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Supporting Information

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Supporting Information

for

Interception of the Enzymatic Conversion of Farnesyl Diphosphate to 5-Epi-aristolochene by Using a Fluoro Substrate Analogue: 1-Fluorogermacrene A from (2*E*,6*Z*)-6-Fluorofarnesyl Diphosphate

Juan A. Faraldos, Yuxin Zhao, Paul E. O'Maille,
Joseph P. Noel, and Robert M. Coates*

Experimental Section

General methods. Optical rotations were measured on a JASCO DIP-370 digital polarimeter at 25 ºC. The UV spectrum was obtained on a Shimadzu UV-2401 PC spectrophotometer. IR spectra were measured on a Perkin Elmer Spectrum BX, FTIR spectrophotometer. GC analyses were conducted on a Rtx-5 30-m fused silica capillary column (split ratio ca 100:1). The following programs were used: Method A = initial temp 50 °C for 3 min, ramp 5 °C/min to 130 °C at an injector temp of 110 °C. Method B = initial temp 60 °C for 3 min, ramp 5 °C/min to 150 °C at an injector temp of 180 °C. ^{1}H, ^{13}C, ^{19}F and ^{31}P NMR spectra were recorded in $CDCl_3$ (^{1}H, 7.26; ^{13}C, 77.0) or CD_3OD {^{1}H, 3.31 (quintet); ^{13}C, 49.2 (septet)} with U400 and U500 spectrometers in the School of Chemical Sciences NMR Spectroscopy Facility at the University of Illinois. Chemical shifts are in ppm and coupling constants are in Hertz. Mass spectra were recorded on 70V-SE instruments. All chemical reactions were performed in flame-dried glassware under nitrogen. THF and Et_2O were dried and distilled from Na/benzophenone; benzene and CH_2Cl_2 were dried and distilled from CaH_2. Hexane and

ethyl acetate were freshly distilled from CaH_2. TLC analyses were performed on silica gel 60 F254 precoated-plates 250 μm. TLC visualizations were performed with 5% phosphomolybdic acid (0.2 M in 2.5% conc. H_2SO_4/EtOH (v/v)), I_2 vapor, 0.1 % berberine·HCl/EtOH or UV light. Commercial reagents were used without further purification unless specifically noted. Column chromatography was performed according to Still's procedure[1] using 100-700 times excess 32-64 μm grade silica gel unless indicated otherwise. Products separated by chromatography are specified in elution order. The purity of all stable products was estimated to be ≥ 90-95 % by inspection and integration of the ^1H and ^{19}F NMR spectra. In some cases the yields of products containing solvents were corrected for the solvent peak integration in ^1H NMR spectra and specified individually in the data sections. Buffered solutions (50% glycerol, 25 mM Tris-HCl (pH 7.5), 2.5 mM $MgCl_2$, 0.5 mM β-mercaptoethanol, 0.5 μg/mL leupeptin and 0.5 mM phenylmethylsulfonyl fluoride) of recombinant TEAS were shipped from the Salk Institute to the University of Illinois and stored at -20 °C. Preparative incubations with TEAS were carried out as previously reported by Schenk et al[2] with modifications.

(*Z*)-1-Bromo-2-fluoro-3,7-dimethyl-octa-2,6-diene (7, X = Br). Known allylic bromide **7**[3] was prepared according to Corey and coworkers.[4] Thus, a solution 2-fluorogeraniol[5] (**6**, 183.0 mg, 1.06 mmol) and triethylamine (218.0 mg, 2.15 mmol) in THF (6 mL) was stirred and cooled at -45 °C as methanesulfonyl chloride (161.0 mg, 1.40 mmol) was added dropwise. The resulting solution was stirred at -45 °C for 50 min, and then a solution of anh. LiBr (360 mg, 4.19 mmol) in THF (2.5 mL) was added via cannula. The mixture was allowed to warm to 0 °C and stirred for an additional 1 h at which time the reaction was judged complete by TLC analysis. Ice water (20 mL) and ice-cold hexane (30 mL) were added, and the aq layer was extracted with hexane (4 x 40 mL). The combined organic extracts were washed with saturated aq $NaHCO_3$ (20 mL) and brine (15 mL) and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave bromide **7** (247 mg, 95%) as a yellow oil. The ^1H NMR spectrum of compound **7** showed that the bromide was essentially pure (>95%), and it was used without further purification. Data for allylic bromide **7**: TLC R_f 0.68 (30 % EtOAc/hexane); ^1H NMR (400 MHz, $CDCl_3$,): δ = 5.09 (t, *J* = 7.0 Hz, 1H, vinyl *H*), 4.07 (d, *J* = 23.0 Hz, 2H, C*H*$_2$Br), 2.05-2.17 (m, 4H, 2C*H*$_2$), 1.68 (s, 3H, C*H*$_3$), 1.67 (d, *J* = 2.8 Hz, 3H, C*H*$_3$), 1.60 ppm (s, 3H, C*H*$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 150.0 (d, *J* = 238.5 Hz), 136.2, 131.5, 124.5, 123.3, 119.1 (d, *J* = 16.3 Hz), 39.9, 30.4 (d, *J* = 5.3 Hz), 26.9, 26.3, 25.93 (d, *J* = 7.6 Hz), 25.91, 17.9, 16.2, 16.1 ppm (d, *J* = 4.6 Hz); ^{19}F NMR

(376 MHz, $CDCl_3$): δ = -116.3 ppm (dt, *J* = 22.9, 3.0 Hz). The ^{1}H NMR data agree reasonably well with those previously reported at 60 MHz for compound **7**.[3b]

