Enzymatic Hydroxylation of an Unactivated Methylene C–H Bond Guided by Molecular Dynamics Simulations

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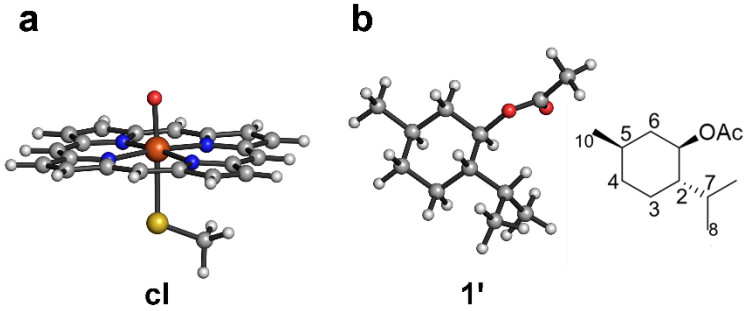
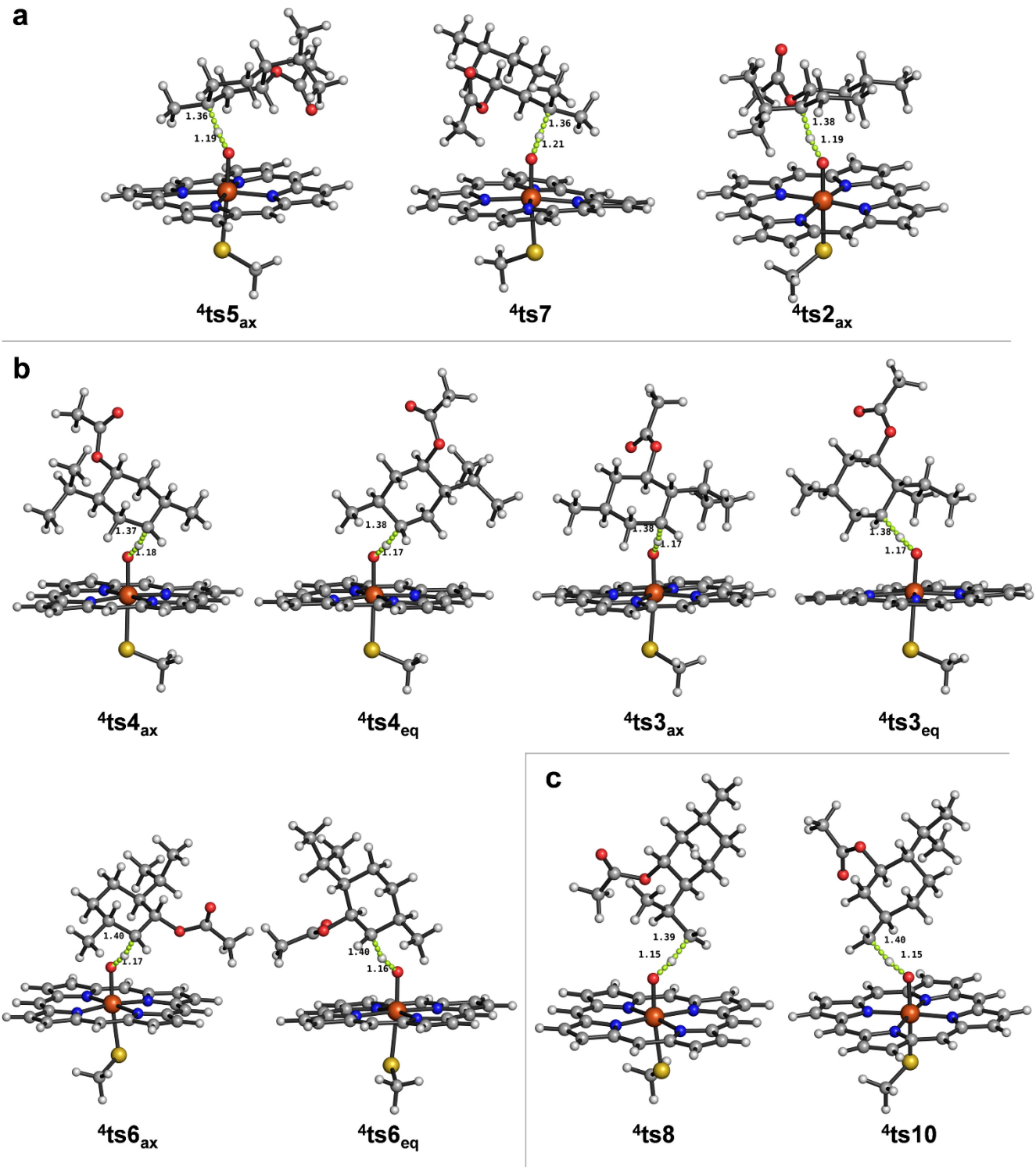
Supporting Information

Supplementary Figure S1. (a) QM modeling of the iron-oxo heme group. The P450 protein-bound porphyrin complex coordinated with iron, and containing an Fe=O moiety is known as compound I (**cI**). In our computational model for compound I substituents at the periphery of the porphyrin moiety were replaced with hydrogen atoms. Additionally, the axial Fe−SCys bond in compound I was modeled as a Fe−SCH_3 bond. For these heme systems, the spin-state energetics, and activation barriers are highly dependent upon both the level of theory employed, as well as the approximation chosen to model compound I *(1, 2)*. In agreement with previous work, our model of compound I shows almost degenerate doublet and quartet states, the sextet state being significantly higher in energy. The quartet C–H abstraction transition-states were calculated to be consistently lower in energy than the doublet spin states. Hence, all the reported activation free-energies ($\Delta G^{\ddagger}$) correspond to C–H abstraction on the quartet potential energy surface. **(b) Model menthol substrate.** An acetyl group was used to replace the different anchoring groups employed experimentally. The different C–H abstraction sites are labeled.



Supplementary Figure S2: QM transition-states for C–H abstraction of (a) primary, (b) secondary and (c) tertiary carbons from the model menthol substrate calculated at the B3LYP/6-311G(d,p)+LanL2DZ(Fe)//B3LYP/6-31G(d)+ LanL2DZ(Fe) in the quartet spin state.



Supplementary Table S1. Energies, enthalpies, free energies, and entropies of the QM structures calculated for the heme iron-catalyzed H-abstraction.[a]

Structure[a]	E_0[b] (Hartree)[f]	E_0[c] (Hartree)[f]	E_0[d] (Hartree)[f]	ZPE[e] (Hartree /particle)[f,g]	H correction[e] (Hartree /particle)[f,h]	S[e] (cal mol^{-1} K^{-1})[h]	G correction[e] (Hartree /particle)[f,h]	Lowest freq.[e] (cm^{-1})
cI	–1625.429856	-1625.588831	-1625.092550	0.317697	0.341284	158.5	0.265983	46.1
1'	–621.1914961	-621.2682711	-620.750481	0.326652	0.343590	128.1	0.282717	28.8
^{4}ts2	–2246.589006	-2246.848654	-2245.834605	0.638415	0.679460	241.7	0.564639	–1812.5
^{4}ts3$_{ax}$	–2246.591242	-2246.847873	-2245.833509	0.638093	0.679081	243.7	0.563277	–1725.3
^{4}ts3$_{eq}$	–2246.588585	-2246.841288	-2245.811992	0.637641	0.678977	245.9	0.562154	–1789.2
^{4}ts4$_{ax}$	–2246.593458	-2246.846869	-2245.830985	0.638267	0.679340	247.4	0.561769	–1717.3
^{4}ts4$_{eq}$	–2246.592847	-2246.843426	-2245.827675	0.638330	0.679468	246.8	0.562198	–1668.2
^{4}ts5	–2246.592876	-2246.848492	-2245.820121	0.637831	0.679099	244.1	0.563116	–1826.0
^{4}ts6$_{ax}$	–2246.588444	-2246.844157	-2245.828430	0.638336	0.679265	243.0	0.563797	–1757.8
^{4}ts6$_{eq}$	–2246.585981	-2246.840738	-2245.825359	0.638040	0.678981	242.6	0.563715	–1747.4
^{4}ts7	–2246.589755	-2246.849199	-2245.835225	0.638607	0.679370	240.4	0.565164	–1803.3
^{4}ts8	–2246.589756	-2246.849199	-2245.835225	0.638512	0.679251	245.6	0.562568	–1651.3
^{4}ts10	–2246.590098	-2246.838515	-2245.822824	0.638410	0.679327	247.6	0.561669	–1644.1

[a] Except for the model menthol substrate (**1'**, singlet), all species correspond to quartet spin states; all species are neutral.
[b] Energy obtained from single-point calculations with **B3LYP/6-311+G(d,p)+LANL2DZ(Fe)**.
[c] Energy obtained from single-point calculations with **B3LYP-D3/6-311+G(2d,p)+LANL2DZ(Fe)**.
[d] Energy obtained from single-point calculations with **M06/6-311+G(2d,p)+SDD(Fe)**.
[e] Vibrational, thermal and entropic corrections obtained from frequency calculations on geometries optimized at the B3LYP/6-31G(d) level.
[f] 1 Hartree = 627.51 kcal mol^{-1}.
[g] Zero-point energy obtained from vibrational frequencies.
[h] Thermal corrections at 298.15 K.

Supplementary Table S2. **Energies, enthalpies, free energies, and entropies of the QM structures calculated for the estimation of the BDE of various C–H bonds in menthol.**

Structure[a]	E_0[b] (Hartree)[d]	ZPE[c] (Hartree /particle)[d,e]	H correction[c] (Hartree /particle)[d,f]	S[c] (cal mol^{-1} K^{-1})[f]	G correction[c] (Hartree /particle)[d,f]	Lowest freq.[c] (cm^{-1})
1	–467.341795	0.288358	0.301842	107.8	0.250604	47.2
H	–0.499810	0.000000	0.002360	27.4	–0.010654	
2	–466.672915	0.273805	0.287692	111.8	0.234572	52.5
3	–466.674067	0.273394	0.287455	113.0	0.233766	45.9
4	–466.672024	0.274335	0.288074	112.8	0.234502	19.7
5	–466.668688	0.273950	0.287649	110.4	0.235206	38.3
6	–466.668687	0.273927	0.287624	110.1	0.235291	44.6
7	–466.669666	0.273630	0.287408	110.4	0.234969	51.8
8	–466.669668	0.273649	0.287412	110.1	0.235080	57.3
9	–466.671031	0.273337	0.287158	110.6	0.234617	45.7
10	–466.671040	0.273388	0.287187	110.4	0.234754	49.2
11	–466.667896	0.273072	0.286884	110.2	0.234510	63.6
12	–466.666649	0.273132	0.287008	111.1	0.234233	47.5

[a] Except for the model menthol substrate (singlet), all species correspond to doublet spin states; all species are neutral

[b] Energy obtained from single-point calculations with SCS-MP2/cc- pVTZ.

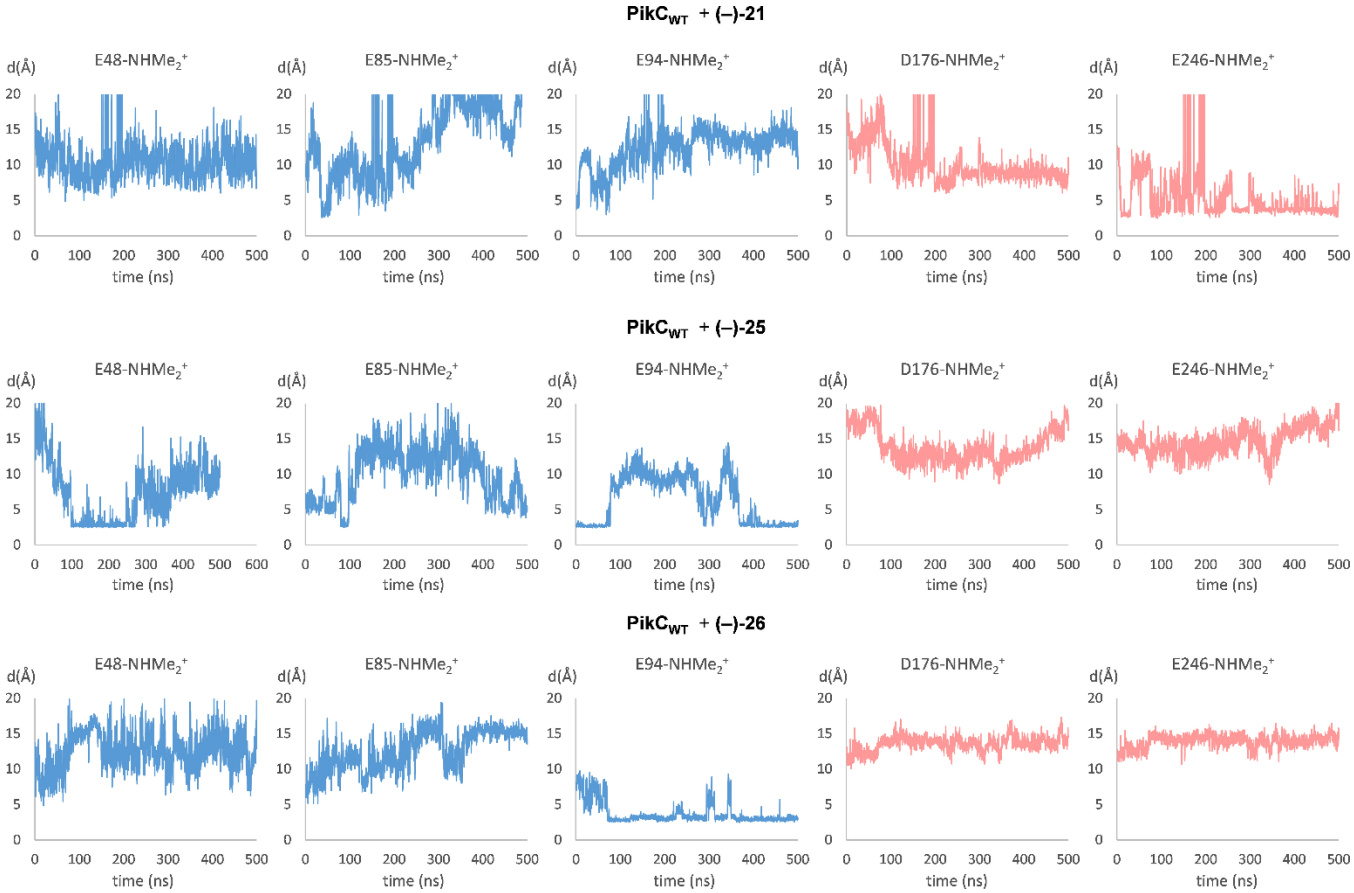
[c] Vibrational, thermal and entropic corrections obtained from frequency calculations on geometries optimized at the B3LYP/6-31G(d) level.

[d] 1 Hartree = 627.51 kcal mol^{-1}.

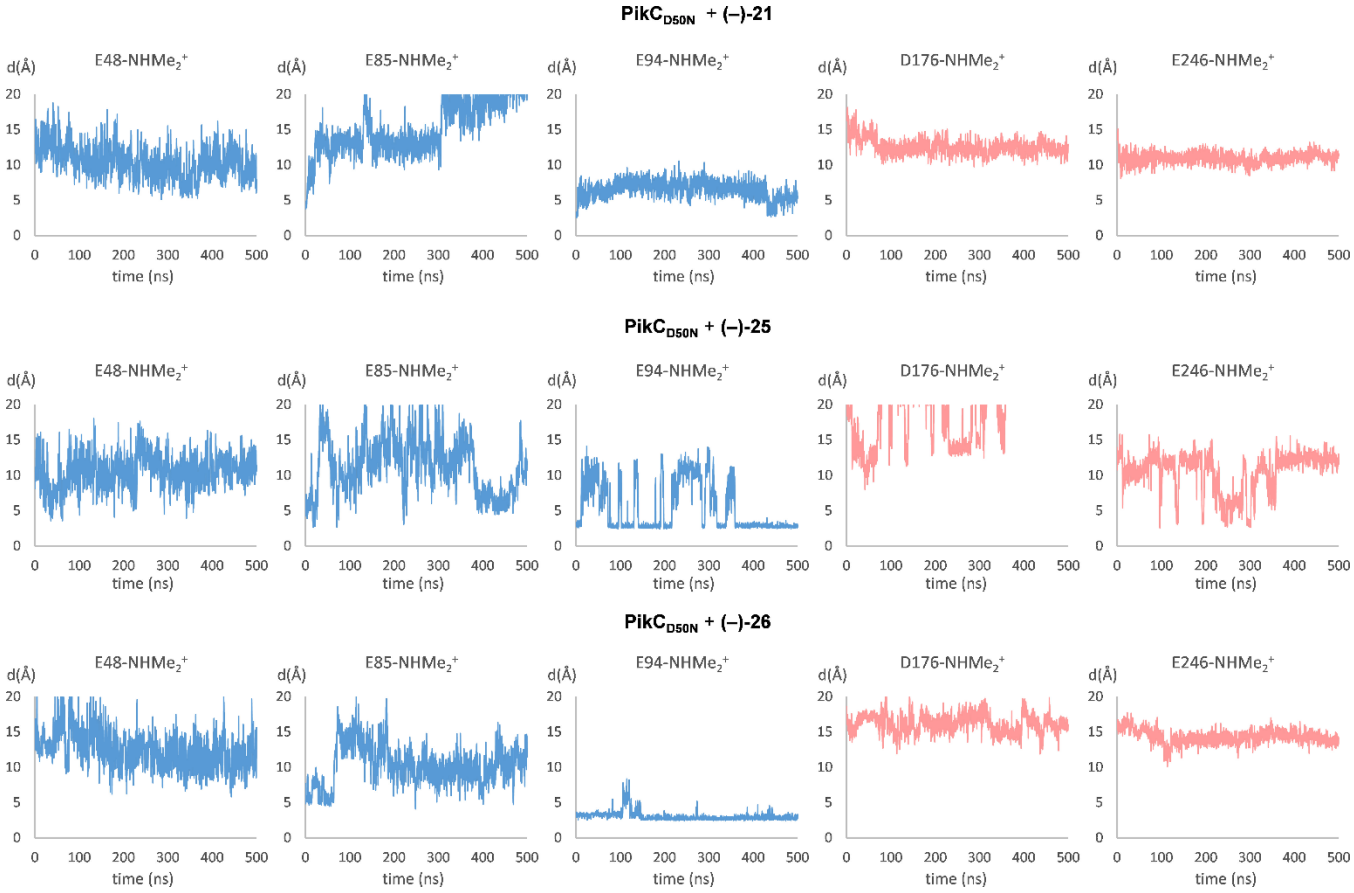
[e] Zero-point energy obtained from vibrational frequencies.

[f] Thermal corrections at 298.15 K.

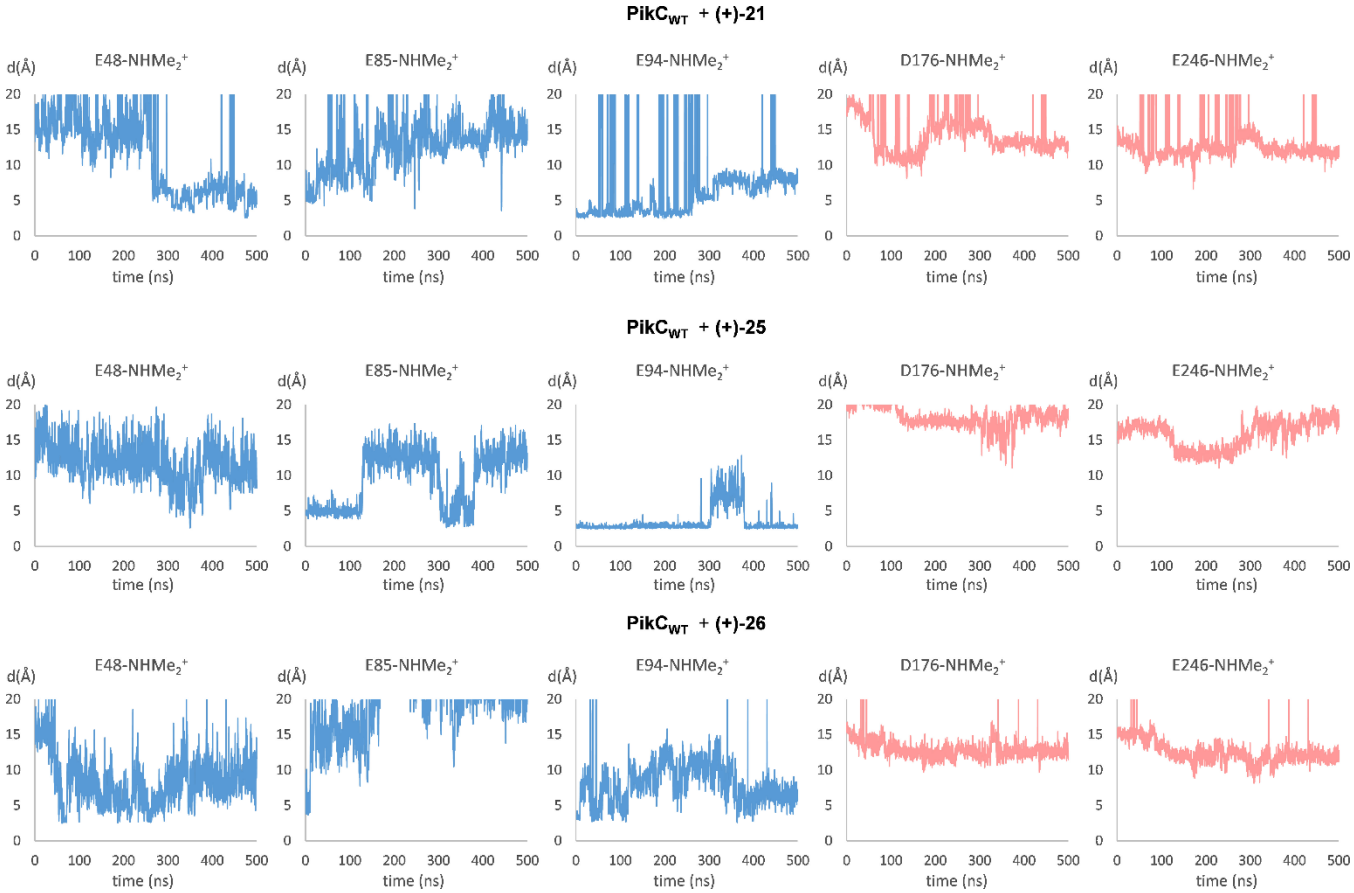
Supplementary Figure S3: Salt bridges between (–)-menthol derivatives 21, 25 and **26 in PikC$_{WT}$ monitored throughout MD simulations.** The distance (in angstroms) between the center of mass of the two carboxylate oxygen atoms of Asp/Glu residues and the nitrogen atom of the dimethylamonium atom of the anchoring group is represented.



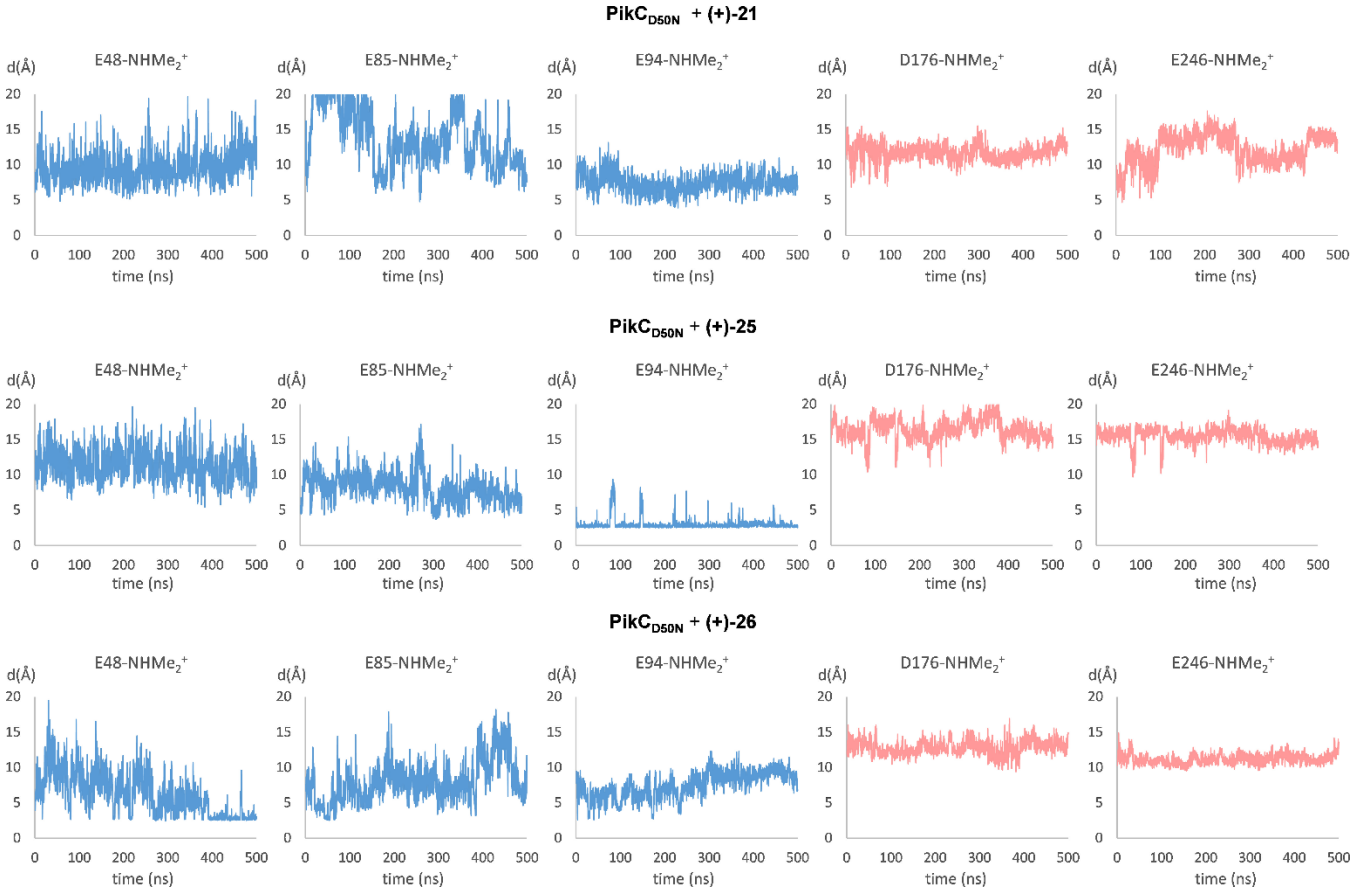
Supplementary Figure S4: Salt bridges between (–)-menthol derivatives 21, 25 and **26 in PikC$_{D50N}$ monitored throughout MD simulations.** The distance (in angstroms) between the center of mass of the two carboxylate oxygen atoms of Asp/Glu residues and the nitrogen atom of the dimethyl ammonium moiety of the anchoring group is represented.



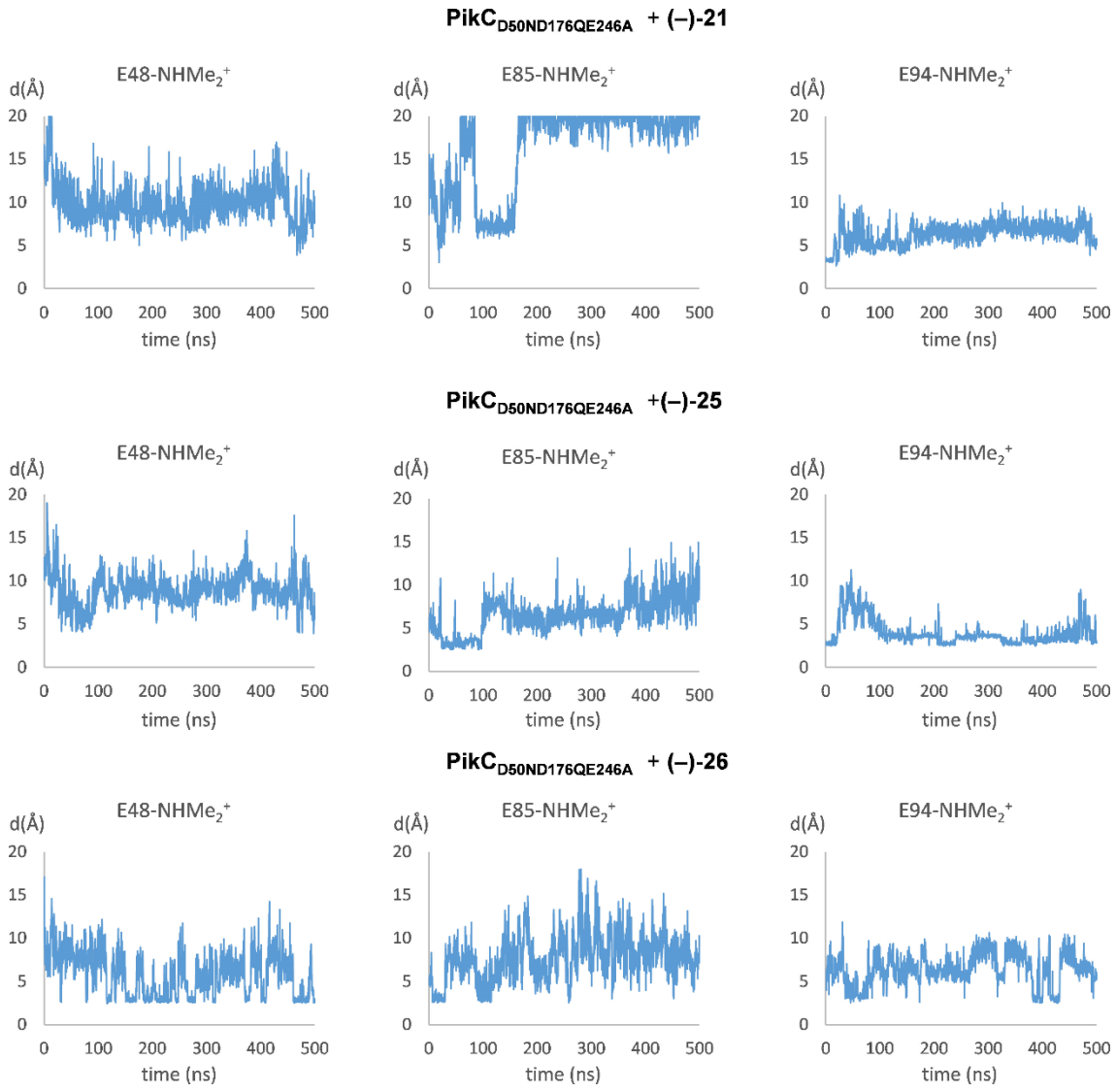
Supplementary Figure S5: Salt bridges between (+)-menthol derivatives 21, 25 and **26 in PikC$_{WT}$ monitored throughout MD simulations.** The distance (in angstroms) between the center of mass of the two carboxylate oxygen atoms of Asp/Glu residues and the nitrogen atom of the dimethyl ammonium moiety of the anchoring group is represented.



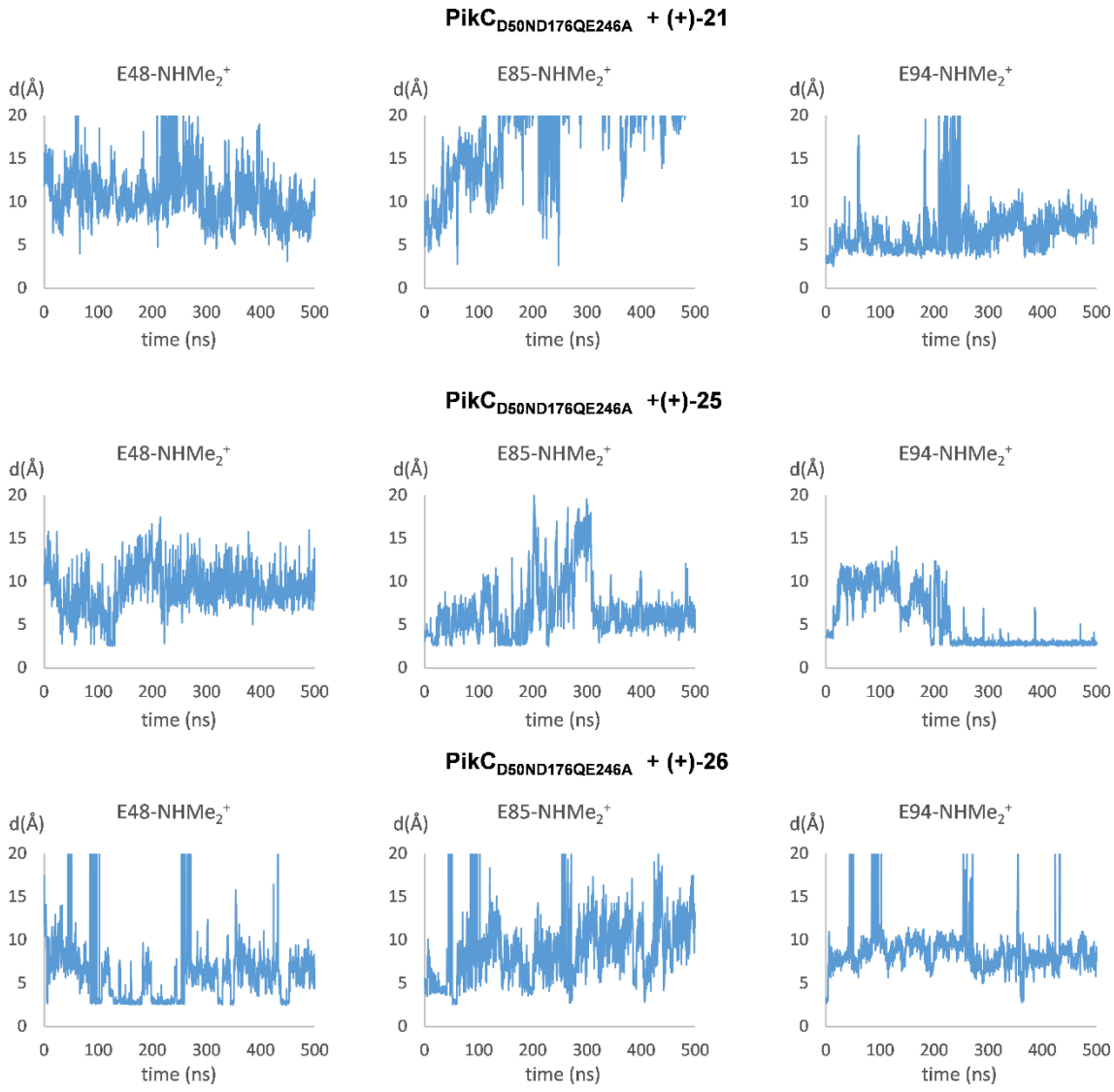
Supplementary Figure S6: Salt bridges between (+)-menthol derivatives 21, 25 and **26 in PikC$_{D50N}$ monitored throughout MD simulations.** The distance (in angstroms) between the center of mass of the two carboxylate oxygen atoms of Asp/Glu residues and the nitrogen atom of the dimethyl ammonium moiety of the anchoring group is represented.



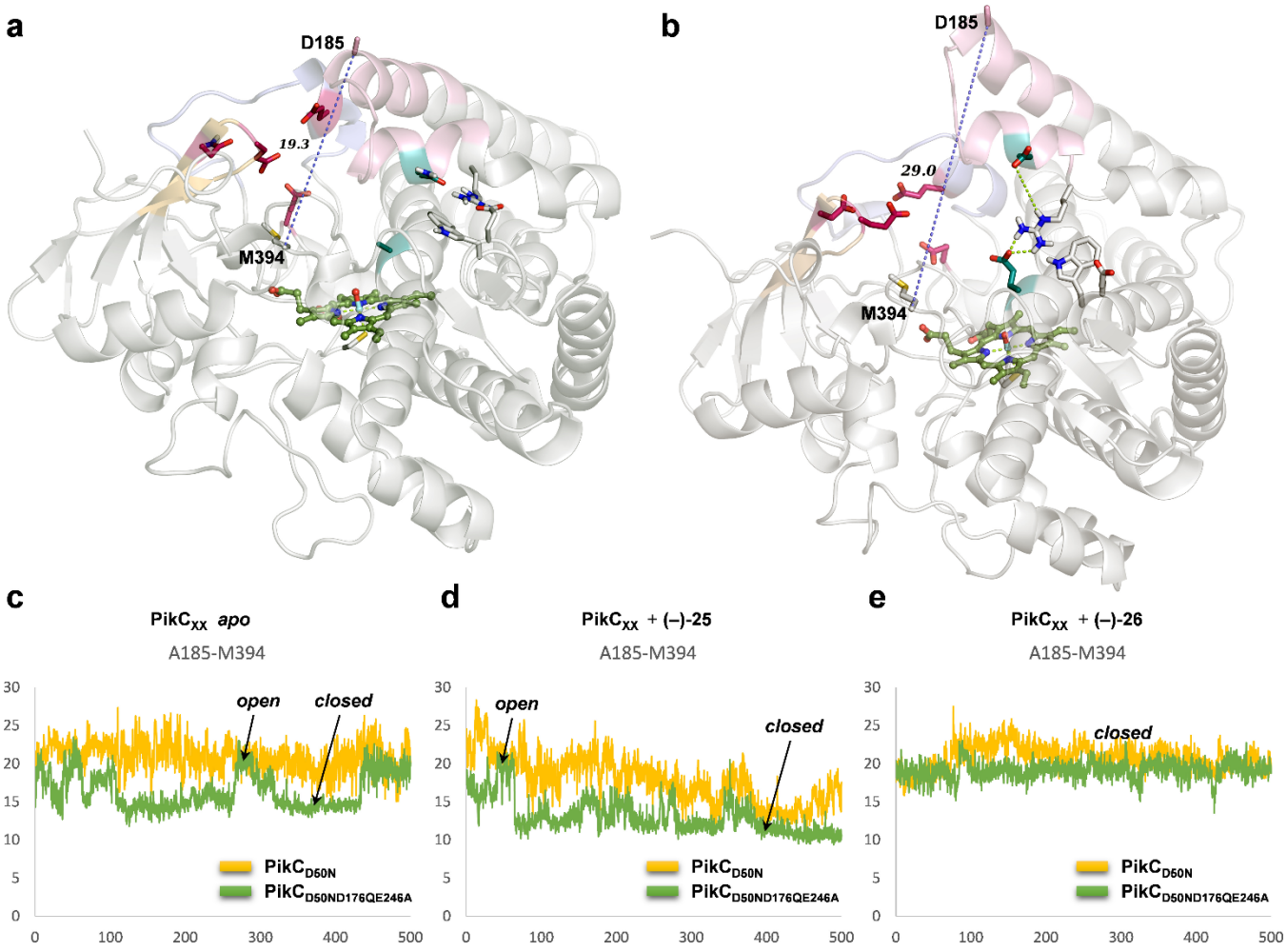
Supplementary Figure S7: Salt bridges between (–)-menthol derivatives 21, 25 and **26 in $PikC_{D50ND176QE246A}$ monitored throughout MD simulations.** The distance (in angstroms) between the center of mass of the two carboxylate oxygen atoms of Asp/Glu residues and the nitrogen atom of the dimethyl ammonium moiety of the anchoring group is represented.



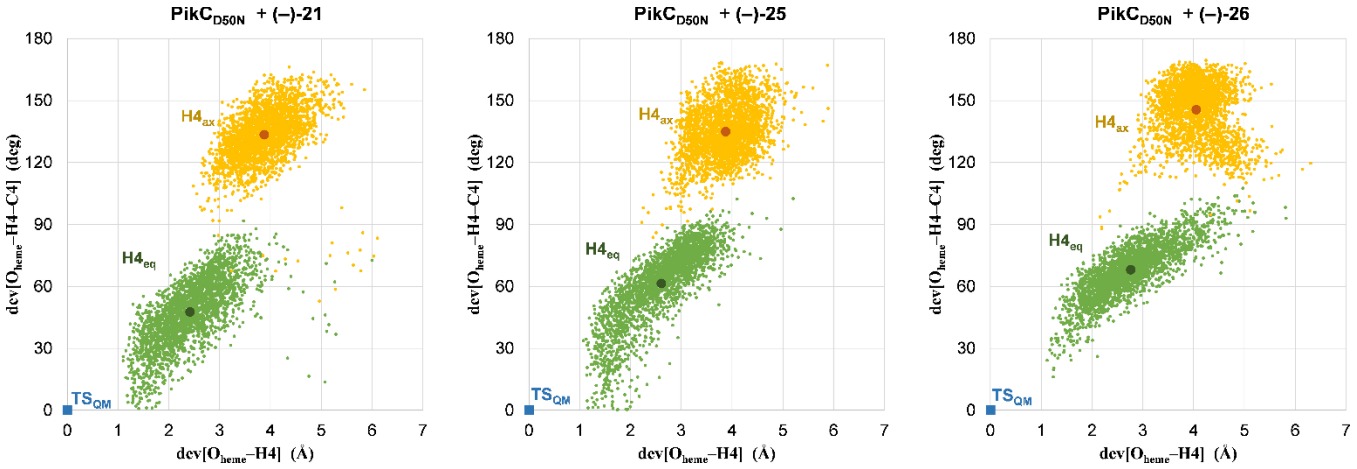
Supplementary Figure S8: Salt bridges between (+)-menthol derivatives 21, 25 and **26 in $PikC_{D50ND176QE246A}$ monitored throughout MD simulations.** The distance (in angstroms) between the center of mass of the two carboxylate oxygen atoms of Asp/Glu residues and the nitrogen atom of the dimethyl ammonium moiety of the anchoring group is represented.



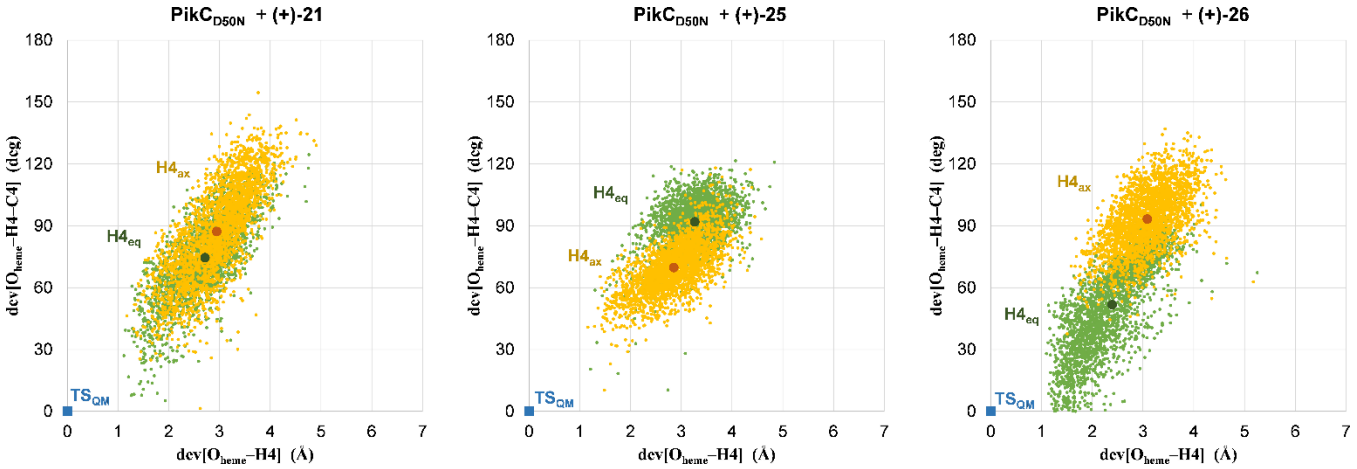
Supplementary Figure S9: Representative (a) open and (b) closed conformations in PikC derived from MD simulations. The distance (in angstroms) between the Cα of A185 and M394 was selected to represent the width of the active site channel and the deviation from the catalytically active closed conformation. (**c-e**) Evolution of the active site channel in PikC variants in the presence and absence of substrates. The closed conformation is more frequently sampled in the $PikC_{D50ND176QE246A}$ mutant even in the *apo* state.



