

Bio- and air-tolerant carbon-carbon bond formations via organometallic ruthenium catalysis

*Louis Adriaenssens, Lukáš Severa, Jan Vávra, Tereza Šálová, Jakub Hývl, Martina Čížková, Radek Pohl, David Šaman and Filip Teplý**

*Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic,
v. v. i., Flemingovo nám. 2, 166 10 Prague 6, Czech Republic*

Electronic Supplementary Data

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Materials

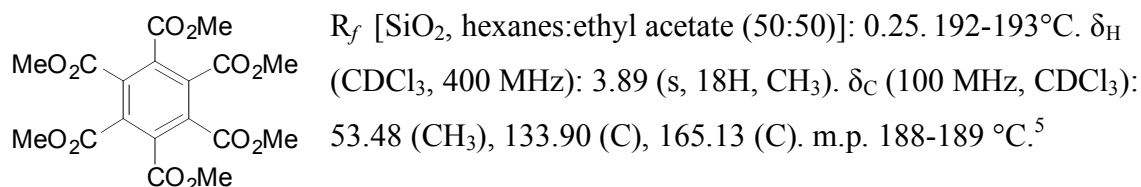
Catalyst **1**, Chloro(1,5-cyclooctadiene)(pentamethylcyclopentadienyl)ruthenium(II) [(C₁₀H₁₅)Ru(C₈H₁₂)Cl], [(Cp**Ru*(cod)Cl] , (Strem, 98%, CAS 92390-26-6)
CDCl₃ (Merck, 99.8%, 102450)
D₂O (Aldrich, 99.96%, 7789-20-0)
Dimethyl sulfoxide (Aldrich, 99+%(GC), 67-68-5)
Dimethyl acetylenedicarboxylate (Dimethyl but-2-ynedioate, Fluka, purum, 96%, 01110)
Propargylether (Aldrich, 99%, 416967)
Malononitrile (Fluka, 98%, 63390)
(Trimethylsilyl)diazomethane solution (2M solution in diethyl ether, Aldrich, 527254)
3-Butyn-1-ol (Aldrich, 97%, 130850)
Allyl alcohol (Fluka, 98%, 05790)
Petrolether, ethyl acetate, diethyl ether, *n*-pentane, hexanes and acetone were purchased from Penta, Czech Republic (www.pentachemicals.eu)
Sodium sulphate (anhydrous Penta)
Enyne **7** was prepared according to the published procedure¹.
Lyophilized bovine serum albumin was obtained from Serva.

Analytical data

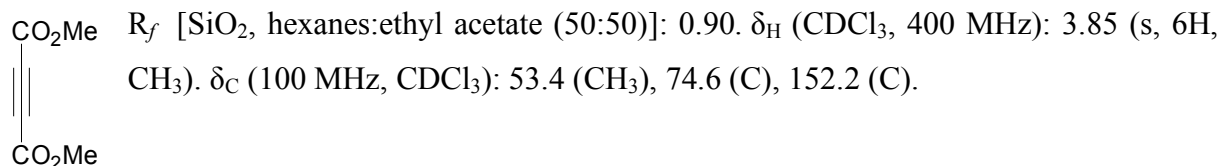
NMR spectra were measured on a Bruker Avance 600 (600 MHz for ¹H, 151 MHz for ¹³C), Bruker Avance 500 (500 MHz for ¹H, 125.7 MHz for ¹³C) or Bruker Avance 400 (400 MHz for ¹H, 100.6 MHz for ¹³C) NMR spectrometer. Chemical shifts are given in δ-scale as parts per million (ppm); coupling constants (*J*) are given in Hertz. Where indicated, the signal assignments in the NMR spectra are unambiguous; the numbering scheme is arbitrary and is shown in the inserts. Where assigned, all ¹H and ¹³C resonance assignments are based on analysis of H,H-COSY; H,H-ROESY; H,C-HSQC and H,C-HMBC spectra. IR spectra were recorded on a Bruker EQUINOX55 (IFS55) spectrometer in CHCl₃, or CCl₄ (cuvette width 0.1 mm), or as KBr pellets. Mass spectral data were obtained at the Mass Spectrometry Facility operated by the Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic. EI MS spectra were measured at an electron energy of 70 eV; *m/z* values are given along with their relative intensities (%). FAB MS spectra were measured using a thioglycerol-glycerol 3:1 matrix; *m/z* values are given. ESI mass spectra were recorded using a

Thermo Scientific LCQ Fleet mass spectrometer equipped with an electrospray ion source and controlled by Xcalibur software. The mobile phase consisted of methanol/water (9:1), flow rate of 200 $\mu\text{L}/\text{min}$. The sample was dissolved, diluted with the mobile phase and injected using a 5- μL loop. Spray voltage, capillary voltage, tube lens voltage and capillary temperature were 5.5 kV, 5 V, 80 V and 275 $^{\circ}\text{C}$, respectively. HR MS spectra were obtained with the EI or APCI instruments.

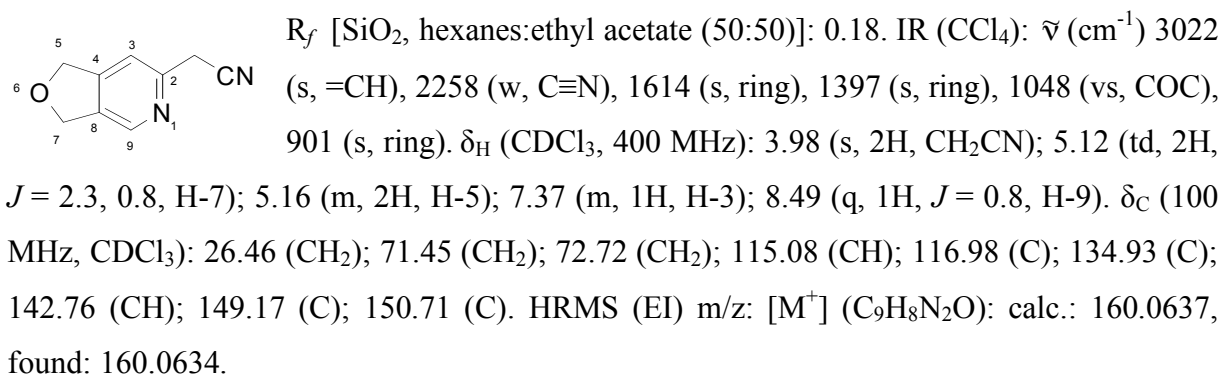
Analytical data for hexamethyl benzene-1,2,3,4,5,6-hexacarboxylate (3)³



Analytical data of recovered dimethyl acetylenedicarboxylate (2)

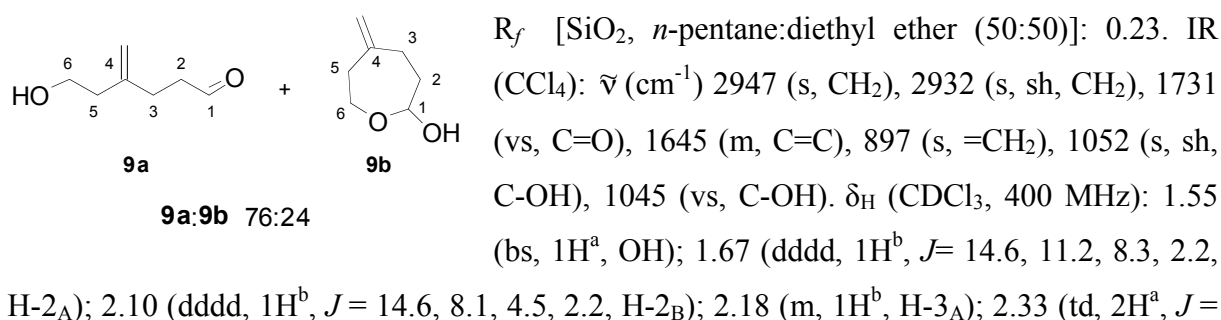


Analytical data for 2-(1,3-Dihydrofuro[3,4-c]pyridin-6-yl)acetonitrile (6)⁵



Analytical data for

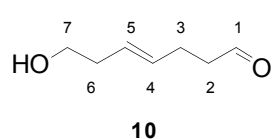
mixture of 6-hydroxy-4-methylenehexanal (9a) and 5-methyleneoxepan-2-ol (9b)⁶



