

Supplementary Material

Structure Elucidation of Metabolite x17299 by Interpretation of Mass Spectrometric Data

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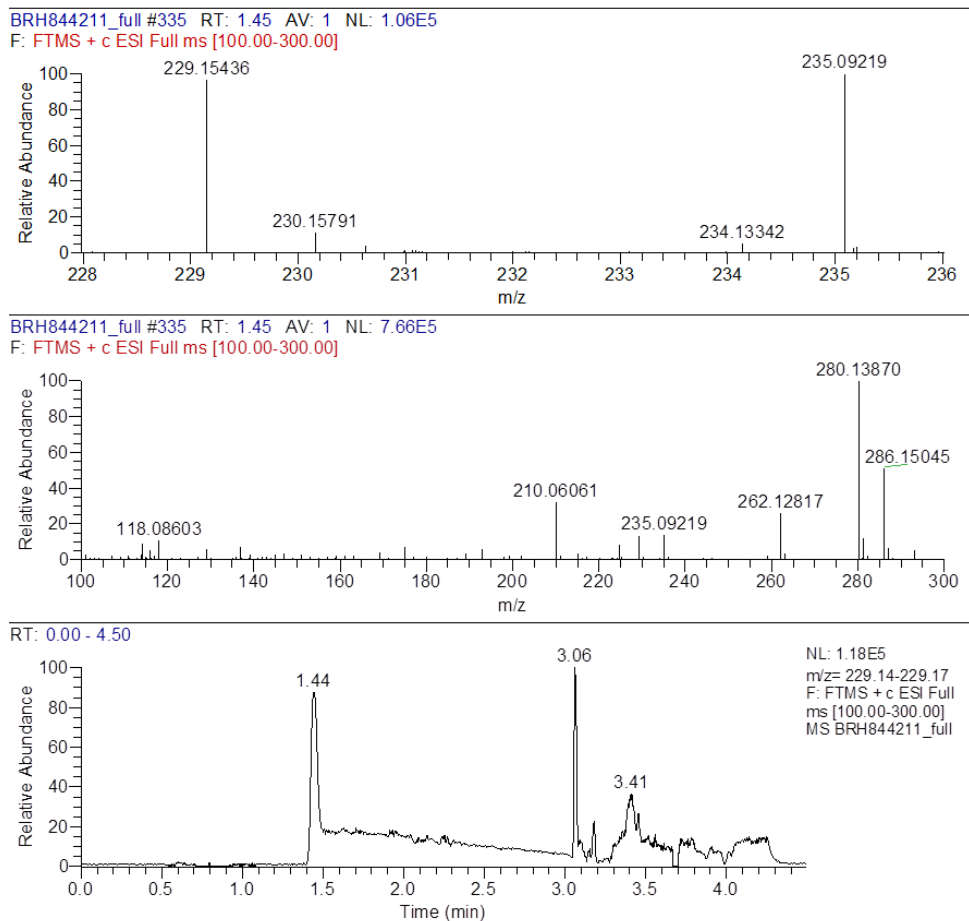


Figure S1. LC/MS chromatogram and spectrum of x17299 (1.44 min) in a plasma extract with expansion (top).

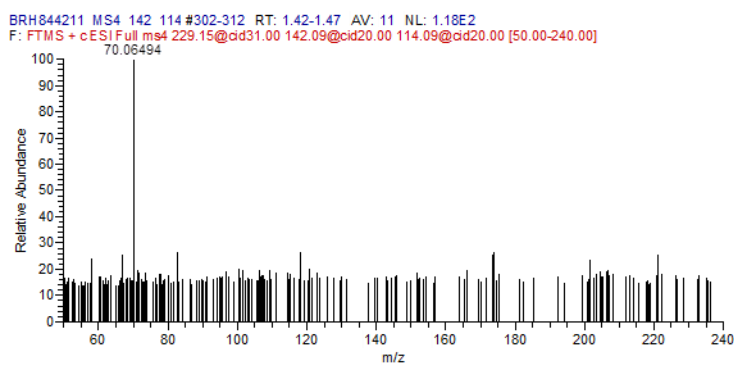


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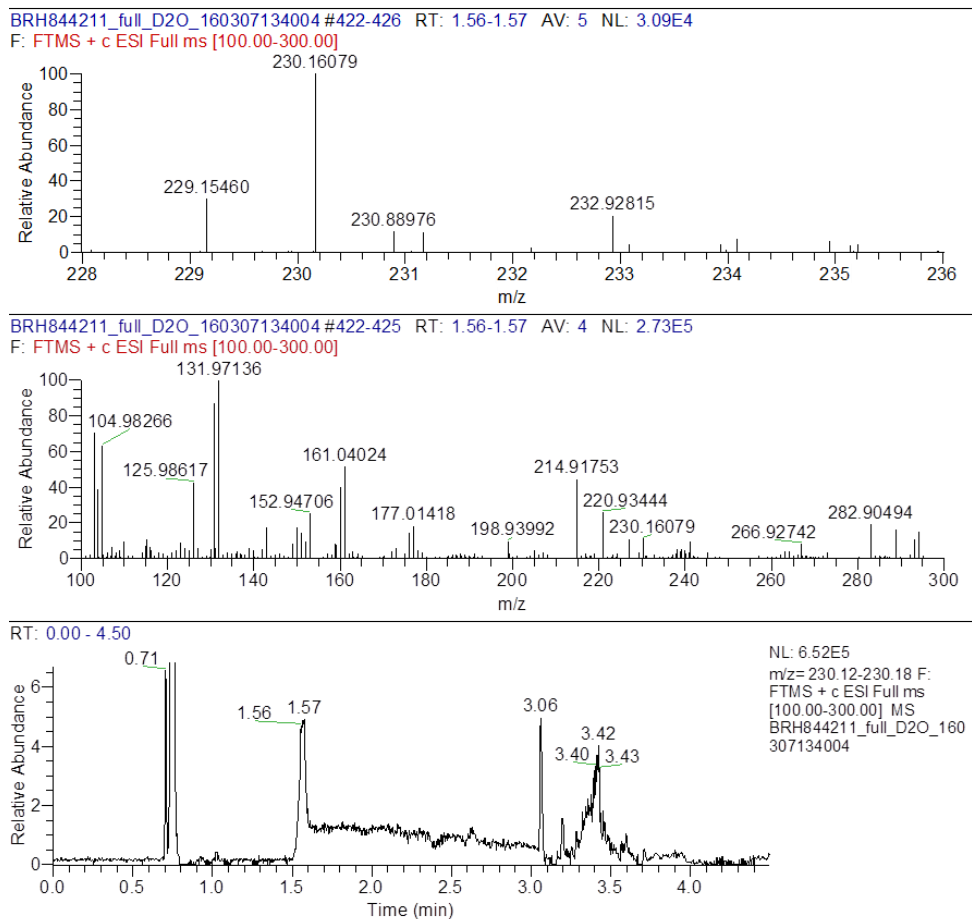


Figure S3. LC/MS chromatogram and spectrum of deuterated x17299 (1.57 min) with expansion (top).

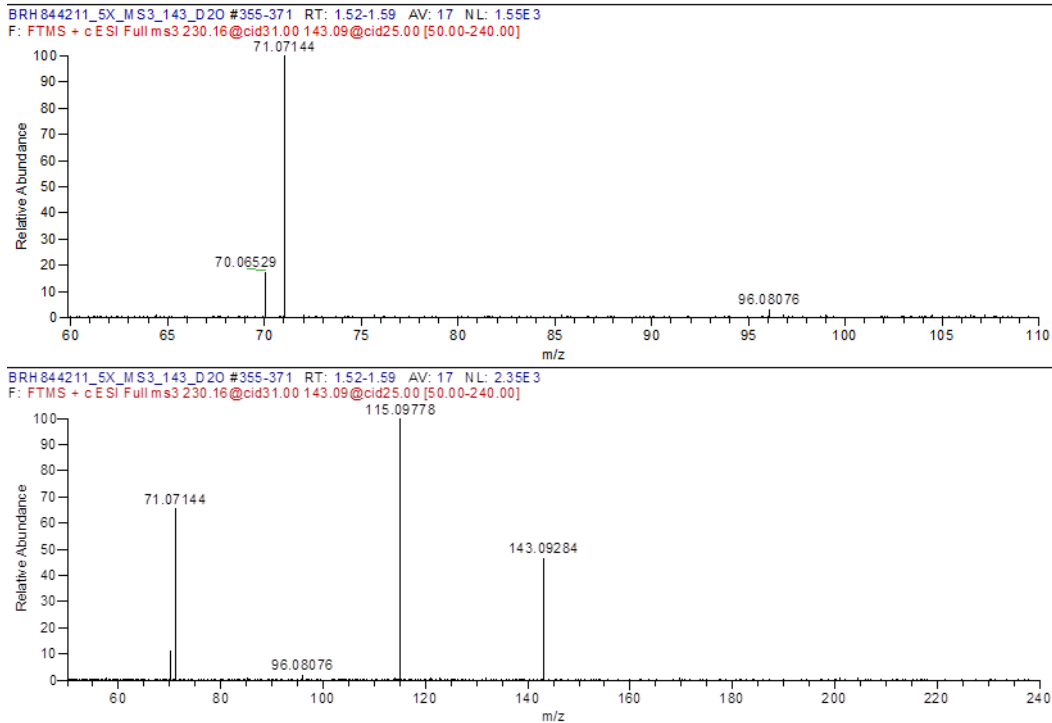


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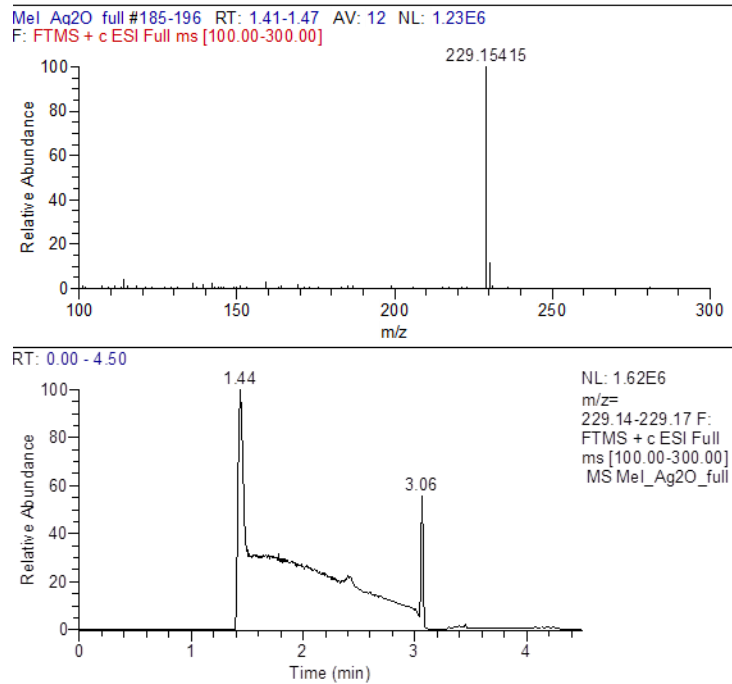


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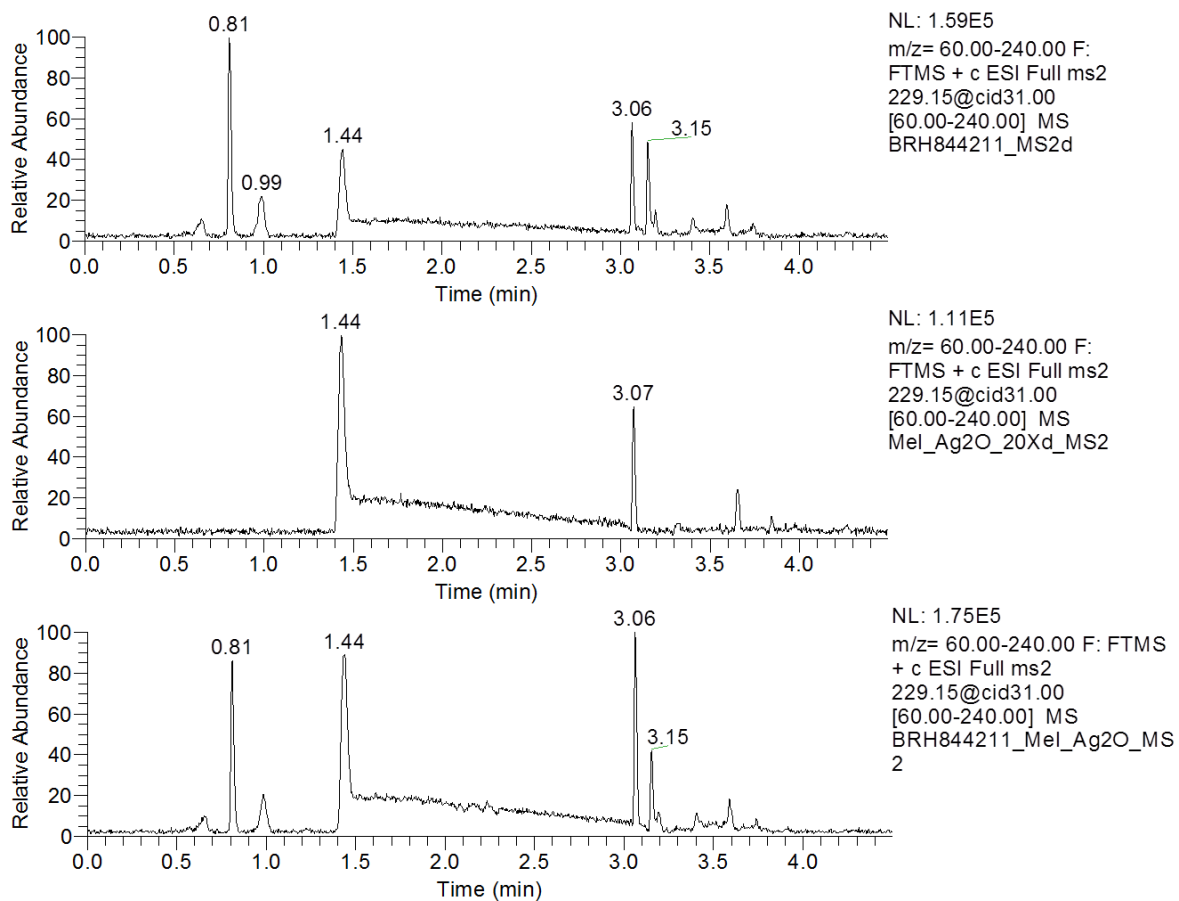


Figure S6. LC-MS/MS chromatograms of x17299 (1.44 min) in a plasma extract (top), synthetic L,L-TMAP (1.44 min, middle), and their co-injection (bottom).

