Electronic supplementary material for:

Characterisation of 6-DMATS$_{Mo}$ from *Micromonospora olivasterospora* leading to identification of divergence in enantioselectivity, regioselectivity and multiple prenylation of tryptophan prenyltransferases

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Structure elucidation of enzyme products of 6-DMATS$_{Mo}$ by NMR analysis

Inspection of the NMR spectra of the isolated peaks revealed the presence of a unique product each from the reaction mixtures of **1a**, **1b**, **2a**, **3a**, **4**, **5**, **8**, and **9a**, whereas three products **5-C5**, **-C6,** and **-C7** were found from that of **5** and two products each **6-C6** and **6-C7** or **7-C5** and **7-C6** from those of **6** and **7** (Table S5-S7, Fig. S4-S22). The presence of the signals for dimethylallyl moieties at δ_H 3.30 - 3.56 (d/ or m, 2H-1'), 5.09 - 5.41 (t sept or m, H-2'), 1.74 - 1.83 (s, 3H-4'), 1.68 - 1.75 ppm (s, 3H-5') verified a regular *C*-prenylation in all the structures (Table S5-S7).[2,3,5-7] In comparison to the respective substrates, signals for one aromatic proton was absent in the spectra of the enzyme products. The presence of the singlet in the range of δ_H 7.06 - 7.17 ppm for H-2 implies the prenylation at the benzene ring.

Comparison of the spectra of **1a**, **1b**, **2a**, **3a**, and **4** with each other (Table S5, Fig. S4-S8) showed similar chemical shifts of the three coupling aromatic protons at δ_H 7.49 - 7.59, 6.89 - 6.91, and 7.14 - 7.15 ppm. The two coupling constants of 8.2 and 1.4 - 1.5 Hz indicates *C5*- or *C6*-prenylation in their structures. Considering the relative positions of the signals of the aromatic protons and comparison of the spectra with those of *C5*- and *C6*-prenylated tryptophan and analogues [6,8] led to identification of **1a-C6,** **1b-C6**, **2a-C6**, **3a-C6**, and **4-C6** to be *C6*-prenylated derivatives. **1a-C6**, **2a-C6,** and **3a-C6** have been identified as enzyme products of **1a**, **2a**, and **3a** with 6-DMATS$_{Sa}$.[6]

Signals for three products **5-C5**, **-C6**, and **-C7** with a ratio of 0.6:1:0.6 were detected in the ^{1}H NMR spectrum of the isolated peak from the enzyme assay of **5**. Due to different coupling pattern, it was possible to determine the prenylation positions in their structures. The three singlets at δ_H 7.06, 6.96, and 6.60 ppm of the main product **5-C6** verified a *C6*-prenylation in its structure (Table S6, Fig S9). The correlations in ^{1}H-^{1}H

COSY confirmed this conclusion and facilitated the assignment of the protons (Fig S10-S14). **5-C5** and **5-C7** were identified as *C5*- and *C7*-prenylated products by interpretation of the ^{1}H-^{1}H COSY correlations and by comparison of their coupling pattern with those published previously.[4,6,8]

Two products **6-C6** and **6-C7** with a ratio of 1:0.4 were identified as products in the reaction mixture of **6** (Table S6, Fig. S15). The chemical shifts and the coupling pattern of the main product **6-C6** were nearly the same as those of 6-DMA-5-methyl-DL-tryptophan, the product of 6-DMATS$_{Sa}$ with **6**.[6] This result was further confirmed by the interpretation of correlations in ^{1}H-^{1}H COSY (Fig S16-S19). Three singlets at δ_H 7.15, 7.35, and 6.76 ppm for three aromatic protons were observed for **6-C7**, which are distinct from those of **6-C6** and correspond very well to those of the *C7*-prenylated product reported previously for TyrPT.[1] Thus, MolI14.36 catalyses mainly a *C6*-prenylation of **6** rather than a *C7*-prenylation. From the reaction mixture of MolI14.36 with **7**, two products **7-C5** and **7-C7** with a ratio of 0.12:1 were isolated as a mixture. The ^{1}H NMR data of the main product **7-C7** correspond very well to those observed for the *C7*-prenylated product of **7** reported for 6-DMATS$_{Sa.}$[6] Signals of **7-C5** had a very low intensity. The observed three singlets of the indole moiety at δ_H 7.14, 7.45, and 7.07 ppm indicates a *C4*- or *C5*-prenylation of **7** (Table S7, Fig S20). Comparison of these data with those of the *C5*-prenylated derivative proved unequivocally the *C5*-prenylation in **7-C5**.[8] Interpretation of the ^{1}H NMR spectra of **8-C6** and **9a-C6** revealed the attachment of the dimethylallyl moiety at position C-6 of the indole ring (Table S7, Fig. S21 – S22)

Reference List

1 A. Fan, H. Chen, R. Wu, H. Xu, and S.-M. Li, *Appl. Microbiol. Biotechnol.*, 2014, **98**, 10119-10129.

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5 S. Takahashi, H. Takagi, A. Toyoda, M. Uramoto, T. Nogawa, M. Ueki, Y. Sakaki, and H. Osada, *J. Bacteriol.*, 2010, **192**, 2839-2851.

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7 X. Yu and S.-M. Li, *Methods Enzymol.*, 2012, **516**, 259-278.

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Table S1 HPLC conditions for analyses of enzyme assays.

Condition 1		
Column	Multospher 120 RP-18 column (250×4 mm, 5 µm, C+S Chromatography Service, Langerwehe, Germany)	
Flow rate	1 ml*min^{-1}	
Solvent A	water	
Solvent B	methanol	
Elution profile	solvent B in A [v/v]	duration [min]
	from 40 % to 100 %	15 min
	100 %	5 min
	40 %	5 min
Condition 2		
Column	CHIRALPAK®Zwix(+) column (150 × 3 mm, 3 µm, Chiral technologies Europe, Daicel Group, Illkirch Cedex, France)	
Flow rate	0.5 ml*min^{-1}	
Solvent A	water:methanol (1:1), 25 mM diethylamine, 50 mM formic acid	
Solvent B	methanol, 25 mM diethylamine, 50 mM formic acid	
Elution profile	solvent B in A [v/v]	duration [min]
	0%	25 min
	100 %	5 min
	0 %	5 min
Condition 3		
Column	Multospher 120-C18 column (250 x 2 mm, 5 µm; C+S Chromatography Service, Langenfeld, Germany))	
Flow rate	0.5 ml*min^{-1}	
Solvent A	water, 0.1 % (v/v) formic acid	
Solvent B	acetonitrile, 0.1 % (v/v) formic acid	
Elution profile	solvent B in A [v/v]	duration [min]
	from 5 % to 100 %	40 min
	100 %	10 min
	5 %	5 min
Condition 4		
Column	Eclipse XDB-C18 column (5 µm, 4.6 x 150 mm, Agilent)	
Flow rate	0.5 ml*min^{-1}	
Solvent A	water, 0.5 % (v/v) trifluoroacetic acid	
Solvent B	acetonitrile, 0.5 % (v/v) trifluoroacetic acid	
Elution profile	solvent B in A [v/v]	duration [min]
	30 %	5 min
	from 30 % to 45 %	30 min
	100 %	5 min
	30 %	5 min
Condition 5		
Column	Eclipse Plus-C18 column (3.5 µm, 4.6 x 150 mm, Agilent)	
Flow rate	0.5 ml*min^{-1}	
Solvent A	water, 0.5 % (v/v) trifluoroacetic acid	
Solvent B	acetonitrile, 0.5 % (v/v) trifluoroacetic acid	
Elution profile	solvent B in A [v/v]	duration [min]
	30 %	5 min
	From 30 % to 35 %	30 min
	100 %	5 min
	30 %	5 min
Condition 6		
Column	Eclipse Plus-C18 column (3.5 µm, 4.6 x 150 mm, Agilent)	
Flow rate	0.5 ml*min^{-1}	
Solvent A	water, 0.5 % (v/v) trifluoroacetic acid	
Solvent B	acetonitrile, 0.5 % (v/v) trifluoroacetic acid	
Elution profile	solvent B in A [v/v]	duration [min]
	30 %	5 min

	from 30 % to 35 %	15 min
	from 35 % to 70 %	25 min
	100 %	5 min
	30 %	5 min
Condition 7		
Column	CHIRALPAK®Zwix(+) column (150 × 3 mm, 3 µm, Chiral technologies Europe, Daicel Group, Illkirch Cedex, France)	
Flow rate	0.5 ml*min^{-1}	
Solvent A	methanol	
Elution profile	solvent A	duration [min]
	100 %	25 min
Condition 8		
Column	Multospher 120 RP-18 column (250×10 mm, 5 µm, C+S Chromatography Service, Langerwehe, Germany)	
Flow rate	2.5 ml*min^{-1}	
Solvent A	water	
Solvent B	methanol	
Elution profile	solvent B in A [v/v]	duration [min]
	60 %	5 min
	from 60 % to 100 %	25 min
	100 %	5 min
	60 %	5 min
Condition 9		
Column	Multospher 120 RP-18 column (250×10 mm, 5 µm, C+S Chromatography Service, Langerwehe, Germany)	
Flow rate	2.5 ml*min^{-1}	
Solvent A	water	
Solvent B	methanol	
Elution profile	solvent B in A [v/v]	duration [min]
	from 70 % to 100 %	20 min
	100 %	5 min
	70 %	5 min

Table S2 Enzyme activities of 6-DMATS$_{Mo}$ towards different prenyl donors.

prenyl donor	relative conversion yield [%]	
	(4 µM, 4 h, 1 mM donor)	(6 µM, 6 h, 2 mM donor)
DMAPP	100	100
GPP	7.8	11.7
FPP	≤0.5	≤0.5

The enzyme assays were analyzed on HPLC under condition 1. The conversion yields of L-tryptophan in the presence of DMAPP at 51.2 % (1 mM DMAPP) or 98.3 % (2 mM DMAPP) were defined as 100 % relative activity.

Table S3 Comparison of enzyme activities of 6-DMATS$_{Mo}$, 6-DMATS$_{Sa}$ and 6-DMATS$_{Sv}$ towards tryptophan-containing cyclic dipeptides.

substrate	relative conversion yield [%]		
	6-DMATS$_{Mo}$	**6-DMATS$_{Sv}$**	**6-DMATS$_{Sa}$**
cyclo-L-Trp-Gly	7.1±0.5	0.8±0.2	1.8±0.3
cyclo-L-Trp-L-Leu	1.3±0.2	1.3±0.1	9.1±1.2
cyclo-L-Trp-L-Trp	2.7±0.3	2.5±0.1	13.3±0.01
cyclo-L-Trp-L-Phe	2.0±0.01	2.3±0.4	6.9±0.8
cyclo-L-Trp-L-Ala	4.4±0.1	0.8±0.01	1.7±0.1
cyclo-L-Trp-L-His	≤0.5	≤0.5	≤0.5
cyclo-L-Trp-L-Tyr	0.9±0.1	1.6±0.1	17.8±14.8
L-Trp	100.0±5.00	100.0±0.1	100.0±10.1

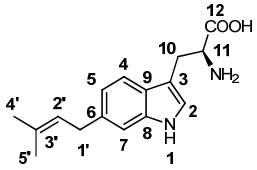
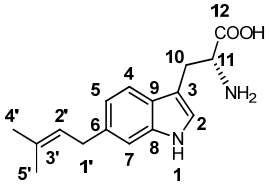
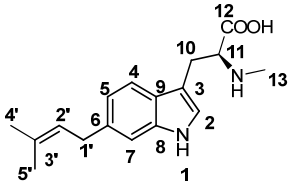
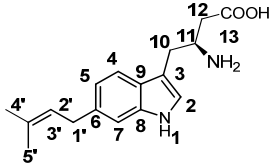
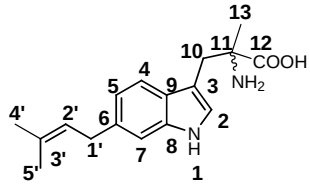
The enzyme assays contained 0.5 mM aromatic substrate and 1 mM DMAPP were incubated at 37 °C for 2 h with 1 µM of the purified protein of 6-DMATS$_{Mo}$, 6-DMATS$_{Sa}$ and 6-DMATS$_{Sv}$, respectively. Relative product yields were measured in duplicate on HPLC with Multospher 120 RP-18 column. The conversion yields of 6-DMATS$_{Mo,}$ 6-DMATS$_{Sv}$ and 6-DMATS$_{Sa}$ with L-tryptophan at 86.6, 99.5 and 90.3 % were defined as 100 % of relative activity, respectively.

Table S4 HR-ESI-MS analysis of the enzyme products of MolI14.36 (6-DMATS$_{Mo}$).

Product	HR-ESI-MS of the prenylated products ([M+H$^+$])		
	Calculated	Measured	Deviation [ppm]
1a-C6	273.1598	273.1601	-1.1
1b-C6	273.1598	273.1590	2.9
2a-C6	287.1754	287.1775	-7.3
3a-C6	287.1754	287.1757	-1.0
4-C6	287.1754	287.1757	-1.0
5-C5, 5-C6, 5-C7	287.1754	287.1768*	-4.9
6-C6, 6-C7	287.1754	287.1766*	-4.2
7-C5, 7-C7	287.1754	287.1768*	-4.9
8-C6	287.1754	287.1762	-2.8
9a-C6	291.1503	291.1519	-5.5

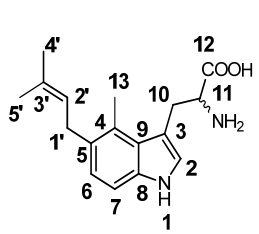
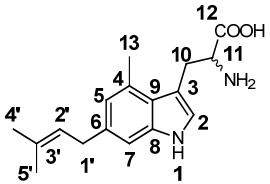
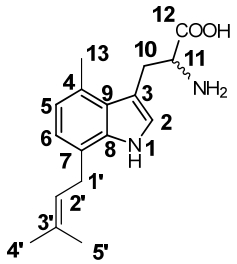
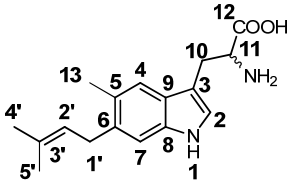
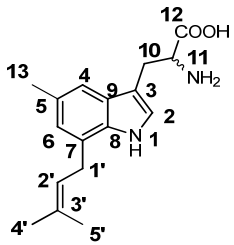
*Mass obtained from a product mixture.

Table S5 ^{1}H NMR data of the enzyme products of 6-DMATS$_{Mo}$ **1a-C6**, **1b-C6**, **2a-C6**, **3a-C6**, and **4-C6** in CD_3OD

Comp	6-DMA-L-Trp (**1a-C6**)	6-DMA-D-Trp (**1b-C6**)	6-DMA-L-abrine (**2a-C6**)	6-DMA-L-β-homo-Trp (**3a-C6**)	6-DMA-α-methyl-DL–Trp (**4-C6**)
					
Pos.	δ_H, *multi*, *J*	δ_H, *multi*, *J*	δ_H, *multi*, *J*	δ_H, *multi*, *J*	δ_H, *multi*, *J*
2	7.12, s	7.13, s	7.14, br s	7.09, s	7.12, s
4	7.59, d, 8.2	7.57, d, 8.1	7.58, dd, 8.2, 0.8	7.49, dd, 8.2, 0.6	7.56, d, 8.2
5	6.89, dd, 8.2, 1.4	6.90, dd, 8.1	6.89, dd, 8.2, 1.5	6.89, dd ,8.2, 1.5	6.88, dd ,8.2, 1.5
7	7.15, d, 1.4	7.16, s	7.14, br s	7.15, dd, 1.5, 0.6	7.14, s
10	3.49, dd, 15.2, 4.0, 0.8	3.49, dd, 15.2, 4.8	3.42, ddd, 15.4, 4.8, 0.8	2.51, dd, 16.7, 4.0	3.12, d, 15.0
	3.12, dd, 15.2, 9.4	3.17, dd, 15.2, 9.0	3.23, ddd, 15.4, 7.8, 0.6	2.34, dd , 16.7, 8.9	3.31-3.36, m*
11	3.84, dd, 9.4, 4.0	3.95, m	3.71, dd, 7.8, 4.8	3.46-3.50, m	-
12	-	-	-	3.02, d, 7.1	-
13	-	-	2.66, s	-	1.51, s
1′	3.41, d, 7.3	3.41, d, 7.3	3.41, d, 7.4	3.42, d, 7.3	3.41, d, 7.4
2′	5.35, tsept, 7.3, 1.4	5.35, tsept, 7.3, 1.4	5.34, tsept, 7.4, 1.5	5.36, tsept, 7.3, 1.5	5.36, tsept, 7.4, 1.5
4′	1.74, br s	1.75, br s	1.74, s	1.75, s	1.75, br s
5′	1.74, br s	1.75, br s	1.74, s	1.75, s	1.75, br s

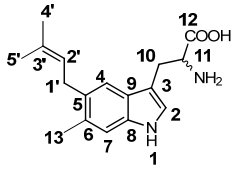
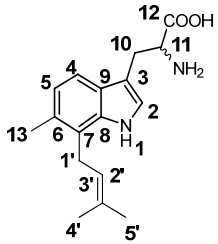
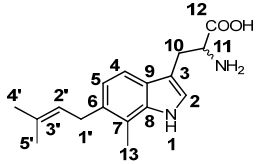
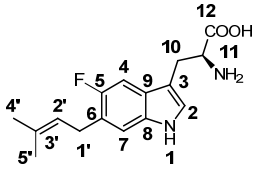
Chemical shifts (δ) are given in ppm and coupling constants (*J*) in Hz. *Signals are overlaying with solvent signal.

Table S6 ^{1}H NMR data of the enzyme products of 6-DMATS$_{Mo}$ **5-C5** - **5-C7**, **6-C6** and **6-C7** in CD_3OD

Comp.	5-DMA-4-methyl-DL-Trp (**5-C5**)	6-DMA-4-methyl-DL-Trp (**5-C6**)	7-DMA-4-methyl-DL-Trp (**5-C7**)	6-DMA-5-methyl-DL-Trp (**6-C6**)	7-DMA-5-methyl-DL-Trp (**6-C7**)
					
Pos.	δ_H, *multi*, *J*	δ_H, *multi*, *J*	δ_H, *multi*, *J*	δ_H, *multi*, *J*	δ_H, *multi*, *J*
2	7.09, s	7.06, s	7.15, s	7.08, s	7.15, s
4	-	-	-	7.47, s	7.35, s
5	-	6.96, s	6.76, d, 7.3	-	-
6	6.90, d, 8.2	-	6.69, d, 7.3	-	6.76, s
7	7.10, d, 8.2	6.60, s	-	7.14, s	-
10	3.53-3.61, m	3.73, m	3.53-3.61, m	3.47, dd, 15.1, 3.8	3.56-3.59, m
	3.02-3.12, m	3.05, dd, 16.0, 11.1	3.02-3.12, m	3.07, dd, 15.1, 9.6	3.07, m
11	3.74-3.82, m	3.73, m	3.74-3.82, m	3.83, dd, 9.6, 3.8	3.5-3.54, m
13	2.58, s	2.69, s	2.70, s	2.36, s	2.40, s
1´	3.30-3.36*	3.34, d, 7.4	3.39, d, 7.1	3.37, d, 7.1	3.35-3.37, m
2´	5.20, tsept, 7.0, 1.5	5.33, tsept, 7.4, 1.5	5.40, tsept, 7.1, 1.5	5.25, tsept, 7.1, 1.6	5.41, m
4´	1.74, br s	1.74, br s	1.74, br s	1.75, s	1.75, s
5´	1.74, br s	1.74, br s	1.74, br s	1.74, s	1.74, s

Chemical shifts (δ) are given in ppm and coupling constants (*J*) in Hz.*Signals are overlaying with solvent signal.

Table S7 ^{1}H NMR data of the enzyme products of 6-DMATS$_{Mo}$ **7-C5**, **7-C7**, **8-C6** and **9a-C6** in CD_3OD.

Comp	5-DMA-6-methyl-DL-Trp (**7-C5**)	7-DMA-6-methyl-DL-Trp (**7-C7**)	6-DMA-7-methyl-DL-Trp (**8-C6**)	6-DMA-5-Fluoro-L-Trp (**9a-C6**)
				
Pos.	δ_H, *multi*, *J*	δ_H, *multi*, *J*	δ_H, *multi*, *J*	δ_H, *multi*, *J*
2	7.14, s	7.13, s	7.14, s	7.17, s
4	7.45, s	7.43, d ,8.2	7.44, d, 8.0	7.36, d, 11.0
5	-	6.89, d, 8.2	6.88, d, 8.0	-
6	-	-	-	-
7	7.07, s	-	-	7.15, d, 6.4
10	3.48-3.52, m	3.48, dd, 15.3, 4.0	3.46-3.64, m	3.39-3.43, m
	3.03-3.09, m	3.10, dd, 15.3, 9.5	3.09, dd, 15.3, 9.4	3.12, dd, 15.3, 9.1
11	3.83, dd, 9.8, 3.9	3.83, dd, 9.5, 4.0	3.81, dd, 9.4, 4.0	3.81, dd, 9.1, 3.9
13	2.34, s	2.34, s	2.39, s	-
1´	3.42, d,7.1	3.56, d, 6.7	3.42, d, 7.2	3.40, d, 7.5
2´	5.24, m	5.09, tsept, 6.7, 1.4	5.20, m	5.32, m
4´	1.78, s	1.83, s	1.77, s	1,74, s
5´	1.73, s	1.68, s	1.71, s	1.73, s

Chemical shifts (δ) are given in ppm and coupling constants (*J*) in Hz

Table S8 ^{1}H NMR data of the enzyme products of 5-DMATS$_{Sc}$ **1b-C5**, **1b-C7**, **1a-C5,C6**, **1a-C5,C7**, and **1b-C5,C6** in CD_3OD

Comp	5-DMA-D-Trp (**1b-C5**)	7-DMA-D-Trp (**1b-C7**)	5,6-di-DMA-L-Trp (**1a-C5,C6**)	5,7-di-DMA-L-Trp (**1a-C5,C7**)	5,6-di-DMA-D-Trp (**1b-C5,C6**)
Pos.	δ_H, *multi, J*	δ_H, *multi, J*	δ_H, *multi, J*	δ_H, *multi, J*	δ_H, *multi, J*
2	7.14, br s	7.19, s	7.08, s	7.15, s	7.10, s
4	7.49, s	7.53, d, 7.1	7.45, s	7.33, br s	7.45, s
5	-	6.98, t, 7.8	-	-	-
6	6.95, dd, 8.5, 1.7	6.91, dd, 7.3	-	6.75, br s	-
7	7.26, d, 8.5	-	7.14, s	-	7.15, s
10	3.50, dd, 15.3, 4.2	3.56, m	3.48, m[a]	3.48, m [a]	3.49, dd, 15.2, 3.9
	3.08, m	3.13, m	3.06, dd, 15.3, 9.6 [b]	3.07, dd, 15.3, 9.6 [b]	3.09, dd, 15.2, 9.6
11	3.84, m	3.81-3.86, m	3.82, dd, 9.6, 4.4	3.82, dd, 9.6, 4.4	3.86, dd, 9.6, 3.9
1′	3.42, m	3.54, d, 7.3	3.42, d, 6.8 [c]	3.39, m [c]	3.42, d, 6.7 [g]
2′	5.38, m	5.42, m	5.25, t, 6.8 [d]	5.36, t, 7.3 [f]	5.24, t, 6.7 [h]
4′	1.73-1.76, m	1.73-1.76, m	1.74, s [e]	1.75, s [e]	1.74, s [i]
5′	1.73-1.76, m	1.73-1.76, m	1.71, s [e]	1.75, s [e]	1.71, s [i]
1”	-	-	3.39, m [c]	3.39, m [c]	3.38, d, 6.8 [g]
2”	-	-	5.27, t, 7.0 [d]	5.41, t, 7.0 [f]	5.25, t, 6.8 [h]
4”	-	-	1.75, s [e]	1.75, s [e]	1.74, s [i]
5”	-	-	1.73, s [e]	1.75, s [e]	1.72, s [i]

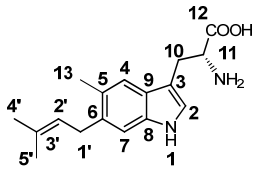
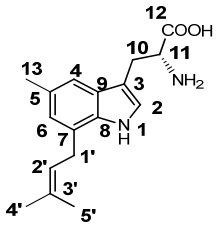
Chemical shifts (δ) are given in ppm and coupling constants (J) in Hz. Signals with the same letters are interchangeable.

Table S9 Conditions for enzyme assays to identify enzyme products of DMATSs.

Substrate	Protein amount of DMATS	Incubation time
1 mM **1a**	0.5 μM FgaPT2 8.5 μM 5-DMATS 1.4 μM 5-DMATS$_{Sc}$ 1.2 μM 6-DMATS$_{Sa}$ 3.1 μM 6-DMATS$_{Sv}$ 4.0 μM 6-DMATS$_{Mo}$ 0.6 μM 7-DMATS	2 h
1 mM **1b**	2.0 μM FgaPT2, 5-DMATS, 5-DMATS$_{Sc}$, 6-DMATS$_{Sa}$, 6-DMATS$_{Sv}$, 6-DMATS$_{Mo}$, 7-DMATS	4 h
0.5 mM **6a**	2.7 μM FgaPT2 3.0 μM 5-DMATS 3.5 μM 5-DMATS$_{Sc}$ 3.7 μM 6-DMATS$_{Sa}$ 3.5 μM 6-DMATS$_{Sv}$ 3.5 μM 6-DMATS$_{Mo}$ 2.8 μM 7-DMATS	16 h
0.5 mM **6b**	3.5 μM 5-DMATS$_{Sc}$ 3.7 μM 6-DMATS$_{Sa}$ 3.5 μM 6-DMATS$_{Sv}$ 3.5 μM 6-DMATS$_{Mo}$ 2.8 μM 7-DMATS	
0.5 mM, **7a**	2.7 μM FgaPT2 3.0 μM 5-DMATS 3.5 μM 5-DMATS$_{Sc}$ 3.5 μM 6-DMATS$_{Sv}$ 3.5 μM 6-DMATS$_{Mo}$ 2.8 μM 7-DMATS	
0.5 mM, **7b**	3.0 μM 5-DMATS 3.5 μM 5-DMATS$_{Sc}$ 3.5 μM 6-DMATS$_{Mo}$	
0.5 mM, **8a**	2.7 μM FgaPT2 3.0 μM 5-DMATS 3.5 μM 5-DMATS$_{Sc}$ 3.5 μM 6-DMATS$_{Sv}$ 3.5 μM 6-DMATS$_{Mo}$	
0.5 mM, **8b**	3.0 μM 5-DMATS 3.5 μM 5-DMATS$_{Sc}$ 3.5 μM 6-DMATS$_{Mo}$	

Enzyme assays of 100μl contained 1 mM DMAPP and 5 mM $CaCl_2$.

Table S10 ^{1}H NMR data of the enzyme products of 5-DMATS$_{Sc}$ **6b-C6** and **6b-C7** in CD_3OD.

Comp	6-DMA-5-methyl-D-Trp (**6b-C6**)	7-DMA-5-methyl-D-Trp (**6b-C7**)
		
Pos.	δ_H, *multi*, *J*	δ_H, *multi*, *J*
2	7.07, s	7.14, s
4	7.47, s	7.34, s
5	-	-
6	-	6.75, s
7	7.13, s	-
10	3.4, dd, 14.9, 3.3 3.08, dd, 14.9, 9.7	3.47-3.52, m 3.08, m
11	3.83, dd, 9.7, 3.3	3.51-3.54, m
13	2.36, s	2.39, s
1′	3.36, d, 7.2	3.38, m
2′	5.25, tsept, 7.2, 1.6	5.34, m
4′	1.74, s	1.74, s
5′	1.73, s	1.73, s

Chemical shifts (δ) are given in ppm and coupling constants (*J*) in Hz.