9a:9b 76:24

6.3, 1.1, H-5); 2.34 (m, 1H^b, H-3_B); 2.36 - 2.42 (m, 2H^b, H-5); 2.38 (tt, 2H^a, *J* = 7.2, 1.1, H-3); 2.52 (d, 1H^b, *J* = 3.6, OH); 2.65 (td, 2H^a, *J* = 7.2, 1.5, H-2); 3.59 (ddd, 1H^b, *J* = 12.6, 5.0, 3.9, H-6_A); 3.76 (m, 2H^a, H-6); 3.95 (ddd, 1H^b, *J* = 12.6, 9.3, 3.0, H-6_B); 4.69 (m, 1H^b, =CH_AH_B); 4.74 (h, 1H^b, *J* = 1.2, =CH_AH_B); 4.86 (q, 1H^a, *J* = 1.1, =CH_AH_B); 4.90 (m, 1H^a, =CH_AH_B); 5.17 (ddd, 1H^b, *J* = 8.3, 4.5, 3.6, H-1); 9.80 (t, 1H^a, *J* = 1.5, H-1). δ_C (100 MHz, CDCl₃): 27.61 (CH₂); 30.78 (CH₂); 34.41 (CH₂); 39.07 (CH₂); 39.46 (CH₂); 41.68 (CH₂); 60.39 (CH₂); 61.35 (CH₂); 96.96 (CH); 111.30 (CH₂); 112.12 (CH₂); 144.20 (C); 148.91 (C); 201.86 (CH). MS (EI) *m/z*: 128 [M⁺] (20), 110 [M⁺-H₂O] (30), 70 (100). HRMS (EI) *m/z*: [M⁺] (C₇H₁₂O₂) calc.: 128.0837, found: 128.0836.

Analytical data for (*E*)-7-hydroxyhept-4-enal (**10**)⁶

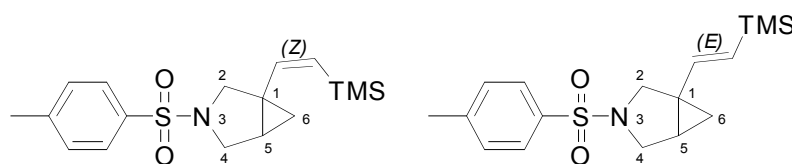


R_f [SiO₂, *n*-pentane:diethyl ether (50:50)]: 0.10. IR (CCl₄): $\tilde{\nu}$ (cm⁻¹) 3636 (vw, OH), 1050 (m), 1731 (m, C=O), 971 (m, =CH). δ_H (CDCl₃, 400 MHz): 2.27 (m, 2H, H-6); 2.37 (m, 2H, H-3); 2.53 (tdd, 2H, *J* = 7.2, 1.6, 0.8, H-2); 3.64 (t, 2H, *J* = 6.3, H-7); 5.47 (dt, 1H, *J* = 15.3, 6.7, 1.1, H-5); 5.56 (dt, 1H, *J* = 15.3, 6.4, 1.3, H-4); 9.77 (t, 1H, *J* = 1.6, H-1). δ_C (100 MHz, CDCl₃): 25.16 (CH₂); 35.86 (CH₂); 43.29 (CH₂); 61.94 (CH₂); 127.65 (CH); 131.31 (CH); 202.01 (CH). MS (EI) *m/z*: 128 [M⁺] (5), 110 [M⁺-H₂O] (25), 80 (100). HRMS (FAB) *m/z*: [M+H⁺] (C₇H₁₃O₂) calc.: 129.0916, found: 129.0913.

Analytical data for mixture of

(*Z*)-3-Tosyl-1-(2-(trimethylsilyl)vinyl)-3-azabicyclo[3.1.0]hexane (**13**) and

(*E*)-3-Tosyl-1-(2-(trimethylsilyl)vinyl)-3-azabicyclo[3.1.0]hexane (**14**)^{7,8}



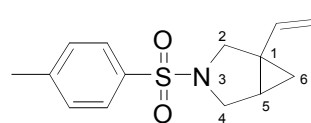
13:14 5:1

R_f [SiO₂, hexanes-ethyl acetate (80:20)]: 0.57. IR (CCl₄): $\tilde{\nu}$ (cm⁻¹) 3044 (w), 1600 (m), 841 (vs). δ_H (CDCl₃, 600 MHz): *Z* stereoisomer **13** 0.08 (s, 9H, (CH₃)₃Si); 0.85 (dd, 1H, *J* = 5.0, 4.5, H-6_A); 0.90 (ddt, 1H, *J* = 8.2, 5.0, 1.0, H-6_B); 1.33 (ddd, 1H, *J* = 8.2, 4.5, 3.9, H-5); 2.44 (s, 3H, CH₃); 2.98 (dd, 1H, *J* = 9.3, 1.0, H-2_A); 3.11 (ddt, 1H, *J* = 9.3, 3.9, 1.0, H-4_A); 3.52 (d, 1H, *J* = 9.3, H-2_B); 3.55 (d, 1H, *J* = 9.3, H-4_B); 5.60 (d, 1H, *J* = 14.6, CH=CH-TMS); 6.27 (d, 1H, *J* = 14.6, CH=CH-TMS); 7.33 (m, 2H, H arom.); 7.68 (m, 2H, H arom.) *E* stereoisomer **14** 0.02 (s, 9H, (CH₃)₃Si); 0.90 (ddt, 1H, *J* = 8.2, 5.0, 1.0, H-6_A); 0.93 (dd, 1H, *J* = 5.0, 4.5, H-6_B); 1.46 (ddd, 1H, *J* = 8.2, 4.5, 3.9, H-5); 2.44 (s, 3H, CH₃); 3.10 (m, 1H, H-4_A); 3.19 (dd, 1H, *J* = 8.9, 1.0, H-2_A); 3.54 (d, 1H, *J* = 8.9, H-4_B); 3.55 (d, 1H, *J* = 8.9, H-2_B); 5.52 (d, 1H, *J* = 19.0, CH=CH-

TMS); 5.69 (d, 1H, $J = 19.0$, CH=CH-TMS); 7.34 (m, 2H, H arom.); 7.70 (m, 2H, H arom.). δ_C (CDCl₃, 151 MHz): *Z* stereoisomer **13** 0.35 (CH₃); 15.81 (CH₂); 21.53 (CH₃); 23.56 (CH); 30.38 (C); 49.91 (CH₂); 52.96 (CH₂); 127.60 (CH); 129.63 (CH); 133.11 (C); 134.12 (CH); 143.53 (C); 144.89 (CH) *E* stereoisomer **14** -1.30 (CH₃); 15.85 (CH₂); 21.53 (CH₃); 24.87 (CH); 31.81 (C); 49.67 (CH₂); 50.73 (CH₂); 127.35 (CH); 127.60 (CH); 129.65 (CH); 133.40 (C); 143.48 (C); 145.68 (CH). MS (FAB) m/z : 336 [M+H⁺] (34), 73 [Me₃Si⁺] (100). HRMS (FAB) m/z : [M+H⁺] C₁₇H₂₆NO₂SSi calc.: 336.1454, found: 336.1445.

