

Stereoselectivity of the Honda-Reformatsky reaction in reactions with ethyl bromodifluoroacetate with α -oxygenated sulfinylimines

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1. General conditions

All air/ moisture sensitive reactions were carried out under an inert atmosphere (Ar), in oven dried glassware. CH₂Cl₂ (from CaH₂), THF (from Na and benzophenone) and MeCN (from CaH₂) were distilled prior to use, and where appropriate, other reagents and solvents were purified by standard techniques. TLC was performed on aluminium-precoated plates coated with silica gel 60 with an F₂₅₄ merck indicator; visualised under UV light (254 nm) and/or by staining with KMnO₄ (10% aq.). Flash column chromatography was performed with Sigma Aldrich 60 silica gel (40-63 nm).

Chemical shifts are reported in δ units using CHCl₃ as an internal standard. The following abbreviations for the multiplicity of the peaks are s (singlet), d (doublet), dd (doublet of doublets), ddd (doublet of doublets of doublets), dddd (doublet of doublets of doublets of doublets) dt (doublet of triplets), t (triplet), q (quartet), qd (quartet of doublets), qt (quartet of triplets), br. s (broad singlet), and m (multiplet).

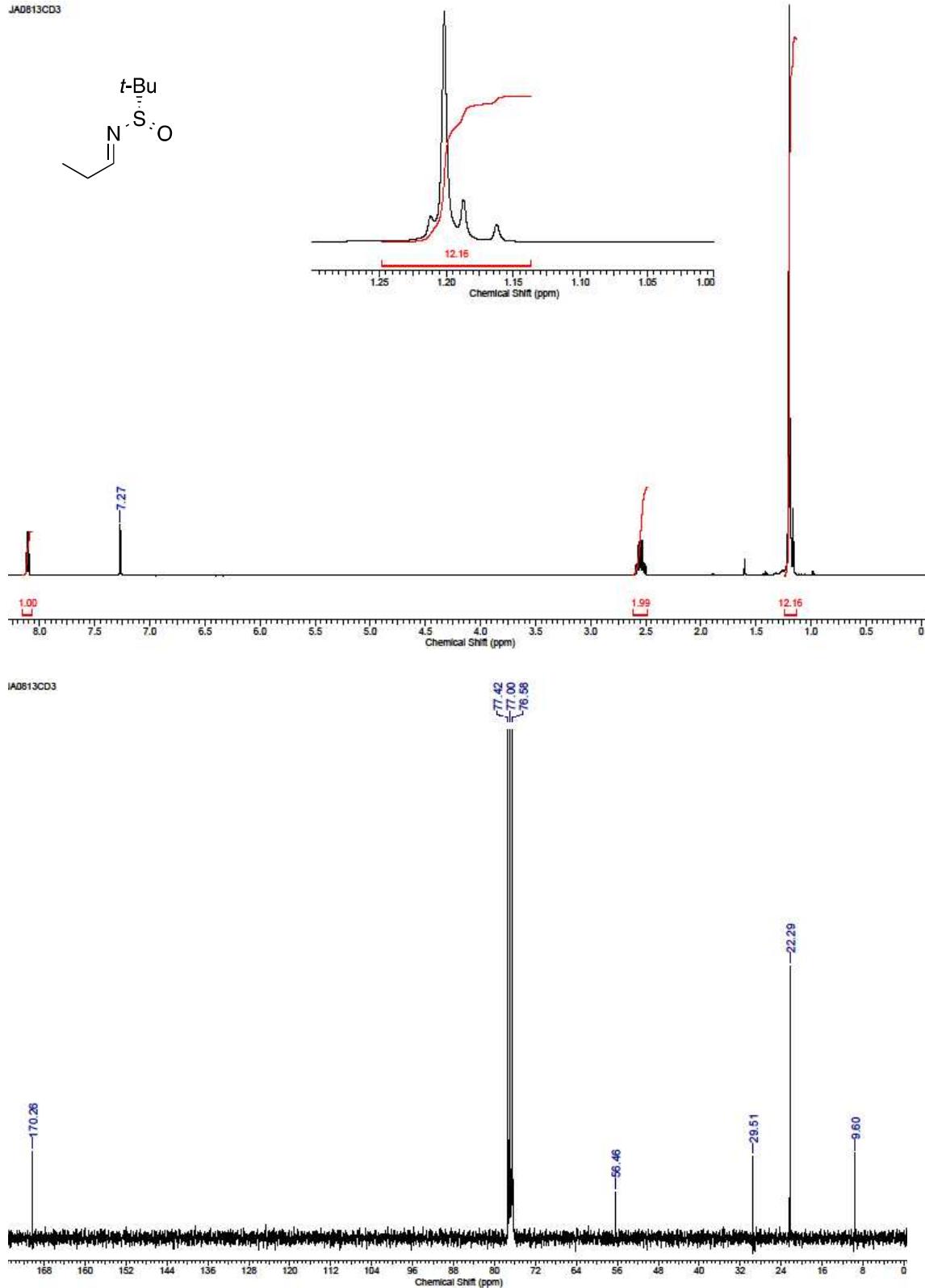
Fourier-transform infrared (FT-IR) spectra were collected using an ATR accessory using neat samples (solids and liquids). The abbreviations s (strong), m (medium), w (weak) and br (followed by either s, m or w to indicate the strength of a broad peak) are used when reporting the spectra.

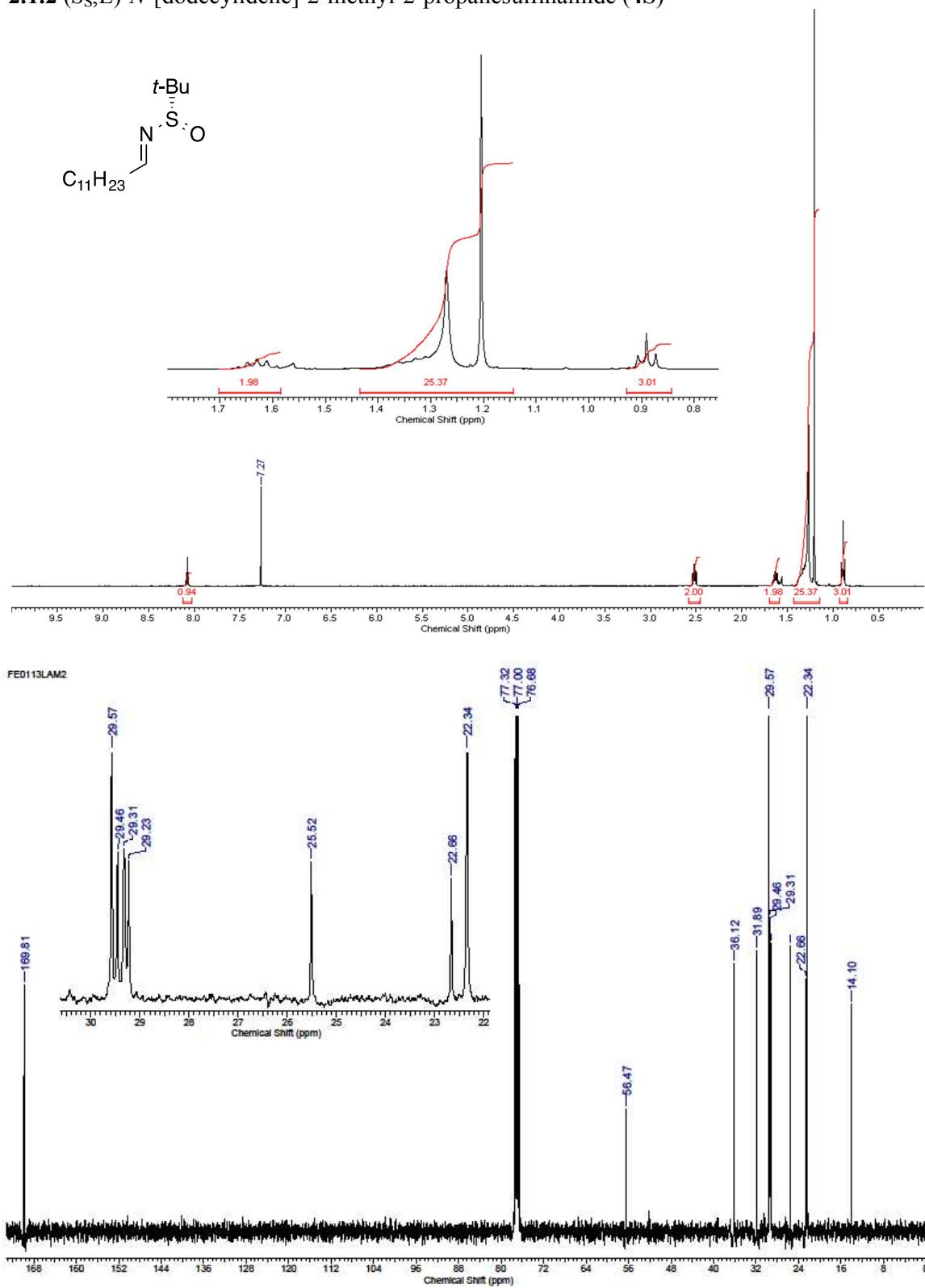
Electrospray mass spectra were ran in HPLC methanol or MeCN, labelled *m/z* (abundance percentage) [M+X]^{+/−}. HRMS samples were run on a ESI-TOF MS or a ESI FT-ICR MS spectrometer.

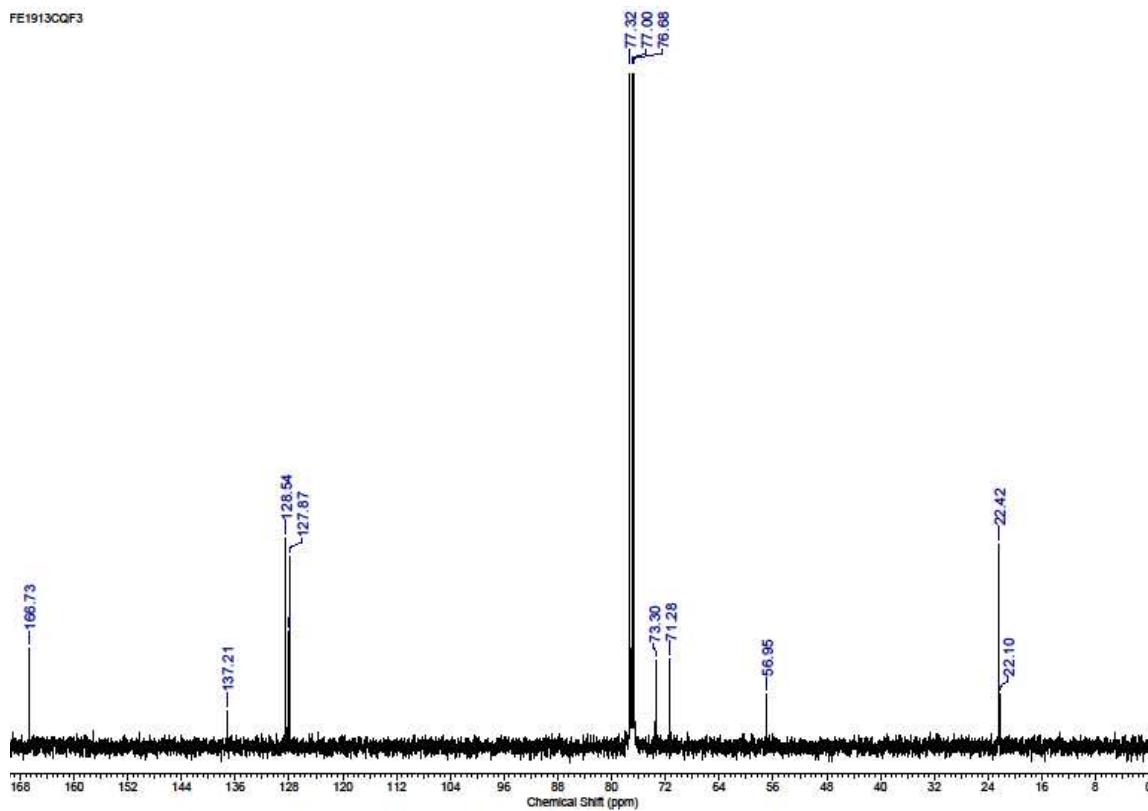
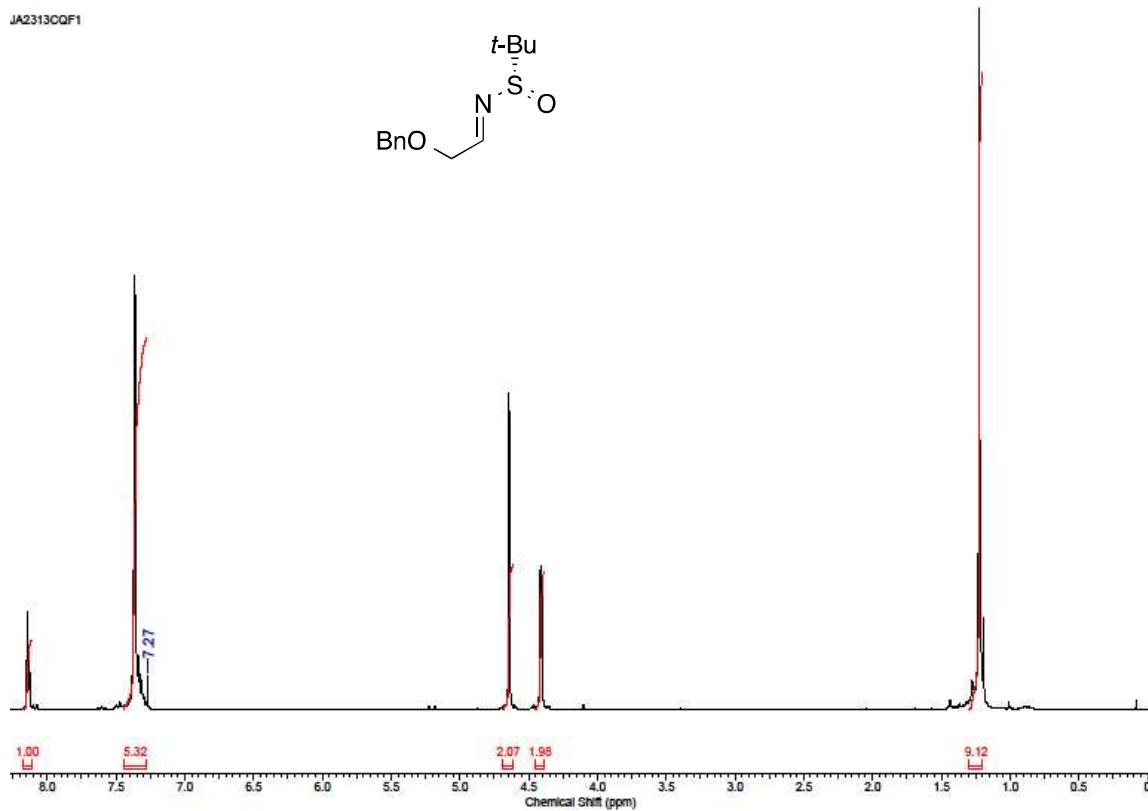
Optical rotations were collected at 589 nm.

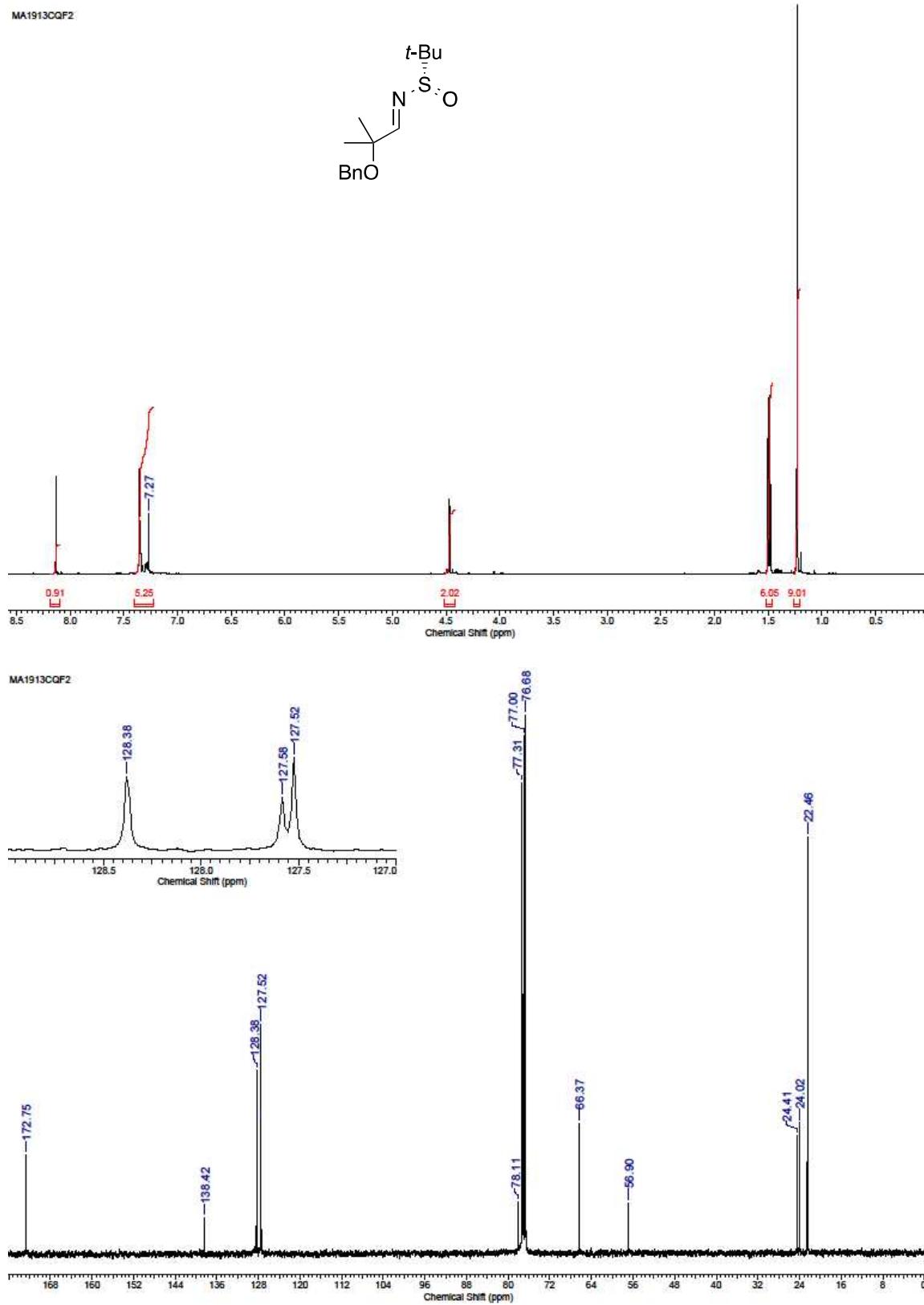
2. Copies of spectra**2.1 Synthesis of tert-butyl sulfinyl imines****2.1.1 (*S_S,E*)-*N*-(propylidene)-2-methyl-2-propanesulfonamide (3S)**

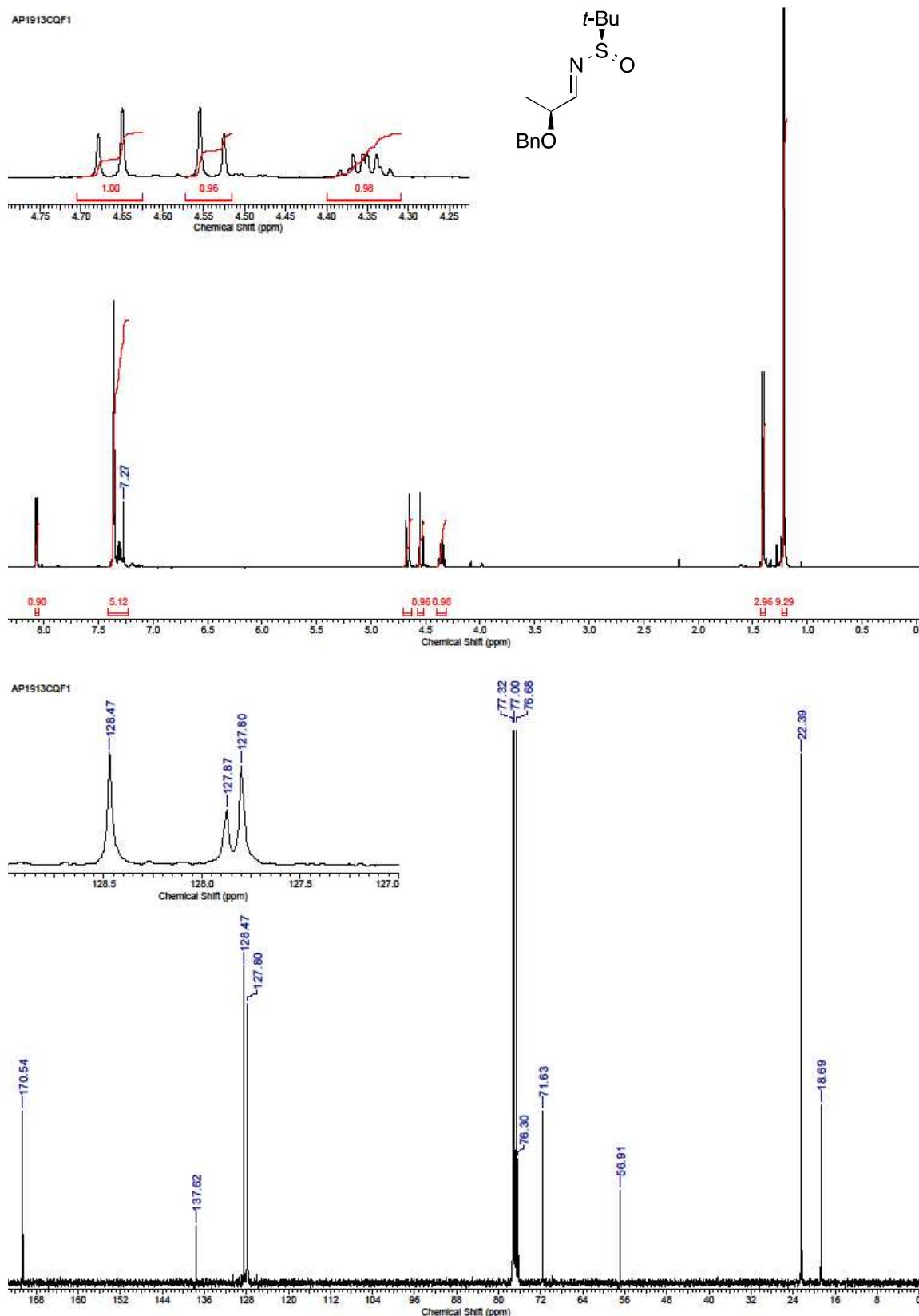
JAD813CD3

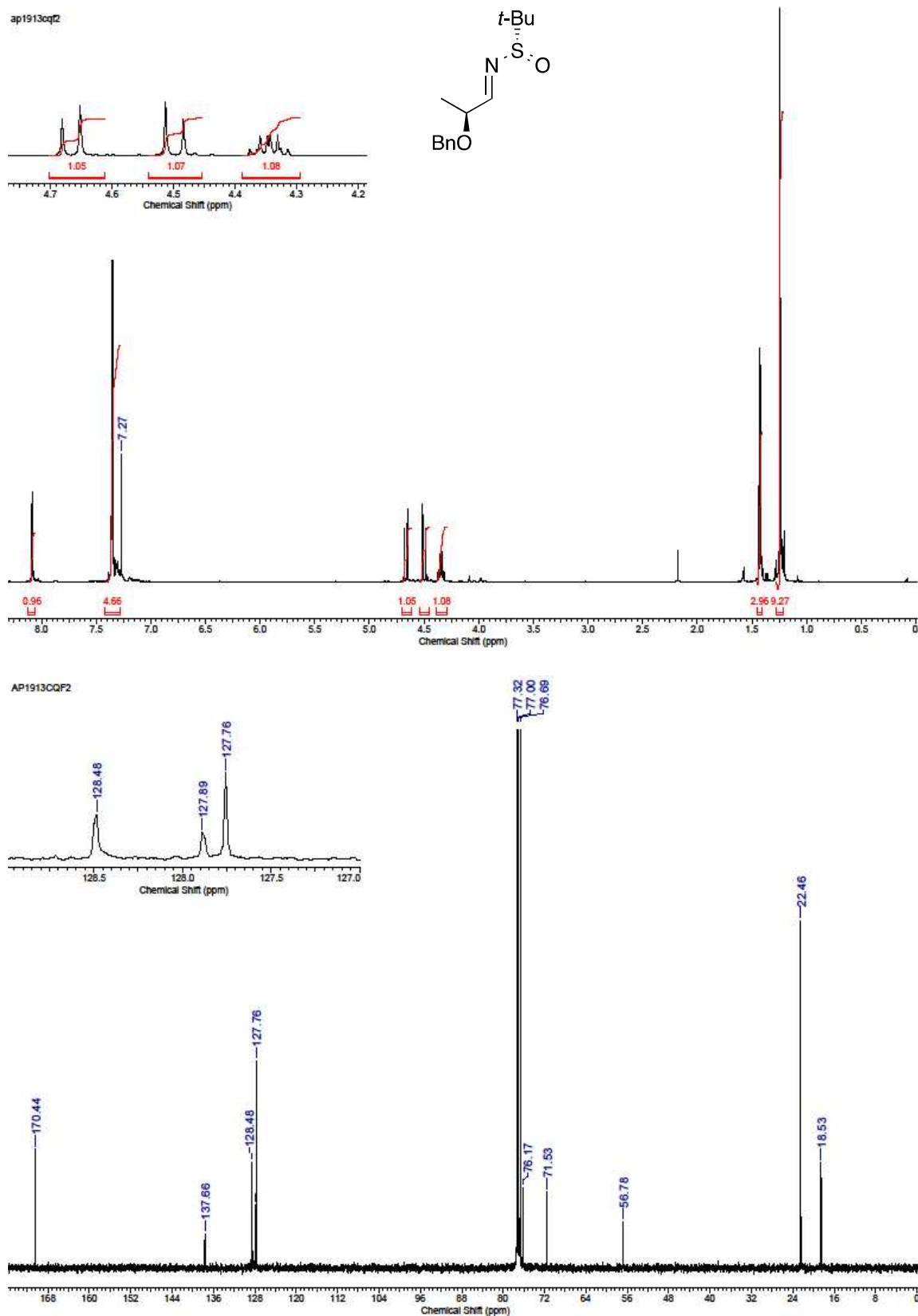


2.1.2 (*S_S,E*)-*N*-[dodecylidene]-2-methyl-2-propanesulfonamide (4S**)**

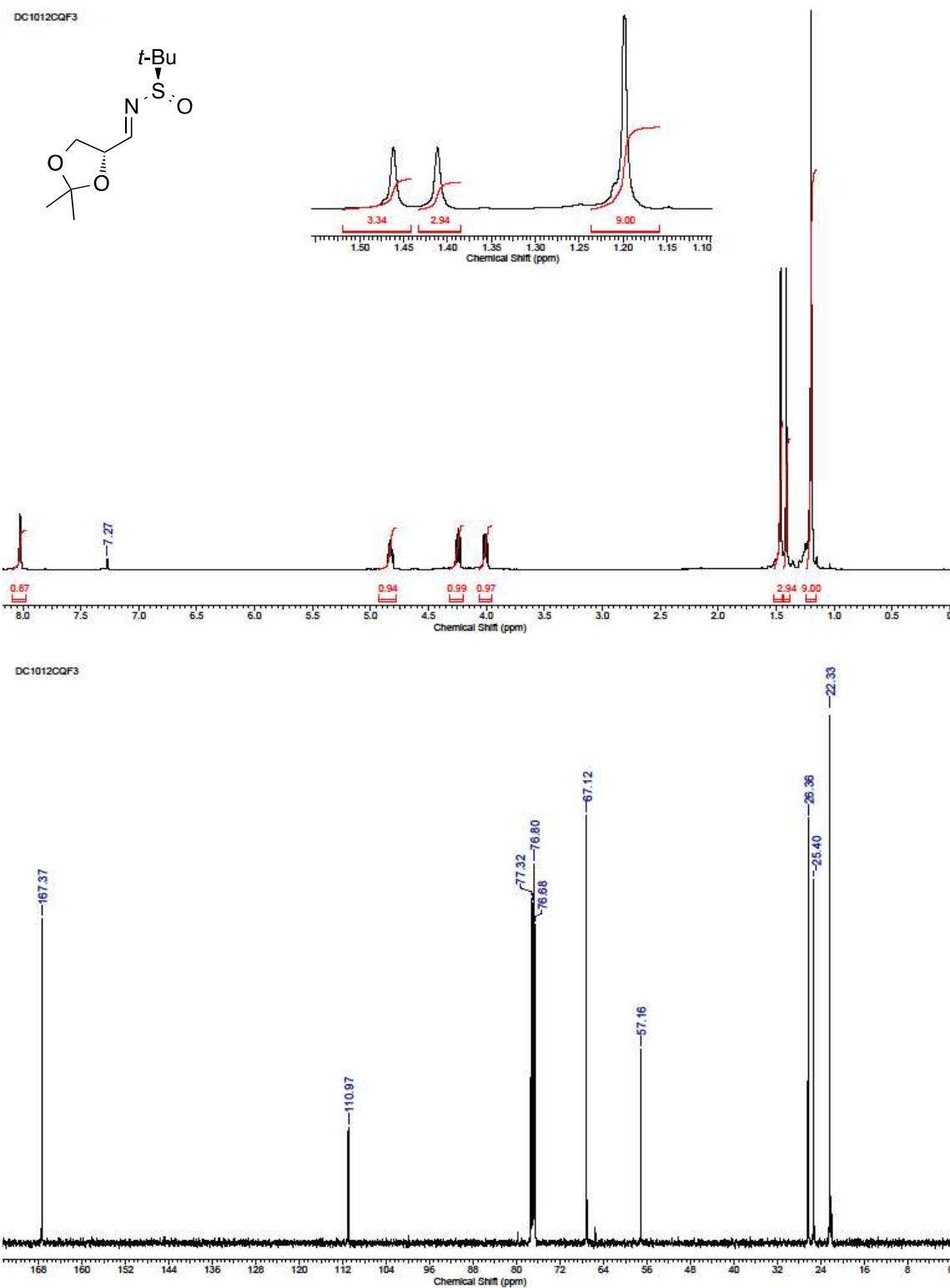
(S_S,E)-N-[2-Benzyloxyethylidene]-2-methyl-2-propanesulfinamide (5S**)**