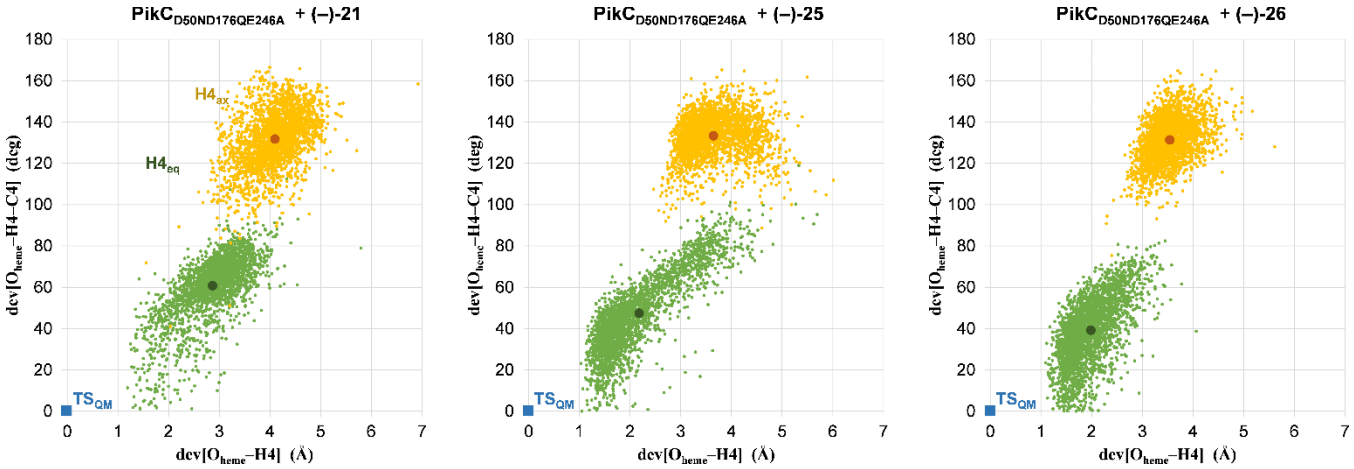
Supplementary Figure S10: Stereoselectivity in the C4–H abstraction catalyzed by $PikC_{D50N}$. Orientation of $H4_{eq}$ (in green) and $H4_{ax}$ (in orange) of (–)-menthol (substrates **21**, **25** and **26**) relative to the iron-heme oxo group in $PikC_{D50N}$, derived from 500 ns MD trajectories. Deviations of the distances (x axis) and angles (y axis) from the quantum mechanically optimized transition structure (in blue) with a hypothetical model heme catalyst are shown.



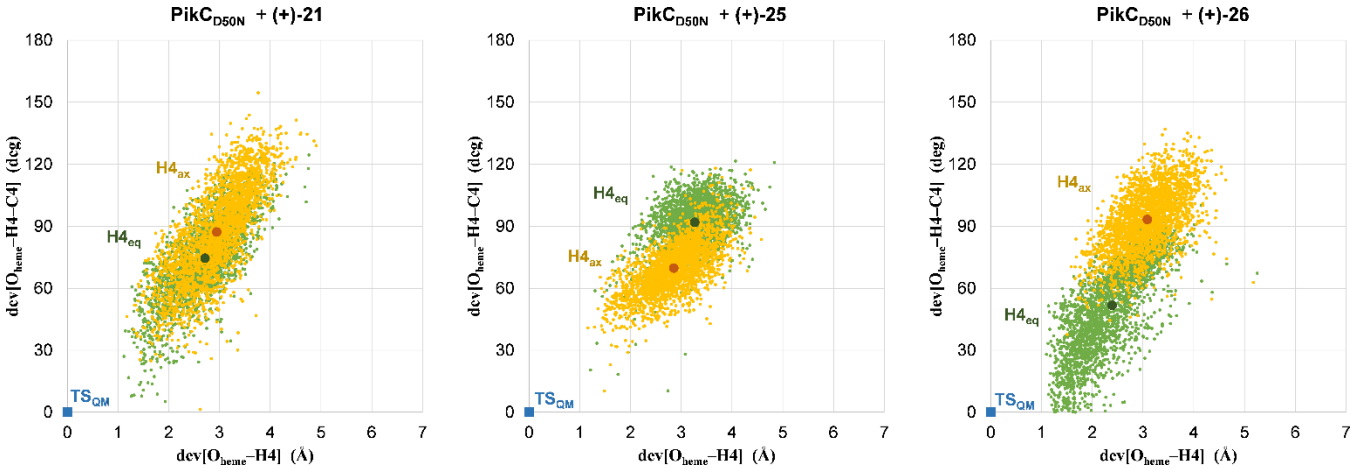
Supplementary Figure S11: Stereoselectivity in the C4–H abstraction catalyzed by $PikC_{D50N}$. Orientation of $H4_{eq}$ (in green) and $H4_{ax}$ (in orange) of (+)-menthol (substrates **21**, **25** and **26**) relative to the iron-heme oxo group in $PikC_{D50N}$, derived from 500 ns MD trajectories. Deviations of the distances (x axis) and angles (y axis) from the quantum mechanically optimized transition structure (in blue) with a hypothetical model heme catalyst are shown.



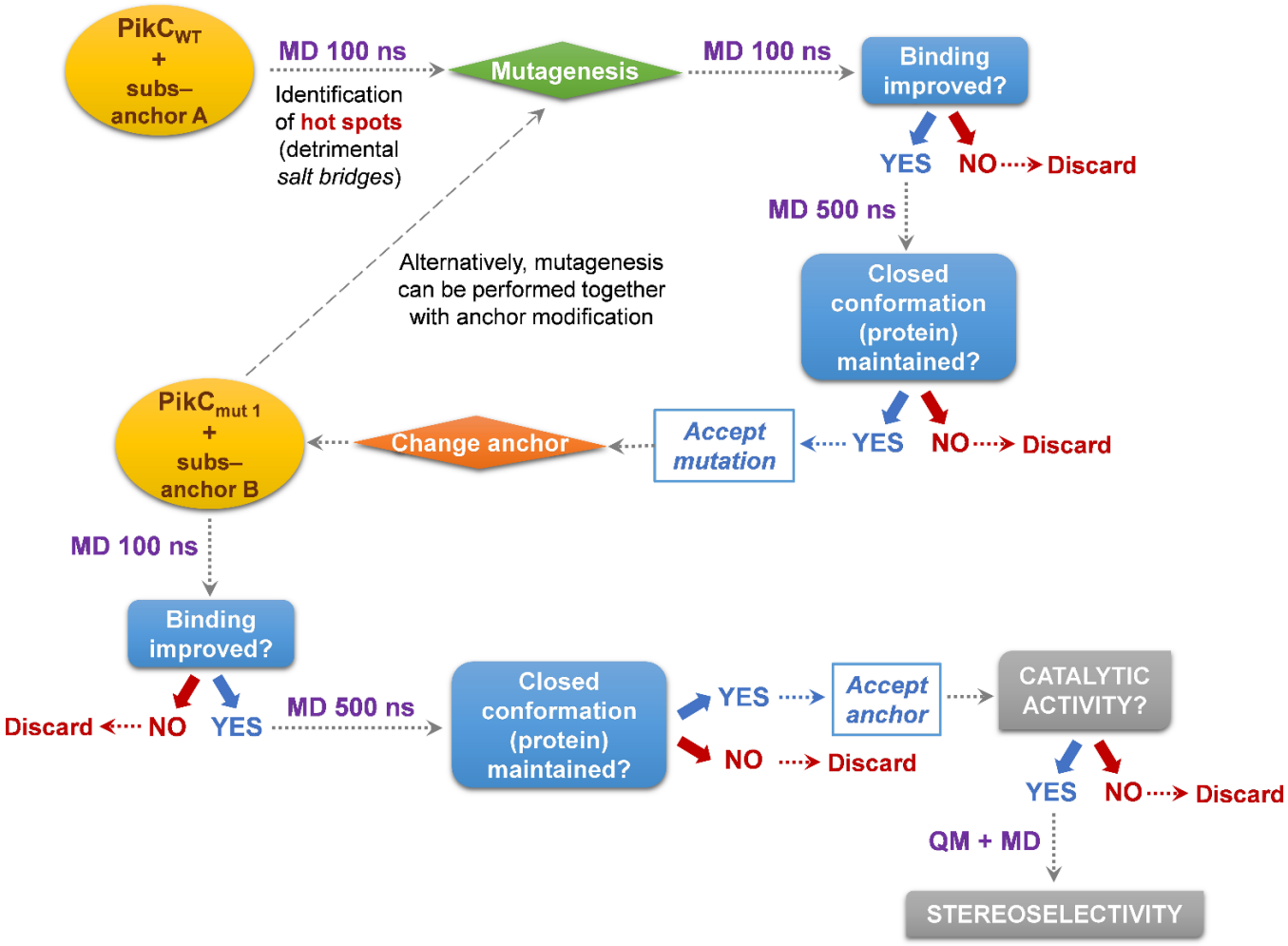
Supplementary Figure S12: Stereoselectivity in the C4–H abstraction catalyzed by PikC$_{D50ND176QE246A}$. Orientation of H4$_{eq}$ (in green) and H4$_{ax}$ (in orange) of (–)-menthol (substrates **21**, **25** and **26**) relative to the iron-heme oxo group in PikC$_{D50ND176QE246A}$, derived from 500 ns MD trajectories. Deviations of the distances (x axis) and angles (y axis) from the quantum mechanically optimized transition structure (in blue) with a hypothetical model heme catalyst are shown.



Supplementary Figure S13: Stereoselectivity in the C4–H abstraction catalyzed by PikC$_{D50ND176QE246A}$. Orientation of H4$_{eq}$ (in green) and H4$_{ax}$ (in orange) of (+)-menthol (substrates **21**, **25** and **26**) relative to the iron-heme oxo group in PikC$_{D50ND176QE246A}$, derived from 500 ns MD trajectories. Deviations of the distances (x axis) and angles (y axis) from the quantum mechanically optimized transition structure (in blue) with a hypothetical model heme catalyst are shown.



Supplementary Figure S14: Protocol for concurrent protein and substrate engineering guided by molecular dynamics (MD) simulations. The wild-type protein and a substrate candidate are subjected to MD in order to identify suitable positions for mutation. The beneficial or detrimental effect of these mutations in both substrate binding and protein structure is re-evaluated through MD. The improved mutants are tested against a modified version of the substrate. Only those candidates with enhanced substrate binding that preserve the protein closed conformation are subjected to experimental evaluation of their catalytic activity; in the positive cases, stereoselectivity is determined by combination of experimental and theoretical (QM, MD) techniques.

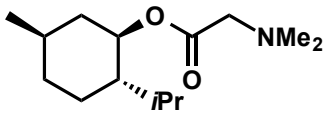


Part II: Substrate synthesis

General Protocols

All reagents were used as received unless otherwise noted. Solvents were purified under nitrogen using a solvent purification system (Innovative Technology, inc., Model # SPS-400-3 and PS-00-3. Reactions were monitored by thin layer chromatography using SiliCycle silica gel 60 F254 precoated plates (0.25 mm) which were visualized using UV light, *p*-anisaldehyde, $KMnO_4$, PMA or CAM stain. Flash column chromatography was performed using Kieselgel 60 (230□400 mesh) silica gel. Eluent mixtures are reported as v:v percentages of the minor constituent in the major constituent. All compounds purified by column chromatography were sufficiently pure for use in further experiments unless otherwise indicated. ^1H and ^{13}C spectra were obtained in $CDCl_3$ at rt (25 °C), unless otherwise noted, on Varian nmrs (500 MHz or 700 MHz), Varian MR400 or Varian Unity 500 MHz. Chemical shifts of ^1H NMR spectra were recorded in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.26 ppm). Chemical shifts of ^{13}C NMR spectra were recorded in ppm from the central peak of $CDCl_3$ (77.0 ppm) on the δ scale. Low resolution electrospray mass spectra were obtained on a Micromass LCT spectrometer and high resolution electrospray mass spectra were obtained on a Micromass AutoSpec Ultima spectrometer at the University of Michigan Mass Spectrometry Laboratory.

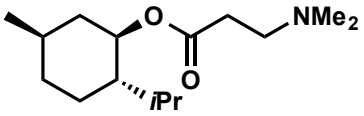
Synthesis of menthol substrates:



(–)-**21**

(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl dimethylglycinate, (–)-21

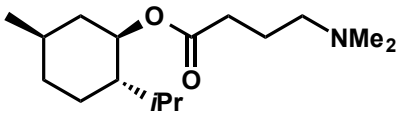
A flame-dried round-bottom flask was charged with (0.42 g) N,N-dimethylamino glycine•HCl (1.5 equiv), 0.62 g DCC (1.5 equiv), and 0.37 g DMAP (1.5 equiv). The contents of the flask were suspended in 20 mL of CH_2Cl_2 and allowed to stir for ~5 min. 0.47 mL of distilled triethylamine (1.7 equiv) was added dropwise and the reaction was allowed to stir for an additional 5 min before 0.31 g of (–)-menthol (1.0 equiv) was added. The reaction was stirred for 7 d and was then filtered through a cotton plug. The solvent was removed by under reduced pressure, and 1 M HCl was added to the resulting yellow residue until the pH was between 2 and 3. The aqueous solution was extracted 3x with 25 mL of 30% EtOAc/hexanes, and the remaining aqueous layer was adjusted to pH 8-9 with a saturated aqueous sodium bicarbonate solution. The solution was extracted 3x with 30 mL of CH_2Cl_2. The resulting organic layers were combined, dried over sodium sulfate, and filtered. The solvent was removed under reduced pressure to afford the crude material, which was purified by column chromatography (the column was packed with 5% EtOAc, 5% triethylamine, and 90% hexanes and run on a gradient of 30% EtOAc/hexanes to 7:2:1 EtOAc: MeCN: MeOH) to yield 0.28 g (57%) of the title compound as a clear oil. ^1H NMR (500 MHz, $CDCl_3$) δ 4.77 (td, J = 10.9, 4.4 Hz, 1H), 3.14 (s, 2H), 2.34 (s, 6H), 2.04 – 1.94 (m, 1H), 1.92 – 1.78 (m, 1H), 1.76 – 1.61 (m, 2H), 1.58 – 1.44 (m, 1H), 1.43 – 1.34 (m, 1H), 1.12 – 0.95 (m, 2H), 0.93 – 0.81 (m, 7H), 0.76 (d, J = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 74.4, 60.8, 46.9, 45.3, 40.9, 34.2, 31.4, 26.3, 23.3, 22.0, 20.7, 16.2; HRMS (ESI) *m/z* calculated for $[M+H]^+$ 242.2115, found 242.2112.



(–)-**22**

(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl 3-(dimethylamino)propanoate, (–)-22

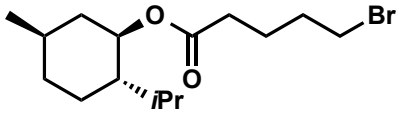
Following the procedure used to synthesize (1R,2S,5R)-2-isopropyl-5-methylcyclohexyl dimethylglycinate, (–)-menthol (0.31 g), 3-(N,N-dimethylamino)propionic acid•HCl (0.46 g), DCC (0.62 g), DMAP (0.37 g), and triethylamine (0.47 mL) was employed to give 0.096 g (19%) of the title compound as a clear oil after purification by column chromatography (SiO_2, packed with 5% EtOAc, 5% triethylamine, and 90% hexanes and run on a gradient of 30% EtOAc/hexanes to 7:2:1 EtOAc: MeCN: MeOH). ^{1}H NMR (401 MHz, $CDCl_3$) δ 4.69 (td, J = 10.9, 4.4 Hz, 1H), 2.83 – 2.70 (m, 2H), 2.67 – 2.51 (m, 2H), 2.36 (s, 6H), 2.03 – 1.92 (m, 1H), 1.92 – 1.78 (m, 1H), 1.75 – 1.61 (m, 2H), 1.56 – 1.42 (m, 1H), 1.42 – 1.30 (m, 1H), 1.13 – 0.93 (m, 2H), 0.93 – 0.79 (m, 8H), 0.75 (d, J = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.1, 74.2, 54.8, 47.0, 45.2, 40.9, 34.3, 33.3, 31.4, 26.2, 23.4, 22.0, 20.8, 16.3; HRMS (ESI) *m/z* calculated for $[M+H]^+$ 256.2271, found 256.2274.



(–)-**23**

(*1R*,*2S*,*5R*)-2-isopropyl-5-methylcyclohexyl 4-(dimethylamino)butanoate, (–)-23

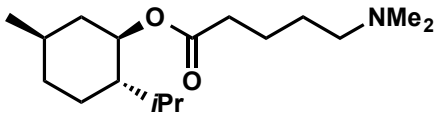
(–)-(*1R*,*2S*,*5R*)-menthol (200 mg, 1.28 mmol), 3-*N,N*-dimethylaminobutyric acid hydrochloride (325 mg, 1.92 mmol), triethylamine (304 μL, 2.18 mmol), DCC (400 mg, 1.92 mmol) and DMAP (237 mg, 1.92 mmol) were dissolved in 12.5 mL of CH_2Cl_2 and stirred at rt for 4 d, then the reaction mixture was filtered through cotton and evaporated to dryness in vacuo. The crude residue was transferred to a separatory funnel by washing the flask with 0.1 M HCl and 30% EtOAc in hexanes. The acidified aqueous phase was extracted three times with 30% EtOAc in hexanes. Then, the aqueous layer was basified with saturated aqueous $NaHCO_3$ solution until it reached a pH of approximately 8-9, measured by pH paper. The aqueous layer was extracted three times with EtOAc. The EtOAc layers were combined, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness in vacuo. The crude residue was chromatographed over silica gel (gradient from 30% EtOAc in hexanes to 20% MeCN, 10% MeOH in EtOAc) to yield 168 mg (49% yield) of the desired ester derivative as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.67 (ddd, J = 10.8, 10.8, 4.4 Hz, 2H), 2.35 – 2.24 (m, 4H), 2.22 (s, 6H), 2.06 – 1.93 (m, 1H), 1.91 – 1.74 (m, 3H), 1.72 – 1.62 (m, 2H), 1.54 – 1.42 (m, 1H), 1.41 – 1.31 (m, 1H), 1.11 – 0.80 (m, 9H), 0.75 (d, J = 6.8 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 173.1, 74.0, 58.9, 47.0, 45.4, 40.9, 34.2, 32.4, 31.3, 26.2, 23.4, 23.1, 22.0, 20.7, 16.3; IR (thin film, cm^{-1}) 2925, 2865, 2812, 2764, 1728, 1456; HRMS (ESI) *m/z* calculated for $[M+H]^+$ 270.2433, found 270.2431.



(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl 5-bromopentanoate, S1

Following the procedure used to synthesize (1R,2S,5R)-2-isopropyl-5-methylcyclohexyl 6-bromohexanoate, (–)-menthol (0.23 g), DCC (0.46 g), DMAP (0.027 g), 5-bromovaleric acid (0.45 g),

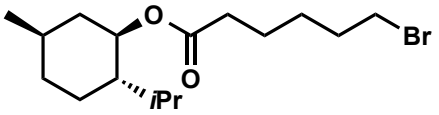
and CH_2Cl_2 (23 mL) were employed. 0.48 g of the title compound was obtained after purification by column chromatography (SiO_2, 5% EtOAc/hexanes to 10% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.68 (td, *J* = 10.9, 4.4 Hz, 1H), 3.42 (t, *J* = 6.6 Hz, 2H), 2.32 (t, *J* = 7.2 Hz, 2H), 2.02 – 1.94 (m, 1H), 1.94 – 1.73 (m, 4H), 1.72 – 1.63 (m, 2H), 1.56 – 1.42 (m, 1H), 1.41 – 1.32 (m, 1H), 1.12 – 0.93 (m, 2H), 0.93 – 0.80 (m, 7H), 0.75 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6, 74.2, 47.0, 40.9, 34.2, 33.7, 33.0, 32.0, 31.4, 26.3, 23.6, 23.5, 23.4, 22.0, 20.7, 16.3; HRMS (ESI) *m/z* calculated for $[M+Na]^+$ 341.1087, found 341.1082.



(–)-**24**

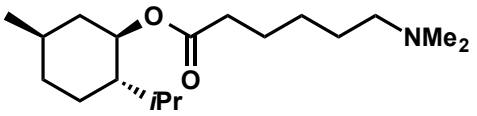
(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl 5-(dimethylamino)pentanoate, (–)-24

Following the procedure to synthesize (1R,2S,5R)-2-isopropyl-5-methylcyclohexyl 6-(dimethylamino)hexanoate, (1R,2S,5R)-2-isopropyl-5-methylcyclohexyl 5-bromopentanoate (0.16 g), 40% w/w aqueous dimethylamine (0.32 mL) and DMF (2.2 mL) was employed to give 0.12 g (88%) of the desired product after purification by column chromatography (SiO_2, 30% EtOAc/hexanes to 98%CH_2Cl_2, 2%, Et_3N). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.68 (td, *J* = 10.9, 4.4 Hz, 1H), 2.36 – 2.16 (m, 10H), 2.03 – 1.93 (m, 1H), 1.93 – 1.78 (m, 1H), 1.75 – 1.57 (m, 4H), 1.56 – 1.41 (m, 3H), 1.41 – 1.30 (m, 1H), 1.13 – 0.92 (m, 2H), 0.92 – 0.78 (m, 7H), 0.75 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.1, 73.9, 59.4, 47.0, 45.5, 41.0, 34.6, 34.3, 31.4, 27.2, 26.3, 23.4, 23.0, 22.0, 20.8, 16.3; HRMS (ESI) *m/z* calculated for $[M+H]^+$ 284.2584, found 284.2595.



(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl 6-bromohexanoate, S2

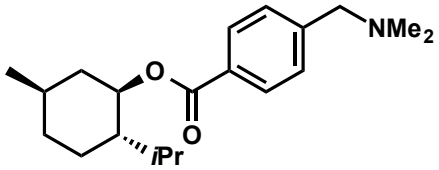
A flame-dried round-bottom flask was charged with 0.62 g of dicyclohexylcarbodiimide (DCC) (3.0 mmol), 0.037 g 4-dimethylaminopyridine (DMAP) (0.30 mmol), and 0.58 g of 6-bromohexanoic acid (3.0 equiv). The contents of the flask were suspended in 21 mL of CH_2Cl_2, and allowed to stir for 10 min. Then, 0.31 g of (–)-menthol (2.0 mmol) was added and the reaction was allowed to stir until all of the (–)-menthol was consumed as judged by TLC. The reaction mixture was filtered through a cotton plug and the solvent was removed under reduced pressure to afford a white residue. The crude material was purified by column chromatography (SiO_2, gradient 5% EtOAc/hexanes to 10% EtOAc/hexanes) to yield 0.66 g (99%) of the title compound as a clear oil. ^{1}H NMR (401 MHz, $CDCl_3$) δ 4.68 (td, *J* = 10.9, 4.4 Hz, 1H), 3.40 (t, *J* = 6.8 Hz, 2H), 2.30 (t, *J* = 7.4 Hz, 2H), 2.02 – 1.93 (m, 1H), 1.93 – 1.78 (m, 3H), 1.75 – 1.59 (m, 4H), 1.55 – 1.42 (m, 3H), 1.41 – 1.31 (m, 1H), 1.12 – 0.93 (m, 2H), 0.93 – 0.79 (m, 6H), 0.75 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.0, 74.0, 47.0, 40.9, 34.4, 34.2, 33.5, 32.4, 31.4, 27.6, 26.3, 24.2, 23.4, 22.0, 20.8, 16.3; HRMS (ESI) *m/z* calculated for $[M+Na]^+$ 355.1243, found 355.1240.



(–)-**25**

(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl 6-(dimethylamino)hexanoate, (–)-25

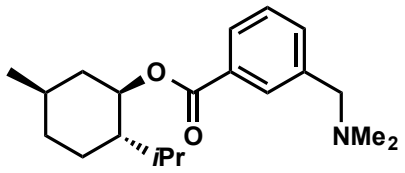
A flame-dried round-bottom flask was charged with 0.16 g of (1R,2S,5R)-2-isopropyl-5-methylcyclohexyl 6-bromohexanoate (0.47 mmol). (1R,2S,5R)-2-isopropyl-5-methylcyclohexyl 6-bromohexanoate was suspended in 2.2 mL DMF and allowed to stir for ~5 min, followed by addition of 0.31 mL of 40% w/w aqueous dimethylamine (2.5 mmol). The mixture was stirred until all of the starting material was consumed as monitored by TLC analysis. The reaction was quenched with 6 mL of saturated sodium bicarbonate solution and extracted with EtOAc (3 x 15 mL). The resulting organic layers were combined, dried with sodium sulfate, filtered and concentrated under reduced pressure. The resulting clear oil was chromatographed (SiO_2, 30% EtOAc/Hex to 99% CH_2Cl_2, 1% Et_3N) to yield 0.13 g (90%) of the title compound as a clear oil. ^{1}H NMR (401 MHz, $CDCl_3$) δ 4.67 (td, *J* = 10.9, 4.4 Hz, 1H), 2.34 – 2.15 (m, 10H), 2.02 – 1.93 (m, 1H), 1.93 – 1.77 (m, 1H), 1.75 – 1.58 (m, 4H), 1.48 (quint, *J* = 7.8 Hz, 3H), 1.41 – 1.26 (m, 3H), 1.15 – 0.93 (m, 2H), 0.93 – 0.79 (m, 7H), 0.75 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3, 73.9, 59.6, 47.0, 45.5, 40.9, 34.7, 34.3, 31.4, 27.4, 27.0, 26.2, 23.4, 22.0, 20.8, 16.3; HRMS (ESI) *m/z* calculated for $[M+H]^+$ 298.2741, found 298.2747.



(–)-**26**

(*1R,2S,5R*)-2-isopropyl-5-methylcyclohexyl 4-((dimethylamino)methyl)benzoate, (–)-26

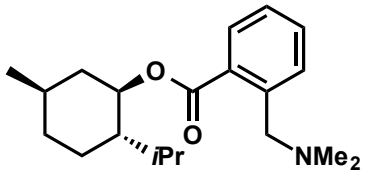
Following the procedure used to synthesize (1R,2S,5R)-2-isopropyl-5-methylcyclohexyl dimethylglycinate, (-)-(*1R,2S,5R*)-menthol (100 mg, 0.640 mmol), 172 mg of 4-((dimethylamino)methyl)benzoic acid (0.960 mmol, 1.50 equiv), 200 mg of dicyclohexylcarbodiimide (0.960 mmol, 1.5 equiv) and 118 mg 4-dimethylaminopyridine (0.960 mmol, 1.5 equiv) were employed to yield 166 mg (82%) of the desired ester derivative as a colorless oil after chromatography over silica gel (gradient from 30% EtOAc in hexanes to 100% EtOAc). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 4.93 (ddd, *J* = 11.2, 11.2, 4.2 Hz, 1H), 3.47 (s, 2H), 2.25 (s, 6H), 2.12 (d, *J* = 11.9 Hz, 1H), 1.96 (sept-d, *J* = 7.0, 2.8 Hz, 1H), 1.75 – 1.70 (m, 2H), 1.61 – 1.53 (m, 2H), 1.14 (td, *J* = 13.7, 3.2 Hz, 1H), 1.09 (t, *J* = 12.0 Hz, 1H), 0.97 – 0.88 (m, 7H), 0.79 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0, 144.1, 129.6, 129.5, 128.8, 74.7, 64.0, 47.2, 45.3, 41.0, 34.3, 31.4, 26.5, 23.6, 22.0, 20.8, 16.5; IR (thin film, cm^{-1}) 2923, 2856, 2767, 1712, 1611, 1454; HRMS (ESI) *m/z* calculated for $[M+H]^+$ 318.2433, found 318.2420.



(–)-**27**

(*1R*,*2S*,*5R*)-2-isopropyl-5-methylcyclohexyl 3-((dimethylamino)methyl)benzoate, (–)-27

Following the procedure used to synthesize (1R,2S,5R)-2-isopropyl-5-methylcyclohexyl dimethylglycinate, (-)-(*1R*,*2S*,*5R*)-menthol (160 mg, 1.02 mmol), 154 mg of 3-((dimethylamino)methyl)benzoic acid (1.54 mmol, 1.50 equiv), 320 mg of dicyclohexylcarbodiimide (1.54 mmol, 1.50 equiv) and 190 mg 4-dimethylaminopyridine (1.54 mmol, 1.50 equiv) to yield 105 mg (33%) of the desired ester derivative as a colorless oil after chromatography over silica gel (gradient from 30% EtOAc in hexanes to 100% EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 – 7.92 (m, 2H), 7.52 (d, *J* = 7.5 Hz, 1H), 7.40 (d, *J* = 7.5 Hz, 2H), 4.94 (ddd, *J* = 11.0, 11.0, 4.5 Hz, 1H), 3.49 (d, *J* = 13.0 Hz, 1H), 3.45 (d, *J* = 13.0 Hz, 1H), 2.25 (s, 6H), 2.11 (dtd, *J* = 11.5, 3.5, 2.0 Hz, 1H), 1.96 (sept-d, *J* = 7.0, 2.5 Hz, 1H), 1.73 – 1.69 (m, 2H), 1.63 – 1.52 (m, 2H), 1.18 – 1.06 (m, 2H), 0.92 (t, *J* = 6.5 Hz, 6H), 0.79 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 166.0, 139.2, 133.3, 130.8, 130.0, 128.3, 128.2, 74.7, 63.9, 47.1, 45.2, 40.9, 34.2, 31.4, 26.4, 23.6, 22.0, 20.7, 16.4; IR (thin film, cm^{-1}) 2949, 2864, 2815, 2767, 1711, 1455, 1360; HRMS (ESI) *m/z* calculated for $[M+H]^+$ 318.2433, found 318.2440.



(–)-**28**

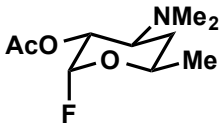
(*1R*,*2S*,*5R*)-2-isopropyl-5-methylcyclohexyl 2-((dimethylamino)methyl)benzoate, (–)-28

2-((dimethylamino)methyl)benzoic acid (57 mg, 0.32 mmol) was dissolved in 1 mL CH_2Cl_2. To this mixture was added one drop of *N,N*-dimethylformamide followed by oxalyl chloride (33 µL, 0.38 mmol). The reaction was allowed to stir at rt for 1.5 h before the solvent was evaporated and the crude acid chloride was resuspended in 1 mL CH_2Cl_2. The acyl chloride suspension was added dropwise to an ice cooled solution of (–)-(*1R*,*2S*,*5R*)-menthol (100 mg, 0.64 mmol), DMAP (0.16 mmol, 20 mg) and triethylamine (180 µL, 1.3 mmol) in 3.4 mL CH_2Cl_2. The reaction mixture was allowed to stir as it was warmed to rt. After 12 h, the reaction was quenched by the addition of saturated sodium bicarbonate solution. The aqueous phase was washed with EtOAc (3x), dried over sodium sulfate, filtered and concentrated. The crude residue was transferred to a separatory funnel by washing the flask with 0.1 M HCl and 30% EtOAc in hexanes. The acidified aqueous phase was extracted three times with 30% EtOAc in hexanes. Then, the aqueous layer was basified with saturated aqueous $NaHCO_3$ solution until it reached a pH of approximately 8-9, measured by pH paper. The basic aqueous layer was extracted three times with EtOAc. The EtOAc organic layers were combined, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness in vacuo. The crude residue was chromatographed over silica gel (gradient from 5% EtOAc in hexanes to 100% EtOAc) to yield 44 mg (44%) of the desired ester as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.0 Hz, 1H), 7.48 (d, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1 H), 7.29 (t, *J* = 7.5 Hz, 1H), 4.91 (ddd, *J* = 11.0, 11.0, 4.5 Hz, 1 H), 3.80 (d, *J* = 14.0 Hz, 1H), 3.65 (d, *J* = 13.5 Hz, 1H), 2.22 (s, 6H), 2.17 (d, *J* = 11.5 Hz, 1H), 2.02 (sept-d, *J* = 7.0, 2.5 Hz, 1H), 1.77 – 1.69 (m, 2H), 1.62 – 1.47 (m, 2H), 1.18 – 1.05 (m, 2H), 0.98 – 0.86 (m, 7H), 0.82 (d, 6.5 Hz, 3H);

^{13}C NMR (175 MHz, $CDCl_3$) δ 167.8, 139.9, 132.0, 130.8, 130.0, 129.3, 126.6, 76.8, 74.6, 61.2, 47.2, 45.2, 40.9, 34.2, 31.4, 26.2, 23.4, 22.1, 20.8, 16.3; IR (thin film, cm^{-1}) 2951, 2868, 2815, 2765, 1715, 1454, 1366; HRMS (ESI) *m/z* calculated for $[M+H]^+$ 318.2433, found 318.2436.

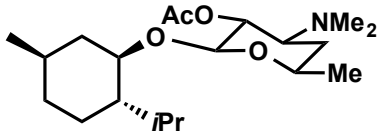
(3R,4S,6R)-4-(dimethylamino)-6-methyltetrahydro-2H-pyran-2,3-diyl diacetate, S3

Following the literature procedure *(5)*, 7.0 g (9.5 mmol) of erythromycin was added to a round bottom flask followed by 50 mL of EtOH. 125 mL of a 6 N HCl solution was added, and the mixture was heated at reflux at 100 °C for 4 h. The reaction mixture was transferred to a separatory funnel and extracted with $CHCl_3$ (3 x 50 mL). The organic layer was discarded, and the solvent was removed from the red/orange aqueous layer. After vacuum drying overnight, crude 4-(dimethylamino)-6-methyltetrahydro-2H-pyran-2,3-diol was obtained as a red/orange solid and was carried on to the next step without further purification. The crude compound was transferred to a round bottom flask and suspended in 50 mL Ac_2O. 2 mL of concentrated sulfuric acid was added at 0 °C. The resulting mixture was stirred overnight at rt. The reaction mixture was poured into ice water and neutralized with solid sodium bicarbonate and extracted with EtOAc. The combined organic layers were concentrated and purified by column chromatography (80% EtOAc 20% Hexanes to 2% MeOH in EtOAc) to afford 4-(dimethylamino)-6-methyltetrahydro-2H-pyran-2,3-diyl diacetate (1.5 g, 5.7 mmol, 60 % over 2 steps) as a yellow oil. Spectral data of the compound was identical with that previously reported *(5)*.



(2R,3R,4S,6R)-4-(dimethylamino)-2-fluoro-6-methyltetrahydro-2H-pyran-3-yl acetate, S4

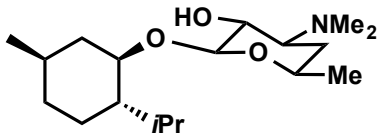
To a stirring solution of HF pyridine (7.2 mL) in a dry polyethylene vial at 0 °C was added 1.2 g (4.4 mmol) of 4-(dimethylamino)-6-methyltetrahydro-2H-pyran-2,3-diyl diacetate as a solution in toluene (4.8 mL). The reaction was allowed to stir at 0 °C for 2.5 h. The reaction mixture was diluted with 10 mL of a brine solution and quenched with a saturated sodium bicarbonate solution. The mixture was extracted with EtOAc and dried over Na_2SO_4, filtered, and concentrated. The crude material was chromatographed (100% EtOAc) to yield 0.48 g (2.2 mmol) of the α-anomer of 4-(dimethylamino)-2-fluoro-6-methyltetrahydro-2H-pyran-3-yl acetate as a clear oil. Spectral data of the compound was identical with that previously reported *(5)*.



(2S,3R,4S,6R)-4-(dimethylamino)-2-(((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)oxy)-6-methyltetrahydro-2H-pyran-3-yl acetate, S5

A suspension of (–)-menthol (0.038 g, 0.24 mmol), 4-(dimethylamino)-2-fluoro-6-methyltetrahydro-2H-pyran-3-yl acetate (0.026 g, 0.12 mmol), and molecular sieves (4Å, 0.15 g) in 2 mL CH_2Cl_2 was allowed to stir for 30 min at rt under an N_2 atmosphere. The suspension was cooled to 0 °C and BF_3•OEt_2 0.060 mL (0.48 mmol, freshly distilled) was added. The reaction was allowed to stir at 0 °C until the starting material was consumed as judged by TLC. The reaction was quenched with a solution of saturated

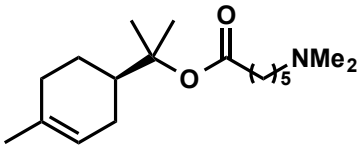
sodium bicarbonate and extracted with EtOAc. The resulting organic layers were combined, dried over Na_2SO_4, filtered, concentrated, and purified by chromatography (5% MeOH in CH_2Cl_2) to yield 0.028 g (65%) of the title compound as a clear oil. ^{1}H NMR (401 MHz, $CDCl_3$) δ 4.77 (dd, *J* = 10.5, 7.6 Hz, 1H), 4.32 (d, *J* = 7.6 Hz, 1H), 3.63 – 3.42 (m, 1H), 3.32 (td, 1H), 2.77 (s, 1H), 2.41 – 2.18 (m, 7H), 2.06 (s, 3H), 2.01 – 1.91 (m, 1H), 1.80 – 1.69 (m, 1H), 1.69 – 1.55 (m, 2H), 1.45 – 1.13 (m, 8H), 1.03 – 0.77 (m, 9H), 0.74 (d, *J* = 6.9 Hz, 3H).



(2S,3R,4S,6R)-4-(dimethylamino)-2-(((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)oxy)-6-methyltetrahydro-2H-pyran-3-ol, S6

To a solution of 2-((1R,2S,5R)-(-)-menthol)-4-(dimethylamino)-6-methyltetrahydro-2H-pyran-3-yl acetate 0.028 g (0.079 mmol) in 1.60 mL of MeOH was added 0.044 g of K_2CO_3 (0.32 mmol). The reaction was allowed to stir at rt until all starting material was consumed as judged by TLC. The reaction was diluted with brine and extracted with EtOAc. The organic layers were combined, dried over Na_2SO_4, concentrated, and purified by chromatography (10% MeOH in CH_2Cl_2) to yield 0.023g (95%) of the title compound. ^{1}H NMR (401 MHz, $CDCl_3$) δ 4.29 (d, *J* = 7.3 Hz, 1H), 3.59 – 3.39 (m, 2H), 3.27 (dd, *J* = 10.2, 7.3 Hz, 1H), 2.63 (ddd, *J* = 12.3, 10.2, 4.1 Hz, 1H), 2.35 (s, 7H), 2.14 – 2.00 (m, 1H), 1.84 – 1.70 (m, 1H), 1.70 – 1.56 (m, 2H), 1.36 – 1.20 (m, 7H), 1.03 – 0.80 (m, 9H), 0.76 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 101.0, 76.6, 69.6, 69.1, 65.3, 47.6, 40.7, 40.3, 34.3, 31.5, 29.4, 24.9, 22.9, 22.1, 21.0, 20.9, 15.3; HRMS (ESI) *m/z* calculated for $[M+H]^+$ 314.2690, found 314.2696.

Synthesis of (+)-menthol derivatives: The parallel set of (+)-menthol substrates were synthesized in an analogous manner to yield products matching the characterization data for the (–)-menthol enantiomer.

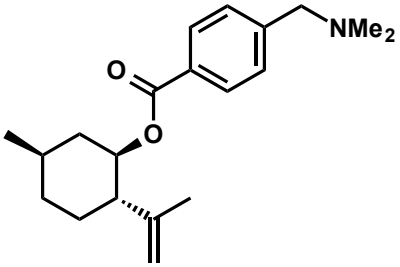


(*R*)-2-(4-methylcyclohex-3-en-1-yl)propan-2-yl 6-(dimethylamino)hexanoate, S7

A flame-dried round bottom flask was charged with 0.771 g (5.00 mmol) of (+)-α-terpineol, 1.545 g (7.50 mmol) of DCC, and 0.122 g (1.00 mmol) of DMAP. The contents of the flask were suspended in 25 mL of DCM and allowed to stir for 5 minutes before 1.460 g (7.50 mmol) of 6-bromohexanoic acid. Upon completion, the reaction was filtered through a plug of cotton and the solvent removed. The crude material was purified by chromatography to yield the ester.

A round bottom flask was charged with 0.404 g (1.22 mmol) of the ester. The contents of the flask were suspended in DMF and cooled to 0 °C. 0.289 g (6.42 mmol) of dimethylamine solution (40 wt. % in H_2O) was then added. Upon completion, the reaction was quenched with ethyl acetate and a solution of sat'd sodium bicarbonate. The organic layer was extracted twice with a solution of sat'd sodium bicarbonate and once with a solution of brine. The solvent was removed from the organic layer and the resulting residue was suspended in 1 M HCl until pH ~2. The aqueous layer was extracted three times with diethyl ether and then basified to pH ~8 with a solution of sat'd sodium bicarbonate. The aqueous

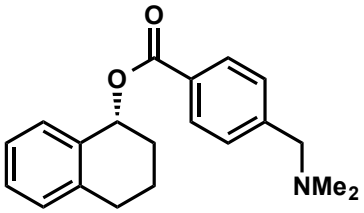
solution was extracted thrice with DCM, the organic layers combined, dried over sodium sulfate, and the solvent removed to yield 0.292 g (81%) of the desired product.[1]H NMR (400 MHz, $CDCl_3$): δ 5.38-5.32 (m, 1H), 2.29-2.16 (m, 11H), 2.07-1.92 (m, 4H), 1.85-1.73 (m, 2H), 1.63-1.54 (m, 4H), 1.52-1.45 (m, 2H), 1.42 (s, 3H), 1.40 (s, 3H), 1.35-1.25 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 133.9, 120.283, 84.6, 59.6, 45.4 (2C), 42.7, 35.6, 30.9, 27.3, 26.9, 26.3, 25.0, 23.8, 23.3, 23.3, 23.1; HRMS (ESI) *m/z* calculated for $[M+H]^+$ 296.2584, found 296.2582.



(1*R*,2*S*,5*R*)-5-methyl-2-(prop-1-en-2-yl)cyclohexyl 4-((dimethylamino)methyl)benzoate, S8

A flame-dried round bottom flask was charged with 0.462 g (3.00 mmol) of (-)-Isopulegol, 0.927 g (4.50 mmol) of DCC, and 0.073 g (0.60 mmol) of DMAP. The contents of the flask were suspended in 15 mL of DCM and allowed to stir for 5 minutes before 0.675 g (4.50 mmol) of 4-formylbenzoic acid. Upon completion, the reaction was filtered through a plug of cotton and the solvent removed. The crude material was purified by chromatography to yield the ester.

A flame-dried round bottom flask was charged with 0.772 g (2.70 mmol) of the ester and 0.284 g (3.51 mmol) of dimethylamine hydrochloride. The contents of the flask were suspended in DCM and cooled to 0 °C. 0.859 g (4.05 mmol) of sodium triacetoxyborohydride was then added over half an hour. Upon completion, the reaction was quenched with ethyl acetate and a solution of sat'd sodium bicarbonate. The organic layer was extracted twice with a solution of sat'd sodium bicarbonate and once with a solution of brine. The solvent was removed from the organic layer and the resulting residue was suspended in 1 M HCl until pH ~2. The aqueous layer was extracted three times with diethyl ether and then basified to pH ~8 with a solution of sat'd sodium bicarbonate. The aqueous solution was extracted thrice with DCM, the organic layers combined, dried over sodium sulfate, and the solvent removed to yield 0.587 g (69%) of the desired product.[1]H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 5.01 (td, J = 10.9, 4.4 Hz, 1H), 4.78-4.75 (m, 1H), 4.71-4.67 (m, 1H), 3.47 (s, 2H), 2.33-2.20 (m, 7H), 2.19-2.11 (m, 1H), 1.90-1.55 (m, 6H), 1.53-1.40 (m, 1H), 1.13 (q, J = 11.8 Hz, 1H), 1.07-0.97 (m, 1H), 0.95 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 146.1, 143.7, 129.7, 129.6, 128.8, 111.9, 74.2, 64.0, 50.9, 45.4 (2C), 40.5, 34.2, 31.4, 30.5, 22.0, 19.5; HRMS (ESI) *m/z* calculated for $[M+H]^+$ 316.2271, found 316.2276.

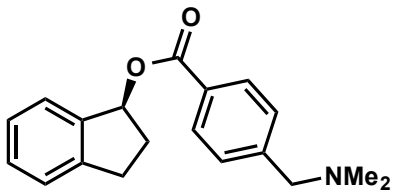


(*R*)-1,2,3,4-tetrahydronaphthalen-1-yl 4-((dimethylamino)methyl)benzoate, S9

A flame-dried round bottom flask was charged with 0.217 g (1.46 mmol) of (R)-1,2,3,4-tetrahydronaphthalen-1-ol, 0.453 g (2.20 mmol) of DCC, and 0.036 g (0.29 mmol) of DMAP. The

contents of the flask were suspended in 10 mL of DCM and allowed to stir for 5 minutes before 0.330 g (2.20 mmol) of 4-formylbenzoic acid. Upon completion, the reaction was filtered through a plug of cotton and the solvent removed. The crude material was purified by chromatography to yield the ester.

A flame-dried round bottom flask was charged with 0.381 g (1.40 mmol) of the ester and 0.143 g (1.78 mmol) of dimethylamine hydrochloride. The contents of the flask were suspended in DCM and cooled to 0 °C. 0.445 g (2.10 mmol) of sodium triacetoxyborohydride was then added over half an hour. Upon completion, the reaction was quenched with ethyl acetate and a solution of sat'd sodium bicarbonate. The organic layer was extracted twice with a solution of sat'd sodium bicarbonate and once with a solution of brine. The solvent was removed from the organic layer and the resulting residue was suspended in 1 M HCl until pH ~2. The aqueous layer was extracted three times with diethyl ether and then basified to pH ~8 with a solution of sat'd sodium bicarbonate. The aqueous solution was extracted thrice with DCM, the organic layers combined, dried over sodium sulfate, and the solvent removed to yield 0.333 g (77%) of the desired product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 8.2 Hz, 2H), 7.40 – 7.31 (m, 3H), 7.29 – 7.20 (m, 1H), 7.16 (m, 2H), 6.23 (t, J = 4.5 Hz, 1H), 3.45 (s, 2H), 2.96 – 2.86 (m, 1H), 2.85 – 2.74 (m, 1H), 2.22 (s, 6H), 2.15 – 1.98 (m, 3H), 1.87 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 144.1, 138.0, 134.7, 129.7, 129.5, 129.5, 129.0, 128.8, 128.0, 126.0, 70.5, 64.0, 45.4, 29.2, 29.0, 19.1; HRMS (ESI) *m/z* calculated for $[M+H]^+$ 310.1802, found 310.1808.

