

Supporting Information for:

Surveying labdane-related diterpenoid biosynthesis in the fungal genus *Aspergillus*

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Table of Contents

Table S1: CPS-PS mutant summary	S1
Figure S1: GC-MS chromatograms for PS _{inact} mutants	S2
Figure S2: Activity of CPS _{inact} mutants with 2	S3
Figure S3: Activity of CPS _{inact} mutants with 3	S3
Table S2: NMR ¹ H and ¹³ C chemical shifts for <i>syn</i> -isopimara-7,15-diene 9	S4
Figure S4: Numbering, ¹ H- ¹ H COSY, HMBC correlations and NOESY correlations for 9	S4
Figure S5: Original 1D ¹ H spectra for 9	S5
Figure S6: Original 1D ¹³ C spectra for 9	S5
Table S3: NMR ¹ H and ¹³ C chemical shifts for <i>syn</i> -manool 10	S6
Figure S7: Numbering, ¹ H- ¹ H COSY, HMBC correlations and NOESY correlations for 10	S6
Figure S8: Original 1D ¹ H spectra for 10	S7
Figure S9: Original 1D ¹³ C spectra for 10	S7
Table S4: Gene accessions	S8
Table S5: Primer sequences	S8
Sequences of synthetic genes	S9-12

Table S1: CPS-PS mutant summary.

Species (cyclase name)	PS _{inact} mutant	CPS _{inact} mutant
<i>A. fumigatus</i> (AfCPS-PS)	D651A	D311A/D313A/D314A
<i>A. oryzae</i> (AoCPS-PS)	D651A	D311A/D313A/D314A
<i>A. niger</i> (AnCPS-PS)	D667A	D327A/D329A/D330A
<i>N. fischeri</i> (NfCPS-PS)	D649A	D314A (middle Asp of DxDD)