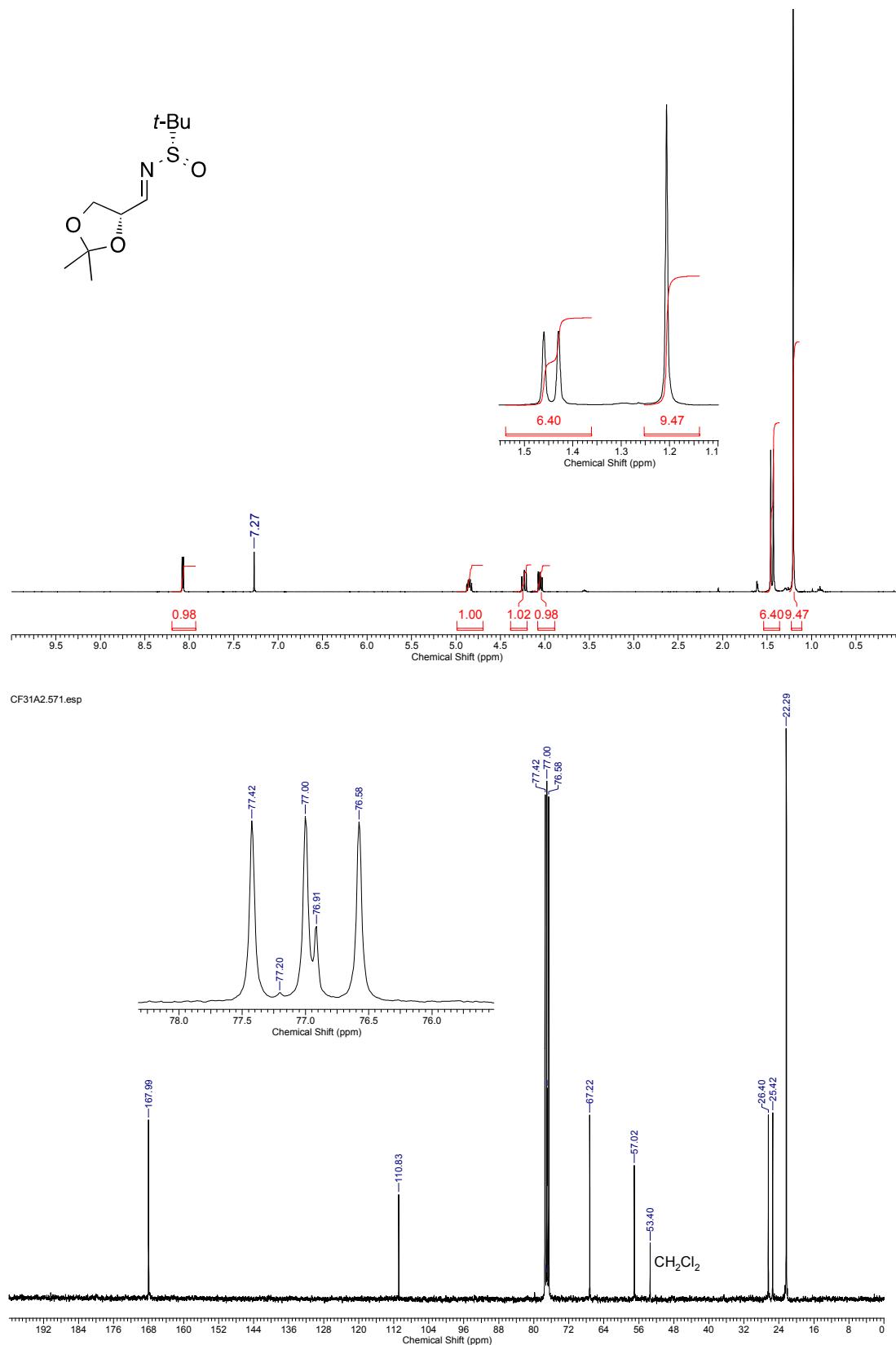
2.1.3 (*S*,*E*)-*N*-[2-(Benzylxy)-2-methylpropylidene]-2-methyl-2-propanesulfinamide (6S**)**

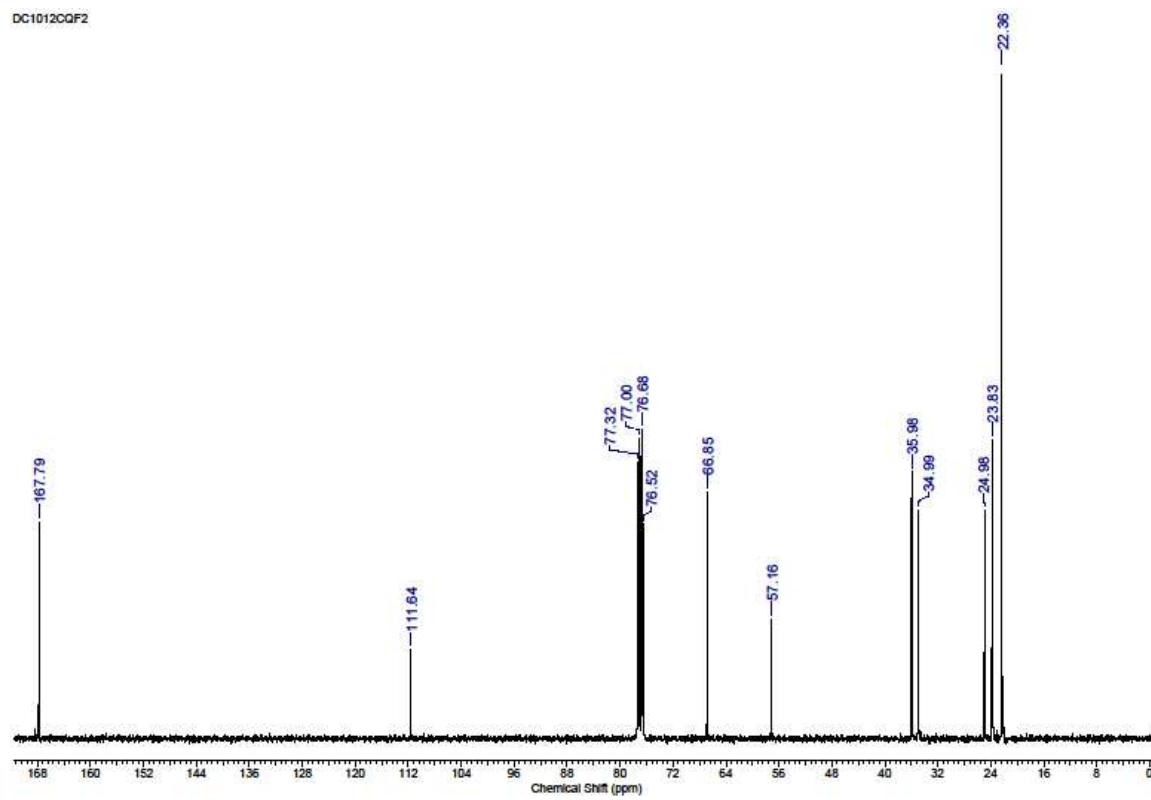
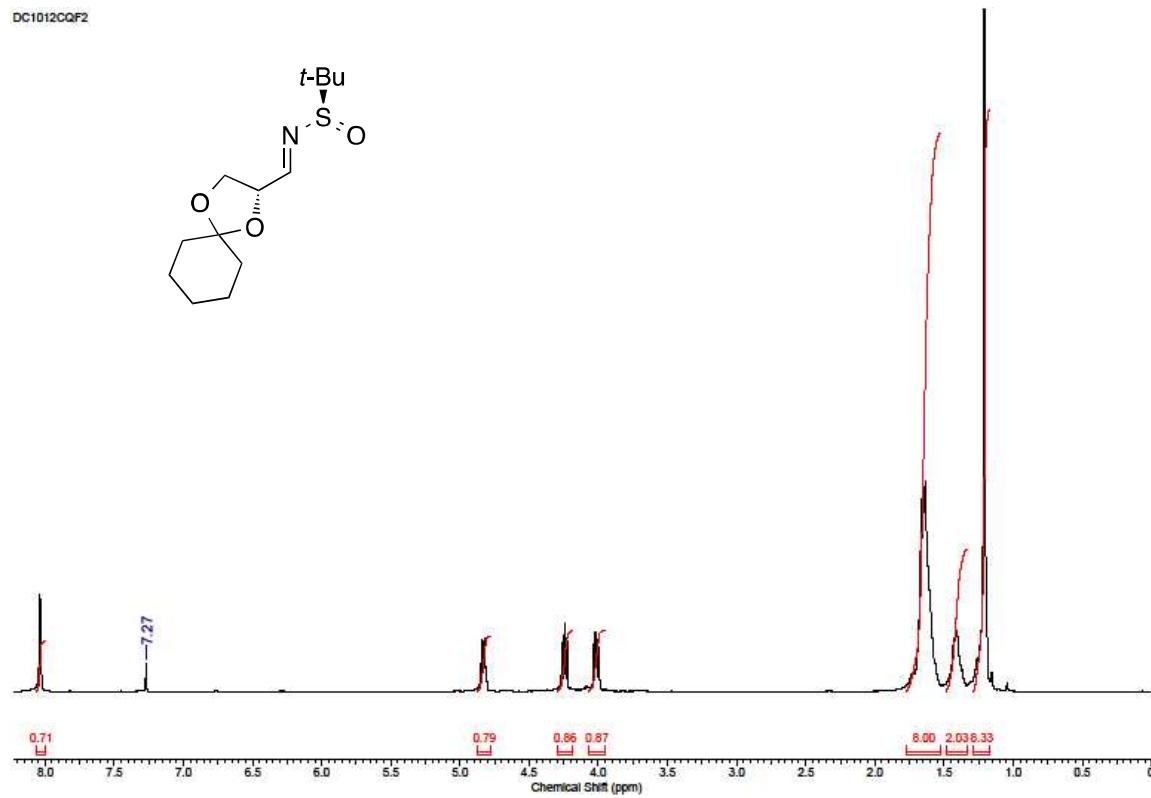
2.1.4 (*R_S,E*)-*N*-(2*S*)-2-(Benzylxy)propylidene]-2-methyl-2-propanesulfonamide (*ent*-7S)

2.1.5 (*S_S,E*)-*N*-[(2*S*)-2-(Benzylxy)propylidene]-2-methyl-2-propanesulfonamide (*ent*-7R)

2.1.6 (*R_S,E*)-*N*-(2*S*)-2,3-(isopropylidenedioxy)propylidene]-2-methyl-2-propanesulfinamide (8R)

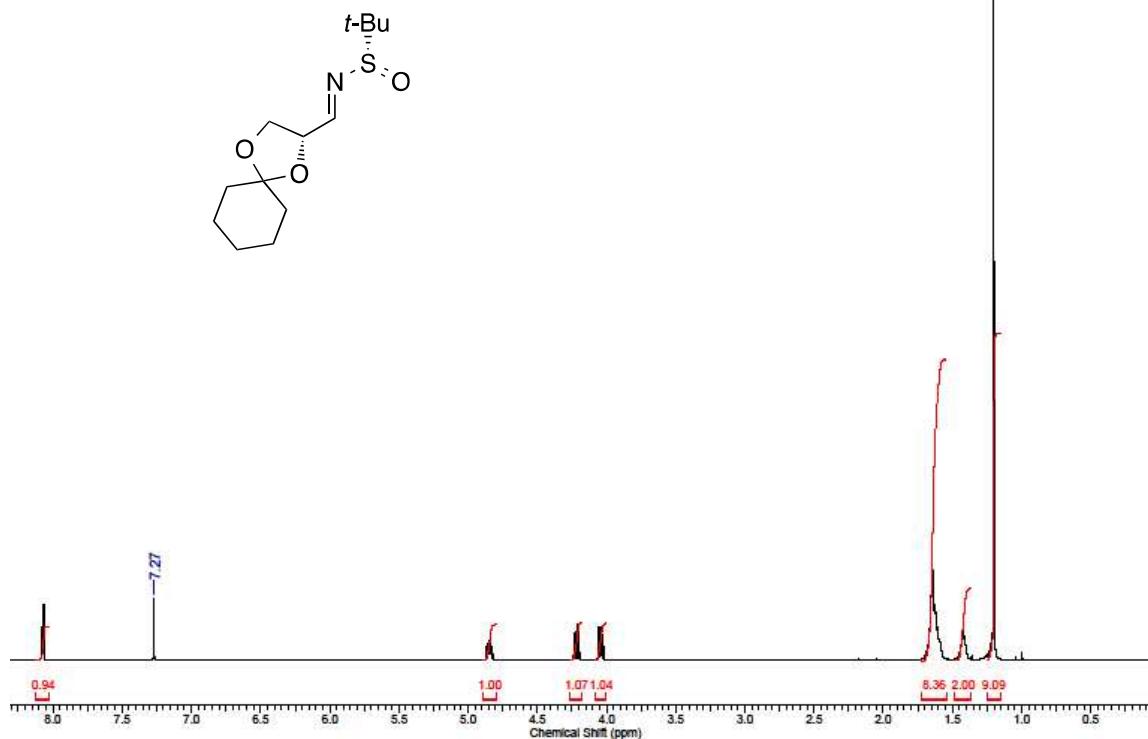


2.1.7 (*S_S,E*)-*N*-[(2*S*)-2,3-(isopropylidenedioxy)propylidene]-2-methyl-2-propanesulfonamide (8S)

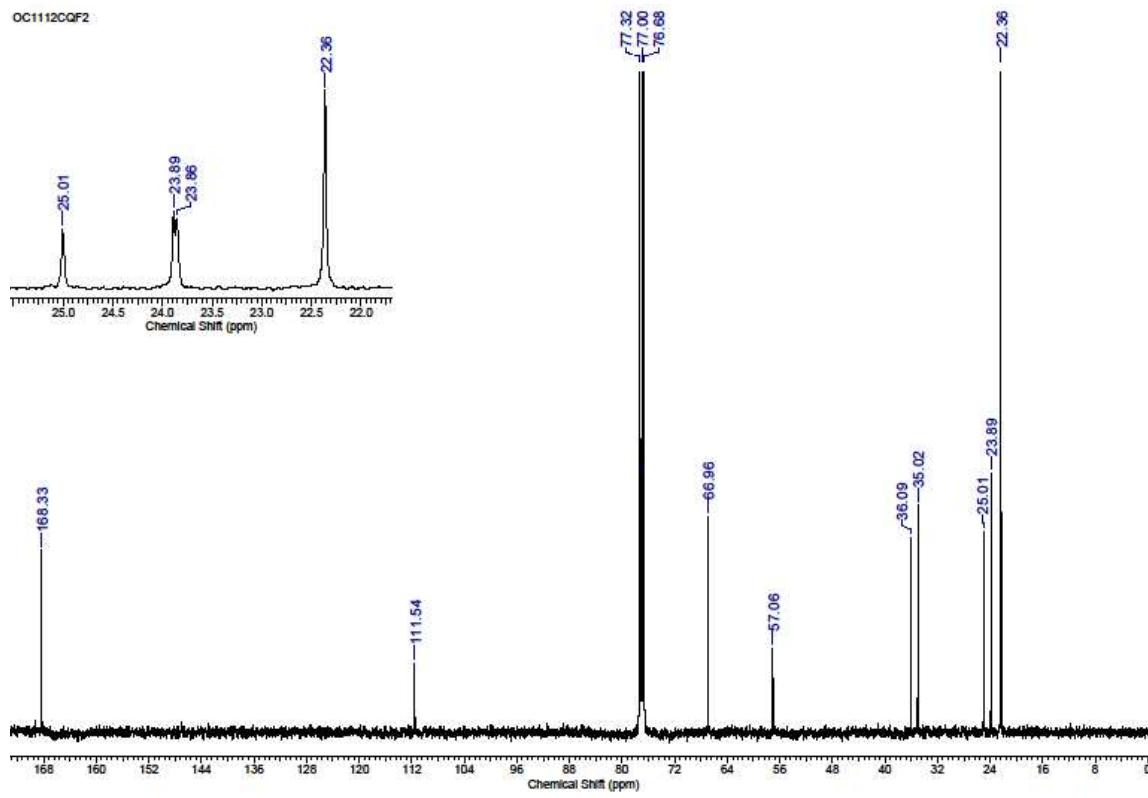
2.1.8 (*R_S,E*)-*N*-[(2*S*)-2,3-(cyclohexyldenedioxy)propylidene]-2-methyl-2-propanesulfinamide (9R**)**

2.1.9 (*S,S,E*)-*N*-[(2*S*)-2,3-(cyclohexyldenedioxy)propylidene]-2-methyl-2-propanesulfinamide (9S**)**

OC1112CQF2

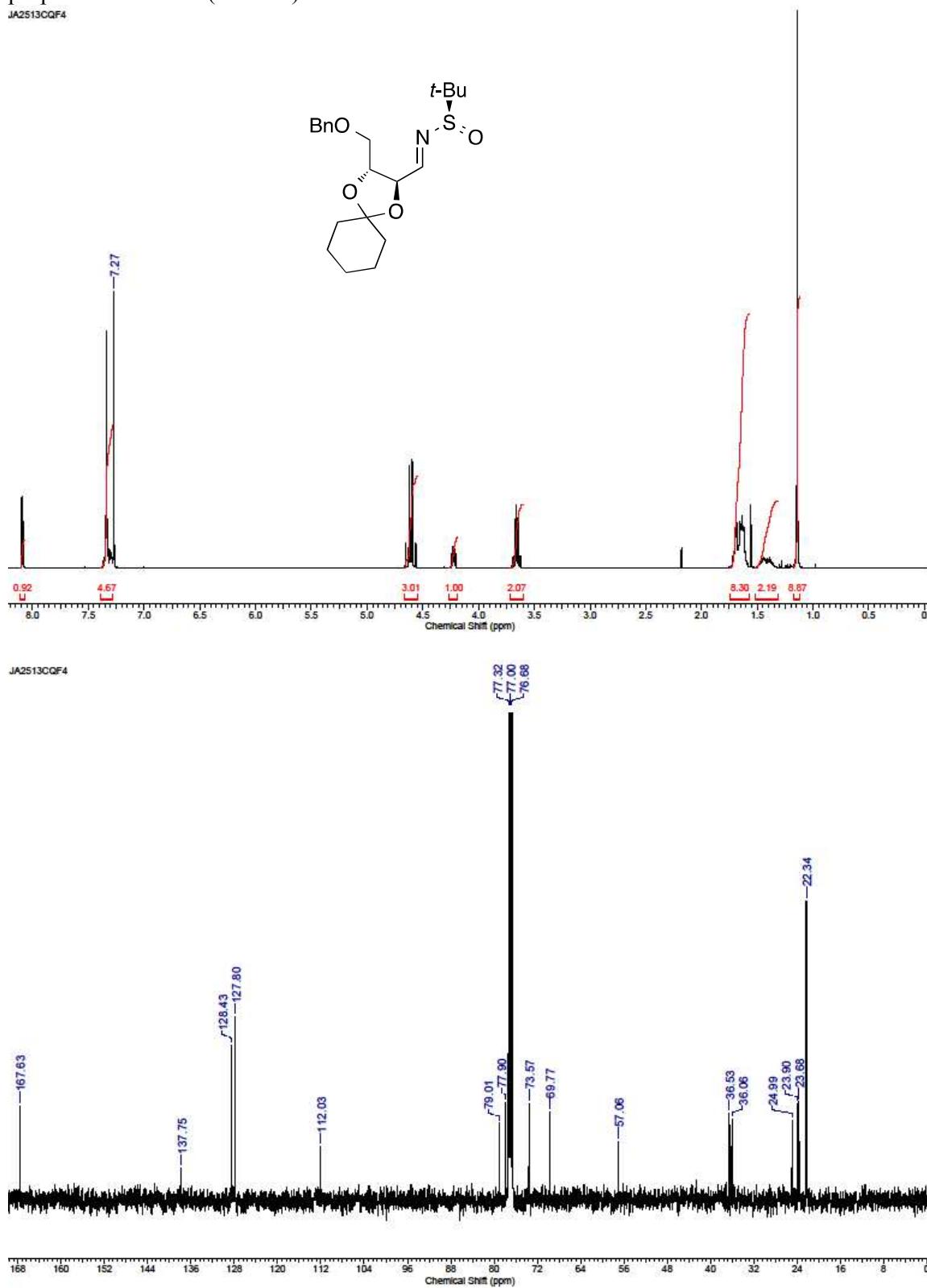


OC1112CQF2



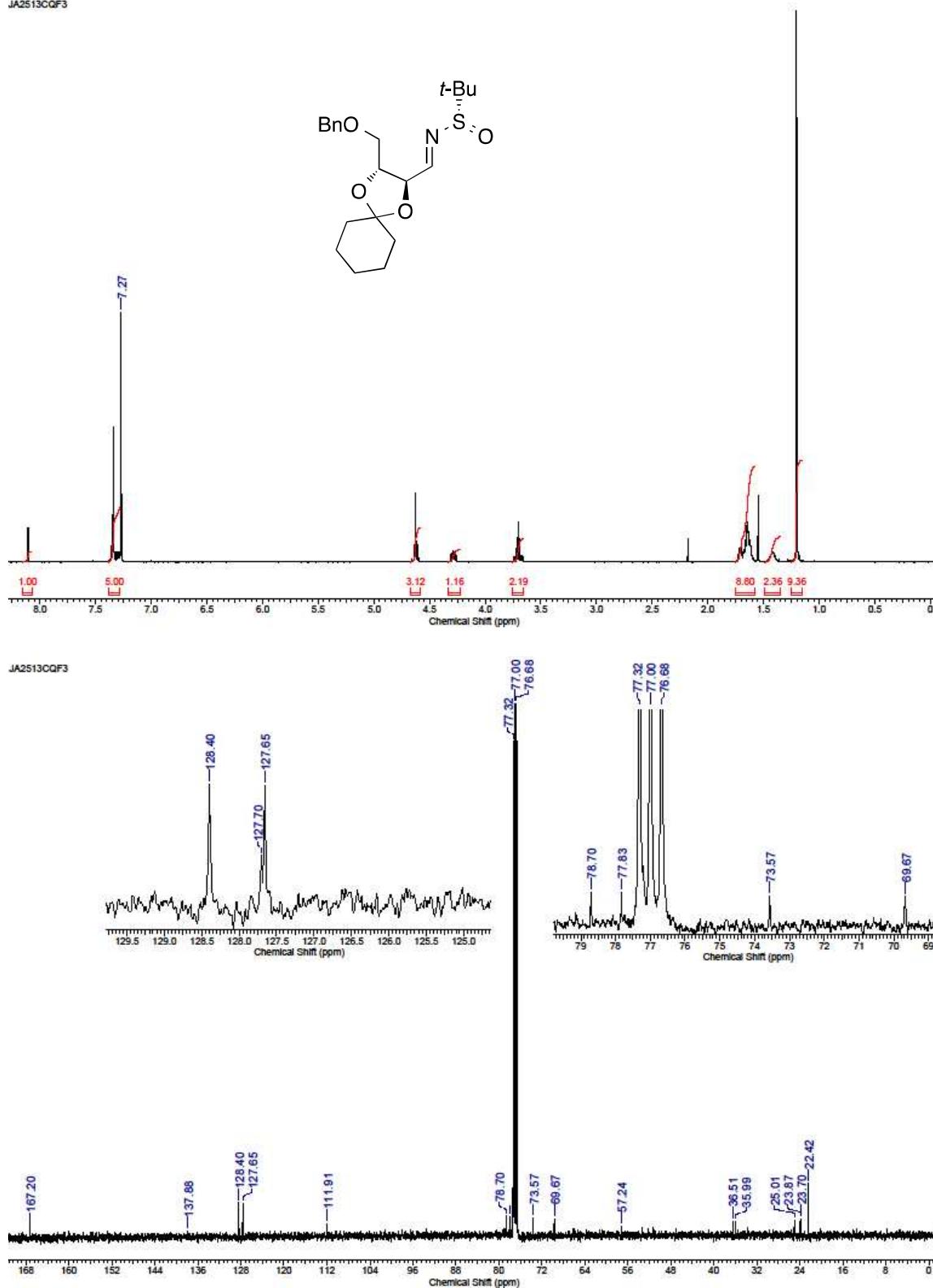
2.1.10 (*R_s,E*)-*N*-[(2*R*,3*R*)-4-(benzyloxy)-2,3-(cyclohexyldenedioxy)butylidene]-2-methyl-2-propanesulfinamide (*ent*-10S)

JA2513CQF4



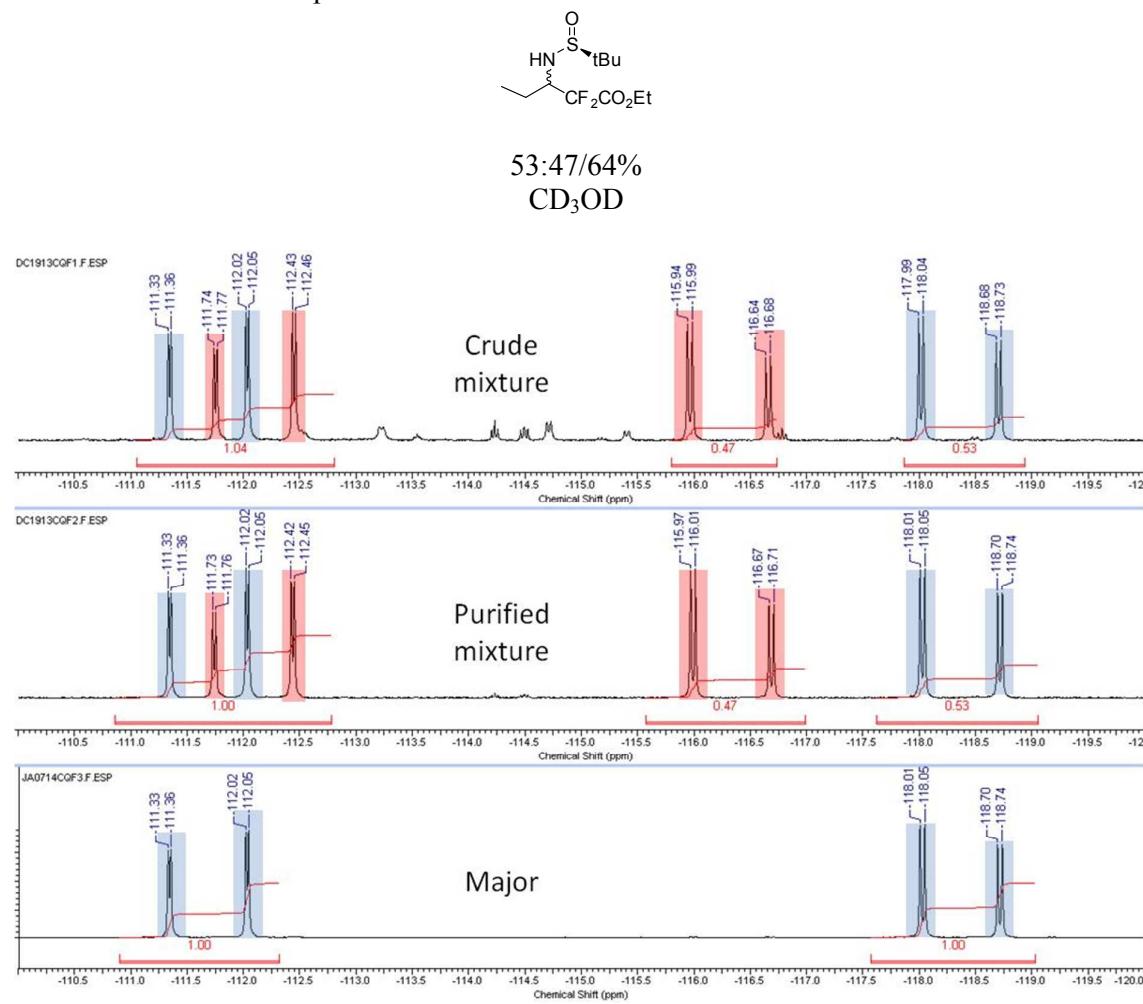
2.1.11 (*S_S,E*)-*N*-[(2*R*,3*R*)-4-(benzyloxy)-2,3-(cyclohexyldenedioxy)butylidene]-2-methyl-2-propanesulfinamide (*ent*-10R)

JA2513CQF3



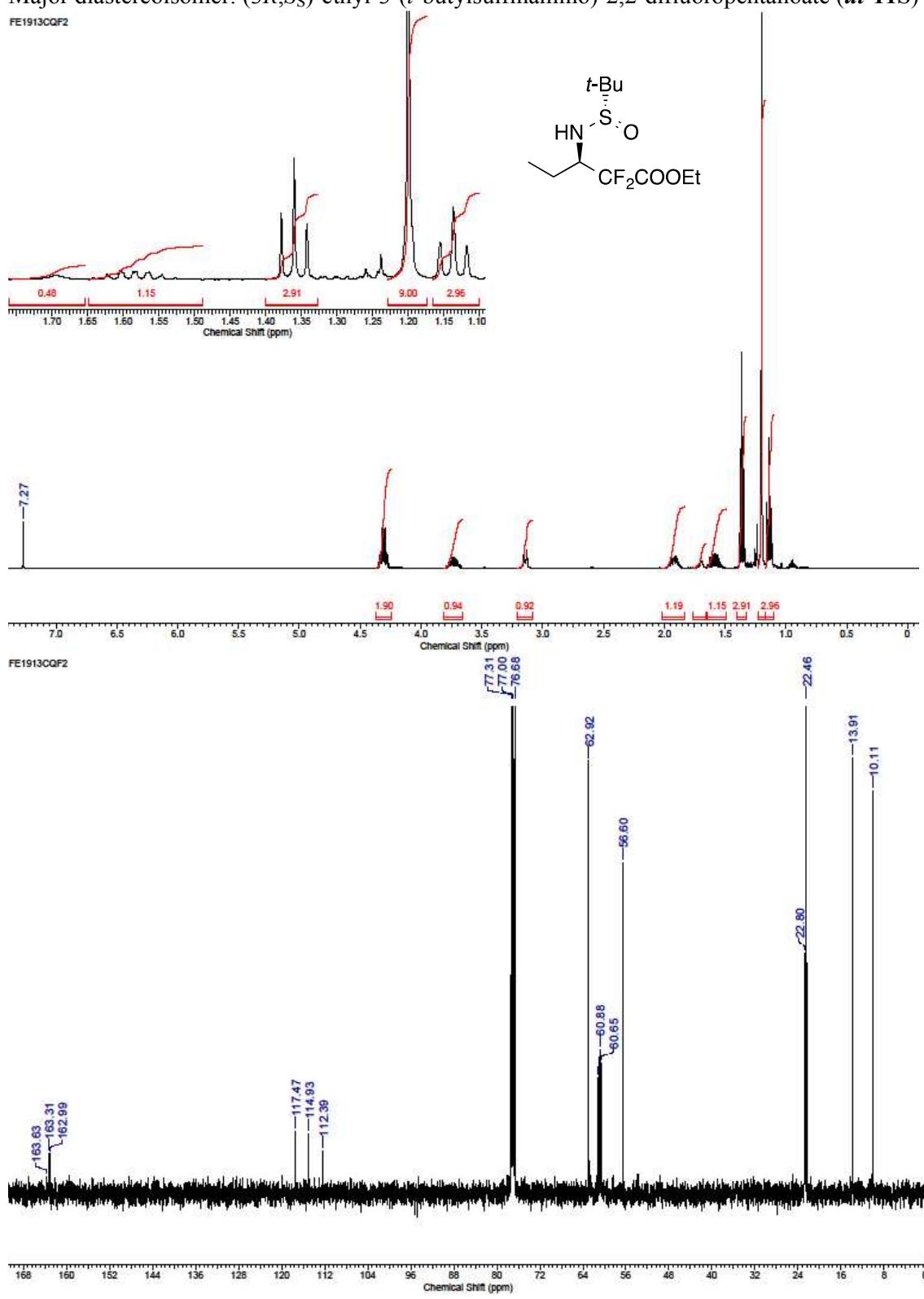
2.2 Reformatsky reaction

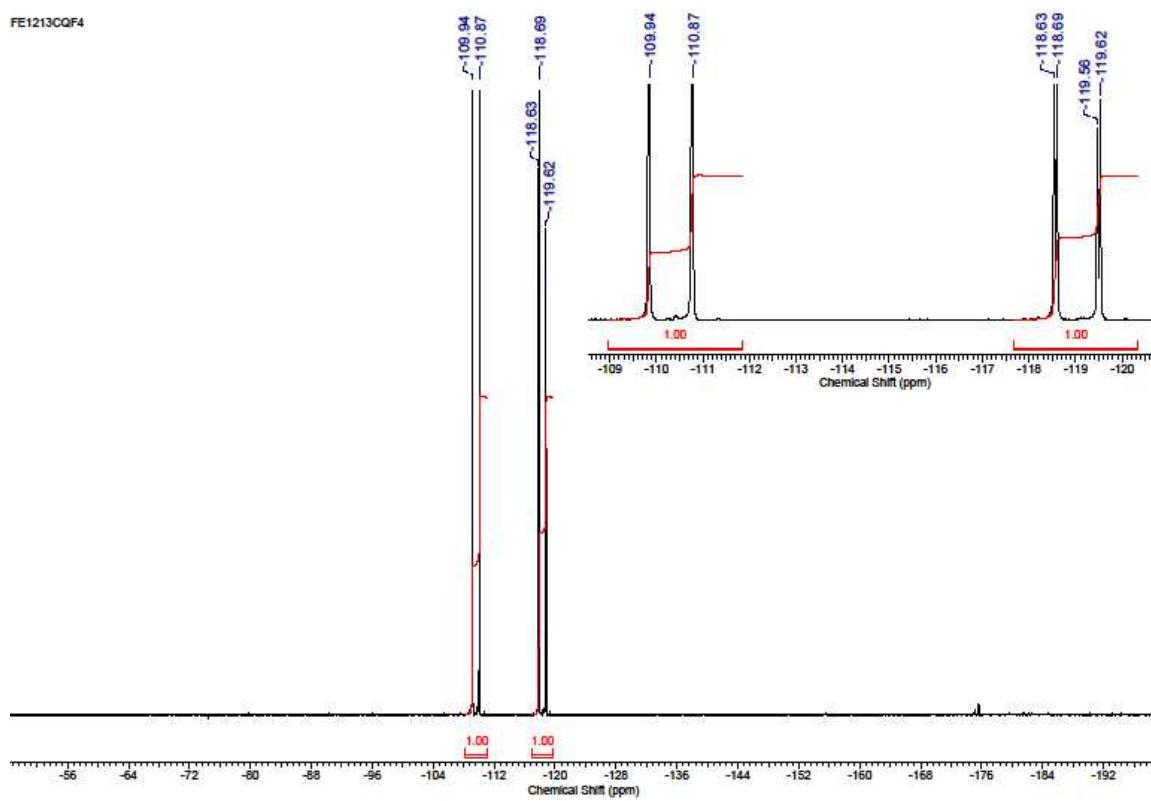
2.2.1 Reaction with 3S: spectra of crude NMR and of the diastereomers 11S



