Electronic Supporting Information

Cyclic β-hydroxy-α-nitrosulfone isomers readily equilibrate via open-chain aldehyde forms

Peter A. Wade,[a]* Ruchi Tandon[a] and Patrick J. Carroll[b]
*wadepa@drexel.edu

[a] Department of Chemistry, Drexel University, Philadelphia, PA 19104
[b] Department of Chemistry, University of Pennsylvania, Philadelphia, PA 19104

Table of Contents

1. Supplemental Figures

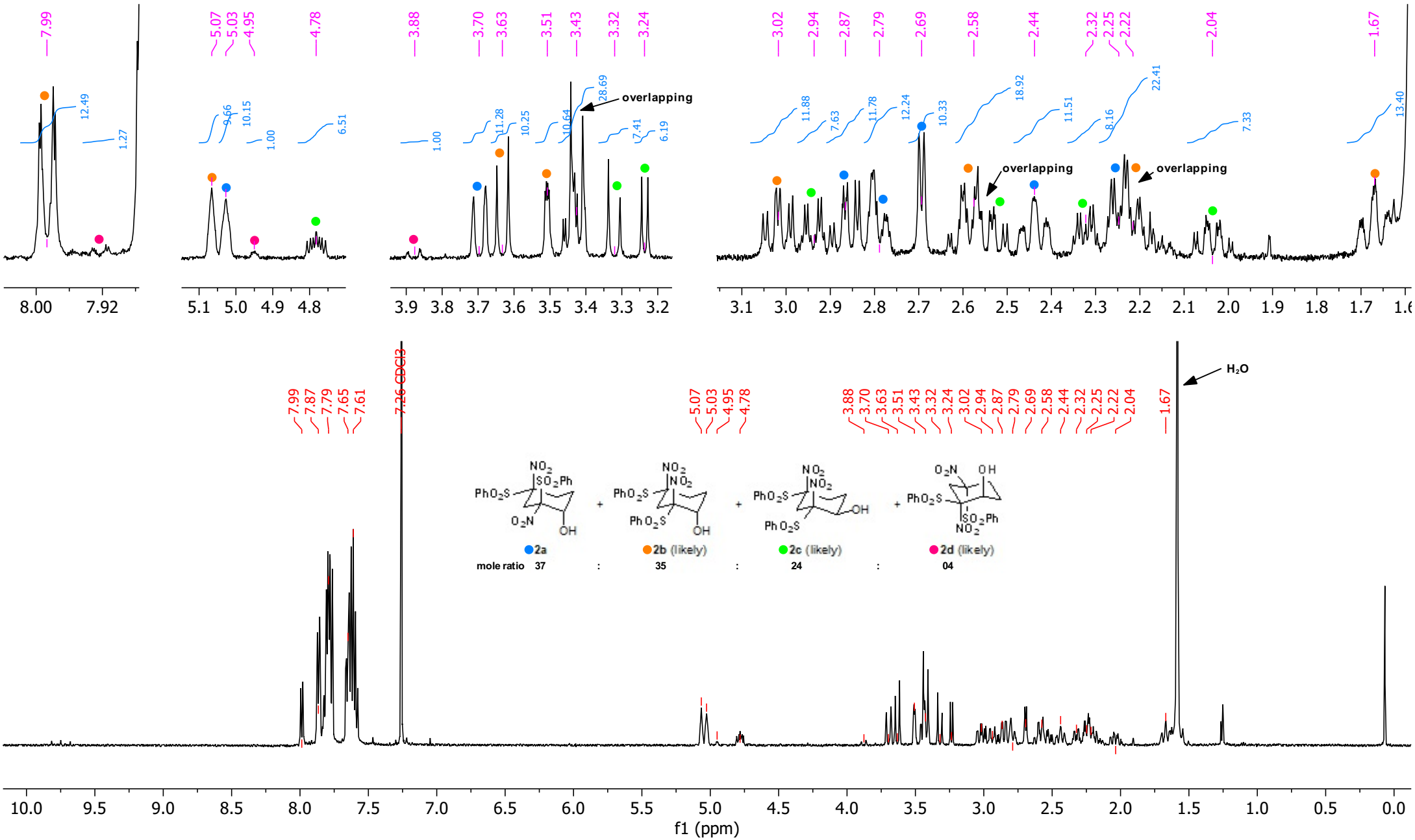


Fig. S1. ^{1}H NMR Spectra (500 MHz, $CDCl_3$) for a crude mixture of **2a-d**. Mole ratio of **2a**/**2b**/**2c**/**2d** is 37:35:24:04 as determined by integration of H-1 signals. Top: expansions. Bottom: spectrum. The chemical shifts are shown as δ_H values.

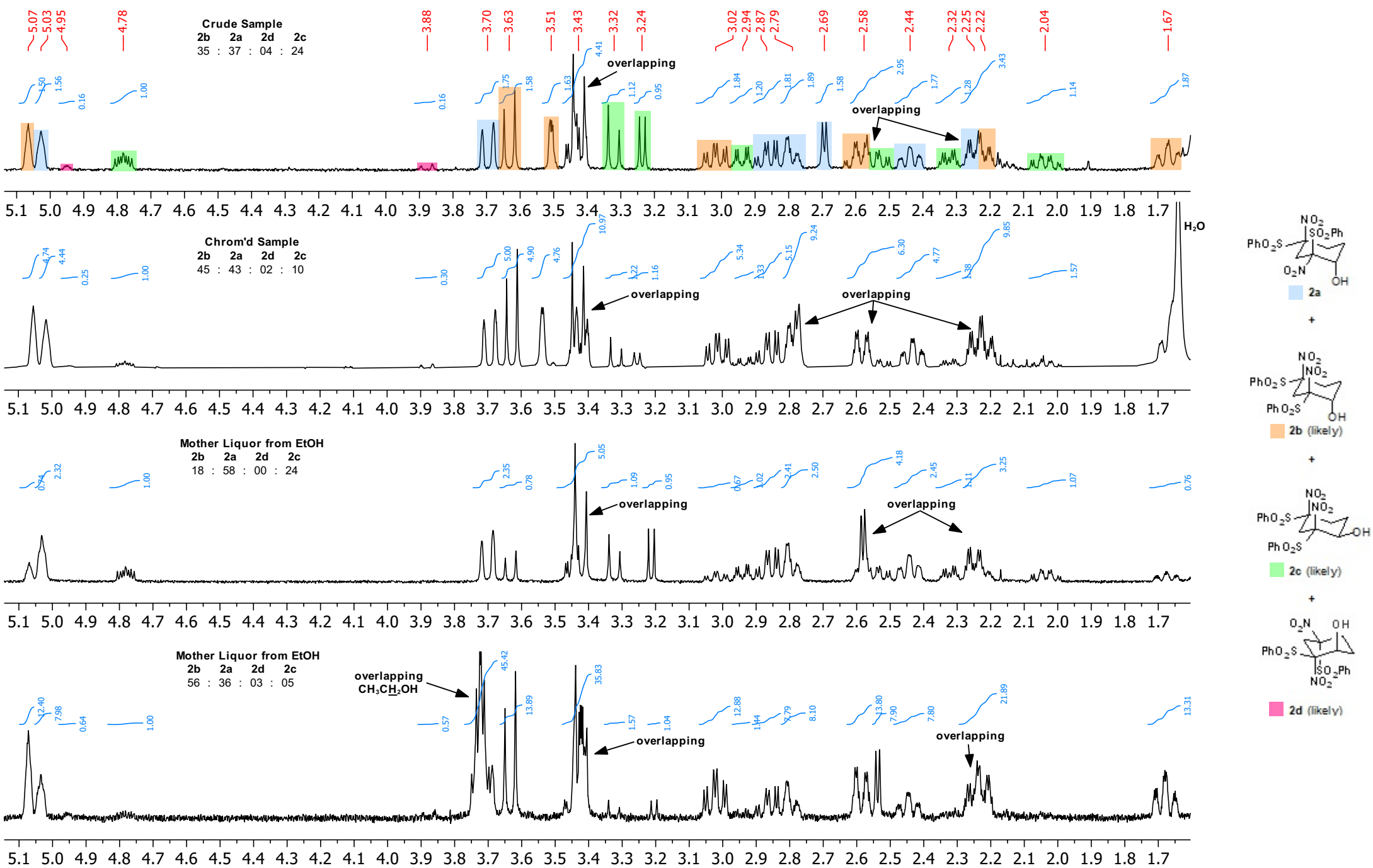


Fig. S2. Stacked ^{1}H NMR Spectra (500 MHz, $CDCl_3$) δ 1.7-5.1 region for mixtures of **2a-d**. Mole ratio of **2a**/**2b**/**2c**/**2d** is shown above each spectrum. Assigned signals are indicated by color. Top spectrum is shown in Fig. 2a of the article.

