

Fluorous Click Chemistry as a Practical Tagging Method

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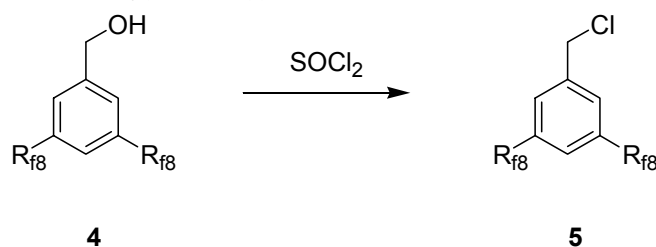
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General Information The ¹H and ¹³C NMR spectra were acquired on a Varian UNITY INOVA instrument (400 MHz and 100 MHz, respectively) and internally referenced to TMS or the residual proton solvent signal. Carbon multiplicities were determined by APT measurements, in some cases by 2D (HSQC and HMQC) experiments, or based on analogies. Infrared spectra were recorded on a Thermo Nicolet Avatar 320 FT-IR spectrometer and are reported in wavenumbers. Mass spectra and high resolution mass spectra were recorded by VG ZAB2-SEQ tandem mass spectrometer. Melting points were determined by a Büchi apparatus and are uncorrected. Thin layer chromatography (TLC) was carried out using Merck TLC aluminium sheets silica gel 60 F₂₅₄. All weights for small scale reactions were measured on a Mettler Toledo AX 105 DeltaRange®.

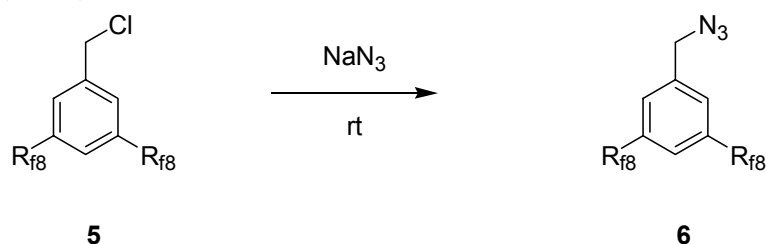
Phenylacetylene, 1-phenyl-2-propyn-1-ol, cinchonidine, thionyl chloride were purchased from Aldich and used as received. Fluorinert R (FC-77) and 1H,1H,2H,2H-perfluorodecyl iodide were purchased from Apollo and used as received. The fluorous reverse phase (FRP) silica was prepared according to literature procedure.¹

1-(Chloromethyl)-3,5-bis(heptadecafluorooctyl)benzene (5).



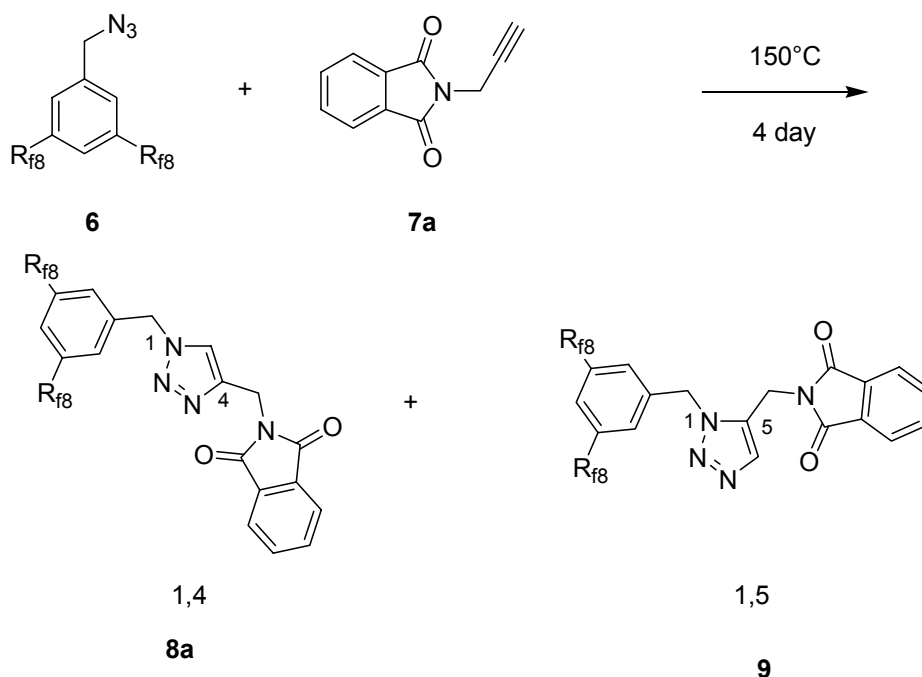
1.416 g (1.50 mmol) of alcohol **4** was refluxed overnight in 60 mL of thionyl chloride. The excess thionyl chloride was distilled off, the residue dissolved in CH₂Cl₂, washed with brine, dried over Na₂SO₄ and evaporated to dryness. Yield: 1.351 g (94 %). mp: 46-47 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.84 (s, 2H, Ar-H), 7.76 (s, 1H, Ar-H), 4.69 (s, 2H, CH₂); ¹³C NMR (partial, 100 Hz, CDCl₃) 139.9 (C), 130.9 (C, t, ²J_{FC} = 26 Hz), 130.5 (CH, t, ³J_{FC} = 7 Hz), 125.6 (CH, t, ³J_{FC} = 7 Hz), 44.3 (CH₂); IR (KBr) 1372, 1245, 1206, 1148, 1118 cm⁻¹; HRMS (EI, 70 eV) calcd. For(C₂₃F₃₄H₅Cl): 961.9537, found: 961.9515.

3,5-Bis(heptafluorooctyl)benzyl azide (6).



A round-bottom flask was charged with chloride **5** (963 mg, 1.0 mmol), sodium azide (650 mg, 10.0 mmol) and TBAB (32 mg, 0.1 mmol), 60 mL of DMF and 20 mL of diethyl ether was added, and stirred overnight at room temperature. The mixture was diluted with diethyl ether, washed with brine, dried over Na_2SO_4 and evaporated to dryness. The azide **6** was purified by column chromatography with hexane-ether 10:1, $R_f=0.85$. Yield: 900 mg (93%) white solid. mp: 28-29 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.77 (s, 3H, Ar-*H*), 4.56 (s, 2H, CH_2); ^{13}C NMR (partial, 100 Hz, CDCl_3) 138.1 (C), 130.8 (C, t, $^2J_{\text{FC}} = 26$ Hz), 129.6 (CH, t, $^3J_{\text{FC}}=7$ Hz), 125.2 (CH, t, $^3J_{\text{FC}}=7$ Hz), 53.5 (CH_2); IR (KBr) 2110, 1245, 1209, 1150, 1118, 664, 559 cm^{-1} . MS (EI, 70 eV) m/z (rel intensity) 950 ($[\text{M-F}]^+$, 10), 941 ($[\text{M-N}_2]^+$, 33), 927 ($[\text{M-N}_3]^+$, 37), HRMS (EI, 70 eV) calcd. for($\text{M-N}_2 = \text{C}_{23}\text{F}_{34}\text{H}_5\text{N}$): 940.9879, found: 940.9926.