Major diastereoisomer: (3*R*,*S*)-ethyl-3-(*t*-butylsulfinamino)-2,2-difluoropentanoate (**ul-11S**)

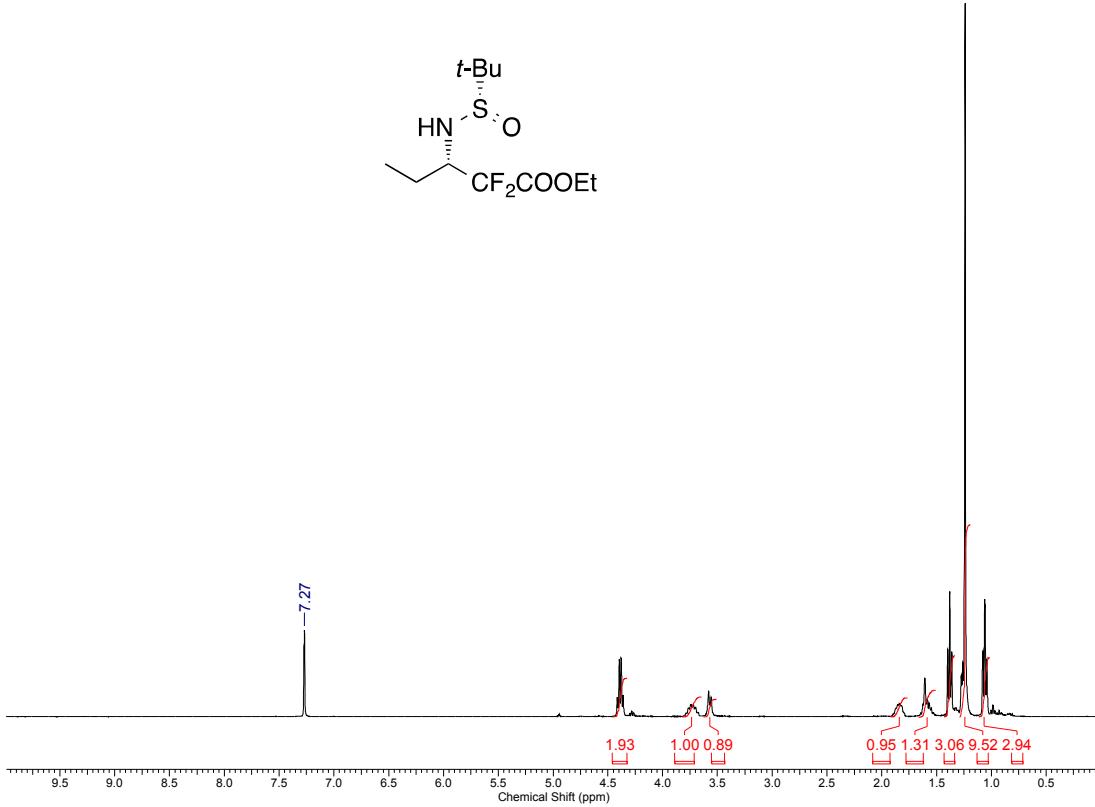
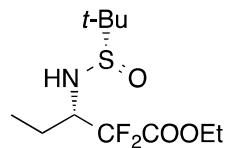
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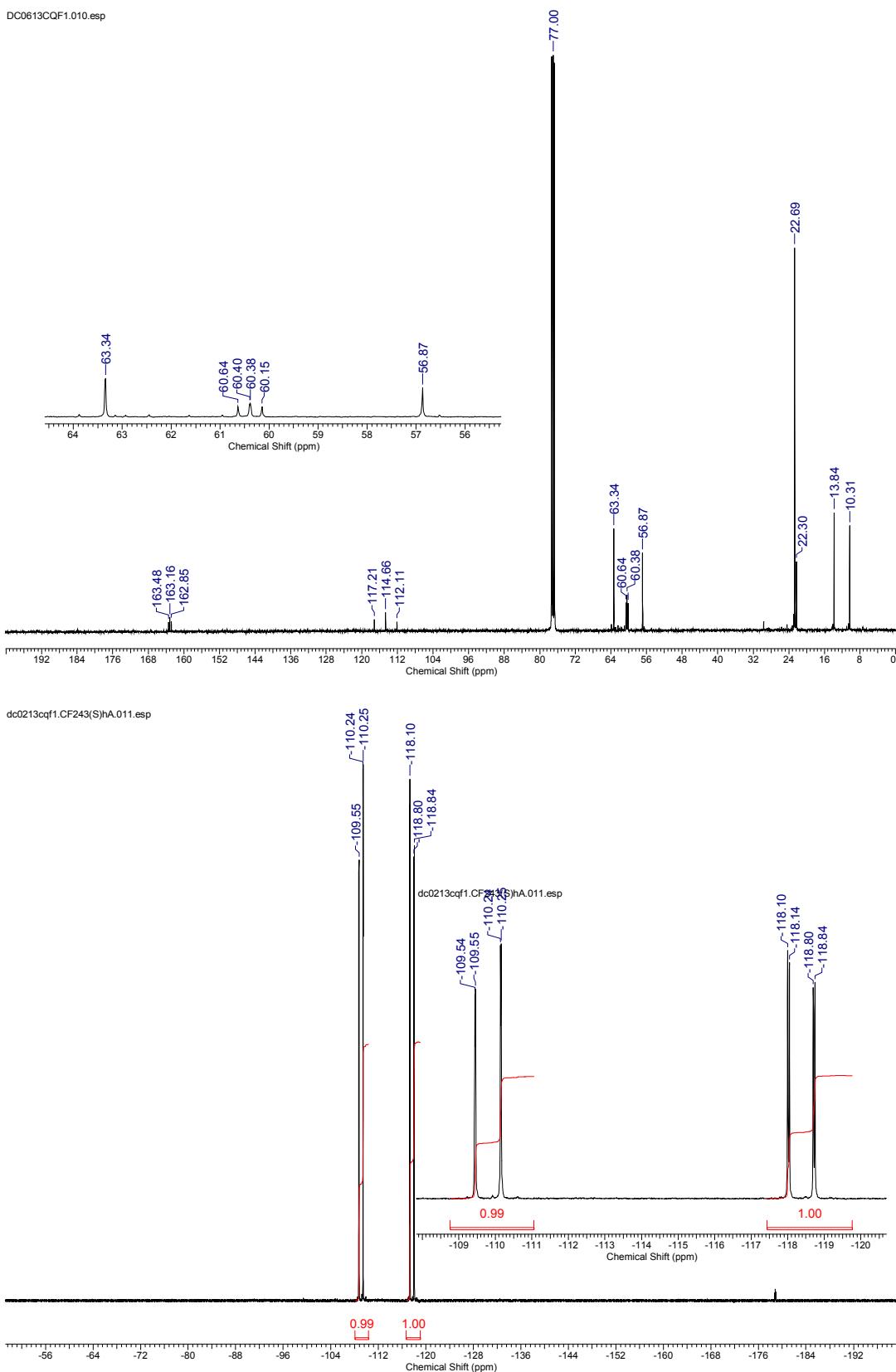




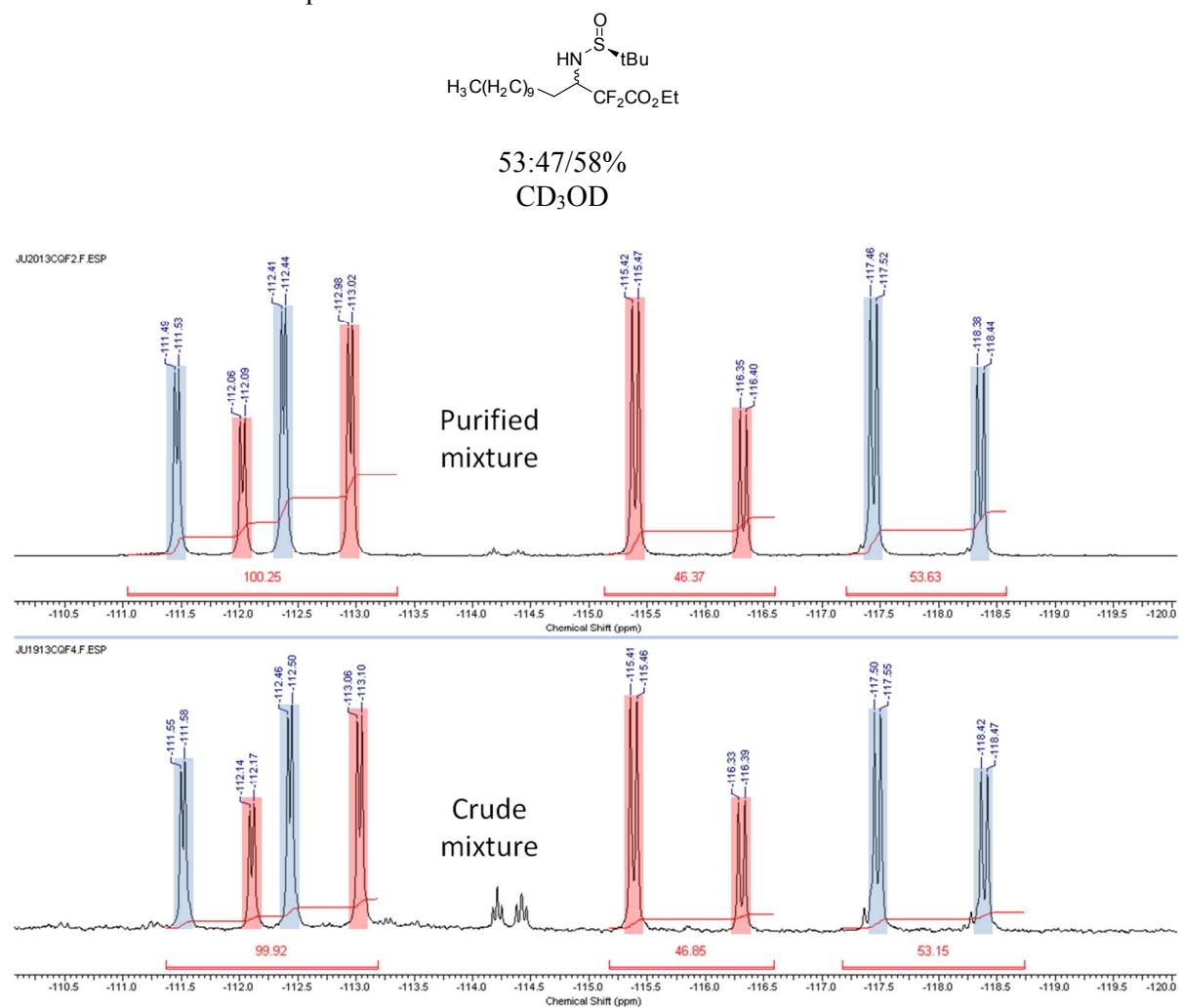
Minor diastereoisomer: (*3S,S_S*)-ethyl-3-(*t*-butylsulfinamino)-2,2-difluoropentanoate (**I-11S**)

DC0213CQF1.H.ESP



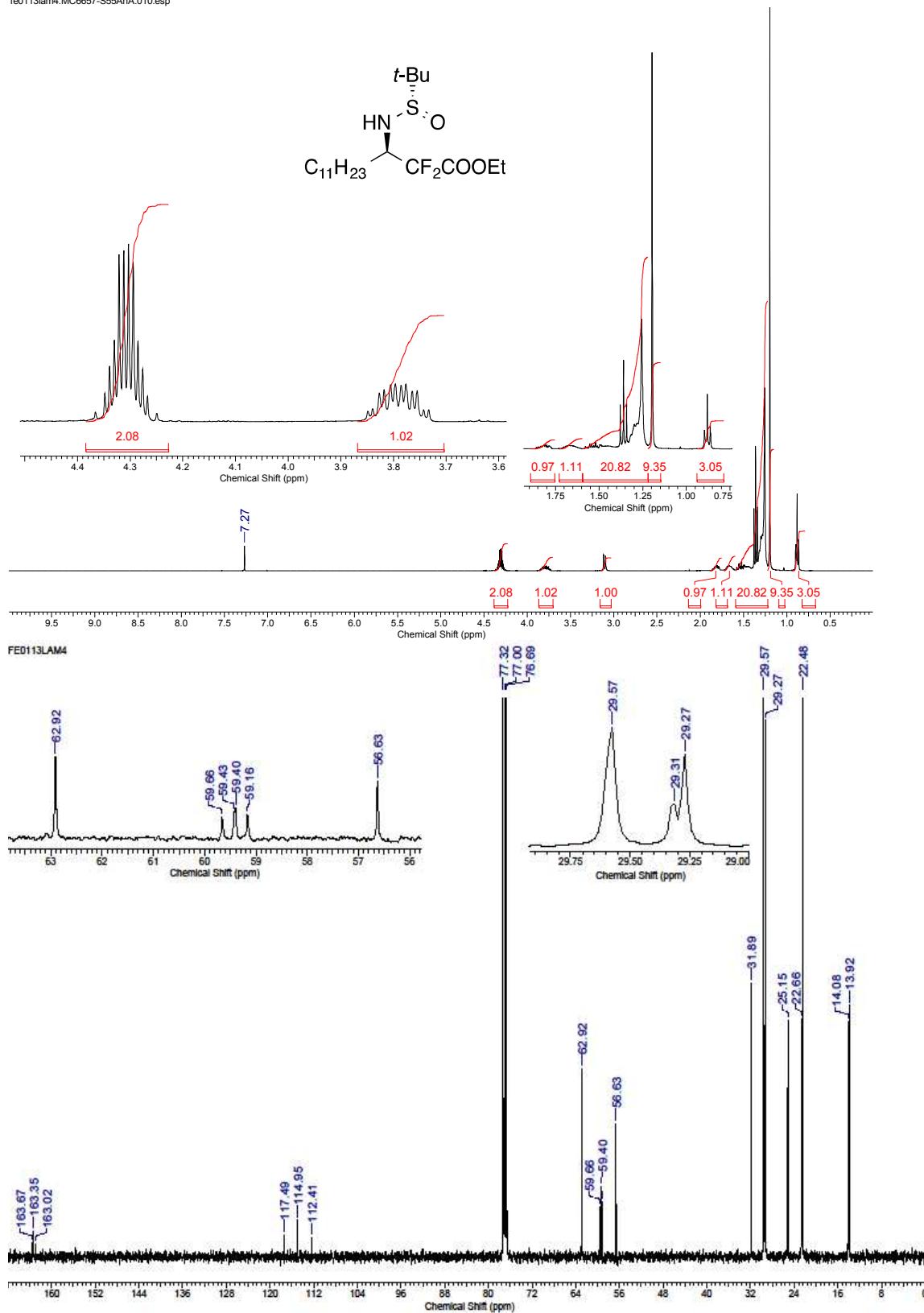


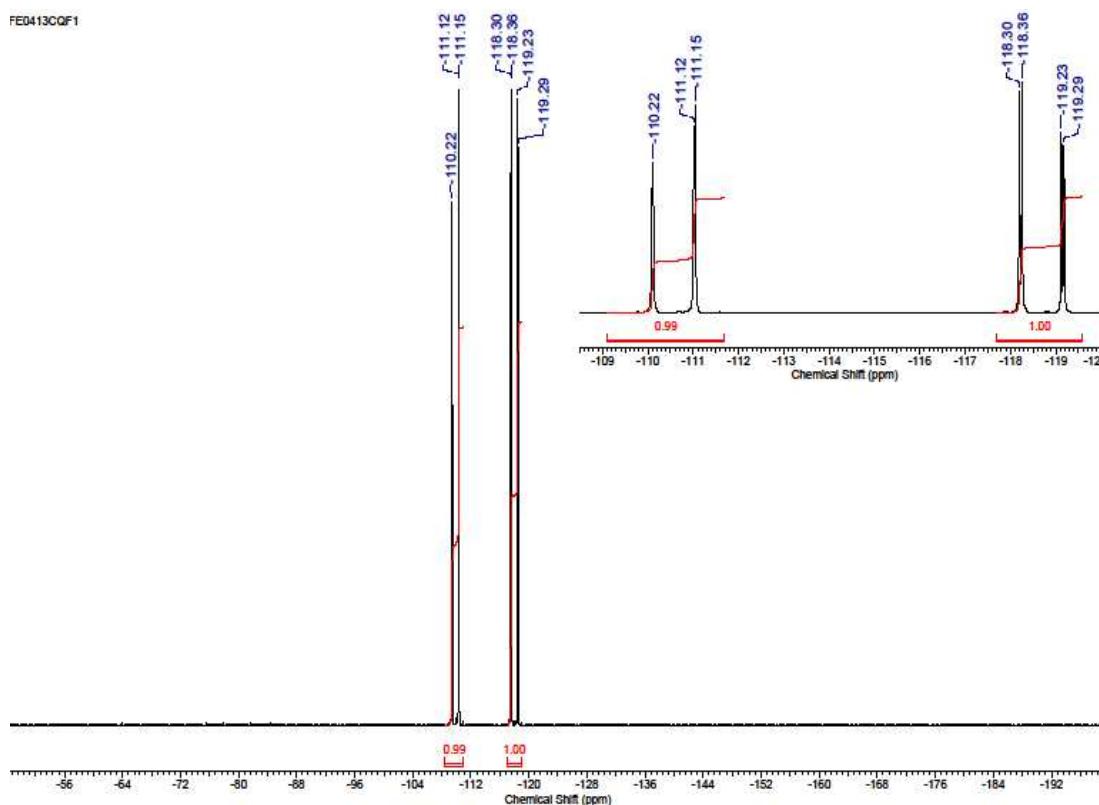
2.2.2 Reaction with **4S**: spectra of crude NMR and of the diastereomers **12S**



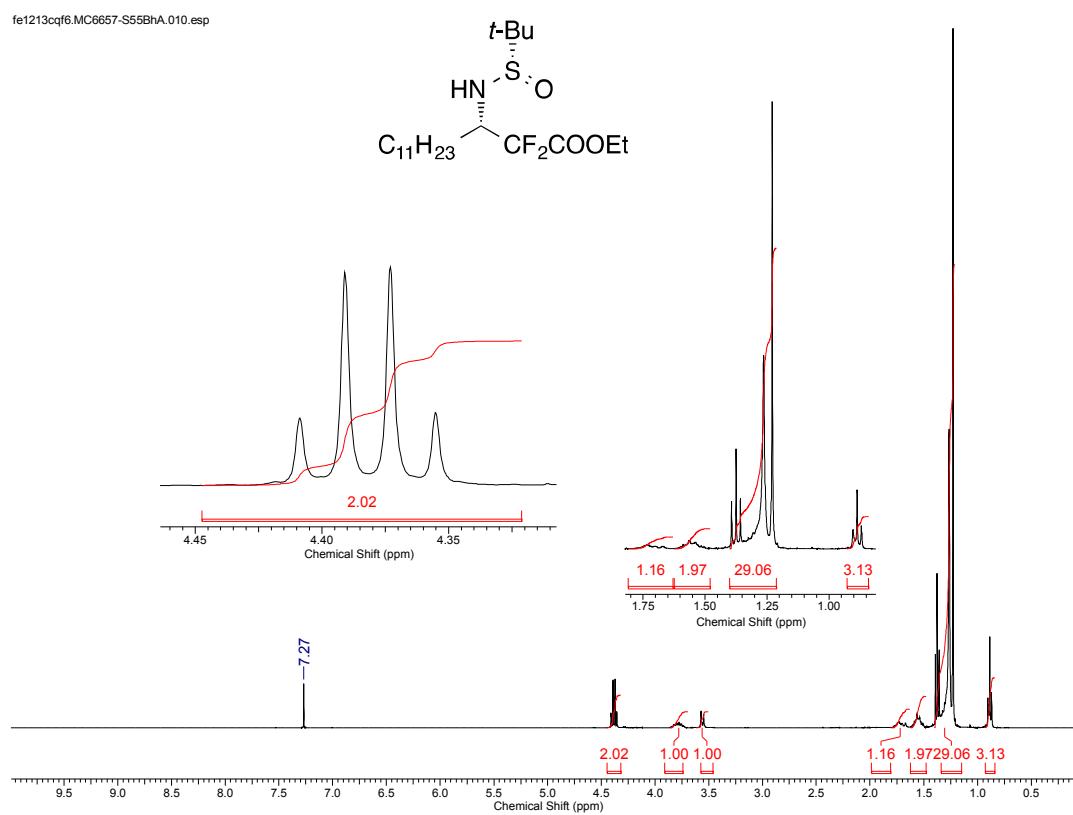
Major diastereoisomer: (3*R*,*S*_S)-ethyl-3-(*t*-butylsulfinamino)-2,2-difluorotetradecanoate (**ul-12S**)

fe0113lam4.MC6657-S55AhA.010.esp

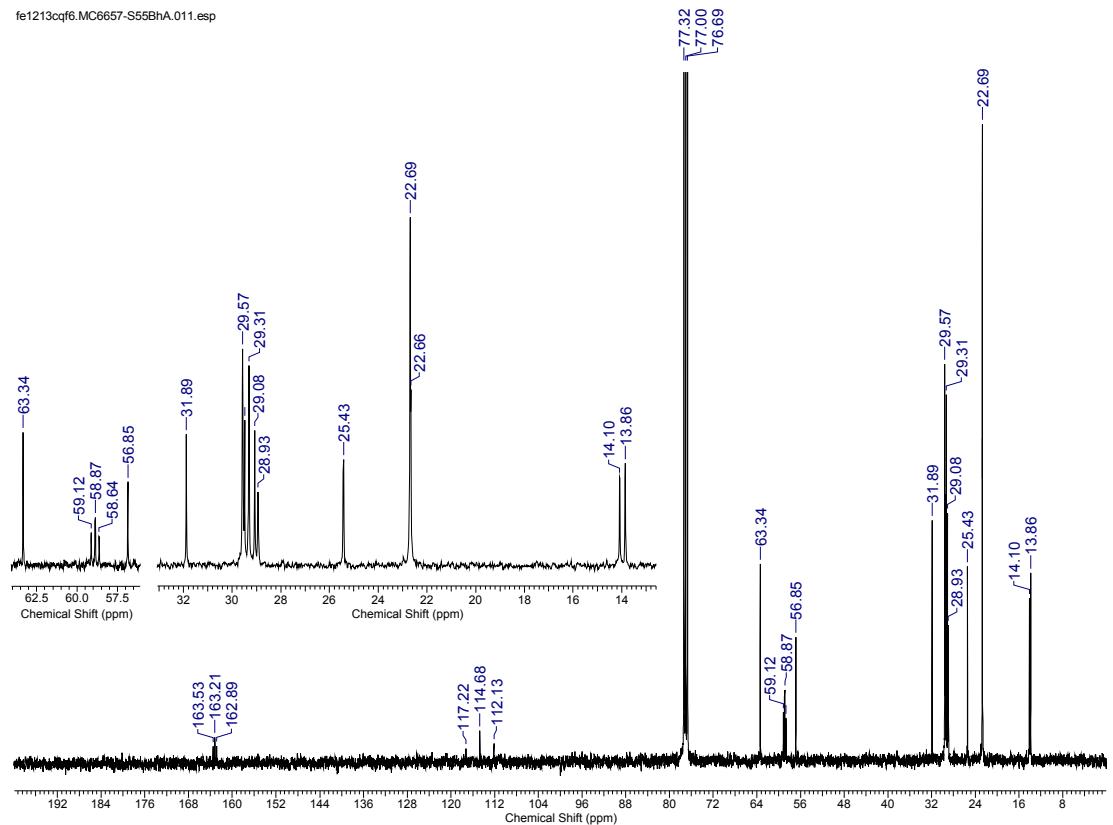




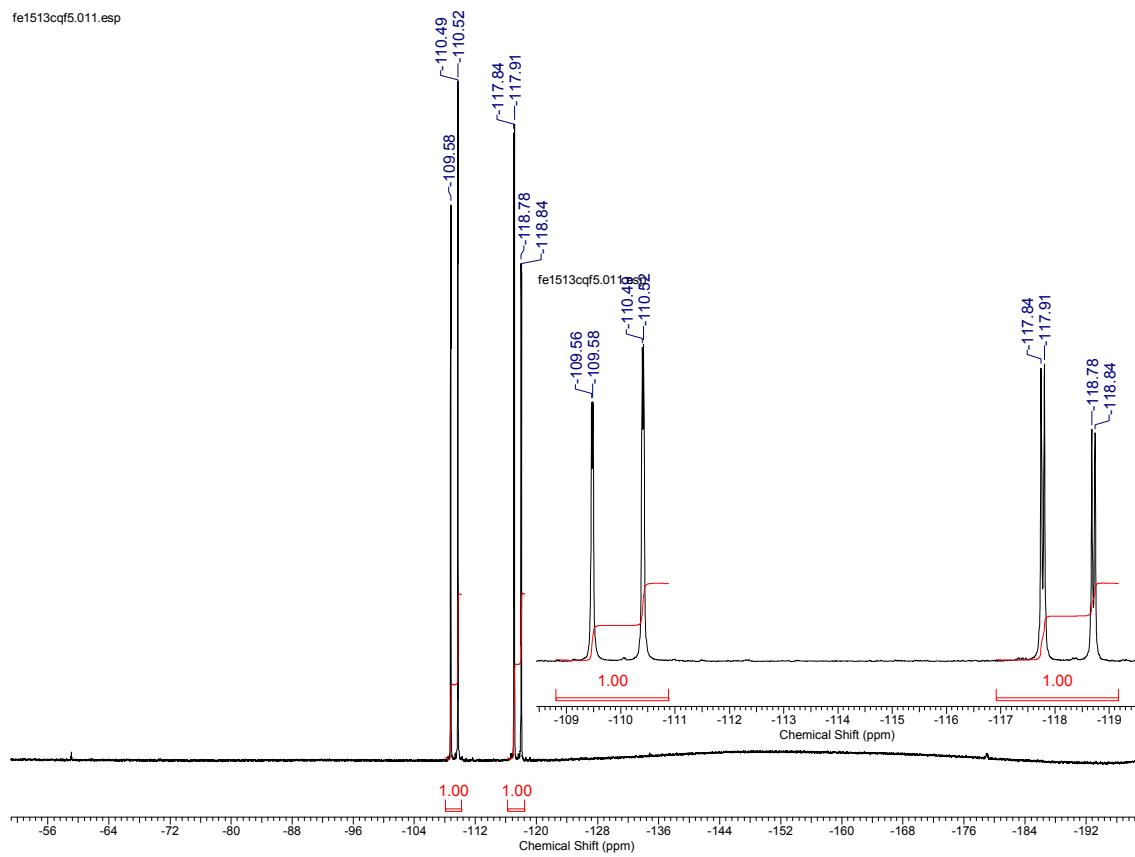
Minor diastereoisomer: (*3S,S_S*)-ethyl-3-(*t*-butylsulfinamino)-2,2-difluorotetradecanoate (*I-12S*)

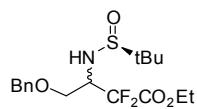
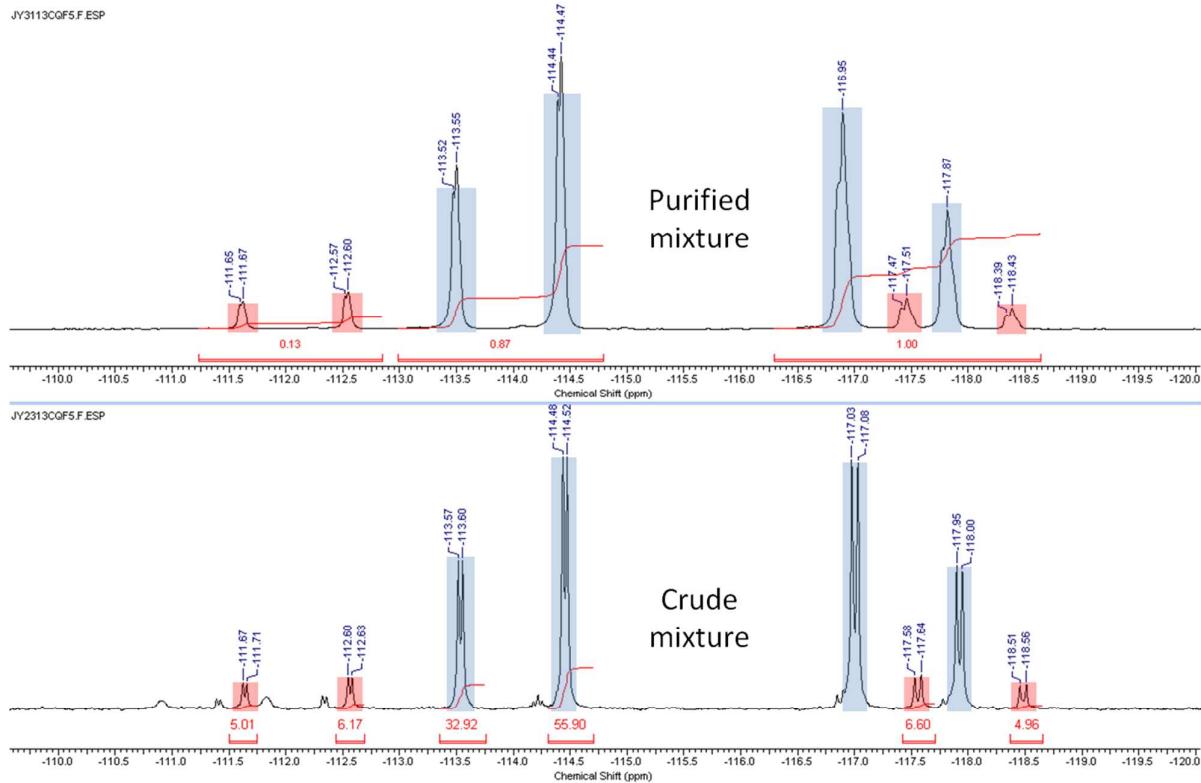


fe1213cqf6.MC6657-S55BhA.011.esp



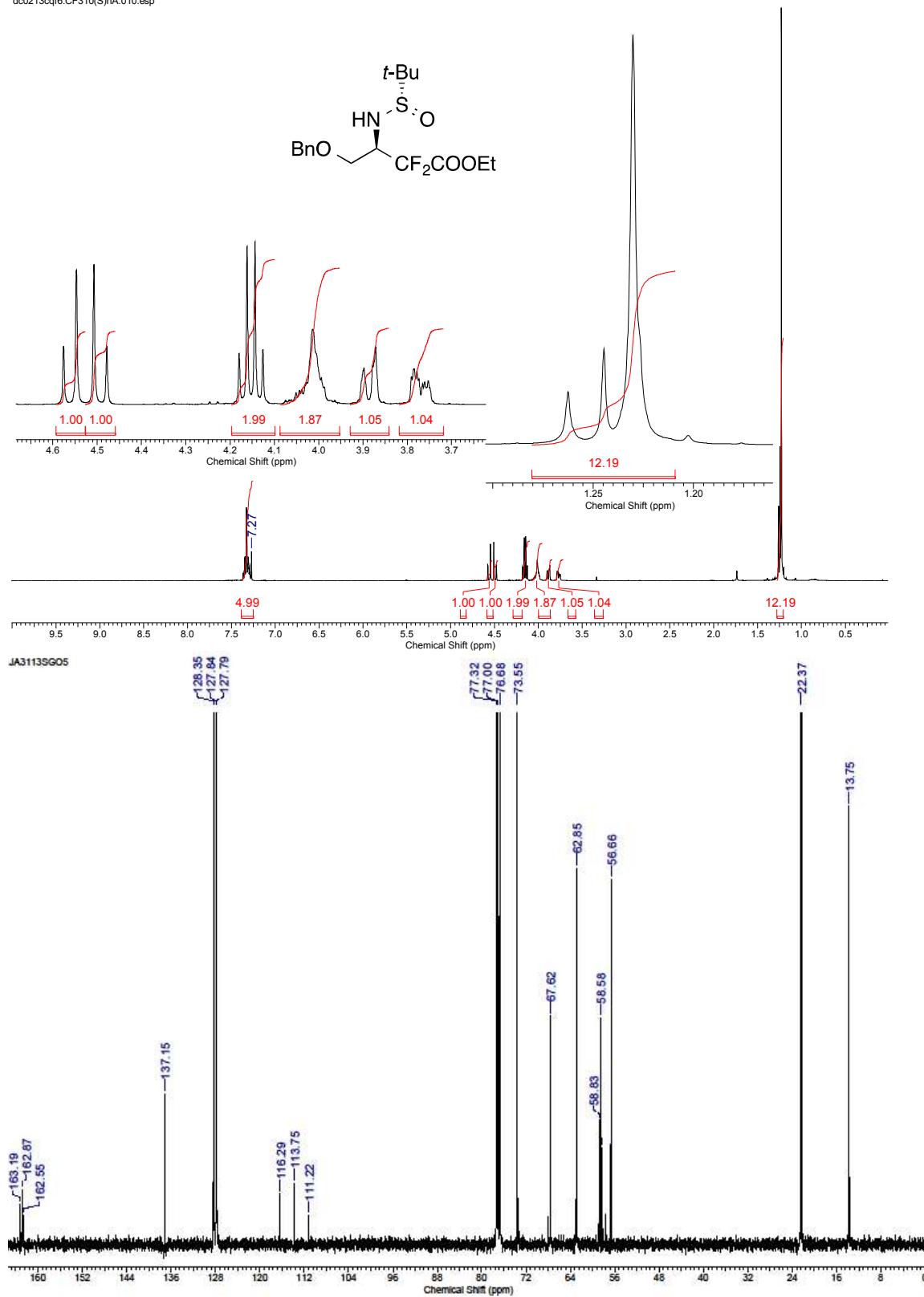
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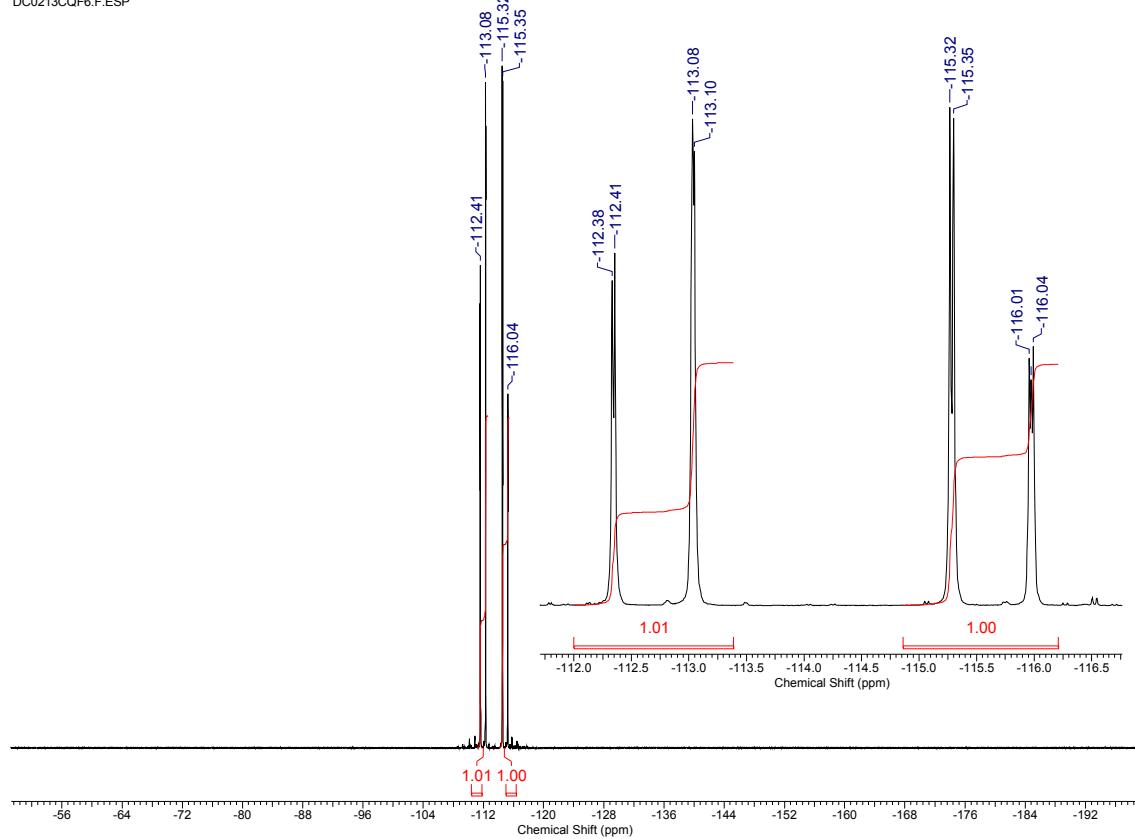
2.2.3 Reaction with **5S: spectra of crude NMR and of the diastereomers **13S****88:12/46%
CD₃OD

