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Resistance-gene-directed discovery of a natural-product herbicide with a new mode of action

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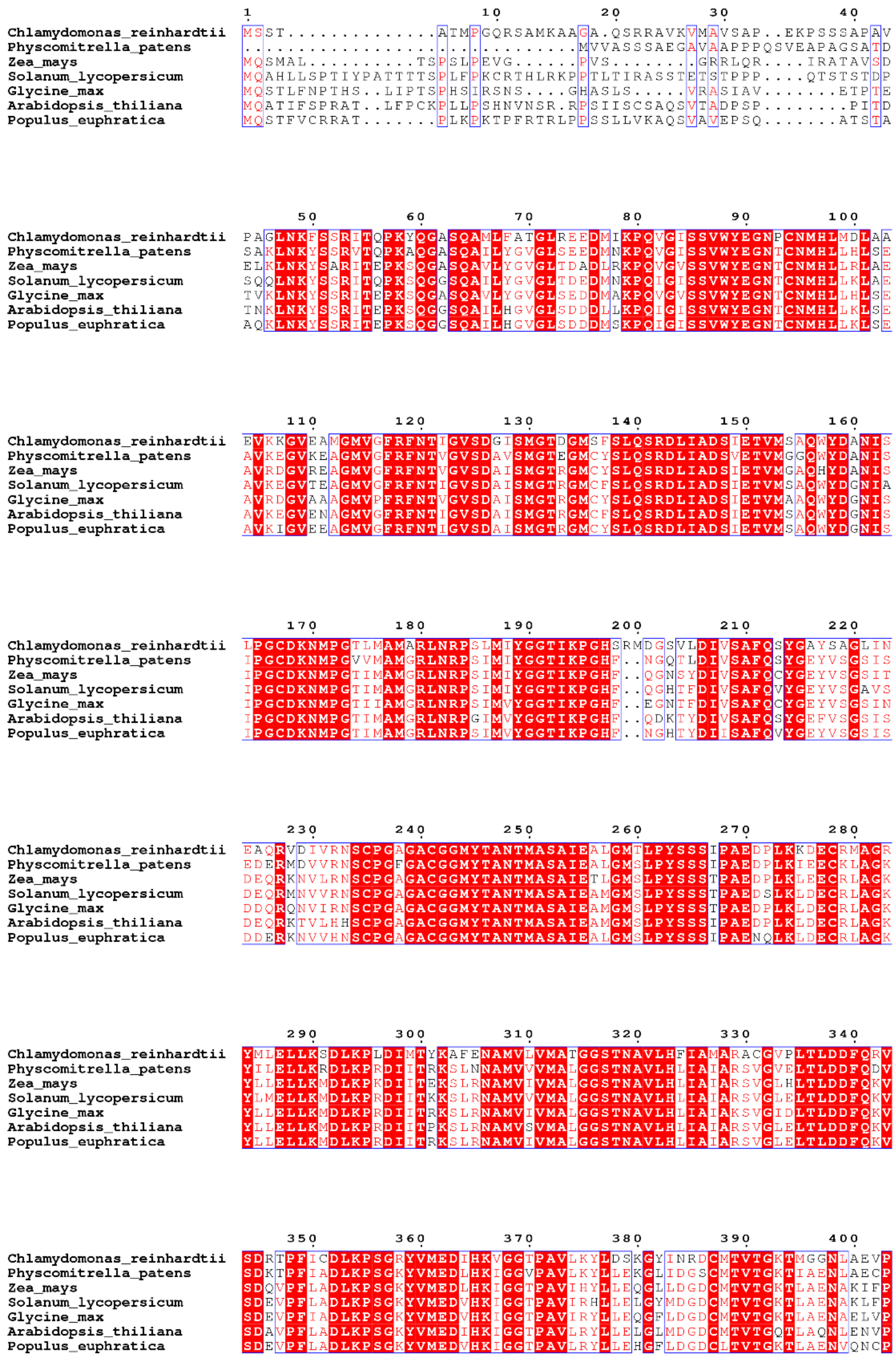
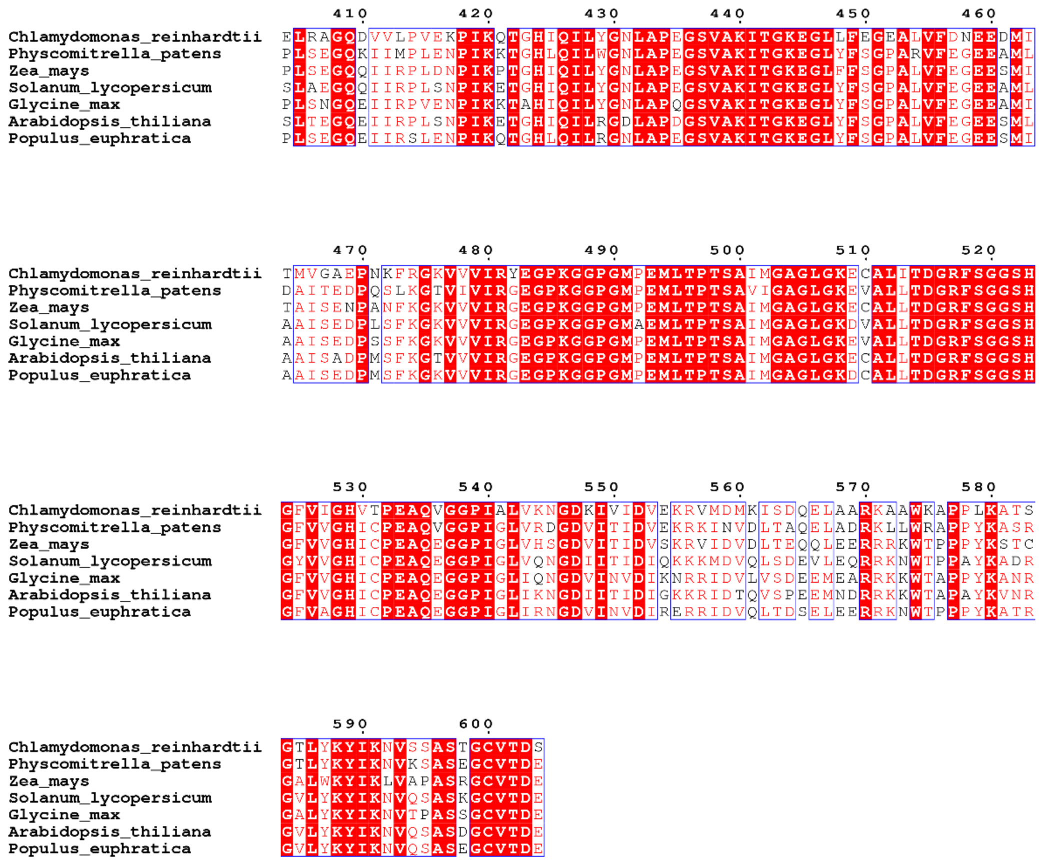
Supplementary Materials:

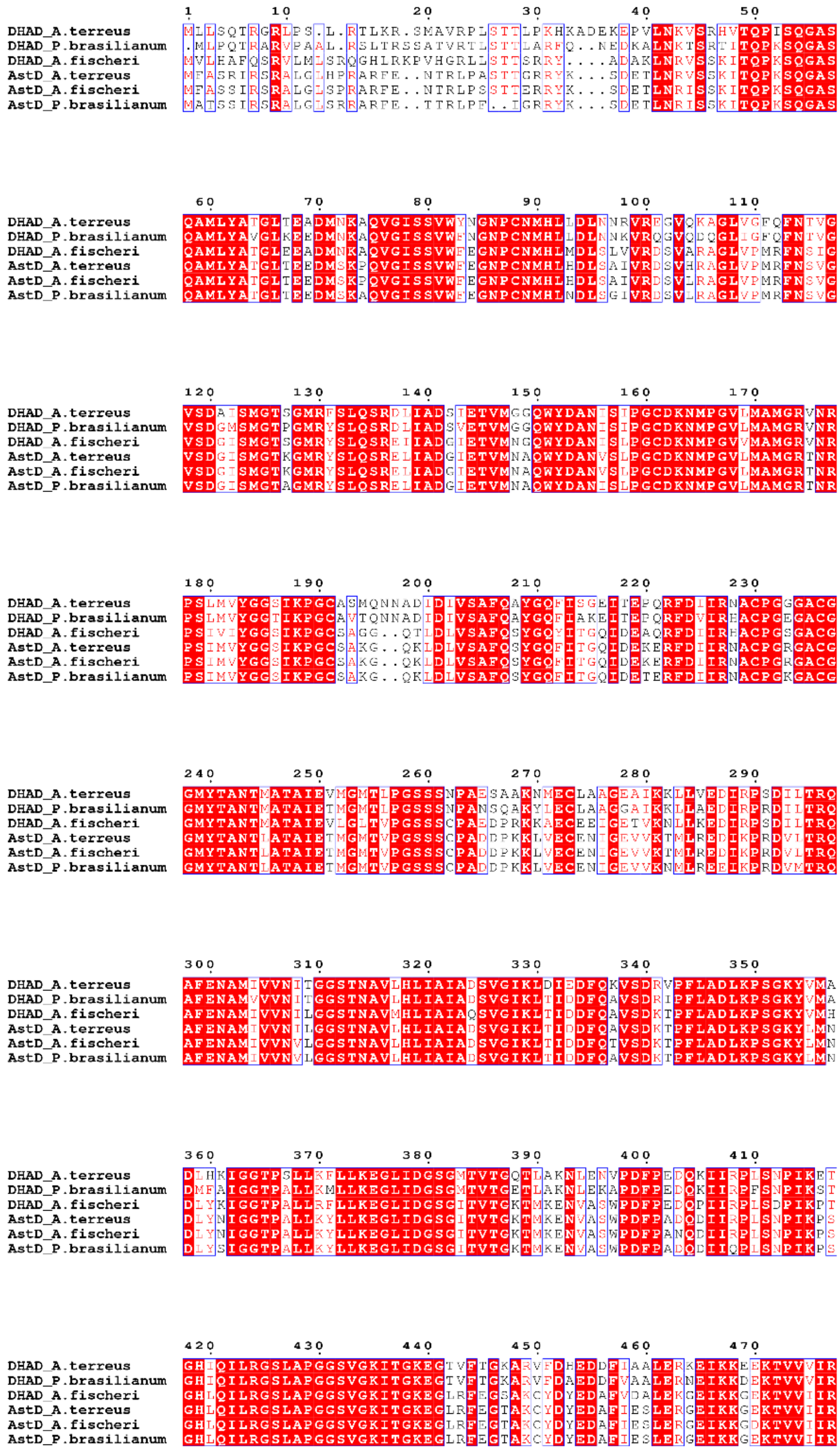
Supplementary Figures

Supplementary Figure 1. Alignment of amino acid sequences of DHADs from different plant species. The identities of DHAD sequences among flowering plant are ~80%. The lack of identity at the *N*-terminal of these DHAD results from the differences in chloroplast localization signals from different species.





