ 6.50 (d, *J* = 2.2, 2H), 6.38 (t, *J* = 2.2, 1H), 5.81 (m, 1H), 4.99 (m, 1H), 4.93 (m, 1H), 4.62 (d, *J* = 6.2, 2H), 3.93 (t, *J* = 6.5, 4H), 3.39 (t, *J* = 6.7, 4H), 2.18 (dt, *J* = 7.1, *J* = 2.6, 2H), 2.03 (apparent q, *J* = 7.2, 2H), 1.94 (t, *J* = 2.7, 1H), 1.76 (m, 6H), 1.64 (t, *J* = 6.2, 1H), 1.54 (m, 6H), 1.44-1.26 (m, 32H); ^{13}C NMR δ 160.52, 143.23, 139.19, 114.07, 105.07, 100.59, 84.72, 70.95, 68.05, 68.02, 65.40, 33.78, 29.75, 29.52, 29.49, 29.45, 29.41, 29.37, 29.32, 29.27, 29.23, 29.10, 28.99, 28.92, 28.69, 28.46, 26.17, 26.00, 18.37; MS 621.6 ($M+Na^+$, 100), 581.6 (M^+-OH, 88), 471.3 (32); HRMS calcd for $C_{39}H_{67}O_4$: 599.5039. Found: 599.5067 (4.7 ppm difference).

1-azido-4-bromobutane (8).[3] A mixture of 1,4-dibromobutane (10.798 g, 50.0 mmol), sodium azide (3.255 g, 50.0 mmol), and DMF (30 mL) was stirred at ambient temperature for 9 days. The heterogeneous reaction mixture was decanted and the liquid was partitioned between PE and H_2O. The organic layer was separated and the aqueous layer was extracted with PE. The combined organic layers were washed with H_2O (4x), brine (1x), dried (Na_2SO_4), and concentrated under reduced pressure to a provide 8.319 g of colorless liquid that contained 1,4-dibromobutane, **8**, and 1,4-diazidobutane. **CAUTION:** The product mixture is potentially explosive and should not be distilled. The product was purified by FC (1% Et_2O/PE) to afford 3.484 g (39%) of **8** as a colorless liquid. The product is known,[3a,3b] although spectral data have not been reported: IR 2941.2, 2870.0, 2090.9, 1483.6, 1350.2, 1259.0, 745.7, 647.0; ^1H NMR δ 3.44 (t, *J* = 6.6, 2H), 3.34 (t, *J* = 6.7, 2H), 1.94 (m, 2H), 1.76 (m, 2H); ^{13}C NMR δ 50.57, 32.83, 29.73, 27.44.

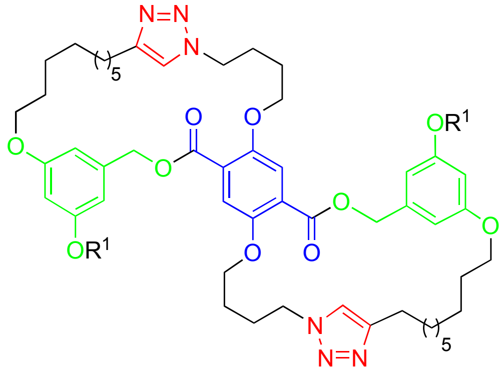
Diethyl 2,5-bis(4-azidobutoxy)terephthalate (9). A mixture of diethyl 2,5-dihydroxyterephthalate (**7**) (1.00 g, 3.9 mmol), 1-azido-4-bromobutane[3] (**8**) (2.134 g, 12.0 mmol), potassium carbonate (3.34 g, 24.2 mmol), potassium iodide (49 mg, 0.30 mmol), 18-crown-6 (32 mg, 0.12 mmol) and dry acetone (30 mL) was heated at 70 °C for 27 h. The reaction mixture was cooled and concentrated under reduced pressure. The mixture was then partitioned between EtOAc and water. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine (1x), dried (Na_2SO_4), and concentrated under reduced pressure. The resulting brown oil was purified by FC (10% EtOAc/PE) to afford 1.407 g (80%) of **9** as a pale yellow oil. The product was crystallized as colorless needles by cooling an ethereal solution that has been layered with PE to -30 °C in a freezer: mp 37-38 °C; IR 2937.1, 2873.3, 2093.1, 1725.8, 1701.8, 1501.7, 1467.1, 1417.5, 1383.3, 1298.3, 1230.9, 1204.7, 1102.3, 1022.2, 789.1; ^1H NMR δ 7.35 (s, 2H), 4.38 (q, *J* = 7.1, 4H), 4.05 (t, *J* = 5.9, 4H), 3.38 (t, *J* = 6.6, 4H), 1.89 (m, 4H), 1.83 (m, 4H), 1.39 (t, *J* = 7.1, 6H); ^{13}C NMR δ 165.72, 151.60, 124.73, 116.60, 69.00, 61.35, 51.12, 26.49, 25.63, 14.29; MS 449.2 (M+1, 100), 409.4 (92), 70.4 (80); HRMS calcd for $C_{20}H_{28}N_6NaO_6$: 472.1968. Found: 472.1952 (3.4 ppm difference); EA calcd. $C_{20}H_{28}N_6O_6$ C: 53.56; H: 6.29; N: 18.74; found C: 53.63; H: 6.03; N: 18.60.

Click cycloaddition[5] product (10a). A mixture of **9** (149.7 mg, 0.33 mmol, 1 eq), **6a** (314.0 mg, 0.67 mmol, 2 eq), copper sulfate (27.3 mg, 0.11 mmol, 0.33 eq), THF (5.5 mL), *t*-butanol (1.5 mL), water (1.5 mL), and sodium ascorbate (79.8 mg, 0.40 mmol, 1.2 eq) was stirred vigorously for 3 days. The mixture was then concentrated under reduced and partitioned between ether/ethyl acetate and water. The organic layer was separated and the aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with water, brine, and dried (Na_2SO_4). Purification by FC (50→100% EtOAc/PE) yielded 302.6 mg (66%) of **10a** as an oil that solidified to a white solid under high vacuum: mp 62-64 °C; IR 3318.6, 2924.3, 2853.1, 1723.6, 1639.6, 1595.7, 1503.5, 1463.0, 1417.4, 1383.9, 1294.6, 1232.1, 1206.7, 1163.1, 1102.2, 1052.6, 908.1, 831.3, 789.9, 721.5; UV (Et_2O) λ_{max} 332 nm; ^1H NMR δ 7.33 (s, 4H), 6.50 (t, *J* = 2.0, 4H), 6.36 (t, *J* = 2.0, 2H), 5.81 (m, 2H), 4.99 (m, 2H), 4.92 (m, 2H), 4.61 (s, 4H), 4.42 (t, *J* = 7.1, 4H), 4.35 (q, *J* = 7.1, 4H), 4.03 (t, *J* = 5.9, 4H), 3.92 (t, *J* = 6.3, 8H), 2.69 (t, *J* = 7.8, 4H), 2.15 (m, 4H), 2.03 (m, 6H), 1.81 (m, 4H), 1.75 (m, 8H), 1.65 (m, 4H), 1.43 (m, 8H), 1.36 (t, *J* = 7.1, 6H), 1.27 (m, 44H); ^{13}C NMR δ 165.22, 160.48, 160.46, 151.67, 148.45, 143.48, 139.24, 124.69, 120.56, 116.62, 105.04, 104.98, 100.44, 68.88, 68.04, 67.98, 65.21, 61.37, 49.66, 33.81, 29.57, 29.49, 29.45, 29.38, 29.27, 29.25, 29.24, 29.21, 29.14, 28.94, 27.10, 26.13, 26.05, 25.97, 25.67; MS 1390.0 (M+1, 57), 695.7 (100); HRMS calcd for $C_{82}H_{129}N_6O_{12}$: 1389.9668. Found: 1389.9630 (2.7 ppm difference); EA calcd. $C_{82}H_{128}N_6O_{12}$ C: 70.86; H: 9.28; N: 6.05; found C: 70.60; H: 9.47; N: 6.10.