Major diastereoisomer: (3*R*,*S*)-ethyl-4-(benzyloxy)-3-(*tert*-butylsulfinamino)-2,2-difluorobutanoate (**ul-13S**)

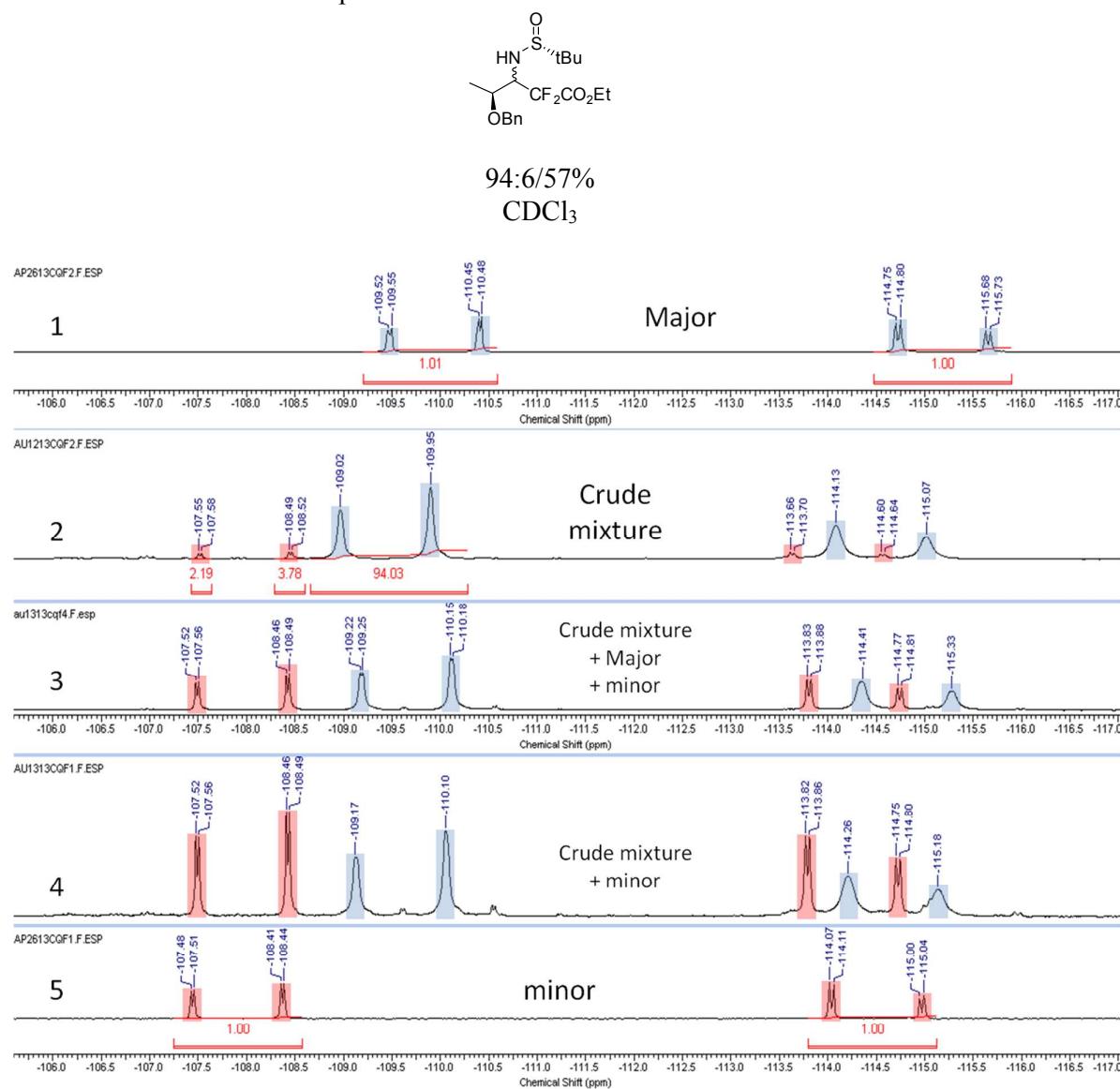
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DC0213CQF6.F.ESP



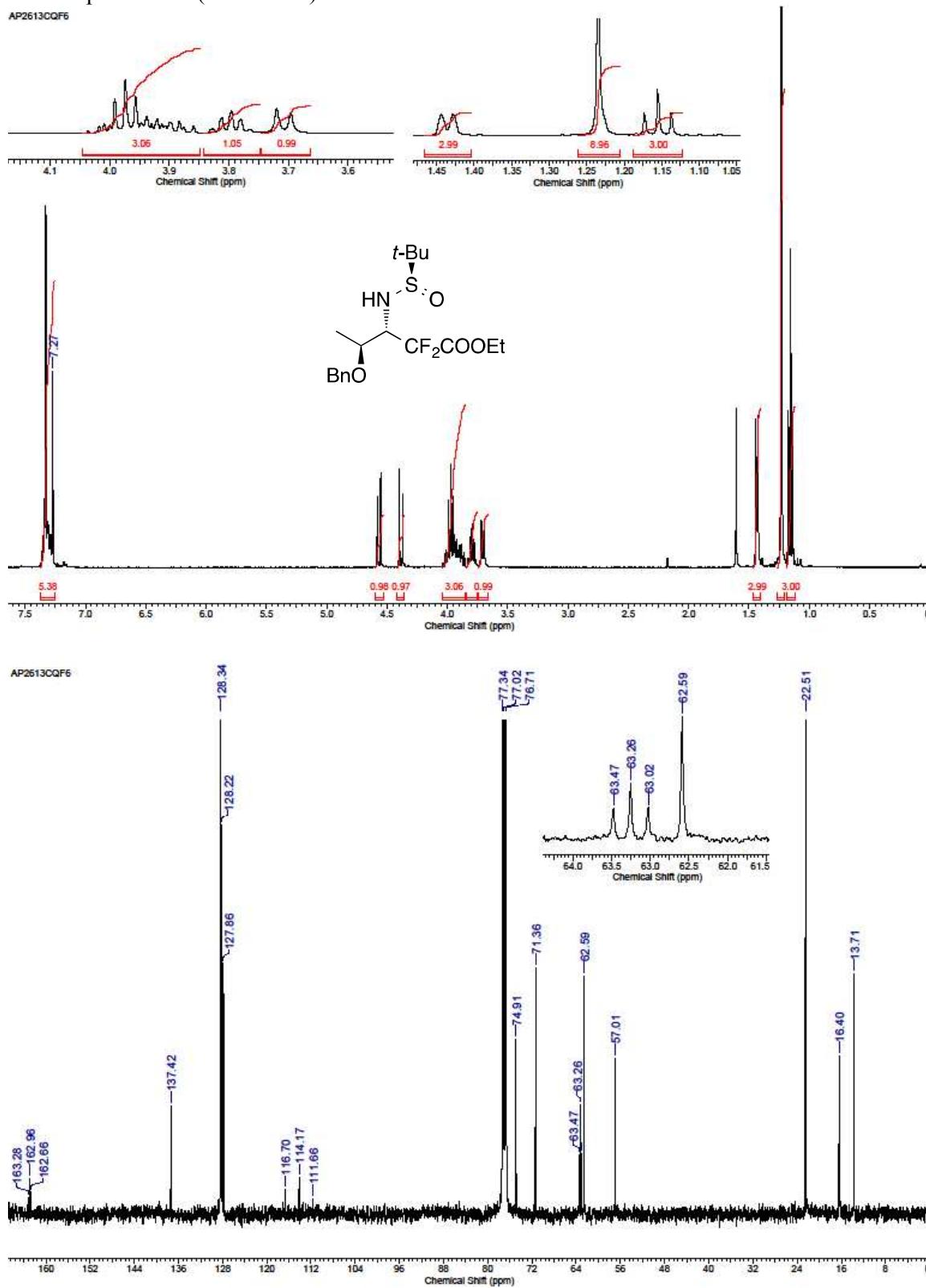
2.2.4 Reaction with *ent*-7S: spectra of crude NMR and of the diastereomers **15S**

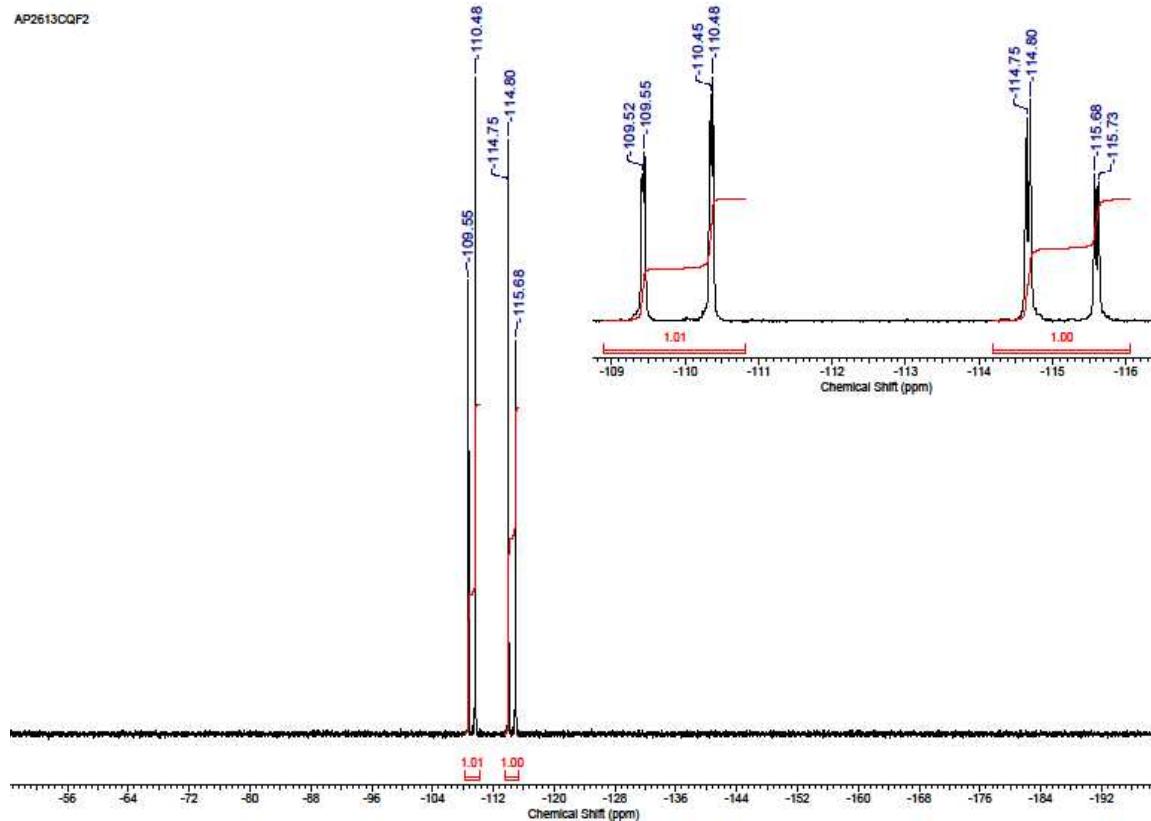


The peaks for both the major and the minor diastereoisomers are shifting comparing the crude mixture (2) and the respective pure diastereoisomers (1 and 5). To ensure that the highlighted peaks in the crude mixture (2) are the right ones, a small amount of the minor diastereoisomer was added to the crude mixture to give spectrum 4. In a second time, a small amount of the major diastereoisomer was added to the previously obtained mixture to give spectrum 3. In both cases, one can see that the peaks whose intensity increases are indeed the highlighted peaks in the crude mixture (2).

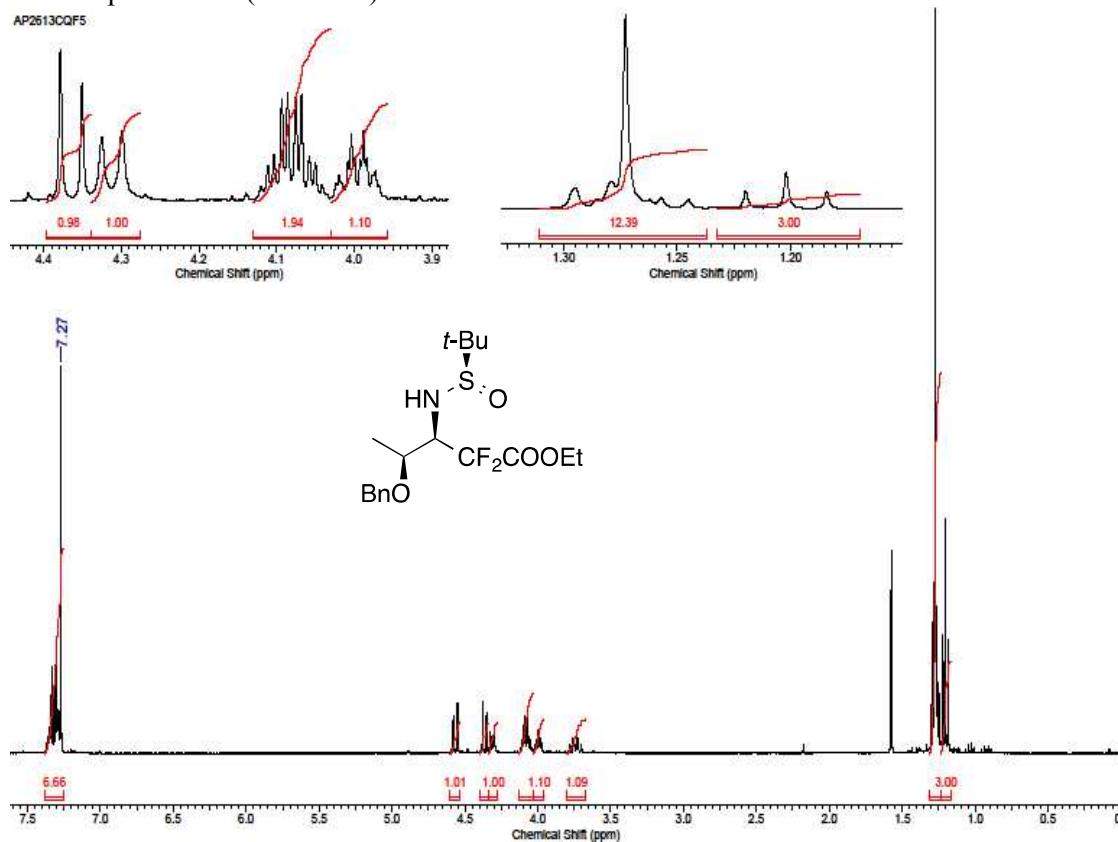
Major diastereoisomer: (3*S*,4*S*,*R*_S)-ethyl-4-(benzyloxy)-3-(*t*-butylsulfamino)-2,2-difluoropentanoate (*ent-ul*-**15S**)

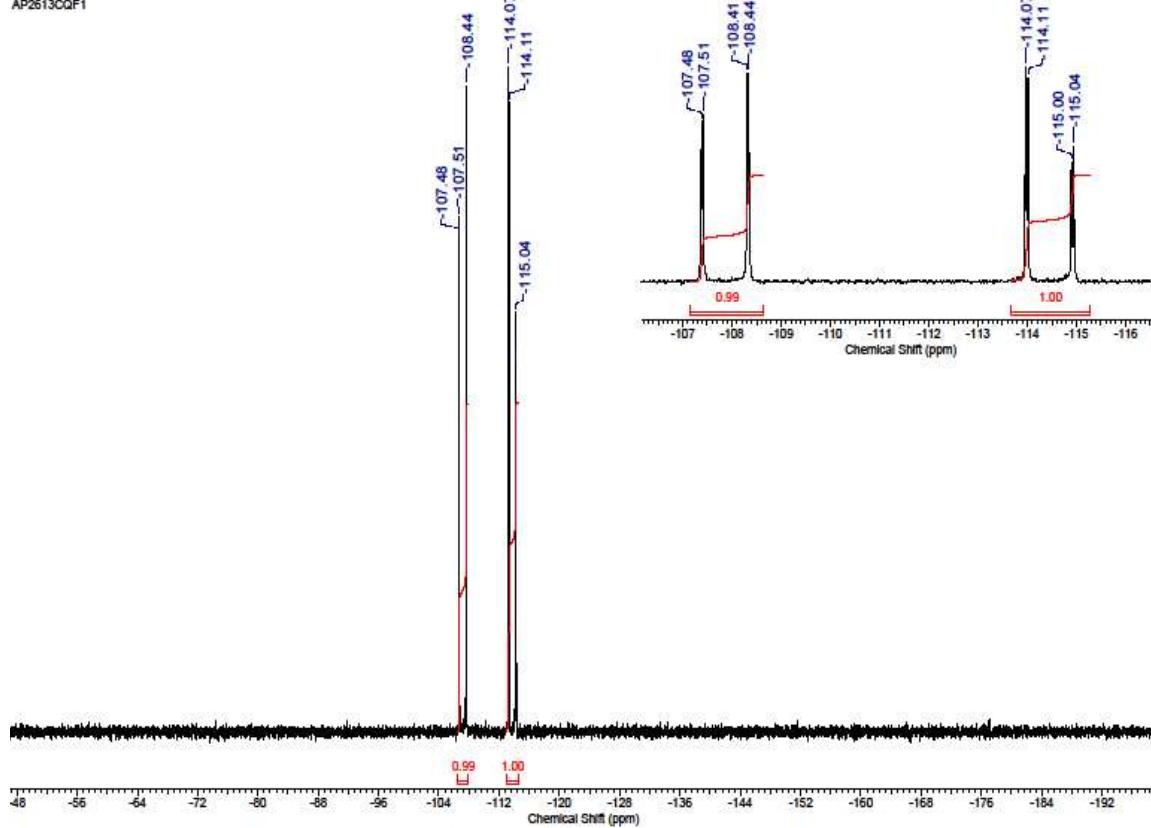
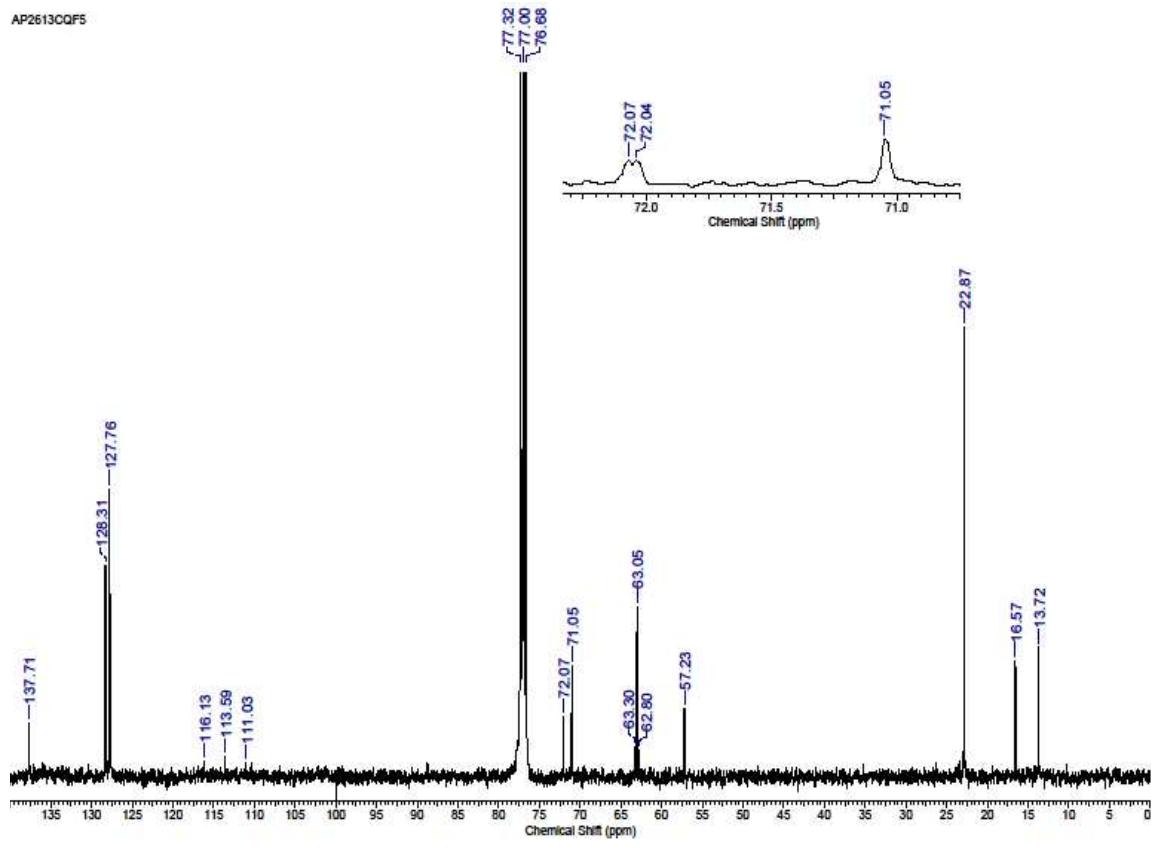
AP2613CQF6

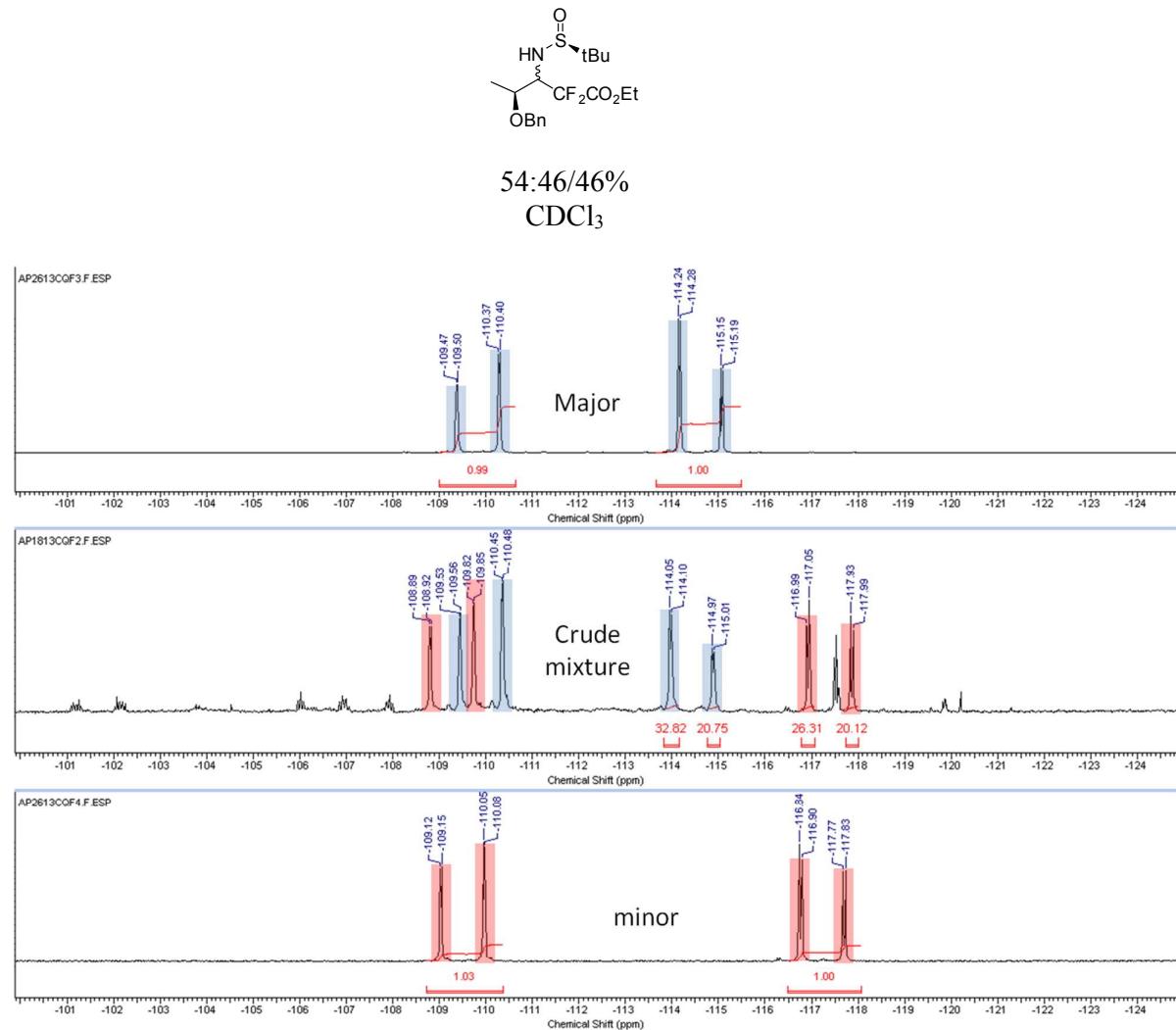




Minor diastereoisomer (3*R*,4*S*,*R*_S)-ethyl-4-(benzyloxy)-3-(*t*-butylsulfinamino)-2,2-difluoropentanoate (*ent*-**I-15S**)