Supplementary Figure 2. Alignment of amino acid sequences of AstD and housekeeping DHAD from different strains.



```
                     480       490       500       510       520       530
DHAD_A.terreus       YTGPKGGPGMPEMLKPSSALMGAGLGGSCALITDGRFSGGSHGFLIGHIVPEAAVGGPIG
DHAD_P.brasilianum   YCGPKGGPGMPEMLKPSSALMGYGLGSSCALITDGRFSGGSHGFLIGHIVPEAATGGPIG
DHAD_A.fischeri      YEGPKGGPGMPEMLKPSAAIMGAGLGQDVALLTDGRFSGGSHGFLIGHIVPEAMDGGPIA
AstD_A.terreus       YEGPKGGPGMPEMLKPSAAIMGAGLGQDVALLTDGRFSGGSHGFLIGHIVPEAMEGGPIA
AstD_A.fischeri      YEGPKGGPGMPEMLKPSAAIMGAGLGQDVALLTDGRFSGGSHGFLIGHIVPEAMEGGPIA
AstD_P.brasilianum   YEGPKGGPGMPEMLKPSAAIMGAGLGQDVALLTDGRFSGGSHGFLIGHIVPEAMEGGPIA
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                     540       550       560       570       580       590
DHAD_A.terreus       LVKDGDVITIDAVKRVLDLDVDETTLAERRKQWEADKEAGRLPPTGLTLRGTLGKYARNV
DHAD_P.brasilianum   LVNDGDVITIDADNRVLDLDVPESELAERRKDWEARKAAGKLPETGLTMRGTLGKYARNV
DHAD_A.fischeri      LVKDGDRVIIDAEKRVVDLDISGEEMQRRKKAWKAPEP........RAKKGTLKKYAALV
AstD_A.terreus       LARDGDRIVIDAEERVVDLDIPTEELEKRRKEWKAPPL........RYQKGTLKKYCTLV
AstD_A.fischeri      LARDGDRIVIDAEERVVDLDIPIEELEKRRKEWKAPPL........RYQKGTLKKYCTLV
AstD_P.brasilianum   LARDGDRIVIDAEEKVVDLDVPTEELDARRKQWKAPPL........RYQKGTLKKYCALV
```

```
                     600       610
DHAD_A.terreus       KDASHGCITDALD
DHAD_P.brasilianum   KDASQGCITDALE
DHAD_A.fischeri      SDASHGCVTDGPL
AstD_A.terreus       SDASHGCVTDGPI
AstD_A.fischeri      SDASHGCVTDGPI
AstD_P.brasilianum   SDASHGCVTDGPI
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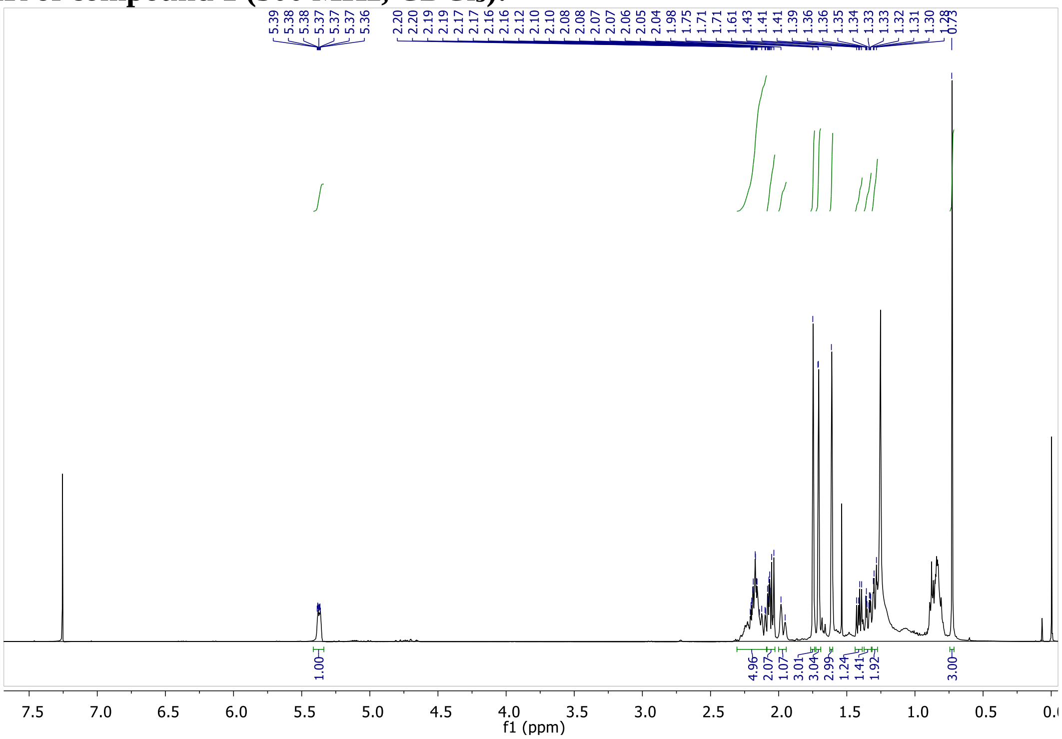
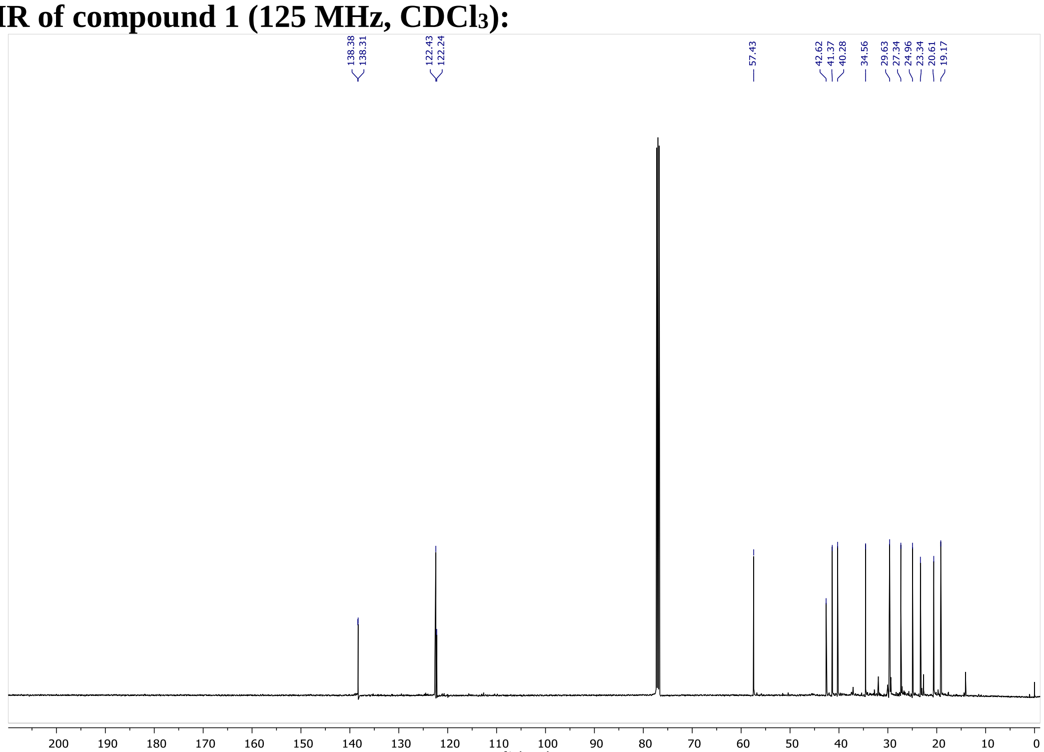
Supplementary Figure 3. NMR analyses of the compounds in this study. The experiments were repeated independently for 3 times with similar results.