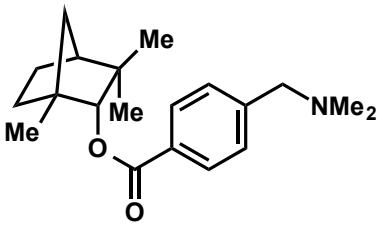


(*S*)-2,3-dihydro-1*H*-inden-1-yl 4-((dimethylamino)methyl)benzoate, S10

A flame-dried round bottom flask was charged with 0.200 g (1.50 mmol) of (S)-2,3-dihydro-1H-inden-1-ol, 0.464 g (2.25 mmol) of DCC, and 0.027 g (0.225 mmol) of DMAP. The contents of the flask were suspended in 16 mL of DCM and allowed to stir for 5 minutes before 0.338 g (2.25 mmol) of 4-formylbenzoic acid. Upon completion, the reaction was filtered through a plug of cotton and the solvent removed. The crude material was purified by chromatography (Hexanes to 20% ethyl acetate in hexanes) to yield 0.323 g (81%) of the desired product. ^{1}H NMR (700 MHz, $CDCl_3$) δ 10.09 (s, 1H), 8.19 (d, J = 8.4 Hz, 2H), 7.93 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 7.5 Hz, 1H), 7.36 – 7.31 (m, 2H), 7.29 – 7.23 (m, 1H), 6.48 (dd, J = 7.1, 3.8 Hz, 1H), 3.21 (ddd, J = 15.3, 8.4, 6.2 Hz, 1H), 2.97 (ddd, J = 16.0, 8.6, 4.9 Hz, 1H), 2.69 – 2.61 (m, 1H), 2.31 – 2.23 (m, 1H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 191.6, 165.5, 144.5, 140.7, 139.1, 135.5, 130.3, 129.4, 129.2, 126.8, 125.7, 124.9, 79.7, 32.4, 30.3; IR (thin film, cm^{-1}) 2933, 2841, 1709, 1264.

A flame-dried round bottom flask was charged with 0.283 g (1.06 mmol) of (S)-2,3-dihydro-1H-inden-1-yl 4-formylbenzoate and 0.112 g (1.38 mmol) of dimethylamine hydrochloride. The contents of the flask were suspended in DCM and cooled to 0 °C. 0.337 g (1.59 mmol) of sodium triacetoxyborohydride was then added over half an hour. Upon completion, the reaction was quenched with ethyl acetate and a solution of sat'd sodium bicarbonate. The organic layer was extracted twice with a solution of sat'd sodium bicarbonate and once with a solution of brine. The solvent was removed from the organic layer and the resulting residue was suspended in 1 M HCl until pH ~2. The aqueous layer was extracted three times with diethyl ether and then basified to pH ~8 with a solution of sat'd sodium bicarbonate. The aqueous solution was extracted thrice with DCM, the organic layers

combined, dried over sodium sulfate, and the solvent removed to yield 0.232 g (74%) of the desired product. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 – 7.96 (m, 2H), 7.49 (d, *J* = 7.5 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.33 – 7.30 (m, 2H), 7.28 – 7.21 (m, 1H), 6.45 (dd, *J* = 7.1, 4.1 Hz, 1H), 3.46 (s, 2H), 3.18 (ddd, *J* = 15.9, 8.5, 5.9 Hz, 1H), 2.95 (ddd, *J* = 16.0, 8.6, 5.2 Hz, 1H), 2.68 – 2.59 (m, 1H), 2.28 – 2.19 (m, 7H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 166.5, 144.4, 144.3, 141.2, 129.7, 129.3, 128.9, 128.8, 126.7, 125.7, 124.8, 78.8, 64.0, 45.4, 32.5, 30.3; IR (thin film, cm^{-1}) 2941, 2878, 2816, 2767, 1711, 1456, 1264; HRMS (ESI) *m/z* calculated for $[M+H]^+$ 296.1645, found 296.1646.



(1*R*,2*R*,4*S*)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl 4-((dimethylamino)methyl)benzoate, S11

A flame-dried round bottom flask was charged with 1.000 g (6.50 mmol) of (+)-fenchol, 2.060 g (10.0 mmol) of DCC, and 0.159 g (1.30 mmol) of DMAP. The contents of the flask were suspended in 30 mL of DCM and allowed to stir for 5 minutes before 1.500 g (10.00 mmol) of 4-formylbenzoic acid. Upon completion, the reaction was filtered through a plug of cotton and the solvent removed. The crude material was purified by chromatography to yield the ester.

A flame-dried round bottom flask was charged with 0.530 g (1.85 mmol) of the ester and 0.195 g (2.41 mmol) of dimethylamine hydrochloride. The contents of the flask were suspended in DCM and cooled to 0 °C. 0.588 g (2.78 mmol) of sodium triacetoxyborohydride was then added over half an hour. Upon completion, the reaction was quenched with ethyl acetate and a solution of sat'd sodium bicarbonate. The organic layer was extracted twice with a solution of sat'd sodium bicarbonate and once with a solution of brine. The solvent was removed from the organic layer and the resulting residue was suspended in 1 M HCl until pH ~2. The aqueous layer was extracted three times with diethyl ether and then basified to pH ~8 with a solution of sat'd sodium bicarbonate. The aqueous solution was extracted thrice with DCM, the organic layers combined, dried over sodium sulfate, and the solvent removed to yield 0.414 g (71%) of the desired product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.1 Hz, 2H), 7.40 (d, *J* = 8.1 Hz, 2H), 4.62 (s, 1H), 3.48 (s, 2H), 2.26 (s, 6H), 1.99 – 1.88 (m, 1H), 1.77 (d, *J* = 9.0 Hz, 2H), 1.67 (d, *J* = 11.7 Hz, 1H), 1.49 (s, 1H), 1.27 (s, 2H), 1.18 (s, 3H), 1.11 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.8, 129.5, 128.9, 86.6, 64.0, 48.6, 48.4, 45.4, 41.5, 39.8, 29.8, 26.9, 25.9, 20.3, 19.5; HRMS (ESI) *m/z* calculated for $[M+H]^+$ 316.2271, found 316.2268.

III. Biochemistry

Preparation of PikC(D50ND176QE246A)-RhFRED: Using previously prepared pET28b-PikC(D50N)-RhFRED as a template, iterative site-directed mutagenesis was performed with the primers: (D176Q) 5'-ccgccttccgcgtctggaccCAGgccttcgtcttcccggacgatc-3' and (E246A) 5'-catcctgctcgtcgcggggcacGCGaccacggtcaatctgatcgccaacgg-3'.

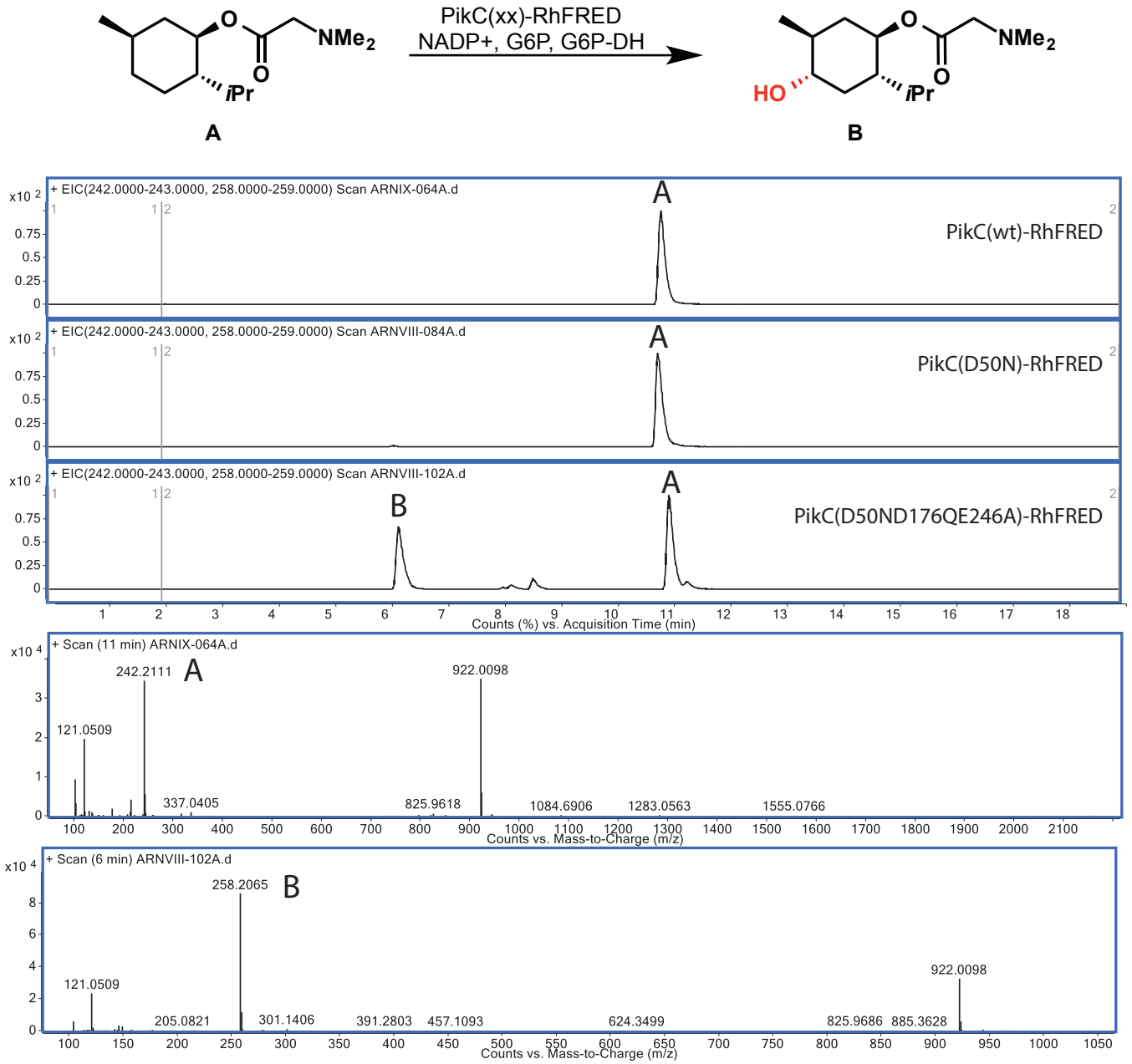
Expression and purification of PikC-RhFRED variants: Protein expression and purification followed a previously described procedure *(6)*.

PikC$_{xx}$-RhFRED analytical-scale enzymatic reactions: The standard assay contained 5 μM PikC$_{xx}$-RhFRED, 1 mM substrate, 1 mM NADP+, 0.05 units of glucose-6-phosphate dehydrogenase, and 5 mM glucose-6-phosphate for NADPH regeneration in of reaction buffer (50 mM NaH_2PO_4, pH 7.3, 1 mM EDTA, 0.2 mM dithoerythritol, and 10% glycerol) total volume 50 μL. The reaction was carried out at 30 °C for 3 h and quenched by addition of 150 μL MeOH. The resulting mixture was briefly vortexed and centrifuged at 10,000 x g for 10 min. The subsequent liquid chromatography mass spectrometry (LC-MS) analysis was performed on an Agilent Q-TOF HPLC-MS (Department of Chemistry, University of Michigan) equipped with an high resolution electrospray mass spectrometry (ESI-MS) source and a Beckmann Coulter reverse-phase HPLC system using an Waters XBridge C18 3.5 μm, 2.1x150 mm under the following conditions: mobile phase (A = deionized water + 0.1% formic acid, B = acetonitrile + 0.1% formic acid), 10% to 100% B over 15 min, 100% B for 4 min; flow rate, 0.2 mL/min. Reactions were scanned for [M+16] (monohydoxylation) and [M+32] (dihydroxylation). The percent conversion was determined as outlined in Li et al. *(7)*. Briefly, the percent conversion was calculated with $AUC_{total\ products}/(AUC_{total\ products} + AUC_{unreacted\ substrate})$ by assuming ionization efficiency of substrate and hydroxylated products are the same, because the ionization site of this series of compounds should be the dimethylamino group *(7)*.

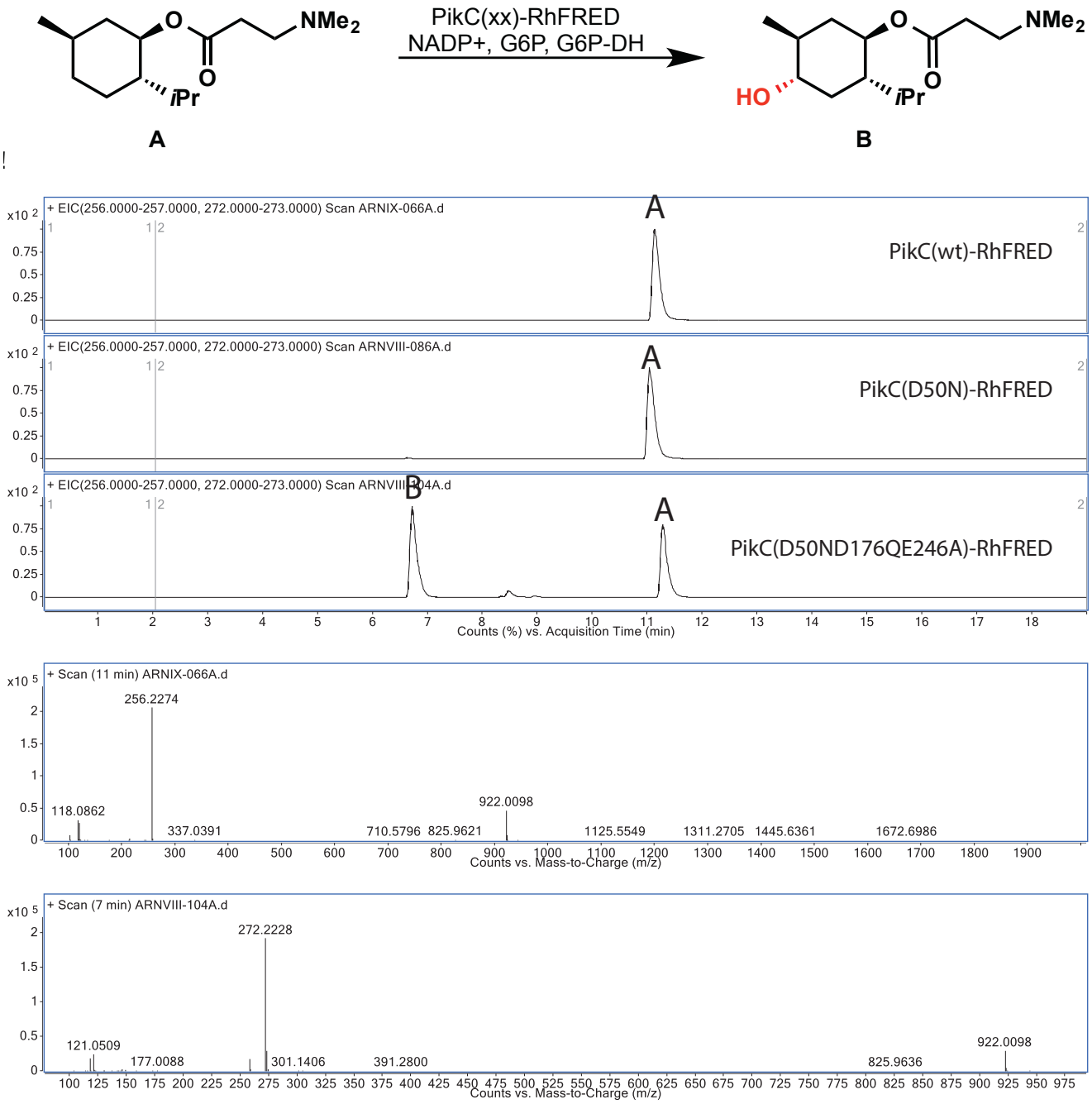
Determination of total turnover number (TTN): Total turnover number was determined by analyzing (# of moles of starting material consumed)/(# of moles of enzyme) under the following conditions: 5 μM PikC$_{D50N}$-RhFRED, 1 mM substrate, 1 mM NADP+, 0.05 units of glucose-6-phosphate dehydrogenase, and 5 mM glucose-6-phosphate for NADPH regeneration in 50 μL of reaction buffer (50 mM NaH_2PO_4, pH 7.3, 1 mM EDTA, 0.2 mM dithoerythritol, and 10% glycerol). The reaction was carried out at 30 °C for 24 h and quenched by addition of 150 μL MeOH. The resulting mixture was briefly vortexed and centrifuged at 10,000 x g for 10 min. The subsequent liquid chromatography mass spectrometry (LC-MS) analysis was performed on an Agilent Q-TOF HPLC-MS (Department of Chemistry, University of Michigan) equipped with an high resolution electrospray mass spectrometry (ESI-MS) source and a Beckmann Coulter reverse-phase HPLC system using an Waters XBridge C18 3.5 μm, 2.1x150 mm under the following conditions: mobile phase (A = deionized water + 0.1% formic acid, B = acetonitrile + 0.1% formic acid), 10% to 100% B over 15 min, 100% B for 4 min; flow rate, 0.2 mL/min. Assuming equal ionization efficiencies of the starting material and product, the percent conversion of the reaction was calculated with $AUC_{total\ products}/(AUC_{total\ products} + AUC_{unreacted\ substrate})$ *(7)*. All reactions were performed and analyzed in triplicate.

PikC$_{D50N}$-RhFRED preparative-scale enzymatic reactions:
Preparative –scale enzymatic reactions were conducted on 20 mg of each substrate under the following conditions: 5 μM PikC$_{D50N}$-RhFRED, 1 mM substrate, 1 mM NADP+, 1 U/mL glucose-6-phosphate dehydrogenase, and 5 mM glucose-6-phosphate for NADPH generation in reaction buffer (50 mM NaH_2PO_4, pH 7.3, 1 mM EDTA, 0.2 mM dithoerythritol, and 10% glycerol). The reaction mixture was divided into 50 mL conical tubes in 7 mL aliquots. Each conical tube was loosely capped and transferred to a shaking incubator. The reaction was carried out at 30 °C for 12 h at 160 rpm. After 12 h, a 50 μL aliquot was removed and processed in an identical manner to the analytical-scale reactions described above to access the outcome of the reaction. The remaining reaction mixture was diluted with acetone (2 x total reaction volume) and cooled to 4 °C for two h. The mixture was then filtered through celite and concentrated under reduced pressure until the acetone had been removed. The remaining solution was adjusted to pH 12, brined and extracted with EtOAc (3 x 200 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated to afford a crude yellow oil. The crude oil was purified through silica flash column chromatography (column conditions from the starting material purification) to afford the mixture of hydroxylated products.

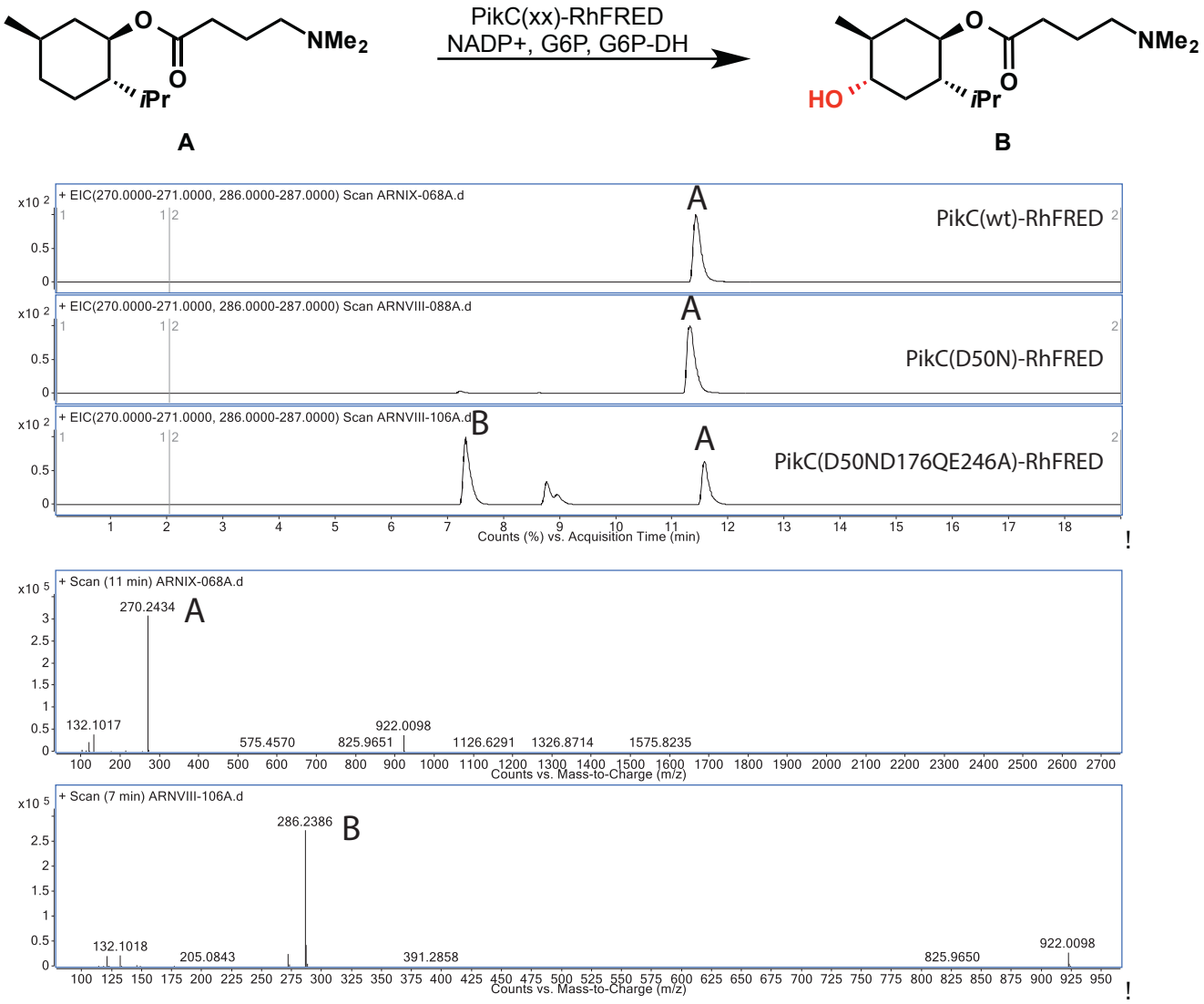
Supplementary Figure S15: Hydroxylation of (–)-21 by PikC-RhFRED variants, LC-MS traces and HRMS of the starting material (A) and product (B).



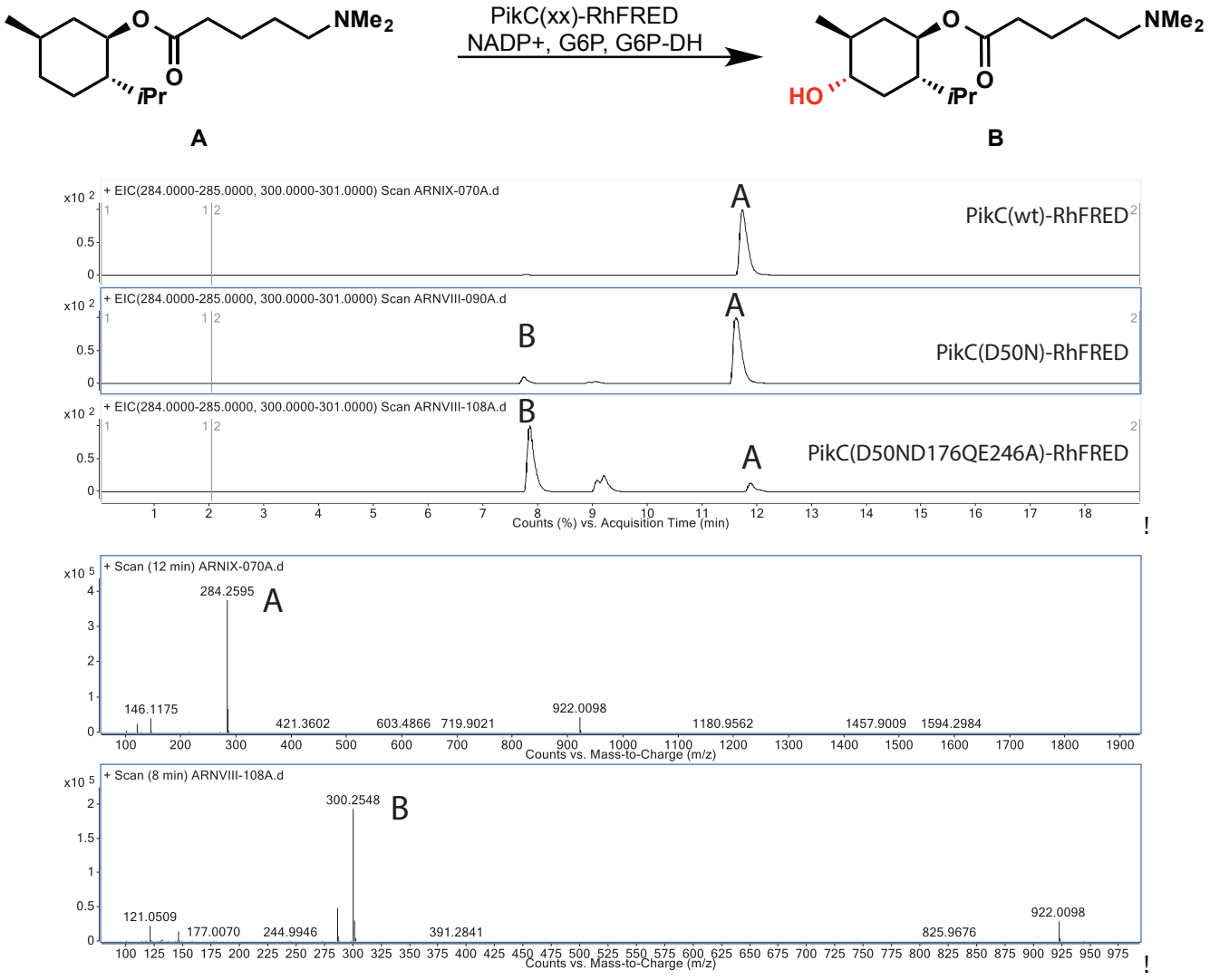
Supplementary Figure S16: Hydroxylation of (–)-22 by PikC-RhFRED variants, LC-MS traces and HRMS of the starting material (A) and product (B).



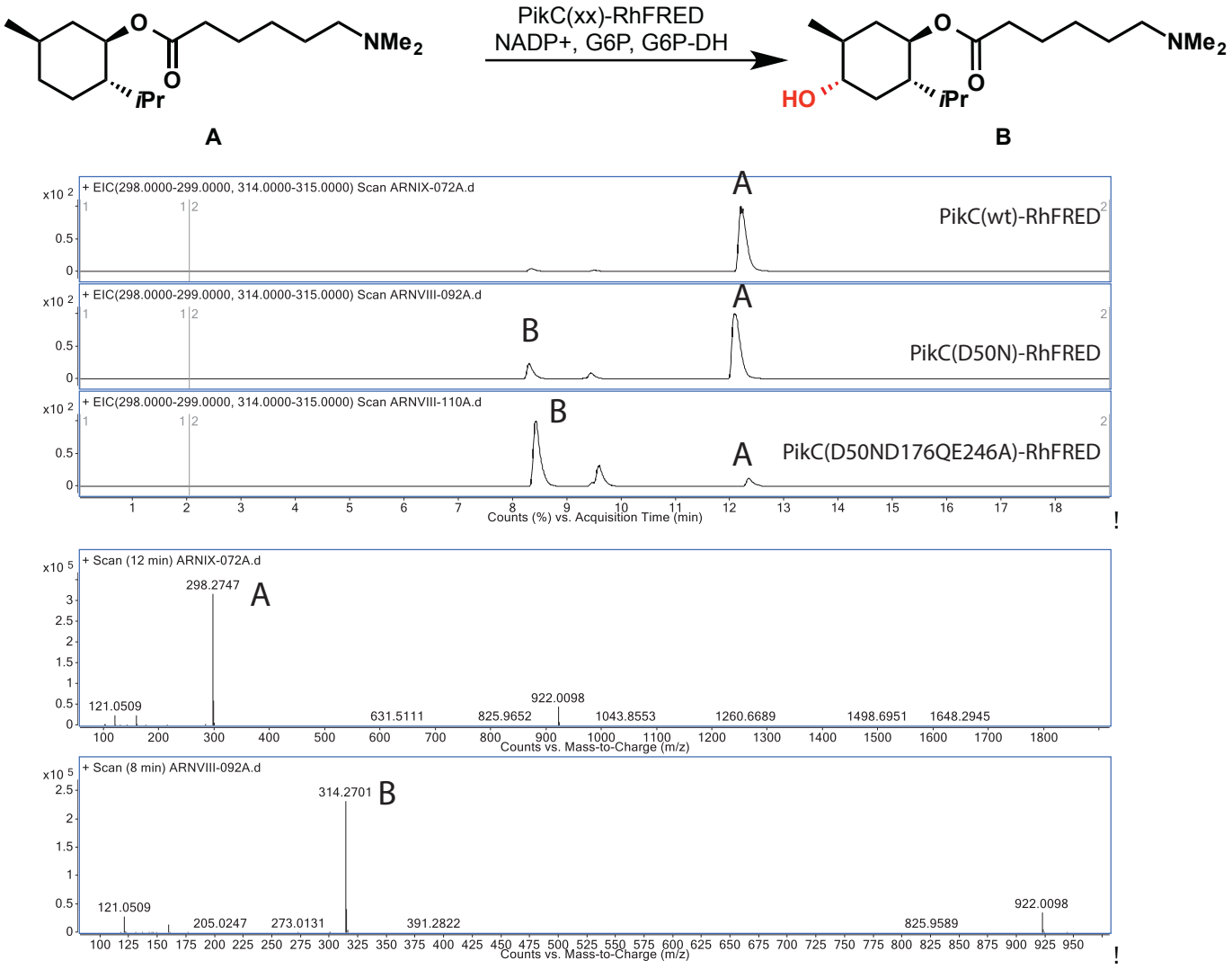
Supplementary Figure S17: Hydroxylation of (–)-23 by PikC-RhFRED variants, LC-MS traces and HRMS of the starting material (A) and product (B).



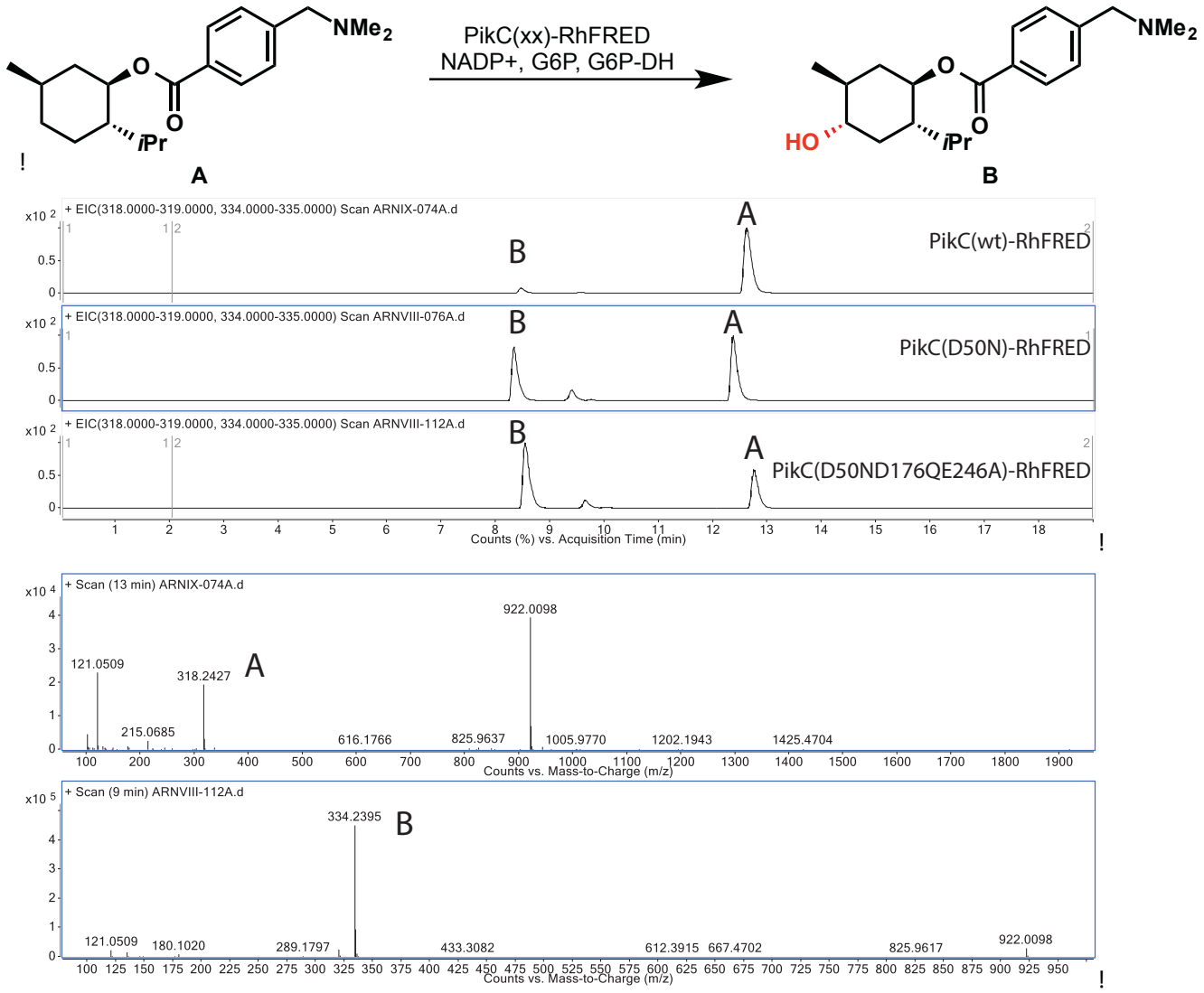
Supplementary Figure S18: Hydroxylation of (–)-24 by PikC-RhFRED variants, LC-MS traces and HRMS of the starting material (A) and product (B).



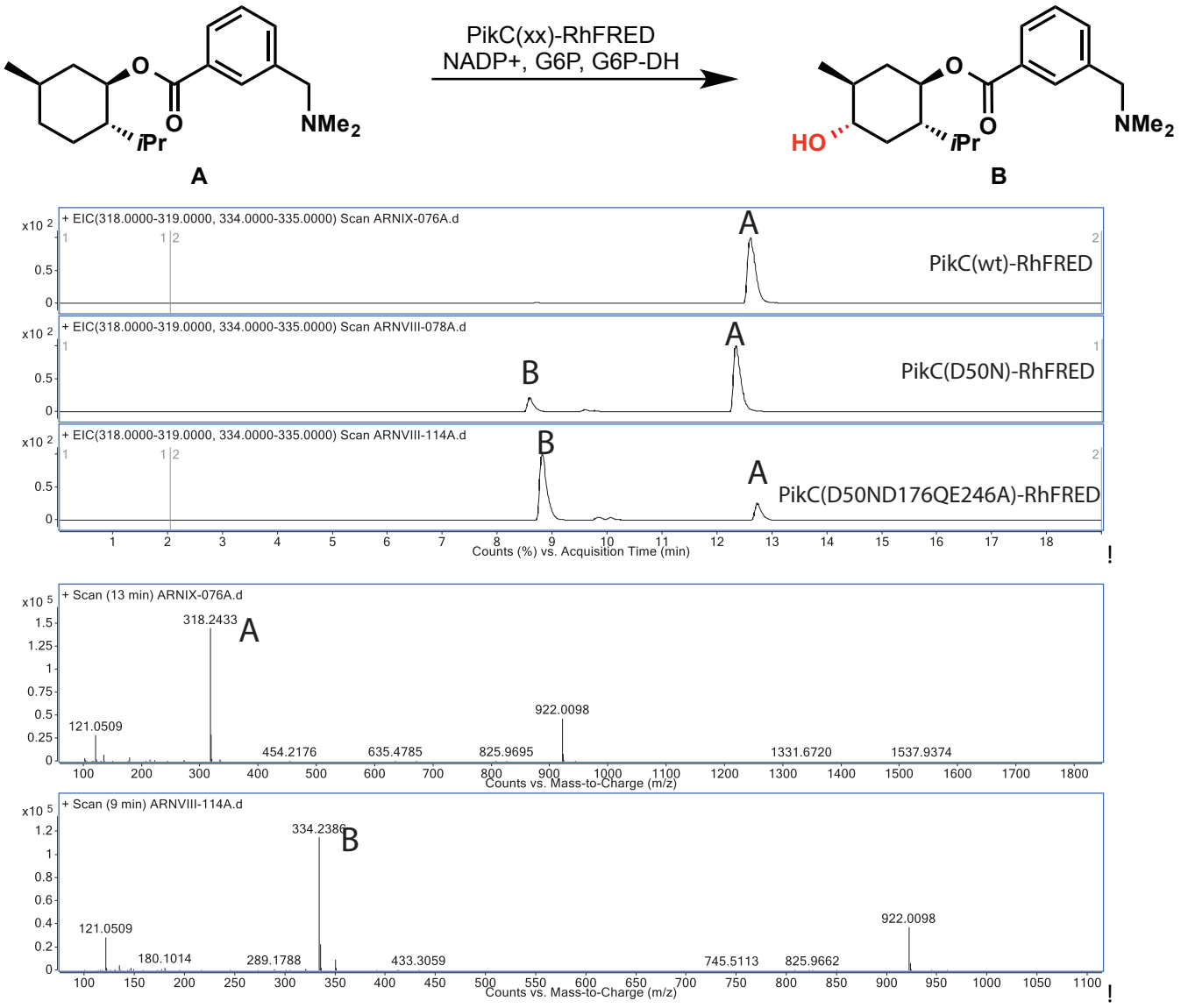
Supplementary Figure S19: Hydroxylation of (–)-25 by PikC-RhFRED variants, LC-MS traces and HRMS of the starting material (A) and product (B).



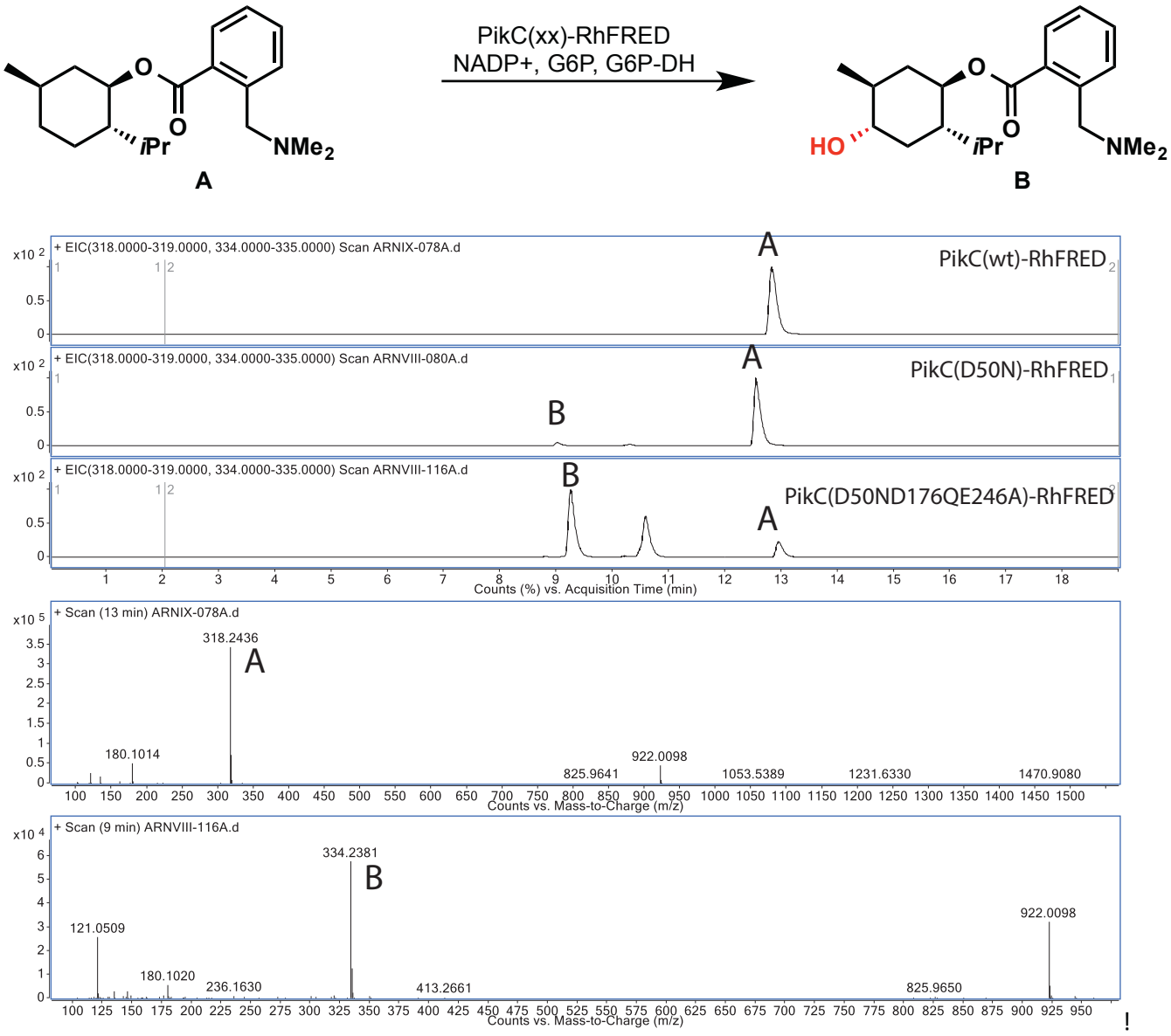
Supplementary Figure S20: Hydroxylation of (–)-26 by PikC-RhFRED variants, LC-MS traces and HRMS of the starting material (A) and product (B).



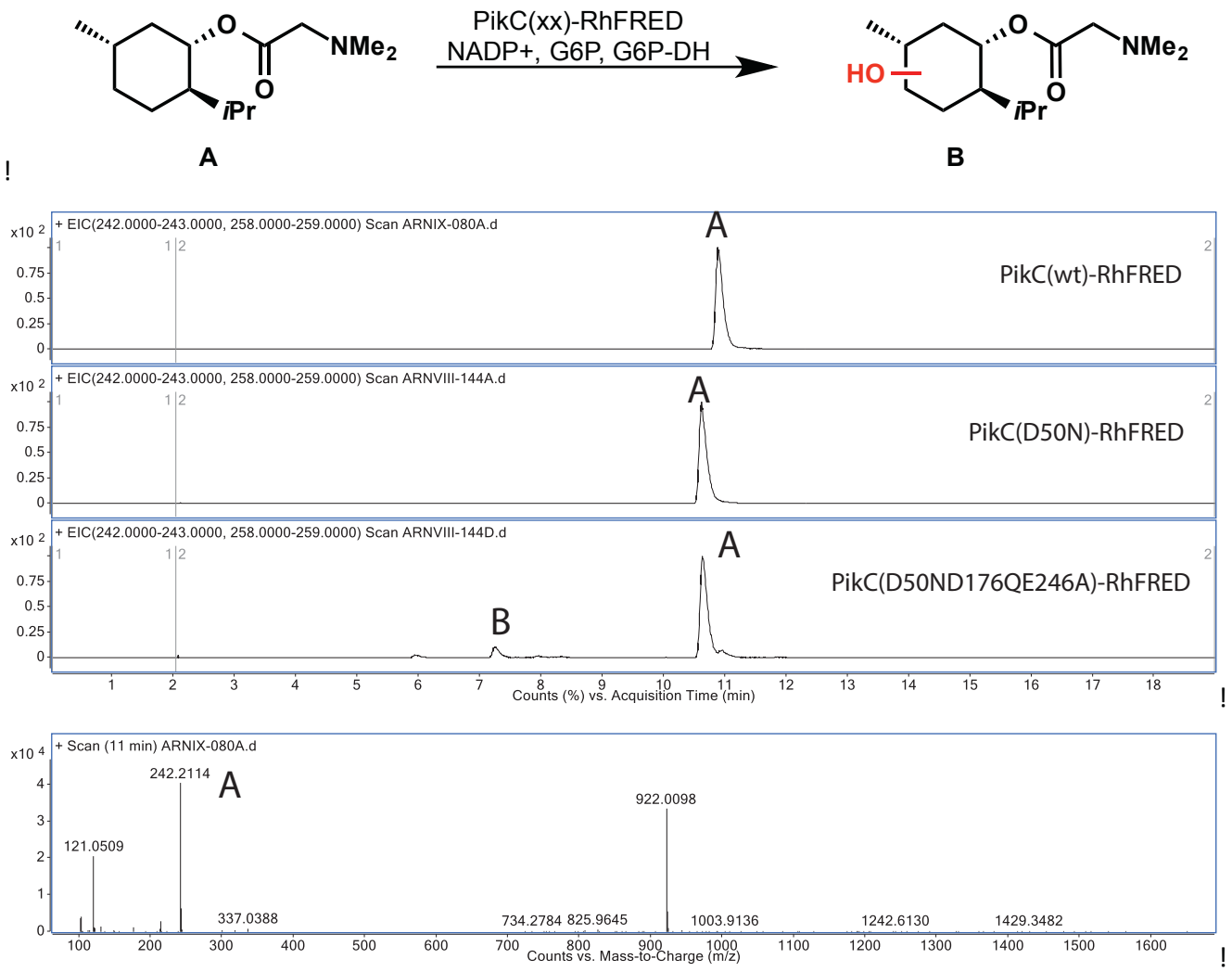
Supplementary Figure S21: Hydroxylation of (–)-27 by PikC-RhFRED variants, LC-MS traces and HRMS of the starting material (A) and product (B).