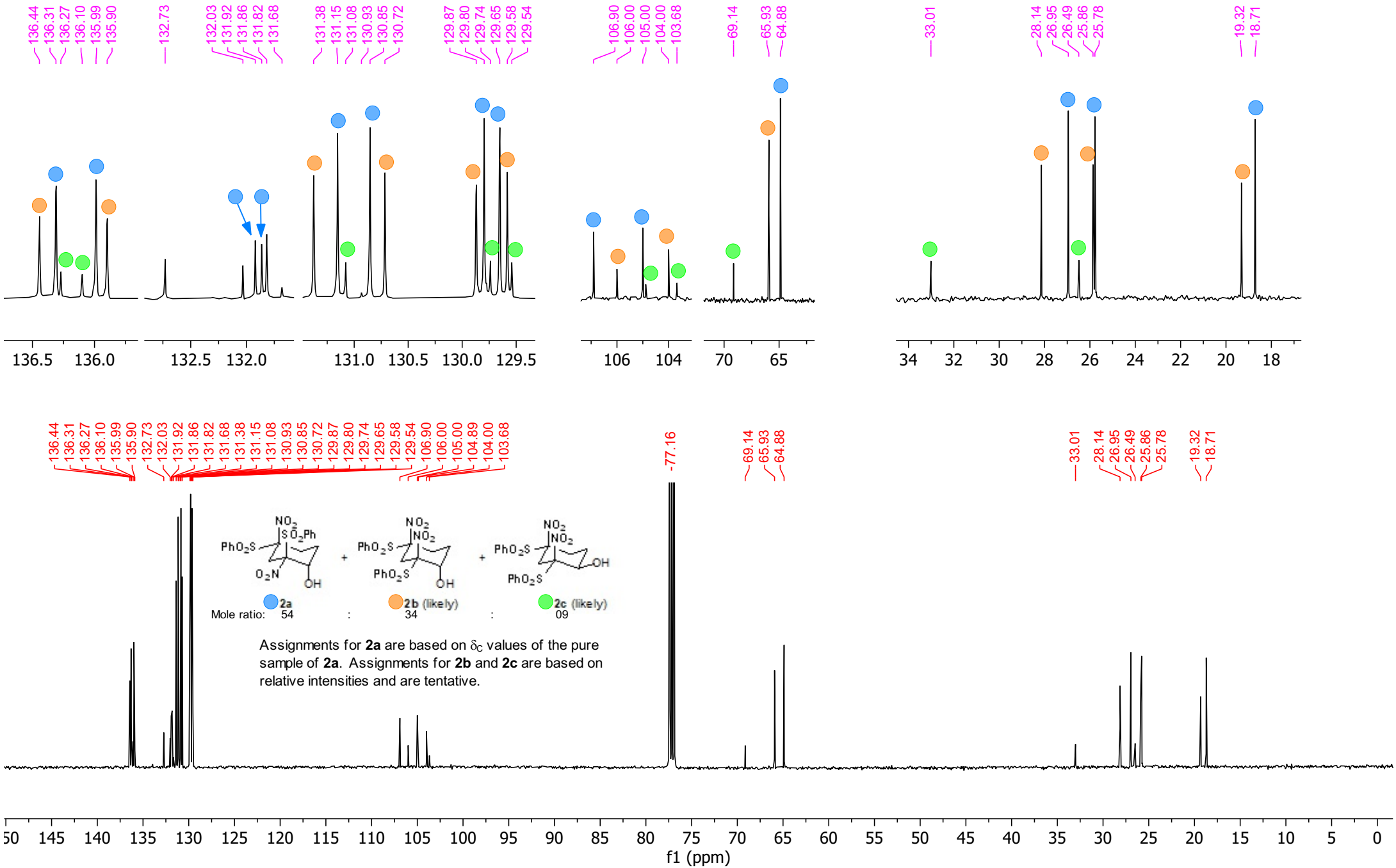


Fig. S3. ^{13}C NMR Spectra (126 MHz, $CDCl_3$) for a crude mixture of **2a-d**. Mole ratio of **2a**/**2b**/**2c**/**2d** is 54:34:09:03, respectively, as determined by ^{1}H NMR. Top: expansions. Bottom: spectrum. The chemical shifts are shown as δ_C values .

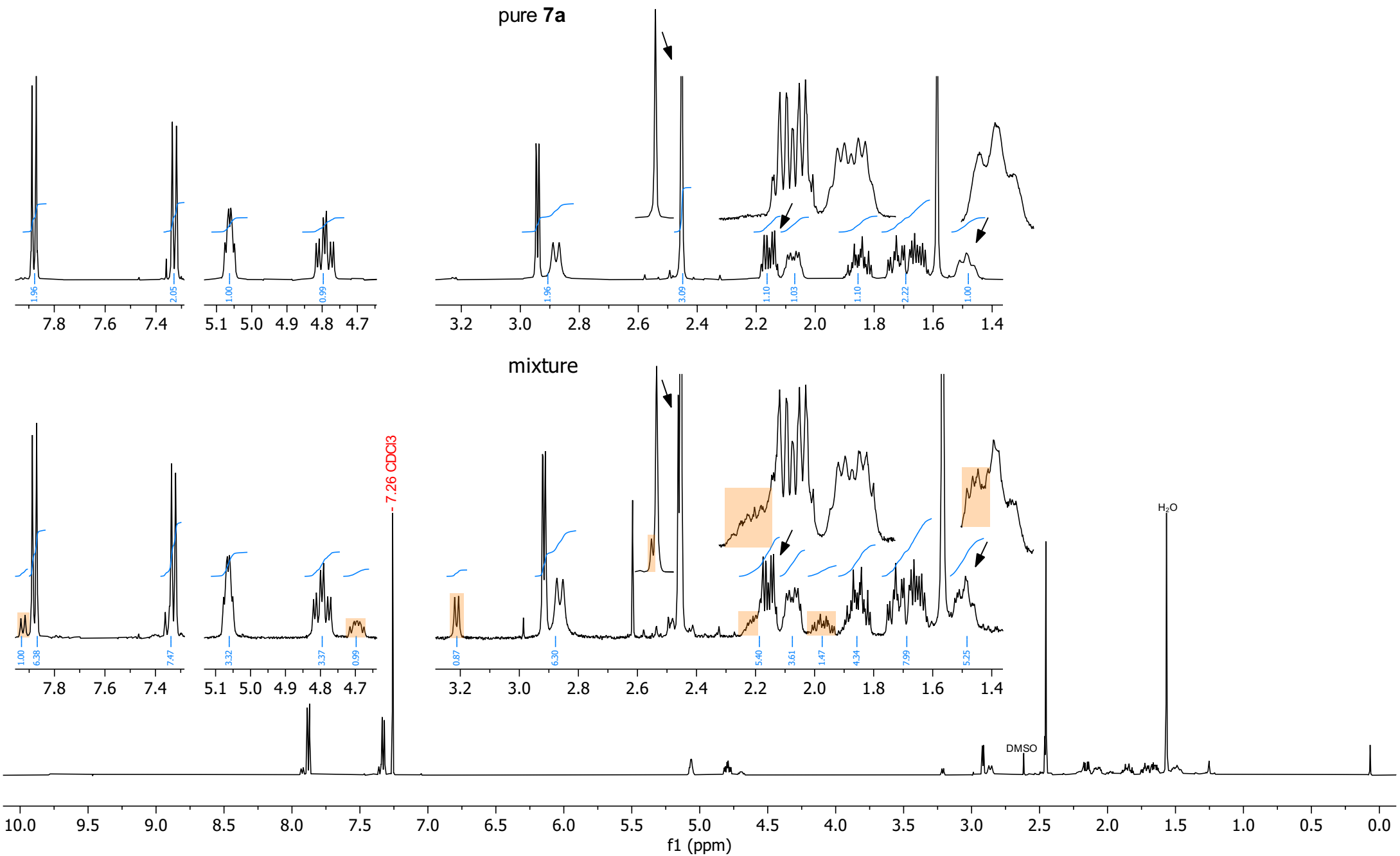


Fig. S4. ^{1}H NMR Spectra (500 MHz, $CDCl_3$). Top: pure **7a**. Bottom: crude mixture of predominantly **7a-b** obtained from DMSO isomerization of **7a**. Mole ratio of **7a**/**7b**/**7c**/**9a-d** is 85:13:01:01. Signals attributed to **7b** are highlighted in orange.

