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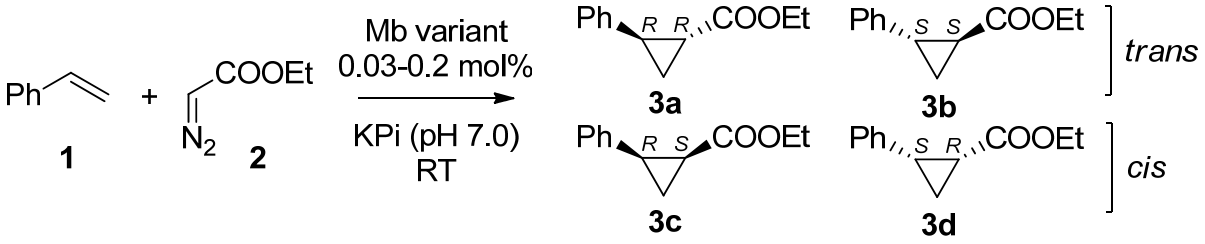
Table S1. Sequence of the oligonucleotides used for the preparation of the myoglobin variants.

No.	Primer	Sequence
1	Myo_H64V_L29(NDT) for	GACGTTGCTGGTCACGGTCAGGACATCNDTATCCGTCTGTTCAA
2	Myo_H64V_L29(VMA) for	GACGTTGCTGGTCACGGTCAGGACATCVMAATCCGTCTGTTCAA
3	Myo_H64V_L29(ATG) for	GACGTTGCTGGTCACGGTCAGGACATCATGATCCGTCTGTTCAA
4	Myo_H64V_L29(TGG) for	GACGTTGCTGGTCACGGTCAGGACATCTGGATCCGTCTGTTCAA
5	Myo_H64V_L29_rev	GACCGTGACCAGCAACGTC
6	Myo_H64V_F43(AHN) rev	TTCAGCTTCGGTTTTCAGGTGTTTGAAACGGTCAHNTTTTTCCAGGGTTTC
7	Myo_H64V_F43(TKB) rev	TTCAGCTTCGGTTTTCAGGTGTTTGAAACGGTCTKBTTTTTCCAGGGTTTC
8	Myo_H64V_F43(CAT) rev	TTCAGCTTCGGTTTTCAGGTGTTTGAAACGGTCCATTTTTTCCAGGGTTTC
9	Myo_H64V_F43(CCA) rev	TTCAGCTTCGGTTTTCAGGTGTTTGAAACGGTCCCATTTTTCCAGGGTTTC
10	Myo_H64V_F43_for	CAAACACCTGAAAACCGAAGCTG
11	Myo_H64V_V68(AHN) rev	CCCTTTTTCTTCAGGATAGCACCCAGAGCGGTCAGAHNGGTAACACCCACTT
12	Myo_H64V_V68(TKB) rev	CCCTTTTTCTTCAGGATAGCACCCAGAGCGGTCAGTKBGGTAACACCCACTT
13	Myo_H64V_V68(CAT) rev	CCCTTTTTCTTCAGGATAGCACCCAGAGCGGTCAGCATGGTAACACCCACTT
14	Myo_H64V_V68(CCA) rev	CCCTTTTTCTTCAGGATAGCACCCAGAGCGGTCAGCCAGGTAACACCCACTT
15	Myo_H64V_V68_for	GGGTGCTATCCTGAAGAAAAAGGGT
16	Myo_H64(NDT) for	AAATGAAGGCTTCTGAAGACC TGAAAAAANDTGGTGTTACCGTTCT
17	Myo_H64(VMA) for	AAATGAAGGCTTCTGAAGACC TGAAAAAAVMAGGTGTTACCGTTCT
18	Myo_H64(ATG) for	AAATGAAGGCTTCTGAAGACC TGAAAAAAATGGGTGTTACCGTTCT
19	Myo_H64(TGG) for	AAATGAAGGCTTCTGAAGACC TGAAAAAATGGGGTGTTACCGTTCT
20	Myo_H64_rev	GGTCTTCAGAAGCCTTCATTT
21	Myo_H64V_I107(NDT) for	ACAAAATCCCGATCAAATACCTGGAGTTCNDTTCTGAAGCTATCAT
22	Myo_H64V_I107(VMA) for	ACAAAATCCCGATCAAATACCTGGAGTTCVMATCTGAAGCTATCAT
23	Myo_H64V_I107(ATG) for	ACAAAATCCCGATCAAATACCTGGAGTTCATGTCTGAAGCTATCAT
24	Myo_H64V_I107(TGG) for	ACAAAATCCCGATCAAATACCTGGAGTTCTGGTCTGAAGCTATCAT

25	Myo_H64V_I107_rev	GGTATTTGATCGGGATTTTGT
26	Myo_H64V_L29D_for	GACGTTGCTGGTCACGGTCAGGACATCGATATCCGTCTGTTCAA
27	Myo_H64V_L29N_for	GACGTTGCTGGTCACGGTCAGGACATCAACATCCGTCTGTTCAA
28	Myo_H64V_L29P_for	GACGTTGCTGGTCACGGTCAGGACATCCCGATCCGTCTGTTCAA
29	Myo_H64V_L29S_for	GACGTTGCTGGTCACGGTCAGGACATCAGCATCCGTCTGTTCAA
30	Myo_H64V_L29M_for	GACGTTGCTGGTCACGGTCAGGACATCATGATCCGTCTGTTCAA
31	Myo_H64V_L29Q_for	GACGTTGCTGGTCACGGTCAGGACATCCAGATCCGTCTGTTCAA
32	Myo_H64V_L29Y_for	GACGTTGCTGGTCACGGTCAGGACATCTATATCCGTCTGTTCAA
33	Myo_H64V_L29T_for	GACGTTGCTGGTCACGGTCAGGACATCACCATCCGTCTGTTCAA
34	Myo_H64V_L29K_for	GACGTTGCTGGTCACGGTCAGGACATCAAAATCCGTCTGTTCAA
35	Myo_H64V_F43Q_for	TCAAATCTCACCCGGAAACCCTGGAAAAACAGGACCGTTTCAAAC
36	Myo_H64V_F43N_for	TCAAATCTCACCCGGAAACCCTGGAAAAAAACGACCGTTTCAAAC
37	Myo_H64V_F43C_for	TCAAATCTCACCCGGAAACCCTGGAAAAATGCGACCGTTTCAAAC
38	Myo_H64V_F43S_for	TCAAATCTCACCCGGAAACCCTGGAAAAAAGCGACCGTTTCAAAC
39	Myo_H64V_F43E_for	TCAAATCTCACCCGGAAACCCTGGAAAAAGAAGACCGTTTCAAAC
40	Myo_H64V_F43D_for	TCAAATCTCACCCGGAAACCCTGGAAAAAGATGACCGTTTCAAAC
41	Myo_H64V_F43G_for	TCAAATCTCACCCGGAAACCCTGGAAAAAGGCGACCGTTTCAAAC
42	Myo_H64V_F43I_for	TCAAATCTCACCCGGAAACCCTGGAAAAAATTGACCGTTTCAAAC
43	Myo_H64V_F43W_for	TCAAATCTCACCCGGAAACCCTGGAAAAATGGGACCGTTTCAAAC
44	Myo_H64V_V68I_for	CTGAAGACCTGAAAAAAGTGGGTGTTACCATTCTGACCGCTCTGG
45	Myo_H64V_V68P_for	CTGAAGACCTGAAAAAAGTGGGTGTTACCCCGCTGACCGCTCTGG
46	Myo_H64V_V68W_for	CTGAAGACCTGAAAAAAGTGGGTGTTACCTGGCTGACCGCTCTGG
47	Myo_H64V_V68G_for	CTGAAGACCTGAAAAAAGTGGGTGTTACCGGCCTGACCGCTCTGG
48	Myo_H64V_V68D_for	CTGAAGACCTGAAAAAAGTGGGTGTTACCGATCTGACCGCTCTGG
49	Myo_H64V_V68E_for	CTGAAGACCTGAAAAAAGTGGGTGTTACCGAACTGACCGCTCTGG
50	Myo_H64V_V68M_for	CTGAAGACCTGAAAAAAGTGGGTGTTACCATGCTGACCGCTCTGG

51	Myo_H64V_V68S_for	CTGAAGACCTGAAAAAAGTGGGTGTTACCAGCCTGACCGCTCTGG
52	Myo_H64V_I107K_for	ACAAAATCCCGATCAAATACCTGGAGTTCAAATCTGAAGCTATCAT
53	Myo_H64V_I107R_for	ACAAAATCCCGATCAAATACCTGGAGTTCCGTTCTGAAGCTATCAT
54	Myo_H64V_I107P_for	ACAAAATCCCGATCAAATACCTGGAGTTCCCGTCTGAAGCTATCAT
55	Myo_H64V_I107S_for	ACAAAATCCCGATCAAATACCTGGAGTTCAGCTCTGAAGCTATCAT
56	Myo_H64V_I107L_for	ACAAAATCCCGATCAAATACCTGGAGTTCCTGTCTGAAGCTATCAT
57	Myo_H64V_I107D_for	ACAAAATCCCGATCAAATACCTGGAGTTCGATTCTGAAGCTATCAT
58	Myo_H64V_I107N_for	ACAAAATCCCGATCAAATACCTGGAGTTCAACTCTGAAGCTATCAT
59	Myo_H64V_I107T_for	ACAAAATCCCGATCAAATACCTGGAGTTCACCTCTGAAGCTATCAT
60	Myo_H64V_I107Y_for	ACAAAATCCCGATCAAATACCTGGAGTTCTATTCTGAAGCTATCAT
61	Myo_H64V_I107H_for	ACAAAATCCCGATCAAATACCTGGAGTTCCATTCTGAAGCTATCAT
62	Myo_H64V_I107V_for	ACAAAATCCCGATCAAATACCTGGAGTTCGTGTCTGAAGCTATCAT
63	Myo_NdeI_for	CAGGTCATATGGTTCTGTCTGAAGGTGAATGGCAGC
64	Myo_XhoI_rev	GGAACCTCGAGAGAACCACCCTGGTAACCCAGTTC

Supplementary Table S2. Activity and selectivity of Mb(H64V)-derived active site variants toward styrene cyclopropanation with ethyl α-diazoacetate (EDA). Reactions conditions: 10 mM styrene, 20 mM EDA, 10 mM dithionite, and Mb variant at the indicated concentration in KPi buffer (50 mM, pH 7.0) for 18 hours at room temperature.



Mb variant	Conc. [μM][a]	Conv. [%][b]	TON	de_{trans} [%]	ee_{trans} [%][c]
Mb(H64V)	20	47	235	93	-10
Mb(L29A,H64V)	20	47	235	84	-2
Mb(L29D,H64V)	6	6	95	80	10
Mb(L29F,H64V)	20	56	280	91	-29
Mb(L29G,H64V)	20	52	260	96	50
Mb(L29K,H64V)	3	1	35	82	-42
Mb(L29M,H64V)	20	43	215	90	-7
Mb(L29N,H64V)	13	43	335	88	-12
Mb(L29Q,H64V)	11	40	355	94	-13
Mb(L29S,H64V)	20	60	300	93	70
Mb(L29T,H64V)	20	93	460	95	59
Mb(F43C,H64V)	3	11	360	85	1
Mb(F43I,H64V)	7	2	30	75	-8
Mb(F43M,H64V)	20	1	5	>99	12
Mb(F43S,H64V)	20	45	225	95	55
Mb(F43W,H64V)	20	14	70	93	3
Mb(F43Y,H64V)	20	52	260	94	-41
Mb(H64V,V68A)	20	>99	510	>99	>-99
Mb(H64V,V68C)	20	21	105	99	>-99
Mb(H64V,V68F)	20	57	285	>99	72
Mb(H64V,V68G)	20	>99	525	81	>-99
Mb(H64V,V68H)	20	14	70	83	-6

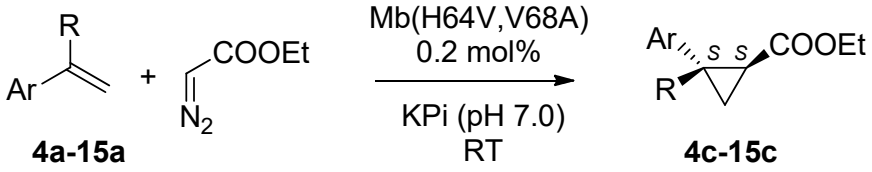
Mb(H64V,V68K)	20	12	60	87	6
Mb(H64V,V68L)	20	53	265	>99	70
Mb(H64V,V68N)	20	6	30	65	-65
Mb(H64V,V68Q)	20	2	10	76	-27
Mb(H64V,V68S)	20	82	410	>99	>-99
Mb(H64V,V68T)	20	70	350	96	-38
Mb(H64V,V68W)	20	24	120	87	5
Mb(H64V,V68Y)	20	23	110	96	59
Mb(H64V,I107H)	13	2	15	71	16
Mb(H64V,I107S)	7.5	2	20	88	-12
Mb(H64V,I107T)	8	1	15	86	-52
Mb(H64V,I107V)	20	34	170	>99	-54
Mb(H64V,I107Y)	20	21	105	91	5

Supplementary Table S3: Activity and selectivity of second-generation Mb variants toward styrene cyclopropanation with ethyl α-diazoacetate (EDA). Reactions conditions: 10 mM styrene, 20 mM EDA, 10 mM dithionite, and Mb variant at the indicated concentration in KPi buffer (50 mM, pH 7.0) for 18 hours at room temperature.

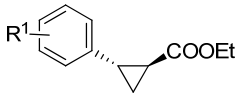
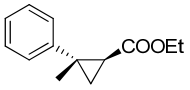
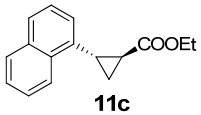
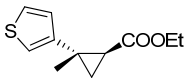
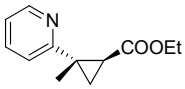
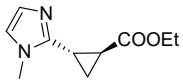
Mb variant	Conc. [μM][a]	Conv. [%][b]	TON	de_{trans} [%]	ee_{trans} [%][c]	ee_{cis} [%][c]
Mb(L29S,H64V,V68L)	20	58	290	97	76	38
Mb(L29S,H64V,V68F) (= RR1)	20	27	135	90	91	12
Mb(H64V,V86F,I107H)	20	26	130	96	20	4
Mb(H64V,V86L,I107H)	20	43	215	>99.9	45	-
Mb(L29T,H64V,V68L) (= RR2)	20	61	305	>99.9	92	-
Mb(L29T,H64V,V68F) (= RR3)	20	58	290	>99.9	92	-
Mb(L29T,F43S,H64V,V68L)	n/a	-	-	-	-	-
Mb(L29T,H64V,V68L,I107H)	n/a	-	-	-	-	-
Mb(L29T,F43S,H64V,V68L, I107H)	n/a	-	-	-	-	-
Mb(L29T,H64V,V68F,I107A)	15	48	320	99	-71	-
Mb(L29T,H64V,V68F,I107C)	15	18	120	99	5	-
Mb(L29T,H64V,V68F,I107L) (= RR4)	15	64	320	97	75	56
Mb(L29T,H64V,V68F,I107T)	15	15	100	>99.9	-16	-
Mb(L29T,H64V,V68F,I107V)	15	37	245	99	57	-
Mb(L29T,H64V,V68F,I107W)	15	26	175	99	75	-
Mb(L29T,H64V,V68F,I107Y)	15	3	20	91	26	8
Mb(L29T,F43W,H64V,V68F) (= RR5)	20	53	265	99	95	-

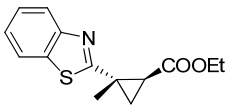
[a] n/a: not expressed in soluble form. [b] % conversion based on GC analysis and relative to olefin.
[c] *trans* = (*1R,2R*); *cis* = (*1S,2R*) as determined by chiral GC or SFC.

Supplementary Table S4. Catalytic activity and selectivity for Mb(H64V,V68A)-catalyzed cyclopropanation of aryl-substituted olefins in the presence of EDA. Reactions conditions: 20 μM Mb(H64V,V68A), 10 mM styrene, 20 mM EDA, 10 mM dithionite, in KPi buffer (50 mM, pH 7.0) for 18 hours at room temperature.



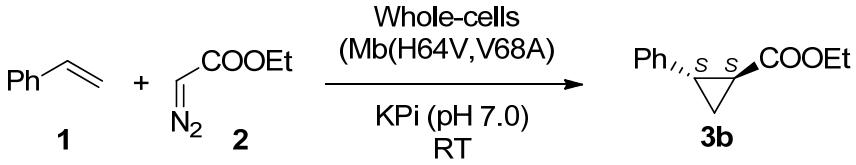
4a-15a **4c-15c**

Entry	Product	Conv. [%]	TON	de_{trans} [%]	$ee_{(1S,2S)}$ [%]
					
1[a]	R^1 = 4-CH_3 (**4c**)	77	1,150	>99.5	98
2[a]	4-MeO (**5c**)	89	1,330	99.9	99
3[a]	4-Cl (**6c**)	92	1,380	>99.5	>99.9
4[a]	4-CF_3 (**7c**)	69	1,035	99.9	>99.9
5[a]	3-Me (**8c**)	73	1,095	>99.5	>99.9
6[a]	2-Me (**9c**)	86	1,275	>99	>99.9
7[a]	 **10c**	86	1,290	97	96
8	 **11c**	87	435	98	99
9	 **12c**	98	490	96	97
10	 **13c**	>99	>500	95	>99.9
11	 **14c**	7	35	99	99

12	 **15c**	97	485	99	96

[a] As reported in Bordeaux et al.[1]. Reaction conditions: 20 uM Mb(H64V,V68A), 30 mM styrene, 60 mM EDA, in KPi (pH 7.0), RT, 16 hours.

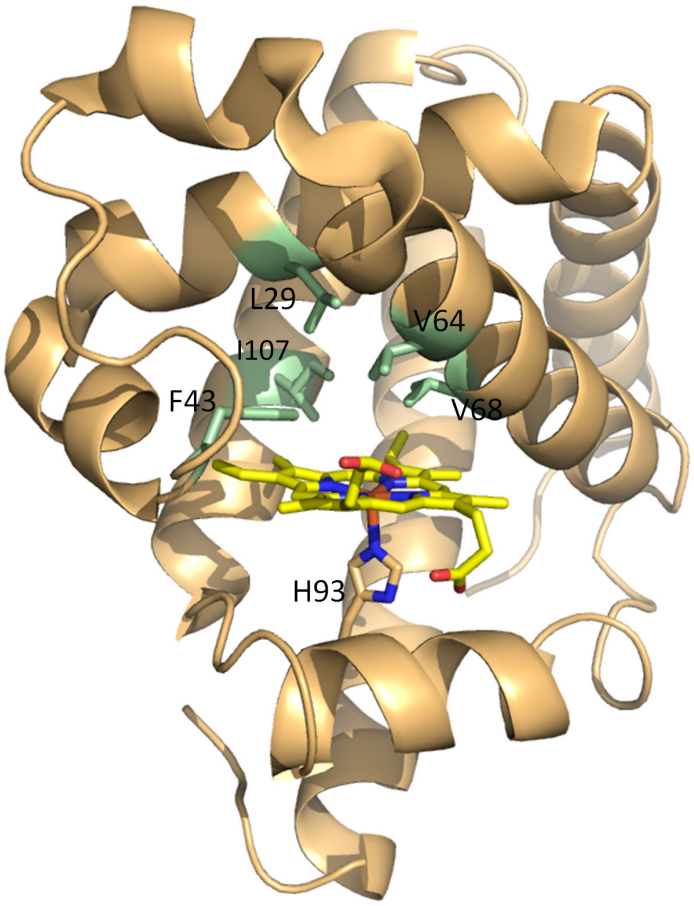
Supplementary Table S5. Product conversion and selectivity for transformation of styrene and EDA into (*1S,2S*)-ethyl 2-phenylcyclopropanecarboxylate (**3b**) as catalyzed by *E. coli* cells expressing Mb(H64V,V64A). The whole-cell reactions were carried out using cell suspensions at the indicated density under aerobic (= open vessel), partially aerobic (= sealed vessel), or anaerobic (= argon atmosphere) conditions.



Cell density (OD_{600})	Conditions	[styrene]	[EDA]	Conv. [%][b]	TON	de_{trans} [%]	$ee_{(1S,2S)}$ [%]
40[a]	Open vessel	0.02 M	0.02 M	68	450	99.9	99.9
40[a]	Sealed vessel	0.02 M	0.02 M	91	600	99.9	99.9
40[a]	Argon atm.	0.02 M	0.02 M	>99	725	99.9	99.9
40[a]	Open vessel + Glucose[c]	0.02 M	0.02 M	76	515	99.9	99.9
40[a]	Sealed vessel + Glucose[c]	0.02 M	0.02 M	54	365	99.9	99.9
40[a]	Ar atm. + Glucose[c]	0.02 M	0.02 M	88	595	99.9	99.9
200[b]	Argon atm.	0.5 M	0.5 M*	50	590	99.9	99.9
200[b]	Argon atm.	0.5 M	0.5 M**	62	730	99.9	99.9

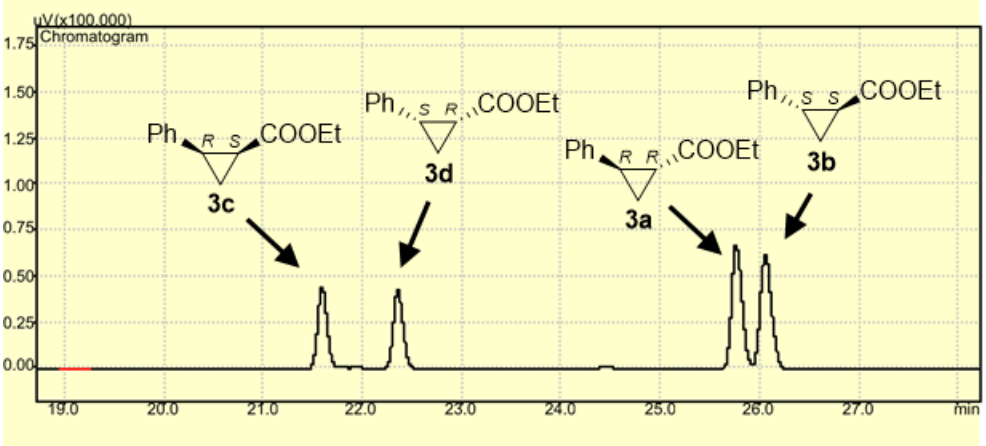
[a] Using BL21(DE3) cells. [b] Using C41(DE3) cells. [c] Glucose added to final concentration of 50 mM. * Slow addition over 4 hours. ** Slow addition over 2 hours.

Supplementary Figure S1. Crystal structure of Mb(H64V) variant (pdb 2MGJ)[2]. The heme (yellow), active site residues (green), and heme-bound histidine are shown as stick models. The figure was prepared with PyMOL (www.pymol.org).

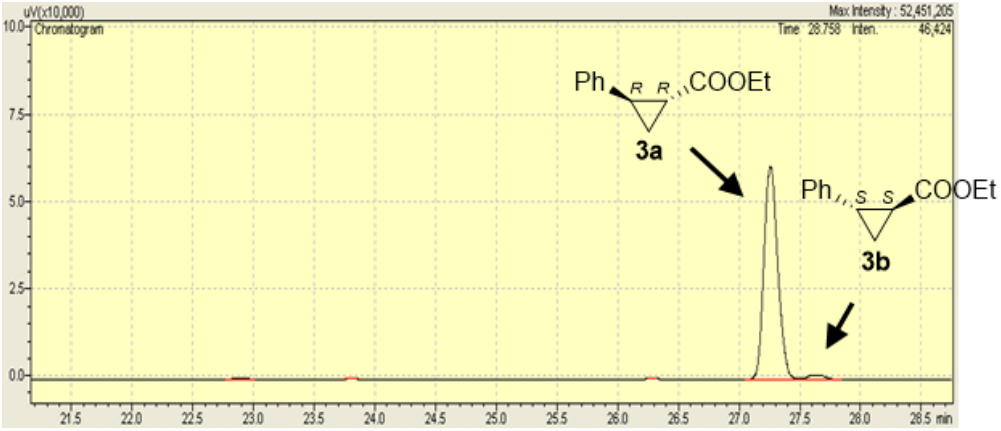


Supplementary Figure S2. Representative chiral GC chromatograms corresponding to products **3a**, **3b**, **3c**, and **3d** as (a) as authentic racemic standards obtained in the presence of $Rh_2(OAc)_4$ catalyst, and (b) as produced from the reaction with Mb(L29T,F43W,H64V,V68F) (= RR5). Product assignment was made using enantiomerically enriched authentic standards as described previously.[1]

(a) $Rh_2(OAc)_4$-catalyzed reaction:



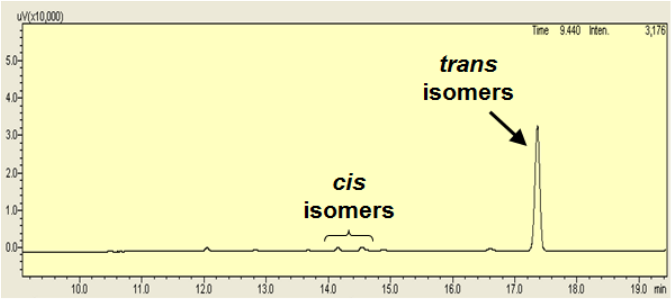
(b) Mb(L29T,F43W,H64V,V68F)-catalyzed reaction:

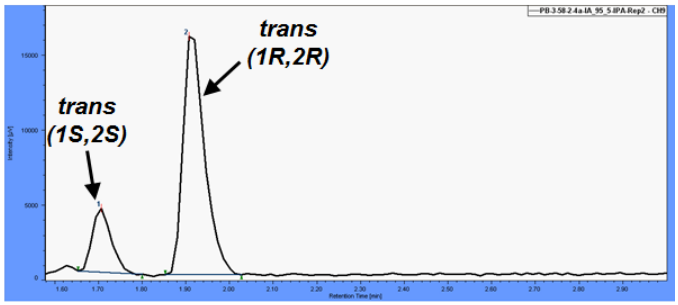


Supplementary Figure S4. GC and SFC chromatograms for determination of diastereomeric and enantiomeric excess in the cyclopropanation reactions catalyzed by the *trans*-(*1R*,*2R*)-selective Mb variants. Reference samples enriched in the *trans*-(*1S*,*2S*) isomer were prepared using Nishiyama's Ru-((+)-ip-PyBox) catalyst[3] as described in the experimental procedures.