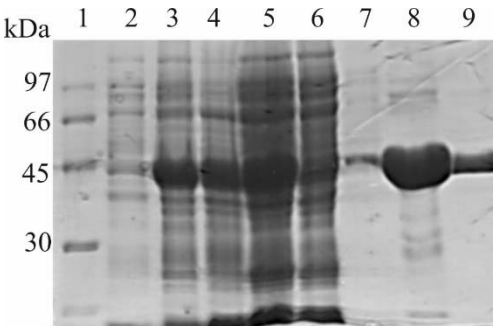


Fig. S1: SDS-PAGE analysis of 6-DMATS$_{Mo}$ from *M. olivasterospora*. Proteins were separated on a 12 % SDS gel and stained with Coomassie Brilliant Blue G-250. Lane 1: molecular mass standard; Lane 2: total protein before IPTG induction; lane 3: total protein after IPTG induction; lane 4: insoluble protein fraction; lane 5: soluble protein fraction; lane 6: flow through fraction; lane 7: wash fraction of Ni-NTA-agarose; lanes 8 and 9: purified His$_8$-tagged recombinant protein.

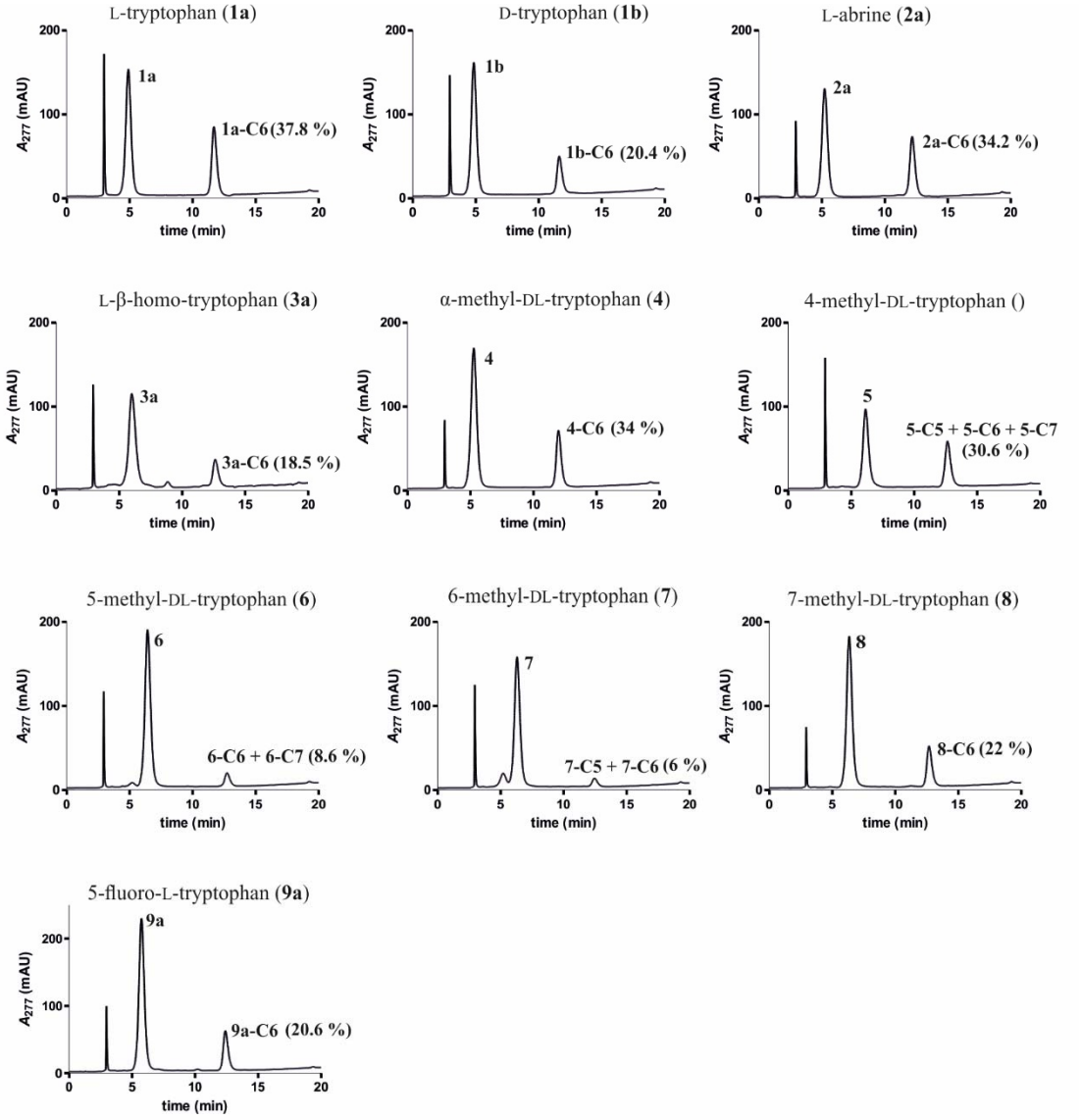


Fig. S2: HPLC analysis of the reaction mixtures of 6-DMATS$_{Mo}$ with L-tryptophan and analogs. For conditions see legends of Table S2. A Multospher 120 RP-18 column was used and an absorption at 277 nm was illustrated. Product yields are given in parentheses after product numbers.

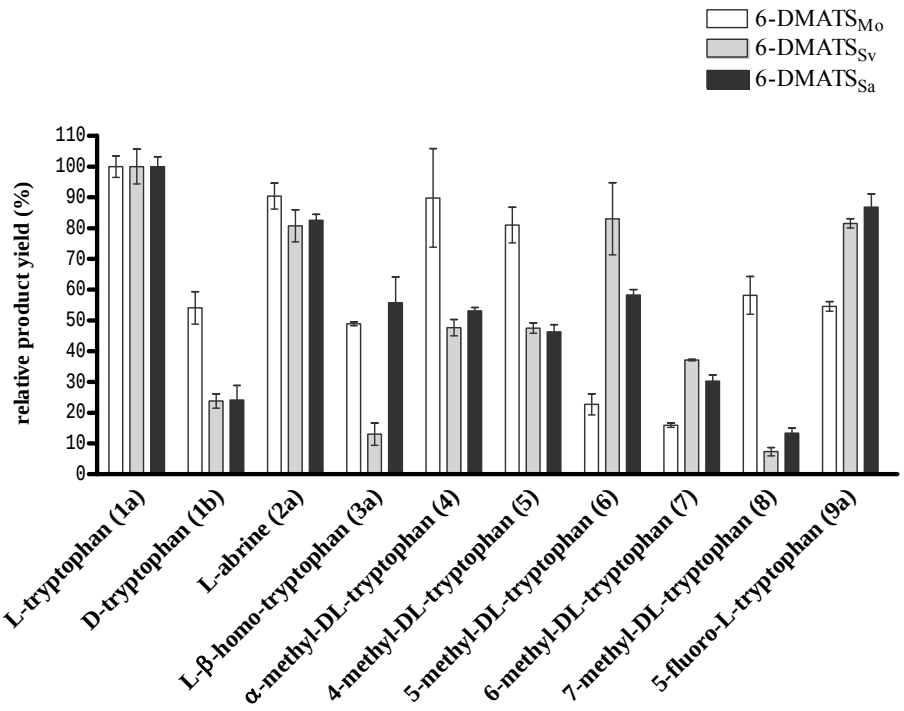


Fig. S3: Comparison of the substrate preferences of 6-DMATS$_{Mo}$, 6-DMATS$_{Sa}$, and 6-DMATS$_{Sv}$ towards tryptophan and analogs. The reaction mixtures contained 0.5 mM aromatic substrate and 1 mM DMAPP were incubated with 1 μM 6-DMATS$_{Mo}$, 6-DMATS$_{Sa}$, or 6-DMATS$_{Sv}$ at 37 °C for 1 h. Relative product yields were measured in duplicate on HPLC with Multospher 120 RP-18 column.

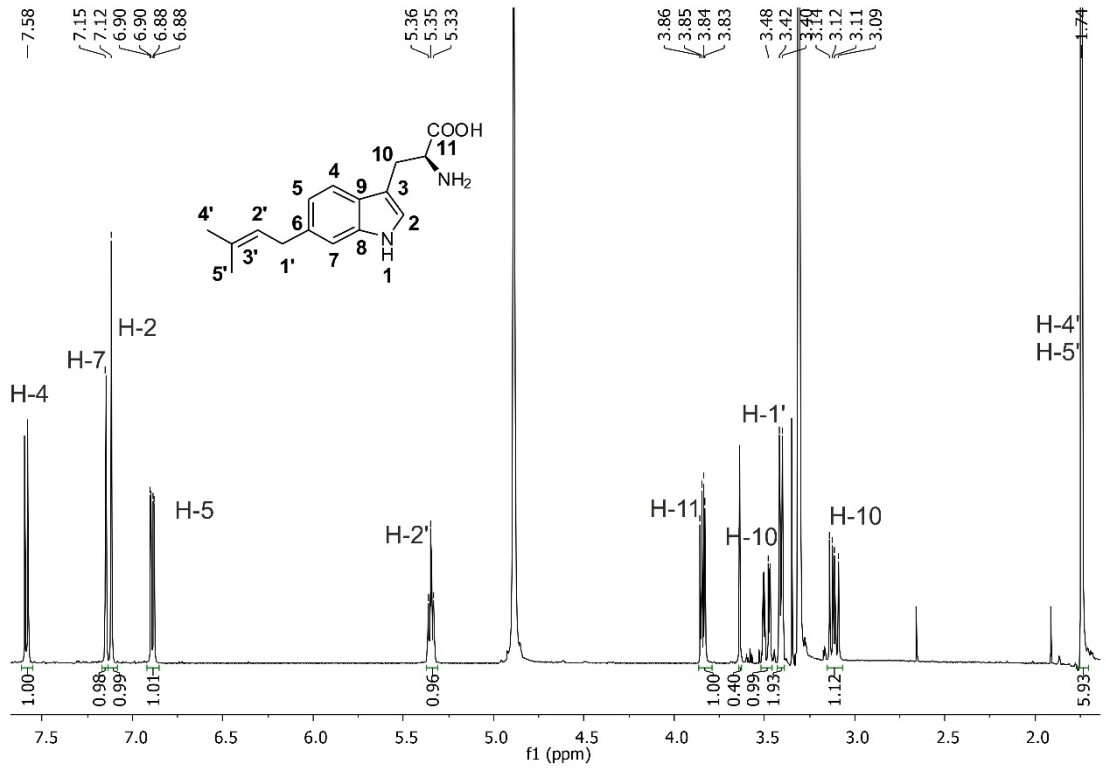


Fig. S4 ^{1}H NMR spectrum of **1a-C6** in CD_3OD (500MHz)

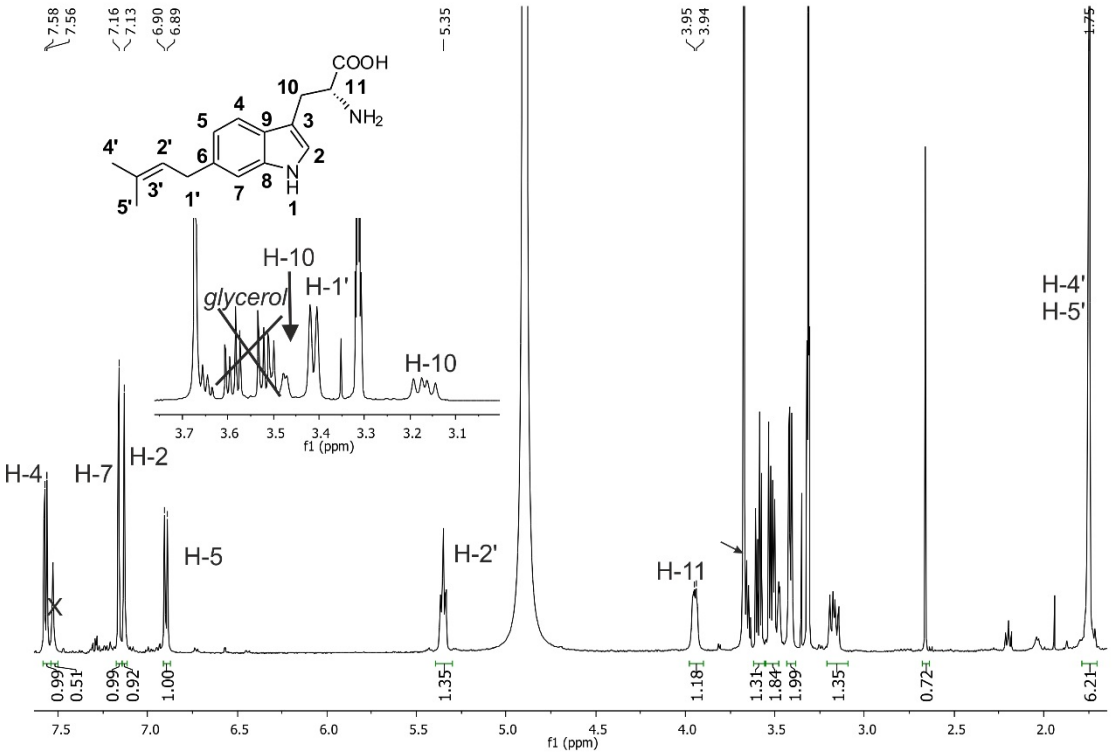


Fig. S5 ^{1}H NMR spectrum of **1b-C6** in CD_3OD (500MHz)

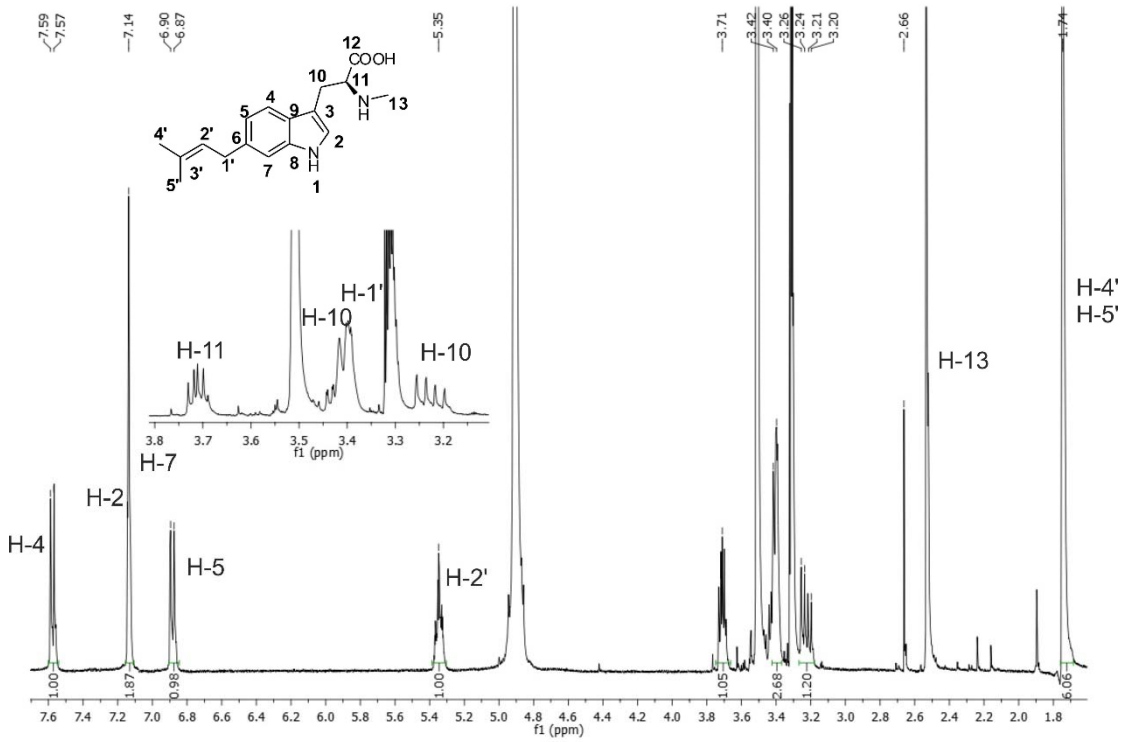


Fig. S6 ^{1}H NMR spectrum of **2a-C6** in CD_3OD (400MHz)

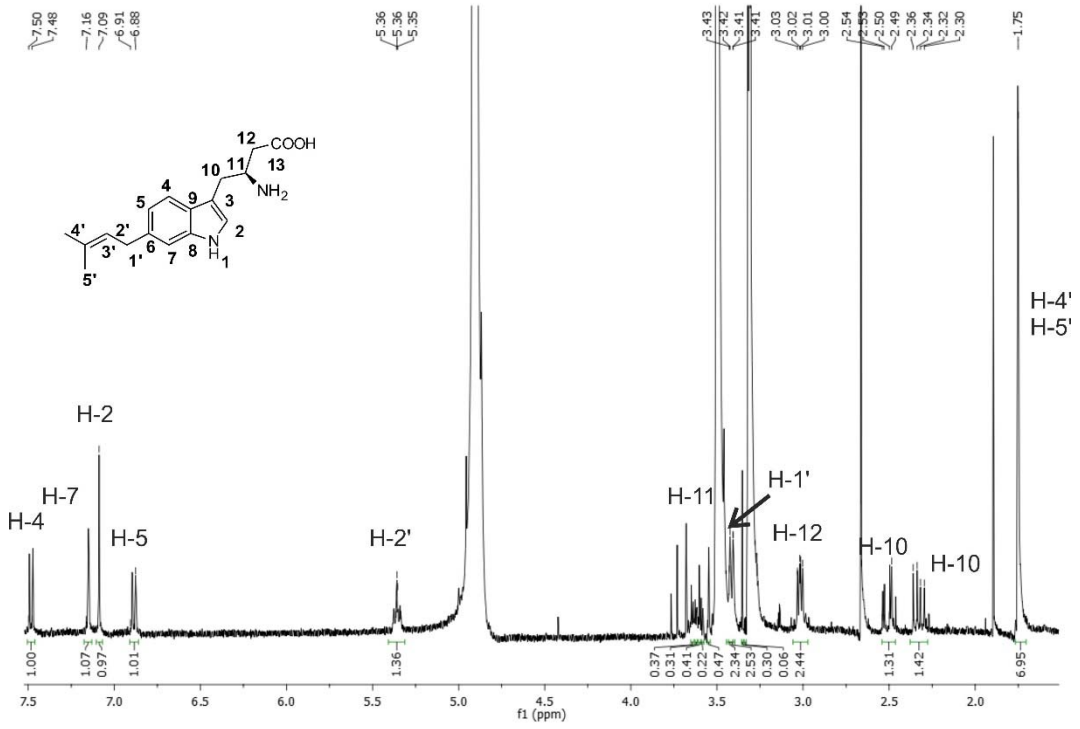


Fig. S7 ^{1}H NMR spectrum of **3a-C6** in CD_3OD (400MHz)

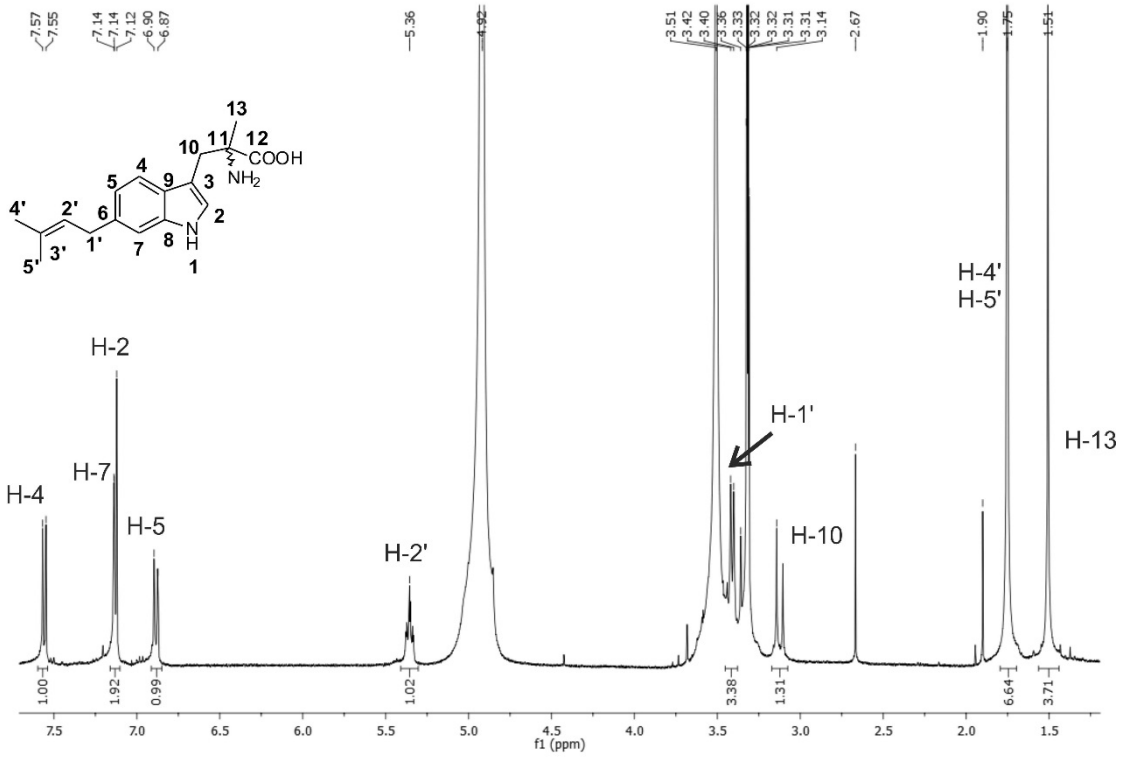


Fig. S8 ^{1}H NMR spectrum of **4-C6** in CD_3OD (400MHz)

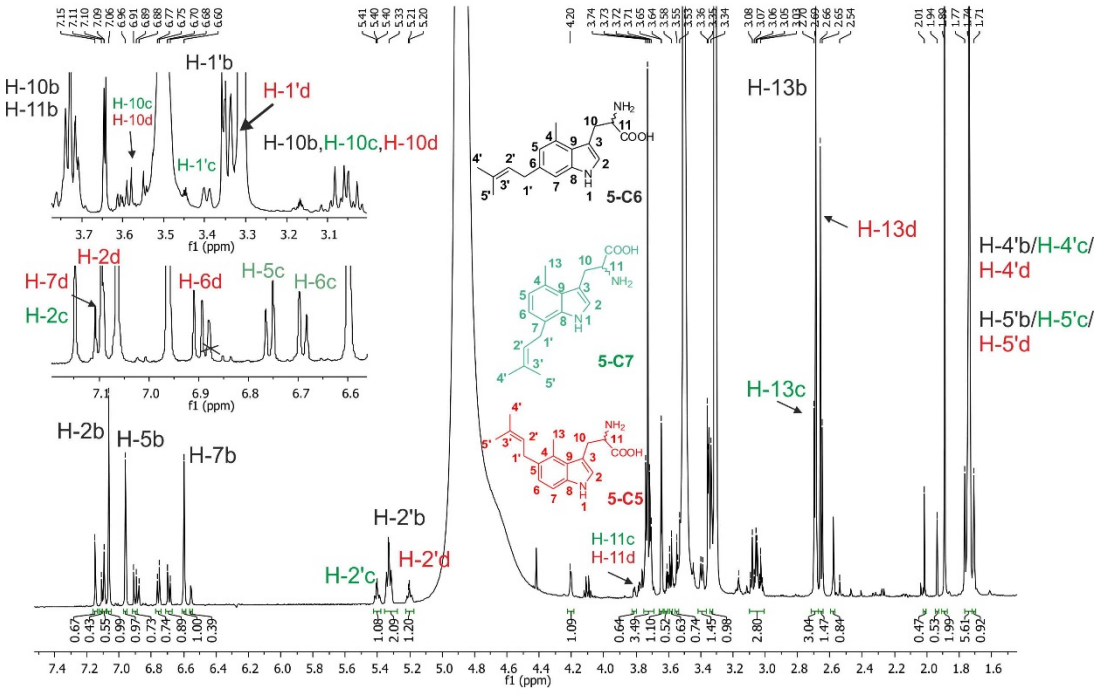


Fig. S9 ^{1}H NMR spectrum of **5-C5**, **5-C6**, and **5-C7** as a mixture in CD_3OD (500MHz)

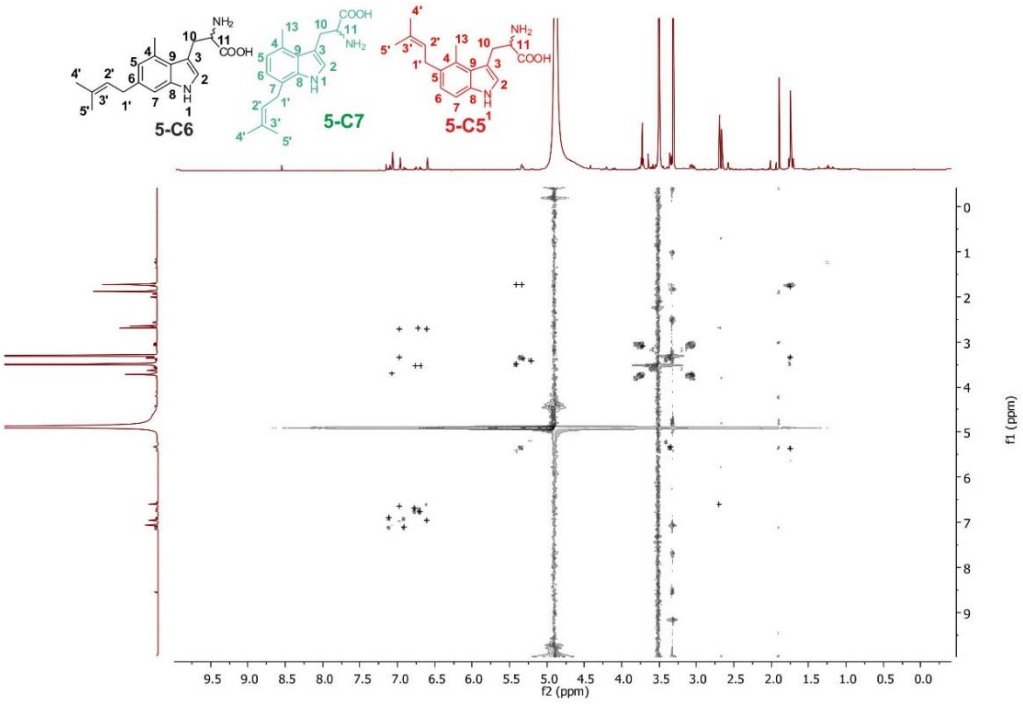


Fig. S10 ^{1}H-^{1}H COSY spectrum of **5-C5, 5-C6,** and **5-C7** as a mixture in CD_3OD (500MHz) (1)

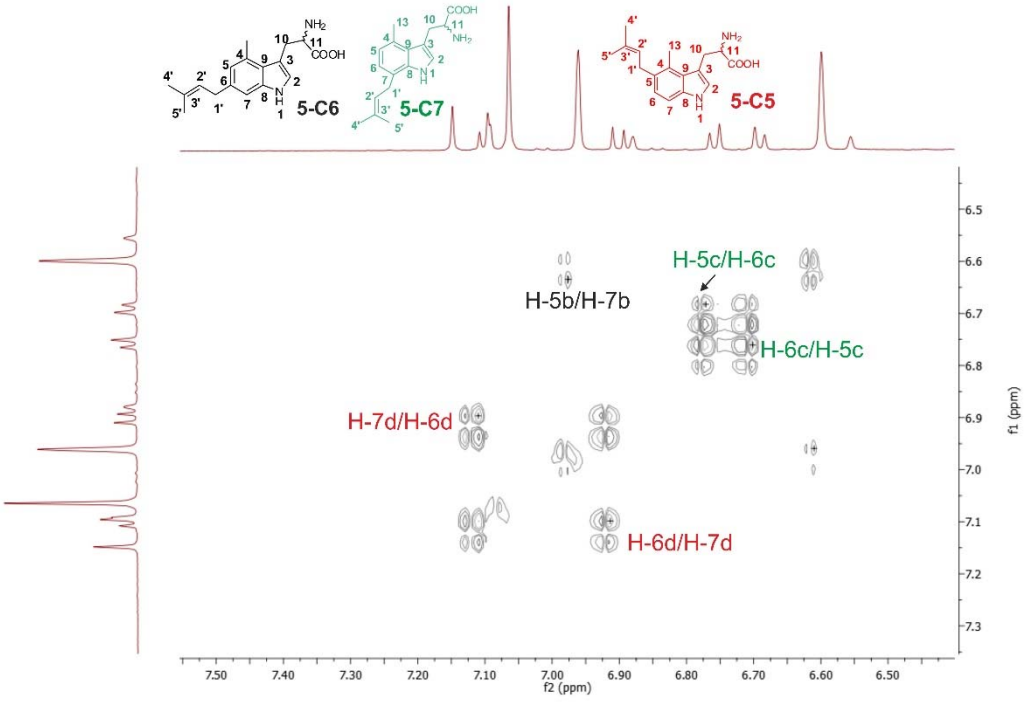


Fig. S11 ^{1}H-^{1}H COSY spectrum of **5-C5, 5-C6,** and **5-C7** as a mixture in CD_3OD (500MHz) (2)