Fluorous Thermal Huisgen Reaction of 6 and 7a.



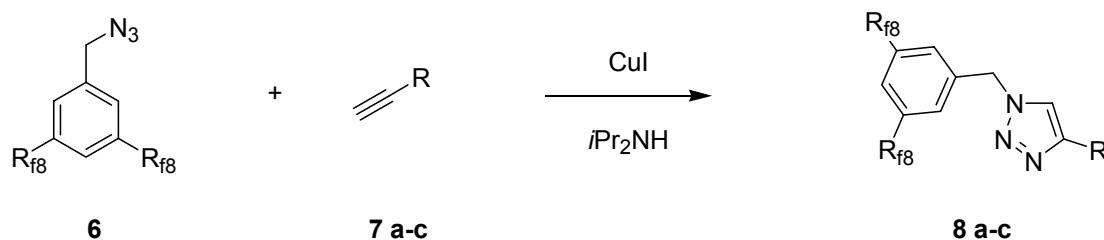
Under Ar atmosphere a Schlenk tube was charged with N-propargyl-phthalimide **7a** (46.0 mg, 0.25 mmol), 3 mL of DMF was added, stirred for a few minutes, and then azide **6** (193.8 mg, 0.20 mmol) was loaded. The mixture was stirred at 150 °C for four days. The mixture was cooled down, washed three times with FC-77, and the combined fluorous phase was evaporated. The regiochemistry and the peak assignment of the products was established by NOE experiments. The irradiation of the CH_2 protons at 5.95 ppm resulted in NOE enhancement of the triazole proton at 7.63 ppm and CH_2 protons at 4.81 ppm, suggesting the 1,5 substitution pattern for compound **9**. On

the other hand, the spatial proximity of the CH₂ protons at 5.64 ppm, the triazole proton at 7.69 ppm and the protons of the R_{f8} substituted aromatic ring at 7.71 ppm approved the 1,4 substitution in compound **8a**.

Data of the **9**: ¹H NMR (400 MHz, CDCl₃) δ 7.91 (s, 1H), 7.78 (m, 2H), 7.71 (m, 2H), 7.63 (br s, 3H), 5.95 (s, 2H), 4.81 (s, 2H).

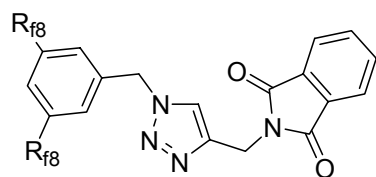
Data of the **8a**: ¹H NMR (400 MHz, CDCl₃) δ 7.84 (m, 2H), 7.79 (br s, 1H), 7.71 (m, 2H), 7.69 (s, 2H), 7.65 (s, 1H), 5.64 (s, 2H), 5.00 (s, 2H).

General procedure for the preparation of compounds **8a-c**.



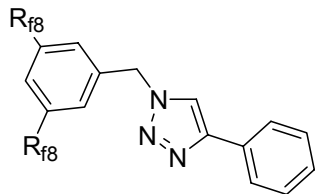
Under Ar atmosphere a Schlenk tube was charged with the corresponding acetylene **7a-c** (0.21 mmol), copper(I) iodide (1.90 mg, 0.01 mmol) and diisopropylamine (20.24 mg, 0.20 mmol). Then 3 mL of trifluoroethanol was added, stirred for a few minutes and azide **6** (193.8 mg, 0.20 mmol) were loaded. The mixture was stirred overnight at room temperature, diluted with diethyl ether, washed with brine and 1 % aqueous EDTA, dried over Na₂SO₄ and evaporated to dryness. The crude product was purified with Fluorous-SPE methodology. A short column packed with FRP silica¹ (2 g) was wetted with ether before washing with methanol/water 8/2. The crude product was loaded to this column. The column was first eluted with methanol/water 8/2 to remove organic compounds. Then the pure **8a-c** was washed out with methanol from the column and evaporated to dryness.

8a 2-({1-[3,5-Bis(heptafluorooctyl)benzyl]-1H-1,2,3-triazol-4-yl)methyl)-1H-isoindole-1,3-dione.



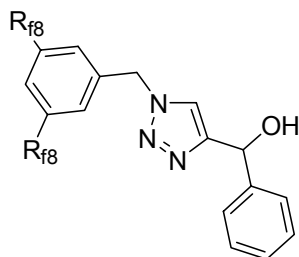
Yield: 215 mg (93%), white solid. mp: 106-107 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.84 (m, 2H, C₆H₄), 7.79 (br s, 1H, f-Ar-H), 7.71 (m, 2H, C₆H₄), 7.69 (s, 2H, f-Ar-H), 7.65 (s, 1H, Tr-H), 5.64 (s, 2H, Tr-CH₂-f-Ar), 5.00 (s, 2H, Tr-CH₂-N); ¹³C NMR (partial, 100 Hz, CDCl₃) δ 167.8 (C), 144.0 (C) 137.1 (C), 134.3 (CH), 132.2 (C), 131.3 (C, t, ²J_{FC} = 26 Hz), 130.0 (CH, t, ³J_{FC} = 7 Hz), 126.2 (CH, t, ³J_{FC} = 7 Hz), 123.7 (CH), 123.3 (CH), 53.2 (CH₂), 33.1 (CH₂); IR (KBr) 2932, 1715, 1219, 1145, 1115, 712 cm⁻¹; MS: (EI, 70 eV) *m/z* (rel intensity) 1154 (M⁺, 34), 1134 ([M-F]⁺, 24), 1126 ([M-N₂]⁺, 33), 1107 ([M-N₂-F]⁺, 11), 979 ([M-N₂-Pht]⁺, 86), 927 ([M-Pht-Tr]⁺, 100); HRMS (EI, 70 eV) calcd. for (C₃₄H₁₂F₃₄N₄O₂): 1154.0417, found: 1154.0360.

8b 1-[3,5-Bis(heptadecafluorooctyl)benzyl]-4-phenyl-1H-1,2,3-triazole.