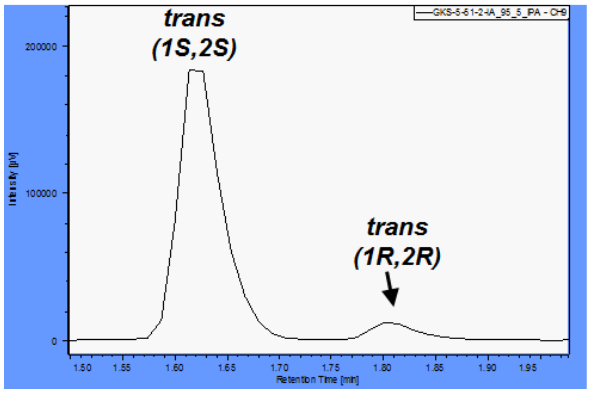
(a) Reaction with 4-methyl-styrene (**4a**) and EDA to give **4b:**

i. Mb(L29T,F43W,H64V,V68F) (= RR5)-catalyzed reaction (GC and SFC):



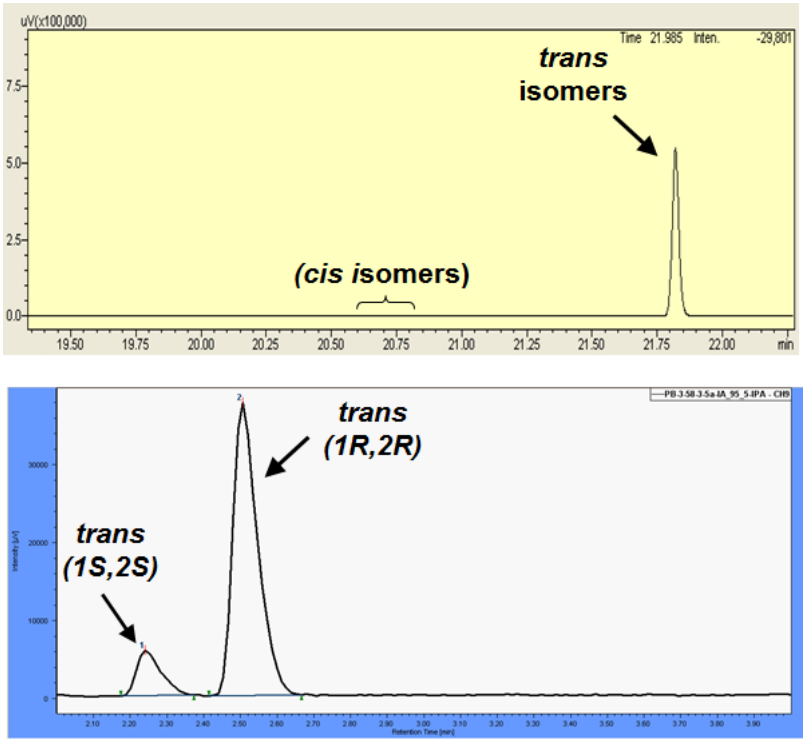


ii. Ru-((+)-ip-PyBox)-catalyzed reaction (SFC):

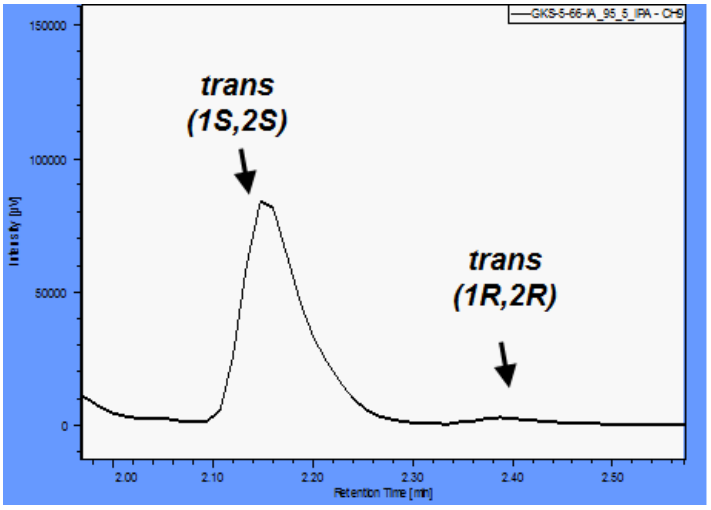


(b) Reaction with 4-methoxy-styrene (**5a**) and EDA to give **5b**:

i. Mb(L29T,F43W,H64V,V68F) (= RR5) catalyzed reaction (GC and SFC):

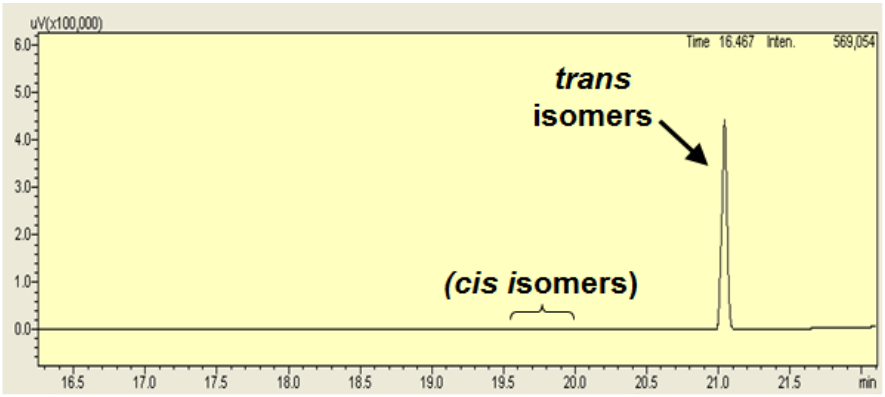


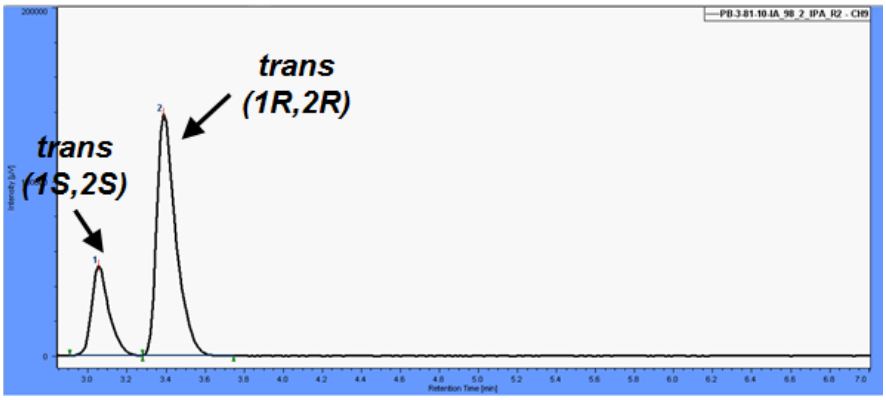
ii. Ru-((+)-ip-PyBox)-catalyzed reaction (SFC):



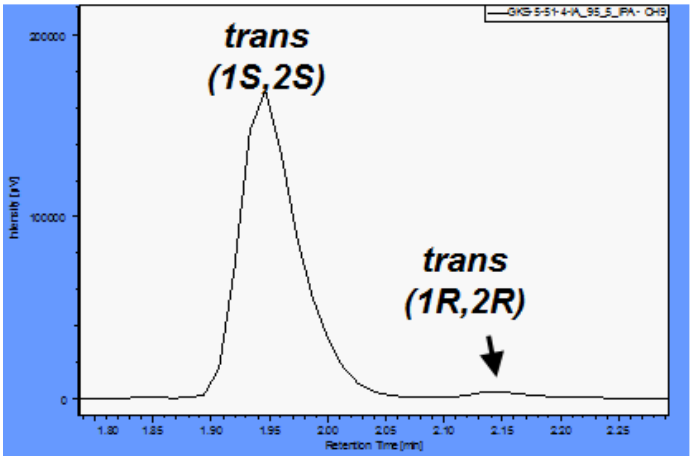
(c) Reaction with 4-chloro-styrene (**6a**) and EDA to give **6b**:

i. Mb(L29T,H64V,V68L) (= RR2) catalyzed reaction (GC and SFC):



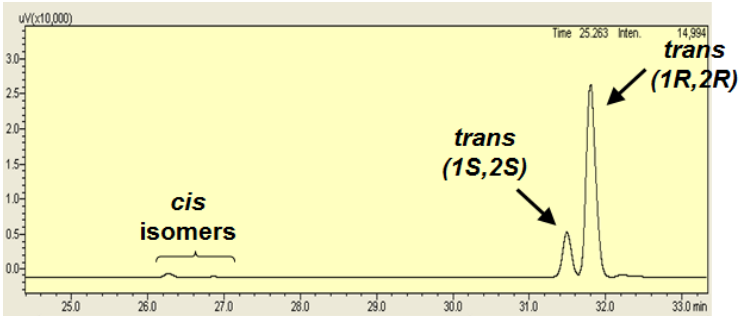


ii. Ru-((+)-ip-PyBox)-catalyzed reaction (SFC):

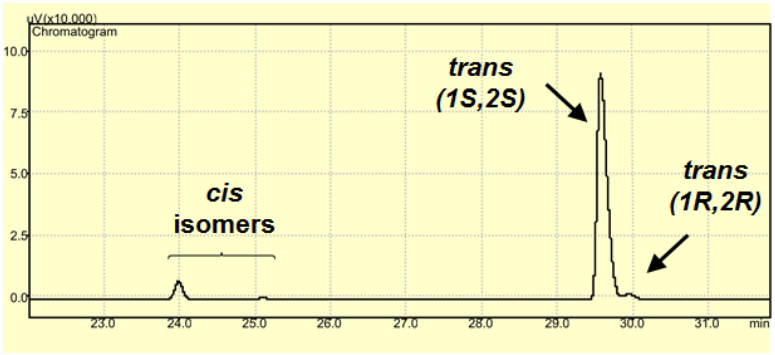


(d) reaction with 4-trifluoromethyl-styrene (**7a**) and EDA to give **7b**:

i. Mb(L29T,H64V,V68F,I107L) (= RR4) catalyzed reaction (GC):

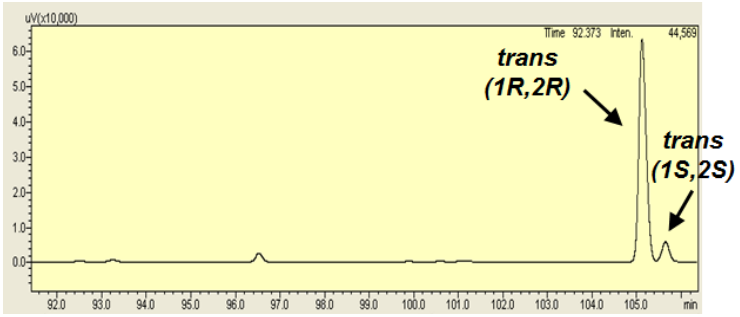


ii. Ru-((+)-ip-PyBox)-catalyzed reaction (GC):

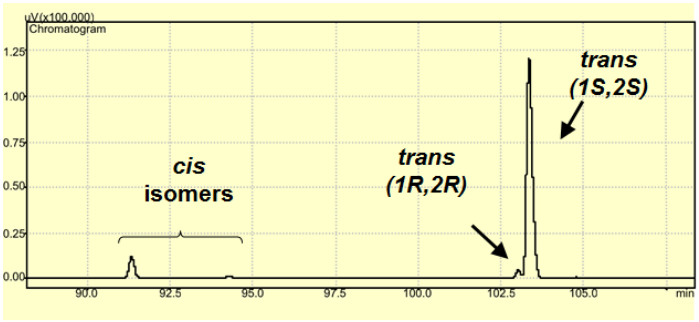


(e) Reaction with 3-methyl-styrene (**8a**) and EDA to give **8b**:

i. Mb(L29T,H64V,V68F,I107L) (= RR4) catalyzed reaction (GC):

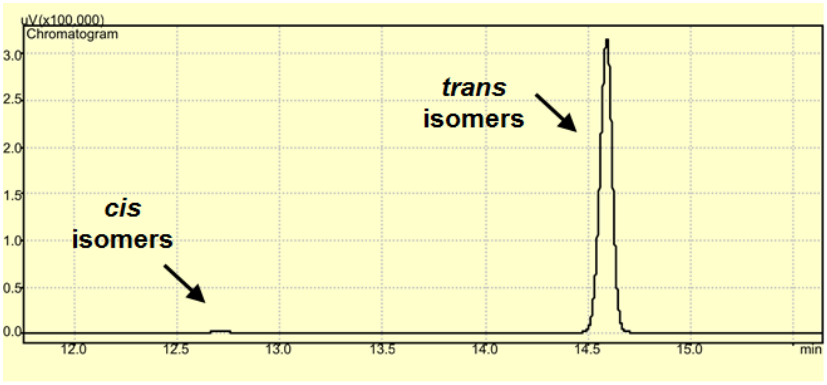


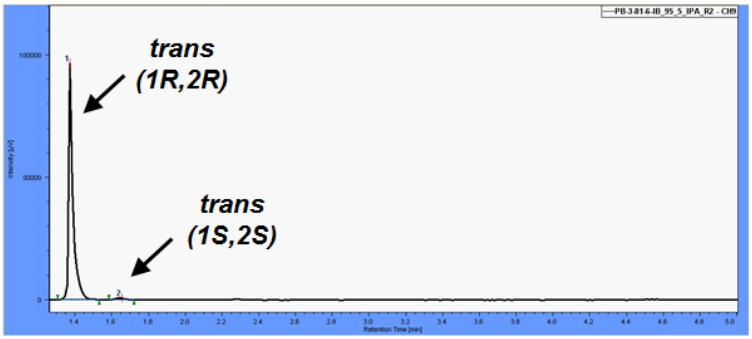
ii. Ru-((+)-ip-PyBox)-catalyzed reaction (GC):



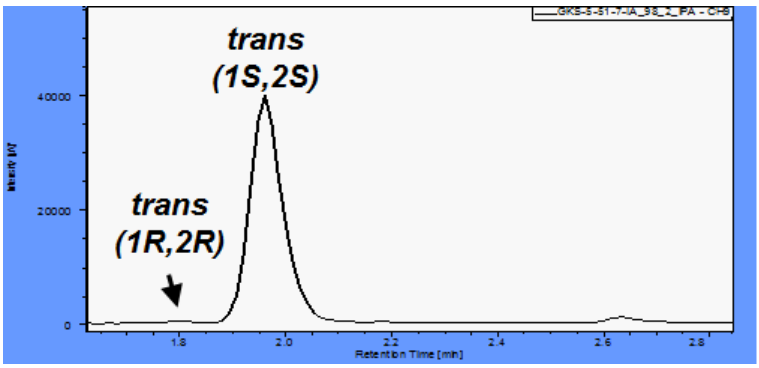
(f) Reaction with 2-methyl-styrene (**9a**) and EDA to give **9b**:

i. Mb(L29T,H64V,V68F) (= RR3) catalyzed reaction (GC and SFC):



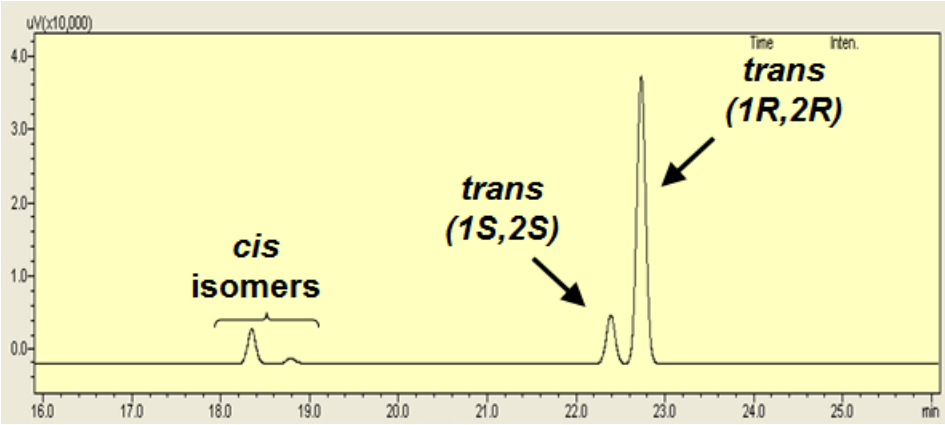


ii. Ru-((+)-ip-PyBox)-catalyzed reaction (SFC):

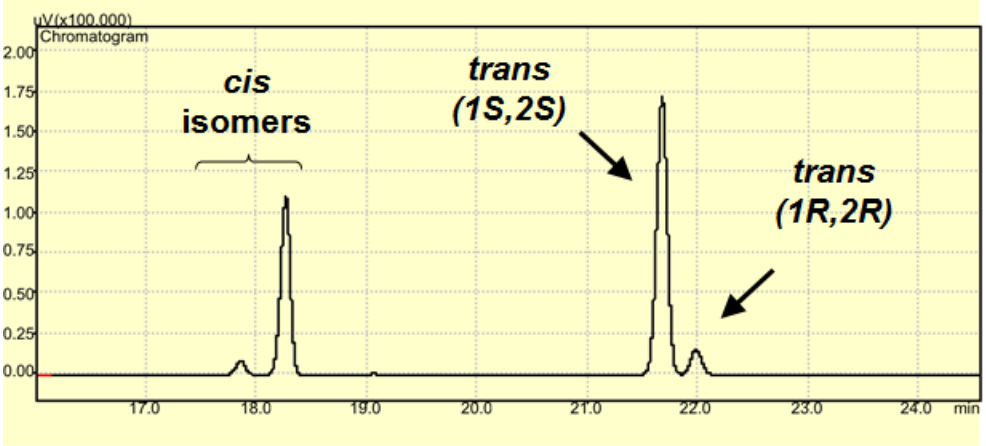


(g) Reaction with alpha-methyl-styrene (**10a**) and EDA to give **10b**:

i. Mb(L29T,H64V,V68F) (= RR3) catalyzed reaction (GC):

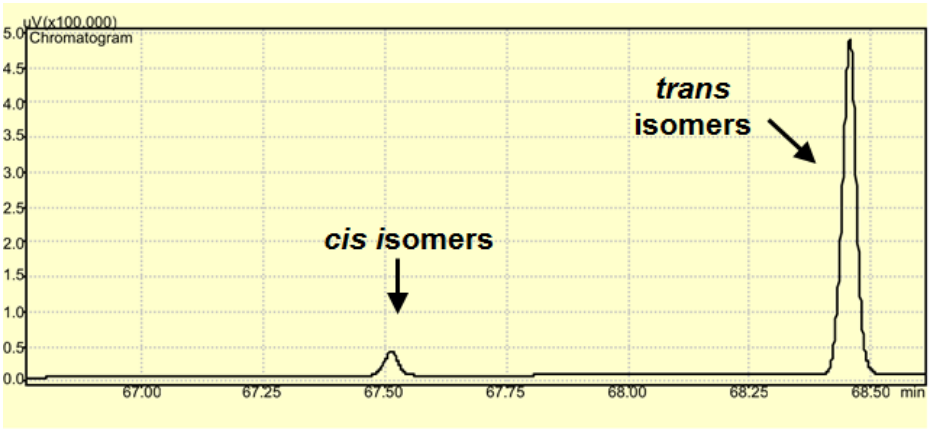


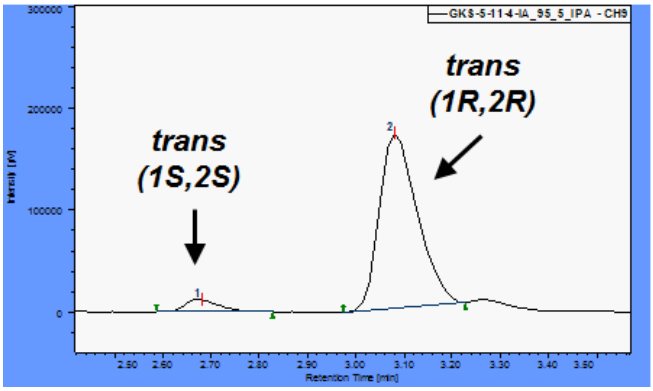
ii. Ru-((+)-ip-PyBox)-catalyzed reaction (GC):



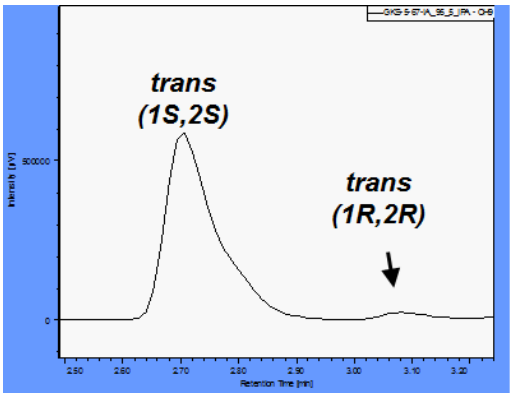
(h) Reaction with 1-vinyl-napthalene (**11a**) and EDA to give **11b**:

i. Mb(L29T,H64V,V68F,I107L (= RR4) catalysed reaction (GC and SFC):



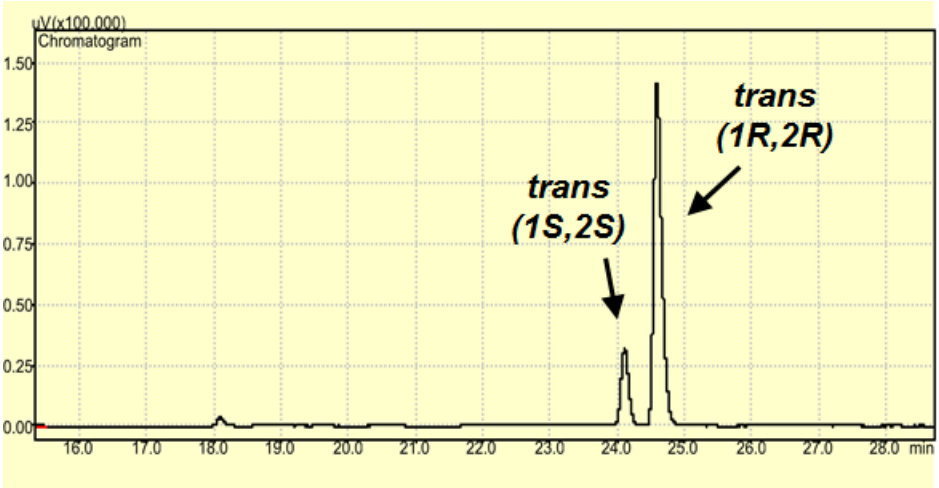


ii. Ru-((+)-ip-PyBox)-catalyzed reaction (SFC):

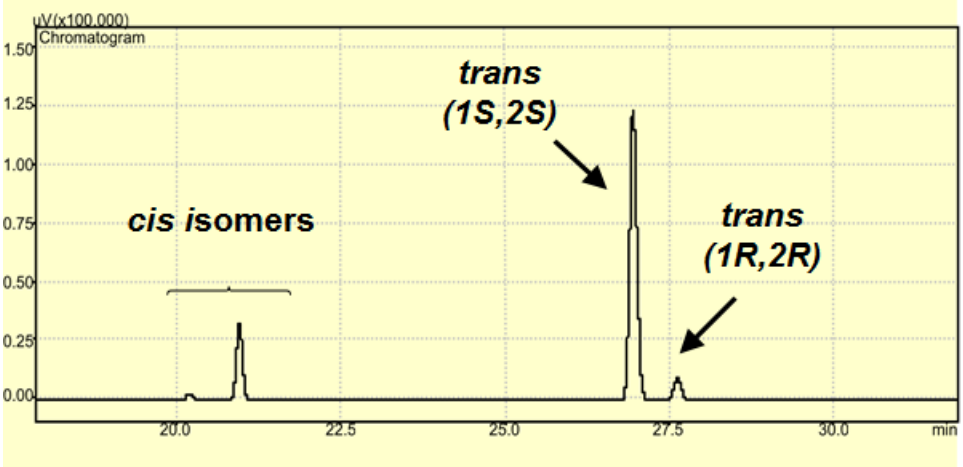


(j) Reaction with 3-(prop-1-en-2-yl)thiophene (**12a**) and EDA to give **12b**:

i. Mb(L29T,H64V,V68L) (= RR2) catalyzed reaction (GC):

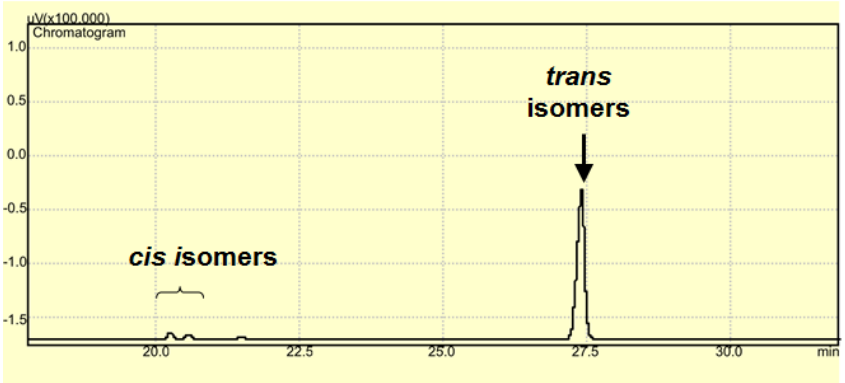


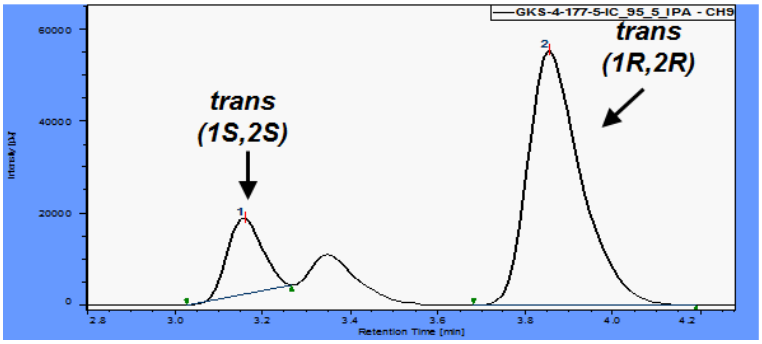
ii. Ru-((+)-ip-PyBox)-catalyzed reaction (GC):



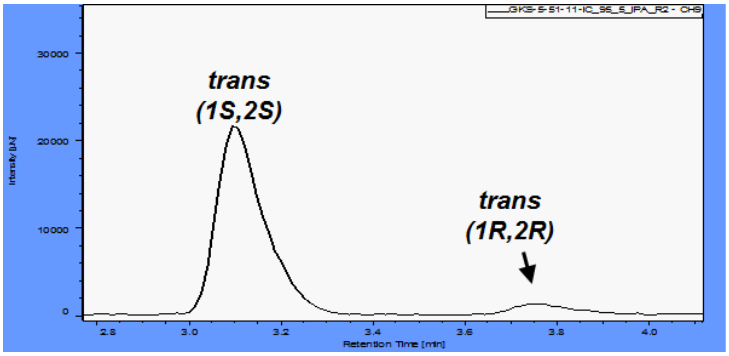
(k) Reaction with 2-(prop-1-en-2-yl)pyridine (**13a**) and EDA to give **13b**:

i. Mb(L29T,H64V,V68L) (= RR2) catalyzed reaction (GC and SFC):



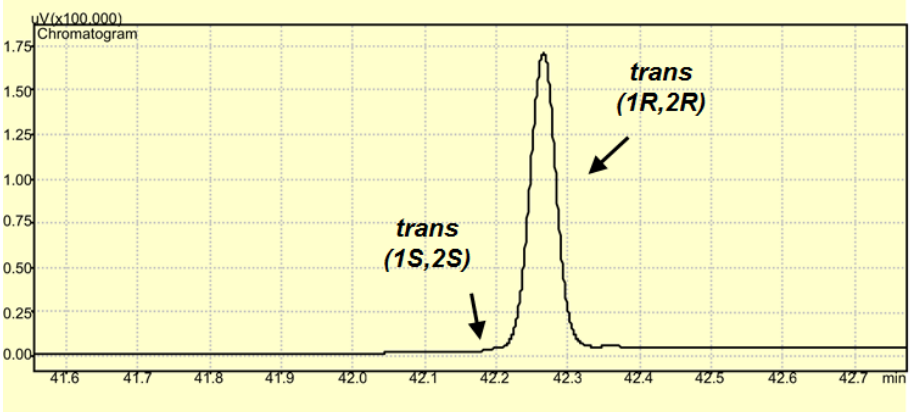


ii. Ru-((+)-ip-PyBox)-catalyzed reaction (SFC):

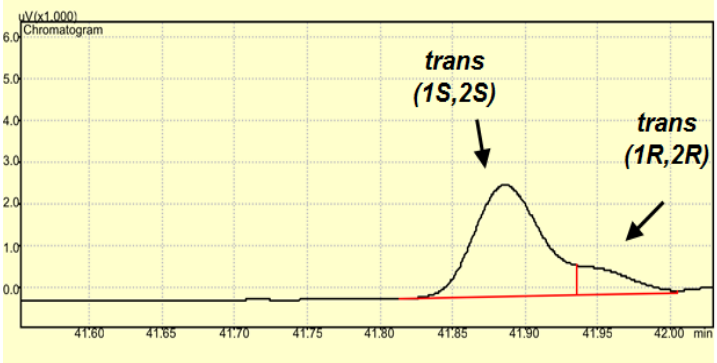


(l) Reaction with 1-methyl-2-vinyl-1H-imidazole (**14a**) and EDA to give **14b**:

i. Mb(L29S,H64V,V68F) (= RR1) catalysed reaction (GC):