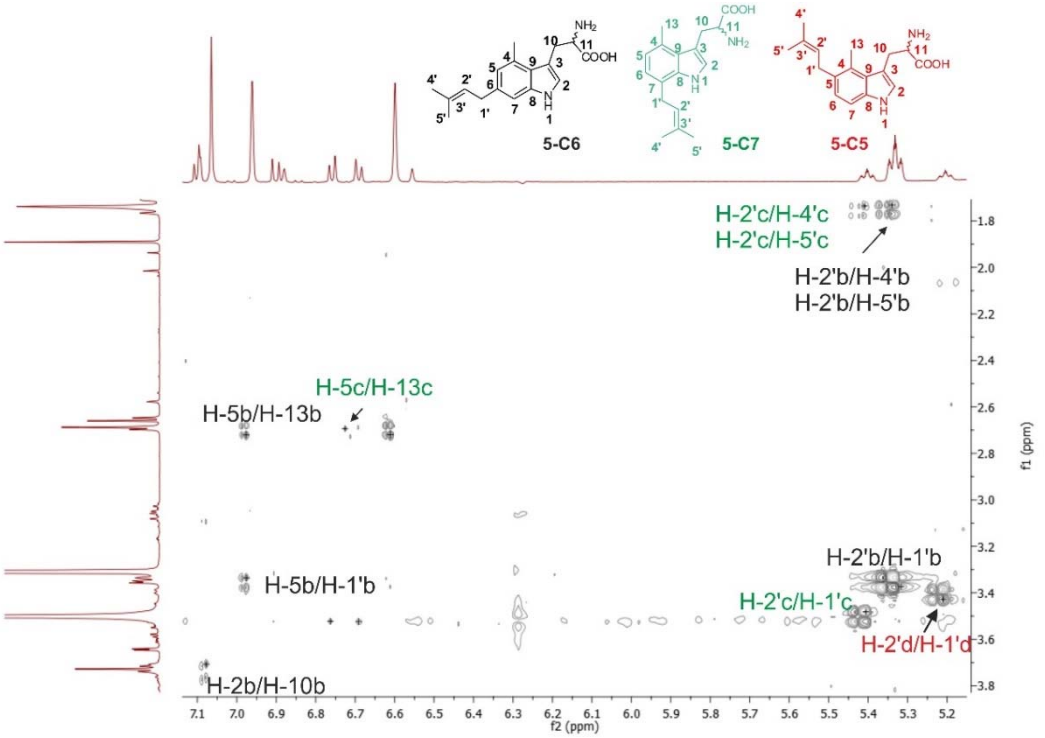


Fig. S12 ^{1}H-^{1}H COSY spectrum of **5-C5**, **5-C6**, and **5-C7** as a mixture in CD_3OD (500MHz) (3)

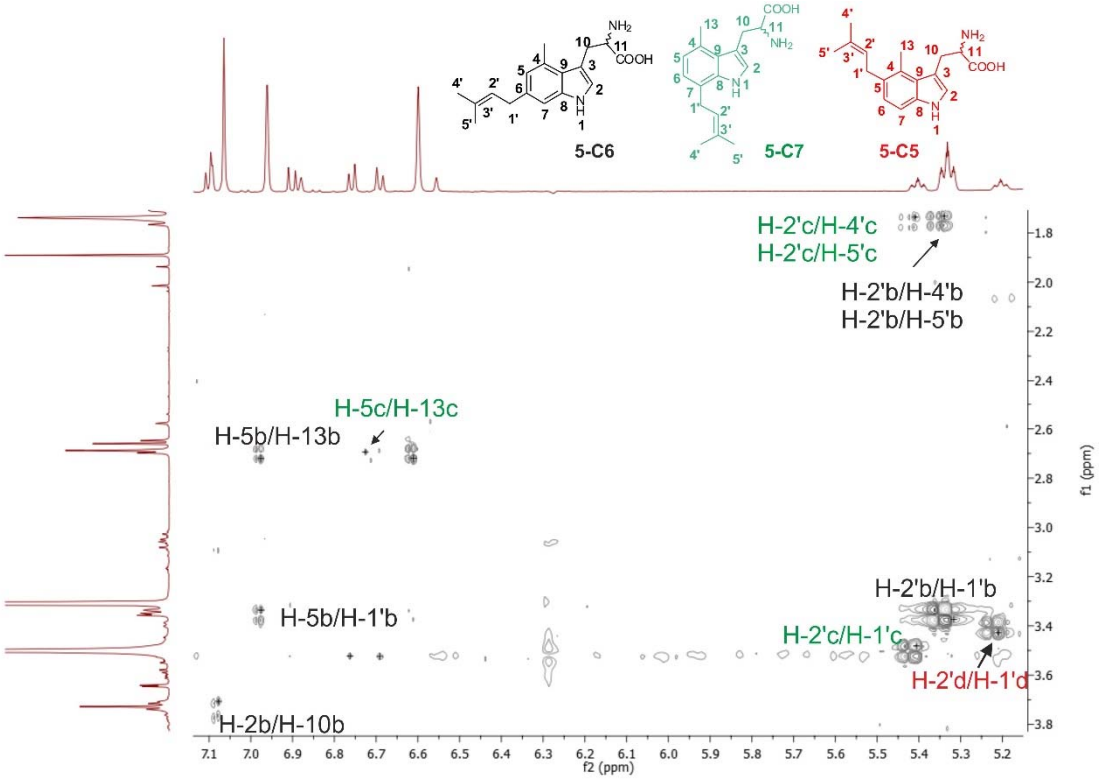


Fig. S13 ^{1}H-^{1}H COSY spectrum of **5-C5, 5-C6,** and **5-C7** as a mixture in CD_3OD (500MHz) (4)

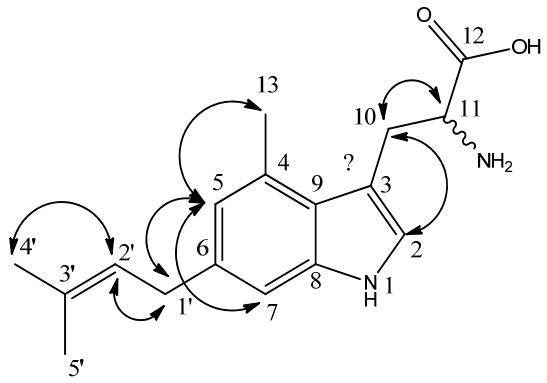


Fig. S14 Selected ^{1}H-^{1}H COSY connectivities of **5-C6**

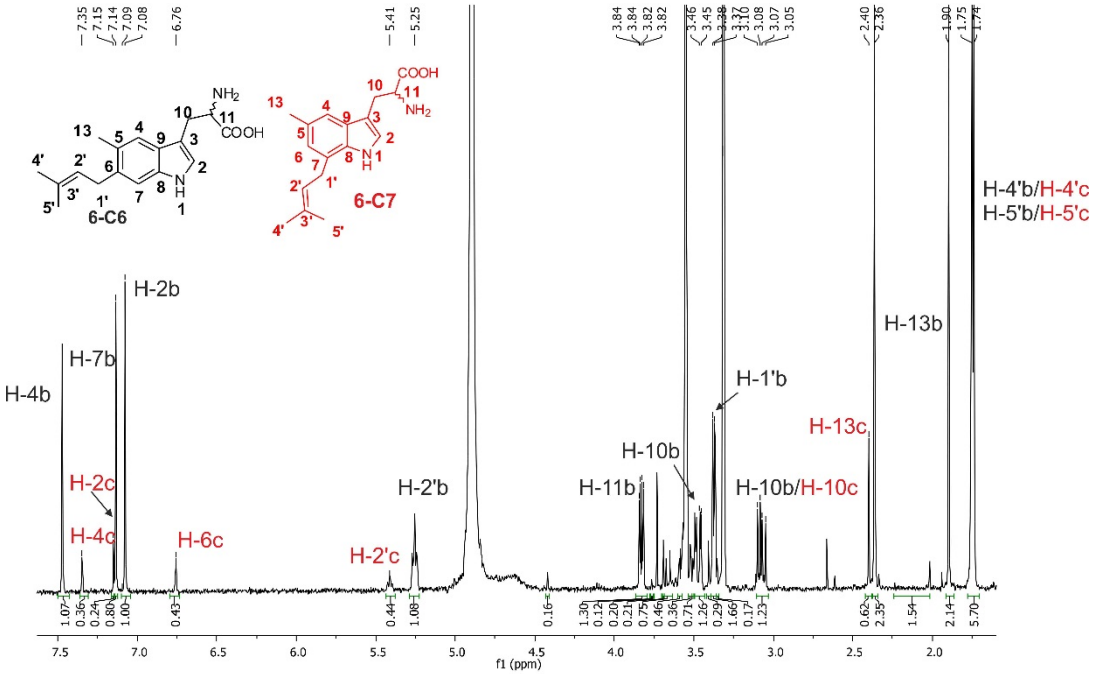


Fig. S15 ^{1}H NMR spectrum of the mixture of **6-C6** and **6-C7** in CD_3OD (500MHz)

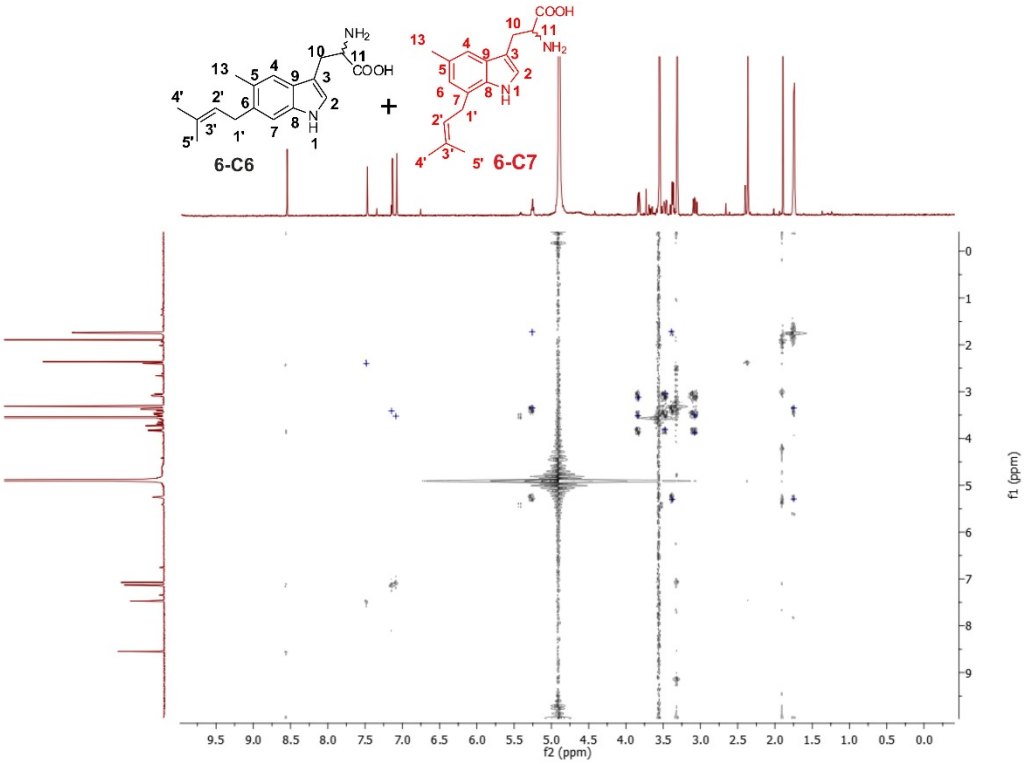


Fig. S16 ^{1}H-^{1}H COSY spectrum of the mixture of **6-C6** and **6-C7** in CD_3OD (500MHz) (1)

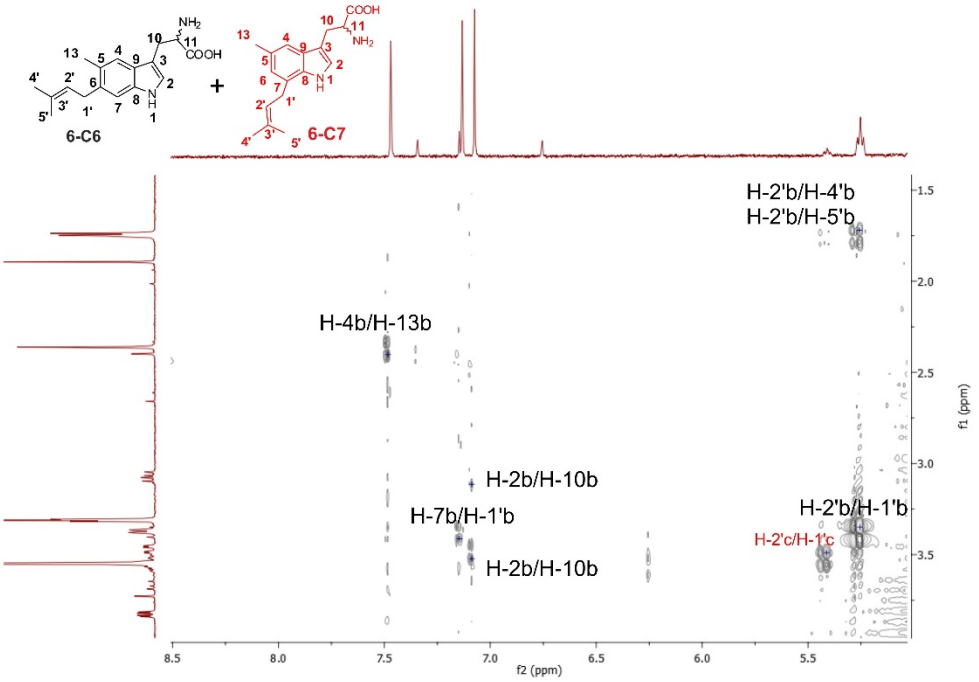


Fig. S17 ^{1}H-^{1}H COSY spectrum of the mixture of **6-C6** and **6-C7** in CD_3OD (500MHz) (2)

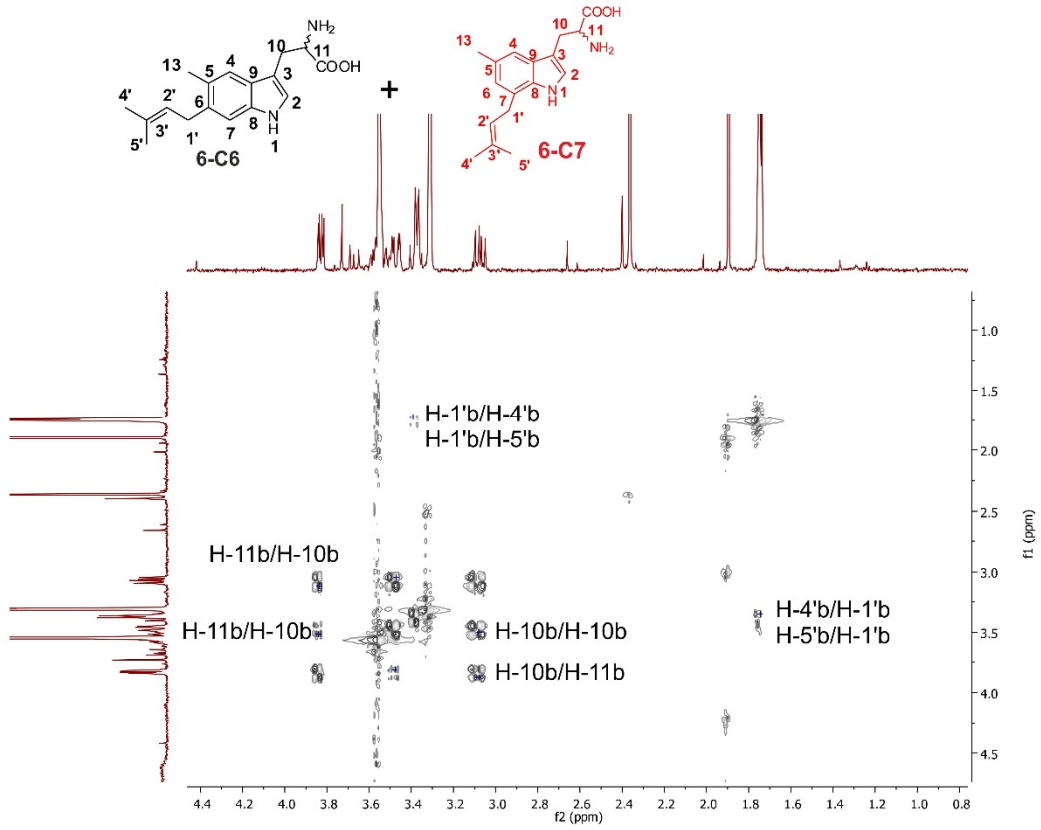


Fig. S18 ^{1}H-^{1}H COSY spectrum of the mixture of **6-C6** and **6-C7** in CD_3OD (500MHz) (3)

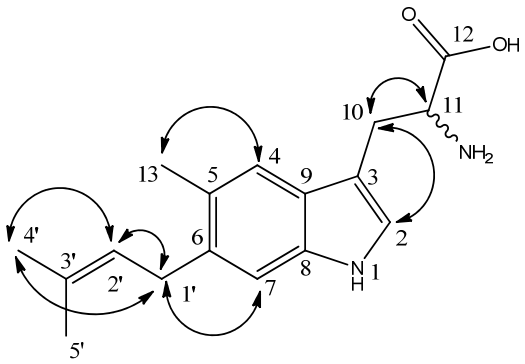


Fig. S19 Selected ^{1}H-^{1}H COSY connectivities of **6-C6**

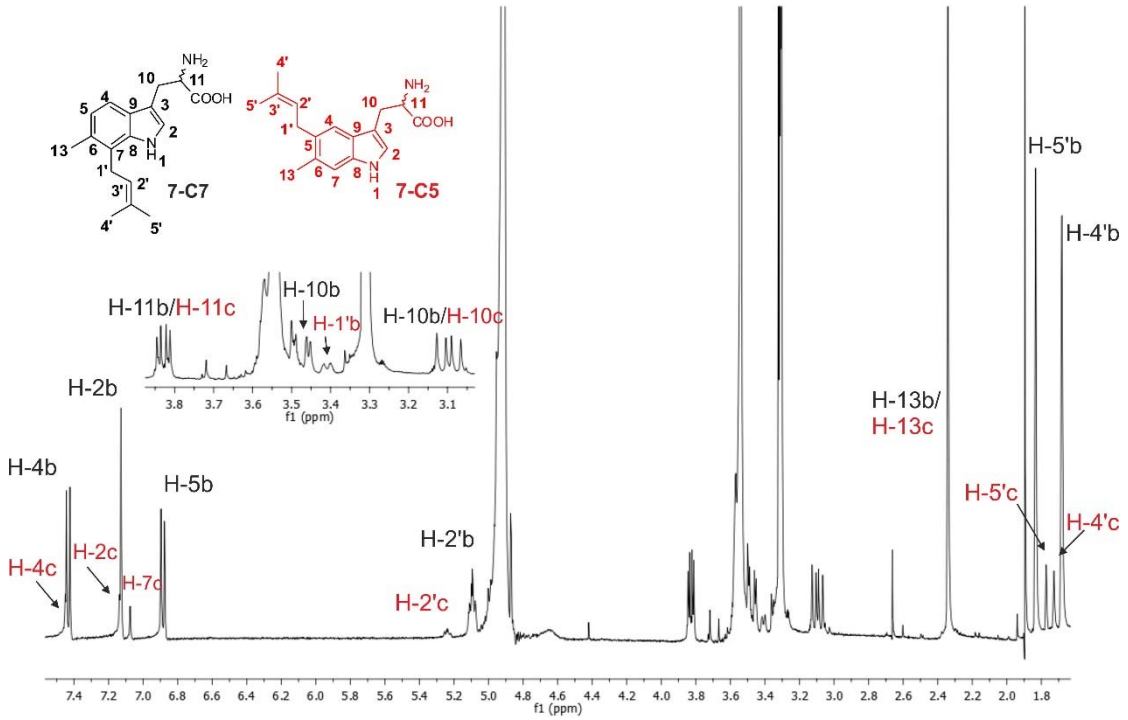


Fig. S20 ^{1}H NMR spectrum of the mixture of **7-C5** and **7-C7** in CD_3OD (400MHz)

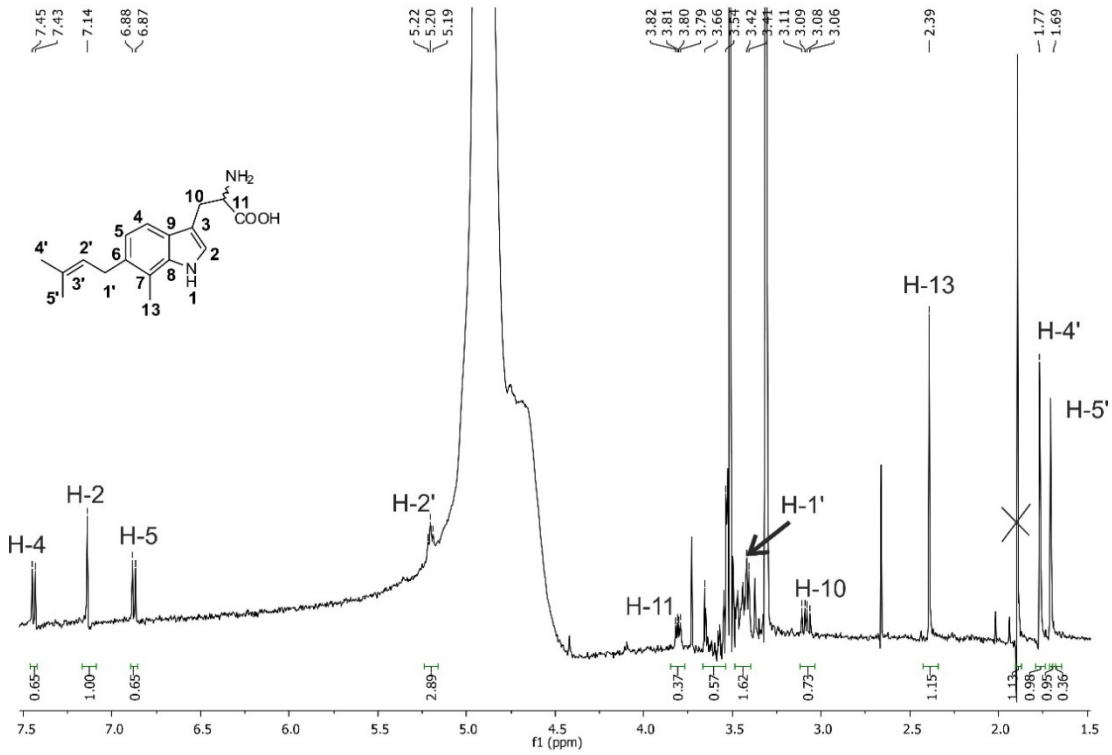


Fig. S21 ^{1}H NMR spectrum of **8-C6** in CD_3OD (500MHz)

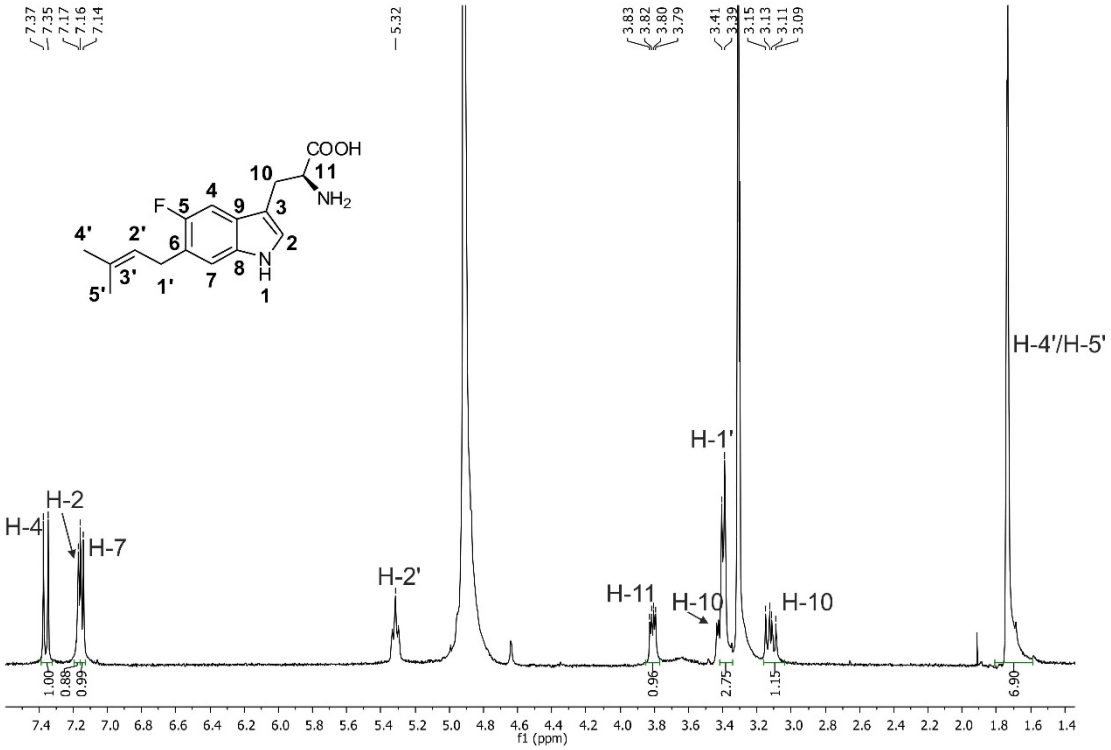


Fig. S22 ^{1}H NMR spectrum of **9a-C6** in CD_3OD (400MHz)

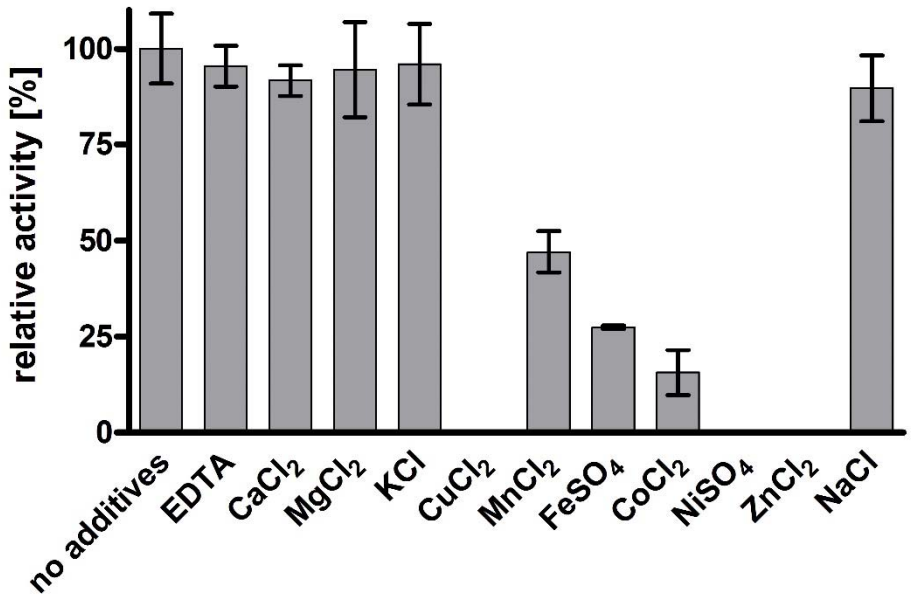


Fig. S23 Ion dependency of the 6-DMATS$_{Mo}$ reaction.
The enzyme assays containing 1 mM L-tryptophan, 1 mM DMAPP, 5 mM metal ions and were incubated with 1 μM of the recombinant protein for 1.5 h. The enzyme activity without additives was defined as 100 %.