Click cycloaddition[5] product (10b). To a mixture of **6b** (904 mg, 1.51 mmol), **9** (334 mg, 0.74 mmol), copper sulfate pentahydrate (19.6 mg, 0.078 mmol), THF (12 mL), *t*-butanol (5 mL), and water (5 mL) was added sodium ascorbate (77 mg, 0.39 mmol). The mixture was stirred vigorously at ambient temperature for 23 h, after which time additional copper sulfate pentahydrate (28 mg, 0.11 mmol) and sodium ascorbate (88 mg, 0.44 mmol) were added and the mixture was stirred for an additional 3 h. The reaction mixture was then diluted with water, Et_2O, and EtOAc. The organic layer was collected and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Purification by FC (compound loaded as a CH_2Cl_2 solution: 30→100% EtOAc/PE) afforded 859 mg (70%) of **10b** as a waxy white solid: mp 48.5-50.5 °C; IR 3411.0, 2925.2, 2853.5, 1724.6, 1639.4, 1596.0, 1551.3, 1503.4, 1463.1, 1417.7, 1383.5, 1294.7, 1233.1, 1207.1, 1163.2, 1104.9, 1054.4, 1024.1, 908.5, 830.1, 790.6; ^1H NMR δ 7.34 (s, 2H), 7.33 (s, 2H), 6.50 (apparent t, *J* = 2.2, 4H), 6.36 (apparent t, *J* = 2.2, 2H), 5.81 (m, 2H), 4.99 (m, 2H), 4.92, m, 2H), 4.61 (s, 4H), 4.42 (t, *J* = 7.0, 4H), 4.35 (q, *J* = 7.1, 4H), 4.03 (t, *J* = 5.9, 4H), 3.92 (t, *J* = 6.6, 8H), 3.39 (t, *J* = 6.7, 8H), 2.69 (t, *J* = 7.7, 4H), 2.15 (m, 4H), 2.03 (m, 4H), 1.82 (m, 4H), 1.75 (m, 8H), 1.65 (m, 4H), 1.56 (m, 8H), 1.43 (m, 8H), 1.36 (t, *J* = 7.1, 6H), 1.30 (m, 60H); ^{13}C NMR δ 165.36, 160.41, 151.59, 148.39, 143.38, 139.17, 124.59, 120.50, 116.52, 114.04, 104.95, 104.90, 100.35, 70.90, 68.78, 67.95, 67.90, 65.17, 61.30, 49.60, 33.74, 29.70, 29.48, 29.46, 29.44, 29.41, 29.38, 29.37, 29.32, 29.29, 29.19, 29.15, 29.13, 29.05, 28.86, 27.04, 26.12, 26.05, 25.96, 25.90, 25.60, 14.27; MS 1647.3 (M+1, 57); 806.4 (100), 727.7 (41); HRMS calcd for $C_{98}H_{161}N_6O_{14}$: 1646.2071. Found: 1646.2034 (2.2 ppm difference); EA calcd. $C_{98}H_{160}N_6O_{14}$ C: 71.49; H: 9.80; N: 5.10; found C: 71.63; H: 9.70; N: 5.13.

Terephthalic acid derivative (11a). A solution of potassium hydroxide (630 mg, 11.3 mmol) in water (5 mL) was added to a solution of **10a** (353 mg, 0.25 mmol) in THF (15 mL) and ethanol (2.7 mL). The resulting mixture was stirred and heated at 80 °C for 18 h. It was then diluted with saturated aqueous ammonium chloride to pH 7 and an ether/ethyl acetate mixture. To help separation, the mixture was washed with brine. The organic layer was collected and the aqueous layer was acidified to pH 1 by 0.5 M HCl and further extracted with CH_2Cl_2 (2x). All organic layers were combined, dried (Na_2SO_4), and concentrated to give 366.6 mg (quantitative) of **11a** as a white solid: mp 43-44 °C; IR 3136.7, 3049.5, 2923.6, 2853.0, 1713.1, 1640.4, 1498.7, 1450.8, 1409.7, 1294.0, 1210.2, 1164.0, 1054.9, 907.3, 830.1, 724.8, 635.7. ^{1}H NMR δ 7.75 (s, 2H), 7.29 (s, 2H), 6.51 (s, 2H), 6.49 (s, 2H), 6.36 (t, *J* = 2.2, 2H), 5.81 (m, 2H), 4.99 (m, 2H), 4.92 (m, 2H), 4.63 (s, 4H), 4.42 (t, *J* = 6.6, 4H), 4.26 (m, 4H), 3.92 (t, *J* = 6.6, 8H), 2.70 (t, *J* = 7.6, 4H), 2.11 (m, 4H), 2.04 (m, 4H), 1.91 (m, 4H), 1.74 (m, 8H), 1.66 (m, 4H), 1.43 (m, 8H), 1.27 (m, 46H); ^{13}C NMR δ 165.24, 160.38, 151.45, 148.40, 143.31, 139.18, 123.67, 120.81, 116.92, 114.07, 114.04, 105.03, 104.95, 100.36, 69.60, 68.00, 65.03, 40.52, 33.75, 29.52, 29.43, 29.34, 29.26, 29.21, 29.12, 29.02, 29.08, 29.06, 28.87, 26.84, 25.99, 25.86, 25.38; MS 1334.5 (M+1, 63), 668.0 (100); HRMS calcd for $C_{78}H_{121}N_6O_{12}$: 1333.9042. Found: 1333.9042 (0.1 ppm difference).

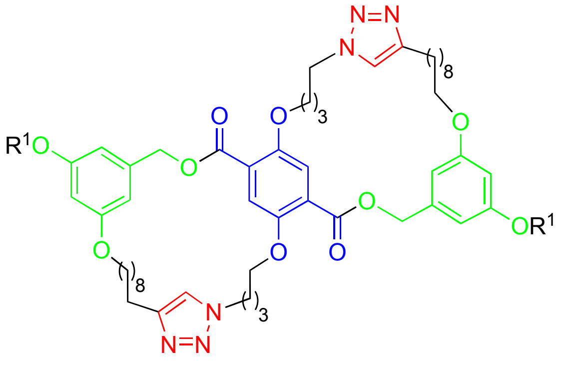
Terephthalic acid derivative (11b). To a solution of **10b** (134 mg, 0.081 mmol) in THF (6 mL) and ethanol (1 mL) was added a solution of KOH (214 mg, 3.82 mmol) in water (2 mL). The resulting solution was heated at reflux for 2 h, cooled to ambient temperature, and diluted with saturated aqueous ammonium chloride, Et_2O, and EtOAc. The organic layer was collected, the aqueous layer was acidified with 0.5 M HCl and then extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give 132.9 mg (quantitative) of **11b** as a white solid that was a single spot via TLC (10% MeOH/CH_2Cl_2): mp 66.5-68 °C; IR 3138.9, 3076.3, 2923.2, 2852.4, 1706.7, 1640.4, 1595.3, 1552.9, 1498.1, 1455.2, 1384.9, 1292.9, 1207.5, 1161.7, 1114.1, 1054.2, 992.8, 829.7, 806.3, 723.4, 683.6; ^{1}H NMR δ 7.41 (s, 2H), 7.32 (s, 2H), 6.49 (s, 2H), 6.45 (s, 2H), 6.33 (t, *J* = 2.1, 2H), 5.80 (m, 2H), 4.98 (m, 2H), 4.92 (m, 2H), 4.59 (s, 4H), 4.34 (t, *J* = 6.5, 4H), 4.04 (br s, 4H), 3.89 (m, 8H), 3.38 (t, *J* = 6.7, 8H), 2.62 (t, *J* = 7.6, 4H), 1.75 (m, 8H), 1.55 (m, 12H), 1.38 (m, 12H), 1.28 (m, 68H); ^{13}C NMR (DMSO-d_6/$CDCl_3$ 2:1) δ 167.37, 157.89, 148.20, 145.07, 143.02, 136.83, 119.69, 113.48, 112.45, 102.54, 97.34, 68.24, 66.79, 65.47, 61.25, 47.15, 31.49, 27.48, 27.29, 27.26, 27.23, 27.21, 27.13, 27.11, 27.09, 27.08, 27.00, 26.95, 26.78, 26.56, 25.01, 23.95, 23.93, 23.87, 23.78, 23.37; MS 1591.3 (M^+, 100), 1390.5 (20), 796.7 (31); HRMS calcd for $C_{94}H_{153}N_6O_{14}$: 1590.1445. Found: 1590.1405 (2.5 ppm difference).



ortho isomer

1a $R^1 = (CH_2)_{11}CH{=}CH_2$

1b $R^1 = (CH_2)_{10}O(CH_2)_9CH{=}CH_2$



meta isomer

1a $R^1 = (CH_2)_{11}CH{=}CH_2$

1b $R^1 = (CH_2)_{10}O(CH_2)_9CH{=}CH_2$

Knot Precursor (*o*-1a & *m*-1a) To a mixture of CH_2Cl_2 (115 mL), MNBA[8] (43.9 mg, 0.13 mmol, 2.5 eq), DMAP (41.6 mg, 0.34 mmol, 6.5) and was added a solution of **11a** (70 mg, 52.3