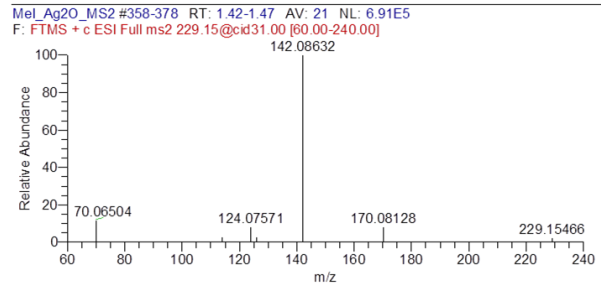
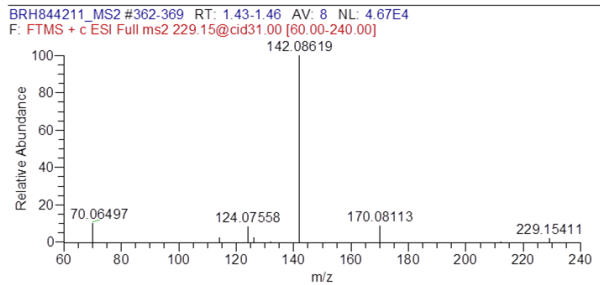
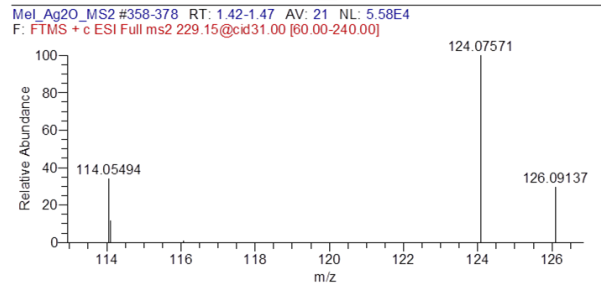
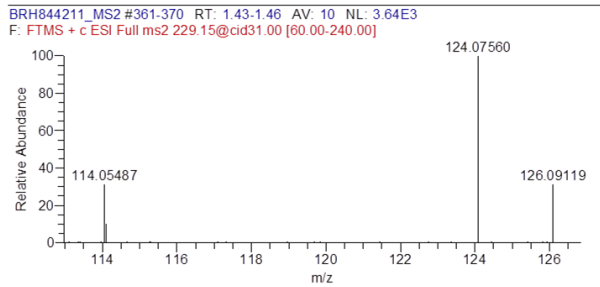
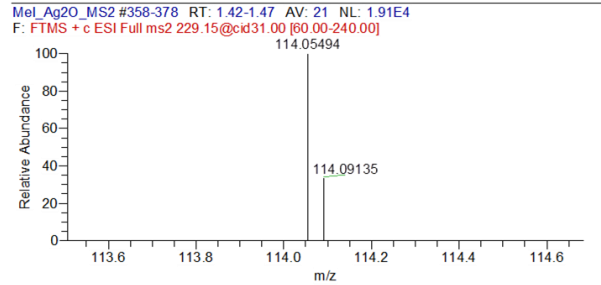
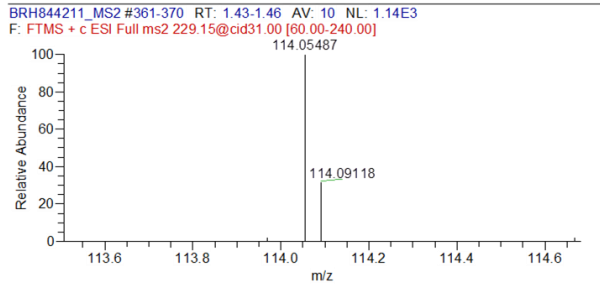


Figure S7. MS² spectra of x17299 (left) and synthetic L,L-TMAP (right) with expansions (top and middle).

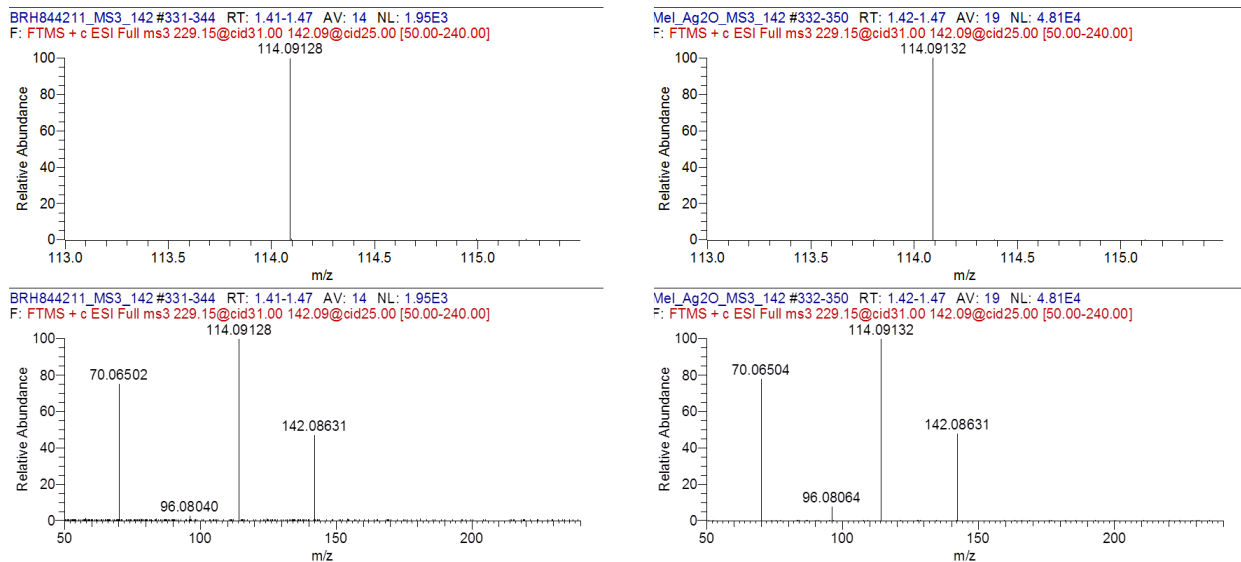


Figure S8. MS³ spectra of m/z 229/142 of x17299 (left) and synthetic L,L-TMAP (right) with expansion (top).

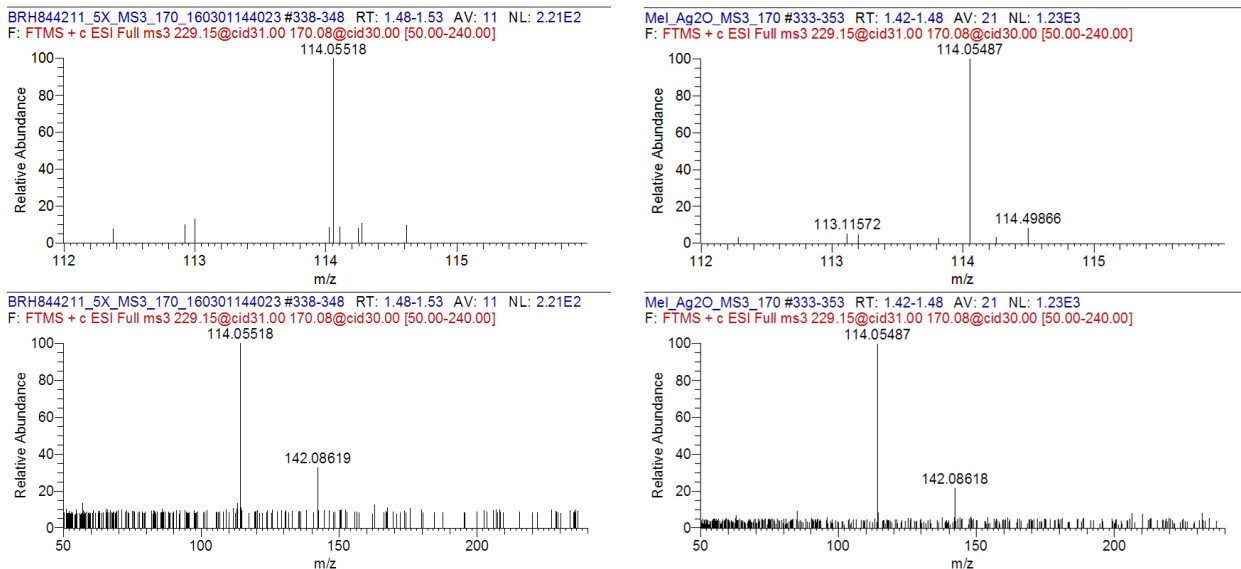


Figure S9. MS³ spectra of m/z 229/170 of x17299 (left) and synthetic L,L-TMAP (right) with expansion (top).

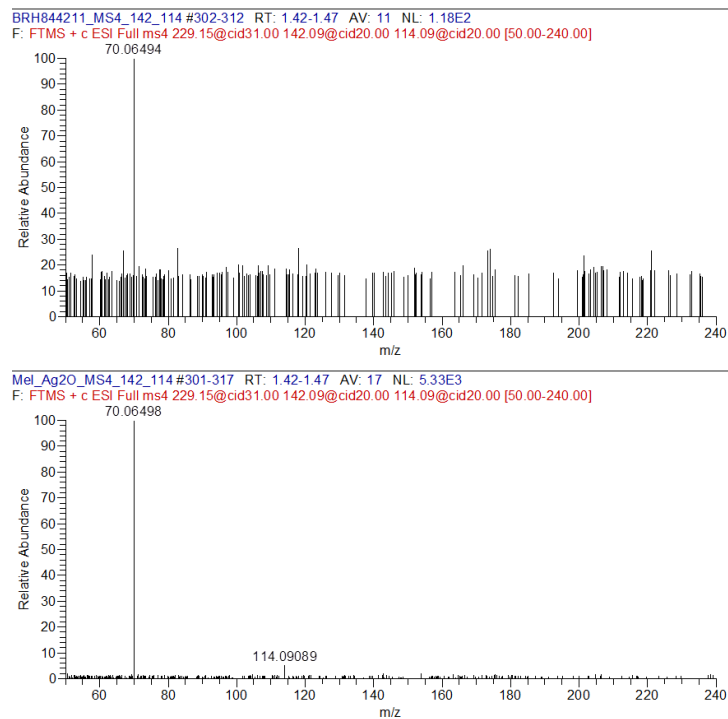


Figure S10. MS⁴ spectra of *m/z* 229/142/114 of synthetic L,L-TMAP (bottom) and x17299 (top) for comparison.

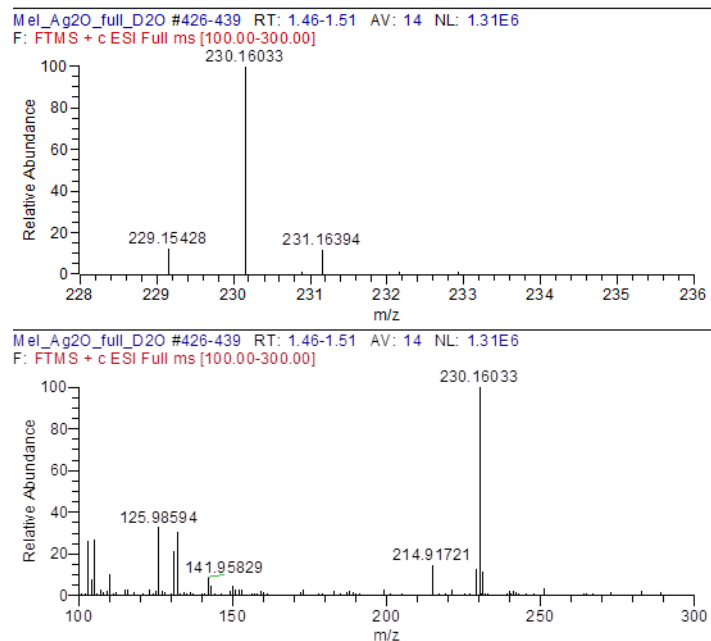


Figure S11. MS spectrum of deuterated synthetic L,L-TMAP with expansion (top).

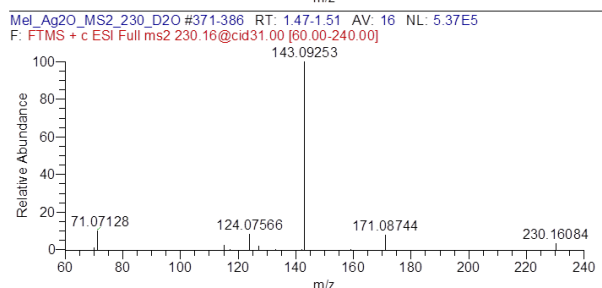
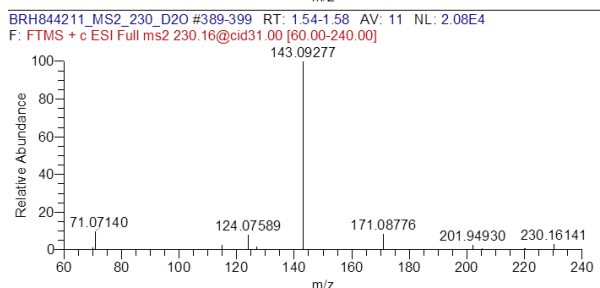
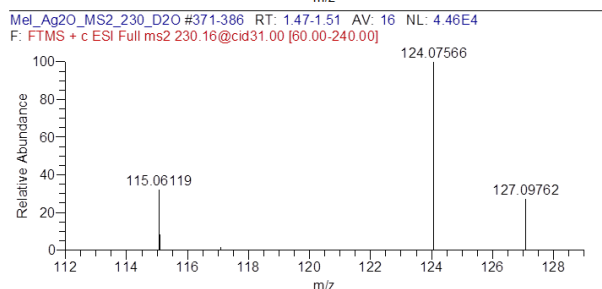
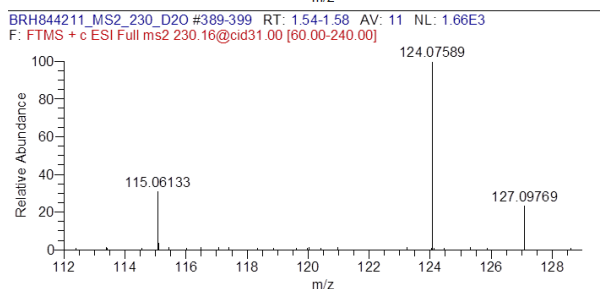
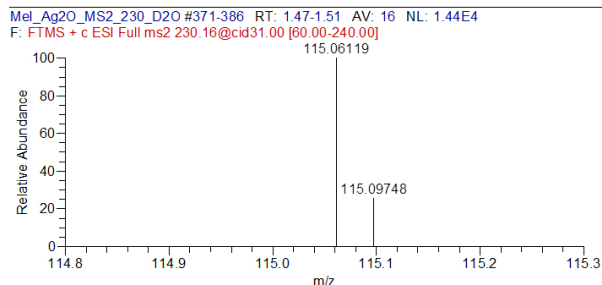
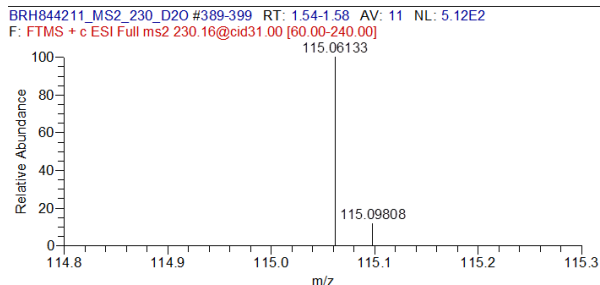


Figure S12. MS² spectra of deuterated x17299 (left) and synthetic L,L-TMAP (right) with expansions (top and middle).