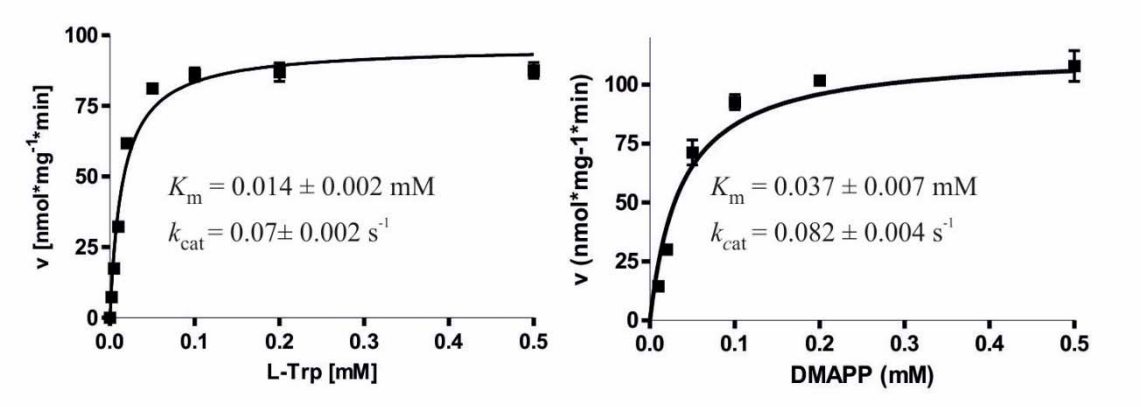


Fig. S24 Determination of the kinetic parameters of 6-DMATS$_{Mo}$ towards L-tryptophan and DMAPP. Reaction mixtures contained 229.9 nM 6-DMATS$_{Mo}$, 5 mM $MgCl_2$ and were incubated for 30 min at 37 °C. 1 mM L-tryptophan and 1 mM DMAPP were used for determination of the kinetic parameters of DMAPP and L-tryptophan, respectively.

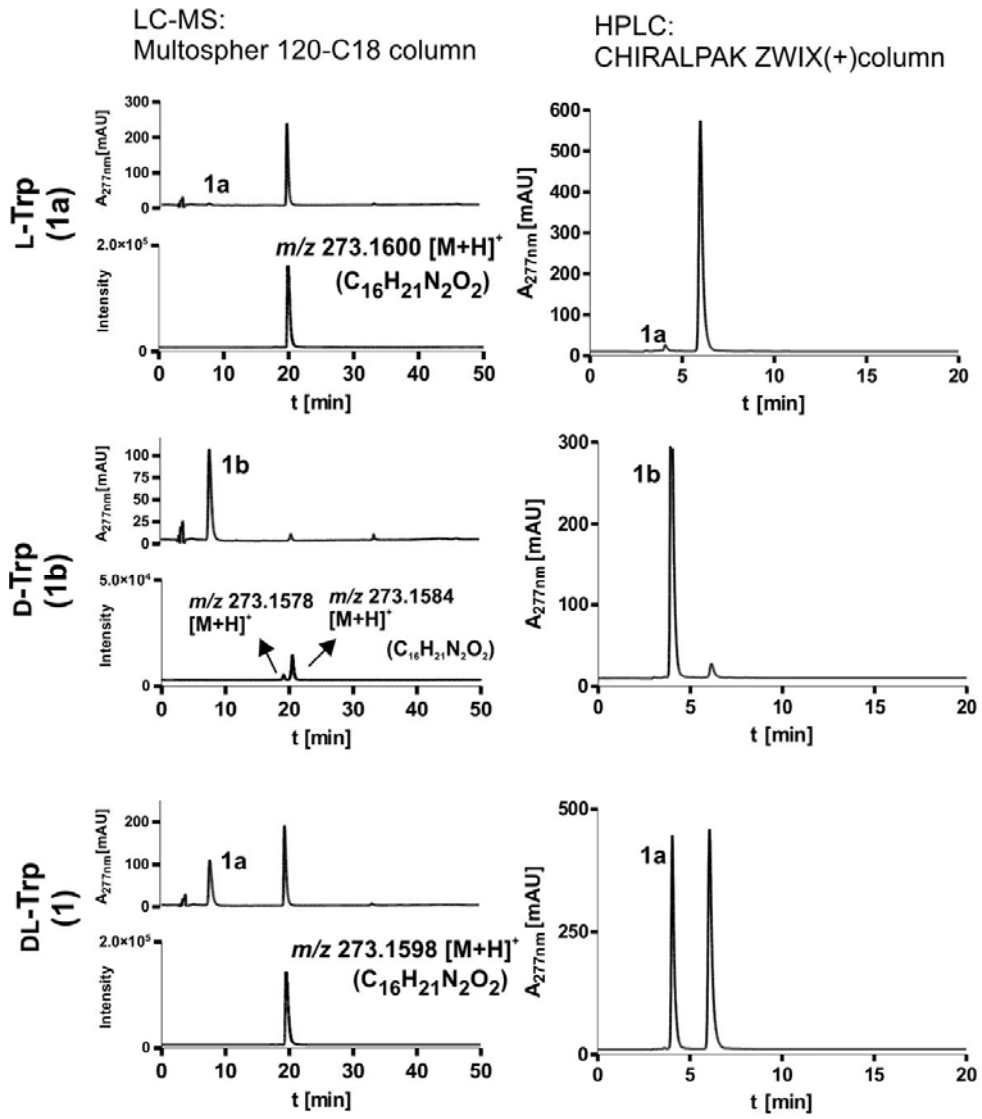


Fig. S25 LC-MS and HPLC analyses of the enzyme assays of tryptophan with FgaPT2. The enzyme assays contained 1 mM DMAPP, 1 µM purified protein, and 0.5 mM of L- or D-isomer, or 1 mM of their racemate and were incubated at 37 °C for 1.5 h. UV-detection was carried out on a Diode Array detector and illustrated for absorption at 277 nm.

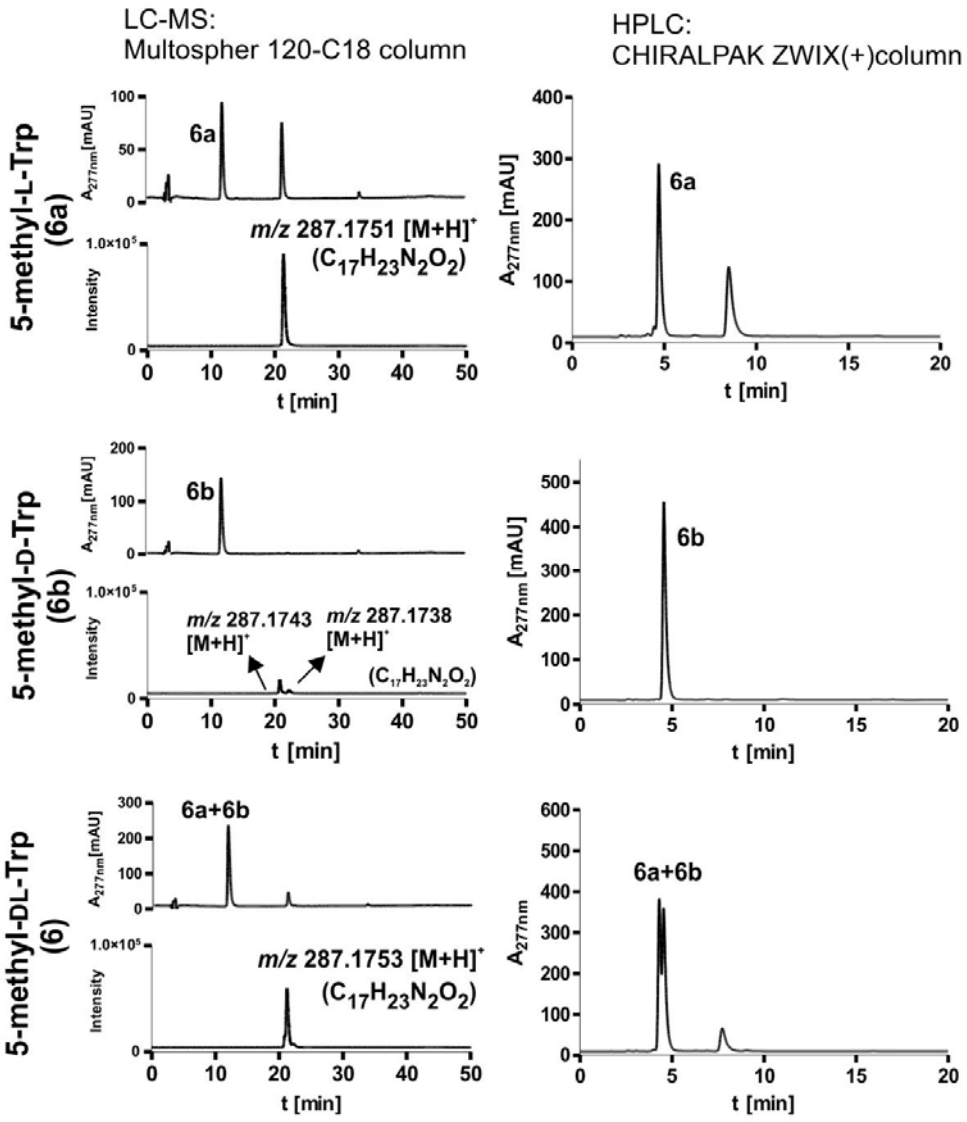


Fig. S26 LC-MS and HPLC analyses of the enzyme assays of 5-methyltryptophan with FgaPT2. The enzyme assays contained 1 mM DMAPP, 1 μM purified protein, and 0.5 mM of L- or D-isomer, or 1 mM of their racemate were incubated at 37 °C for 1.5 h. UV-detection was carried out on a Diode Array detector and illustrated for absorption at 277 nm.

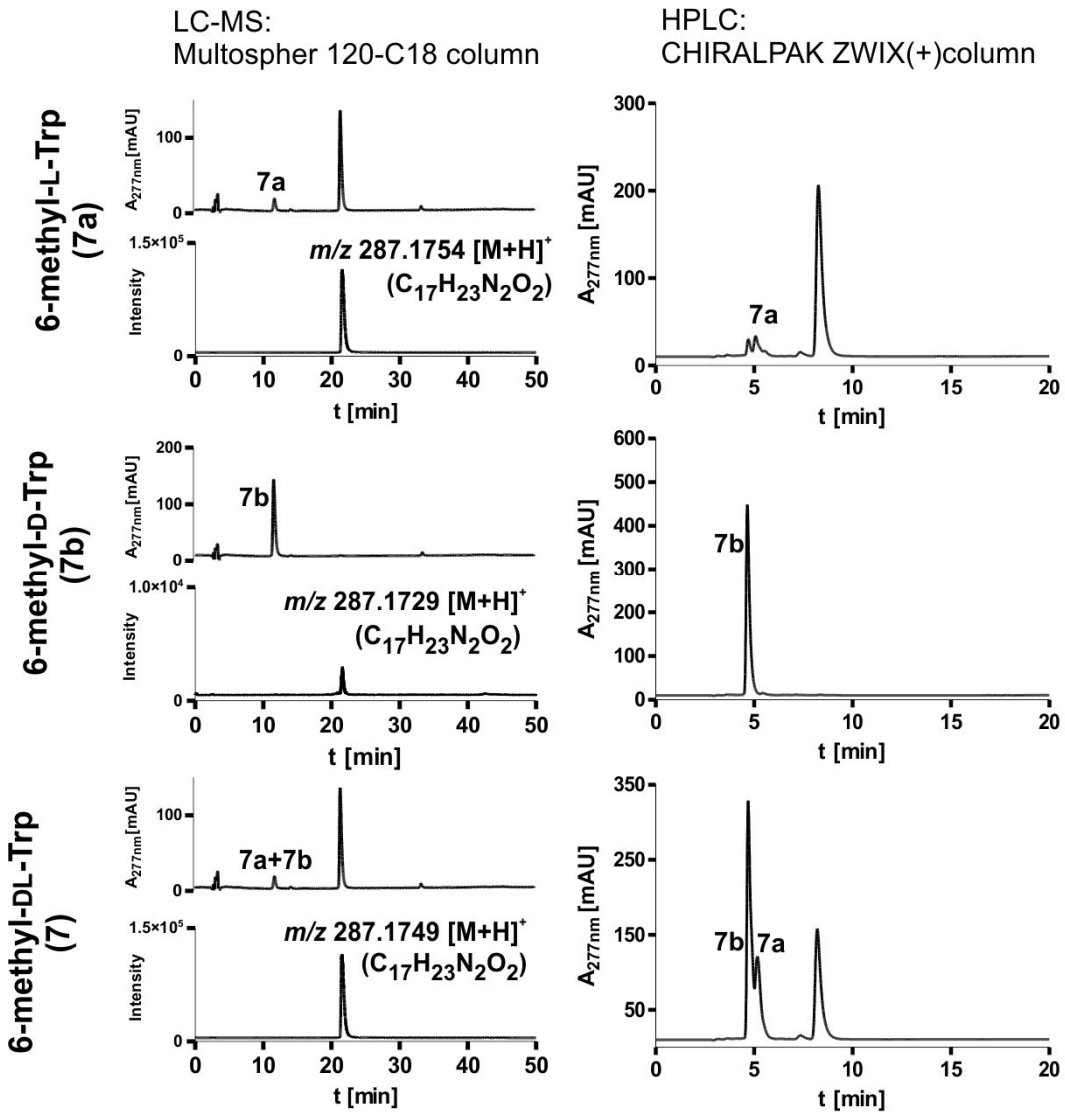


Fig. S27 LC-MS and HPLC analyses of the enzyme assays of 6-methyltryptophan with FgaPT2. The enzyme assays contained 1 mM DMAPP, 1 μM purified protein, and 0.5 mM of L- or D-isomer, or 1 mM of their racemate were incubated at 37 °C for 1.5 h. UV-detection was carried out on a Diode Array detector and illustrated for absorption at 277 nm.

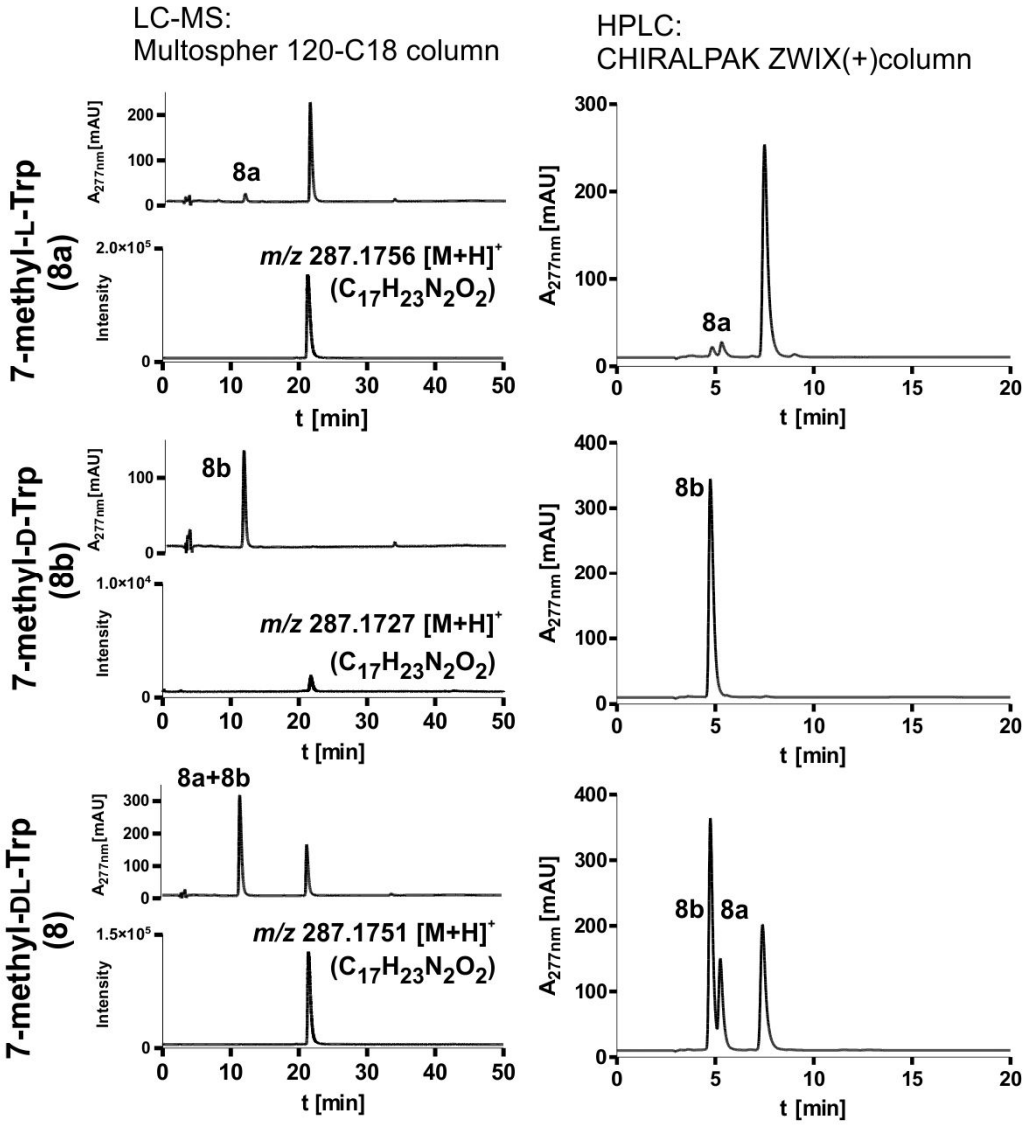


Fig. S28 LC-MS and HPLC analyses of the enzyme assays of 7-methyltryptophan with FgaPT2. The enzyme assays contained 1 mM DMAPP, 1 μM purified protein, and 0.5 mM of L- or D-isomer, or 1 mM of their racemate were incubated at 37 °C for 1.5 h. UV-detection was carried out on a Diode Array detector and illustrated for absorption at 277 nm.

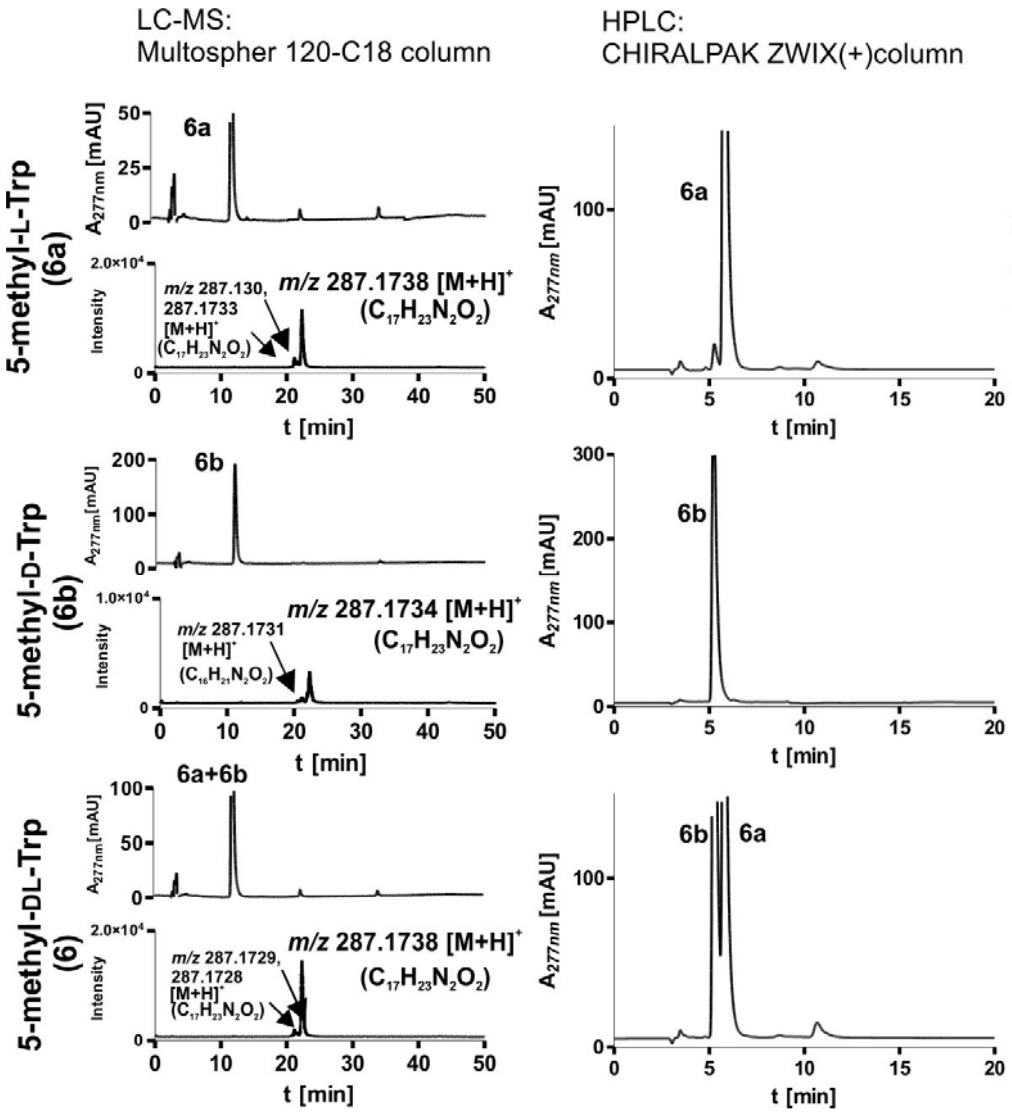


Fig. S29 LC-MS and HPLC analyses of the enzyme assays of 5-methyltryptophan with 5-DMATS. The enzyme assays contained 1 mM DMAPP, 1 μM purified protein, and 0.5 mM of L- or D-isomer, or 1 mM of their racemate were incubated at 37 °C for 1.5 h. UV-detection was carried out on a Diode Array detector and illustrated for absorption at 277 nm.

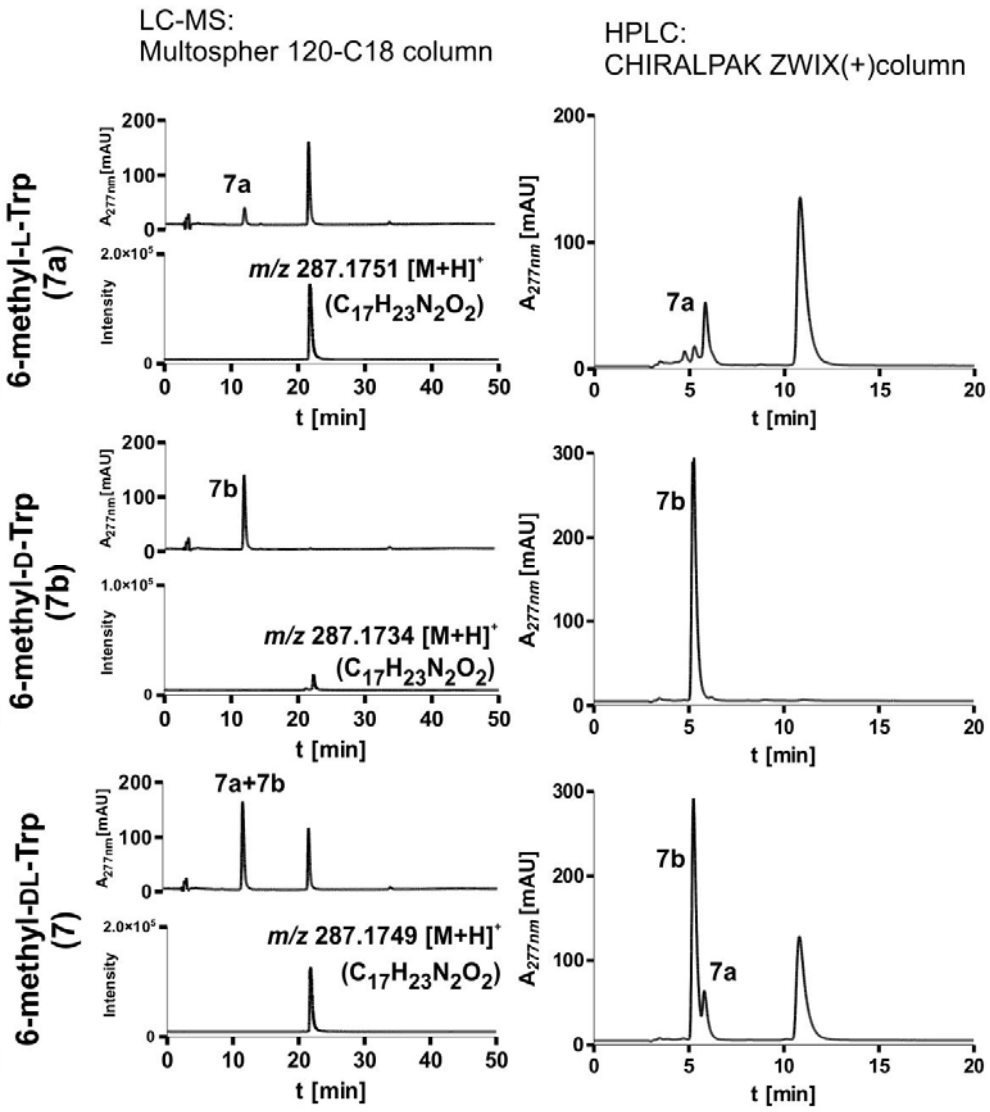


Fig. S30 LC-MS and HPLC analyses of the enzyme assays of 6-methyltryptophan with 5-DMATS. The enzyme assays contained 1 mM DMAPP, 1 μM purified protein, and 0.5 mM of L- or D-isomer, or 1 mM of their racemate were incubated at 37 °C for 1.5 h. UV-detection was carried out on a Diode Array detector and illustrated for absorption at 277 nm.

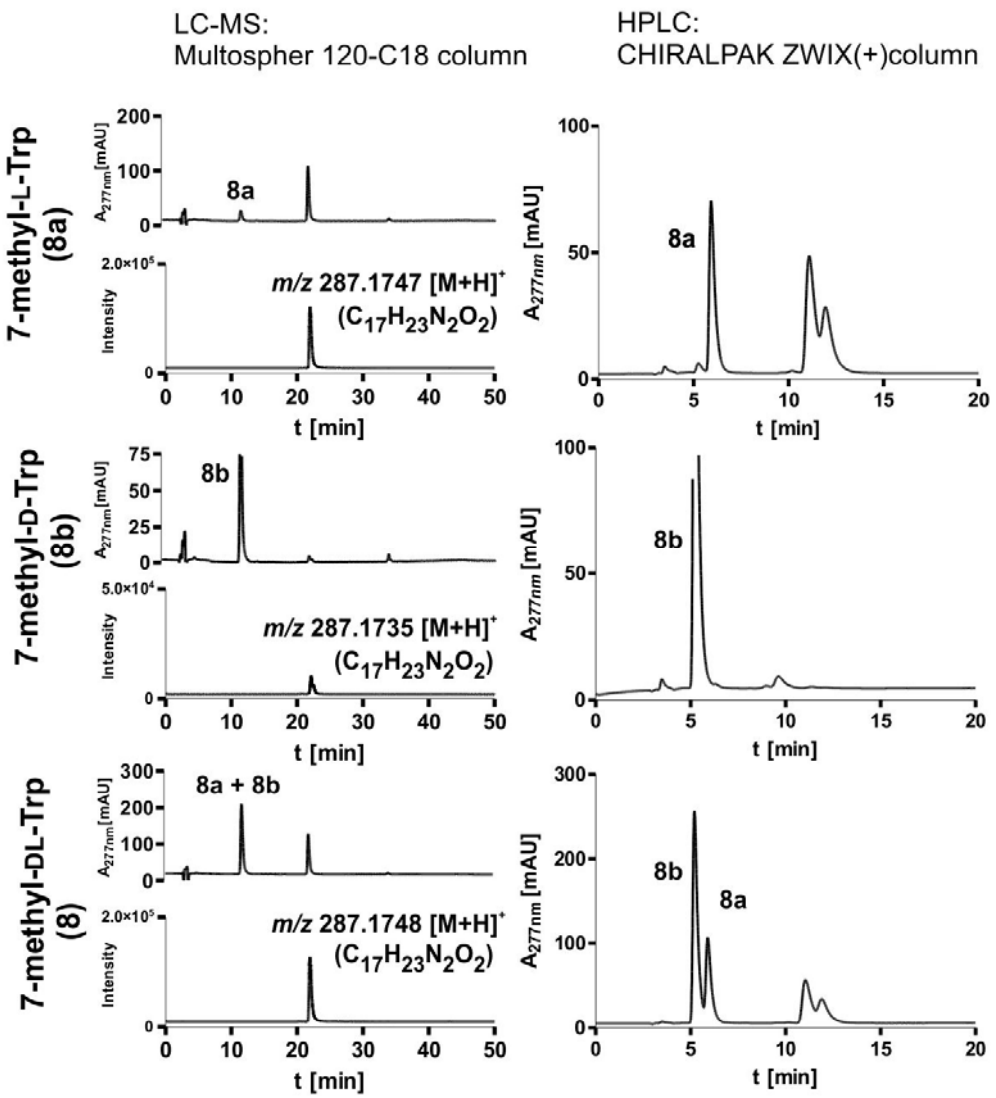


Fig. S31 LC-MS and HPLC analyses of the enzyme assays of 7-methyltryptophan with 5-DMATS. The enzyme assays contained 1 mM DMAPP, 1 µM purified protein, and 0.5 mM of L- or D-isomer, or 1 mM of their racemate were incubated at 37 °C for 1.5 h. UV-detection was carried out on a Diode Array detector and illustrated for absorption at 277 nm.