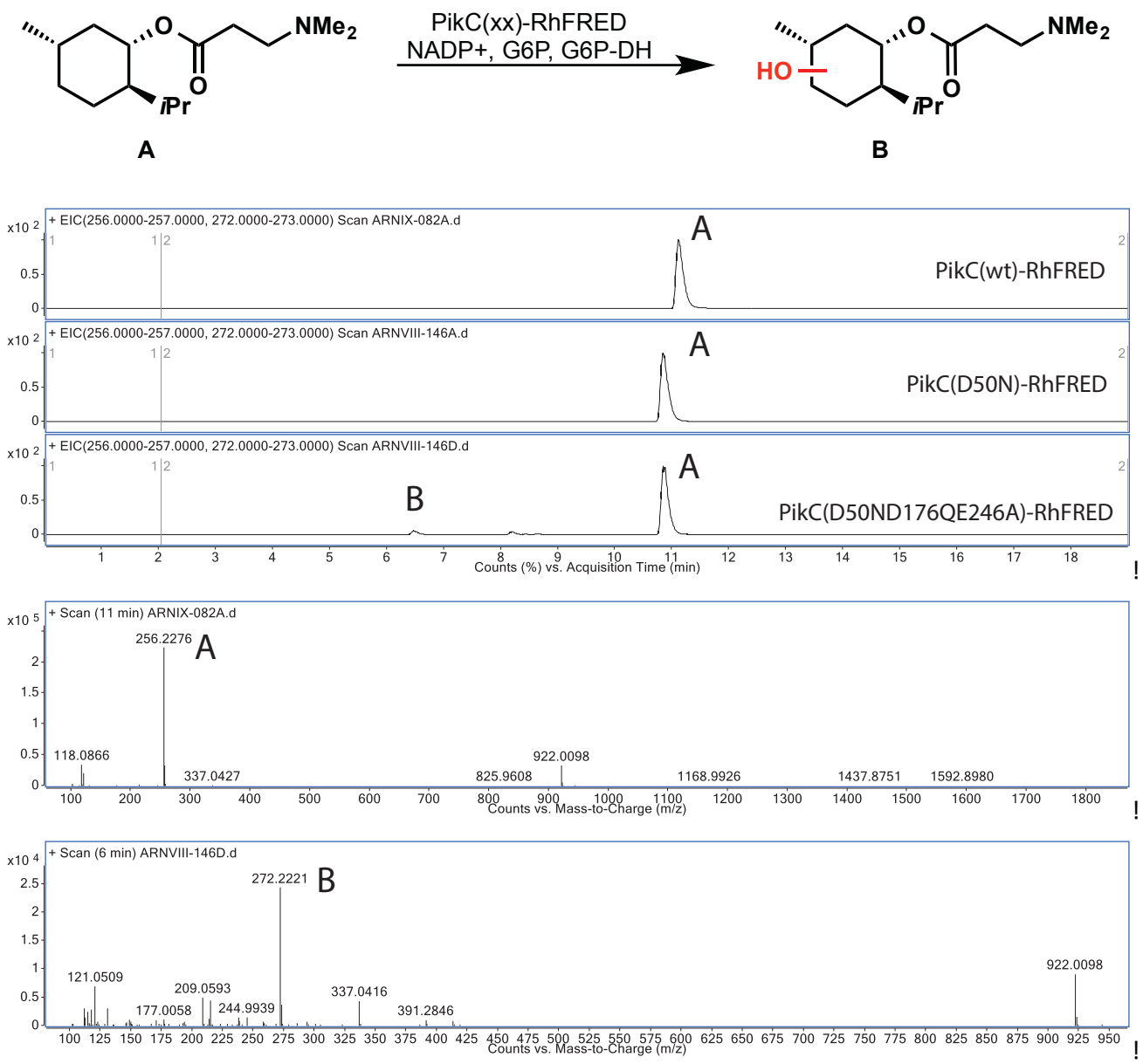
Supplementary Figure S22: Hydroxylation of (–)-28 by PikC-RhFRED variants, LC-MS traces and HRMS of the starting material (A) and product (B).



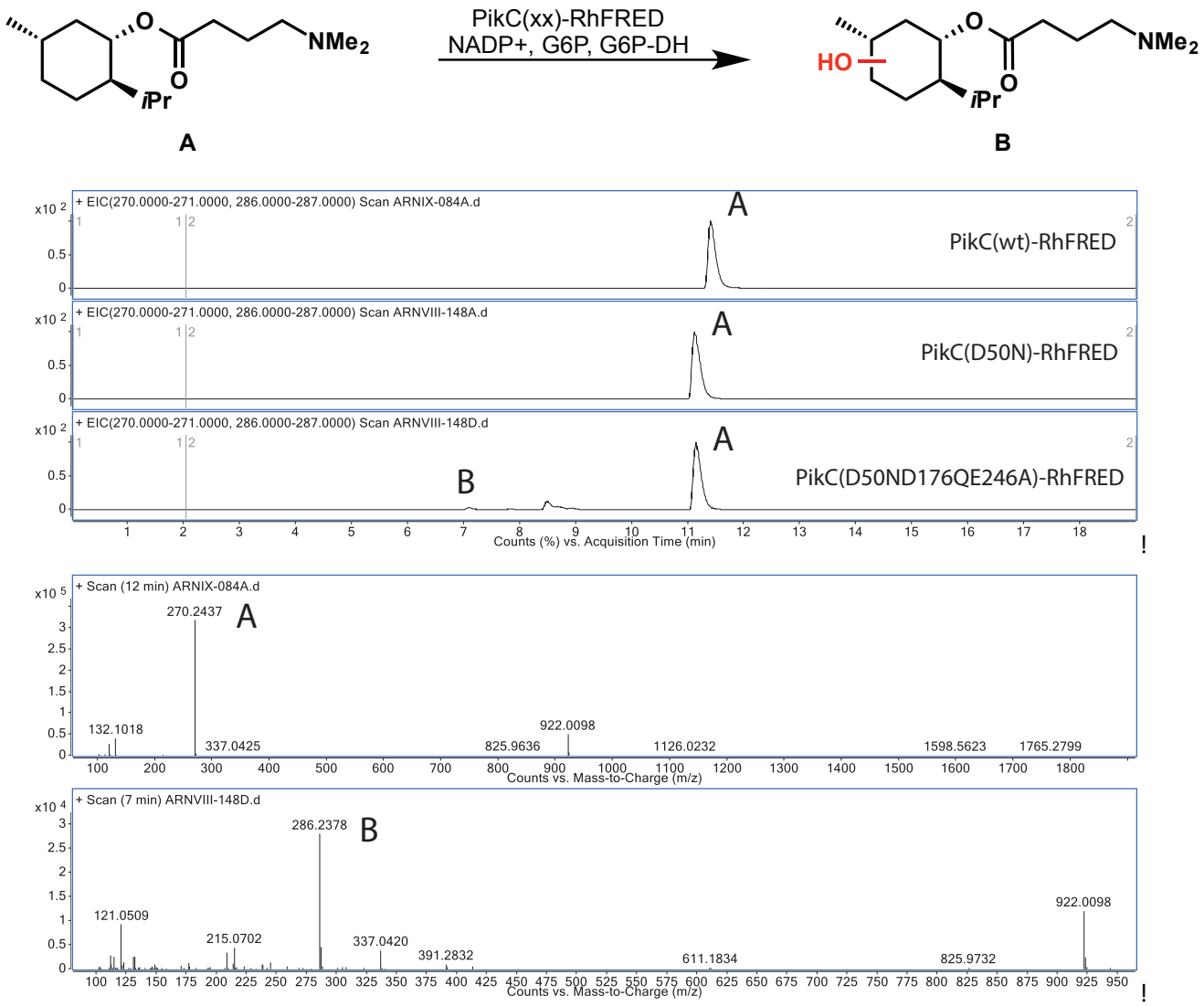
Supplementary Figure S23: Hydroxylation of (+)-21 by PikC-RhFRED variants, LC-MS traces and HRMS of the starting material (A) and product (B).



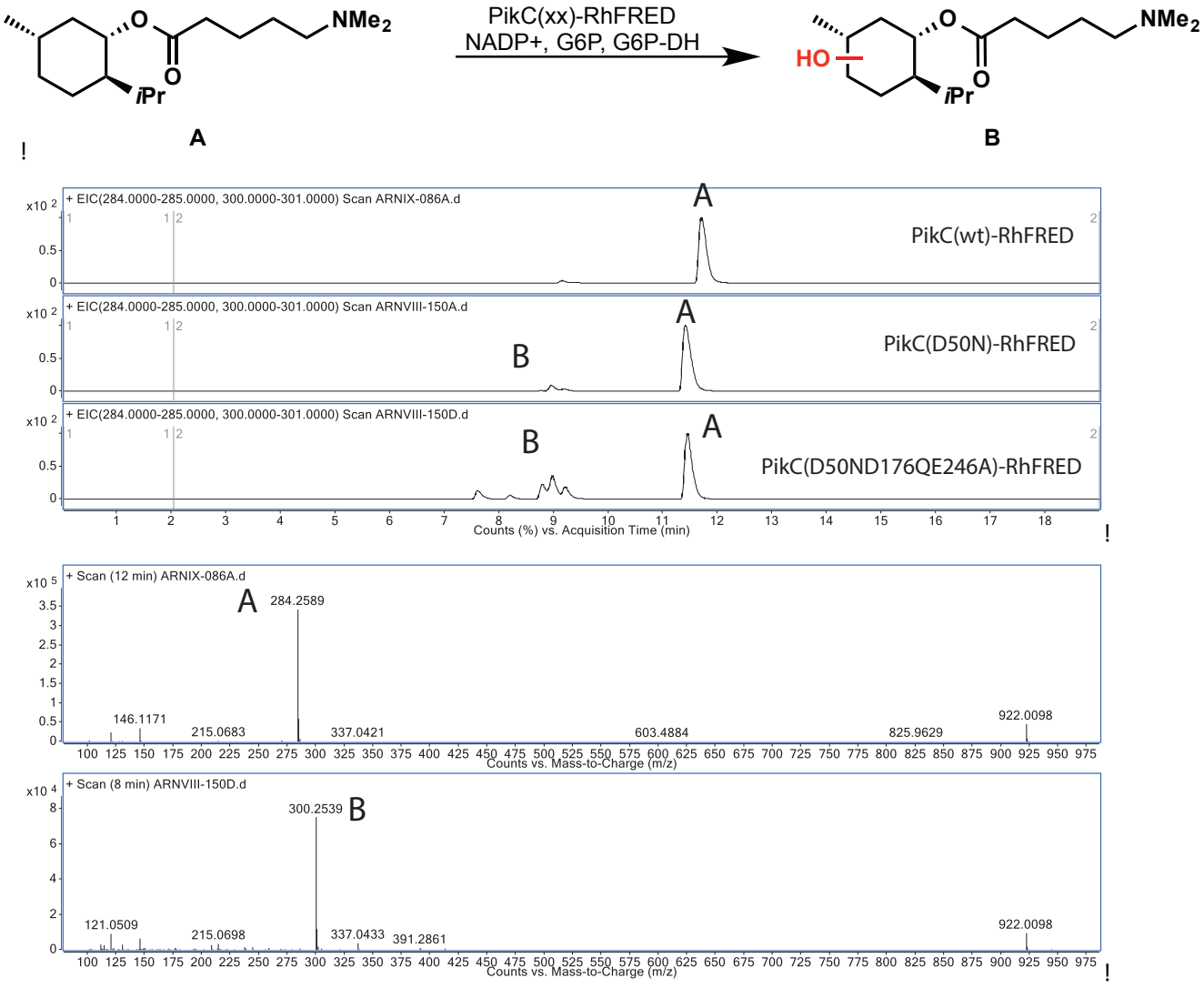
Supplementary Figure S24: Hydroxylation of (+)-22 by PikC-RhFRED variants, LC-MS traces and HRMS of the starting material (A) and product (B).



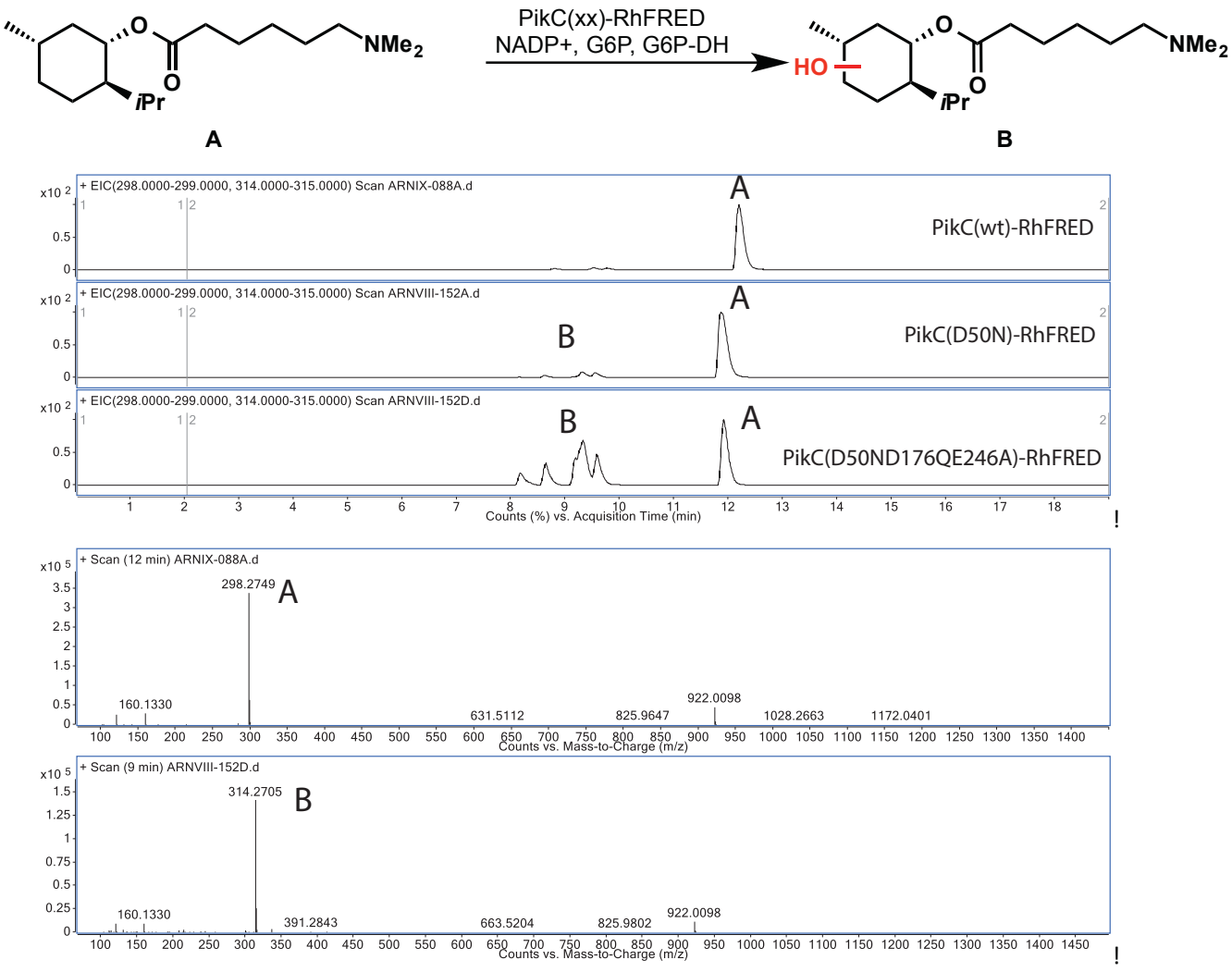
Supplementary Figure S25: Hydroxylation of (+)-23 by PikC-RhFRED variants, LC-MS traces and HRMS of the starting material (A) and product (B).



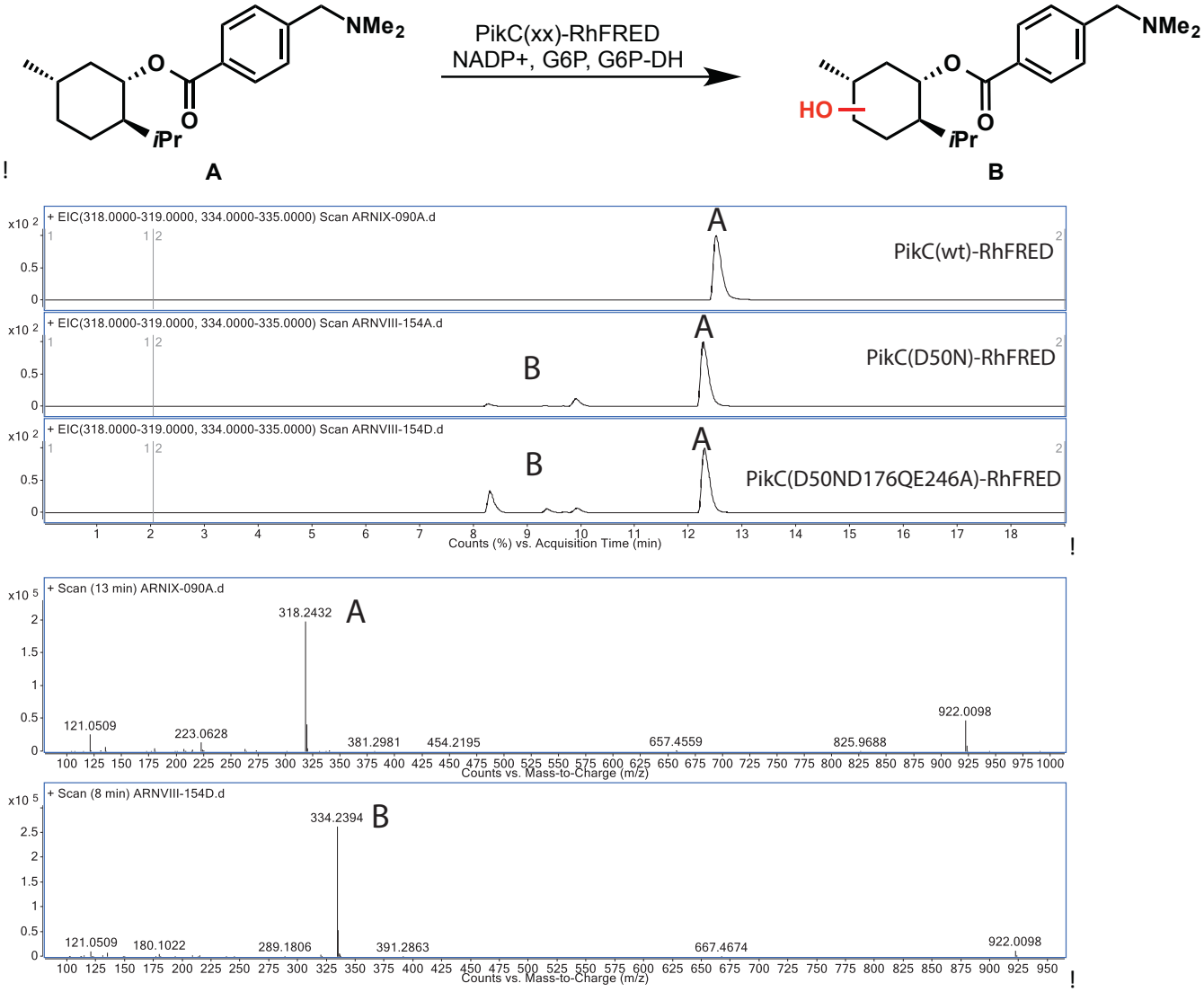
Supplementary Figure S26: Hydroxylation of (+)-24 by PikC-RhFRED variants, LC-MS traces and HRMS of the starting material (A) and product (B).



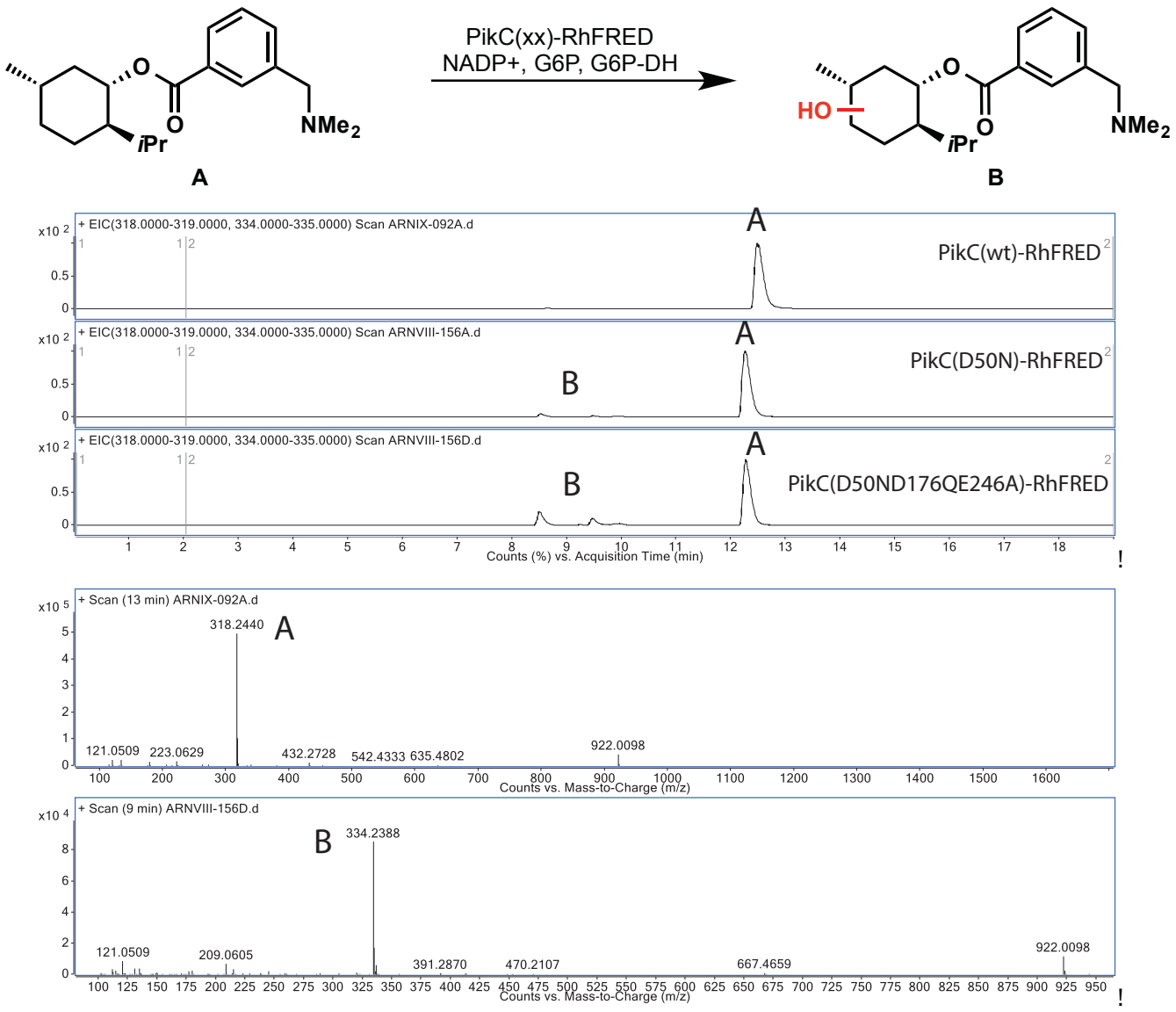
Supplementary Figure S27: Hydroxylation of (+)-25 by PikC-RhFRED variants, LC-MS traces and HRMS of the starting material (A) and product (B).



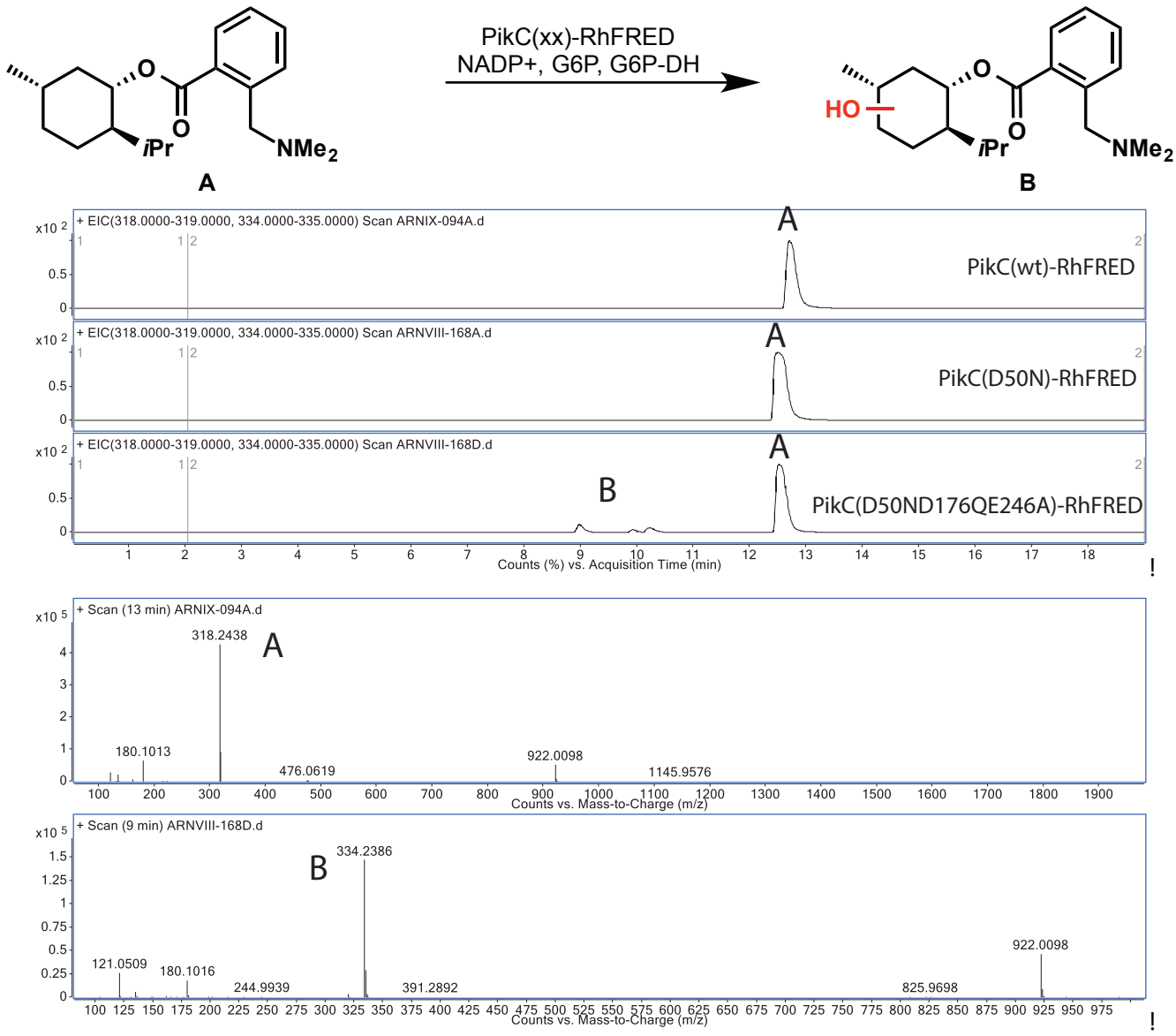
Supplementary Figure S28: Hydroxylation of (+)-26 by PikC-RhFRED variants, LC-MS traces and HRMS of the starting material (A) and product (B).



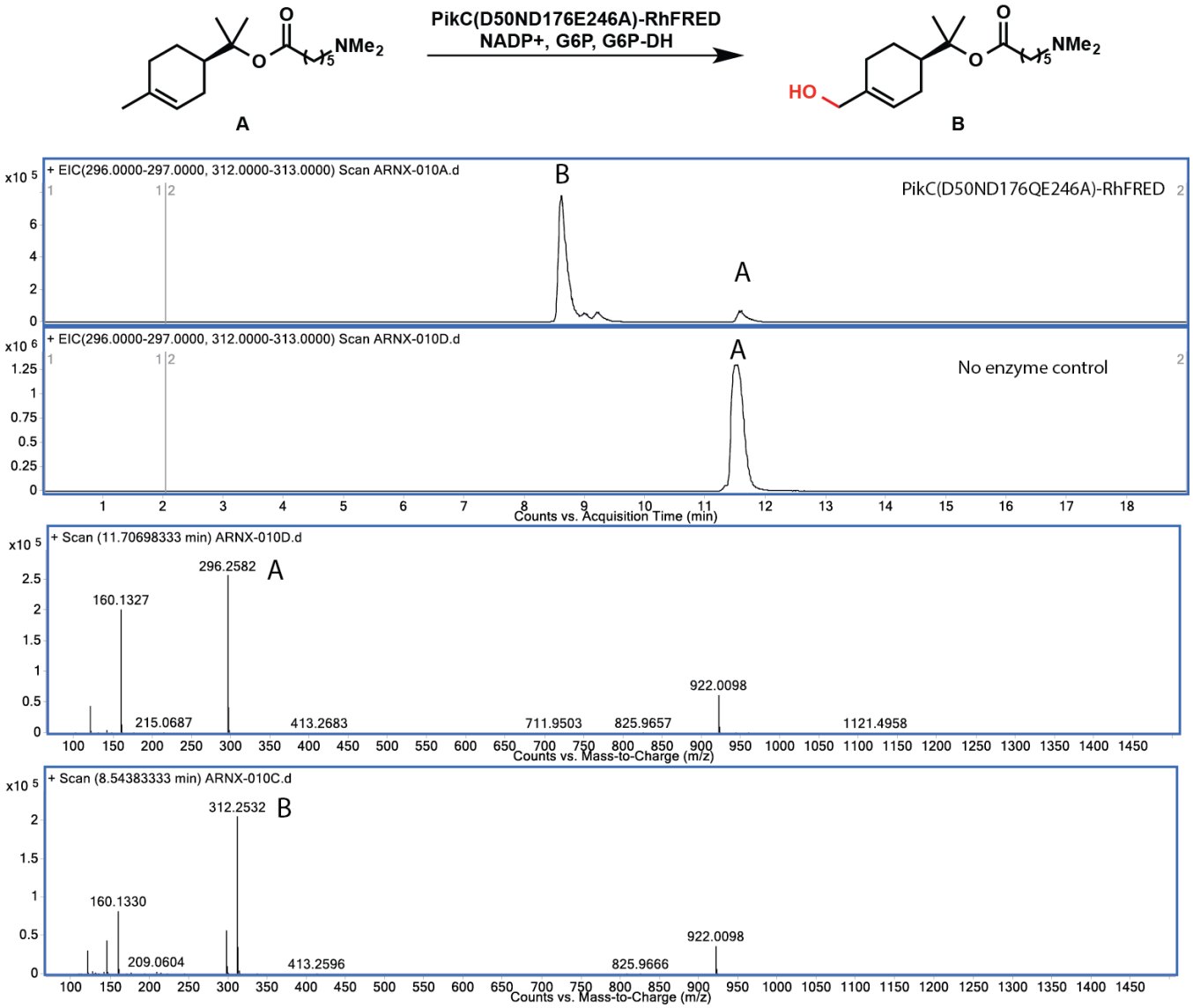
Supplementary Figure S29: Hydroxylation of (+)-27 by PikC-RhFRED variants, LC-MS traces and HRMS of the starting material (A) and product (B).



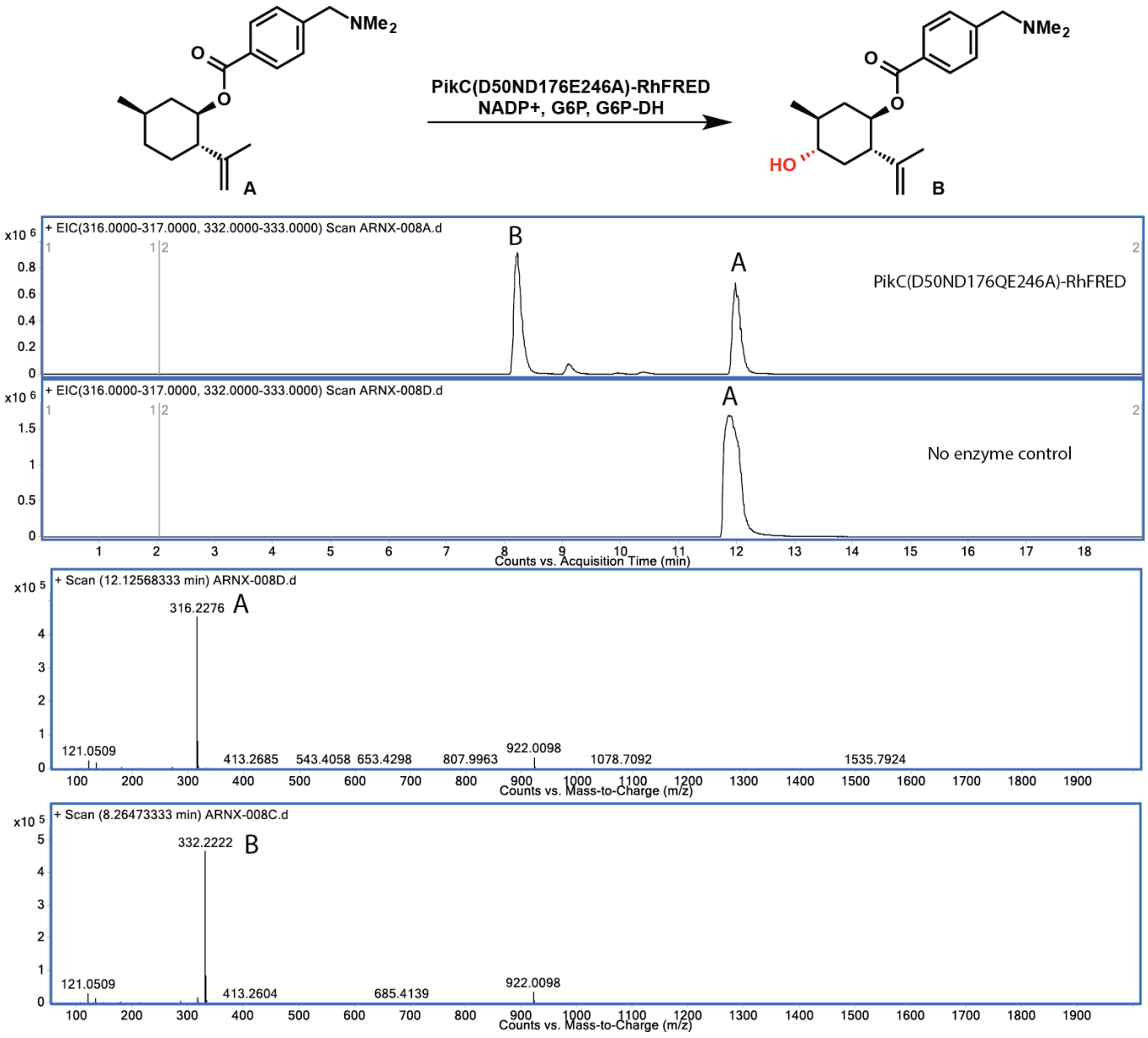
Supplementary Figure S30: Hydroxylation of (+)-28 by PikC-RhFRED variants, LC-MS traces and HRMS of the starting material (A) and product (B).



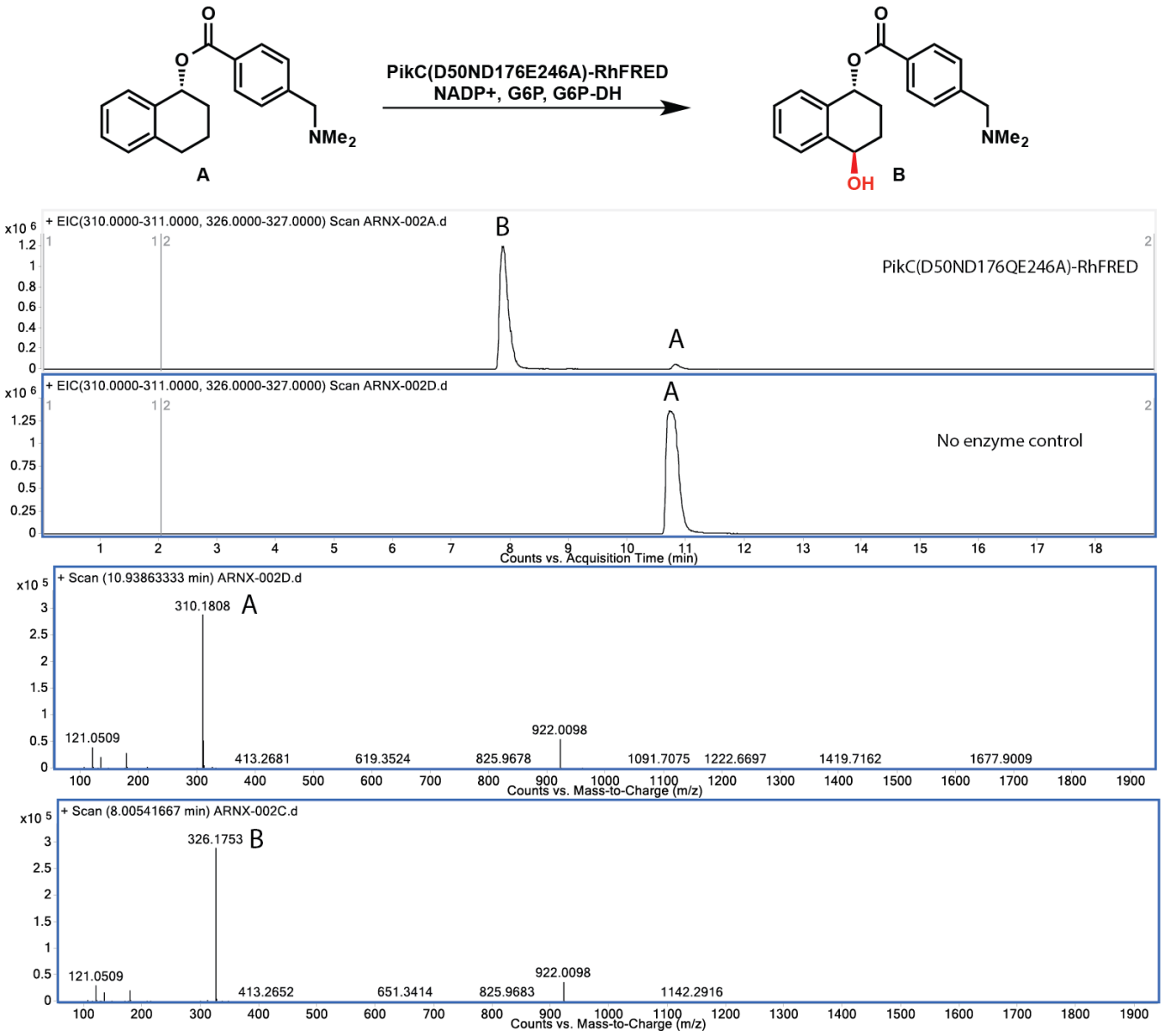
Supplementary Figure S31: Hydroxylation by PikC$_{D50ND176QE246A}$-RhFRED, LC-MS traces and HRMS of the starting material (A) and product (B).



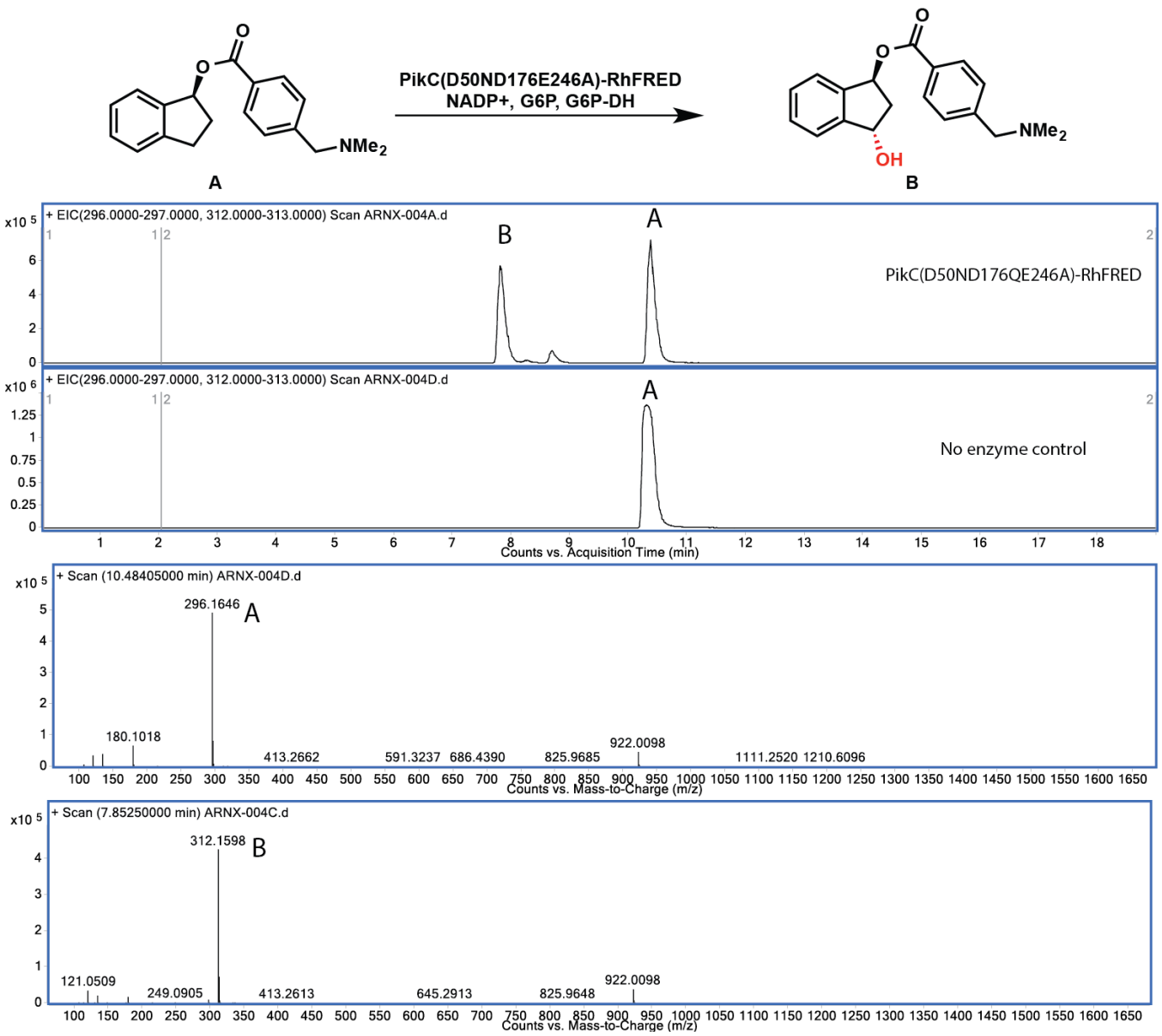
Supplementary Figure S32: Hydroxylation by PikC$_{D50ND176QE246A}$-RhFRED, LC-MS traces and HRMS of the starting material (A) and product (B).



