An Efficient and Recyclable Hybrid Nanocatalyst to Promote Enantioselective Radical Cascade Rearrangements of Enediynes

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1. Preparation of hybrid materials

1.1. MCM41

The MCM-41 mesoporous silica was synthesized by adopting the procedure reported by Grün et al.[1] In a standard method of synthesis, 0.80 g of cetyltrimethylammonium bromide (CTAB), was dissolved in 17.7 mL of water under vigorous stirring at 70 °C for 10 min. After cooling (30 °C), a mixture of 10.3 mL of absolute ethanol and 8.1 mL of ammonium hydroxide 32% was added and the solution was stirred for an additional 10 min. Then, 1.5 g (7.2 mmol) of tetraethyl orthosilicate (TEOS (98%), commercially available from Aldrich) was added dropwise to the solution with stirring for an additional 24 h. The molar composition of the resultant mixture was 1 TEOS: 0.3 CTAB: 11 NH_3: 144 H_2O: 58 EtOH. After hydrothermal treatment at 90 °C for 24 hours, the precipitate was filtered, washed with deionized water, ethanol and diethyl ether. For acidic extraction, the as-obtained material (1 g) was treated with a mixture of ethanol (100 ml) and concentrated HCl (1 mL, 38% in weight) at 70 °C for 8 h. The resulting (surfactant removed) solid product was filtered and washed with ethanol, and then dried at 60 °C.

1.2. SBA15

In a typical synthesis, 4 g of Pluronic P123 were dissolved in 30 mL of deionized water and 120 mL of 2M HCl under constant stirring for three hours, prior to the addition of 8.5 g of TEOS. This mixture was further stirred for 24 hours before hydrothermal treatment at 100 °C for 48 hours. The resulting white precipitate was filtered, which was followed by soxhlet extraction of the polymeric template with ethanol for 24 hours. The molar composition of the synthesis mixture was as follows: 1 TEOS: 0.017M P123 Polymer: 188M H_2O: 5.8M HCl. The resulting (surfactant removed) solid product was filtered and washed with ethanol, acetone and diethyl ether and then dried at 60 °C.

1.3. Passivated SBA15

In a typical synthesis, 4 g of Pluronic P123 were dissolved in 30 mL of deionized water and 120 mL of 2M HCl under constant stirring for three hours, prior to the addition of 8.5 g of TEOS. This mixture was further stirred for 24 hours before hydrothermal treatment at 100 °C for 48 hours. The resulting white precipitate was filtered, and washed with ethanol, acetone and diethyl ether and then dried at 60 °C. The molar composition of the synthesis mixture was as follows: 1 TEOS: 0.017M P123 Polymer: 188M H_2O: 5.8M HCl. SBA15 still containing the surfactant (1 g) was loaded in dry toluene (75 ml) and triethylamine (4.04 g, 40 mmol, then chlorotrimethylsilane (3.56 g, 33.3 mmol) was added, and the mixture was heated at 70 °C overnight. The resulting white precipitate was filtered, which was followed by soxhlet extraction of the polymeric template with ethanol for 24 hours. The resulting (surfactant removed) solid product was filtered and washed with ethanol, acetone and diethyl ether and then dried at 60°C. The grafting procedure is described in § 1.4.4.

[1] M. Grün, K.K. Unger, A. Matsumoto and K. Tsutsumi, *Micropor. Mesopor. Mater.*, 1999, **27**, 207.

1.4. Grafting procedure

1.4.1. Diethylaminopropyltrimethoxysilane (DEAP) was anchored onto the silica surface via post-grafting procedure. After SBA15 (1 g, 16.7 mmol) was loaded in dry toluene (16 ml), DEAP (1.35 g, 5.7 mmol) was added, and mixture was heated at 70 °C overnight. The precipitate was filtered, washed (ethanol and ether) and dried which was referred as **GA-**SBA15. The quantity of organic group was determined by TGA analysis; it is 1.45 mmol/g.

1.4.2. Diethylaminopropyltrimethoxysilane (DEAP) was anchored onto the silica surface via post-grafting procedure. After MCM41 (1 g, 16.7 mmol) was loaded in dry toluene (16 ml), DEAP (1.35 g, 5.7 mmol) was added, and mixture was heated at 70 °C overnight. The precipitate was filtered, washed (ethanol and ether) and dried which was referred as **GA-**MCM41. The quantity of organic group was determined by TGA analysis; it is 1.57 mmol/g.

1.4.3. Diethylaminopropyltrimethoxysilane (DEAP) was anchored onto the silica surface via post-grafting procedure. After Si2000 (1 g, 16.7 mmol) was loaded in dry toluene (16 ml), DEAP (1.35 g, 5.7 mmol) was added, and mixture was heated at 70 °C overnight. The precipitate was filtered, washed (ethanol and ether) and dried which was referred as **GA-**Si2000. The quantity of organic group was determined by TGA analysis; it is 0.21 mmol/g.

1.4.4. Diethylaminopropyltrimethoxysilane (DEAP) was anchored onto the silica surface via post-grafting procedure. After SBA15 (0.6 g) was loaded in dry toluene (11 ml), DEAP (0.78 g, 3.3 mmol) was added, and mixture was heated at 70 °C overnight. The precipitate was filtered, washed (ethanol and ether) and dried which was referred as passivated **GA-**SBA15.

1.5. Characterization of Mesoporous Silicas

Thermogravimetric (TGA) measurements were carried out with a TGA Q500 apparatus (TA Instruments) under dynamic air atmosphere (sample flow rate 60 ml/min). XRD patterns were measured on a Siemens D5000; XRD diffractometer using Cu (40 Kv, 40 mA) Ka radiation and detected by Scintillator (Thêta-2 Thêta). The N_2 adsorption/desorption isotherms were obtained at 77 K on a Micrometrics ASAP2010. The specific surface area was determined with the Brunauer, Emmett, and Teller (BET) method and the pore size distribution was calculated from the desorption isotherms using the Barrett Joyner Halenda (BJH) method1.[2] Prior to adsorption, the samples were out gassed at 393 K overnight under a vacuum pressure of 2×10^{-3} mbar. All solid-state Cross Polarization Magic Angle Spinning (CPMAS) NMR spectra were obtained on a Bruker Avance-400 MHz NMR spectrometer operating at a ^{13}C and ^{29}Si resonance frequency of 101.6 MHz and 79.5MHz, respectively. ^{13}C and ^{29}Si CPMAS experiments were performed with a commercial Bruker Double-bearing probe. About 100 mg of samples were placed in zirconium dioxide rotors of 4-mm outer diameter and spun at a Magic Angle Spinning rate of 10 kHz. The CP technique[3] was applied with a ramped 1H-pulse starting at 100 % power and decreasing until 50% during the contact time in order to

[2] F. Rouquerol, J. Rouquerol, K. S. W. Sing, Adsorption by Powders and Porous Solids: Principles, Methodology and Applications, Academic Press: London, 1999.
[3] J. Schaefer and E. O. R. Stejskal, *J. Am. Chem. Soc*., 1976, ***98***, 1031.

circumvent Hartmann-Hahn mismatches (Peersen *et al.*, 1993; Cook *et al.*, 1996)[4]. The contact times were 2 ms for ^{13}C CPMAS and 5ms for ^{29}Si CPMAS. To improve the resolution, a dipolar decoupling GT8 pulse sequence (Gerbaud *et al.* 2003)[5] was applied during the acquisition time. To obtain a good signal-to-noise ratio, 6144 scans were accumulated using a delay of 2 s in ^{13}C CPMAS experiment, and 4096 scans with a delay of 5 s in ^{29}Si CPMAS experiment. The ^{13}C and ^{29}Si chemical shifts were referenced to tetramethylsilane.

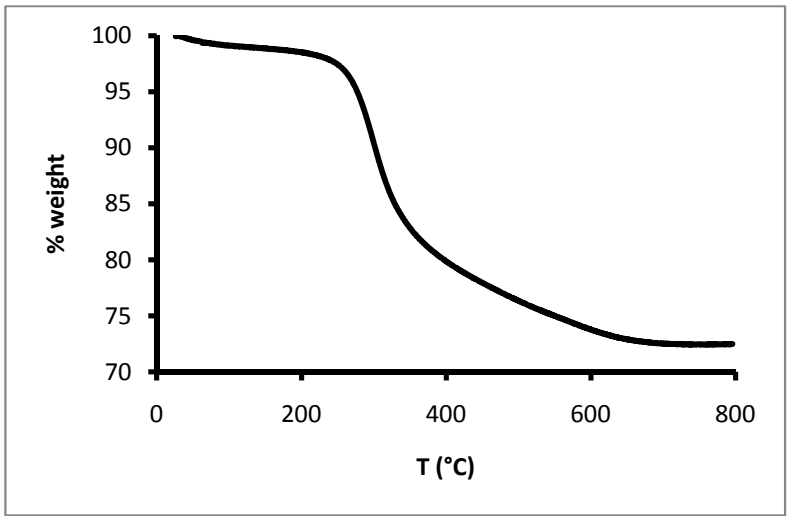


Figure 1: TGA analysis of **GA**-SBA15 (5.8 nm)

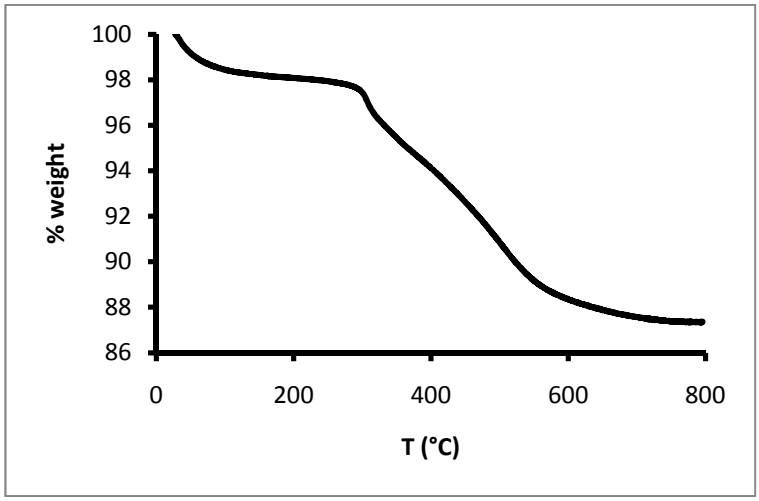


Figure 2: TGA analysis of passivated SBA15 before grafting (5.8 nm)

[4] a) O. B. Peersen, X. Wu, I. Kustanovich and S.O. Smith, *J. Magn. Reson.*, 1993, **104**, 334. b) R. L. Cook, C. H. Langford, R. Yamdagni and C. M. Preston, *Anal. Chem.*, 1996, **68**, 3979.
[5] G. Gerbaud, F. Ziarelli and S. Caldarelli, *Chem. Phys. Lett.*, 2003, **377**, 1.

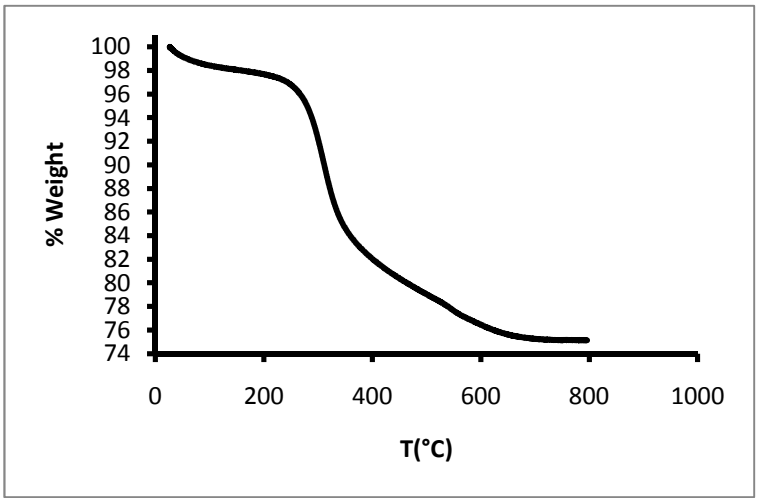


Figure 3: TGA analysis of **GA**-MCM41 (2 nm)

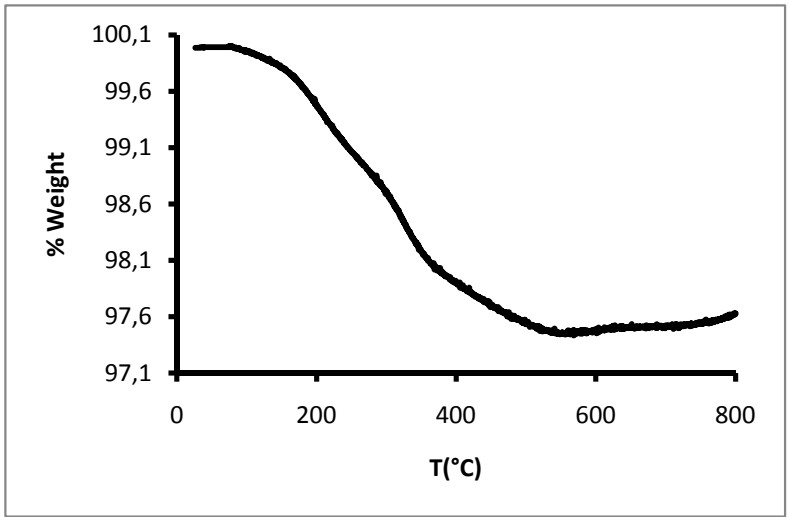


Figure 4: TGA analysis of **GA**-Si2000 (200 nm)

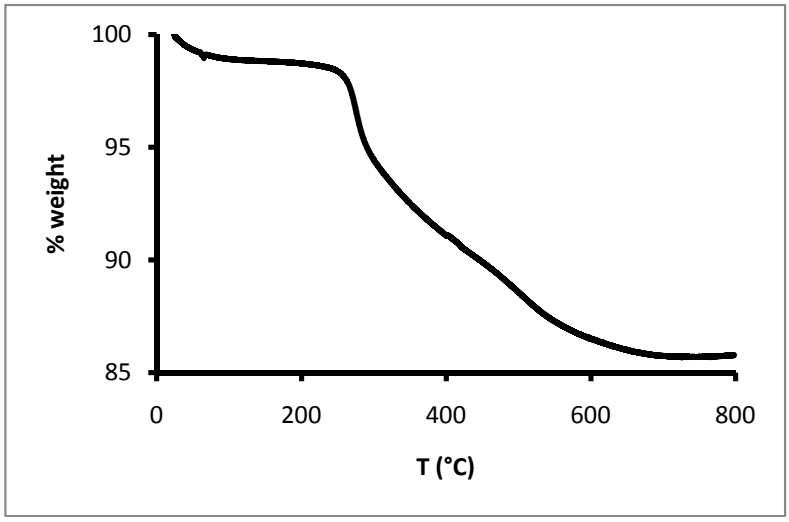


Figure 5: TGA analysis of passivated **GA**-SBA15 (5.8 nm) after grafting

TGA experiments were confirmed by elemental analyses.

GA-SBA15: found %N=3.23, C=20.13, H=4.28 (the experimental ratio between C/N is 7.29, close to the theoretical ratio of 7).

GA-MCM41: found % N=2.71, C=17.29, H=3.77 (the experimental ratio between C/N is 7.46, close to the theoretical ratio of 7).

GA-Si2000: found % N=0.09, C=0.75, H=0.38 (owing the experimental errors the vamues are not significant, but they are in agreement with TGA data).

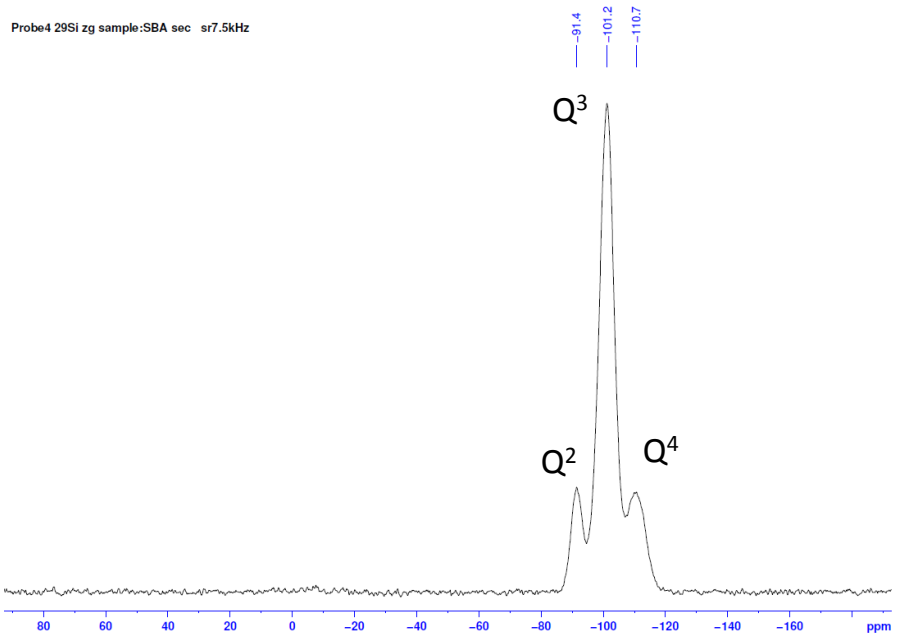


Figure 6: ^{29}Si CP-MAS solid state NMR of SBA15 (7.9 nm)

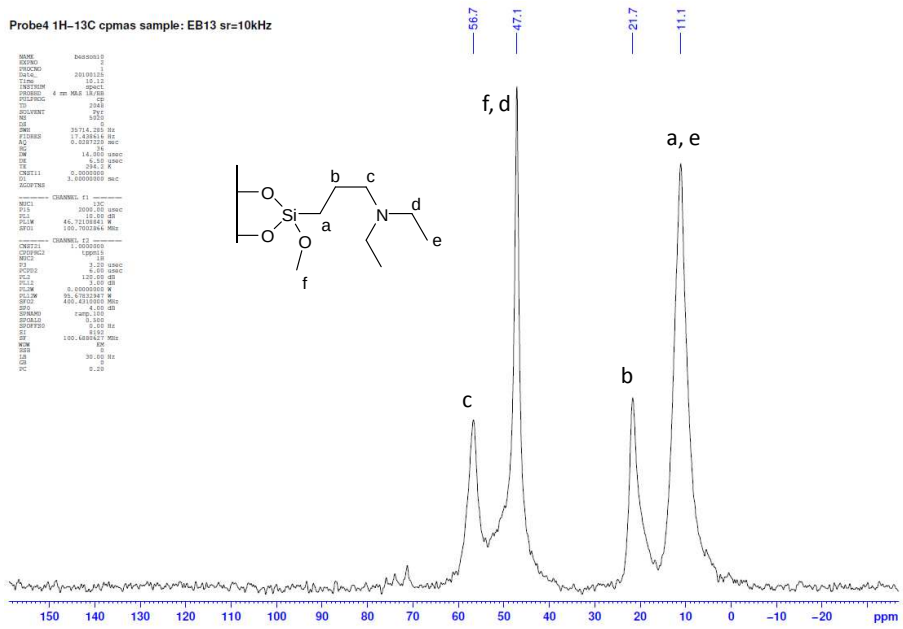


Figure 7: ^{13}C CP-MAS solid state NMR of **GA**-SBA15 (5.8 nm)

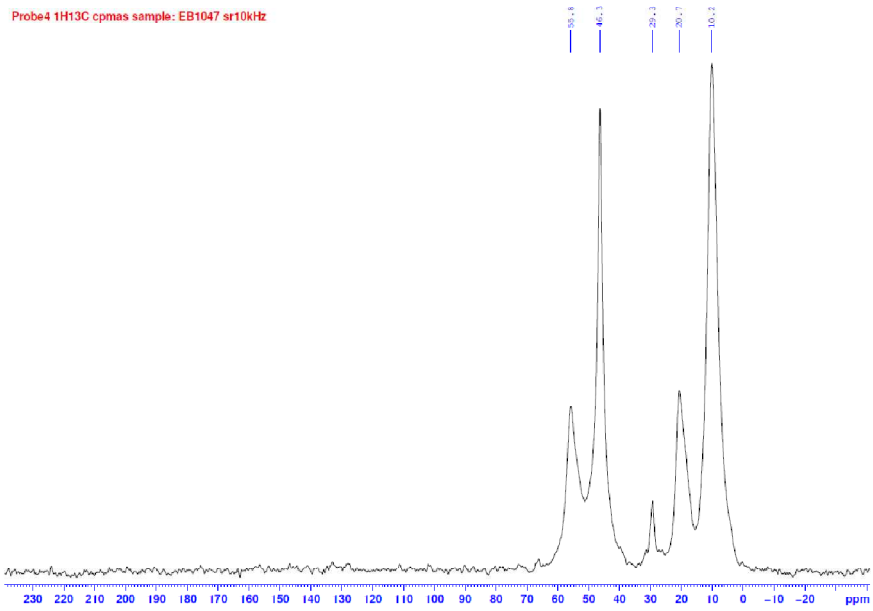


Figure 8: ^{13}C CP-MAS solid state NMR of **GA**-MCM41 (2.0 nm)

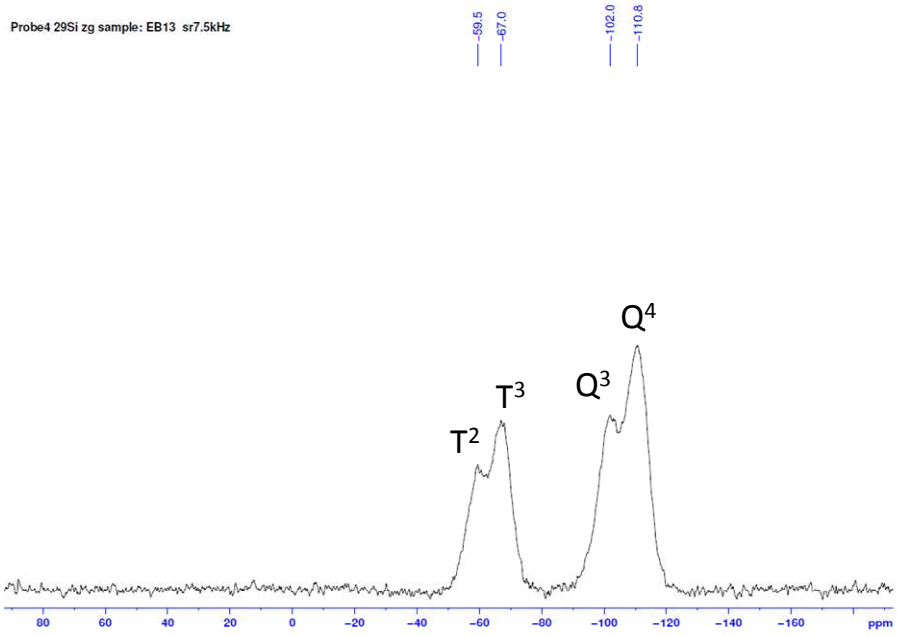


Figure 9: ^{29}Si CP-MAS solid state NMR of **GA**-SBA15 (5.8 nm)

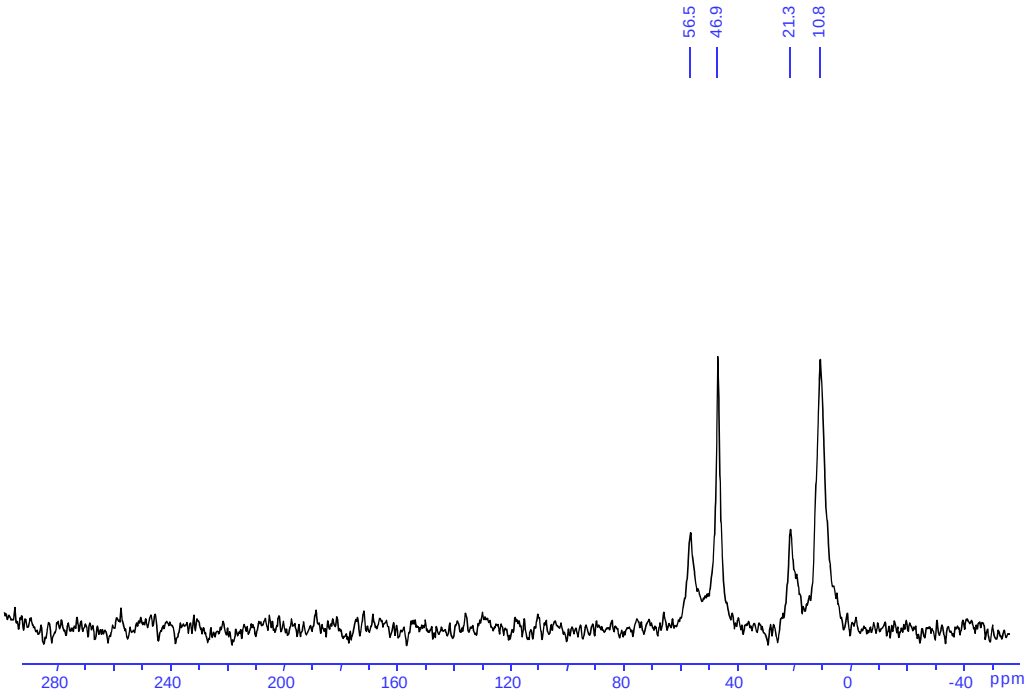


Figure 10: ^{13}C CP-MAS solid state NMR of recycled **GA**-SBA15 (5.8 nm)

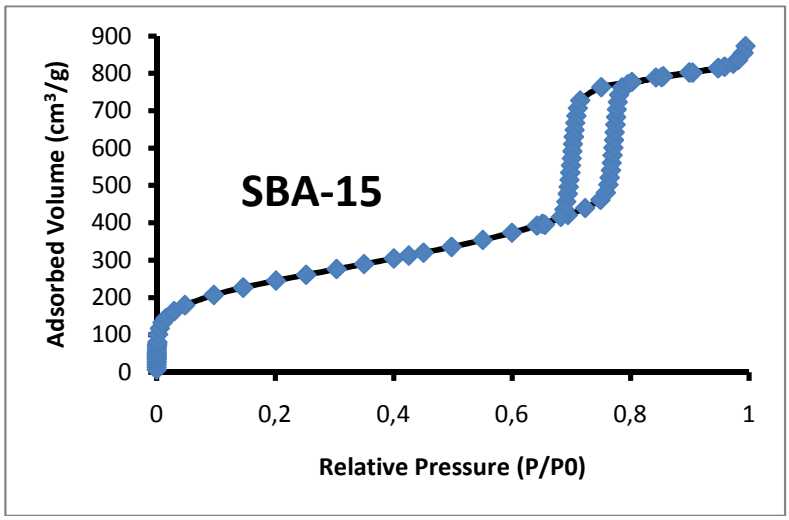


Figure 11: Nitrogen adsorption-desorption isotherm of SBA15. Isotherm of type IV, characteristic of mesoporous materials with a narrow pore size distribution S_{BET}: 874 ± 3 m_2/g, Vp: 1.1 cm_3/g and $Dp_{BJHdes.}$: 7.9 nm.