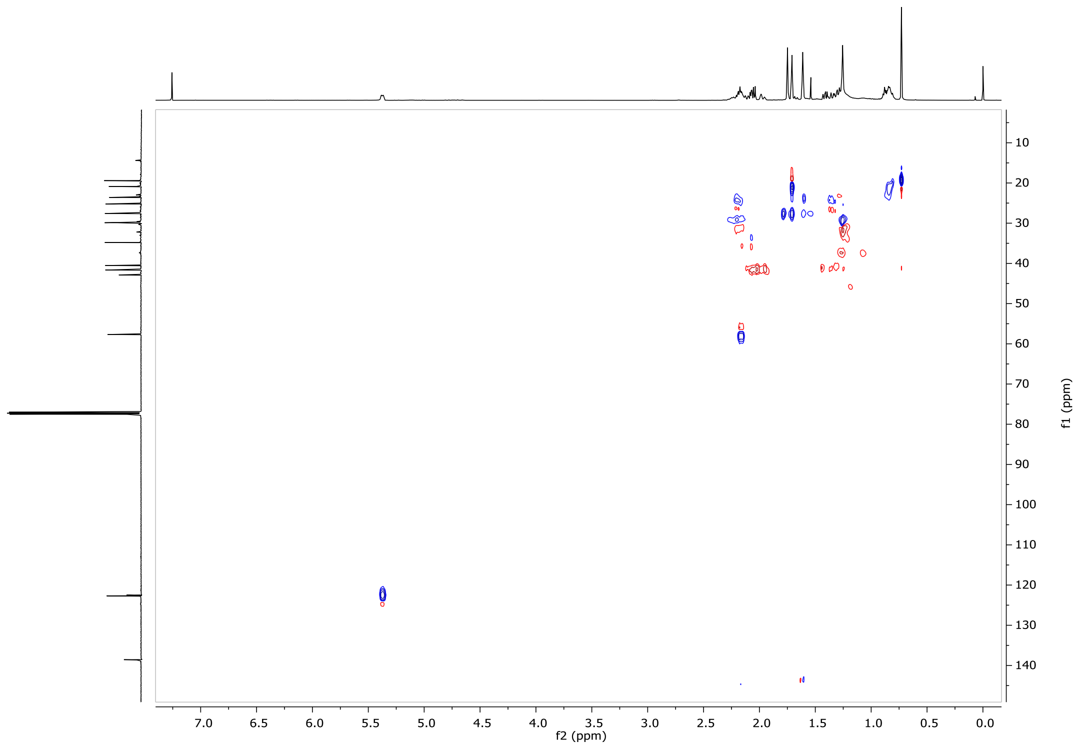
^{1}H NMR of compound 1 (500 MHz, $CDCl_3$):



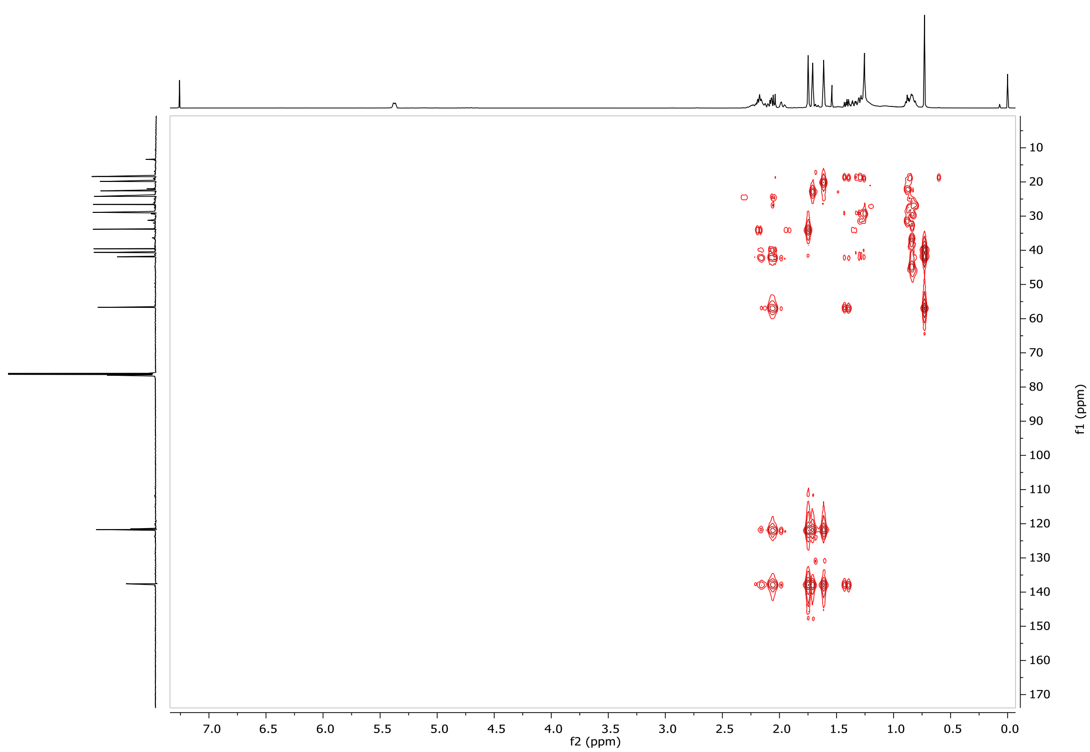
^{13}C NMR of compound 1 (125 MHz, $CDCl_3$):



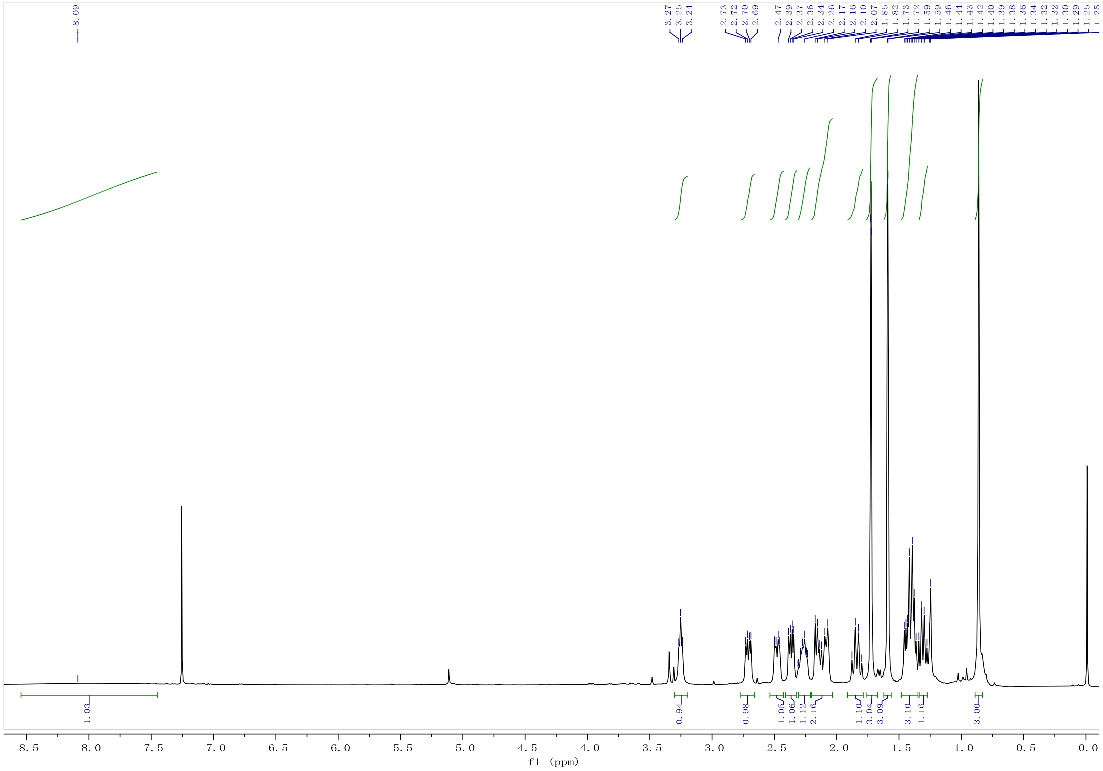
HSQC of compound 1 (500 MHz, $CDCl_3$):



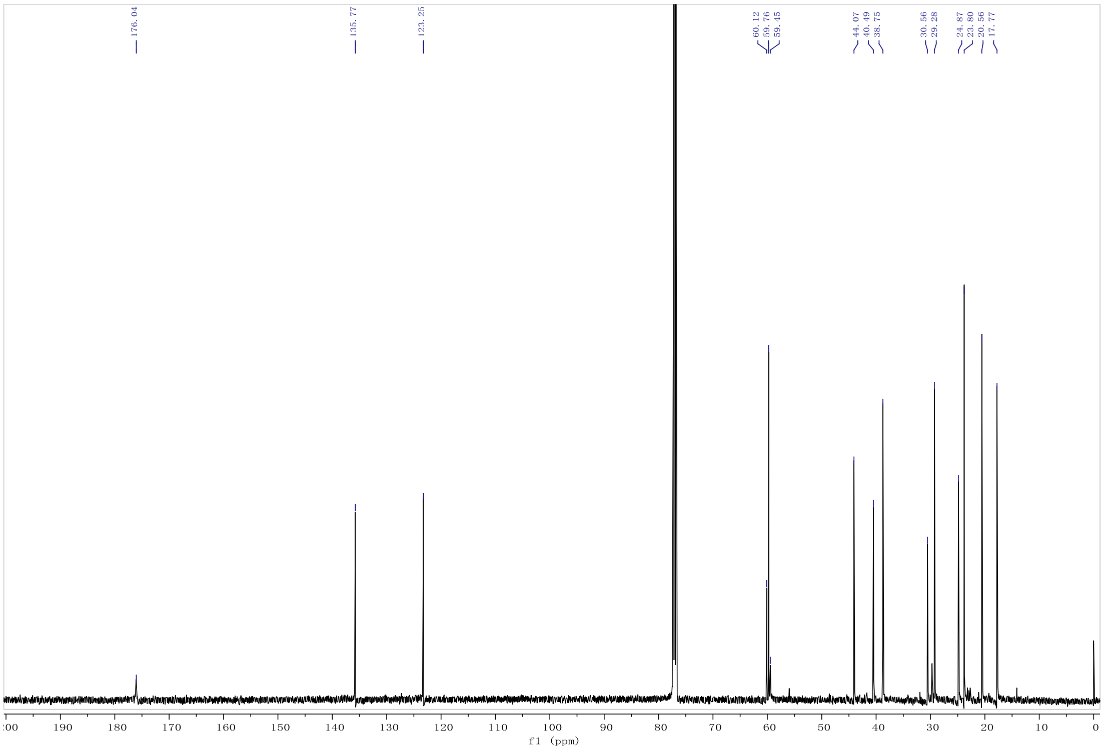
HMBC of compound 1 (500 MHz, $CDCl_3$):



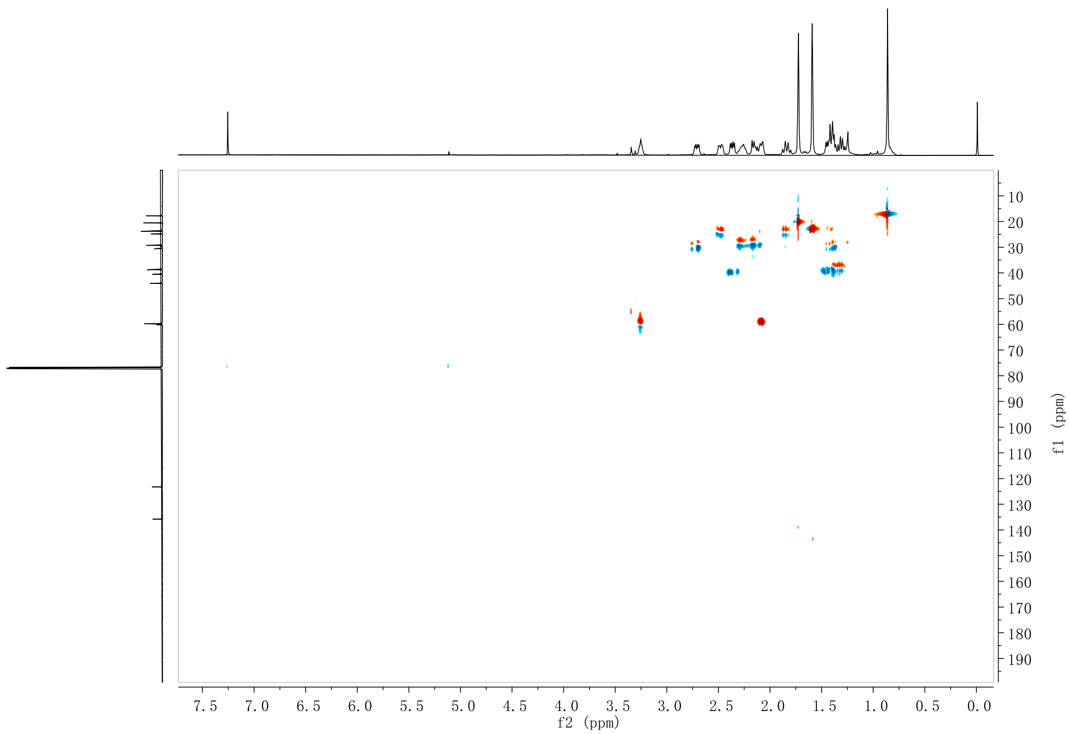
^{1}H NMR of compound 2 (500 MHz, $CDCl_3$):



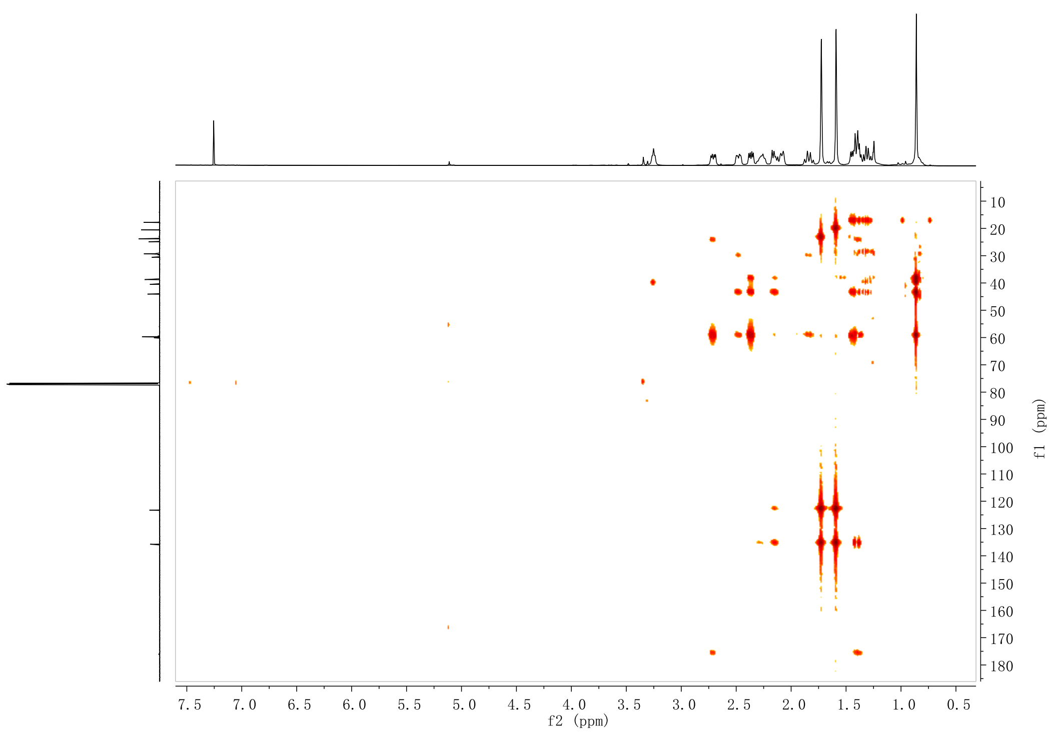
^{13}C NMR of compound 2 (125 MHz, $CDCl_3$):



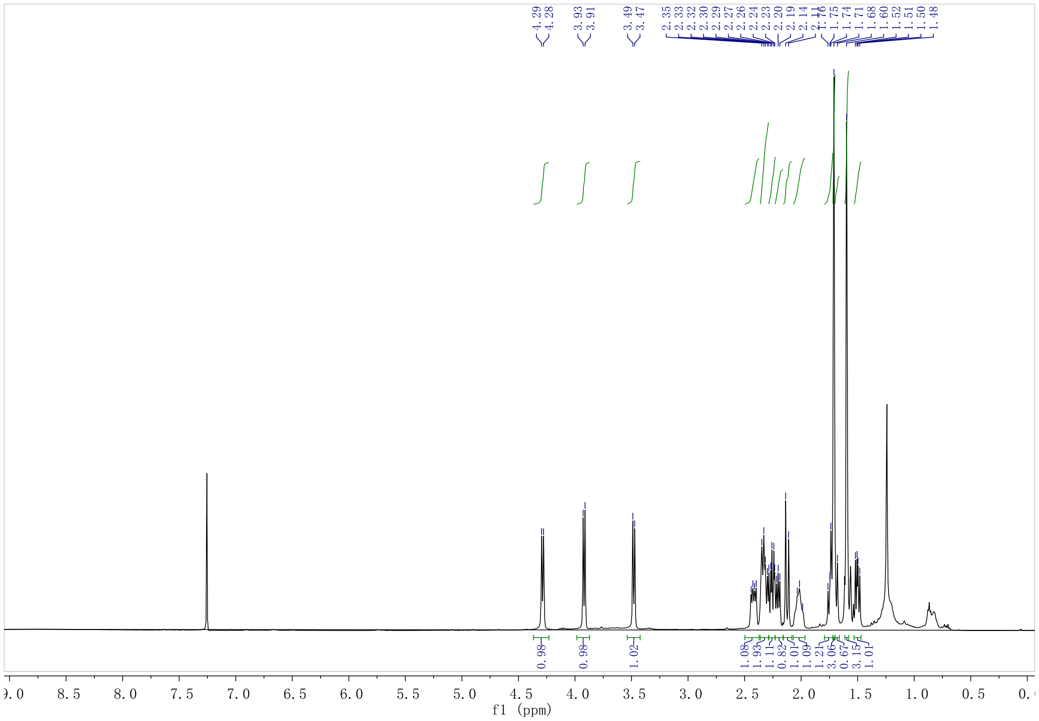