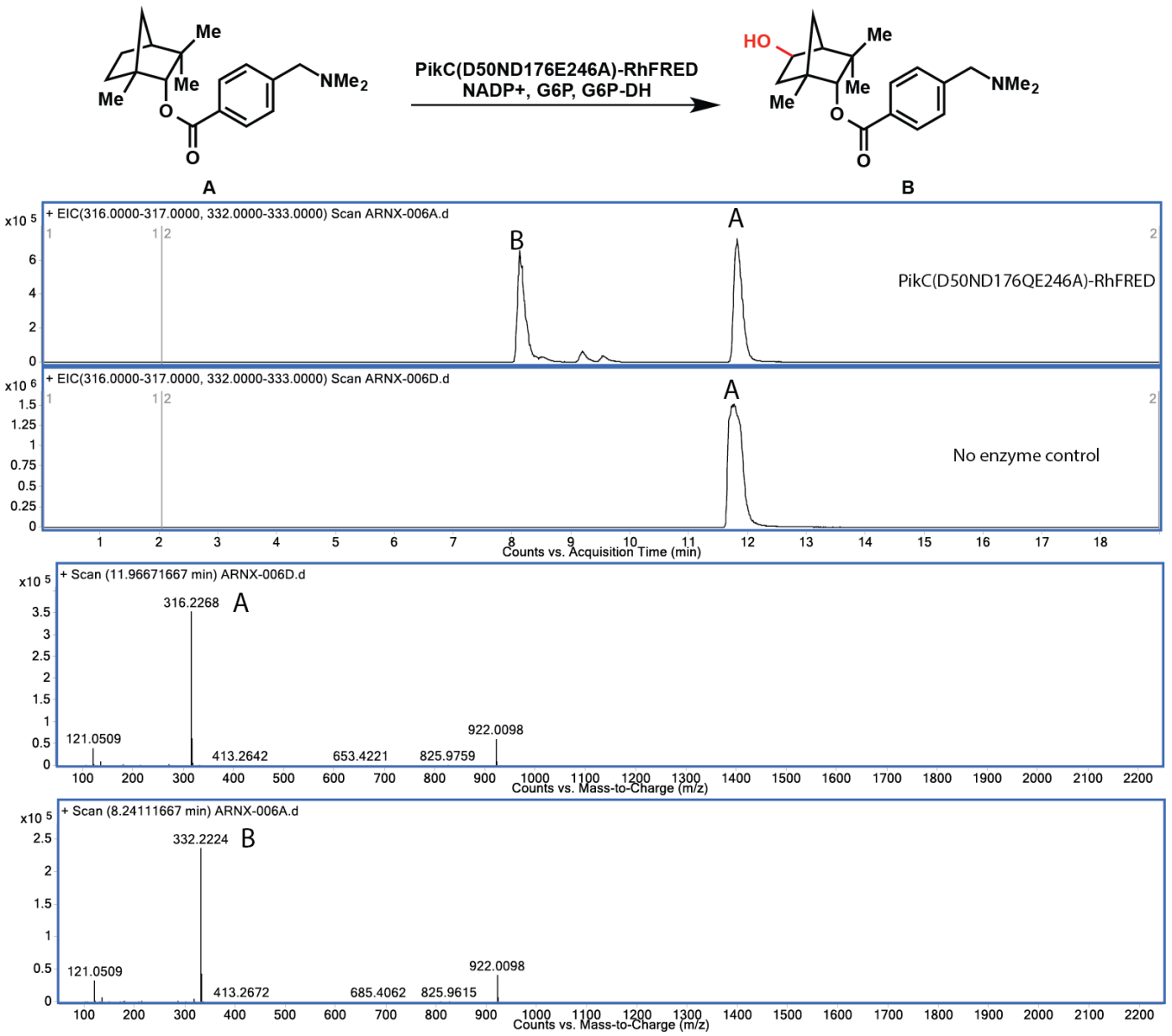
Supplementary Figure S33: Hydroxylation by PikC$_{D50ND176QE246A}$-RhFRED, LC-MS traces and HRMS of the starting material (A) and product (B).



Supplementary Figure S34: Hydroxylation by PikC$_{D50ND176QE246A}$-RhFRED, LC-MS traces and HRMS of the starting material (A) and product (B).



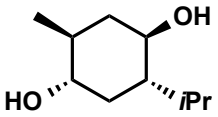
Supplementary Figure S35: Hydroxylation by PikC$_{D50ND176QE246A}$-RhFRED, LC-MS traces and HRMS of the starting material (A) and product (B).



IV. Product Characterization

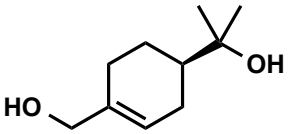
General protocol for anchoring group cleavage

A flame-dried round bottom flask was charged with lithium aluminium hydride (5.0 eq). Under N_2, the contents of the flask were suspended in 2 mL of THF and cooled to 0 °C. The solution of product from P450 oxidation in THF (1 mL) was then added dropwise via cannula. The reaction mixture was warmed to room temperature and stirred overnight, at which point H_2O (0.1 mL), 15% NaOH in H_2O (0.1 mL) and H_2O (0.2 mL) were added sequentially to quench the reaction. The mixture was diluted with EtOAc (10 mL), filtered to remove aluminum salts and the filtrate was concentrated. The residue obtained was purified by column chromatography to yield the product.



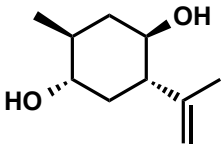
(8)

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.47 (td, *J* = 10.5, 4.4 Hz, 1H), 3.19 (ddd, *J* = 10.9, 9.7, 4.3 Hz, 1H), 2.19-2.10 (m, 1H), 1.96 (dt, *J* = 12.7, 4.1 Hz, 1H), 1.85 (ddd, *J* = 12.6, 4.3, 3.4 Hz, 1H), 1.47-1.23 (m, 4H), 1.17-1.04 (m, 2H), 1.03 (d, *J* = 6.5 Hz, 3H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.83 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (176 MHz, $CDCl_3$): δ 76.0, 70.7, 48.5, 42.5, 38.3, 32.3, 25.8, 21.0, 18.2, 15.9; IR (neat, cm^{-1}): 3230.0, 2926.2, 1456.0, 1095.8, 1026.9. *(8)*



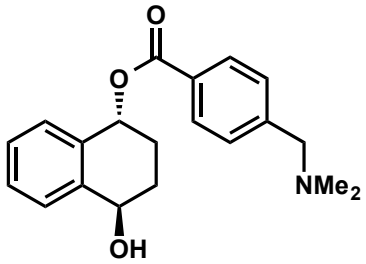
(*R*)-2-(4-(hydroxymethyl)cyclohex-3-en-1-yl)propan-2-ol, S12

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.72-5.66 (m, 1H), 4.01 (t, *J* = 2.6 Hz, 2H), 2.22-2.01 (m, 3H), 2.00-1.93 (m, 1H), 1.92-1.80 (m, 1H), 1.60-1.50 (m, 1H), 1.35 – 1.25 (m, 3H), 1.20 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.5, 122.4, 72.7, 67.1, 45.1, 27.4, 26.6, 26.5, 26.4, 23.6; HRMS (ESI) *m/z* calculated for $[M+H]^+$ 171.1380, found 188.1645.



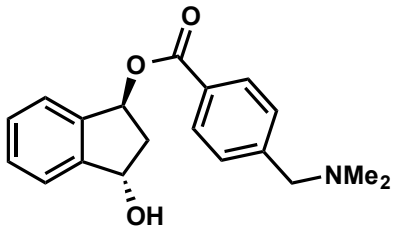
(1*S*,2*S*,4*R*,5*S*)-2-methyl-5-(prop-1-en-2-yl)cyclohexane-1,4-diol, S13

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.94-4.90 (m, 1H), 4.87-4.84 (m, 1H), 3.52 (td, *J* = 10.5, 4.3 Hz, 1H), 3.31-3.21 (m, 1H), 2.13-2.00 (m, 2H), 1.92 (dt, *J* = 12.7, 3.9 Hz, 1H), 1.86-1.80 (m, 1H), 1.74-1.69 (m, 3H), 1.54-1.37 (m, 3H), 1.19-1.09 (m, 1H), 1.06 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.2, 113.6, 75.3, 69.6, 52.5, 40.3, 38.2, 38.0, 19.0, 18.2; HRMS (ESI) *m/z* calculated for $[M+H]^+$ 171.1380, found 188.1654.



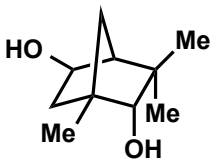
(1*R*,4*R*)-4-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl 4-((dimethylamino)methyl)benzoate, 33

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.2 Hz, 2H), 7.50 (d, *J* = 7.4 Hz, 1H), 7.41 – 7.33 (m, 4H), 7.30 (t, *J* = 7.4 Hz, 1H), 6.26 (t, *J* = 4.8 Hz, 1H), 4.92 (t, *J* = 4.7 Hz, 1H), 3.46 (s, 2H), 2.51 – 2.41 (m, 1H), 2.41 – 2.31 (m, 1H), 2.23 (s, 6H), 2.09 – 1.99 (m, 1H), 1.99 – 1.92 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 144.3, 139.4, 134.4, 129.7, 129.4, 129.2, 128.9, 128.8, 128.6, 128.3, 70.0, 67.5, 64.0, 45.4, 28.4, 25.0; IR (thin film, cm^{-1}) 3398, 2940, 2776, 1708, 1453, 1263; HRMS (ESI) *m/z* calculated for $[M+H]^+$ 326.1751, found 326.1753.



(1*S*,3*S*)-3-hydroxy-2,3-dihydro-1*H*-inden-1-yl 4-((dimethylamino)methyl)benzoate, 34

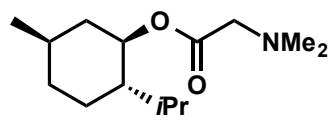
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.1 Hz, 2H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 7.4 Hz, 1H), 7.37 (m, 3H), 6.56 (dd, *J* = 6.7, 2.9 Hz, 1H), 5.56 (t, *J* = 5.7 Hz, 1H), 3.48 (s, 2H), 2.74 – 2.64 (m, 1H), 2.53 – 2.42 (m, 1H), 2.25 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.4, 145.9, 140.6, 129.8, 129.0, 128.9, 126.2, 124.4, 76.7, 74.4, 63.9, 45.3, 43.5; IR (thin film, cm^{-1}) 3388, 2932, 1712, 1611, 1459, 1268, 1175; HRMS (ESI) *m/z* calculated for $[M+H]^+$ 312.1594, found 312.1598.



(1*S*,2*R*,4*S*,5*R*)-1,3,3-trimethylbicyclo[2.2.1]heptane-2,5-diol, S14 ***(9)***

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.17 – 4.13 (m, 1H), 3.23 (d, *J* = 1.6 Hz, 1H), 2.18 (ddd, *J* = 13.8, 6.7, 2.5 Hz, 1H), 1.70 (s, 1H), 1.56 (dd, *J* = 10.6, 1.6 Hz, 1H), 1.37 (d, *J* = 10.6 Hz, 1H), 1.20 (d, *J* = 6.2 Hz, 1H), 1.12 (s, 3H), 1.03 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 83.5, 71.5, 55.6, 48.5, 38.8, 38.1, 36.5, 30.6, 19.5, 18.9; IR (thin film, cm^{-1}) 3341, 2944, 1277, 1071; LRMS (EI) *m/z* calculated for [M] 170.1, found 170.0.

.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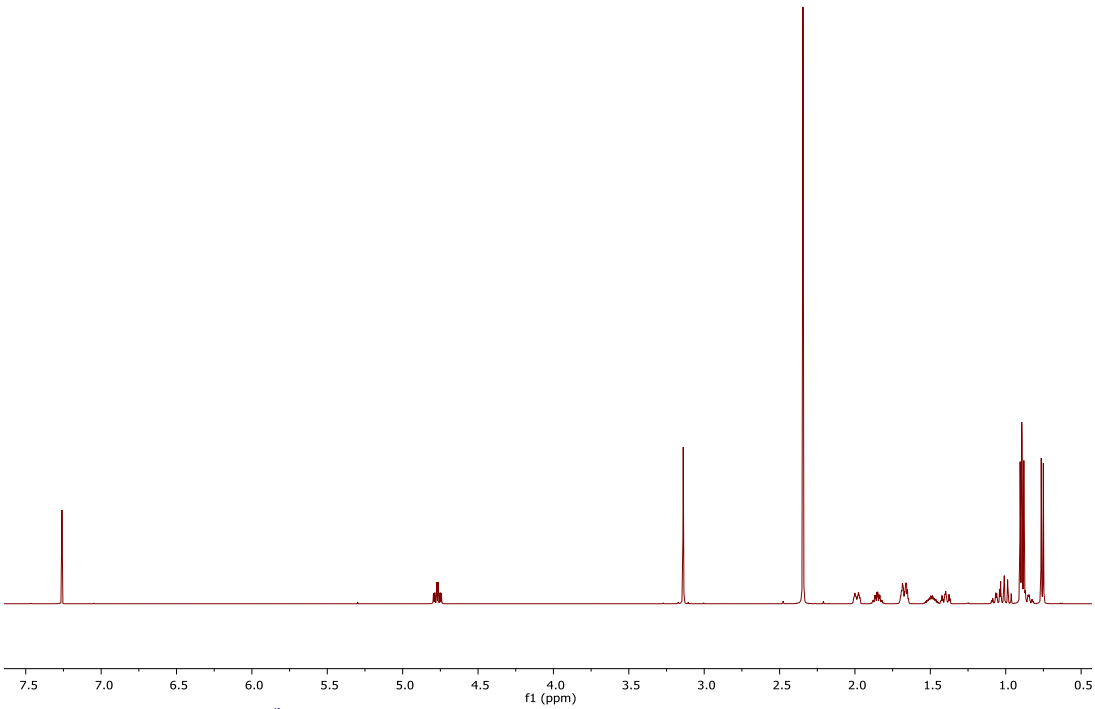
iPr

(–)-**21**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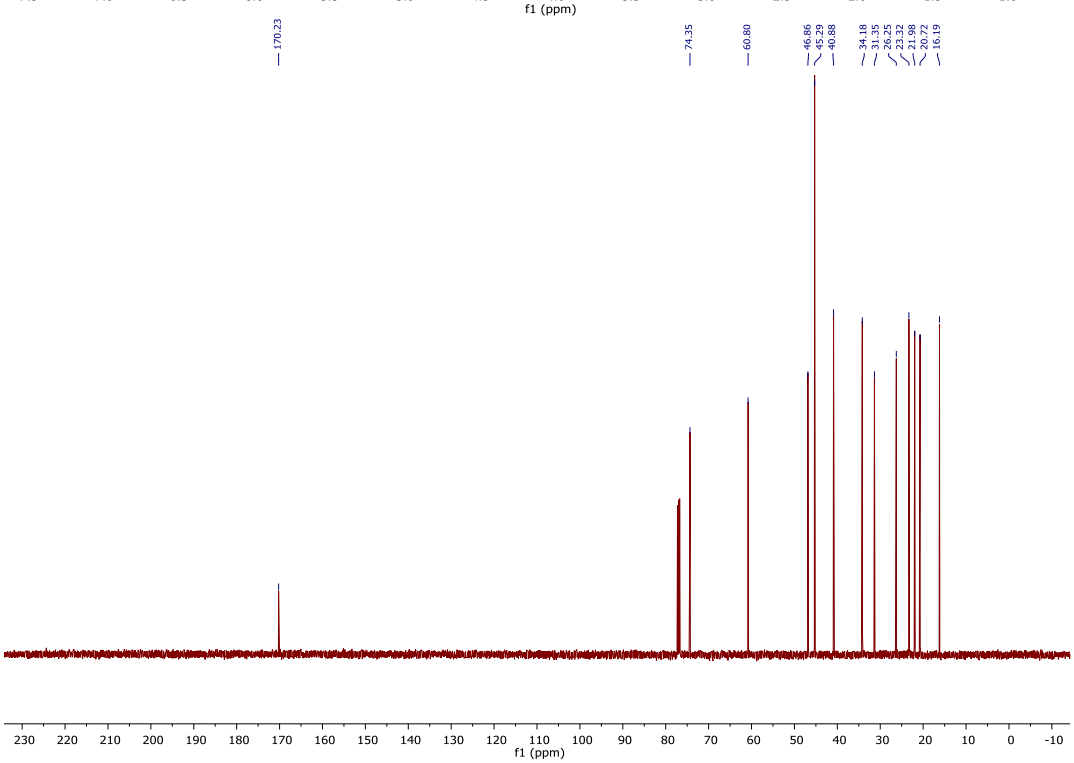
f1 (ppm)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200
190
180
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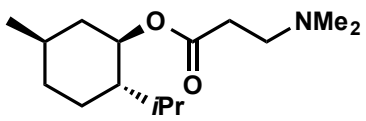
f1 (ppm)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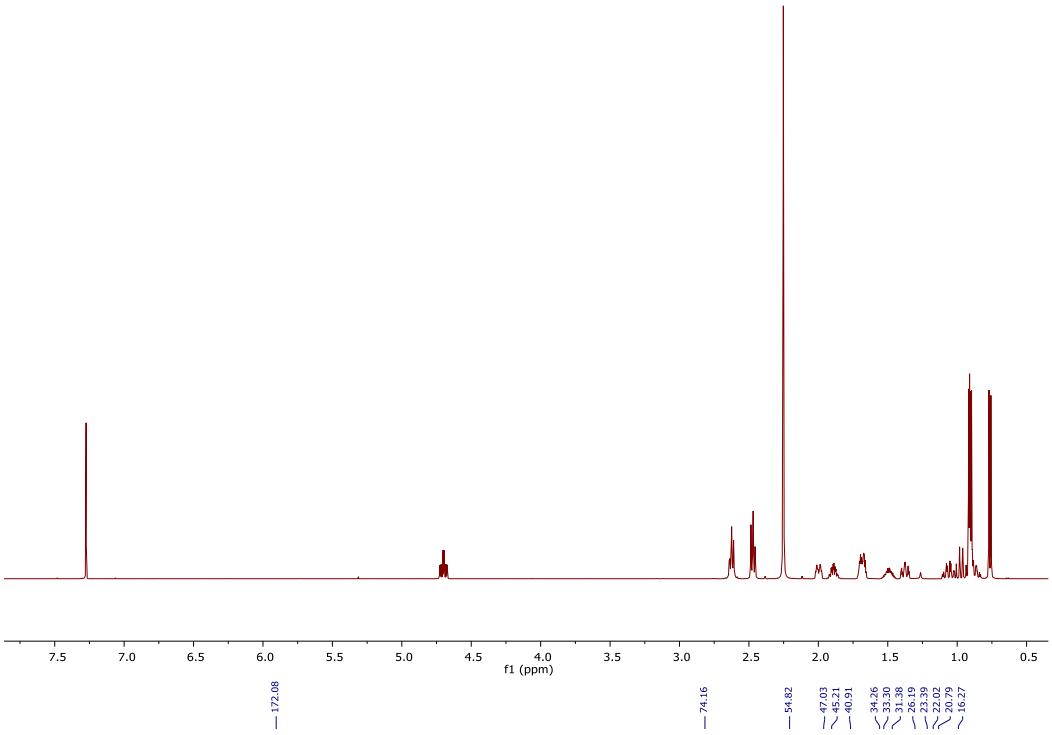
iPr

(–)-**22**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0.5
f1 (ppm)
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74.16
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34.26
33.30
31.38
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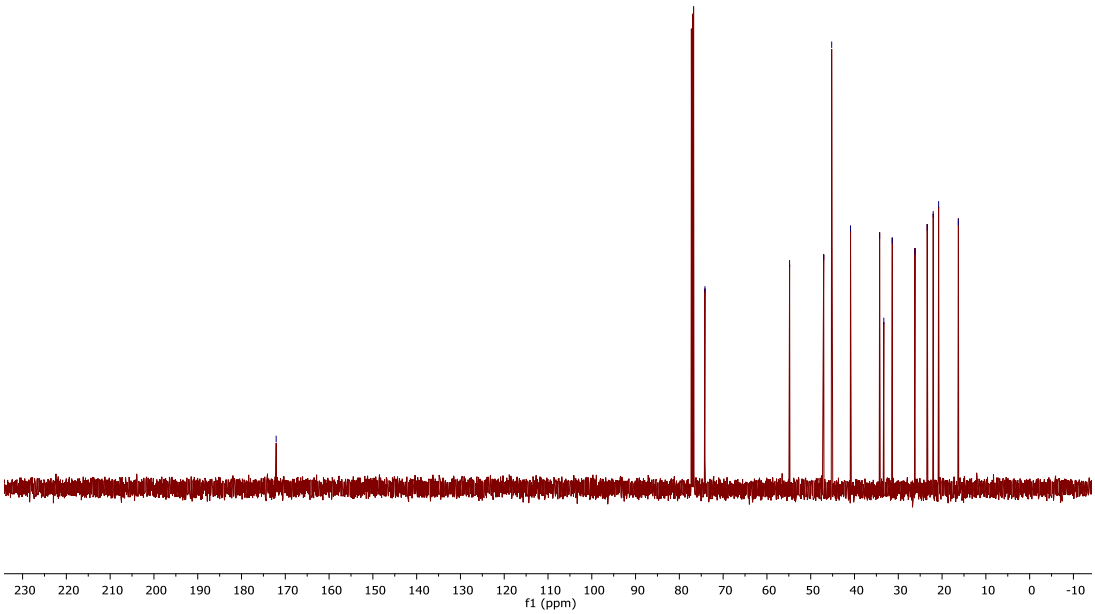
23.39
22.02
20.79
16.27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30
20
10
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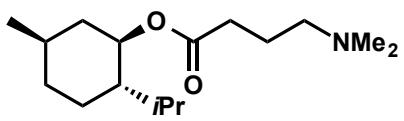
-10
f1 (ppm)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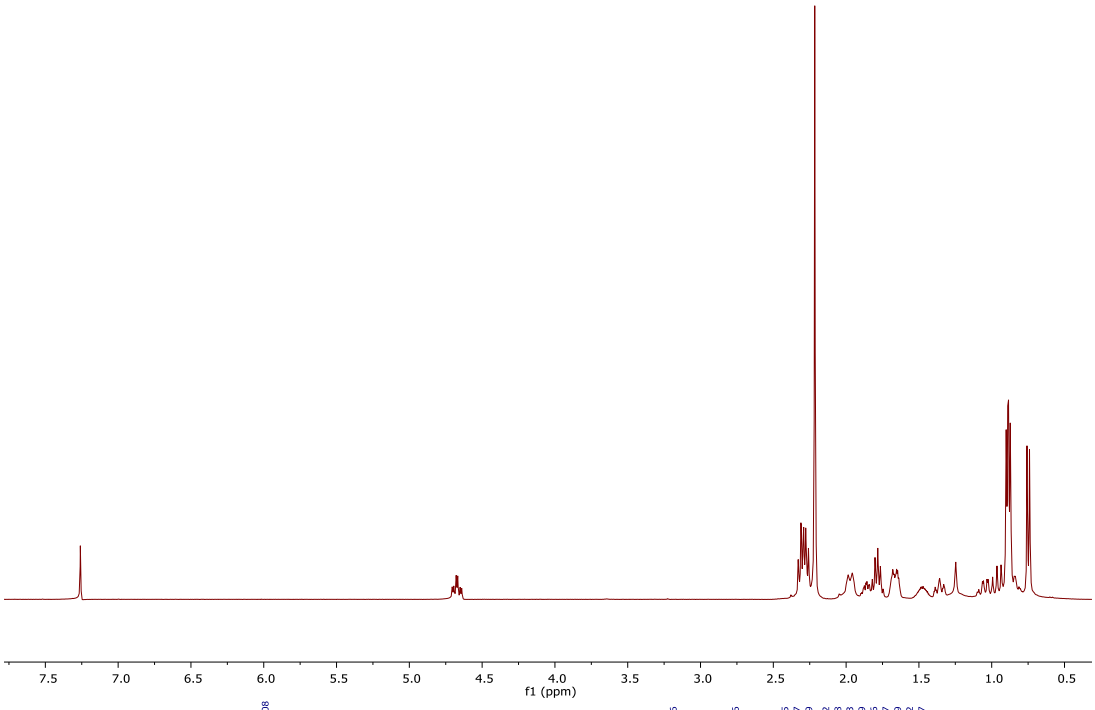
O
iPr

(–)-**23**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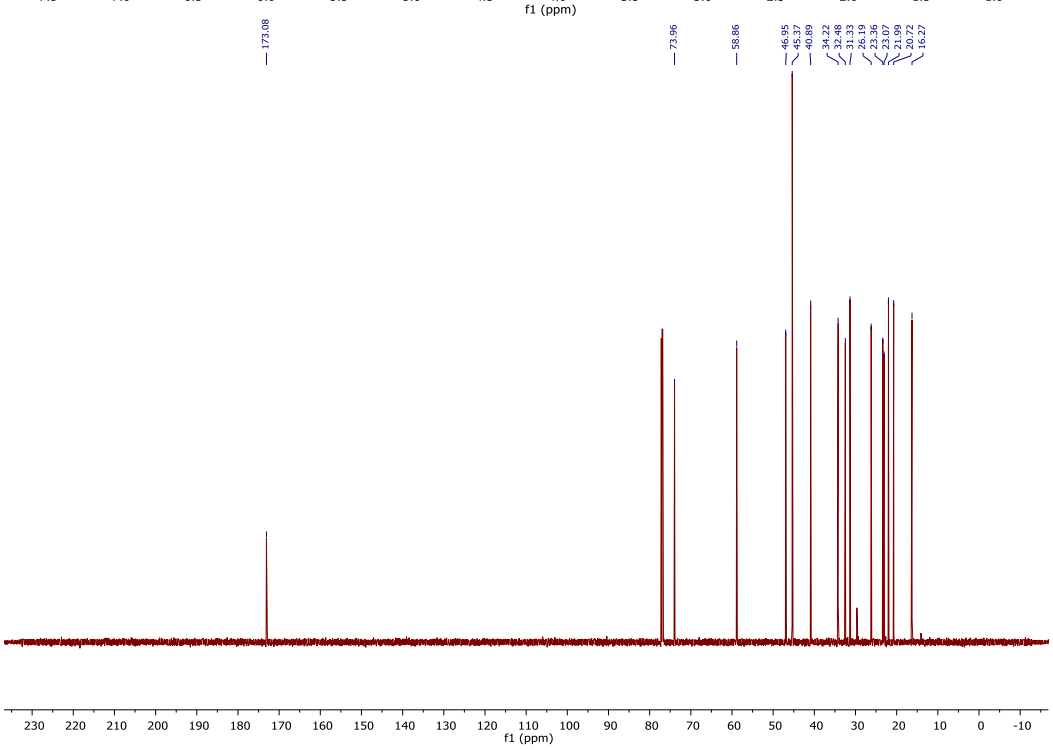
f1 (ppm)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20.72
16.27
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100
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80
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50
40
30
20
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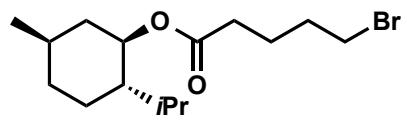
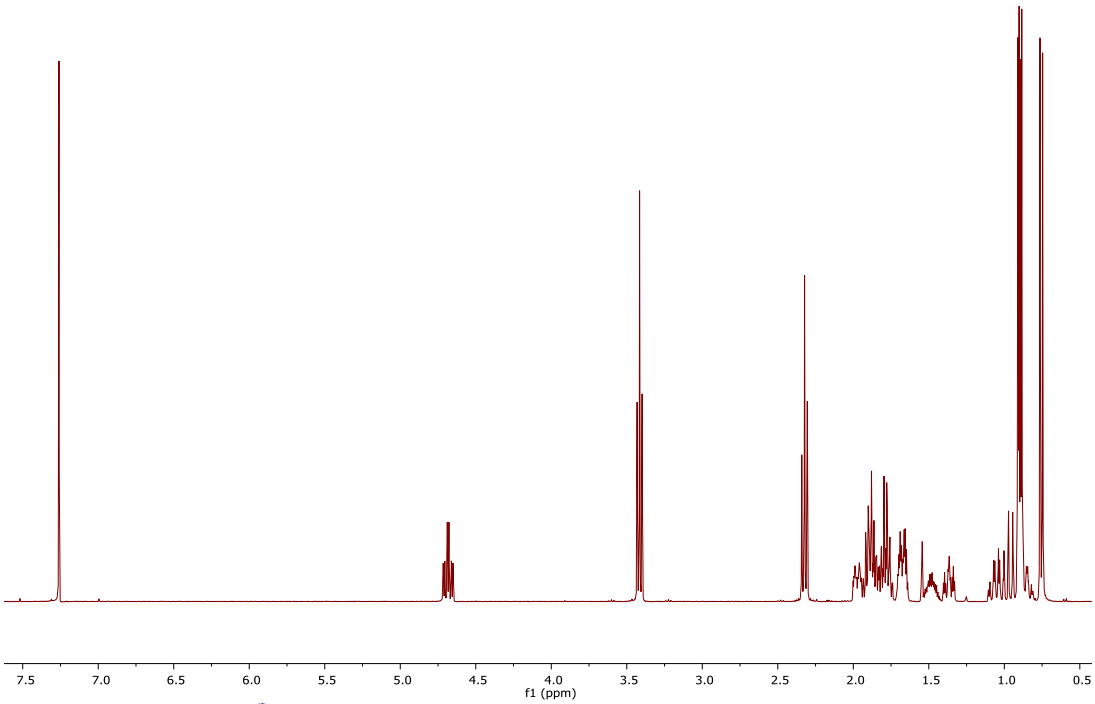
0
-10
f1 (ppm)


O
Br
O
iPr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2.0
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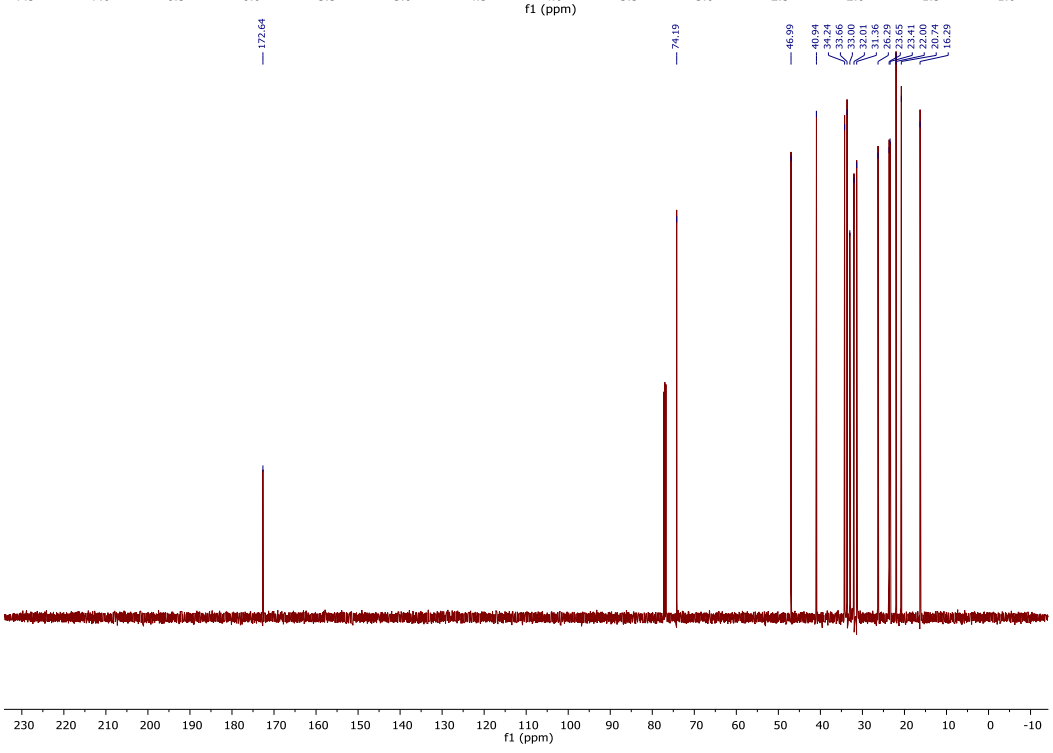
1.0
0.5
f1 (ppm)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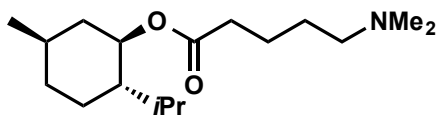
f1 (ppm)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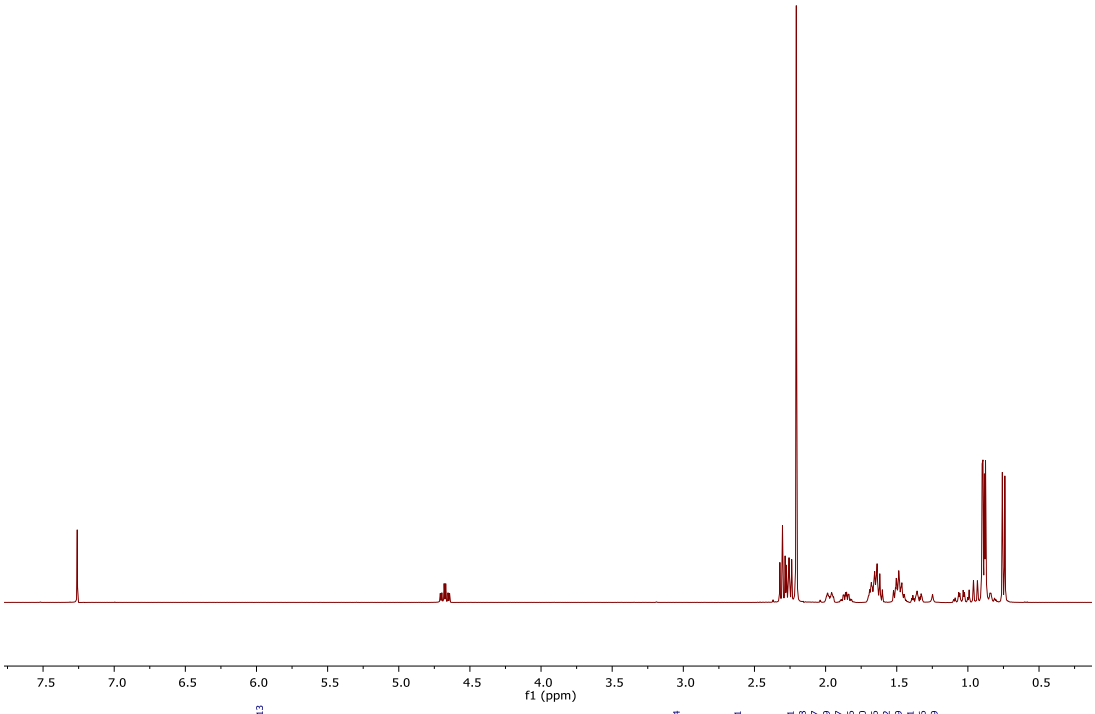
NMe2
O
iPr

(–)-**24**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3.0
2.5
2.0
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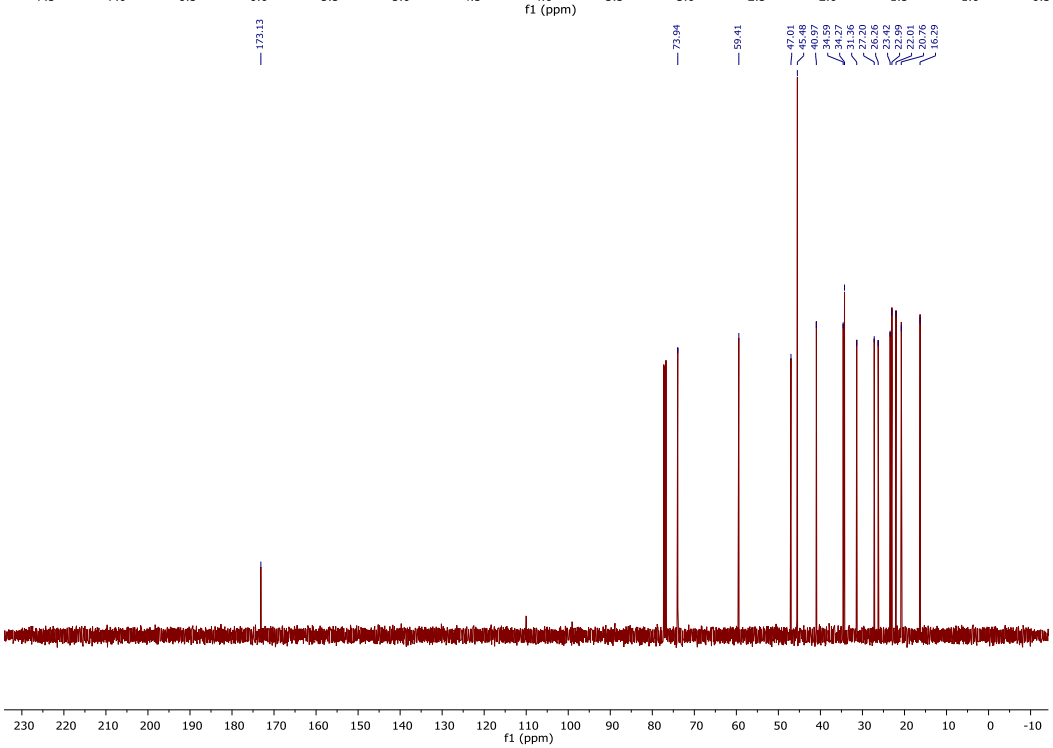
1.0
0.5
f1 (ppm)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21.01
20.76
16.29
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180
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40
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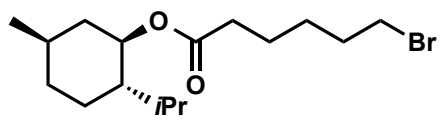
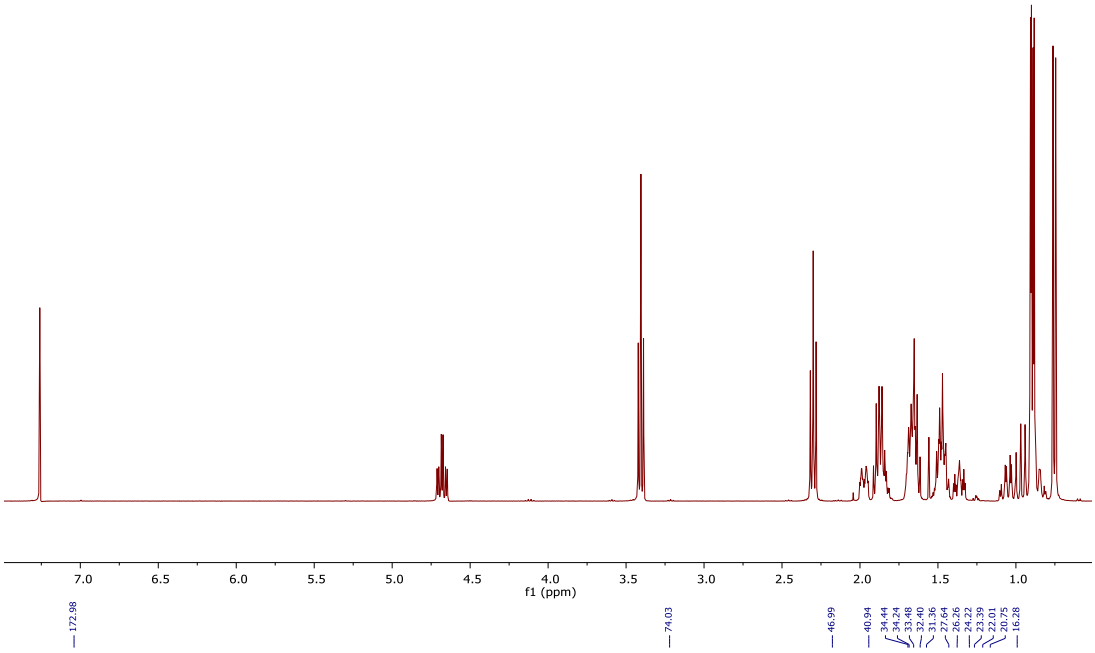
f1 (ppm)


O
Br
O
iPr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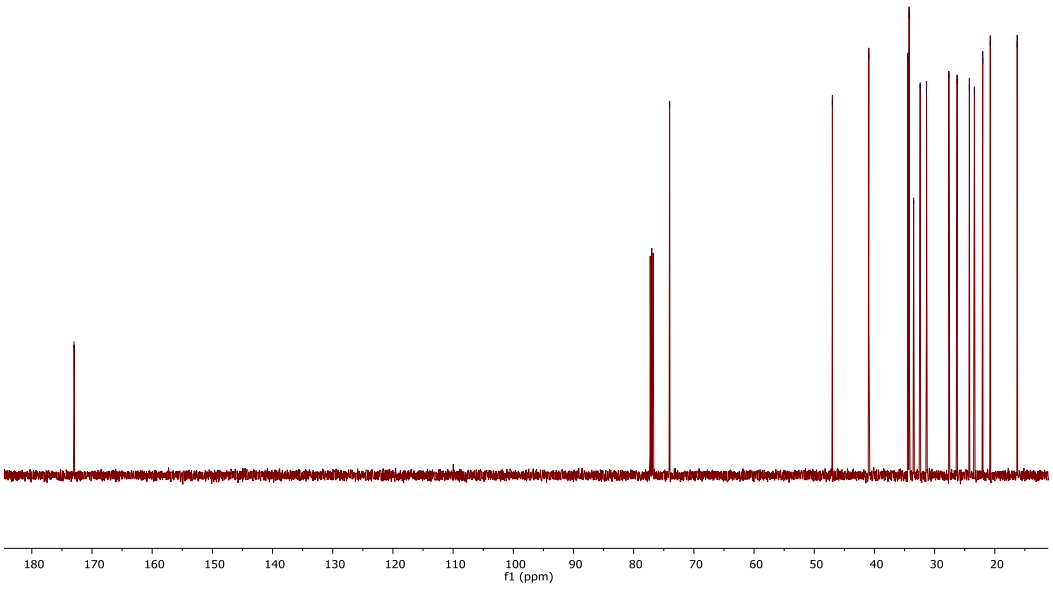
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)
172.98
74.03
46.99
40.94
34.44
34.24
33.48
32.40
31.36
27.64
26.26
24.22
23.39
22.01
20.75
16.28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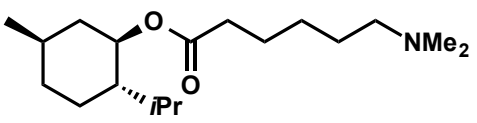
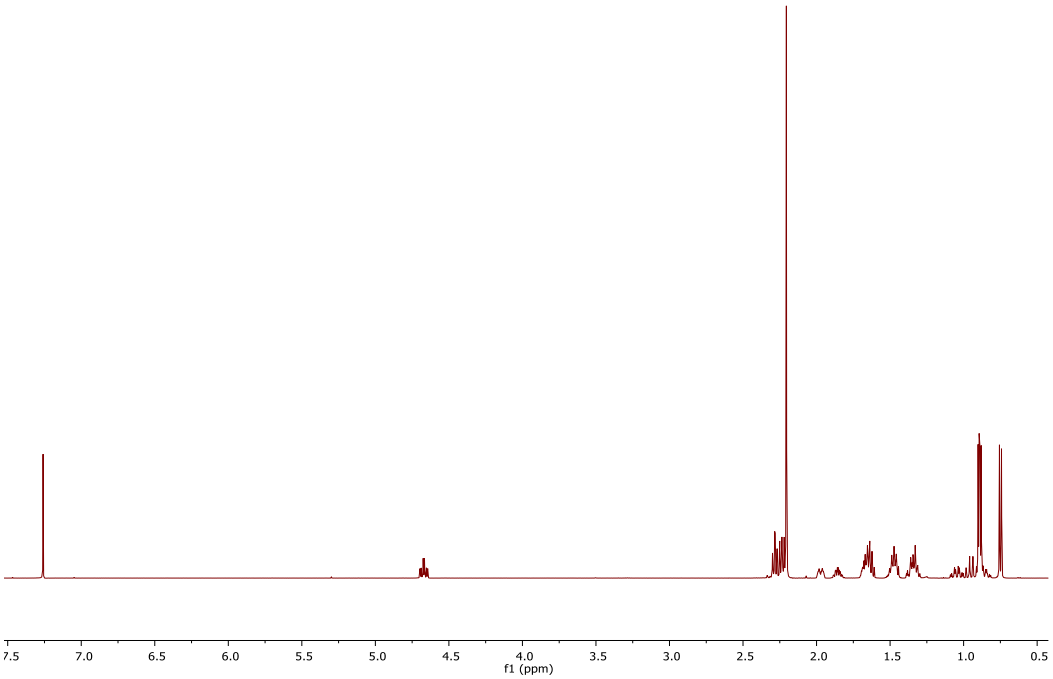
f1 (ppm)