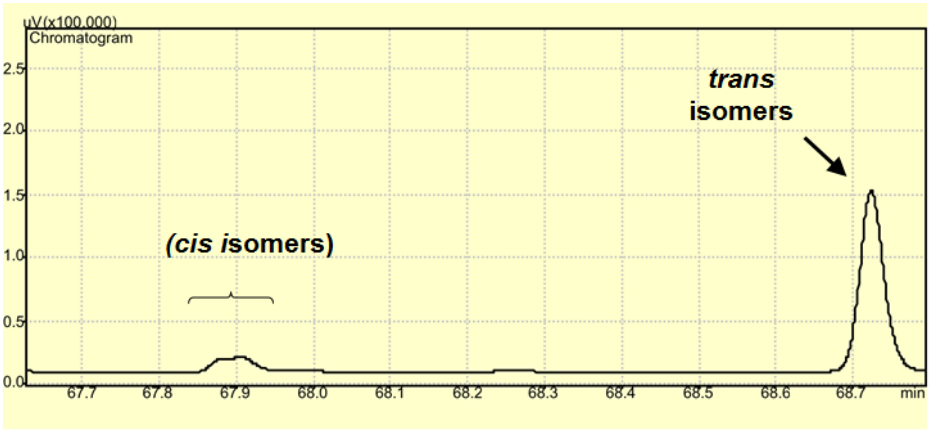


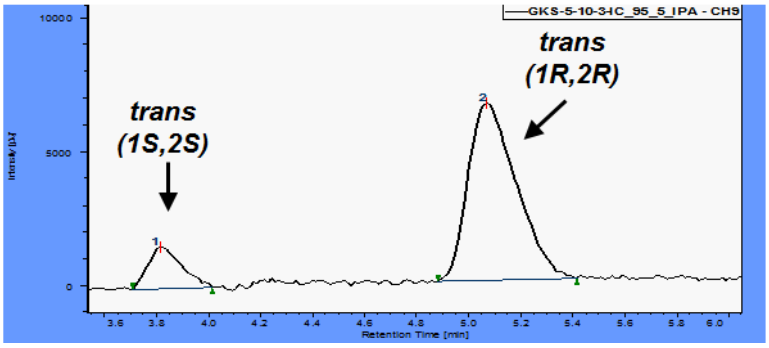
ii. Ru-((+)-ip-PyBox)-catalyzed reaction (GC):



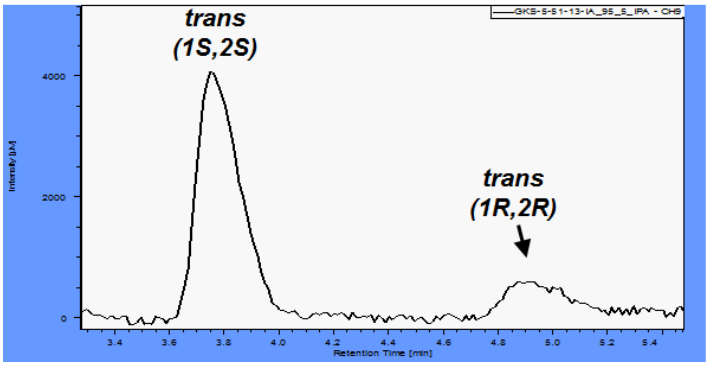
(m) Reaction with 2-(prop-1-en-2-yl)benzo[d]thiazole (**15a**) and EDA to give **15b**:

i. Mb(L29T,H64V,V68F,I107L (= RR4) catalysed reaction (GC and SFC):



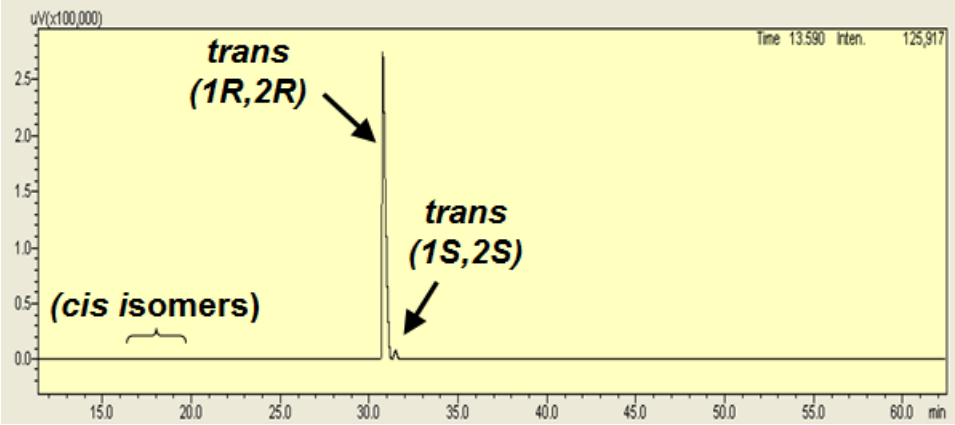


ii. Ru-((+)-ip-PyBox)-catalyzed reaction (SFC):

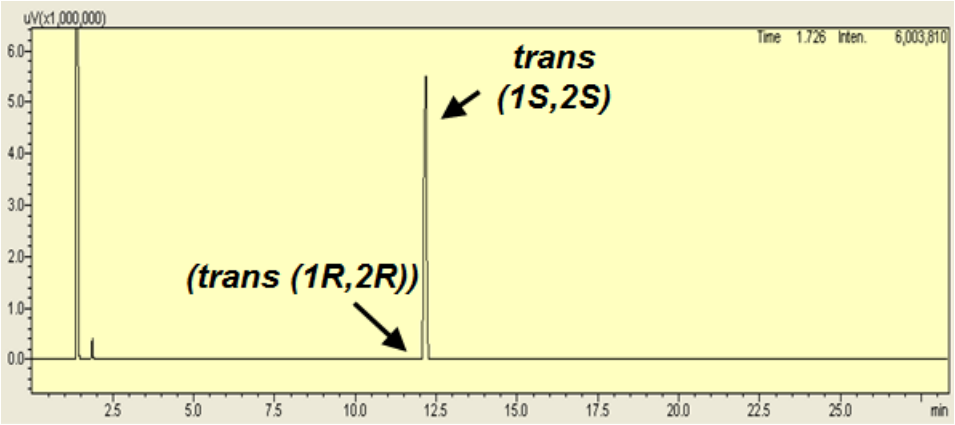


Supplementary Figure S5. GC and SFC chromatograms for determination of diastereomeric and enantiomeric excess in the whole cell cyclopropanation reactions for the synthesis of **3a**, **3b**, **19**, **23**, and **26**. Reference samples enriched in the *trans*-(*1S,2S*) isomer were prepared using Nishiyama's Ru-((+)-ip-PyBox) catalyst[3] as described in the experimental procedures.

(a) Whole-cell reaction with Mb(L29T,H64V,V68L) (= RR2)-expressing cells, styrene (**1**), and EDA to give **3a** (GC):

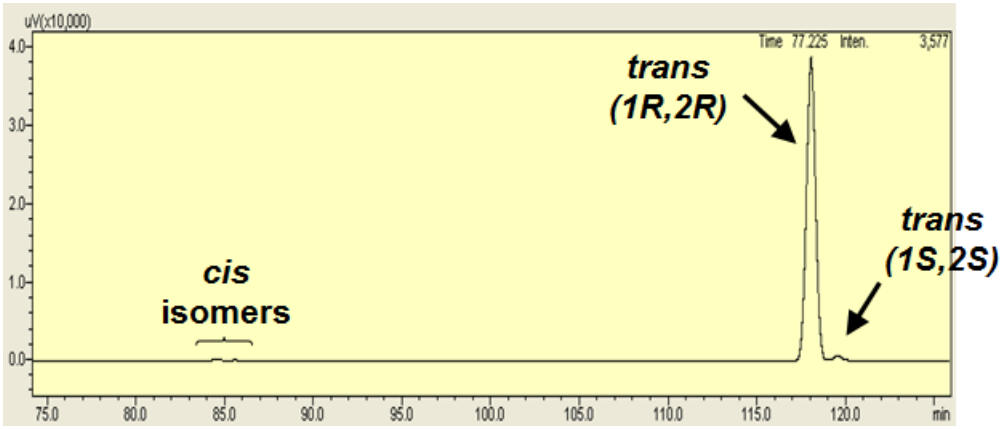


(b) Whole-cell reaction with Mb(H64V,V68A)-expressing cells, styrene (**1**), and EDA to give **3b** (GC):

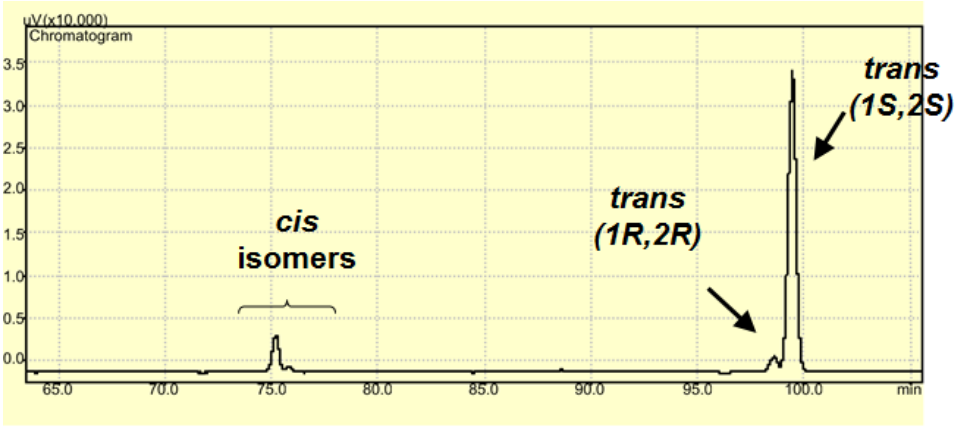


(c) Reaction with 4-vinyl-2,3-dihydrobenzofuran (**18**) and EDA to give **19**:

i. Whole-cell Mb(L29T,H64V,V68F,I107L) (= RR4) catalyzed reaction (GC):

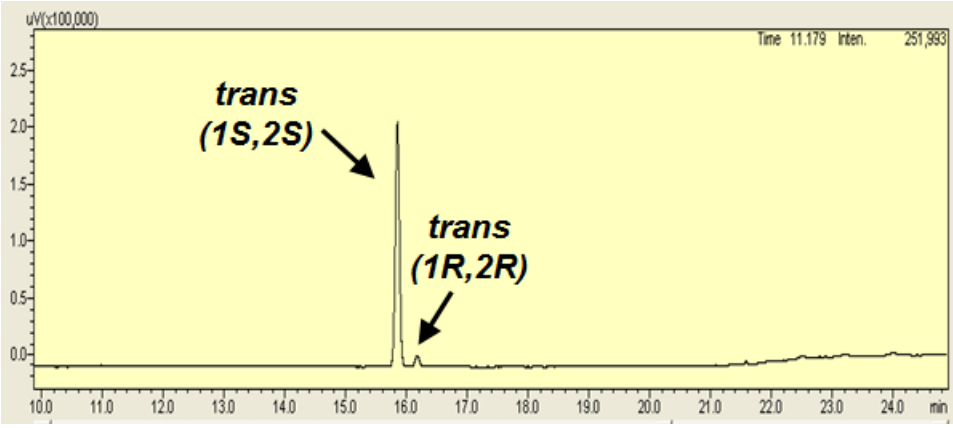


ii. Ru-((+)-ip-PyBox)-catalyzed reaction (GC):

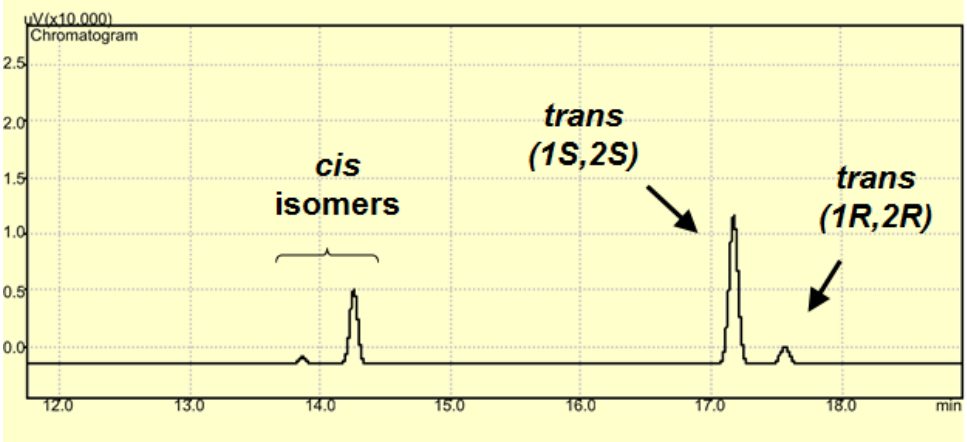


(d) Reaction with 5-(prop-1-en-2-yl)-2-(trifluoromethyl)pyridine (**22**) and EDA to give **23**:

i. Whole-cell Mb(L29T,H64V,V68F,I107L) (= RR4) catalyzed reaction (GC):

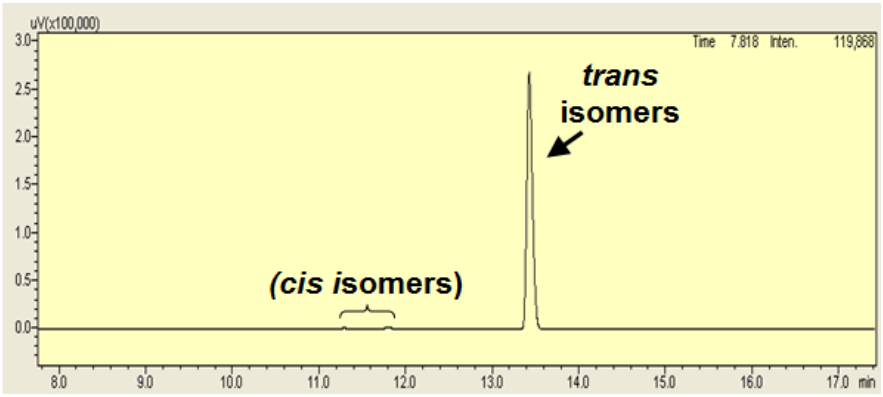


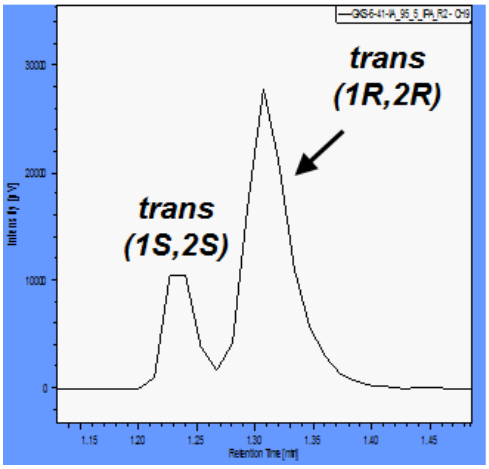
ii. Ru-((+)-ip-PyBox)-catalyzed reaction (GC):



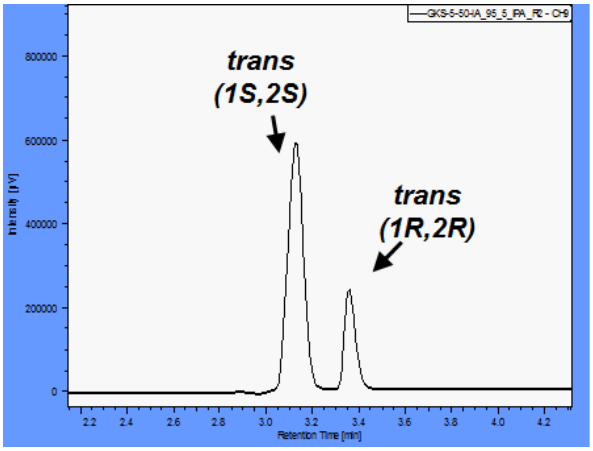
(e) Reaction with 1,2-difluoro-4-vinylbenzene (**25**) and EDA to give **26**:

i. Whole-cell Mb(L29T,H64V,V68F) (= RR3) catalyzed reaction (GC and SFC):

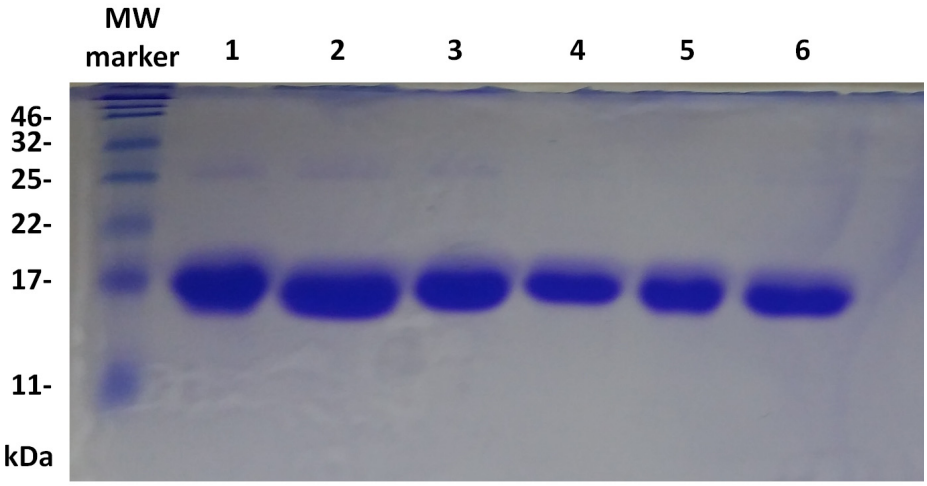




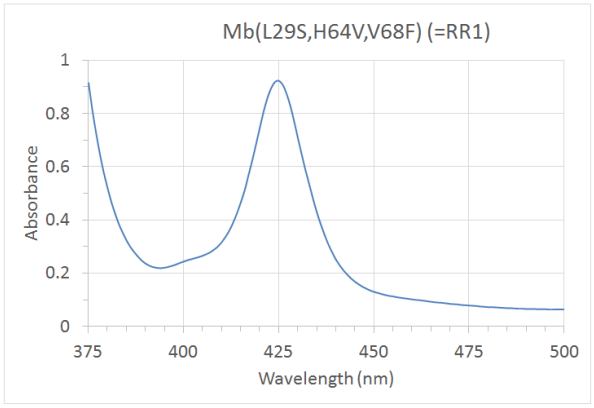
ii. Ru-((+)-ip-PyBox)-catalyzed reaction (SFC, different method):

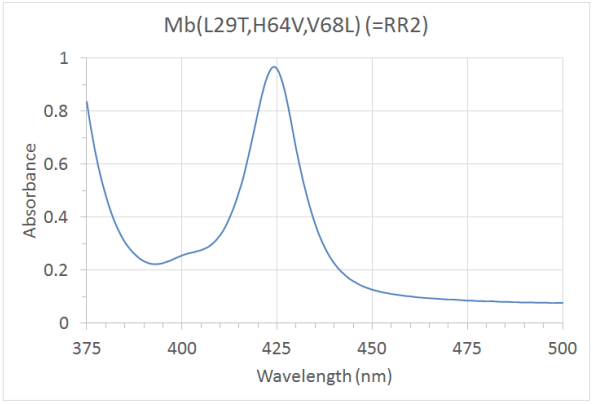


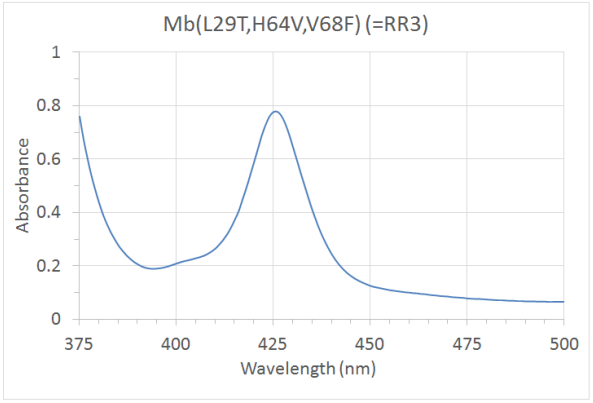
Supplementary Figure S6. SDS-PAGE gel of purified *trans*-(*1R,2R*)-selective Mb variants (RR1-RR5) (lane 1-5) and *trans*-(*1S,2S*)-selective Mb(H64V,V68S) (lane 6) variant.

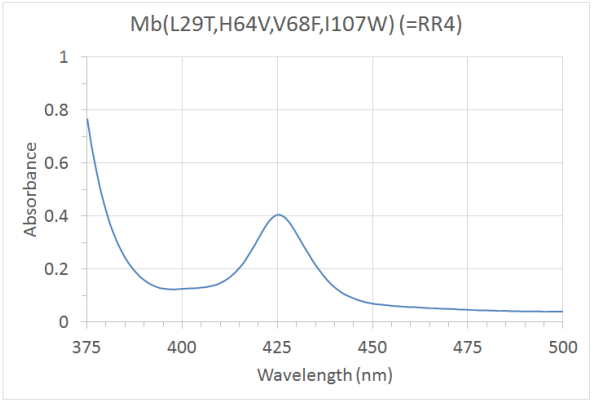


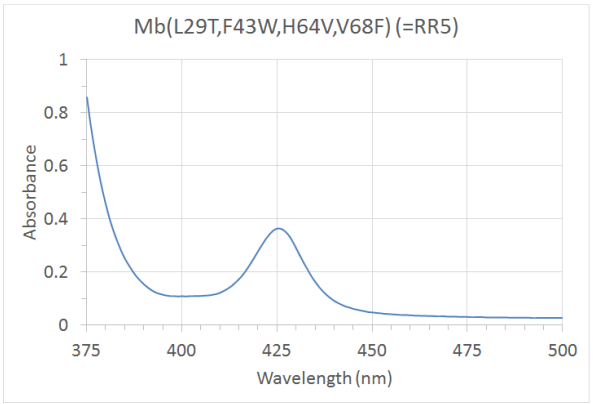
Supplementary Figure S7. Visible-range electronic absorption spectra corresponding to purified *trans*-(*1R,2R*)-selective Mb variants (RR1-RR5) and *trans*-(*1S,2S*)-selective Mb(H64V,V68S) variant in their ferrous CO-bound form.

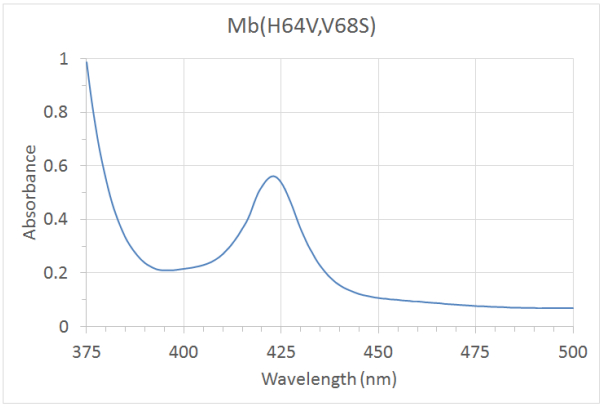




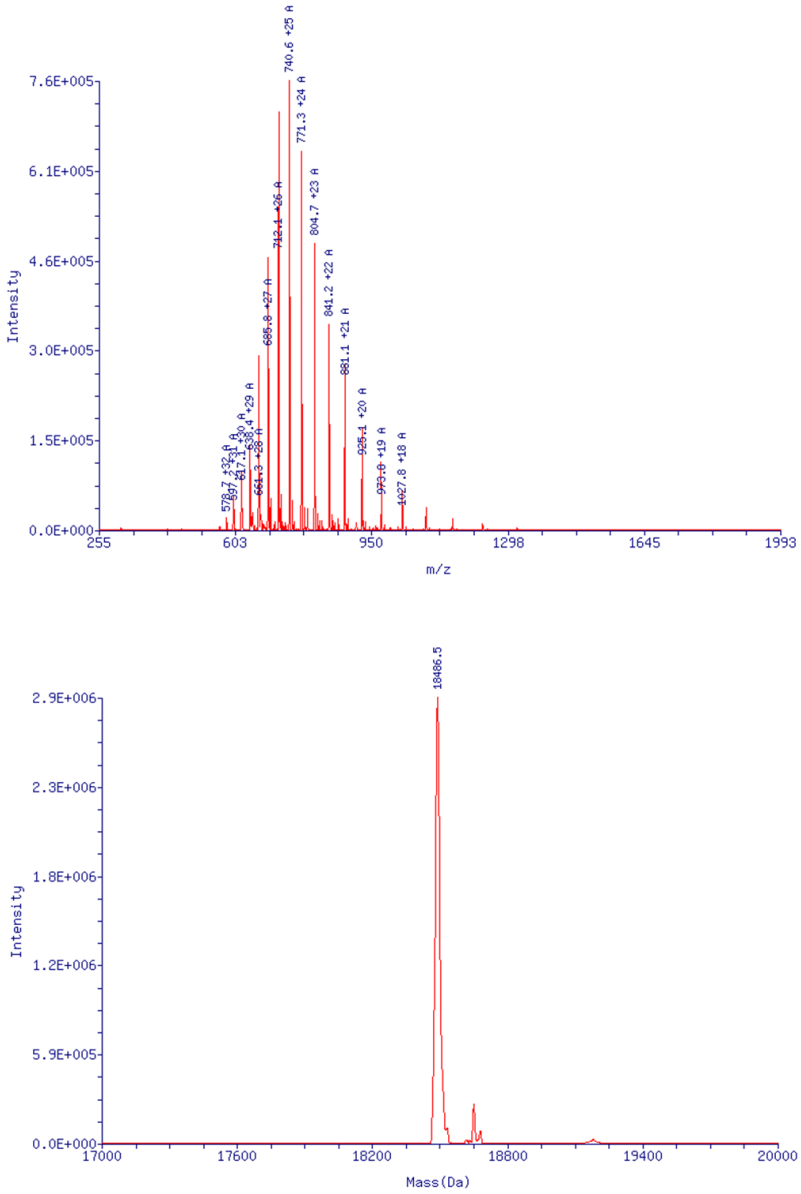




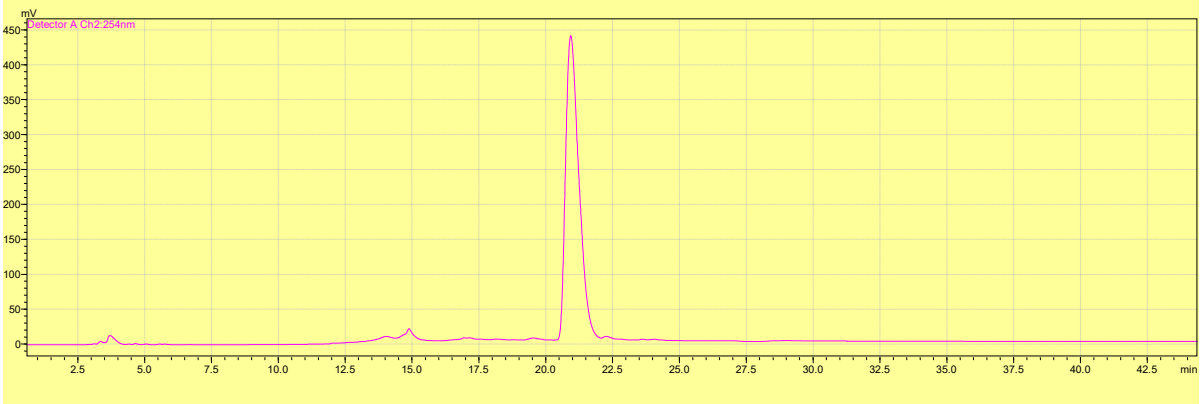




Supplementary Figure S8. Peak envelope (top panel) and deconvoluted MS spectrum (bottom panel) from ESI-MS analysis of Mb(H64V,V64S). Observed: $[M+H]^+$ 18,487 (± 2) Da; Calculated: 18,489 Da.



Supplementary Figure S9. Chiral High Performance Liquid Chromatography (HPLC) analysis of compound **24**. Instrument: Shimadzu LC-2010 HT equipped with a Daicel Chiralpak AD-H column (0.46 cm × 15 cm), and UV-Vis detector. Sample volume: 5 µL. Column temperature: 50°C. Flow rate: 1 ml/min. Detection at λ = 254 nm. Gradient solvent system of hexanes (A) and isopropanol (B): 5 min. (1% B), 10 min. (10% B), 15 min. (20% B), 30 min. (30% B), 40 min. (40% B), 45 min. (50% B), 46 min. (1% B). Total run time was 50 min.