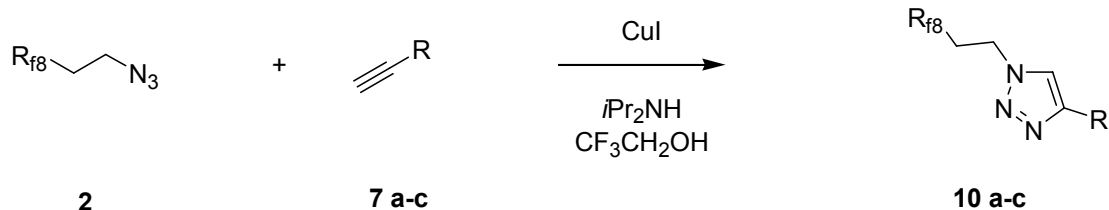
This product was purified by column chromatography with hexane-ether 10:1. Yield: 69 mg (32%), white solid. mp: 145-146 °C. ¹H NMR (400 MHz, CD₃COCD₃/CF₂ClCFCl₂ 1/1) δ 8.40 (s, 1H, f-Ar-H), 8.13 (s, 2H, f-Ar-H), 7.89 (s, 1H, Tr-H), 7.85 (m, 2H, Ar-H), 7.37 (m, 2H, Ar-H), 7.28 (m, 1H, Ar-H), 5.98 (s, 2H, Tr-CH₂-f-Ar); ¹³C NMR² (partial, 100 Hz, CD₃COCD₃/CF₂ClCFCl₂ 1/1) δ 149.0 (C), 148.2 (C), 139.0 (C), 131.2 (CH), 131.0 (C), 129.0 (CH), 128.0 (CH), 125.8 (CH), 125.3 (CH), 121.0 (CH), 52.8 (CH₂). IR (KBr) 2924, 2854, 1245, 1205, 1145, 1116, 650 cm⁻¹; MS (EI, 70 eV) *m/z* (rel intensity) 1071 (M⁺, 65), 1052 ([M-F]⁺, 54), 1043 ([M-N₂]⁺, 66), 1042 ([M-N₂-H]⁺, 78), 927 ([M-Ph-Tr]⁺, 100); HRMS (EI, 70 eV) calcd. for (C₃₁H₁₁F₃₄N₃): 1071.0410, found: 1071.0454.

8c {1-[3,5-bis(heptadecafluorooctyl)benzyl]-1H-1,2,3-triazol-4-yl}(phenyl)methanol.



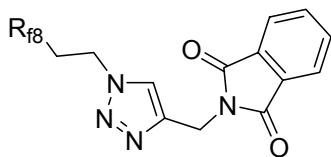
Yield: 190 mg (86%), white solid. mp: 109-110 °C, ¹H NMR (400 MHz, CDCl₃/CF₂ClCFCl₂ 1/1) δ 7.80 (s, 1H, f-Ar-H), 7.67 (s, 2H, f-Ar-H), 7.42 (d, *J* = 6 Hz, 2H, Ar-H), 7.33 (t, *J* = 6 Hz, 2H, Ar-H), 7.30 (t, *J* = 6 Hz, 1H, Ar-H), 7.27 (s, 1H, Tr-H), 6.03 (s, 1H, Tr-CH(OH)-Ar), 5.63 (s, 2H, Tr-CH₂-f-Ar); ¹³C NMR² (partial, 100 Hz, CDCl₃/CF₂ClCFCl₂ 1/1) δ 153.1 (C), 142.4 (C), 137.5 (C), 130.1 (CH), 129.0 (CH), 128.2 (CH), 126.9 (CH), 126.5 (CH), 121.3 (CH), 69.9 (CH), 53.4 (CH₂); IR (KBr) 2920, 1249, 1219, 1146, 1116, 711, 650, 558 cm⁻¹; MS: (EI, 70 eV) *m/z* (rel intensity) 1101 (M⁺, 19), 1082 ([M-F]⁺, 20), 1073 ([M-N₂]⁺, 100), 1056 ([M-45]⁺, 48), 994 ([M-107]⁺, 22), 927 ([M-Ph-Tr]⁺, 89); HRMS (EI, 70 eV) calcd. for (C₃₂H₁₃F₃₄N₃O): 1101.0516, found: 1101.0559.

General procedure for the preparation of compounds 10a-c.



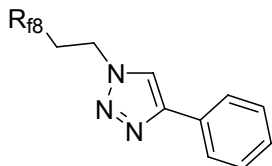
Under Ar atmosphere a Schlenk tube was charged with the correspondig acetylene **7a-c** (0.21 mmol), copper(I) iodide (1.90 mg, 0.01 mmol) and diisopropylamine (20.24 mg, 0.20 mmol). Then 3 mL of trifluoroethanol was filled in, stirred for a few minutes and azide **2** (97.8 mg, 0.20 mmol) were loaded. The mixture was stirred overnight at room temperature, diluted with diethyl ether, washed with brine, and 1 % aqueous EDTA, dried over Na₂SO₄ and evaporated to dryness. The crude product was purified with Fluorous-SPE methodology. A short column packed with FRP silica¹ (2 g) was wetted with ether before washing with methanol/water 8/2. The crude product was loaded to this column. The column was first eluted with methanol/water 8/2 to remove organic compounds. Then the pure **10a-c** was washed out from the column with methanol and evaporated to dryness.

10a 2-[1-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10-Heptadecafluorodecyl)-1H-1,2,3-triazol-4-yl]methyl]-1H-isoindole-1,3(2H)-dione.



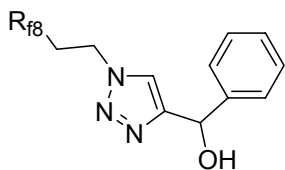
Yield: 130 mg (96%), white solid. mp: 130-131 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.86 (m, 2H, C_6H_4), 7.72 (m, 2H, C_6H_4), 7.64 (s, 1H, Tr-*H*), 5.00 (s, 2H, Tr- CH_2 -N), 4.62 (t, $J = 7$ Hz, 2H, Tr- CH_2), 2.81 (m, 2H, CH_2CF_2); ^{13}C NMR (partial, 100 Hz, CDCl_3) 167.8 (C), 143.4 (C), 134.3 (CH), 132.2 (C), 123.7 (CH), 123.6 (CH), 42.5(CH_2), 33.1 (CH_2), 32.1 (CH_2 , $^2J_{\text{FC}} = 21$ Hz); IR (KBr) 2927, 2854, 1715, 1201, 1143, 1107, 714, 529 cm^{-1} ; MS (EI, 70 eV) m/z (rel intensity) 674 (M^+ , 30), 655 ($[\text{M}-\text{F}]^+$, 15) 646 ($[\text{M}-\text{N}_2]^+$, 65), 213 ($[\text{M}-\text{N}_2-\text{R}_{18}-\text{CH}_2]^+$, 25), 199 ($[\text{M}-\text{N}_2-\text{R}_{18}-\text{CH}_2-\text{CH}_2]^+$, 28), 173 ($[\text{M}-\text{N}_2-\text{R}_{18}-\text{CH}_2-\text{CH}_2-\text{CN}]^+$, 100); HRMS (EI, 70 eV) calcd. for ($\text{C}_{21}\text{H}_{11}\text{F}_{17}\text{N}_4\text{O}_2$): 674.0611, found: 674.0606

10b 1-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptafluorodecyl)-4-phenyl-1H-1,2,3-triazole.