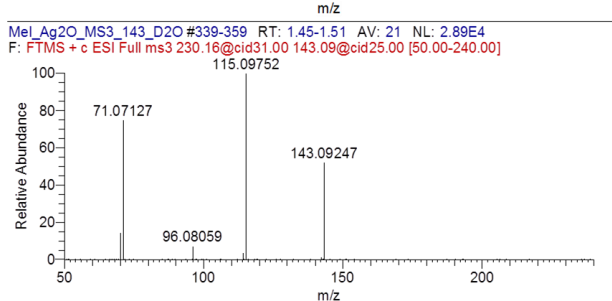
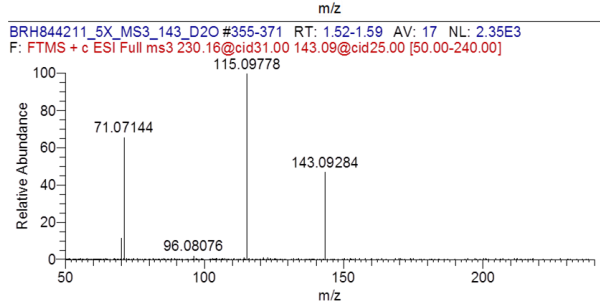
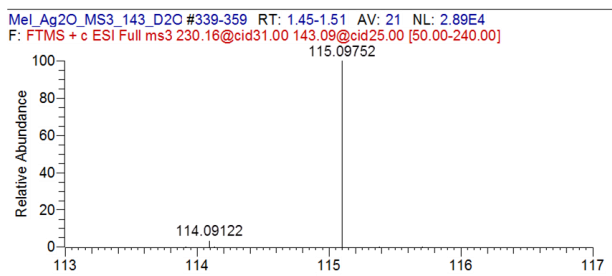
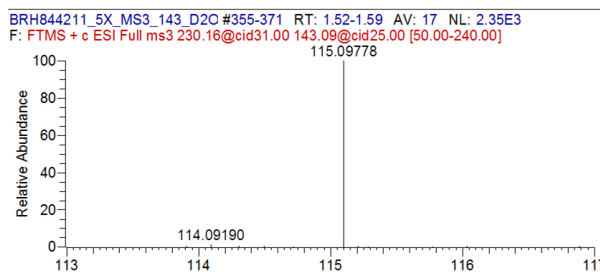


Figure S13. MS³ spectra of *m/z* 230/143 of deuterated x17299 (left) and synthetic L,L-TMAP (right) with expansion (top).

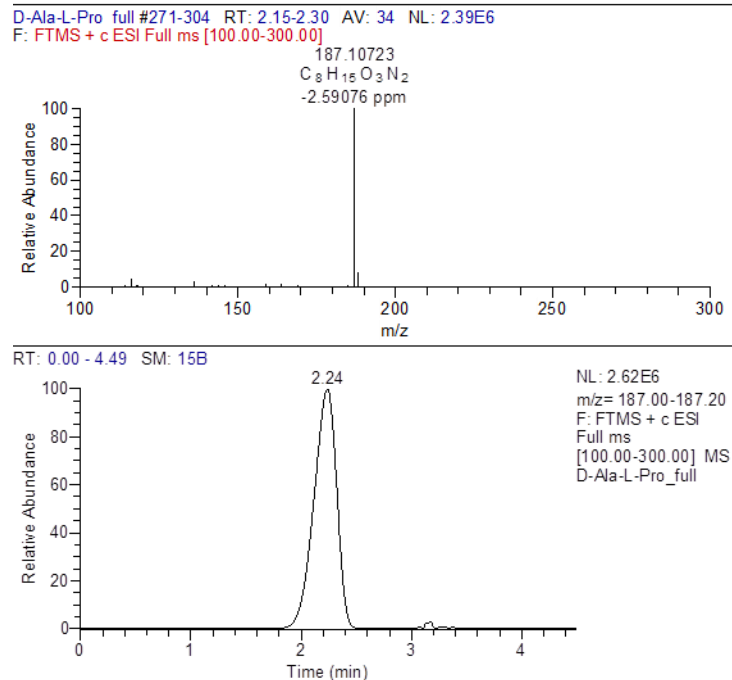


Figure S14. LC/MS chromatogram and spectrum of synthetic D-alanyl-L-proline (2.24 min).

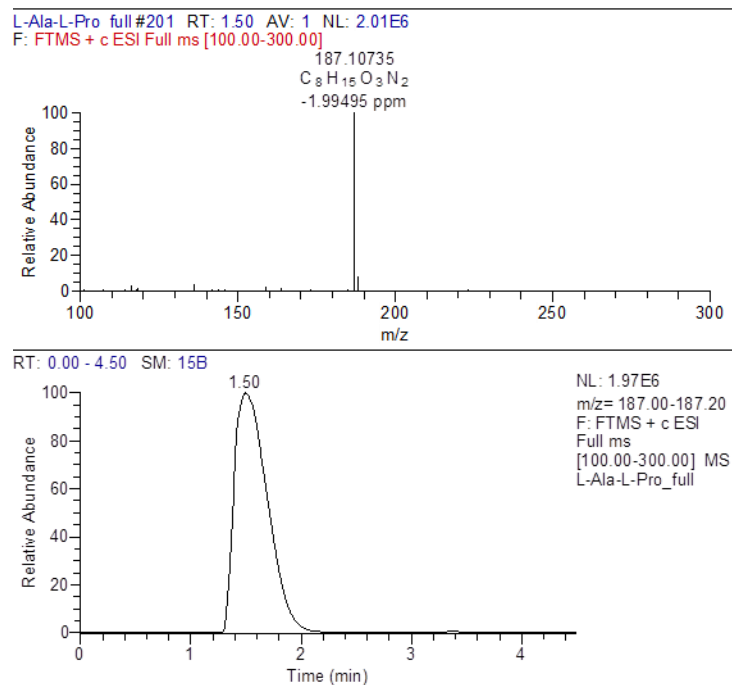


Figure S15. LC/MS chromatogram and spectrum of L-alanyl-L-proline (1.50 min) from TCI for comparison.

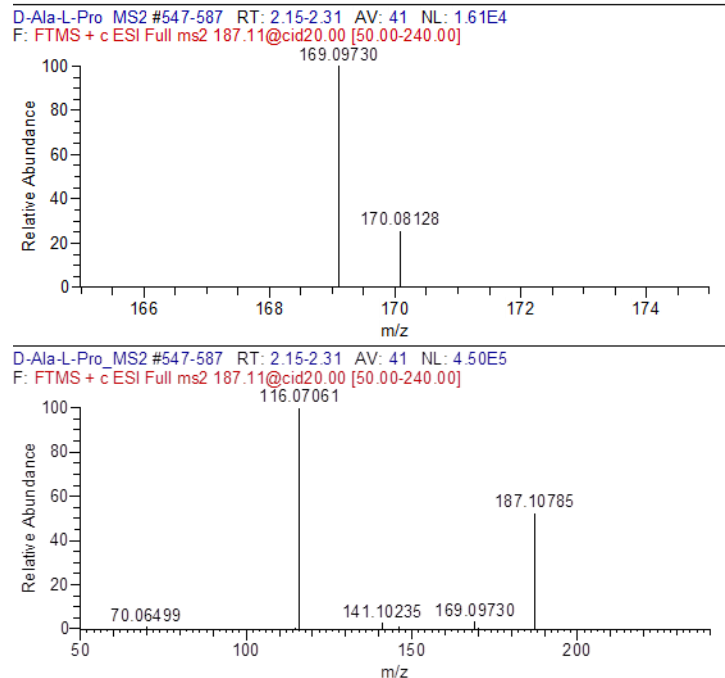


Figure S16. MS² spectrum of synthetic D-alanyl-L-proline with expansion (top).

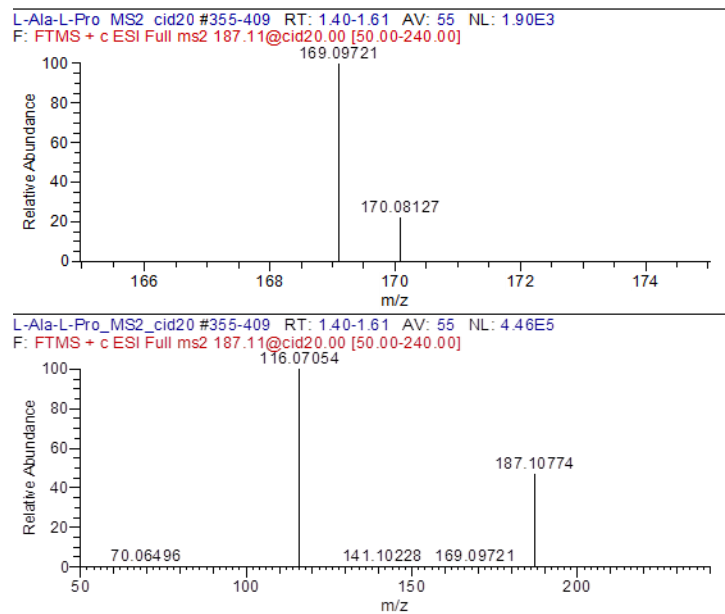


Figure S17. MS² spectrum of L-alanyl-L-proline from TCI with expansion (top) for comparison.

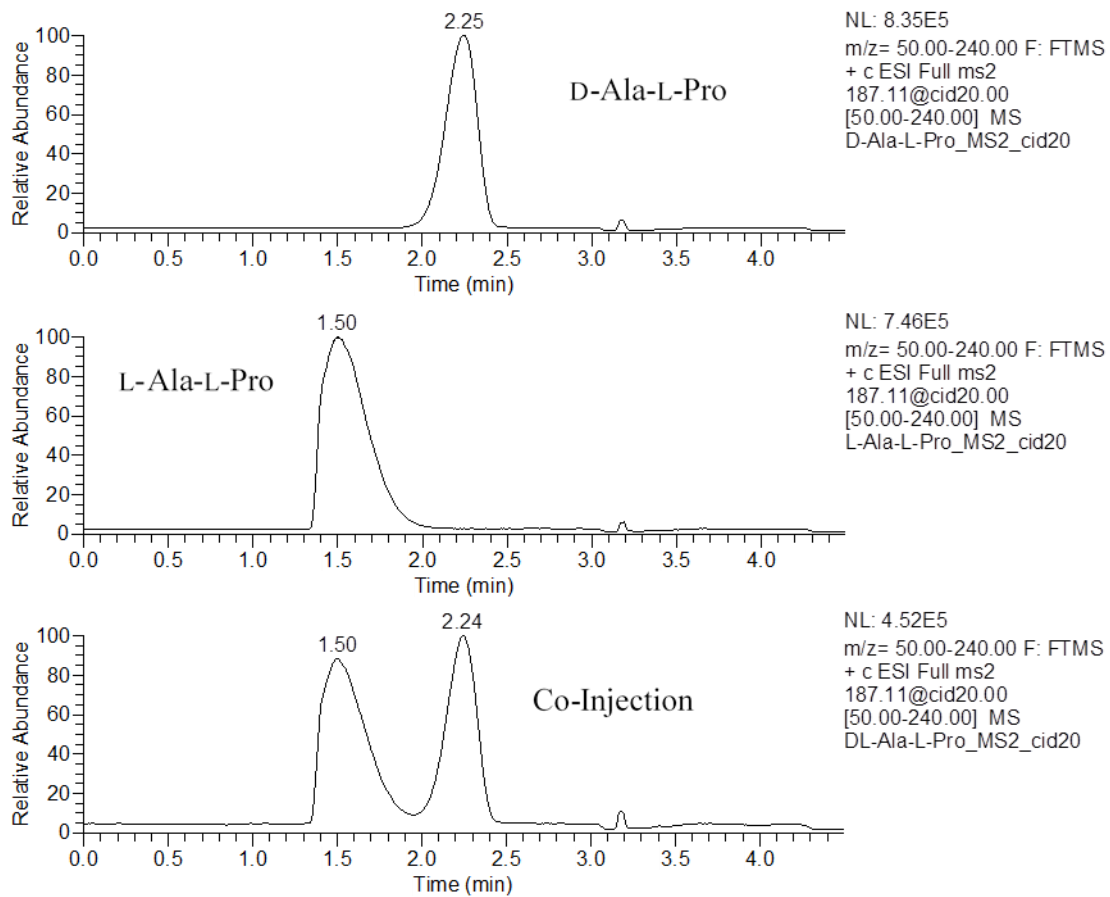


Figure S18. LC-MS/MS chromatograms of D-alanyl-L-proline (top, 2.25 min, synthesized), L-alanyl-L-proline (middle, 1.50 min, from TCI), and a mixture of the two (bottom).

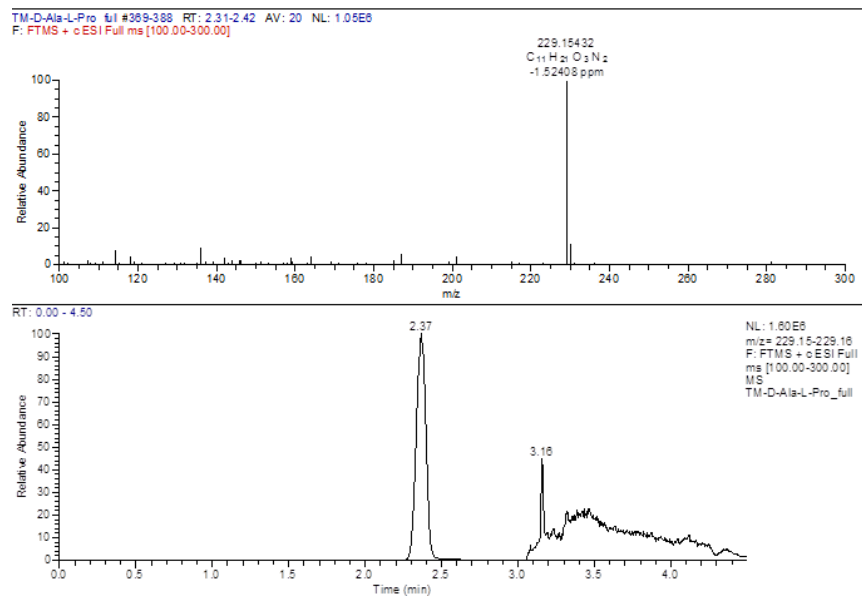


Figure S19. LC/MS chromatogram and spectrum of synthetic D,L-TMAP (2.37 min).

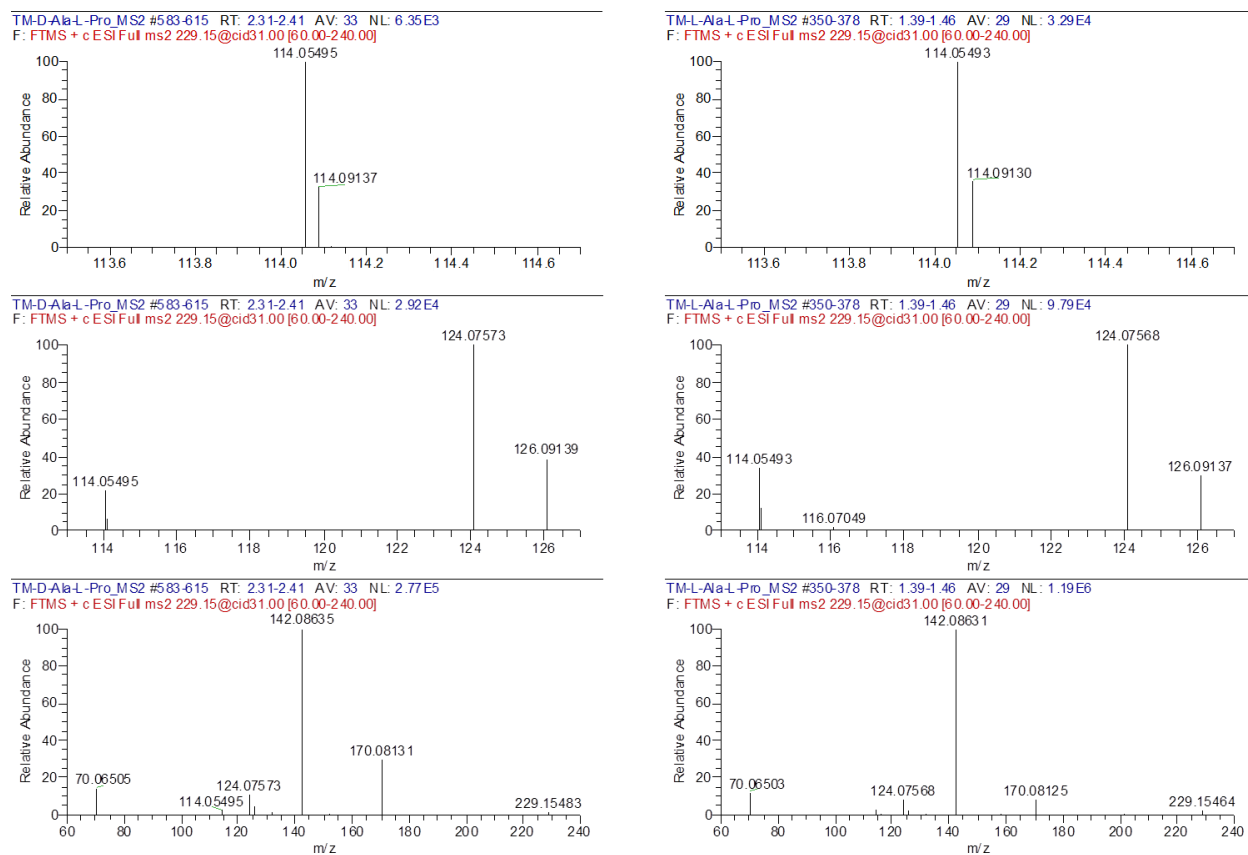


Figure S20. MS² spectra of synthetic D,L-TMAP (left) and L,L-TMAP (right) with expansions (top and middle) for comparison.