Experimental Procedures

Reagents. All the chemicals and reagents were purchased from commercial suppliers (Sigma-Aldrich, ACS Scientific, Acros) and used without any further purification, unless otherwise stated. EDA was purchased from Sigma-Aldrich as 87% solution in dichloromethane. All dry reactions were carried out under argon or nitrogen in oven-dried glassware with magnetic stirring using standard gas-tight syringes, cannulae and septa. ^{1}H and ^{13}C NMR spectra were measured on Bruker DPX-400 (operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C) or Bruker DPX-500 (operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C). Tetramethylsilane (TMS) served as the internal standard (0 ppm) for ^{1}H NMR and $CDCl_3$ was used as the internal standard (77.0 ppm) for ^{13}C NMR. Silica gel chromatography purifications were carried out using AMD Silica Gel 60 230-400 mesh. Thin Layer Chromatography (TLC) were carried out using Merck Millipore TLC silica gel 60 F254 glass plates.

Analytical Methods. Gas chromatography (GC) analyses were carried out using a Shimadzu GC-2010 gas chromatograph equipped with a FID detector, and a Cyclosil-B column (30 m x 0.25 mm x 0.25 μm film). The following GC methods were used for TON analysis: a) for **4b**-**10b**: 1 μL injection, injector temp.: 200 ºC, detector temp: 300 ºC. Gradient: column temperature set at 140 ºC for 3 min, then to 160 ºC at 1.8 ºC/min, then to 165 ºC at 1 ºC/min, then to 245 ºC at 25 ºC/min. Total run time was 28.31 min; b) for **11b**-**15b**: 1 μL injection, injector temp.: 200 ºC, detector temp: 300 ºC. Gradient: column temperature set at 120 ºC for 3 min, then to 150 ºC at 0.5 ºC/min, then to 245 ºC at 25 ºC/min. Total run time was 69 min. The following GC methods were used for stereoisomer separation: c) for **2a**, **2b**, **7b, 10b**, and **12b**: 1 μL injection, injector temp.: 200 ºC, detector temp: 300 ºC. Gradient: column temperature set at 120 ºC for 3 min, then to 150 ºC at 0.8 ºC/min, then to 245 ºC at 25 ºC/min. Total run time was 46.30 min. d) For **8b**: 1 μL injection, injector temp: 200 ºC, detector temp: 300 ºC. Gradient: column temperature set at 60 ºC for 3 min, then to 180 ºC at 0.8 ºC/min, then to 240 ºC at 4 ºC/min and then to 245 ºC at the rate of 20 ºC for 1 min. Total run time was 169.50 min. e) For **14b**: 1 μL injection, injector temp: 200 ºC, detector temp: 300 ºC. Gradient: column temperature set at 120 ºC for 3 min, then to 160 ºC at 0.35 ºC/min, and then to 245 ºC at the rate of 25 ºC for 2 min. Total run time was 122.69 min. f) For **19**: 1 μL injection, injector temp: 200 ºC, detector temp: 300 ºC. Gradient: column temperature set at 120 ºC for 3 min, then to 140 ºC at 0.8 ºC/min, then

to 1500 ºC at 0.1 ºC/min and then to 245 ºC at the rate of 25 ºC for 2 min. Total run time was 133.80 min. g) For **23**: 1 µL injection, injector temp.: 200 ºC, detector temp: 300 ºC. Gradient: column temperature set at 140 ºC for 3 min, then to 160 ºC at 1.8 ºC/min, then to 165 ºC at 1 ºC/min, then to 245 ºC at 25 ºC/min. Total run time was 28.31 min.

Products	**t_R for (*1R,2R*) isomer (min)**	**t_R for (*1S,2S*) isomer (min)**
3a,3b	27.22	27.61
7b	31.91	31.56
8b	105.19	105.66
10b	23.20	22.86
12b	24.61	24.11
14b	42.27	42.20
19	118.06	119.61
23	16.16	15.84

Stereoisomer resolution for compound **4b**, **5b**, **6b, 9b, 11b, 13b, 15b**, and **26** was performed by Supercritical Fluid Chromatography (SFC) analysis, using a JASCO Analytical and Semi-Preparative SFC instrument equipped with a column oven (35 °C), photodiode array detector, a backpressure regulator (12.0 MPa), a carbon dioxide pump and a sample injection volume of 3 µL. Daicel Chiralpak IA, IB or IC column (0.46 cm ID × 25 cm L) were used for separation of enantiomers. All samples were eluted using an isocratic solvent system with the indicated modifier (see table below) in liquid CO_2 at an elution rate of 4 mL/min and detected at λ = 220 nm. Total run time was 10.2 min.

Product	Column	Modifier Solvent	t_R for (*1R,2R*) isomer (min)	t_R for (*1S,2S*) isomer (min)
4b	IA	5% isopropanol	1.91	1.71
5b	IA	5% isopropanol	2.52	2.24
6b	IA	2% isopropanol	3.41	3.25
9b	IB	5% isopropanol	1.37	1.65
11b	IA	5% isopropanol	3.12	2.69
13b	IC	5% isopropanol	3.88	3.19
15b	IC	5% isopropanol	5.07	3.82
26	IA	5% isopropanol	1.31	1.24

Gas chromatography-Mass spectrometry (GC-MS) analyses were carried out using a Shimadzu GCMS-QP2010 gas chromatograph equipped with an EI detector, and a RTX-XLB column (30 m × 0.25 mm × 0.28 μm). Method: 1 μL injection, injector temp.: 250 ºC, detector temp: 300 ºC. Gradient: column temperature set at 80 ºC for 1 min, then to 290 ºC at 20 ºC/min. Total run time was 15.5 min. MS ion source temp. 220 ºC, interface temp. 250 ºC with m/z scan from 100 to 400. Total run time was 12 min.

Cloning and Mutagenesis. pET22b(+) (Novagen) was used as the recipient plasmid vector for cloning of all of the myoglobin variants. The plasmid encoding for the H64V variant of sperm whale myoglobin, Mb(H64V), was prepared as described previously.[1] The Mb(H64V)-derived single-site mutants described in **Table S2** were prepared by using a combination of "small-intelligent mutagenesis"[4] and site-directed mutagenesis.

Using the Mb(H64V)-encoding gene as template, small-intelligent mutagenesis libraries for each of the four target active site positions (i.e., 29, 43, 68, and 107) were prepared using a mixture of four primers containing the codon NDT, VMA, ATG and TGG at the target position in a 12 : 6 : 1 : 1 ratio. After gene assembly via SOE PCR, the corresponding library was cloned into the *Nde* I / *Xho* I cassette of pET22b(+), followed by transformation into DH5α cells, as described previously.[1] As an example, for preparing the site-saturation mutagenesis library at position 29, a 3'-terminal fragment of the target gene was prepared by PCR (NEB Phusion

Polymerase) using a 12 : 6 : 1 : 1 mixture of forward primers #1 through #4 (Table S1), the reverse mega primer #64, and vector pET22_Mb(H64V) as the template. In a separate PCR reaction, the 5'-terminal gene fragment was prepared using forward mega primer #63, reverse primer #5, and vector pET22_Mb(H64V) as the template. The two fragments were then fused together using overlap extension PCR (SOE PCR) and mega primers #63 and #64 to yield the target gene encoding for Mb(L29X,H64V) where X is the randomized position. The plasmid pET22b(+) and gene library were digested with *Nde* I and *Xho* I for 2 hr at 37ºC. The gene insert and plasmid were then ligated with T4 DNA ligase. The ligation mix was transformed into chemically competent DH5α cells. The other site-saturation libraries were also prepared using a similar procedure.

From each library, 30-40 colonies were randomly sequenced, resulting in the isolation of about 40-60% of the desired recombinants. The remaining single-site mutants were prepared via conventional site-directed mutagenesis. The triple, quadruple and quintuple mutants were prepared via site-directed mutagenesis and SOE PCR. The sequence of the oligonucleotide primers used in this project are given in **Table S1**.

Protein expression and purification. The engineered Mb variants were expressed in *E. coli* C41(DE3) cells as described previously.[1] Briefly, cells were grown in TB medium (ampicillin, 100 mg L^{-1}) at 37 °C (150 rpm) until OD_{600} reached 0.6. Cells were then induced with 0.25 mM isopropyl-β-D-1-thiogalactopyranoside (IPTG) and 0.3 mM δ-aminolevulinic acid (ALA). After induction, cultures were shaken at 150 rpm and 27 °C and harvested after 20 hours by centrifugation at 4,000 rpm at 4 °C. After cell lysis by sonication, the proteins were purified by Ni-affinity chromatography using the following buffers: loading buffer (50 mM KPi, 800 mM NaCl, pH 7.0), wash buffer 1 (50 mM KPi, 800 mM NaCl, pH 6.2), wash buffer 2 (50 mM KPi, 800 mM NaCl, 250 mM glycine, pH 7.0) and elution buffer (50 mM KPi, 800 mM NaCl, 300 mM L-histidine, pH 7.0). After buffer exchange (50 mM KPi, pH 7.0), the enzymes were stored at +4 °C. Myoglobin concentration was determined using an extinction coefficient ε_{410} = 157 mM^{-1} cm^{-1}.[5]

Cyclopropanation reactions: Initial reactions (**Table 1, 2, S2, S3**) were carried out at a 400 μL scale using different concentrations of myoglobin, 10 mM styrene, 20 mM EDA, and 10 mM

sodium dithionite. In a typical procedure, a solution containing sodium dithionate (100 mM stock solution) in potassium phosphate buffer (KPi 50 mM, pH 7.0) was degassed by bubbling argon into the mixture for 5 min in a sealed vial. A buffered solution containing myoglobin was degassed in a similar manner in a separate vial. The two solutions were then mixed together via cannulation. Reactions were initiated by addition of 10 μL of styrene (from a 0.4 M stock solution in ethanol), followed by the addition of 10 μL of EDA (from a 0.8 M stock solution in ethanol) with a syringe, and the reaction mixture was stirred for 18 hours at room temperature, under positive argon pressure.

Whole-cell cyclopropanation reactions. Initial whole-cell experiments (**Table S4**) were carried out at a 400 μL-scale using 380 μL of *E. coli* cells expressing Mb(H64V,V68A), 10 mM alkene, and 20 mM EDA. In a typical procedure, reactions were initiated by addition of 10 μL of alkene (from a 0.4 M stock solution in ethanol), followed by the addition of 10 μL of EDA (from a 0.8 M stock solution in ethanol) with a syringe to a suspension of Mb(H64V,V68A)-expressing cells (OD_{600} = 40 or 200 in KPi pH 7.2 buffer), with or without 10 μL D-glucose solution (from a stock of 2 M solution in water). The reaction mixture was stirred for 16 hours at room temperature under aerobic, semi-aerobic, or anaerobic conditions. Aerobic conditions were obtained by carrying out the reaction in open vessels, semi-aerobic conditions were obtained using sealed vessels with an argon-filled headspace, and anaerobic conditions were obtained using sealed vessels with argon-degassed solutions. The TON for the whole-cell reactions were calculated based on Mb concentration in the reaction mixture as measured via UV-vis spectroscopy (ε_{410} = 157 mM^{-1} cm^{-1}) after cell lysis.

Product analysis. The reactions were analyzed by adding 20 μL of internal standard (benzodioxole, 100 mM in methanol) to the reaction mixture, followed by extraction with 400 μL of dichloromethane (DCM) and analyzed by GC-FID (see **Analytical Methods** section for details on GC analyses). Calibration curves of the different cyclopropane products were constructed using synthetically produced authentic standards (see **Synthetic Procedures**). All measurements were performed at least in duplicate. For each experiment, negative control samples containing either no enzyme or no reductant were included. For stereoselectivity

determination, the samples were analyzed by GC-FID or SFC using a chiral column as described under **Analytical Methods** section.

Synthetic Procedures:

Alkenes **4a**-**11a** and **25** were purchased from chemical suppliers as mentioned in **Reagents and Analytical Methods** and used without further purification. Alkenes **12a**-**15a** were synthesized according to reported procedures.[6] Racemic standards for analysis of the cyclopropane products **3b**, **4b**, **5b**, **6b**, **7b**, **8b**, **9b**, and **10b** were prepared as described previously.[1] Racemic standards for analysis of the cyclopropane products **11b**, **12b**, **13b**, **15b**, **19**, **23**, and **26** were prepared via cyclopropanation with $Rh_2(OAc)_4$ catalyst according to the general procedure provided below (Procedure A). The synthesis of racemic (±)-**14b** using $Rh_2(OAc)_4$ catalysis failed. Enantiopure **14b** (98% *ee*) and the drug intermediates described in **Scheme 1** (**3a**, **3b**, **19**, **23**, and **26**) were prepeared and isolated from whole-cell reactions according to the general procedure provided below (Procedure B). For stereochemical assignment of the *trans* cyclopropanation products, reference samples enriched in the *trans-(1S,2S)* isomer were prepared using the well characterized Nishiyama's Ru-((+)-ip-PyBox) catalyst[3] as described in Procedure C.

Chemical synthesis of racemic standards for cyclopropanation products (Procedure A).

To a flame dried round bottom flask under argon, equipped with a stir bar was added alkene (2 equiv.) and $Rh_2(OAC)_4$ (2 mol%) in dry CH_2Cl_2 (1-2 mL). To this solution was added a solution of EDA (1 equiv.) in dry CH_2Cl_2 (1-2 mL) over 30 minutes at 0ºC. The resulting mixture was stirred at 25ºC for another 12-14 hours. The solvent was removed under reduced pressure and the crude mixture was purified by flash column chromatography (hexanes/ethyl acetate) to provide the cyclopropanation product as a mixture of *trans* and *cis* isomers (0-29% de_{trans}) both in racemic form. The products were characterized by GC-MS, ^{1}H NMR and ^{13}C NMR techniques.

General procedure for the large-scale whole-cell cyclopropanation reactions (Procedure B).

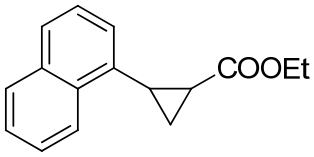
E. coli C41(DE3) cells expressing the appropriate engineered Mb variant were prepared according to the protocol described above. After harvesting, the cells were suspended in phosphate buffer (KPi pH 7.2) and diluted to an OD_{600} of 40. The cell suspension was transferred

to an open Erlenmeyer flask equipped with a stir bar and supplemented with 50 mM D-glucose solution (from a 2 M stock solution). Reactions were initiated by addition of alkene (indicated amount dissolved in 1/100 of total reaction volume) in one portion, followed by the addition of EDA (indicated amount dissolved in 1/100 of total reaction volume) with a syringe pump over a period of 2-4 hours at room temperature. Reaction mixtures were stirred at room temperature for 14-16 hours and extracted with ethyl acetate (100 mL x 3). Combined organic layers were dried over sodium sulfate and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel) with 5-10% diethyl ether/hexanes as the eluent.

Chemical synthesis of *trans-(1S,2S)* enriched references for cyclopropanation products (Procedure C).

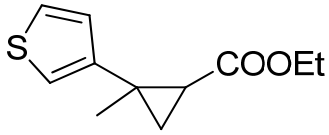
To a flame dried round bottom flask under argon, equipped with a stir bar was added alkene (4 equiv.) dichloro(*p*-cymene)ruthenium(II) dimer (0.015 equiv.) and 2,6-*bis*[(4*R*)-(+)-isopropyl-2-oxazolin-2-yl]pyridine (0.06 equiv.) in dry CH_2Cl_2 (3 mL). To this solution was added a solution of EDA (1 equiv.) in dry CH_2Cl_2 (1-2 mL) over 60 minutes at 0 ºC. The resulting mixture was stirred at 25 ºC for another 12-14 hours. The solvent was removed under reduced pressure and the crude mixture was purified by a pad of silica gel (CH_2Cl_2) to provide the crude cyclopropanation product as a mixture of *trans* and *cis* isomers with the *trans*-(1*S,2S*) isomer as the major product. The products were analyzed by GC and SFC techniques.

Ethyl 2-(naphthalen-1-yl) cyclopropane-1-carboxylate (11b + 11c):



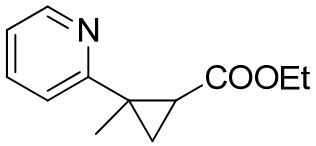
Following the standard procedure **A**, racemic, *trans* isomer of ethyl 2-(naphthalen-1-yl) cyclopropane-1-carboxylate was isolated as a colorless liquid, 50% yield, GC-MS m/z (% relative intensity): 240(34.3), 167(100), 152(54.1), 115(7.2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.22 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.61-7.52 (m, 2H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 8 Hz, 1H), 4.32-4.26 (m, 2H), 3.06-3.01 (m, 1H), 1.99-1.95 (m, 1H), 1.77-1.72 (m, 1H), 1.48-1.43 (m, 1H), 1.37 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.0, 138.1, 135.9, 133.7, 137.7, 133.1, 128.7, 127.7, 126.4, 126.0, 125.5, 124.2, 60.9, 24.2, 22.4, 15.6, 14.5 ppm.

Ethyl 2-methyl-2-(thiophen-3-yl)cyclopropane-1-carboxylate (12b + 12c):



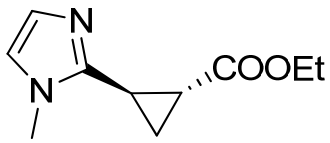
Following the standard procedure **A**, racemic, *trans* isomer of ethyl 2-methyl-2-(thiophen-3-yl)cyclopropane-1-carboxylate was isolated as light brown liquid, 67% yield, GC-MS m/z (% relative intensity): 210(24.6), 165(14.6), 137(100), 103(6.9); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.22-7.20 (m, 1H), 6.98-6.97 (m, 1H), 6.84 (d, *J* = 4.8 Hz, 1H), 1.94 (dd, *J* = 8.4, 6.4 Hz, 1H), 1.54 (s, 3H), 1.46-1.44 (m, 1H), 1.39-1.36 (m, 1H), 1.24 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.5, 146.9, 125.7, 125.3, 119.3, 60.4, 29.1, 25.9, 22.1, 17.8, 14.2 ppm.

Ethyl 2-methyl-2-(pyridin-2-yl)cyclopropane-1-carboxylate (13b + 13c):



Following the standard procedure **A**, racemic, *trans* isomer of ethyl 2-methyl-2-(pyridin-2-yl)cyclopropane-1-carboxylate was isolated as a light red liquid, % yield (45), GC-MS m/z (% relative intensity): 205(25.1), 176(43.4), 132(100), 117(68.7), 104(9.2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 68.48 (d, J = 4.0 Hz, 1H), 7.62-7.59 (m, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.08 (dd, J = 8.0, 4.0 Hz 1H), 4.19-4.13 (m, 2H), 2.39-2.37(m, 1H), 1.80-1.78 (m, 1H), 1.63 (s, 3H), 1.49-1.47 (m, 1H), 1.26 (t, J = 8.0 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.9, 162.4, 149.0, 136.1, 120.9, 120.2, 60.5, 29.9, 29.3, 22.5, 15.7, 14.4 ppm.

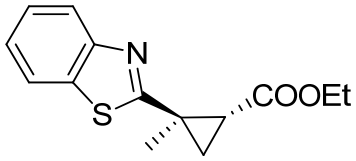
Ethyl (*1R,2R*)-2-(1-methyl-1*H*-imidazol-2-yl) cyclopropane-1-carboxylate (14b):



A solution (18 mL) containing 10 mM sodium dithionite in potassium phosphate buffer (KPi 50 mM, pH 7.0) was degassed by purging with argon for 10 min in a sealed round bottom flask. A buffered solution containing 20 μM Mb(L29S,H64V,V68F) (1.6 mL of 250 μM stock solution) was degassed in a similar manner in a separate vial. The two solutions were then mixed together through cannula under argon pressure. The reaction mixture was added with 30 μL of alkene **14a** (1.2 equivalent, dissolved in 0.5 mL ethanol), followed by the addition of 24 μL of EDA (1 equivalent, dissolved in 0.5 mL ethanol) with a syringe. The reaction mixture was stirred for 16 hours at room temperature, under positive argon pressure, and then extracted with dichloromethane (40 mL x 3), dried over sodium sulfate, and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel) with acetone/dichloromethane (9:1). **14b** was isolated as a colorless 1iquid (21 mg, 46% yield), GC-MS m/z (% relative intensity): 194(35.9), 149(45.2), 121(100), 107(14.5); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.89 (s, 1H), 6.80 (s, 1H), 4.18 (q, J = 9.0 Hz, 2H), 3.68 (s, 3H), 2.43-2.38 (m, 1H),

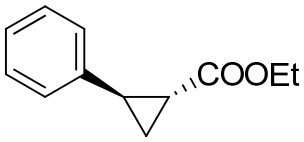
2.24-2.19 (m, 1H), 1.68-1.63 (m, 1H), 1.60-1.55 (m, 1H), 1.28 (t, *J* = 8.5 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.8, 146.3, 126.4, 120.8, 60.8, 32.5, 22.2, 16.9, 15.4, 14.1 ppm.

Ethyl 2-(benzo[*d*]thiazol-2-yl)-2-methylcyclopropane-1-carboxylate (15b + 15c):



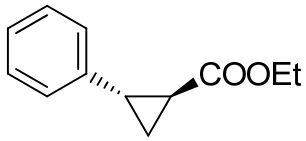
Following the standard procedure **A**, racemic, *trans* isomer of ethyl 2-(benzo[d]thiazol-2-yl)-2-methylcyclopropane-1-carboxylate was isolated as a pale yellow solid, 58% yield, GC-MS m/z (% relative intensity): 261(36.9), 216(27.0), 188(100), 173(41.0), 109(5.6); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.91 (d, *J* = 8.4 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.45-7.42 (m, 1H), 7.35-7.31 (m, 1H), 4.21-4.16 (m, 2H), 2.61 (dd, *J* = 8.4, 6.8 Hz, 1H), 1.93 (dd, *J* = 8.4, 4.4 Hz, 1H) 1.79 (s, 3H), 1.68 (dd, *J* = 6.4, 4.4 Hz, 1H), 1.28 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.4, 170.4, 152.9, 134.6, 125.9, 124.4, 122.4, 121.2, 60.8, 31.1, 28.2, 23.9, 16.3, 14.2 ppm.

Ethyl (1*R*, 2*R*)-2-phenylcyclopropane-1-carboxylate (3a):



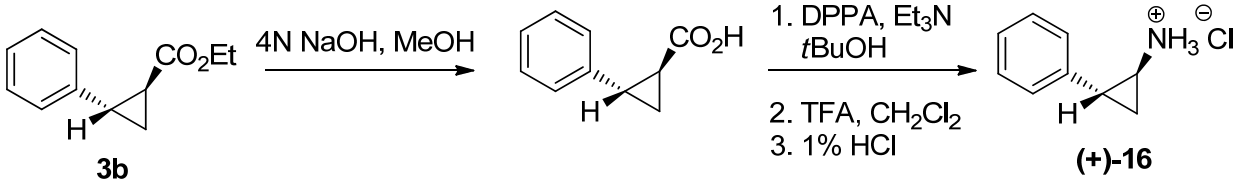
Following the general procedure **B**, **3a** was prepared via whole-cell biotransformation of styrene (1.0 g, 1 equiv) and EDA (1.1 g, 1 equiv) with *E. coli* cells expressing Mb(L29T,H64V,V68L) (120 mL; OD_{600} = 40), and isolated by flash chromatography as a colorless oil (1.2 g, 80% yield, >99.9% *de*, 95% *ee*); GC-MS m/z (% relative intensity): 190(29.5), 144(28.3), 135(20.7), 117(100), 107(7.3); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32-7.28 (m, 2H), 7.24-7.20 (m, 1H), 7.12 (d, *J* = 7.2 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 2.57-2.52 (m, 1H), 1.95-1.90 (m, 1H), 1.65-1.60 (m, 1H), 1.35-1.28 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.3, 140.0, 128.3, 126.3, 126.0, 60.6, 26.1, 24.1, 17.0, 14.2 ppm. $[a]_D^{26}$ = - 299° (c = 0.71, $CHCl_3$) (lit. $[a]_D^{20}$ = - 308° (c=0.78, $CHCl_3$))[7].

Ethyl (1*S*, 2*S*)-2-phenylcyclopropane-1-carboxylate (3b):



Following the general procedure **B**, **3b** was prepared via whole-cell biotransformation of styrene (2.9 g, 1 equiv) and EDA (3.15 g, 1 equiv) with *E. coli* cells expressing Mb(H64V,V68A) (290 mL; OD_{600} = 40), and isolated by flash chromatography as a colorless oil (4.7 g, 91% yield, >99.9% *de,* >99.9% *ee*); GC-MS m/z (% relative intensity): 190(29.5), 144(28.3), 135(20.7), 117(100), 107(7.3); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34-7.28 (m, 2H), 7.23-7.20 (m, 1H), 7.11 (d, *J* = 7.2 Hz, 2H), 4.19 (q, *J* = 7.2 Hz, 2H), 2.56-2.51 (m, 1H), 1.94-1.90 (m, 1H), 1.64-1.59 (m, 1H), 1.35-1.30 (4H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.2, 140.0, 128.3, 126.3, 126.0, 60.6, 26.1, 24.1, 17.0, 14.2 ppm. $[a]_D^{26}$ = + 315° (c = 1.08, $CHCl_3$) (lit. $[a]_D^{20}$ = + 236° (75% ee))[8].

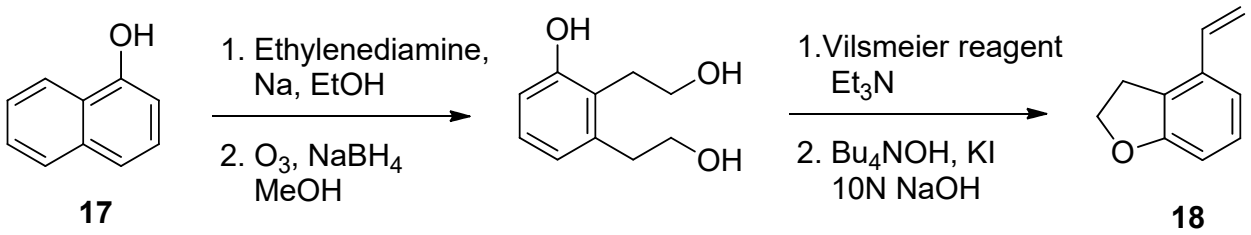
(+)-Tranylcypromine ((+)-16):



3b **(+)-16**

(+)-Tranylcypromine ((+)-**16**) was synthesized from ethyl (1*S*, 2*S*)-2-phenylcyclopropane-1-carboxylate (**3b**) following reported literature procedures,[7] and isolated by flash chromatography as a light brown solid (3.9 g, 93% yield over four steps). GC-MS m/z (% relative intensity): 133(100), 115(58.1), 104(13.4); $(\alpha)_D^{26}$ = + 0.44° (c = 0.26, MeOH); 1H NMR (MeOD d^4, 400 MHz): δ 7.30-7.27 (m, 2H), 7.22-7.20 (m, 1H), 7.18-7.14 (m, 2H), 2.83-2.81(m, 1H), 2.39-2.37 (m, 1H), 1.44-1.39 (m, 1H), 1.33-1.30 (m, 1H) ppm; ^{13}C NMR (MeOD d^4, 100 MHz): δ 139.7, 129.6, 127.8, 127.3, 31.9, 22.5, 13.8 ppm. $[a]_D^{26}$ = + 58.5° (c = 0.21, MeOH) (lit. $[\alpha]_D^{25}$ = - 67.7° (c = 0.882, H_2O))[9].

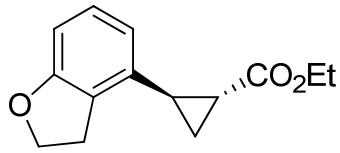
4-vinyl-2,3-dihydrobenzofuran (18):



17 **18**

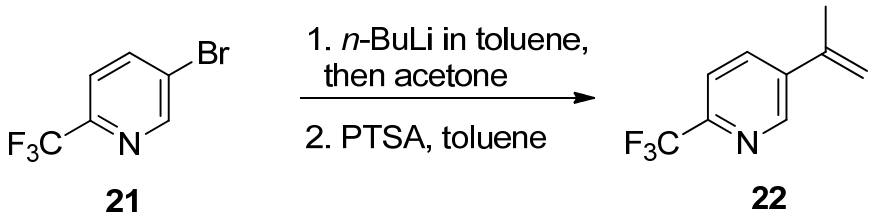
4-vinyl-2,3-dihydrobenzofuran (**18**) was synthesized from naphthalen-1-ol (**17**) according to published procedures,[10] and isolated as a light brown oil (1.5 g, 50% yield over four steps); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.11-7.07 (m, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.73-6.65 (m, 2H), 5.71-5.66 (m, 1H), 5.32 (dd, *J* = 11.2, 0.4 Hz, 1H), 4.58 (t, *J* = 8.4 Hz 2H), 3.25 (t, *J* = 8.4 Hz, 2H) ppm.; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.0, 134.5, 134.2, 127.9, 124.7, 117.5, 115.5, 108.3, 70.9, 28.9 ppm.