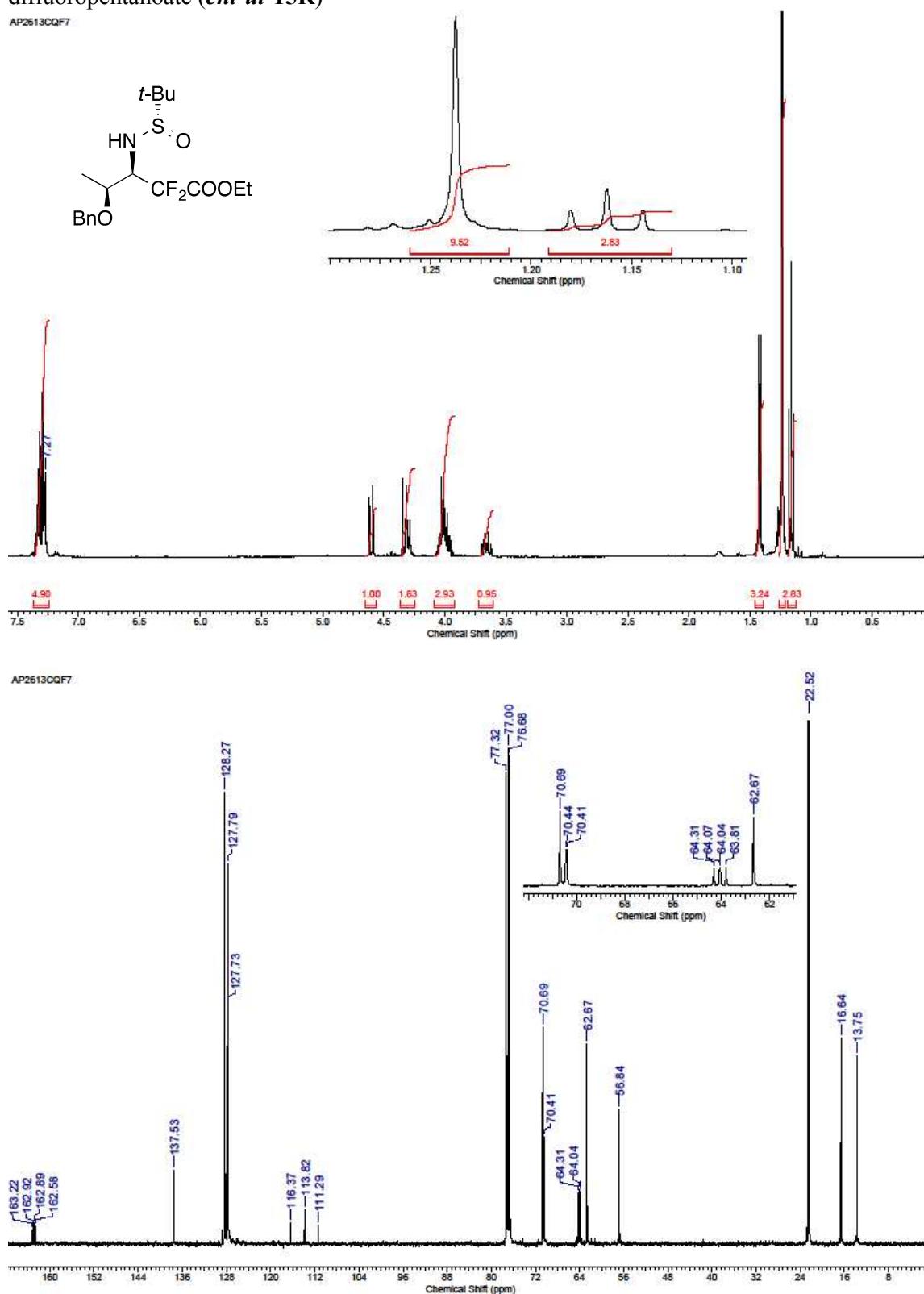


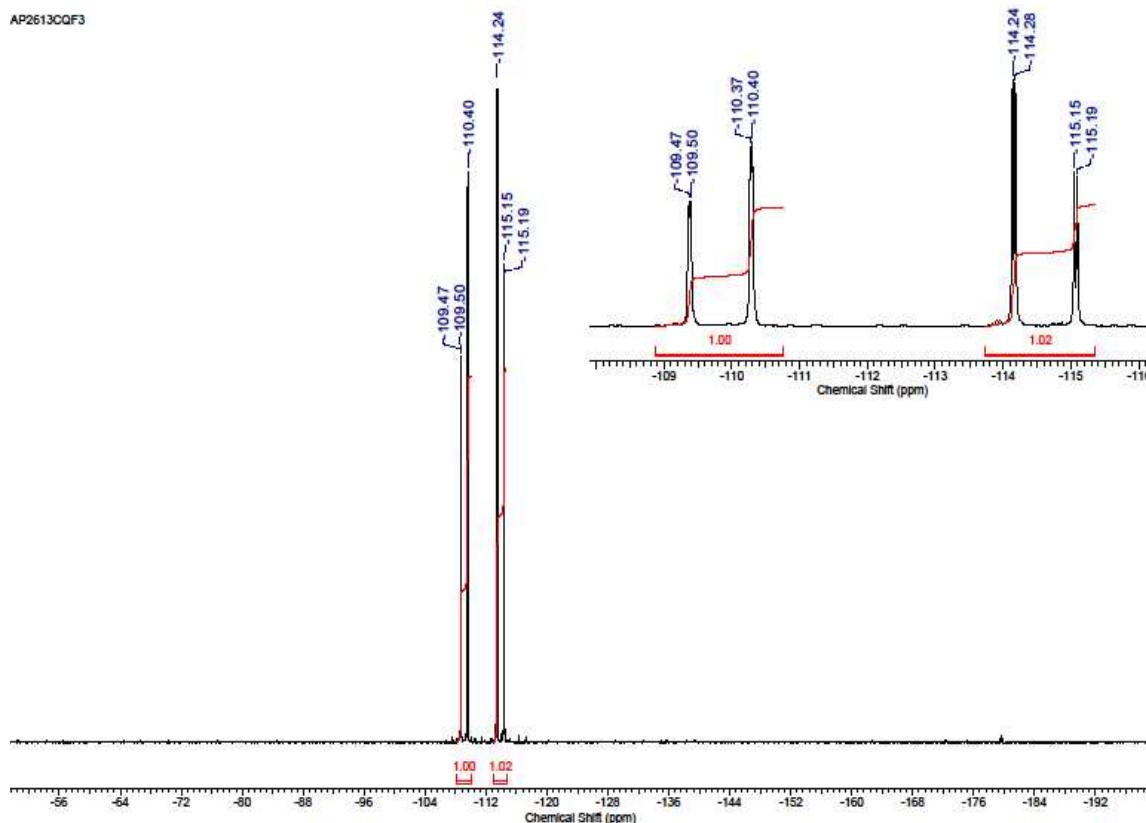


2.2.5 Reaction with *ent*-7R**: spectra of crude NMR and of the diastereomers **15R****

Major diastereoisomer: (*3R,4S,S_S*)-ethyl-4-(benzyloxy)-3-(*t*-butylsulfamino)-2,2-difluoropentanoate (*ent-ul-15R*)

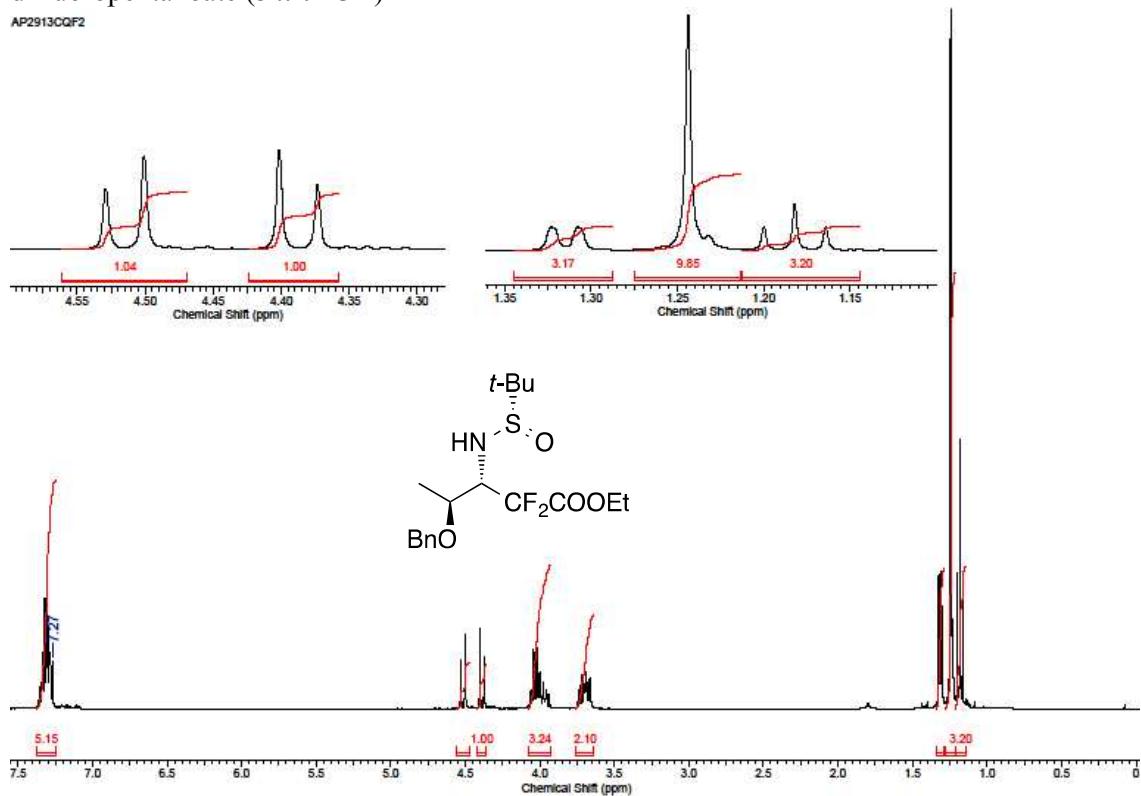
AP2613CQF7



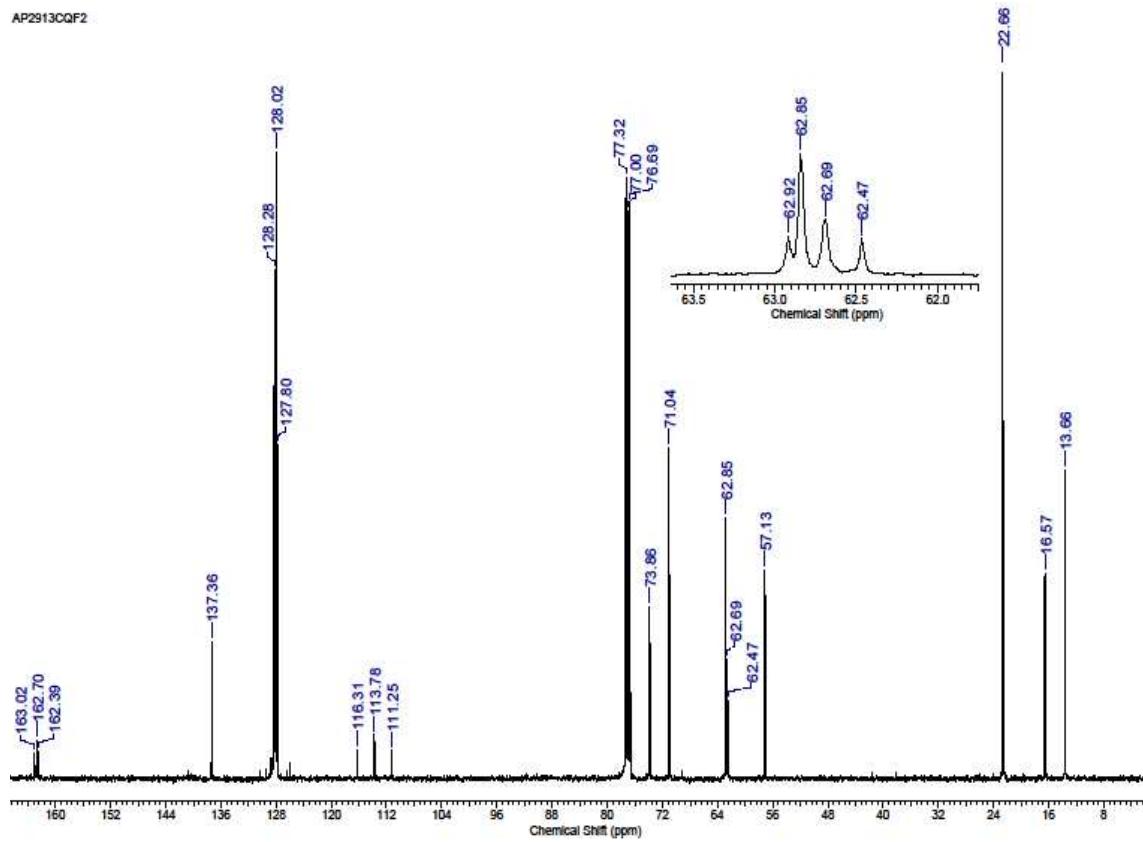


Minor diastereoisomer: (3*S*,4*S*,*S*_S)-ethyl-4-(benzyloxy)-3-(*t*-butylsulfinamino)-2,2-difluoropentanoate (*ent*-**15R**)

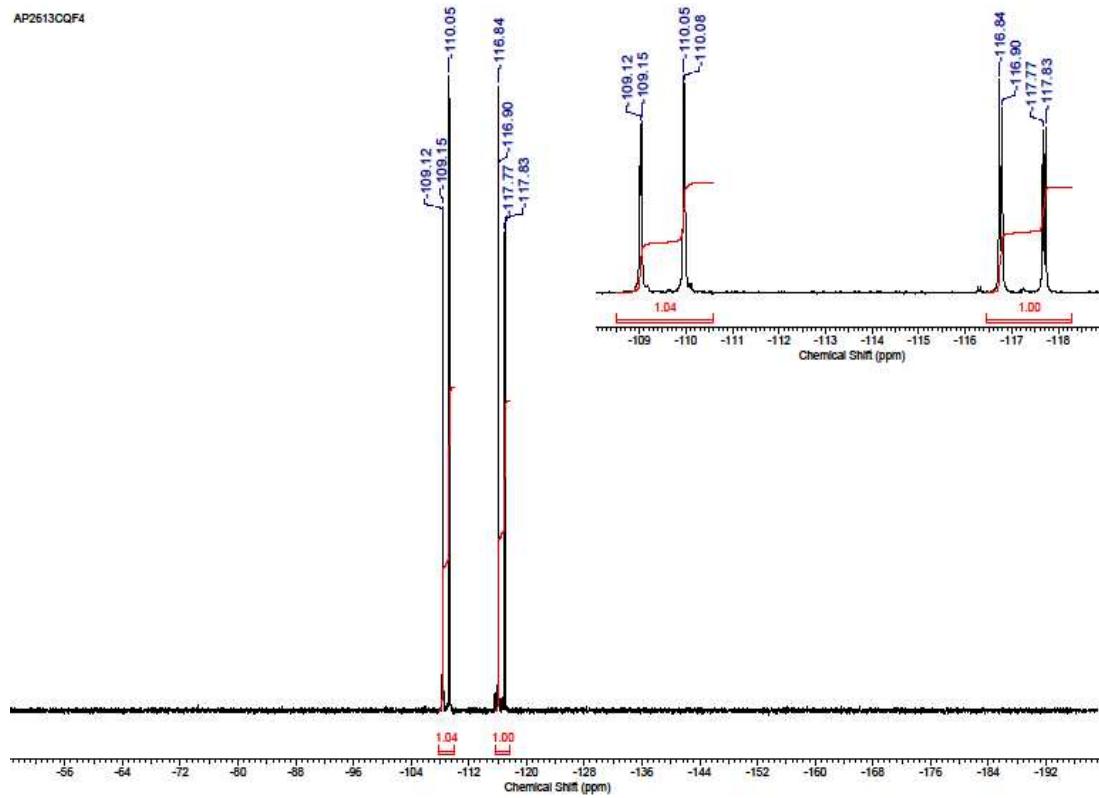
AP2913CQF2



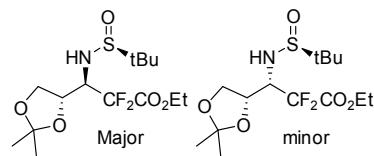
AP2913CQF2



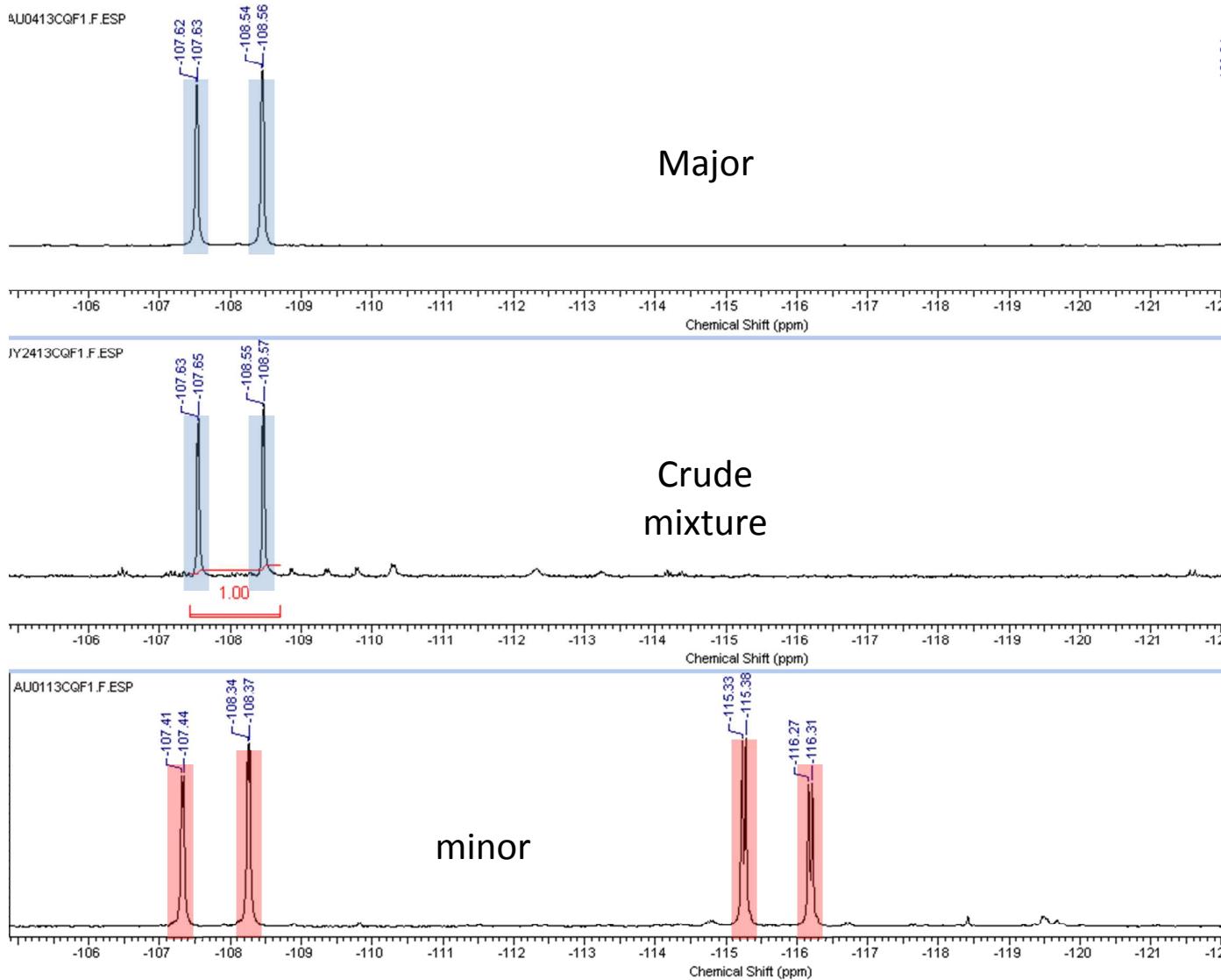
AP2613CQF4



2.2.6 Reaction with **8S**: spectra of crude NMR and of the diastereomers **16S**



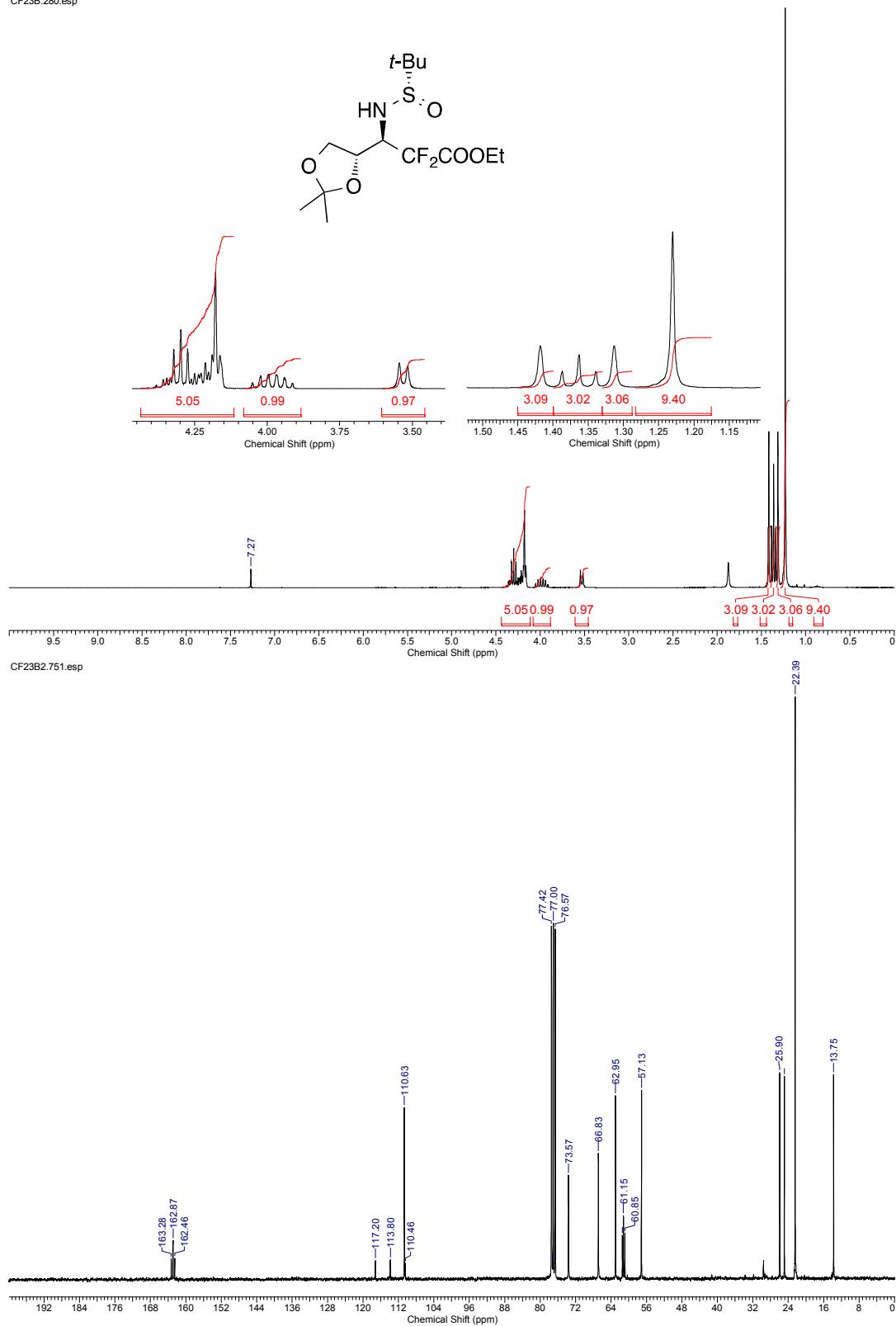
>95:5/62%
CD₃OD



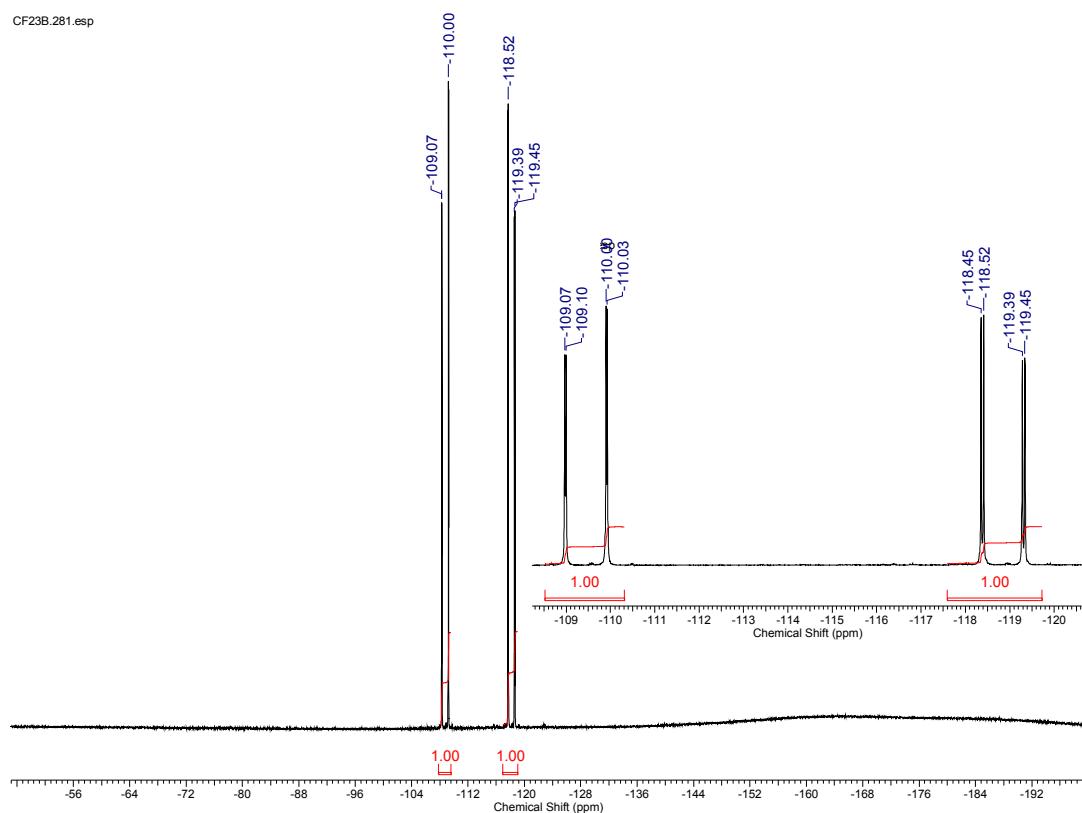
The minor diastereoisomer was isolated from an unselective Honda-Reformatsky reaction using Zn dust (see manuscript, table 2, entries 2-4).

Major diastereoisomer: (3*R*,4*S*,*S*₅)-ethyl-4,5-isopropylidenedioxy-3-(*t*-butylsulfinylamino)-2,2-difluoropentanoate (**ul-16S**)

CF23B.280.esp

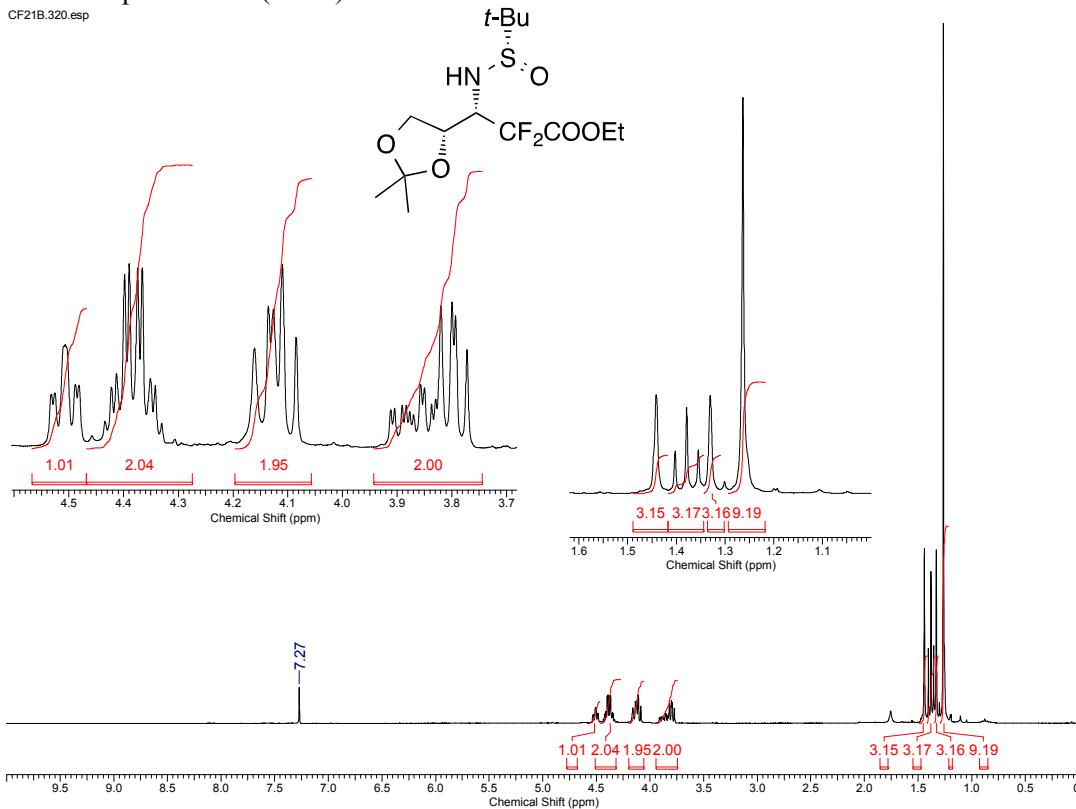


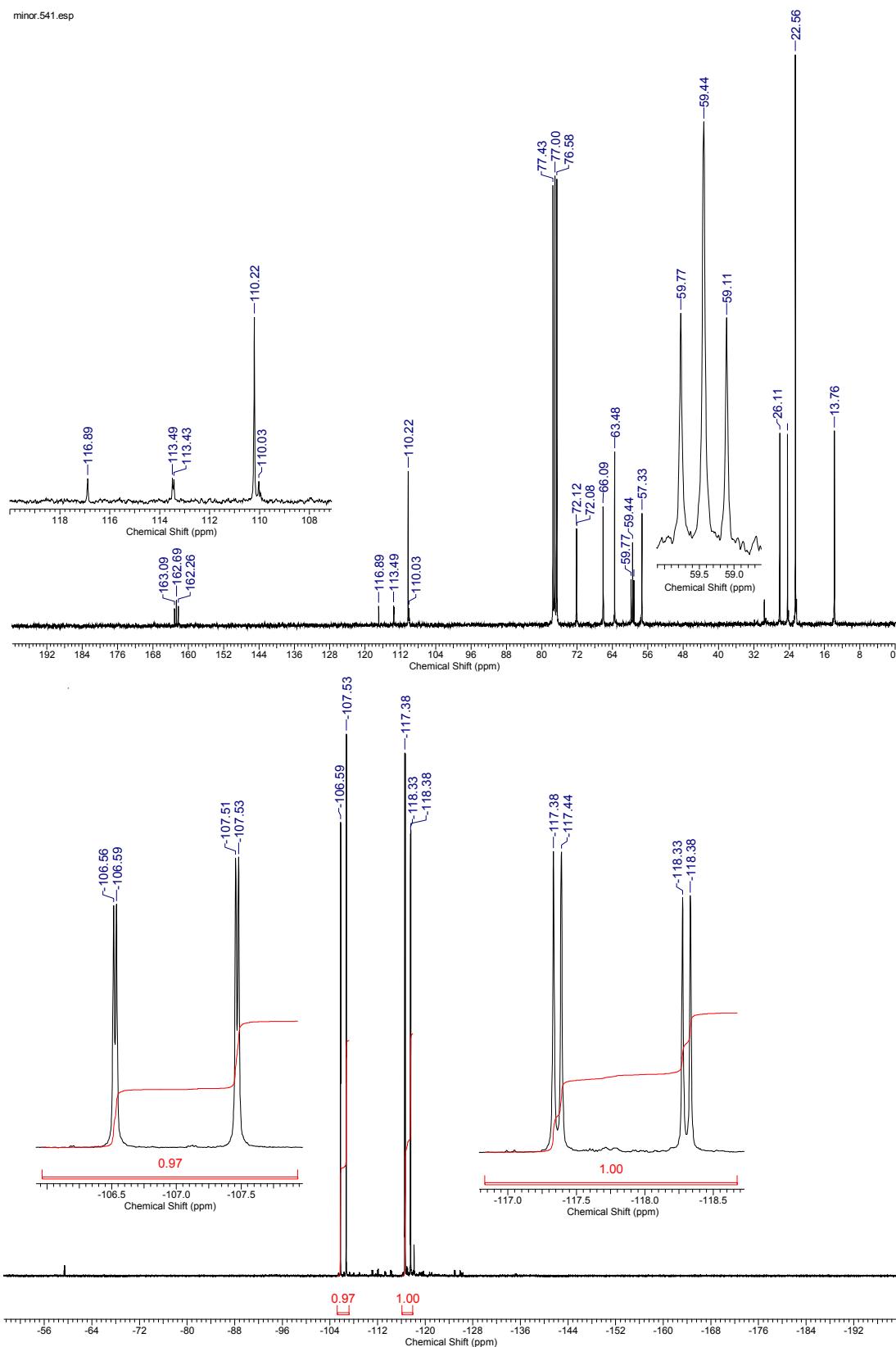
CF23B.281.esp



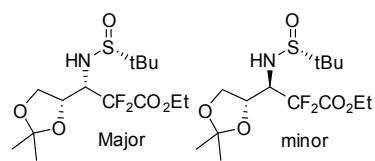
Minor diastereoisomer: (3*S*,4*S*,*S*_S)-ethyl-4,5-isopropylidenedioxy-3-(*t*-butylsulfinylamino)-2,2-difluoropentanoate (**I-16S**)