HSQC of compound 2 (500 MHz, $CDCl_3$):



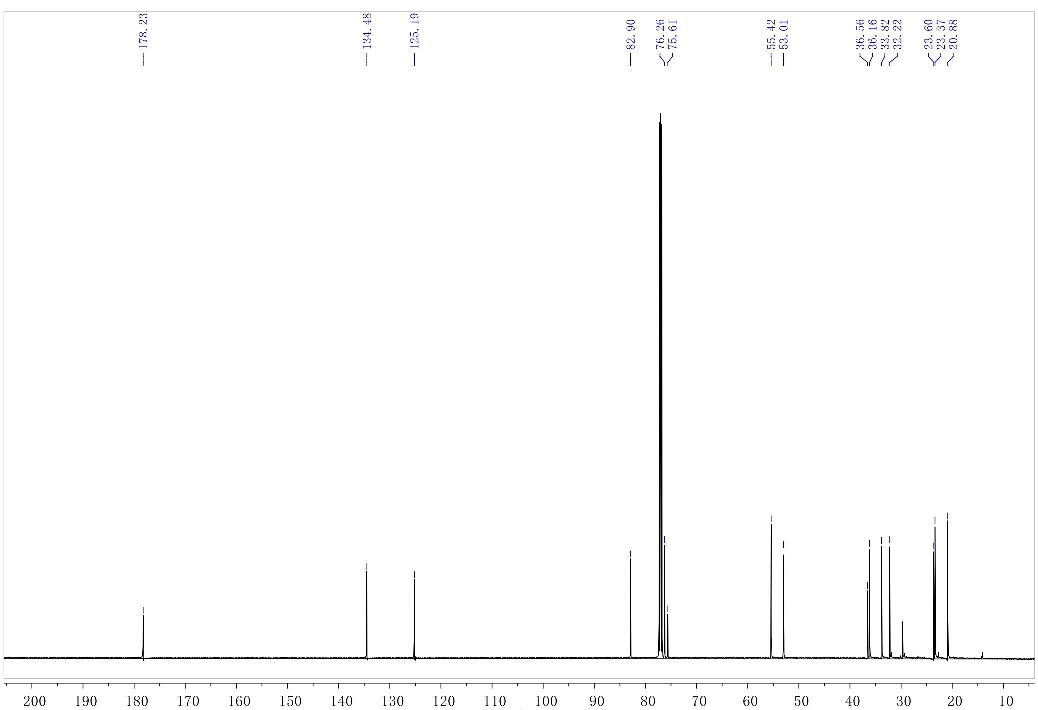
HMBC of compound 2 (500 MHz, $CDCl_3$):



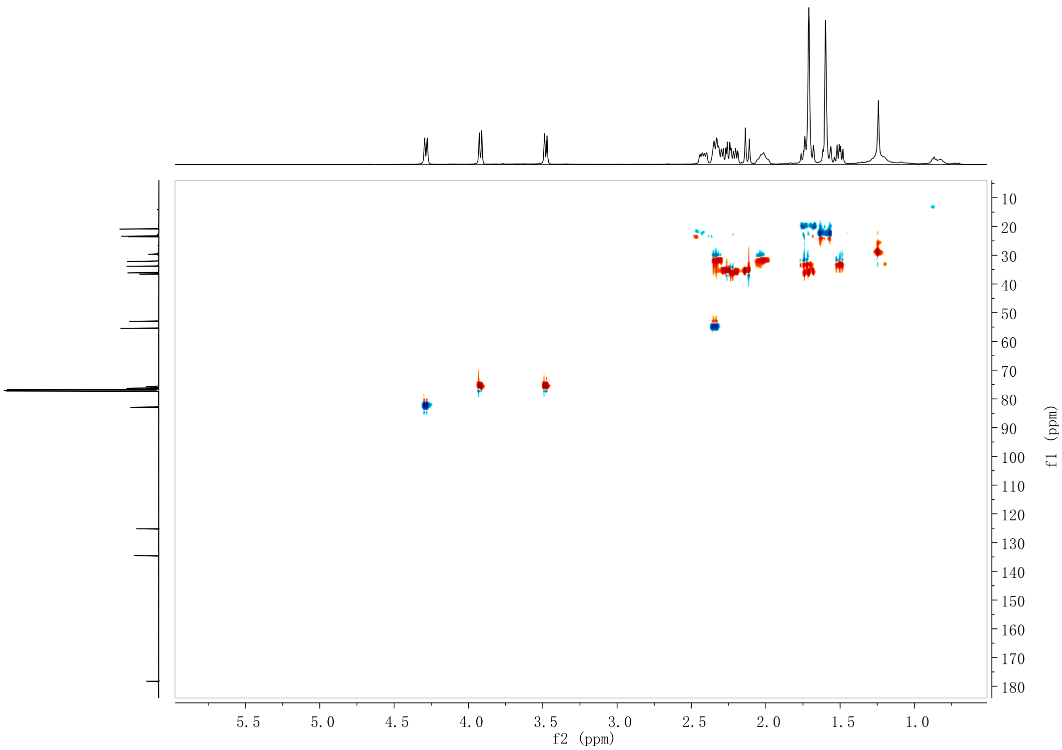
[1]H NMR of compound 3 (aspterric acid, AA) (500 MHz, $CDCl_3$):



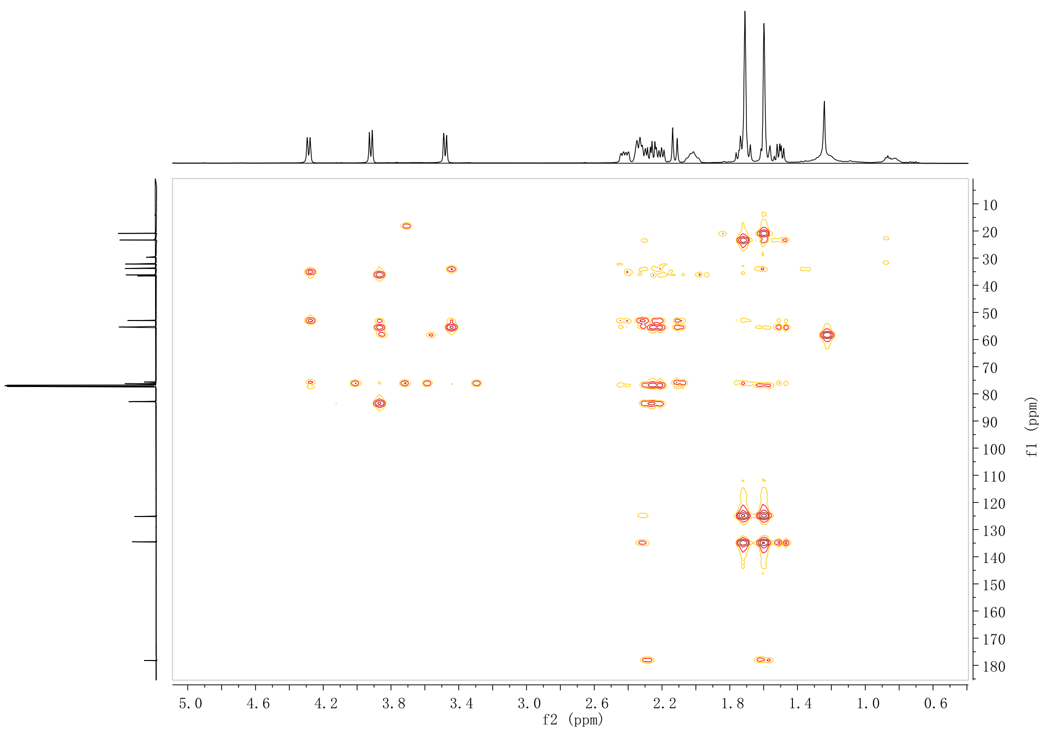
[13]C NMR of compound 3 (aspterric acid, AA) (125 MHz, $CDCl_3$):



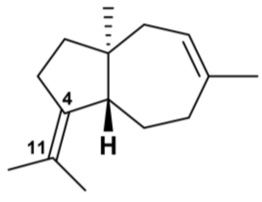
HSQC of compound 3 (aspterric acid, AA) (500 MHz, $CDCl_3$):



HMBC of compound 3 (aspterric acid, AA) (500 MHz, $CDCl_3$):

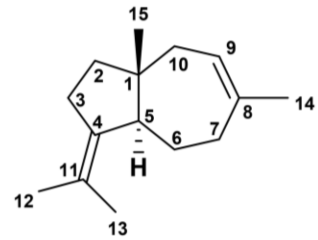


Supplementary Figure 4. EI-MS of compound 1 by GC-MS analysis. The structure of compound **1** (top right) and its known enantiomer (+)-Dauca-4(11),8-diene (top left). The EI-MS of compound **1** (bottom). The EI-MS spectrum of (+)-Dauca-4(11),8-diene is reported as m/z (rel.int): 204 $[M]^+$ (22), 189 $[M\text{-}Me]^+$ (2), 161 (18), 148 (3), 136 (100), 133 (10), 121 (60), 119 (10), 107 (17) 105 (15), 93 (19), 91 (18), 79 (12), 77 (11), 55 (10), 41 (22). The EI-MS of both compound **1** and (+)-Dauca-4(11),8-diene are identical[1]. The experiment was repeated independently with similar results for 7 times.