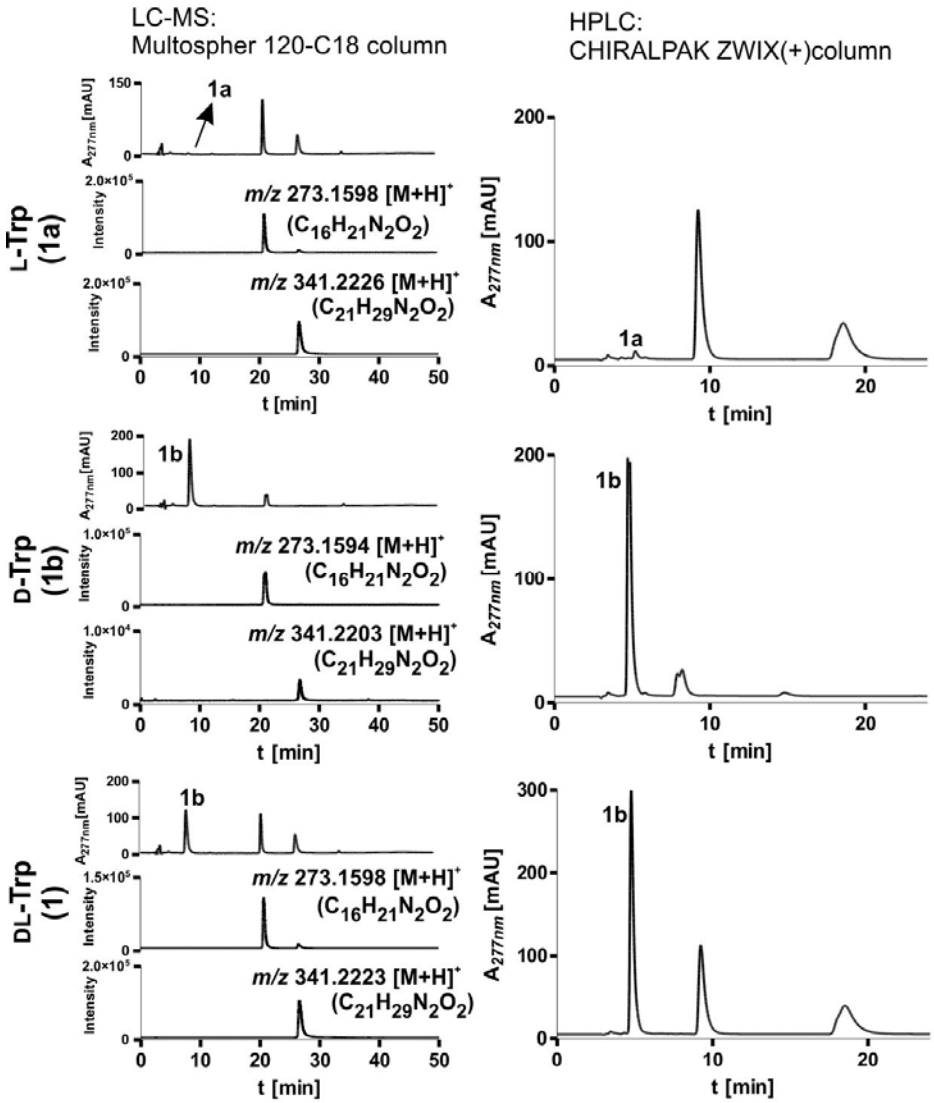


Fig. S32 LC-MS and HPLC analyses of the enzyme assays of tryptophan with 5-DMATS$_{Sc}$. The enzyme assays contained 1 mM DMAPP, 1 µM purified protein, and 0.5 mM of L- or D-isomer, or 1 mM of their racemate were incubated at 37 °C for 1.5 h. UV-detection was carried out on a Diode Array detector and illustrated for absorption at 277 nm.

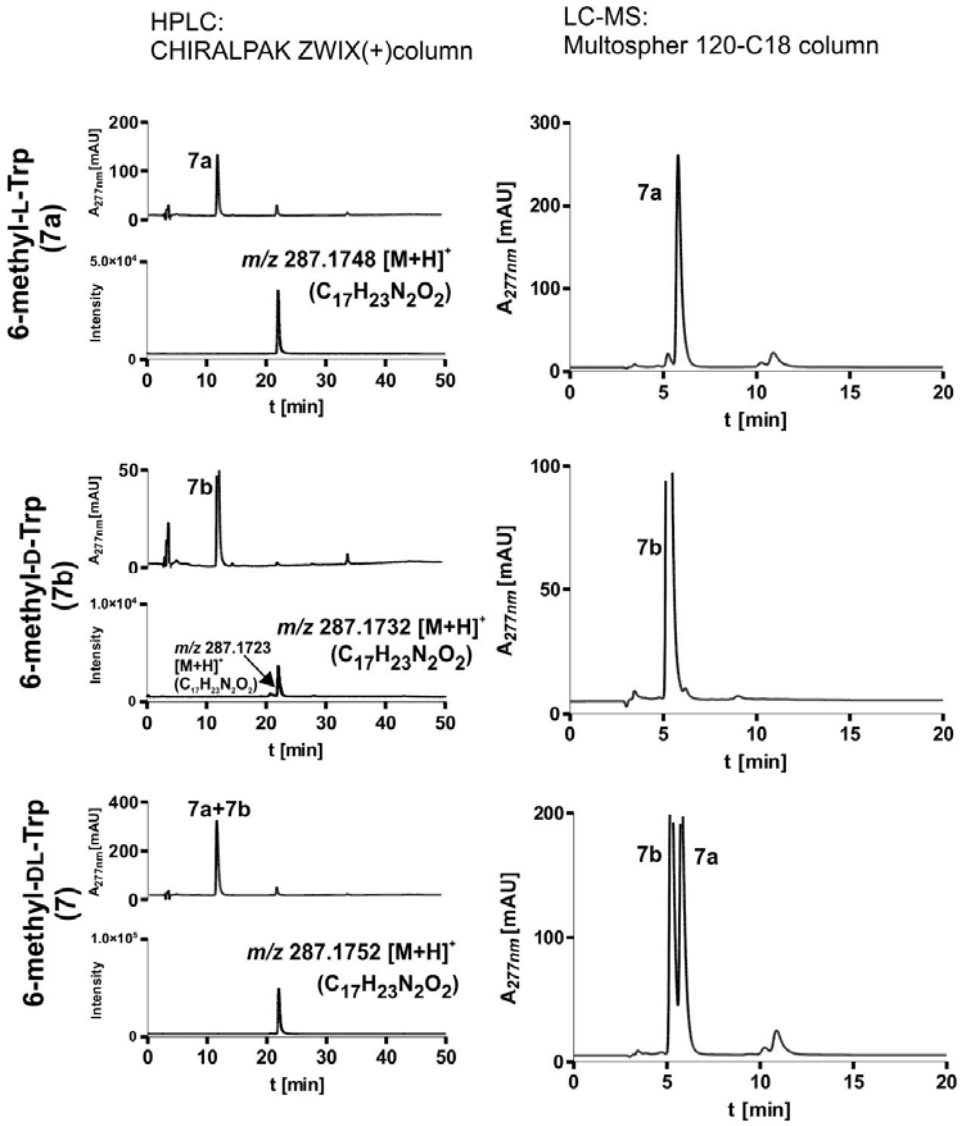


Fig. S33 LC-MS and HPLC analyses of the enzyme assays of 6-methyltryptophan with 5-DMATS$_{Sc}$. The enzyme assays contained 1 mM DMAPP, 1 µM purified protein, and 0.5 mM of L- or D-isomer, or 1 mM of their racemate were incubated at 37 °C for 1.5 h. UV-detection was carried out on a Diode Array detector and illustrated for absorption at 277 nm.

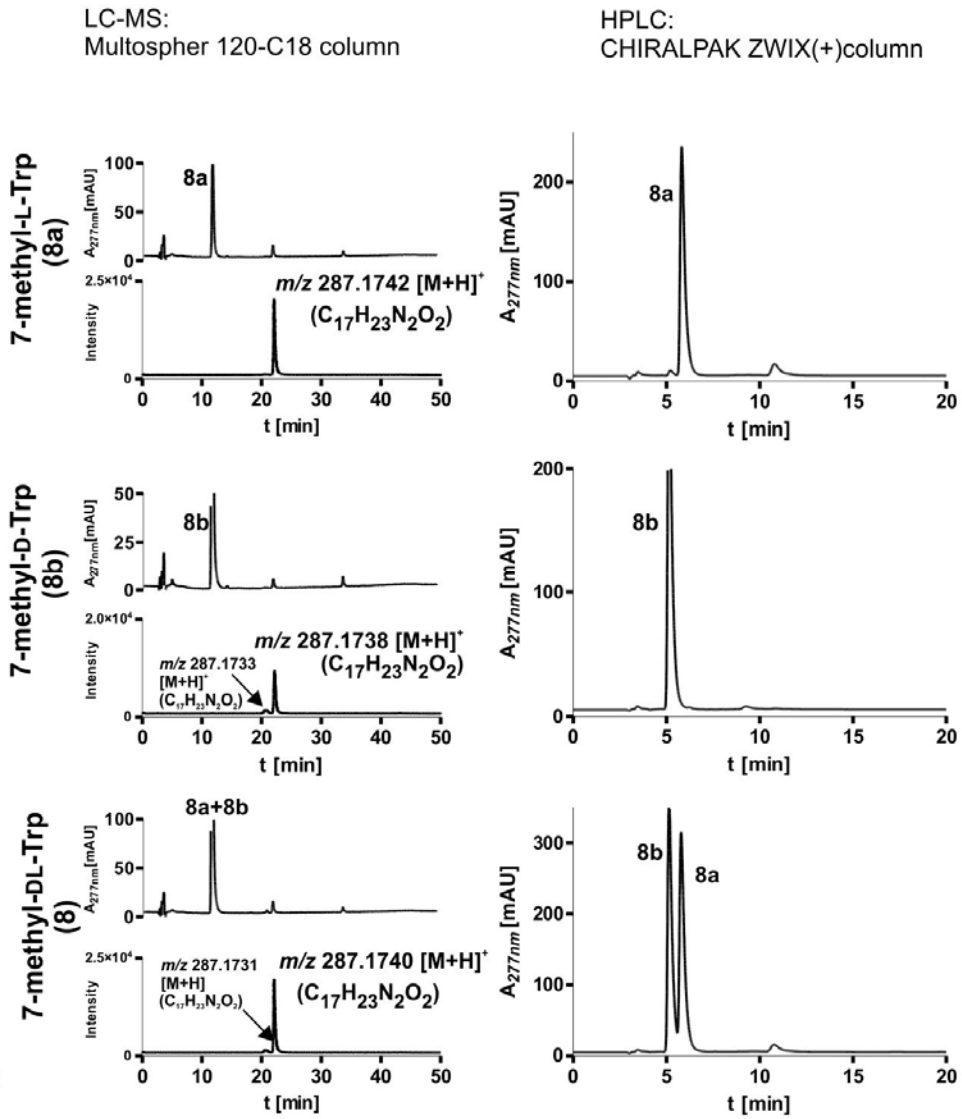


Fig. S34 LC-MS and HPLC analyses of the enzyme assays of 7-methyltryptophan with 5-DMATS$_{Sc}$. The enzyme assays contained 1 mM DMAPP, 1 µM purified protein, and 0.5 mM of L- or D-isomer, or 1 mM of their racemate were incubated at 37 °C for 1.5 h. UV-detection was carried out on a Diode Array detector and illustrated for absorption at 277 nm.

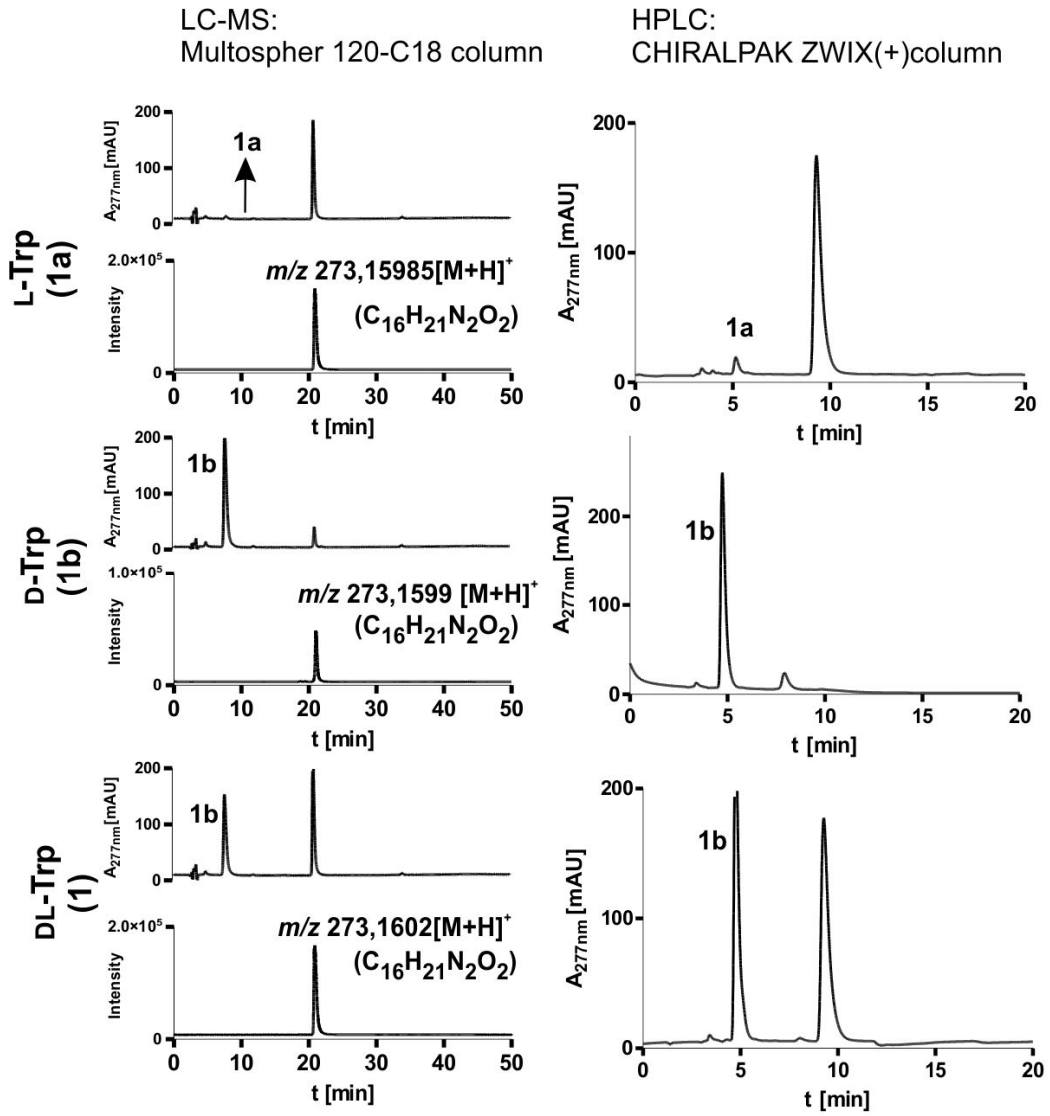


Fig. S35 LC-MS and HPLC analyses of the enzyme assays of tryptophan with 6-DMATS$_{Sa}$. The enzyme assays contained 1 mM DMAPP, 1 μM purified protein, and 0.5 mM of L- or D-isomer, or 1 mM of their racemate were incubated at 37 °C for 1.5 h. UV-detection was carried out on a Diode Array detector and illustrated for absorption at 277 nm.

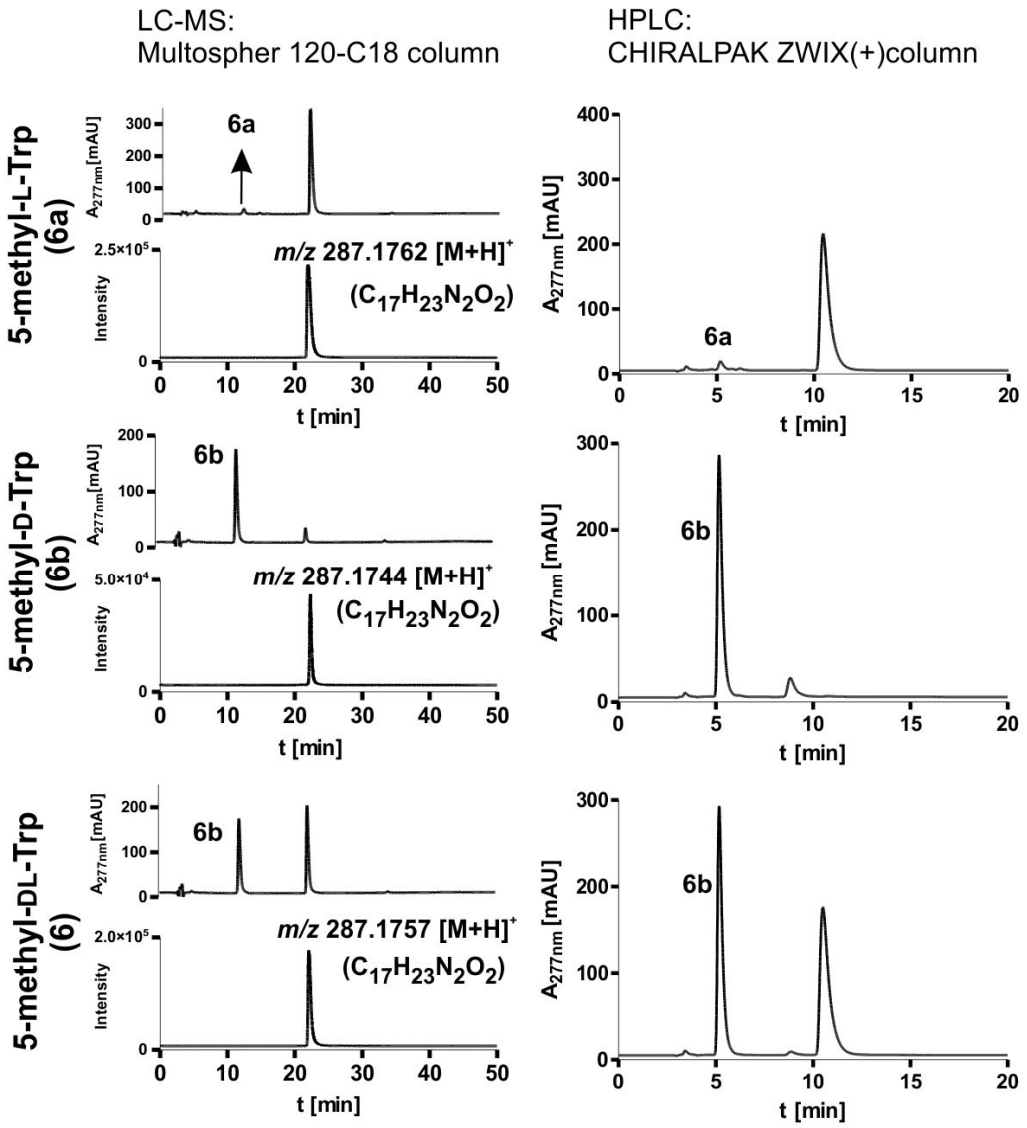


Fig. S36 LC-MS and HPLC analyses of the enzyme assays of 5-methyltryptophan with 6-DMATS$_{Sa}$. The enzyme assays contained 1 mM DMAPP, 1 µM purified protein, and 0.5 mM of L- or D-isomer, or 1 mM of their racemate were incubated at 37 °C for 1.5 h. UV-detection was carried out on a Diode Array detector and illustrated for absorption at 277 nm.

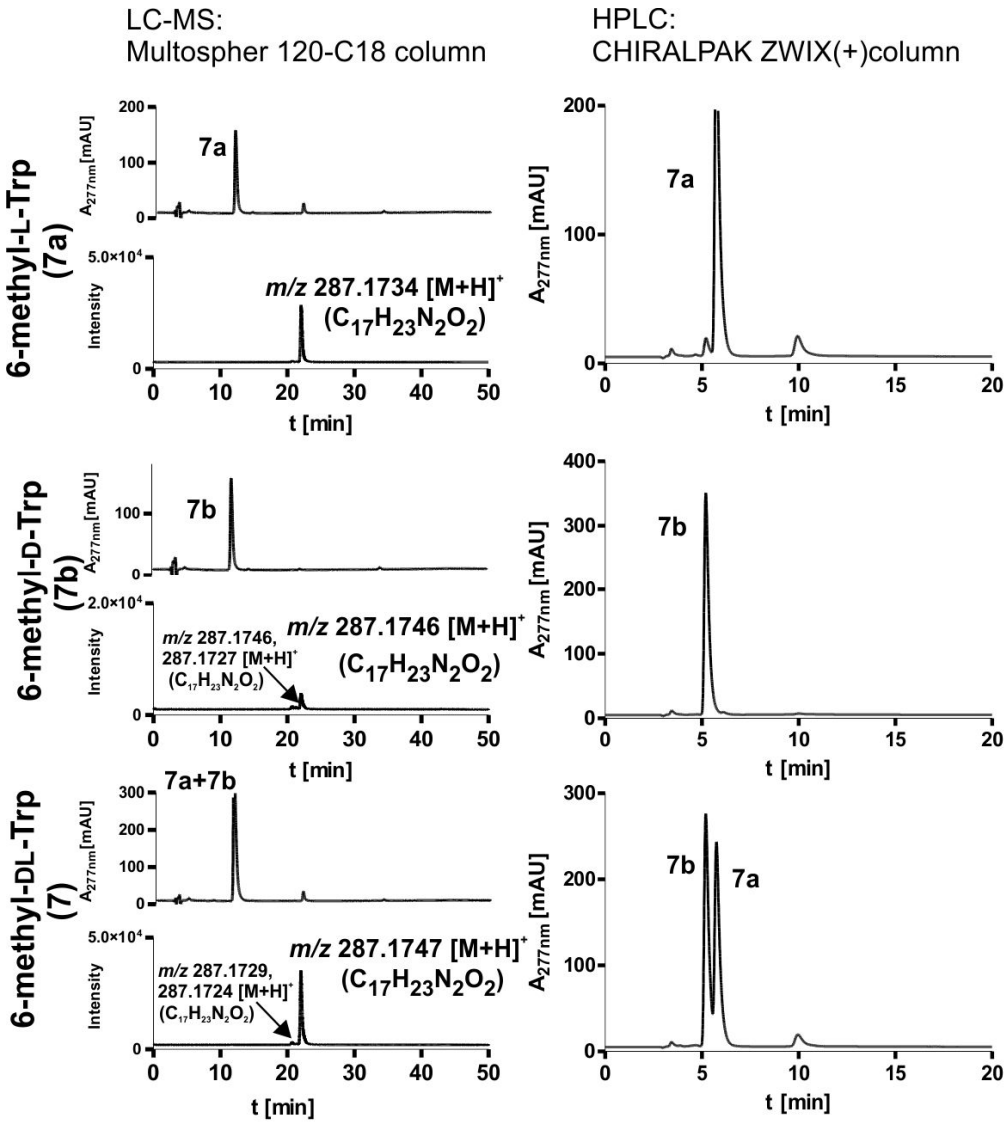


Fig. S37 LC-MS and HPLC analyses of the enzyme assays of 6-methyltryptophan with 6-DMATS$_{Sa}$. The enzyme assays contained 1 mM DMAPP, 1 µM purified protein, and 0.5 mM of L- or D-isomer, or 1 mM of their racemate were incubated at 37 °C for 1.5 h. UV-detection was carried out on a Diode Array detector and illustrated for absorption at 277 nm.

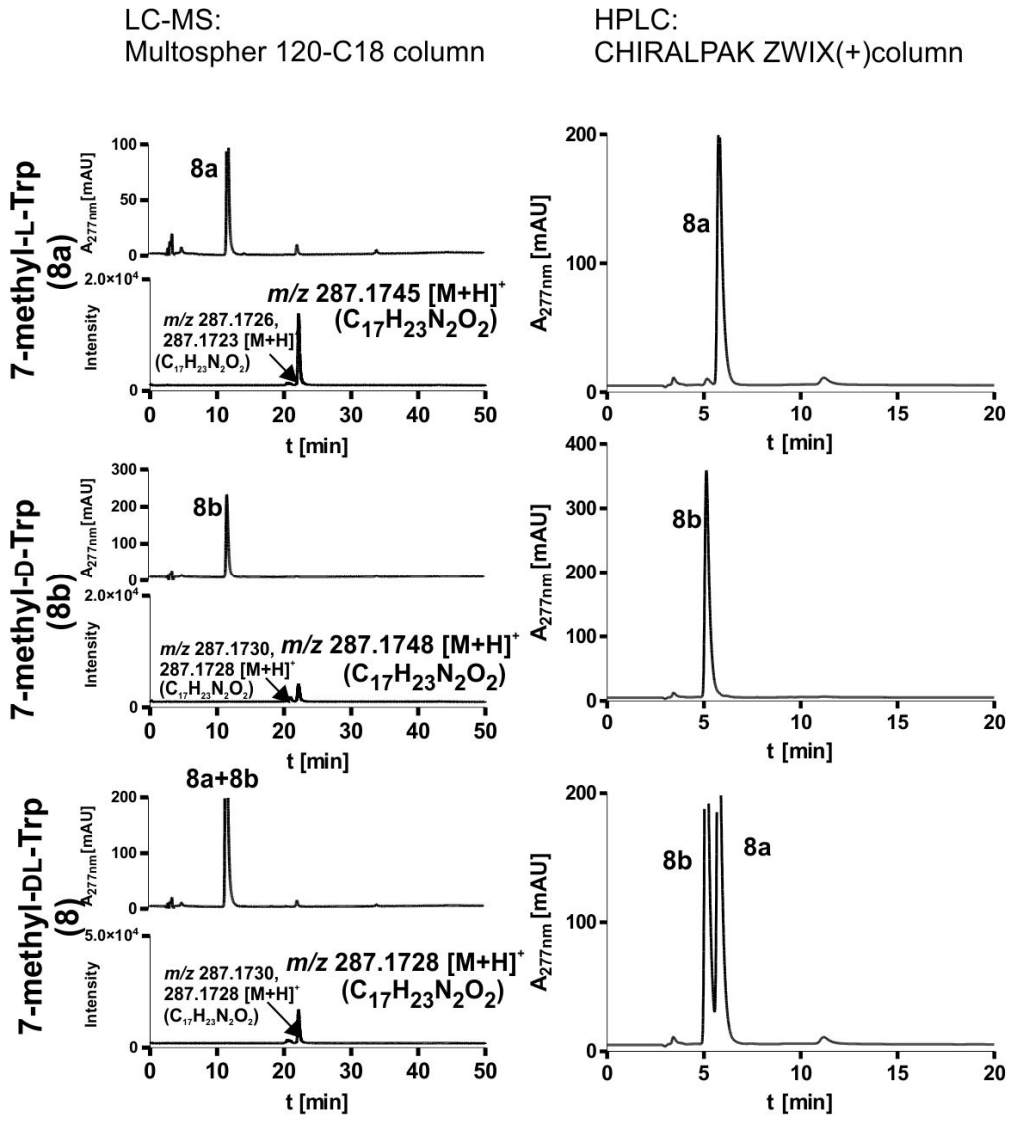


Fig. S38 LC-MS and HPLC analyses of the enzyme assays of 7-methyltryptophan with 6-DMATS$_{Sa}$. The enzyme assays contained 1 mM DMAPP, 1 µM purified protein, and 0.5 mM of L- or D-isomer, or 1 mM of their racemate were incubated at 37 °C for 1.5 h. UV-detection was carried out on a Diode Array detector and illustrated for absorption at 277 nm.