Ethyl (1*R*, 2*R*)-2-(2,3-dihydrobenzofuran-4-yl)cyclopropane-1-carboxylate (19):



Following the general procedure **B**, **19** was prepared via whole-cell biotransformation of styrene 4-vinyl-2,3-dihydrobenzofuran **18** (0.73 g, 1.1 equiv) and EDA (0.52 g, 1 equiv) with *E. coli* cells expressing Mb(L29T,H64V,V68F,I107L) (330 mL; OD_{600} = 40), and isolated by flash chromatography as a colorless oil (0.96 g, 91% yield, >99.9% *de,* 96% *ee*); GC-MS m/z (% relative intensity): 232(100), 159(90.1), 144(68.9), 132(70.2), 115(43.5), 101(16.7); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.04 (t, *J* = 8.0 Hz, 1H), 6.65 (d, *J* = 8.0 Hz, 1H), 6.41 (d, *J* = 8.0 Hz, 1H), 4.59 (t, *J* = 8.4 Hz, 2H), 4.19 (q, *J* = 7.2 Hz, 2H), 3.24 (t, *J* = 8.4 Hz, 2H), 32.44-2.39 (m, 1H), 1.93-1.88 (m, 1H), 1.60-1.56 (m, 1H), 1.32 (t, *J* = 4.4 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.4, 159.7, 136.5, 128.1, 126.4, 116.0, 107.4, 70.9, 60.6, 28.4, 23.8, 22.7, 15.9, 14.1 ppm.

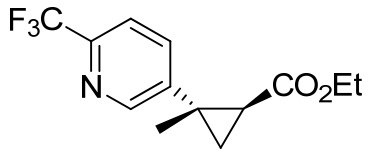
5-(prop-1-en-2-yl)-2-(trifluoromethyl)pyridine (22):



21 **22**

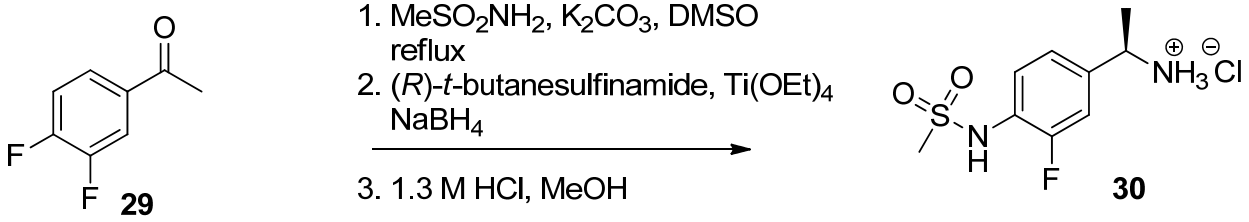
Compound **22** was synthesized from 5-bromo-2-(trifluoromethyl)pyridine (**21**) according to published procedures,[11] and isolated by flash chromatography as a colorless oil (0.95 g, 57% yield over two steps); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.78 (s, 1H), 7.86 (d, *J* = 7.6 Hz 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 5.48 (s, 1H), 5.27 (s, 1H), 2.16 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.0, 139.4, 134.8, 129.1, 128.4, 125.5, 119.9, 116.4, 21.1.

Ethyl (1*S*, 2*S*)-2-methyl-2-(6-(trifluoromethyl)pyridin-3-yl)cyclopropane-1-carboxylate (23):



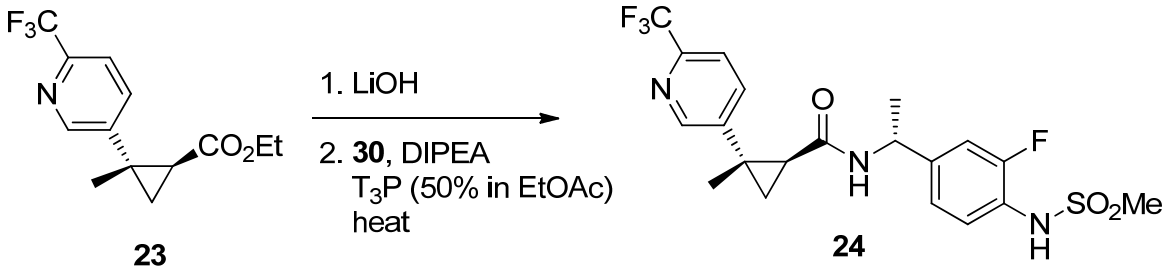
Following the general procedure **B**, **23** was prepared via whole-cell biotransformation of styrene 5-(prop-1-en-2-yl)-2-(trifluoromethyl)pyridine **22** (0.83 g, 1.2 equiv) and EDA (0.42 g, 1 equiv) with *E. coli* cells expressing Mb(H64V,V68A) (220 mL; OD_{600} = 40), and isolated by flash chromatography as a colorless oil (0.75 g, 75% yield, >99.9% *de,* >99.9% *ee*); GC-MS m/z (% relative intensity): 273(20.8), 244(76.4), 228(43.3), 200(100), 180(68.3), 130(20.7); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.63 (d, *J* =1, Hz, 1H), 7.74 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 4.21-4.15 (m, 2H), 1.96 (dd, *J* = 8.5, 6.0 Hz, 1H), 1.52 (s, 3H), 1.44 (dd, *J* = 8.5, 5.5 Hz, 3H), 1.27 (t, *J* = 7.5 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.1, 149.3, 146.7, 146.4, 146.1, 145.9, 144.4, 136.1, 124.8, 122.6, 120.4, 120.2, 120.1, 60.9, 27.7, 20.3, 19.1, 14.3 ppm.

(*R*)-1-(3-fluoro-4-(methylsulfonamido)phenyl)ethan-1-aminium chloride (30):



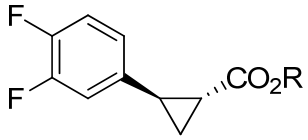
Compound **30** was synthesized from 1-(3,4-difluorophenyl)ethan-1-one (**29**) according to reported literature procedures,[11] and isolated as an off-white solid (0.97g, 45% yield over three steps);); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.98 (t, *J* = 8.0 Hz, 1H), 8.77 (d, *J* = 11.5 Hz, 1H), 8.7 (d, *J* = 8.5 Hz, 1H), 5.89-5.88 (m, 1H), 4.43 (s, 3H), 3.03 (d, *J* = 7.0 Hz, 3H) ppm.

(1*S*,2*S*)-*N*-((*R*)-1-(3-fluoro-4-(methylsulfonamido)phenyl)ethyl)-2-methyl-2-(6-(trifluoromethyl)pyridin-3-yl)cyclopropane-1-carboxamide (24):



The TRPV1 inhibitor **24** was synthesized from ethyl (1*S*,2*S*)-2-methyl-2-(6-(trifluoromethyl)pyridin-3-yl)cyclopropane-1-carboxylate (**23**) according to reported literature procedures,[11] and isolated as a white solid (102 mg, 45% yield over two steps). $(\alpha)_D^{26}$ = + 0.40° (c = 0.44, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.64 (s, 1H), 7.72-7.70 (m, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.53-7.49 (m, 1H), 7.14-7.12 (m, 2H), 6.69 (s, 1H), 6.27 (d, *J* = 7.2, 1H), 5.13-5.10 (m, 1H), 3.01(s, 3H), 1.77 (dd, *J* = 8.4 Hz, 6 Hz, 1H), 1.64-1.61(m, 1H), 1.59 (s, 3H), 1.50 (d, *J* = 6.8 Hz, 1H), 1.44-1.40 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.4, 155.3, 152.8, 148.4, 144.7, 142.7, 135.3, 123.8, 123.3, 122.4, 120.1, 113.7, 113.5, 48.5, 39.7, 30.3, 29.6, 26.5, 21.9, 19.6, 18.0 ppm. $[a]_D^{26}$ = + 66.9° (c = 0.29, $CHCl_3$). Chiral HPLC analysis: see Figure S9.

Ethyl (1*R*, 2*R*)-2-(3,4-difluorophenyl)cyclopropane-1-carboxylate (26):



Following the general procedure **B**, **26** was prepared via whole-cell biotransformation of styrene 1,2-difluoro-4-vinylbenzene **25** (0.28 g, 1.1 equiv) and EDA (0.22 g, 1 equiv) with *E. coli* cells expressing Mb(L29T,H64V,V68L) (210 mL; OD_{600} = 40), and isolated by flash chromatography as a colorless oil (0.41 g, 94% yield, 98% *de,* 58% *ee*); GC-MS m/z (% relative intensity): 226(56.1), 198(18.3), 181(25.7), 153(100), 133(53.3), 125(39.1), 101(6.8); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.04-6.98 (m, 1H), 6.87-6.78 (m, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 2.46-2.41 (m, 1 H), 1.82-1.78 (m, 1H), 1.57-1.52 (m, 1H), 1.24 (t, *J* = 6.8 Hz, 3H), 1.21-1.17 (m, 1H) ppm, ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.7, 151.4, 151.3, 150.2, 150.1, 148.9, 148.8, 147.8, 147.7, 137.0, 122.2, 177.1, 116.9, 115.1, 114.9, 60.7, 24.9, 23.9, 16.7, 14.1 ppm.