CF21B.320.esp

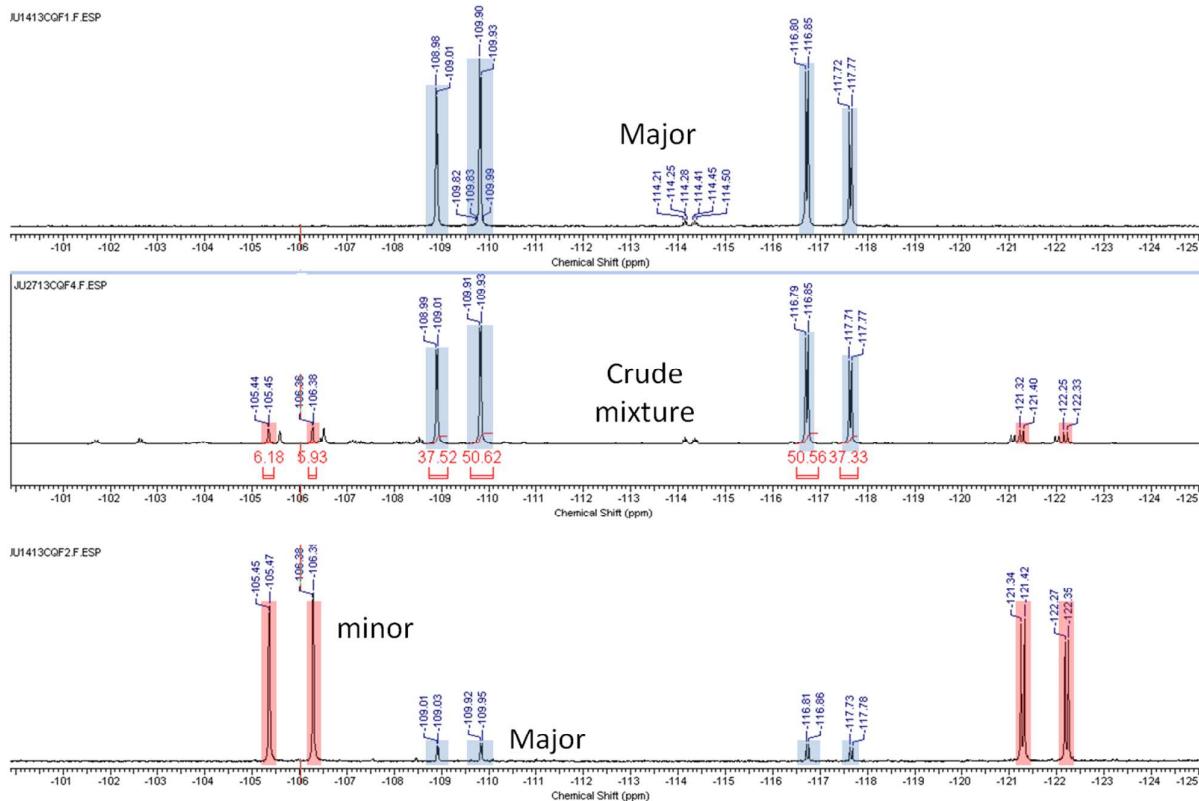




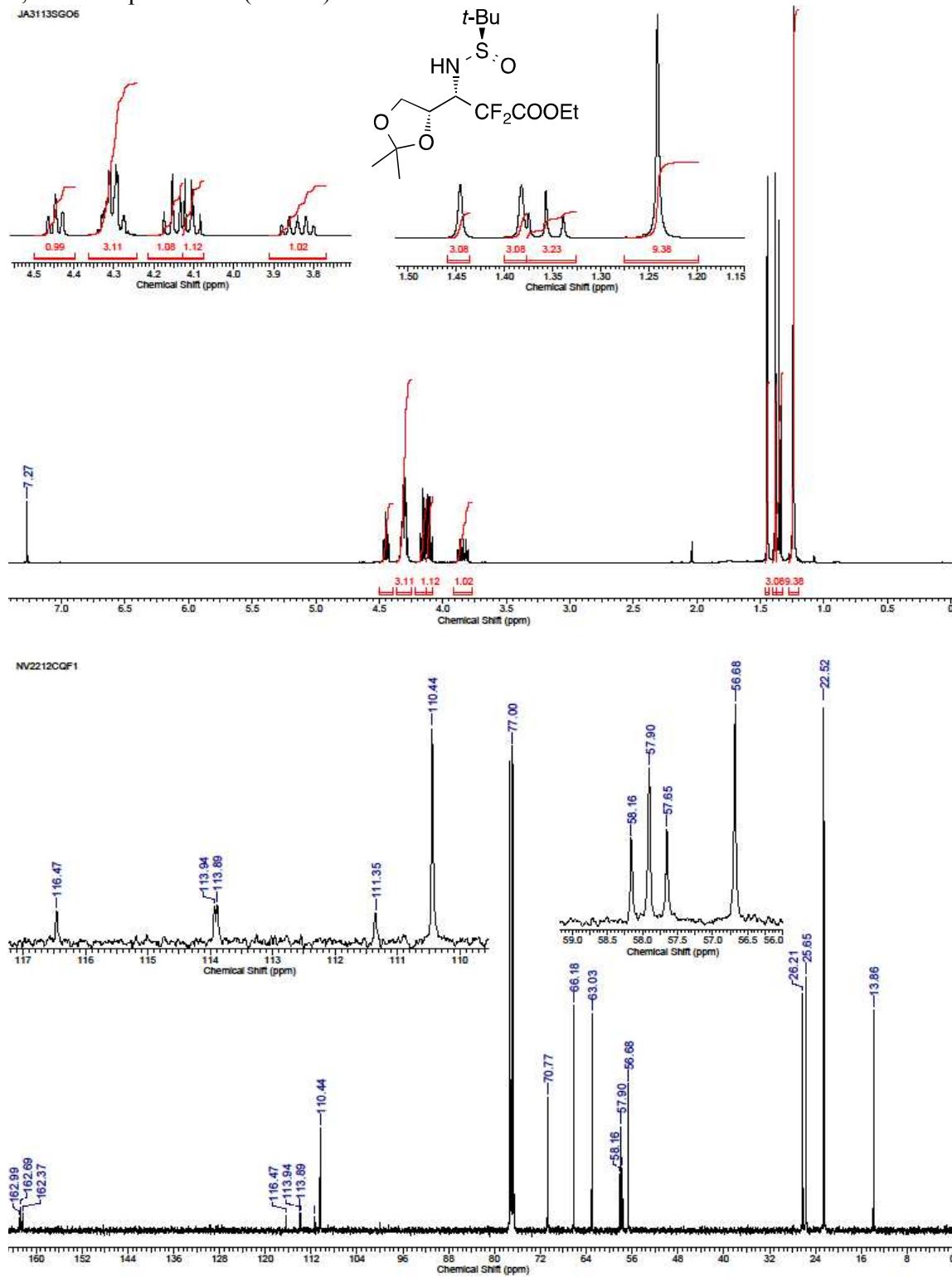
2.2.7 Reaction with **8R**: spectra of crude NMR and of the diastereomers **16R**

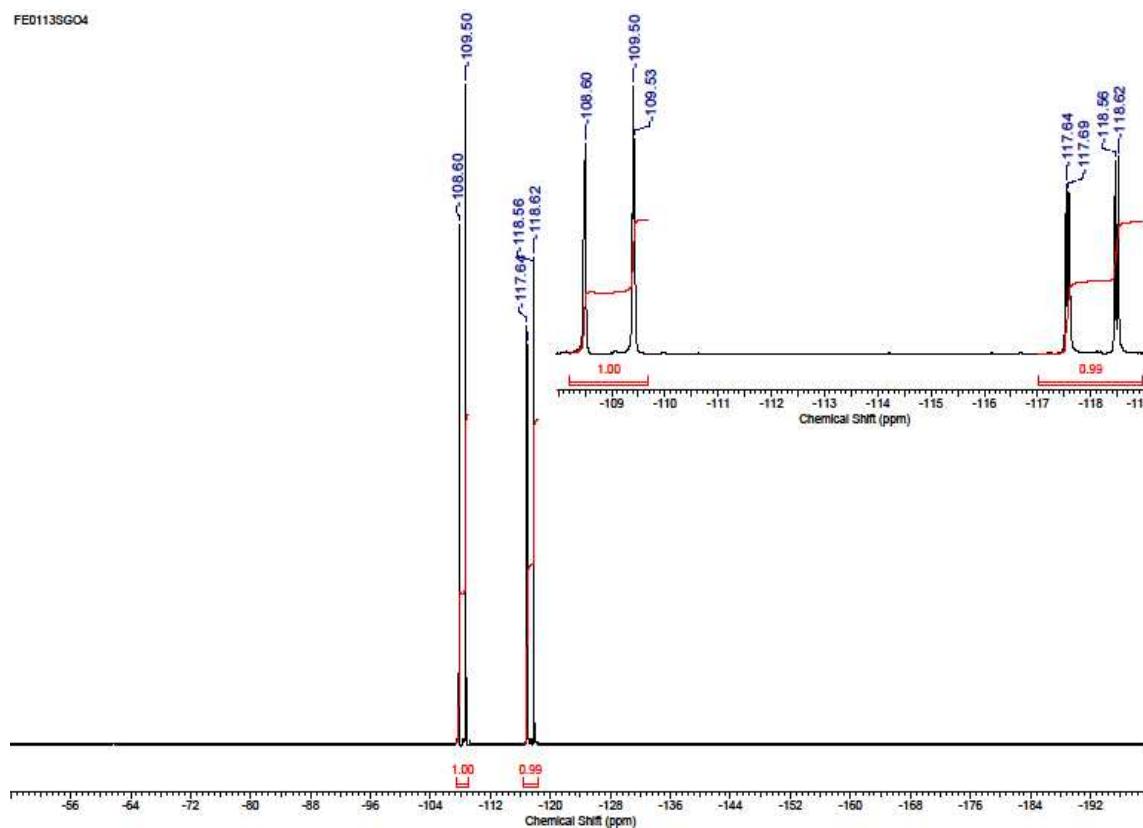


88:12/59%
CD₃OD

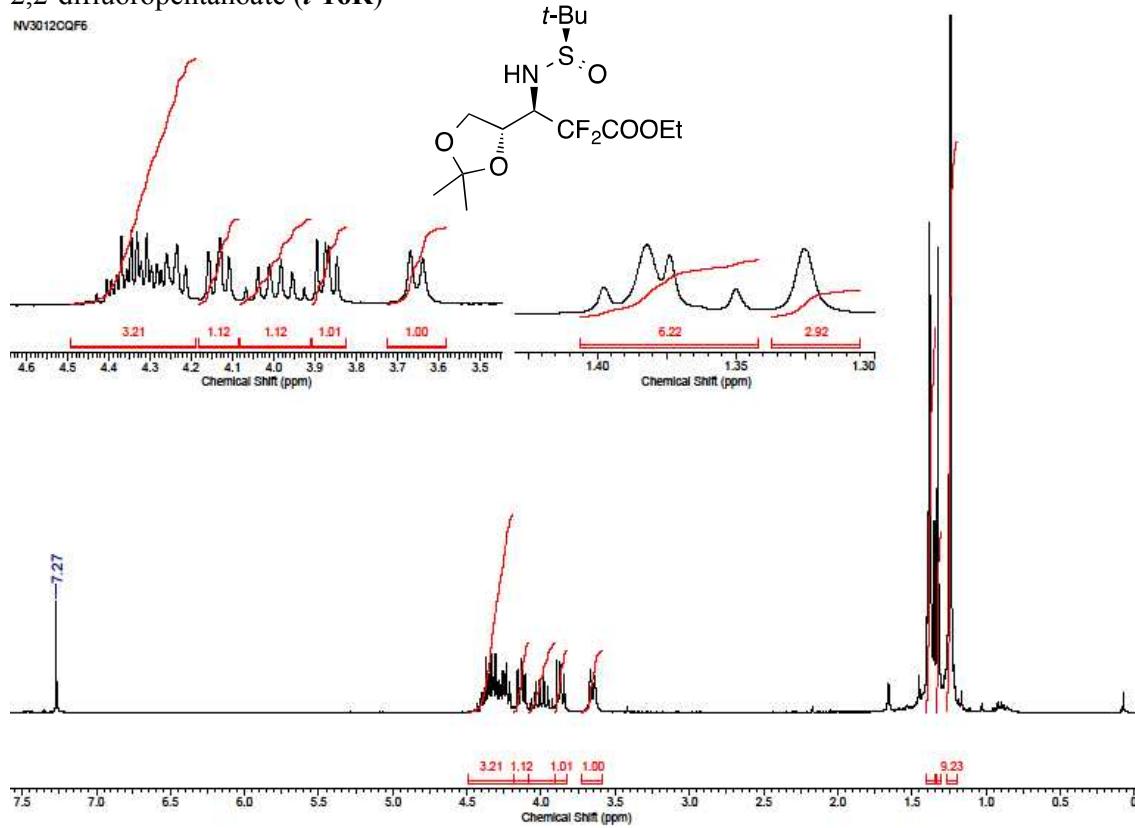


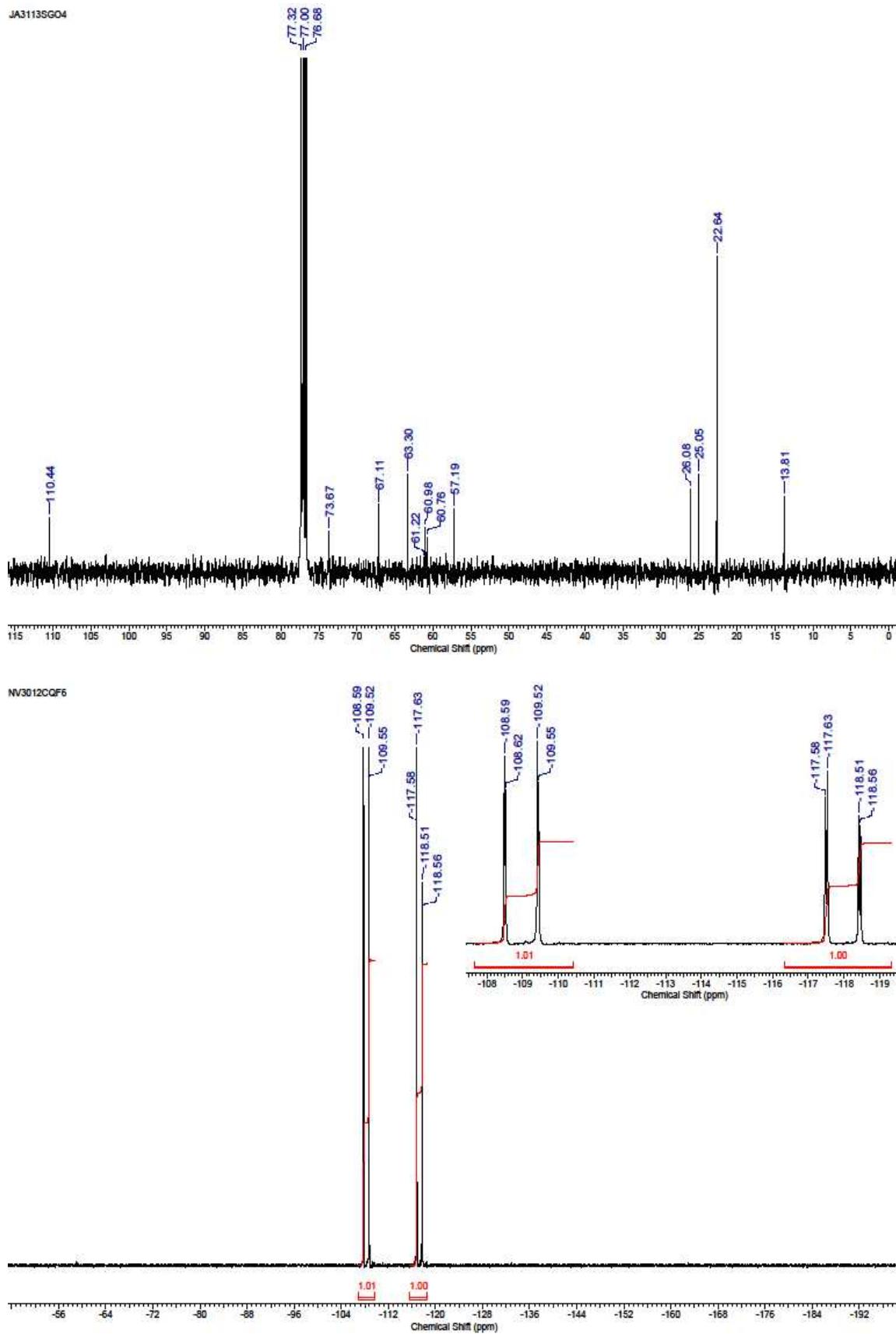
Major diastereoisomer: (*3S,4S,R_S*)-ethyl-4,5-isopropylidenedioxy-3-(*t*-butylsulfinylamino)-2,2-difluoropentanoate (**ul-16R**)

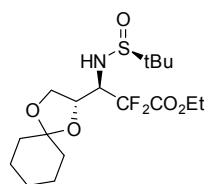




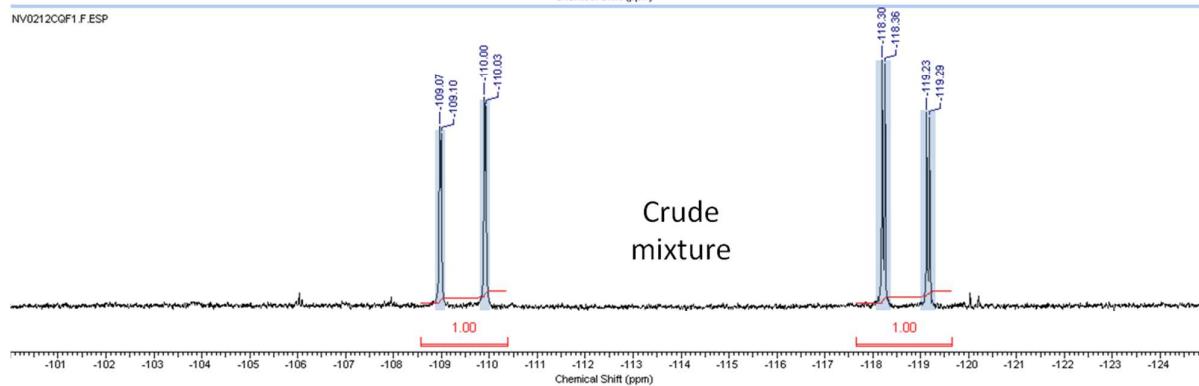
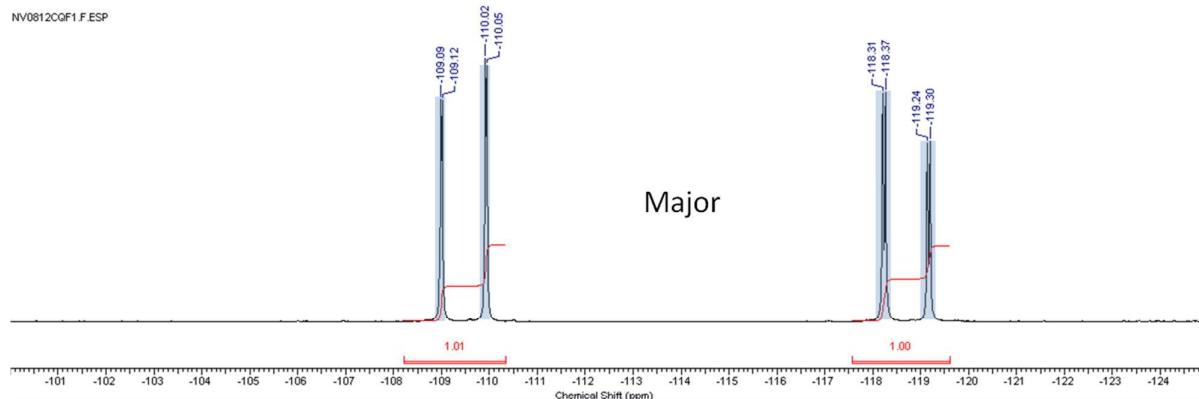
Minor diastereoisomer: (3*R*,4*S*,*R*_S)-ethyl-4,5-isopropylidenedioxy-3-(*t*-butylsulfinylamino)-2,2-difluoropentanoate (**I-16R**)





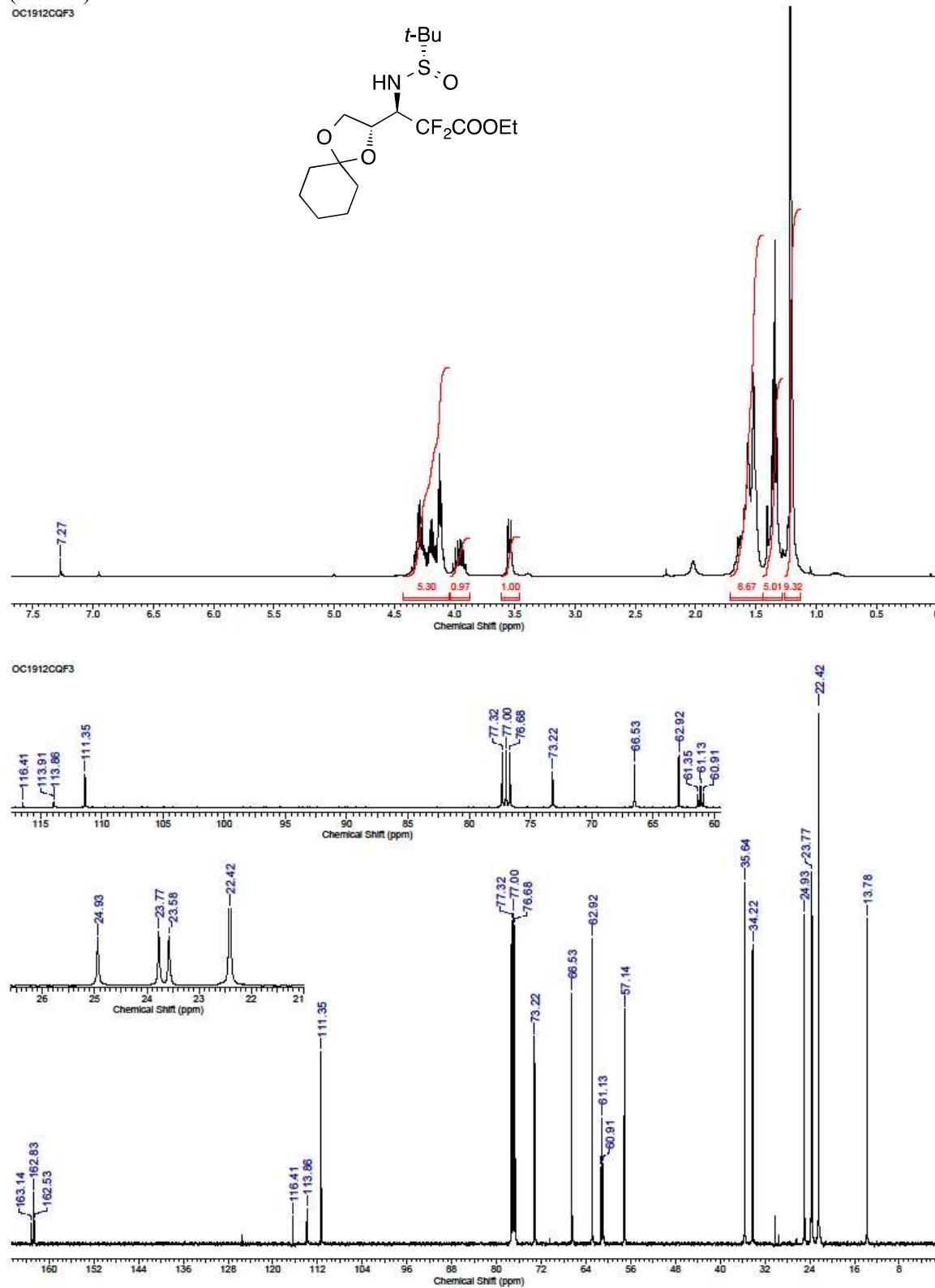
2.2.8 Reaction with **9S: spectra of crude NMR and of the diastereomers **17S****

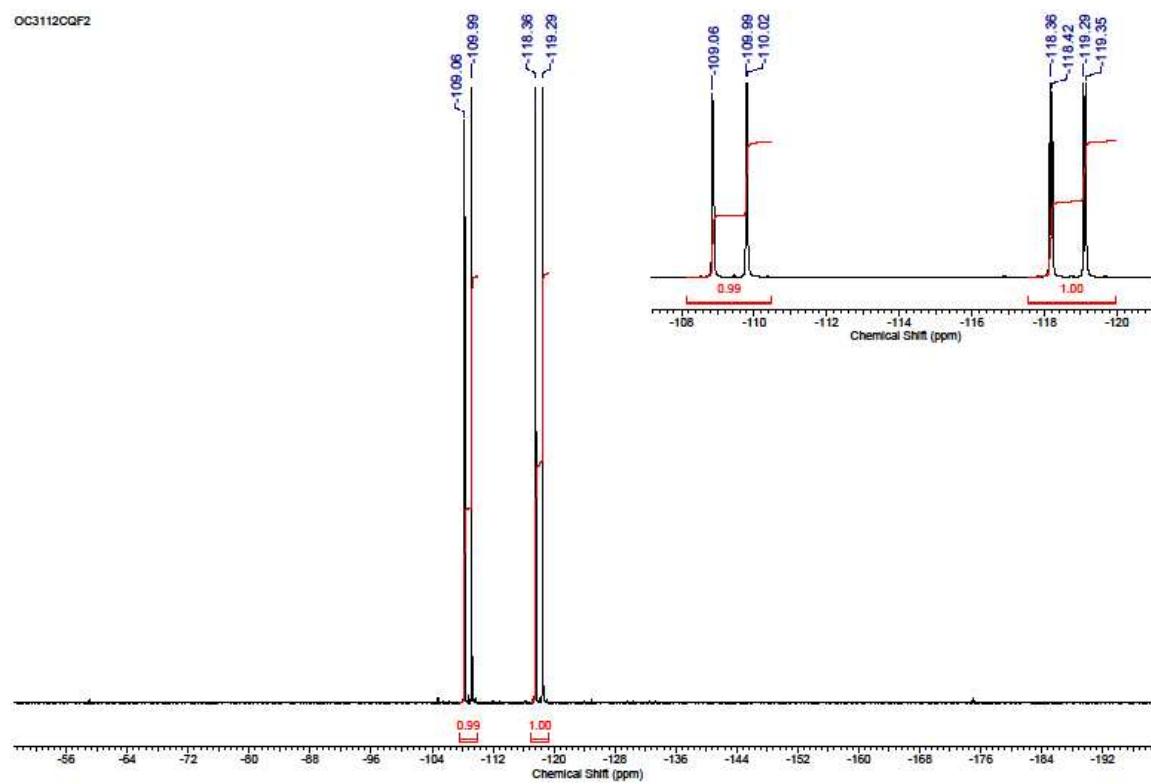
>95:5/52%
CDCl₃

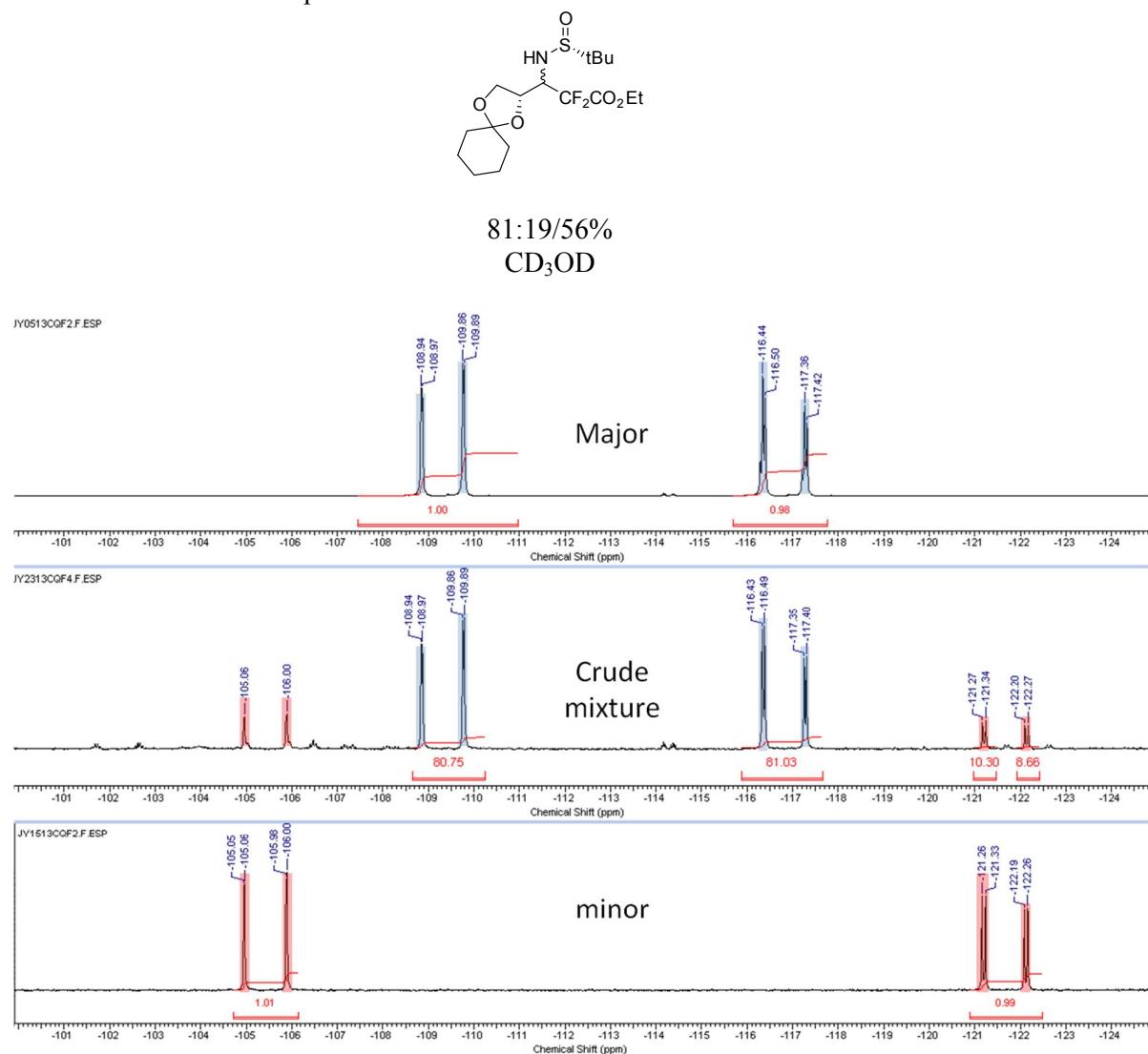


(*3R,4S,S_S*)-ethyl-4,5-cyclohexyldenedioxy-3-(*t*-butylsulfinylamino)-2,2-difluoropentanoate
(ul-17S)

OC1912CQF3

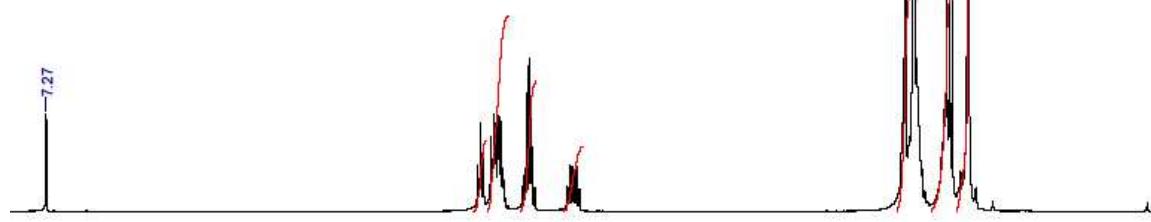
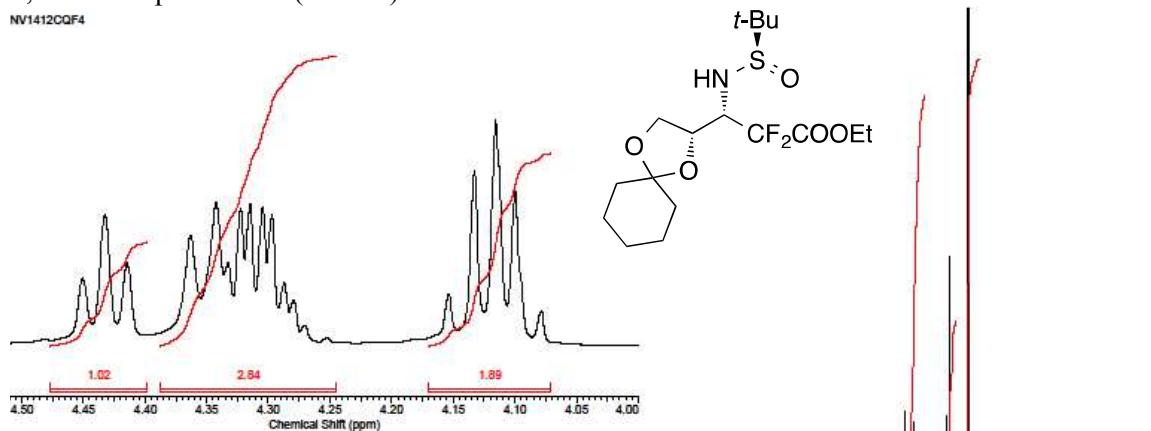