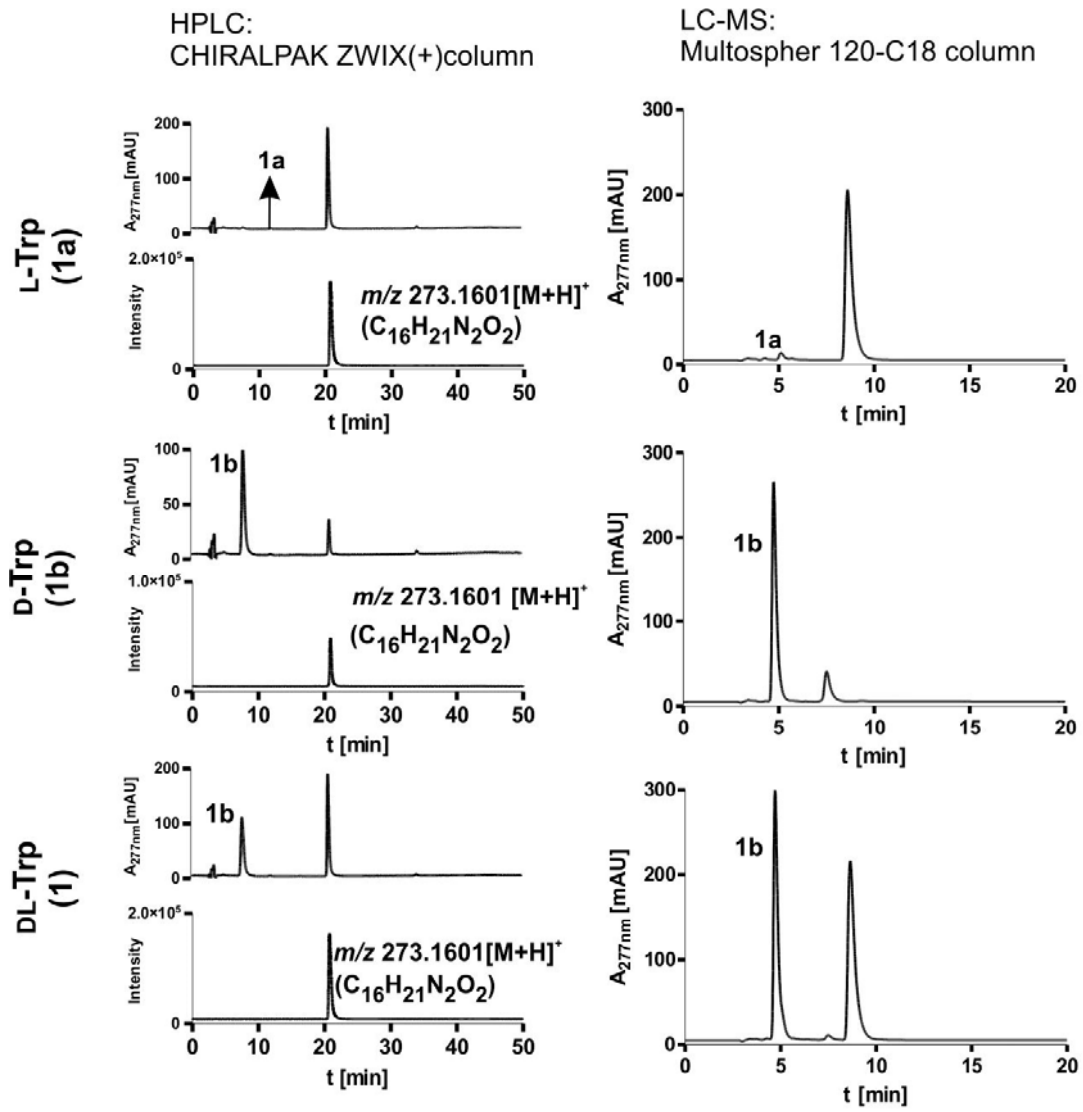


Fig. S39 LC-MS and HPLC analyses of the enzyme assays of tryptophan with 6-DMATS$_{Sv}$. The enzyme assays contained 1 mM DMAPP, 1 µM purified protein, and 0.5 mM of L- or D-isomer, or 1 mM of their racemate were incubated at 37 °C for 1.5 h. UV-detection was carried out on a Diode Array detector and illustrated for absorption at 277 nm.

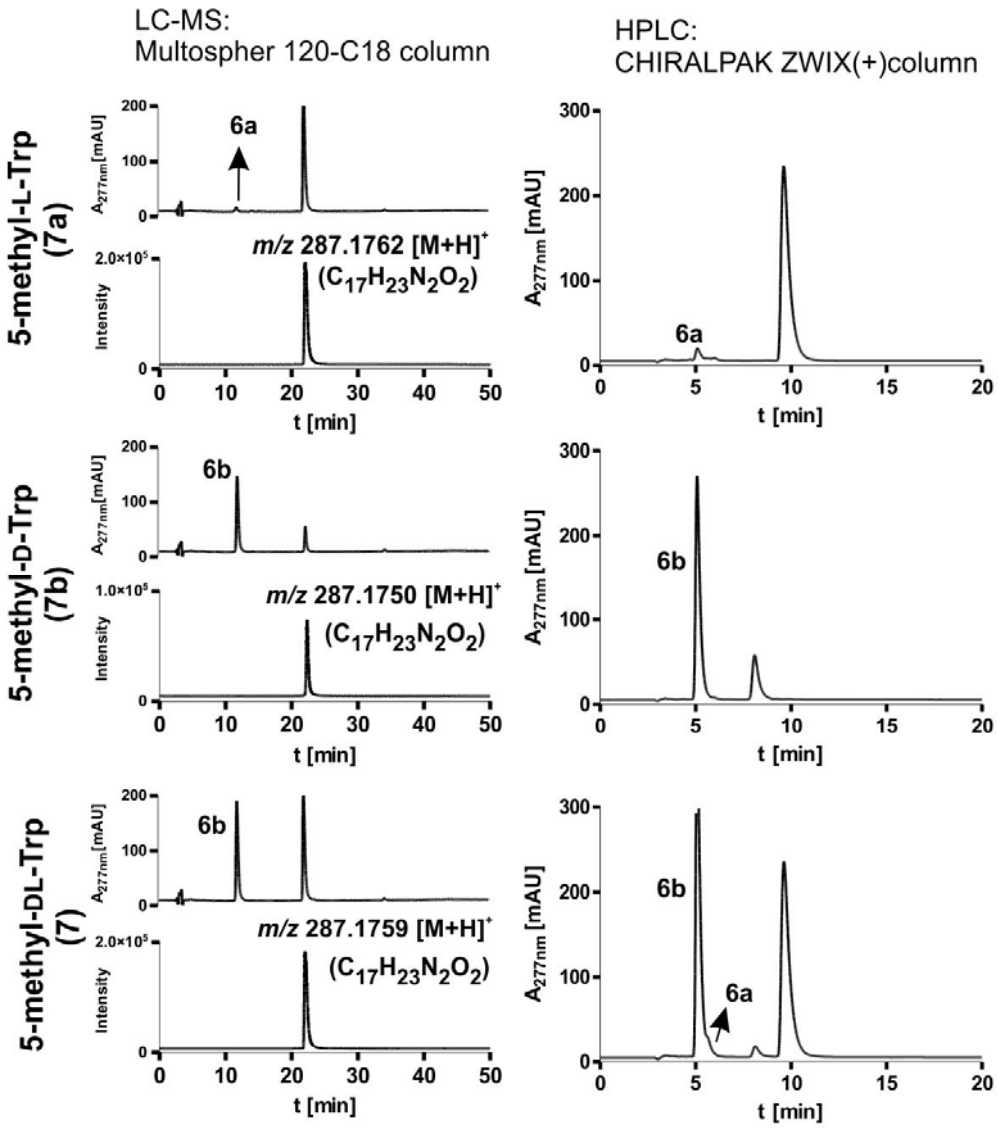


Fig. S40 LC-MS and HPLC analyses of the enzyme assays of 5-methyltryptophan with 6-DMATS$_{Sv}$. The enzyme assays contained 1 mM DMAPP, 1 µM purified protein, and 0.5 mM of L- or D-isomer, or 1 mM of their racemate were incubated at 37 °C for 1.5 h. UV-detection was carried out on a Diode Array detector and illustrated for absorption at 277 nm.

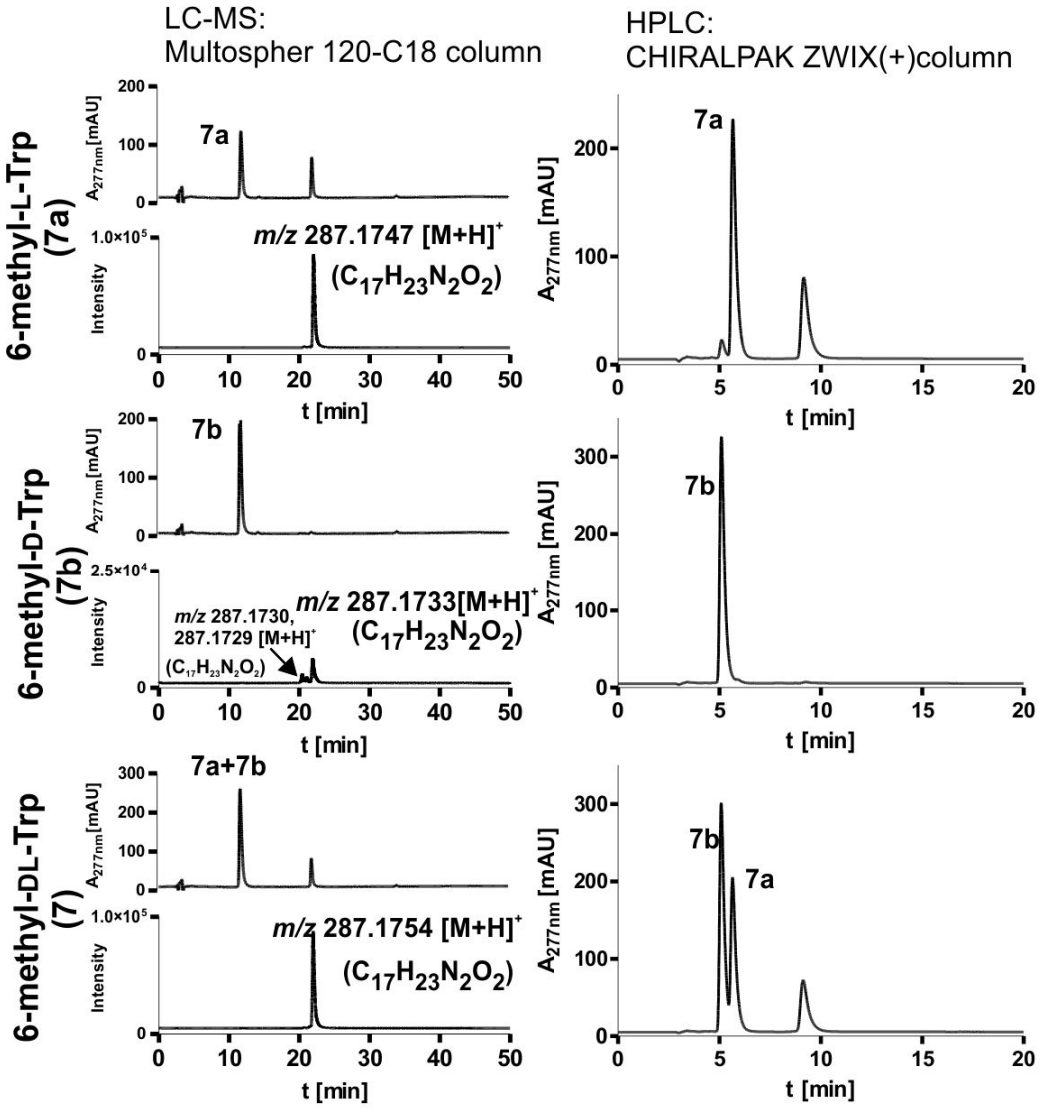


Fig. S41 LC-MS and HPLC analyses of the enzyme assays of 6-methyltryptophan with 6-DMATS$_{Sv}$. The enzyme assays contained 1 mM DMAPP, 1 μM purified protein, and 0.5 mM of L- or D-isomer, or 1 mM of their racemate were incubated at 37 °C for 1.5 h. UV-detection was carried out on a Diode Array detector and illustrated for absorption at 277 nm.

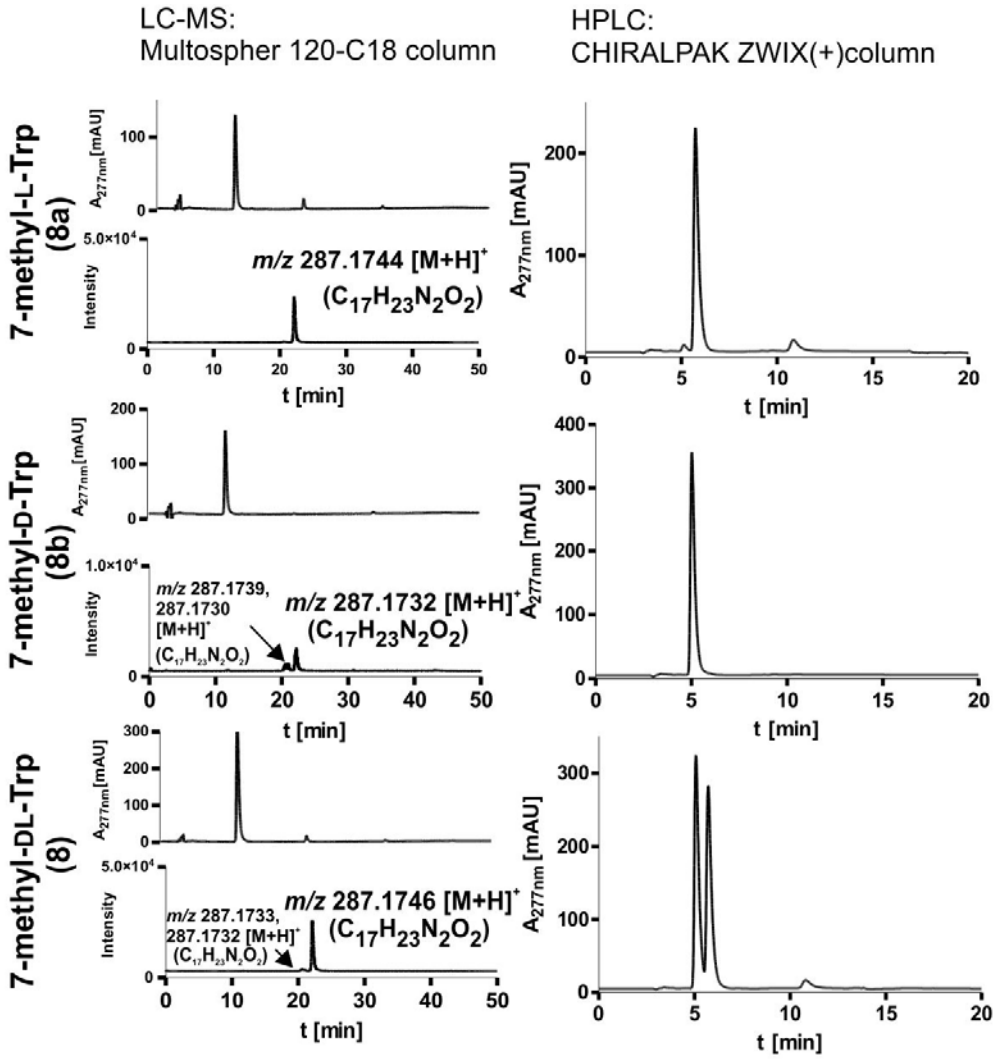


Fig. S42 LC-MS and HPLC analyses of the enzyme assays of 7-methyltryptophan with 6-DMATS$_{Sv}$. The enzyme assays contained 1 mM DMAPP, 1 µM purified protein, and 0.5 mM of L- or D-isomer, or 1 mM of their racemate were incubated at 37 °C for 1.5 h. UV-detection was carried out on a Diode Array detector and illustrated for absorption at 277 nm.

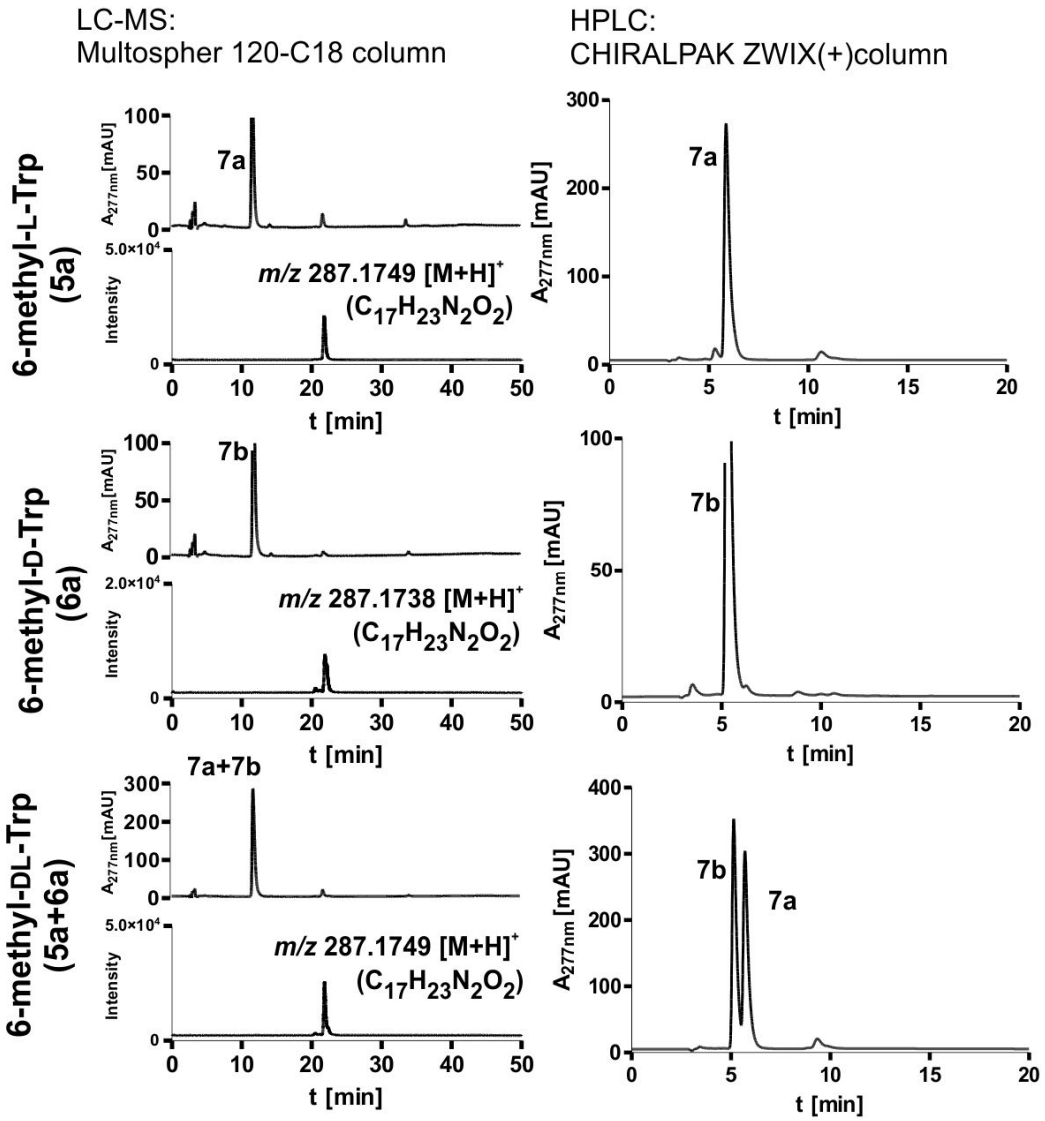


Fig. S43 LC-MS and HPLC analyses of the enzyme assays of 6-methyltryptophan with 6-DMATS$_{Mo}$. The enzyme assays contained 1 mM DMAPP, 1 μM purified protein, and 0.5 mM of L- or D-isomer, or 1 mM of their racemate were incubated at 37 °C for 1.5 h. UV-detection was carried out on a Diode Array detector and illustrated for absorption at 277 nm.

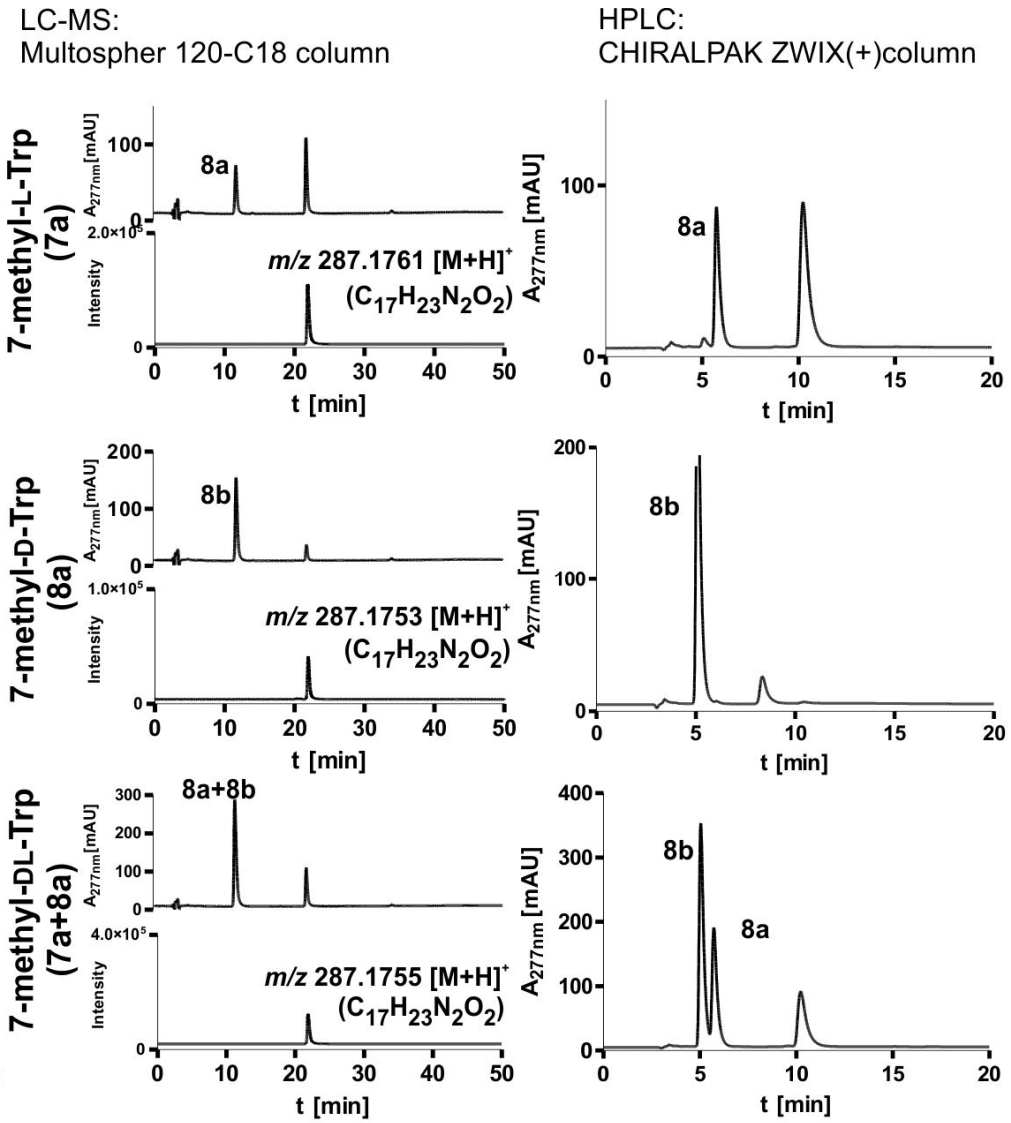


Fig. S44 LC-MS and HPLC analyses of the enzyme assays of 7-methyltryptophan with 6-DMATS$_{Mo}$. The enzyme assays contained 1 mM DMAPP, 1 µM purified protein, and 0.5 mM of L- or D-isomer, or 1 mM of their racemate were incubated at 37 °C for 1.5 h. UV-detection was carried out on a Diode Array detector and illustrated for absorption at 277 nm.

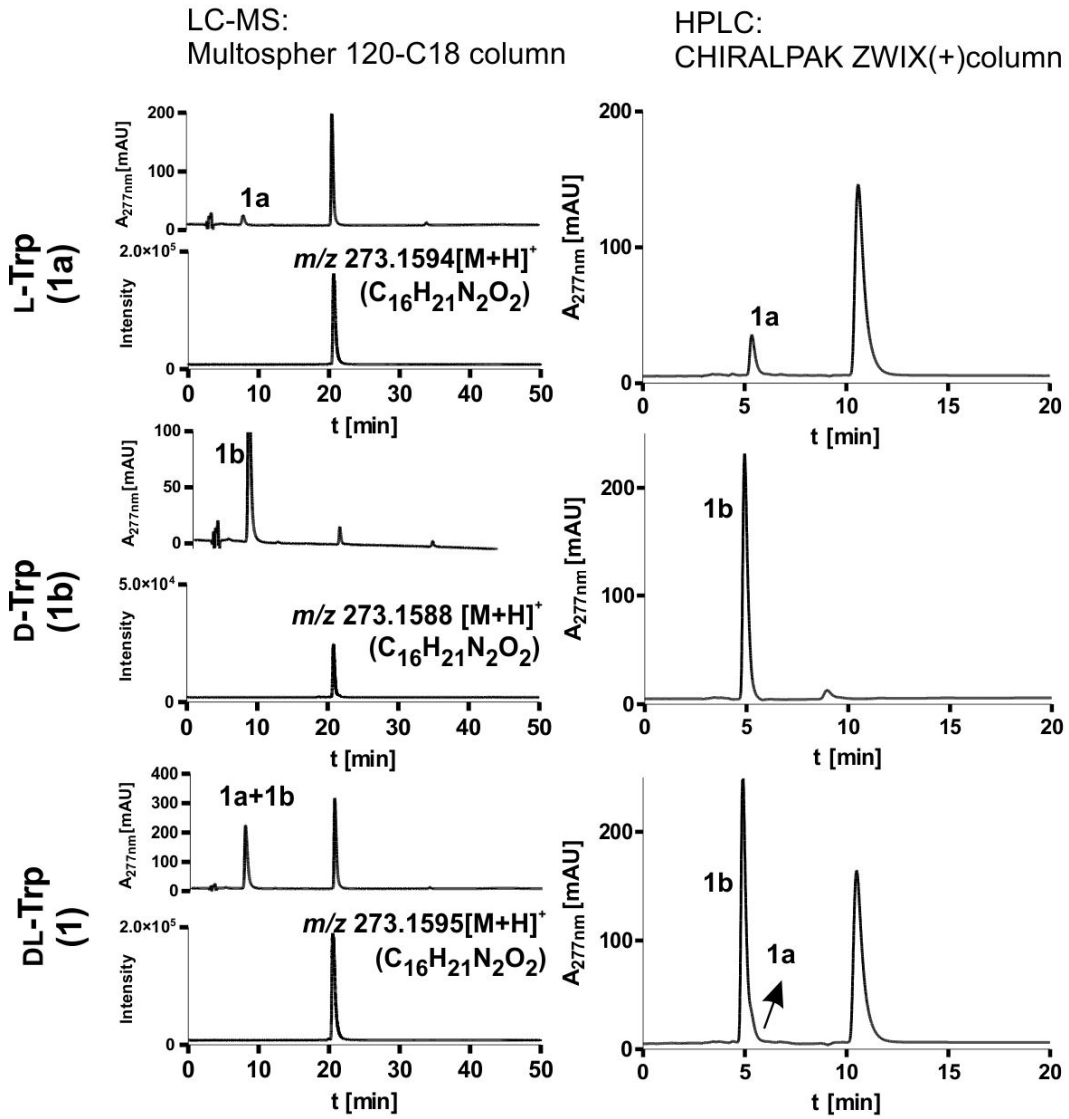


Fig. S45 LC-MS and HPLC analyses of the enzyme assays of tryptophan with 7-DMATS. The enzyme assays contained 1 mM DMAPP, 1 μM purified protein, and 0.5 mM of L- or D-isomer, or 1 mM of their racemate were incubated at 37 °C for 1.5 h. UV-detection was carried out on a Diode Array detector and illustrated for absorption at 277 nm.