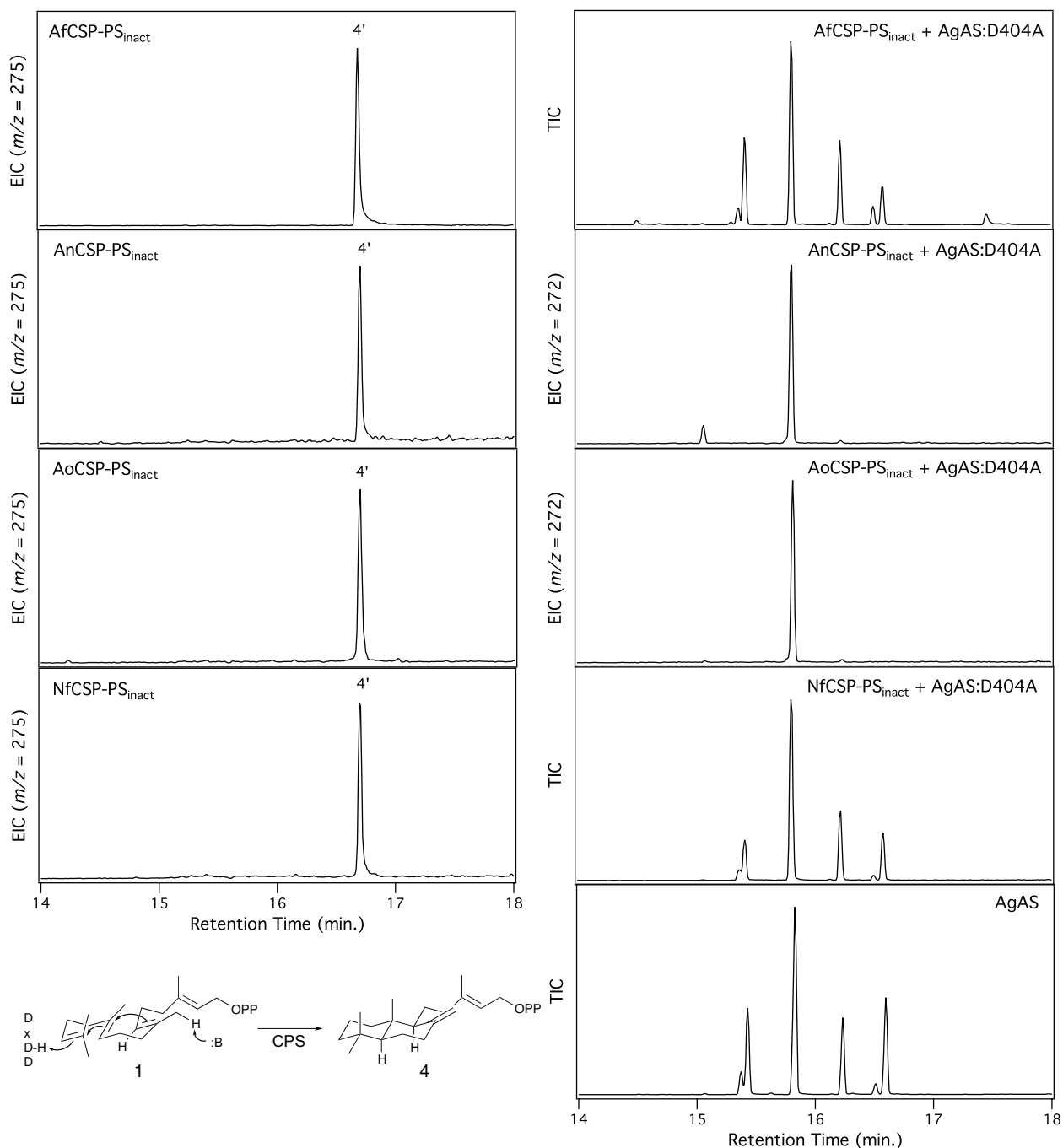


Figure S1: CPS activity of the fungal CPS-PS. GC-MS chromatograms for the PS_{inact} mutants, either expressed alone or with class I diterpene synthases specific for CPP **4** (AtKS, data not shown) or *ent*-CPP **2** (i.e., AgAS:D404A) in *E. coli* engineered to produce **1**. The production of abietadiene (double bond isomers) observed upon co-expression with AgAS:D404A indicates the specific production of **4** by the CPS active site, by comparison to the product outcome mediated by the wild-type AgAS (note that single isomer seen in chromatograms for AnCPS- PS_{inact} and AoCPS- PS_{inact} result from use of 272 (m/a) ion extraction due to lower activity of these enzymes). Also shown is the reaction catalyzed by the CPS active sites of these fungal bifunctional enzymes.

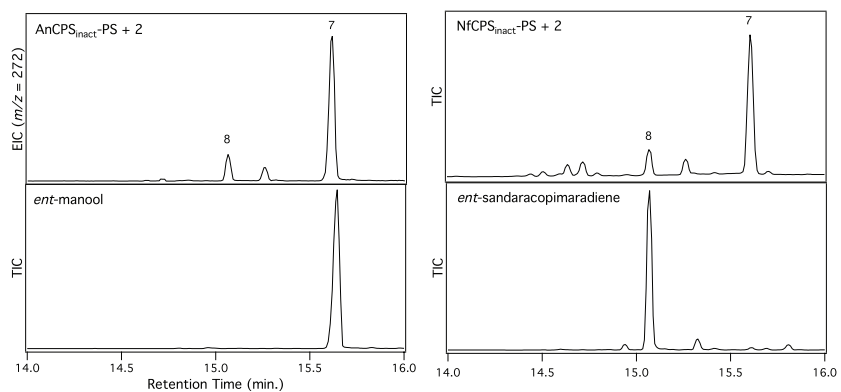


Figure S2: PS activity of fungal CPS-PS with *ent*-CPP **2**. GC-MS chromatograms for the CPS_{inact} mutants when expressed in *E. coli* engineered to produce **2**, along with those of authentic standards.