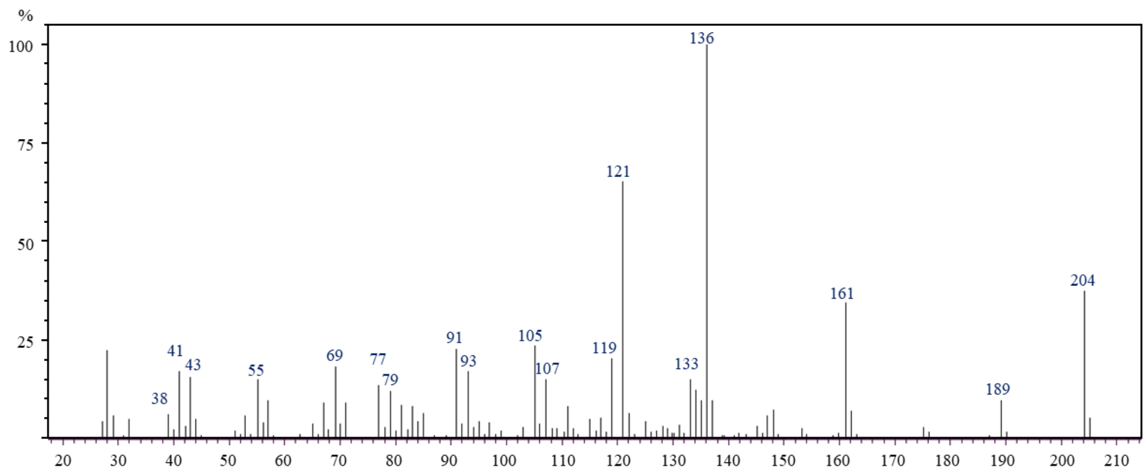
(+)-dauca-4(11),8-diene

$[\alpha]_D^{22} > +40°$ (*n*-hexane; $c < 0.1$)

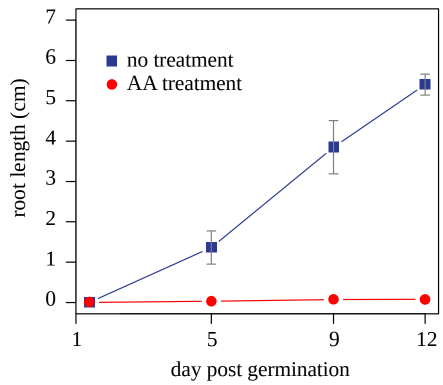


1, (-)-dauca-4(11),8-diene

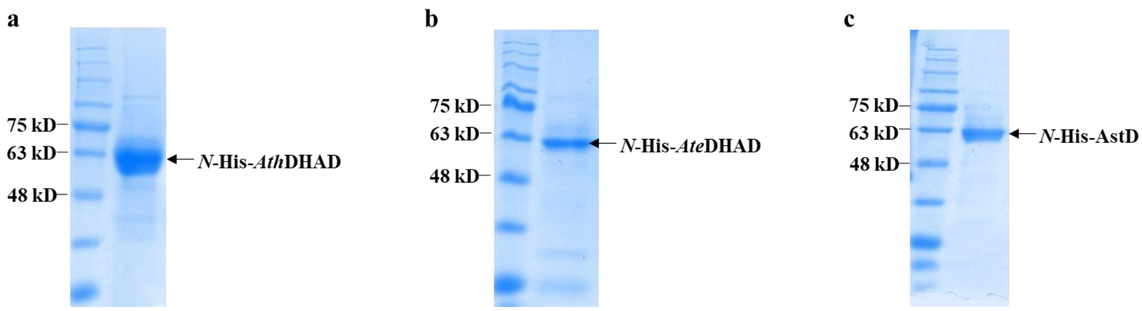
$[\alpha]_D^{22} = -30°$ (*n*-hexane; $c = 0.1$)



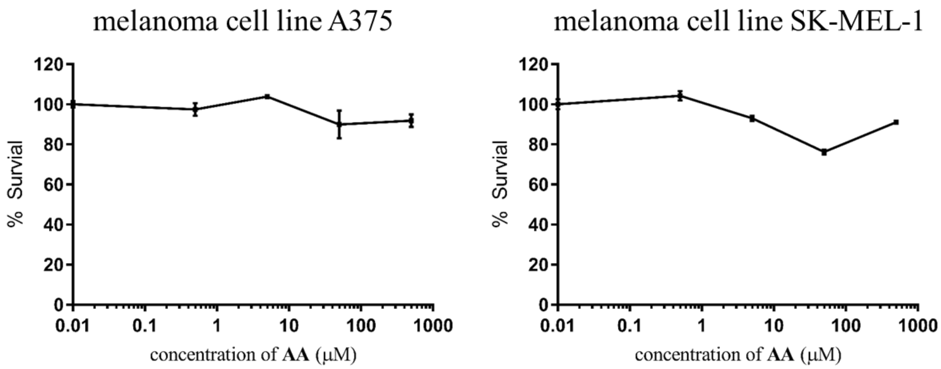
Supplementary Figure 5. Root length of aspterric acid treated *Arabidopsis*. Wild type *A. thaliana* was grown on MS media with and without 250 µM aspterric acid (AA**)**. The lengths of roots were measured at four different time points after seed germination. The plot shows mean values ± s.d. (error bars); n=18 biologically independent samples.



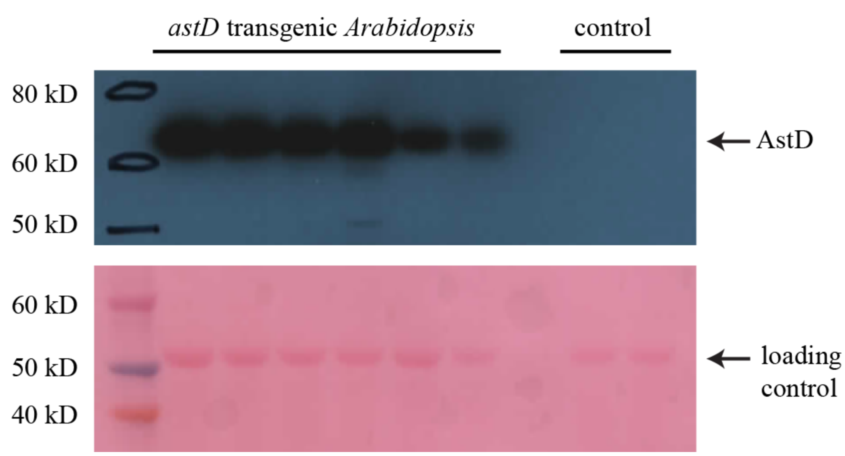
Supplementary Figure 6. SDS-PAGE analysis of purified proteins. SDS-PAGE analysis of purified *Ath*DHAD (**a**), *Ate*DHAD (**b**) and AstD (**c**) from *E. coli* BL21 (DE3). The experiments were repeated independently with similar results for 5 times.



Supplementary Figure 7. Cytotoxicity assay of aspterric acid. Percent growth inhibition of melanoma cell line A375 (left) and SK-MEL-1 (right) indicate aspterric acid (AA**)** has no significant cytotoxicity. Treatments of AA was initiated at 24 h postseeding for 72 h, cell viability was measured by CellTiter-GLO Luminescence (Promega) following the manufacturer's recommendations. Results are representative data in duplicate from three independent experiments (center values are averages, errors bars are s.d., n = 5 biologically independent experiments, error bars were determined from independent biological replicates).

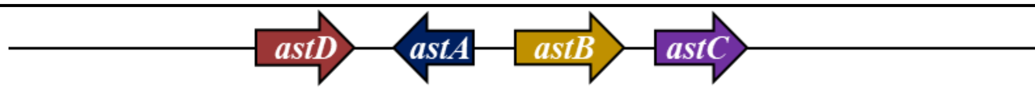


Supplementary Figure 8. Verification of AstD expression in *A. thaliana* using western blot. Western blot verification of AstD expression in *A. thaliana* using anti-FLAG antibody (top); Ponceau staining shows equal loading (bottom). Six independent T1 transgenic plants (lane 1 to 6) and two wild-type plants (lane 8, and 9) were assayed. Lane 7 does not contain any sample. The experiment was not repeated.