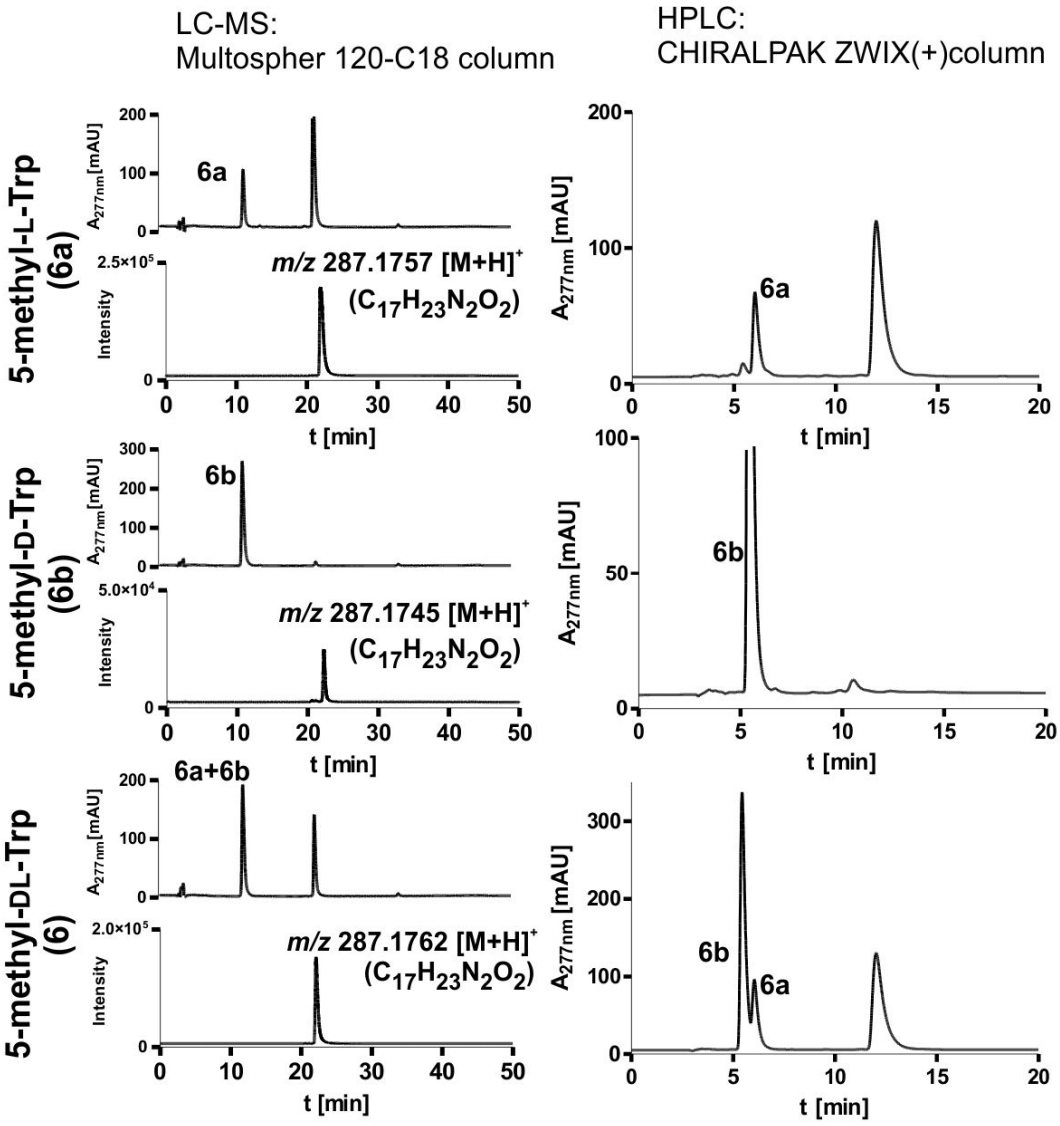


Fig. S46 LC-MS and HPLC analyses of the enzyme assays of 5-methyltryptophan with 7-DMATS. The enzyme assays contained 1 mM DMAPP, 1 μM purified protein, and 0.5 mM of L- or D-isomer, or 1 mM of their racemate were incubated at 37 °C for 1.5 h. UV-detection was carried out on a Diode Array detector and illustrated for absorption at 277 nm.

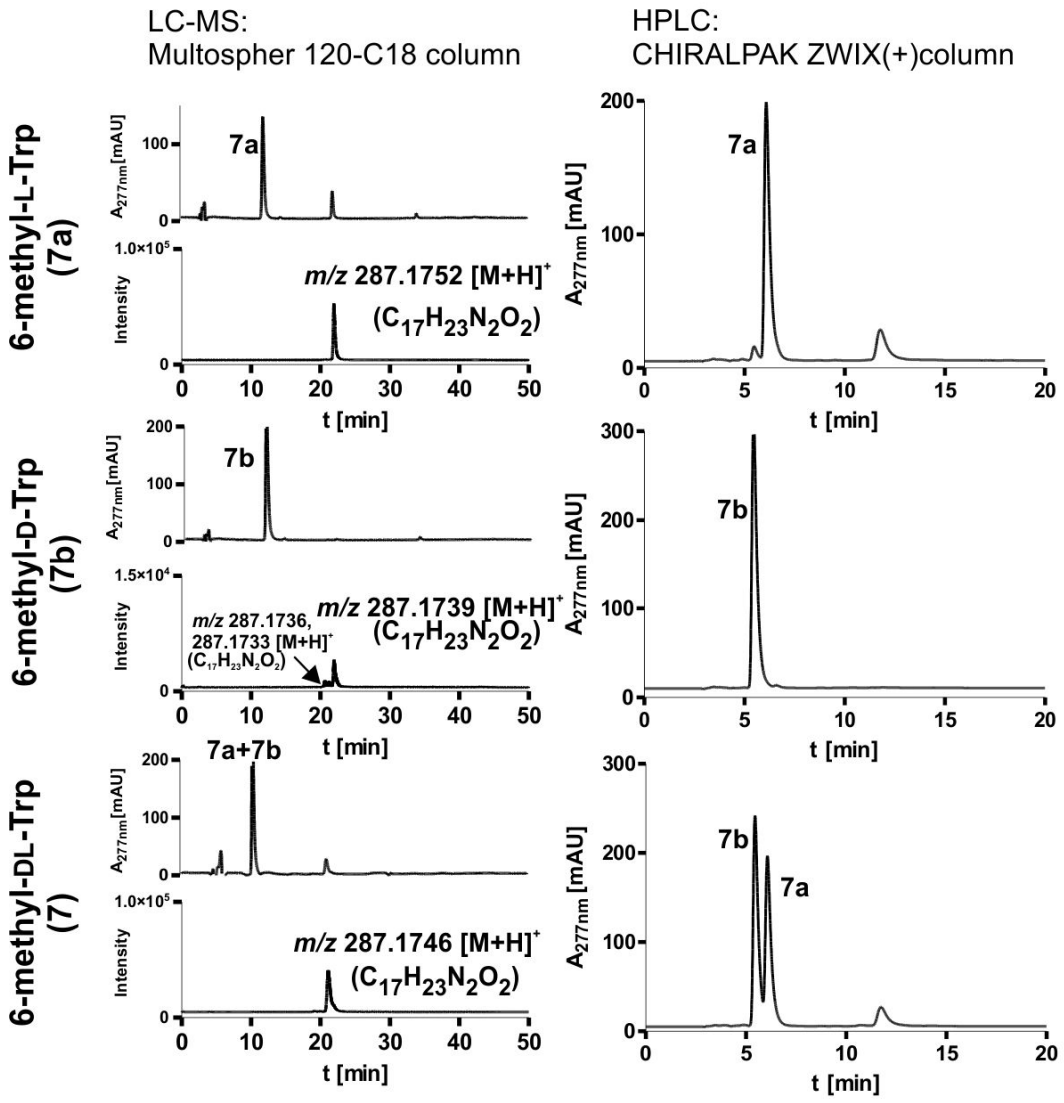


Fig. S47 LC-MS and HPLC analyses of the enzyme assays of 6-methyltryptophan with 7-DMATS. The enzyme assays contained 1 mM DMAPP, 1 µM purified protein, and 0.5 mM of L- or D-isomer, or 1 mM of their racemate were incubated at 37 °C for 1.5 h. UV-detection was carried out on a Diode Array detector and illustrated for absorption at 277 nm.

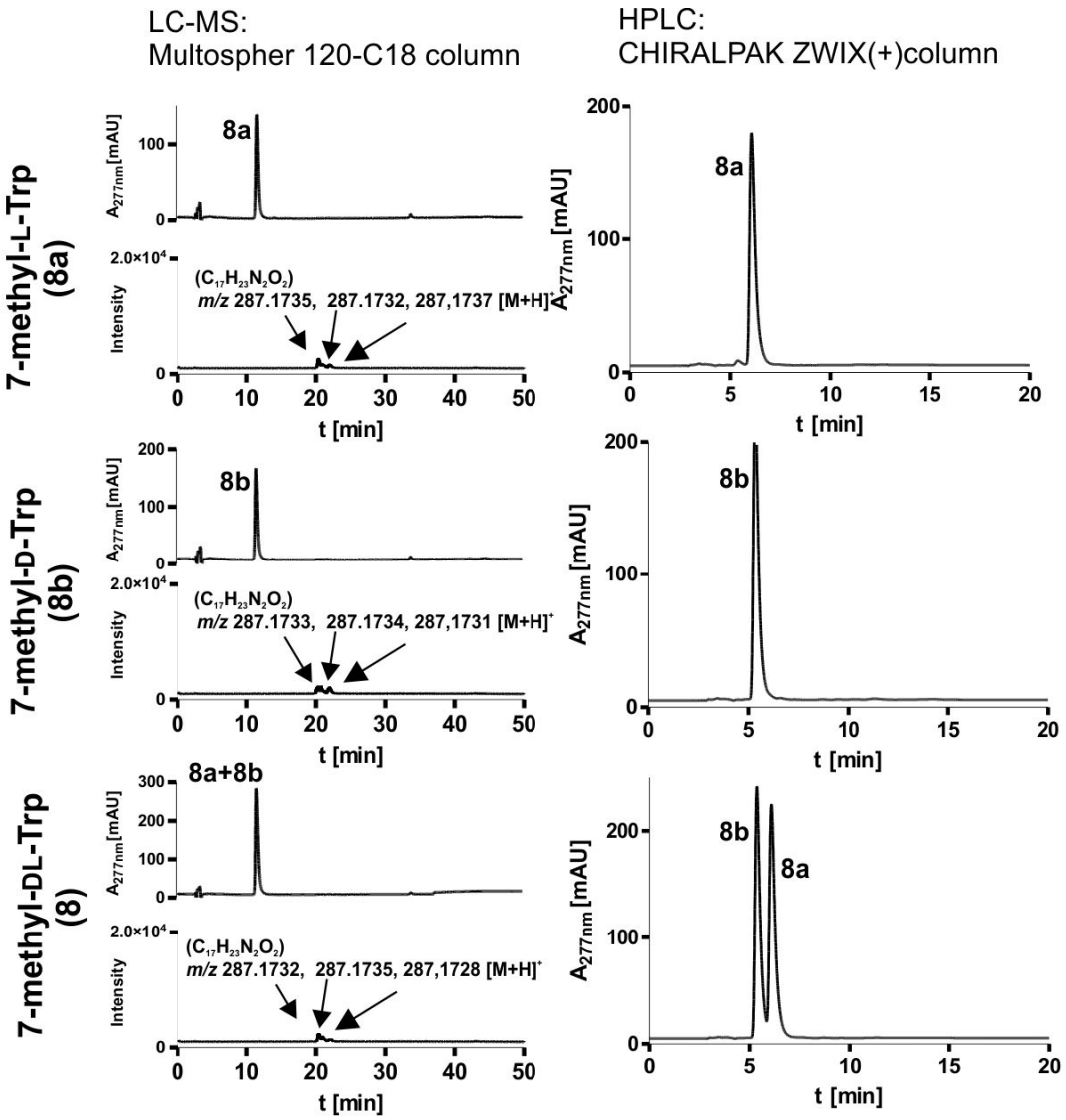


Fig. S48 LC-MS and HPLC analyses of the enzyme assays of 7-methyltryptophan with 7-DMATS. The enzyme assays contained 1 mM DMAPP, 1 µM purified protein, and 0.5 mM of L- or D-isomer, or 1 mM of their racemate were incubated at 37 °C for 1.5 h. UV-detection was carried out on a Diode Array detector and illustrated for absorption at 277 nm.

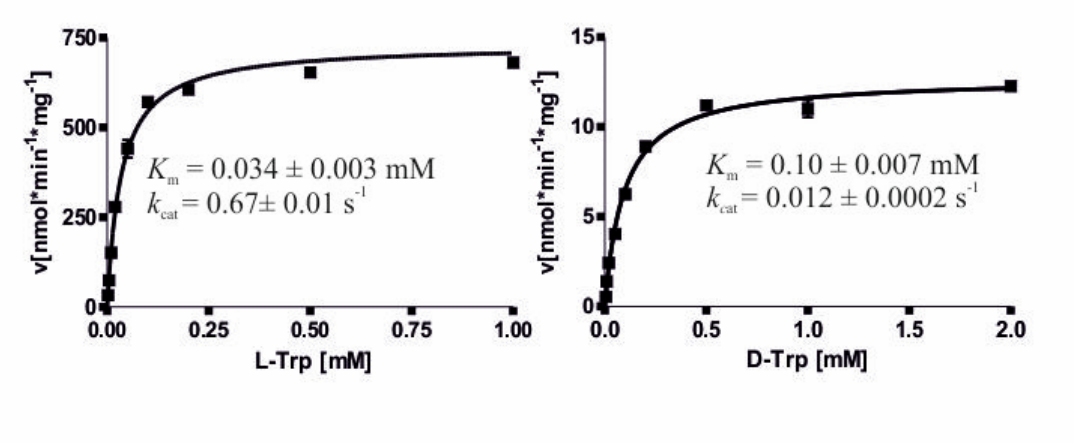


Fig. S49 Determination of the kinetic parameters of FgaPT2 towards L- and D-tryptophan. The reaction mixtures with L-tryptophan contained 1 mM DMAPP, 5 mM $CaCl_2$, and 36.2 nM of the purified protein and were incubated at 37 °C for 15 min. The reaction mixtures with D-tryptophan contained 1 mM DMAPP, 5 mM $CaCl_2$, and 905.8 nM of the purified protein and were incubated at 37 °C for 30 min.

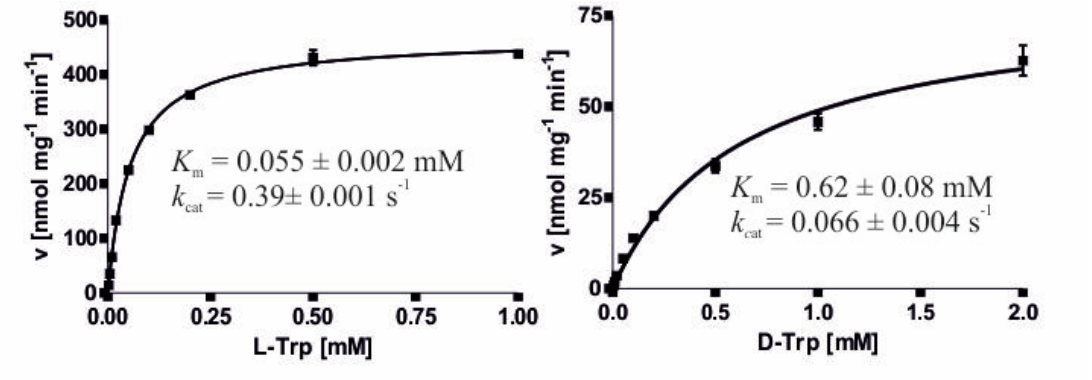


Fig. S50 Determination of the kinetic parameters of 5-DMATS towards L- and D-tryptophan. The reaction mixtures with L -tryptophan contained 1 mM DMAPP, 5 mM $CaCl_2$, and 99.2 nM of the purified protein and were incubated at 37 °C for 15 min. The reaction mixtures with D-tryptophan contained 1 mM DMAPP, 5 mM $CaCl_2$, and 396.8 nM of the purified protein and were incubated at 37 °C for 30 min.

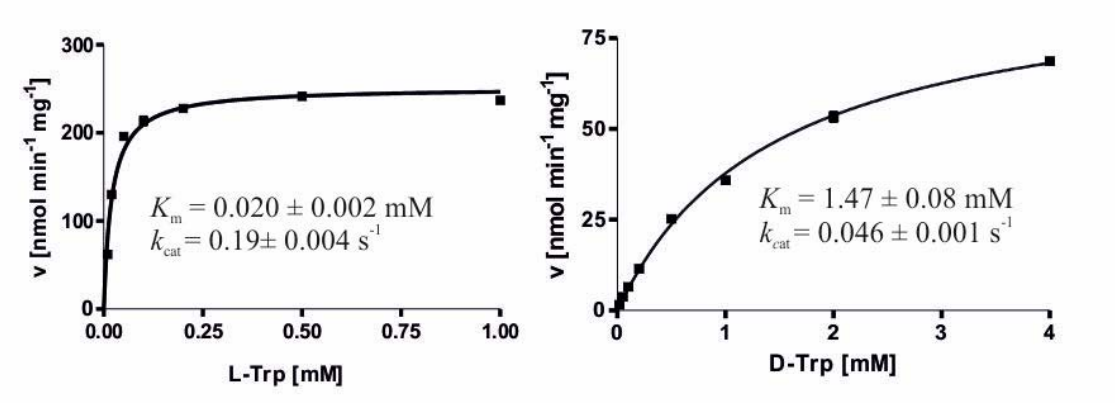


Fig. S51 Determination of the kinetic parameters of 5-DMATS$_{Sc}$ towards L- and D-tryptophan. The reaction mixtures with L-tryptophan contained 1 mM DMAPP, 5 mM $MgCl_2$, and 118.5 nM of the purified protein and were incubated at 37 °C for 15 min. The reaction mixtures with D-tryptophan contained 1 mM DMAPP, 5 mM $MgCl_2$, and 473.9 nM of the purified protein and were incubated at 37 °C for 15 min.

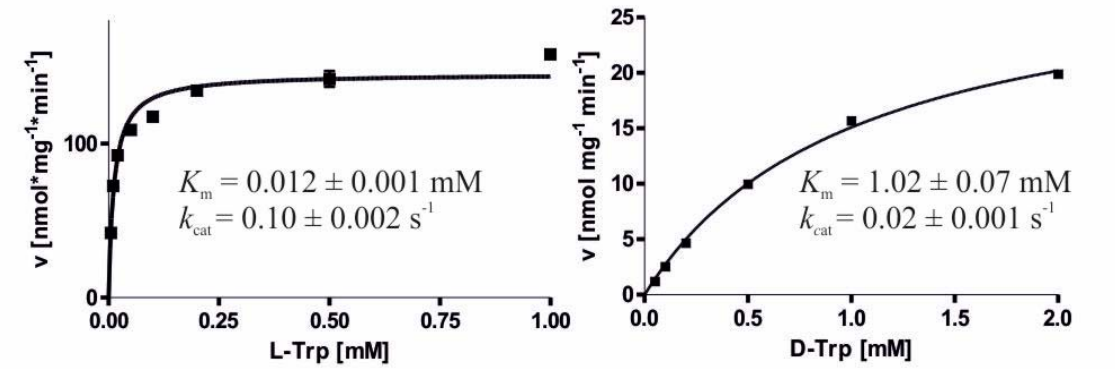


Fig. S52 Determination of the kinetic parameters of 6-DMATS$_{Sa}$ towards L- and D-tryptophan. The reaction mixtures with L-tryptophan contained 1 mM DMAPP, 5 mM $MgCl_2$, and 121.7 nM of the purified protein and were incubated at 37 °C for 15 min. The reaction mixtures with D-tryptophan contained 1 mM DMAPP, 5 mM $MgCl_2$, and 486.6 nM of the purified protein and were incubated at 37 °C for 30 min.

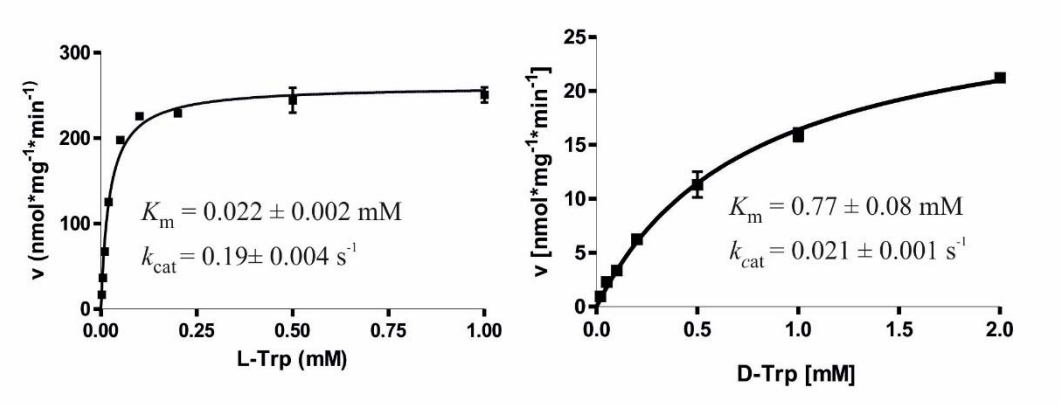


Fig. S53 Determination of the kinetic parameters of 6-DMATS$_{Sv}$ towards L- and D-tryptophan. The reaction mixtures with L-tryptophan contained 1 mM DMAPP, 5 mM $MgCl_2$, and 231.0 nM of the purified protein and were incubated at 37 °C for 15 min. The reaction mixtures with D-tryptophan contained 1 mM DMAPP, 5 mM $MgCl_2$, and 461.9 nM of the purified protein and were incubated at 37 °C for 30 min.

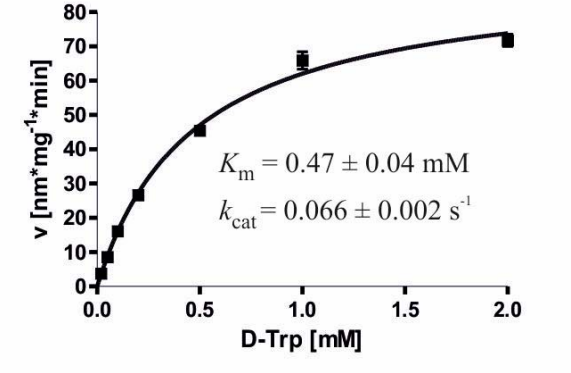


Fig. S54 Determination of the kinetic parameters of 6-DMATS$_{Mo}$ towards D-tryptophan. The reaction mixtures contained 1 mM DMAPP, 5 mM $MgCl_2$, and 459.8 nM of the purified protein and were incubated at 37 °C for 30 min.

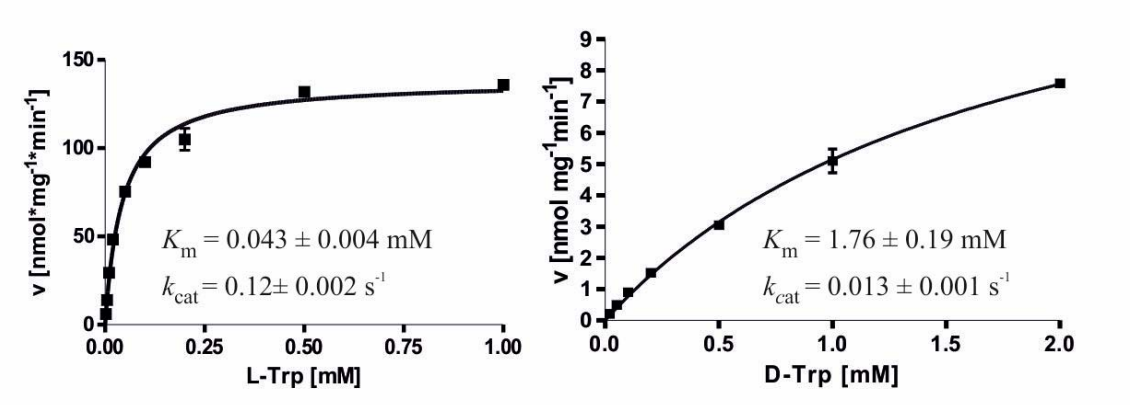


Fig. S55 Determination of the kinetic parameters of 7-DMATS towards L- and D-tryptophan. The reaction mixtures with L-tryptophan contained 1 mM DMAPP, 5 mM $CaCl_2$, and 228.8 nM of the purified protein and were incubated at 37 °C for 15 min. The reaction mixtures with D-tryptophan contained 1 mM DMAPP, 5 mM $CaCl_2$, and 1.4 μM of the purified protein and were incubated at 37 °C for 30 min.

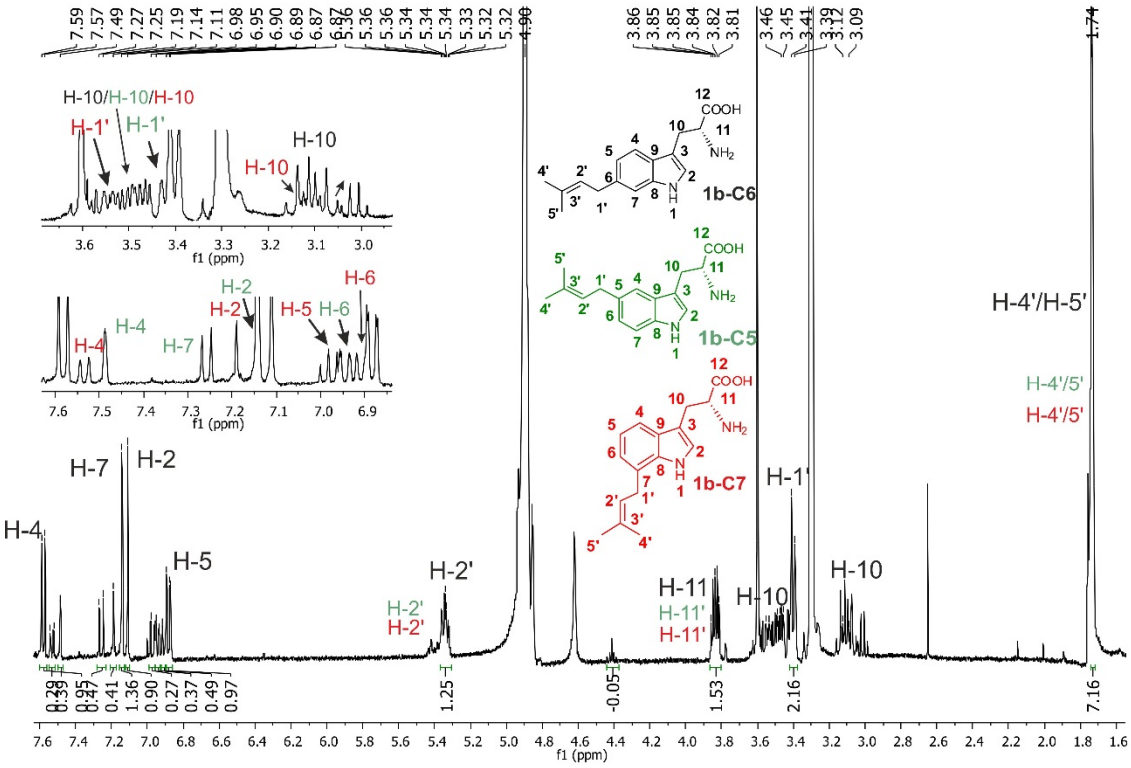


Fig. S56 ^{1}H NMR spectrum of the isolated enzyme product mixture of **1b-C5**, **1b-C6**, and -**1b-C7** of 5-DMATS$_{Sc}$ in CD_3OD (400MHz).