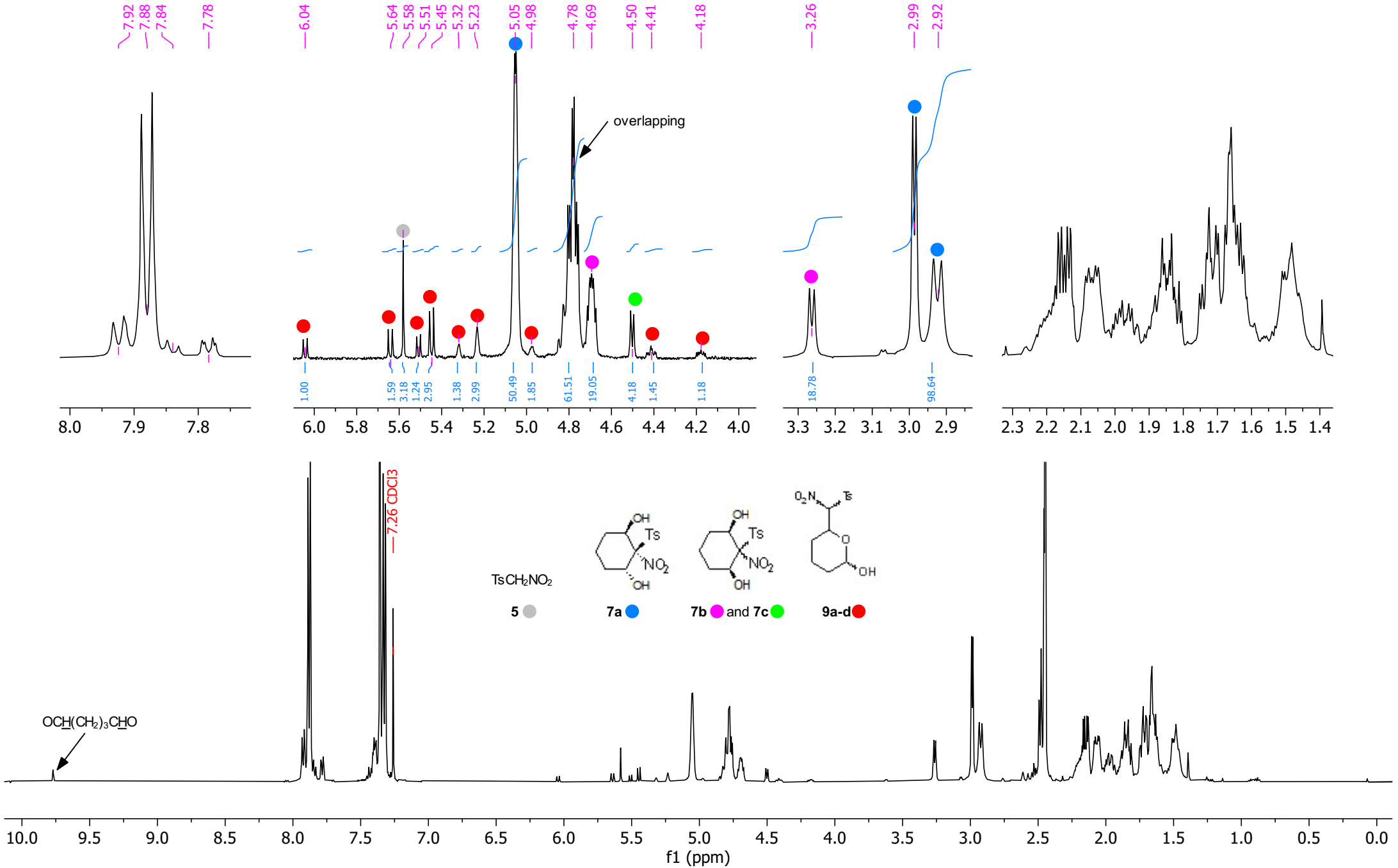


Fig. S5. ^{1}H NMR Spectra (500 MHz, $CDCl_3$) of a chrom'd mixture of **5**, **7a-c** and **9a-d**. Mole ratio **5**/**7a**/**7b**/**7c**/**9a**/**9b**/**9c**/**9d** is 02:72:13:03:01:02:02:04. Top: expansions. Assigned signals are shown in color. Fig. 5 of the main document is based on the second expansion. Bottom: spectrum.

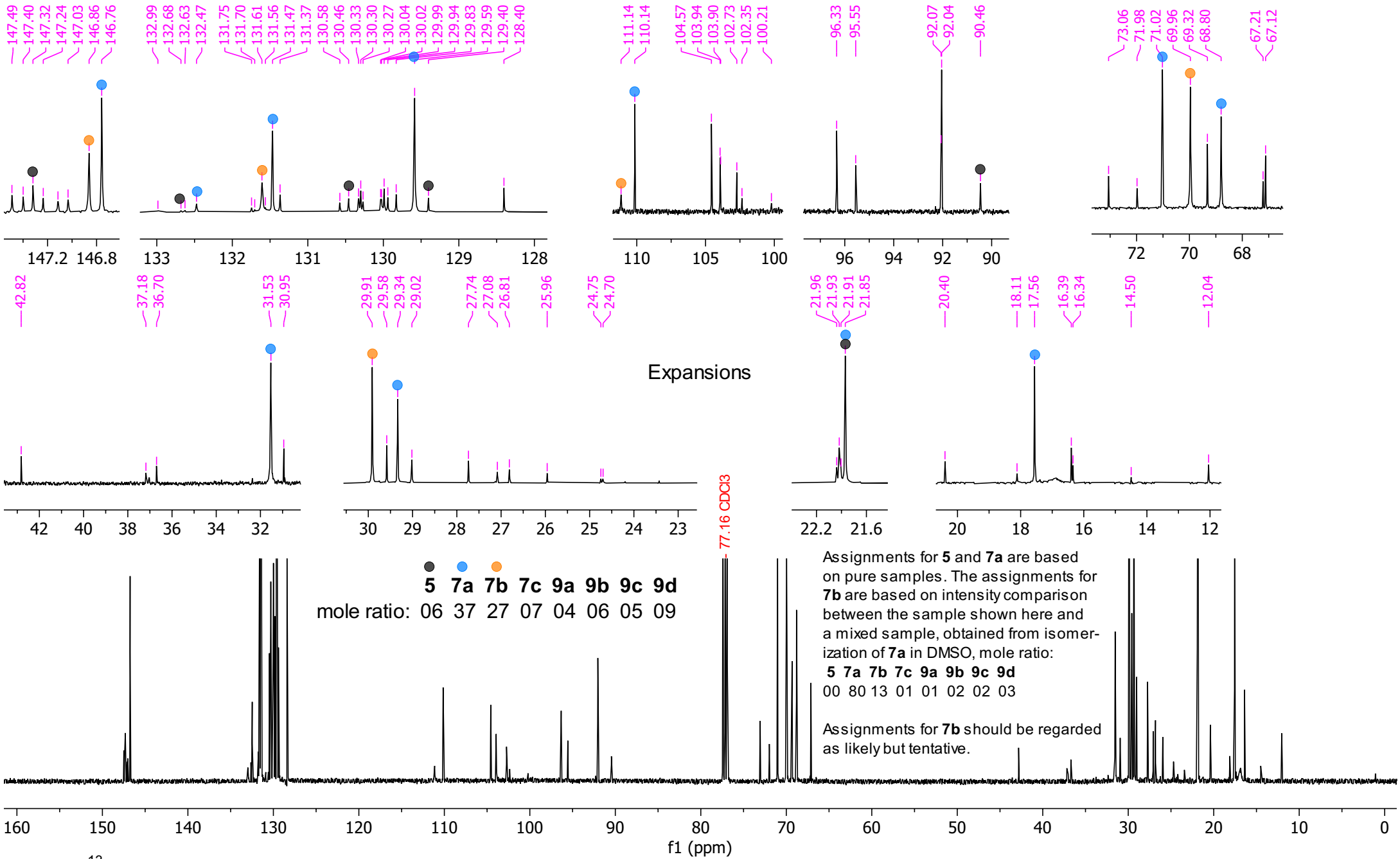


Fig. S6. ^{13}C NMR Spectra (126 MHz, $CDCl_3$) for a concentrated mother liquor containing **5**, **7a-c** and **9a-d**. The mother liquor was obtained by recrystallizing chrom'd product from benzene-CH_2Cl_2 and separating crystalline **7a**. Top and middle: expansions. Bottom: spectrum, mole ratio indicated. The chemical shifts are shown as δ_C values. Assigned signals are indicated by color.