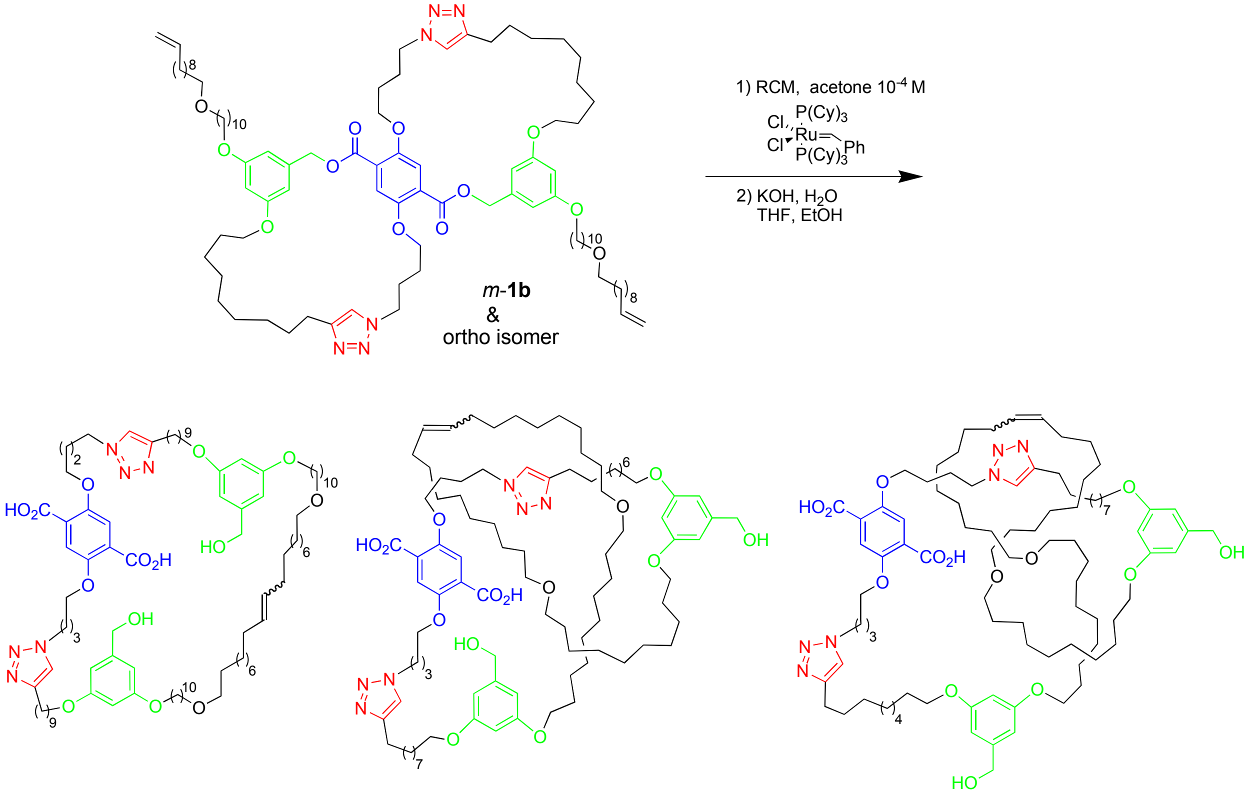
μmol, 1 eq) dissolved in CH_2Cl_2 (100 mL) over a period of 1 h. The mixture was stirred at ambient temperature for an additional 18 h and concentrated under reduced pressure. The residue was dissolved in methylene chloride and the organic layer was washed with saturated sodium bicarbonate, 0.5 M HCl, water, brine, and dried (Na_2SO_4). Purification by FC ($CH_2Cl_2 \rightarrow$1.5% MeOH/CH_2Cl_2) gave 41.8 mg (62%) of **_o_-1a** & **_m_-1a** as white crystals. Based on ^{1}H NMR integrations of the benzylic protons, the ratio of the two isomers is approximately 64:36. The isomers proved to be inseparable and it is unknown whether the *ortho-* or *meta-* is the major isomer: mp 144-146 °C; IR 3114.8, 3064.9, 2920.9, 2852.2, 1723.4, 1700.2, 1640.1, 1595.8, 1504.0, 1457.7, 1420.9, 1404.0, 1379.7, 1330.7, 1300.5, 1240.8, 1201.8, 1167.5, 1100.9, 1056.1, 996.3, 968.5, 909.1, 872.1, 824.2, 810.6, 784.8, 757.5, 720.9, 681.2; UV (CH_2Cl_2) λ_{max} 281 nm, 337 nm; ^{1}H NMR δ 7.39 (s, 2H major), 7.34 (s, 2H), 7.20 (s, 2H minor), 6.59 (s, 2H major), 6.57 (d, *J* =2.2, 4H minor), 6.48 (s, 2H major), 6.43 (t, *J* =2.2, 2H minor), 6.41 (t, *J* =2.2, 2H major), 5.81 (m, 2H), 5.28 (s, 4H minor), 5.26 (s, 4H major), 4.99 (m, 2H), 4.92 (m, 2H), 4.40 (t, *J* =6.6, 4H minor), 4.24 (t, *J* = 7.1, 2H major), 4.00 (t, *J* = 5.6, 2H major), 3.96 (m, 8H), 2.68 (t, *J* = 7.1, 4H), 2.14-1.96 (m, 8H), 1.78-1.70 (m, 12H), 1.65-1.59 (m, 12H), 1.43-1.27 (m, 32H); ^{13}C NMR δ 165.50, 164.43, 160.50, 160.42, 160.36, 151.90, 151.67, 148.29, 148.11, 139.17, 137.82, 137.67, 124.50, 124.33, 120.65, 120.59, 116.74, 114.04, 107.22, 107.08, 106.39, 106.17, 100.68, 100.45, 69.06, 68.64, 67.67, 66.96, 49.56, 49.36, 33.74, 33.73, 29.63, 29.51, 29.42, 29.32, 29.19, 29.07, 29.04, 28.87, 28.85, 28.82, 28.79, 28.66, 28.49, 28.30, 28.30, 27.56, 27.31, 27.21, 26.89, 25.99, 25.90, 25.71, 25.29, 25.10, 24.78; MS 1297.8 (M+1, 100), 649.8 (39); HRMS calcd for $C_{78}H_{117}N_6O_{10}$: 1297.8831. Found: 1297.8795 (2.8 ppm difference).

Knot Precursor (_o_-1b & _m_-1b). To a mixture of DMAP (58 mg, 0.47 mmol) and MNBA[8] (71 mg, 0.21 mmol), 4Å molecular sieves, and CH_2Cl_2 (150 mL) was added a solution of **11b** (109 mg, 0.069 mmol) in CH_2Cl_2 (150 mL) over a period of 100 min. The resulting mixture was stirred at ambient temperature for 45 h. The reaction mixture was then concentrated under reduced pressure and the product was purified by FC (5% MeOH/CH_2Cl_2) to yield 86.3 mg (81%) of **_o_-1b** & **_m_-1b** as a white solid. Based on ^{1}H NMR integrations of the benzylic protons, the ratio of the two isomers is approximately 63:37. The isomers proved to be inseparable and it is unknown whether the *ortho-* or *meta-* is the major isomer: mp 126-127 °C; IR 3116.3, 3064.4, 2924.6, 2853.3, 1723.6, 1701.1, 1640.4, 1596.5, 1536.1, 1504.4, 1485.5, 1421.2, 1379.5, 1300.8, 1241.5, 1204.2, 1169.1, 1102.6, 1057.2, 996.3, 969.3, 909.2, 872.0, 824.4, 810.1, 784.9, 722.2, 680.8; ^{1}H NMR δ 7.39 (s, 2H of major isomer), 7.34 (s, 2H), 7.21 (s, 2H of minor isomer), 6.60 (s, 2H major), 6.58 (d, *J* = 2.1, 4H minor), 6.48 (s, 2H major), 6.43 (t, *J* = 2.1, 2H minor), 6.41 (t, *J* = 2.2, 2H major), 5.81 (m, 2H), 5.28 (s, 4H minor), 5.26 (s, 4H major), 4.99 (m, 2H), 4.92 (m, 2H), 4.40 (t, *J* = 6.5, 4H minor), 4.24 (t, *J* = 7.1, 2H major), 4.00 (t, *J* = 5.7, 2H major), 3.97 (m, 8H), 3.39 (t, *J* = 6.7, 8H), 2.68 (t, *J* = 7.1, 4H), 2.14-1.95 (m, 8H), 1.78-1.70 (m, 12H), 1.65-1.53 (m, 12H), 1.43-1.26 (m, 72H); ^{13}C NMR δ 165.41, 165.08, 160.42, 160.36, 160.34, 160.28, 151.81, 151.59, 148.18, 148.00, 145.94, 139.05, 137.81, 137.74, 137.60, 136.12, 130.18, 127.90, 124.43, 124.26, 121.75, 120.59, 120.54, 116.67, 113.97, 107.11, 107.02, 106.31, 106.10, 100.60, 100.38, 80.85, 70.81, 70.79, 68.98, 68.57, 68.02, 67.60, 66.87, 66.72, 49.48, 49.28, 33.66, 29.65, 29.40, 29.37, 29.35, 29.34, 29.28, 29.27, 29.24, 29.12, 28.98, 28.78, 28.74, 28.72, 28.60, 28.58, 28.42, 28.23, 28.15, 27.49, 27.30, 27.23, 27.14, 26.80, 26.07, 26.05, 25.93, 25.91, 28.82, 25.64, 25.21, 25.02, 24.71; MS 1555.2 (M+1, 72), 1398.2 (7), 778.3 (100); HRMS calcd for $C_{94}H_{149}N_6O_{12}$: 1554.1234. Found: 1554.1184 (3.2 ppm difference).

Preliminary Thread & Cut Results

Initial RCM/ester hydrolysis experiments on **1a** and **1b** have produced isomeric products whose full structure elucidation is currently under investigation. Three possible products for the thread & cut sequence on **1b** are shown in Scheme 1S. Two isomeric products were isolated in this experiment (see manuscript text).