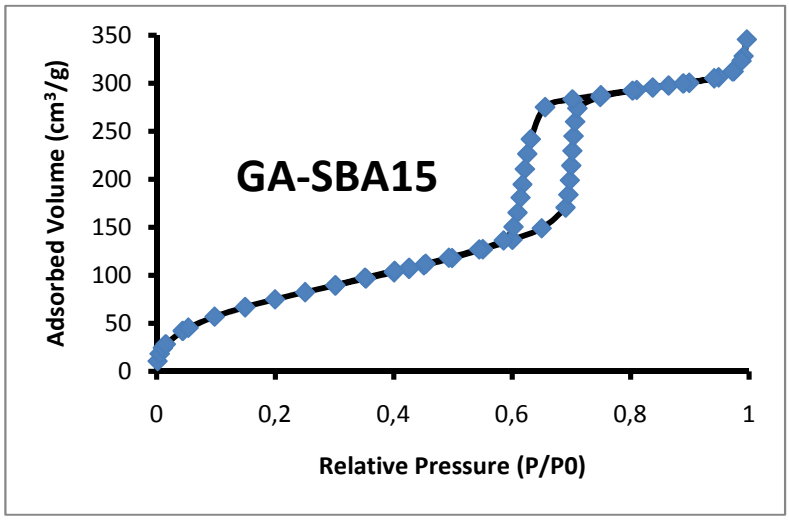


Figure 12: Nitrogen adsorption-desorption isotherm of **GA**-SBA15. Isotherm of type IV, characteristic of mesoporous materials with a narrow pore size distribution S_{BET}: 296 ± 3 m_2/g, Vp: 0.51 cm^3/g and $Dp_{BJHdes.}$: 5.8 nm.

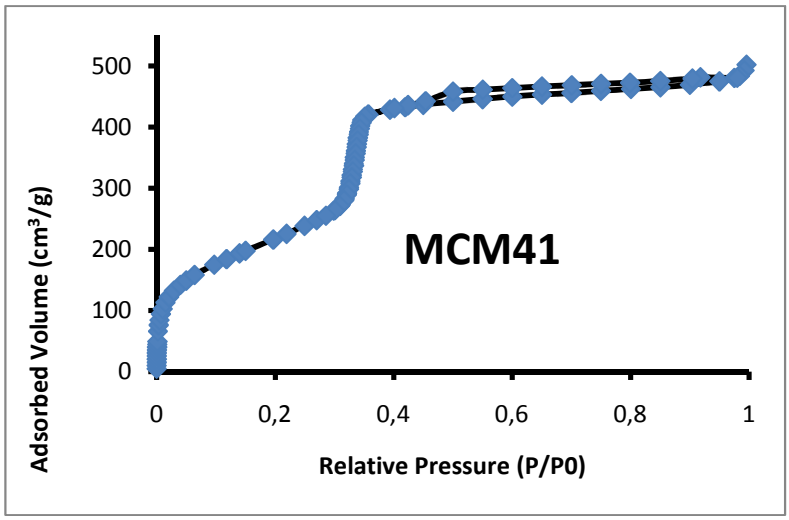


Figure 13: Nitrogen adsorption-desorption isotherm of **GA**-MCM41. Isotherm of type IV, characteristic of mesoporous materials with a narrow pore size distribution S_{BET}: 720 ± 3 m^2/g , Vp: 0.78 cm^3/g and Dp_{BJHdes} .: 2,4 nm.

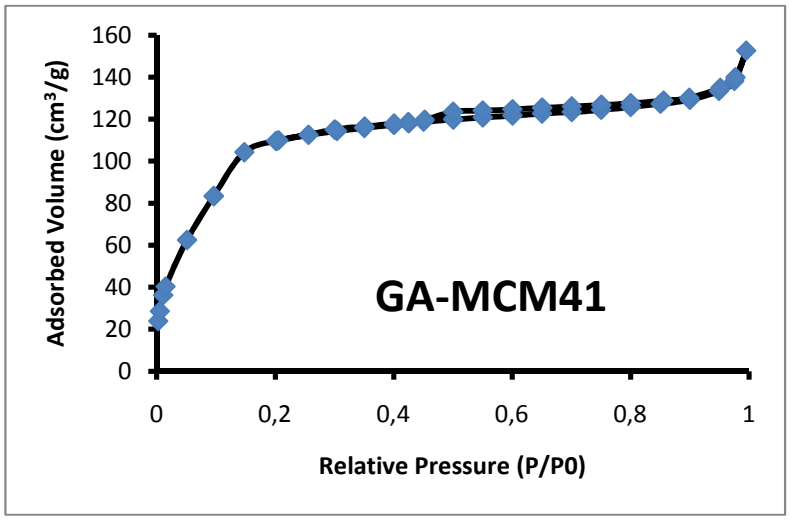


Figure 14: Nitrogen adsorption-desorption isotherm of **GA**-MCM41. Isotherm of type IV, characteristic of mesoporous materials with a narrow pore size distribution S_{BET}: 200 ± 3 m^2/g and $Dp_{est.}$: 2 nm.

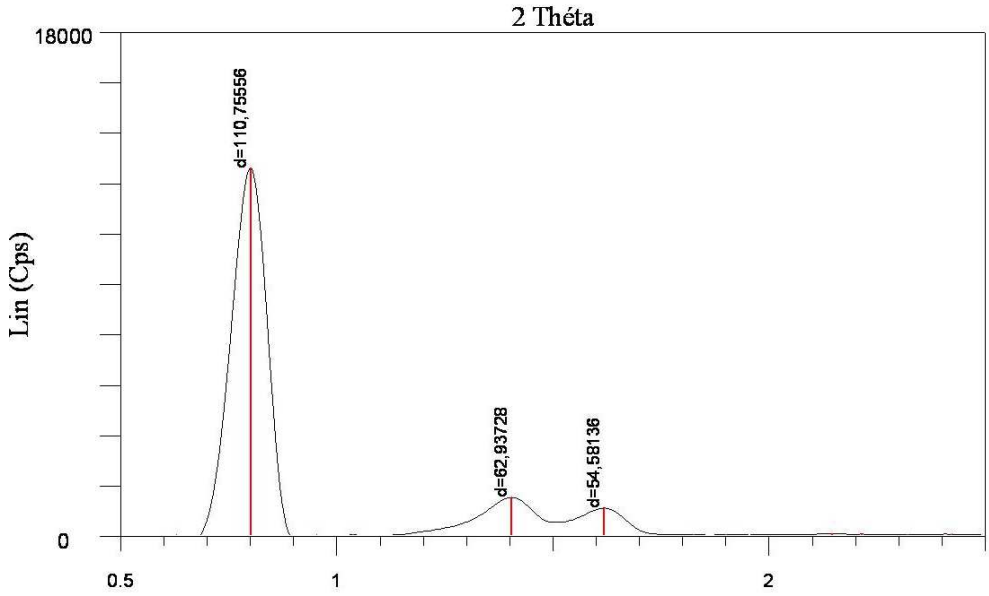


Figure 15: Powder Small Angle X-Ray Diffraction pattern of SBA15

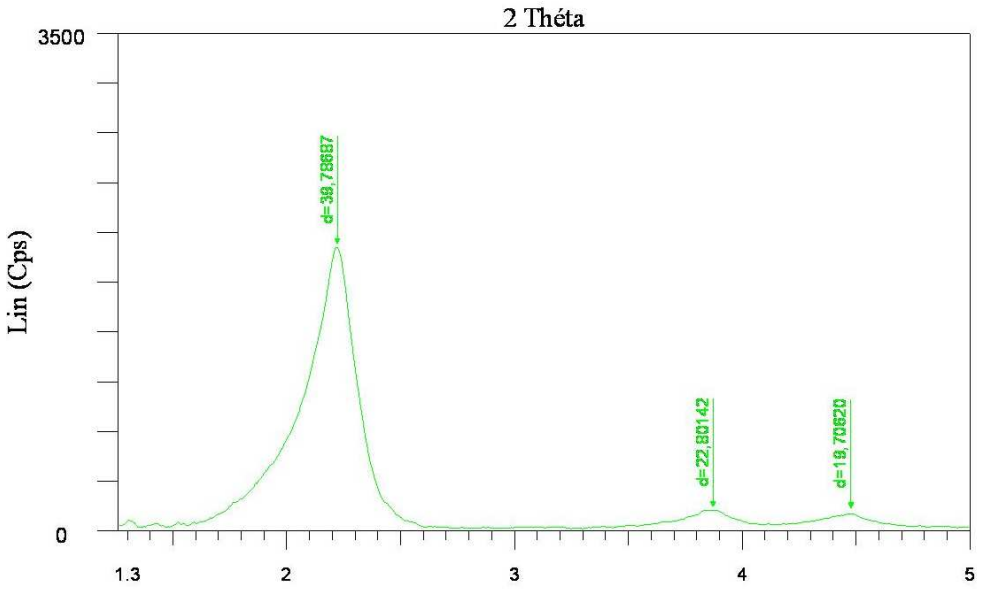


Figure 16: Powder Small Angle X-Ray Diffraction pattern of MCM41

2. Synthesis and rearrangement of substrates 1a, 5a, and 5c

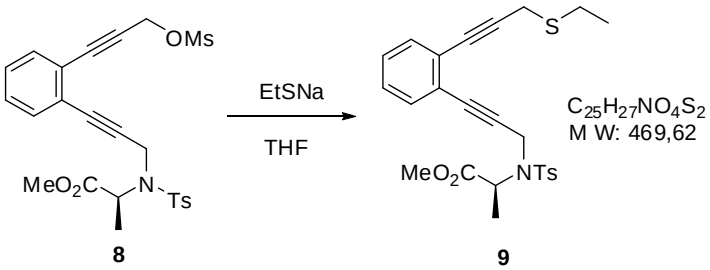
General information

All reactions were carried out in dry glassware using magnetic stirring and a positive pressure of argon. Solvents are commercially available, most of them were used as purchased (analytic grade), without further purification. THF was distilled over sodium benzophenone ketyl prior to use. Dry state adsorption conditions and purification were performed on silica gel 60 Å (70-230 mesh). Analytical thin layer chromatography was performed on pre-coated silica gel plates. Visualization was accomplished by UV (254 nm) and with phosphomolybdic acid in ethanol. ^{1}H NMR spectra were recorded on 400 MHz-spectrometers. ^{13}C spectra were recorded at 100 MHz. Chemical shifts (δ) are reported in ppm. Signals due residual protonated solvent (^{1}H NMR) or to the solvent (^{13}C NMR) served as the internal standard: $CDCl_3$ (7.26 ppm and 77.16 ppm). Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). The lists of coupling constants (*J*) correspond to the order of multiplicity assignment and are reported in Hertz (Hz). APT was used for ^{13}C spectra assignment. All melting points were uncorrected and were recorded in open capillary tubes using a Buchi melting point apparatus.
High resolution mass spectra were obtained on QStar Elite (Applied Biosystems SCIEX).
Crude mixture and purified compounds were analysed by chiral HPLC with double detection, with UV and circular dichroism detectors. The solvents for chiral chromatography (*n*-hexane, 2-PrOH, ethanol) were HPLC grade, they were degassed and filtered on a 0.45 µm membrane before use. The columns used are Chiralpak IC (250*4.6 mm, cellulose tris(3,5-dichlorophenylcarbamate)), Chiralpak AS-3 (250*4.6 mm, amylose tris[(*S*)alpha-phenethyl]carbamate), and Chiralpak IA (250*4.6 mm, amylose tris-(3,5-dimethylphenylcarbamate)). Enantiomeric excesses were determined by integration of the peaks on the chromatograms obtained by UV detection at 254, 240, 230 or 220 nm, and confirmed by circular dichroism detection at 254 nm. The sign given by the on-line circular dichroism detector for one enantiomer is the sign in the solvent used for the chromatographic separation.

The rotatory powers were measured on a 241 MC Perkin-Elmer polarimeter with a sodium lamp and a double-jacketed cell thermostated at the given temperature.
The syntheses of racemic starting materials and rearranged products were achieved according to the procedures described for optically pure materials in the following.

1.6. Synthesis of **1a**

(*S*)-2-[{3-[2-(3-Ethylsulfanyl-prop-1-ynyl)-phenyl]-prop-2-ynyl}-(toluene-4-sulfonyl)-amino]-propionic acid methyl ester (9)

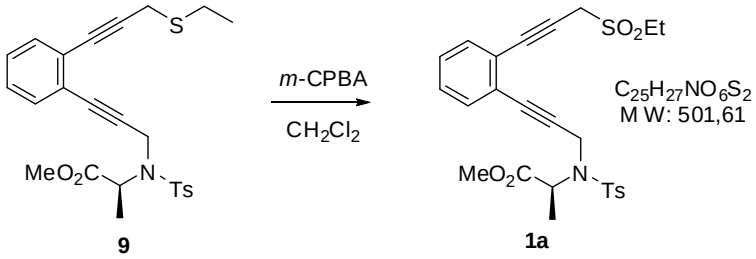


8 **9**

To a solution of ethanethiol (100 µL, 1.32 mmol) in freshly distilled anhydrous THF (20 mL), a 16.2 M aqueous sodium hydroxide solution (325 µL, 52.5 mg, 1.32 mmol) was added at room temperature. Then a solution of **8**[6] (565 mg, 1.12 mmol) in THF (10 mL) was slowly added *via* syringe and the reaction mixture was vigorously stirred overnight. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (pentane/Et_2O, 80/30 to 60/40). This afforded **9** as a yellow oil (363 mg, 69%). $[\alpha]_D^{20}$= -22.1 (c=0.9, $CHCl_3$). **HRMS** (ESI): *m/z*: calcd for $[M+NH_4]^+$ $C_{25}H_{31}N_2O_4S_2$: 487.1720, found: 487.1708.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.82 (2H, br d, *J*=8.5, CH_{ar}), 7.41-7.38 (1H, m, CH_{ar}), 7.24-7.17 (5H, m, CH_{ar}), 4.69 (1H, q, *J*=7.3, $CHCH_3$), 4.59 (1H, d, *J*=18.6, CH_2N, A part of an AB pattern), 4.38 (1H, d, *J*=18.6, CH_2N, B part of an AB pattern), 3.62 (3H, s, CH_3O), 3.51 (2H, s, CH_2SEt), 2.77 (2H, q, *J*=7.5, SCH_2CH_3), 2.35 (3H, s, CH_3C), 1.54 (3H, d, *J*=7.3, CH_3CH), 1.32 (3H, t, *J*=7.5, SCH_2CH_3).
^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.9 (CO_2Me), 143.6 (C_{ar}), 137.3 (C_{ar}), 132.2 (CH_{ar}), 132.1 (CH_{ar}), 129.6 (2xCH_{ar}), 128.2 (CH_{ar}), 127.8 (CH_{ar}), 127.7 (2xCH_{ar}), 125.8 (C_{ar}), 125.0 (C_{ar}), 89.8 ($C_{C\equiv C}$), 88.3 ($C_{C\equiv C}$), 83.4 ($C_{C\equiv C}$), 81.3 ($C_{C\equiv C}$), 55.1 (CHN), 52.4 (CH_3O), 35.2 (CH_2N), 25.8 (CH_2S), 21.6 (CH_3), 20.0 (SCH_2), 16.4 (CH_3), 14.4 (CH_3).

(*S*)-2-[{3-[2-(3-Ethanesulfonyl-prop-1-ynyl)-phenyl]-prop-2-ynyl}-(toluene-4-sulfonyl)-amino]-propionic acid methyl ester (1a)

[6] M. Nechab, D. Campolo, J. Maury, P. Perfetti, N. Vanthuyne, D. Siri, and M. P. Bertrand, *J. Am. Chem. Soc.*, 2010, **132**, 14742.



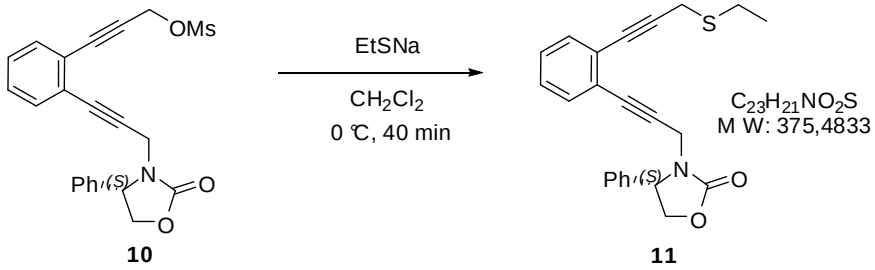
m-Chloroperbenzoic acid (75%) (346 mg, 1.5 mmol) was dissolved in dichloromethane (15 mL), and the solution was cooled to 0 °C. To this mixture a solution of **9** (323 mg, 0.688 mmol) in dichloromethane (5 mL) was added *via* syringe, and the reaction mixture was stirred for 40 min at 0 °C. The crude product was purified by flash chromatography on silica gel (pentane/CH_2Cl_2, 50/50 to 15/85) then the product was washed with a saturated solution of $NaHCO_3$, dried over $MgSO_4$ and concentrated to afford **1a** as a yellow oil (334 mg, 97%). ee=88% (Chiralpak AS-3, hexane/EtOH 50/50, $R_t(S)$ = 13.22 min, $R_t(R)$ = 10.54 min). $[\alpha]_D^{20}$= -11.1 (c=0.9, $CHCl_3$). **HRMS** (ESI): *m/z*: calcd for $[M+NH_4]^+$ $C_{25}H_{31}N_2O_6S_2$: 519.1618, found: 519.1619.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.79 (2H, d, *J*=8.3, CH_{ar}), 7.47-7.43 (1H, m, CH_{ar}), 7.30-7.24 (5H, m, CH_{ar}), 4.67 (1H, q, *J*=7.3, $CHCH_3$), 4.52 (1H, d, *J*=18.8, CH_2N, A part of an AB pattern), 4.37 (1H, d, *J*=18.8, CH_2N, B part of an AB pattern), 4.15 (2H, AB pattern, *J*=17.1, Δν=10.6, CH_2SO_2Et), 3.58 (3H, s, CH_3O), 3.32 (2H, q, *J*=7.5, $SO_2CH_2CH_3$), 2.38 (3H, s, CH_3C), 1.53 (3H, d, *J*=7.3, CH_3CH), 1.47 (3H, t, *J*=7.5, $SO_2CH_2CH_3$).

^{13}C NMR (100 MHz, CDCl3) δ: 171.8 (CO_2Me), 143.8 (C_{ar}), 137.1 (C_{ar}), 132.4 (CH_{ar}), 132.1 (CH_{ar}), 129.6 (2xCH_{ar}), 128.9 (CH_{ar}), 128.4 (CH_{ar}), 127.6 (2xCH_{ar}), 125.7 (C_{ar}), 124.4 (C_{ar}), 89.4 ($C_{C\equiv C}$), 85.9 ($C_{C\equiv C}$), 82.6 ($C_{C\equiv C}$), 80.8 ($C_{C\equiv C}$), 55.0 (CHN), 52.4 (CH_3O), 46.2 (CH_2SO_2), 45.5 (CH_2SO_2), 35.1 (CH_2N), 21.6 (CH_3), 16.5 (CH_3), 6.8 (CH_3).

1.7. Synthesis of **5a**

(*S*)-3-{3-[2-(3-Ethylsulfanyl-prop-1-ynyl)-phenyl]-prop-2-ynyl}-4-phenyl-oxazolidin-2-one (11)

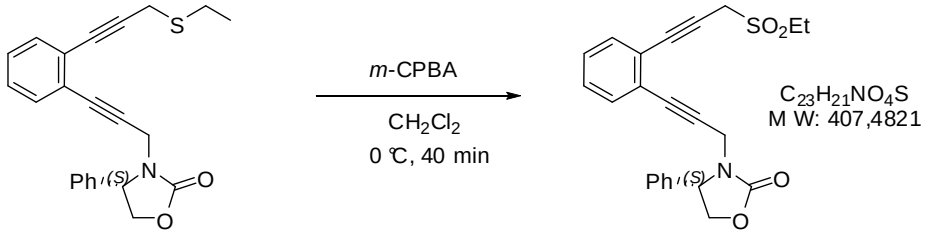


Sulfide **11** was prepared according to the procedure already described for the synthesis of **9**, using ethanethiol (130 µL, 1.72 mmol) in THF (10 mL), 210 µL of a 16 M solution of NaOH and **10**[6] (600 mg, 1.46 mmol). After work-up, purification by liquid chromatography on silica gel (pentane/CH_2Cl_2, 100/0 to 40/60) led to **11** (407 mg, 74%) as a pale yellow oil. $[\alpha]_D^{20}$= +227 (c=0.8, CH_2Cl_2). **HRMS** (ESI): *m/z*: calcd for $[M+H]^+$ $C_{23}H_{22}NO_2S$: 376.1366, found: 376.1365.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.45-7.36 (7H, m, CH_{ar}), 7.29-7.22 (2H, m, CH_{ar}), 5.13 (1H, pseudo t, X part of an ABX pattern, *J*=8.3), 4.71 (1H, t, *J*=8.8), 4.67 (1H, superimposed d, *J*=17.8, CH_2N, A part of an AB pattern), 4.18 (1H, pseudo t, *J*=8.3), 3.67 (1H, d, *J*=17.6,

CH_2N, B part of an AB pattern), 3.52 (2H, s, CH_2SEt), 2.73 (2H, q, *J*=7.5, CH_3CH_2S), 1.28 (3H, t, *J*=7.5, $CH_3CH_2SO_2$).
^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.9 (CO), 137.1 (C_{ar}), 132.4 (CH_{ar}), 132.3 (CH_{ar}), 129.5 ($2xCH_{ar}$), 129.3 (CH_{ar}), 128.4 (CH_{ar}), 128.0 (CH_{ar}), 127.4 ($2xCH_{ar}$), 125.9 (C_{ar}), 124.8 (C_{ar}), 89.8 (C≡C), 85.8 (C≡C), 83.9 (C≡C), 81.5 (C≡C), 70.1 (CH_{2oxa}), 59.1 (CH_{oxa}), 33.1 (CH_2N), 25.7 (CH_2S), 20.0 (CH_2S), 14.4 (CH_3).

(*S*)-3-{3-[2-(3-Ethanesulfonyl-prop-1-ynyl)-phenyl]-prop-2-ynyl}-4-phenyl-oxazolidin-2-one (5a)

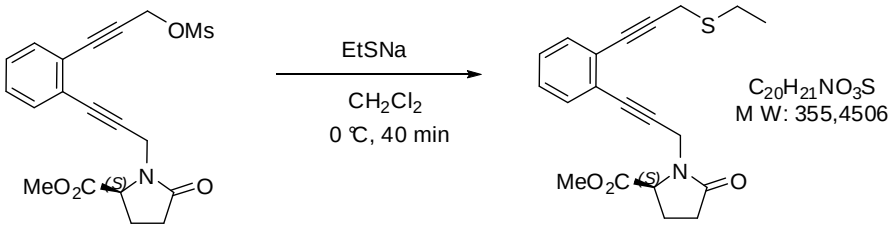


11 **5a**

The procedure already described for the synthesis of **1a** was followed, starting from **11** (375 mg, 1 mmol) and 75% *m*-CPBA (540 mg, 2.2 mmol) in dichloromethane (10 mL). Substrate **5a** was isolated as a pale yellow oil (355 mg, 87%) after purification by flash chromatography on silica gel (pentane/CH_2Cl_2,50/50 to 0/100). ee>99% (Chiralpak IA, hexane/EtOH 50/50, R_t(*S*) = 9.83 min, R_t(*R*) = 7.61 min). **$[\alpha]_D^{20}$**= +143.8 (c=0.675, $CHCl_3$). **HRMS** (ESI): *m/z*: calcd for $[M+H]^+$ $C_{23}H_{22}NO_4S$: 408.1264, found: 408.1266.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.47-7.36 (7H, m, CH_{ar}), 7.33-7.27 (2H, m, CH_{ar}), 5.06 (1H, t, *J*=8.5), 4.71 (1H, t, *J*=8.8), 4.62 (1H, d, *J*=17.8, CH_2N), 4.14 (1H, t, *J*=8.5), 4.11 (2H, superimposed AB pattern, *J*=17.1, Δν=11, CH_2SO_2Et), 3.69 (1H, d, *J*=17.8, CH_2N), 3.25 (2H, q, *J*=7.5, $CH_3CH_2SO_2$), 1.43 (3H, t, *J*=7.5, $CH_3CH_2SO_2$).
^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.1 (CO), 136.9 (C_{ar}), 132.5 (CH_{ar}), 132.3 (CH_{ar}), 129.5 ($2xCH_{ar}$), 129.4 (CH_{ar}), 128.9 (CH_{ar}), 128.5 (CH_{ar}), 127.4 ($2xCH_{ar}$), 125.3 (C_{ar}), 124.5 (C_{ar}), 86.5 (C≡C), 85.9 (C≡C), 83.1 (C≡C), 80.6 (C≡C), 70.2 (CH_{2oxa}), 59.4 (CH_{oxa}), 46.1 (CH_2S), 45.2 (CH_2S), 33.1 (CH_2N), 6.8 (CH_3).