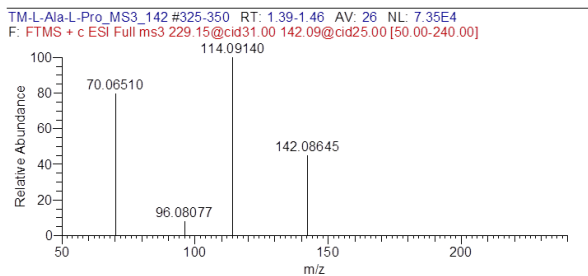
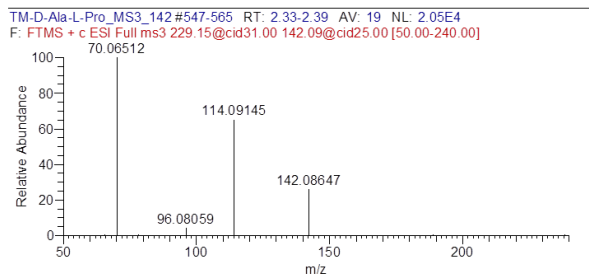
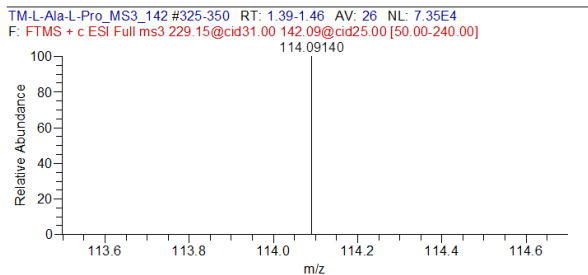
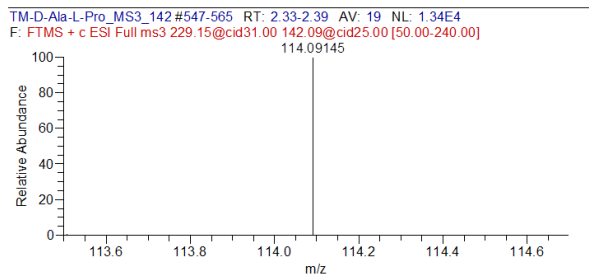


Figure S21. MS³ spectra of m/z 229/142 of synthetic D,L-TMAP (left) and L,L-TMAP (right) with expansion (top) for comparison.

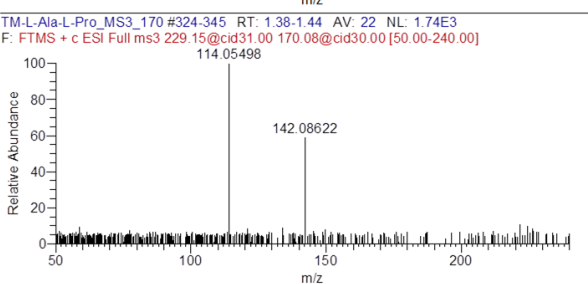
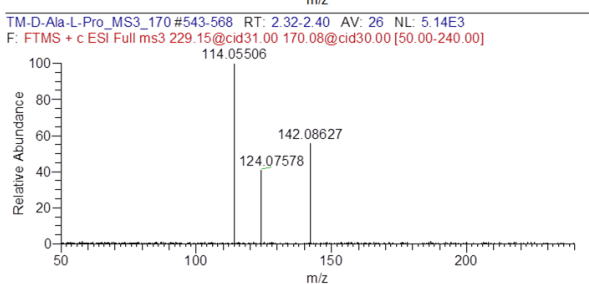
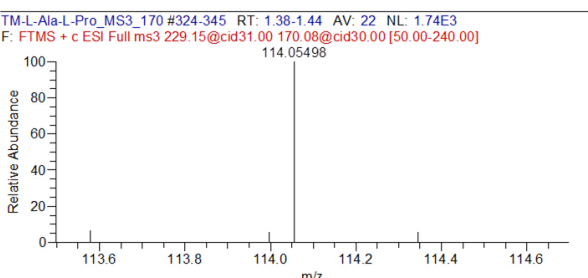
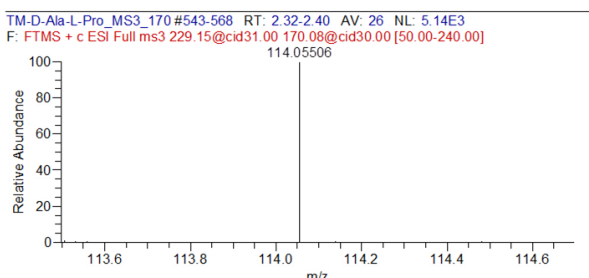


Figure S22. MS³ spectra of m/z 229/170 of synthetic D,L-TMAP (left) and L,L-TMAP (right) with expansion (top) for comparison.

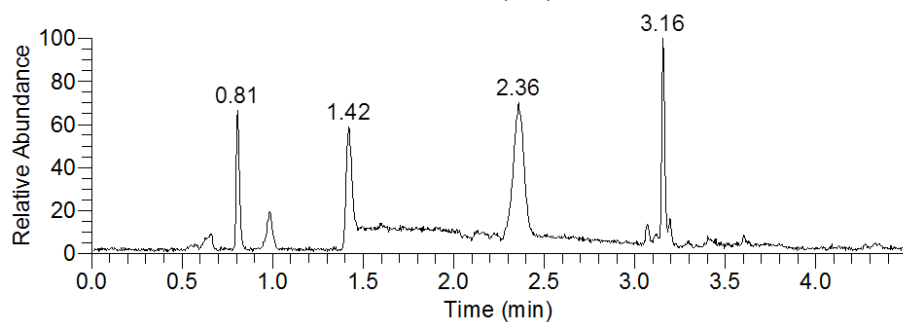
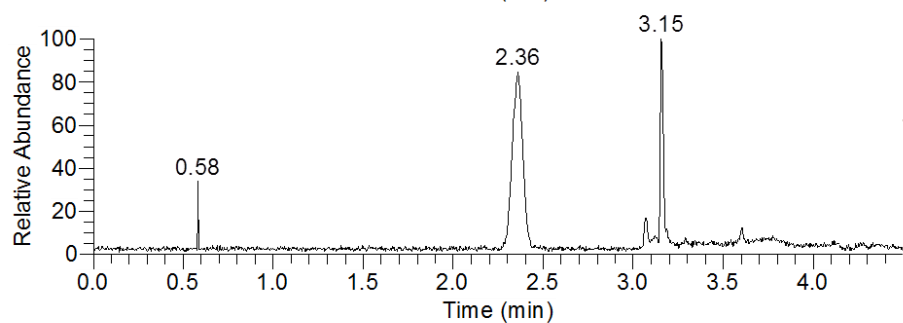
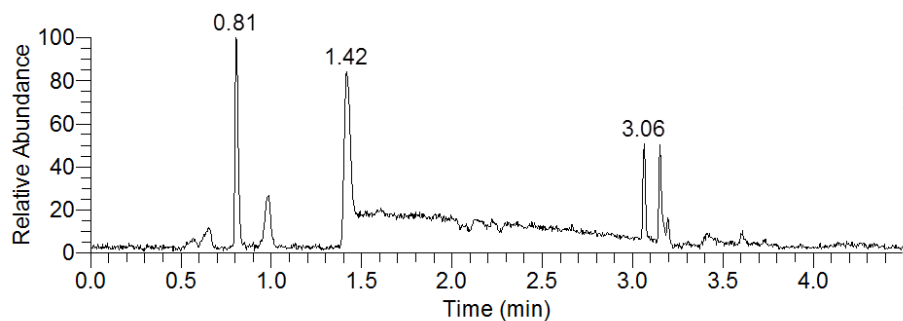


Figure S23. LC-MS/MS chromatograms of x17299 (1.42 min) in a plasma extract (top), synthetic D,L-TMAP (2.36 min, middle), and their co-injection (bottom).

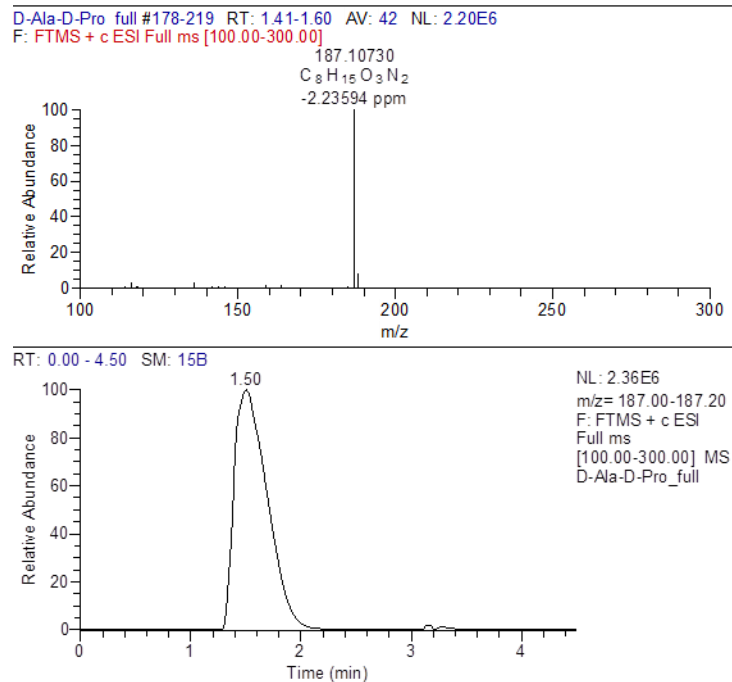


Figure S24. LC/MS chromatogram and spectrum of synthetic D-alanyl-D-proline (1.50 min).

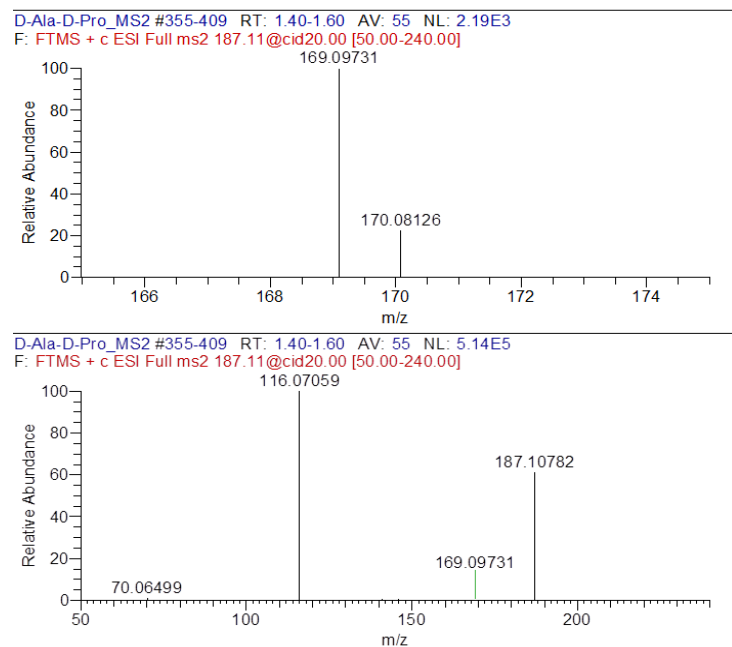


Figure S25. MS² spectrum of synthetic D-alanyl-D-proline with expansion (top).

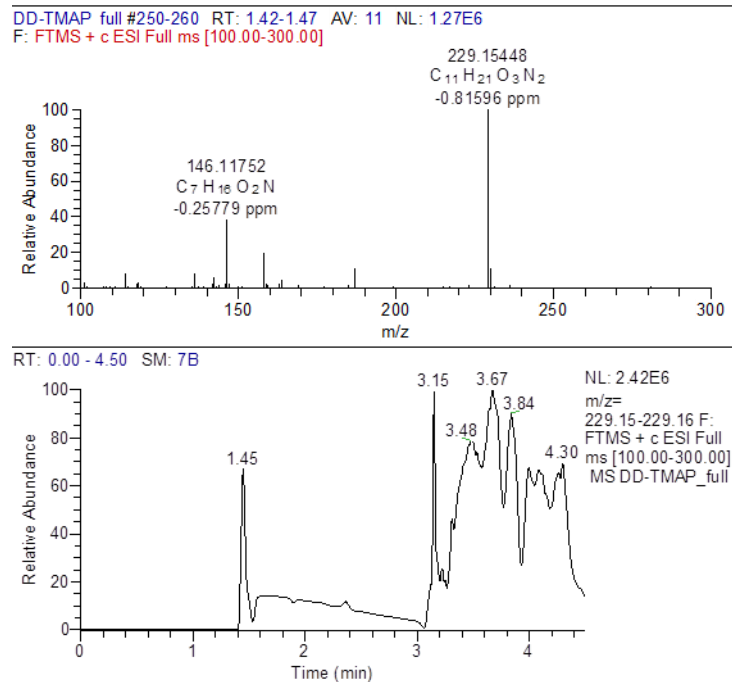


Figure S26. LC/MS chromatogram and spectrum of synthetic D,D-TMAP (1.45 min).