O
O
NMe2
iPr

(–)-**25**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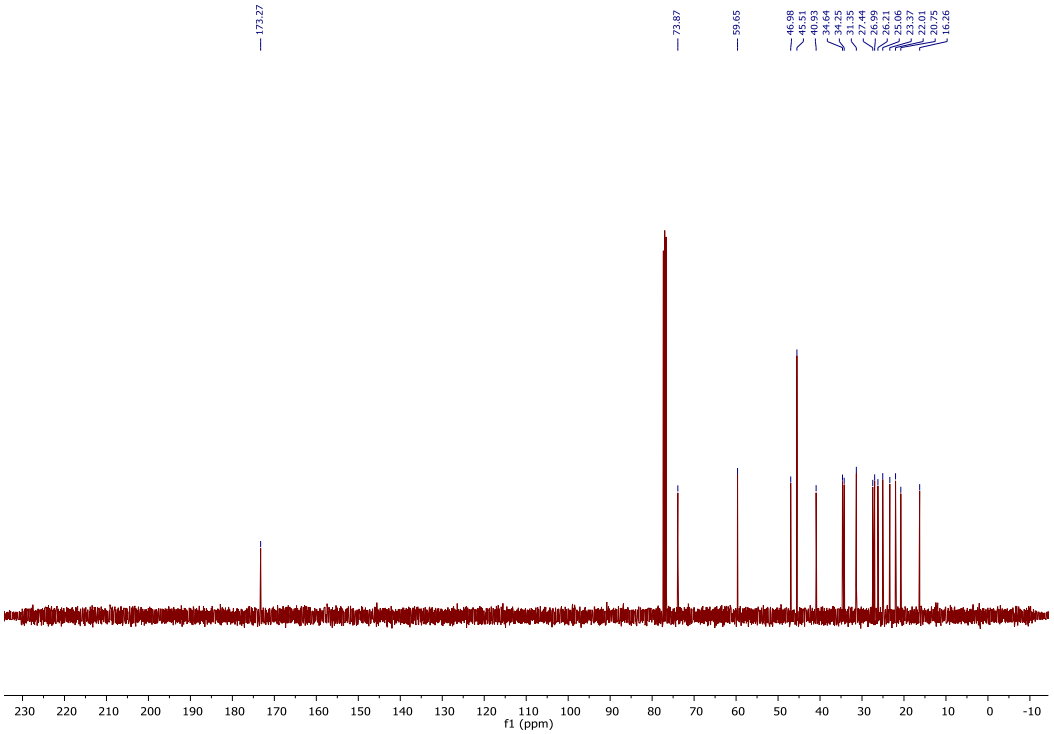
f1 (ppm)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100
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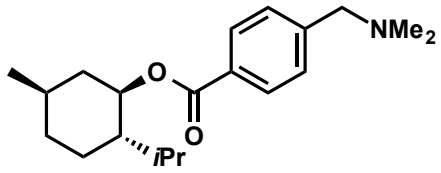
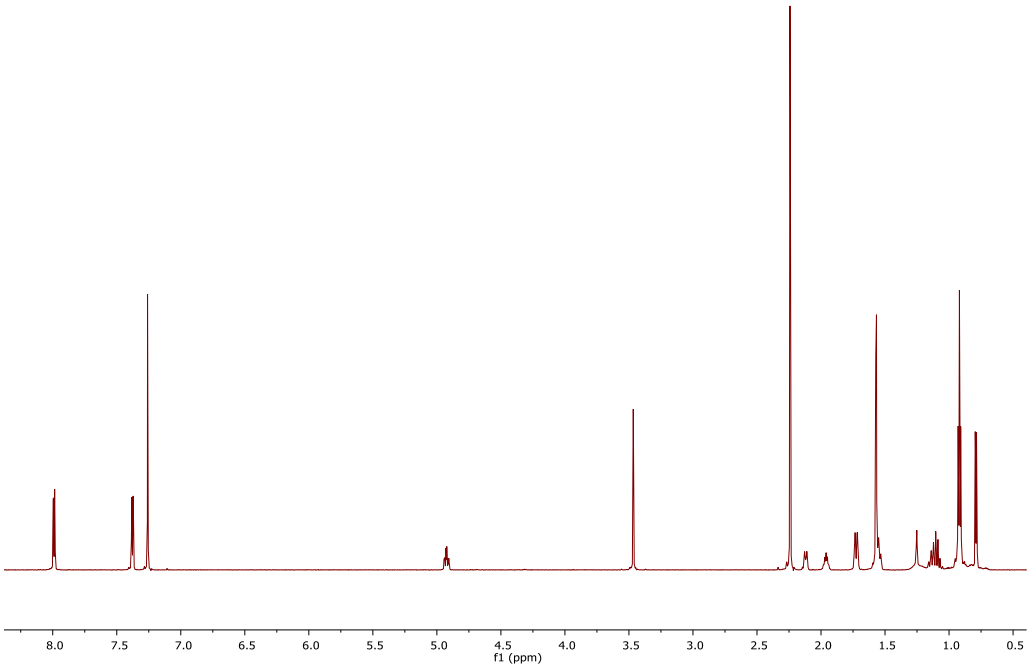
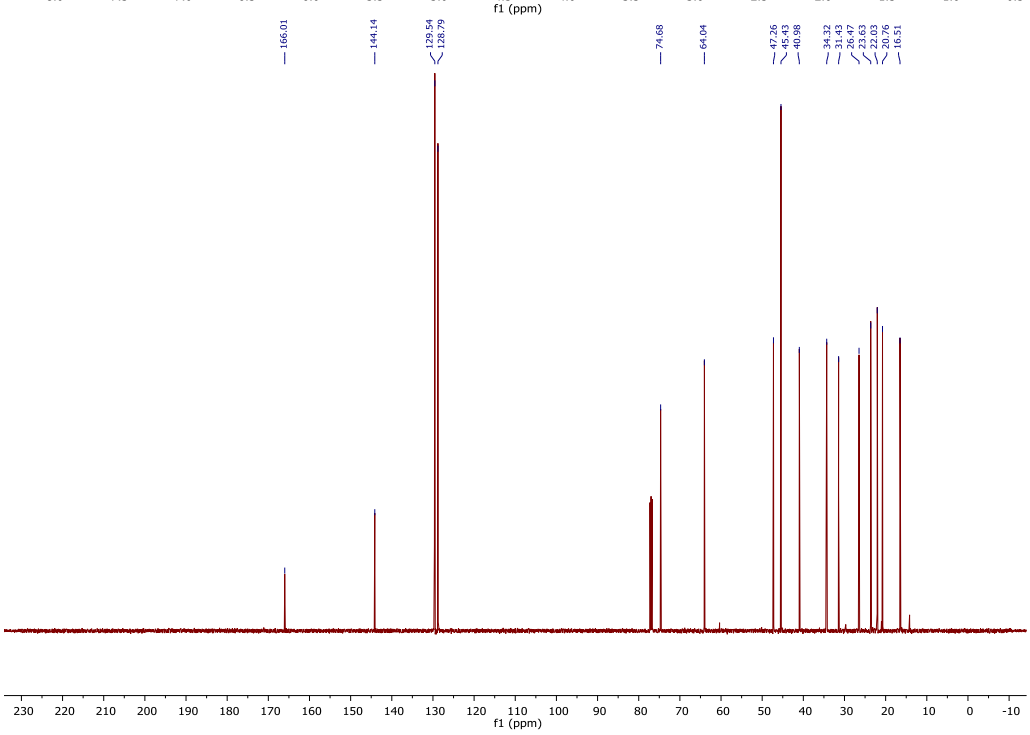
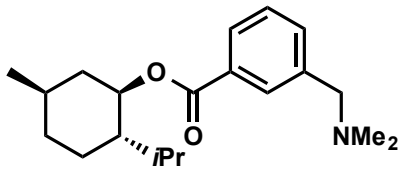
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


NMe2
O
O
iPr

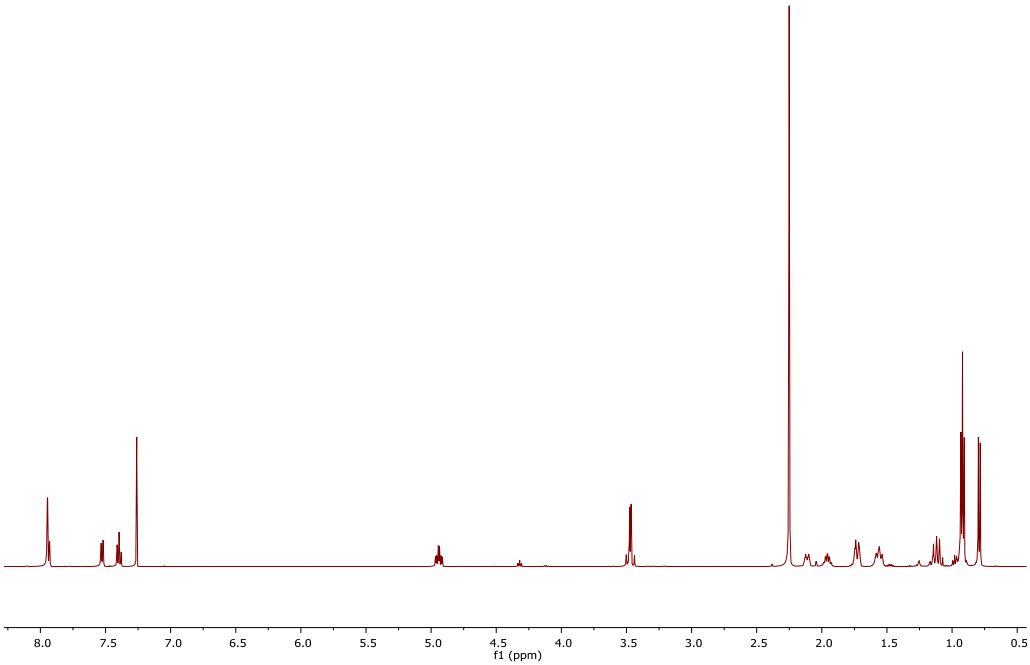
(–)-**26**

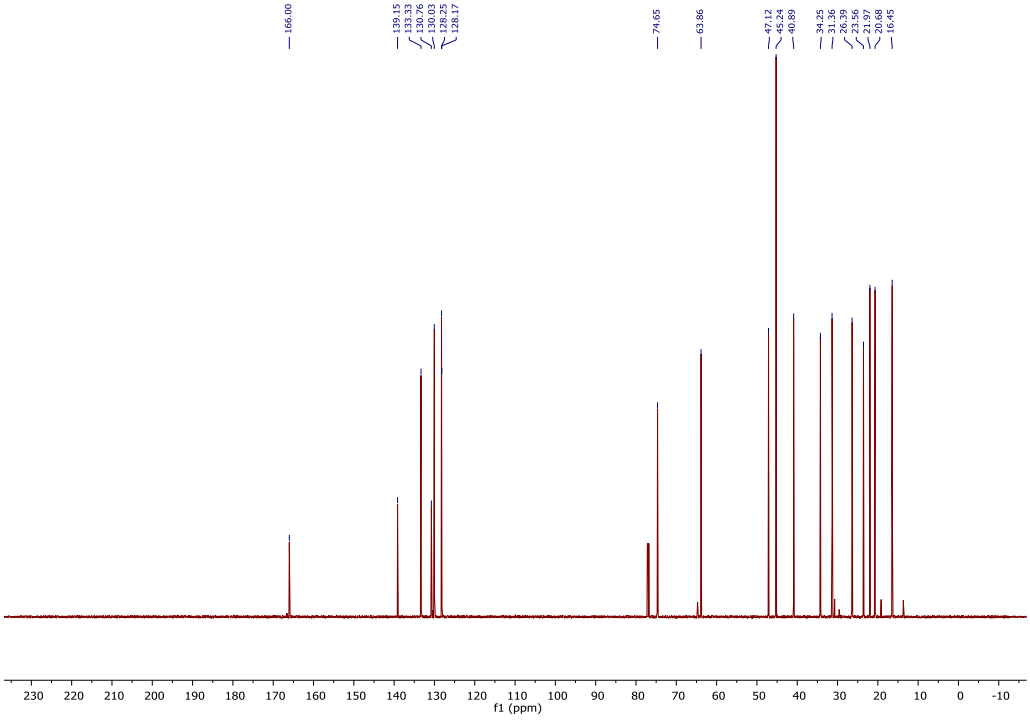

8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

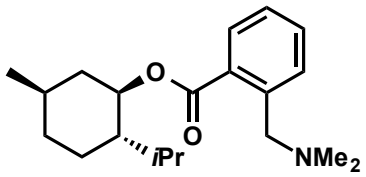

166.01
144.14
129.54
128.79
74.68
64.04
47.26
45.43
40.98
34.32
31.48
26.47
23.63
22.03
20.76
16.51
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


O
O
NMe2
iPr

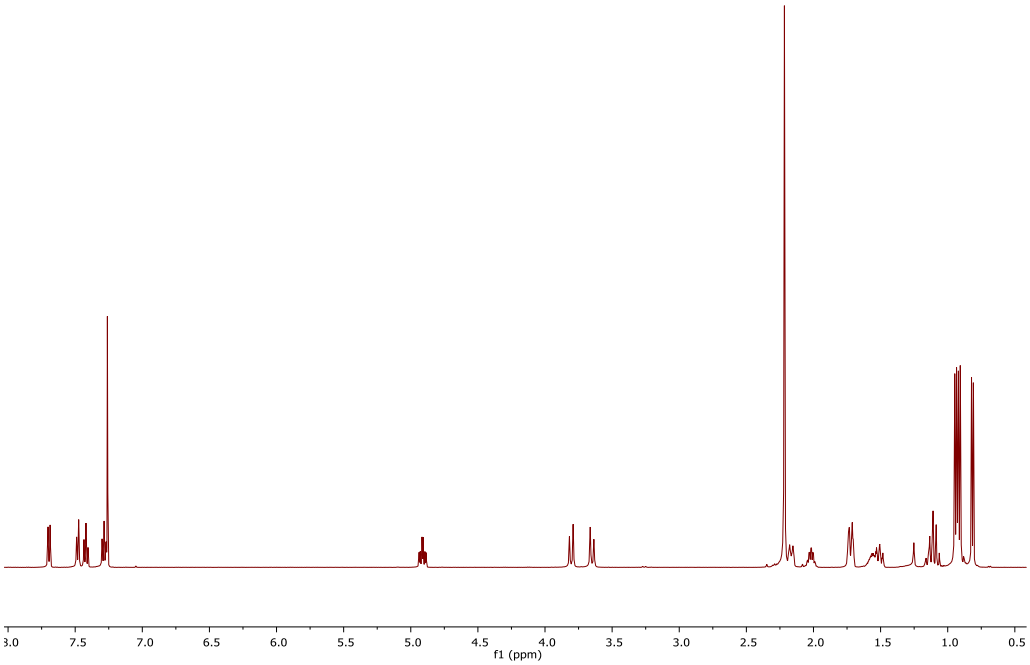
(–)-**27**

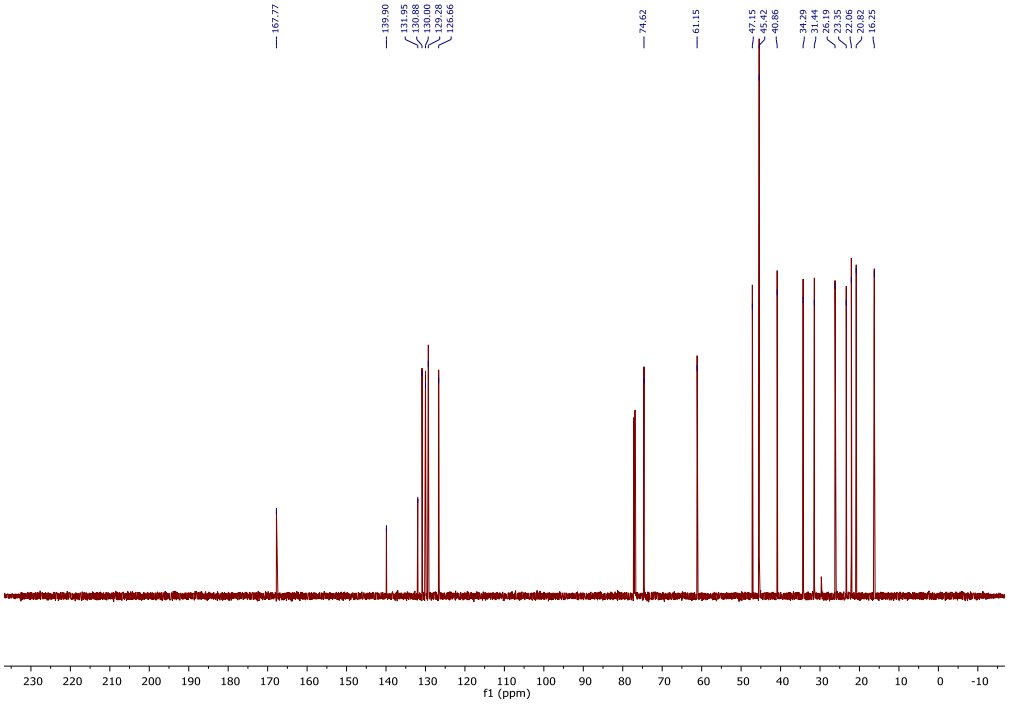

8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

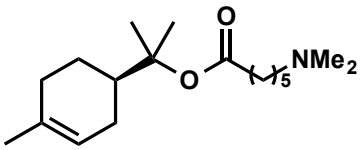

166.00
139.15
133.33
130.56
130.03
128.25
128.17
74.65
63.86
47.12
45.24
40.89
34.25
31.36
26.39
23.56
21.89
20.68
16.45
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


O
O
iPr
NMe2

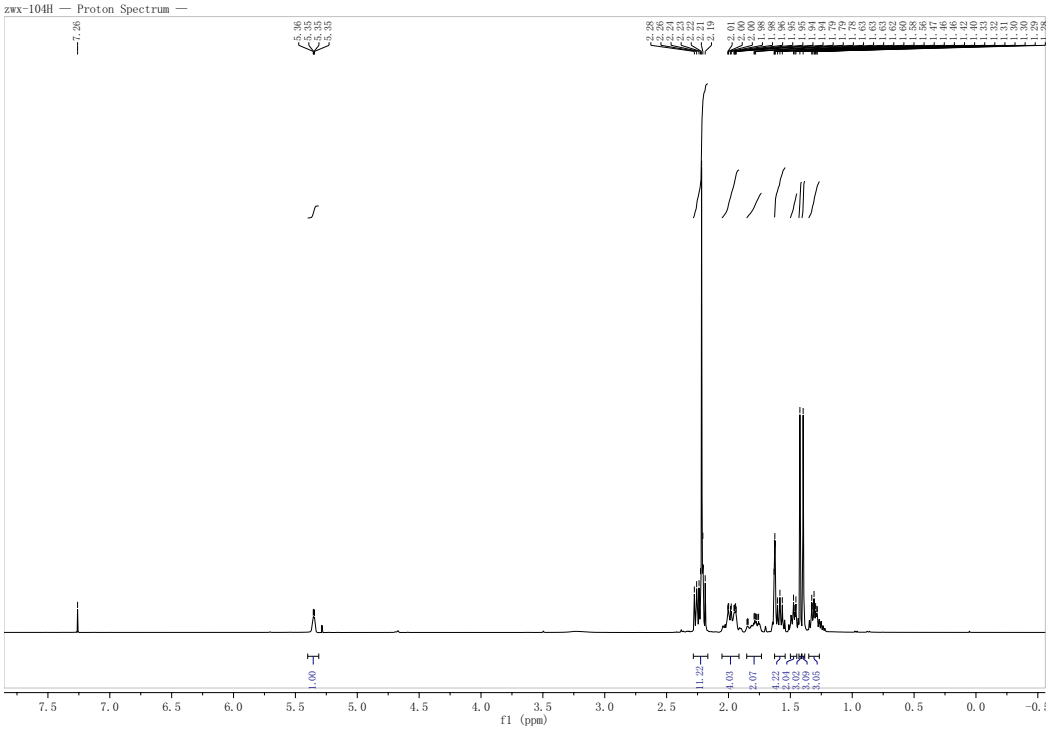
(–)-**28**


f1 (ppm)

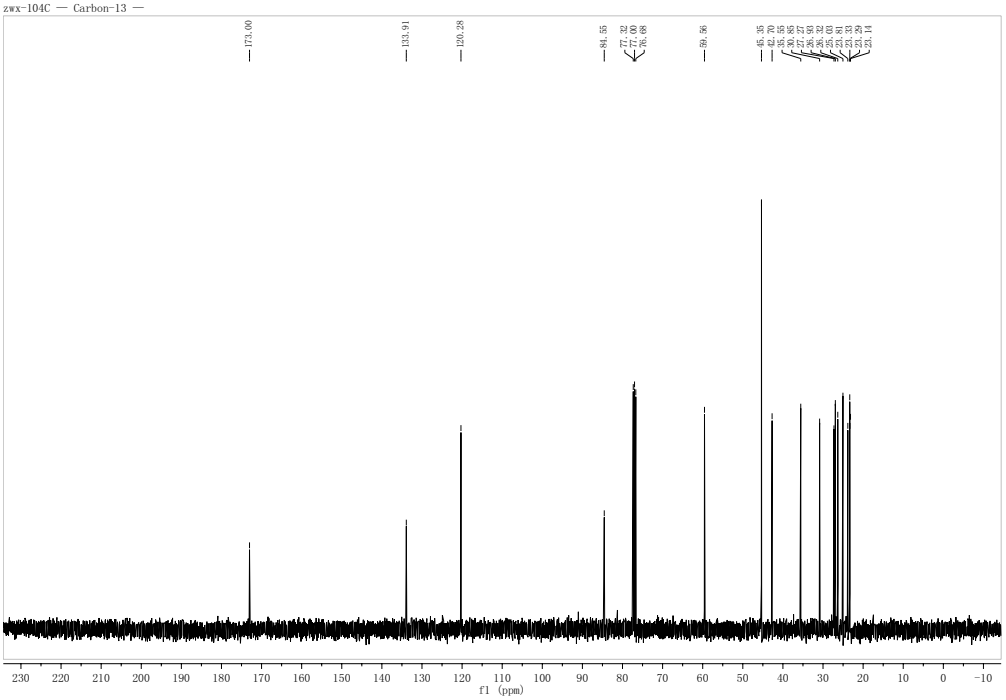

167.77
139.90
131.95
130.88
130.00
129.28
126.66
74.62
61.15
47.15
45.42
40.86
34.29
31.44
28.19
23.35
22.06
20.82
16.25
f1 (ppm)

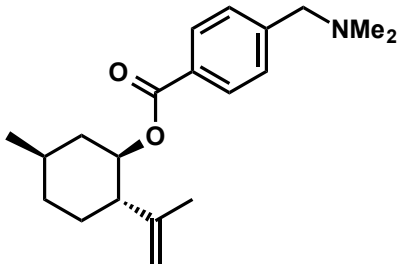


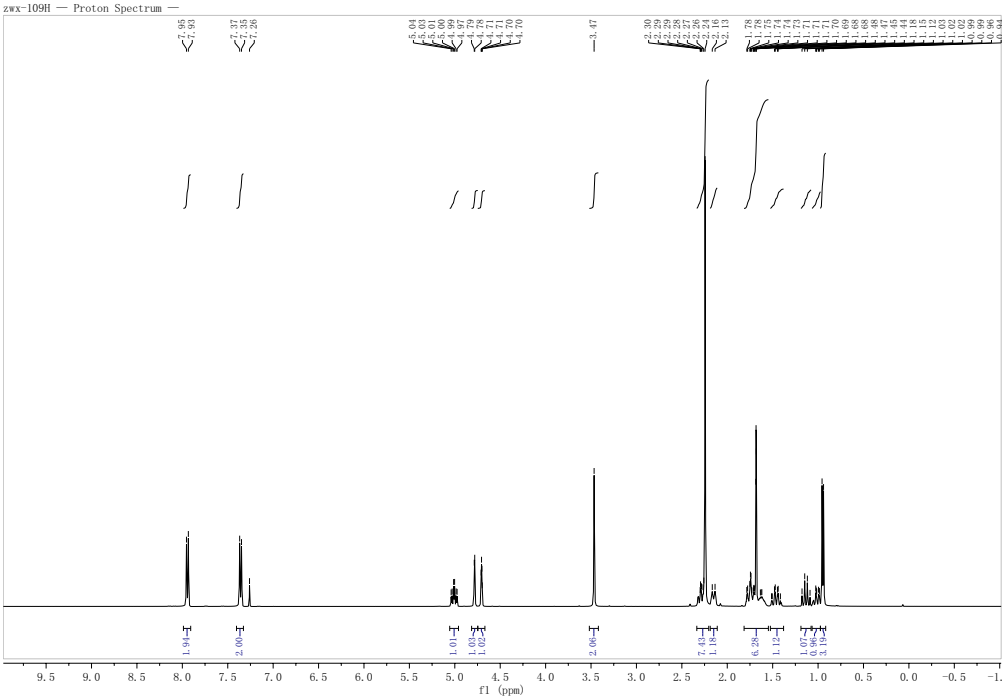
zwx-104H — Proton Spectrum —

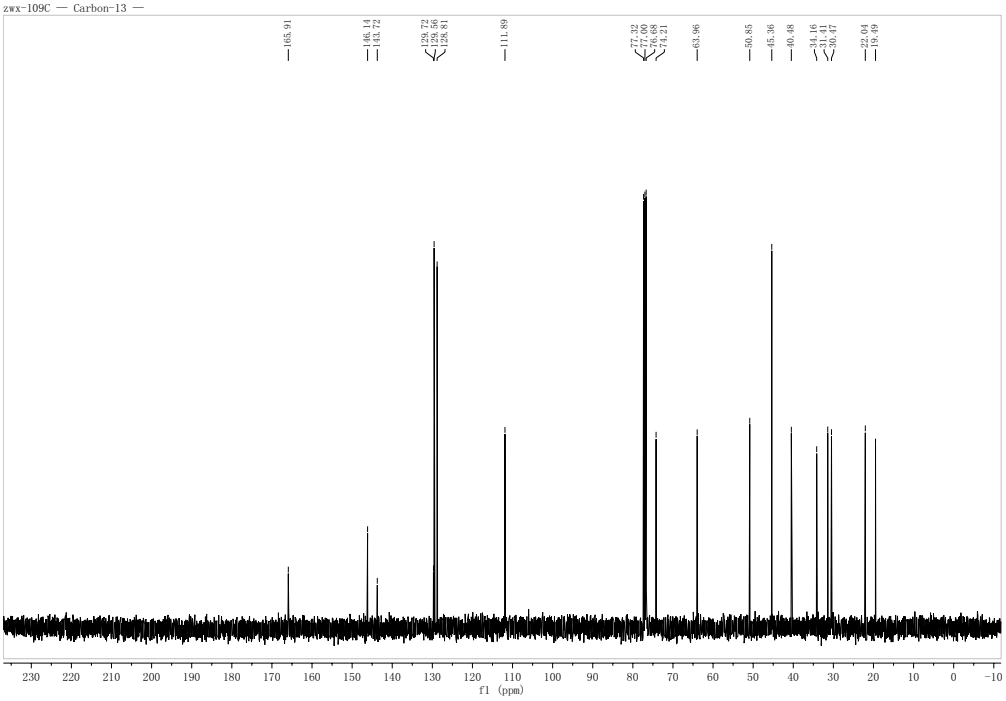


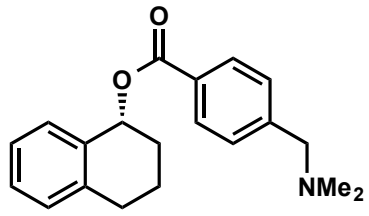
zwx-104C — Carbon-13 —

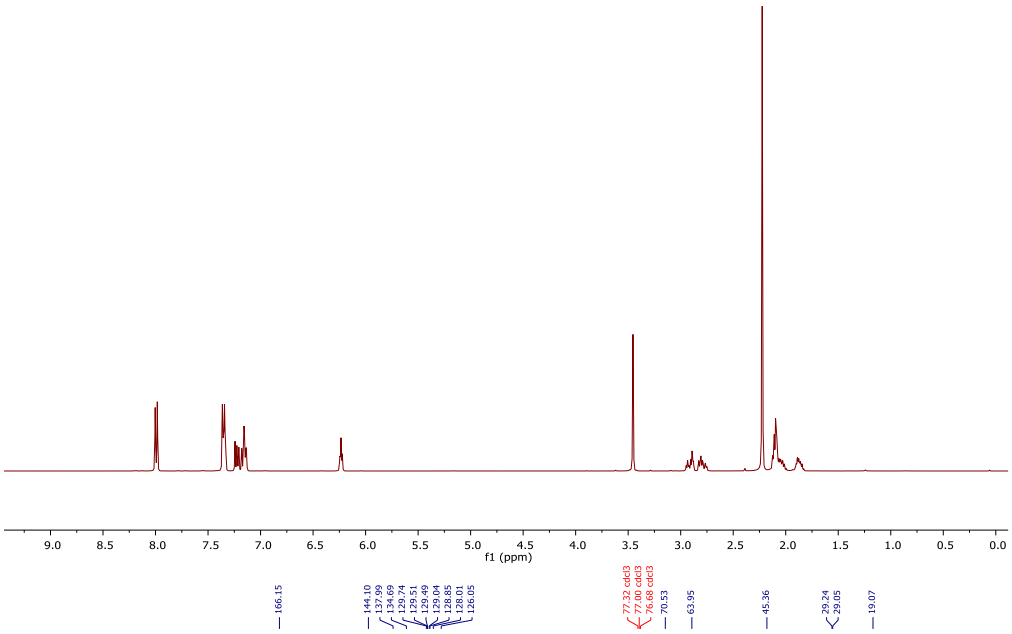


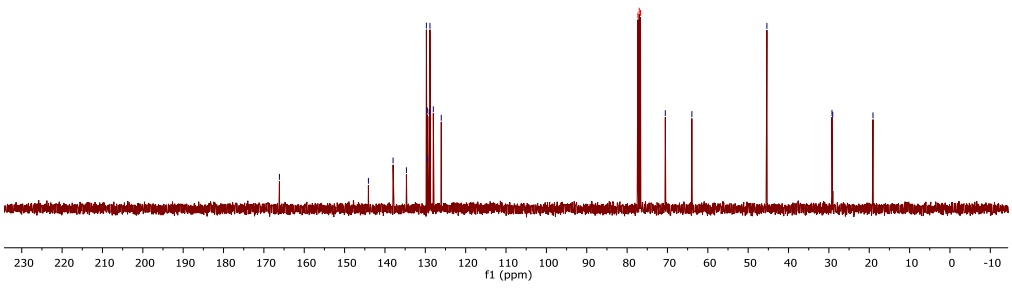

NMe2
O
O

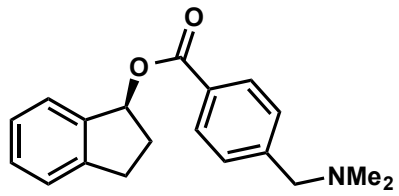

zwx-109H — Proton Spectrum —
f1 (ppm)

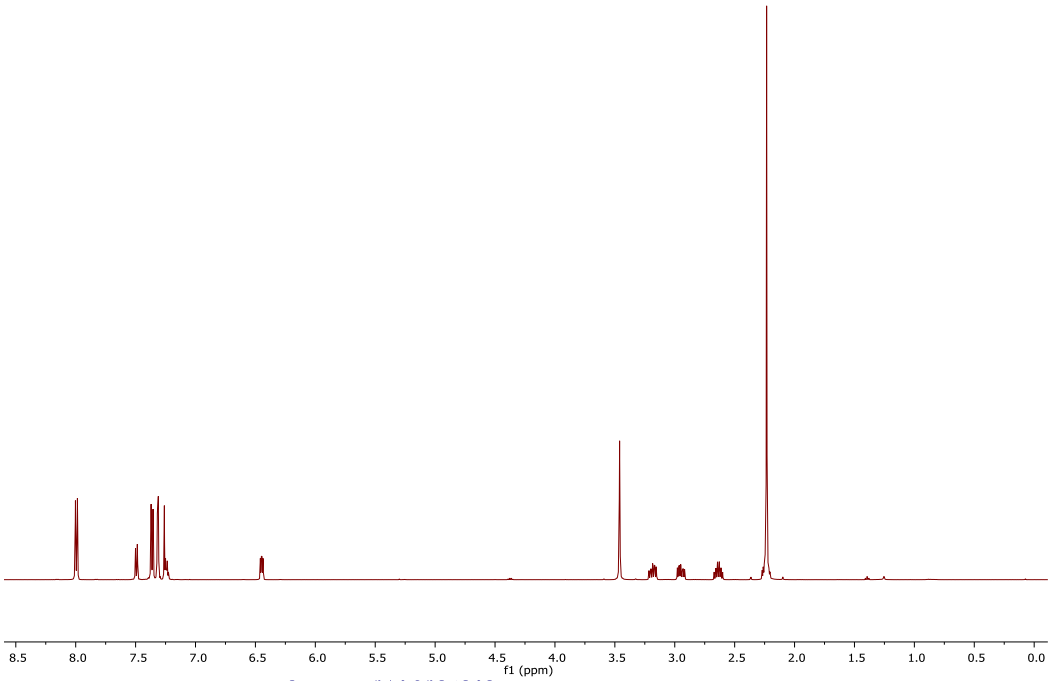

zwx-109C — Carbon-13 —
f1 (ppm)

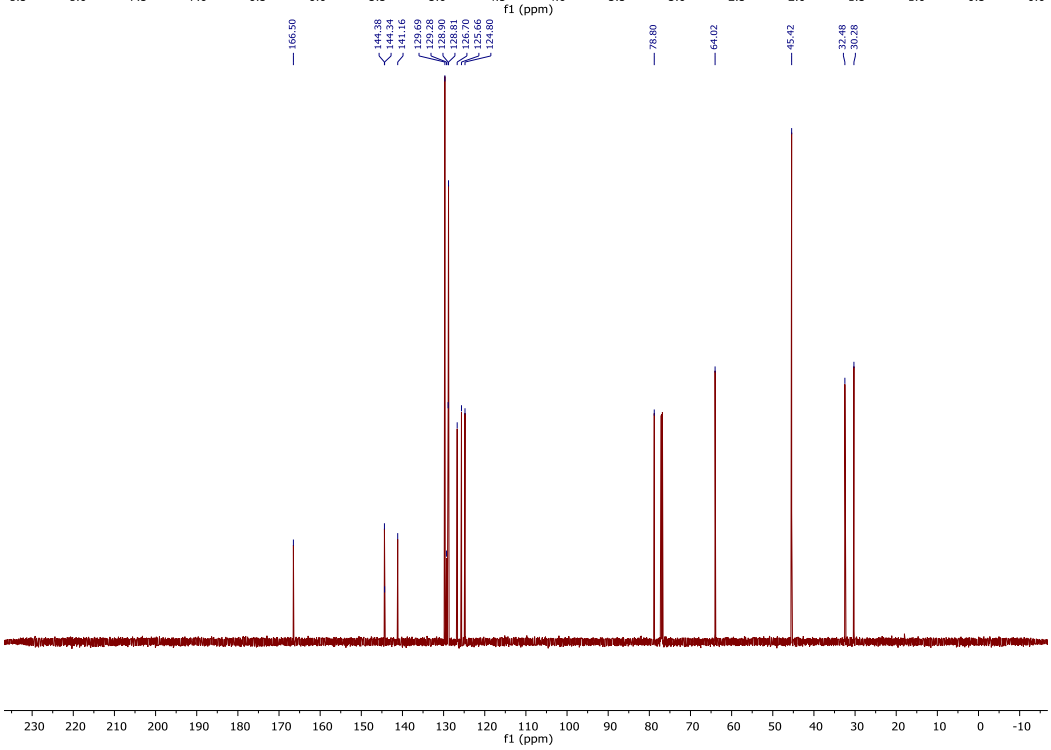

O
O
NMe2

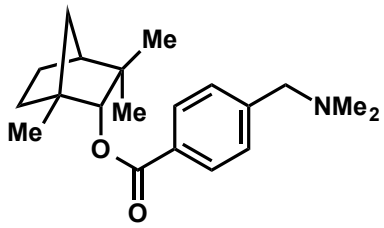

9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
166.15
144.10
137.99
134.68
129.74
129.51
129.49
129.04
128.65
128.01
126.05
77.32 cdcl3
77.00 cdcl3
76.68 cdcl3
70.53
63.95
45.36
29.34
29.05
19.07

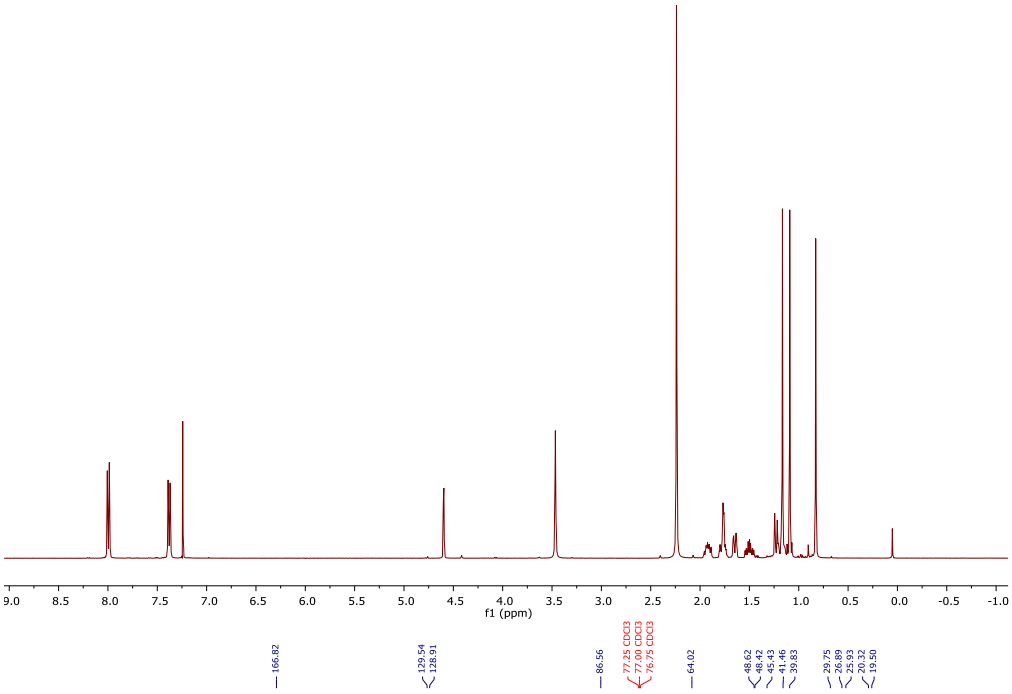

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

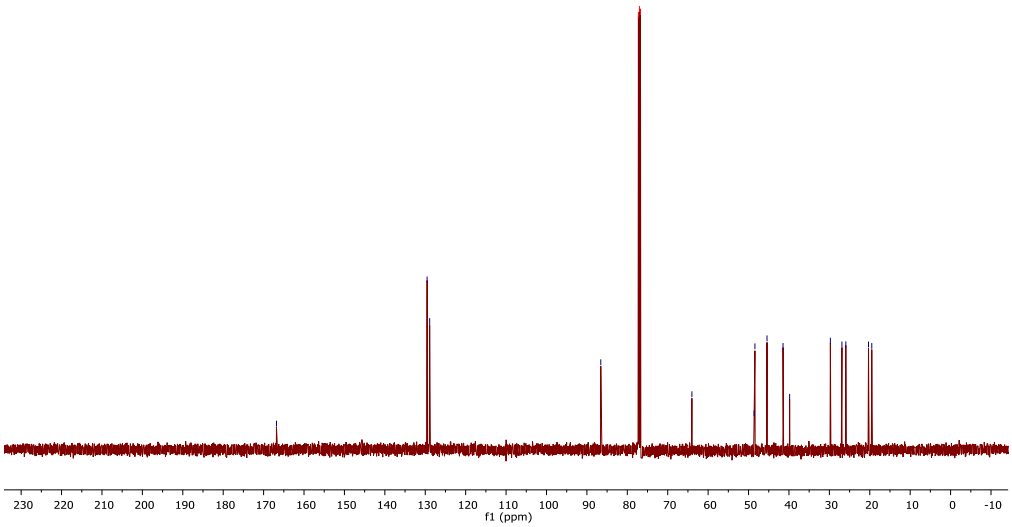

O
O
NMe2

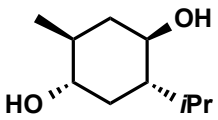

8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


166.50
144.38
144.34
141.16
129.69
129.28
128.90
128.81
126.70
125.66
124.80
78.80
64.02
45.42
32.48
30.28
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

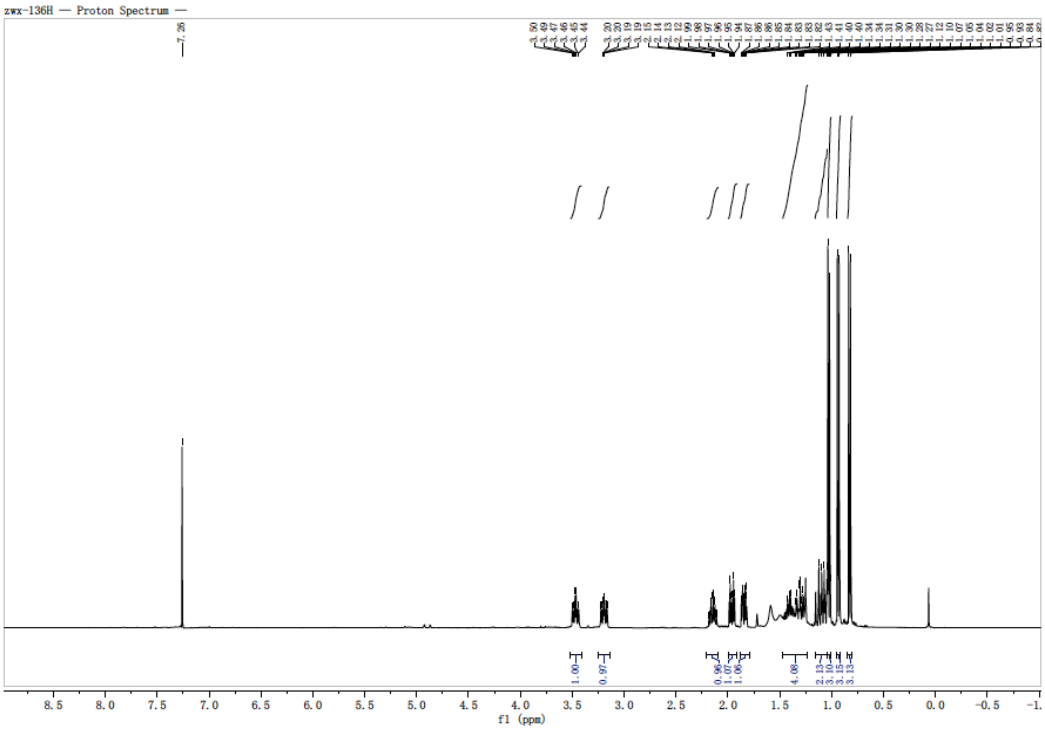

Me
Me
Me
O
O
NMe2

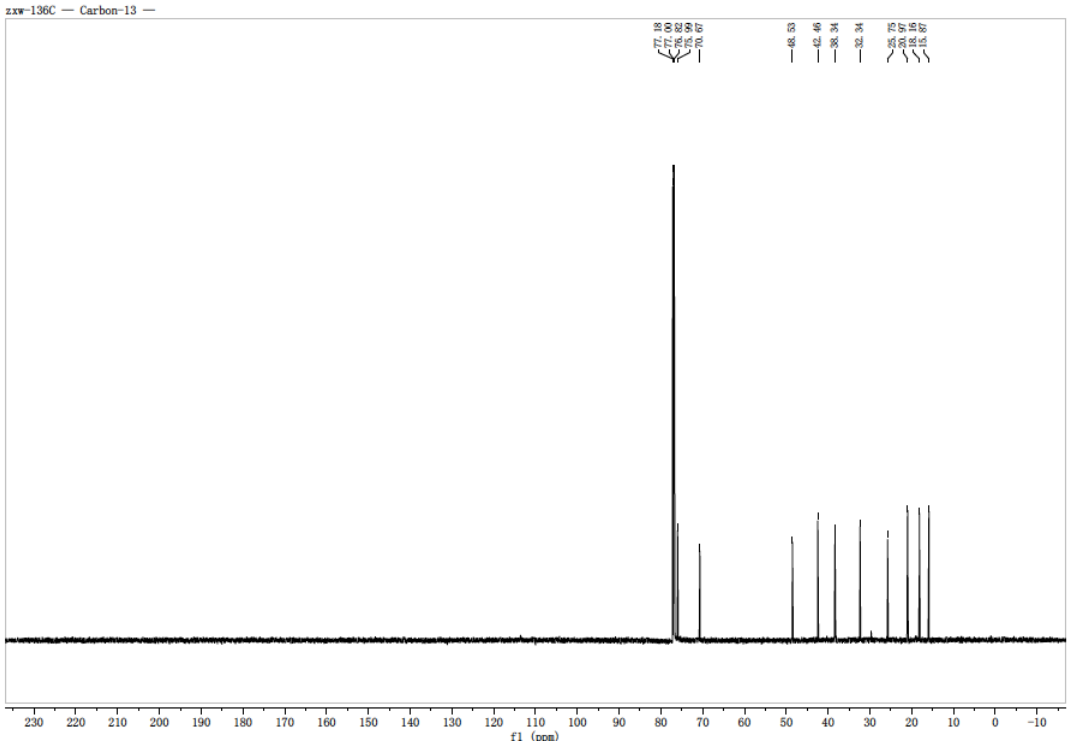

9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)
166.82
129.54
128.91
86.56
77.25 CDCl3
77.00 CDCl3
76.75 CDCl3
64.02
48.62
48.42
45.43
41.46
39.83
29.75
26.88
25.93
20.32
19.50