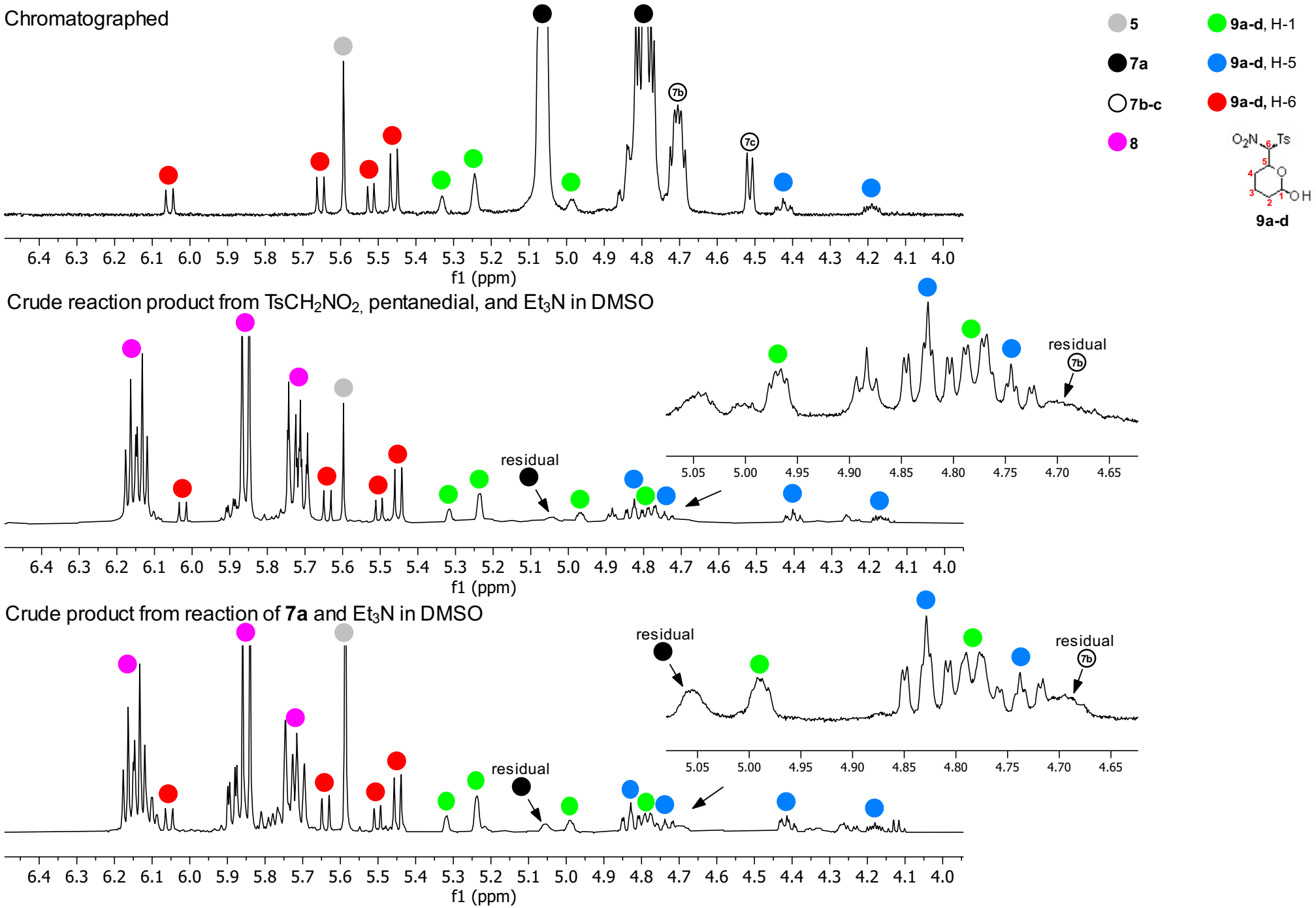


Fig. S7. ^{1}H NMR δ_C 4.0-6.4 spectral region with **9a-d** assigned signals. Chrom'd **7** (top) and two crude products (middle and bottom) containing **8**, **9a-d** and only traces of **7a-b**.

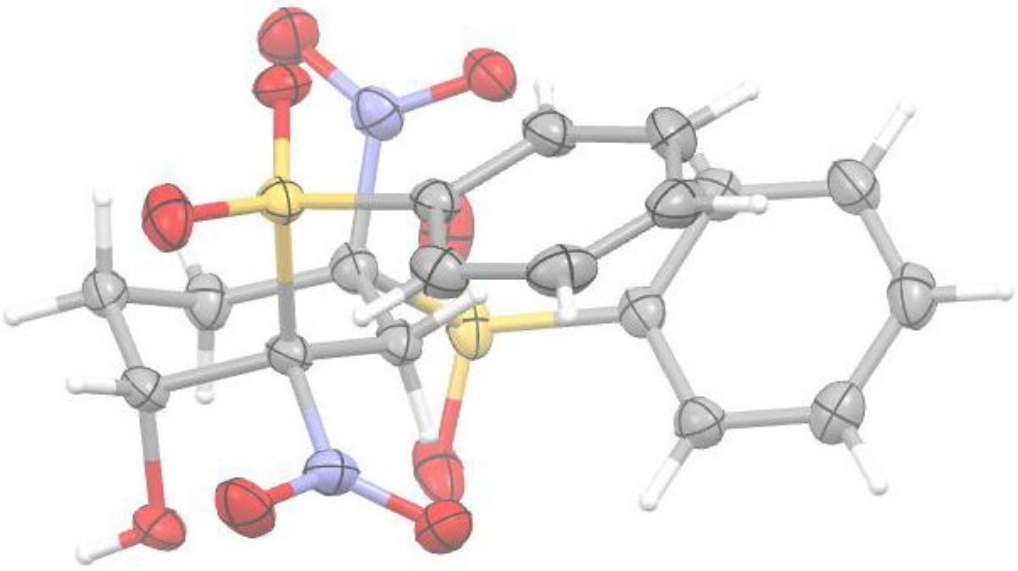


Fig. S8. ORTEP drawing of **2a**. Thermal ellipsoids are drawn at 50% probability level.

2. General experimental methods

^{1}H NMR signals were determined at 500 MHz in $CDCl_3$ and are referenced to residual $CHCl_3$ (δ_H 7.26) unless otherwise noted. Mole ratios were determined by ^{1}H NMR integration and are listed in the same order as the constituents in all cases. ^{13}C NMR signals were determined at 126 MHz in and referenced to $CDCl_3$ (δ_C 77.16). HSQC spectra were taken for **7a** to determine ^{1}H, ^{13}C signal correlations. ^{1}H, ^{1}H correlations were determined by 1D-decoupling with COSY confirmation. HRMS were performed using either CI with CH_4 as carrier gas or APCI ionization techniques as noted. Infrared spectra (ATR-IR) spectra were taken using attenuated total reflectance sampling methodology and FT data treatment. Reagents and solvents were used as received unless otherwise noted. Ethyl acetate, CH_2Cl_2, $CHCl_3$, benzene, 1,2-dichlorobenzene and hexanes were distilled. DMSO was used as received or stored over molecular sieves prior to use as a dry solvent. Acetonitrile was distilled and stored over molecular sieves. Reactions and isomerizations were run under N_2. Organic layers were dried over anhydrous $MgSO_4$.

3. Experimental Procedures

3.1 Synthetic procedures

3.1.1 Synthesis of (1*R*, 2*R*, 4*S*)-rel-2,4-dinitro-2,4-bis(phenylsulfonyl)cyclohexanol (2a). A solution containing **1**[1] (50:50 diastereomer mix; 1.16 g, 2.8 mmol), propenal (0.57 g**,** 10 mmol), and Et_3N (0.54 g, 5 mmol) in CH_2Cl_2 (60 mL) was refluxed for 3 h. The cooled reaction solution was poured into water (55 mL and 5% HCl (15 mL). Layers were separated and the aqueous layer was extracted with CH_2Cl_2 (two 30-mL portions). The combined organic layers were washed with water (60 mL), dried and concentrated to give **2** (1.4 g) as a solid mixture of diastereomers (**2a**/**2b**/**2c**/**2d**, 37:35:24:4 mole ratio). The crude product was flash chromatographed on silica gel eluted with an EtOAc-hexanes gradient. A 1.29 g portion (98% yield) of **2** was obtained (EtOAc-hexanes 50:50 elution) as a white solid diastereomer mixture (**2a**/**2b**/**2c**/**2d**, 54:35:10:2 mole ratio). This material was recrystalized from ethanol and then from $CHCl_3$ to give pure **2a**: mp 224-225 °C (dec); ATR-IR: 3512 (OH), 1557 (NO_2 asym), 1336 (NO_2 sym, SO_2 asym), 1150 (SO_2 sym) cm^{-1}; ^{1}H NMR δ_H 7.85-7.88 (m, 2H), 7.75-7.83 (m, 4H), 7.62-7.66 (m, 2H), 7.57-7.62 (m, 2H), 5.03 (m, 1H), 3.69 (d, 1H, *J* = 16.1 Hz), 3.43 (d, 1H, *J* = 16.1 Hz), 2.86 (td, 1H, *J* = 4.9, 13.7 Hz), 2.79 (m, 1H), 2.72 (d, 1h, *J* = 4.9 Hz), 2.25 (dq, 1H, *J* = 3.4, 14.7 Hz), 2.44 (m, 1H); ^{13}C NMR δ_C 136.32, 135.99, 131.90, 131.86, 131.16, 130.86, 129.81, 129.66, 106.90, 104.98, 64.89, 26.97, 25.77, 18.72; HRMS (CI) *m/z* calcd. for $C_{18}H_{19}N_2O_9S_2$ $(M + H^+)^+$ 471.0527, found 471.0532; anal. calcd. for $C_{18}H_{18}N_2O_9S_2$ (470.47): C 45.95, H 3.86, N 5.95; found: C 45.89, H 3.94, N 5.83.