Ethyl (6*Z*)-6-Fluoro-7,11-dimethyl-3-oxo-undeca-6,10-dienoate (8). The procedure developed by Huckin and Weiler[6] and modified by Jin et al.[7] was followed. To a cold (0 °C) suspension of NaH (325.0 mg, 8.14 mmol) in THF (12. mL) was added ethyl acetoacetate (950 μL, 7.40 mmol) dropwise. After stirring 10 min, *n*-BuLi (1.5 M in hexane, 5.4 mL, 8.14 mmol) was slowly added via syringe. The resulting suspension was stirred for an additional 15 min at 0 °C, and then neat bromide **7** (580 mg, 2.47 mmol) was added via syringe. After 30 min, the reaction was quenched by careful addition of 3 M aq HCl (3 mL), water (80 mL) and ether (80 mL). The aq layer was extracted with ether (50 mL x 3). The combined ethereal extracts were washed with brine (100 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure and purification by flash chromatography on silica gel (11% EtOAc-hexane) gave the known ß-keto ester **8**[3b] (593 mg, 85 %) as a yellow oil: TLC R_f 0.58 (30 % EtOAc-hexane); ^{1}H NMR (400 MHz, $CDCl_3$,): δ = 5.08 (m, 1H, vinyl *H*), 4.19 (q, *J* = 7.1 Hz, 2H, C*H*$_2$), 3.44 (s, 2H, C*H*$_2$), 2.73 (t, *J* = 7.2 Hz, 2H, C*H*$_2$), 2.52 (dt, *J* = 22.1, 7.5 Hz, 2H, C*H*$_2$), 1.99-2.09 (m, 4H, 2C*H*$_2$), 1.67 (s, 3H, C*H*$_3$), 1.59 (s, 3H, C*H*$_3$), 1.58 (d, *J* = 2.9 Hz, 3H, CH3), 1.27 ppm (t, *J* = 7.0 Hz, 3H, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.6, 167.0, 153.6, 131.7, 123.8, 112.5 (d, *J* = 16.4 Hz), 61.4, 49.3, 39.6, 29.6 (d, *J* = 7.3 Hz), 26.1, 25.7, 22.8, 17.6, 15.4 (d, *J* = 6.1 Hz), 14.1 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ = -115.2 ppm (t, *J* = 21.8 Hz); HRMS (FAB): calcd for $C_{16}H_{25}FO_3Na$: 307.1685 [*M*+Na], found 307.1685.

Ethyl (2*E,* 6*Z)*-6-Fluoro-3,7,11-trimethylundeca-2,6,10-trienoate (9). The procedure developed by Sum and Weiler[8,9] modified by Jin et al.[7] was followed. To a cold (0 °C) and well-stirred suspension of NaH (37.0 mg, 0.93 mmol) in Et_2O (6 mL) was added a solution of ß-keto ester **8** (170.0 mg, 0.60 mmol) in Et_2O (4 mL) dropwise. The mixture was stirred for 30 min, and neat diethyl chlorophosphate (115.0 mg, 0.66 mmol) was slowly added via syringe. After 2 h at 0 °C, the reaction was quenched by adding saturated aq NH_4Cl (15 mL). The mixture was diluted with water (15 mL), and the product was extracted with ether (3 x 50 mL). The combined ethereal extracts were washed with water (25 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (15 % EtOAc-hexane, 1 % Et_3N) gave the pure enol phosphate intermediate: yield, 260 mg (ca. 100%);

TLC R_f 0.26 (30 % EtOAc-hexane, 1 % Et_3N); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.35 (s, 1H, vinyl *H*), 5.07 (m, 1H, vinyl *H*), 4.25 (dt, *J* = 7.8, 7.0 Hz, 2H CH_2), 4.13 (q, *J* = 7.2 Hz, 2H, CH_2), 2.45-2.61 (m, 4H, 2CH_2), 1.99-2.08 (m, 4H, 2CH_2), 1.66 (d, *J* = 0.9 Hz, 3H, CH_3), 1.58 (s, 3H, CH_3), 1.56 (d, *J* = 2.6 Hz, 3H, CH_3), 1.35 (dt, *J* = 7.1, 1.2 Hz, 6H, CH_3), 1.24 ppm (t, *J* = 6.9 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 163.7, 160.3 (d, *J* = 7.3 Hz), 153.4, 150.9, 132.0, 124.1, 113.4 (d, *J* = 16.1 Hz), 106.3 (d, *J* = 7.6 Hz), 65.0 (d, *J* = 6.1 Hz), 60.1, 32.7, 29.9 (d, *J* = 7.0 Hz), 26.4, 26.0, 25.9, 17.8, 16.3 (d, *J* = 7.4 Hz), 14.4 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -114.8 ppm (t, *J* = 18.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ = -7.5 ppm (s); IR (neat film): ν = 2981.6, 2916.2, 1726.8, 1664.1, 1444.8, 1370.8, 1279.2, 1207.1, 1148.0, 1034.9, 986.3, 818.7, 802.7 cm^{-1}; HRMS (FAB): calcd for $C_{20}H_{35}FO_6P$: 421.2155 [*M*+H], found 421.2166.