Analytical data for the desilylated minor product:

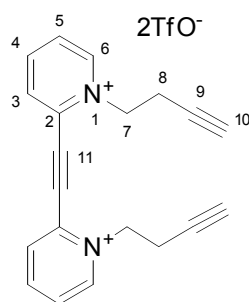
3-Tosyl-1-vinyl-3-azabicyclo[3.1.0]hexane



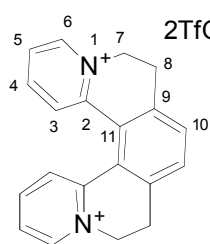
R_f [SiO₂, hexanes:ethyl acetate (80:20)]: 0.48. IR (CCl₄): $\tilde{\nu}$ (cm⁻¹) 1639 (m, C=C), 1599 (m), 1358 (vs, SO₂), 1169 (vs, SO₂), 1105 (s, benzene), 665 (vs, benzene). δ_H (CDCl₃, 600 MHz): 0.83 (dddd, 1H, $J = 8.0, 5.1, 1.1, 0.7$, H-6_A); 0.91 (dd, 1H, $J = 5.1, 4.4$, H-6_B); 1.43 (ddd, 1H, $J = 8.0, 4.4, 3.9$, H-5); 2.44 (s, 3H, CH₃); 3.09 (m, 1H, H-4_A); 3.14 (dd, 1H, $J = 9.0, 1.1$, H-2_A); 3.53 (d, 1H, $J = 9.2$, H-4_B); 3.56 (d, 1H, $J = 9.0$, H-2_B); 4.92 (dd, 1H, $J = 17.4, 1.0$, =CH_AH_B); 4.95 (dd, 1H, $J = 10.8, 1.0$, =CH_AH_B); 5.58 (dd, 1H, $J = 17.4, 10.8$, =CH); 7.34 (m, 2H, H arom.); 7.70 (m, 2H, H arom.). δ_C (CDCl₃, 151 MHz): 15.12 (CH₂); 21.53 (CH₃); 24.38 (CH); 29.98 (C); 49.69 (CH₂); 50.81 (CH₂); 112.67 (CH₂); 127.57 (CH); 129.65 (CH); 133.25 (C); 138.07 (CH); 143.53 (C). MS (EI) m/z : 263 [M⁺] (6), 155 [CH₃-*p*-C₆H₄-SO₂] (18), 139 [CH₃-*p*-C₆H₄-SO] (6), 91 (100). HRMS (EI) m/z : [M⁺] C₁₄H₁₇NO₂S calc.: 263.0980, found: 263.0976.

Analytical data for

2,2'-(ethyne-1,2-diyl)bis(1-(but-3-ynyl)pyridinium)bis(trifluoromethanesulfonate) (**15**)²