3.1.2 Synthesis of (1*R*, 3*R*)-rel-[(4-methylphenyl)sulfonyl]2-nitro-1,3-cyclohexanediol (7a). A solution containing 1-methyl-4-[(nitromethyl)sulfonyl]benzene[2] (0.73 g, 3.4 mmol), acetic acid (5 mL), pentanedial (aq 50%, 4 mL; 22 mmol), and DMSO (50 mL) was stirred for 50 h at room temperature. The solution was added to ice water (500 mL) layered with CH_2Cl_2 (100 mL). Layers were separated and the aqueous phase was extracted with CH_2Cl_2 (two 100-mL portions). The organic layers were combined, washed with water (three 100-mL portions), dried and concentrated to give 1.15 g of a viscous oil containing **7a**, **7b**, excess pentanedial, and small amounts of other materials. The crude product could be purified by either procedure A or procedure B.

Purification: Procedure A. 1,2-Dichlorobenzene (5 mL) and CH_2Cl_2 (5mL) were added to the crude product and the sample was concentrated (0.1 mm Hg). The process was repeated two times and the crystals were triturated with hexanes (5 mL) to give 0.73 g of white semi-crystalline material. This was recrystallized from 50:50 $CHCl_3$-C_6H_6 (10 mL) to give 0.59 g (55% yield) of pure **7a**: mp 146.5-147 °C; ATR-IR: 3510 (OH), 3289 (OH), 1548 (NO_2 asym), 1329 (NO_2 sym, SO_2 asym), 1153 (SO_2 sym); ^{1}H NMR δ 7.88 (d, 2H, *J* = 8.3 Hz), 7.33 (d, 2H, *J* = 8.3 Hz), 5.05 (m, 1H, H-3), 4.78 (dt, 1H, *J* = 10.8, 4.4 Hz, H-1), 3.04 (d, 1H, *J* = 4.4 Hz),2.95 (d, 1H, *J* = 10.8 Hz), 2.45 (s, 3H), 2.15 (m, 1H), 2.06 (m, 1H), 1.85 (m, 1H), 1.72 (m, 1H), 1.64 (m, 1H), 1.48 (m, 1H); ^{13}C NMR δ 146.85, 132.46, 131.51, 129.66, 110.17 (C-2), 71.19 (C-3), 68.89 (C-1), 31.67, 29.35, 21.93, 17.66; HRMS (CI) *m/z* calcd. for $C_{13}H_{18}NO_6S$ $(M + H^+)^+$ 316.0849, found 316.0851; anal. calcd. for $C_{13}H_{17}NO_6S$ (315.34): C 49.51, H 5.43, N 4.44; found: C 49.49, H 5.41, N 4.42.

Purification: Procedure B. The crude product was flash chromatographed on silica gel eluted with an EtOAc-hexanes gradient. An 0.59 g portion of semi-crystalline material (EtOAc-hexanes 50:50 elution) was obtained in the main fraction. This was recrystallized from $CHCl_3$-PhH to give 0.25 g (23% yield) of pure **7a** as a white solid: mp 146.5-147 °C.

3.1.3 Synthesis of 6-[(4-methylphenyl)sulfonyl]-4-nitro-3-pentenal (8). A stirred solution containing **5**[2] (0.41 g, 1.9 mmol), pentanedial (aq 50%, 2 mL; 11 mmol), Et_3N (1.09 g, 10 mmol) and DMSO (12 mL) was heated at 35-40 °C for 90 m. The resulting dark solution was cooled and added to ice water (120 mL) and 5% HCl (20 mL) layered with CH_2Cl_2 (20 mL). Layers were separated and the aqueous phase was extracted with CH_2Cl_2 (two 20-mL portions). The combined organic layers were washed with water (three 50-mL portions), dried and concentrated to afford 0.59 g of crude product. This consisted of **8**/**9a-d**/**5** 70:27:3 mol ratio. Excess pentanedial and small amounts of unidentified materials were also present. Flash chromatography on silica gel (EtOAc-hexanes, 50:50) gave 0.11 g of a mixture of **9a-d**/**8**/**7a**/**7b**/**7c**/**5**, 8:64:13:6:6 mole ratio followed closely by **8** (0.31 g; 54% yield). The main product **8** required a second chromatography to provide a pure colorless oil: ATR-IR: 1715 (C=O), 1558 (NO_2 asym), 1335 (NO_2 sym, SO_2 asym), 1152 (SO_2 sym); ^{1}H NMR δ_H 9.77 (s, 1H), 7.73 (d, 2H, *J* = 8.3 Hz), 7.41 (d, 2H, *J* = 8.3 Hz), 6.14 (dt, 1H, *J* = 6.6, 15.4 Hz), 5.84 (d, 1H, *J* = 9.5 Hz), 5.71 (ddt, 1H, *J* = 1.6, 9.5, 15.4 Hz), 2.62 (t, 2H, *J* = 7.1 Hz), 2.46-2.52 (m, 5H); ^{13}C NMR δ_C 200.12, 147.19, 144.37, 131.19, 130.42, 130.23, 116.44, 103.25, 41.95, 25.07, 21.98; HRMS (APCI) *m/z* calcd. for $C_{13}H_{16}NO_5S$ $(M + H^+)^+$ 298.0744, found 298.0749.

3.2 Isomerization procedures

3.2.1 Isomerization reactions of compounds 2 and 7a in neutral solution.

Procedure A. A 5 mg (0.01mmol) portion of **2** enriched in **2a** (**2a**/**2b**/**2c**, 90:9:1 mol ratio) was dissolved in the appropriate solvent: EtOH, CH_3CN or EtOAc (1 mL). Alternatively, a 6 mg (0.02 mmol) portion of **7a** was dissolved in CH_3CN (1 mL). Stirring was carried out for the indicated time (see Table 1, entries 4-7 and Table 3, entries 5-6). The isomerization solution was concentrated at reduced pressure to give a quantitative recovery of isomerized material in each case.

Procedure B. For $CDCl_3$ isomerization (Table 1 entries 12-15, Table 3 entries 12-13), the solution was prepared with $CDCl_3$ (0.6 mL) and either **2** or **7a** as listed in Procedure A. Alternatively, a 6 mg mixture of **7a**/**7b**, 87:12 mole ratio was used (Table 3 entry 14). The solution was kept directly in the capped NMR

tube at room temperature for the indicated time. On long runs, partially evaporated solvent was replenished from time to time.

Procedure C. For DMSO isomerization, the solutions were prepared with dry DMSO (1 mL) and either **2** or **7a** as listed in Procedure A. Solutions were stirred for the indicated time (Table 1 entry 3, Table 3 entries 7-8). Ice water (10 mL) and CH_2Cl_2 (5mL) were added and layers were separated. The aqueous layer was further extracted with CH_2Cl_2 (two 5-mL portions). The combined organic layers were washed with water (three 5-mL portions), dried and concentrated. Recovery of isomerized **2** and **7a** was greater than 95% in all cases.

Procedure D. For aqueous acetone isomerization, a solution containing 6 mg (0.02 mmol) of **7a** in acetone (1 mL) was treated with water (0.5 mL). The resulting solution was stirred for 3 h and was partially concentrated. To the residue was added CH_2Cl_2 (5mL). Layers were separated and the organic layer was dried and concentrated to give a quantitative recovery of material (Table 3 entry 4).

3.2.2 Isomerization of 2 with silica gel. A mixture containing 0.37 g (0.8 mmol) of **2a-d** (**2a**/**2b**/**2c**/**2d**, 43:46:10:2 mole ratio), EtOAc (10 mL), hexanes (20 mL) and silica gel (10 g) was stirred for 90 m. The silica gel mixture was filtered and washed with Et-OAc-hexanes, 50:50 (five 20-mL portions). The combined filtrates were concentrated to give 0.18 g of a solid containing **2a-d** (**2a**/**2b**/**2c**/**2d**, 68:23:8:1 mole ratio). The silica gel was further washed with EtOAc (five 20-mL portions). These combined filtrates were concentrated to give 0.11 g of a solid containing **2a-d** (**2a**/**2b**/**2c**/**2d**, 54:34:10:2 mole ratio).

3.2.3 Base-induced Isomerization of 2. A 5 mg (0.01 mmol) portion of **2** enriched in **2a** (**2a**/**2b**/**2c**, 90:9:1 mol ratio) was dissolved in CH_2Cl_2 (1mL). The solution was treated with base. Use of Et_3N (25 μL) gave a homogenous solution whilst use of aqueous 5% Na_2CO_3 (1 mL) and 5% $NaHCO_3$ (1 mL) gave heterogenous mixtures. All were stirred under N_2 for the indicated time (see Table 1, entries 8-11). All reaction media were acidified with aqueous 5% HCl (1.5 mL) and diluted with CH_2Cl_2 (1 mL). Layers were separated and the organic layer was washed with water (1 mL), dried over anhydrous $MgSO_4$, and concentrated. Recovery of isomerized **2** was greater than 95% in all cases (Table 1 entries 8-11).