To a cold (0 °C) and well-stirred suspension of CuI (789.0 mg, 4.15 mmol) in Et_2O (8 mL) was added MeLi (1.6 M in Et_2O, 5.2 mL, 8.30 mmol) via syringe. After 30 min, the initial yellow precipitate that formed had redissolved, and a nearly colorless solution was obtained. This solution was then cooled to -78 °C and an ethereal solution (7 mL) of the enol phosphate (870 mg, 2.1 mmol) described above was slowly added. After 2.5 h at -78 °C, the reaction mixture was poured into an ice-cooled saturated solution of NH_4Cl (20 mL) and conc. NH_4OH (20 mL) was added. The mixture was extracted with ether (4 x 60 mL), and the combined extracts were washed with water (70 mL) and dried over $MgSO_4$. Evaporation under reduced pressure followed by purification by flash chromatography on silica gel (10% EtOAC/hexane) afforded starting enol phosphate (143 mg, 15%) and the known conjugated ethyl ester **9**[3b] (405 mg, 70%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.67 (q, *J* = 1.2 Hz, 1H, C*H*CO_2Et), 5.08 (tq, *J* = 5.4, 1.3 Hz, 1H, vinyl *H*), 4.13 (q, *J* = 7.1 Hz, 2H, CH_2O), 2.32 (t, *J* = 7.3 Hz, 2H, CH_2), 2.37-2.25 (m, 2H, CH_2), 2.17 (d, *J* = 1.2 Hz, 3H, CH_3), 2.07-2.02 (m, 4H, CH_2), 1.67 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 1.55 (d, *J* = 2.6 Hz, 3H, CH_3), 1.26 (t, *J* = 7.1 Hz, 3H, CH_3CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.9 (*C*O_2Et), 158.6 (vinyl *C*), 153.0 (d, $^1J_{F\text{-}C}$ = 219.0 Hz, vinyl *C*F), 131.9 (vinyl *C*), 124.1 (vinyl *C*H), 116.4 (vinyl *C*H), 112.5 (d, $^2J_{F\text{-}C}$ = 16.9 Hz, vinyl *C*), 59.8 (*C*H_2O), 37.9 (*C*H_2), 27.3 (*C*H_2), 27.0 (*C*H_2), 26.4 (*C*H_2), 25.9 (*C*H_3), 18.9 (*C*H_3), 17.8 (*C*H_3), 15.7 (d, $^3J_{F\text{-}C}$ = 6.1 Hz, *C*H_3), 14.5 (*C*H_3CH_2); ^{19}F NMR (376 MHz, $CDCl_3$): δ = -113.9 (t, *J* = 21.6 Hz).

Acid-catalyzed cyclization of germacrene A. A solution of (+)-germacrene A[10] (29.0 mg, 0.142 mmol) in anhydrous $CDCl_3$ (700 µL) was treated with 30 µL of a 0.64

M solution of trifluoroacetic acid (0.02 mmol) in $CDCl_3$ (final conc, 26.3 mM) at room temp. After 10 min, integration of the well-separated and diagnostic ^{1}H NMR signals[11] for the angular methyls of β-selinene (**18a**, 0.73 ppm), α-selinene (**19a**, 0.80 ppm), and α-cyperene (**20a**, 1.05 ppm) showed a mixture of these eudesmanes in an approximately 5:2.5:1 ratio, respectively, and no starting material was detected. The isomers were not separable on TLC and were identified by comparison of the ^{1}H NMR data extracted from the mixture with the reported data.[11]

Acid-catalyzed cyclization of 1-fluorogermacrene A. A solution of 1-fluorogermacrene A (**13**, 3.0 mg, 0.014 mmol) in anhydrous $CDCl_3$ (1 mL) was initially treated with 10 μL of a 1.2 M solution of trifluoroacteric acid (0.012 mmol) in $CDCl_3$ (final conc, 12 mM) at room temp but no reaction was detected (^{1}H NMR, 500 MHz) after 10 min. Then a second (10 μL) and 10 min later a third (10 μL) 0.86 equiv of trifluoroacetic acid (1.2 M in $CDCl_3$) were added, but again no reaction was observed after an additional 12 min. The cyclization reaction was triggered by the addition of another 20 μL of a 1.2 M solution of trifluoroacetic acid (4.3 eq, 0.06 mmol) in $CDCl_3$ (final conc, 60 mM) leading, after 3.5 h at room temp, to a separable (silica gel prep. TLC, *n*-pentane) 2:2:1 mixture of the 1a-fluoro analogues of eudesmanes β-selinene, α-selinene and α-cyperene respectively.

1a-Fluoro-β-selinene (18b): yield, 0.6-0.7 mg (23 %); TLC R_f (n-pentane) 0.594; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 4.78 (d, *J* = 1.5 Hz, 1H, H15), 4.73 (s, 1H, H12), 4.71 (s, 1H, H12), 4.50 (d, *J* = 1.5 Hz, 1H, H15), 4.25 (dt, *J* = 48.6 and 2.4 Hz, 1H, H1), 2.40 (ddd, *J* = 13.4 and 5.4 Hz, 1H, H5), 2.35 (br d, *J* = 12.2 Hz, 1H, H3eq), 2.17 (ddd, *J* = 13.7, 5.4, 1.4 Hz, 1H, H3ax), 2.02-1.86 (m, 4H), 1.79 (ddd, *J* = 14.3, 5.4 and 1.9 Hz, 1H), 1.76 (s, 3H, H13), 1.66 (br d, *J* = 13.5 Hz, 2H), 1.45-1.42 (m, 1H), (br d, *J* = 13.5 Hz, 2H), 0.72 ppm (s, 3H, H14); ^{19}F NMR (376 MHz, $CDCl_3$): δ = -191.33 ppm (dt, *J* = 47.4, 12.4 Hz); MS (EI): *m/e* (rel. int.) 222 ([*M*]$^+$, 100), 207 (30), 193 (36), 179 (56), 165 (56), 151 (24), 119 (20), 105 (31), 93 (38), 67 (24), 55 (21); HRMS (EI): calcd for $C_{15}H_{23}F$: 222.1784, found 222.1785.