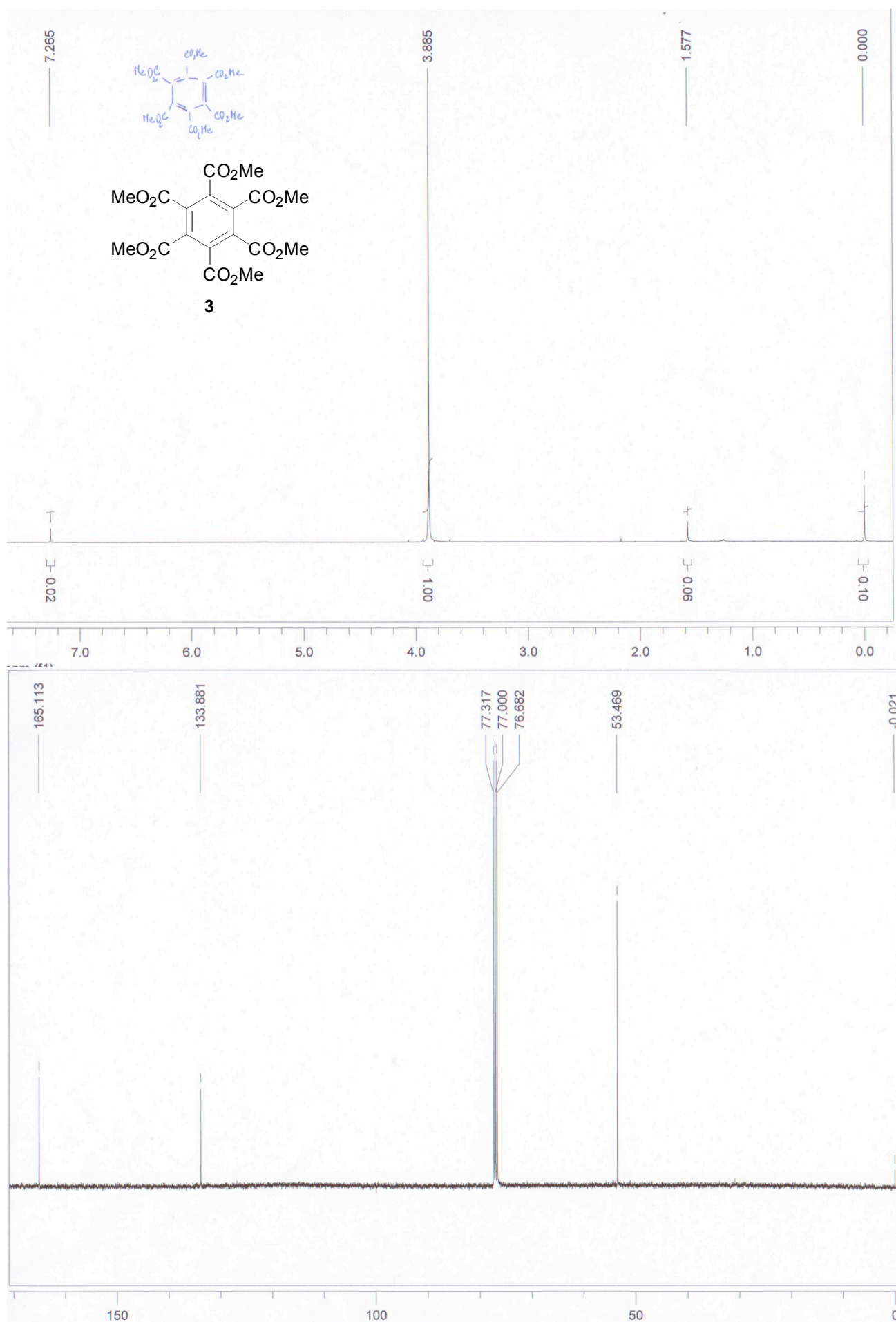


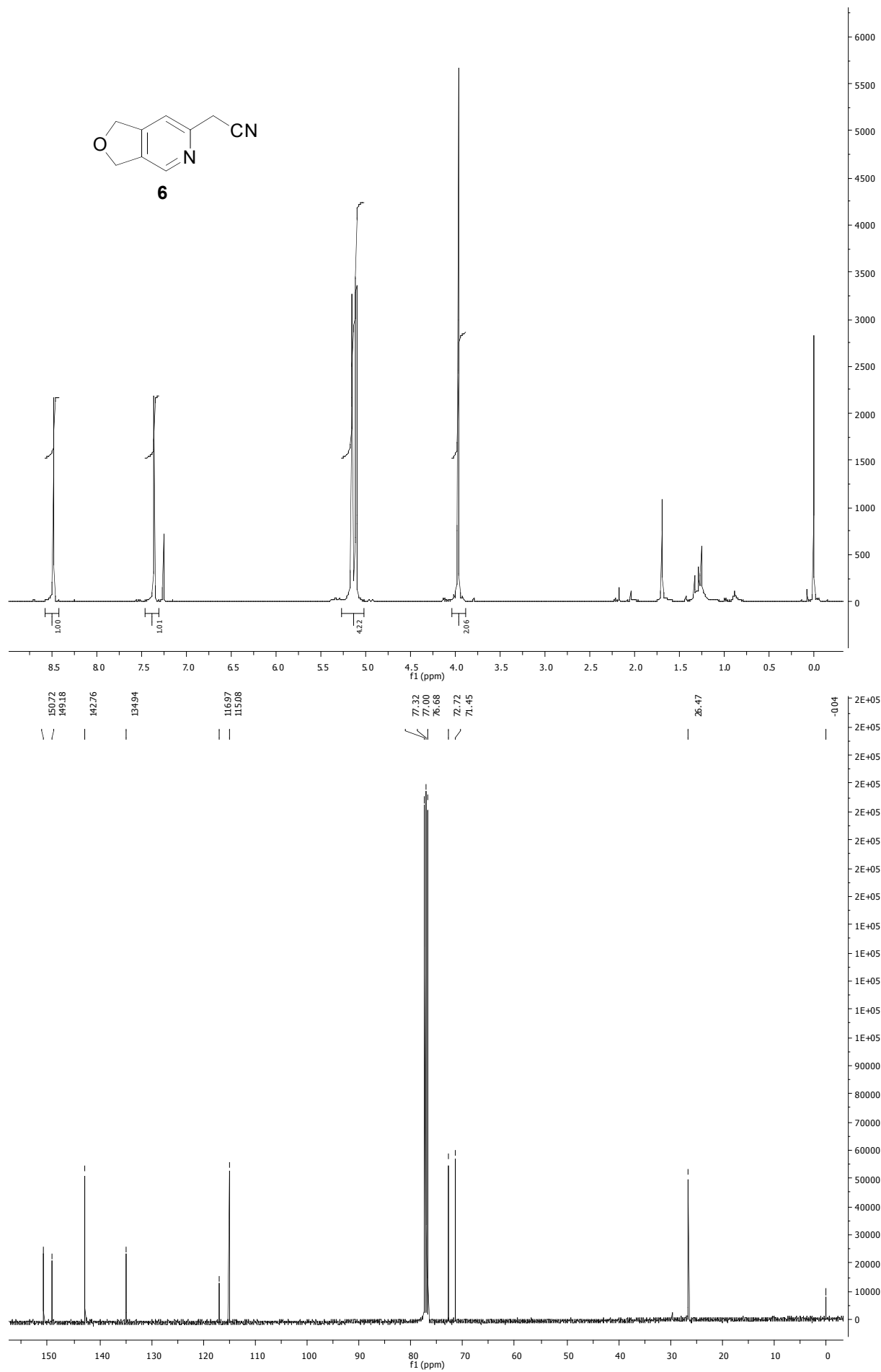
IR (KBr): $\tilde{\nu}$ (cm⁻¹) 1030 s, 1164 s, 1225 s, 1255 vs, 1278 s, 1518 s, 1618 m, 3236 m. δ_H (500 MHz, D₂O): 3.12 (t, 4H, $J = 6.4$, H-8); 5.08 (t, 4H, $J = 6.4$, H-7); 8.27 (ddd, 2H, $J = 8.0, 6.2, 1.5$; H-5); 8.55 (dd, 2H, $J = 8.0, 1.5$, H-3); 8.72 (td, 2H, $J = 8.0, 1.4$, H-4); 9.18 (ddd, 2H, $J = 6.2, 1.4, 0.7$, H-6). δ_C (125.7 MHz, D₂O): 22.74 (CH₂); 61.54 (CH₂); 76.87 (t, $J = 40$, CH); 80.37 (t, $J = 8$, C); 93.80 (C); 122.36 (q, $J = 318$, CF₃); 132.27 (CH); 136.89 (CH); 137.07 (C); 149.05 (CH); 150.31 (CH). MS (ES⁺) m/z : 435 [(M-OTf)⁺] (100), 349 (45), 317 (70), 303 (50), 286 (30). HRMS (ES⁺) m/z : [(M-OTf)⁺] C₂₁H₁₈F₃N₂O₃S calc.: 435.0990, found: 435.1002. m.p. 147-148 °C.

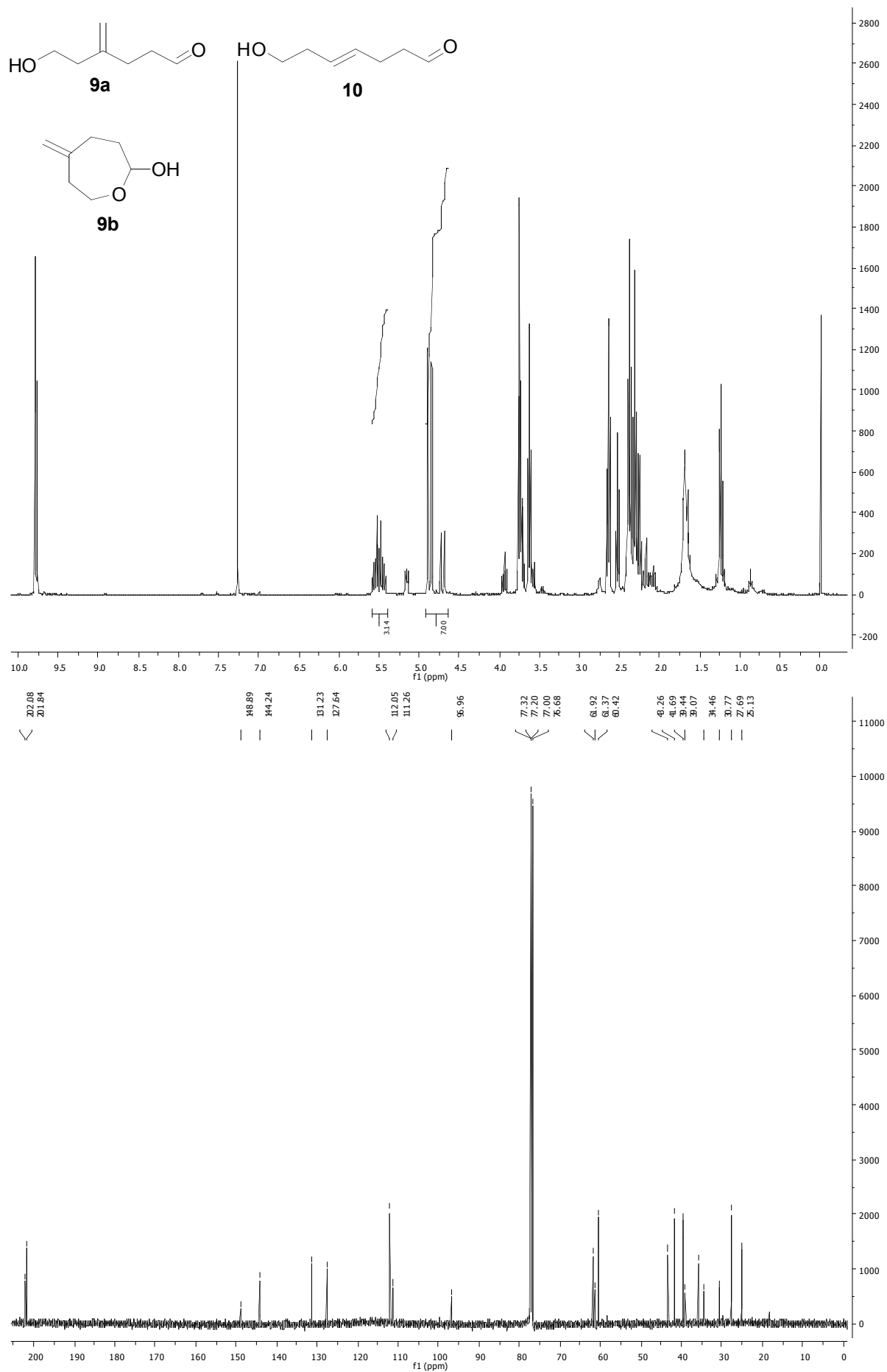
Analytical data for**6,7,12,13-Tetrahydro-5,14-diaza[5]helicinium trifluoromethanesulfonate (16)**²