3.2.4 Attempted Isomerization of 2 with acid.

Procedure A. A solution containing **2** (10 mg, 0.02 mmol, enriched in **2a** (**2a**/**2b**/**2c**, 90:9:1 mol ratio), trifluoroacetic acid (1 mg, 0.01 mmol) and $CDCl_3$ (0.6 mL) was prepared and kept in a capped NMR tube for 2 d. Integration of the H-1 signals showed no detectable isomerization (Table 1, entry 16).

Procedure B. A CH_2Cl_2 (5 mL) solution of **2** (15 mg, 0.03 mmol) enriched in **2a** (**2a**/**2b**/**2c**, 90:9:1 mol ratio) was prepared in a 25-mL RB flask. A stream of dry HCl gas was generated by dropwise addition of concentrated HCl (3 mL, 37 mmol HCl) to $CaCl_2$ (5.03 g, 45 mmol).[3] Over 5 min, the gas stream was bubbled through the solution of **2** saturating the solution and replacing much of the atmosphere. The flask containing the resulting solution and gas was stoppered and left standing for 6 d. Volatile materials were removed at reduced pressure and 15 mg of recovered **2** (**2a**/**2b**/**2c**, 79:15:6 mol ratio, Table 1 entry 17) was obtained (Table 1 entry 17).

3.2.4 Isomerization, dehydration and cycloreversion of 7a.

Procedure A. A 6 mg (0.02 mmol) portion of **7a** was dissolved in CH_2Cl_2 (1 mL) and Et_3N (20 ml) was added. After stirring for 20 m, CH_2Cl_2 (5 mL) and 5% aqueous HCl (1 mL) were added. Layers were separated and the organic layer was washed with water (3 mL), dried, and concentrated to give 6 mg of a mixture of isomers, **5** and pentanedial (Table 3 entry 10).

Procedure B. A 13 mg (0.04 mmol) portion of **7a** was dissolved in DMSO (2 mL). The solution was heated at 50-55 ^oC with stirring for 24 h (see Table 3, entry 8). Ice water (20 mL) and CH_2Cl_2 (5mL) were added and layers were separated. The aqueous layer was further extracted with CH_2Cl_2 (two 5-mL portions). The combined organic layers were washed with water (three 5-mL portions), dried and concentrated to give 12 mg of crude product (Table 3 entry 9).

Procedure C. Procedure B was repeated except Et_3N (10 μL) was added before heating at 34-37 ^oC for 90 m. Ice water (20 mL), aqueous 5% HCl (1 mL) and CH_2Cl_2 (5mL) were added and layers were separated. The aqueous layer was further extracted with CH_2Cl_2 (two 5-mL portions). The combined organic layers were washed with water (three 5-mL portions), dried and concentrated to give 11 mg of crude product (Table 3 entry 11).

4. Data used in tables

4.1 Data for Table 2.

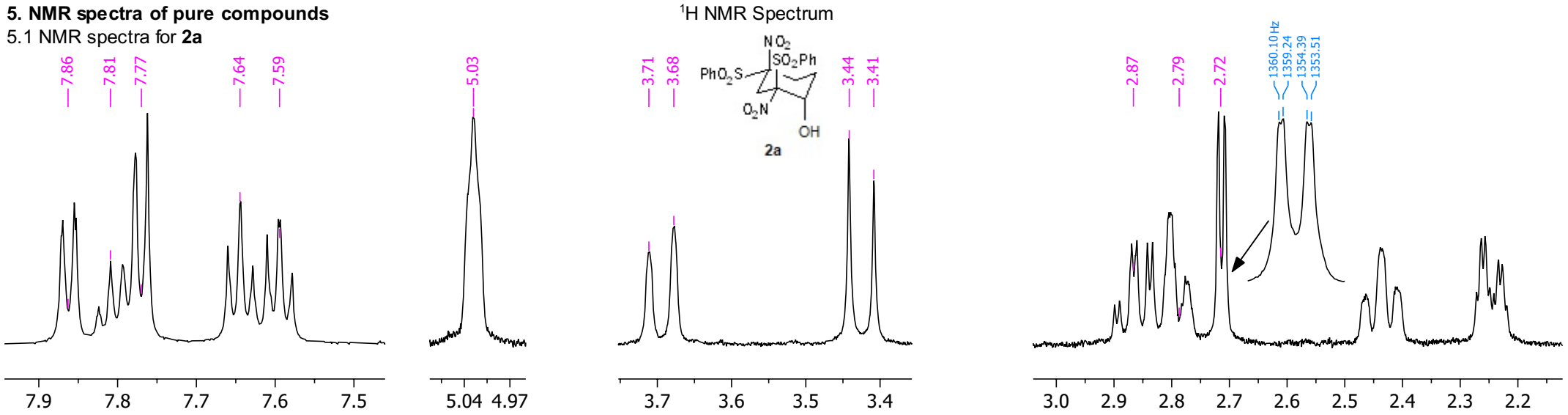
Purified **2a** was used to enter data for this isomer. The crude product (**2a**/**2b**/**2c**/**2d** 37:35:24:4 mole ratio) obtained in the preparation of **2a** was a mixed sample of all isomers. Data entered in Table 2 for **2b-d** are from this spectrum with comparison to data for chromatographed product (mole ratio **2a**/**2b**/**2c**/**2d** 43:45:10:2) and for two samples obtained as mother liquors from ethanol recrystallization of chromatographed product (see Fig. S2). These mother liquor samples had varied isomer concentrations. They contained mole ratios of **2a**/**2b**/**2c** 58:18:24 and **2a**/**2b**/**2c**/**2d** 36:56:5:3. ^1H, ^1H-Decoupling experiments were run on multiple samples to determine correlations and assign signals as listed in Table 2.

4.2 Data for Table 5

^{13}C NMR data were recorded at 126 MHz for $CDCl_3$ solutions of pure **7a**, pure **5** and two mixtures. The mixtures contained dissimilar amounts of the products: one mixture, obtained as a mother liquor from recrystallization of **7a**, had **7a**/**7b**/**7c**/**5**/**9a**/**9b**/**9c**/**9d**, 37:27:7:6:4:6:5:9 mole ratio and the second mixture, obtained from isomerization of **7a** in aqueous acetone, had **7a**/**7b**/**7c**/**5**/**9a**/**9b**/**9c**/**9d**, 80:12:1:4:1:1:1:1 mole ratio. Data from the first mixture were entered into the table for **9a-d** and **7b-c**, using data from the second mixture to partially assign the signals. The concentration differences resulted in significantly different relative intensities allowing for many peak assignments of **7b** but not **7c** or **9a-d**.