Scheme 1S



0_1 Unknot (macrocycle) **3_1** Trefoil Knot **4_1** Figure-Eight Knot

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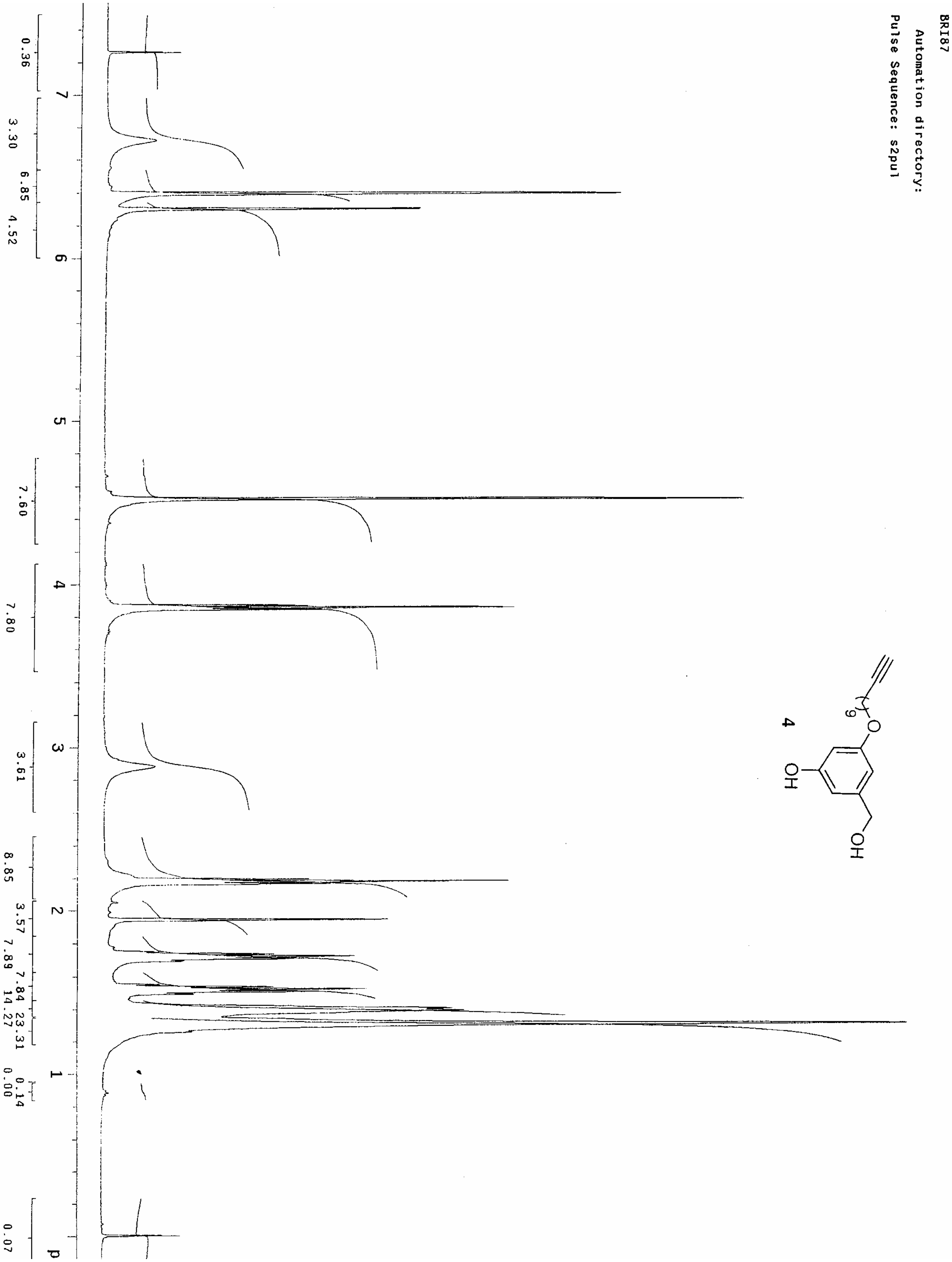
Spectra



BRI87

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EEF571
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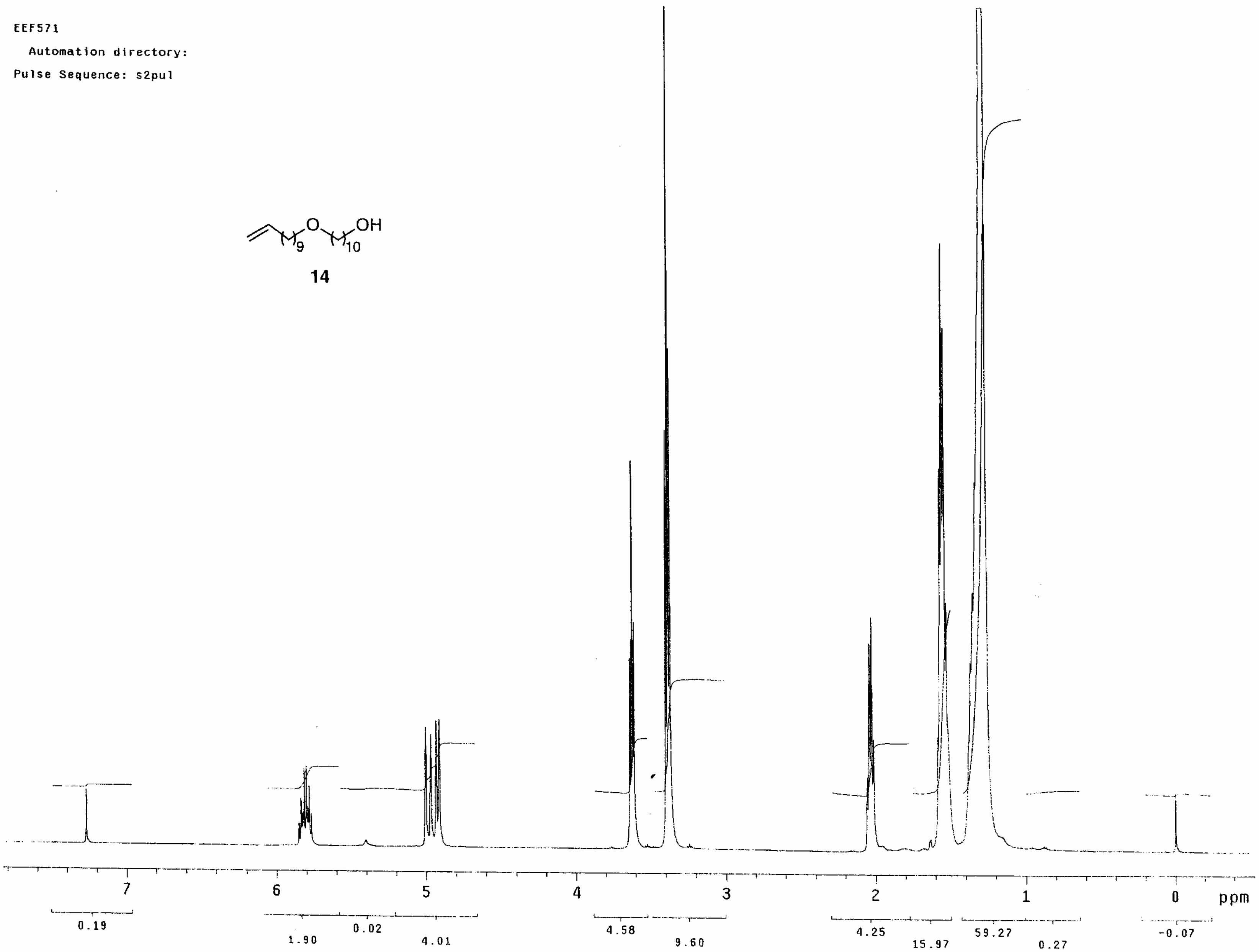

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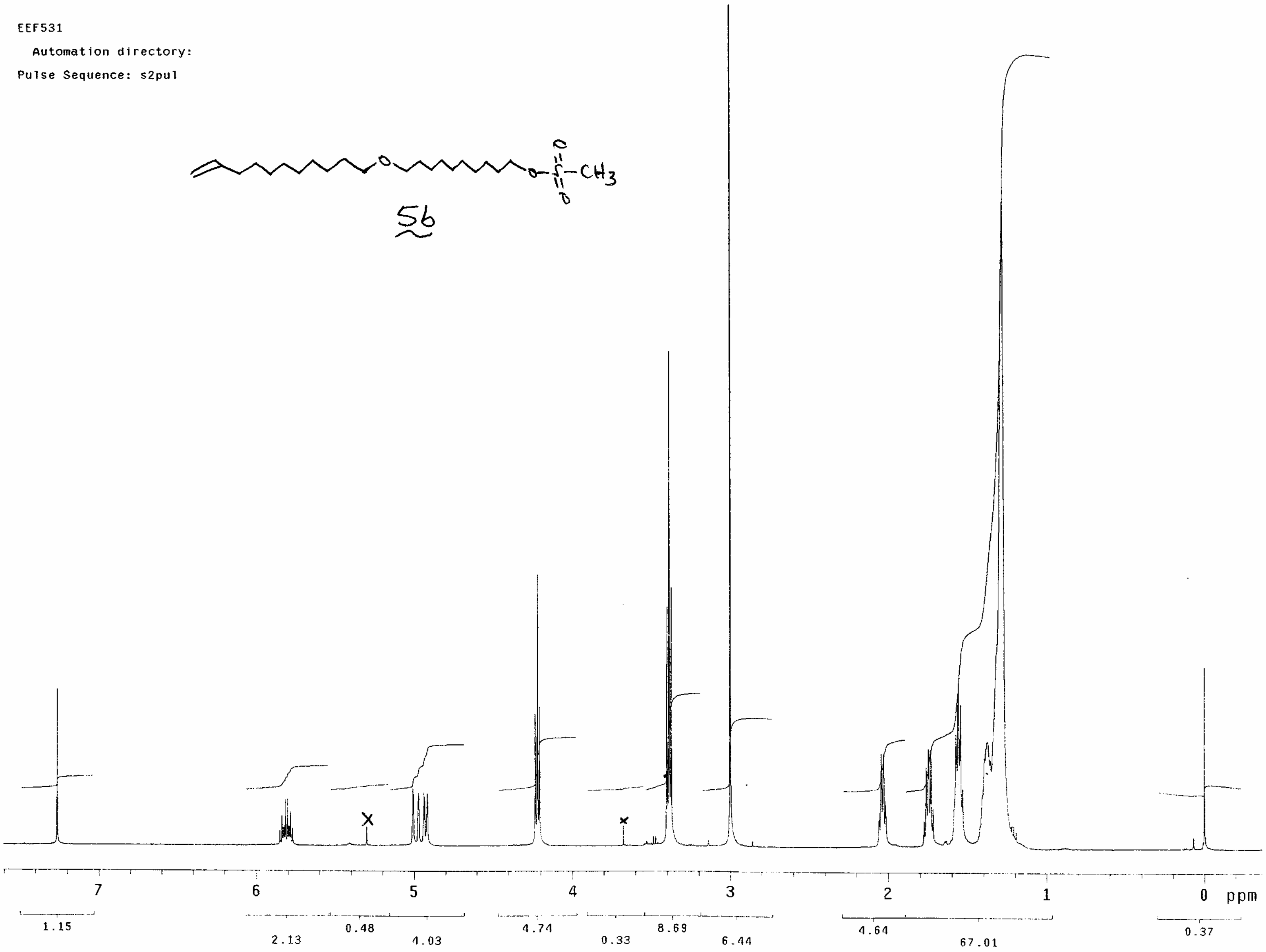