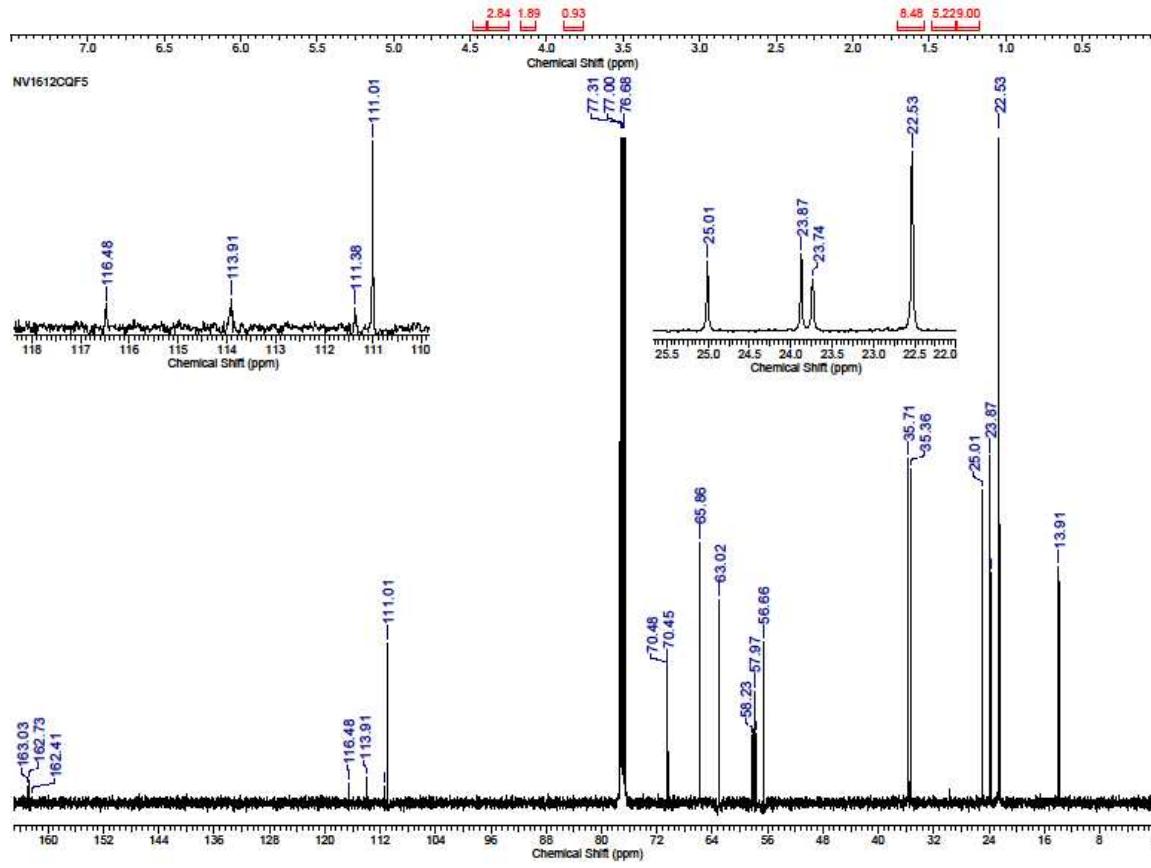
2.2.9 Reaction with 9R: spectra of crude NMR and of the diastereomers 17R

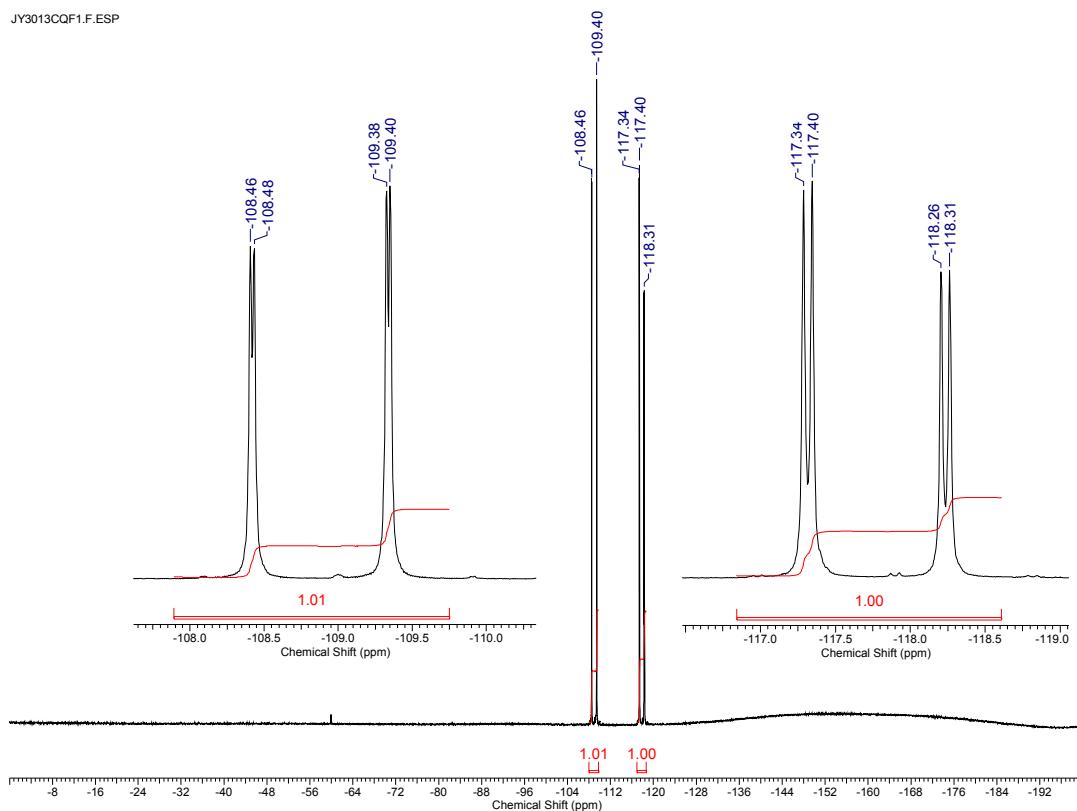
Major diastereoisomer: (3*S*,4*S*,*R*_S)-ethyl-4,5-cyclohexyldenedioxy-3-(*t*-butylsulfinylamino)-2,2-difluoropentanoate (**ul-17R**)

NV1412CQF4

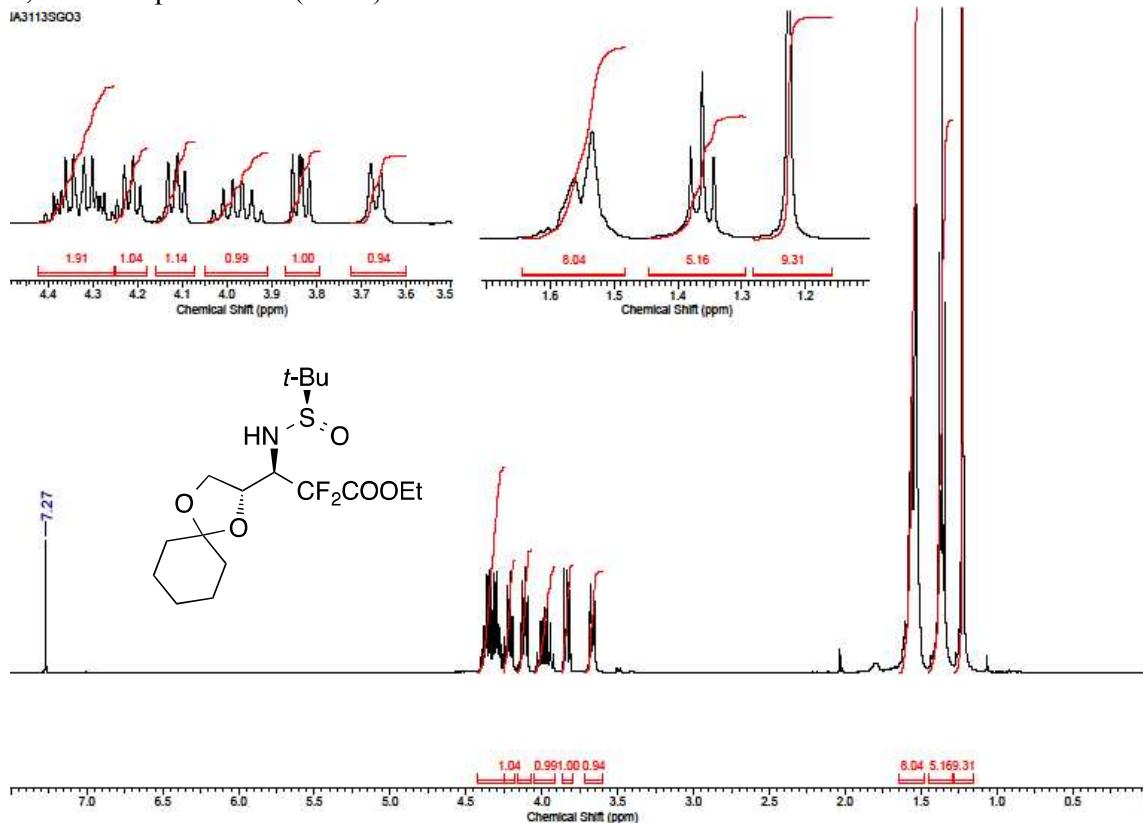


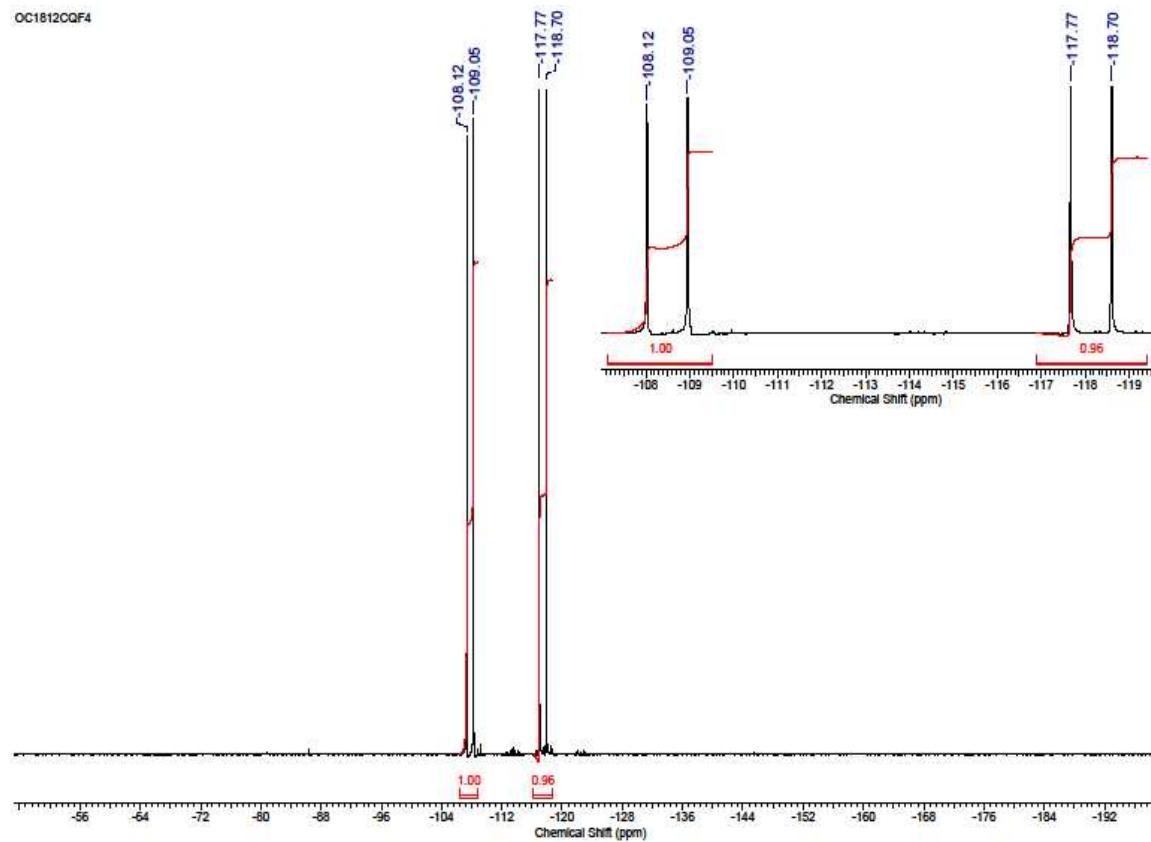
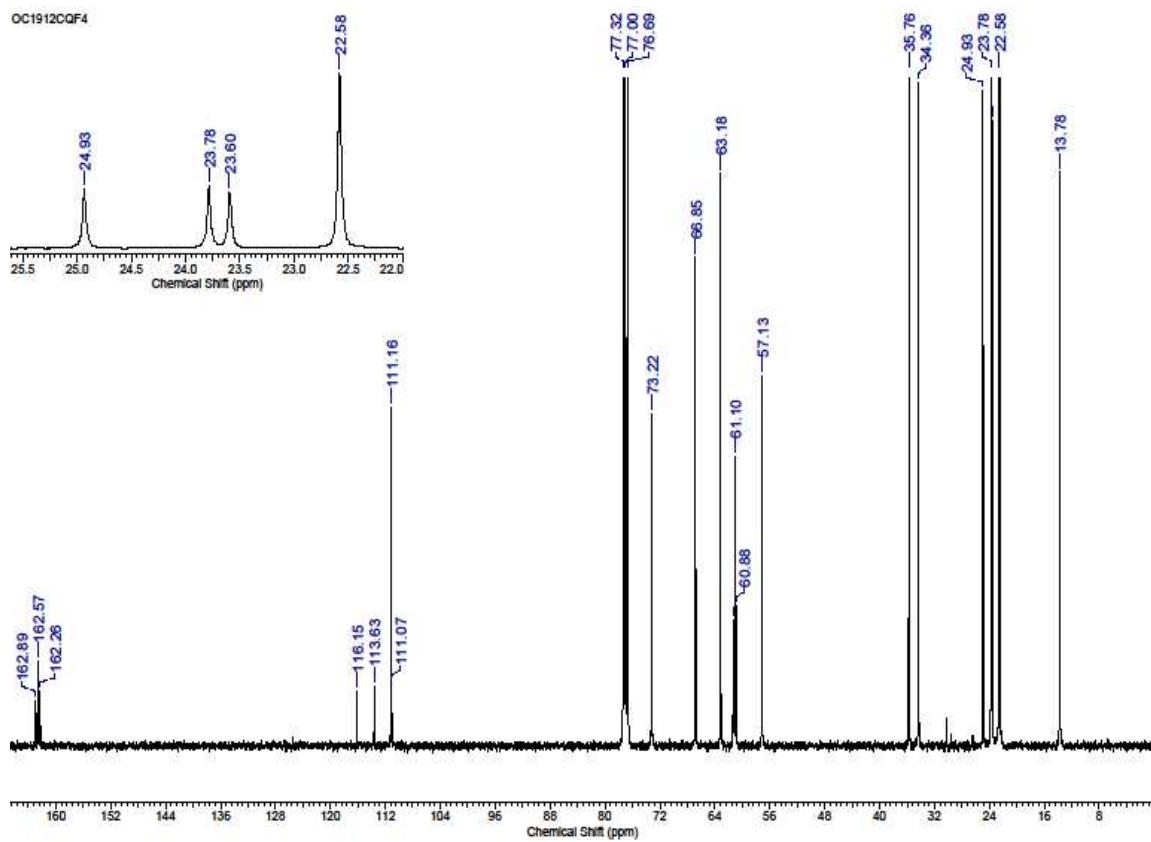
NV1612CQF5

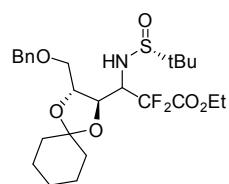




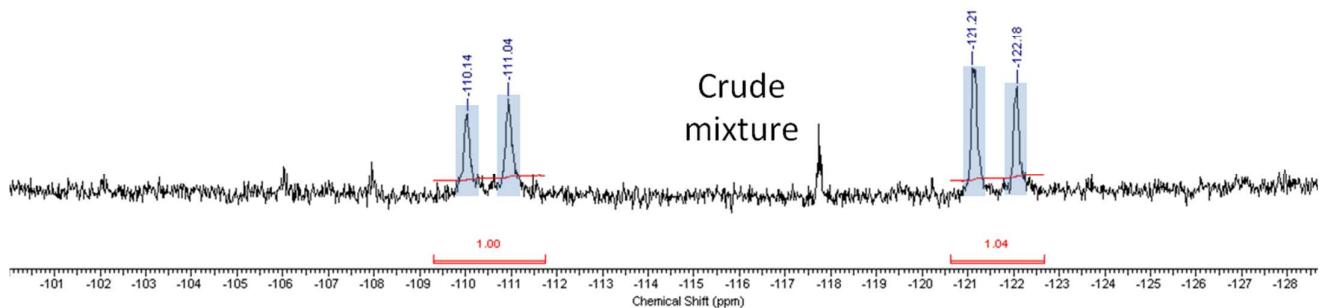
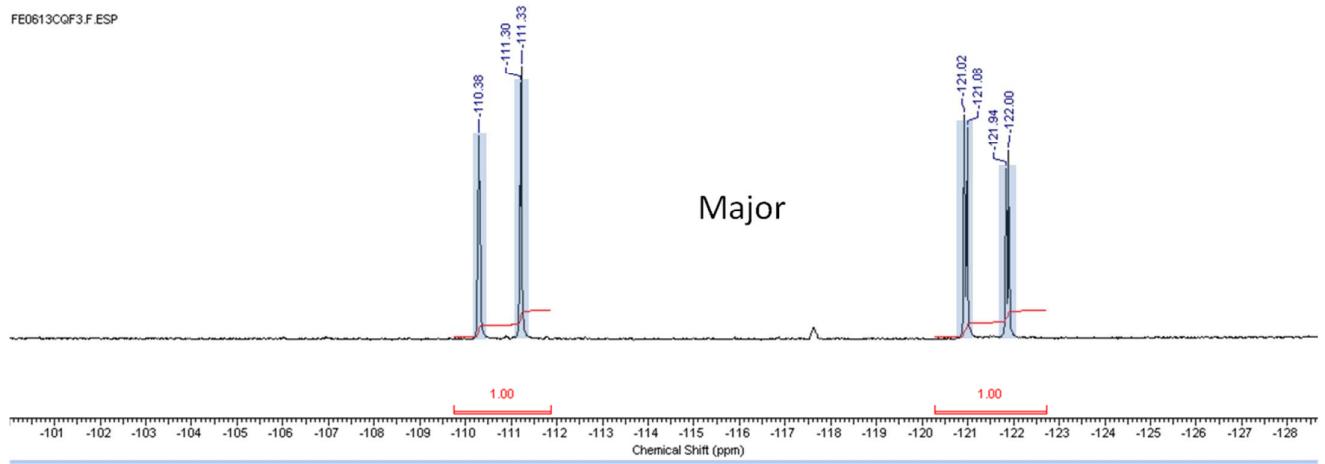
Minor diastereoisomer: (*3R,4S,R_S*)-ethyl-4,5-cyclohexyldenedioxy-3-(*t*-butylsulfinylamino)-2,2-difluoropentanoate (**I-17R**)



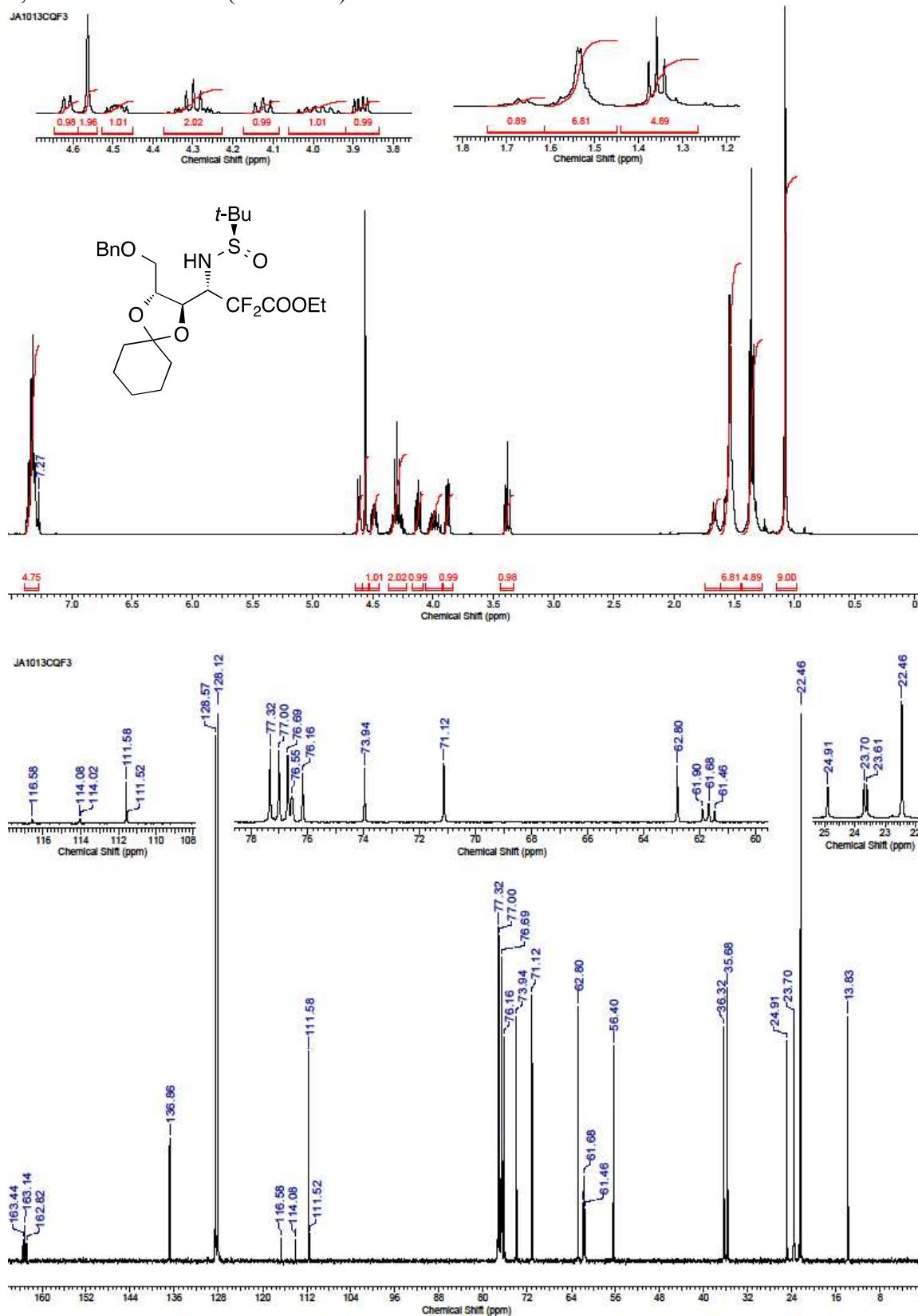


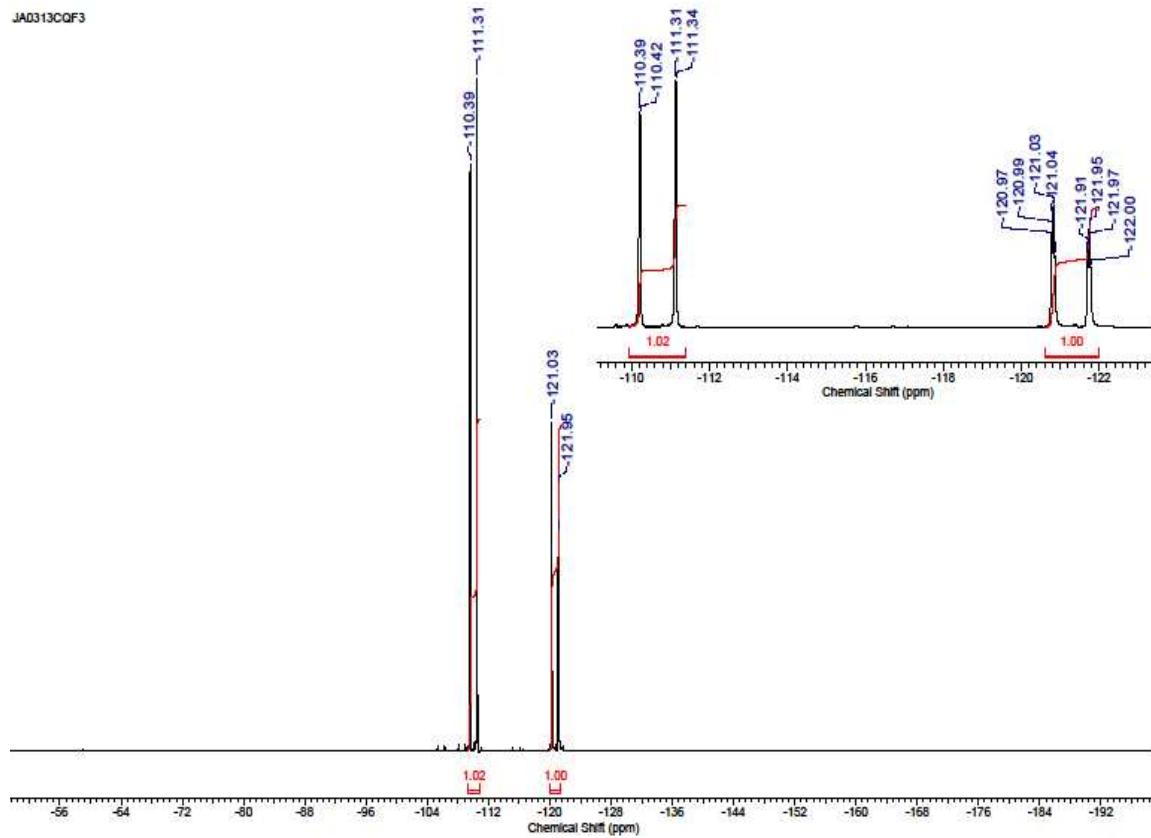
2.2.10 Reaction with *ent*-10S**: spectra of crude NMR and of the diastereomers **18S****

>95:5/67%
CDCl₃

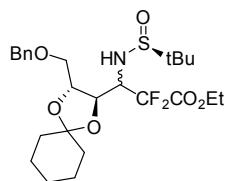


(3*S*,4*R*,5*R*,*R*_S)-Ethyl-[6-(benzyloxy)-3-(*t*-butylsulfinylamino)-4,5-(cyclohexylidenedioxy)-2,2-difluorohexanoate (*ent-ul-18S*)

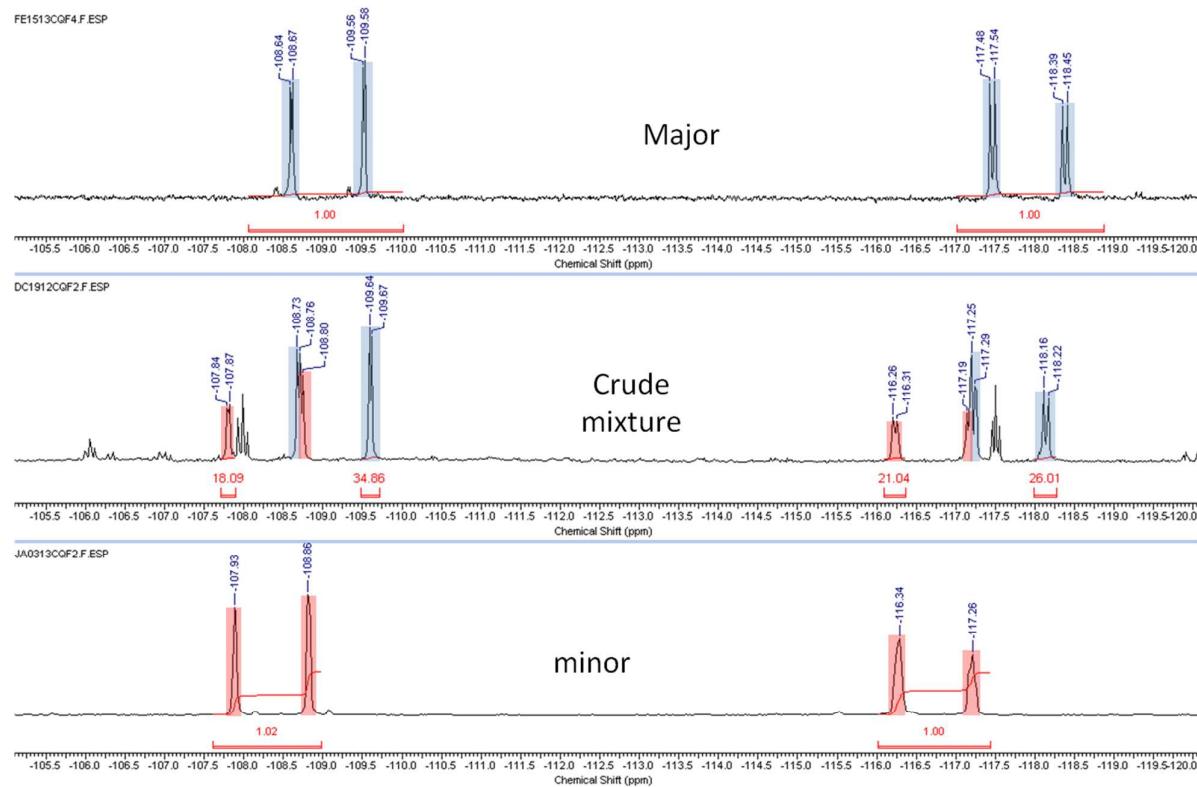




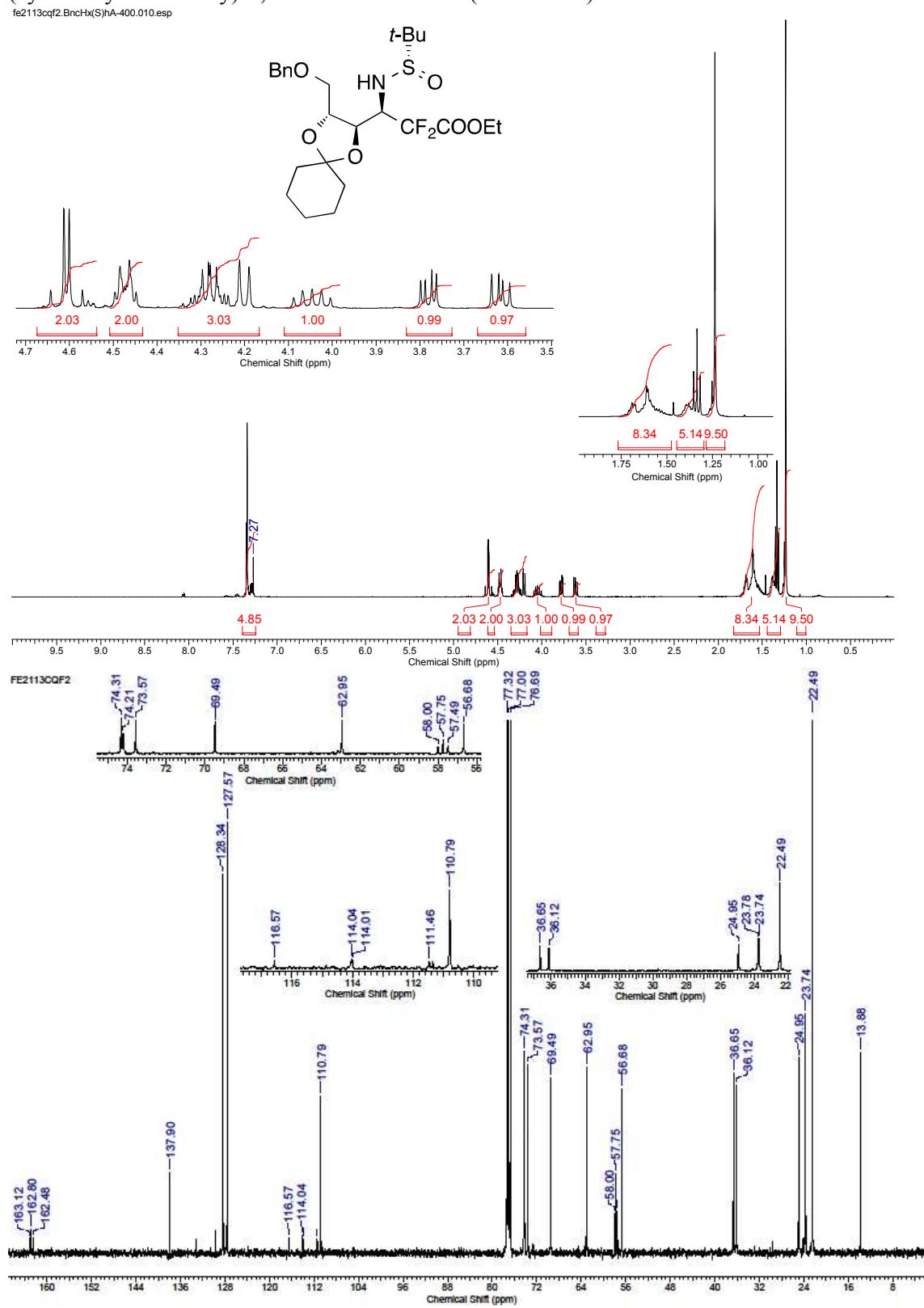
2.2.11 Reaction with *ent*-10R**: spectra of crude NMR and of the diastereomers **18R****