1.8. Synthesis of **5c**

(*S*)-1-{3-[2-(3-Ethylsulfanyl-prop-1-ynyl)-phenyl]-prop-2-ynyl}-5-oxo-pyrrolidine-2-carboxylic acid methyl ester (13)



12 **13**

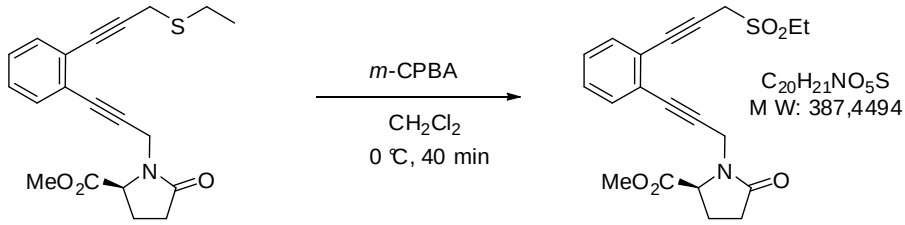
Sulfide **13** was prepared according to the procedure already described for the synthesis of **9**, using ethanethiol (30 µL, 0.39 mmol) in THF (2 mL), 57 µL of a 7 M solution of NaOH and

12[6](150 mg, 0.385 mmol). After work-up, purification by liquid chromatography on silica gel (pentane /CH_2Cl_2, 100/0 to 40/60) led to **13** (91 mg, 67%) as a pale yellow oil. $[\alpha]_D^{20}$= -11.7 (c=0.366, CH_2Cl_2). **HRMS** (ESI): *m/z*: calcd for $[M+H]^+$ $C_{20}H_{22}NO_3S$: 356.1315, found: 356.1314.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.43-7.37 (2H, m, CH_{ar}), 7.27-7.21 (2H, m, CH_{ar}), 4.89 (1H, d, *J*=17.8, CH_2N), 4.62-4,59 (1H, m, CH), 4.04 (1H, br d, *J*=17.8, CH_2N), 3.77 (3H, s, CH_3O), 3.55 (2H, s, CH_2SEt), 2.78 (2H, q, *J*=7.5, SCH_2CH_3), 2.57-2.38 (3H, m), 2.15-2.09 (1H, m), 1.33 (3H, t, *J*=7.5, SCH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.5 (CO), 172.4 (CO), 132.3 (CH_{ar}), 132.3 (CH_{ar}), 128.3 (CH_{ar}), 128.0 (CH_{ar}), 125.8 (C_{ar}), 125.0 (C_{ar}), 89.8 ($C_{C\equiv C}$), 86.3 ($C_{C\equiv C}$), 83.6 ($C_{C\equiv C}$), 81.5 ($C_{C\equiv C}$), 58.6 (CH), 52.6 (CH_3O), 32.4 (CH_2N), 29.6 (CH_2), 25.7 (CH_2SEt), 23.0 (CH_2), 19.9 (CH_2), 14.4 (CH_3).

(*S*)-1-{3-[2-(3-Ethanesulfonyl-prop-1-ynyl)-phenyl]-prop-2-ynyl}-5-oxo-pyrrolidine-2-carboxylic acid methyl ester (5c)



13 **5c**

The procedure already described for the synthesis of **1a** was followed, when reacting **13** (80 mg, 0.225 mmol) with 75% *m*-CPBA (113 mg, 0.49 mmol) in dichloromethane (3 mL). Substrate **5c** was isolated as a yellow solid (68 mg, 78%) after purification by flash chromatography on silica gel (CH_2Cl_2/Et_2O, 100/0 to 80/20). ee=97% (Chiralpak IA, hexane/EtOH 50/50, 1mL/min, R_t(*S*) = 7.63 min, R_t(*R*) = 8.99 min). $[\alpha]_D^{30}$= -2.1 (c=0.6, CH_2Cl_2). **HRMS** (ESI): *m/z*: calcd for $[M+H]^+$ $C_{20}H_{22}NO_5S$: 388.1213, found: 388.1210.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46-7.40 (2H, m, CH_{ar}), 7.32-7.27 (2H, m, CH_{ar}), 4.82 (1H, d, *J*=17.8, CH_2N), 4.54-4.52 (1H, m, CH), 4.15 (2H, s, CH_2SO_2Et), 4.07 (1H, br d, *J*=17.8, CH_2N), 3.76 (3H, s, CH_3O), 3.30 (2H, q, *J*=7.5, $SO_2CH_2CH_3$), 2.56-2.36 (3H, m), 2.15-2.03 (1H, m), 1.47 (3H, t, *J*=7.5, $SO_2CH_2CH_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.7 (CO), 172.4 (CO), 132.5 (CH_{ar}), 132.4 (CH_{ar}), 129.0 (CH_{ar}), 128.5 (CH_{ar}), 125.5 (C_{ar}), 124.3 (C_{ar}), 87.1 ($C_{C\equiv C}$), 86.0 ($C_{C\equiv C}$), 82.7 ($C_{C\equiv C}$), 80.6 ($C_{C\equiv C}$), 58.8 (CH), 52.7 (CH_3O), 46.0 (CH_2SO_2), 45.2 (CH_2SO_2), 32.2 (CH_2N), 29.5 (CH_2), 23.0 (CH_2), 6.9 (CH_3).

1.9. General procedure for the stoichiometric cyclisation

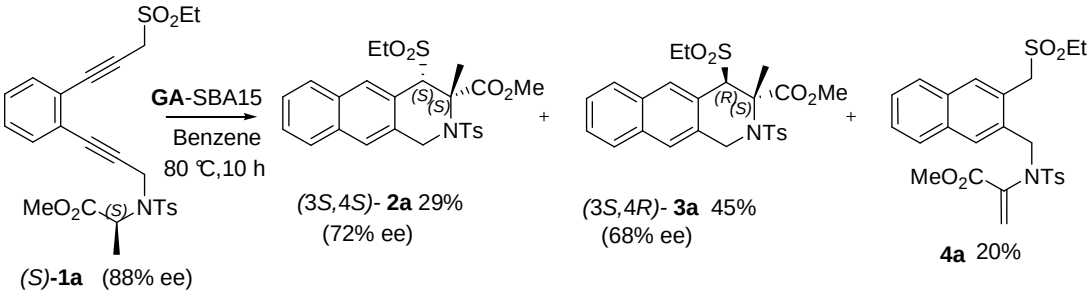
In a typical experiment, 400 mg (0.566 mmol of amine) of mesoporous silica grafted with the tertiary amine group (**GA**-SBA15) were added to a solution of enediyne (*S*)-**1b** (130 mg, 0.259 mmol) in benzene (20 mL). The mixture was stirred at 80 °C for 10h. The reaction was monitored by CCM (CH_2Cl_2/Et_2O, 98/2). After filtration and recovery of silica (rinsed with ether), purification by liquid chromatography on silica gel (pentane/CH_2Cl_2, from 70/30 to

0/100) led to the isolation of (3*S*,4*R*)-**3a** (58 mg, 45%, ee=68%) as a yellowish oil, **4a** (26 mg, 20%), and (3*S*,4*S*)- **2a** (38 mg, 29%, ee=72%) as yellowish oil.

1.10. General procedure for the catalytic cyclisation

In a typical experiment, 26 mg (0.037 mmol, 20 mol %) of mesoporous silica grafted with the tertiary amine group (**GA**-SBA15) were added to a solution of enediyne (*S*)-**5c** (100 mg, 0.184 mmol) in benzene (4 mL). The mixture stirred at 80 °C for 13h. The reaction was monitored by CCM (CH_2Cl_2/Et_2O, 95/5). The crude was then purified by liquid chromatography on silica gel (pentane/ CH_2Cl_2, from 70/30 to 0/100). This led to the isolation of (*R*,*S*)-**6c** (45 mg, 60%, ee=93.5%) as colourless oil and (*S*,*S*)-**7c** (22 mg, 30%, ee=62%) as a colourless oil.

1.11. Cycloaromatisation of (*S*)-**1a**



(3*S*,4*S*)-4-Ethanesulfonyl-3-methyl-2-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-benzo[*g*]isoquinoline-3-carboxylic acid methyl ester (2a)

ee=72% (Chiralpak IC, hexane/EtOH 50/50, 1mL/min R_t(*major)* = 16.93 min, R_t(*minor)* = 22.23 min). $[\alpha]_D^{30}$= +9.6 (c=0.3, CH_2Cl_2). **HRMS** (ESI): *m/z*: calcd for $[M+NH_4]^+$ $C_{25}H_{31}N_2O_6S_2$: 519.1618, found: 519.1614.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (2H, d, *J*=8.3, CH_{ar}), 7.86-7.82 (2H, m, CH_{ar}), 7.82 (1H, superimposed s, CH_{ar}), 7.69 (1H, s, CH_{ar}), 7.59-7.53 (2H, m, CH_{ar}), 7.32 (2H, d, *J*=8.0, CH_{ar}), 4.96 (1H, br d, *J*=14.3, CH_2N, A part of an AB pattern), 4.65 (1H, d, *J*=15.1, CH_2N, B part of an AB pattern), 4.59 (1H, s, $CHSO_2Et$), 3.93 (3H, s, CH_3O), 2.96 (1H, dq, *J*=13.3 and 7.5, $SO_2CH_2CH_3$, A part of ABX_3 pattern), 2.85 (1H, dq, *J*=13.3 and 7.5, $SO_2CH_2CH_3$, B part of an ABX_3 pattern), 2.42 (3H, s), 1.79 (3H, s), 1.26 (3H, t, *J*=7.5, $SO_2CH_2CH_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.2 (CO_2Me), 143.7 (C_{ar}), 137.8 (C_{ar}), 134.0 (C_{ar}), 132.6 (C_{ar}), 131.8 (C_{ar}), 130.6 (CH_{ar}), 129.8 (2xCH_{ar}), 128.0 (CH_{ar}), 127.99 (2xCH_{ar}), 127.95 (CH_{ar}), 127.8 (CH_{ar}), 127.2 (CH_{ar}), 126.5 (CH_{ar}), 124.8 (C_{ar}), 74.4 ($CHSO_2$), 64.7 (C), 53.4 (CH_3O), 48.0 (CH_2), 46.7 (CH_2), 29.3 (CH_3), 21.7 (CH_3), 5.7 (CH_3).

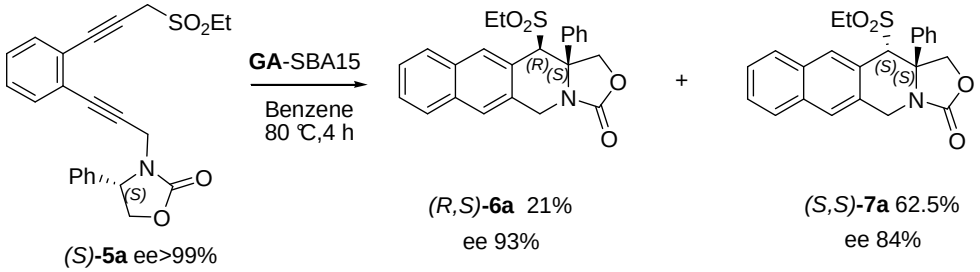
(3*S*,4*R*)-4-Ethanesulfonyl-3-methyl-2-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-benzo[*g*]isoquinoline-3-carboxylic acid methyl ester (3a)

ee=68% (Chiralpak IC, hexane/EtOH 50/50, 1mL/min, R_t(*major)* = 13.44 min, R_t(*minor)* = 18.32 min). **$[\alpha]_D^{30}$**= +63.7 (c=0.85, $CHCl_3$). **HRMS** (ESI): *m/z*: calcd for $[M+NH_4]^+$ $C_{25}H_{31}N_2O_6S_2$: 519.1618, found: 519.1609.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.91 (1H, s, CH_{ar}), 7.86 (2H, d, *J*=8.5, CH_{ar}), 7.84 (1H, d, *J*=7.8, CH_{ar}), 7.78 (1H, d, *J*=7.8, CH_{ar}), 7.67 (1H, s, CH_{ar}), 7.54-7.46 (2H, m, CH_{ar}), 7.35 (2H, d, *J*=8.0), 5.29 (1H, d, *J*=15.9, CH_2N, A part of an AB pattern), 4.98 (1H, d, *J*=15.9, CH_2N, B part of an AB pattern), 4.72 (1H, s, $CHSO_2Et$), 3.24 (3H, s, CH_3O), 3.09 (1H, dq, *J*=13.3 and 7.5, $SO_2CH_2CH_3$, A part of ABX_3 pattern), 2.69 (1H, dq, *J*=13.3 and 7.5, $SO_2CH_2CH_3$, B part of an ABX_3 pattern), 2.44 (3H, s), 2.32 (3H, s), 1.21 (3H, t, *J*= 7.5, $SO_2CH_2CH_3$).
^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.5 (CO_2Me), 143.8 (C_{ar}), 138.0 (C_{ar}), 133.6 (C_{ar}), 132.1 (C_{ar}), 131.0 (CH_{ar}), 130.2 (C_{ar}), 129.6 (2xCH_{ar}), 128.3 (CH_{ar}), 127.8 (2xCH_{ar}), 127.6 (CH_{ar}), 127.5 (CH_{ar}), 126.7 (CH_{ar}), 125.4 (CH_{ar}), 125.1 (C_{ar}), 72.1 ($CHSO_2$), 66.5 (C), 53.1 (CH_3O), 49.3 (CH_2), 46.1 (CH_2), 23.2 (CH_3), 21.7 (CH_3), 5.1 (CH_3).

2-[(3-Ethanesulfonylmethyl-naphthalen-2-ylmethyl)-(toluene-4-sulfonyl)-amino]-acrylic acid methyl ester (4a)

HRMS (ESI): *m/z*: calcd for $[M+NH_4]^+$ $C_{25}H_{31}N_2O_6S_2$: 519.1618, found: 519.1615.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.90 (1H, br s, CH_{ar}), 7.83-7.81 (1H, m, CH_{ar}), 7.75 (2H, d, *J*=8.5, CH_{ar}), 7.69-7;67 (1H, m, CH_{ar}), 7.51-7.44 (2H, m, CH_{ar}), 7.41 (1H, s, CH_{ar}), 7.35 (2H, d, *J*=8.0, CH_{ar}), 6.18 (1H, s, =CH), 5.45 (1H, s, =CH), 4.89 (2H, s, CH_2), 4.85 (2H, s, CH_2), 3.57 (3H, s, CH_3O), 3.29 (2H, q, *J*=7.5, $SO_2CH_2CH_3$), 2.47 (3H, s), 1.56 (3H, t, *J*= 7.5, $SO_2CH_2CH_3$).
^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.3 (CO_2Me), 144.4 (C_{ar}), 135.9 (C_{ar}), 134.4 (C_{ar}), 133.2 (CH_{ar}), 133.1 (C=), 133.0 (C_{ar}), 131.7 (CH_{ar}), 131.4 (C_{ar}), 129.8 (2xCH_{ar}), 128.2 (2xCH_{ar}), 127.9 (CH_{ar}), 127.6 (CH_{ar}), 127.4 (CH_2), 127.1 (CH_{ar}), 127.0 (CH_{ar}), 124.5 (C_{ar}), 54.4 (CH_2), 52.5 (CH_3O), 52.3 (CH_2), 48.2 (CH_2), 21.8 (CH_3), 6.9 (CH_3).

1.12. Cycloaromatisation of (*S*)-5a



(*S*)-**5a** ee>99%

(*R,S*)-**6a** 21%
ee 93%

(*S,S*)-**7a** 62.5%
ee 84%

(11*R*,11a*S*)-11-Ethanesulfonyl-11a-phenyl-1,4,11,11a-tetrahydro-2-oxa-3a-aza-cyclopenta[*b*]anthracen-3-one (6a)

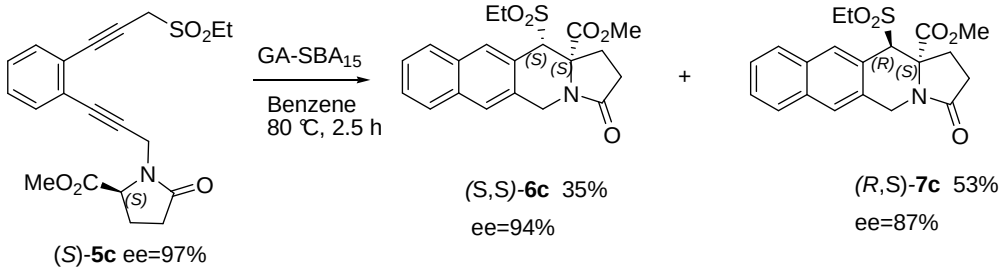
ee=93% (Chiralpak IC, hexane/EtOH 50/50, 1mL/min R_t(*minor)* = 12.77 min, R_t(*major)* =14.31 min). **$[\alpha]_D^{30}$**= +106.6 (c=0.9, $CHCl_3$). **HRMS** (ESI): *m/z*: calcd for $[M+H]^+$ $C_{23}H_{22}NO_4S$: 408.1264, found: 408.1265.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.26 (1H, s, CH_{ar}), 7.88 (1H, d, *J*=7.5, CH_{ar}), 7.82 (1H, d, *J*=7.5, CH_{ar}), 7.72 (1H, s, CH_{ar}), 7.59-7.49 (4H, m, CH_{ar}), 7.32-7.29 (3H, m, CH_{ar}), 5.12 (1H,

d, *J*=9.5, CH_2O, A part of an AB pattern), 5.09 (1H, s, $CHSO_2Et$), 4.99 (1H, d, *J*=16.5, CH_2N, A part of an AB pattern), 4.74 (1H, d, *J*=9.8, CH_2O, B part of an AB pattern), 4.65 (1H, br d, *J*=16.5, CH_2N, B part of an AB pattern), 2.99 (1H, dq, *J*=13.8 and 7.5, $CH_3CH_2SO_2$, A part of an ABX_3 pattern), 2.57 (1H, dq, *J*=13.8 and 7.5, $CH_3CH_2SO_2$, B part of an ABX_3 pattern), 1.31 (3H, t, *J*=7.5, $CH_3CH_2SO_2$).
^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.2 (CO), 137.1 (C_{ar}), 132.8 (C_{ar}), 132.4 (C_{ar}), 130.8 (C_{ar}), 129.3 (CH_{ar}), 129.0 (CH_{ar}), 128.8 (2xCH_{ar}), 128.3 (CH_{ar}), 127.9 (CH_{ar}), 127.5 (CH_{ar}), 127.4 (2xCH_{ar}), 126.9 (CH_{ar}), 126.3 (CH_{ar}), 124.9 (C_{ar}), 76.9 (CH_2O), 71.1 ($CHSO_2Et$), 64.6 (C), 49.8 (CH_2), 43.6 (CH_2), 6.1 (CH_3).

(11*S*,11a*S*)-11-Ethanesulfonyl-11a-phenyl-1,4,11,11a-tetrahydro-2-oxa-3a-aza-cyclopenta[*b*]anthracen-3-one (7a)

ee=84% (Chiralpak IC, hexane/EtOH 50/50, 1mL/min R_t (*major)* = 32.96 min, R_t *(minor)*=53.62 min). **$[\alpha]_D^{30}$**= +33 (c=1.5, $CHCl_3$). **HRMS** (ESI): *m/z*: calcd for $[M+H]^+$ $C_{23}H_{22}NO_4S$: 408.1264, found: 408.1270.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.75-7.72 (2H, m, CH_{ar}), 7.70 (2H, br s, CH_{ar}), 7.50-7.42 (2H, m, CH_{ar}), 7.21 (4H, m, CH_{ar}), 7.14-7.09 (1H, m, CH_{ar}), 5.90 (1H, d, *J*=9.3, CH_2O), 5.31 (1H, d, *J*=16.8, CH_2N, A part of an AB pattern), 5.07 (1H, s, $CHSO_2Et$), 4.86 (1H, d, *J*=17.0, CH_2N, B part of an AB pattern), 4.31 (1H, d, *J*=9.0, CH_2O), 2.98 (1H, dq, *J*=13.5 and 7.5, $CH_3CH_2SO_2$, A part of an ABX_3 pattern), 2.82 (1H, dq, *J*=13.5 and 7.5, $CH_3CH_2SO_2$, B part of an ABX_3 pattern), 1.27 (3H, t, *J*=7.5, $CH_3CH_2SO_2$).
^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.4 (CO), 142.4 (C_{ar}), 133.5 (C_{ar}), 131.8 (C_{ar}), 131.3 (CH_{ar}), 129.5 (2xCH_{ar}), 129.3 (C_{ar}), 128.3 (CH_{ar}), 127.8 (CH_{ar}), 127.7 (CH_{ar}), 127.5 (CH_{ar}), 126.7 (CH_{ar}), 126.6 (CH_{ar}), 124.6 (C_{ar}), 124.0 (2xCH_{ar}), 72.5 (CH_2O), 67.5 ($CHSO_2Et$), 65.2 (C), 46.5 (CH_2), 44.9 (CH_2), 5.3 (CH_3).

1.13. Cycloaromatisation of (*S*)-**5c**



(*S*)-**5c** ee=97%

(*S*,S)-**6c** 35%
ee=94%

(*R*,S)-**7c** 53%
ee=87%

(11*S*,11a*S*)-11-Ethanesulfonyl-3-oxo-2,3,4,11-tetrahydro-1*H*-3a-aza-cyclopenta[*b*]anthracene-11a-carboxylic acid methyl ester (6c)

ee=94% (Chiralpak IC, hexane/EtOH 50/50, 1mL/min R_t (*major)* = 13.43 min, R_t *(minor)*=18.46 min). **$[\alpha]_D^{30}$**=-172 (c=0.186, CH_2Cl_2). **HRMS** (ESI): *m/z*: calcd for $[M+H]^+$ $C_{20}H_{22}NO_5S$: 388.1213, found: 388.1211.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.15 (1H, s, CH_{ar}), 7.85-7.80 (2H, m, CH_{ar}), 7.72 (1H, s, CH_{ar}), 7.56-7.49 (2H, m, CH_{ar}), 5.18 (1H, d, *J*=16.3, CH_2N, A part of an AB pattern), 4.93

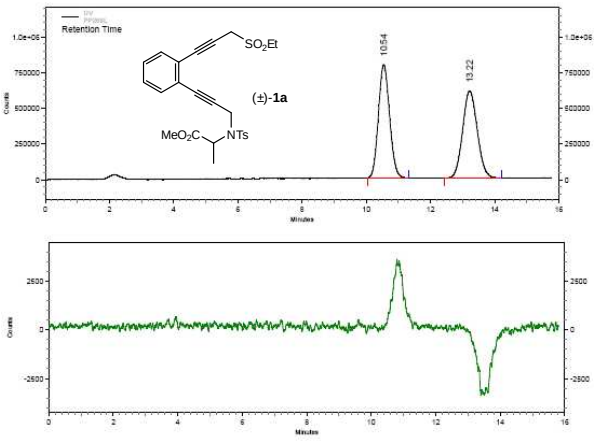
(1H, s, $CHSO_2Et$), 4.38 (1H, d, *J*=16.3, CH_2N, B part of an AB pattern), 3.83 (3H, s, OCH_3), 3.19-3.13 (1H, m), 3.17 (2H, superimposed q, *J*=7.5, $SO_2CH_2CH_3$), 2.69-2.59 (1H, m), 2.44-2.37 (1H, m), 2.25-2.17 (1H, m), 1.34 (3H, t, *J*=7.5, $SO_2CH_2CH_3$).
^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.3 (CO), 170.6 (CO), 133.0 (C_{ar}), 132.3 (C_{ar}), 131.4 (C_{ar}), 129.0 (CH_{ar}), 128.1 (CH_{ar}), 127.7 (CH_{ar}), 127.6 (CH_{ar}), 126.8 (CH_{ar}), 126.1 (CH_{ar}), 124.5 (C_{ar}), 74.0 ($CHSO_2Et$), 67.6 (C), 53.5 (OCH_3), 47.5 (CH_2), 41.3 (CH_2), 33.7 (CH_2), 30.0 (CH_2), 5.9 (CH_3).

(11*R*,11a*S*)-11-Ethanesulfonyl-3-oxo-2,3,4,11-tetrahydro-1*H*-3a-aza-cyclopenta[*b*]anthracene-11a-carboxylic acid methyl ester (7c)

ee=87% (Chiralpak IC, hexane/EtOH 50/50, 1mL/min R_t(*minor)* =17.46 min, R_t(*major)* =24.17 min). **$[\alpha]_D^{30}$**= -11.1 (c=0.18, CH_2Cl_2). **HRMS** (ESI): *m/z*: calcd for $[M+H]^+$ $C_{20}H_{22}NO_5S$: 388.1213, found: 388.1212.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.87 (1H, s, CH_{ar}), 7.78-7.74 (2H, m, CH_{ar}), 7.69 (1H, br s, CH_{ar}), 7.57-7.49 (2H, m, CH_{ar}), 5.12 (1H, d, *J*=17.6, CH_2N, A part of an AB pattern), 5.02 (1H, s, $CHSO_2Et$), 4.74 (1H, d, *J*=17.6, CH_2N, B part of an AB pattern), 3.66-3.56 (1H, ddd, *J*=14.0, 10.5 and 6.0), 3.51 (3H, s, OCH_3), 2.84-2.54 (4H, m superimposed to the ABX_3 pattern of $SO_2CH_2CH_3$), 2.34-2.26 (1H, ddd, *J*=14.0, 10.5 and 6.0), 1.24 (3H, t, *J*=7.5, $SO_2CH_2CH_3$).
^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.1 (CO), 171.8 (CO), 133.9 (C_{ar}), 132.0 (C_{ar}), 131.4 (CH_{ar}), 129.7 (C_{ar}), 128.0 (CH_{ar}), 127.9 (CH_{ar}), 127.6 (CH_{ar}), 126.9 (CH_{ar}), 126.9 (CH_{ar}), 124.6 (C_{ar}), 67.9 (C), 66.7 ($CHSO_2Et$), 53.5 (OCH_3), 47.9 (CH_2), 43.5 (CH_2), 29.6 (CH_2), 26.3 (CH_2), 5.2 (CH_3).