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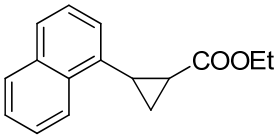
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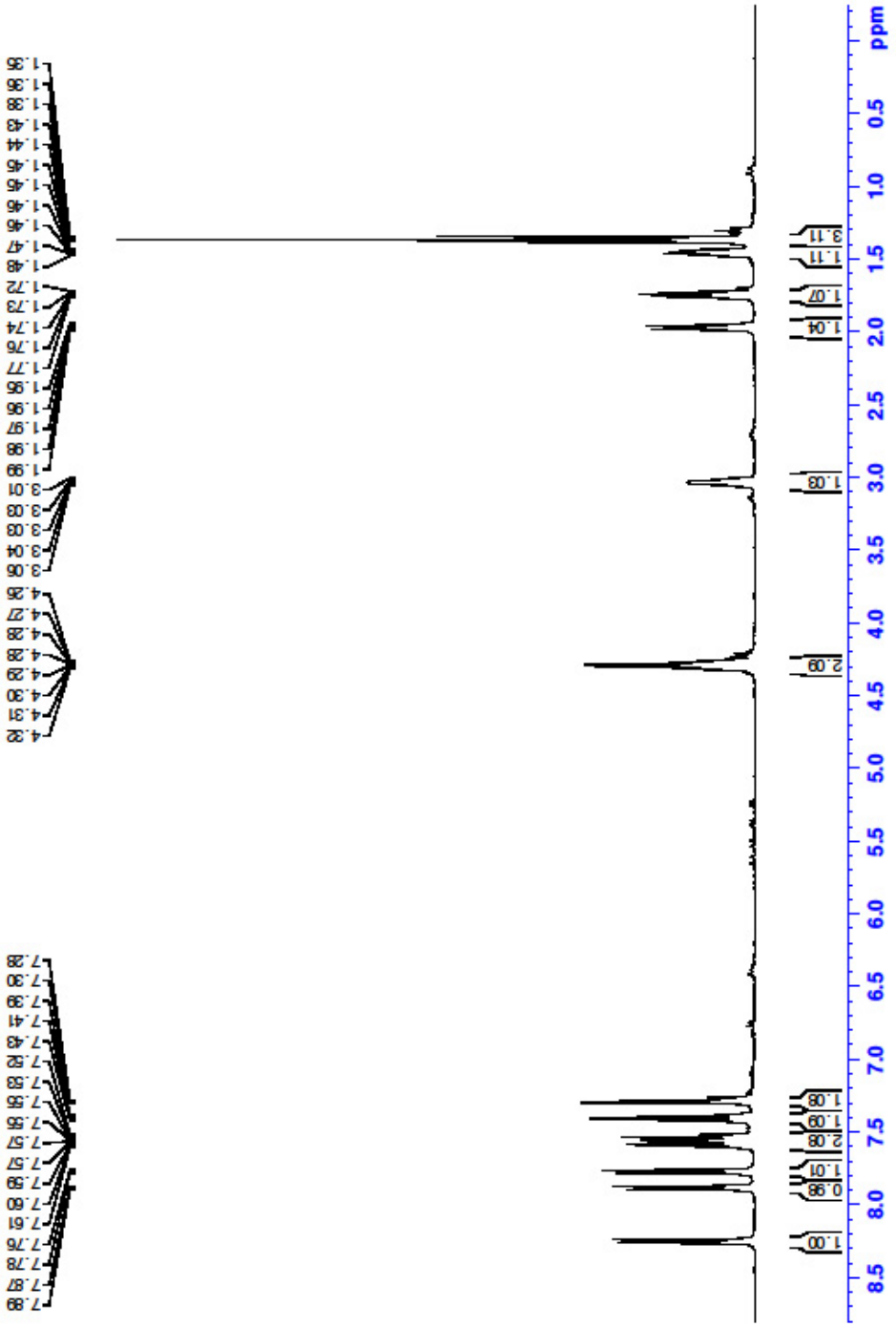
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1.5
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0.5
1.00
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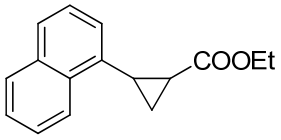
1.08
1.04
1.07
1.11
3.11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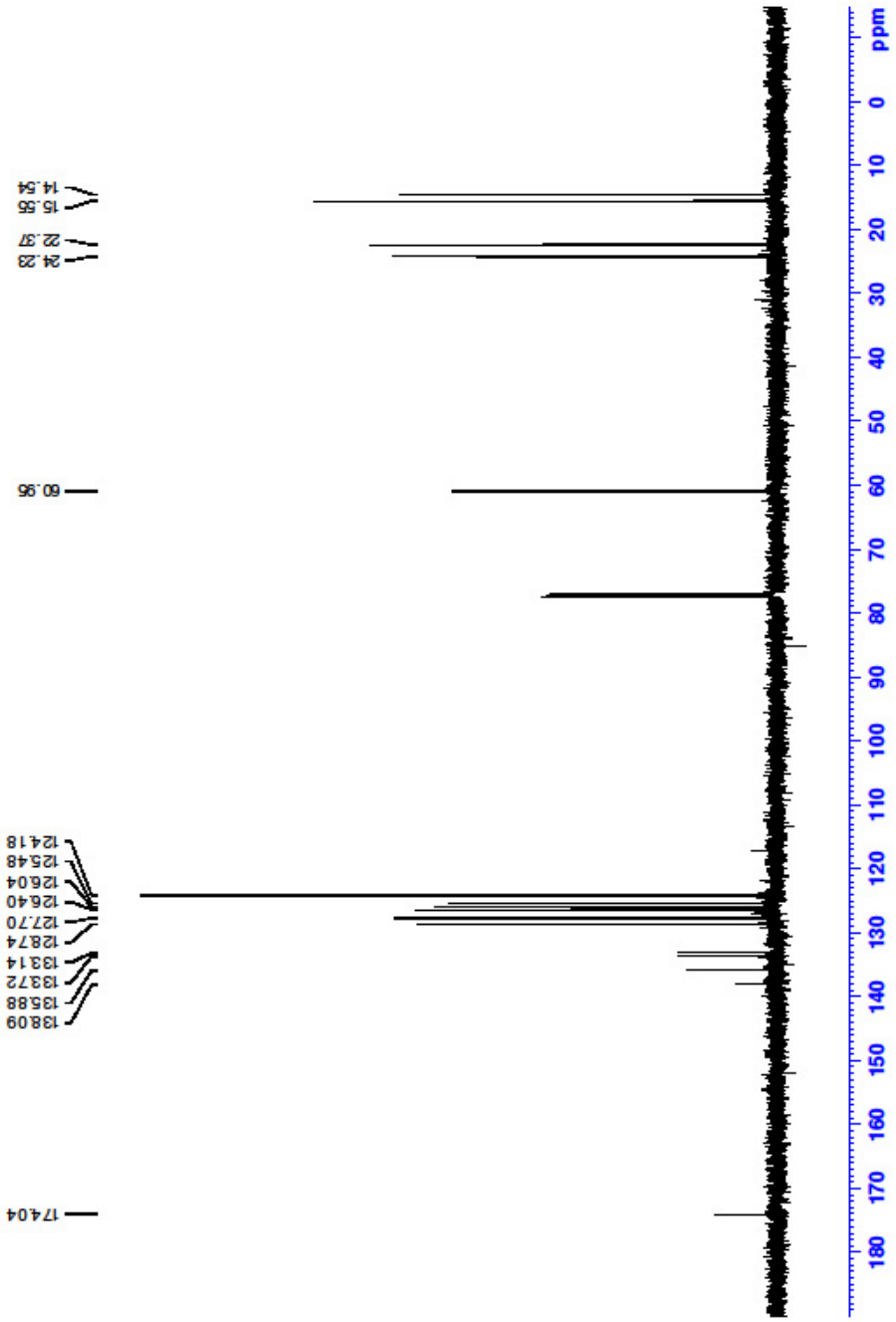
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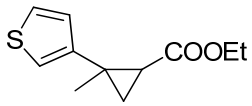
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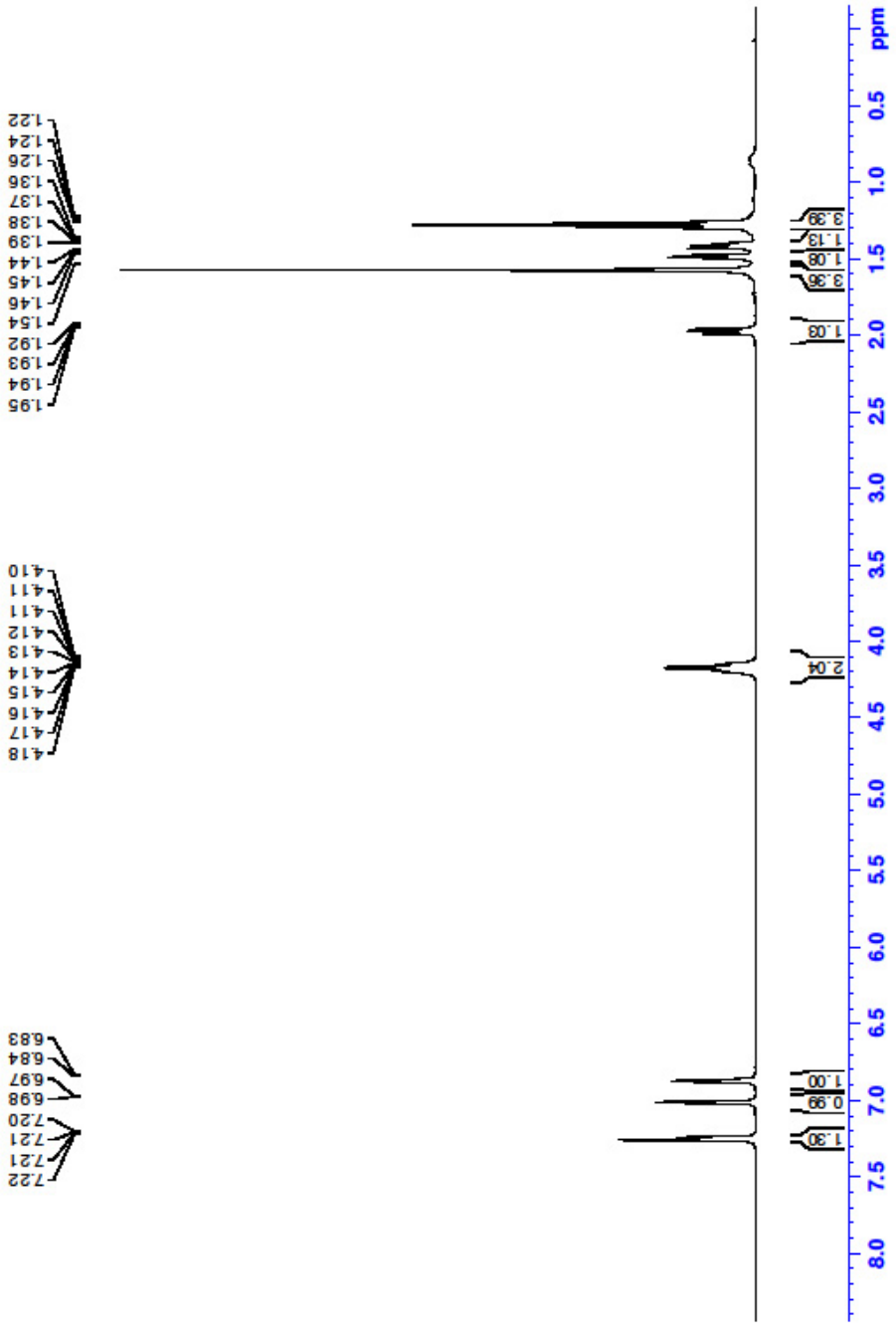
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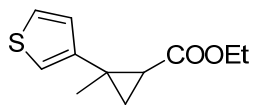
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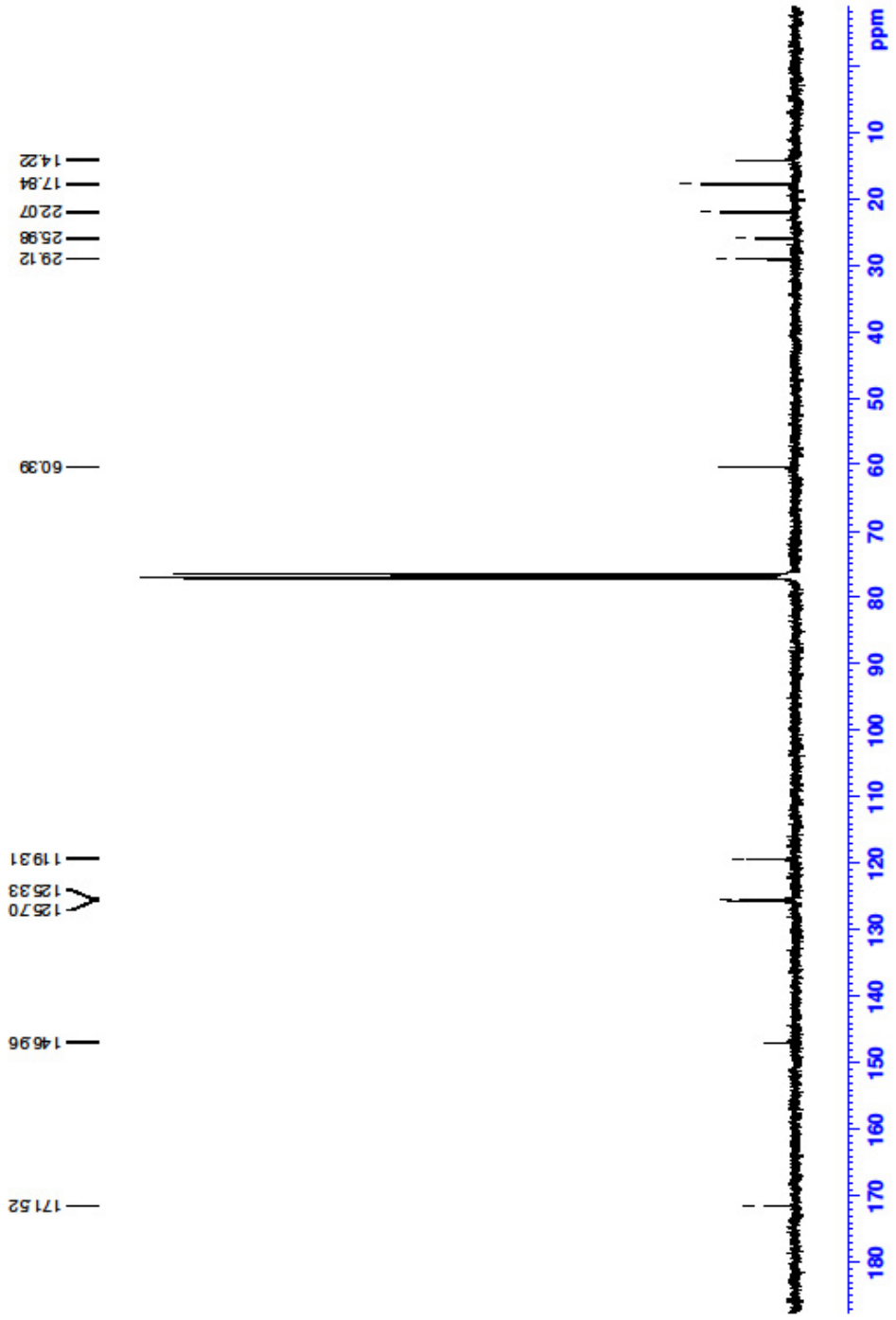
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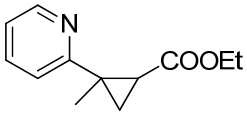
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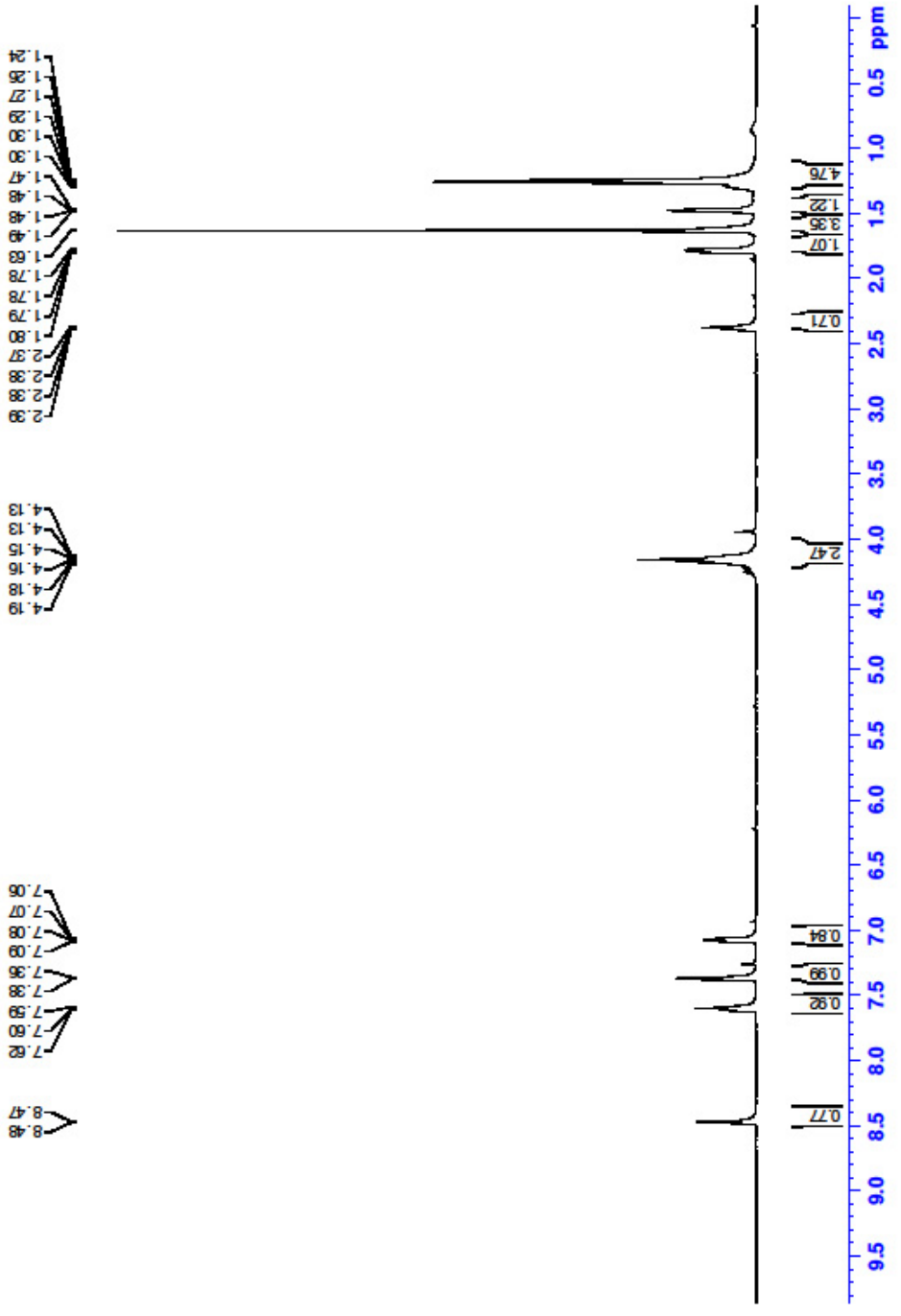
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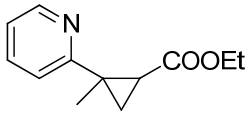
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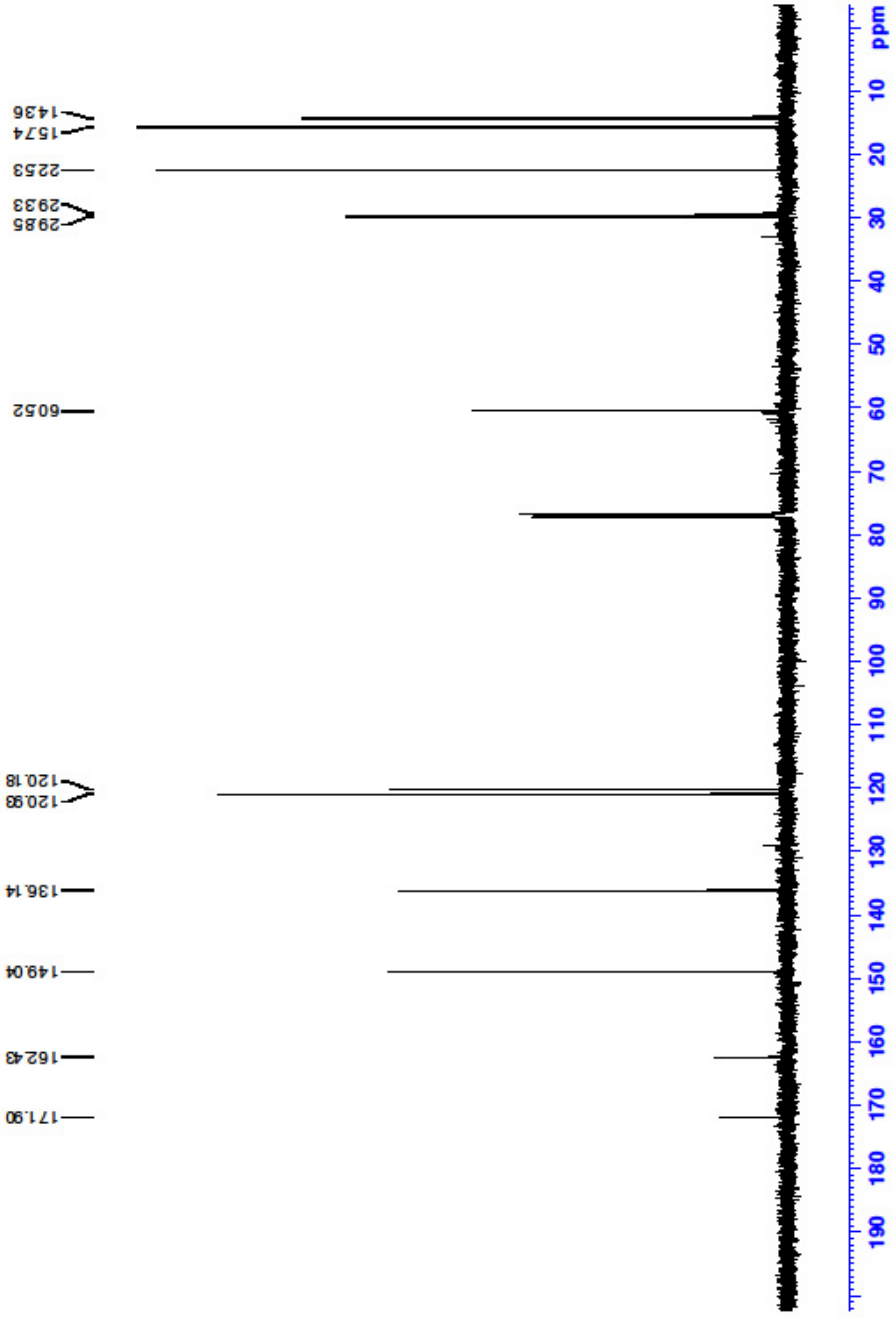
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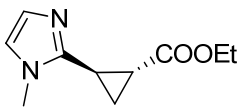
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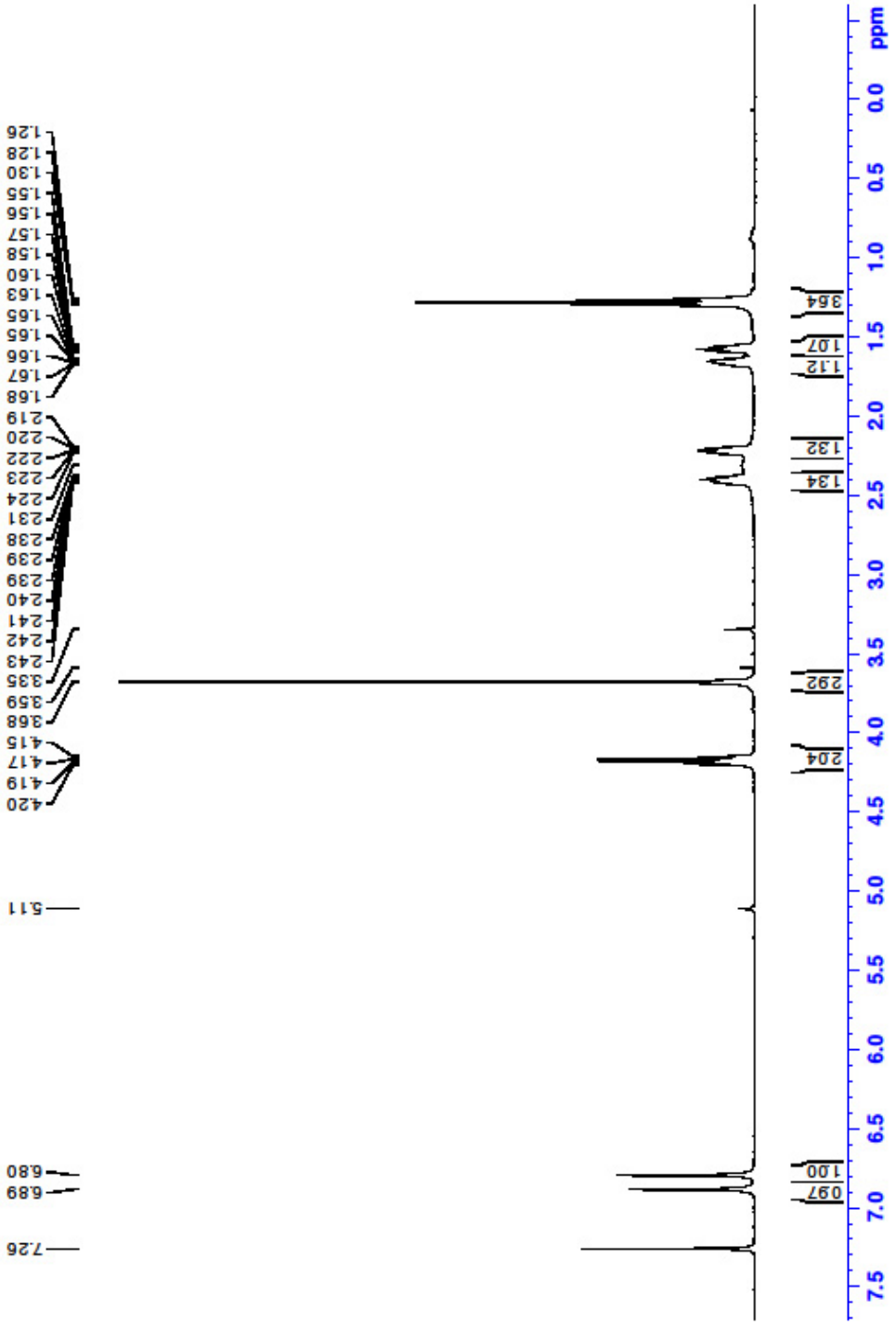
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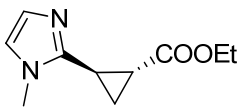
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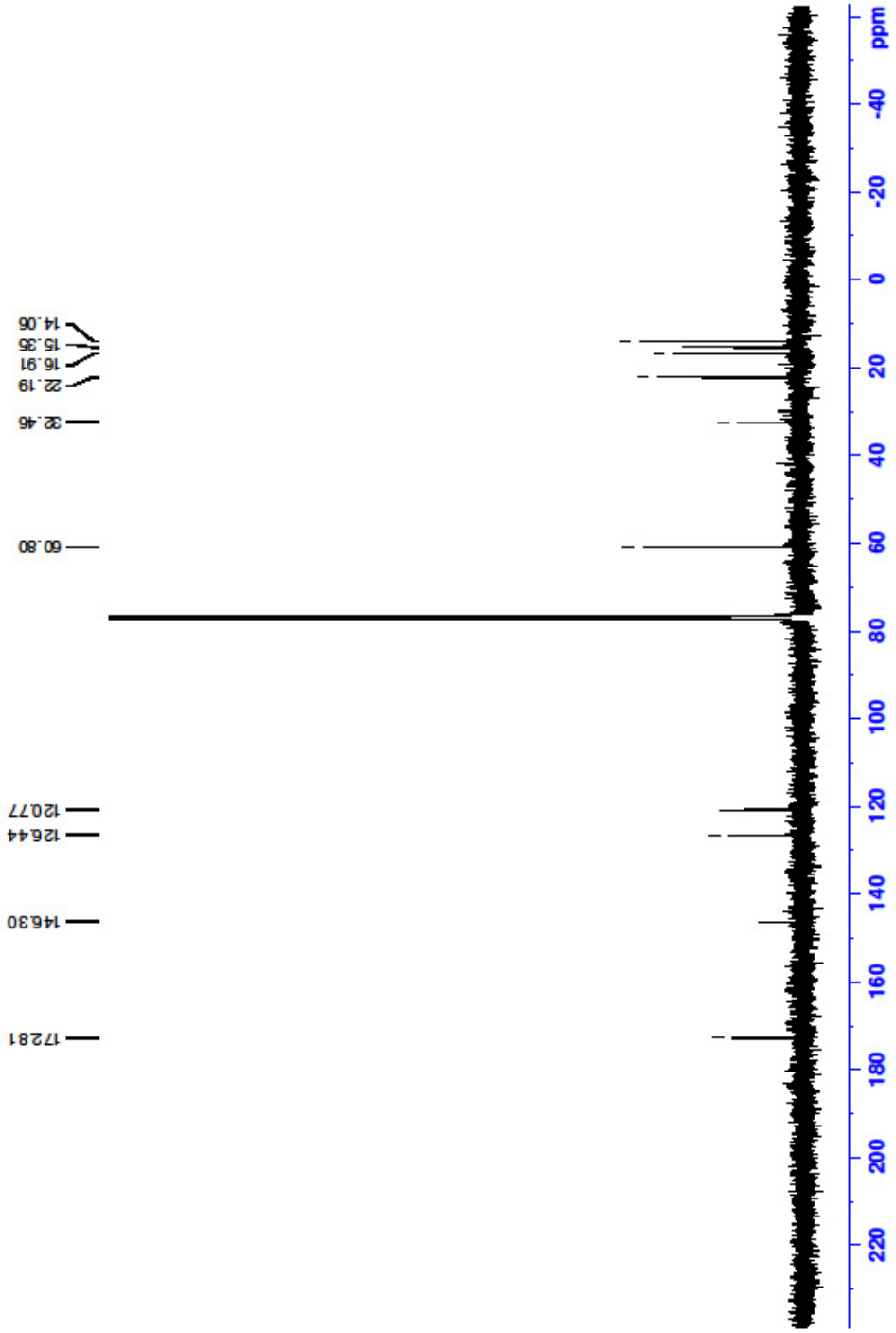
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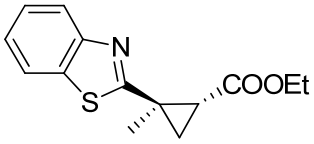
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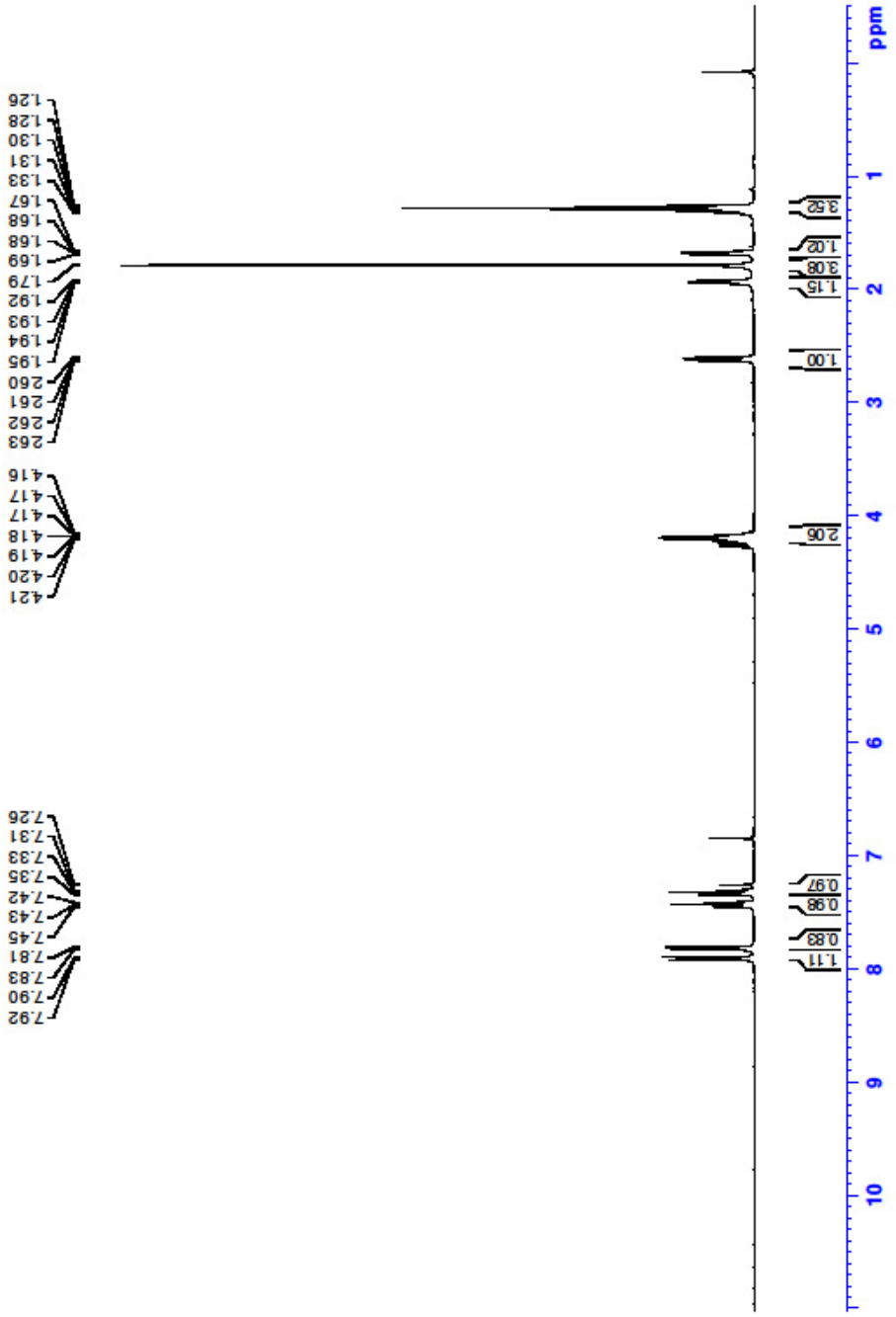
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1.94
1.95
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2.61
2.62
2.63
4.16
4.17
4.17
4.18
4.19
4.20
4.21
7.26
7.31
7.33
7.35
7.42
7.43
7.45
7.81
7.83
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3.08
1.15
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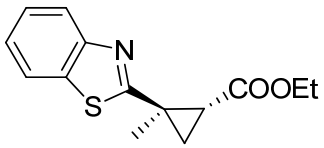
0.83
1.11
ppm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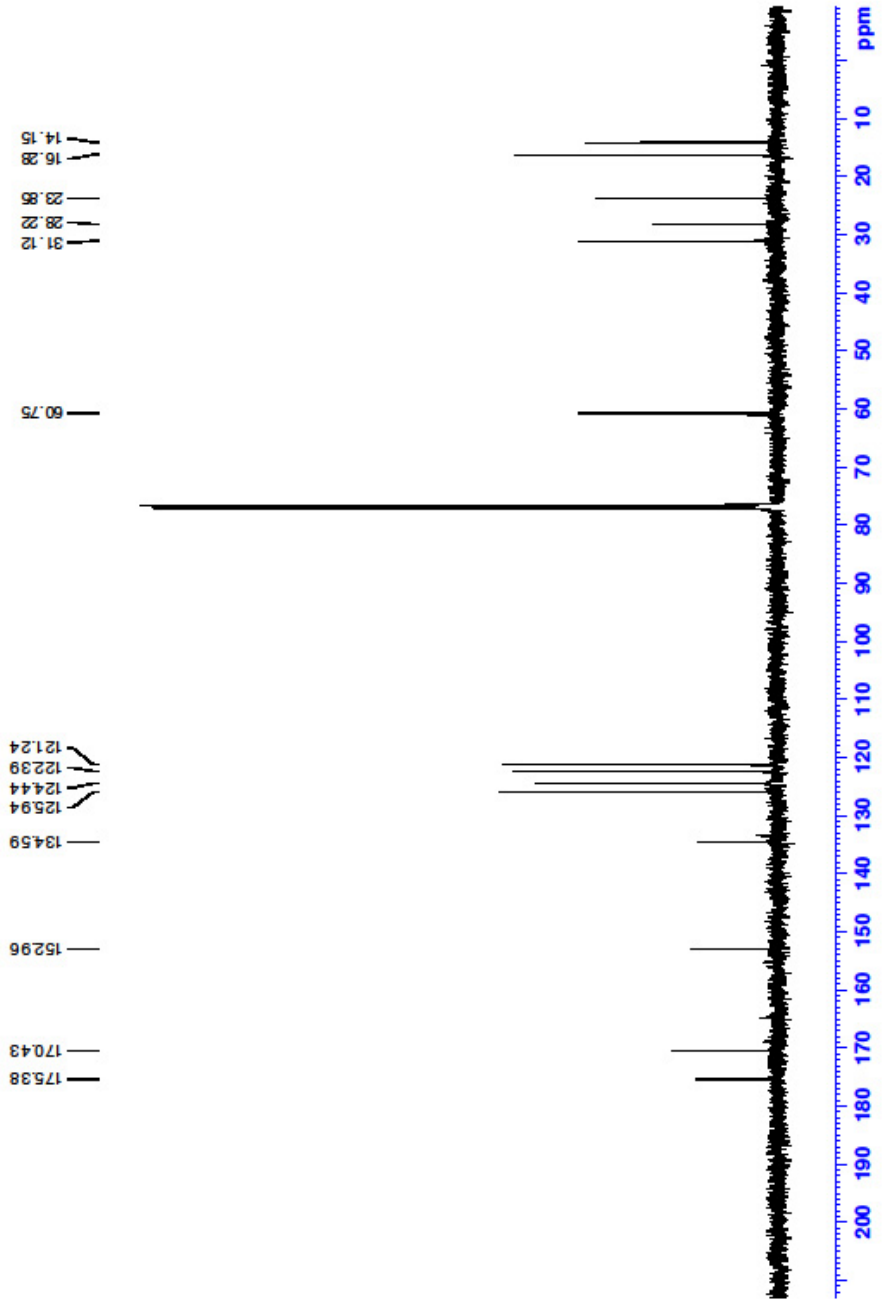
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175.38
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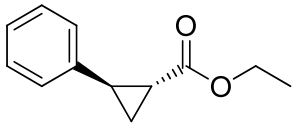
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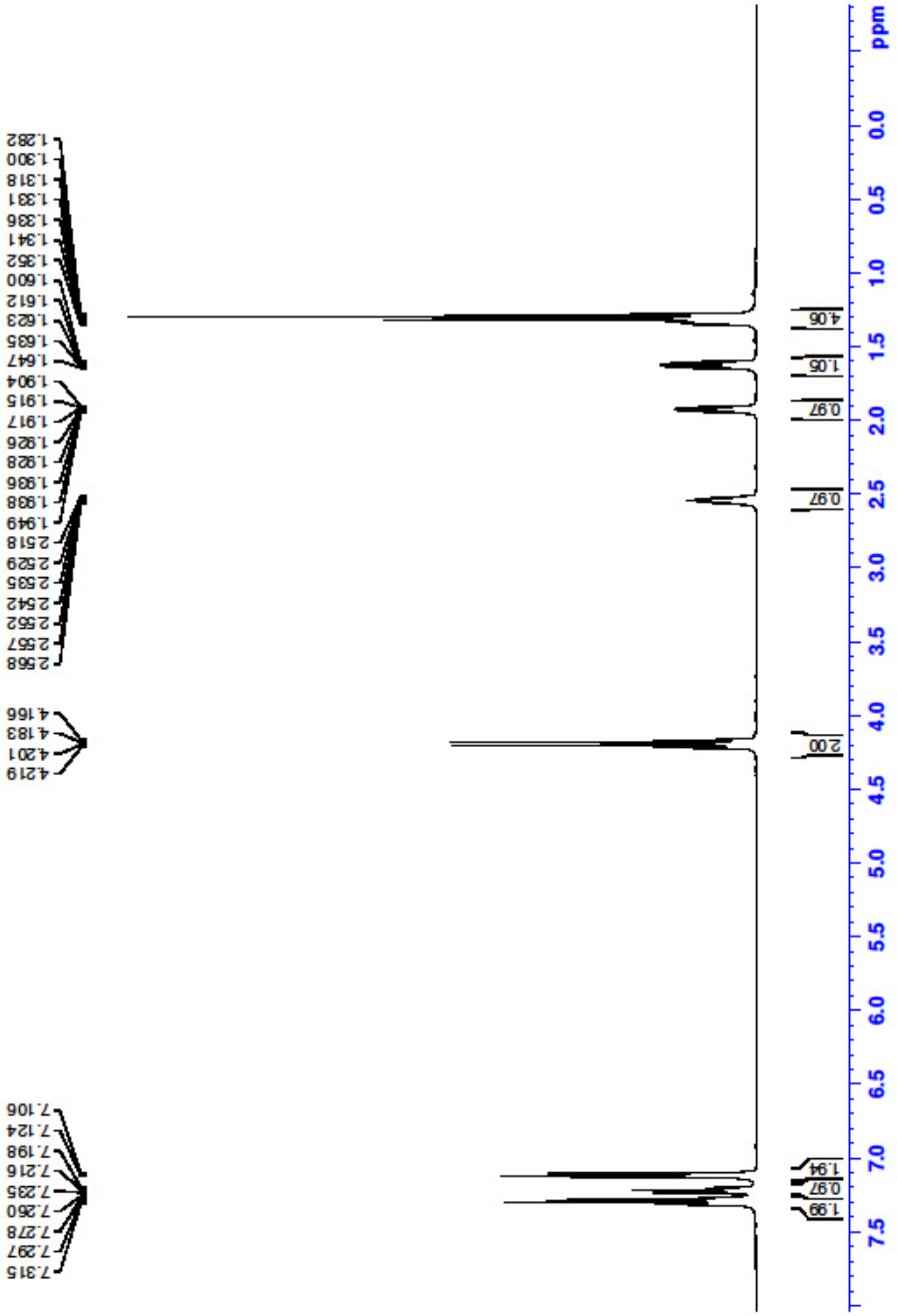
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7.124
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4.201
4.183
4.166
2.568
2.557
2.562
2.542
2.535
2.529
2.518
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1.938
1.936
1.928
1.926
1.917
1.915
1.904
1.647
1.635
1.623
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1.600
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1.336
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1.318
1.300
1.282
4.06
1.05
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0.97
2.00
1.94
0.97
1.99
ppm
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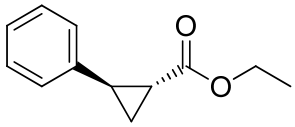
7.0
7.5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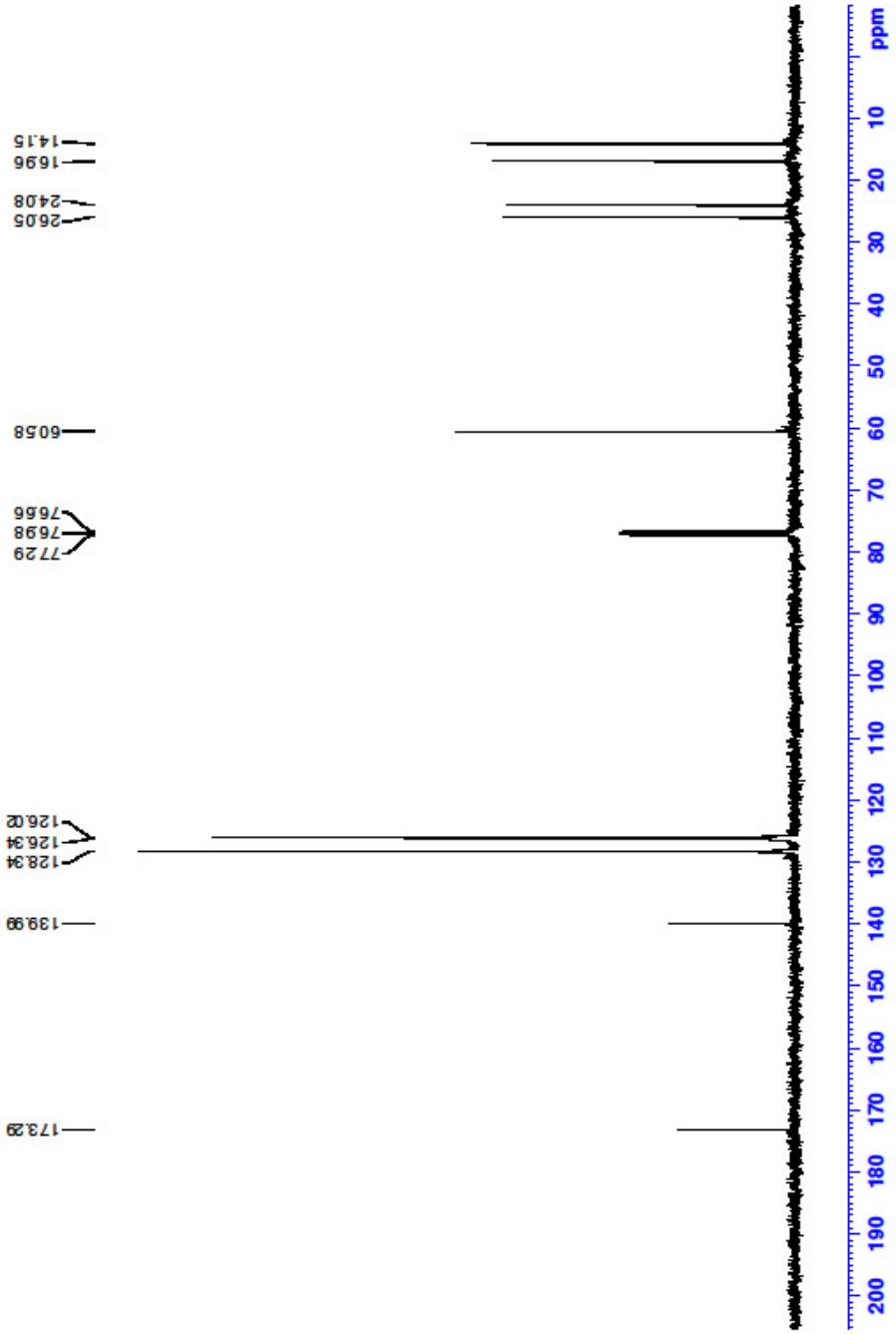
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76.98
77.29
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128.34
139.99
173.29
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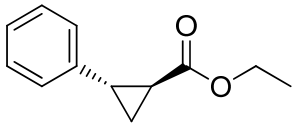