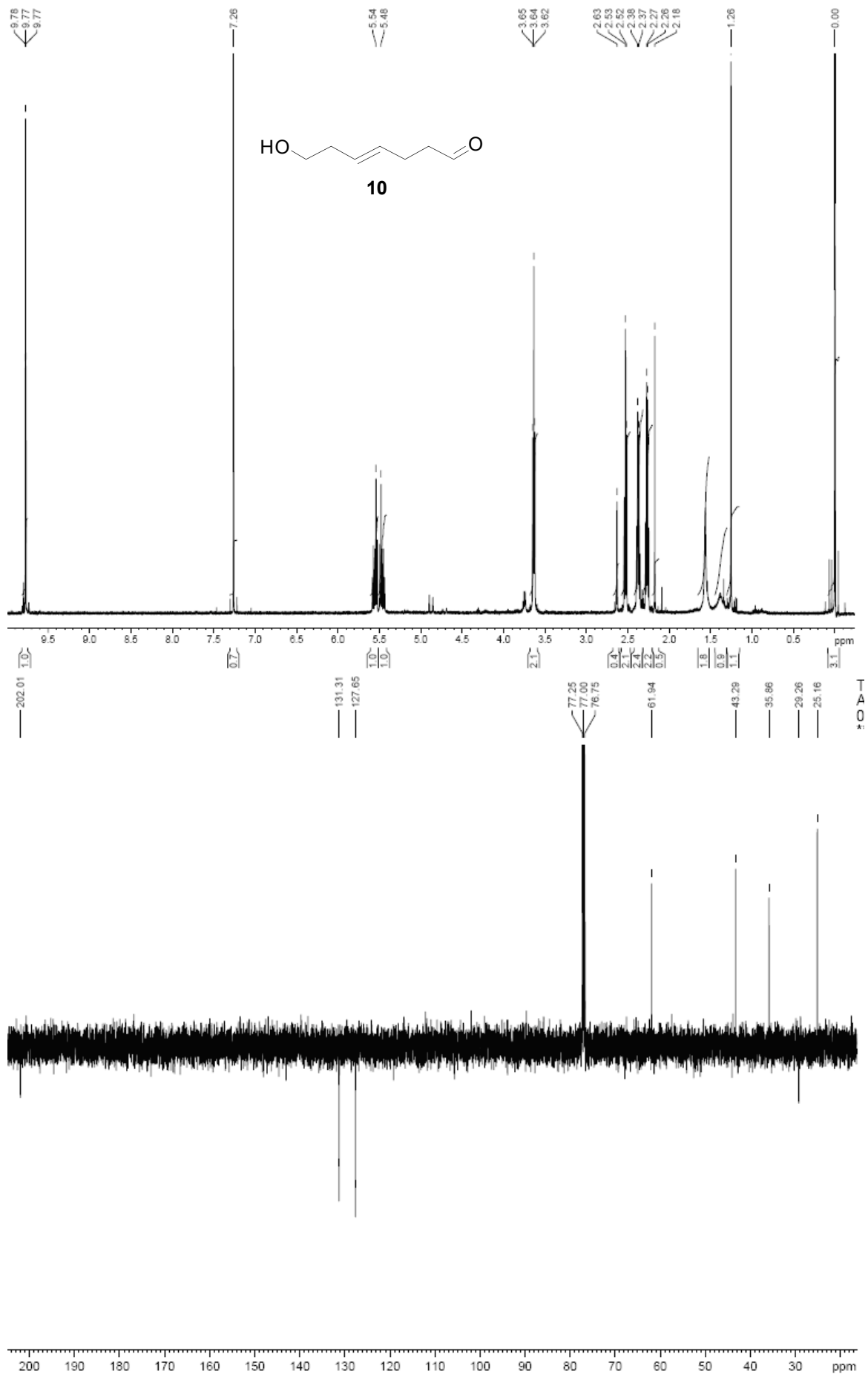
IR (KBr): $\tilde{\nu}$ (cm⁻¹) 1030 s, 1162 s, 1263 vs, 1510 m, 1625 m. δ_{H} (600 MHz, D₂O): 3.24-3.44 (m, 4H, H-8); 4.79-5.04 (m, 4H, H-7); 7.74 (s, 2H, H-10); 7.91 (ddd, 2H, $J = 7.7, 6.2, 1.4$, H-5); 7.94 (dd, 2H, $J = 8.3, 1.4$, H-3); 8.21 (td, 2H, $J = 8.0, 1.4$, H-4); 8.93 (ddd, 2H, $J = 6.2, 1.4, 0.5$, H-6). δ_{C} (151 MHz, D₂O): $\delta = 29.91$ (CH₂); 57.88 (CH₂); 122.33 (q, $J = 317$, CF₃); 128.60 (C); 129.11 (CH); 132.40 (CH); 135.25 (CH); 143.24 (C); 147.59 (CH); 148.28 (C); 149.67 (CH). MS (EI⁺) m/z : 435 [(M-OTf)⁺] (100), 416 (55), 372 (30), 343 (25), 332 (60). HRMS (EI⁺) m/z : [(M-OTf)⁺] C₂₁H₁₈F₃N₂O₃S calc.: 435.0990, found: 435.0975. m.p. 241-244 °C.