56

x = Solvent impurity

BRI89
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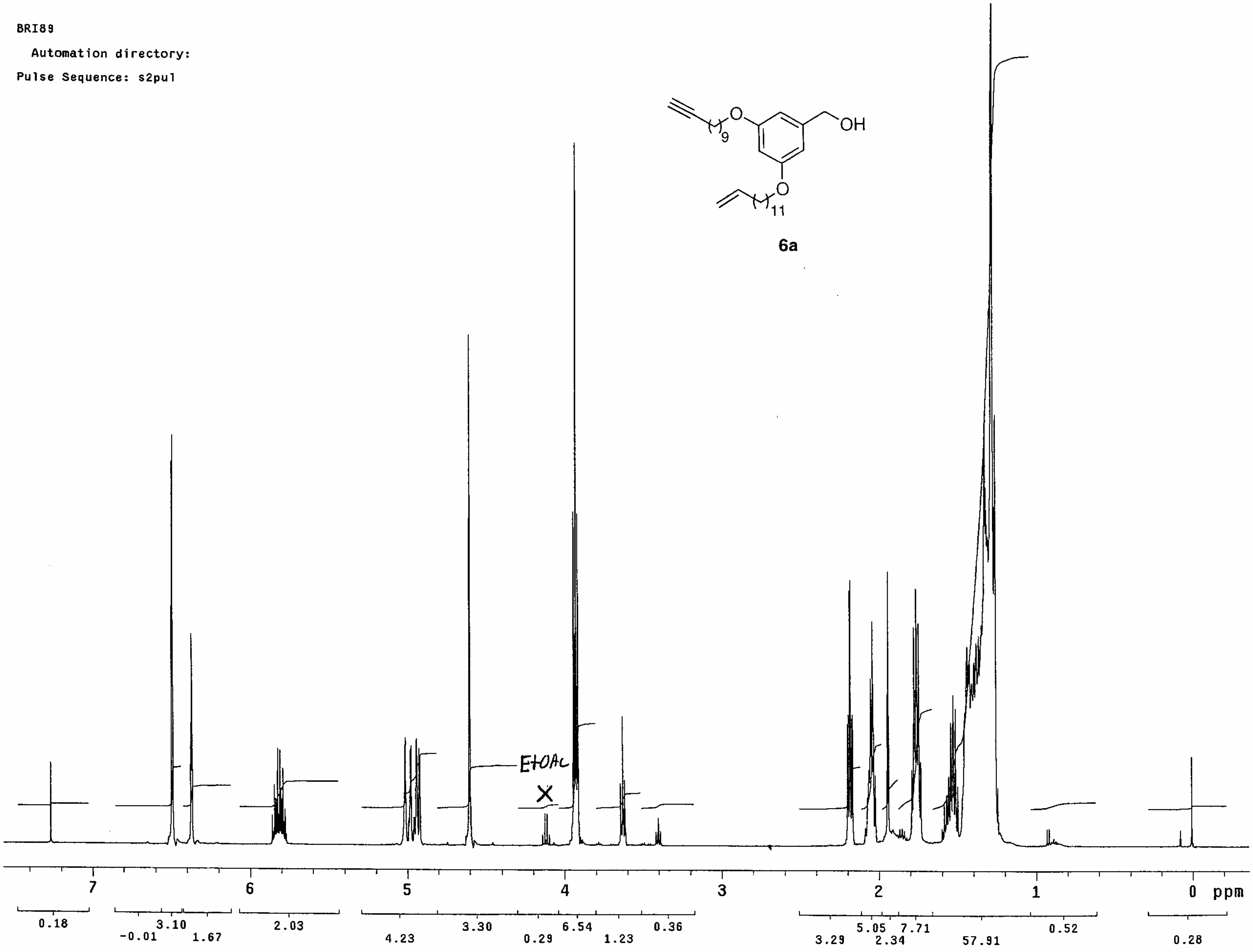
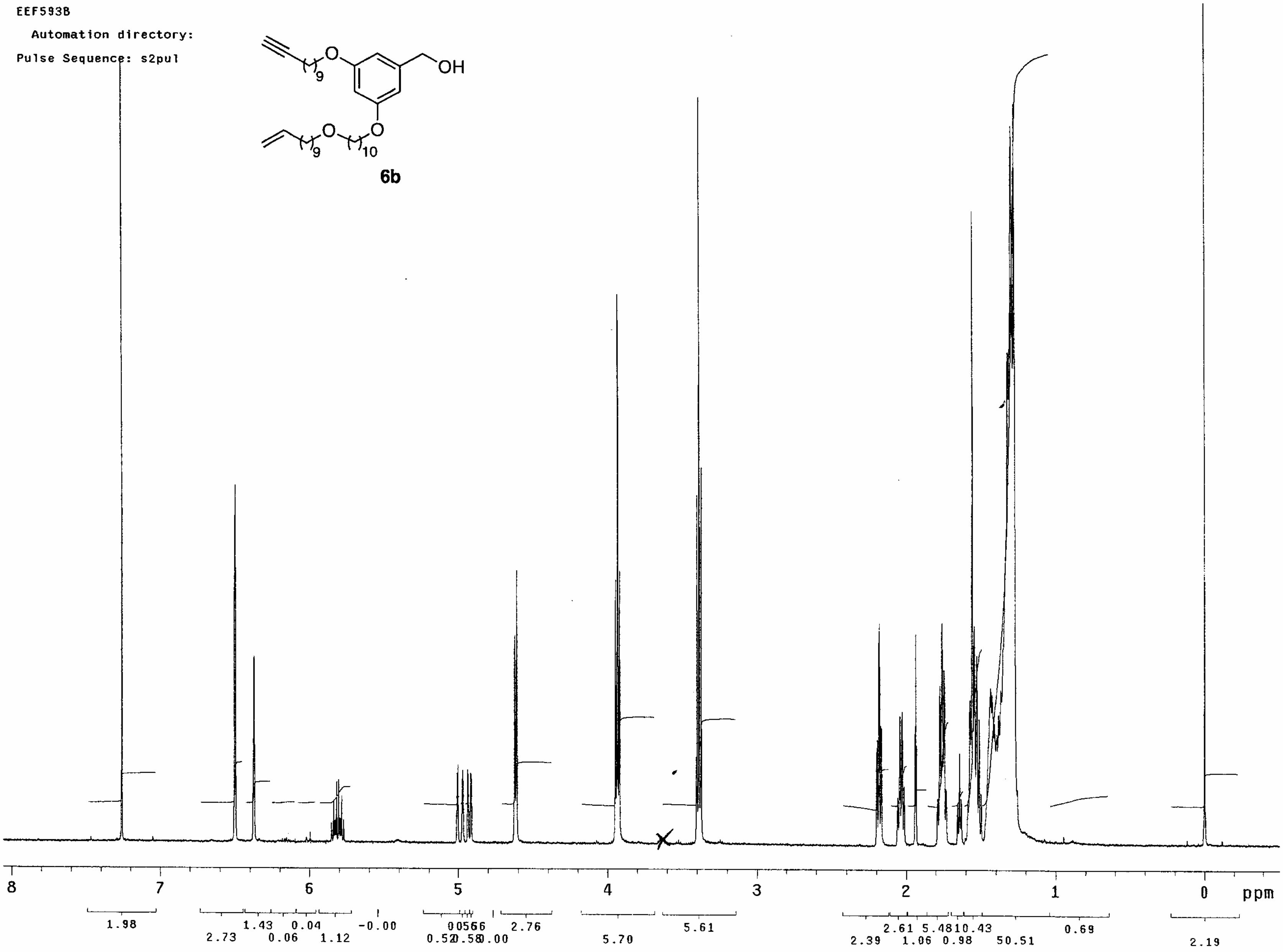


6a


EEF593B
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9
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6b
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7
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1
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ppm
1.98
2.73
1.43
0.06
0.04
1.12
-0.00
0.52
0.05
0.58
0.66
0.00
2.76
5.70
5.61
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50.51
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2.19