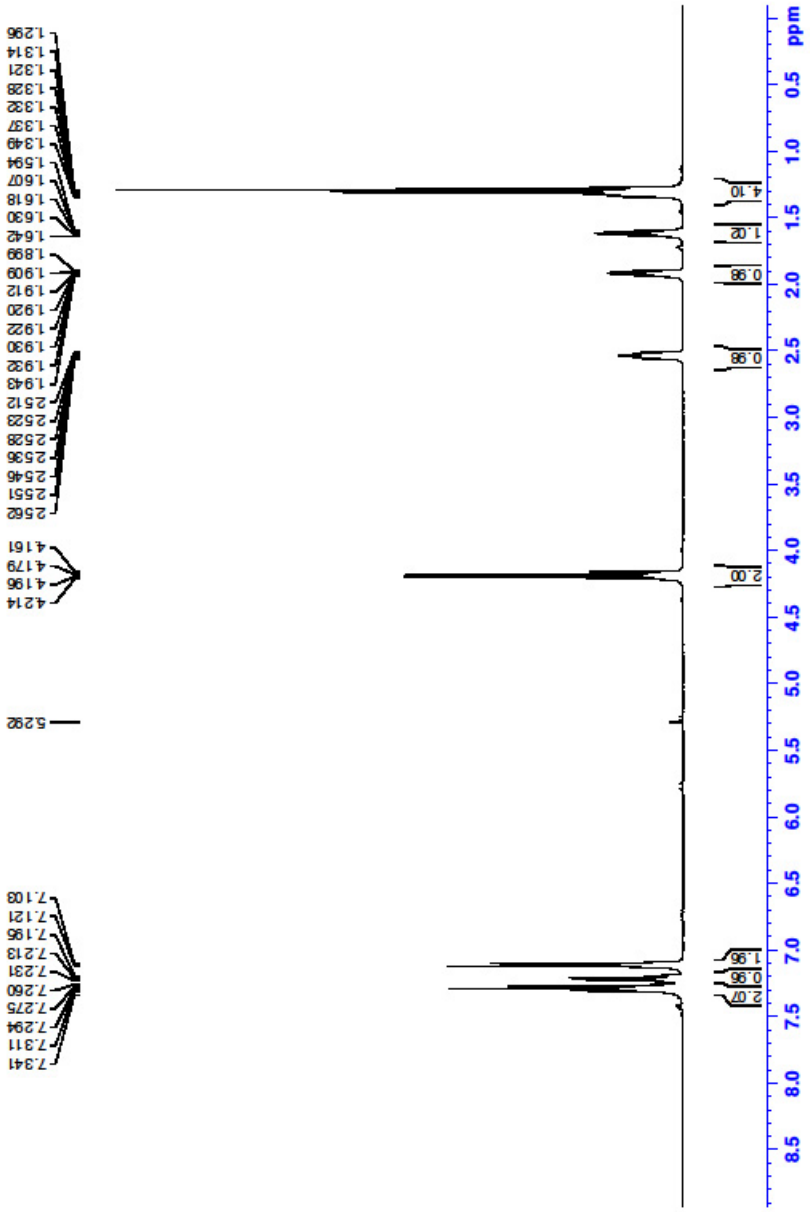
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1.630
1.642
1.899
1.909
1.912
1.920
1.922
1.930
1.932
1.943
2.512
2.523
2.528
2.536
2.546
2.551
2.562
4.161
4.179
4.196
4.214
5.292
7.108
7.121
7.196
7.213
7.231
7.260
7.275
7.294
7.311
7.341
4.10
1.02
0.98
0.98
2.00
1.98
0.96
2.07
ppm
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1.0
1.5
2.0
2.5
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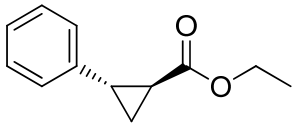
8.5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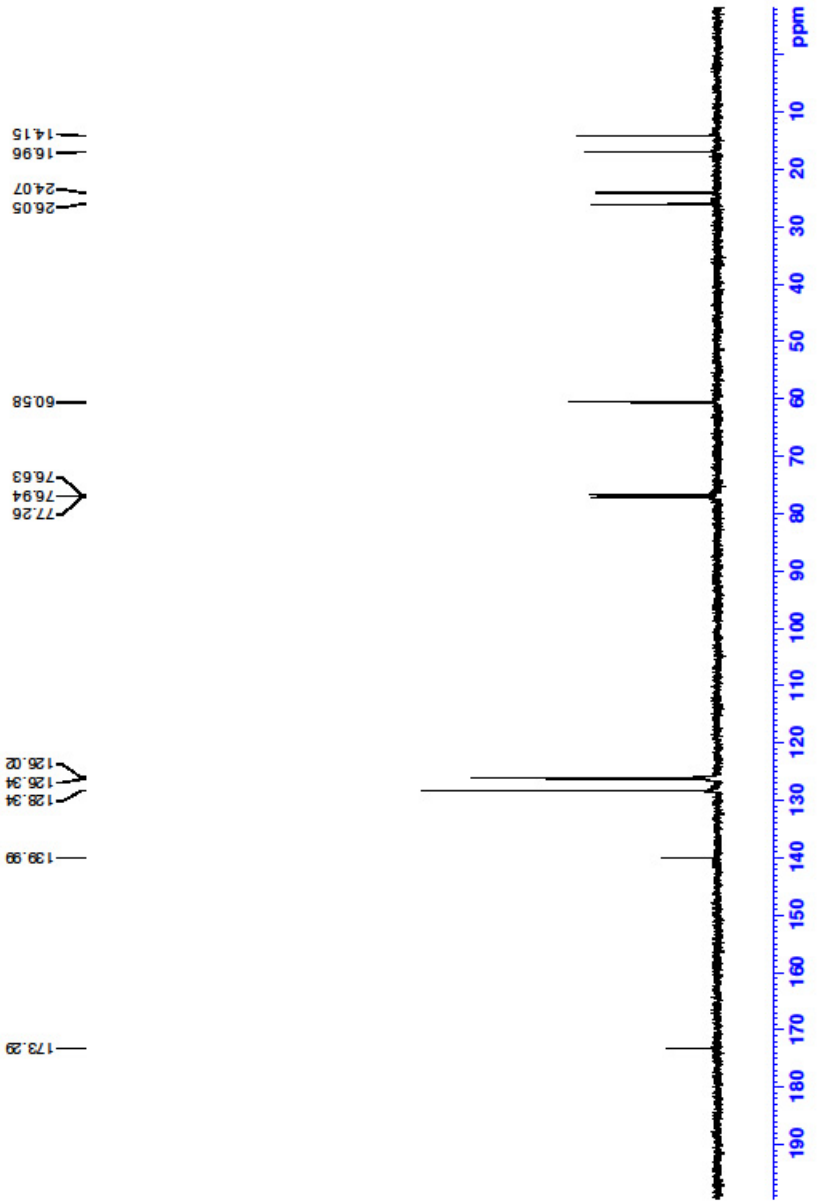
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16.96
24.07
26.05
60.58
76.63
76.94
77.26
126.02
126.34
128.34
139.99
173.29
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80
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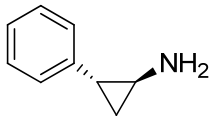
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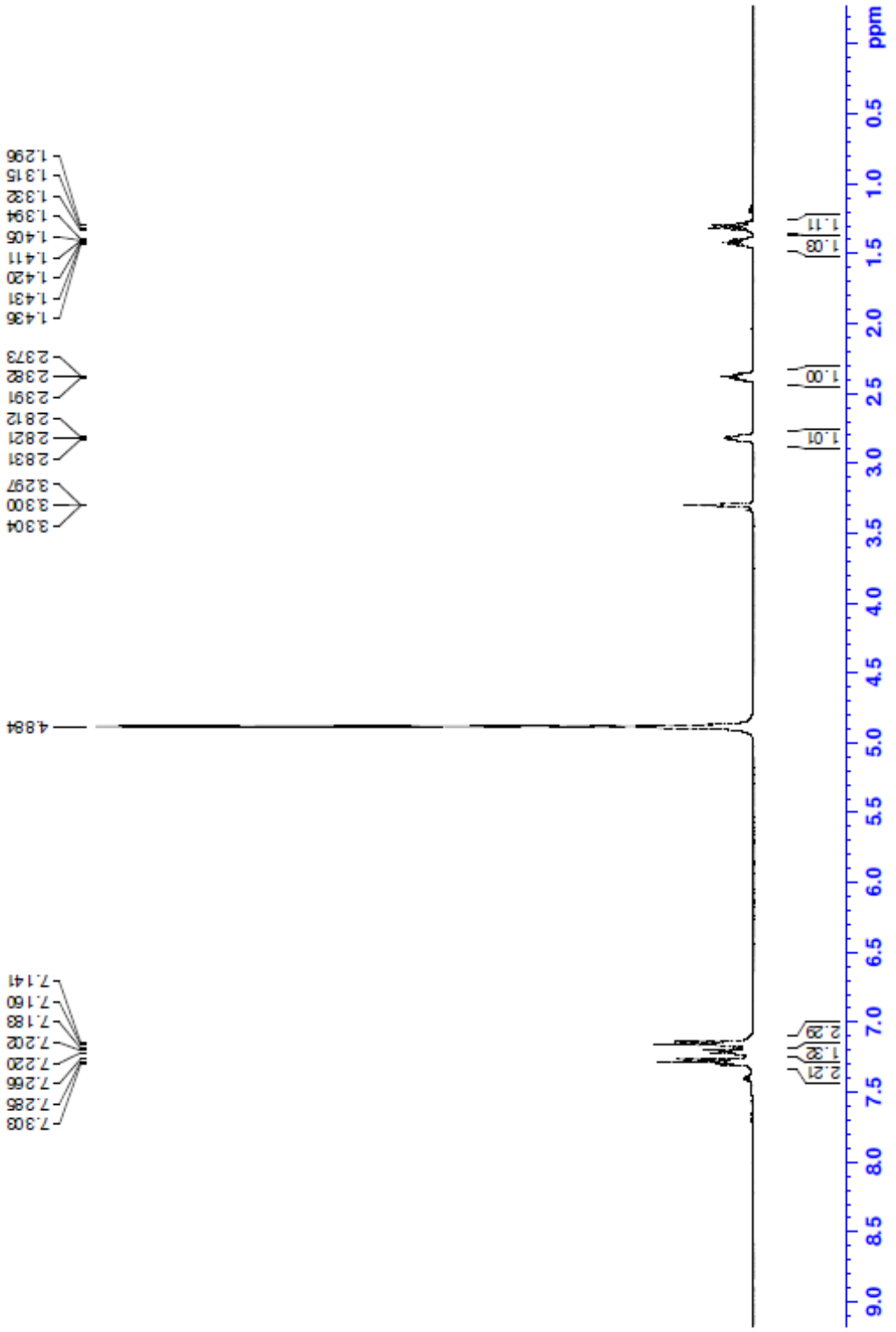
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2.821
2.812
2.391
2.382
2.373
1.436
1.431
1.420
1.411
1.406
1.394
1.382
1.315
1.296
2.29
1.82
2.21
1.00
1.01
1.11
1.08
9.0
8.5
8.0
7.5
7.0
6.5
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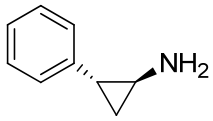
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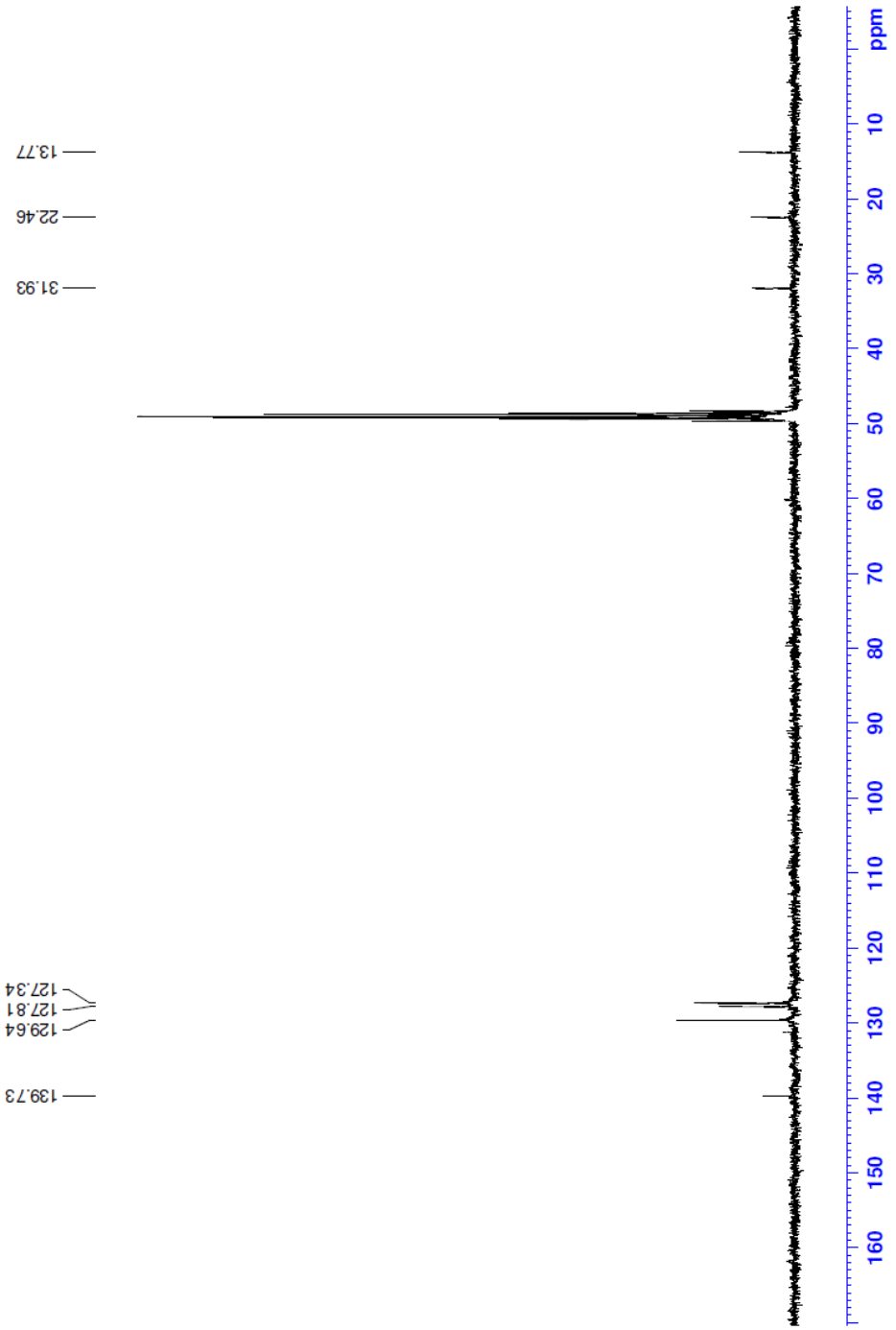
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90
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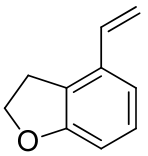

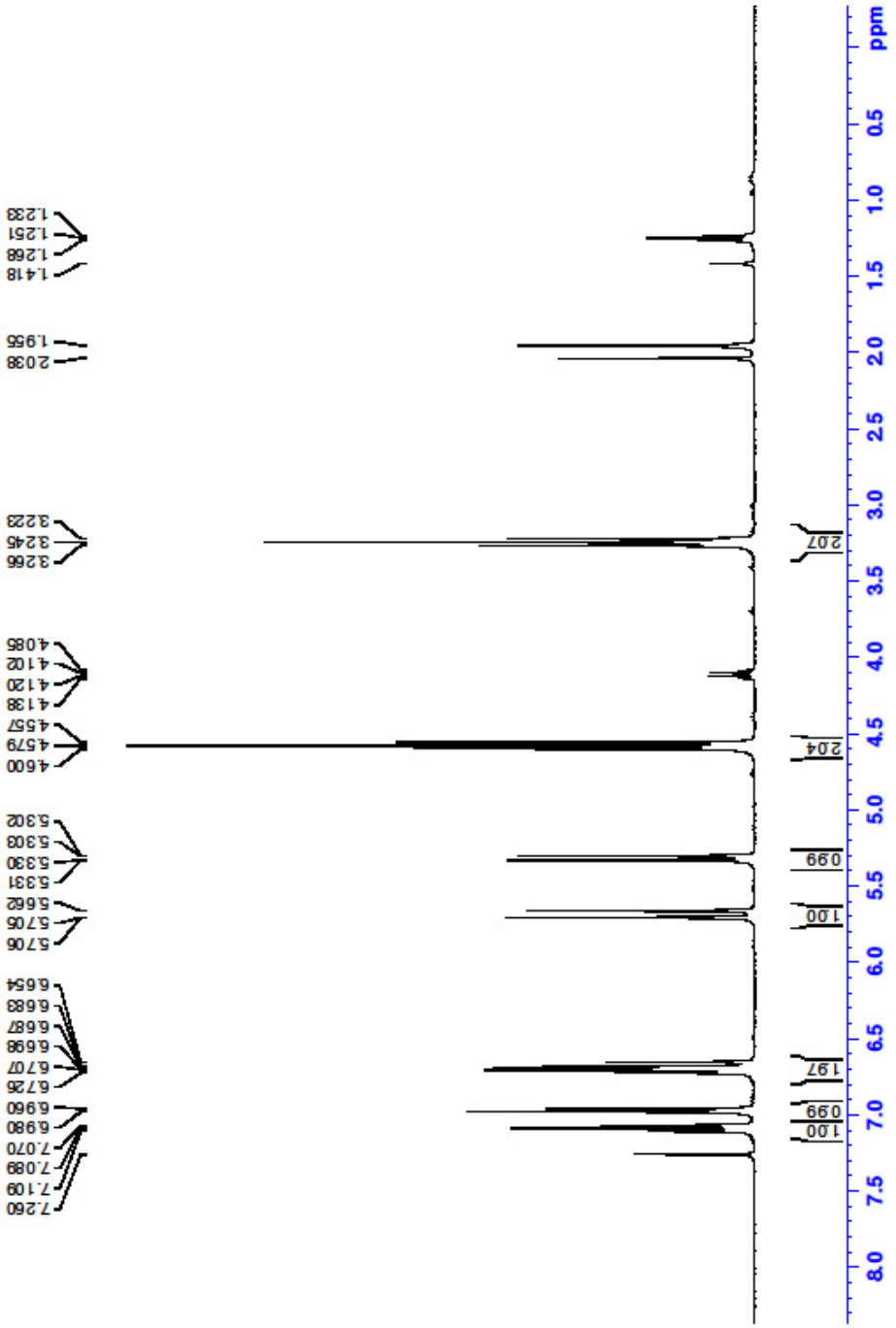
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4.138
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4.579
4.600
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5.308
5.330
5.331
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5.705
5.706
6.654
6.683
6.687
6.698
6.707
6.726
6.960
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7.109
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1.00
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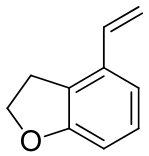
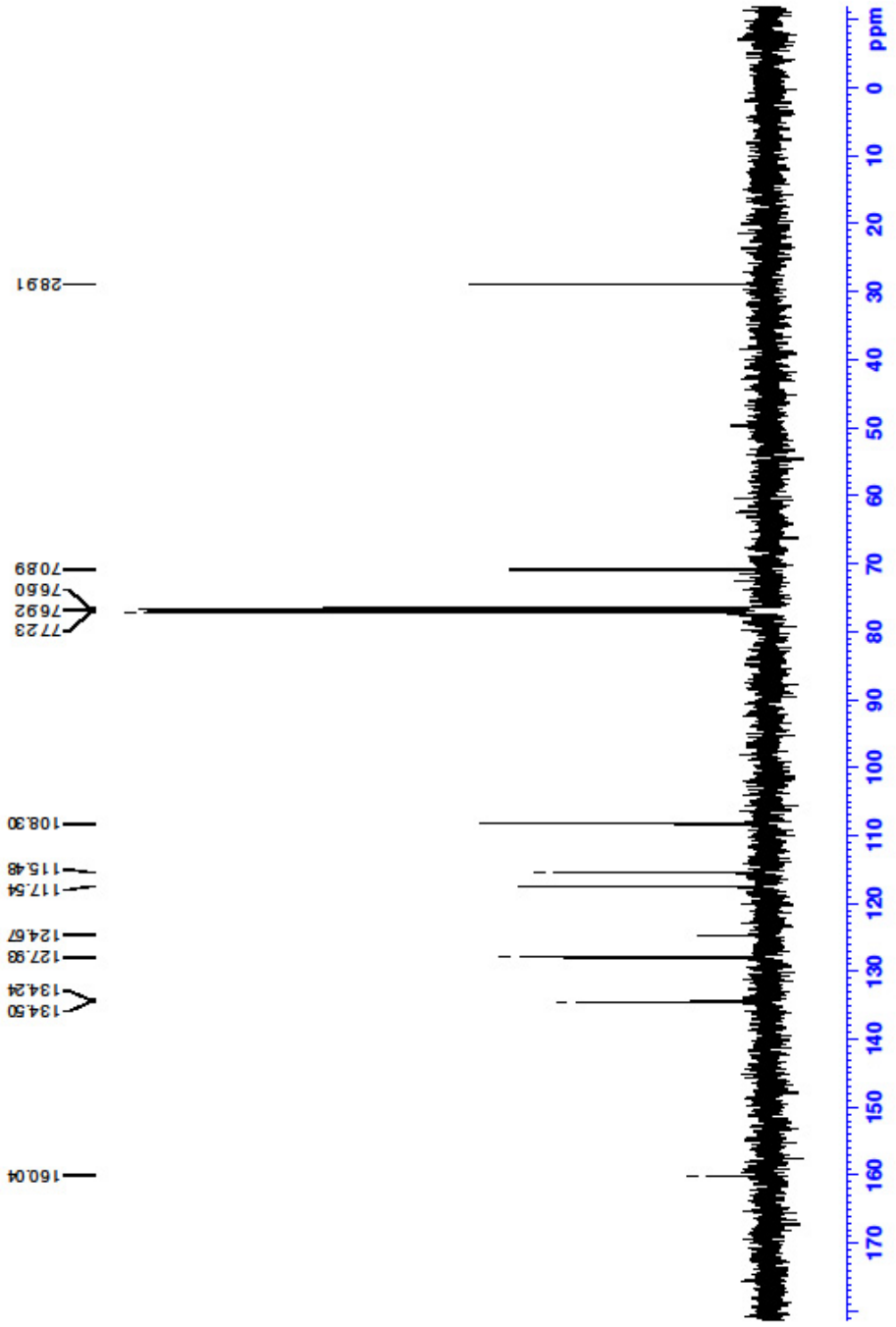
0.99
1.00
ppm