3. Chiral HPLC Spectra

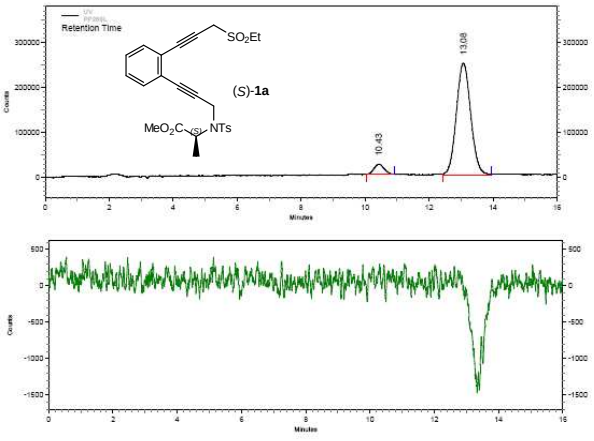
Method description :Chiralpak AS-3, Hexane/ethanol 50/50, 1 ml/min, UV 254 nm et CD254



UV Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
10.54	19197391	49.71	2.51	1.00	0.00
13.22	19420628	50.29	3.41	1.35	3.56
Totals	38618019	100.00			

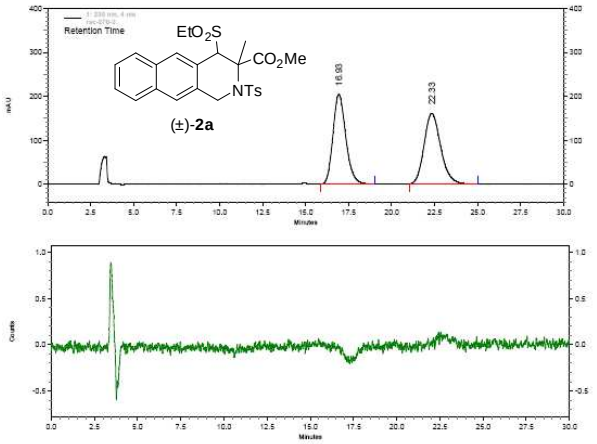
Method description :Chiralpak AS-3, Hexane/ethanol 50/50, 1 ml/min, UV 254 nm et CD254



UV Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
10.43	499974	6.09	2.48	0.00	0.00
13.08	7715680	93.91	3.36	0.00	3.71
Totals	8215654	100.00			

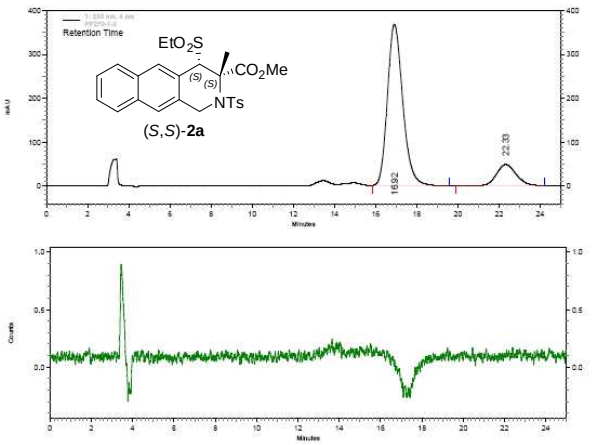
Method description : Chiralpak IC, Hexane/Ethanol 50/50, 1 ml/min, DAD and CD 254nm



1: 230 nm, 4 nm
Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
16.93	42435389	49.44	4.64	0.00	0.00
22.33	43390341	50.56	6.44	0.00	3.43
Totals	85825730	100.00			

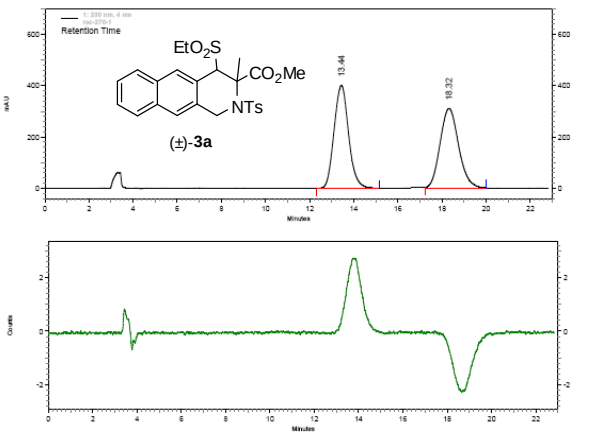
Method description : Chiralpak IC, Hexane/Ethanol 50/50, 1 ml/min, DAD and CD 254nm



1: 230 nm, 4 nm
Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
16.92	76175172	85.76	4.64	0.00	0.00
22.33	12650006	14.24	6.44	0.00	3.46
Totals	88825178	100.00			

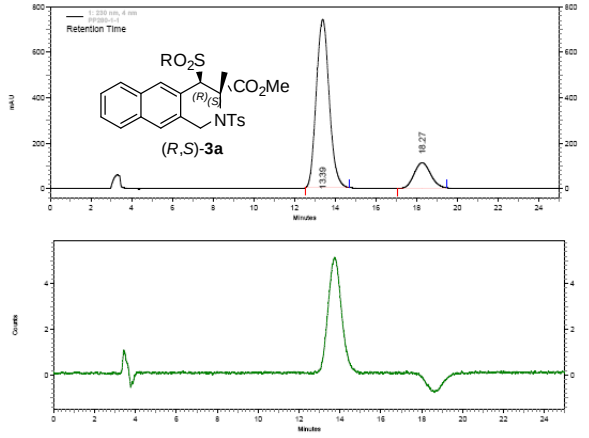
Method description : Chiralpak IC, Hexane/Ethanol 50/50, 1 ml/min, DAD and CD 254nm



1: 230 nm, 4 nm
Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
13.44	73231572	50.38	3.48	0.00	0.00
18.32	72129016	49.62	5.11	0.00	3.54
Totals	145360588	100.00			

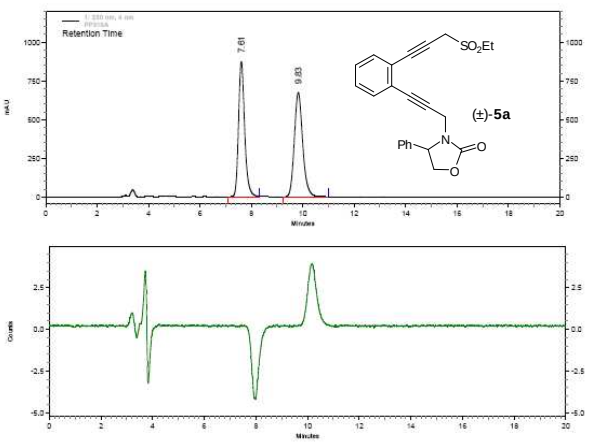
Method description : Chiralpak IC, Hexane/Ethanol 50/50, 1 ml/min, DAD and CD 254nm



1: 230 nm, 4 nm
Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
13.39	131052673	83.92	3.46	1.00	0.00
18.27	25113774	16.08	5.09	1.47	3.64
Totals	156166447	100.00			

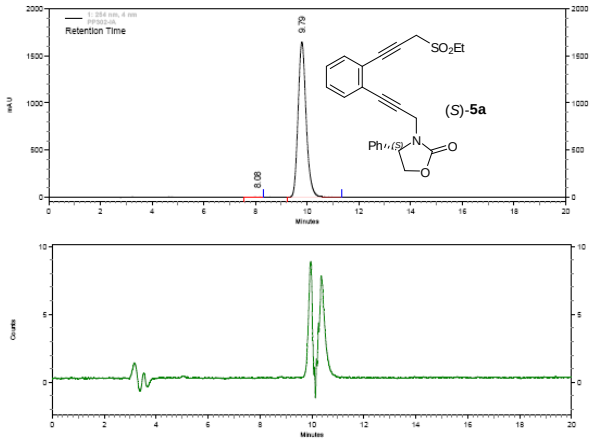
Method description : Chiralpak IA, Hexane/Ethanol 50/50, 1 ml/min, DAD and CD 254nm



1: 230 nm, 4 nm
Results

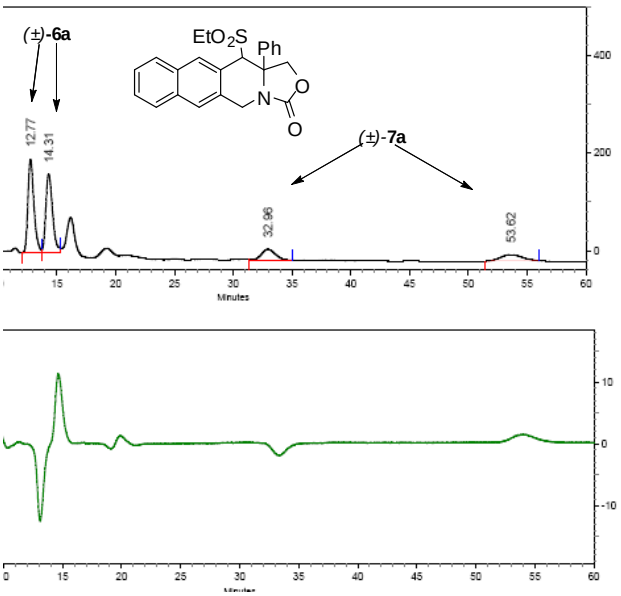
Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
7.61	57976728	48.65	1.54	0.00	0.00
9.83	61182287	51.35	2.28	0.00	4.35
Totals	119159015	100.00			

Method description : Chiralpak IA, Hexane/Ethanol 50/50, 1 ml/min, DAD and CD 254nm



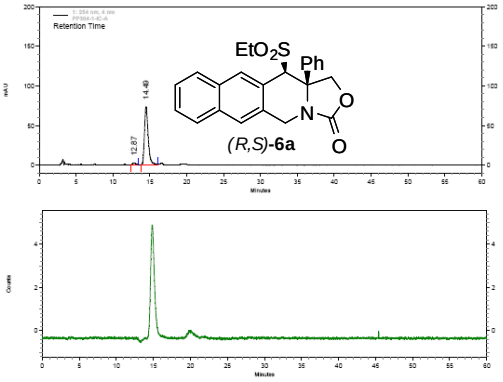
1: 254 nm, 4 nm
Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
8.08	341994	0.24	1.69	1.00	0.00
9.79	142436364	99.76	2.26	1.34	0.00
Totals	142778358	100.00			



Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
12.77	27408866	40.66	3.26	0.00	0.00
14.31	26047444	38.64	3.77	0.00	1.55
32.96	7426692	11.02	9.99	0.00	11.46
53.62	6522680	9.68	16.87	0.00	7.27
Totals	67405682	100.00			

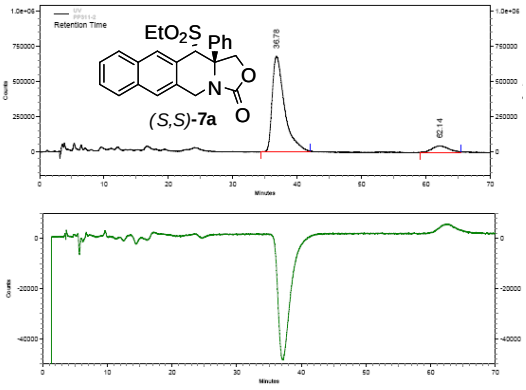
Method description : Chiralpak IC, Hexane/Ethanol 50/50, 1 ml/min, DAD and CD 254nm



1: 254 nm, 4 nm
Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
12.87	329364	3.07	3.29	1.00	0.00
14.49	10407176	96.93	3.83	1.16	1.82
Totals	10736540	100.00			

Method description :Chiralpak IC, Hexane/ethanol 50/50, 1 ml/min, UV 254 nm et CD254

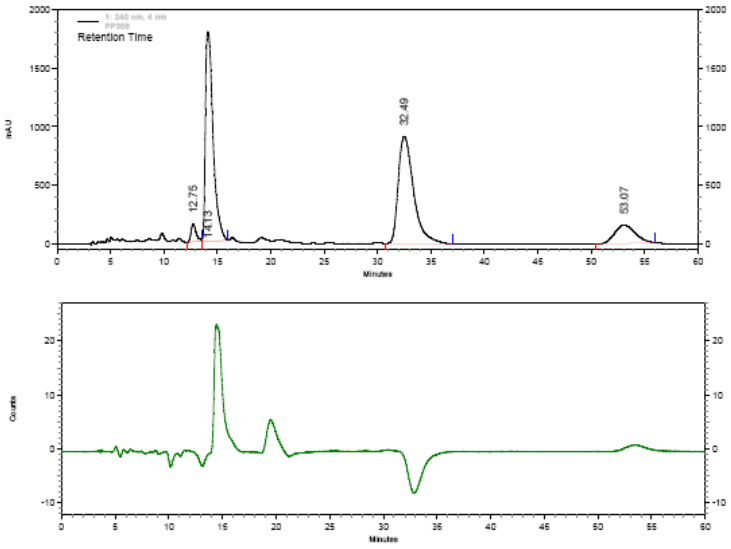


UV Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
36.78	90997649	91.78	11.26	1.00	0.00
62.14	8154687	8.22	19.71	1.75	6.14
Totals	99152336	100.00			

Crude of the cyclization of **5a** (catalytic version)

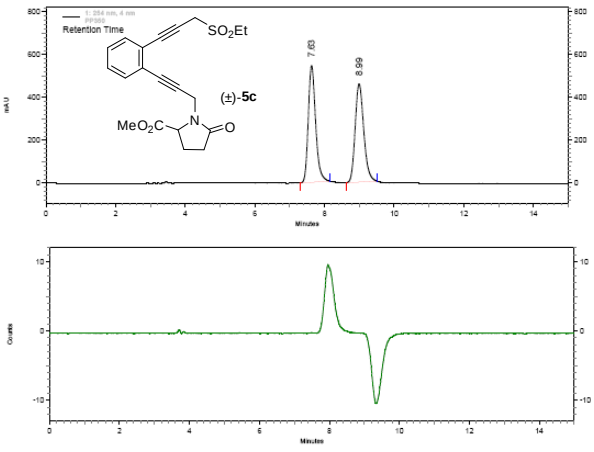
Method description : Chiralpak IC, Hexane/Ethanol 50/50, 1 ml/min, DAD and CD 254nm



1: 240 nm, 4 nm
Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
12.75	20766024	2.52	3.25	0.00	0.00
14.13	356360957	43.23	3.71	0.00	1.34
32.49	363249939	44.06	9.83	0.00	9.83
53.07	84018930	10.19	16.69	0.00	6.69
Totals	824395850	100.00			

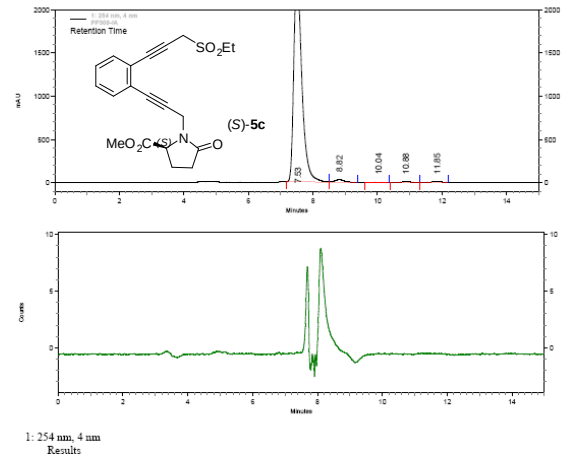
Method description : Chiralpak IA, Hexane/Ethanol 50/50, 1 ml/min, DAD and CD 254nm



1: 254 nm, 4 nm
Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
7.63	32003960	50.36	1.54	1.00	0.00
8.99	31547370	49.64	2.00	1.30	3.27
Totals	63551330	100.00			

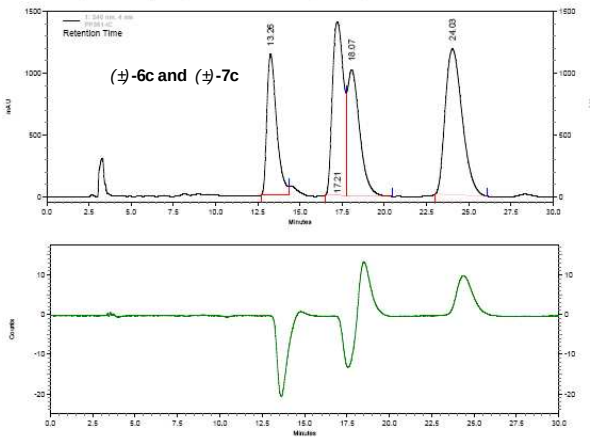
Method description : Chiralpak IA, Hexane/ethanol 50/50, 1 ml/min, UV 254 nm et CD 254nm



1: 254 nm, 4 nm
Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
7.53	159147398	98.02	0.00	0.00	
8.82	2311169	1.42	0.00	0.00	
10.04	82410	0.05	0.00	0.00	
10.88	414360	0.26	0.00	0.00	
11.85	407759	0.25	0.00	0.00	
Totals	162363096	100.00			

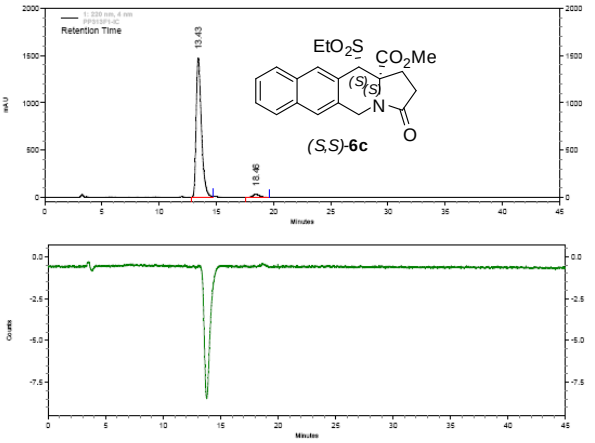
Method description : Chiralpak IC, Hexane/Ethanol 50/50, 1 ml/min, DAD and CD 254nm



1: 240 nm, 4 nm
Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
13.26	180674909	18.59	3.42	0.00	0.00
17.21	254014493	26.14	4.74	0.00	3.17
18.07	208118076	21.42	5.02	0.00	0.49
24.03	328896300	33.85	7.01	0.00	3.04
Totals	971703778	100.00			

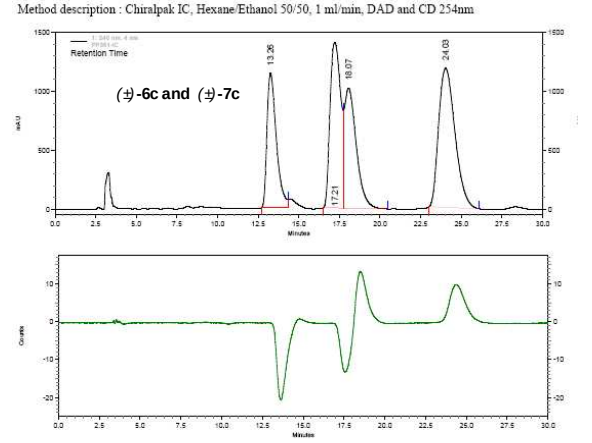
Method description : Chiralpak IC, Hexane/Ethanol 50/50, 1 ml/min, DAD and CD 254nm



1: 220 nm, 4 nm
Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
13.43	190666299	97.21	3.48	1.00	0.00
18.46	5469928	2.79	5.15	1.48	5.06
Totals	196136227	100.00			

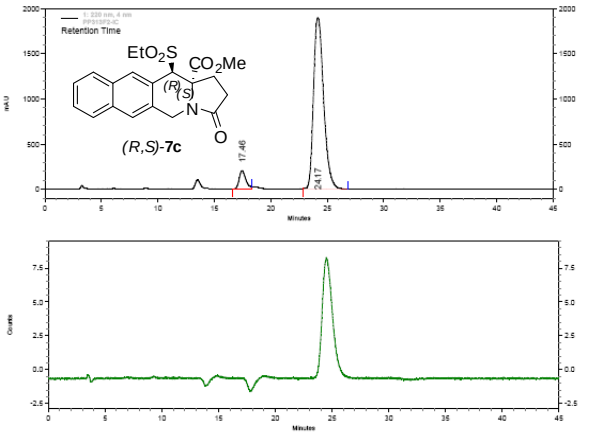
Method description : Chiralpak IC, Hexane/Ethanol 50/50, 1 ml/min, DAD and CD 254nm



1: 240 nm, 4 nm
Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
13.26	180674909	18.59	3.42	0.00	0.00
17.21	254014493	26.14	4.74	0.00	3.17
18.07	208118076	21.42	5.02	0.00	0.49
24.03	328896300	33.85	7.01	0.00	3.04
Totals	971703778	100.00			

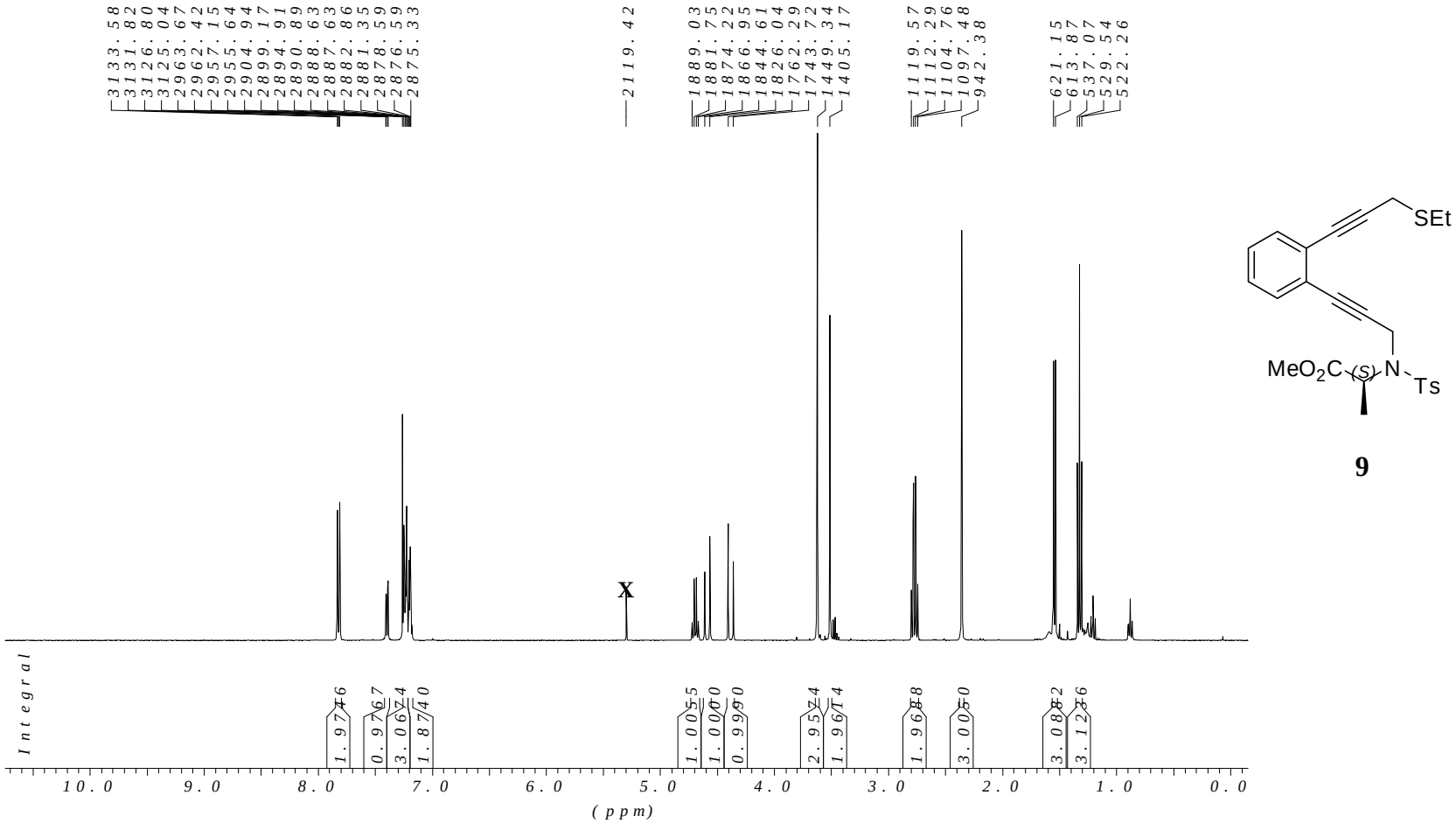
Method description : Chiralpak IC, Hexane/ethanol 50/50, 1 ml/min, UV 254 nm et CD 254nm