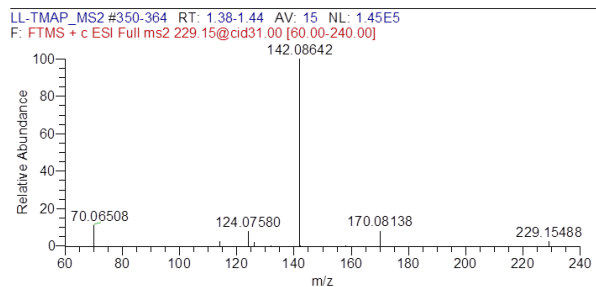
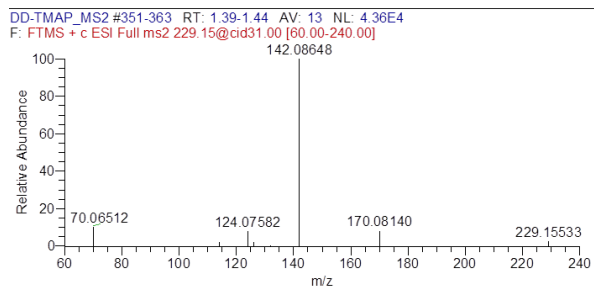
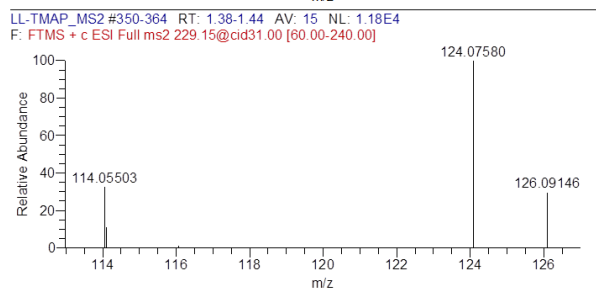
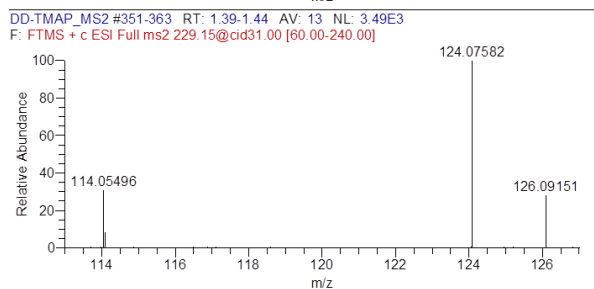
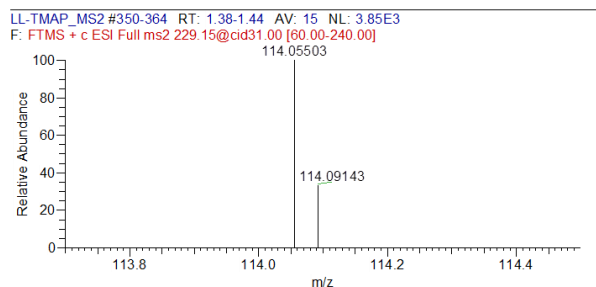
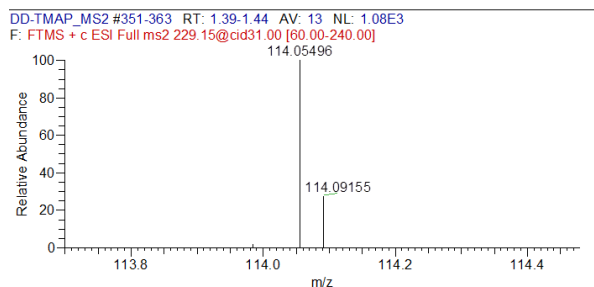


Figure S27. MS² spectra of synthetic D,D-TMAP (left) and L,L-TMAP (right) with expansions (top and middle) for comparison.

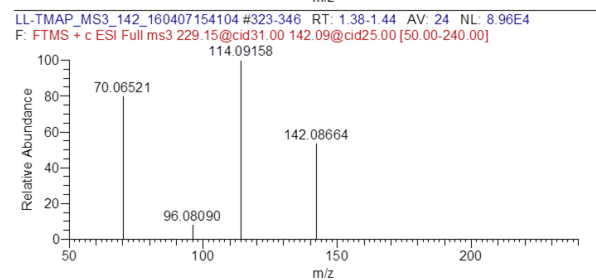
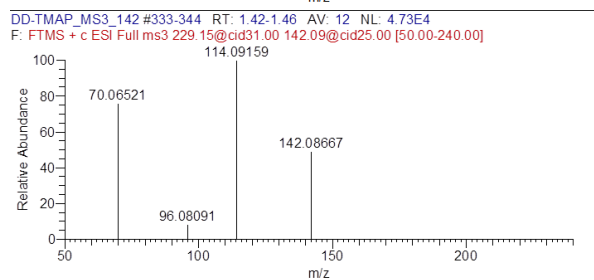
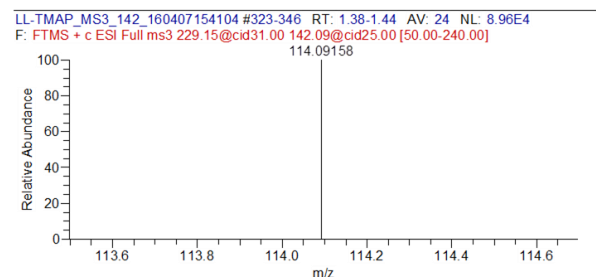
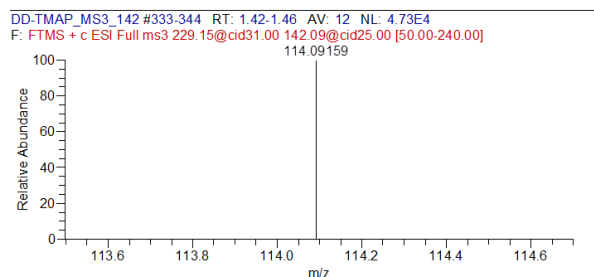
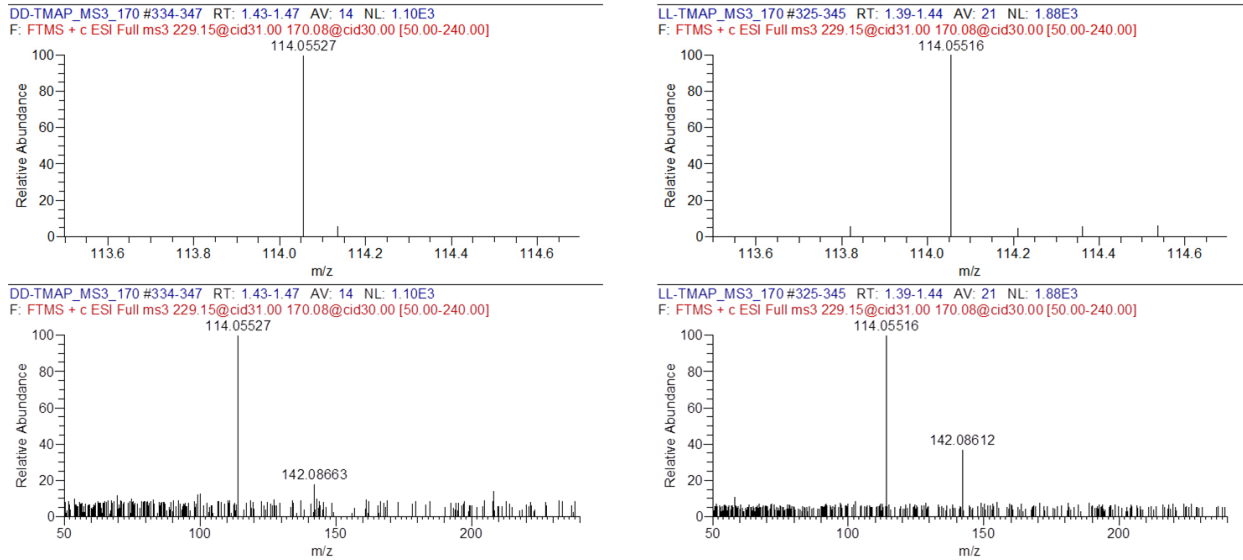


Figure S28. MS³ spectra of *m/z* 229/142 of synthetic D,D-TMAP (left) and L,L-TMAP (right) with expansion (top) for comparison.



S-Figure S29. MS³ spectra of *m/z* 229/170 of synthetic D,D-TMAP (left) and L,L-TMAP (right) with expansion (top) for comparison.

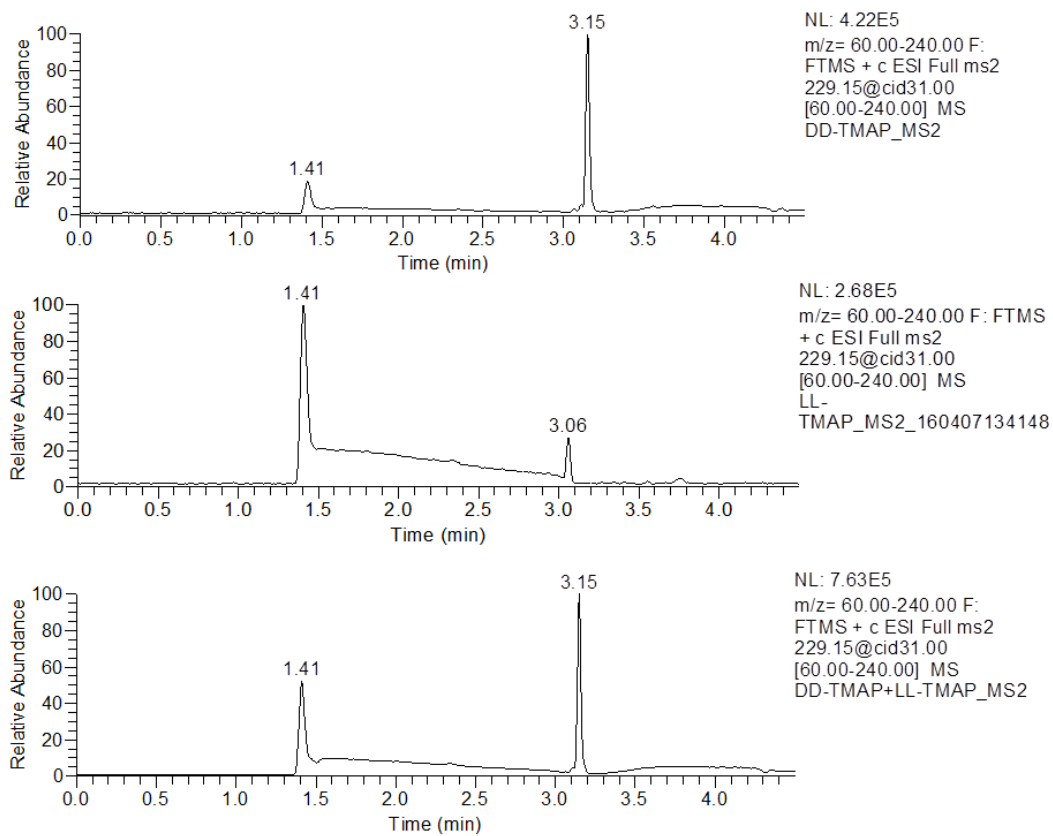


Figure S30. LC-MS/MS chromatograms of synthetic D,D-TMAP (1.41 min, top), L,L-TMAP (1.41 min, middle), and their co-injection (bottom).

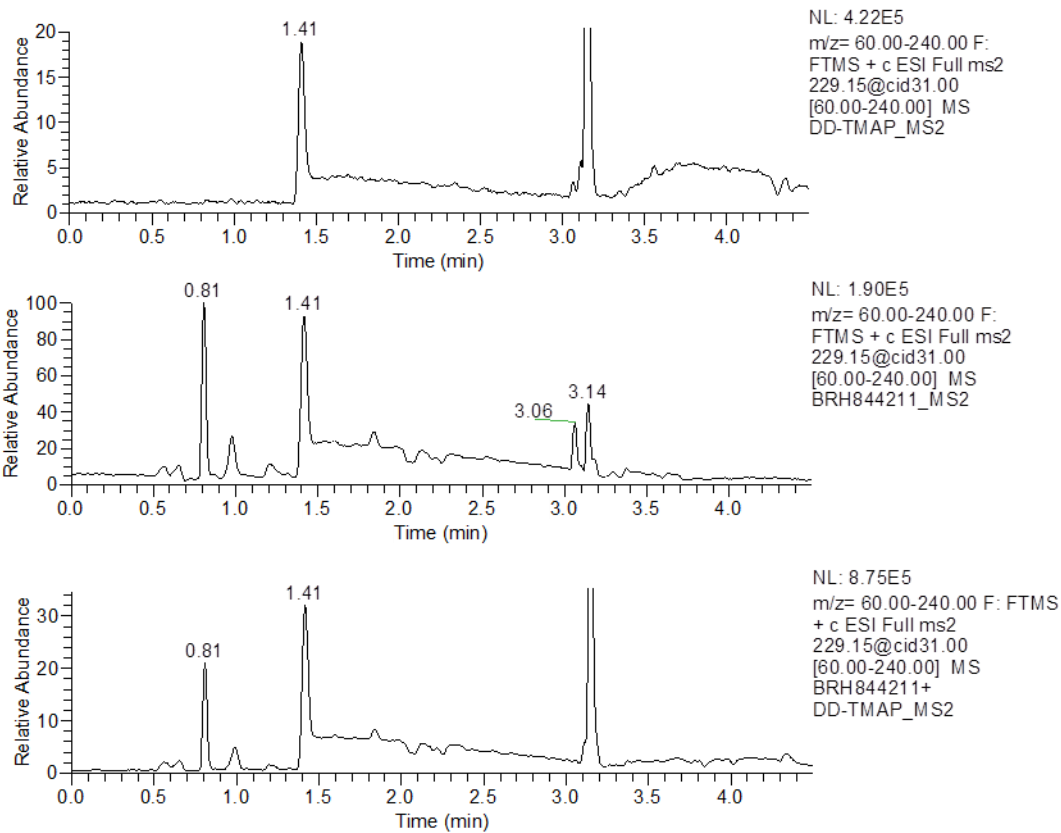


Figure S31. LC-MS/MS chromatograms of synthetic D,D-TMAP (1.41 min, top), x17299 (1.41 min, middle) in a plasma extract, and their co-injection (bottom).