EEF579

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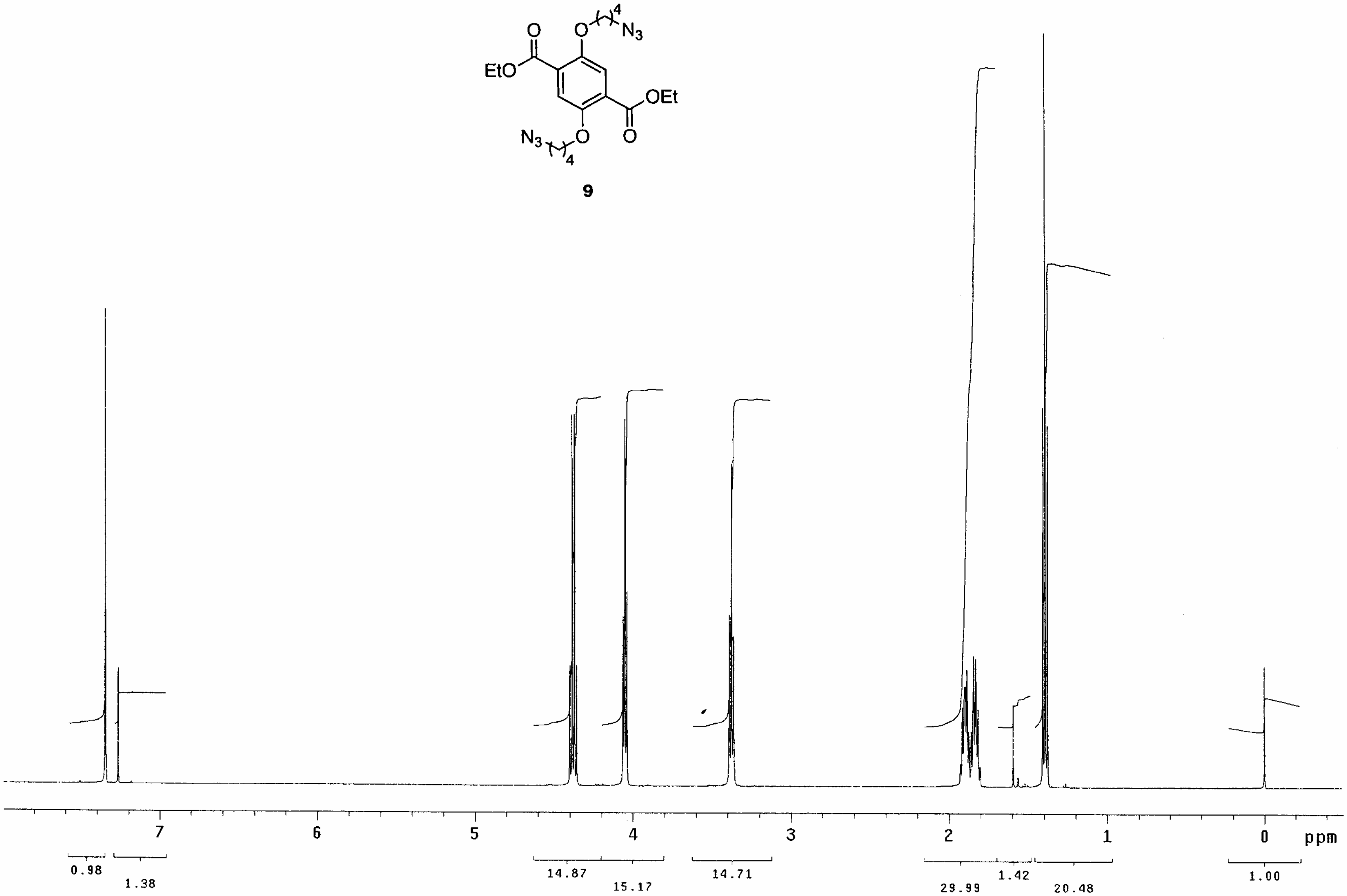

9

BRI97

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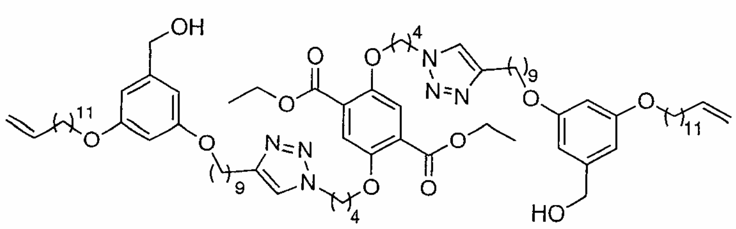
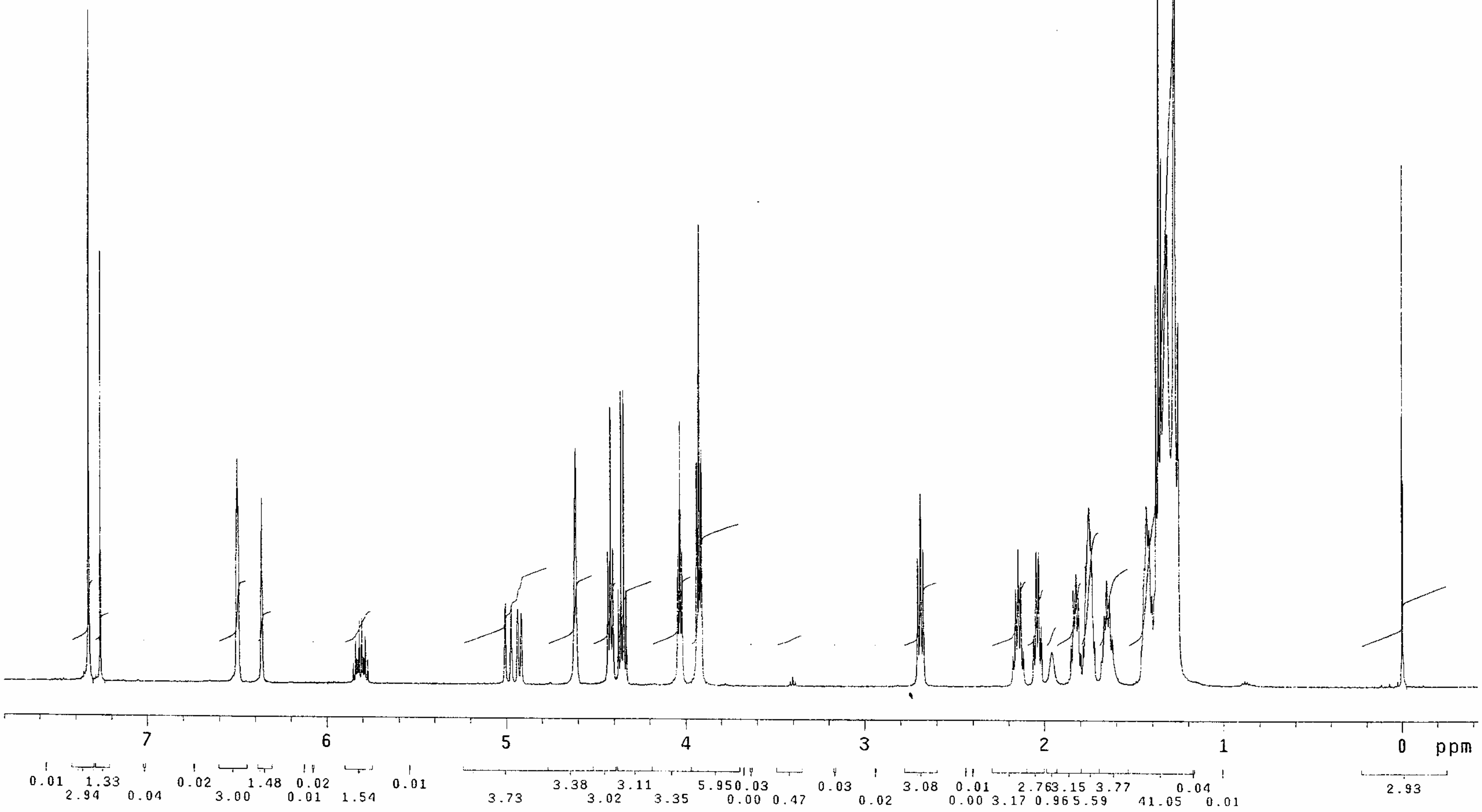