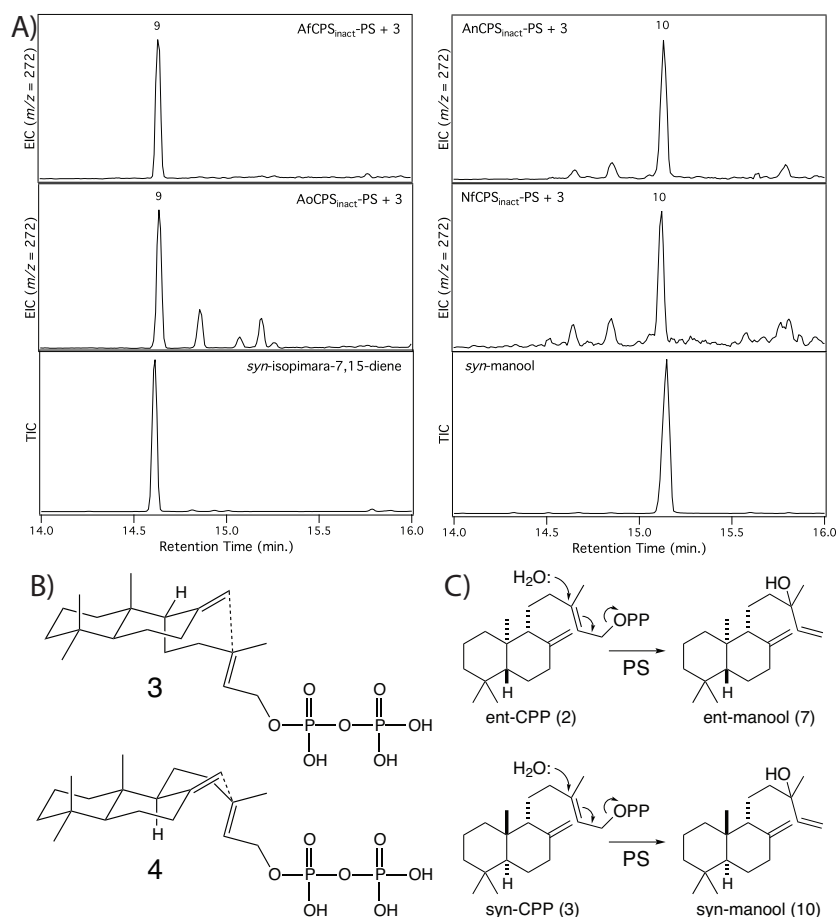


Figure S3: PS activity of fungal CPS-PS with *syn*-CPP **3**. A) GC-MS chromatograms for the CPS_{inact} mutants when expressed in *E. coli* engineered to produce **3**. B) Comparison of the active site configurations of the native substrate **4** and alternative substrate **3** indicated by the observed production of **9** from **3** by both AfCPS-PS and AoCPS-PS. C) Indirect hydrolytic reactions catalyzed by both AnCPS-PS and NfCPS-PS with either **2** or **3** as alternative substrates.

Table S2: ^1H and ^{13}C NMR assignments for *syn*-isopimara-7,15-diene **9** in CDCl_3

<i>syn</i> -isopimara-7,15-diene 9		
Position	δ_{C} (ppm)	δ_{H} (ppm)
1	37.04	1.141(m); 1.395(m)
2	19.95	1.276(m); 1.530(m)
3	46.80	1.116(m); 1.255(m)
4	35.16	
5	43.70	1.155(dt), $J=3.4, 12.5$
6	23.94	1.811(m); 1.953(m)
7	119.78	5.265(bs)
8	137.06	
9	53.38	1.376(m)
10	35.39	
11	33.71	1.216(m); 1.704(m)
12	39.09	1.366(m); 1.374(m)
13	39.80	
14	49.87	1.686(d); 1.978(m), $J=11.5$
15	146.15	5.886(ddt), $J= 1.8, 12.3, 17.9$
16	111.13	4.910(m), 4.939(m)
17	22.41	0.978(s)
18	29.88	0.851(s)
19	22.96	0.878(s)
20	25.55	0.915(s)