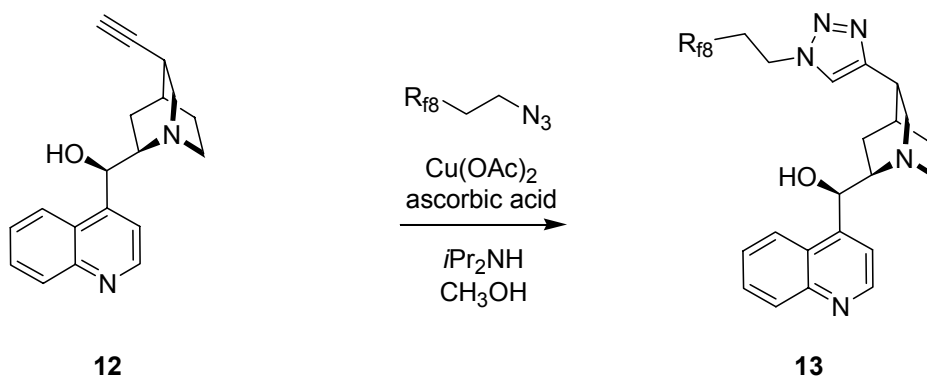
This product was purified by column chromatography with hexane-ether 10:1. Yield: 81 mg (69%), white solid. mp: 148-149 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.83 (d, $J = 8$ Hz, 2H, Ar-*H*), 7.81 (s, 1H, Tr-*H*), 7.43 (t, $J = 8$ Hz, 2H, Ar-*H*), 7.35 (t, $J = 8$ Hz, 1H, Ar-*H*), 4.73 (t, $J = 7$ Hz, 2H, Tr- CH_2), 2.88 (m, 2H, CH_2CF_2); ^{13}C NMR (partial, 100 Hz, CDCl_3) 148.4 (C), 130.2 (C), 129.1 (CH), 128.6 (CH), 126.0 (CH), 120.1 (CH), 42.5 (CH_2), 32.1 (CH_2) (t, $^2J_{\text{FC}} = 21$ Hz); IR (KBr) 3123, 3094, 1339, 1206, 1146, 1115, 1098, 986, 970, 768, 706, 693, 678, 663 cm^{-1} ; MS (EI, 70 eV) m/z (rel intensity) 591 (M^+ , 20), 572 ($[\text{M}-\text{F}]^+$, 15) 563 ($[\text{M}-\text{N}_2]^+$, 62), 144 ($[\text{M}-\text{R}_{18}-\text{CH}_2-\text{CH}_2]^+$, 30), 116 ($[\text{M}-\text{R}_{18}-\text{CH}_2-\text{CH}_2-\text{N}_2]^+$, 100); HRMS (EI, 70 eV) calcd. for ($\text{C}_{18}\text{H}_{10}\text{F}_{17}\text{N}_3$): 591.0603, found: 591.0622.

10c [1-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptafluorodecyl)-1H-1,2,3-triazol-4-yl] (phenyl)methanol.