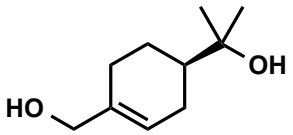

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


OH
HO
iPr

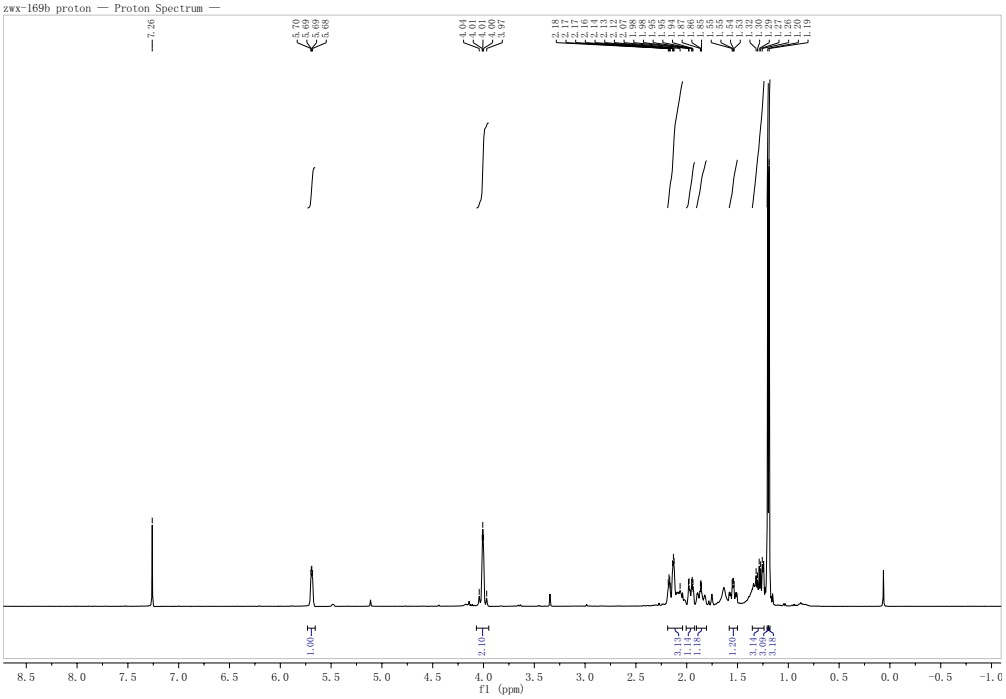
(–)-8


zwx-136H — Proton Spectrum —
f1 (ppm)

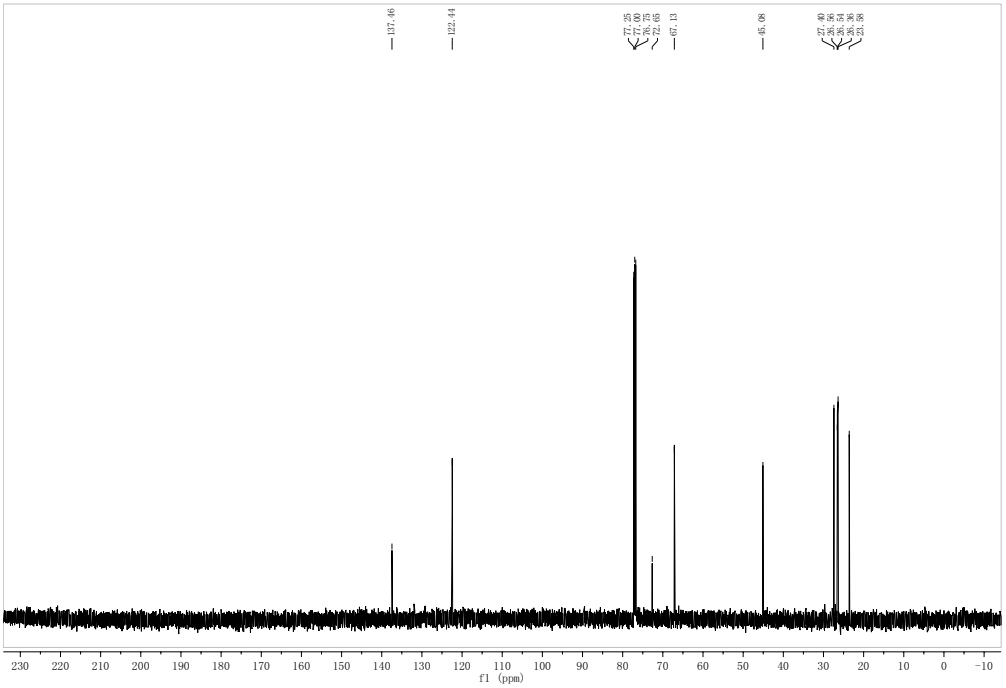

zxw-136C — Carbon-13 —
f1 (ppm)

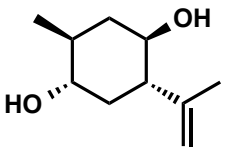


zwx-169b proton — Proton Spectrum —

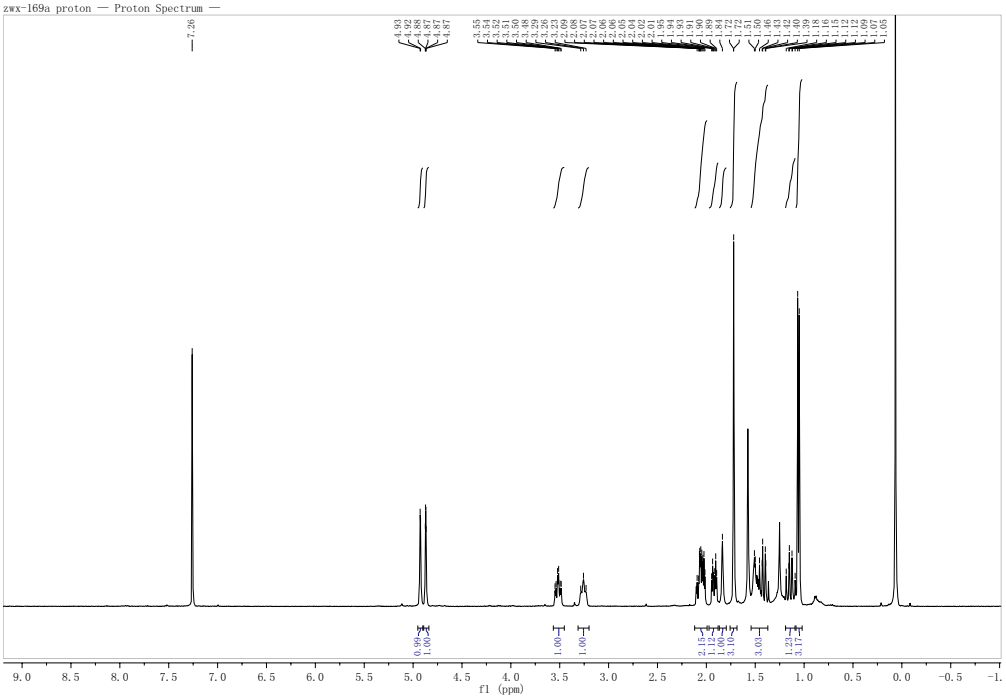


zwx-169b carbon — Carbon-13 —

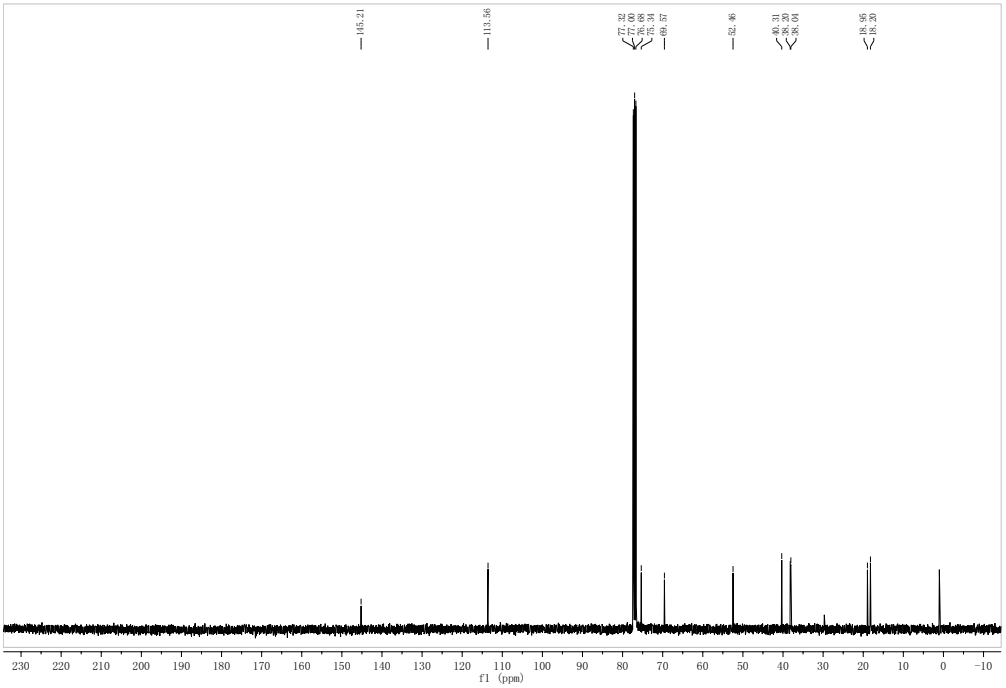


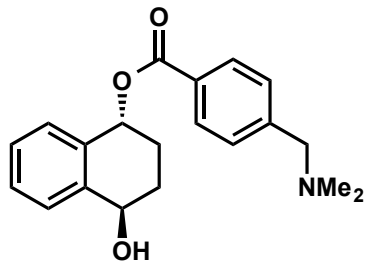


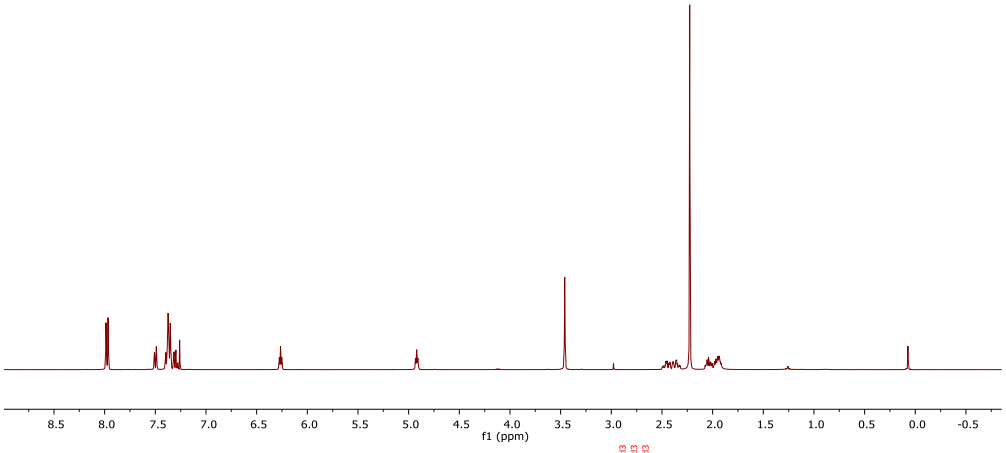
zwx-169a proton — Proton Spectrum —

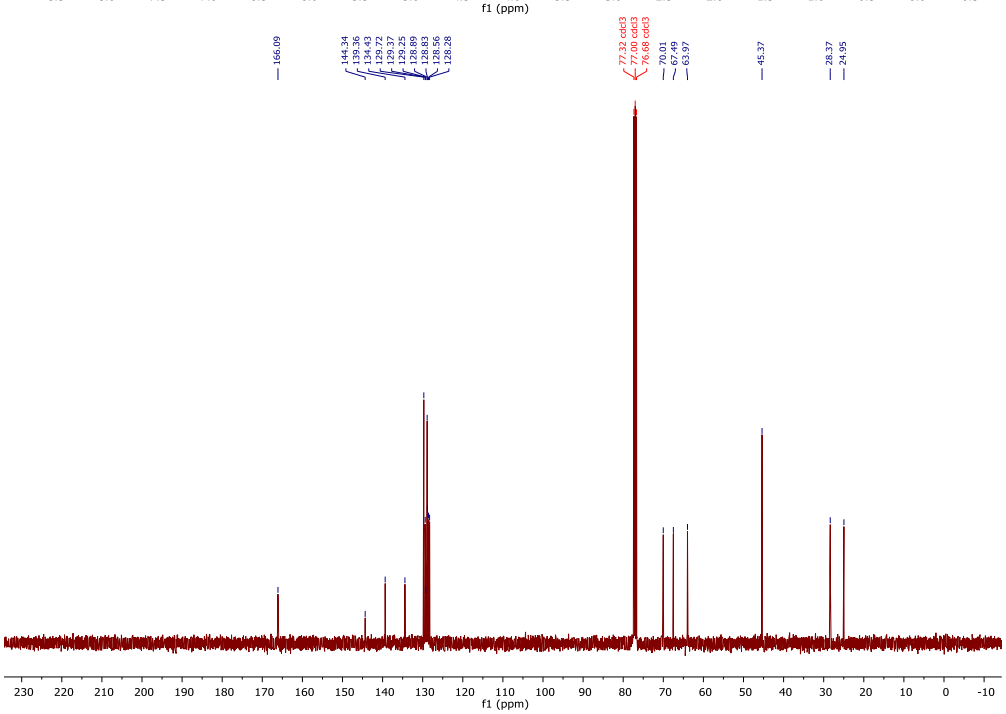


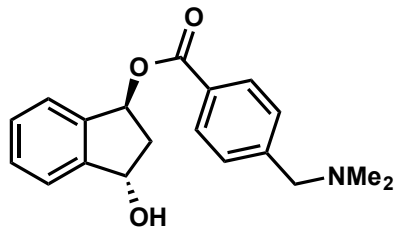
zwx-169a carbon — Carbon-13 —

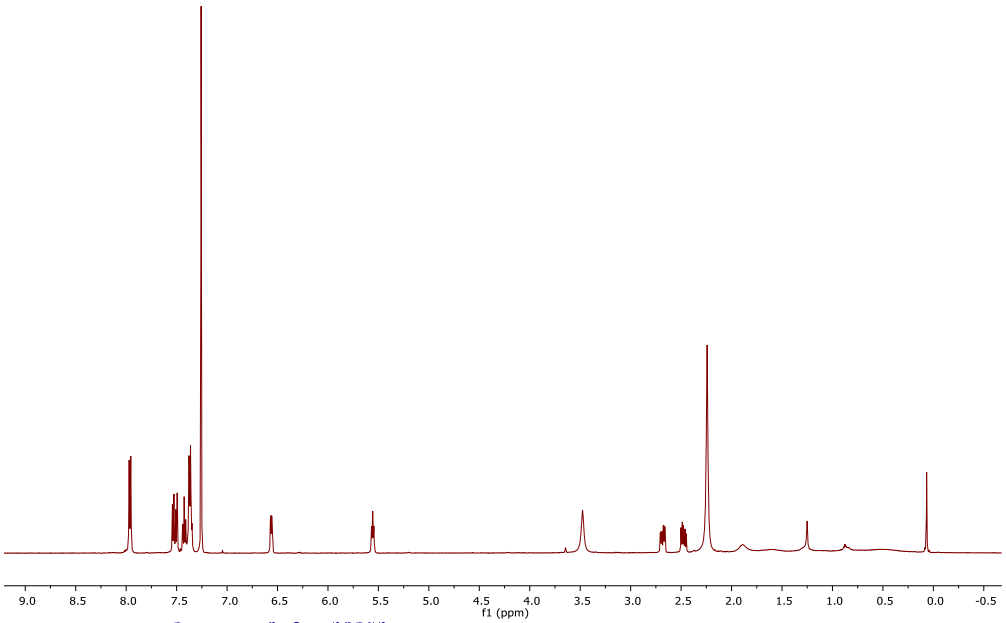


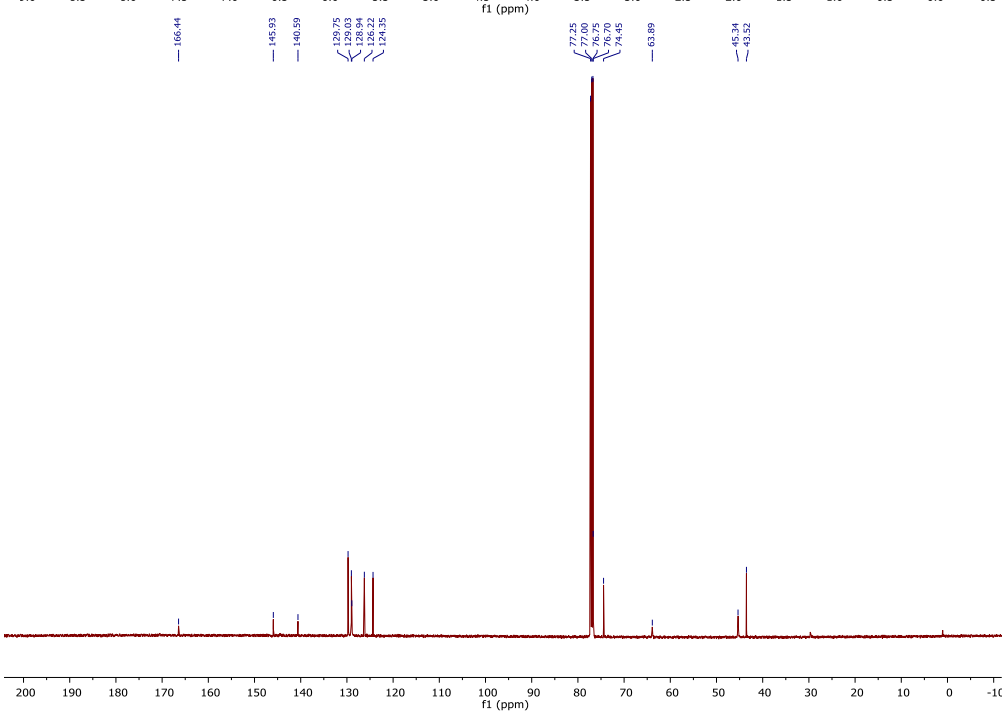

O
O
NMe2
OH

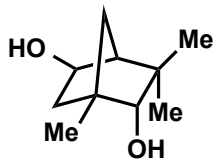

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

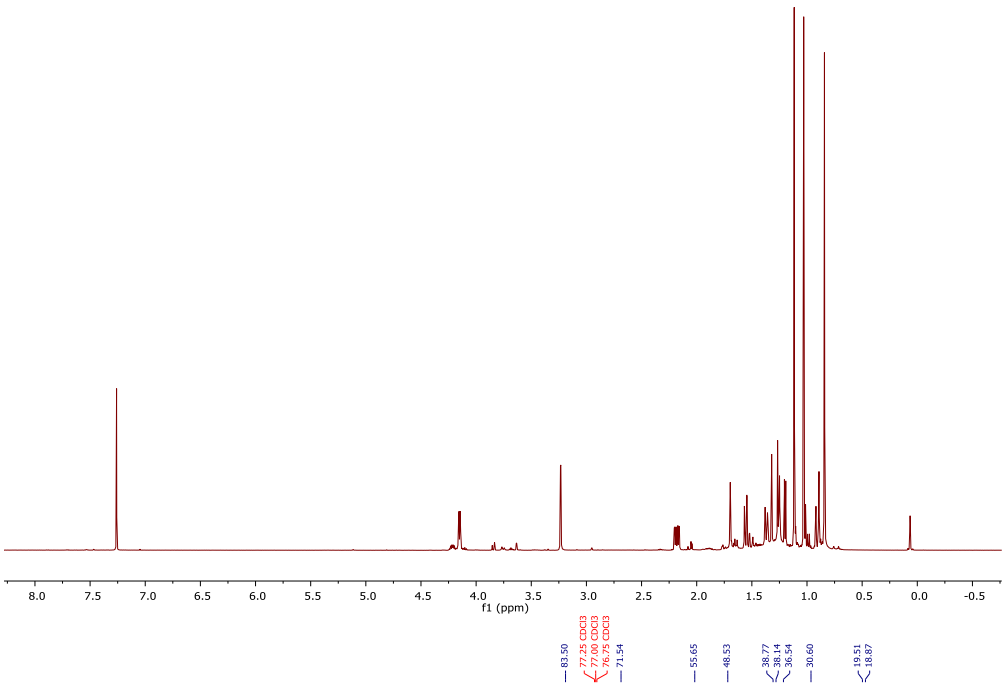

166.09
144.34
139.36
134.43
130.72
130.22
129.25
128.89
128.83
126.56
126.28
77.32 cdcl3
77.00 cdcl3
76.68 cdcl3
70.01
67.49
63.97
45.37
28.37
24.95
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

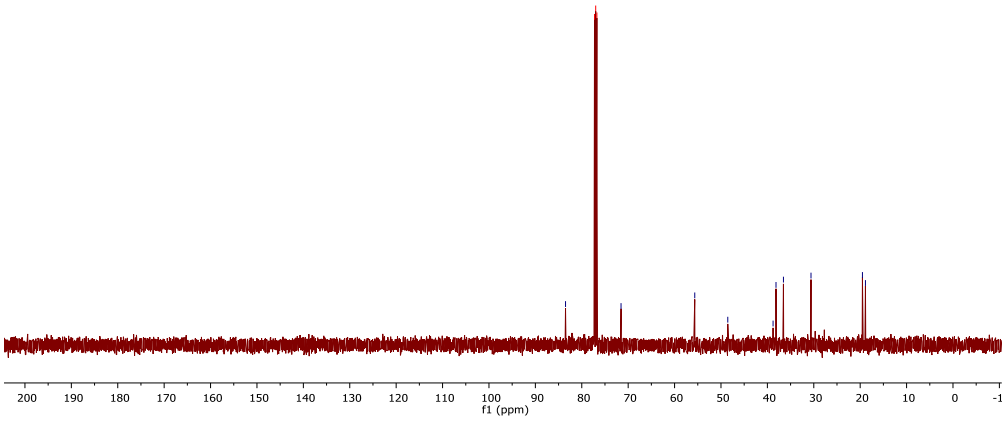

O
O
NMe2
OH


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
f1 (ppm)

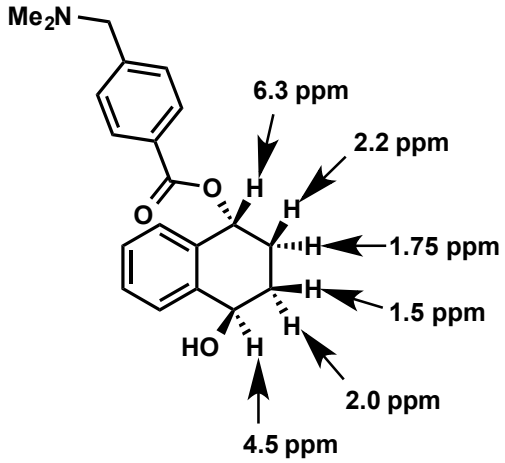

166.44
145.93
140.59
130.75
129.03
128.94
126.22
124.35
77.25
77.00
76.75
76.70
74.45
63.89
45.34
43.52
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

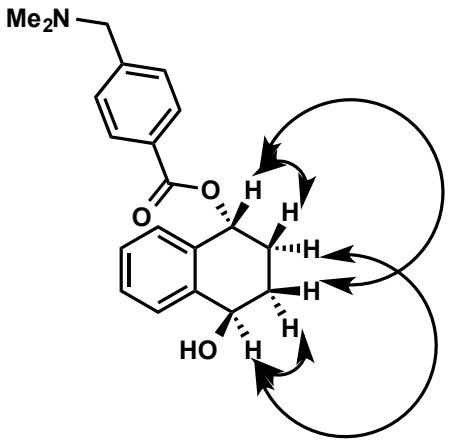

HO
Me
Me
Me
OH

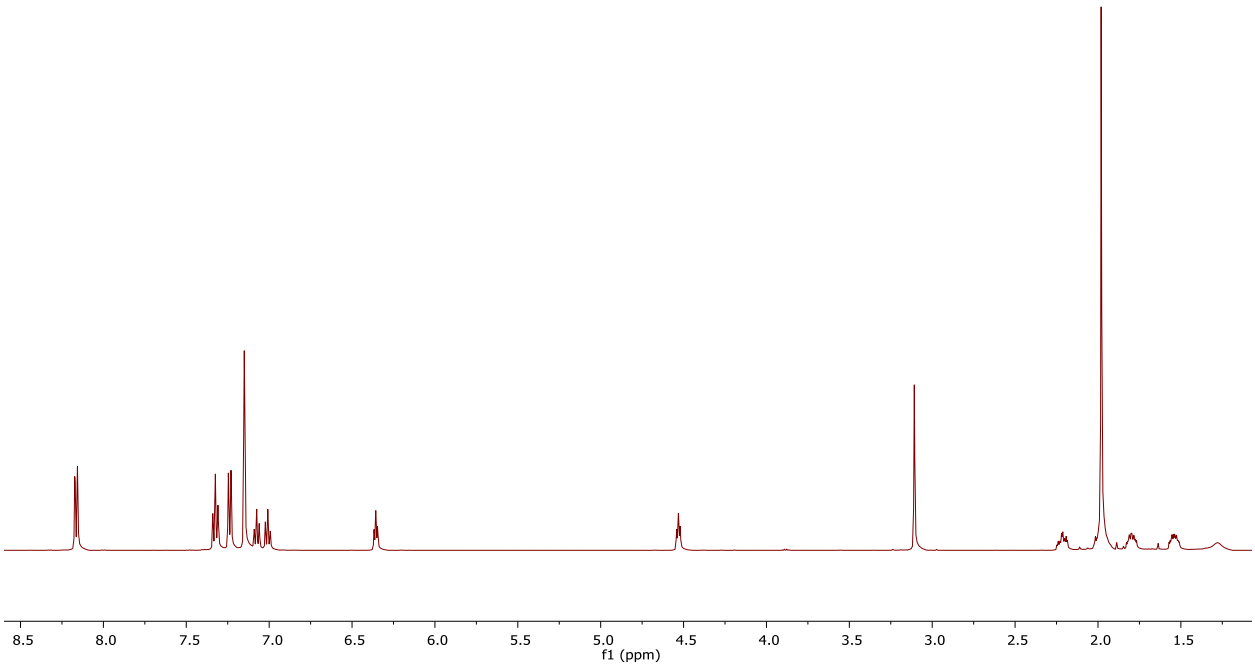

8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)
83.50
77.25 CDCl3
77.00 CDCl3
76.75 CDCl3
71.54
55.65
48.53
38.77
38.14
36.54
30.60
19.51
18.87


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
f1 (ppm)

^{1}H in C_6D_6


Me2N
6.3 ppm
2.2 ppm
1.75 ppm
1.5 ppm
2.0 ppm
4.5 ppm
O
H
HO


Me2N
O
H
HO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8.0
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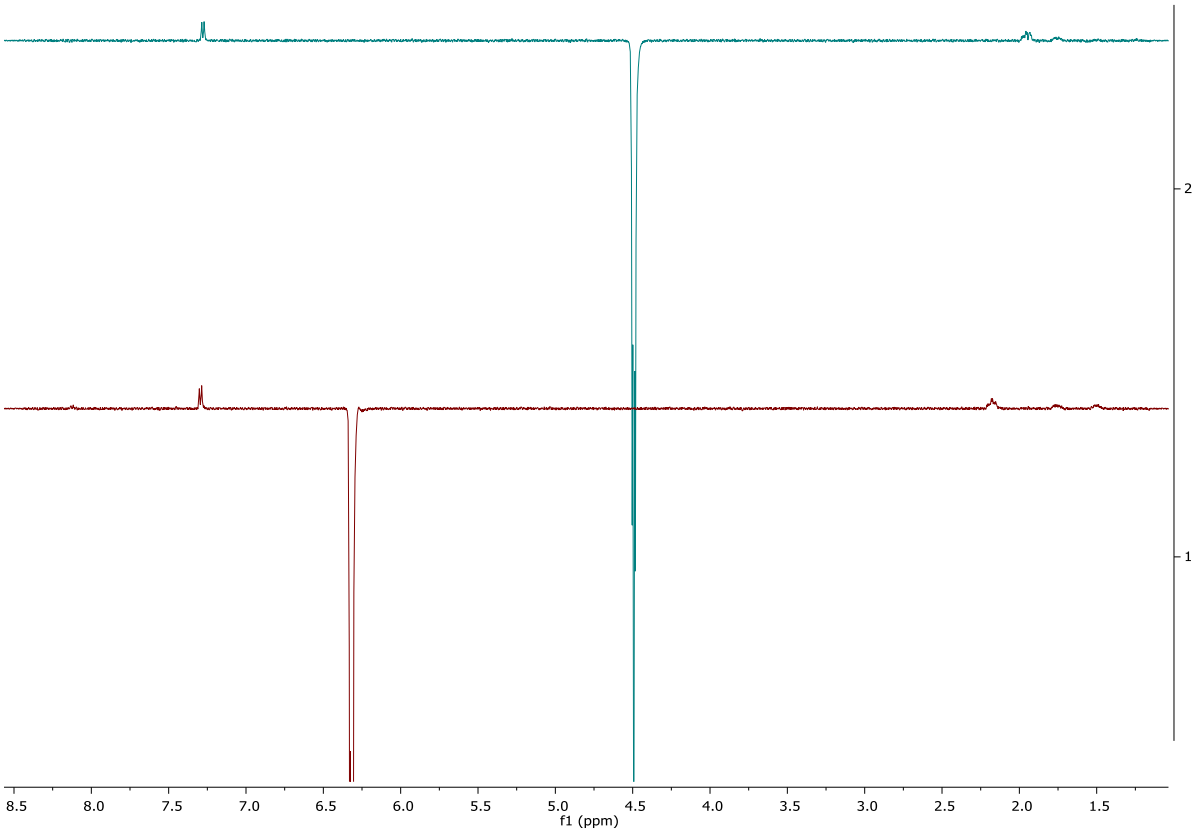
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)


2
1
8.5
8.0
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6.0
5.5
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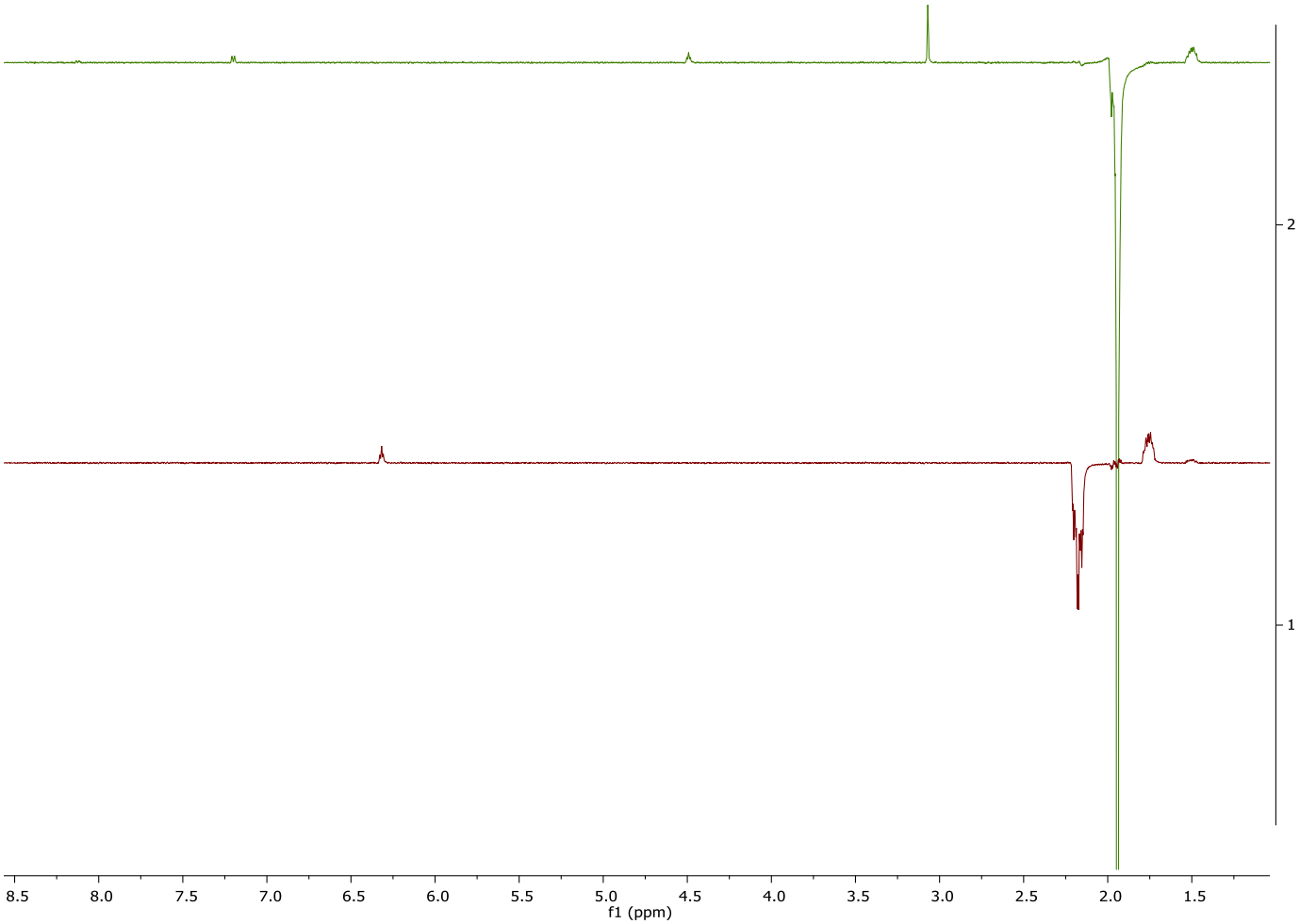
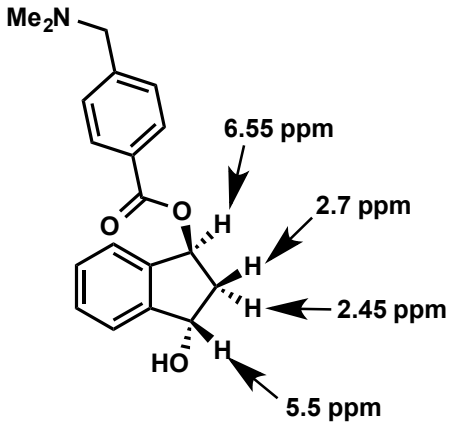
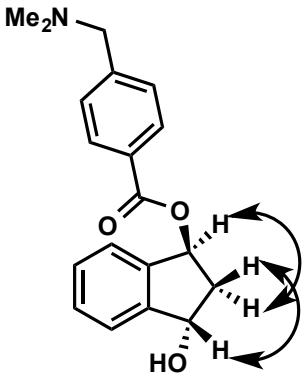
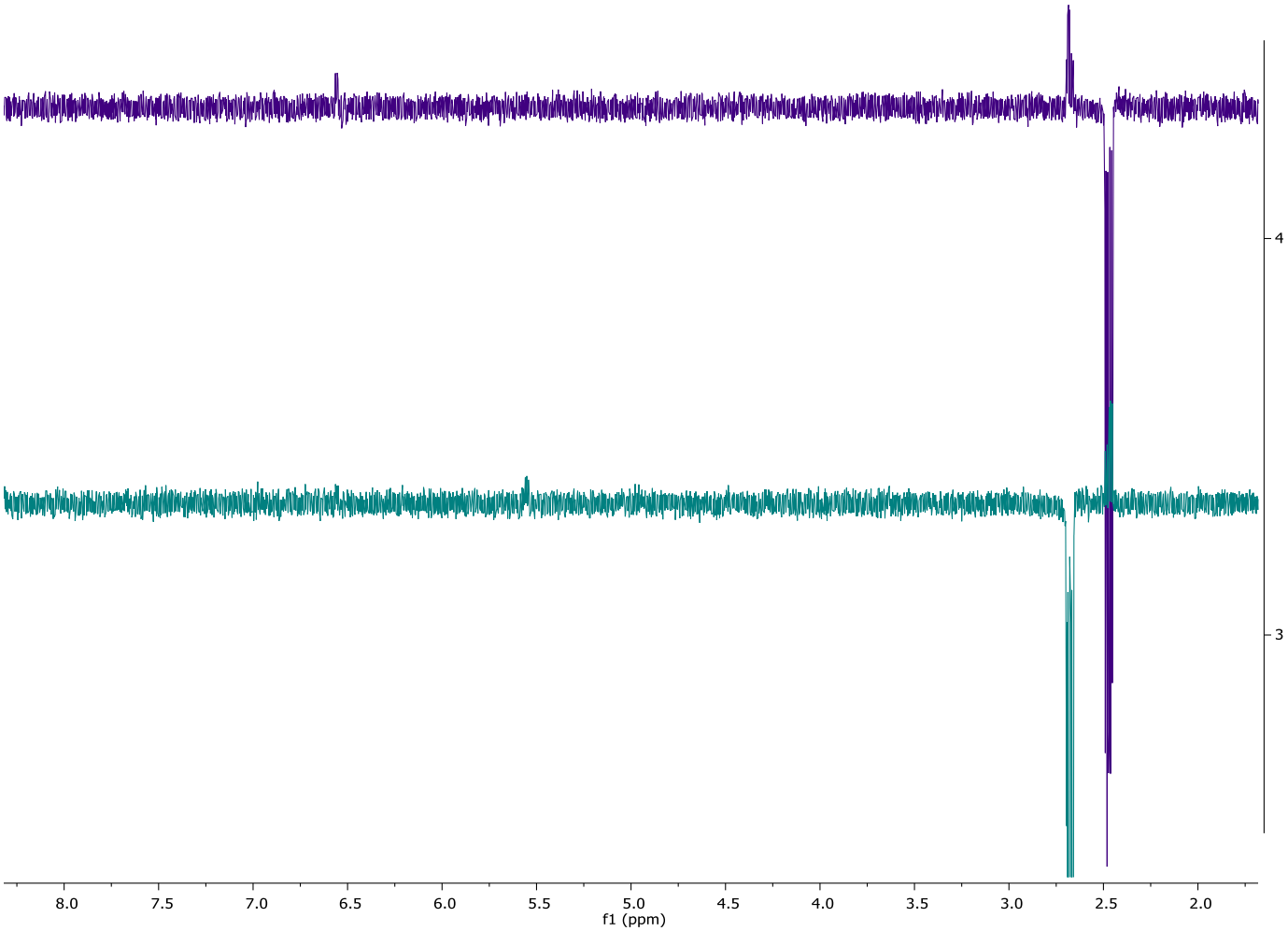
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)



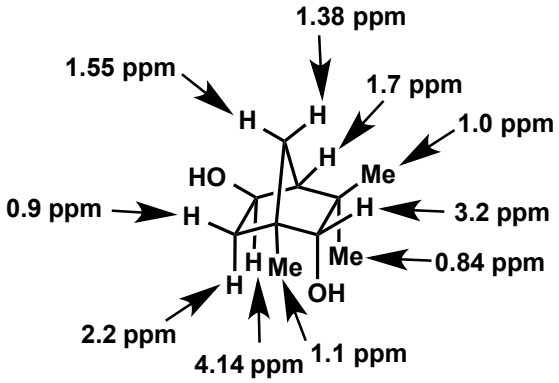
Selected NOEs CDCl3

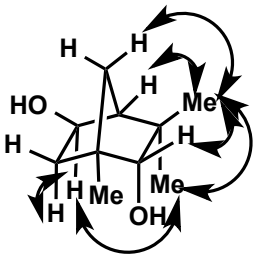


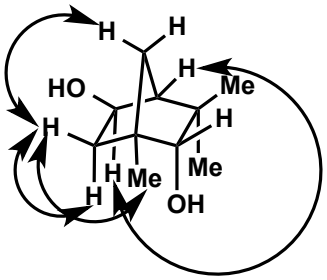


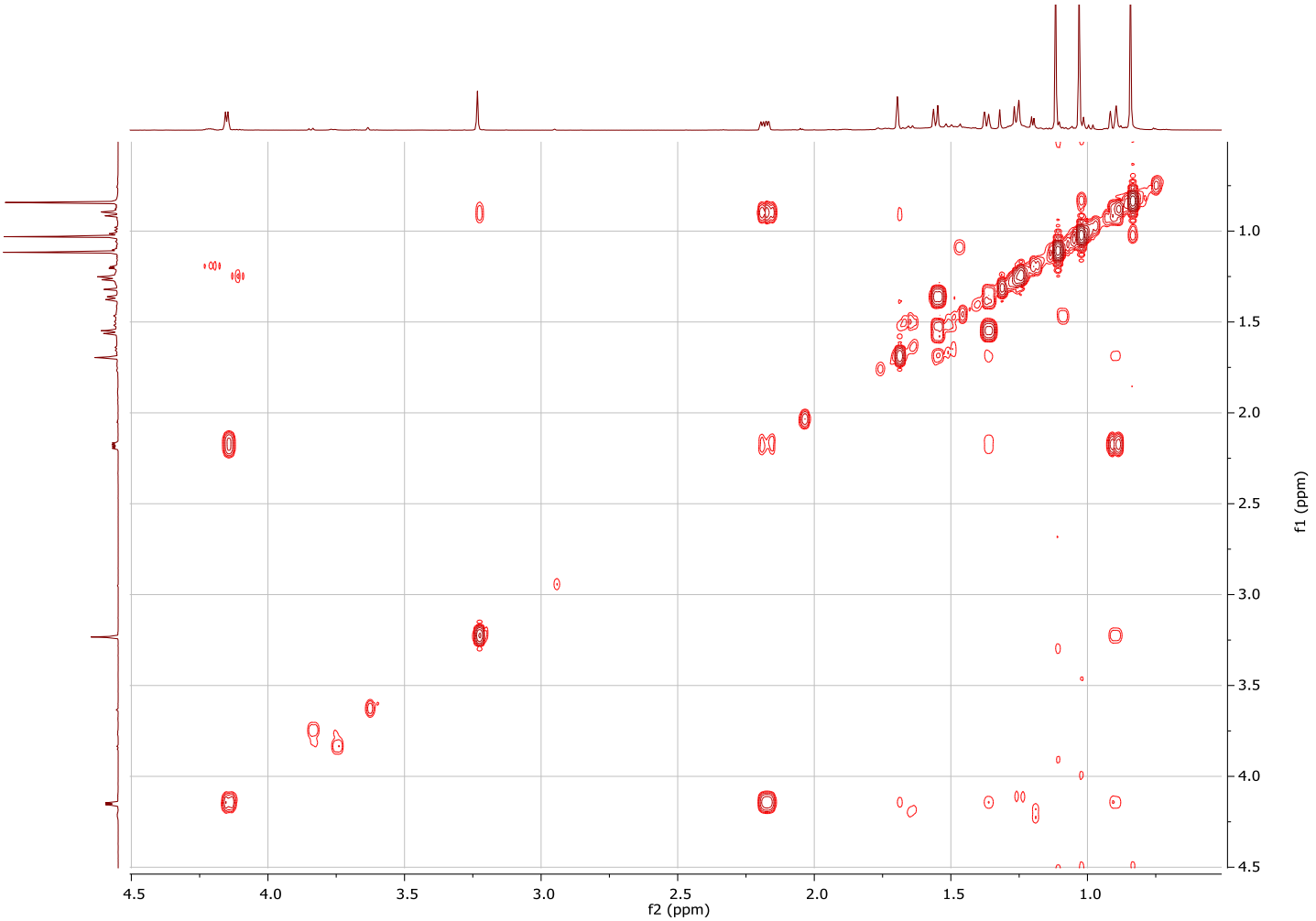


ARN-IX-204
COSY, HMQC in CDCl3





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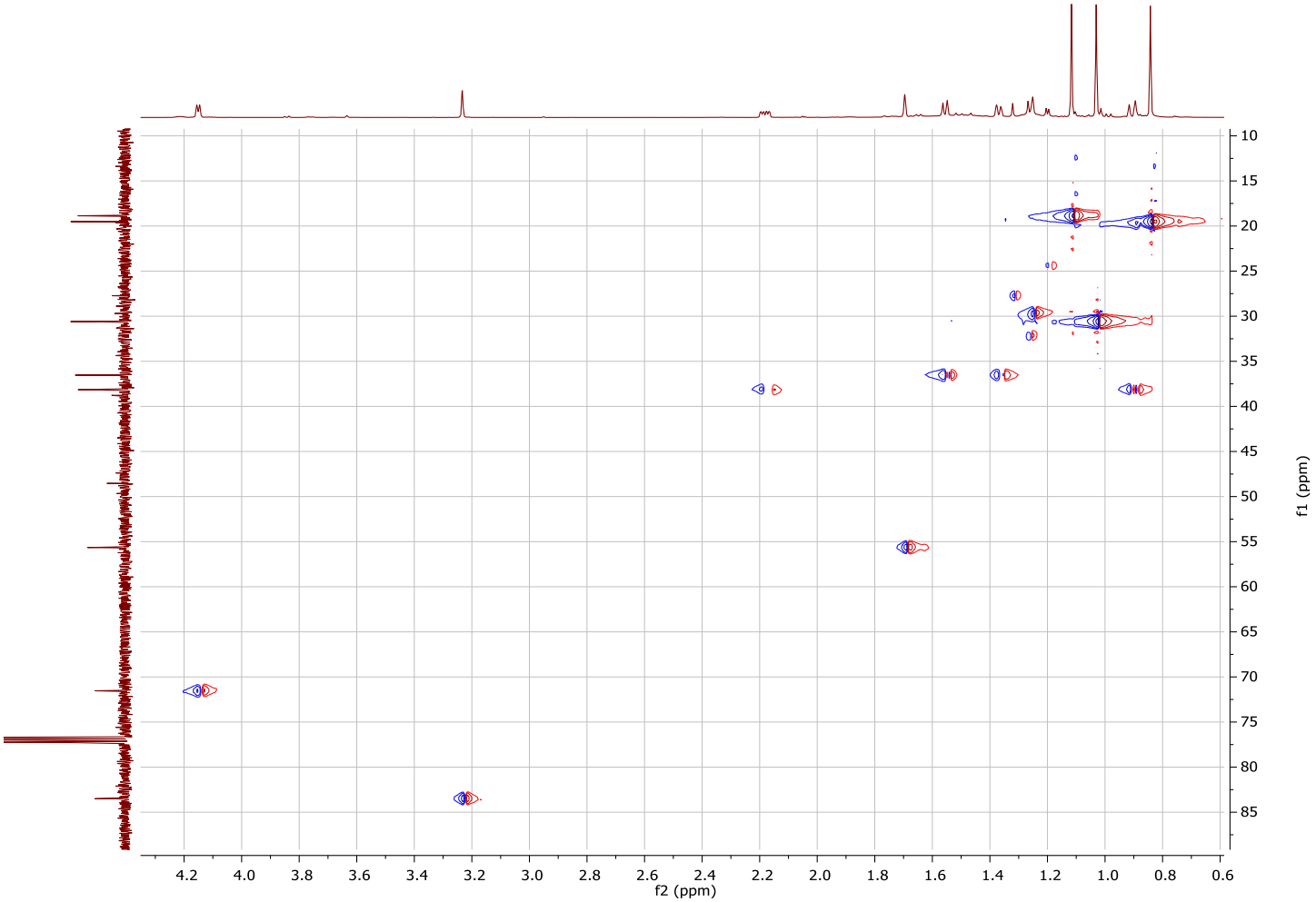
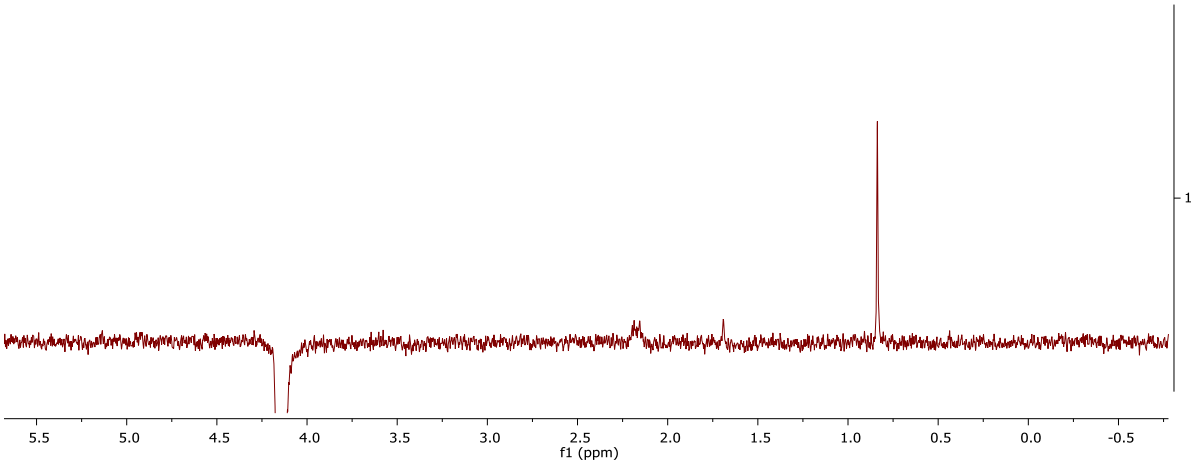
3.0
2.5
2.0
1.5
1.0
f2 (ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
f1 (ppm)