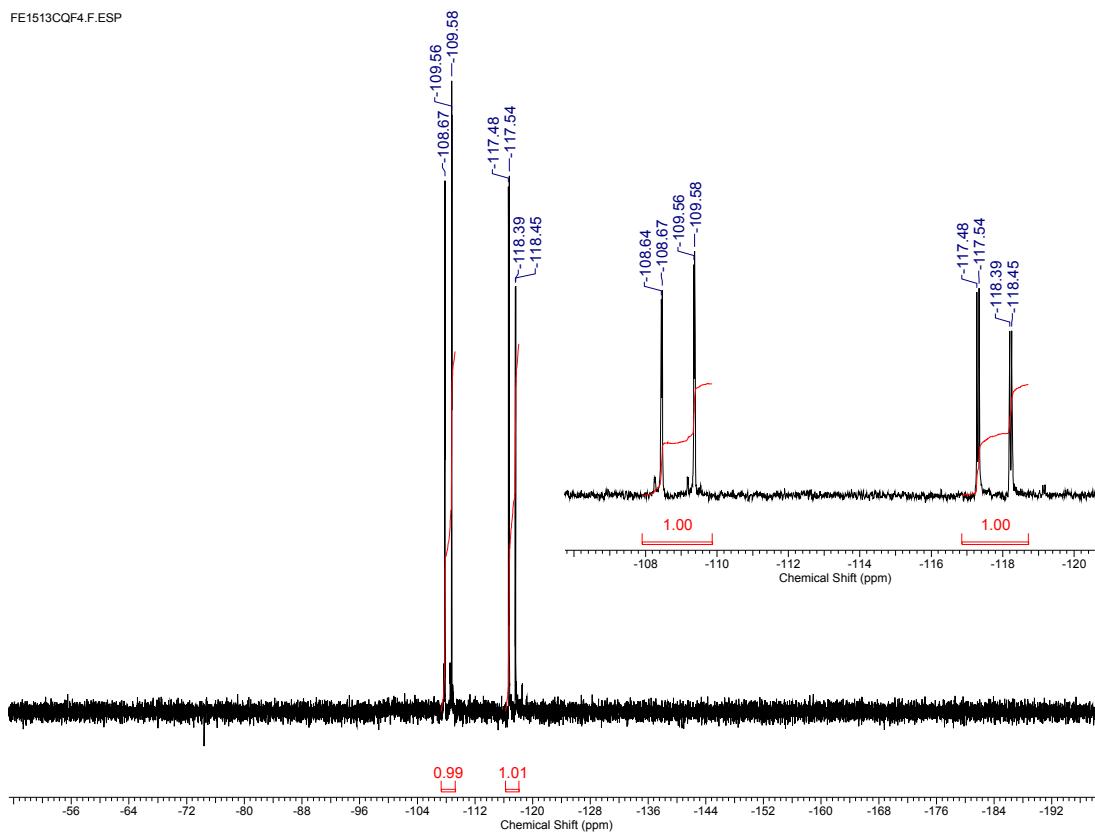


60:40/48%
 CDCl_3



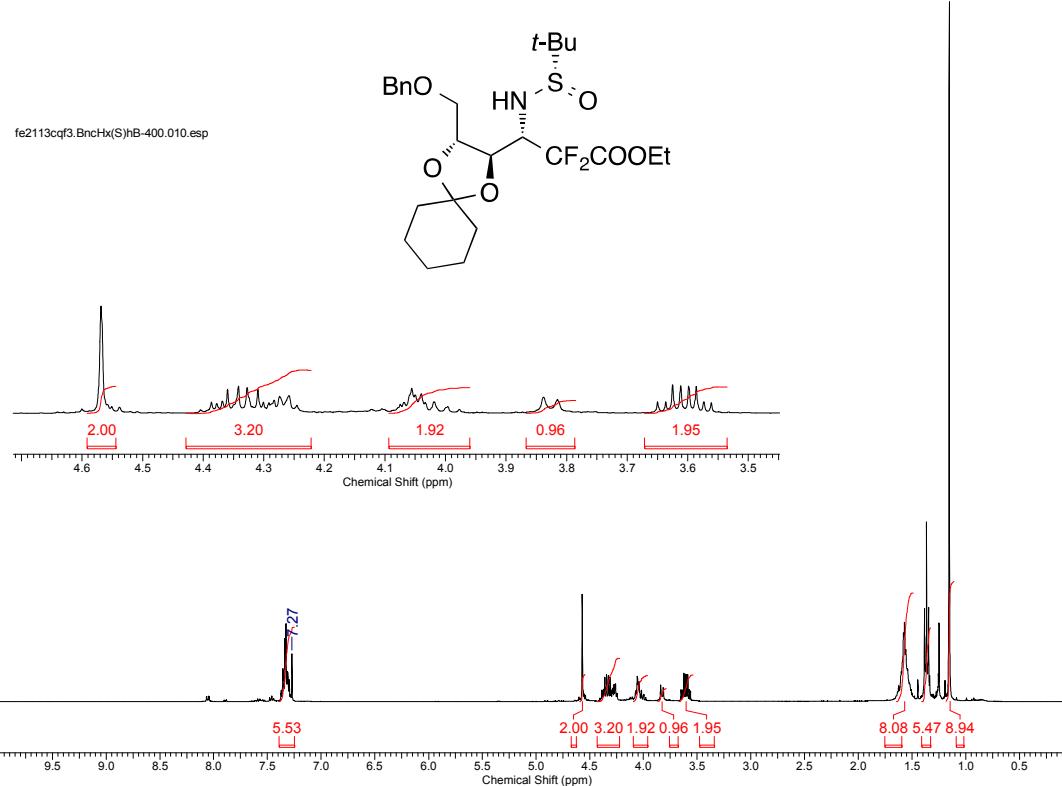
Major diastereoisomer: (3*R*,4*R*,5*R*,*S*_S)-ethyl-6-(benzyloxy)-3-(*t*-butylsulfinylamino)-4,5-(cyclohexyldenedioxy)-2,2-difluorohexanoate (*ent-ul*-**18R**)

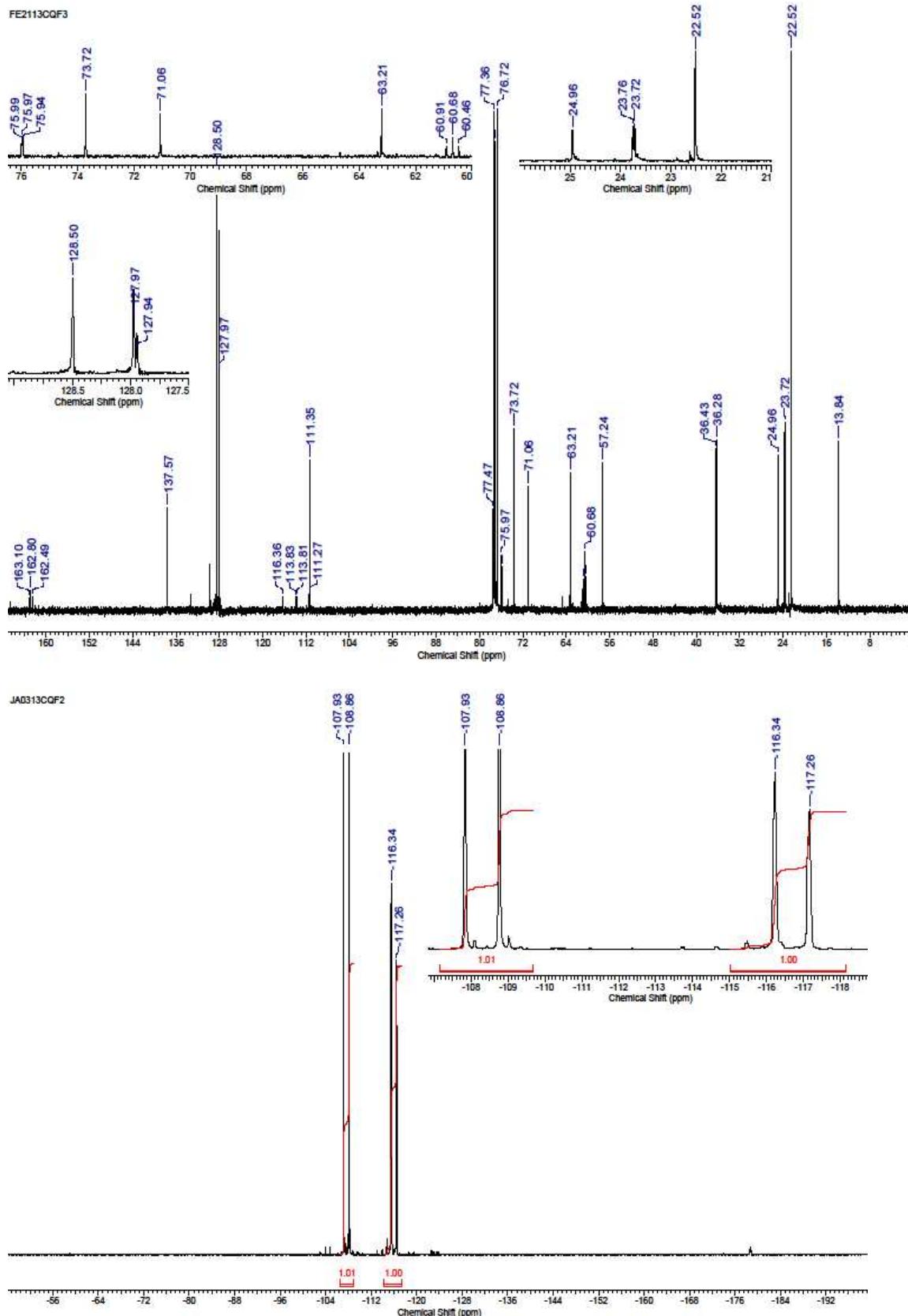


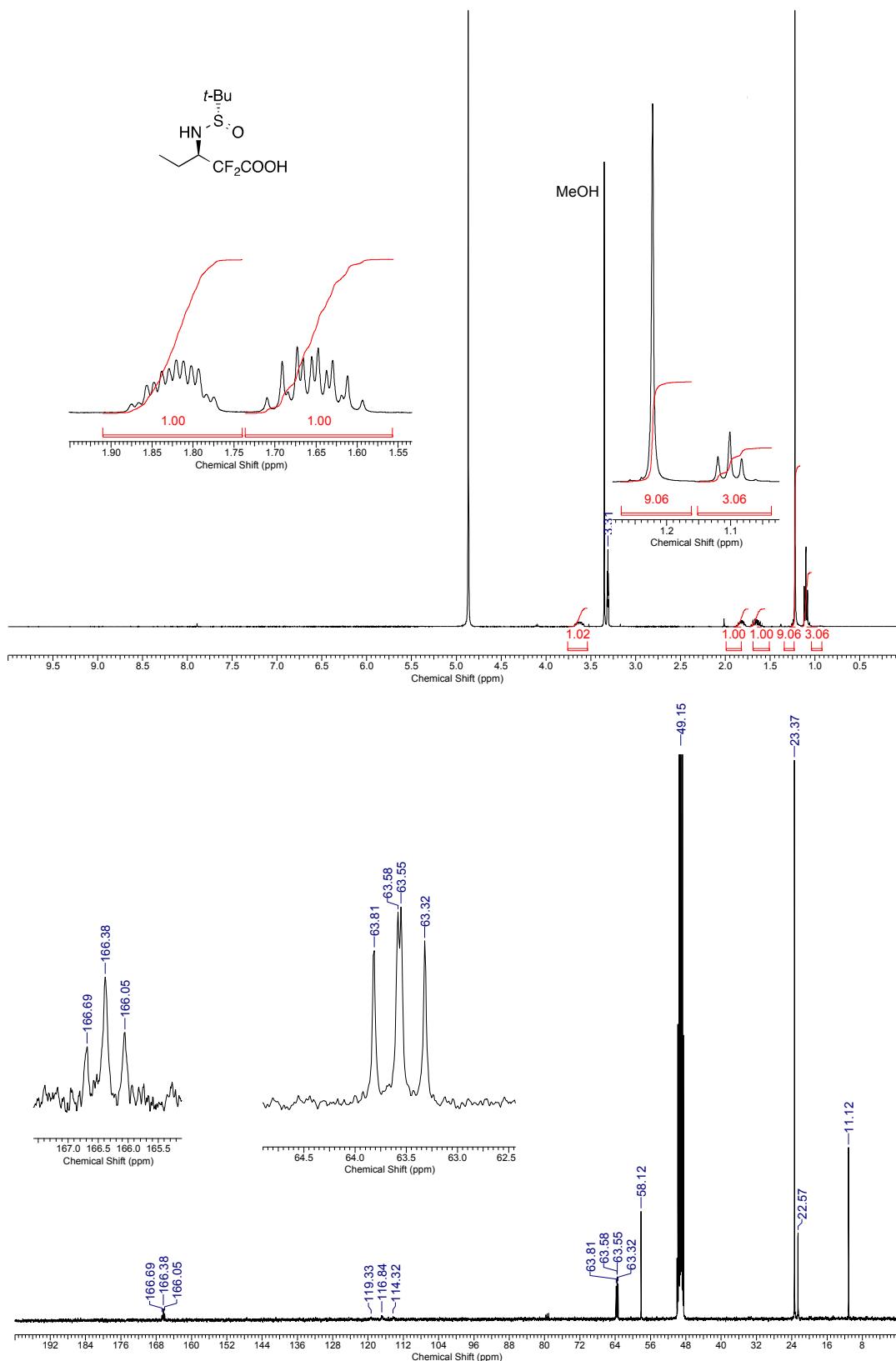


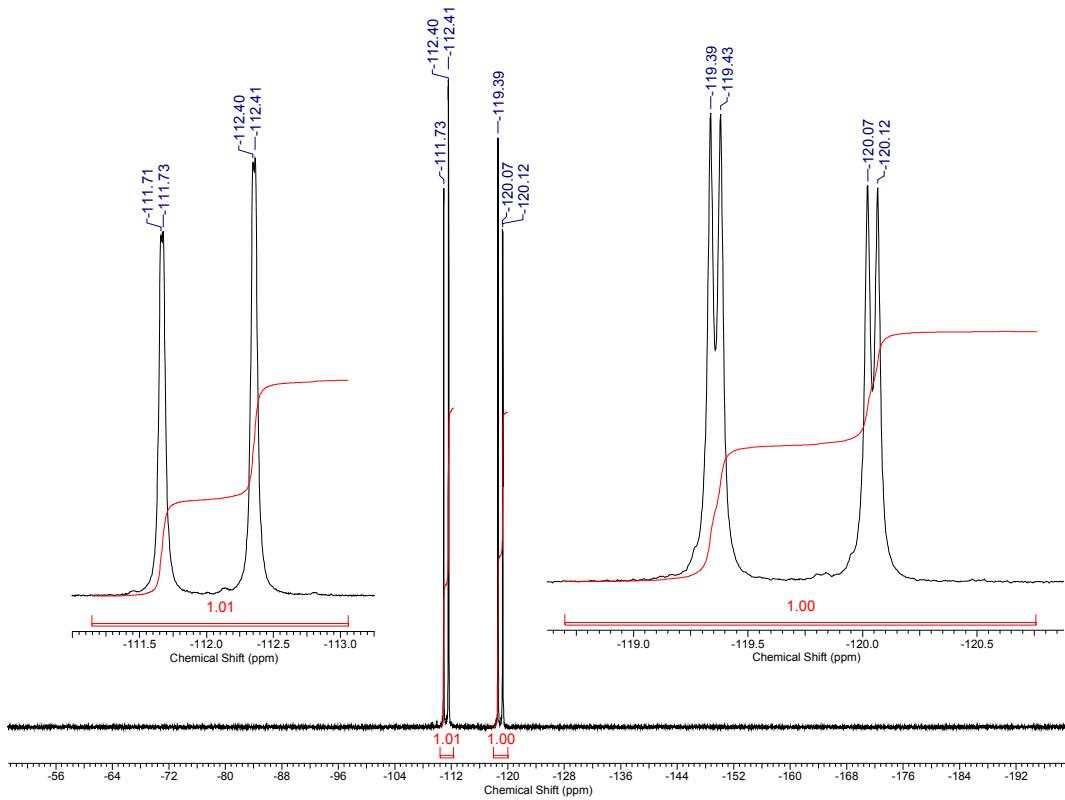
Minor diastereoisomer: (3*S*,4*R*,5*R*,*S*_S)-Ethyl-6-(benzyloxy)-3-(*t*-butylsulfinylamino)-4,5-(cyclohexyldenedioxy)-2,2-difluorohexanoate (*ent-l*-**18R**)

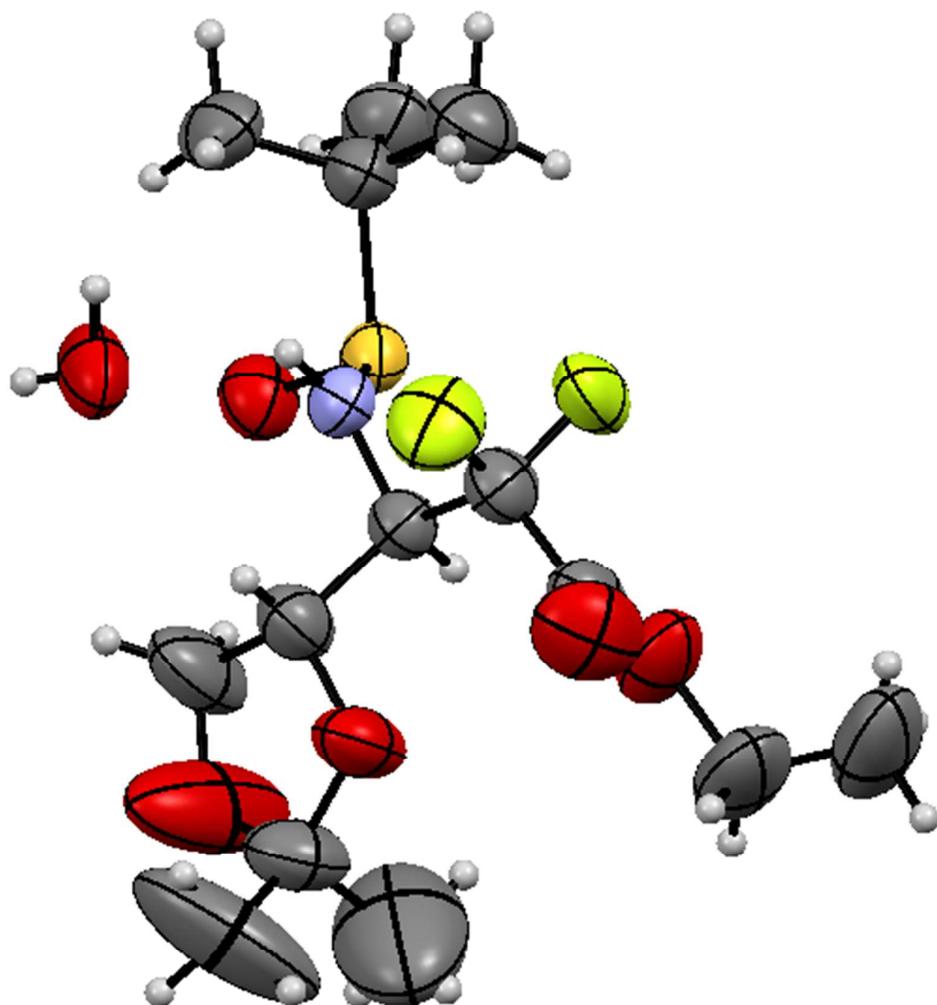
fe2113cqf3.BnchX(S)hB-400.010.esp



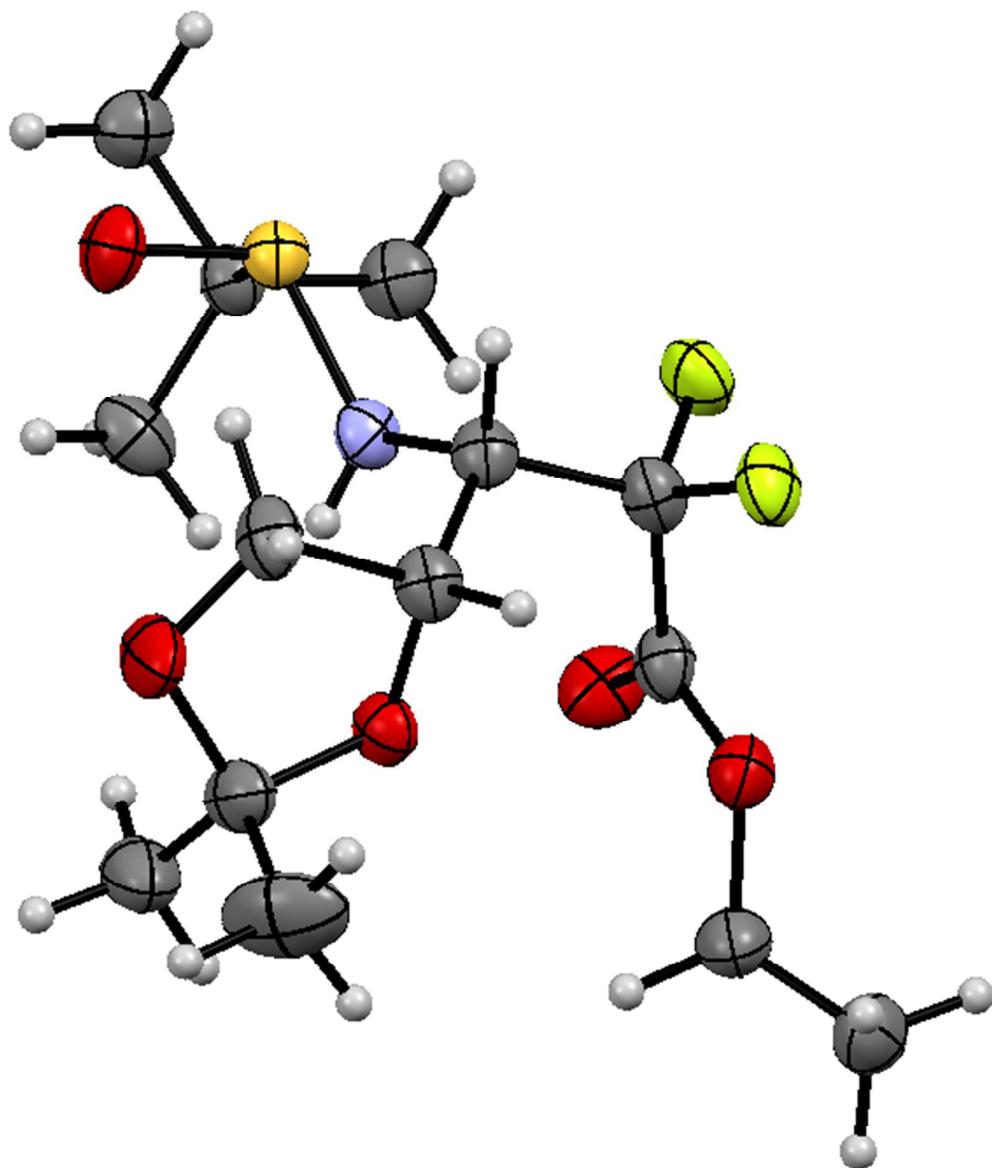


2.2.12 (*3R,S_S*)-3-(*t*-butylsulfinylamino)-2,2-difluoropentanoic acid (19**)**



3. X-ray analysis:**3.1 Crystal data for *ul-16S*:**

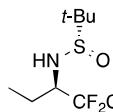
Formula $[C_{14}H_{25}F_2NO_5S].H_2O$, colorless, Monoclinic, space group $P2_1$ (n^o4), $a = 12.221(2)$ Å, $b = 6.0654(11)$ Å, $c = 13.752(2)$ Å, $\alpha = 90.00^\circ$, $\beta = 96.378(3)^\circ$, $\gamma = 90.00^\circ$, $V = 1013.1(3)$ Å 3 , $Z = 2$, $\rho_{\text{calc}} = 1.231$ g.cm $^{-3}$, $F(000) = 400$, $\mu(\text{MoK}\alpha) = 0.203$ mm $^{-1}$. 3726 reflections collected, 3486 independent reflections with $I > 2\sigma(I)$ ($2\theta_{\text{max}} = 27.57^\circ$), and 229 parameters were used for the solution of structure. The non-hydrogen atoms were refined anisotropically. $R_1 = 0.0497$ and $wR_2 = 0.1360$. GOF = 1.078. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-987550. Copies of data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code +44(1223)336-033; E-mail: deposit@ccdc.cam.ac.uk].

3.2 Crystal data for ul-16R:

Formula $C_{14}H_{25}F_2NO_5S$, colorless, crystal dimensions $0.210 \times 0.190 \times 0.150$ mm 3 , Orthorhombic, space group $P2_12_12_1$, $a = 8.329(6)$ Å, $b = 9.292(7)$ Å, $c = 23.430(16)$ Å, $\alpha = \beta = \gamma = 90.00^\circ$, $V = 1813(2)$ Å 3 , $Z = 4$, $\rho_{\text{calc}} = 1.309$ g cm $^{-3}$, $F(000) = 760$, $\mu(\text{MoK}\alpha) = 0.219$ mm $^{-1}$, $T = 100$ K. 11848 reflections collected, 4090 independent reflections with $I > 2\sigma(I)$, and 219 parameters were used for the solution of structure. The non-hydrogen atoms were refined anisotropically. $R_1 = 0.0555$ and $wR_2 = 0.1230$. GOF = 1.096. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-987643. Copies of data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44(1223)336-033; E-mail: deposit@ccdc.cam.ac.uk].

3.3 Crystal data for *ul*-11S (derivatized as the acid 19):

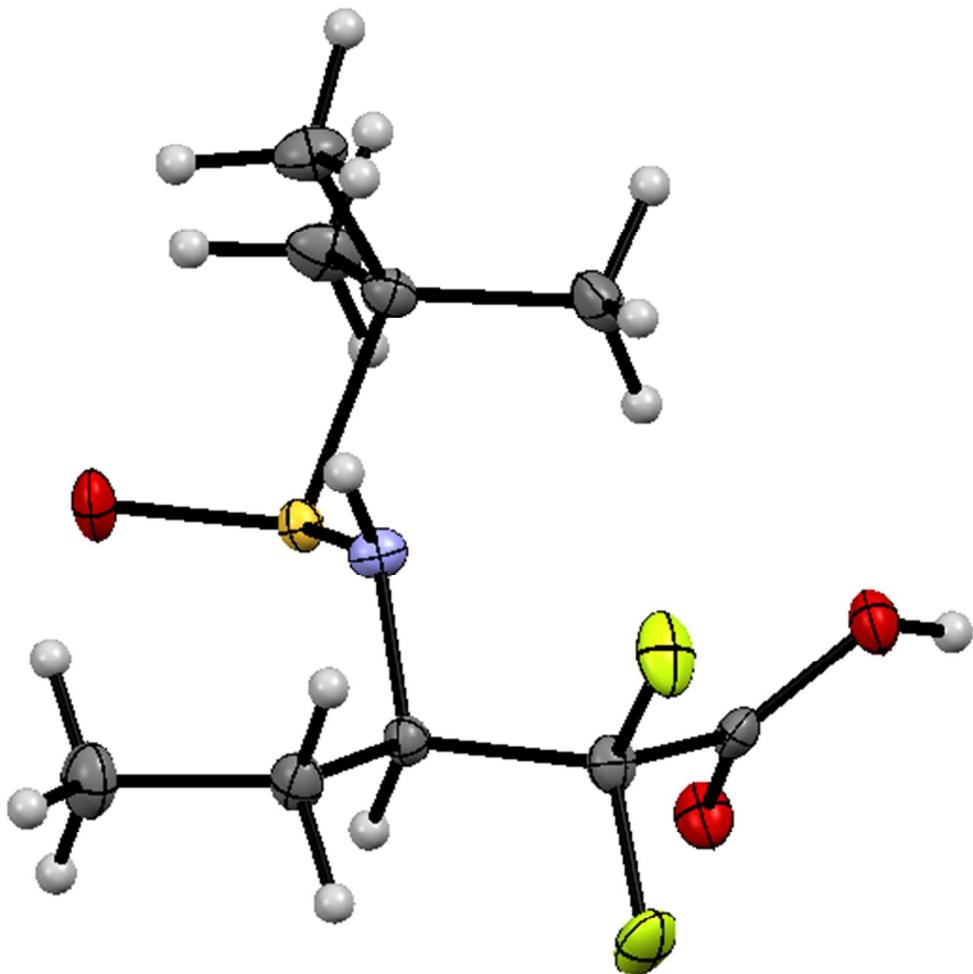
***ul*-11S** was hydrolysed to the corresponding carboxylic acid (*3R,Ss*)-3-(*t*-butylsulfinylamido)-2,2-difluoropentanoic acid (**19**):



To a round-bottomed flask containing ***ul*-11S** (36 mg, 0.126 mmol, 1 equiv) in THF/H₂O (1:2, 3 mL) was added LiOH (15.1 mg, 0.63 mmol, 5 equiv) at 0 °C. The resulting solution was stirred at 0 °C for 1 h then acidified with 2M aq. HCl to pH = 2 and extracted with EtOAc. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give **19** (31 mg, 0.121 mmol, 96%) as a white solid. Recrystallisation from CHCl₃ afforded crystals suitable for X-ray analysis.

Mp: 126–128 °C. [α]_D +50.8 (c 0.90, CH₃OH). IR (neat) 3275 (w, br), 2969 (w), 1748 (m), 1096 (m), 1002 (s). ¹H NMR (400 MHz, CD₃OD) δ 3.70–3.56 (m, 1H), 1.83 (dqd, ²J_{HH}=14.4 Hz, ³J_{HH}=7.4, ³J_{HH}=3.5 Hz, 1H), 1.65 (ddq, ²J_{HH}=14.4 Hz, ³J_{HH}=10.2, ³J_{HH}=7.4 Hz, 1H), 1.22 (s, 9H), 1.10 (t, ³J_{HH}=7.4 Hz, 3H) ppm. ¹³C NMR (101 MHz, CD₃OD) δ 166.4 (t, ²J_{CF}=33.0 Hz), 119.7–113.7 (m), 63.6 (dd, ²J_{CF}=26.4, 23.5 Hz), 58.1, 23.4, 22.6 (3C), 11.1 ppm. ¹⁹F NMR (376 MHz, CD₃OD) δ -112.1 (dd, ²J_{FF}=258.4 Hz, ³J_{HF}=6.1 Hz, 1F), -119.8 (dd, ²J_{FF}=258.4 Hz, ³J_{HF}=16.5 Hz, 1F) ppm. MS (ESI+) (*m/z*) 258 (M+H)⁺. HRMS (MS+) for C₉H₁₇F₂NNaO₃S (M+Na)⁺ calcd 280.0789, found 280.0789.

Crystal structure:



Formula $C_9H_{17}F_2NO_3S$, colorless, crystal dimensions $0.120 \times 0.070 \times 0.020$ mm 3 , Monoclinic, space group $P2_1$, $a = 5.742(4)$ Å, $b = 17.689(11)$ Å, $c = 6.193(4)$ Å, $\alpha = 90.00^\circ$, $\beta = 100.655(14)^\circ$, $\gamma = 90.00^\circ$, $V = 618.1(7)$ Å 3 , $Z = 2$, $\rho_{\text{calc}} = 1.382$ g cm $^{-3}$, $F(000) = 272$, $\mu(\text{MoK}\alpha) = 0.280$ mm $^{-1}$, $T = 100$ K. 5534 reflections collected, 2056 independent reflections with $I > 2\sigma(I)$, and 155 parameters were used for the solution of structure. The non-hydrogen atoms were refined anisotropically. $R_1 = 0.0244$ and $wR_2 = 0.0659$. GOF = 1.032. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-987644. Copies of data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code +44(1223)336-033; E-mail: deposit@ccdc.cam.ac.uk].