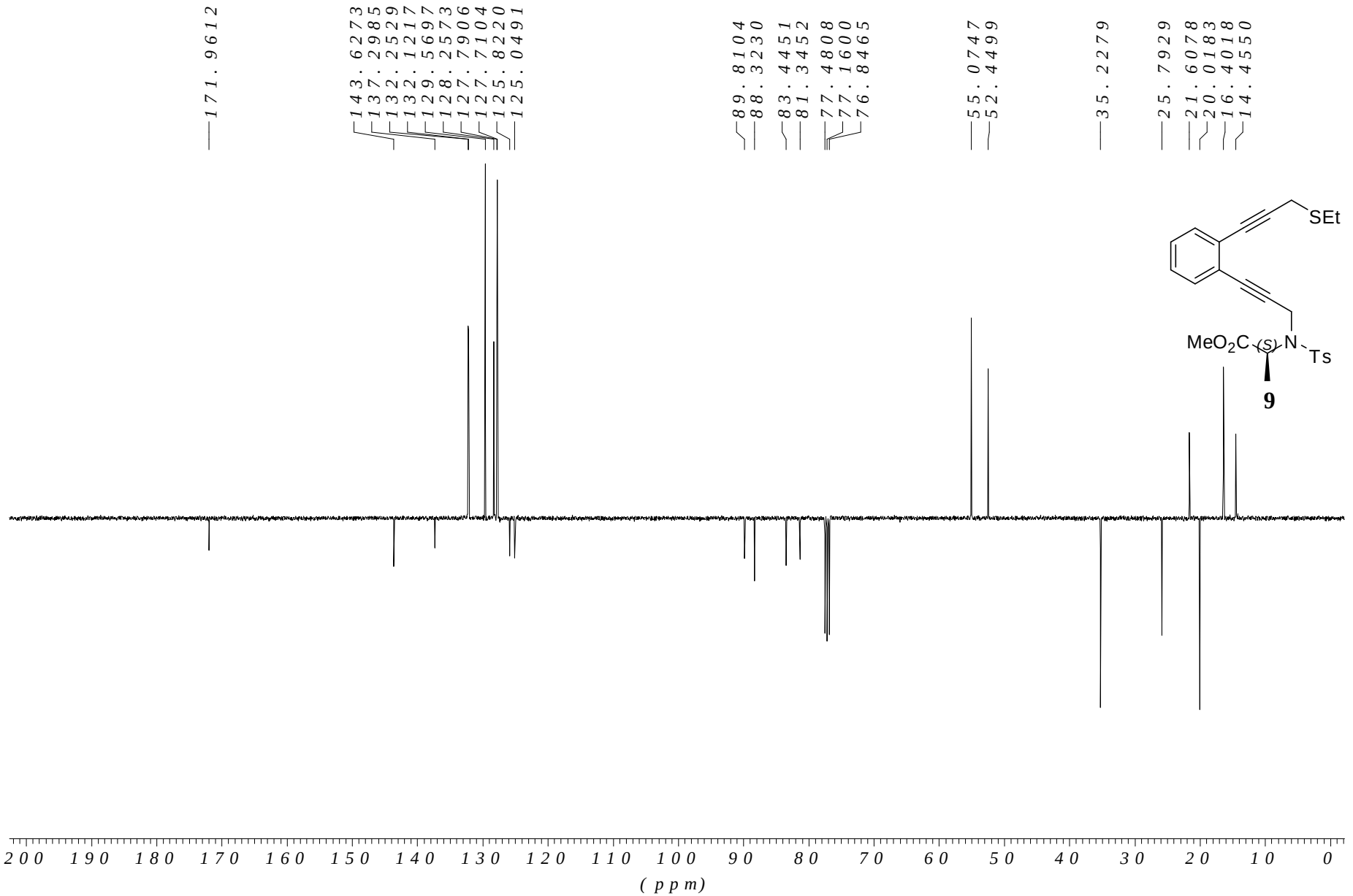
1: 220 nm, 4 nm
Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
17.46	33877384	6.71	0.00	0.00	
24.17	470906845	93.29	0.00	0.00	
Totals	504784229	100.00			

4. NMR Spectra



9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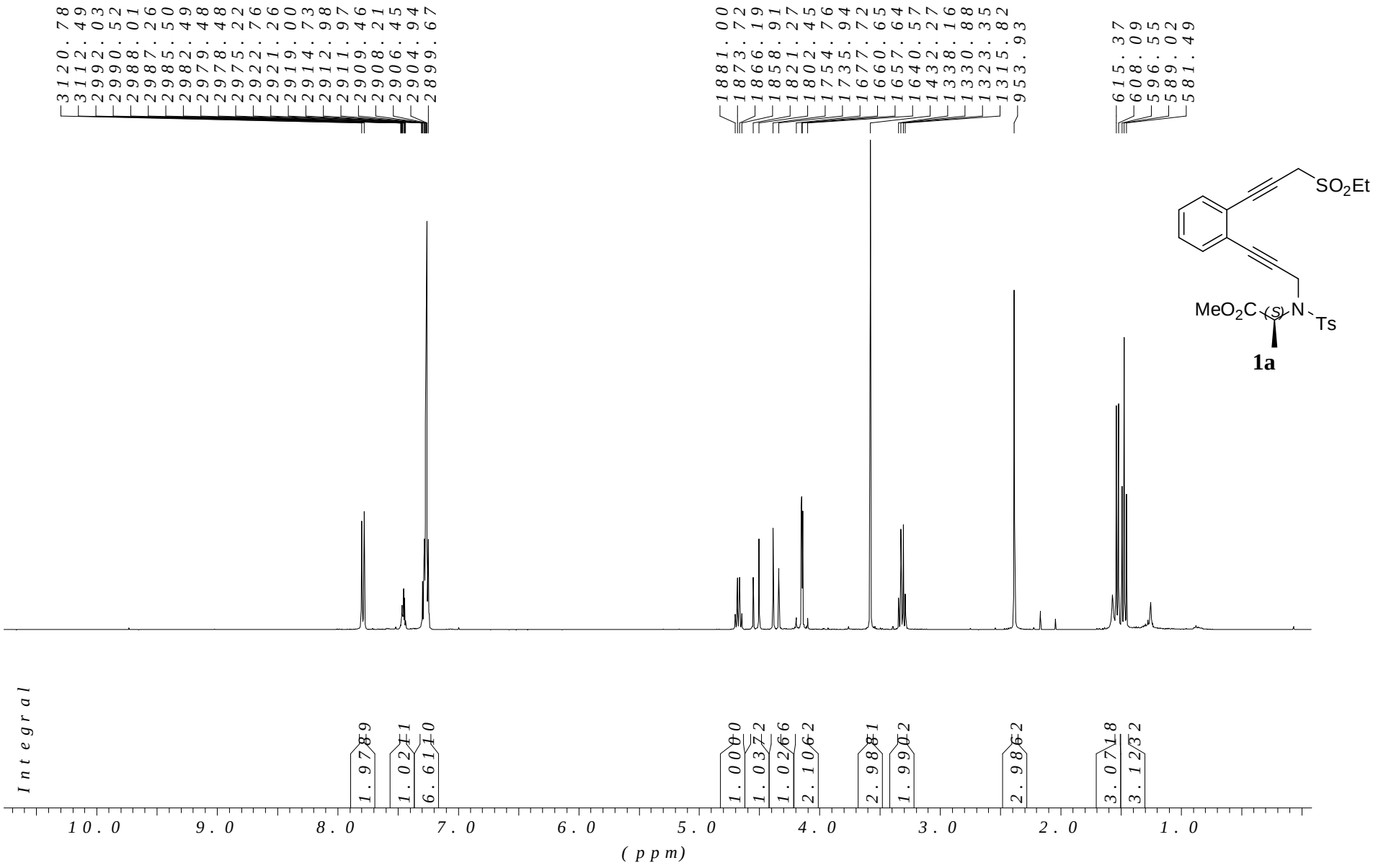
143.6273
137.2985
132.2529
132.1217
129.5697
128.2573
127.7906
127.7104
125.8220
125.0491
89.8104
88.3230
83.4451
81.3452
77.4808
77.1600
76.8465
55.0747
52.4499
35.2279
25.7929
21.6078
20.0183
16.4018
14.4550
SEt
MeO2C
(S)
N
Ts
9
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)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2992.03
2990.52
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2979.48
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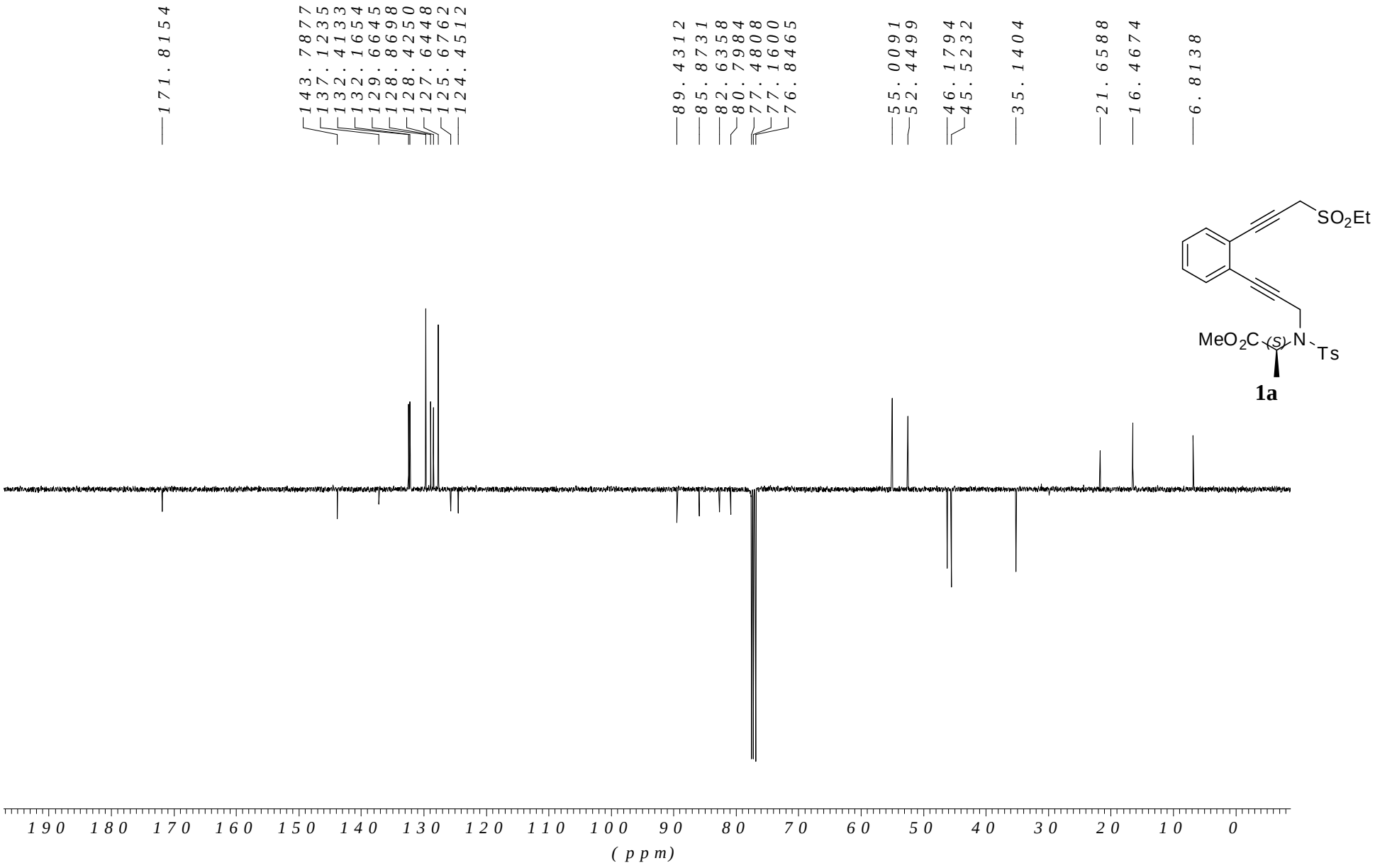
2975.22
2922.76
2921.26
2919.00
2914.73
2912.98
2911.97
2909.46
2908.21
2906.45
2904.94
2899.67
1881.00
1873.72
1866.19
1858.91
1821.27
1802.45
1754.76
1735.94
1677.72
1660.65
1657.64
1640.57
1432.27
1338.16
1330.88
1323.35
1315.82
953.93
615.37
608.09
596.55
589.02
581.49
SO2Et
MeO2C
(S)
N
Ts
1a
Integral
1.97
1.02
6.61
1.00
1.03
1.02
2.10
2.98
1.99
2.98
3.07
3.12
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
(ppm)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127.6448
125.6762
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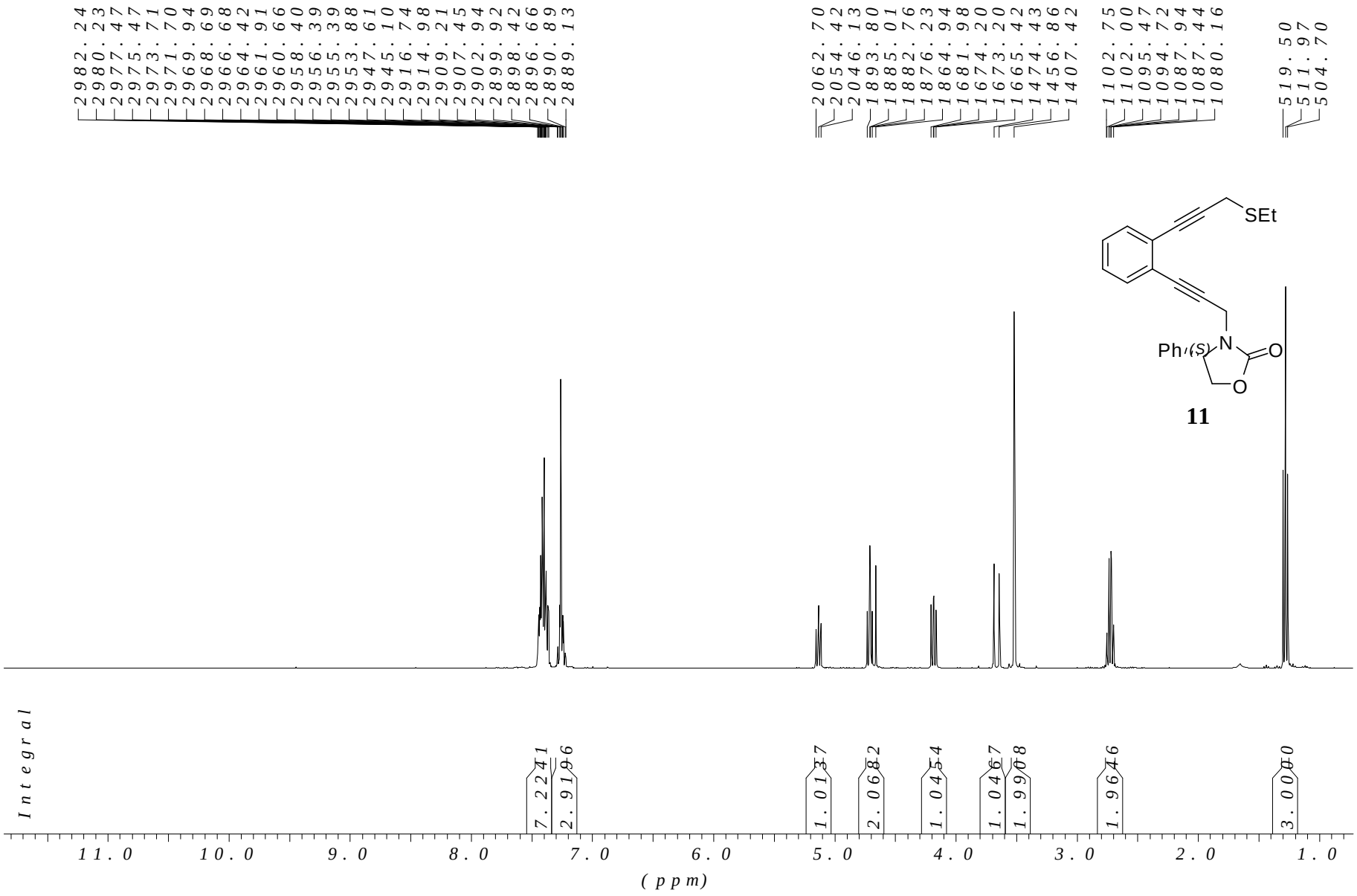
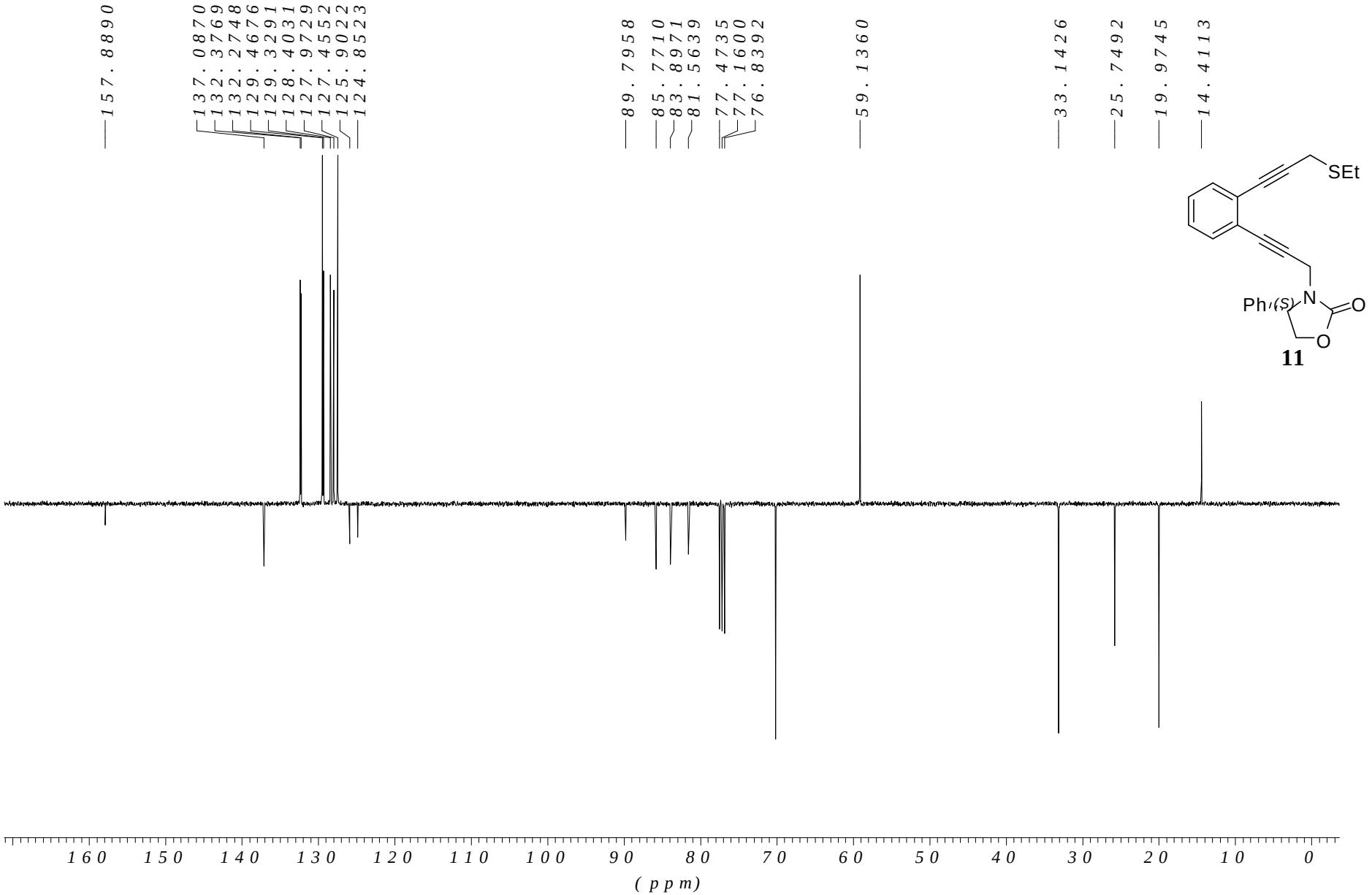
89.4312
85.8731
82.6358
80.7984
77.4808
77.1600
76.8465
55.0091
52.4499
46.1794
45.5232
35.1404
21.6588
16.4674
6.8138
SO2Et
MeO2C
(S)
N
Ts
1a
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)