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127.98
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134.50
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150
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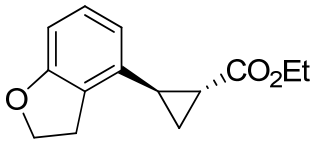
ppm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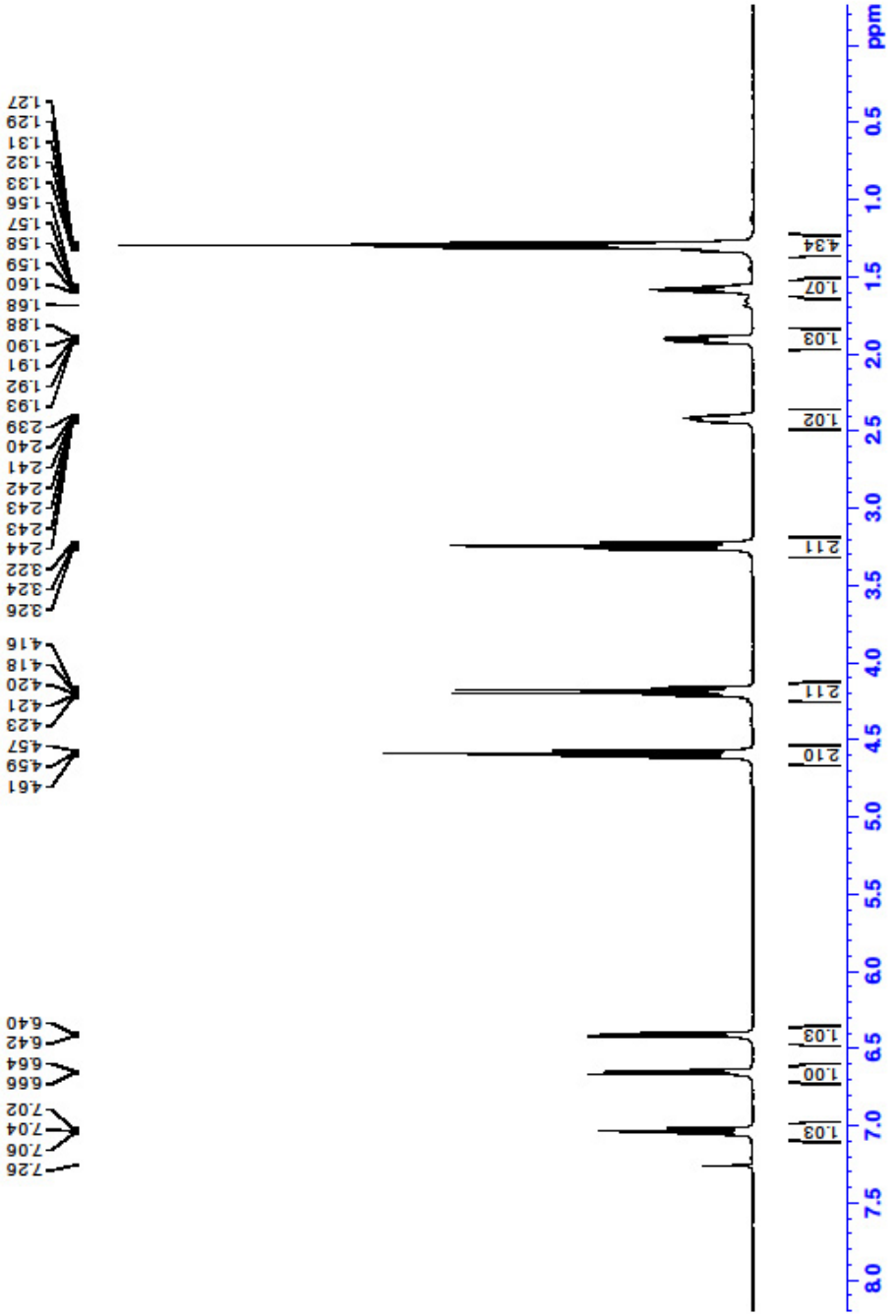
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1.91
1.92
1.93
2.39
2.40
2.41
2.42
2.43
2.43
2.44
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3.24
3.26
4.16
4.18
4.20
4.21
4.23
4.57
4.59
4.61
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6.64
6.66
7.02
7.04
7.06
7.26
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1.02
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2.11
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7.5
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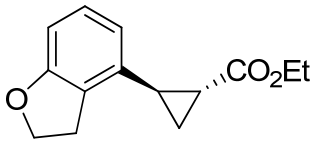
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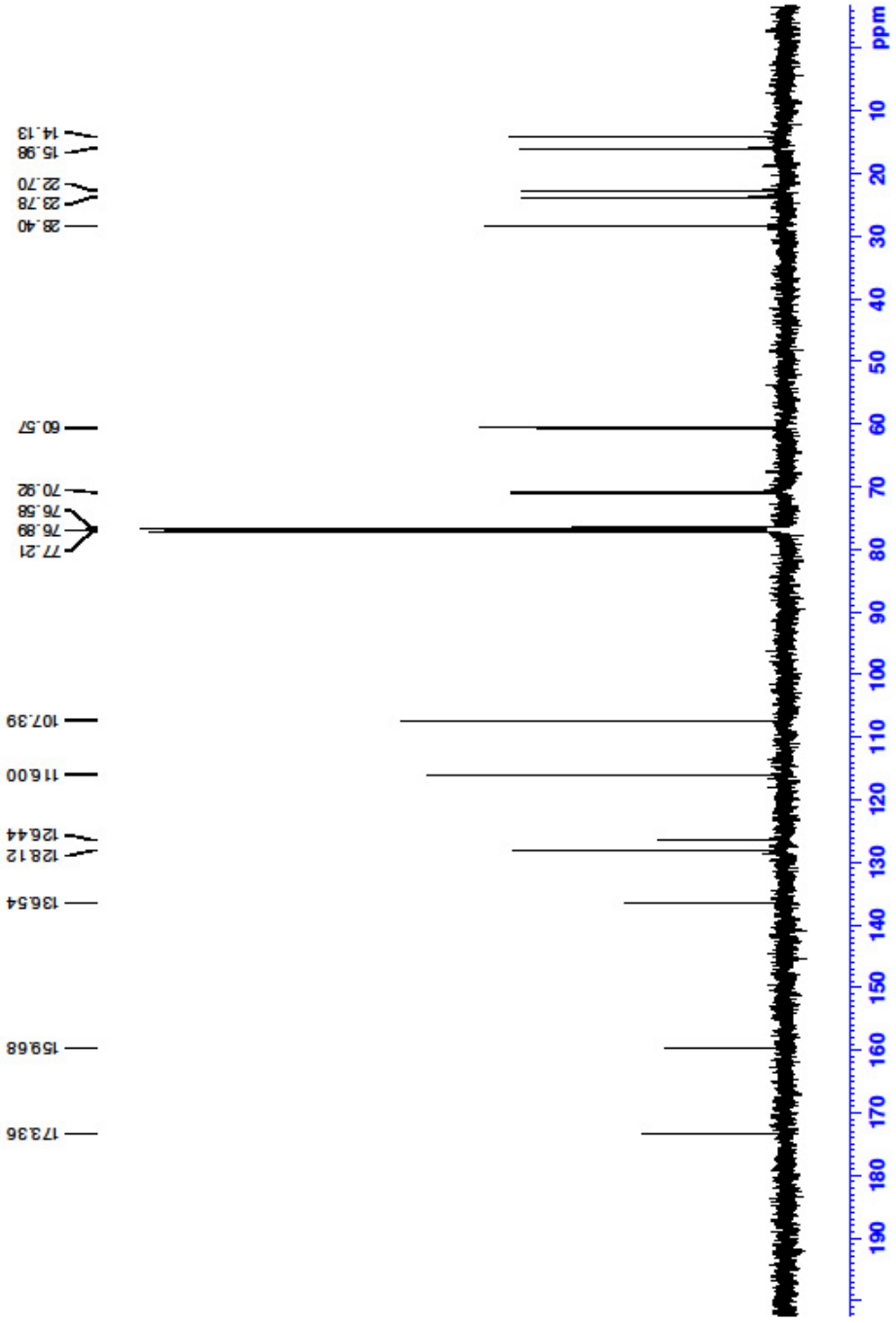
CO2Et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77.21
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136.54
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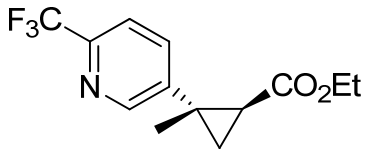
F3C
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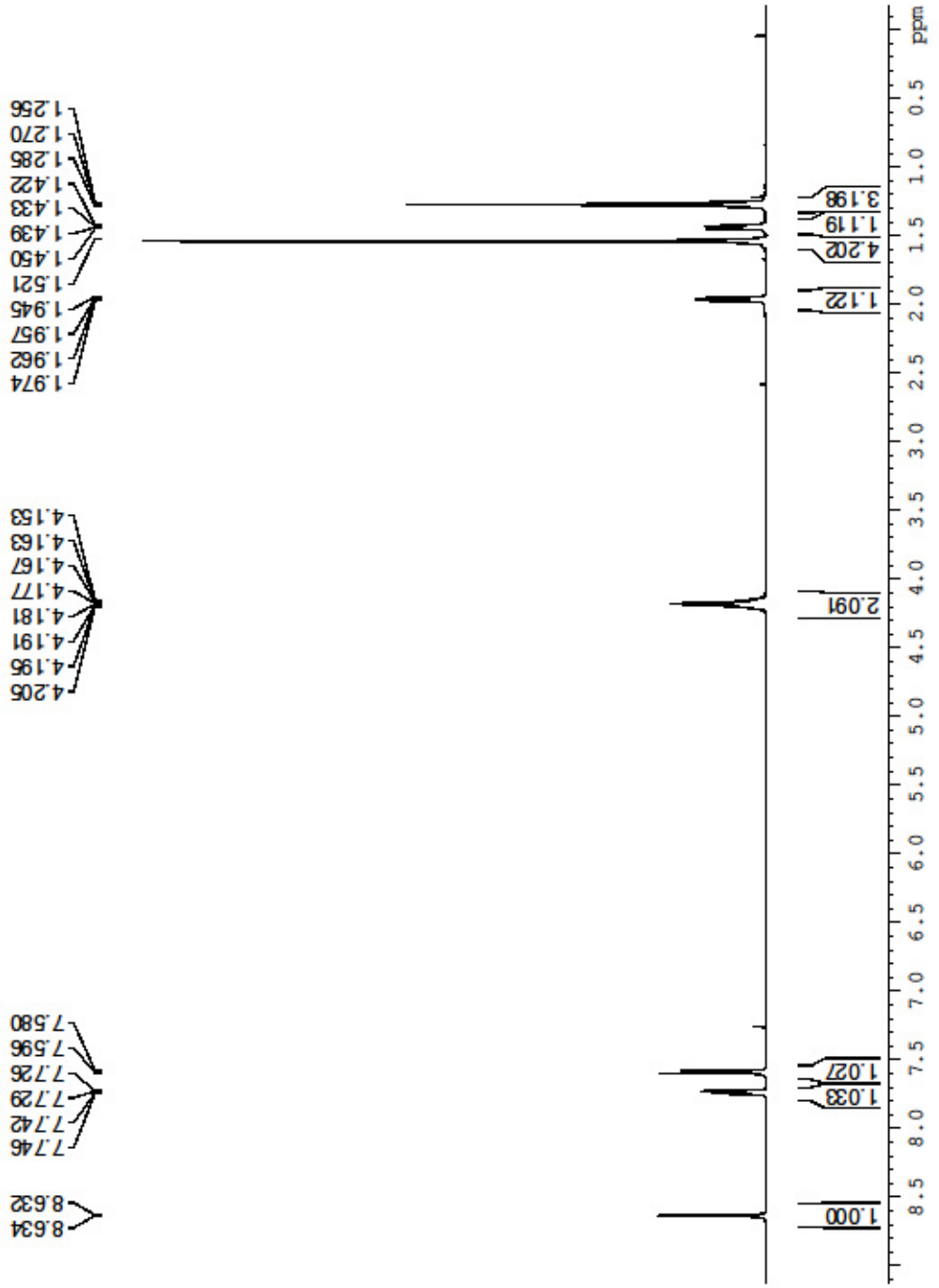
CO2Et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7.580
4.205
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4.191
4.181
4.177
4.167
4.163
4.153
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1.962
1.957
1.945
1.521
1.450
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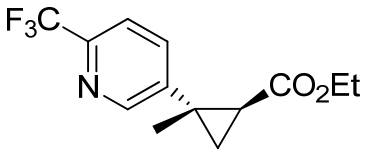
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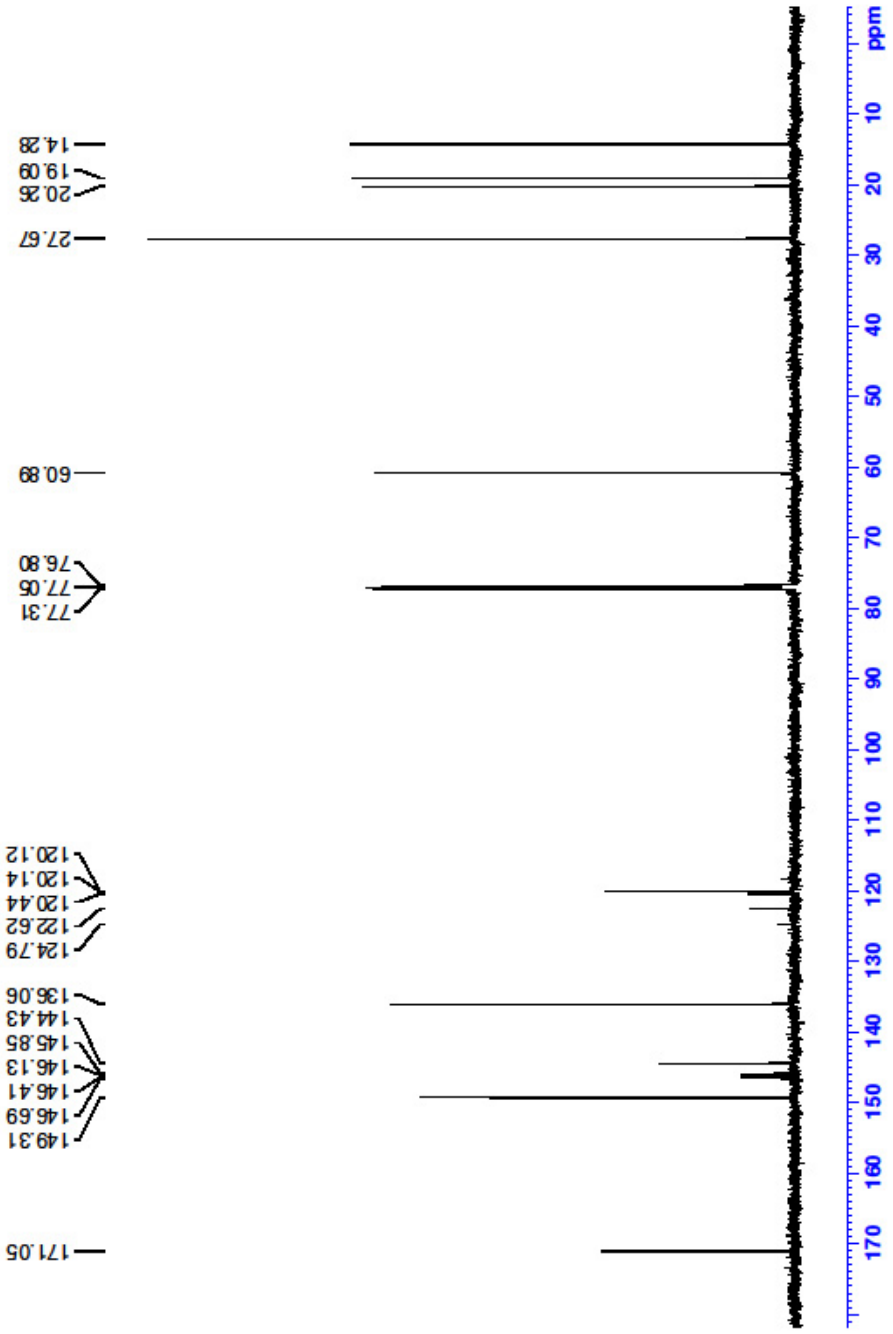
N
CO2Et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120.14
120.44
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124.79
136.06
144.43
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146.13
146.41
146.69
149.31
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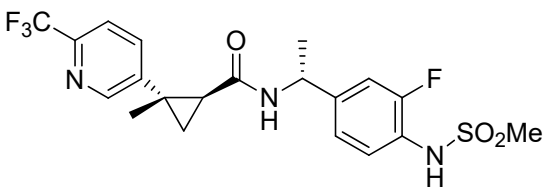
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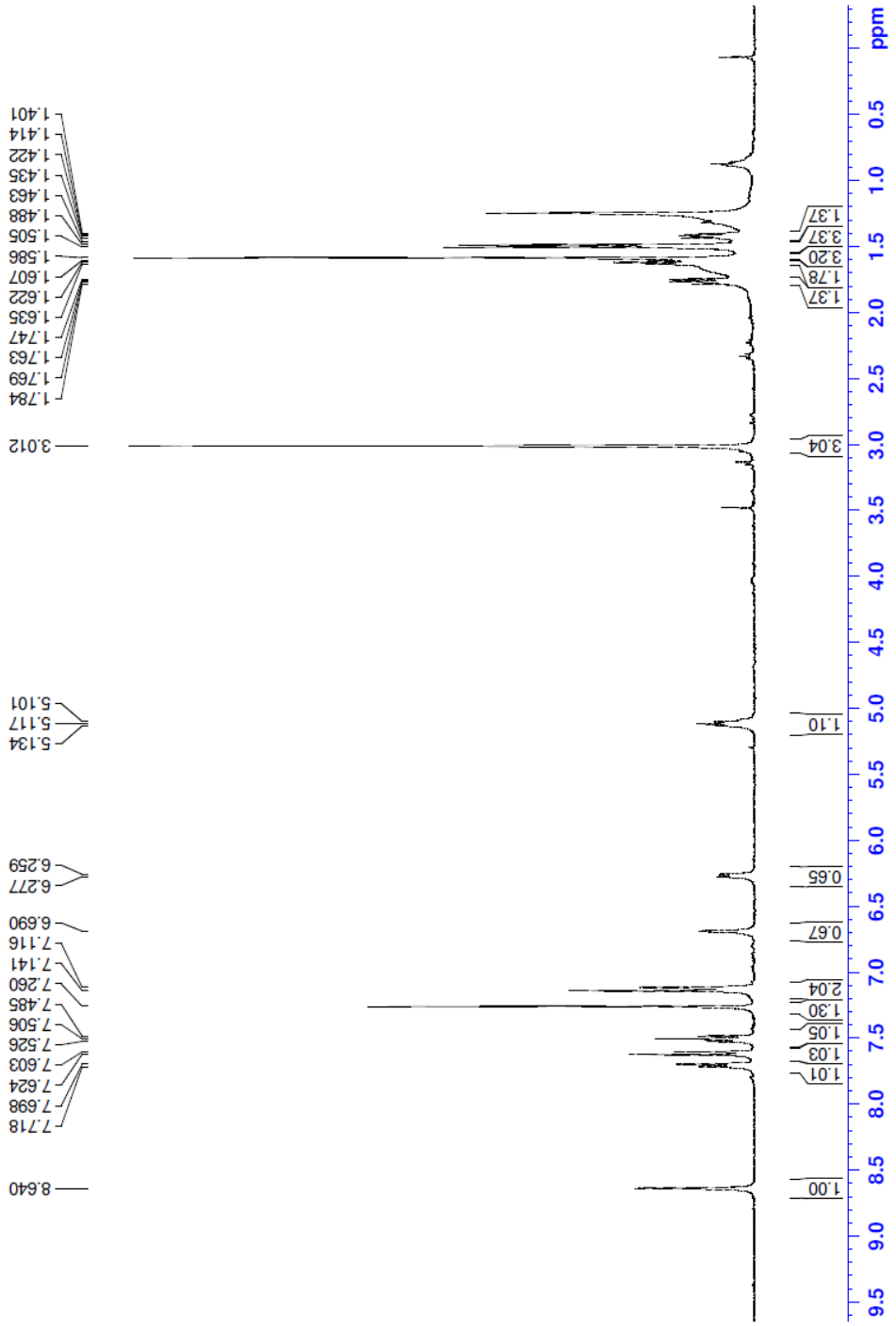
F
N
H
SO2Me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1.769
1.784
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5.117
5.134
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6.277
6.690
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7.141
7.260
7.485
7.506
7.526
7.603
7.624
7.698
7.718
8.640
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3.37
3.20
1.78
1.37
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1.10
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0.67
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1.30
1.05
1.03
1.01
1.00
ppm
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1.5
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2.5
3.0
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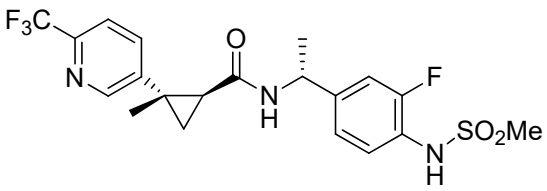
9.5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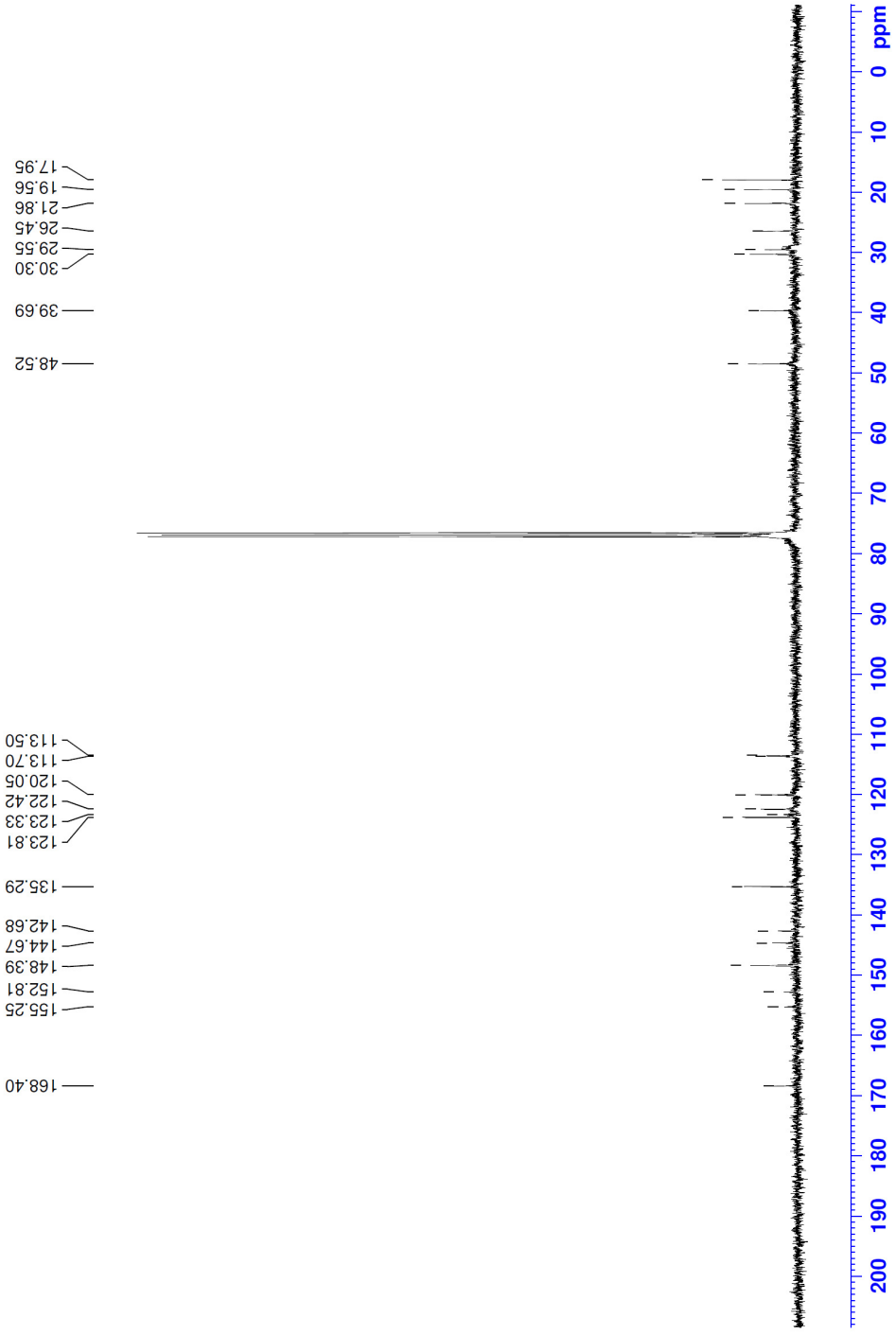
F
N
H
SO2Me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123.81
135.29
142.68
144.67
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152.81
155.25
168.40
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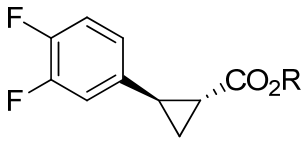
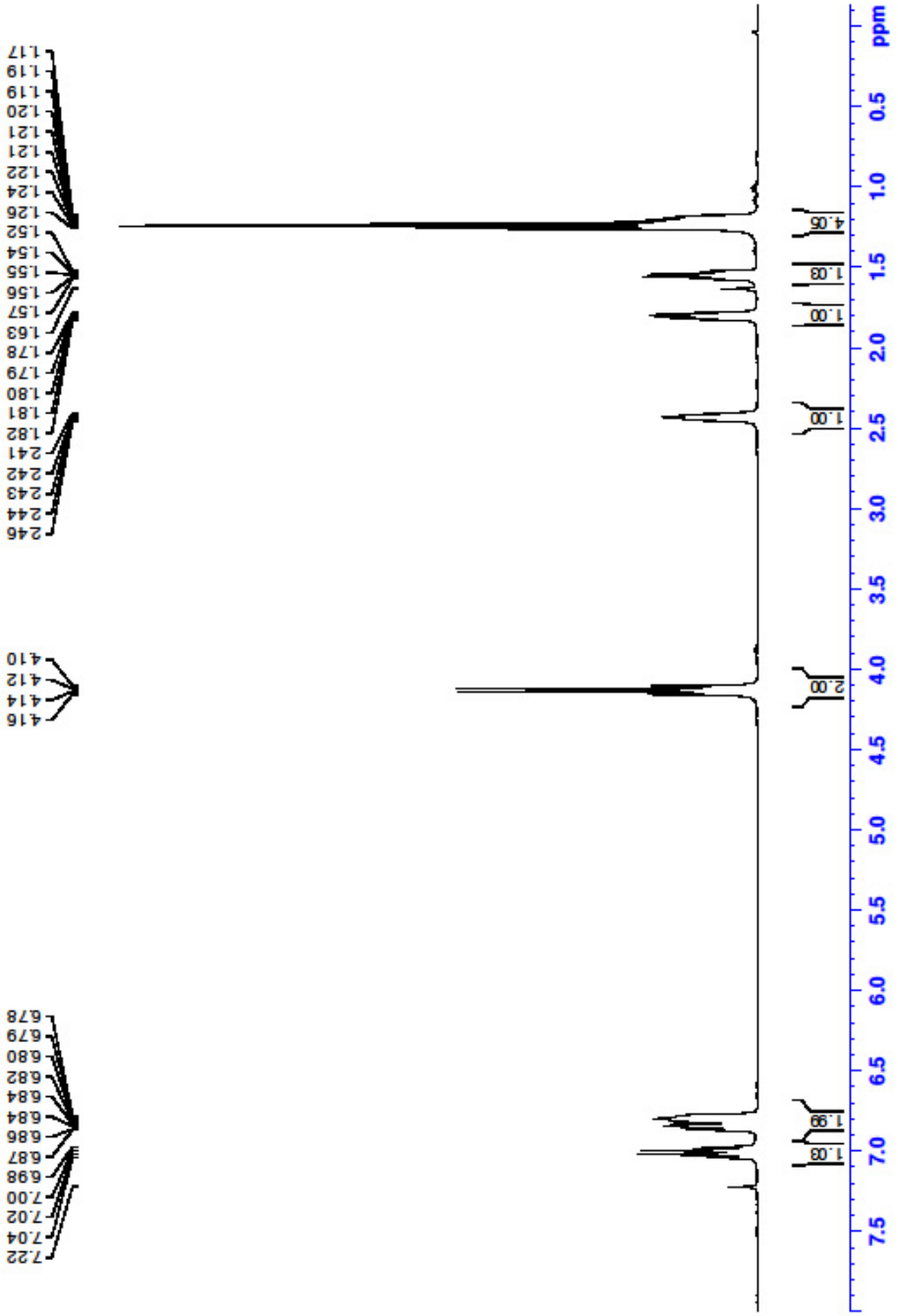
200


F
F
CO2R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1.57
1.63
1.78
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1.80
1.81
1.82
2.41
2.42
2.43
2.44
2.46
4.10
4.12
4.14
4.16
6.78
6.79
6.80
6.82
6.84
6.84
6.86
6.87
6.98
7.00
7.02
7.04
7.22
4.06
1.08
1.00
1.00
2.00
1.99
1.08
ppm
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1.0
1.5
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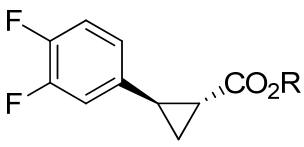
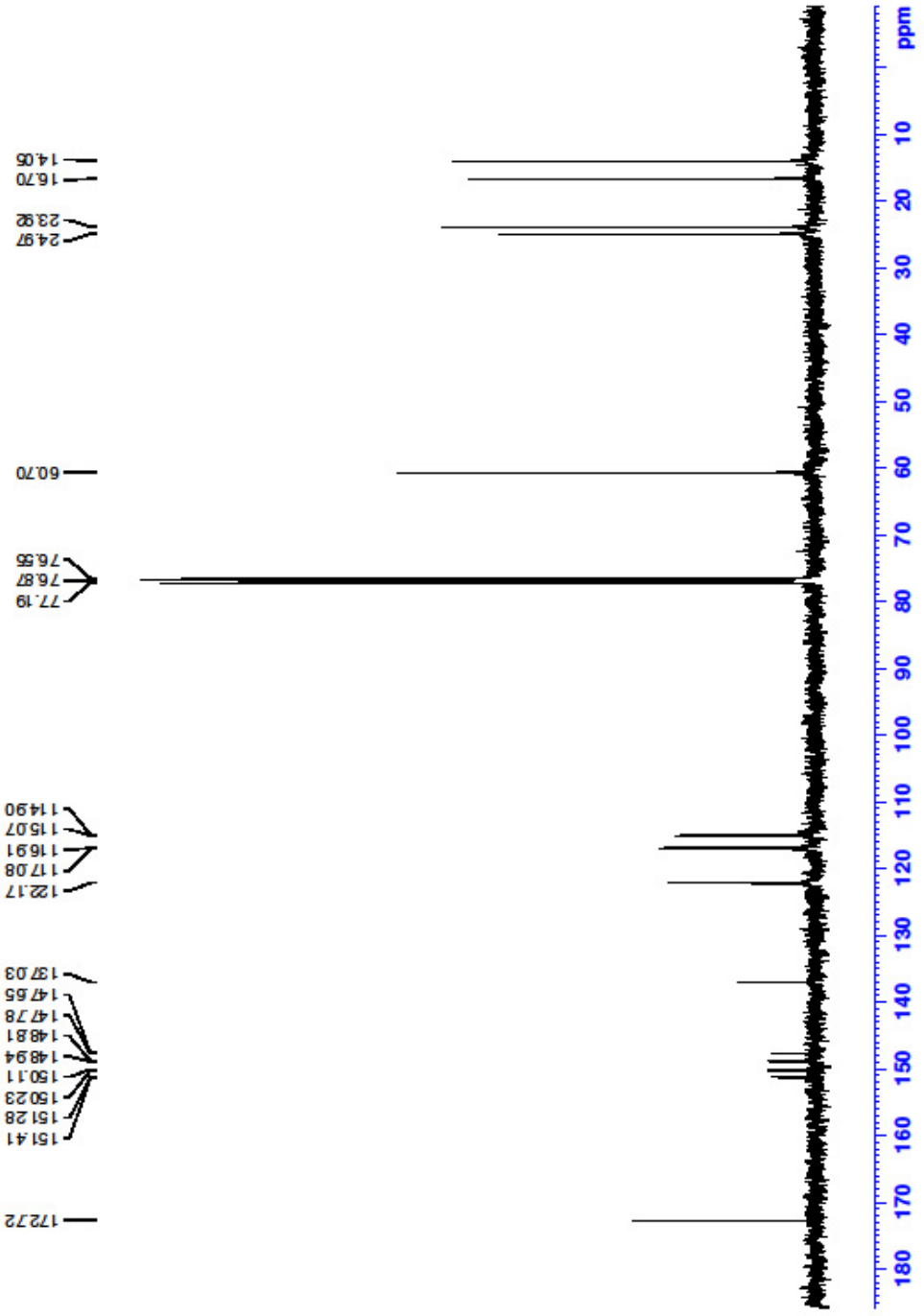

F
F
CO2R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137.03
147.65
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150.23
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151.41
172.72
ppm