5. NMR spectra of pure compounds

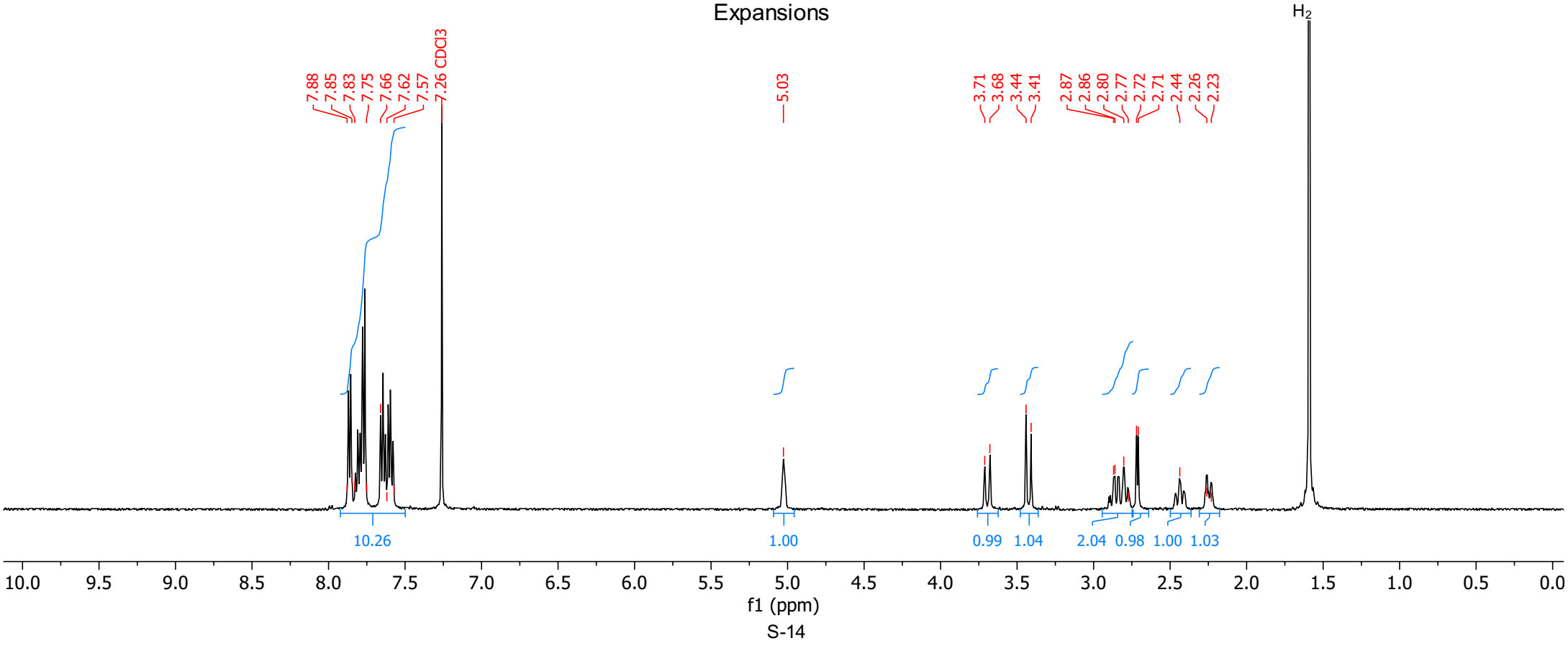
5.1 NMR spectra for **2a**

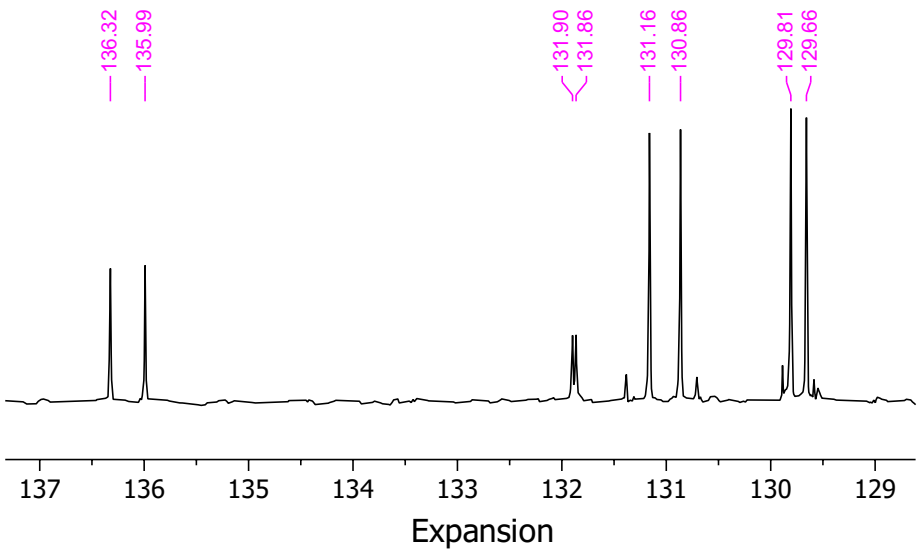


^{1}H NMR Spectrum

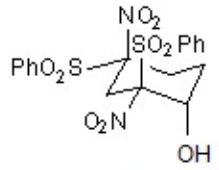
2a

Expansions

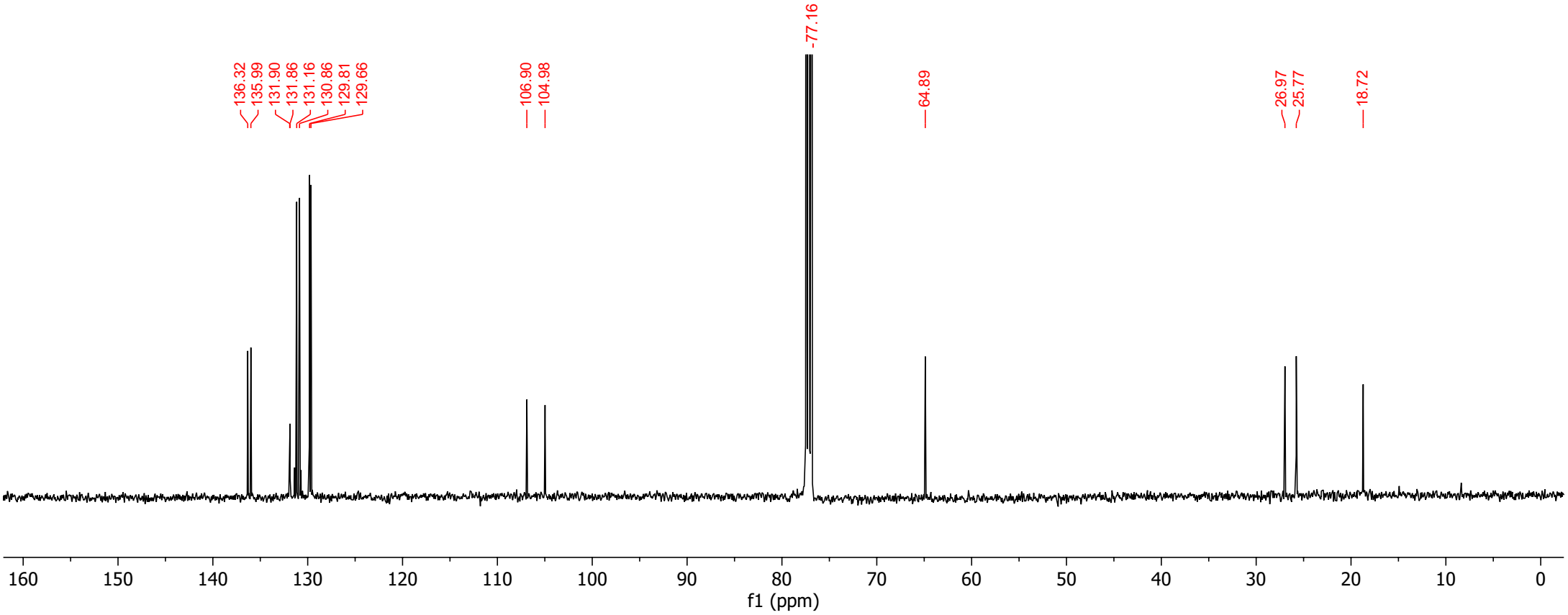




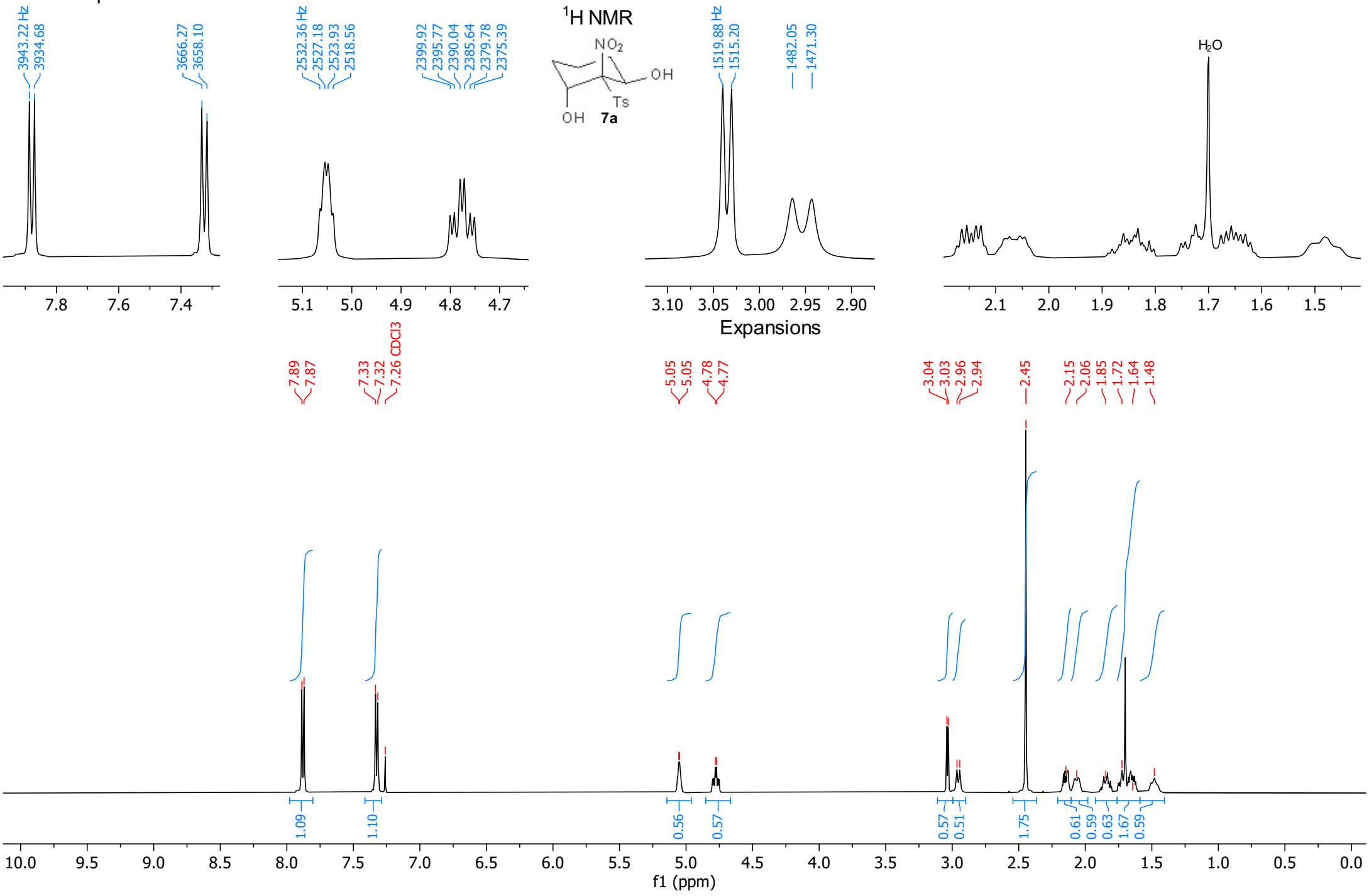
^{13}C NMR Spectrum



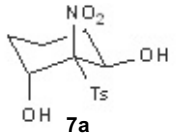
2a



5.2 NMR spectra for **7a**



^{13}C NMR Spectrum



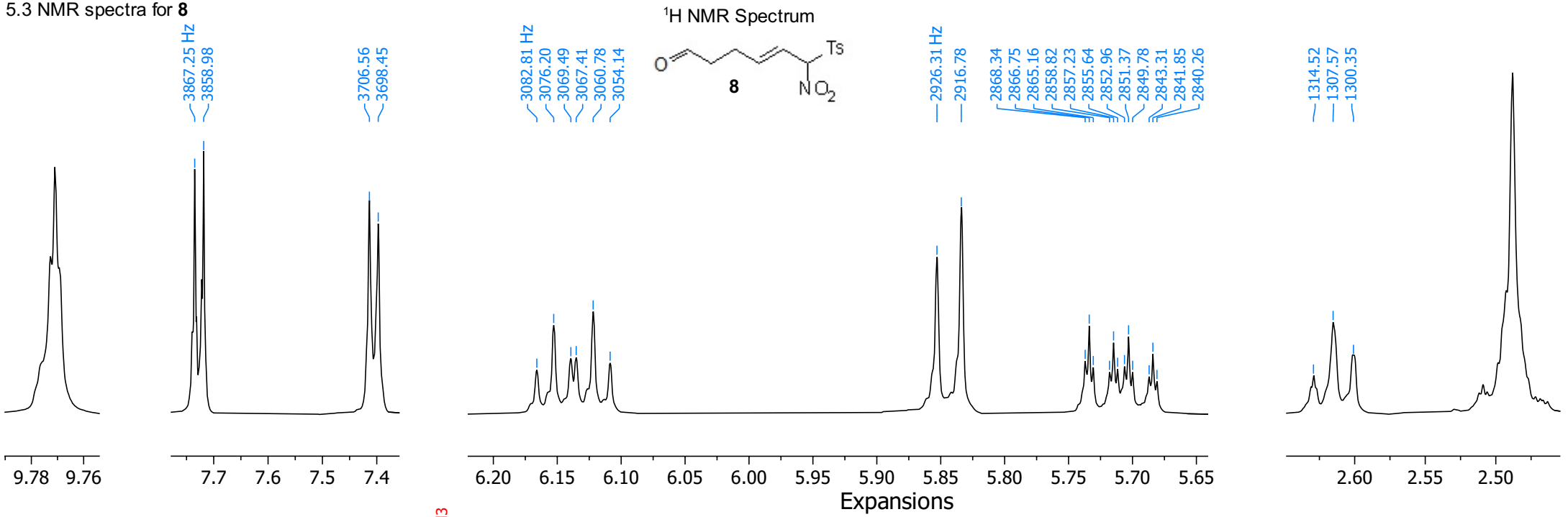
7a

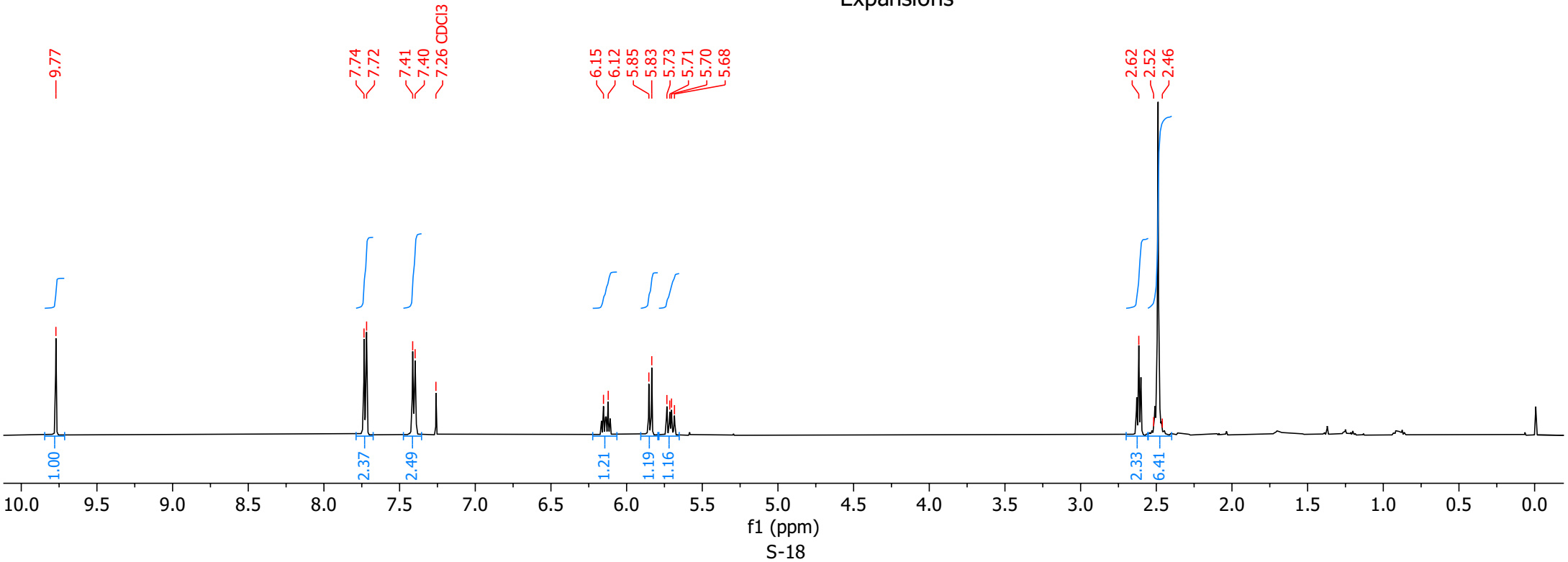
146.85
132.46
131.51
129.66
110.17
77.16 CDCl3
71.19
68.89
31.67
29.35
21.93
17.66

160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

f1 (ppm)

5.3 NMR spectra for **8**

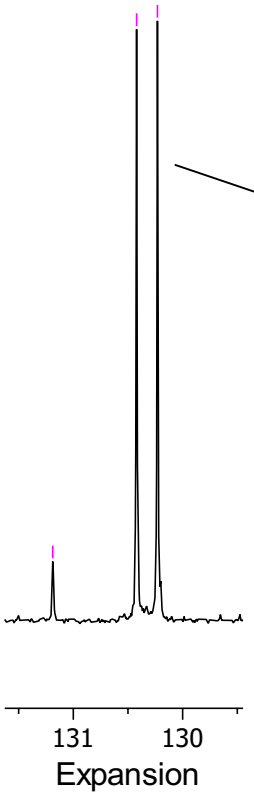




^{13}C NMR Spectrum

8

200.12
131.19
130.42
130.23
147.19
144.37
131.19
130.42
130.23
116.44
103.25
77.16 CDCl3
41.95
25.07
21.98



6. Notes and references

1 P. A. Wade, J. K. Murray, A. Pipic, R. J. Arbaugh and A. Jeyarajasingam, *J. Phys, Org. Chem.* **2009**, *22*, 337-342.

2 Prepared as described for [(nitromethyl)sulfonyl]benzene using sodium 4-methylbenzenesulfinate rather than sodium benzenesulfinate: P. A. Wade, H. R. Hinney, N. V. Amin, P. D. Vail, S. D. Morrow, S. A. Hardinger and M. S. Saft, *J. Org. Chem.* **1981**, *46*, 765-70. See also: J. L. Kelley, E. W. McLean and K. F. Williard, *J. Het. Chem*., **1977**, *14*, 1415-16.

3 F. J. Arnáiz, *J. Chem. Ed.* **1995**, *72*, 1139.