2982.24
2980.23
2977.47
2975.47
2973.71
2971.70
2969.94
2968.69
2966.68
2964.42
2961.91
2960.66
2958.40
2956.39
2955.39
2953.88
2947.61
2945.10
2916.74
2914.98
2909.21
2907.45
2902.94
2899.92
2898.42
2896.66
2890.89
2889.13
2062.70
2054.42
2046.13
1893.80
1885.01
1882.76
1876.23
1864.94
1681.98
1674.20
1673.20
1665.42
1474.43
1456.86
1407.42
1102.75
1102.00
1095.47
1094.72
1087.94
1087.44
1080.16
519.50
511.97
504.70
SEt
Ph
(S)
N
O
O
11
Integral
7.22
2.91
1.01
2.06
1.04
1.04
1.99
1.96
3.00
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
(ppm)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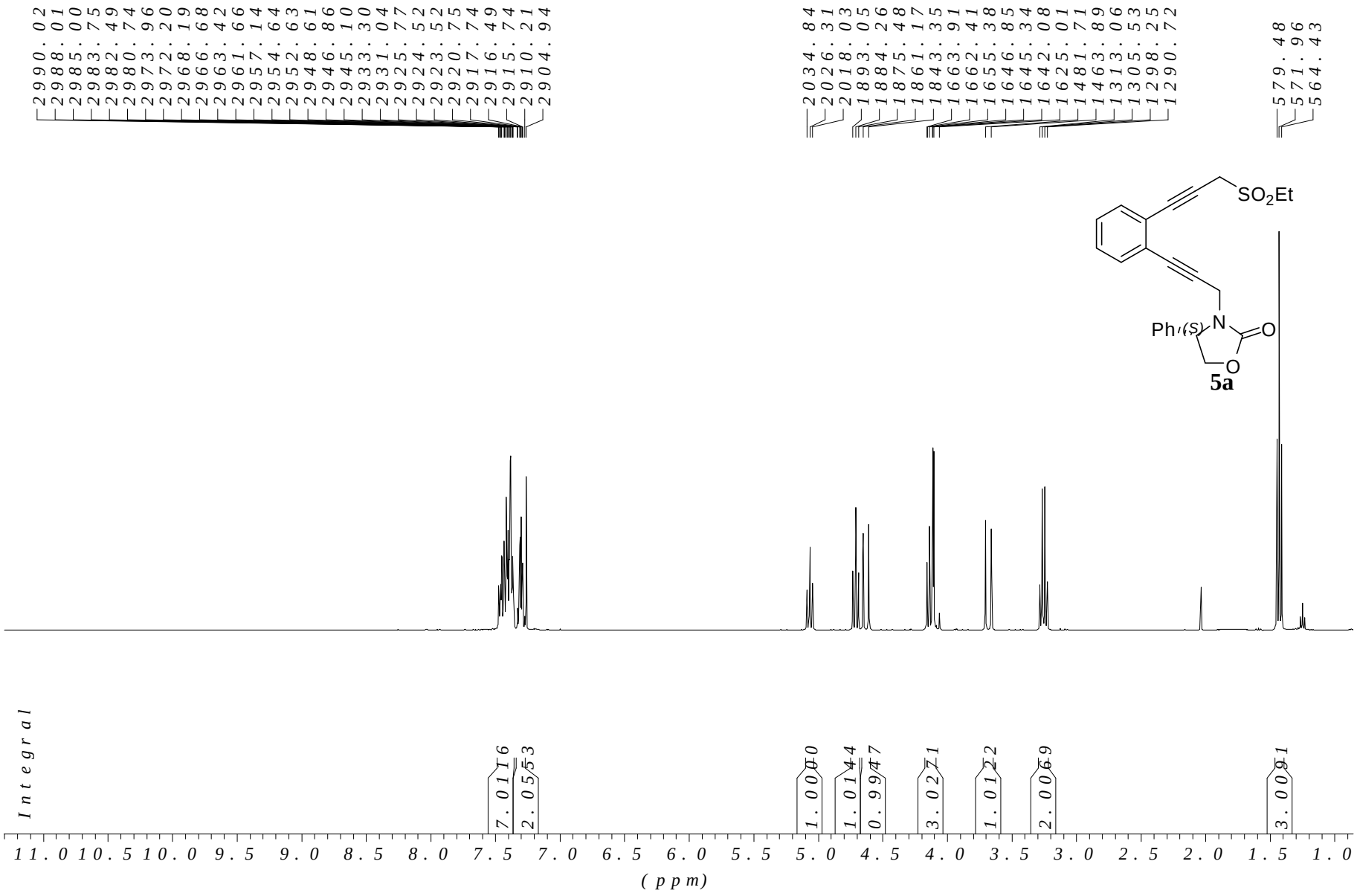
137.0870
132.3769
132.2748
129.4676
129.3291
128.4031
127.9729
127.4552
125.9022
124.8523
89.7958
85.7710
83.8971
81.5639
77.4735
77.1600
76.8392
59.1360
33.1426
25.7492
19.9745
14.4113
SEt
Ph
(S)
N
O
O
11
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)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2985.00
2983.75
2982.49
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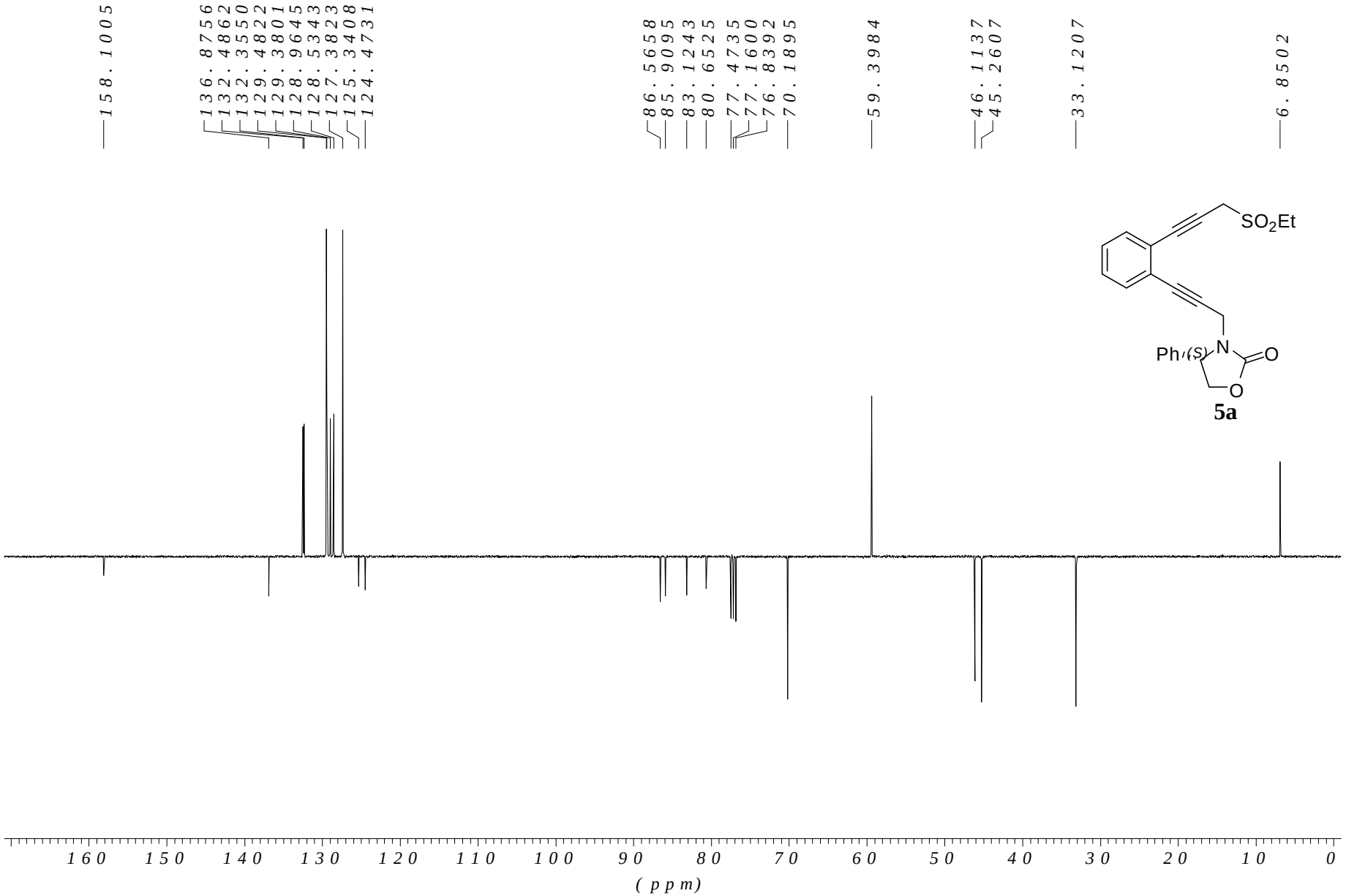
2972.20
2968.19
2966.68
2963.42
2961.66
2957.14
2954.64
2952.63
2948.61
2946.86
2945.10
2933.30
2931.07
2925.52
2924.52
2923.52
2920.75
2917.74
2916.49
2915.74
2910.21
2904.94
2034.84
2026.31
2018.03
1893.05
1884.26
1875.48
1861.17
1843.35
1663.91
1662.41
1655.38
1646.85
1645.34
1642.08
1625.01
1481.71
1463.89
1313.06
1305.53
1298.25
1290.72
579.48
571.96
564.43
SO2Et
Ph
(S)
N
O
O
5a
Integral
7.01
2.05
1.00
1.01
0.99
3.02
1.01
2.00
3.00
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
(ppm)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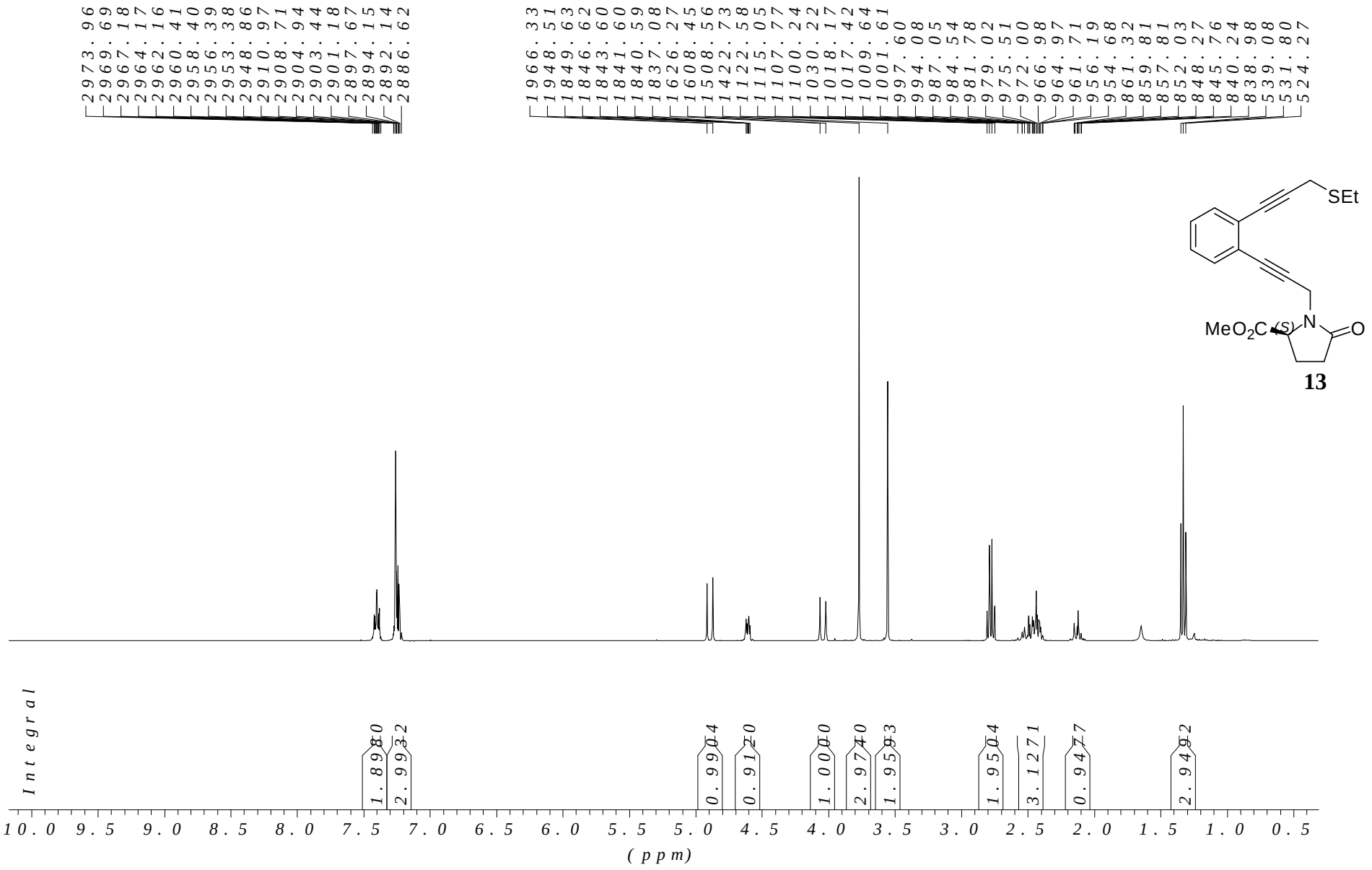
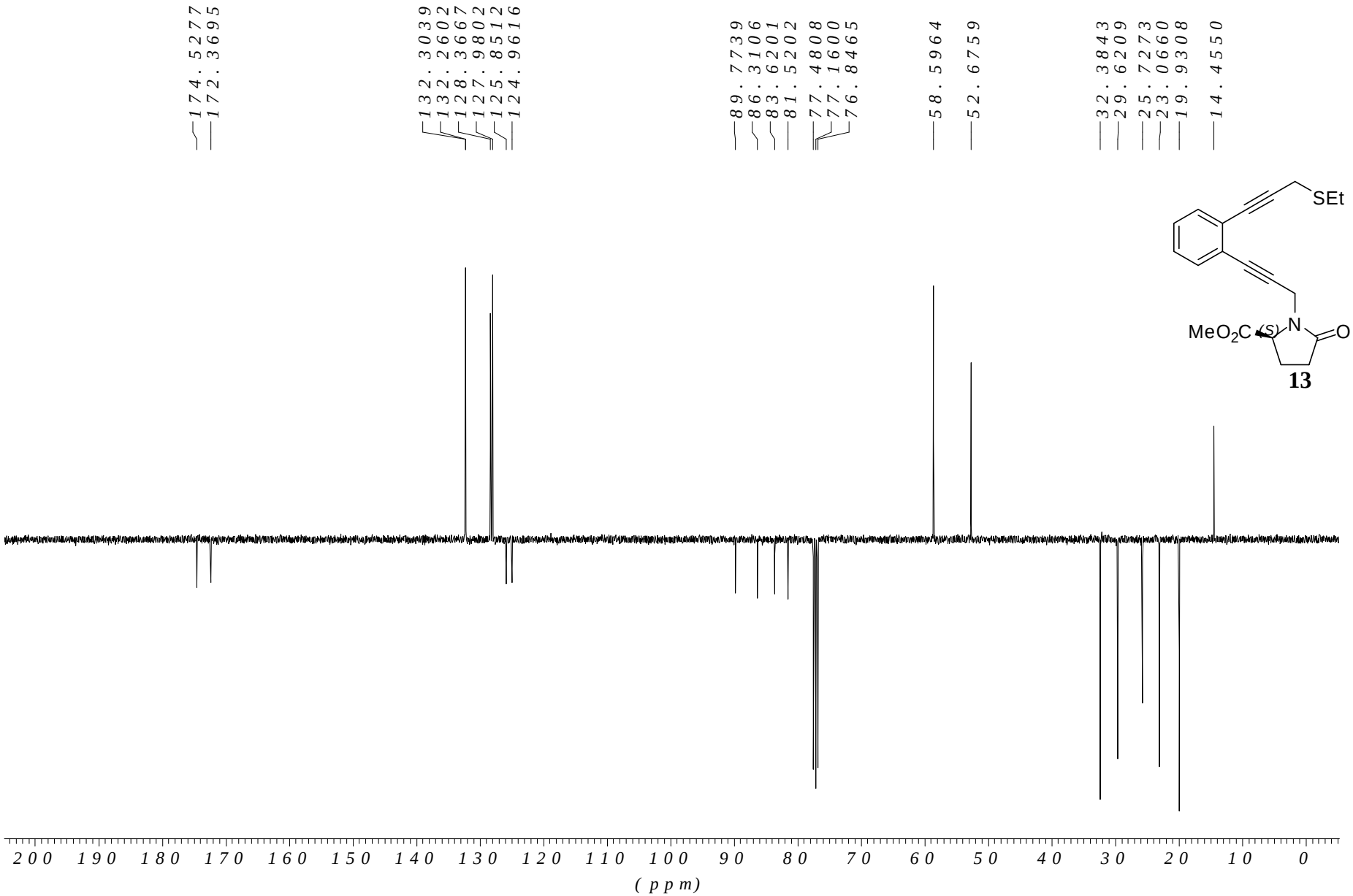
132.4862
132.3550
129.4822
129.3801
128.9645
128.5343
127.3823
125.3408
124.4731
86.5658
85.9095
83.1243
80.6525
77.4735
77.1600
76.8392
70.1895
59.3984
46.1137
45.2607
33.1207
6.8502
SO2Et
Ph
(S)
N
O
O
5a
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)


2973.96
2969.69
2967.18
2964.17
2962.16
2960.41
2958.40
2956.39
2953.38
2948.86
2910.97
2908.71
2904.94
2903.44
2901.18
2897.67
2894.15
2892.14
2886.62
1966.33
1948.51
1849.63
1846.62
1843.60
1841.60
1840.59
1837.08
1626.27
1608.45
1508.56
1422.73
1122.58
1115.05
1107.77
1100.24
1030.22
1018.17
1017.42
1009.64
1001.61
997.60
994.08
987.05
984.54
981.78
979.02
975.51
972.00
966.98
964.97
961.71
956.19
954.68
861.32
859.81
857.03
852.27
848.27
845.76
840.24
838.98
539.08
531.80
524.27
SEt
MeO2C
(S)
N
O
13
Integral
1.8980
2.9932
0.9904
0.9120
1.0000
2.9740
1.9593
1.9504
3.1271
0.9477
2.9492
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)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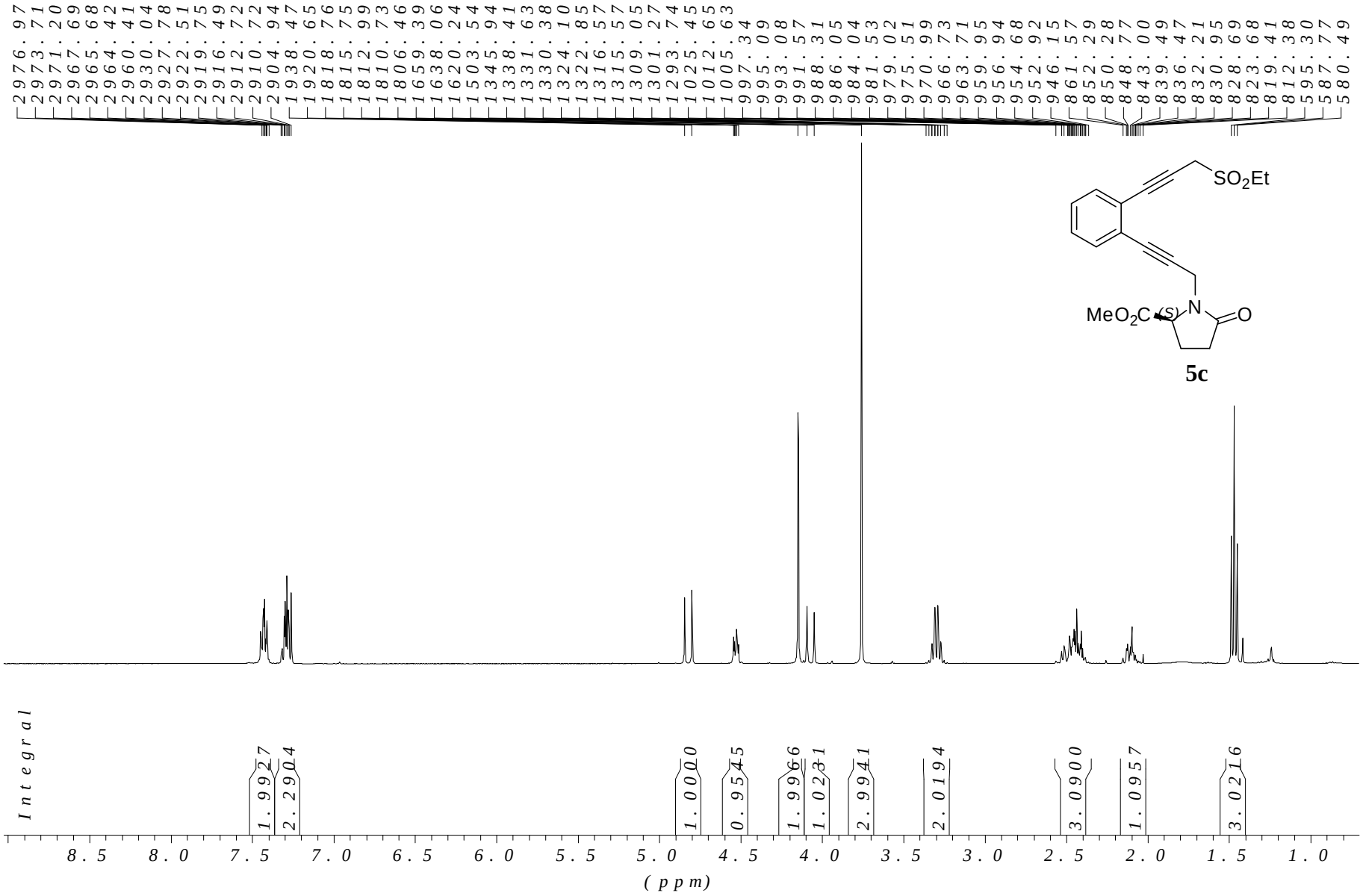
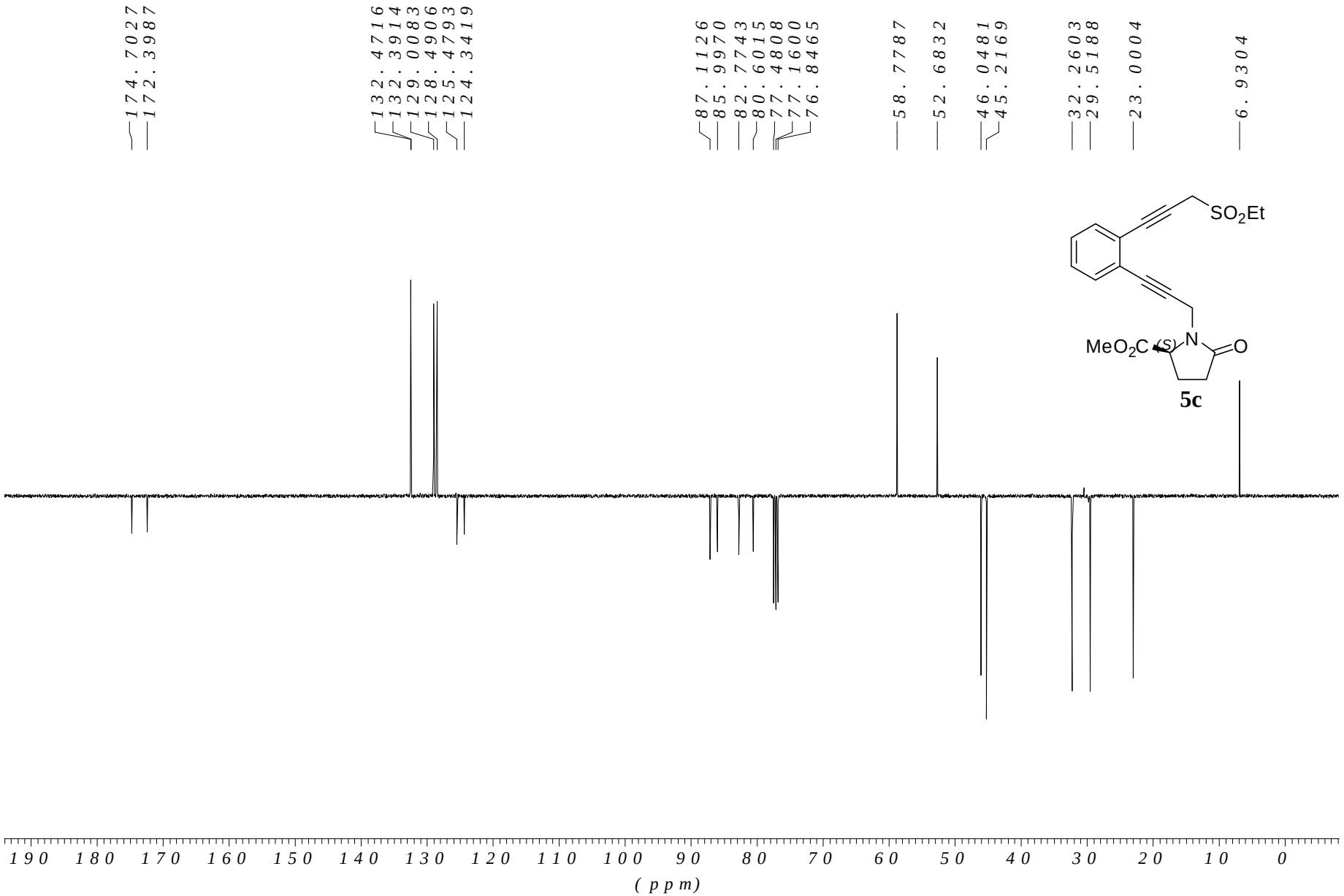
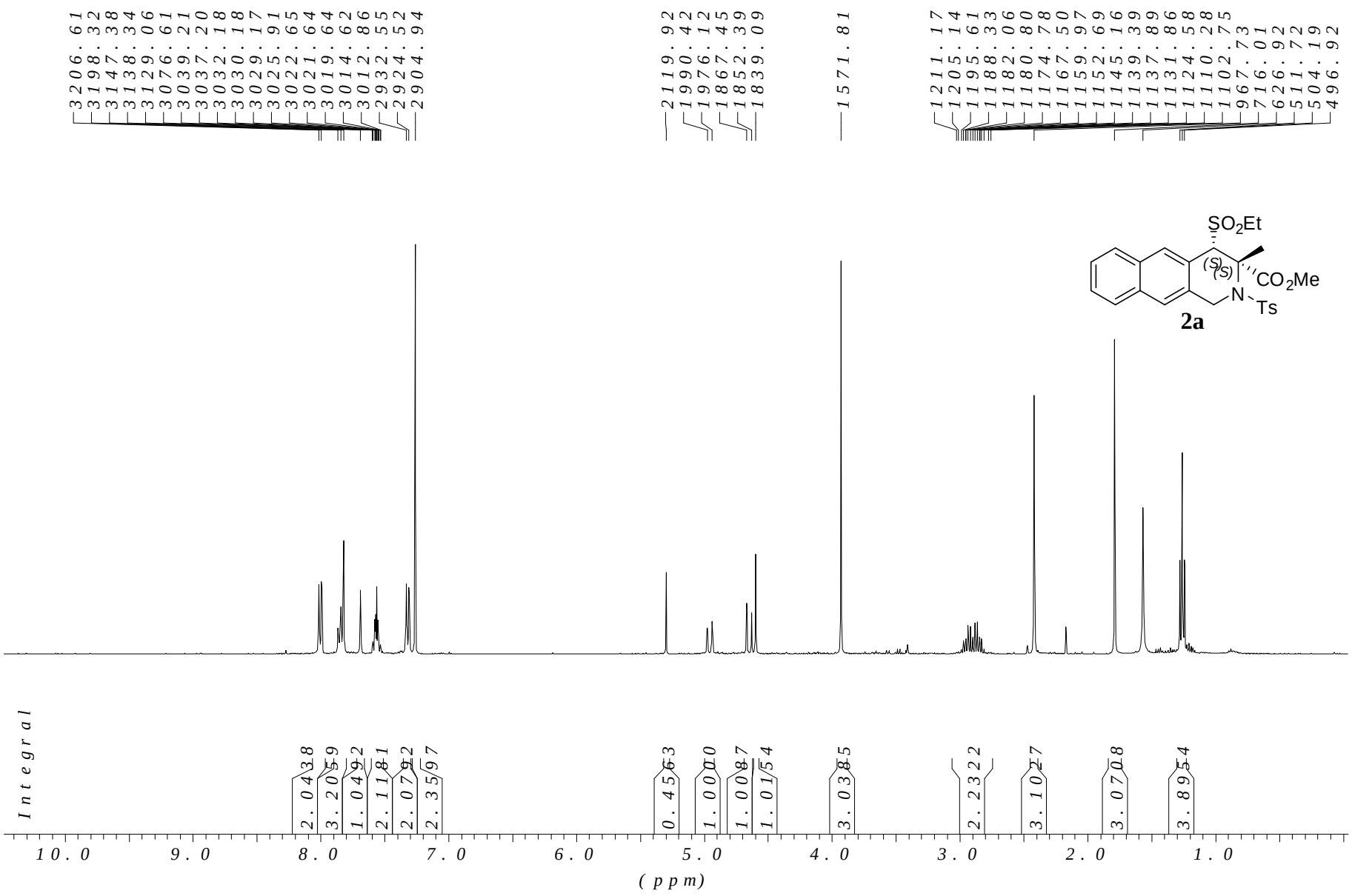
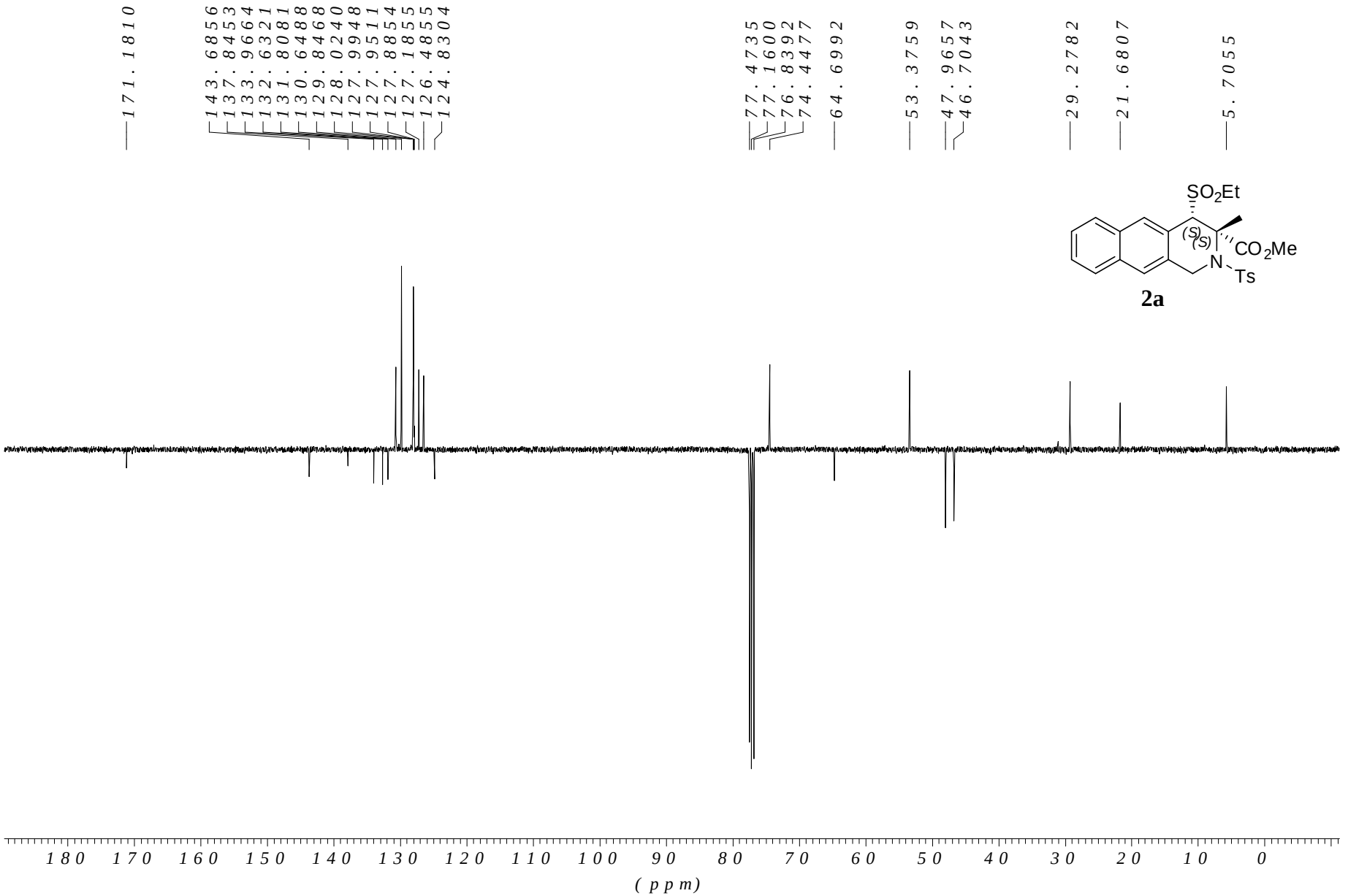
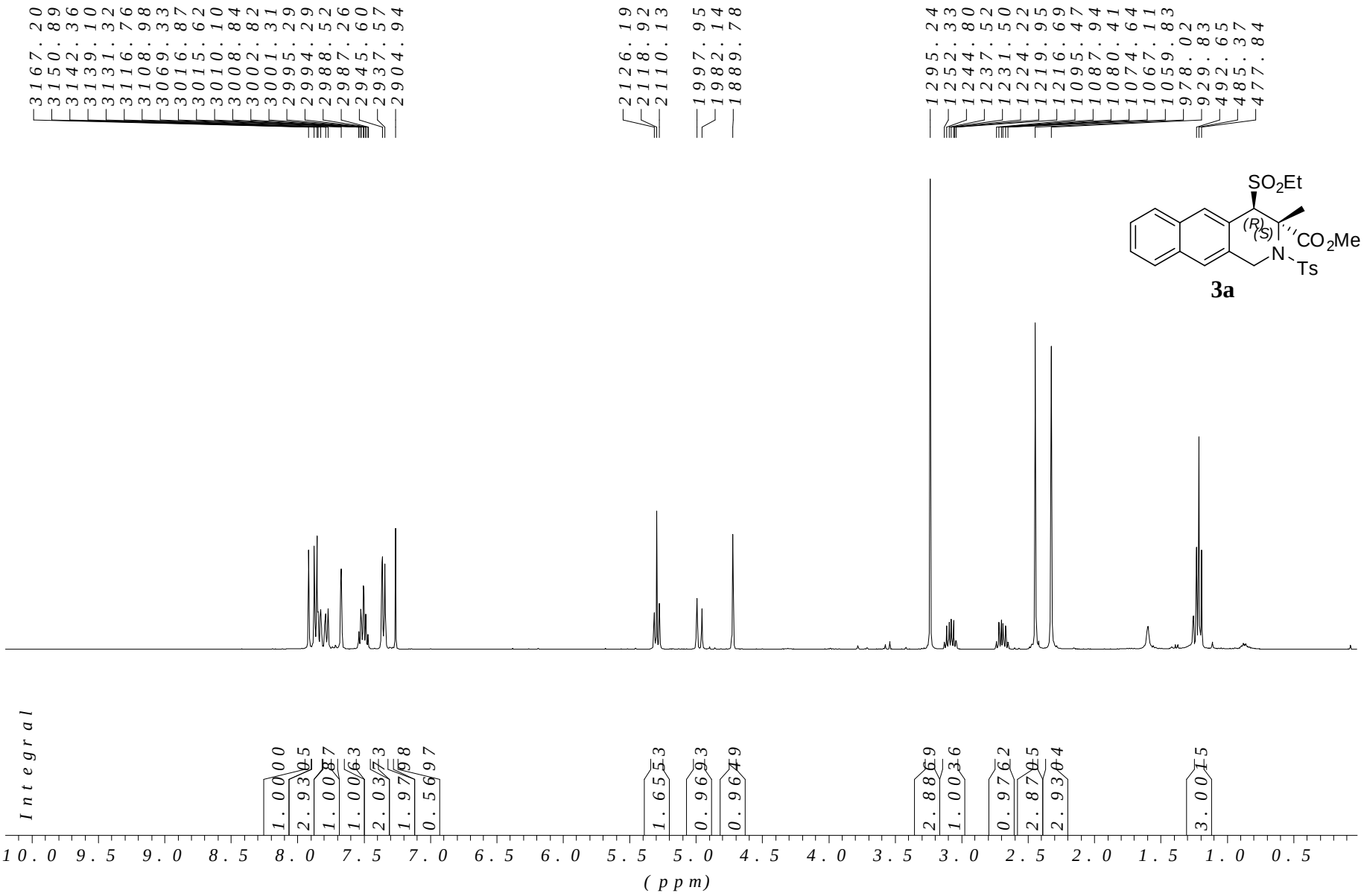
172.3695
132.3039
132.2602
128.3667
127.9802
125.8512
124.9616
89.7739
86.3106
83.6201
81.5202
77.4808
77.1600
76.8465
58.5964
52.6759
32.3843
29.6209
25.7273
23.0660
19.9308
14.4550
SEt
MeO2C
(S)
N
O
13
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(p p m)