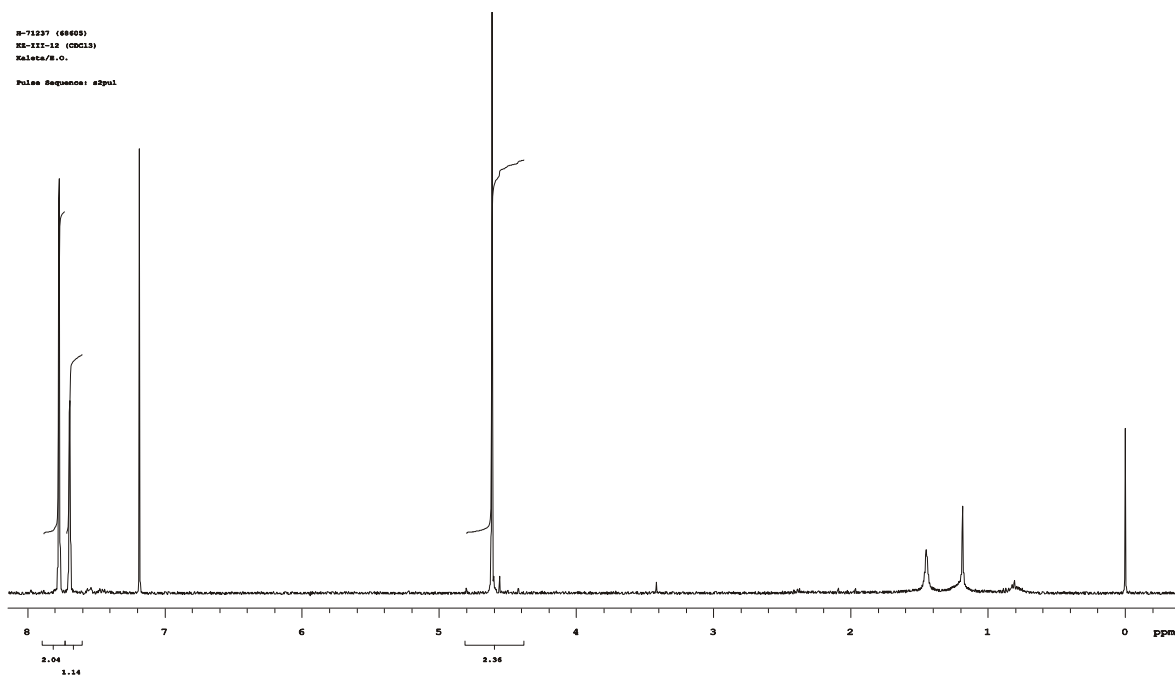


Yield: 114 mg (92%), white solid. mp: 103-104 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.45 (m, 2H, Ar-*H*), 7.38 (m, 2H, Ar-*H*), 7.32 (s, 1H, Tr-*H*), 7.30 (m, 1H, Ar-*H*), 6.03 (s, 1H, Tr- $\text{CH}(\text{OH})-\text{Ph}$), 4.62 (t, $J = 7$ Hz, 2H, Tr- CH_2), 3.20 (br s, 1H, OH), 2.81 (m, 2H, CH_2CF_2); ^{13}C NMR (partial, 100 Hz, CDCl_3) 152.0 (C), 141.9 (C), 128.9 (CH), 128.3 (CH), 126.5 (CH), 121.9 (CH), 69.3 (CH), 42.5 (CH_2), 32.0 (CH_2) (t, $^2J_{\text{FC}} = 21$ Hz); IR (KBr) 2926, 1202, 1148, 1117, 1042, 705, 662, 530 cm^{-1} ; MS (EI, 70 eV) m/z (rel intensity) 621 (M^+ , 44), 602 ($[\text{M}-\text{F}]^+$, 22) 593 ($[\text{M}-\text{N}_2]^+$, 67), 592 ($[\text{M}-\text{N}_2-\text{H}]^+$, 95), 576 ($[\text{M}-\text{N}_2-\text{OH}]^+$, 60), 515 (M^+-106 , 29), 174 ($[\text{M}-\text{R}_{18}-\text{CH}_2-\text{CH}_2]^+$, 50), 102 (M^+-519 , 100); HRMS (EI, 70 eV) calcd. for ($\text{C}_{19}\text{H}_{12}\text{F}_{17}\text{N}_3\text{O}$): 621.0709, found: 621.0723.

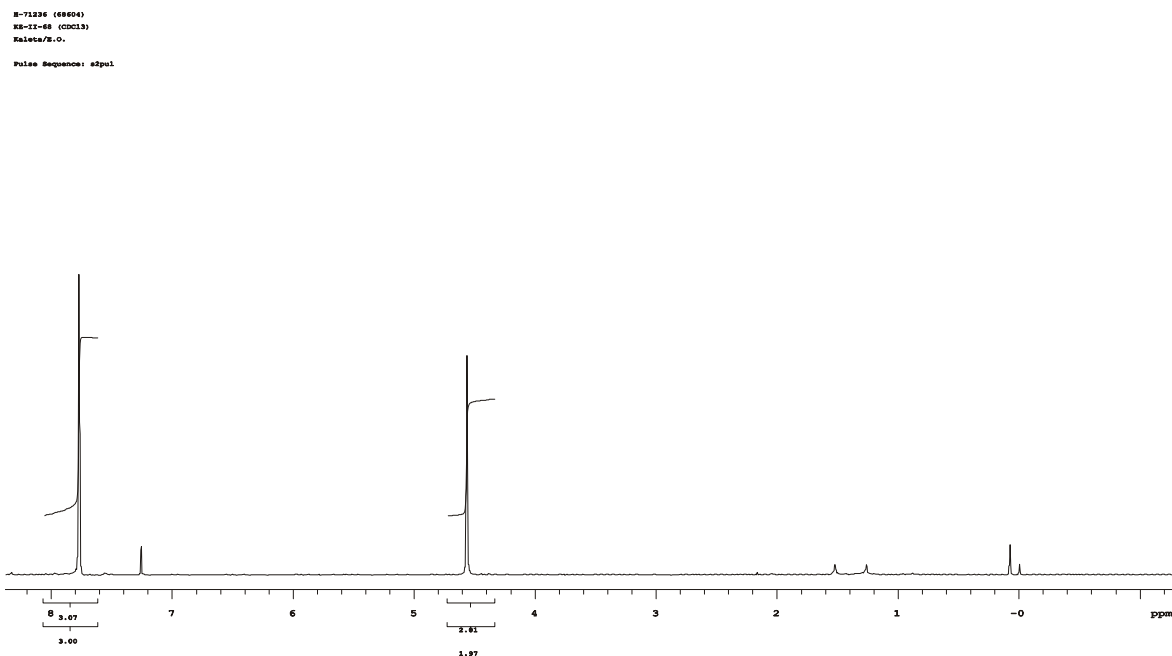
Preparation of fluoros cinchonidine 13.



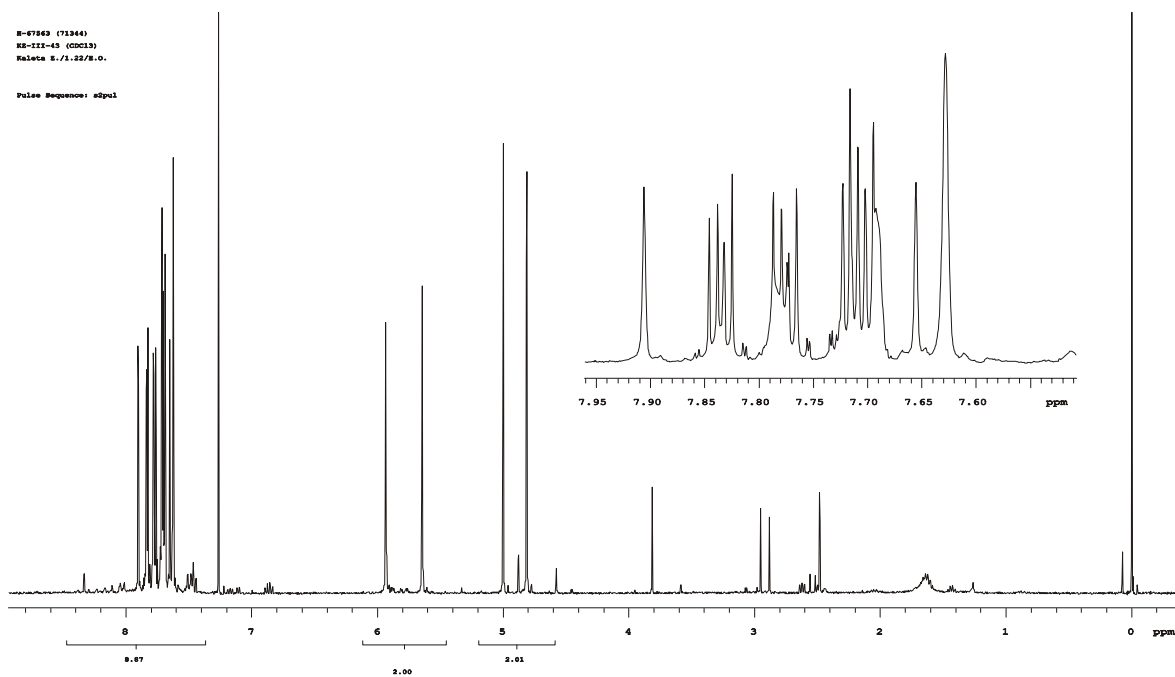
Under Ar atmosphere a Schlenk tube was charged with the didehydrocinchonidine **12** (61.40 mg, 0.21 mmol), copper(II) acetate (1.80 mg, 0.01 mmol) and diisopropylamine (40.48 mg, 0.40 mmol). Then 5 mL of methanol was added, stirred