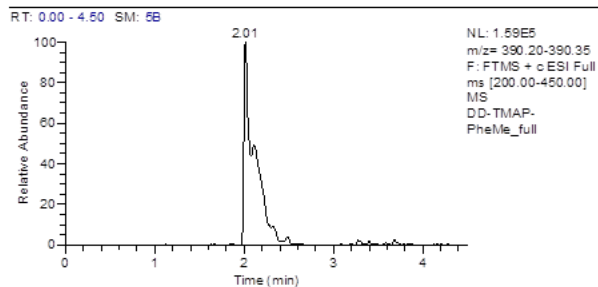
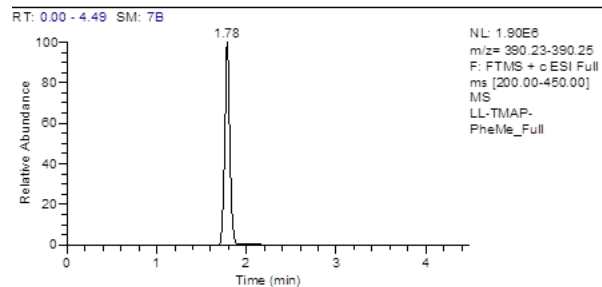
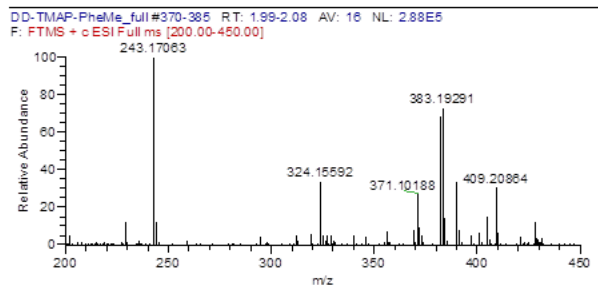
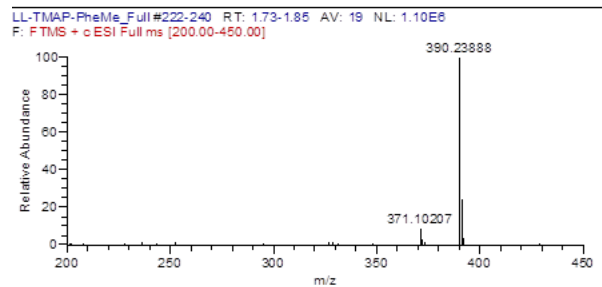
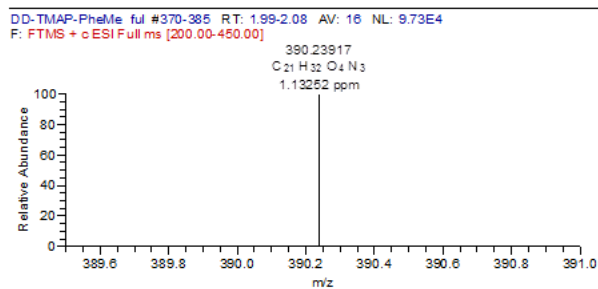
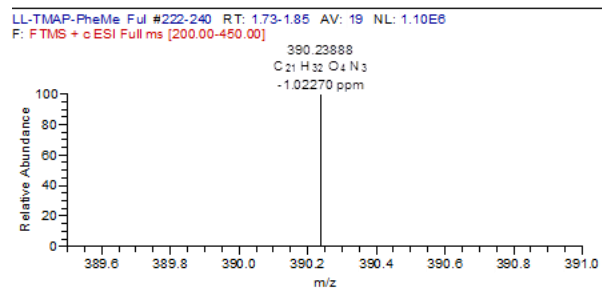
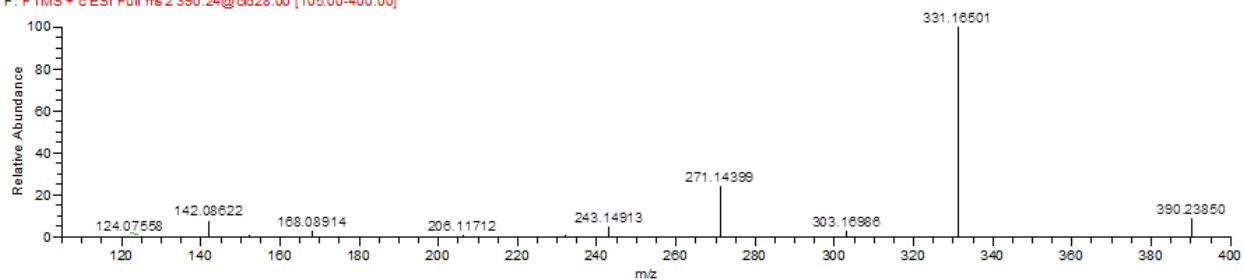
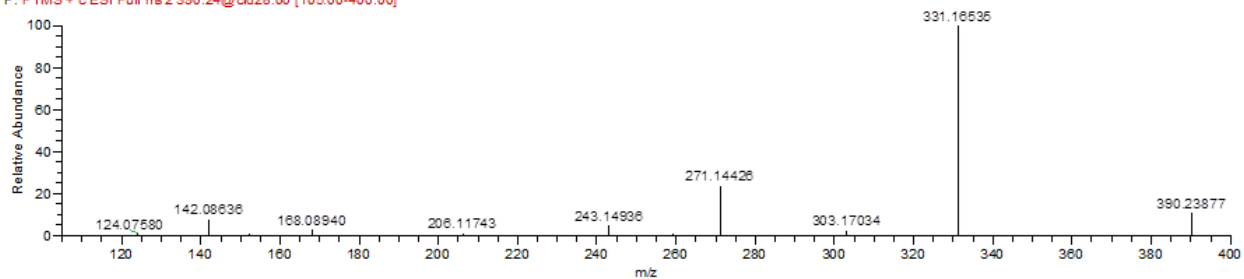


Figure S32. LC/MS chromatograms and mass spectra of L,L-TMAP-L-Phe-OMe (1.78 min, left) and D,D-TMAP-L-Phe-OMe (2.01 min, right) with expansions (top).

BRH844211-PheMe_MS2 #442-462 RT: 1.74-1.82 AV: 21 SB: 15 1.66-1.72 NL: 2.63E4
F: FTMS + c ESI Full ms 2 390.24@cid28.00 [105.00-400.00]



LL-TMAP-PheMe_MS2 #440-469 RT: 1.75-1.82 AV: 20 NL: 4.67E4
F: FTMS + c ESI Full ms 2 390.24@cid28.00 [105.00-400.00]



DD-TMAP-PheMe_MS2 #500-523 RT: 1.98-2.08 AV: 24 NL: 5.98E4
F: FTMS + c ESI Full ms 2 390.24@cid28.00 [105.00-400.00]

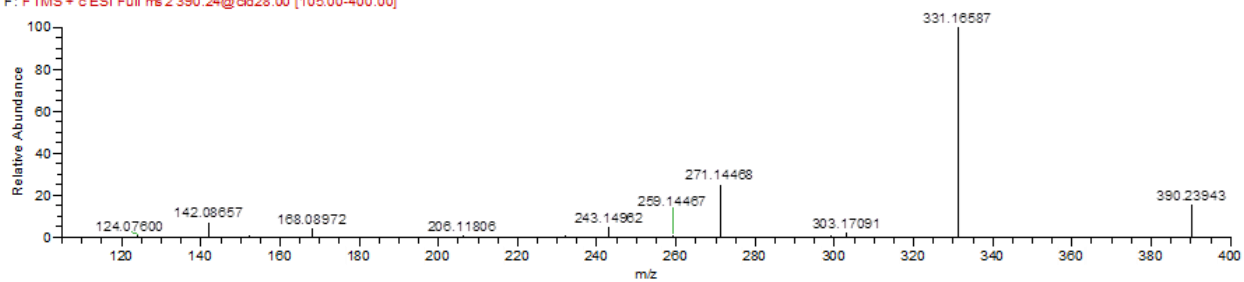
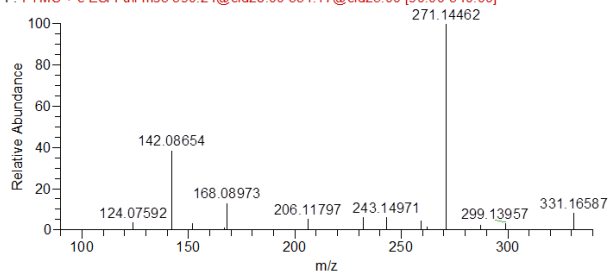
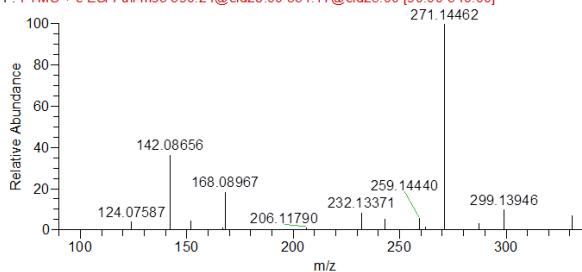


Figure S33. MS² spectra of L,L-TMAP-L-Phe-OMe (middle), D,D-TMAP-L-Phe-OMe (bottom), and x17299-L-Phe-OMe (top).

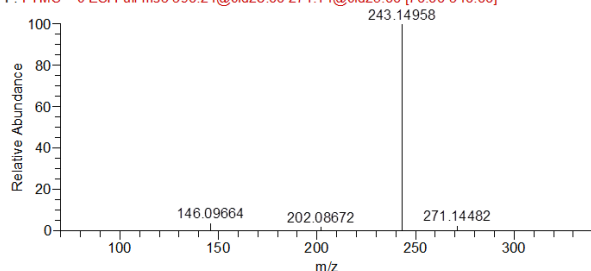
LL-TMAP-PheMe_MS3_331 #411-436 RT: 1.75-1.82 AV: 26 NL: 2.53E5
F: FTMS + c ESI Full ms3 390.24@cid28.00 331.17@cid25.00 [90.00-340.00]



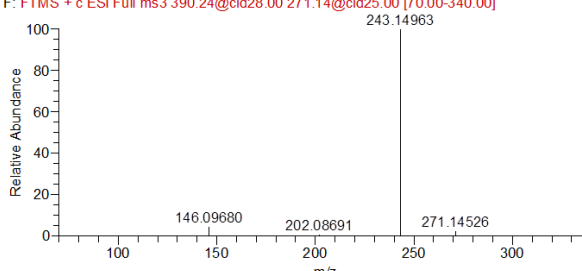
DD-TMAP-PheMe_MS3_331 #467-487 RT: 1.99-2.07 AV: 21 NL: 1.28E4
F: FTMS + c ESI Full ms3 390.24@cid28.00 331.17@cid25.00 [90.00-340.00]



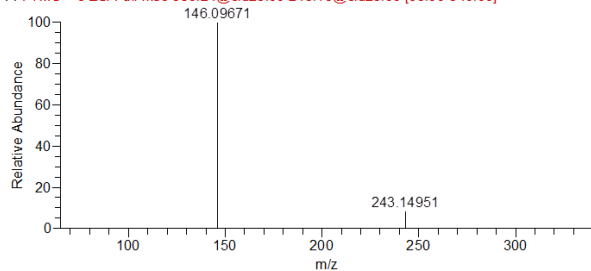
LL-TMAP-PheMe_MS3_271 #410-437 RT: 1.74-1.82 AV: 28 NL: 2.25E5
F: FTMS + c ESI Full ms3 390.24@cid28.00 271.14@cid25.00 [70.00-340.00]



DD-TMAP-PheMe_MS3_271 #469-491 RT: 1.99-2.09 AV: 23 NL: 1.26E4
F: FTMS + c ESI Full ms3 390.24@cid28.00 271.14@cid25.00 [70.00-340.00]



LL-TMAP-PheMe_MS3_243 #411-440 RT: 1.75-1.83 AV: 30 NL: 3.81E4
F: FTMS + c ESI Full ms3 390.24@cid28.00 243.15@cid25.00 [65.00-340.00]



DD-TMAP-PheMe_MS3_243 #465-480 RT: 1.98-2.04 AV: 16 NL: 1.86E3
F: FTMS + c ESI Full ms3 390.24@cid28.00 243.15@cid25.00 [65.00-340.00]

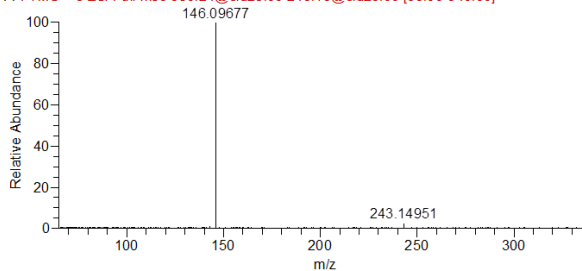


Figure S34. MS³ spectra of m/z 390/331 (top), m/z 390/271 (middle), and m/z 390/243 (bottom) of L,L-TMAP-L-Phe-OMe (left) and D,D-TMAP-L-Phe-OMe (right).

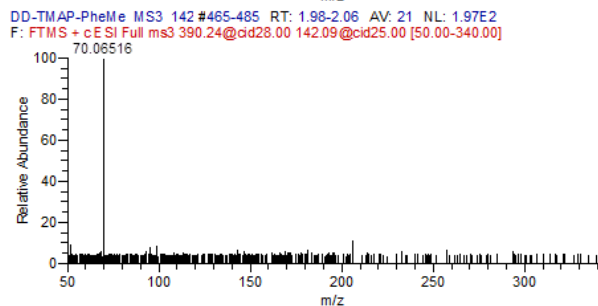
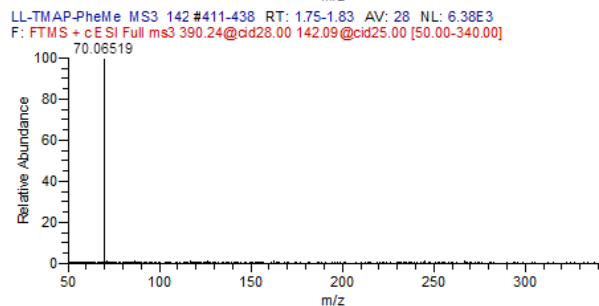
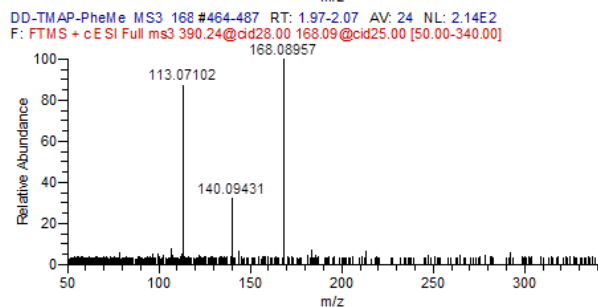
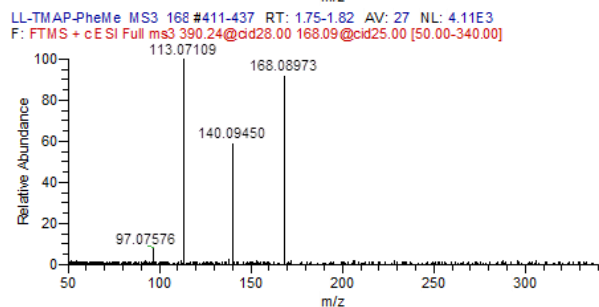
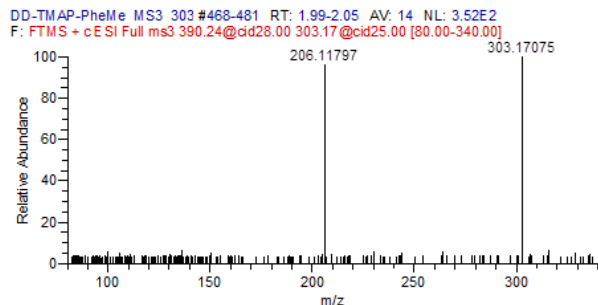
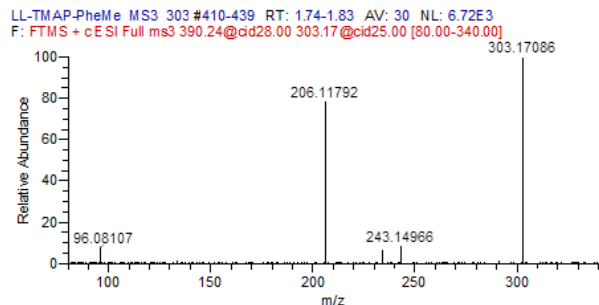


Figure S35. MS³ spectra of *m/z* 390/303 (top), *m/z* 390/168 (middle), and *m/z* 390/142 (bottom) of L,L-TMAP-L-Phe-OMe (left) and D,D-TMAP-L-Phe-OMe (right).