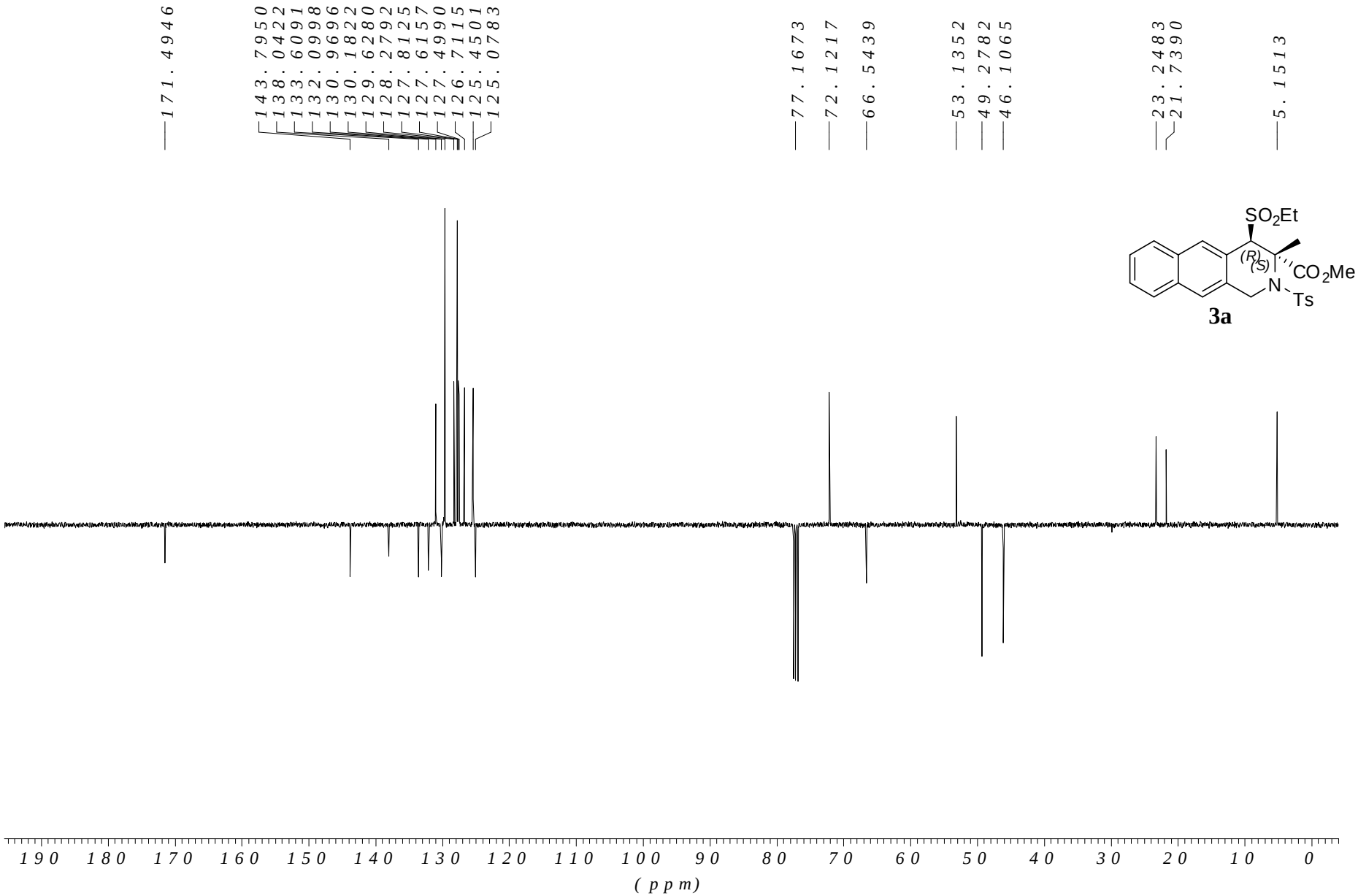

SO2Et
MeO2C
(S)
N
O
5c
Integral
1.9927
2.2904
1.0000
0.9545
1.9966
1.0231
2.9941
2.0194
3.0900
1.0957
3.0216
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
(ppm)

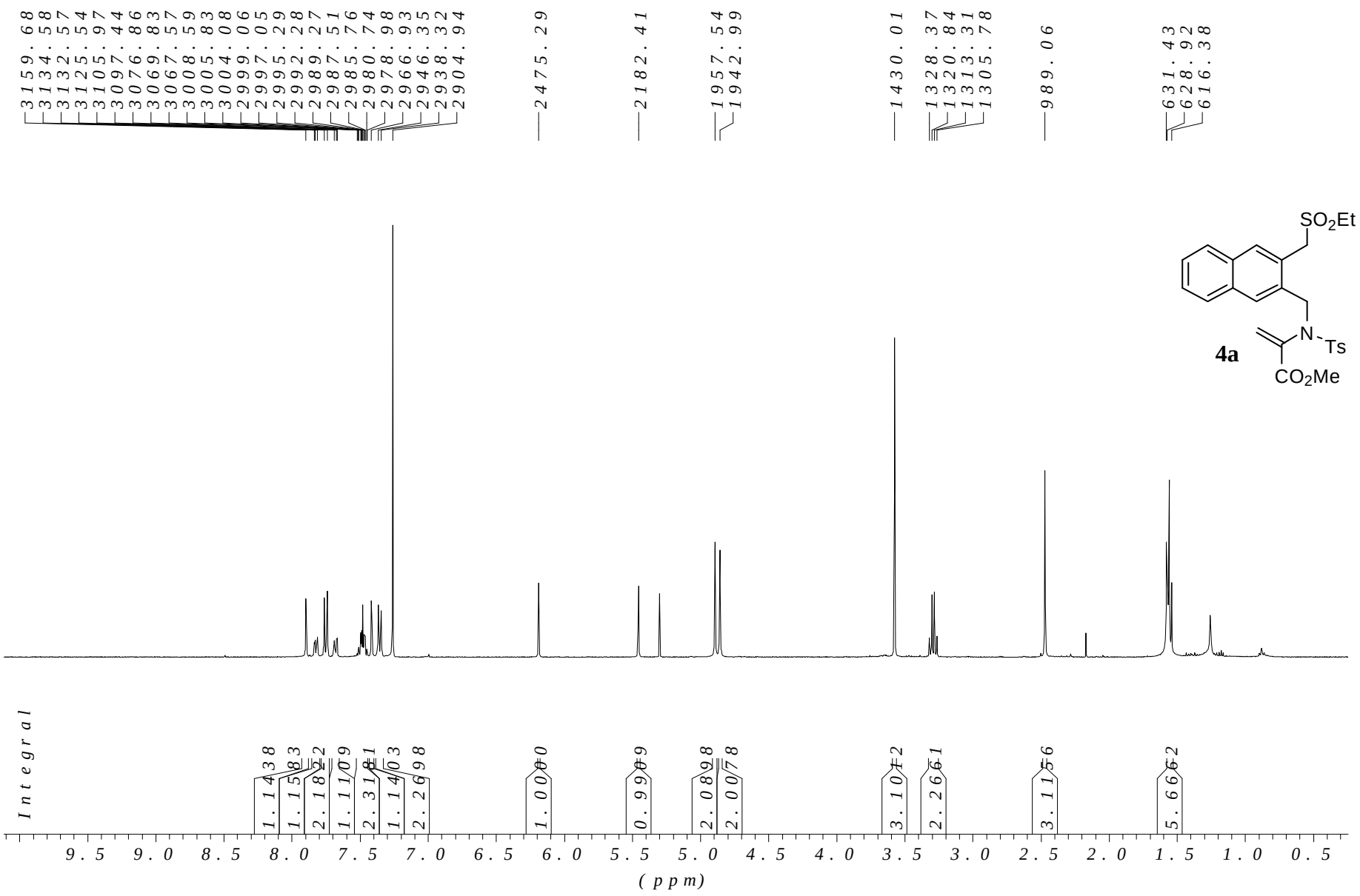

174.7027
172.3987
132.4716
132.3914
129.0083
128.4906
125.4793
124.3419
87.1126
85.9970
82.7743
80.6015
77.4808
77.1600
76.8465
58.7787
52.6832
46.0481
45.2169
32.2603
29.5188
23.0004
6.9304
SO2Et
MeO2C
(S)
N
O
5c
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)

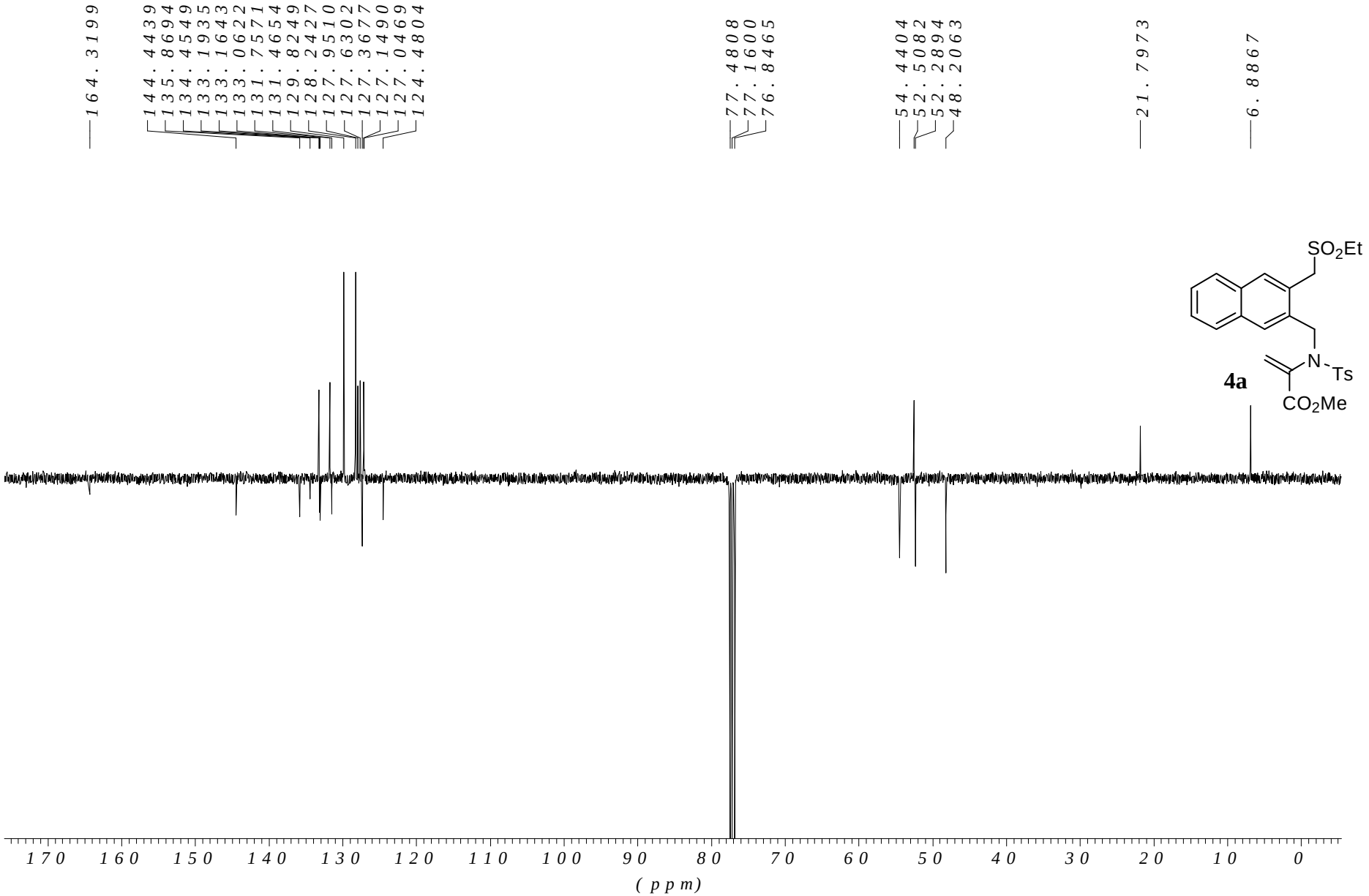

3206.61
3198.32
3147.38
3138.34
3129.06
3076.61
3039.21
3037.20
3032.18
3030.18
3029.17
3025.91
3022.65
3021.64
3019.64
3014.62
3012.86
2932.55
2924.52
2904.94
2119.92
1990.42
1976.12
1867.45
1852.39
1839.09
1571.81
1211.17
1205.14
1195.61
1188.33
1182.06
1180.80
1174.78
1167.50
1159.97
1152.69
1145.16
1139.39
1137.89
1131.86
1124.58
1110.28
1102.75
967.73
716.01
626.92
511.72
504.19
496.92
SO2Et
(S)
(S)
CO2Me
N
Ts
2a
Integral
2.04 3.20 1.04 2.11 2.07 2.35
0.45 1.00 1.00 1.01 3.03 2.23 3.10 3.07 3.89
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
(ppm)

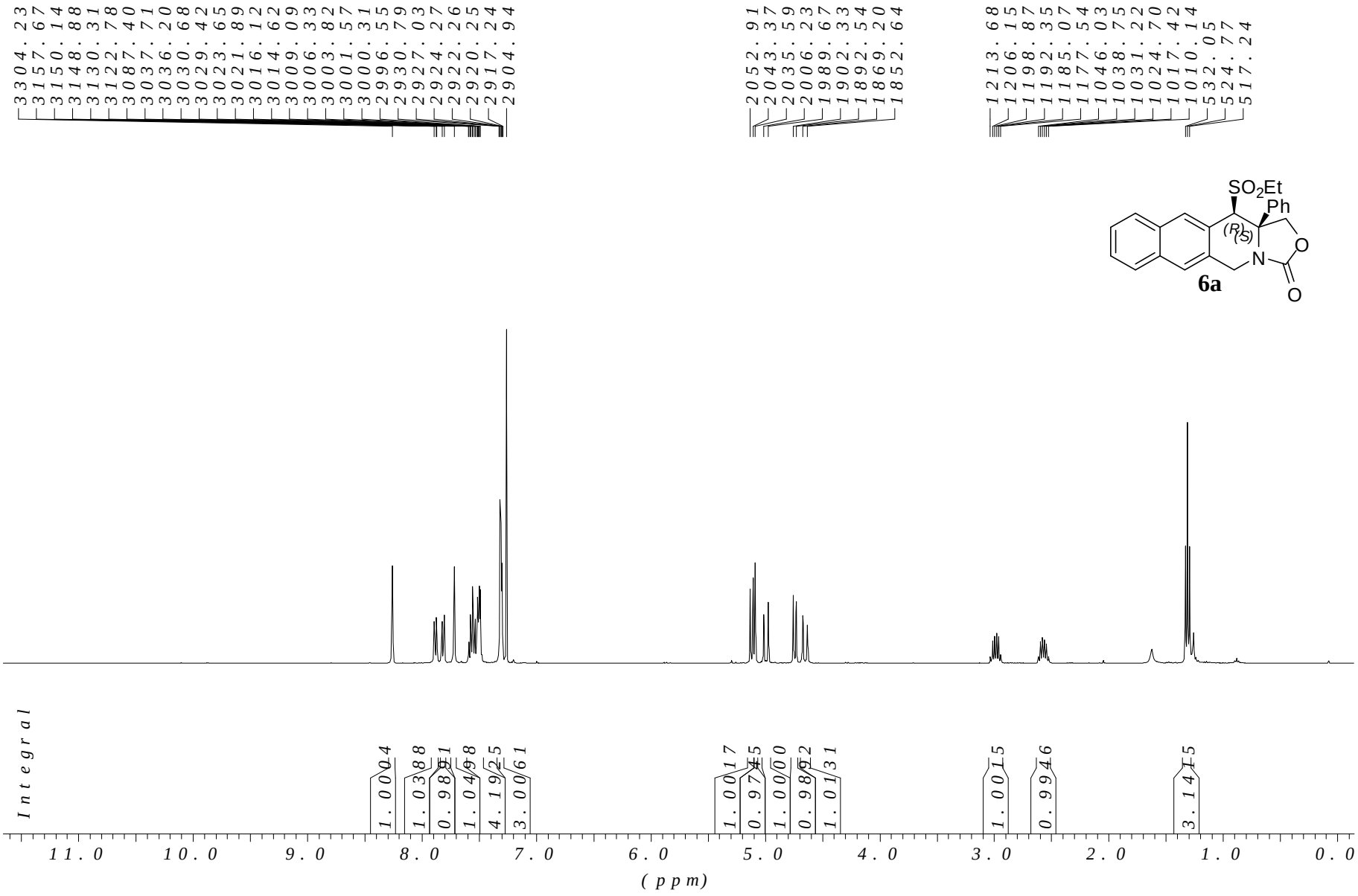

171.1810
143.6856
137.8453
133.9664
132.6321
131.8081
130.6488
129.8468
128.0240
127.9948
127.9511
127.8854
127.1855
126.4855
124.8304
77.4735
77.1600
76.8392
74.4477
64.6992
53.3759
47.9657
46.7043
29.2782
21.6807
5.7055
SO2Et
(S)
(S)
CO2Me
N
Ts
2a
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)


3167.20
3150.89
3142.36
3139.10
3131.32
3116.76
3108.98
3069.33
3016.87
3015.62
3010.84
3008.82
3002.82
3001.31
2995.29
2994.29
2988.52
2987.26
2945.60
2937.57
2904.94
2126.19
2118.92
2110.13
1997.95
1982.14
1889.78
1295.24
1252.33
1244.80
1237.52
1231.50
1224.22
1219.95
1216.69
1095.47
1087.94
1080.41
1074.64
1067.11
1059.83
978.02
929.83
492.65
485.37
477.84
SO2Et
(R)
(S)
CO2Me
N
Ts
3a
Integral
1.000
2.935
1.008
1.006
2.037
1.978
0.569
1.655
0.963
0.964
2.886
1.003
0.976
2.870
2.930
3.001
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)


171.4946
143.7950
138.0422
133.6091
132.0998
130.9696
130.1822
129.6280
128.2792
127.8125
127.6157
127.4990
126.7115
125.4501
125.0783
77.1673
72.1217
66.5439
53.1352
49.2782
46.1065
23.2483
21.7390
5.1513
SO2Et
(R)
(S)
CO2Me
N
Ts
3a
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)


3159.68
3134.58
3132.57
3125.54
3105.97
3097.44
3076.86
3069.83
3067.57
3008.59
3005.83
3004.08
2999.06
2997.05
2995.29
2992.28
2989.27
2987.51
2985.76
2980.74
2978.98
2966.93
2946.35
2938.32
2904.94
2475.29
2182.41
1957.54
1942.99
1430.01
1328.37
1320.84
1313.31
1305.78
989.06
631.43
628.92
616.38
SO2Et
N
Ts
CO2Me
4a
Integral
1.1438
1.1583
2.1822
1.1109
2.3101
1.1403
2.2698
1.0000
0.9909
2.0898
2.0078
3.1012
2.2661
3.1156
5.6662
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)




3304.23
3157.67
3150.14
3148.88
3130.31
3122.78
3087.40
3037.71
3036.20
3030.68
3029.42
3023.65
3021.89
3016.12
3014.62
3009.09
3006.33
3003.82
3001.57
3000.31
2996.55
2930.79
2927.03
2924.27
2922.26
2920.25
2917.24
2904.94
2052.91
2043.37
2035.59
2006.23
1989.67
1902.33
1892.54
1869.20
1852.64
1213.68
1206.15
1198.87
1192.35
1185.07
1177.54
1046.03
1038.75
1031.22
1024.70
1017.42
1010.14
532.05
524.77
517.24
SO2Et
Ph
(R)
(S)
N
O
O
6a
Integral
1.0004
1.0388
0.9891
1.0498
4.1925
3.0061
1.0017
0.9745
1.0000
0.9862
1.0131
1.0015
0.9946
3.1415
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)

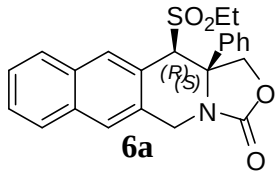
157.1818
137.1526
132.8508
132.4133
130.8092
129.2781
129.0375
128.7823
128.3667
127.9000
127.4917
127.4115
126.9813
126.2886
124.9616