1a-Fluoro-α-selinene (19b): yield, 0.6-0.7 mg (23 %); TLC R_f (n-pentane) 0.514; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 5.23 (br s, 1H, H3), 4.73 (s, 1H, H12), 4.71 (s, 1H, H12), 4.27 (dd, *J* = 50.0 and 3.5 Hz, 1H, H1), 2.48-2.18 (m, 3H), 1.99 (tt, *J* = 12.7, 3.4 Hz, 1H), 1.87 (br d, *J* = 12.7 Hz, 1H) 1.81 (dd, *J* = 13.3, 4.3 Hz, 1H), 1.76 (s, 3H, H13), 1.65 (s, 3H, H15), 1.64 (dd, *J* = 4.1, 1.8 Hz, 1H), 1.54 (dd, *J* = 13.2, 4.0 Hz, 1H), 1.31

(ddd, *J* = 13.9, 4.1, 2.9 Hz, 1H), 1.25 (br d, *J* = 5.2 Hz, 1H), 0.75 ppm (s, 3H, H14); ^{19}F NMR (376 MHz, $CDCl_3$): δ = -183.90 ppm (dt, *J* = 48.9, 22.9 Hz); EIMS *m/e* (rel. int.) 222 ([*M*]$^+$, 100), 207 (40), 205 (84), 193 (15), 179 (40), 165 (20), 151 (21), 141 (23), 121 (18), 105 (26), 91 (22), 81 (23), 55 (20); HRMS (EI): calcd for $C_{15}H_{23}F$: 222.1784, found 222.1785.

1a-Fluoro-α-cyperene (20b): yield, 0.3-0.4 mg (15 %); TLC R_f (n-pentane) 0.351; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.73 (2H, s, H12), 4.29 (d, *J* = 48.0 Hz, 1H, H1), 2.60 (br d, *J* = 11.8 Hz, 2H), 2.44-2.13 (m, 4H), 1.76 (s, 3H, H13), 1.61 (s, 3H, H15), 0.99 ppm (s, 3H, H14); ^{19}F NMR (376 MHz, $CDCl_3$): δ = -194.66 ppm (t, *J* = 50.0, Hz); EIMS *m/e* (rel. int.) 222 ([*M*]$^+$, 100), 205 (36), 193 (25), 179 (37), 165 (15), 151 (11), 121 (17), 105 (29), 91 (22), 55 (17); HRMS (EI): calcd for $C_{15}H_{23}F$: 222.1784, found 222.1785.

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[5] a) C. D. Poulter, J. C. Argyle, E. A. Mash, *J. Biol. Chem.* **1978**, *253*, 7227-7232. In this work 2-fluorogeraniol was synthesized by condensation[5b] of 6-methylhept-5-en-2-one with triethyl fluorophosphonoacetate[5c] followed by $LiAlH_4$ reduction, and flash chromatography on silica gel to separate the resulting 2-fluoronerol and 2-fluorogeraniol. b) Y. Komatsu, T. Kitazume, *J. Fluorine Chem*. **2000**, *102*, 61-67. c) Prepared by the Michaelis-Arbuzov reaction: H.-J. Tsai, A. Thenappan, D. J. Burton, *J. Org. Chem.* **1994**, *59*, 7085-7091.

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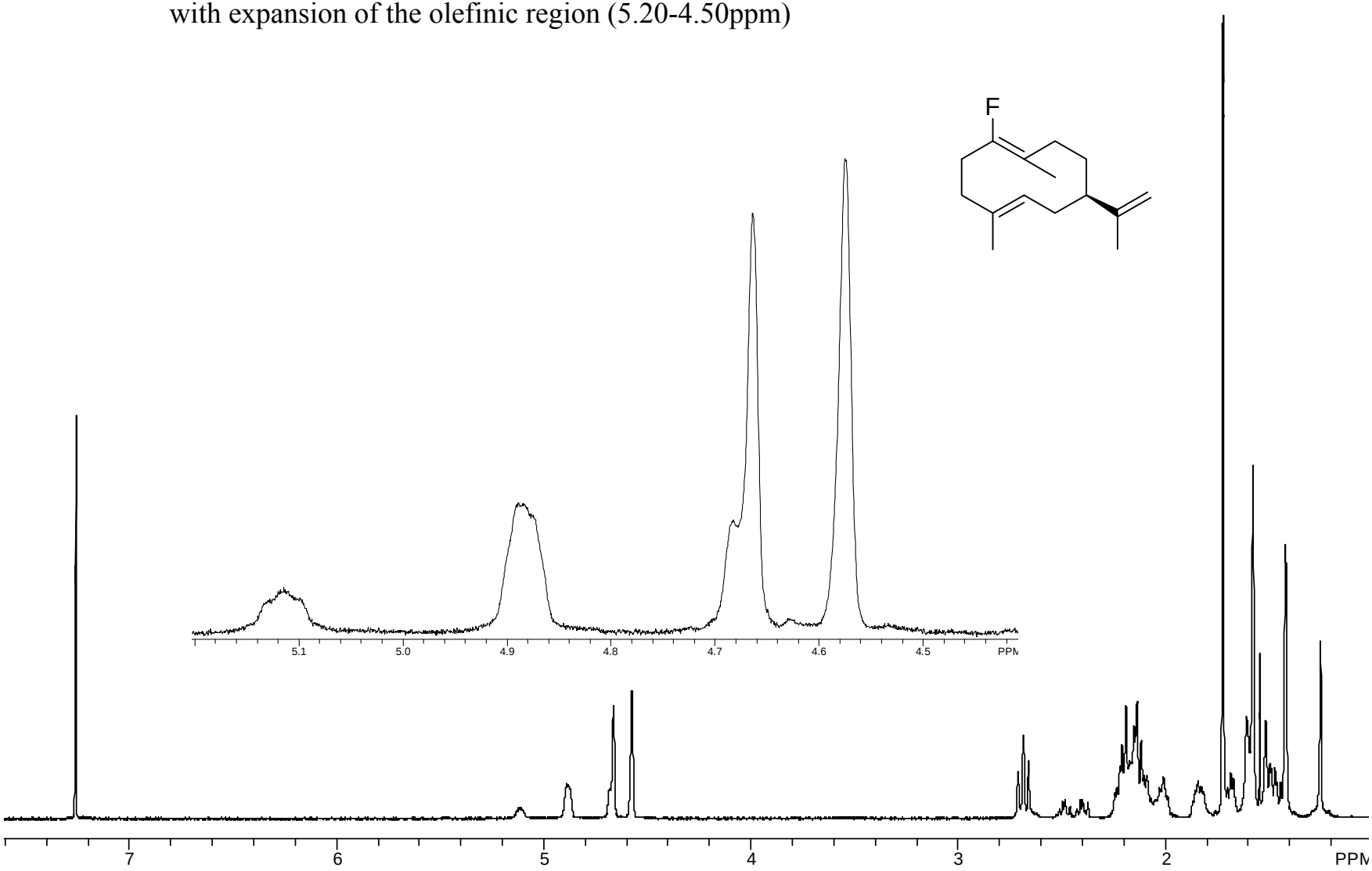
Figure 1. ^{1}H NMR spectrum (500 MHz, $CDCl_3$, 25 ^{o}C) of 1-fluorogermacrene A (**13**) with expansion of the olefinic region (5.20-4.50ppm)