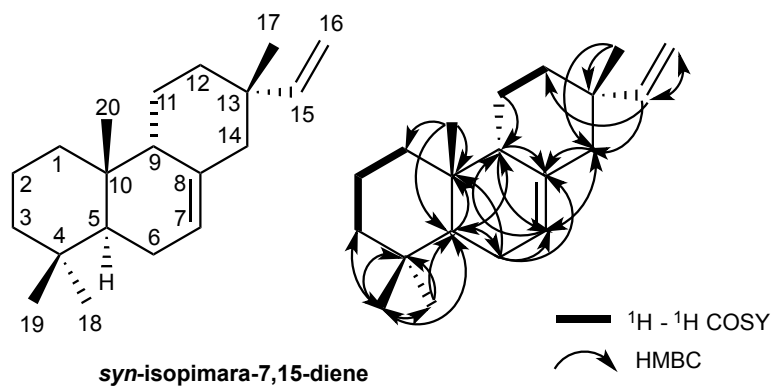


Figure S4: ^1H spectra obtained for *syn*-isopimara-7,15-diene **9**. Carbon numbering and HMBC correlations and COSY correlations used to verify the chemical structure. Note: All chiral centers were predetermined by the use of *syn*-CPP **4** as substrate with the exception of C13, which was assigned based on chemical shift differences and difference in GC-MS retention time compared to an authentic sample of *syn*-pimara-7,15-diene.

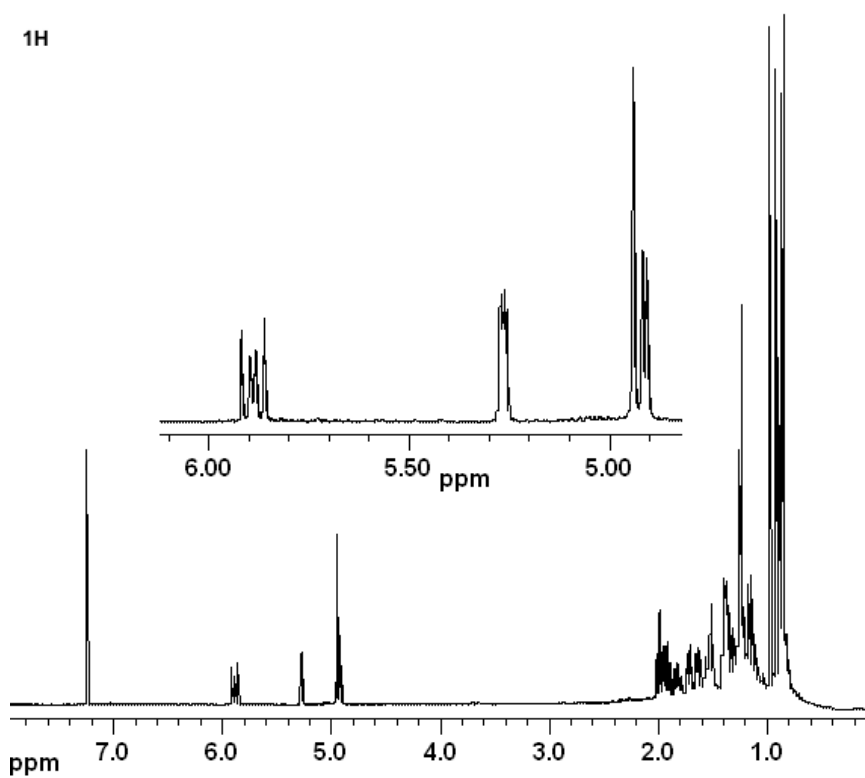


Figure S5: ¹H Spectrum of *syn*-isopimara-7,15-diene **9**. All spectra were acquired in CDCl₃ solvent.