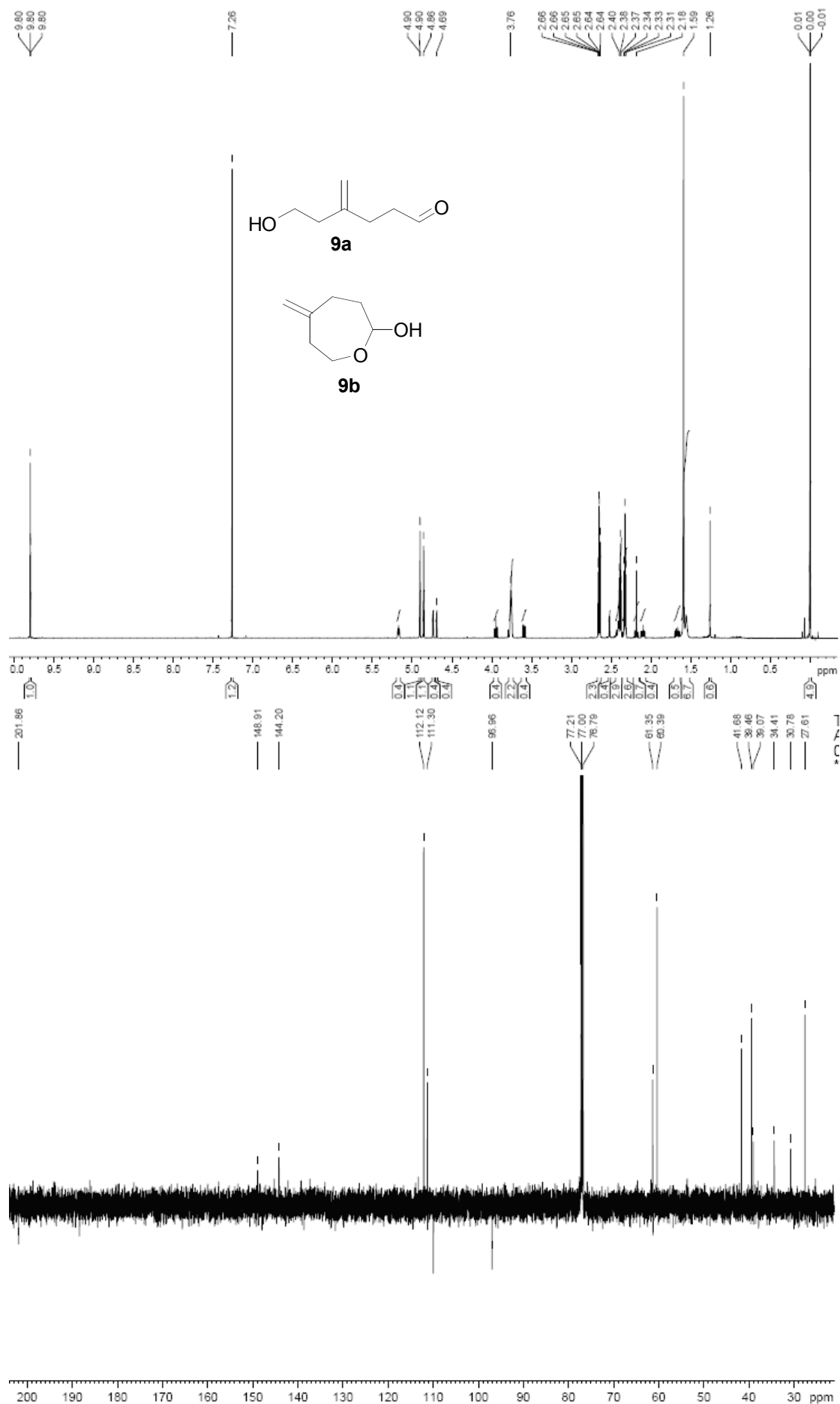
Scanned NMR spectra

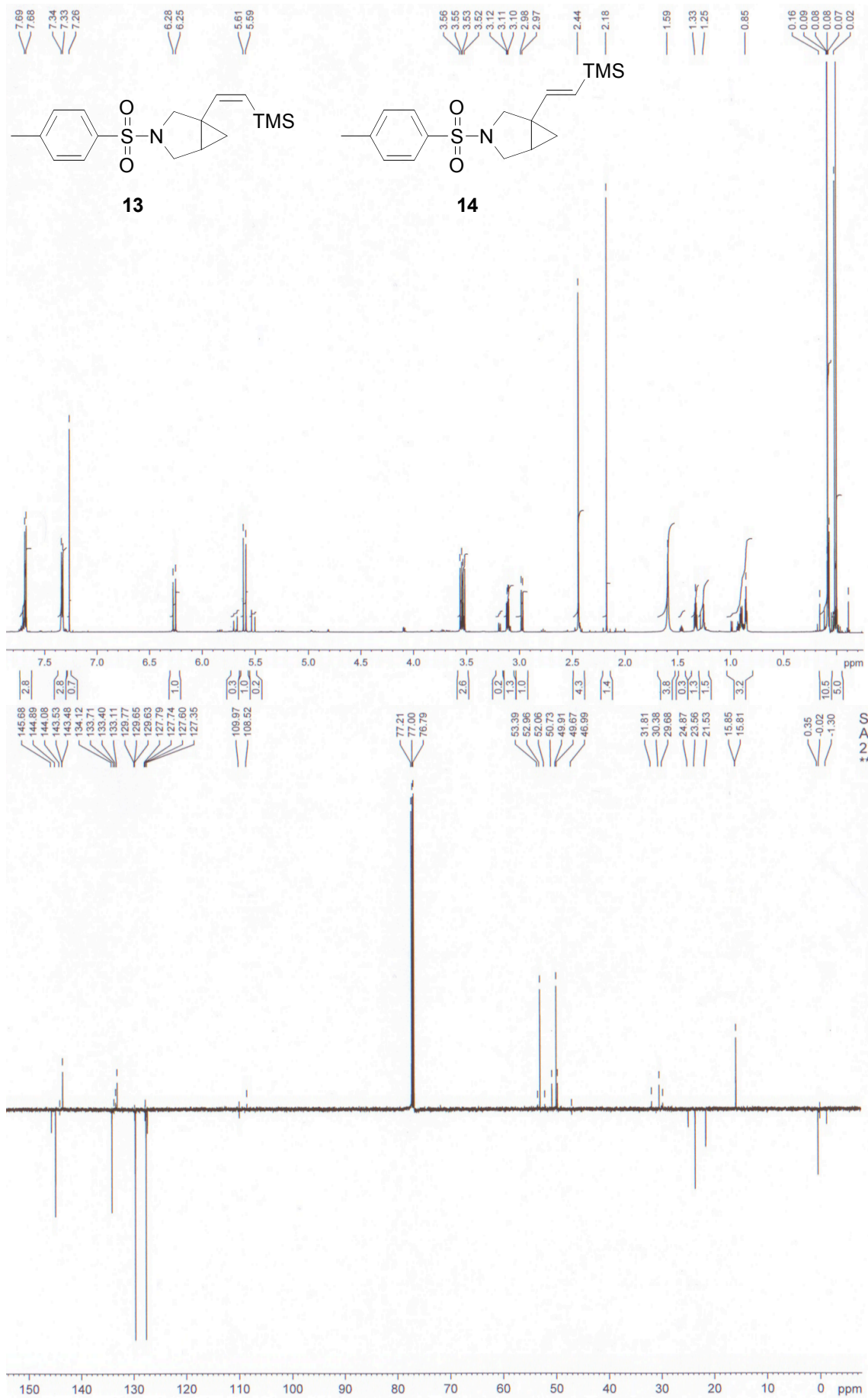


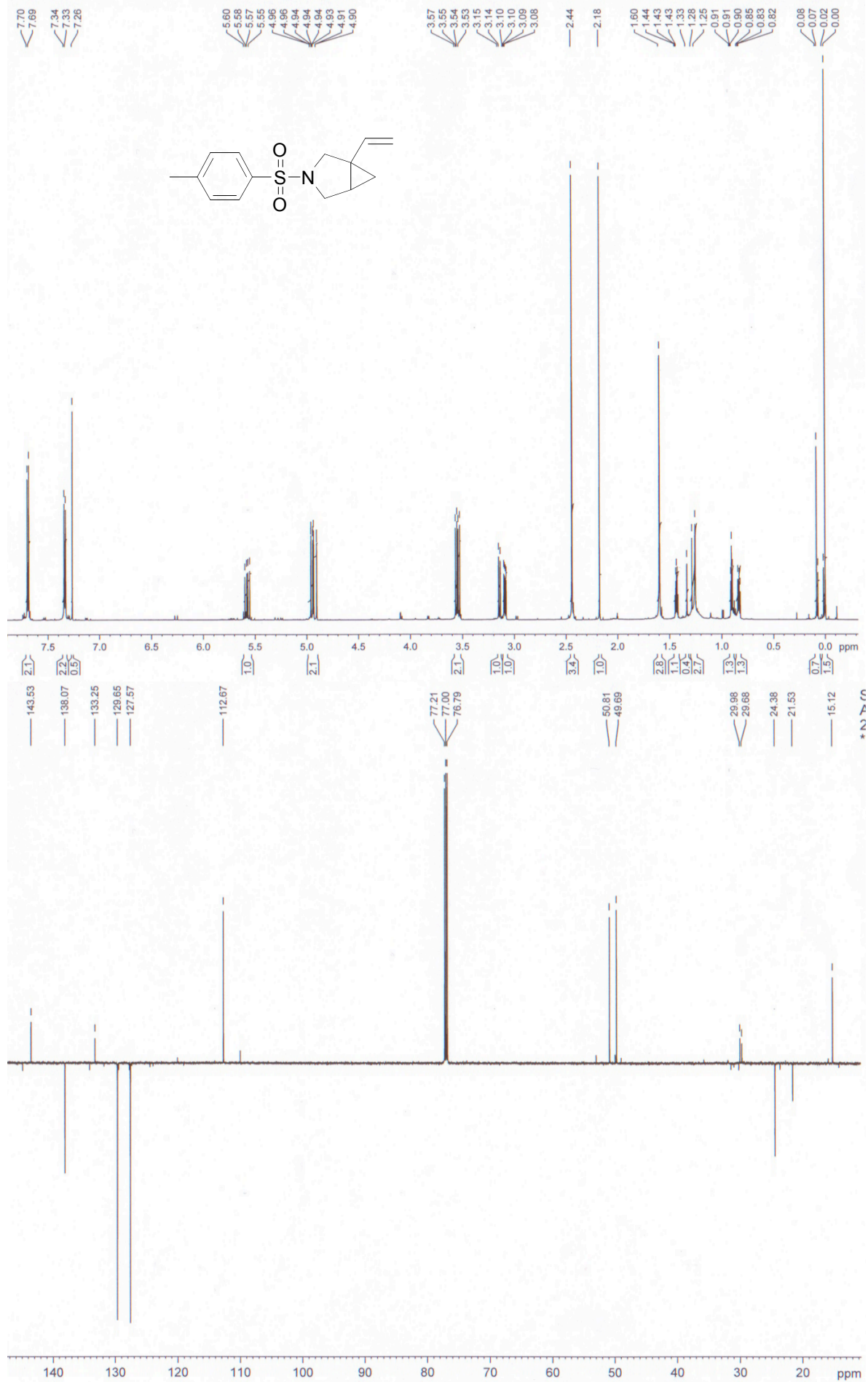


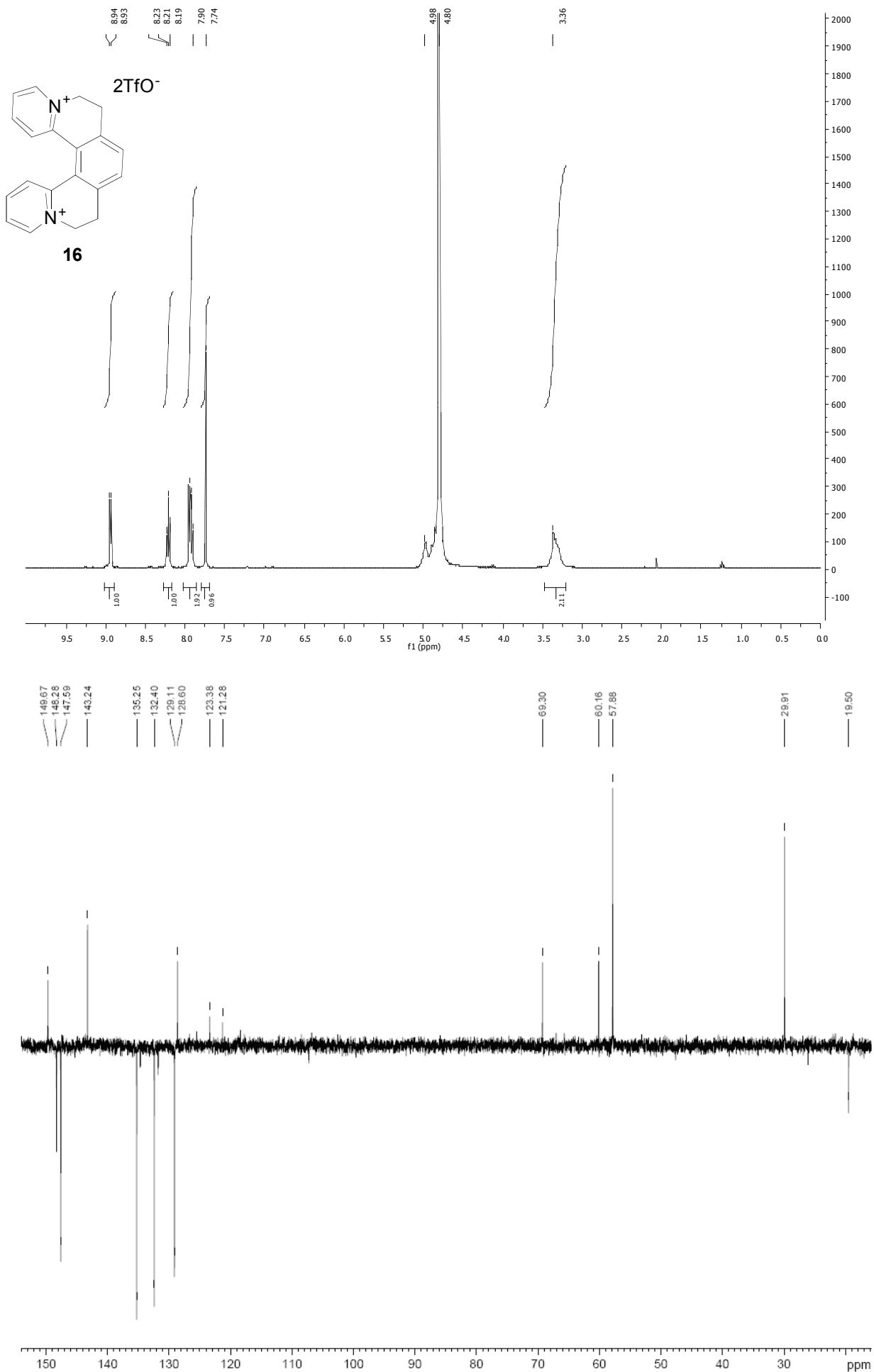


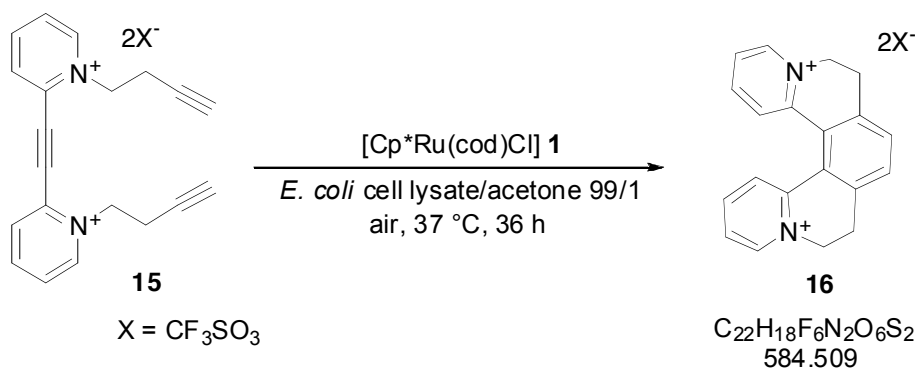










Procedure for yield determination in transformation 15 → 16

One drop of acetone (0.01 ml) was added directly to the bottom of a RBF containing $[\text{Cp}^*\text{Ru}(\text{cod})\text{Cl}] \mathbf{1}$ (1.6 mg, 4.28 μmol , 25 mol%). A solution of 2,2'-(ethyne-1,2-diyl)bis(1-(but-3-ynyl)pyridinium)bis(trifluoromethanesulfonate) **15** (10.0 mg, 17.1 μmol , 1 equiv)² in *E. coli* DH5 α cell lysate (1.5 ml) was added to the mixture of catalyst and acetone. The resulting solution was stirred at 37 °C for 36 h. The yield of this reaction was determined by ¹H NMR with comparison to DMSO as an internal standard.

Preparation of the internal standard

Step 1) 10 μl of DMSO was diluted to 1 ml with D₂O.

Step 2) A 50 μl amount of the standard solution prepared in Step 1 was diluted to 2 ml with D₂O.

Step 3) Step 2 was repeated 3 more times, thus, four separate 2 ml solutions comprised of 7.042×10^{-6} mol of DMSO in D₂O were prepared.

Preparation of the sample

Step 1) The crude reaction mixture from transformation **15** → **16** *vide supra* was diluted to a volume of 20 ml.

Step 2) This was divided into 2 fractions of 2 ml each (samples 2A and 2B), 2 fractions of 4 ml each (samples 4A and 4B), and 1 fraction of 8 ml.

Step 3) The separate fractions were evaporated to dryness *in vacuo*.

Step 4) The samples 2A, 2B, 4A, and 4B were dissolved separately in the four solutions of DMSO in D₂O, see “Preparation of the internal standard” above.

Step 5) ¹H NMR determined the amount of helquat **16** in samples 2A, 2B, 4A, and 4B *via* comparison of the integrations of peaks corresponding to helquat **16** to the peak corresponding to the DMSO internal standard.