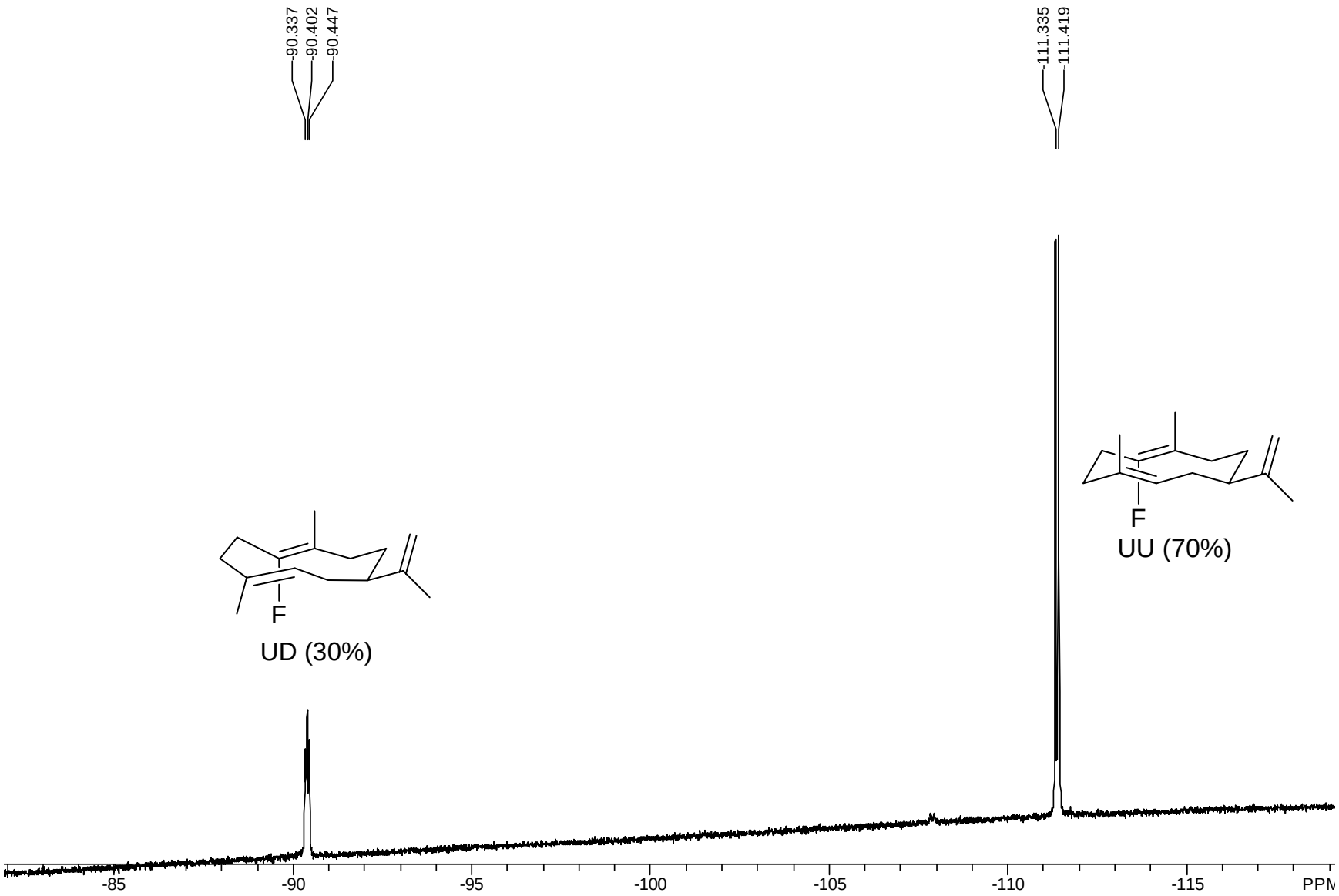


Figure 2. ^{19}F NMR spectrum (376 MHz, $CDCl_3$, 25 °C) of 1-fluorogermacrene A (**13**) as a 7:3 mixture of UU (up-up) and UD (up-down) conformers.