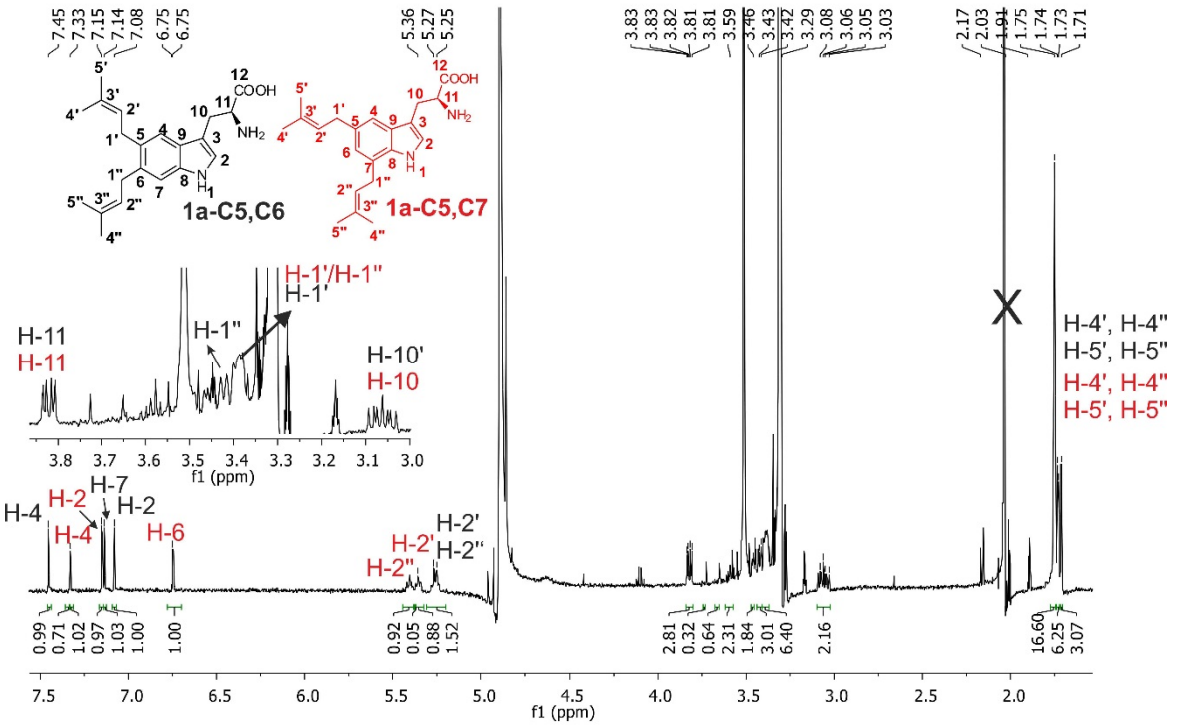


Fig. S57 ^{1}H NMR spectrum of the mixture of **1a-C5,C6** and **1a-C5,C7** in CD_3OD (500MHz)

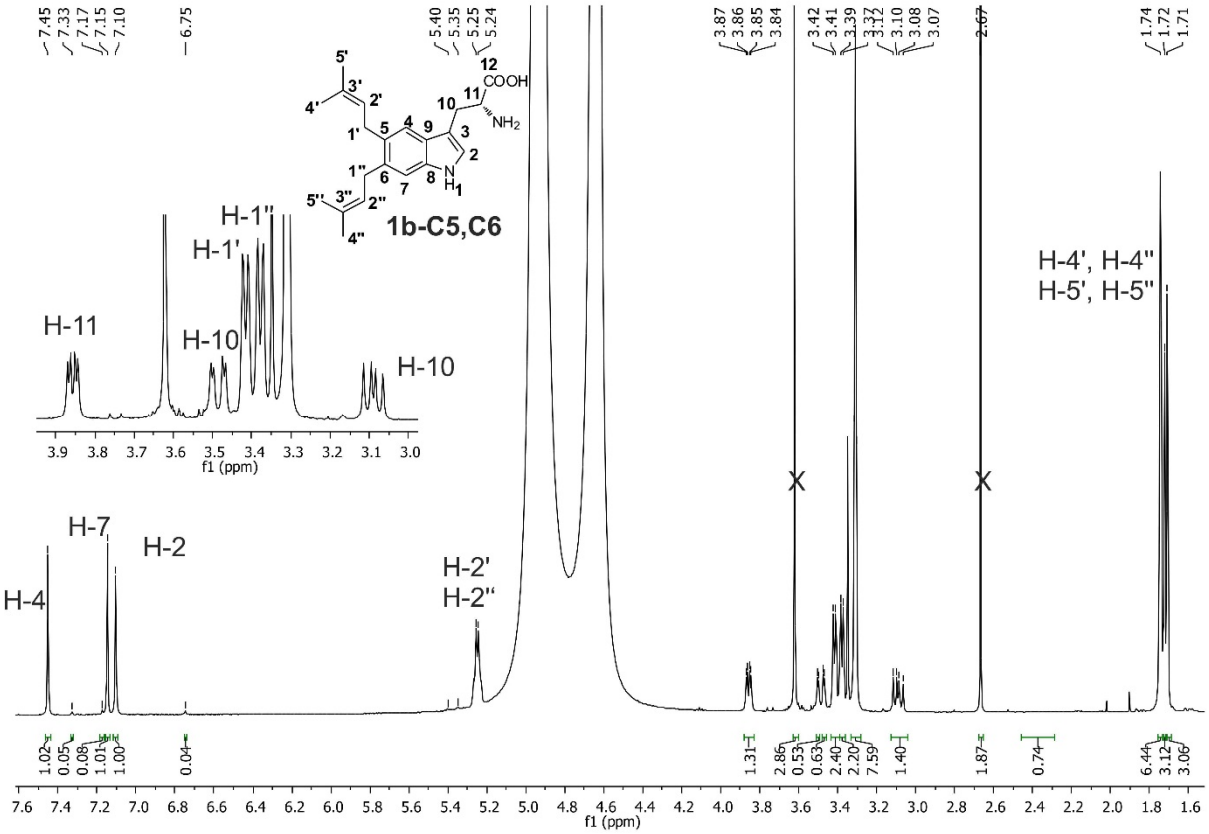


Fig. S58 ^{1}H NMR spectrum of **1b-C5,C6** in CD_3OD (500MHz)

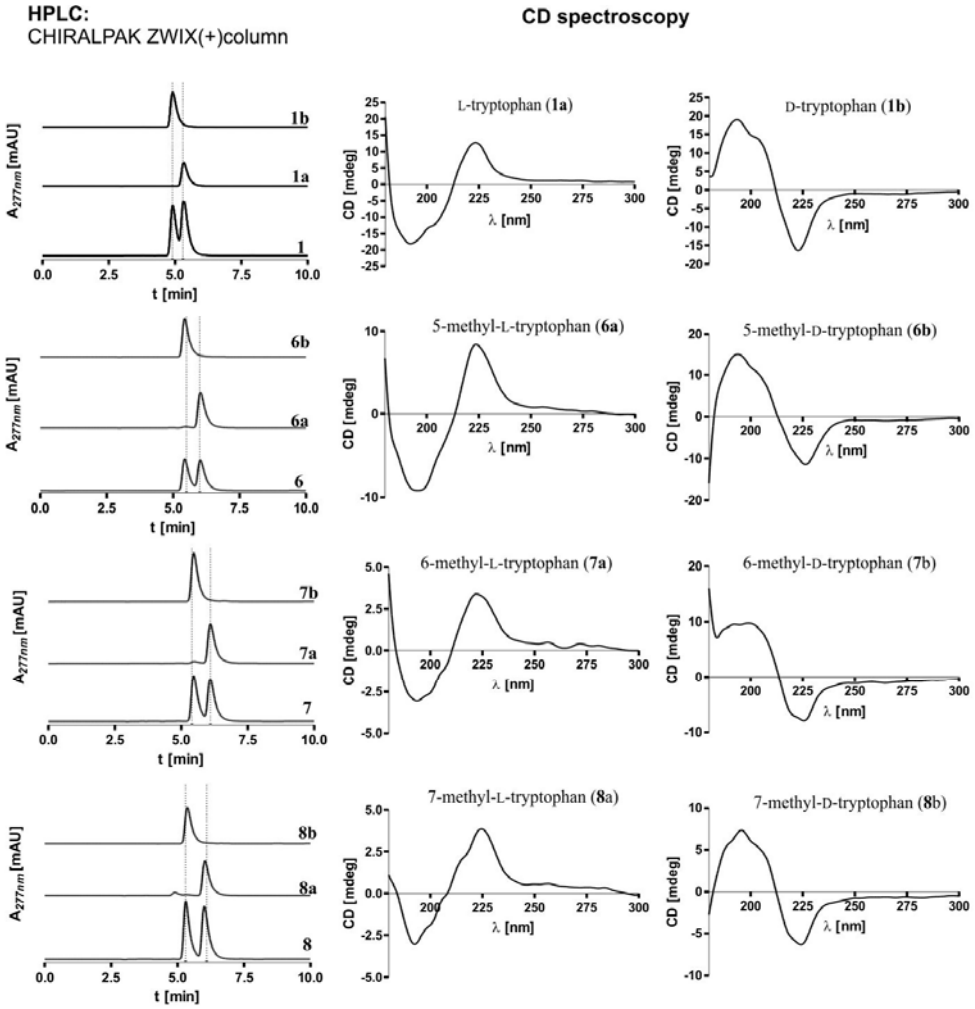


Fig. S59 CD spectra of the isolated L- and D-enantiomers. The enantiomers were isolated from racemate on a CHIRALPAK®Zwix(+) column and dissolved in water. CD spectra were recorded on a Jasco J-810 CD spectrometer in the wavelength range of 180-350 nm.

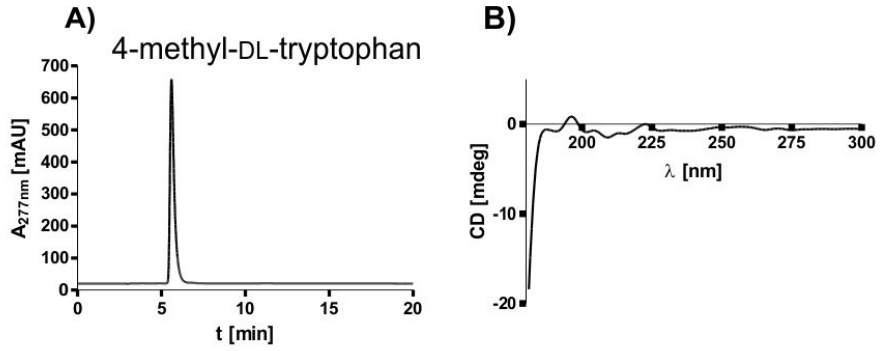


Fig. S60 HPLC chromatogram with CHIRALPAK®Zwix(+) column A) and CD-spectrum B) of 4-methyl-DL-tryptophan (**5**).

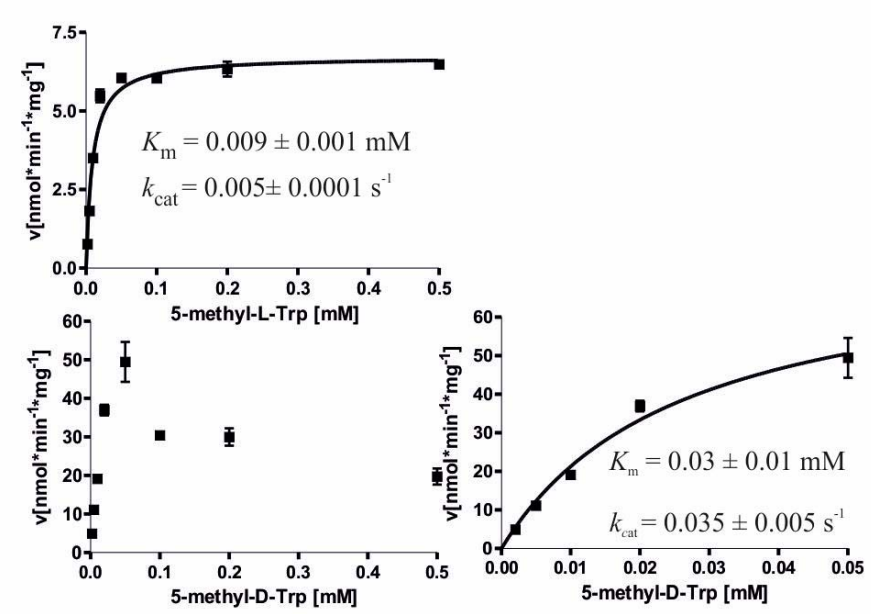


Fig. S61 Determination of the kinetic parameters of 5-DMATS$_{Sc}$ towards 5-methyl-L-tryptophan and 5-methyl-D-tryptophan. The reaction mixtures with 5-methyl-L-tryptophan contained 1 mM DMAPP, 5 mM $MgCl_2$ and 7.1 µM of the purified protein and were incubated at 37 °C for 15 min. The reaction mixtures with 5-methyl-D-tryptophan contained 1 mM DMAPP, 5 mM $MgCl_2$ and 473.9 nM of the purified protein and were incubated at 37 °C for 15 min.

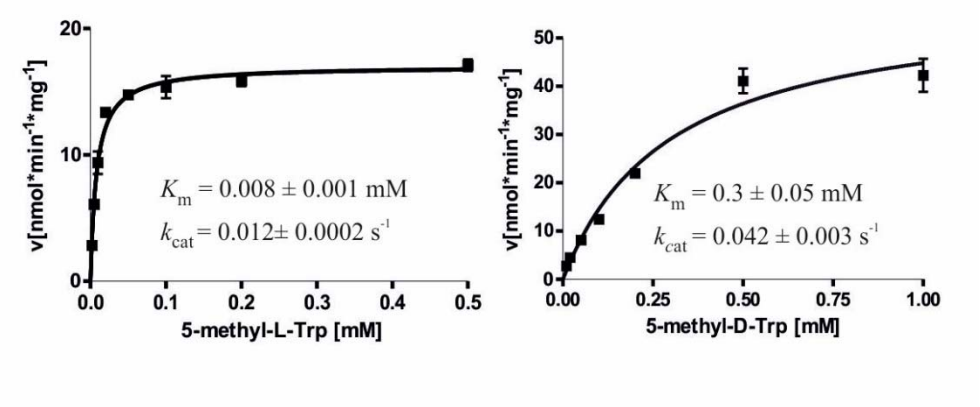


Fig. S62 Determination of the kinetic parameters for 6-DMATS$_{Mo}$ towards 5-methyl-L-tryptophan and 5-methyl-D-tryptophan. The reaction mixtures contained 1 mM DMAPP, 5 mM $MgCl_2$ and 459.8 nM of the purified protein and were incubated at 37 °C for 30 min.

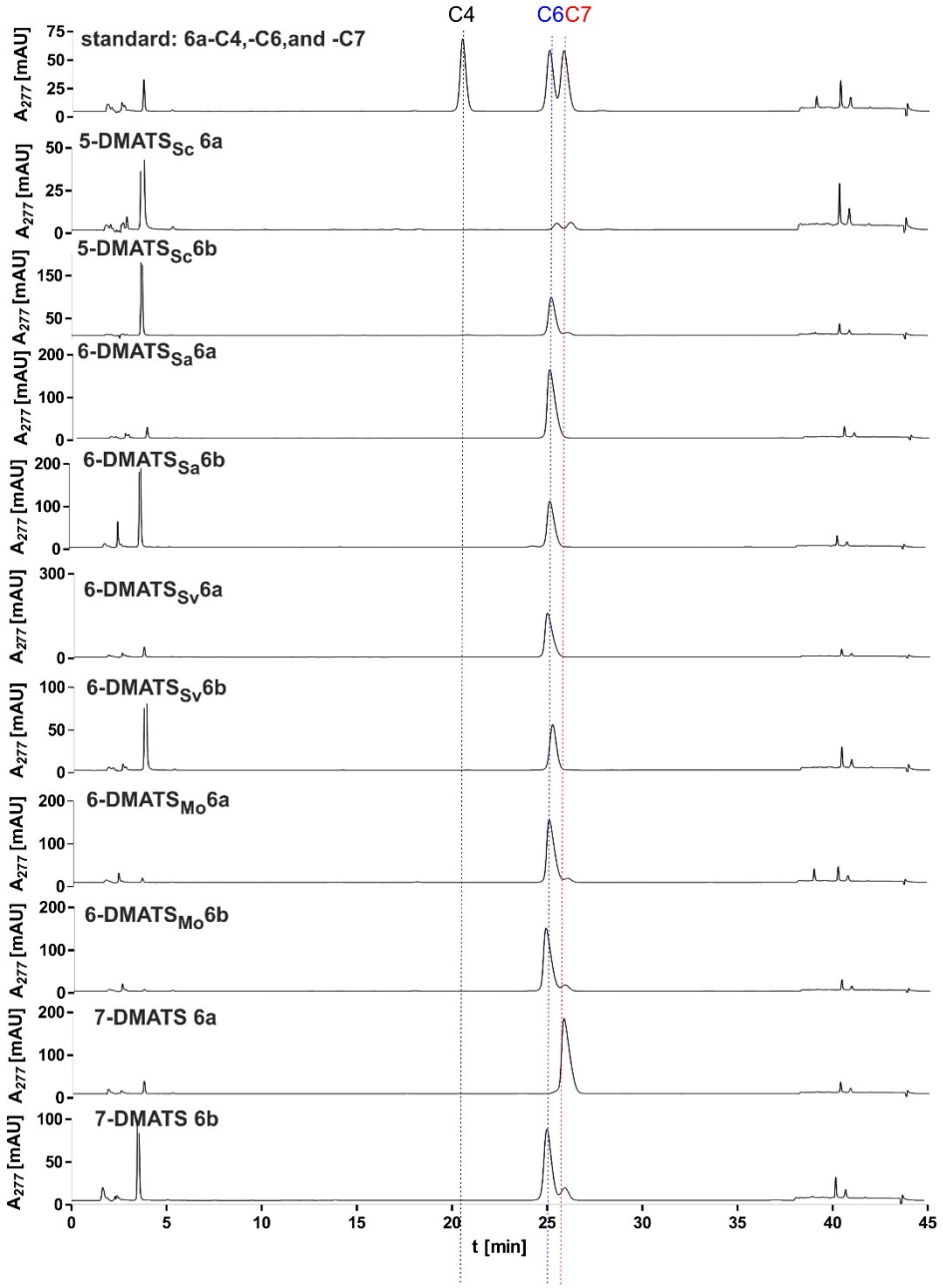


Fig. S63 HPLC analysis for identification of the enzyme products of 5-methyltryptophan. The enzyme assays contained 1 mM DMAPP and 0.5 mM of 5-methyl-L-tryptophan (**6a**) and 5-methyl-D-tryptophan (**6b**). Detailed conditions for the incubation mixtures are given in Table S9. For HPLC analysis, an Eclipse XDB-C18 column was used (condition 5 in Table S1). Detection was carried out with a Diode Array detector and illustrated for absorption at 277 nm.

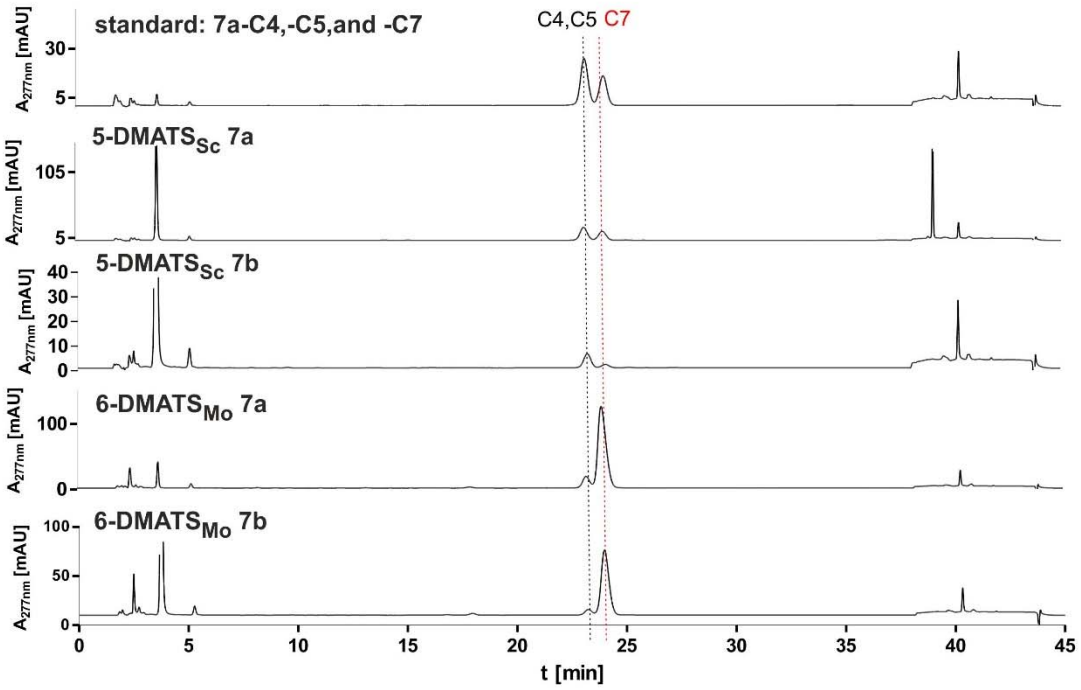


Fig. S64 HPLC analysis for identification of the enzyme products of 6-methyltryptophan. The enzyme assays contained 1 mM DMAPP and 0.5 mM of 6-methyl-L-tryptophan (**7a**) and 6-methyl-D-tryptophan (**7b**). Detailed conditions for the incubation mixtures are given in Table S9. For HPLC analysis, an Eclipse Plus-C18 column was used (condition 5 in Table S1). Detection was carried out with a Diode Array detector and illustrated for absorption at 277 nm.

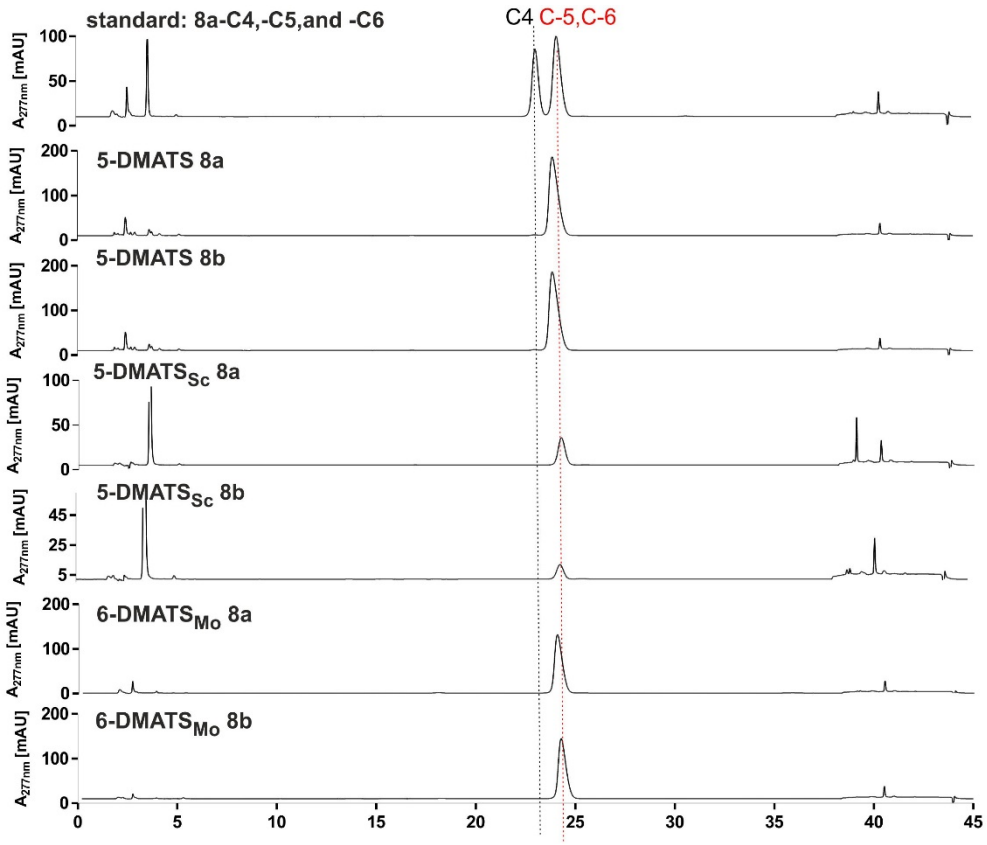


Fig. S65 HPLC analysis for identification of the enzyme products of 7-methyltryptophan. The enzyme assays contain 1 mM DMAPP and 0.5 mM of 7-methyl-L-tryptophan (**8a**) and 7-methyl-D-tryptophan (**8b**). Detailed conditions for the incubation mixtures are given in Table S9. For HPLC analysis, an Eclipse Plus-C18 column was used (condition 5 in Table S1). Detection was carried out with a Diode Array detector and illustrated for absorption at 277 nm.

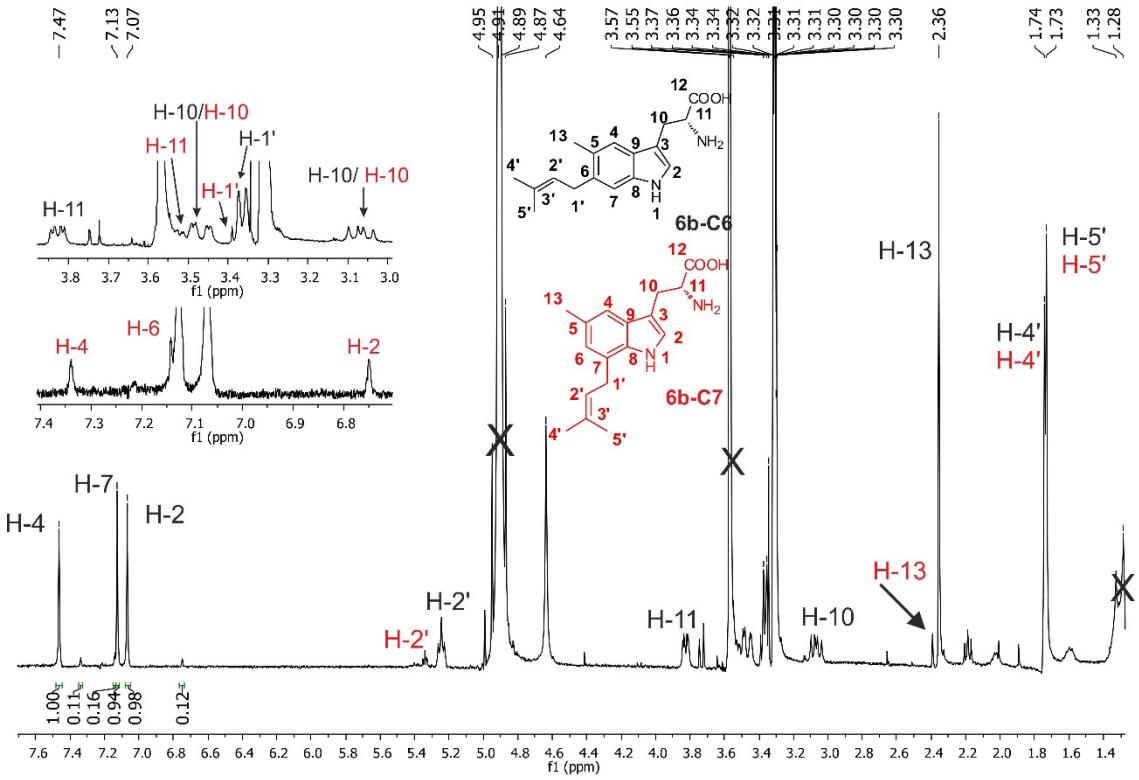


Fig. S66 ^{1}H NMR spectrum of the isolated enzyme product mixture of **6b-C6** and **6b-C7** of 5-DMATS$_{Sc}$ in CD_3OD (400MHz).