Supplementary Tables

Supplementary Table 1. Proposed functions of genes within the *ast* cluster in *A. terreus*



A. terreus NIH 2624, scaffold 6 (NT_165929.1, 469,00-486,00), 17 kb

Gene	Accession number	Size (gene/protein)	BLASTP homologs	Identity/similarity (%)	Putative function
astA	XP_001213594.1	1230/409	XP_001266526.1	94/97	Terpene synthase
astB	XP_001213595.1	1760/512	XP_001266527.1	94/96	Cytochrome P450
astC	XP_001213596.1	1716/538	CEJ61176.1	84/89	Cytochrome P450
astD	XP_001213593.1	1874/598	OJJ72940.1	98/98	Dihydroxy-acid dehydratase

Supplementary Table 2. Microbial strains used in this study

Strain	Genotype	Source
Fungi		
Aspergillus terreus NIH2624		FGSC
Aspergillus nidulans A1145	*ΔpyrG, ΔpyroA, ΔriboB*	[2]
TY01	*Aspergillus nidulans* A1145 carrying AstD+AstA-pYTU, AstB-pYTR, AstC-pYTP	this study
Saccharomyces cerevisiae		
RC01	*MATα ura3-52 his3-Δ200 leu2-Δ1 trp1 pep4::HIS3 ura3-52::atCPR prb1 Δ1.6R can1 GAL*	[3]
TY02	RC01 carrying pAstA-xw55	this study
TY03	TY02 carrying pAstB-xw06	this study
TY04	TY03 carrying pAstC-xw02	this study
DHY *ΔURA3*	*MATα ura3Δ0*	this study
UB01	DHY *ΔURA3 ilv3::URA3*	this study
UB02	DHY *ΔURA3 ΔILV3*	this study
TY05	UB02 carrying pXP318	this study
TY06	UB02 carrying *Ate*DHAD-pXP318	this study
TY07	UB02 carrying AstD-pXP318	this study
Escherichia coli		
DH10β		NEB
BL21 (DE3)		NEB
TY08	BL21 (DE3) carrying AstD-pET28a	this study
TY09	BL21 (DE3) carrying *Ath*DHAD-pET28a	this study
TY10	BL21 (DE3) carrying *Ate*DHAD-pET28a	this study

Supplementary Table 3. Primers for PCR amplification in this study

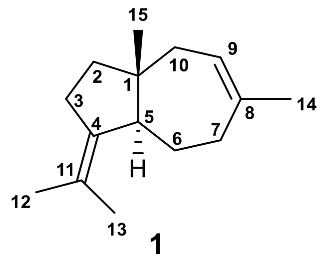
Primer	Sequences of primer (5'→3')
AstD-pYTU-recomb-F	gagagcctgagcttcatccccagcatcattacacctcagcaatgttcgcgtcgaggatcc
AstA-pYTU-recomb-R	gactaaccattaccccgccacatagacacatctaaacaatggacatgaataccttccccg
Gpda-pYTU-F	gtggaggacatacccgtaattttctgggcatttaaatactccggtgaattgatttgggtg
Gpda-R	tgtttagatgtgtctatgtggcggg
AstB-pYTR-recomb-F	aaccattaccccgccacatagacacatctaaacaatgctattccaagacctgtcttttcc
AstB-pYTR-recomb-R	gctaaagggtatcatcgaaagggagtcatccaggtactgcttgtattgaatcctagtttg
AstC-pYTP-recomb-F	cccttctctgaacaataaaccccacagaaggcatttatgggagcttctactttctcccag
AstC-pYTP-recomb-R	caacaaccatgataccaggggatttaaatttaattaaggttggggtttcatgcatatagc
AstA-xw55-recomb-F	tggctagcgattataaggatgatgatgataagactagtatggacatgaataccttccccg
AstA-xw55-recomb-R	atttgtcatttaaattagtgatggtgatggtgatgcacgtgttatgcgttgcctagcggg
AstB-xw06-recomb-F	caactatcaactattaactatatcgtaataccatatgctattccaagacctctcgtttcc
AstB-xw06-recomb-R	tacttgataatggaaactataaatcgtgaaggcatctacttgcagagacccataactcgc
AstC-xw02-recomb-F	atcaactatcaactattaactatatcgtaataccatatgggagcttctactttctccctg
AstC-xw02-recomb-R	ttgataatgaaaactataaatcgtgaaggcatgtttaaacctagcctcgtctctttattc
ILV3p-URA3-F	gtatttttttgtaaacagccaagaaaaaagtagagatgtcgaaagctacatataaggaac
ILV3t-URA3-R	atctctatatatatattcatcgattggggcctataatgcattagttttgctggccgcatc
ILV3KO-ck-F	agcggtgttcatgtgatcaagc
ILV3KO-ck-R	tttagtggcagcaaagcagag
ILV3KO-F	tatgcattgtagcgcctgtaatctttagtaacggattcttgtatttttttgtaaacagccaagaa aaaagtagagtgcattataggcccc
ILV3KO-R	aagattgcgaacaaaaaagatgatggaaaaggagaatctctatatatatattcatcgattg gggcctataatgcactctacttttttctt
*Ath*DHAD-pET-F	atagctagcatgcaagccaccatcttctctcc
*Ath*DHAD-pET-R	atagcggccgcttactcgtcagtcacacatccatctg
*Ate*DHAD-pET-F	atacatatgcttctctctcagacccgg
*Ate*DHAD-pET-R	atagcggccgcttagtcaagagcatcggtgatgcag
AstD-pET-F	atacatatgttcgcgtcgaggatcc
AstD-pET-R	atagcggccgcctagatcggtccgtccgtgac
*Ate*DHAD-pXP318-F	gcatagcaatctaatctaagttttaattacaaaactagtatgcttctctctcagacccgg
*Ate*DHAD-pXP318-R	gaatgtaagcgtgacataactaattacatgactcgagttagtcaagagcatcggtgatgc
AstD-pXP318-F	tagcaatctaatctaagttttaattacaaaactagtatggactacaaagacgatgacgac
AstD-pXP318-R	gcgtgaatgtaagcgtgacataactaattacatgactcgagctagatcggtccgtccgtg
DHAD-F	acaggatccgcccaatccgtaaccgc
DHAD-R	cacgtcgacttactcgtcagtcacacatccat
K559AK560A-F	acataggagcagcaagaatagacacacaagtctcacccg
K559AK560A-R	gtctattcttgctgctcctatgtcaatggtgattatgtctc

Supplementary Table 4. Plasmids used in this study

plasmids	Features	source
pYTU	protein expression vector in *A. nidulans* (*pyrG* marker)	[2]
pYTR	protein expression vector in *A. nidulans* (*riboB* marker)	[2]
pYTP	protein expression in *A. nidulans* (*pyroA* marker)	[2]
pAstD+AstA-pYTU	pYTU expressing *astA* and *astD*	this study
pAstB-pYTR	pYTR expressing *astB*	this study
pAstC-pYTP	pYTP expressing *astC*	this study
pXW55	protein expression vector in *S. cerevisiae* (*URA3* marker)	[3]
pXW06	protein expression vector in *S. cerevisiae* (*TRP2* marker)	[3]
pXW02	protein expression vector in *S. cerevisiae* (*LEU2* marker)	[3]
pAstA-xw55	pXW55 expressing *astA*	this study
pAstB-xw06	pXW06 expressing *astB*	this study
pAstC-xw02	pXW02 expressing *astC*	this study
pET28a	protein expression vector in *E. coli* BL21 (DE3)	Addgene
*Ath*DHAD-pET	pET28a expressing *Ath*DHAD (pDHAD)	this study
*Ate*DHAD-pET	pET28a expressing *Ate*DHAD (fDHAD)	this study
AstD-pET	pET28a expressing AstD	this study
pXP318	protein expression vector in *S. cerevisiae* (*URA3* marker)	Addgene
*Ate*DHAD-pXP318	pXP318 expressing *Ate*DHAD (fDHAD)	this study
AstD-pXP318	pXP318 expressing AstD	this study
pEG202	protein expression vector in *A. thaliana* (*blp*^{R} marker)	Addgene
pAstDo-pEG	pEG202 expressing codon optimized AstD	this study