Figure 3. ^{1}H NMR spectrum (500 MHz, $CDCl_3$, 25 °C) of 1-fluoro-β-elemene (**14**) with expansion of the olefinic region (5.00-4.20 ppm)

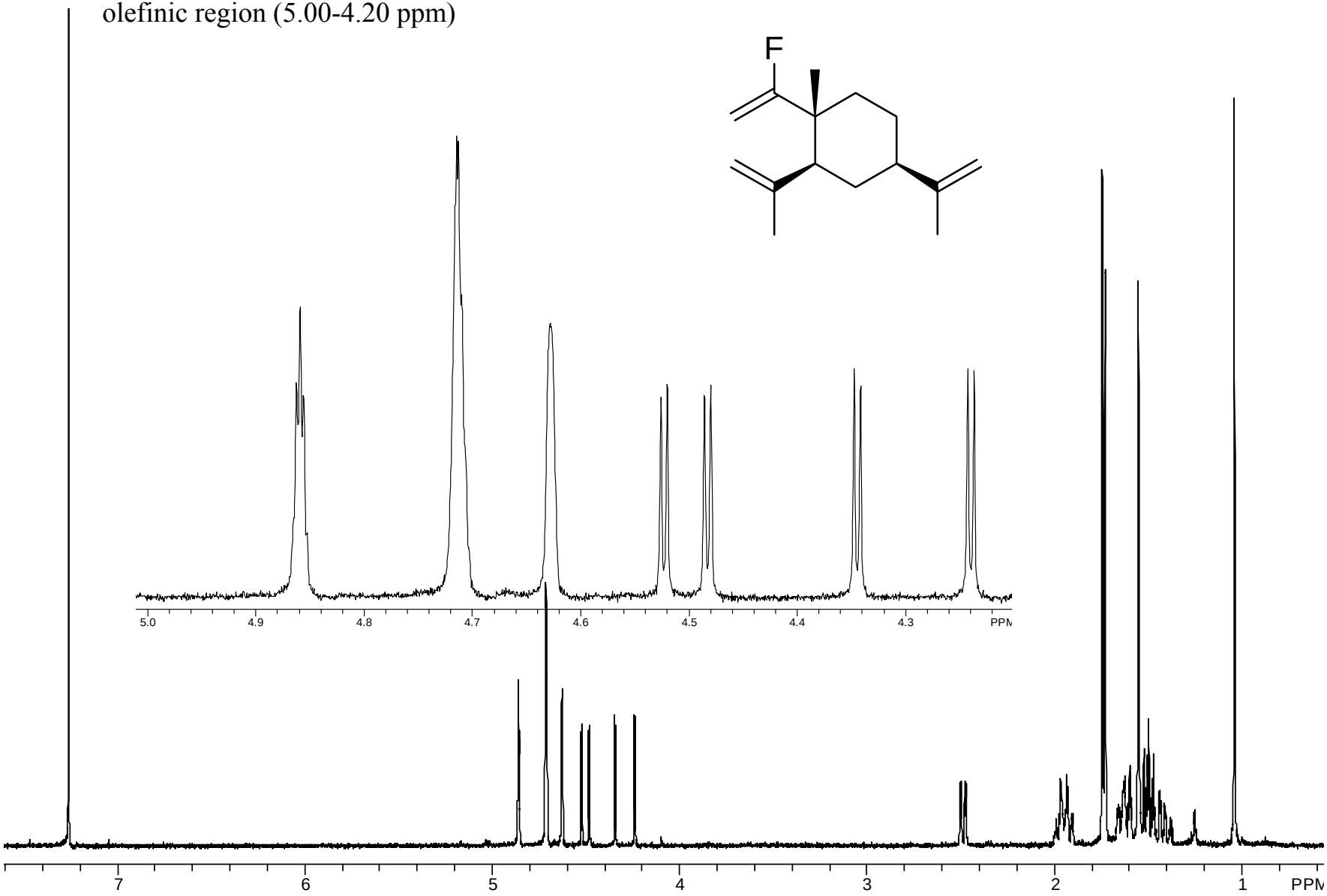


Figure 4. ^{1}H NMR spectrum (500 MHz, $CDCl_3$, 25 °C) of 1α-fluoro–β-selinene (**18b**) with expansion of the olefinic and fluorine region (4.80-4.20 ppm)