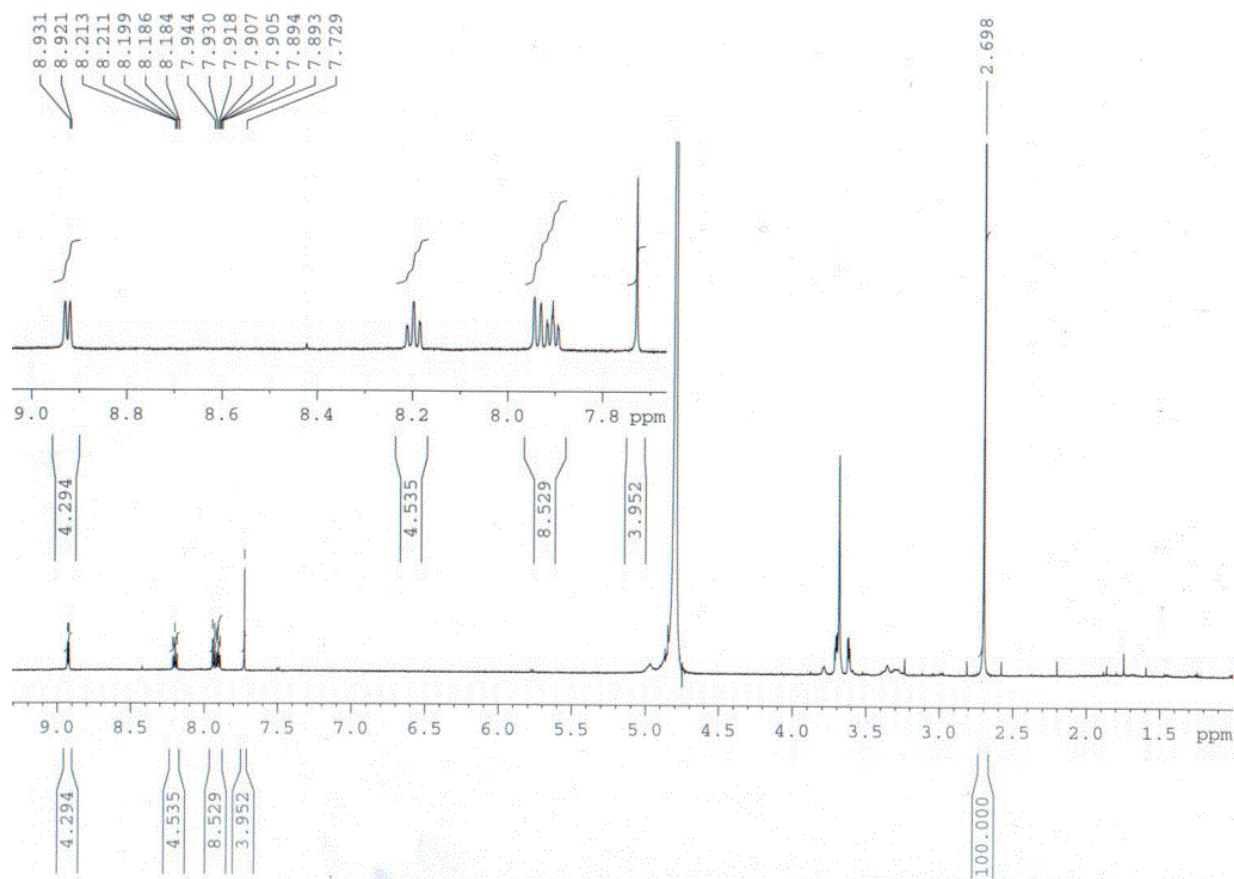


Fig 2. ^1H NMR (600 MHz, D_2O) spectrum of helquat sample 2B

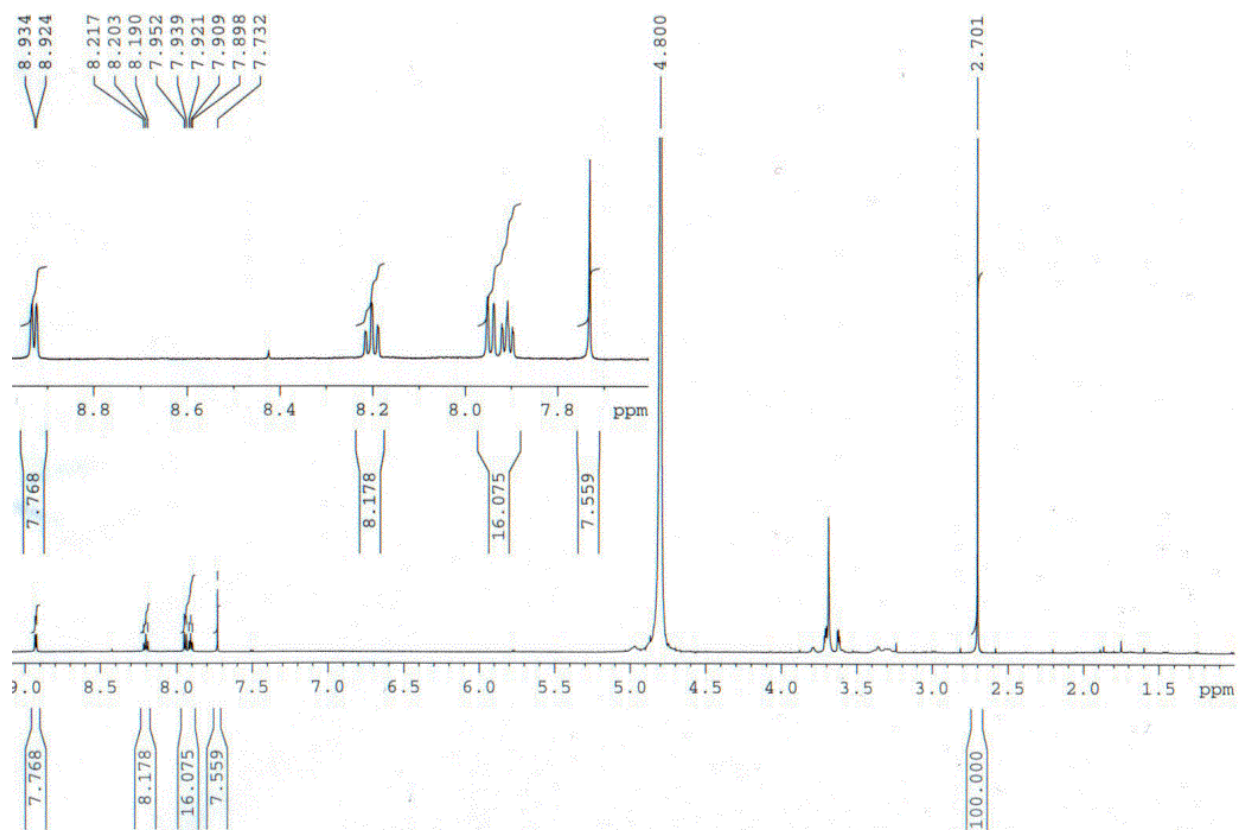


Fig 3. ^1H NMR (600 MHz, D_2O) spectrum of helquat sample 4B

Table 1. Integrations of helquat **16** protons relative to DMSO internal standard

sample	H-6 (%) [8.93 ppm]	H-4 (%) [8.20 ppm]	H-3 & H-5 (%) [7.89-7.95 ppm]	H-10 (%) [7.73 ppm]
2A	3.767	4.038	8.227	3.829
2B	4.294	4.535	8.529	3.952
4A	8.644	9.079	17.432	8.316
4B	7.768	8.178	16.075	7.559

Table 2. Amount (molar%) of **16** relative to DMSO internal standard (7.042×10^{-6} mol) based on ^1H NMR integrations

sample	H-6 (%)	H-4 (%)	H-3 & H-5 (%)	H-10 (%)	average (%)	16 (mols)	Yield 16 (%)
2A	11.301	12.114	24.681	11.487	11.917	8.389×10^{-7}	49.060
2B	12.882	13.605	25.587	11.856	12.786	9.001×10^{-7}	52.639
4A	25.932	27.237	52.296	24.948	26.083	1.836×10^{-6}	53.690
4B	23.304	24.534	48.225	22.677	23.748	1.672×10^{-6}	48.885

From the data presented above (Table 1 and Table 2), obtained from ^1H NMR spectra of samples 2A, 2B, 4A, and 4B, (see Fig. 1 and Fig. 2 for two representative spectra) we can estimate that the yield of the reaction is between 48% and 54% with a mean value of 51%.

Determination of yield for transformation **15** \rightarrow **16** after 2.5 hours

The procedure is performed exactly as outlined above with a reaction time of 2.5 h instead of 36 h. We estimate that the yield of the reaction after 2.5 h is between 32% and 36% with a mean value of 33%.

References

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