Supplementary Table 5. NMR data and structure

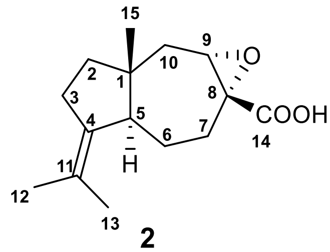
^{1}H (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) of compound 1:



1

no.	δ_H (mult., *J* in Hz)	δ_C	mult.	HMBC
1	-	42.6	C	-
2	1.44 (1H, dd, 11.4, 7.2)	40.3	CH_2	138.4, 57.4, 42.6, 29.6, 19.2
2’	1.31 (1H, dd, 11.3, 2.6)			42.6, 41.4, 29.6, 19.2
3	2.20 (1H, m)	29.6	CH_2	138.4, 42.6, 34.5
3’	2.15 (1H, m)			138.4, 122.2, 57.4, 42.6, 40.3
4	-	138.4	C	-
5	2.16 (1H, m)	57.4	CH	138.4, 42.6, 40.3, 34.5, 25.0
6	2.19 (1H, m)	25.0	CH_2	138.4,138.3, 57.4, 42.6, 34.5
6’	1.36 (1H, m)			34.5
7	2.15 (1H, m)	34.5	CH_2	138.3, 122.4, 57.4
7’	2.07 (1H, m)			138.3, 122.4, 57.4, 27.3, 25.0
8	-	138.3	C	-
9	5.37 (1H, m)	122.4	CH	
10	2.00 (1H, m)	41.4	CH_2	138.3, 122.4, 57.4, 42.6, 40.3, 19.2
10’	1.95 (1H, d, 15.3)			138.3, 122.4, 57.4, 42.6
11	-	122.2	C	-
12	1.61 (3H, brs)	23.3	CH_3	138.4, 122.2, 20.6
13	1.71 (3H, q, 1.7)	20.6	CH_3	138.4, 122.2, 23.3
14	1.75 (3H, s)	27.3	CH_3	138.3, 122.4, 34.5
15	0.73 (3H, s)	19.2	CH_3	57.4, 42.6, 41.4, 40.3

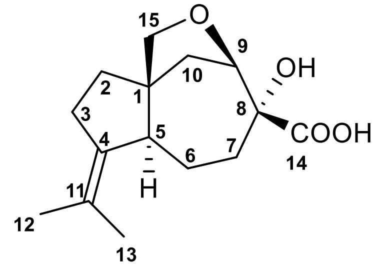
^{1}H (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) of compound 2:



2

no.	δ_H (mult., *J* in Hz)	δ_C	mult.	HMBC
1	-	44.1	C	-
2	1.41 (1H, m)	38.8	CH_2	135.8, 60.1, 44.1, 29.3, 17.8
2’	1.31 (1H, td, 11.5, 9.0)			44.1, 40.5, 29.3, 17.8
3	2.26 (1H, m)	29.3	CH_2	135.8
3’	2.15 (1H, dd, 16.3, 8.9)			135.8, 123.2, 60.1, 44.1, 38.8
4	-	135.8	C	-
5	2.08 (1H, d, 12.0)	60.1	CH	
6	2.48 (1H, dd, 14.8, 6.3)	24.9	CH_2	59.4, 44.1, 30.6
6’	1.84 (1H, q, 13.1)			59.4, 30.6
7	2.71 (1H, dd, 14.6, 6.5)	30.6	CH_2	176.0, 60.1, 59.8, 59.4, 24.9
7’	1.39 (1H, m)			176.0, 60.1, 59.8, 59.4, 24.9
8	-	59.4	C	-
9	3.25 (1H, t, 7.4)	59.8	CH	176.0, 59.4, 40.5
10	2.36 (1H, dd, 14.0, 6.6)	40.5	CH_2	60.1, 59.8, 59.4, 44.1, 38.8
10’	1.44 (1H, m)			60.1, 59.8, 59.4, 44.1, 17.8
11	-	123.2	C	-
12	1.59 (3H, d, 2.2)	23.8	CH_3	135.8, 123.2, 20.6
13	1.73 (3H, d, 2.3)	20.6	CH_3	135.8, 123.2, 23.8
14	-	176.0	C	-
15	0.86 (3H, s)	17.8	CH_3	59.8, 44.1, 40.5, 38.8
14-COOH	8.09 (1H, brs)	-	COOH	

^{1}H (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) of compound 3 (aspterric acid, AA):



3

no.	δ_H (mult., *J* in Hz)	δ_C	mult.	HMBC
1	-	53.0	C	-
2	1.73 (1H, m)	33.8	CH_2	134.5, 76.3, 53.0, 23.6
2’	1.50 (1H, m)			134.5, 76.3, 55.4, 53.0, 23.6
3	2.42 (1H, dd, 14.9, 7.3)	23.6	CH_2	76.3, 55.4, 53.0, 33.8
3’	1.61 (1H, m)			134.5, 55.4, 53.0, 33.8
4	-	134.5	C	-
5	2.34 (1H, m)	55.4	CH	134.5, 125.2, 76.3, 53.0, 33.8, 23.6
6	2.20 (1H, m)	36.6	CH_2	75.6, 55.4, 53.0
6’	1.70 (1H, m)			75.6, 53.0
7	2.32 (1H, m)	32.2	CH_2	178.2, 82.9, 75.6, 55.4
7’	2.01 (1H, m)			75.6, 55.4
8	-	75.6	C	-
9	4.29 (1H, d, 8.5)	82.9	CH	76.3, 75.6, 53.0, 36.2
10	2.26 (1H, m)	36.2	CH_2	82.9, 76.3, 75.6, 55.4
10’	2.12 (1H, d, 13.4)			76.3, 75.6, 55.4, 53.0
11	-	125.2	C	-
12	1.71 (3H, s)	20.9	CH_3	134.5, 125.2, 23.4
13	1.60 (3H, s)	23.4	CH_3	134.5, 125.2, 20.9
14	-	178.2	C	-
15	3.92 (1H, d, 8.3)	76.3	CH_2	82.9, 55.4, 53.0, 36.2
15’	3.48 (1H, d, 8.3)			55.4, 53.0, 33.8

Supplementary Table 6. The codon-optimized sequence of *astD* for expression in *A. thaliana*. The *Ath*DHAD chloroplast localization signal is in blue, and the FLAG-tag is in red.

ATGCAAGCCACCATCTTCTCTCCACGCGCCACTCTCTTCCCCTGTAAACCTCTCCTCC
CTTCCCACAATGTCAACTCTCGCCGTCCCTCAATCATCTCCTGCTCCGACTACAAAG
ACGATGACGACAAACACATGGACTACAAAGACGATGACGACAAAGACTACAAAGA
CGATGACGACAAATTCGCATCTCGTATCCGATCAAGAGCCCTTGGTCTTCACCCCCG
AGCTCGATTTGAAAACACTCGACTTCCGGCCAGTACTACCGGAAGGAGGTATAAGA
GCGACGAGACCCTGAACAGAATTAGCTCAAAAATCACTCAGCCGAAGTCCCAGGGG
GCATCTCAGGCGATGCTCTATGCTACCGGCTTGACAGAGGAAGACATGTCAAAGCC
GCAGGTCGGAATCTCATCCGTTTGGTTTGAGGGGAATCCATGCAACATGCATCTTCA
CGATTTGTCCGCCATCGTTCGTGACTCTGTTCACCGAGCAGGTCTTGTCCCCATGAGG
TTTAATTCAGTTGGCGTTTCAGACGGGATCTCTATGGGTACGAAGGGGATGAGATAT
TCCCTCCAGTCCAGAGAACTGATAGCTGACGGTATTGAGACCGTAATGAACGCTCAA
TGGTATGATGCCAACGTGTCTCTGCCTGGCTGTGACAAAAATATGCCGGGCGTCCTC
ATGGCGATGGGTAGAACCAATCGTCCTTCCATCATGGTCTACGGAGGTAGCATCAAA
CCCGGTTGCTCTGCCAAGGGACAAAAATTAGATCTGGTATCTGCTTTTCAAAGCTAT
GGACAGTTCATAACGGGTCAGATAGATGAAAAGGAACGATTTGATATAATTAGAAA
CGCATGTCCTGGTCGTGGAGCTTGCGGTGGAATGTACACGGCAAACACACTAGCTAC
CGCTATAGAGACTATGGGTATGACAGTGCCCGGCTCTTCTAGCTGTCCGGCGGATGA
CCCTAAAAAACTAGTGGAGTGCGAGAATATAGGCGAGGTGGTAAAGACGATGCTCC
GAGAAGATATCAAACCGCGAGACGTTCTCACCCGTCAGGCTTTTGAAAATGCGATG
ATTGTGGTCAACATACTAGGGGGTTCTACAAATGCCGTACTCCATCTAATAGCCATA
GCTGATTCCGTAGGGATCAAACTGACGATAGATGATTTCCAAGCCGTATCTGATAAA
ACACCGTTCTTGGCCGATCTAAAACCCTCAGGGAAGTACTTAATGAACGATTTGTAC
AACATCGGCGGCACCCCGGCGCTTTTAAAGTATCTCCTTAAGGAAGGACTTATTGAC
GGAAGTGGCATAACTGTCACTGGTAAAACCATGAAAGAAAACGTGGCCTCTTGGCC
CGATTTTCCCTCAGATCAAGACATAATCCGACCGCTCTCAAACCCGATTAAGCCCTC
CGGCCATTTACAAATTCTCAGGGGGTCTCTAGCGCCGGGAGGGTCAGTAGGTAAGA
TTACGGGTAAGGAGGGGCTCAGATTTGAGGGCACCGCAAAGTGCTATGACTACGAG
GATGCCTTCATAGAGAGTCTTGAGAGAGGTGAGATTAAAAAGGGAGAGAAGACAGT
GGTGATAATAAGGTATGAAGGCCCAAAGGGGGGCCCGGGCATGCCTGAAATGCTCA
AACCAAGCGCCGCGATTATGGGTGCGGGCTTAGGTCAAGACGTTGCACTTCTGACA
GATGGGCGTTTCTCAGGGGGATCACACGGCTTTCTAATAGGTCACATTGTACCAGAG
GCGATGGAGGGGGGTCCCATAGCTTTAGCACGTGACGGGGATCGTATTGTCATCGA
CGCCGAGGAGCGAGTAGTCGATCTTGAGATACCGACCGAAGAGTTGGAGAAACGTC
GAAAGGAGTGGAAAGCCCCCCCACTTCGATACCAAAAGGGCACGCTCAAAAAATAT
TGCACGCTTGTTAGCGATGCATCTCACGGTTGCGTGACAGACGGGCCGATTTAG

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