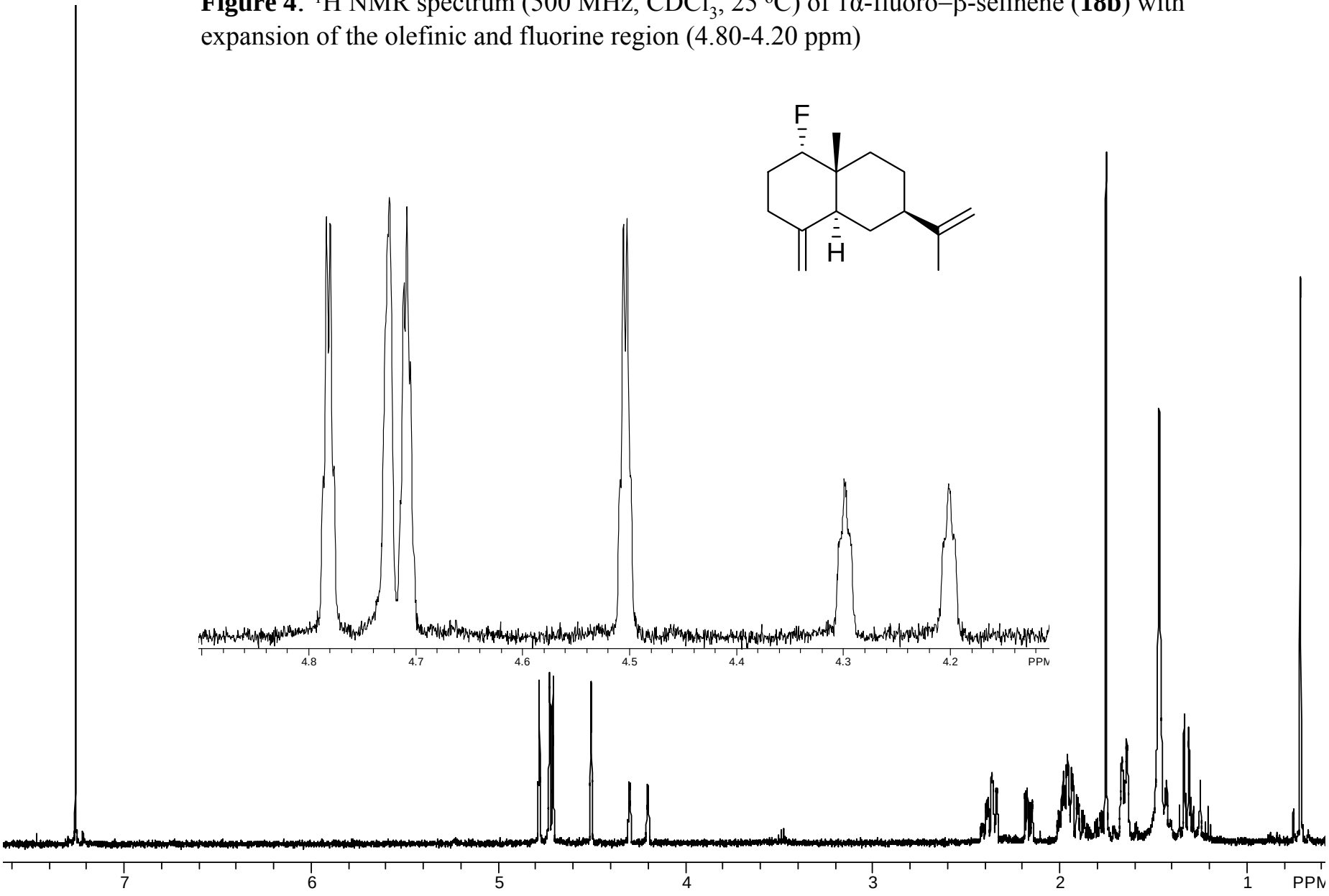


Figure 5. ^{1}H NMR (500 MHz, $CDCl_3$, 25° C of 1α-fluoro-α-selinene (**19b**) with expansion of the olefinic and fluorine region (5.40-4.20 ppm)