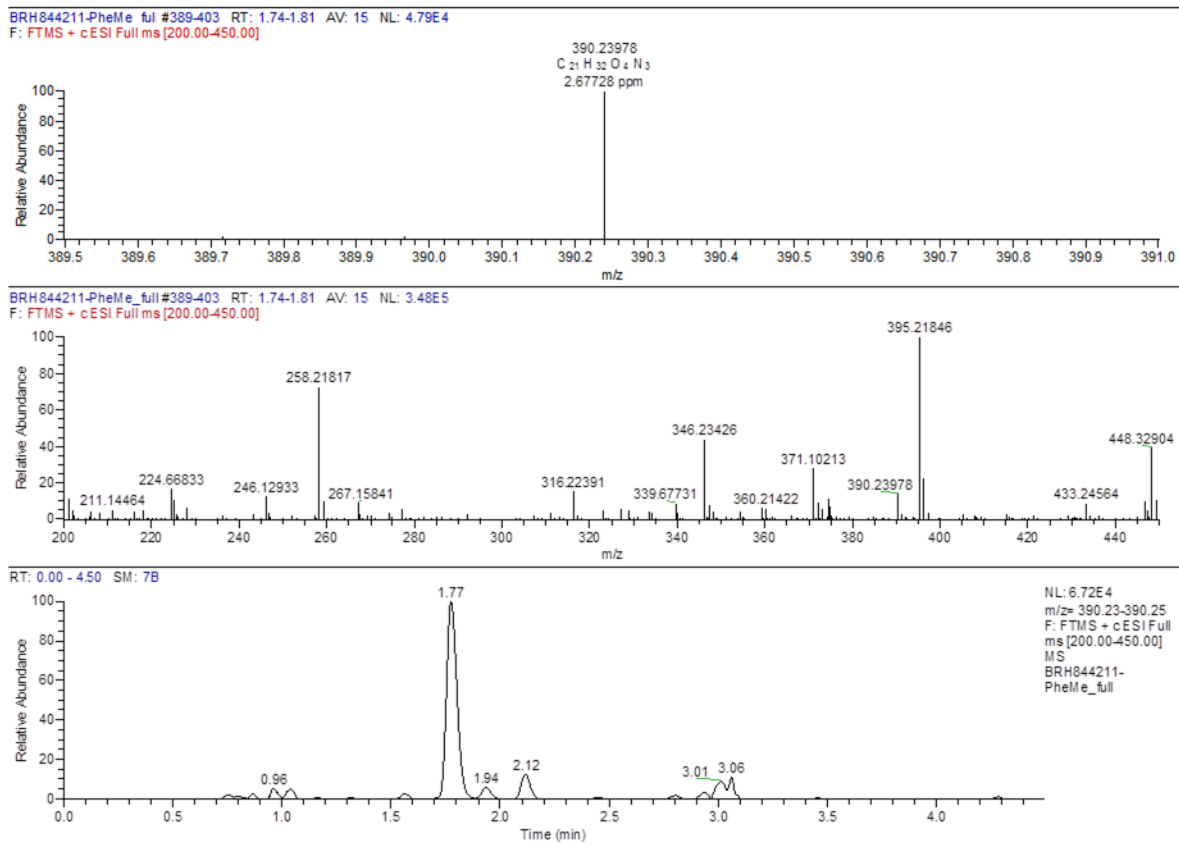
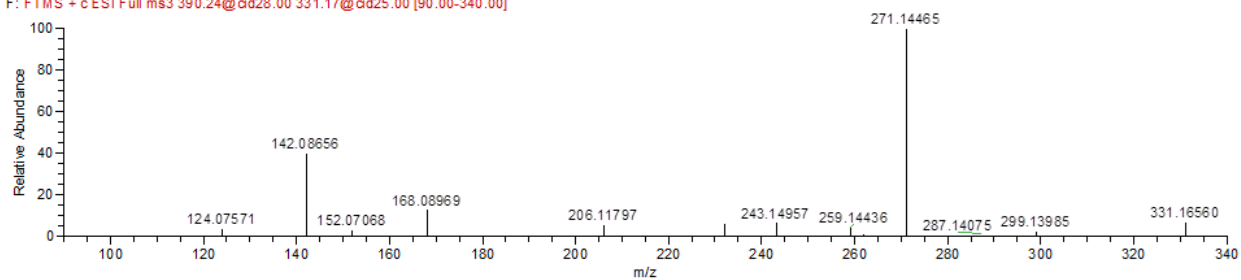
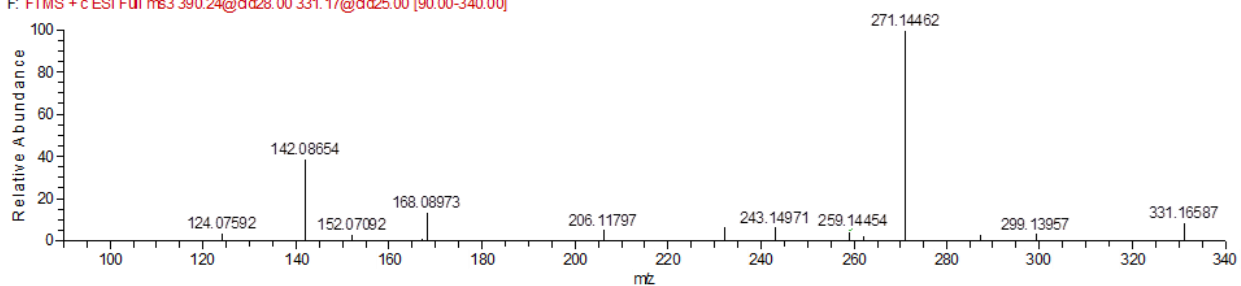


Figure S36. LC/MS chromatograms and mass spectrum of x17299-L-Phe-OMe (1.77 min) with expansion (top).

BRH844211-PheMe_MS3_331#419-426 RT: 1.76-1.79 AV: 8 NL: 9.52E3
F: FTMS + c ESI Full ms3 390.24@cid28.00 331.17@cid25.00 [90.00-340.00]



LL-TMAP-PheMe_MS3_331#411-436 RT: 1.75-1.82 AV: 26 NL: 2.53E5
F: FTMS + c ESI Full ms3 390.24@cid28.00 331.17@cid25.00 [90.00-340.00]



DD-TMAP-PheMe_MS3_331#471-489 RT: 2.00-2.08 AV: 19 NL: 1.35E4
F: FTMS + c ESI Full ms3 390.24@cid28.00 331.17@cid25.00 [90.00-340.00]

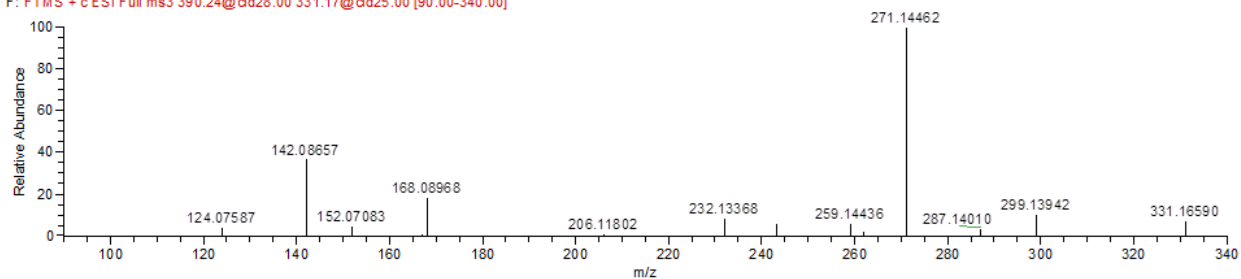
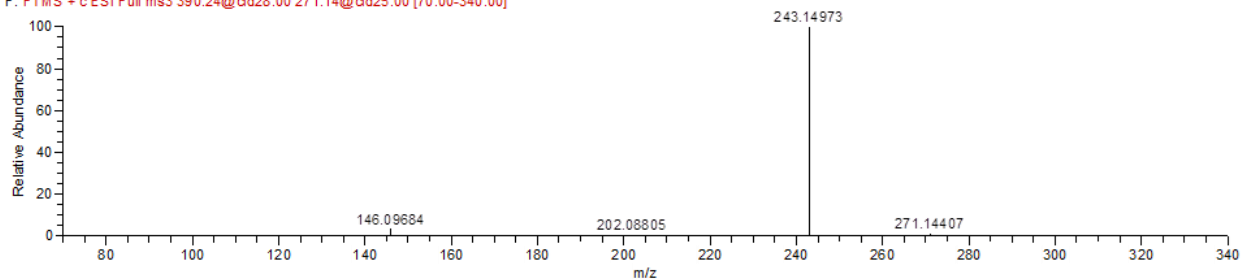
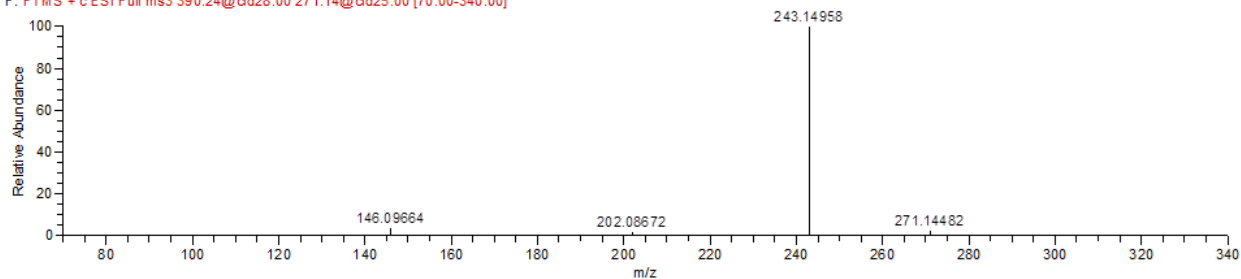


Figure S37. MS³ spectra of *m/z* 390/331 of x17299-L-Phe-OMe (top), L,L-TMAP-L-Phe-OMe (middle), and D,D-TMAP-L-Phe-OMe (bottom).

BRH844211-PheMe_MS3_271 #413-433 RT: 1.74-1.82 AV: 21 NL: 4.64E3
F: FTMS + c ESI Full ms3 390.24@cid28.00 271.14@cid25.00 [70.00-340.00]



LL-TMAP-PheMe_MS3_271 #410-437 RT: 1.74-1.82 AV: 28 NL: 2.25E5
F: FTMS + c ESI Full ms3 390.24@cid28.00 271.14@cid25.00 [70.00-340.00]



DD-TMAP-PheMe_MS3_271 #469-491 RT: 1.99-2.09 AV: 23 NL: 1.26E4
F: FTMS + c ESI Full ms3 390.24@cid28.00 271.14@cid25.00 [70.00-340.00]

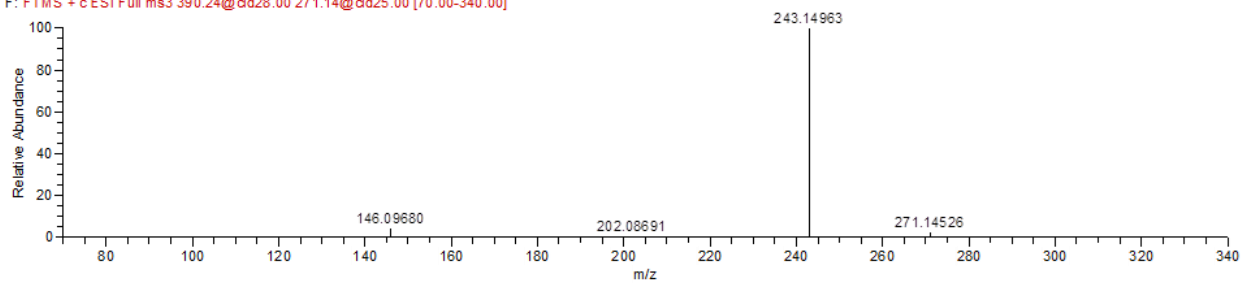


Figure S38. MS³ spectra of *m/z* 390/271 of x17299-L-Phe-OMe (top), L,L-TMAP-L-Phe-OMe (middle), and D,D-TMAP-L-Phe-OMe (bottom).

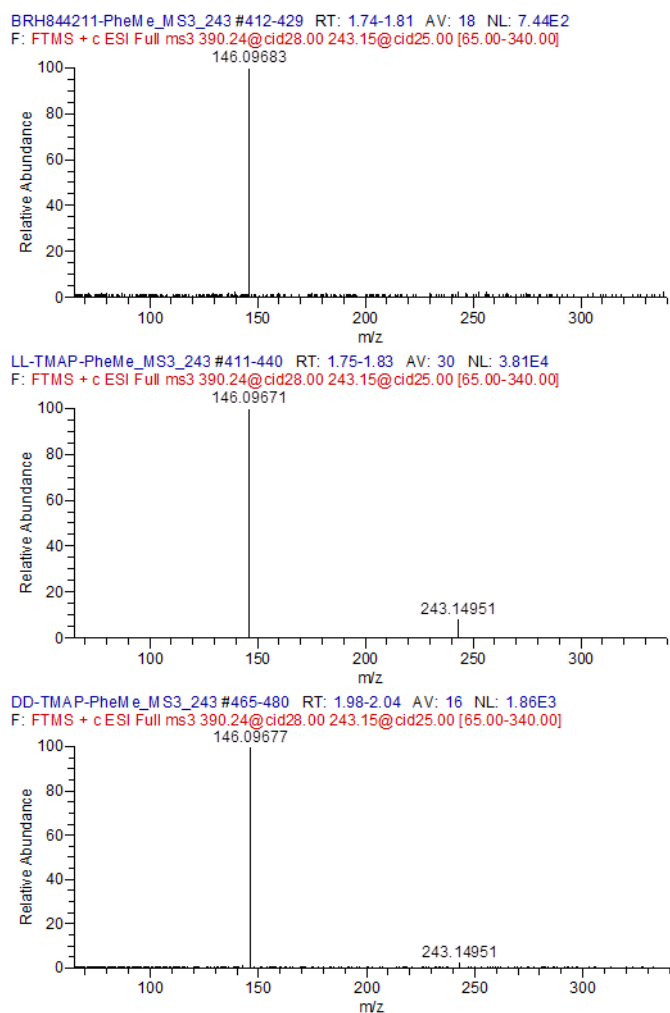


Figure S39. MS³ spectra of m/z 390/243 of x17299-L-Phe-OMe (top), L,L-TMAP-L-Phe-OMe (middle), and D,D-TMAP-L-Phe-OMe (bottom).

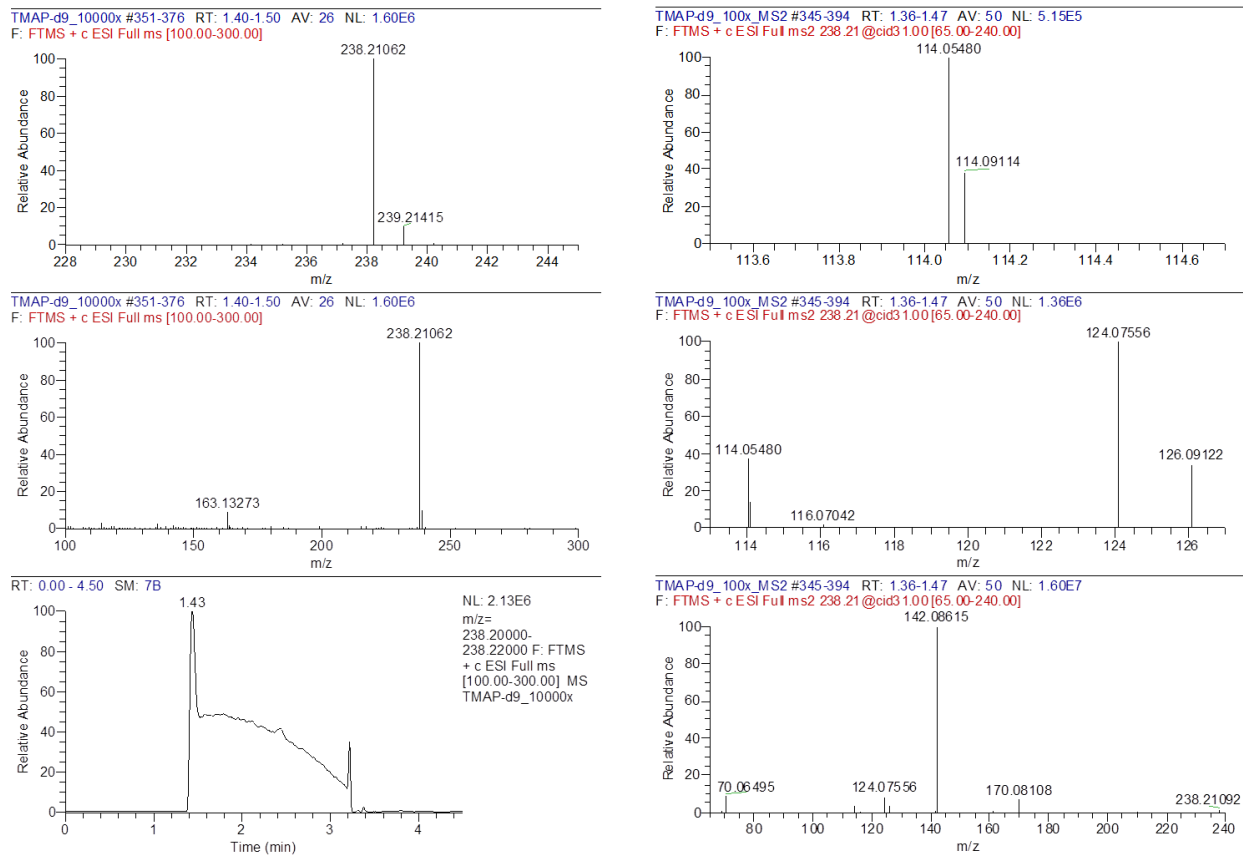


Figure S40. LC/MS chromatogram and MS spectrum (left), and MS² spectrum (right) of synthetic L,L-TMAP-*d*₉ (1.43 min) with expansions (middle and top).