77.4808
77.1600
76.9413
76.8465
71.0864
64.5680

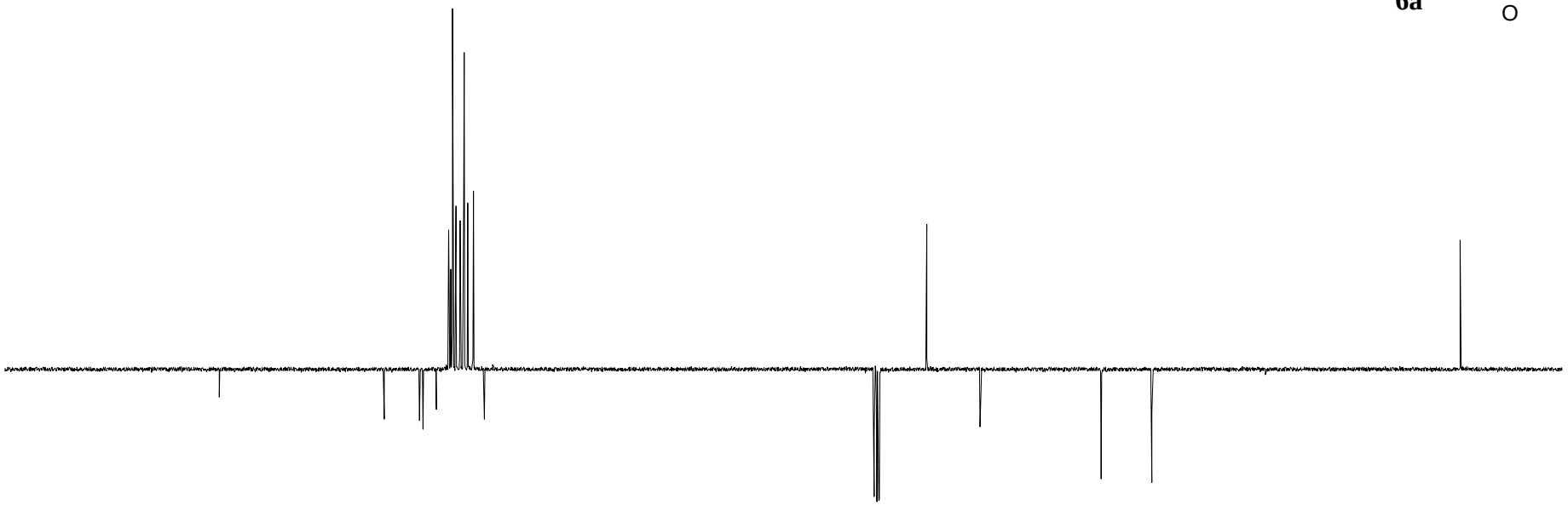
49.8250

43.6493

6.1138

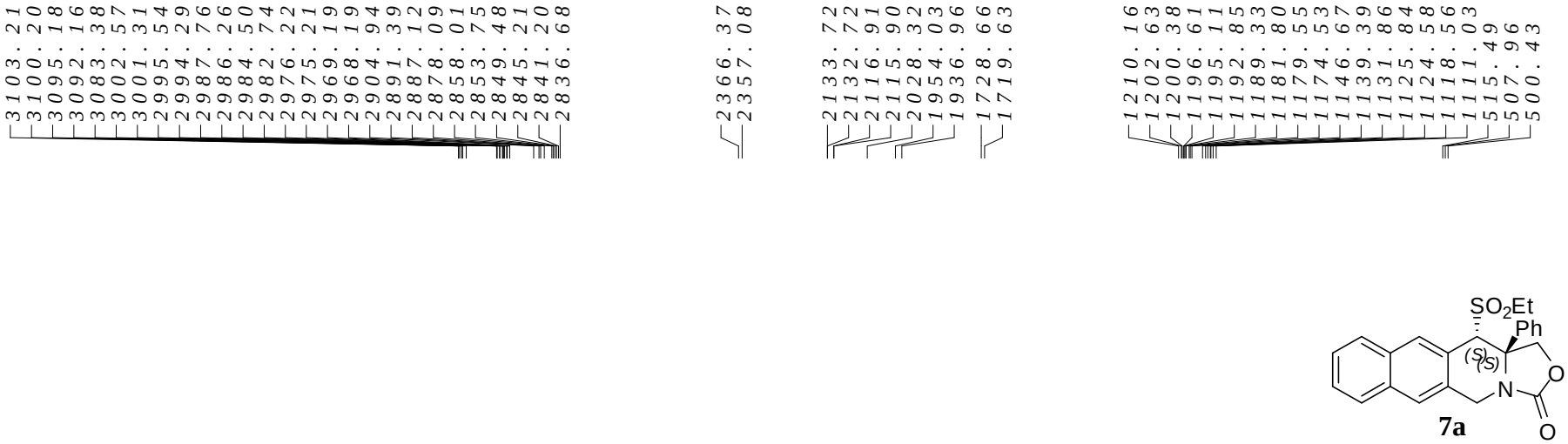


6a



180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

(p p m)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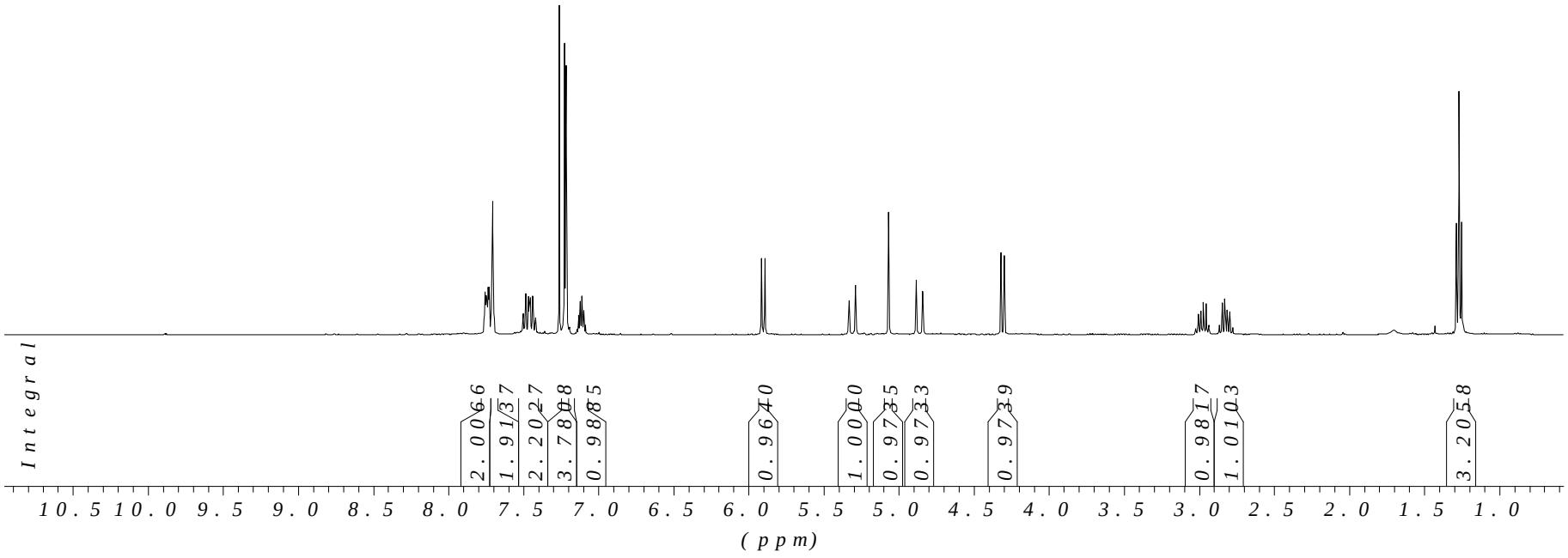
3092.16
3083.38
3002.57
3001.31
2995.54
2994.29
2987.76
2986.26
2984.50
2982.74
2976.22
2975.21
2969.19
2968.19
2904.94
2891.39
2887.12
2878.09
2858.01
2853.75
2849.48
2845.21
2841.20
2836.68
2366.37
2357.08
2133.72
2132.72
2116.91
2115.90
2028.32
1954.03
1936.96
1728.66
1719.63
1210.16
1202.63
1200.38
1196.61
1195.11
1192.85
1189.33
1181.80
1179.55
1174.53
1146.67
1139.39
1131.86
1125.84
1124.58
1118.56
1111.03
515.49
507.96
500.43

SO2Et
Ph
(S)
(S)
N
O
O

7a


Integral
2.0066
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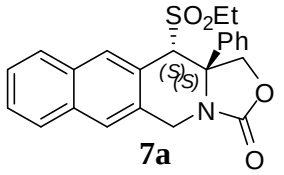
2.2027
3.7808
0.9885
0.9640
1.0000
0.9735
0.9733
0.9739
0.9817
1.0103
3.2058
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
(ppm)

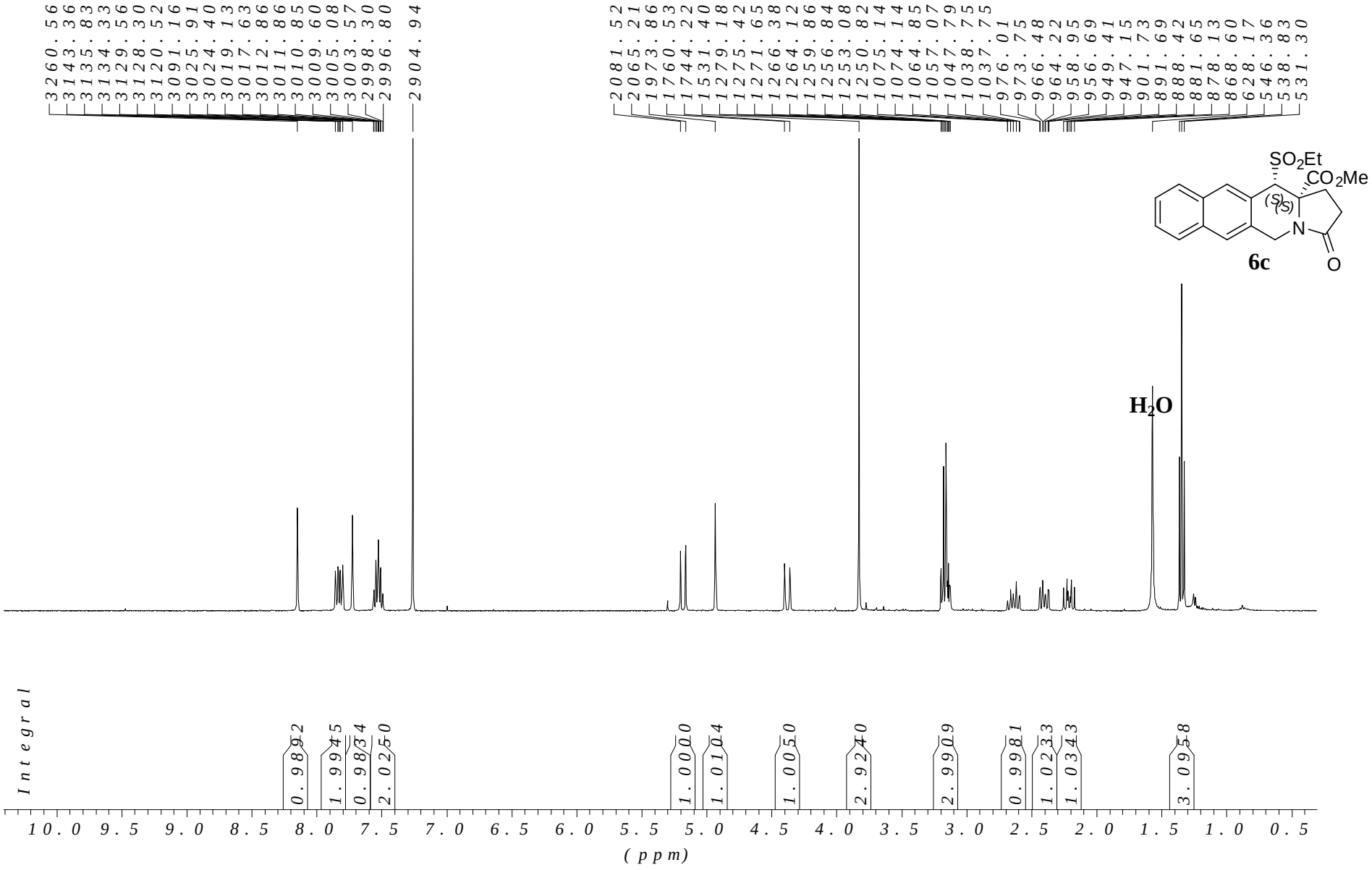
158.3994
142.4024
133.5580
131.8300
131.2905
129.5624
129.3364
128.3521
127.7761
127.6959
127.5136
126.7626
126.6022
124.6044
123.9773
77.4735
77.1600
76.8392
72.4863
67.4772
65.1877
46.5148
44.9617
5.2899

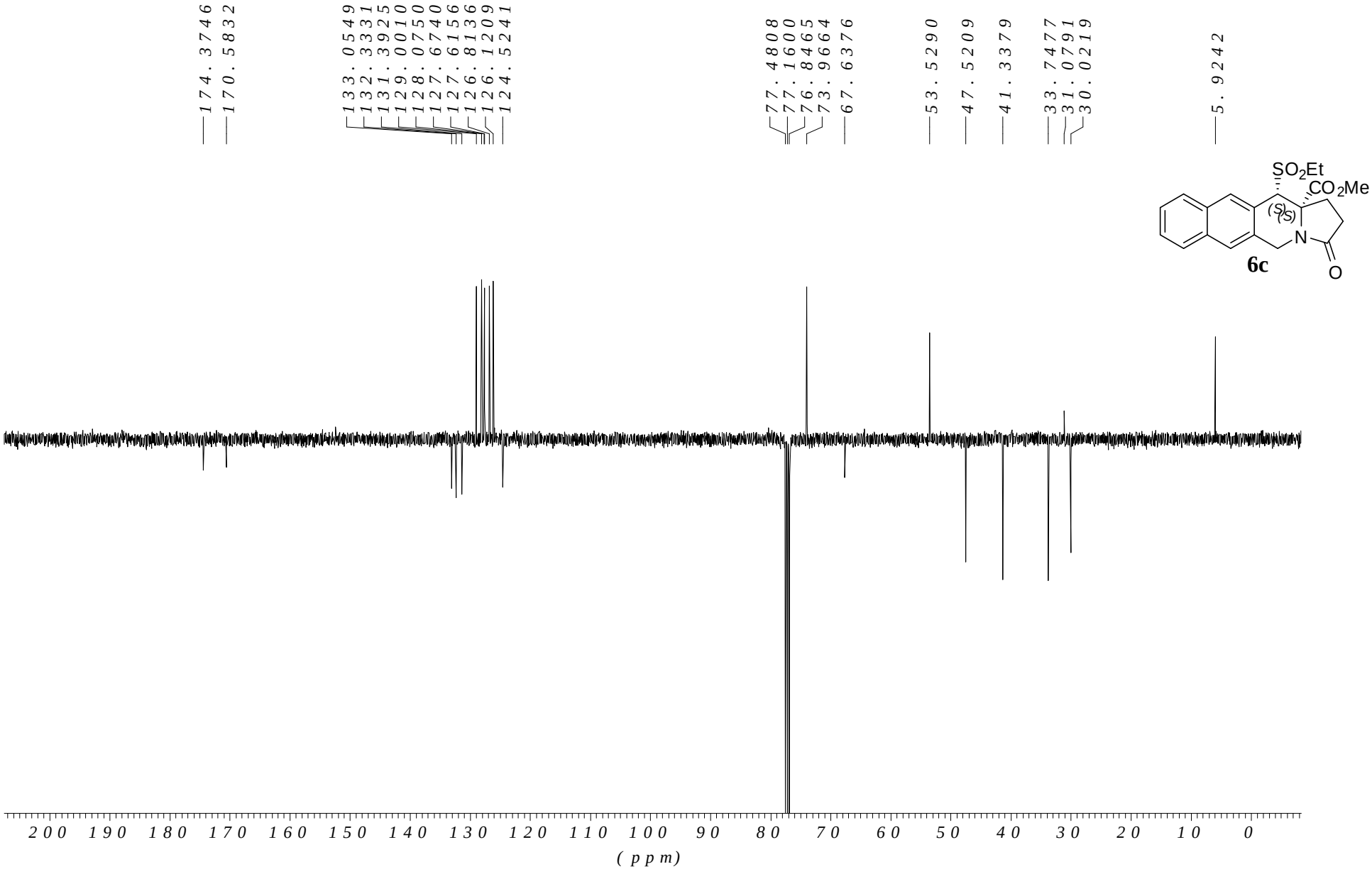


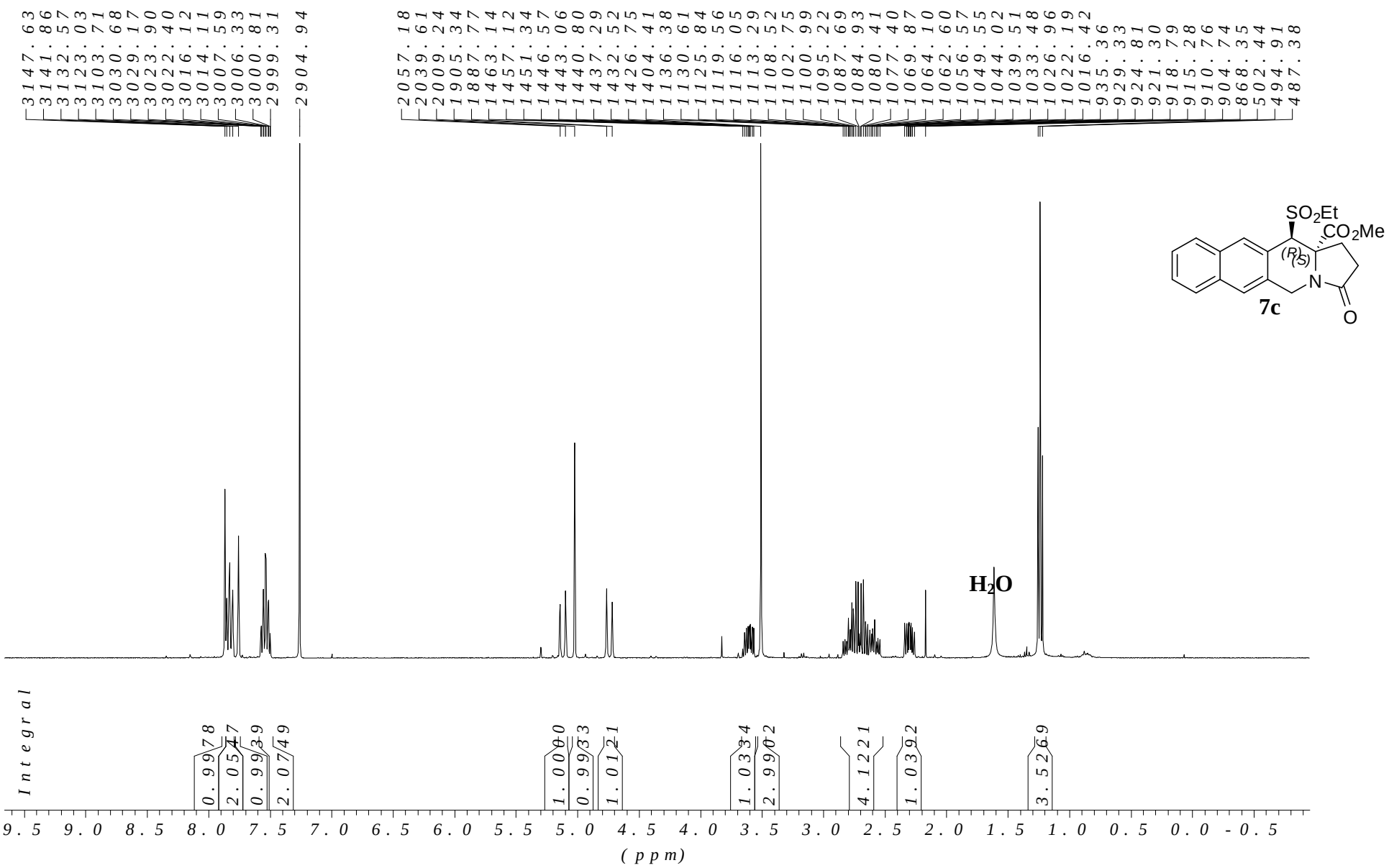
7a

170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

(p p m)


3260.56
3143.36
3135.83
3134.33
3129.56
3128.30
3120.52
3091.16
3025.91
3024.40
3019.13
3017.63
3012.86
3011.86
3010.85
3009.60
3005.08
3003.57
2998.30
2996.80
2904.94
2081.52
2065.21
1973.86
1760.53
1744.22
1531.40
1279.18
1275.42
1271.65
1266.38
1264.12
1259.86
1256.84
1253.08
1250.82
1075.14
1074.85
1064.85
1057.07
1047.79
1038.75
1037.75
976.01
973.75
966.48
964.22
958.95
956.69
949.41
947.15
901.73
891.69
888.42
881.65
878.13
868.60
628.17
546.36
538.83
531.30
H2O
6c
SO2Et
CO2Me
(S)
(S)
N
O
Integral
0.9892
1.9945
0.9834
2.0250
1.0000
1.0104
1.0050
2.9240
2.9909
0.9981
1.0233
1.0343
3.0958
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)

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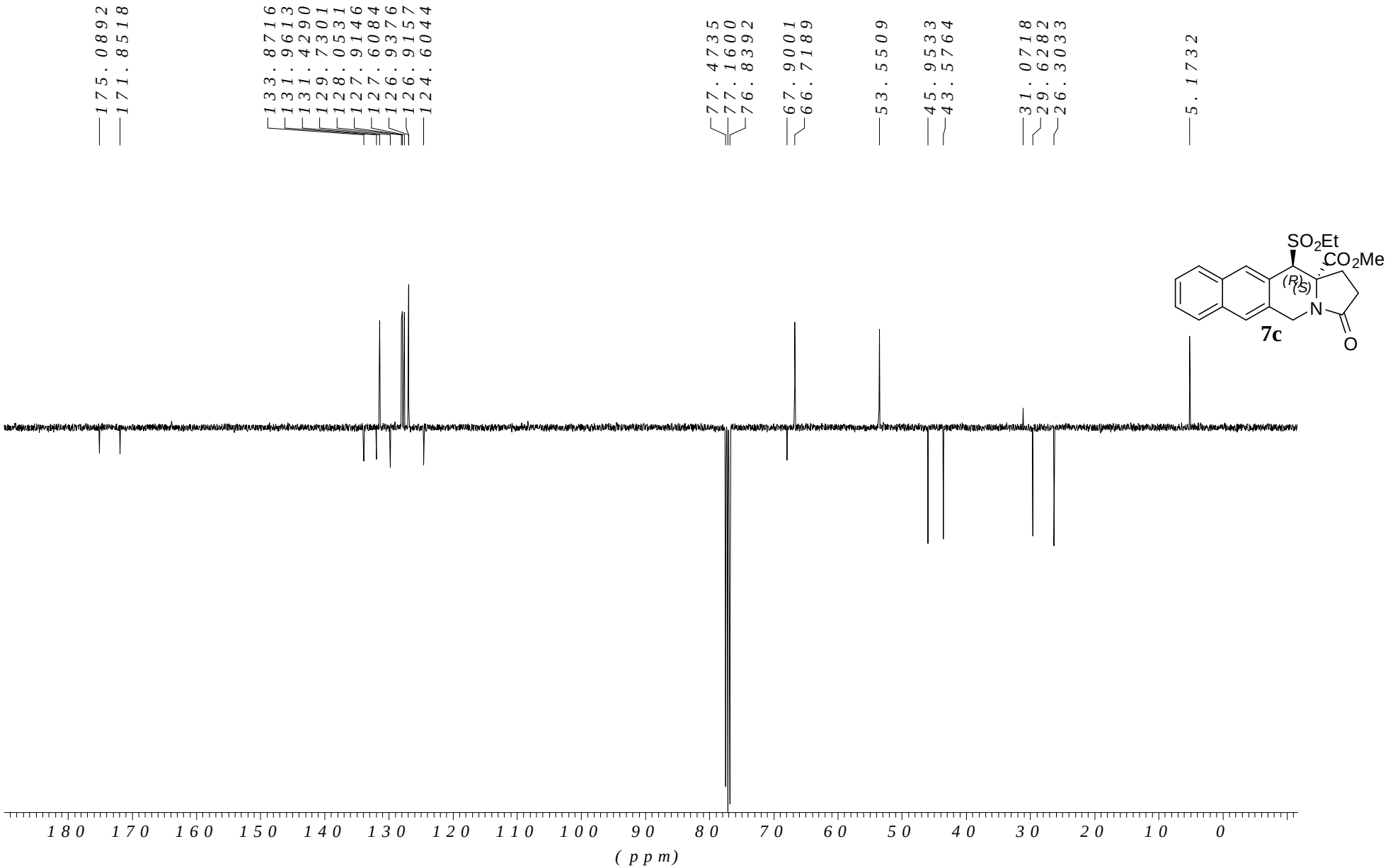
3014.11
3007.59
3006.33
3000.81
2999.31
2904.94
2057.18
2039.61
2009.24
1905.34
1887.77
1463.14
1457.12
1451.34
1446.57
1443.06
1440.80
1437.29
1432.52
1426.75
1404.41
1136.38
1130.61
1125.84
1119.56
1116.05
1113.29
1108.52
1102.75
1100.99
1095.22
1087.69
1084.93
1080.41
1077.40
1069.87
1064.10
1062.60
1056.57
1049.55
1044.02
1039.51
1033.48
1026.96
1022.19
1016.42
935.36
929.33
924.81
921.30
918.79
915.28
910.76
904.74
868.35
502.44
494.91
487.38
SO2Et
CO2Me
(R)
(S)
N
O
7c
H2O
Integral
0.9978
2.0547
0.9939
2.0749
1.0000
0.9933
1.0121
1.0334
2.9902
4.1221
1.0392
3.5269
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)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131.4290
129.7301
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126.9157
124.6044
77.4735
77.1600
76.8392
67.9001
66.7189
53.5509
45.9533
43.5764
31.0718
29.6282
26.3033
5.1732
SO2Et
CO2Me
(R)
(S)
N
O
7c
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)