10a



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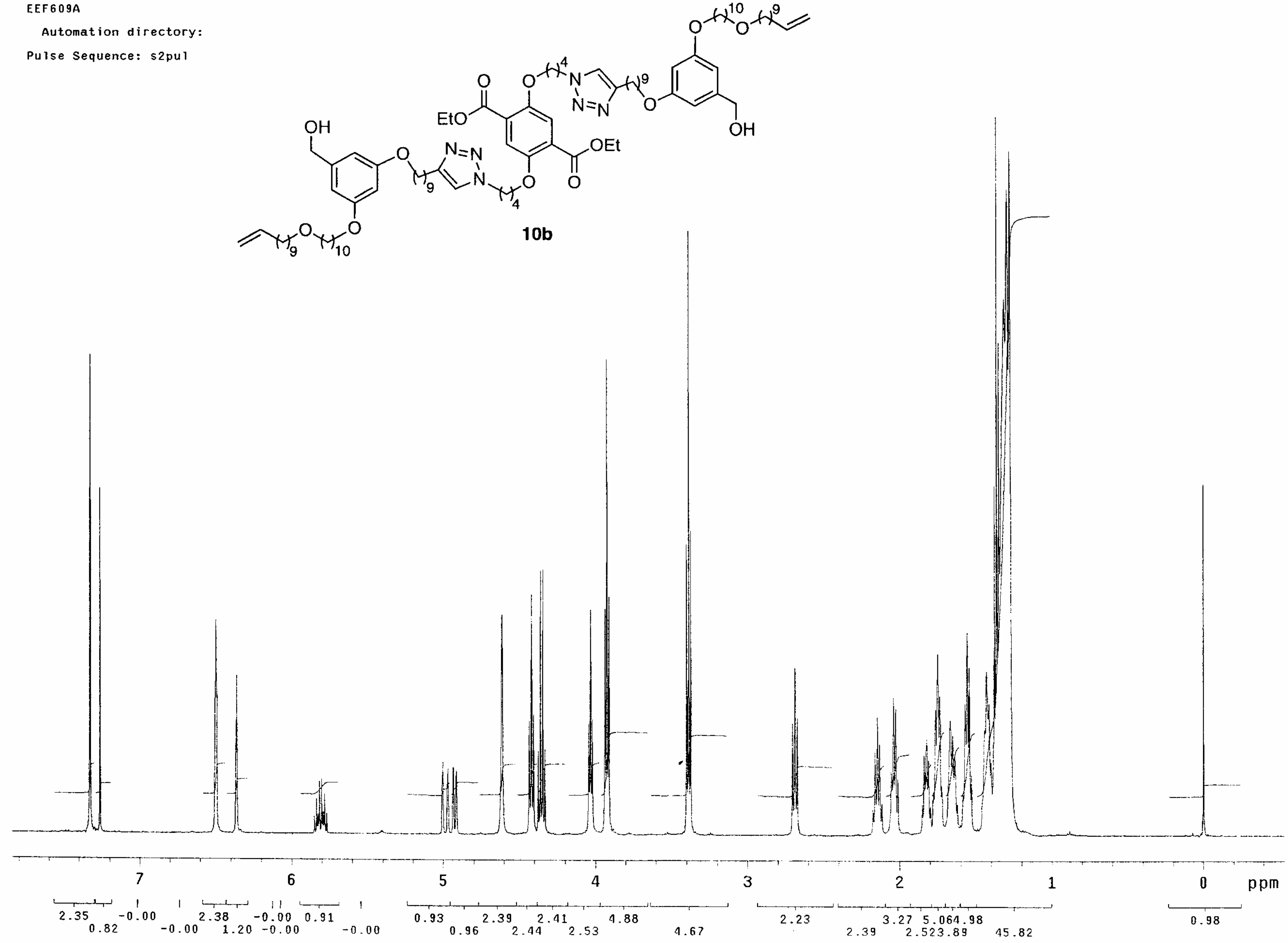

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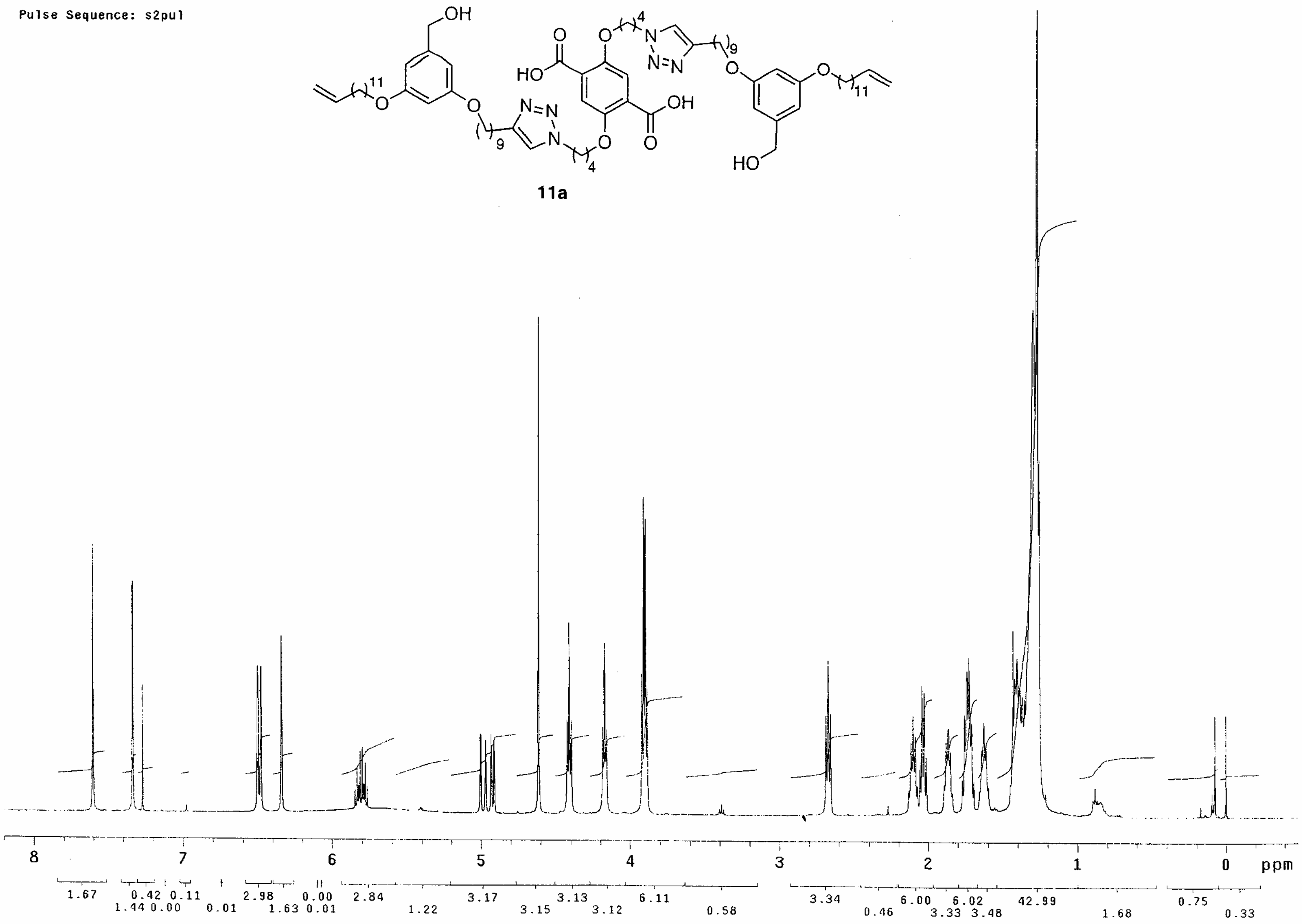

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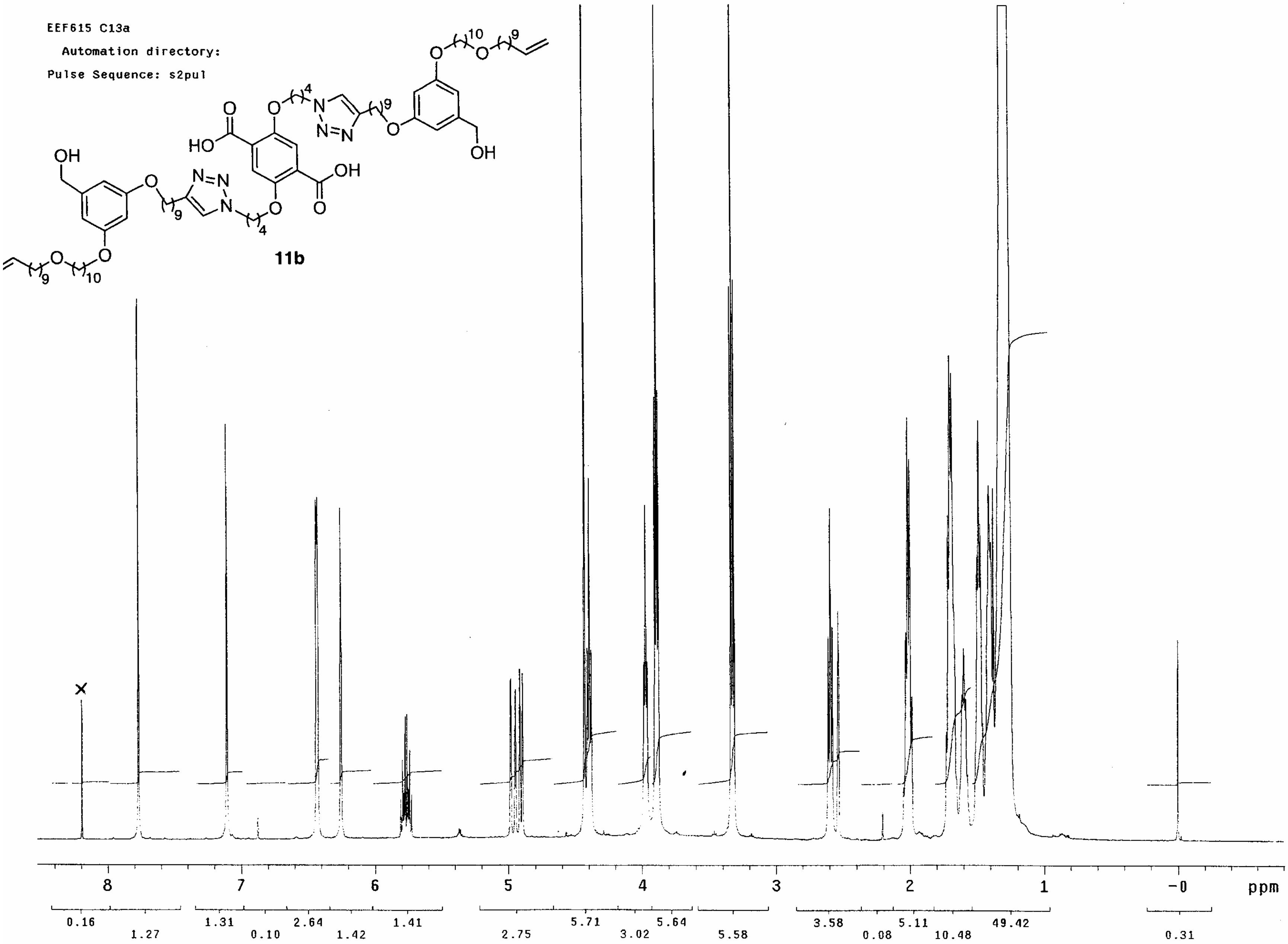
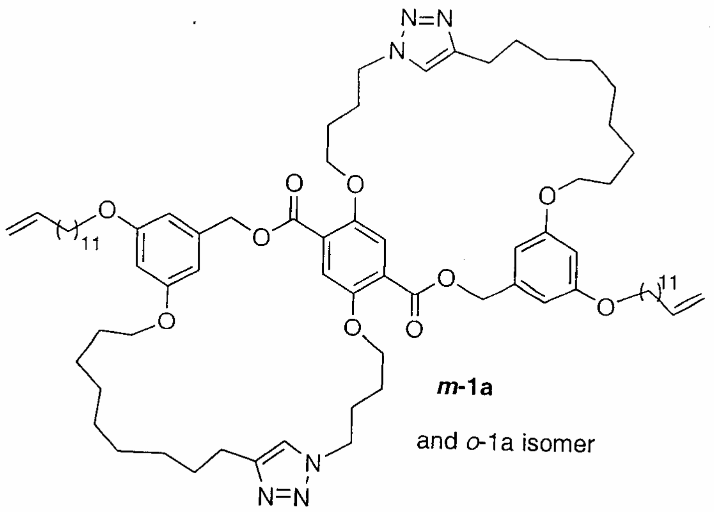