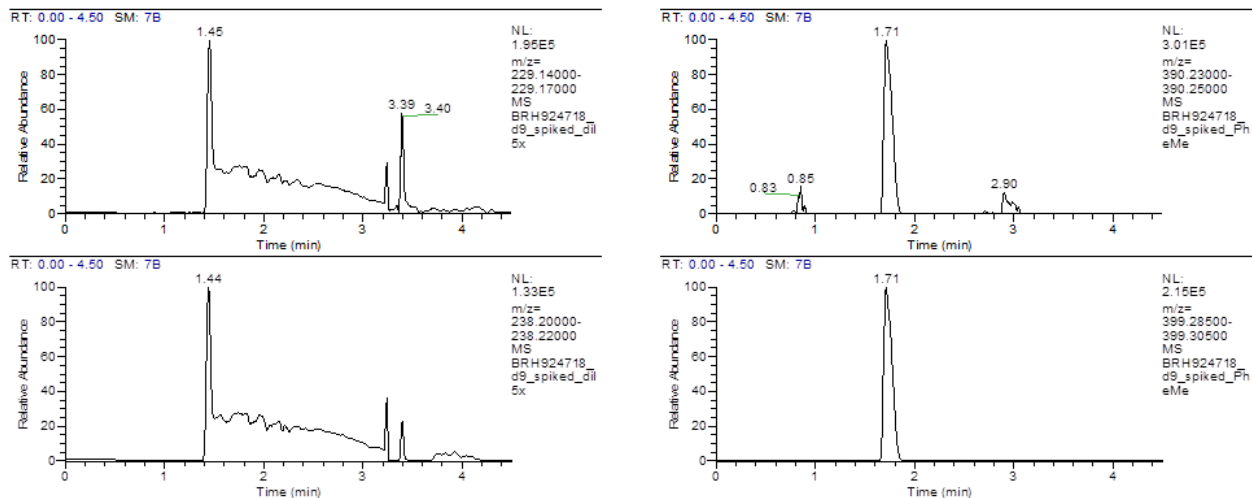
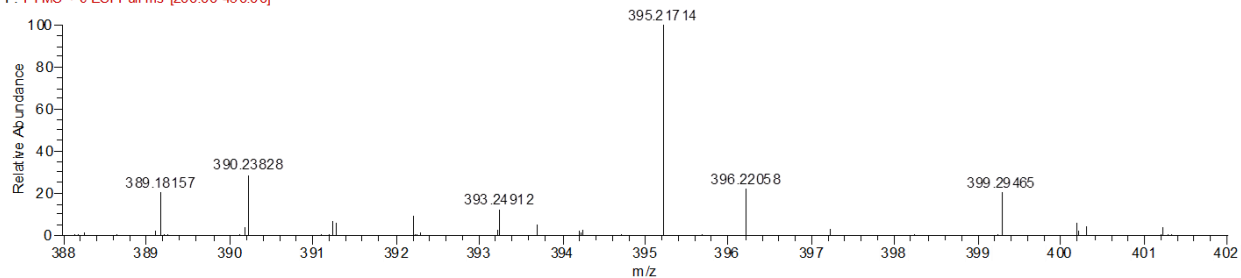


Figure S41. LC/MS chromatograms of x17299 (1.45 min, left top) and L,L-TMAP-*d*₉ (1.44 min, left bottom) in a spiked plasma extract, and x17299-L-Phe-OMe (1.71 min, right top) and L,L-TMAP-*d*₉-L-Phe-OMe (1.71 min, right bottom) in a coupling reaction mixture of the spiked plasma extract.

BRH924718_d9_spiked_PheMe #596-650 RT: 1.67-1.82 AV: 55 NL: 6.41E5
 F: FTMS + c ESI Full ms [200.00-450.00]



BRH924718_d9_spiked_PheMe_MS2 #424-449 RT: 1.70-1.80 AV: 13 NL: 4.65E4
 F: FTMS + c ESI Full ms2 399.30@cid28.00 [105.00-400.00]

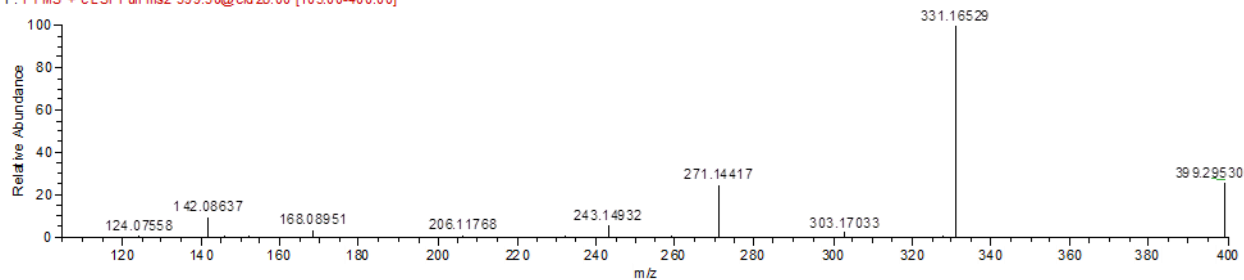


Figure S42. MS (top) and MS² (bottom) spectra of L,L-TMAP-*d*₉-L-Phe-OMe.

Scheme S1. Proposed fragmentation pathways of TMAP-L-Phe-OMe.

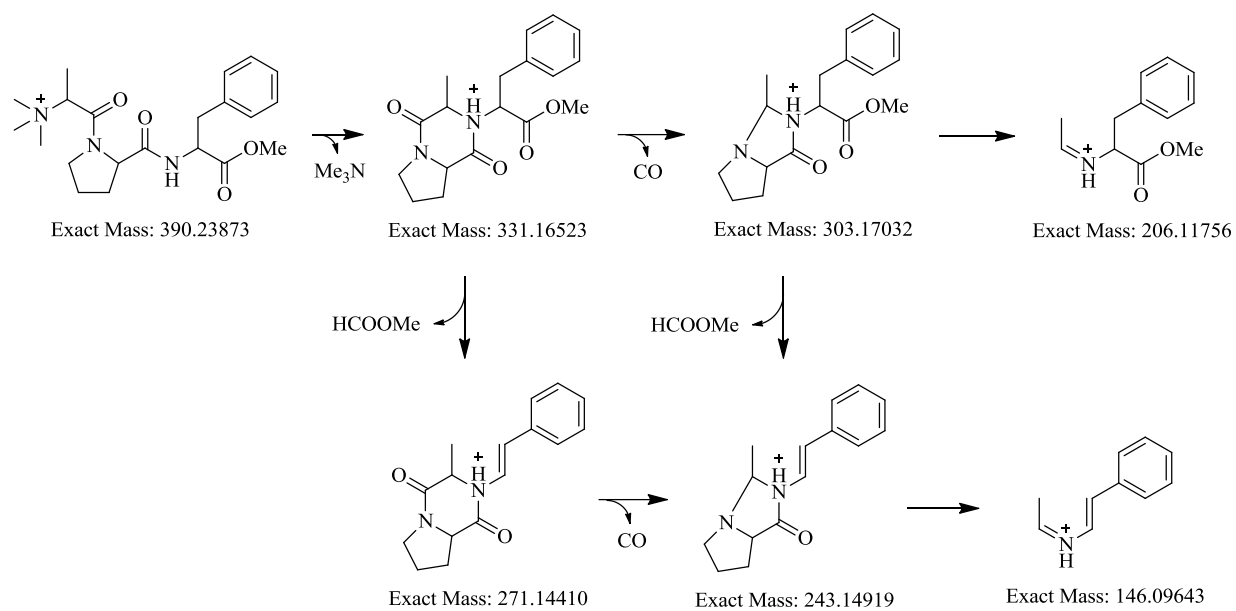


Table S1. Spectrum list of MS² of x17299.

FTMS + c ESI Full ms2 229.15@cid31.00 [60.00-240.00]

Scan #: 370-384

RT: 1.46-1.52

AV: 15

m/z	Intensity	Relative
70.06502	6062.9	10.74
114.05491	1535.7	2.72
114.09139	496.9	0.88
124.07568	4837.1	8.57
126.09128	1445.6	2.56
142.08628	56456.1	100.00
170.08120	4787.5	8.48
229.15460	1149.9	2.04

Table S2. Spectrum list of MS² of deuterated x17299.

FTMS + c ESI Full ms2 230.16@cid31.00 [60.00-240.00]

Scan #: 389-399

RT: 1.54-1.58

AV: 11

m/z	Intensity	Relative
70.06515	238.4	1.15
71.07140	2016.4	9.70
115.06133	512.3	2.47
115.09808	61.5	0.30
124.07589	1658.9	7.98
127.09769	387.7	1.87
143.09277	20781.8	100.00
171.08776	1729.7	8.32
201.94930	529.3	2.55
205.14789	161.4	0.78
219.96103	221.1	1.06
220.16469	230.3	1.11
230.16141	659.6	3.17

Table S3. Spectrum list of MS² of synthetic L,L-TMAP.

FTMS + c ESI Full ms2 229.15@cid31.00 [60.00-240.00]

Scan #: 350-363

RT: 1.38-1.44

AV: 14

m/z	Intensity	Relative
70.06508	16802.5	11.13
114.05503	4028.1	2.67
114.09144	1338.5	0.89
124.07580	12318.8	8.16
126.09147	3656.0	2.42
142.08642	151013.7	100.00
170.08138	12405.1	8.21
229.15488	3817.4	2.53

Table S4. Spectrum list of MS² of deuterated synthetic L,L-TMAP.

FTMS + c ESI Full ms2 230.16@cid31.00 [60.00-240.00]

Scan #: 372-388

RT: 1.47-1.51

AV: 17

m/z	Intensity	Relative
70.06498	6927.0	1.33
71.07128	53715.9	10.31
115.06118	13927.7	2.67
115.09750	3632.2	0.70
124.07565	43278.7	8.31
127.09761	11681.4	2.24
143.09252	520918.2	100.00
171.08743	42265.2	8.11
230.16083	18802.8	3.61

Table S5. Spectrum list of MS² of synthetic D,L-TMAP.

FTMS + c ESI Full ms2 229.15@cid31.00 [60.00-240.00]

Scan #: 583-615

RT: 2.31-2.41

AV: 33

m/z	Intensity	Relative
70.06505	39033.4	14.10
114.05495	6350.1	2.29
114.09137	2050.1	0.74
124.07573	29236.2	10.56
126.09139	11389.1	4.11
132.10199	3184.4	1.15
142.08635	276778.9	100.00
170.08131	81733.8	29.53
229.15483	2809.2	1.01

Table S6. Spectrum list of MS² of synthetic D,D-TMAP.

FTMS + c ESI Full ms2 229.15@cid31.00 [60.00-240.00]

Scan #: 351-363

RT: 1.39-1.44

AV: 13

m/z	Intensity	Relative
70.06512	4449.0	10.21
114.05496	1077.3	2.47
114.09155	296.5	0.68
124.07582	3489.2	8.01
126.09151	983.4	2.26
142.08648	43558.4	100.00
170.08140	3615.5	8.30
229.15533	1044.3	2.40

Table S7. Spectrum list of MS² of L,L-TMAP-L-Phe-OMe.

FTMS + c ESI Full ms2 390.24@cid28.00 [105.00-400.00]

Scan #: 440-459

RT: 1.75-1.82

AV: 20

m/z	Intensity	Relative
124.07580	346.0	0.76
142.08636	3664.1	8.01
152.07061	296.2	0.65
168.08940	1324.5	2.90
206.11743	485.4	1.06
232.13357	292.5	0.64
243.14936	2279.7	4.99
259.14427	321.0	0.70
271.14426	10861.6	23.75
303.17034	1104.7	2.42
331.16535	45726.0	100.00
390.23877	4967.2	10.86

Table S8. Spectrum list of MS² of D,D-TMAP-L-Phe-OMe.

FTMS + c ESI Full ms2 390.24@cid28.00 [105.00-400.00]

Scan #: 500-523

RT: 1.98-2.08

AV: 24

m/z	Intensity	Relative
124.07600	577.3	0.96
142.08657	4296.1	7.17
152.07107	540.9	0.90
168.08972	2505.3	4.18
206.11806	394.6	0.66
232.13390	662.1	1.11
243.14962	2857.4	4.77
259.14467	741.8	1.24
271.14468	15148.8	25.29
299.13955	817.1	1.36
303.17091	1296.1	2.16
331.16587	59895.0	100.00
390.23943	9307.6	15.54

Table S9. Spectrum list of MS² of x17299-L-Phe-OMe.

FTMS + c ESI Full ms2 390.24@cid28.00 [105.00-400.00]

Scan #: 442-462

RT: 1.74-1.82

AV: 21

m/z	Intensity	Relative
124.07558	166.0	0.63
142.08622	2102.2	8.00
152.07030	170.2	0.65
168.08914	768.8	2.93
206.11712	240.3	0.91
232.13340	197.2	0.75
243.14913	1296.6	4.93
259.14347	141.6	0.54
271.14399	6378.1	24.27
277.15486	157.8	0.60
303.16986	660.6	2.51
319.18594	523.0	1.99
331.16501	26278.2	100.00
390.23850	2336.8	8.89

Table S10. Spectrum list of MS² of synthetic L,L-TMAP-*d*₉.

FTMS + c ESI Full ms2 238.21@cid31.00 [65.00-240.00]

Scan #: 345-394

RT: 1.36-1.47

AV: 50

m/z	Intensity	Relative
70.06495	1479674.6	9.23
114.05480	514823.2	3.21
114.09114	198927.7	1.24
124.07556	1363974.4	8.51
126.09122	468917.8	2.93
142.08615	16028258.0	100.00
170.08108	1176932.0	7.34
238.21092	296029.2	1.85

Table S11. Spectrum list of MS² of L,L-TMAP-*d*₉-L-Phe-OMe.

FTMS + c ESI Full ms2 399.30@cid28.00 [105.00-400.00]

Scan #: 424-448

RT: 1.70-1.80

AV: 13

m/z	Intensity	Relative
124.07558	423.3	0.91
142.08637	4517.1	9.72
152.07072	279.2	0.60
168.08951	1722.6	3.71
206.11768	529.7	1.14
232.13337	207.5	0.45
243.14932	2729.3	5.87
259.14395	352.0	0.76
271.14417	11416.8	24.56
303.17033	1152.3	2.48
328.13257	417.7	0.90
331.16529	46483.5	100.00
399.29530	12117.9	26.07