for a few minutes and azide **9** (97.8 mg, 0.20 mmol) and ascorbic acid (7.04 mg, 0.04 mmol) were loaded. The mixture was stirred overnight at room temperature, diluted with diethyl ether, washed with brine and 1 % aqueous EDTA, dried over Na₂SO₄ and evaporated to dryness. The crude product was washed with 1 mL of ethylacetate and dried to afford **13** as a white solid. Yield: 148 mg (95%), mp: 164-166 °C; ¹H NMR (400 MHz, CD₃OD) δ 8.76 (d, *J* = 4 Hz, 1H), 8.24 (d, *J* = 8.5 Hz, 1H), 8.03(d, *J* = 8 Hz, 1H), 7.81 (s, 1H), 7.74 (dd, *J* = 8.5, 8 Hz, 1H), 7.69 (d, *J* = 4 Hz, 1H), 7.64 (t, *J* = 8 Hz, 1H), 5.70 (d, *J* = 4 Hz, 1H), 4.60 (t, *J* = 7 Hz, 2H, CH₂-CH₂-CF₂), 3.70 (m, 1H), 3.37 (m, 1H), 3.22 (m, 2H), 3.15 (m, 1H), 2.80 (m, 1H), 2.70 (m, 2H, CH₂-CH₂-CF₂), 2.05 (br s, 1H), 1.90 (m, 2H), 1.78 (m, 1H), 1.30 (m, 1H). ¹³C NMR (partial, 100 Hz, CD₃OD) 150.8 (C), 150.5 (C), 149.6 (CH), 147.6 (C), 129.4 (CH), 128.8 (CH), 127.0 (CH), 125.9 (C), 123.4 (CH), 122.3 (CH), 118.8 (CH), 70.7 (CH), 60.4 (CH), 55.6 (CH₂) 42.9 (CH₂), 42.1 (CH₂), 32.8 (CH), 30.9 (CH₂), 28.0 (CH), 26.5 (CH₂), 20.9 (CH₂); IR (KBr) 3412, 3268, 2937, 2566, 1508, 1463, 1242, 1202, 1146, 657, cm⁻¹; MS (EI, 70 eV) *m/z* (rel intensity) 781 (M⁺, 100), 762 ([M-F]⁺, 17) 623 ([M-158]⁺, 60), 595 ([M-158-N₂]⁺, 51), 159 ([M-623]⁺, 40); HRMS (EI, 70 eV) calcd. for (C₂₉H₂₄F₁₇N₅O): 781.1709, found: 781.1692.