BRI29

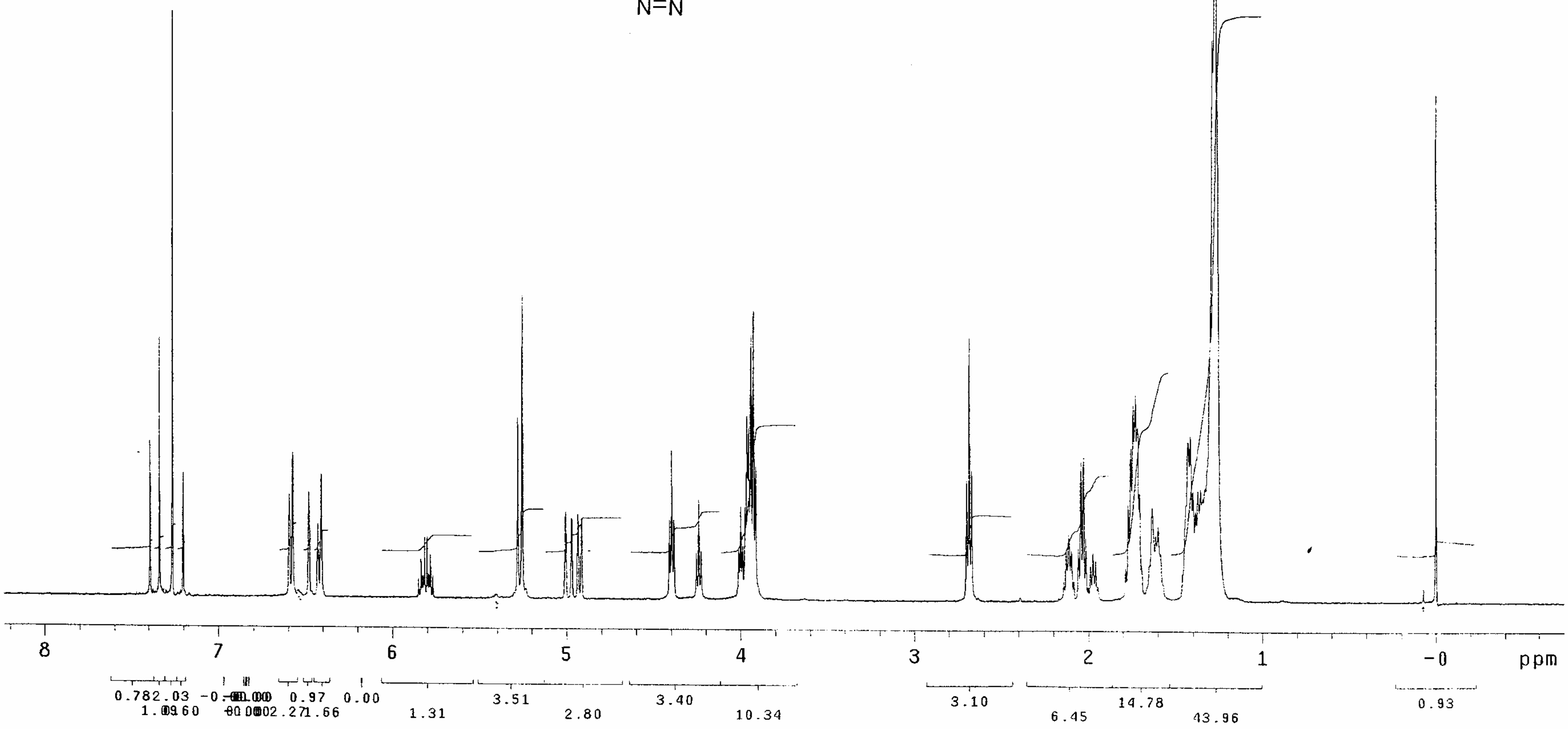
Automation directory:

Pulse Sequence: s2pul

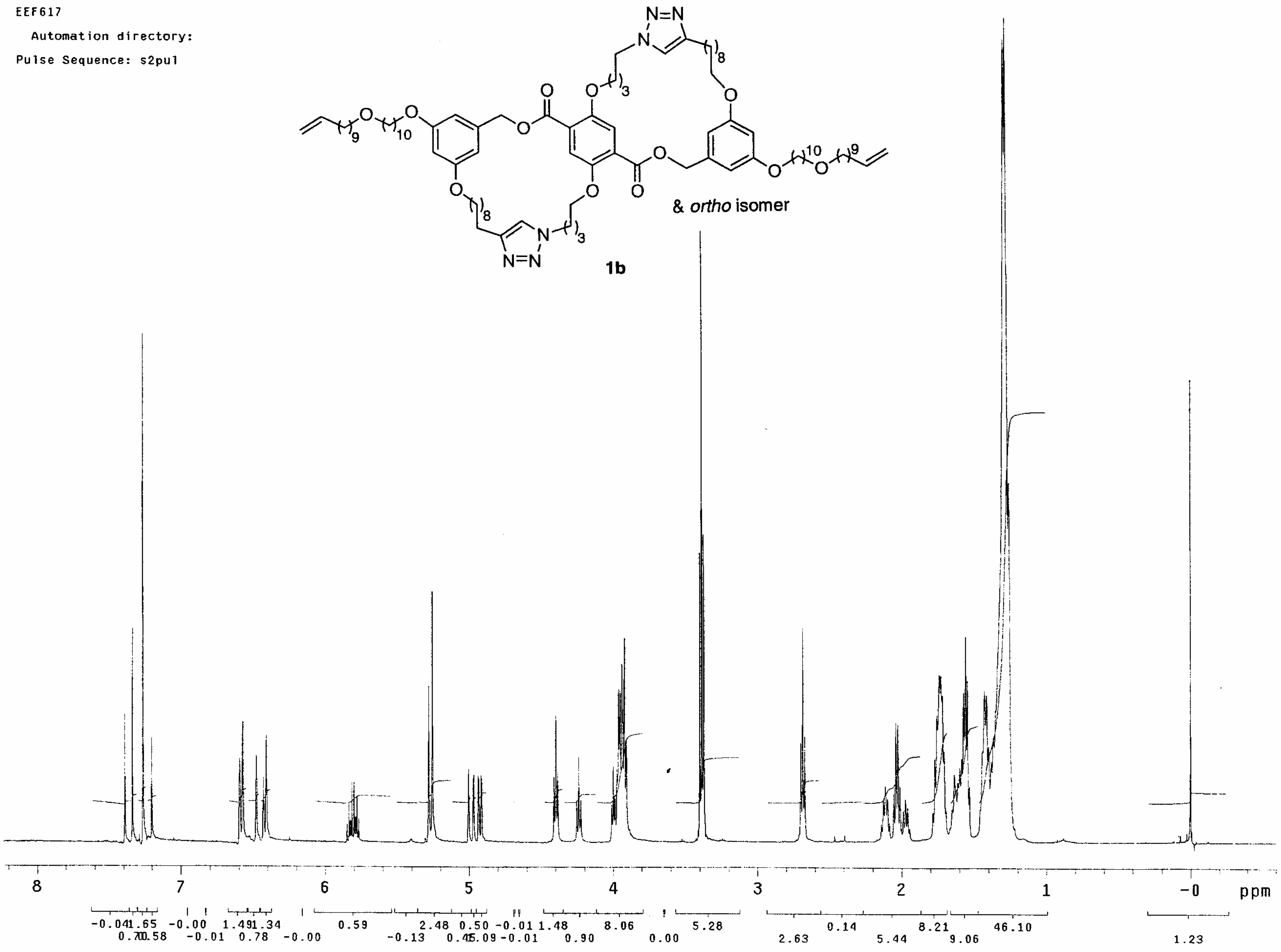


***m*-1a**

and *o*-1a isomer



EEF617
Automation directory:
Pulse Sequence: s2pul



1b

& *ortho* isomer