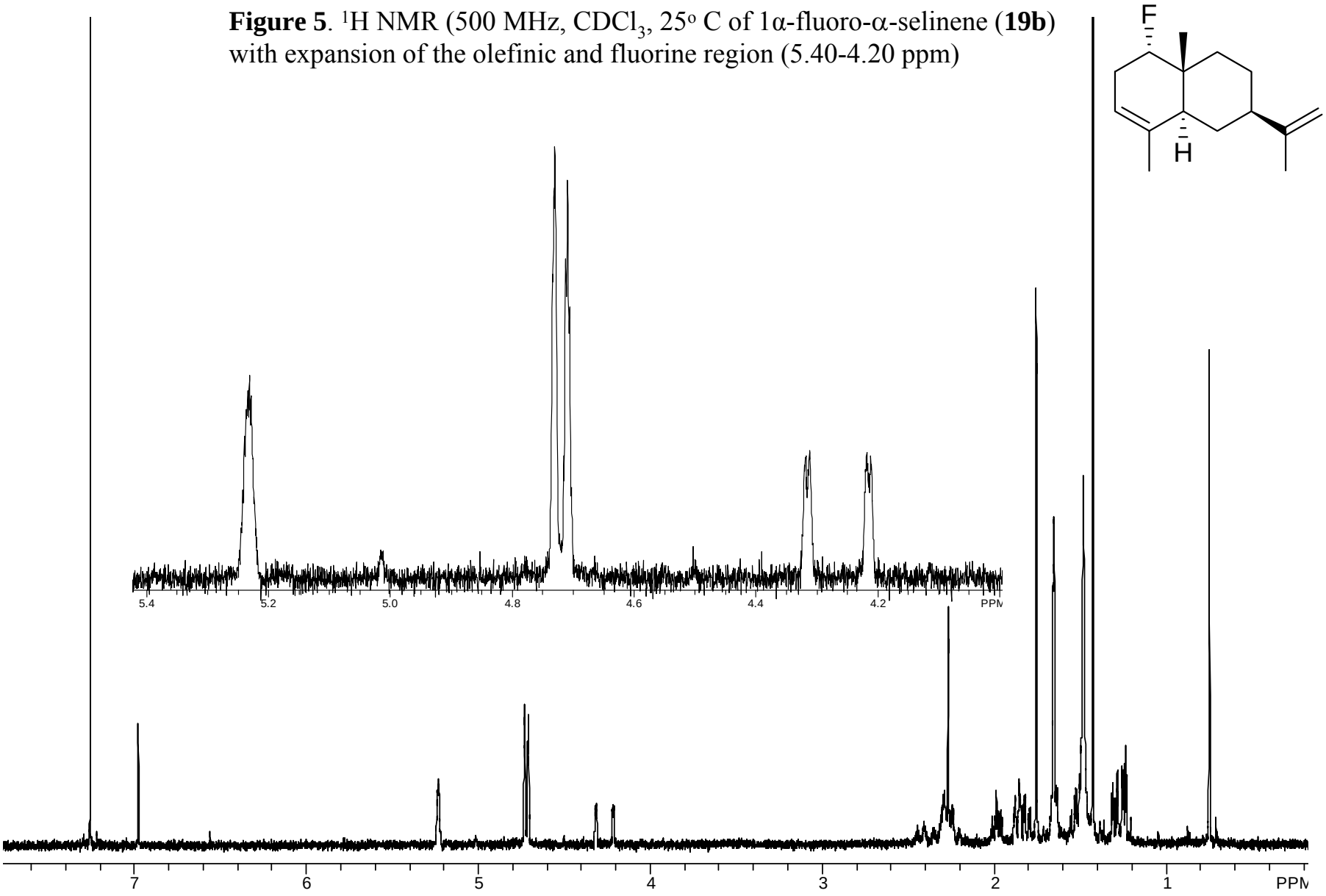
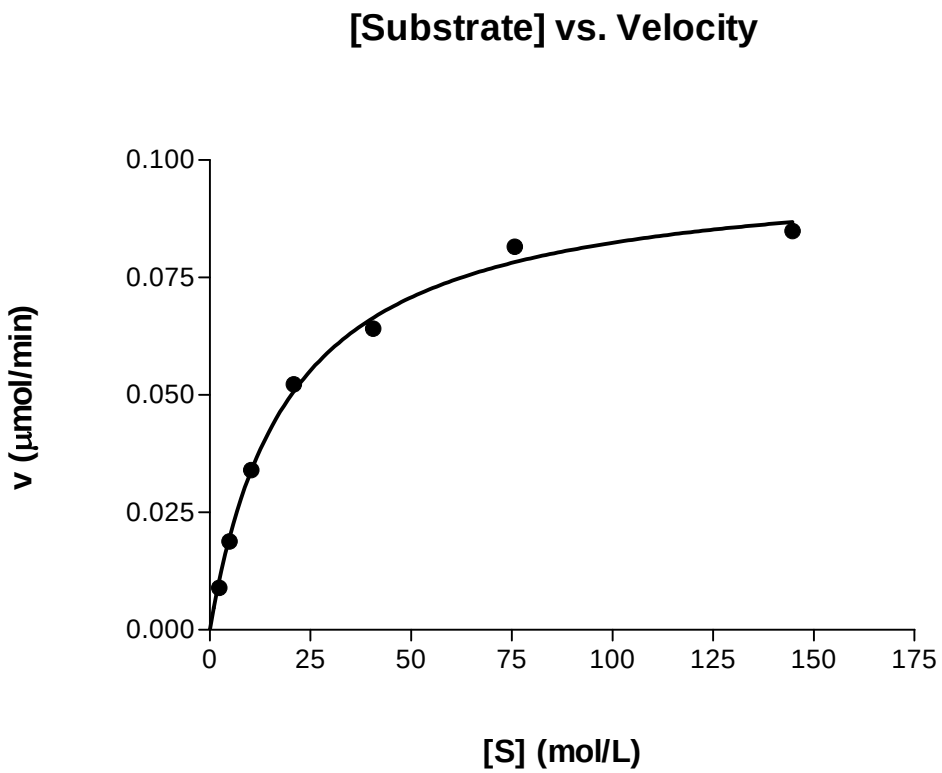


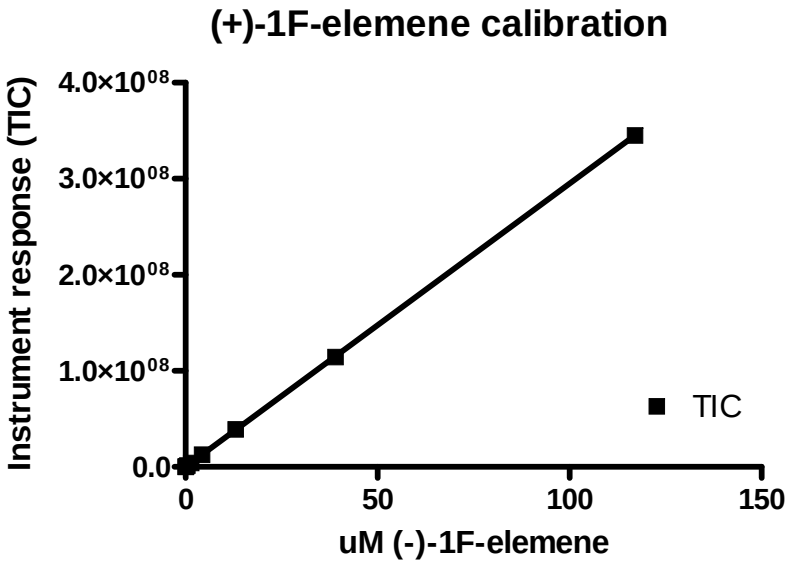
Figure 6. Michaelis-Menten Plot for the TEAS-catalyzed reaction using 6-fluorofarnesyl PP (**12**) as substrate.



Michaelis-Menten Kinetics

Best-fit values	
VMAX	0.09862
KM	19.67
Std. Error	
VMAX	0.00275
KM	1.717
95% Confidence Intervals	
VMAX	0.09155 to 0.1057
KM	15.26 to 24.09
Goodness of Fit	
Degrees of Freedom	5
R^2	0.9953

Figure 7. Calibration of (+)-1-fluoro-β-elemene (**14**)



Calibration statistics

Best-fit values	
Slope	2738000 ± 25960
Y-intercept	3308000 ± 3056000
X-intercept	-1.208
1/slope	3.652E-07
95% Confidence Intervals	
Slope	2679000 to 2798000
Y-intercept when X=0.0	-3740000 to 10360000
X-intercept when Y=0.0	-3.820 to 1.353
Goodness of Fit	
r^2	0.9993
Sy.x	8644000