¹H-NMR spectra of **5**

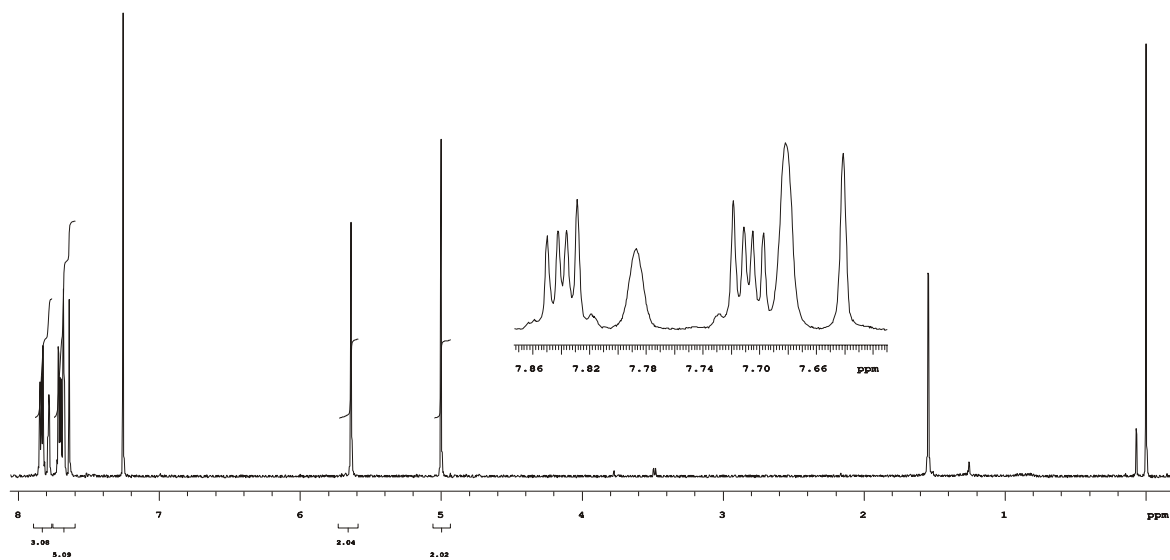


¹H-NMR spectra of **6**



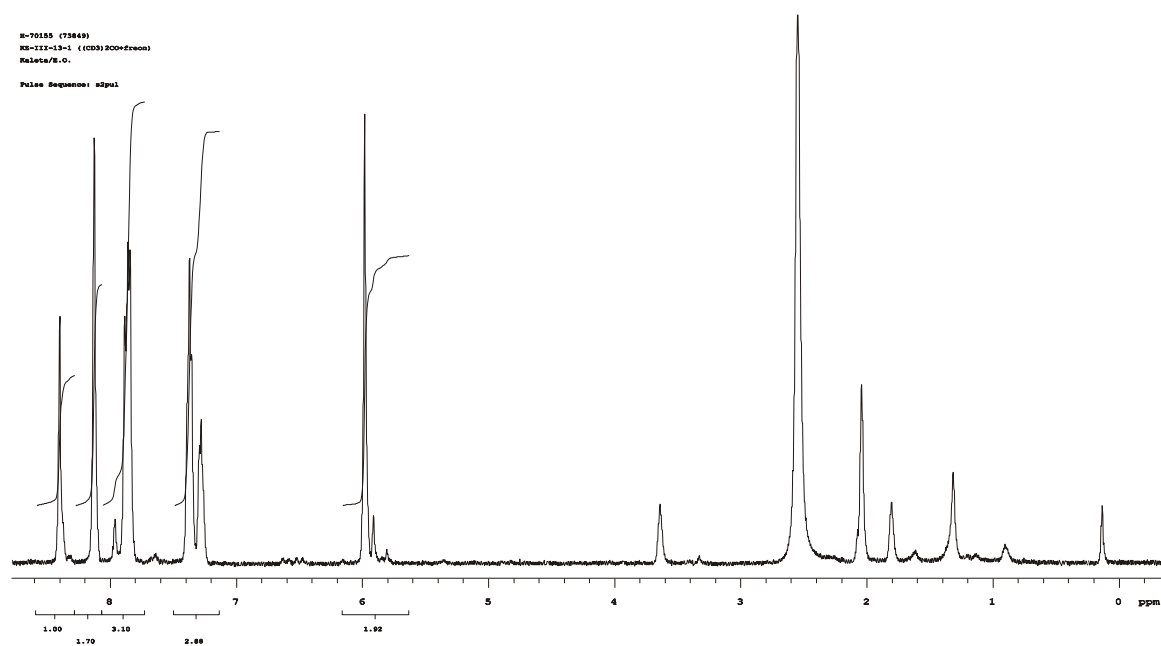
$^1\text{H-NMR}$ spectra of **8a+9**

H-71260
MS-III-13-1 (CDCl₃)
Kaleta/R.O.
Pulse Sequence: s2puls



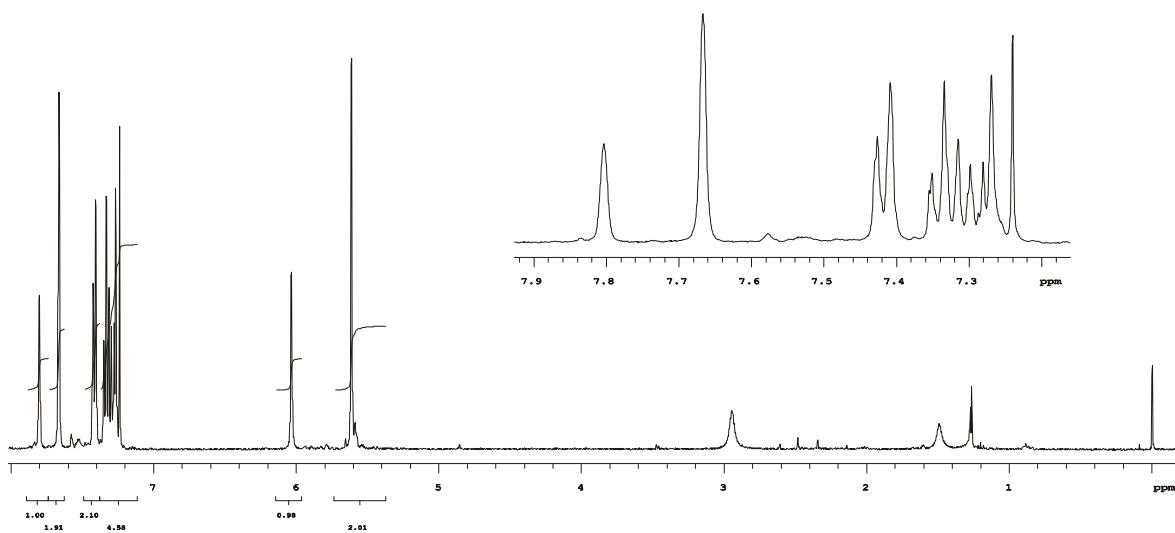
¹H-NMR spectra of **8a**

H-70155 (73849)
MS-III-13-1 ((CD₃)₂SO-d₆)
Kaleta/R.O.
Pulse Sequence: s2puls



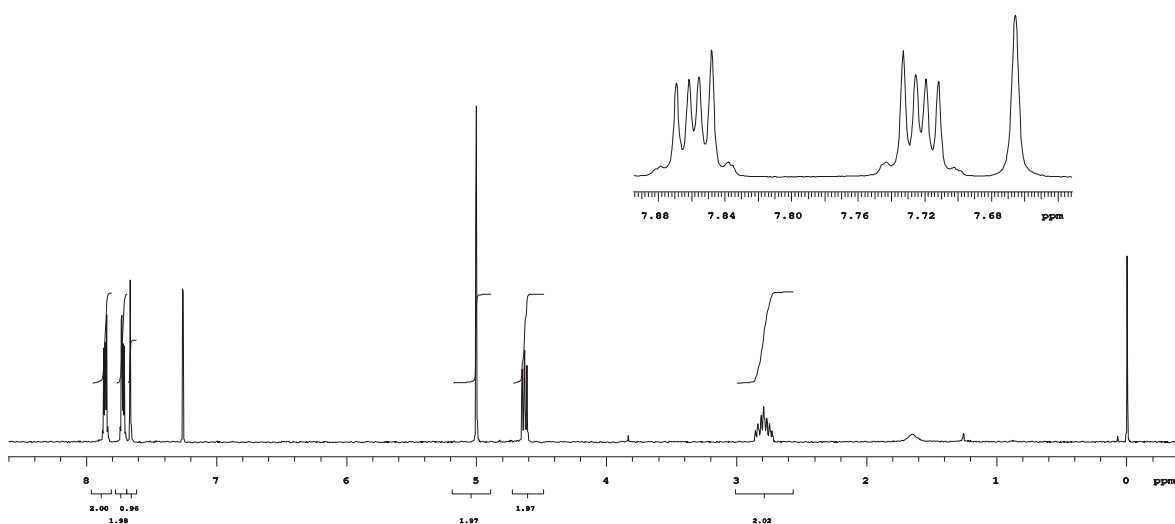
¹H-NMR spectra of **8b**

S-70110 (75882)
HE-111-14-1 (CDCl₃+TMS)
Malate/H₂O.
Pulse Sequence: s2pul



¹H-NMR spectra of **8c**

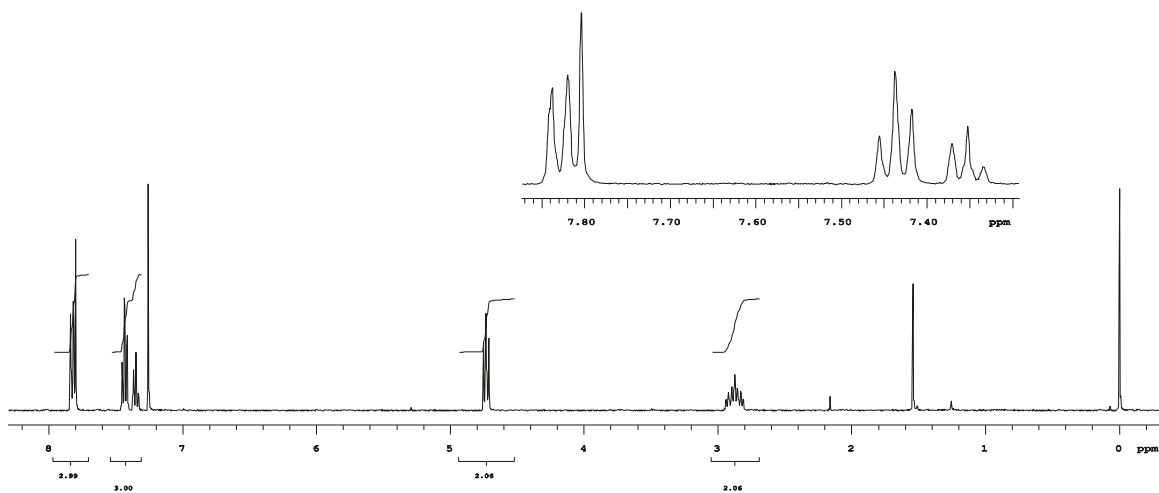
S-71299
HE-111-15-2 (CDCl₃)
Malate/H₂O.
Pulse Sequence: s2pul