f2 (ppm)
f1 (ppm)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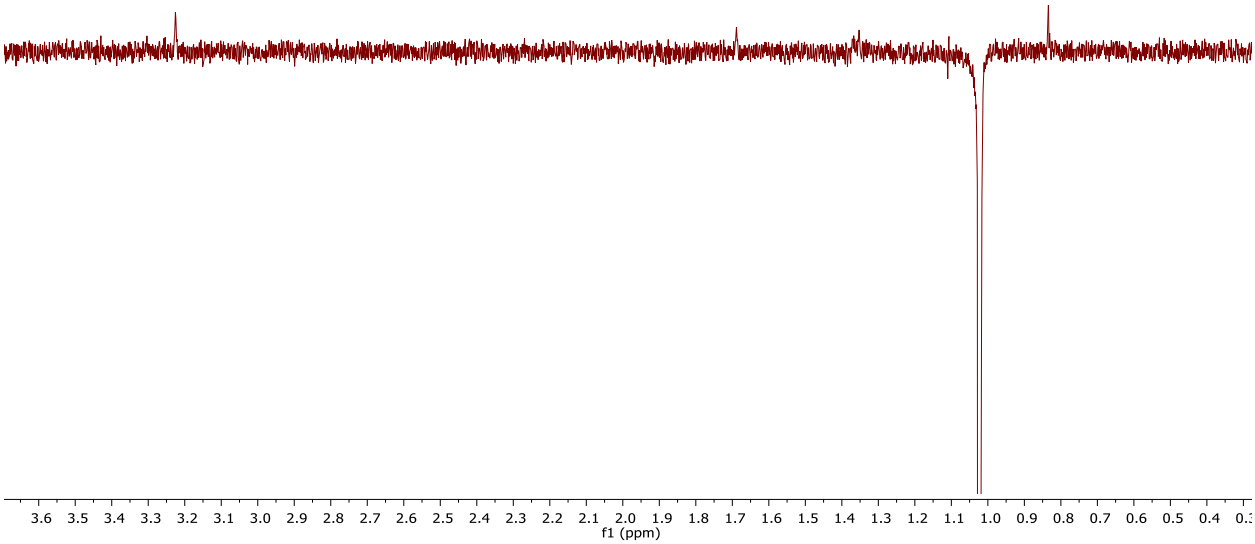
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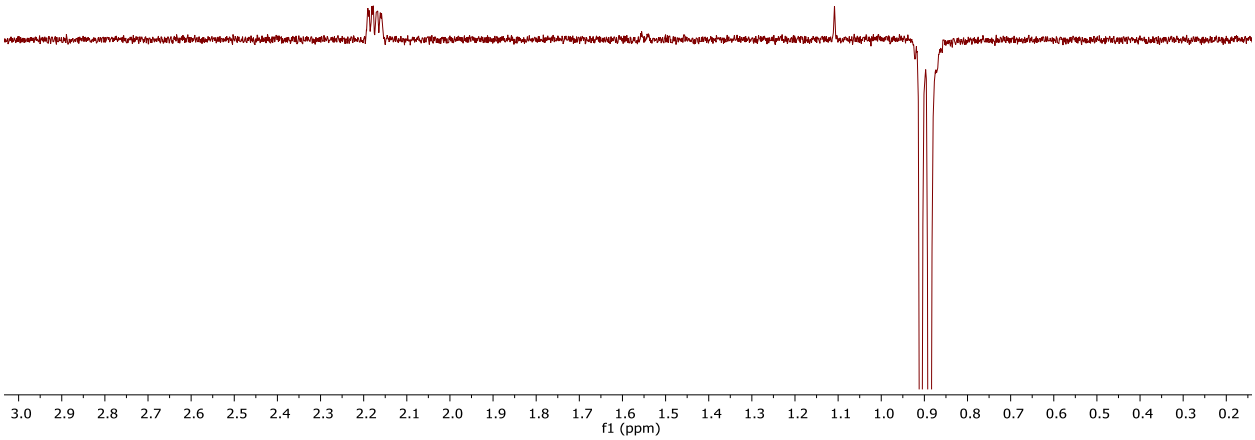
f1 (ppm)


3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.0 0.9 0.8 0.7 0.6 0.5 0.4 0.3 0.2
f1 (ppm)

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Cartesian coordinates of geometries optimized at the B3LYP/6-31G(d)+LanL2DZ(Fe) level

cI

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1□

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H	-2.545837	1.954903	-2.805147
C	-3.102031	-2.003363	-1.257212
C	-2.500590	-2.666632	-2.507027
H	-1.413009	-2.539043	-2.554250
H	-2.701954	-3.744527	-2.498400
H	-2.929333	-2.255964	-3.430512
C	-2.655911	3.930933	-0.888688
H	-3.102879	4.406964	-0.007642
H	-1.677606	4.395589	-1.061400
H	-3.294884	4.160466	-1.751999
H	-4.156873	-2.303989	-1.212702
C	-2.424845	-2.522881	0.022008
H	-2.988567	-2.244350	0.919288
H	-2.367442	-3.618369	-0.000669
H	-1.412210	-2.126612	0.136674
H	-0.922900	2.151629	-2.148675
H	-1.290393	-0.267520	-2.588204

$^{4}ts3_{eq}$

Fe	-0.18018019	0.06006006	0.00000000
N	-0.64884019	1.81713406	0.88028500
N	0.68044981	1.06094806	-1.53236600
N	-0.81083719	-0.91096494	1.64909500
N	0.49097981	-1.67947194	-0.78785700
C	-1.19799719	2.00706106	2.12655900
C	1.30193181	0.51974406	-2.63343600
C	-0.51423119	3.06703506	0.33419400
C	0.61674881	2.41764306	-1.76216600
C	-1.33874919	-0.36774094	2.78964200
C	1.11486781	-1.85998594	-1.98967600
C	-0.81454019	-2.26735394	1.83994000
C	0.28330281	-2.93484894	-0.27524500
C	-1.41930419	3.41269006	2.36766800
C	1.66610181	1.56296606	-3.56360400
C	-1.00218919	4.07063206	1.25078100
C	1.23595681	2.73654806	-3.02677100
C	-1.69612219	-1.40731694	3.72444100
C	1.31955181	-3.26748594	-2.24611500
C	-1.37390619	-2.59049394	3.13112300
C	0.80153981	-3.93606394	-1.17984700
H	-1.83751919	3.82502806	3.27717000
H	2.17261681	1.39860506	-4.50629400
H	-1.00419619	5.13549206	1.05533300
H	1.32016181	3.73535706	-3.43595000
H	-2.13438619	-1.23838894	4.69979600
H	1.79621281	-3.67204194	-3.13002200
H	-1.49198219	-3.59405794	3.51959300
H	0.76422281	-5.00406894	-1.00630000
C	-1.51046319	0.99441006	3.02278500
C	1.51153281	-0.83560694	-2.84758500
C	-0.31924419	-3.21188594	0.94449500
C	0.04822081	3.34827806	-0.90775200
H	-1.93642519	1.28677606	3.97798800
H	2.00222681	-1.12301094	-3.77282600
H	-0.40111719	-4.25592494	1.23205400
H	0.07550781	4.38902706	-1.21626600
O	-1.66913819	-0.13589294	-0.89165500
S	2.11083681	0.56195006	1.00128300
C	3.35711681	-0.50944594	0.22808000
H	3.38465681	-0.30815094	-0.84997200
H	4.34061881	-0.28193694	0.64904500
H	3.11553581	-1.56585394	0.37212800
C	-6.40394719	0.16810306	-0.51677700
C	-6.50917419	1.65670706	-0.85487200
C	-5.47119119	2.49761206	-0.09825800
C	-4.05830119	1.92797106	-0.36372700
C	-3.98569819	0.45187306	-0.02632200
C	-4.99092319	-0.41827594	-0.77700400
H	-6.36157919	1.77899506	-1.93776800
H	-7.52484919	1.99951306	-0.62353600
H	-6.70093619	0.00416406	0.52319100
H	-2.70356319	0.10681906	-0.39754500
H	-3.95329619	0.25820106	1.05027800
H	-4.80685219	-0.29136694	-1.85492800
H	-5.67469619	2.40205906	0.97969900
O	-7.34112919	-0.56159894	-1.35988000
C	-8.60336119	-0.72012694	-0.90116900
O	-9.00692919	-0.28966894	0.15834800
C	-9.43215919	-1.50873694	-1.89132700
H	-8.98807719	-2.49689594	-2.05184100
H	-10.44852419	-1.61647294	-1.51062400
H	-9.44864819	-0.99860894	-2.86011500
H	-3.81566719	2.07433206	-1.42676400
C	-4.93802219	-1.94384194	-0.47446900
C	-3.80148919	-2.63707594	-1.24294000
H	-2.82302019	-2.22916994	-0.97420100
H	-3.80055319	-3.71493194	-1.03581900
H	-3.92541419	-2.50621894	-2.32505400
C	-5.56129419	3.98232706	-0.47033600
H	-6.55757119	4.38708006	-0.25478300
H	-4.82732719	4.57341006	0.09018300
H	-5.36332919	4.13033106	-1.53971200
H	-5.87970219	-2.35447294	-0.85999100

C	-4.87564019	-2.28026994	1.02459400
H	-5.66684219	-1.78057494	1.59722700
H	-5.00124019	-3.35984894	1.17134600
H	-3.91223219	-2.00265594	1.46551100
H	-3.31775519	2.49099006	0.21261400

$^{4}ts4_{ax}$

Fe	0.30411448	0.95706618	0.00000000
N	-0.17577852	2.90781418	0.15995400
N	0.48805948	1.19508518	-2.02792300
N	0.19540548	0.75133018	1.98912700
N	1.02923348	-0.91181882	-0.16992800
C	-0.45818752	3.58455318	1.31879300
C	0.88458248	0.24646018	-2.93440900
C	-0.35405452	3.80892218	-0.86292600
C	0.19645448	2.32194118	-2.75547000
C	-0.16458152	1.70991418	2.89797200
C	1.34542948	-1.57769782	-1.32930400
C	0.44097048	-0.38527582	2.71304700
C	1.16147348	-1.82592982	0.84383000
C	-0.80002052	4.95465418	1.02351800
C	0.82682648	0.78279818	-4.27514700
C	-0.74056052	5.09212018	-0.32982300
C	0.39519748	2.06954118	-4.16374700
C	-0.16609852	1.15769218	4.23556700
C	1.72044648	-2.93866682	-1.03239100
C	0.20704748	-0.14381282	4.12043500
C	1.60345948	-3.09349582	0.31605800
H	-1.05944252	5.69862118	1.76592300
H	1.08844848	0.23475518	-5.17157200
H	-0.93773652	5.97295718	-0.92761300
H	0.23200348	2.79592218	-4.94977800
H	-0.41694952	1.71233818	5.13088200
H	2.02010848	-3.67079582	-1.77158900
H	0.32816448	-0.88382682	4.90127300
H	1.78817648	-3.97826582	0.91202400
C	-0.45575452	3.03294118	2.59504200
C	1.29342448	-1.04341982	-2.61207600
C	0.89193848	-1.58726882	2.18713700
C	-0.20278152	3.53839418	-2.21750600
H	-0.71037752	3.69037918	3.42078200
H	1.58071948	-1.69525782	-3.43176900
H	1.04657448	-2.40965382	2.87906600
H	-0.39211552	4.35275118	-2.91038400
O	-1.34487352	0.41832718	-0.13213000
S	2.54630548	1.89794818	0.02206900
C	3.73982048	0.70240518	-0.65196200
H	3.56104748	0.57466318	-1.72552600
H	4.74424248	1.11570518	-0.51703900
H	3.66191848	-0.27050282	-0.16257300
C	-5.28561752	-0.00206582	-0.69320500
C	-4.30261452	-1.16767682	-0.82596400
C	-3.46533152	-1.06604282	-2.11463300
C	-2.80759152	0.30109218	-2.21204500
C	-3.74026252	1.47820918	-2.00001300
C	-4.58122052	1.36357018	-0.70779600
H	-3.63151652	-1.16308182	0.04187400
H	-4.86098552	-2.11098182	-0.81613300
H	-6.03863752	-0.06333182	-1.48452400
H	-3.16541152	2.41050718	-1.99158300
H	-4.41334752	1.54120618	-2.87328400
H	-3.87491252	1.36060418	0.13358500
H	-4.16411452	-1.13814182	-2.97043700
O	-5.98191252	-0.12528182	0.58136900
C	-7.16187652	-0.78219482	0.59655600
O	-7.68960652	-1.27302882	-0.37966600
C	-7.74960652	-0.78328382	1.99115100
H	-8.19199852	0.19892418	2.19724600
H	-8.52867052	-1.54374282	2.05741300
H	-6.97425452	-0.95518582	2.74261600
H	-1.91997852	0.35180118	-1.16328600
C	-5.55870552	2.55090118	-0.47887100
C	-4.80333952	3.86428818	-0.21947600
H	-4.27118652	4.21566318	-1.11109800
H	-5.50003952	4.65764818	0.07793400
H	-4.06181552	3.74860318	0.57990500
C	-2.46766952	-2.22524382	-2.22829800
H	-2.98680752	-3.19084182	-2.20580400
H	-1.89992452	-2.16784582	-3.16442900
H	-1.75383752	-2.20134382	-1.39795000
H	-6.10489752	2.30893918	0.44201600
C	-6.60275752	2.73734318	-1.59378700
H	-7.21713152	1.84206518	-1.74141000
H	-7.28083452	3.56194318	-1.34255200
H	-6.13360452	2.98642518	-2.55366700
H	-2.14388152	0.41499818	-3.07422400

$^{4}ts4_{eq}$

Fe	0.30499077	0.13863216	0.00000000
N	1.01326277	-1.73989084	-0.08830200
N	-0.43658723	-0.24339584	1.86786400
N	1.11165577	0.54029216	-1.79093300
N	-0.21913823	2.07608116	0.21735600
C	1.71474877	-2.30142584	-1.12463100
C	-1.05821723	0.64309216	2.71158500
C	0.80087977	-2.74858184	0.82113700
C	-0.45201223	-1.45586284	2.51076400
C	1.79361377	-0.32520484	-2.60131800
C	-0.88856423	2.64596416	1.27076400
C	1.06103277	1.73140816	-2.46458300
C	-0.09470823	3.05835716	-0.73144400
C	1.97294077	-3.69485684	-0.85331500
C	-1.48270023	-0.02970184	3.91765100
C	1.40078377	-3.97345984	0.34994400
C	-1.11177723	-1.33345084	3.78965500
C	2.17625277	0.33331216	-3.83171700
C	-1.17154223	4.03249016	0.98979000
C	1.71738777	1.60974116	-3.74852400

C	-0.68075523	4.28757416	-0.25558400
H	2.51378577	-4.36088084	-1.51355500
H	-1.99548223	0.44765916	4.74321800
H	1.37724777	-4.91517084	0.88346300
H	-1.25392123	-2.14640284	4.49044800
H	2.72418577	-0.13691984	-4.63838200
H	-1.68478323	4.70676616	1.66380400
H	1.81057977	2.41011716	-4.47160300
H	-0.70889823	5.21433416	-0.81461200
C	2.09136377	-1.64580384	-2.29057800
C	-1.26332123	1.99123516	2.44100300
C	0.50009777	2.90437816	-1.97929500
C	0.11022477	-2.62719584	2.02005400
H	2.64523077	-2.21986984	-3.02720200
H	-1.77981823	2.57834716	3.19469900
H	0.53176877	3.77679316	-2.62515500
H	0.02207377	-3.51818484	2.63431700
O	-1.19147523	-0.26731484	-0.78620700
S	2.38201477	0.48874716	1.23969600
C	2.32237477	2.05689216	2.15790900
H	1.52144277	2.01160016	2.90476700
H	3.27479477	2.18734416	2.68035100
H	2.13464277	2.90439116	1.49445900
C	-6.25123623	-0.46877884	-0.45241800
C	-5.56357523	-1.81203684	-0.18956100
C	-4.04326023	-1.75744784	-0.48275200
C	-3.44744723	-0.60628484	0.30560100
C	-4.10616623	0.73056116	0.04115500
C	-5.62809523	0.68523816	0.34876500
H	-5.72430823	-2.09003384	0.86179100
H	-6.03590023	-2.58345184	-0.80975500
H	-6.22899623	-0.25528184	-1.52492300
H	-3.62941923	1.51328316	0.63876800
H	-3.95412223	0.99803716	-1.01291800
H	-5.74292823	0.42521016	1.41268300
H	-3.92055823	-1.53174284	-1.55316900
O	-7.64930423	-0.57095784	-0.05406800
C	-8.52816423	-1.03412884	-0.97211600
O	-8.23076923	-1.35745384	-2.10218400
C	-9.92401023	-1.08953784	-0.39090800
H	-10.22993623	-0.09748784	-0.04261500
H	-10.61995223	-1.44799284	-1.15026300
H	-9.94308623	-1.75884984	0.47579000
H	-3.30056523	-0.83181084	1.36784700
H	-2.15982723	-0.44835784	-0.15718800
C	-6.35654823	2.04236316	0.14249600
C	-5.89079623	3.09436816	1.16274200
H	-4.85164323	3.39908716	0.98936000
H	-6.51039623	3.99662416	1.09582600
H	-5.96333523	2.71506316	2.18968700
C	-3.36542223	-3.10096784	-0.19493000
H	-3.81800723	-3.90554484	-0.78670600
H	-2.29916023	-3.05396384	-0.43804600
H	-3.46035523	-3.36966984	0.86515400
H	-7.41675723	1.84277716	0.34734200
C	-6.26102623	2.59997816	-1.28771600
H	-6.63107123	1.89043716	-2.03619300
H	-6.86332723	3.51193716	-1.37756900
H	-5.23045423	2.86256716	-1.55396700

^{4}ts5

Fe	0.68914955	-0.07331378	0.00000000
N	1.53327455	-1.80476078	0.60102800
N	2.01608355	0.95859022	1.12550800
N	-0.45398545	-1.10425278	-1.29175600
N	0.01841355	1.67071322	-0.76838000
C	1.29440355	-3.06652378	0.11083000
C	2.14772255	2.32460022	1.21643800
C	2.45256755	-1.95795678	1.60620900
C	2.86358855	0.43150922	2.07352500
C	-0.45066245	-2.45333078	-1.52469800
C	0.38859055	2.93568622	-0.40944500
C	-1.43638545	-0.58369078	-2.09111600
C	-1.04359845	1.81289422	-1.62604000
C	2.08166555	-4.03923578	0.82893700
C	3.12655355	2.66471822	2.22292000
C	2.78783655	-3.35287178	1.76936700
C	3.56074355	1.49306222	2.76099500
C	-1.46669345	-2.79851478	-2.49071200
C	-0.44166145	3.91199122	-1.07639200
C	-2.09153045	-1.63619578	-2.83046500
C	-1.33779545	3.21322122	-1.82654100
H	2.07779555	-5.10386178	0.63214300
H	3.41879855	3.67455122	2.48201700
H	3.49033655	-3.73732078	2.49798000
H	4.28791255	1.34237822	3.54888500
H	-1.66717845	-3.80192678	-2.84478300
H	-0.34500745	4.98471122	-0.96589300
H	-2.91682445	-1.48167878	-3.51244900
H	-2.12854645	3.59207822	-2.46140400
C	0.38985455	-3.37017678	-0.89803700
C	1.40504955	3.24745322	0.49299600
C	-1.73138345	0.77017222	-2.23201900
C	3.04446555	-0.92033278	2.32141700
H	0.29845855	-4.41210178	-1.19057200
H	1.59857055	4.29954922	0.68062200
H	-2.56680745	1.02658922	-2.87378700
H	3.75226355	-1.19344878	3.09837900
O	-0.52436245	0.04061522	1.24782300
S	2.71559455	-0.06568978	-1.56165600
C	2.89919555	1.58303222	-2.30193500
H	3.09771555	2.31396322	-1.50807300
H	3.75115355	1.57758522	-2.98809500
H	1.98864655	1.88575922	-2.82579800
C	-4.09005145	-0.66206978	0.90834900
C	-3.28523245	-1.91800578	1.26431600
C	-2.12076345	-1.66395678	2.21098600
C	-2.49132745	-0.78200278	3.39409300

C	-3.26569645	0.47585622	2.97562500
C	-4.52460545	0.13225922	2.15188700
H	-3.97701745	-2.63036578	1.74851300
H	-2.93918645	-2.40164778	0.34267700
H	-3.52361645	-0.03193878	0.22151500
H	-3.54891945	1.04145722	3.87083000
H	-2.59543545	1.11298622	2.38820500
H	-5.14251045	-0.55257878	2.75582400
H	-1.22559645	-0.87062178	1.55374200
O	-5.28785445	-1.13271778	0.21420900
C	-5.51943845	-0.75503978	-1.05696300
O	-4.81396545	-0.00988978	-1.70768900
C	-6.79296845	-1.39304778	-1.57068500
H	-7.63695445	-1.12194078	-0.92800000
H	-6.98214745	-1.06050178	-2.59208500
H	-6.70274045	-2.48418678	-1.54496000
C	-5.42197145	1.35709422	1.82008400
C	-6.06792045	1.94079322	3.08849200
H	-5.32697645	2.41696422	3.74151900
H	-6.80783545	2.70608922	2.82524600
H	-6.58094645	1.16621422	3.67211300
C	-1.34158945	-2.91026678	2.58035600
H	-1.04063445	-3.47906778	1.69526500
H	-0.43848645	-2.66088878	3.14798400
H	-1.95748545	-3.57403178	3.20978400
H	-6.24239445	0.97437422	1.19749600
C	-4.71172745	2.46161222	1.01840300
H	-4.31714145	2.09010722	0.06752900
H	-5.41582745	3.27088922	0.78918700
H	-3.88129845	2.90029422	1.58353400
H	-1.58378245	-0.50001878	3.94172900
H	-3.10678045	-1.37731978	4.09357800

^{4}ts6$_{ax}$

Fe	1.17302051	-0.74780058	0.00000000
N	2.22840451	-0.80136958	-1.71413100
N	0.73210551	1.18395542	-0.30881800
N	1.55060151	-2.73992158	0.26387000
N	-0.09306249	-0.79635058	1.56570300
C	2.88795451	-1.87737258	-2.25686500
C	-0.07738149	1.97903942	0.45741300
C	2.48668251	0.26234942	-2.53991200
C	1.21469051	1.98432042	-1.30910800
C	2.32332551	-3.54836458	-0.53256500
C	-0.79973249	0.26295742	2.07670500
C	1.09303151	-3.53509258	1.28308500
C	-0.32953849	-1.85499958	2.40834100
C	3.55687051	-1.48479158	-3.47316700
C	-0.09353749	3.32842142	-0.06395500
C	3.31321251	-0.15611758	-3.64553900
C	0.71072551	3.33224142	-1.15959400
C	2.37425951	-4.88414758	0.01422700
C	-1.52423549	-0.14481958	3.25562400
C	1.61318251	-4.87598458	1.14269000
C	-1.23106049	-1.45905258	3.46226300
H	4.13414651	-2.15125758	-4.10143300
H	-0.65722349	4.14783442	0.36377600
H	3.65218251	0.49446642	-4.44171200
H	0.94543551	4.15534342	-1.82252400
H	2.91749951	-5.71068058	-0.42616000
H	-2.16187549	0.50416042	3.84245600
H	1.40407951	-5.69362958	1.82086800
H	-1.57830149	-2.11146858	4.25343400
C	2.94106551	-3.15302758	-1.71086500
C	-0.80227649	1.55456042	1.56227000
C	0.21679951	-3.12754658	2.28283600
C	2.02868851	1.56148142	-2.35107700
H	3.50759651	-3.90322358	-2.25379500
H	-1.41162549	2.29284342	2.07478600
H	-0.06514949	-3.86433058	3.02905500
H	2.32313551	2.30334342	-3.08723200
O	2.52390451	-0.24291758	0.97577800
S	-0.57078449	-1.57602358	-1.49504600
C	-1.90904449	-2.35358058	-0.54079900
H	-2.34110849	-1.65888958	0.18326900
H	-2.67593249	-2.69501258	-1.24270600
H	-1.51956149	-3.22542158	-0.00330400
C	5.69073551	-1.07028858	1.46043700
C	4.40630251	-1.48798258	2.14511900
C	4.25483551	-0.90048658	3.54094400
C	4.43286751	0.62995942	3.49281500
C	5.73287851	1.03808542	2.78408300
C	5.82794951	0.46279042	1.35407300
H	3.34801551	-0.95402258	1.40901900
H	4.20240851	-2.56077858	2.06948800
H	6.53536451	-1.47848958	2.03081700
H	5.80025851	2.13159442	2.74740200
H	6.59117051	0.69279342	3.37823800
H	4.95124651	0.81634542	0.79420900
H	5.08808851	-1.30950558	4.14429600
O	5.75533951	-1.66752558	0.13692200
C	6.71710451	-2.59089258	-0.08798900
O	7.51784451	-2.97297858	0.74077000
C	6.65569151	-3.10929858	-1.50753100
H	6.01587951	-3.99899558	-1.53308000
H	6.23431951	-2.36650158	-2.18766100
H	7.65884751	-3.40297158	-1.82282600
C	7.08529351	0.91902442	0.56500300
C	7.03224951	2.42359042	0.24996000
H	7.13297951	3.03590242	1.15411300
H	7.85020651	2.70441242	-0.42441200
H	6.08761151	2.69646942	-0.23592400
C	2.94415751	-1.30740458	4.22269100
H	2.84095651	-2.39810858	4.26938900
H	2.90605851	-0.92114258	5.24853200
H	2.08579351	-0.90930058	3.67340300
H	7.04262351	0.39463842	-0.39903800
C	8.42444551	0.55015742	1.22695200

H	8.51574851	-0.52715558	1.40062600
H	9.25854651	0.84877942	0.58023100
H	8.56020451	1.06339242	2.18668000
H	4.42302551	1.03133042	4.51479500
H	3.57450151	1.06155742	2.96355900

$^{4}ts6_{eq}$

Fe	-1.555339	0.232583	0.053667
N	-0.674025	0.949208	1.737089
N	-1.849193	-1.531690	1.020754
N	-1.448338	2.048681	-0.804393
N	-2.610768	-0.435993	-1.516431
C	-0.271431	2.242087	1.947269
C	-2.508449	-2.629613	0.526786
C	-0.369996	0.263853	2.884950
C	-1.378535	-1.897749	2.263646
C	-0.896203	3.175303	-0.259970
C	-3.131167	-1.694410	-1.679199
C	-1.838715	2.389355	-2.069026
C	-2.852644	0.229766	-2.692325
C	0.296833	2.378520	3.268031
C	-2.468476	-3.708681	1.485339
C	0.249818	1.145350	3.844418
C	-1.760237	-3.257331	2.556970
C	-0.937410	4.263583	-1.211647
C	-3.729043	-1.822816	-2.988093
C	-1.516246	3.772502	-2.339636
C	-3.552192	-0.629767	-3.618252
H	0.674318	3.303717	3.685007
H	-2.919263	-4.681893	1.337163
H	0.580290	0.848969	4.831784
H	-1.517220	-3.781046	3.472846
H	-0.560161	5.260961	-1.025228
H	-4.212135	-2.717550	-3.360120
H	-1.719517	4.282841	-3.272424
H	-3.860866	-0.340705	-4.614855
C	-0.375367	3.278176	1.024717
C	-3.103776	-2.708777	-0.728452
C	-2.489509	1.542930	-2.959078
C	-0.666851	-1.074449	3.122836
H	-0.002514	4.251362	1.330047
H	-3.573603	-3.650939	-0.995134
H	-2.744579	1.943521	-3.935520
H	-0.360692	-1.492463	4.077042
O	-0.063960	-0.222113	-0.728397
S	-3.585415	0.843086	1.340444
C	-5.022792	-0.047530	0.673205
H	-4.866849	-1.127669	0.777093
H	-5.907774	0.230956	1.253060
H	-5.174778	0.180588	-0.384891
C	3.141961	-0.394083	-0.311041
C	2.047034	-1.369725	0.067047
C	2.011000	-2.624620	-0.790256
C	3.402926	-3.299586	-0.778136
C	4.508079	-2.322558	-1.189129
C	4.540099	-1.078504	-0.281564
H	1.987925	-1.552461	1.145947
H	0.835326	-0.723284	-0.196221
H	2.946510	0.031178	-1.299245
H	5.480825	-2.827747	-1.160009
H	4.346580	-2.017079	-2.231977
H	4.678068	-1.427711	0.753859
H	1.812192	-2.311773	-1.827119
O	3.144847	0.690908	0.652614
C	3.174070	1.961940	0.187148
O	3.115661	2.274660	-0.982511
C	3.356833	2.939297	1.327136
H	3.002122	3.924668	1.019943
H	2.836410	2.602101	2.225377
H	4.426409	3.012798	1.559618
H	3.606493	-3.688618	0.230754
C	5.719910	-0.110849	-0.580907
C	7.066952	-0.734841	-0.174645
H	7.331452	-1.588683	-0.810069
H	7.874225	0.001172	-0.269059
H	7.052158	-1.082940	0.865615
C	0.911786	-3.603291	-0.369362
H	-0.074583	-3.146307	-0.471391
H	0.937903	-4.505798	-0.992386
H	1.037858	-3.914257	0.675552
H	5.575479	0.762455	0.068467
C	5.773401	0.395563	-2.032002
H	4.848446	0.902829	-2.321446
H	6.591471	1.117019	-2.146558
H	5.961604	-0.421717	-2.738533
H	3.389849	-4.166376	-1.452878

$^{4}ts7$

Fe	1.522920	-0.053930	0.234146
N	2.318097	-1.685383	-0.650728
N	0.413756	-1.282871	1.428776
N	2.710312	1.134600	-0.856904
N	0.901873	1.526628	1.299495
C	3.165822	-1.683752	-1.726975
C	-0.507552	-0.892758	2.364241
C	2.067521	-3.004273	-0.358252
C	0.418546	-2.656434	1.443066
C	3.492487	0.757045	-1.914942
C	-0.088418	1.539857	2.250766
C	2.882882	2.485449	-0.714685
C	1.332893	2.821907	1.174600
C	3.463736	-3.038982	-2.125503
C	-1.119521	-2.051696	2.974251
C	2.791258	-3.857458	-1.269650
C	-0.536375	-3.145366	2.409484
C	4.159520	1.911157	-2.478208
C	-0.279850	2.881889	2.746161
C	3.791393	2.981610	-1.725182

C	0.614079	3.674963	2.091196
H	4.110934	-3.310518	-2.949889
H	-1.879875	-2.015443	3.744285
H	2.767333	-4.939636	-1.250550
H	-0.724331	-4.191479	2.615945
H	4.831512	1.881822	-3.326508
H	-0.999314	3.161366	3.505564
H	4.092097	4.016456	-1.828831
H	0.772334	4.741043	2.194632
C	3.692845	-0.550306	-2.337646
C	-0.766295	0.425368	2.729489
C	2.271500	3.272701	0.252061
C	1.200622	-3.462671	0.625912
H	4.352243	-0.704168	-3.186459
H	-1.523565	0.593408	3.489363
H	2.509976	4.332003	0.261002
H	1.101333	-4.537717	0.741370
O	0.270682	0.125216	-0.954219
S	3.268254	-0.508338	1.859485
C	2.807456	0.159706	3.488925
H	1.886582	-0.319170	3.838773
H	3.609458	-0.081814	4.193066
H	2.652426	1.240510	3.453307
C	-3.550727	0.542408	-0.937909
C	-4.696762	0.839022	0.032931
C	-5.853661	-0.162724	-0.117608
C	-5.314263	-1.594831	0.018568
C	-4.155050	-1.877046	-0.948787
C	-2.979346	-0.874154	-0.768701
H	-4.307759	0.804959	1.061161
H	-5.051262	1.861518	-0.145644
H	-3.909285	0.681790	-1.961559
H	-3.794297	-2.898979	-0.795315
H	-4.522451	-1.825666	-1.984239
H	-2.632053	-0.975601	0.270391
O	-2.493350	1.503647	-0.709734
C	-2.447609	2.583274	-1.527535
O	-3.262463	2.808528	-2.399769
C	-1.236913	3.427432	-1.227770
H	-1.178146	3.653058	-0.159294
H	-0.338878	2.854454	-1.480979
H	-1.278855	4.347631	-1.812527
C	-1.785719	-1.195074	-1.686607
C	-1.342953	-2.649123	-1.660523
H	-2.016622	-3.271448	-2.269923
H	-0.338054	-2.754548	-2.081685
H	-1.331027	-3.061672	-0.647824
C	-6.985420	0.124896	0.875540
H	-7.376722	1.141486	0.750224
H	-7.818802	-0.574995	0.740013
H	-6.633899	0.028054	1.911108
H	-0.716540	-0.545231	-1.153737
C	-1.821529	-0.643961	-3.104286
H	-1.988310	0.434500	-3.150535
H	-0.875824	-0.856783	-3.614364
H	-2.622372	-1.127400	-3.687189
H	-6.122790	-2.318690	-0.151957
H	-4.968666	-1.751171	1.052076
H	-6.259300	-0.054718	-1.136064

^{4}ts8

Fe	0.96774192	-0.46920820	0.00000000
N	1.92352992	-2.08380020	-0.72944900
N	0.09446592	-1.65546820	1.41923900
N	1.89414092	0.70371180	-1.33643100
N	0.17419792	1.15415980	0.89160800
C	2.79569592	-2.10468020	-1.78675500
C	-0.72981608	-1.25075320	2.43865200
C	1.75056992	-3.39310020	-0.34964500
C	0.17502692	-3.02256020	1.51319600
C	2.76930392	0.30762780	-2.31111600
C	-0.68192508	1.17574180	1.96421600
C	1.76116992	2.05957180	-1.47419100
C	0.26157892	2.44889480	0.44654200
C	3.20308492	-3.45985720	-2.06915700
C	-1.18517408	-2.39403120	3.19557500
C	2.54971592	-4.25928020	-1.18201400
C	-0.62761708	-3.49357320	2.61741100
C	3.19361192	1.44547480	-3.09806900
C	-1.12148608	2.52521280	2.22235000
C	2.56413292	2.53301680	-2.58082800
C	-0.53731808	3.31575780	1.27760600
H	3.89183792	-3.74497920	-2.85423100
H	-1.84444008	-2.34398120	4.05303000
H	2.59317892	-5.33674920	-1.08579500
H	-0.73237308	-4.53220620	2.90458400
H	3.88351792	1.39595180	-3.93092100
H	-1.78997608	2.81340280	3.02388500
H	2.62853192	3.56608280	-2.89814800
H	-0.62904408	4.38610980	1.14276700
C	3.20355092	-0.99493720	-2.51752300
C	-1.09057408	0.06647180	2.69822300
C	1.00063392	2.87736680	-0.65065600
C	0.93237592	-3.83669320	0.68130600
H	3.90379692	-1.16487620	-3.32974600
H	-1.76579808	0.24335980	3.53017600
H	0.98196892	3.93869280	-0.87919500
H	0.89868592	-4.90649020	0.86378700
O	-0.37413808	-0.63292120	-1.09248200
S	2.83413892	-0.51219720	1.56373100
C	2.47488292	0.54673880	2.99818700
H	1.61442492	0.14455680	3.54518700
H	3.34400992	0.53240380	3.66266600
H	2.24722392	1.57046080	2.69158500
C	-6.02243308	-0.15899020	-0.58662200
C	-7.38664908	-0.58644520	-0.03784400
C	-7.94118108	-1.82331820	-0.76752900
C	-6.90729008	-2.96138720	-0.72275000

C	-5.54189908	-2.51928420	-1.26948100
C	-4.98476808	-1.29104420	-0.52059300
H	-7.28156708	-0.80784020	1.03428100
H	-8.08633708	0.25449980	-0.12519300
H	-6.13738608	0.20104280	-1.61166000
H	-4.82575708	-3.34668120	-1.19999800
H	-5.64313208	-2.28502920	-2.33826800
H	-4.88698908	-1.56620420	0.54142600
O	-5.53738708	0.95144280	0.21840800
C	-5.59668108	2.19651380	-0.31073800
O	-6.04265508	2.45686280	-1.40773200
C	-5.01410908	3.20740180	0.65147800
H	-3.93634608	3.03817280	0.75865500
H	-5.18886808	4.21417180	0.26974800
H	-5.46427108	3.09531580	1.64280800
C	-3.56486308	-0.84356820	-0.99468000
C	-2.53108208	-1.90427020	-0.67837600
H	-2.41386208	-2.70652620	-1.41157600
H	-1.30406908	-1.25541520	-0.80890100
H	-2.51955408	-2.26785320	0.35103300
C	-9.29646408	-2.25166220	-0.19313800
H	-10.03214908	-1.44120220	-0.25962600
H	-9.70010608	-3.11647220	-0.73322700
H	-9.20375108	-2.53212320	0.86411800
C	-3.48770708	-0.41781720	-2.47058500
H	-4.18481608	0.39495080	-2.70177000
H	-2.47565508	-0.06544420	-2.69229900
H	-3.70313108	-1.25516620	-3.14559800
H	-7.27712908	-3.82479120	-1.29172000
H	-6.79323008	-3.29971820	0.31866700
H	-8.09064608	-1.55044320	-1.82438600
H	-3.32025908	0.03497580	-0.38251300

^{4}ts10

Fe	-1.09970673	-0.05865103	0.00000000
N	0.12674227	0.53523597	1.49383000
N	-0.48568273	-1.98311003	0.30975700
N	-1.76022673	1.82118197	-0.23132500
N	-2.45934073	-0.70667703	-1.32695500
C	0.32301927	1.82555397	1.91301900
C	-0.90914773	-3.09355103	-0.37353800
C	1.00357327	-0.23906003	2.21503400
C	0.47031427	-2.42089503	1.19531600
C	-1.30585373	2.93495197	0.42265000
C	-2.60102673	-1.98787103	-1.80032800
C	-2.73363273	2.25599397	-1.08989700
C	-3.33525073	0.06488397	-2.04756500
C	1.33779427	1.86683297	2.93793600
C	-0.19942673	-4.26438803	0.08761100
C	1.76073627	0.58594197	3.12458800
C	0.65588527	-3.84642103	1.06131800
C	-2.00287473	4.11217997	-0.04811400
C	-3.61237473	-2.02833403	-2.82883600
C	-2.89084873	3.69026297	-0.98648800
C	-4.07063773	-0.75498403	-2.97962500
H	1.67330627	2.76716797	3.43689800
H	-0.35022573	-5.26698903	-0.29235100
H	2.51572727	0.21663797	3.80692900
H	1.35225327	-4.43478203	1.64520700
H	-1.82551973	5.11804197	0.31096200
H	-3.91601673	-2.92187003	-3.35957700
H	-3.59590273	4.27649697	-1.56205800
H	-4.82658573	-0.38604503	-3.66120000
C	-0.34050873	2.94377097	1.42041200
C	-1.88945873	-3.09837903	-1.36077200
C	-3.47839073	1.44232997	-1.93252000
C	1.16875927	-1.61265303	2.08152100
H	-0.08210573	3.90476297	1.85494000
H	-2.11979673	-4.05120203	-1.82817000
H	-4.21838073	1.92142097	-2.56642000
H	1.90632727	-2.09006703	2.71928000
O	0.08719127	0.22039597	-1.24239600
S	-2.56773873	-0.55236303	1.87460300
C	-3.85067773	-1.73344603	1.35790000
H	-3.37906173	-2.66468903	1.02481200
H	-4.48524573	-1.95498203	2.22096500
H	-4.45209373	-1.33482003	0.53718200
C	5.76282327	-0.43598403	-0.66860000
C	4.58971827	-1.23537003	-1.24680300
C	3.25963627	-0.45217903	-1.12592500
C	3.40607727	0.92836397	-1.78626900
C	4.59579527	1.70979897	-1.21057900
C	5.92761227	0.93731097	-1.33640100
H	4.79729727	-1.45346903	-2.30367600
H	4.51701127	-2.19364003	-0.72037100
H	5.62867327	-0.33140303	0.41195000
H	4.68069227	2.67735097	-1.71866800
H	4.39527627	1.93183397	-0.15306500
H	6.09559527	0.74284897	-2.40775700
H	3.07068227	-0.29911803	-0.05225800
O	6.99272427	-1.18638903	-0.88555300
C	7.34372027	-2.09561403	0.05130200
O	6.70707627	-2.32219903	1.05873100
C	8.63679327	-2.78155803	-0.33144300
H	8.52472127	-3.28222203	-1.29888200
H	9.43881127	-2.04351703	-0.43798000
H	8.90320627	-3.51042703	0.43487900
H	3.54470327	0.79255297	-2.86992300
C	7.17331627	1.71861197	-0.83071500
C	7.47275827	2.93878097	-1.71707600
H	6.69977127	3.71109697	-1.62496200
H	8.42683127	3.39776897	-1.43168600
H	7.54079927	2.65781097	-2.77520200
C	2.10867827	-1.24861303	-1.69381600
H	1.93484327	-2.22419703	-1.23693900
H	0.95128627	-0.53050103	-1.37850000
H	2.04695927	-1.27643103	-2.78550000
H	8.02172827	1.03011197	-0.93579500

C	7.10029627	2.13327397	0.64885600	H	6.29630327	2.85666897	0.82946500
H	6.93697727	1.27702997	1.31302000	H	2.47702527	1.49396397	-1.65481600
H	8.04007327	2.60819297	0.95510200				