¹H-NMR spectra of **10a**

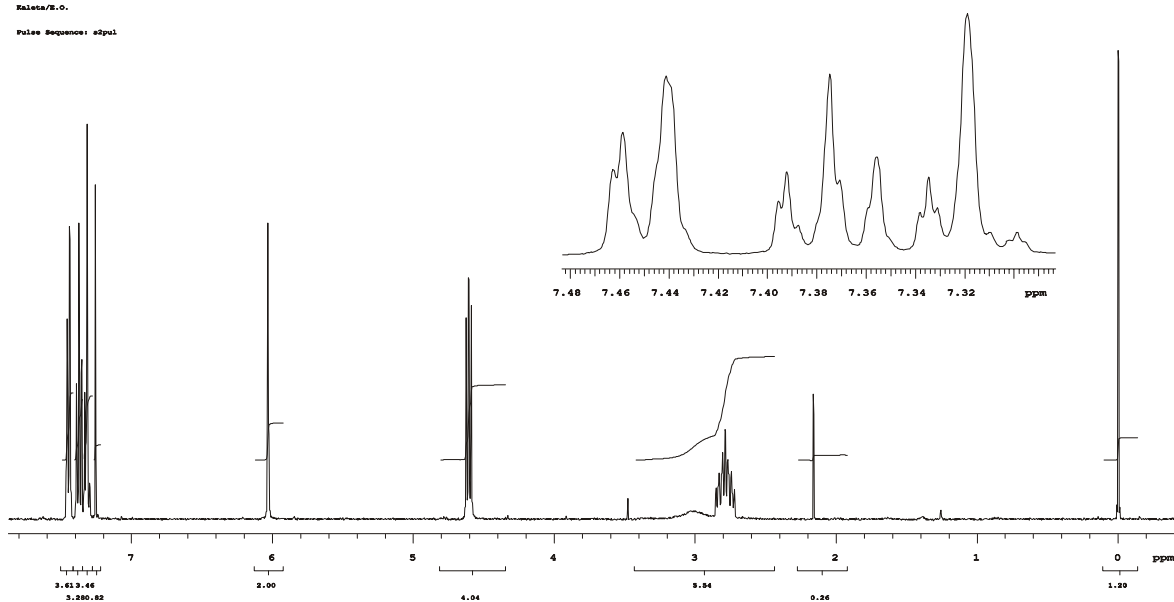
Electronic Supplementary Material for Organic & Biomolecular Chemistry
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S-71261
MS-111-13-2 (CDCl₃)
Malata/S.O.
Pulse Sequence: s2pul

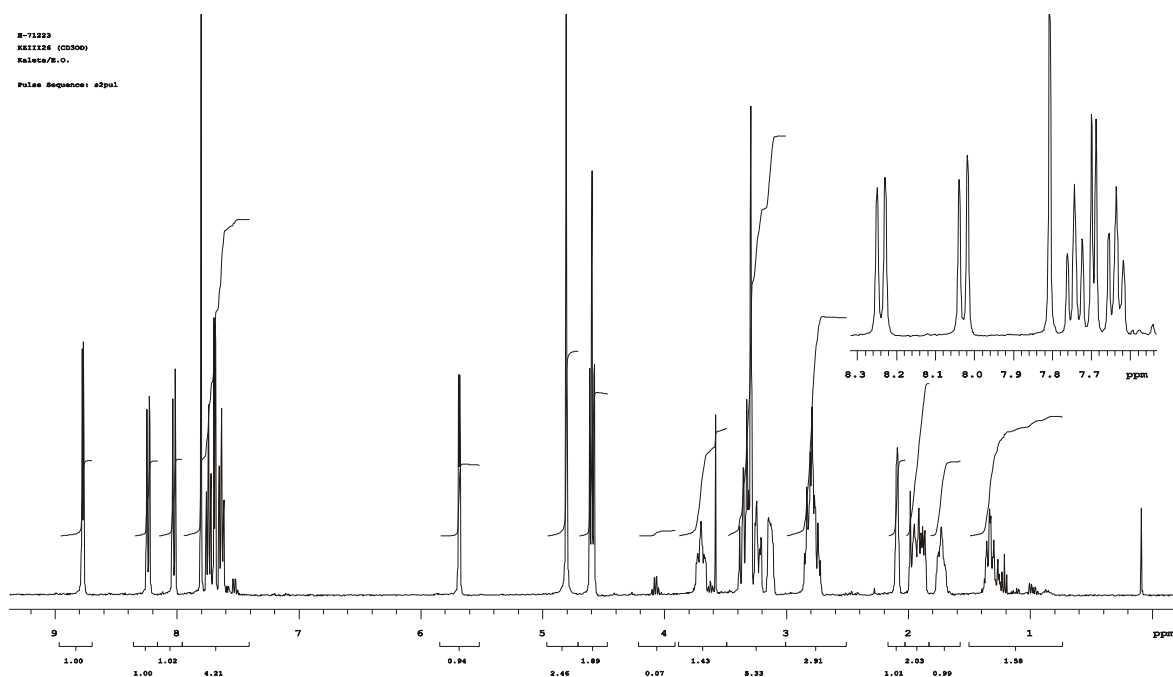


¹H-NMR spectra of **10b**

S-71233 (69907)
MS-111-14-2 (CDCl₃)
Malata/S.O.
Pulse Sequence: s2pul



¹H-NMR spectra of **10c**



¹H-NMR spectra of **13**

¹ S.Kainz, Z. Luo, D. P. Curran, W. Leitner, *Synthesis*, 1998, 1425.

² Compound **8b** and **8c** were poorly soluble, only very dilute solution of them in CD₃COCD₃ or CDCl₃ +CF₂ClCFCl₂ mixture could be prepared. Instead of the direct ¹³C detection of the ¹³C spectra the more sensitive inverse ¹H detection has been applied. Carbon assignments were based on heteronuclear 2D NMR measurements (HSQC, HMQC). For cpd. **8c** the quaternary carbon atoms adjacent to R₈ chains could not be detected, they were probably hidden by other signals, as the resolution in f2 dimension was insufficient for the detection of closely appearing carbon resonances.