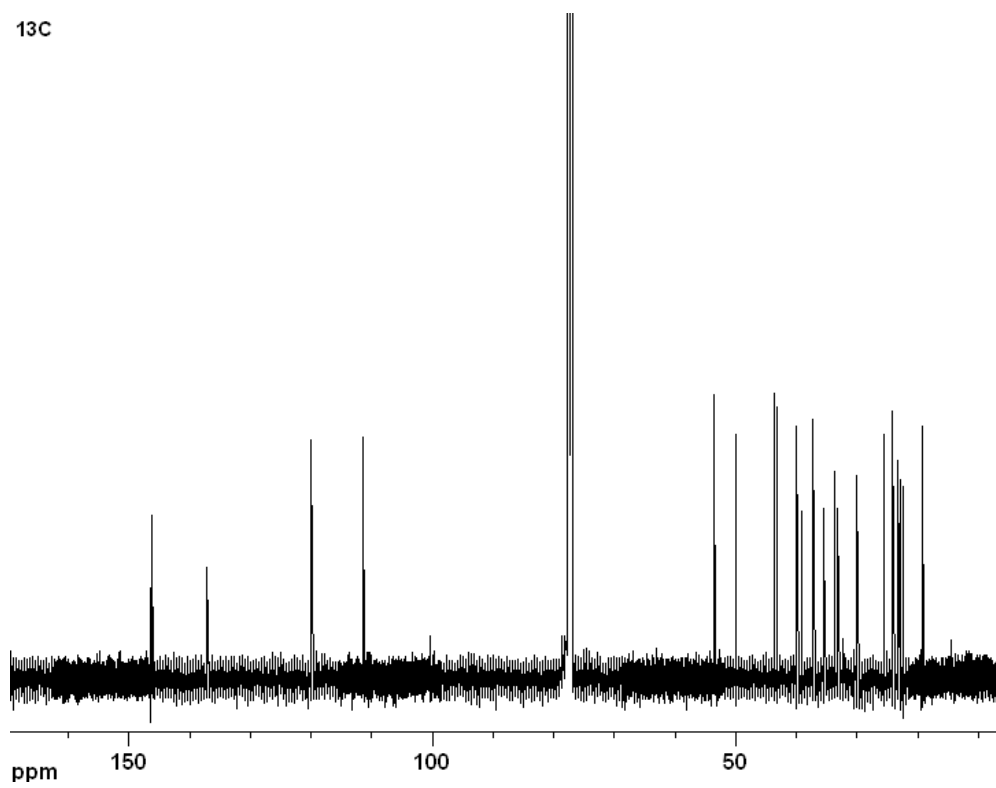


Figure S6: ¹³C Spectrum of *syn*-isopimara-7,15-diene **9**.

Table S3: ^1H and ^{13}C NMR assignments for *syn*-manool **10** in CDCl_3

<i>syn</i> -manool 10		
Position	δ_{C} (ppm)	δ_{H} (ppm), J (Hz)
1	36.98	1.086(m); 1.550(m)
2	19.44	1.428(m); 1.622(m)
3	42.85	1.165(m); 1.385(m)
4	33.47	
5	46.00	1.291(m)
6	23.92	1.289(m); 1.611(m)
7	31.93	2.067(m); 2.185(m)
8	149.44	
9	58.70	1.459(m)
10	38.33	
11	20.44	1.332(m); 1.590(m)
12	41.24	1.224(m), 1.428(m)
13	73.58	
14	145.50	5.899(dt), $J=10.7, 17.4$
15	111.72	5.048(d), $J=10.7$; 5.205(d), $J=17.4$
16	28.10	1.269(s)
17	109.64	4.539(t), $J=1.7$; 4.720(t), $J=2.2$
18	33.68	0.869(s)
19	22.63	0.802(s)
20	22.93	0.907(s)

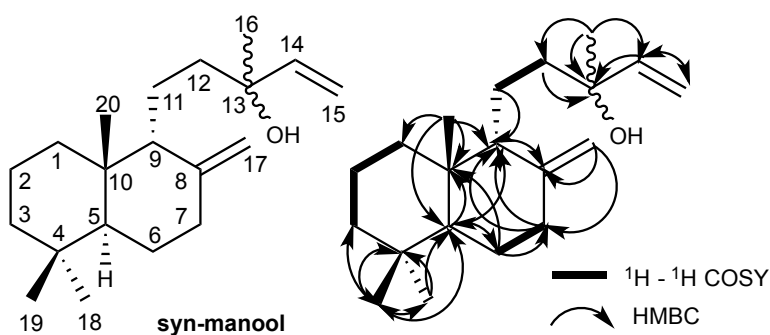


Figure S7: ^1H spectra obtained for *syn*-manool **10**. Carbon numbering and HMBC correlations and COSY correlations used to assign configurations.

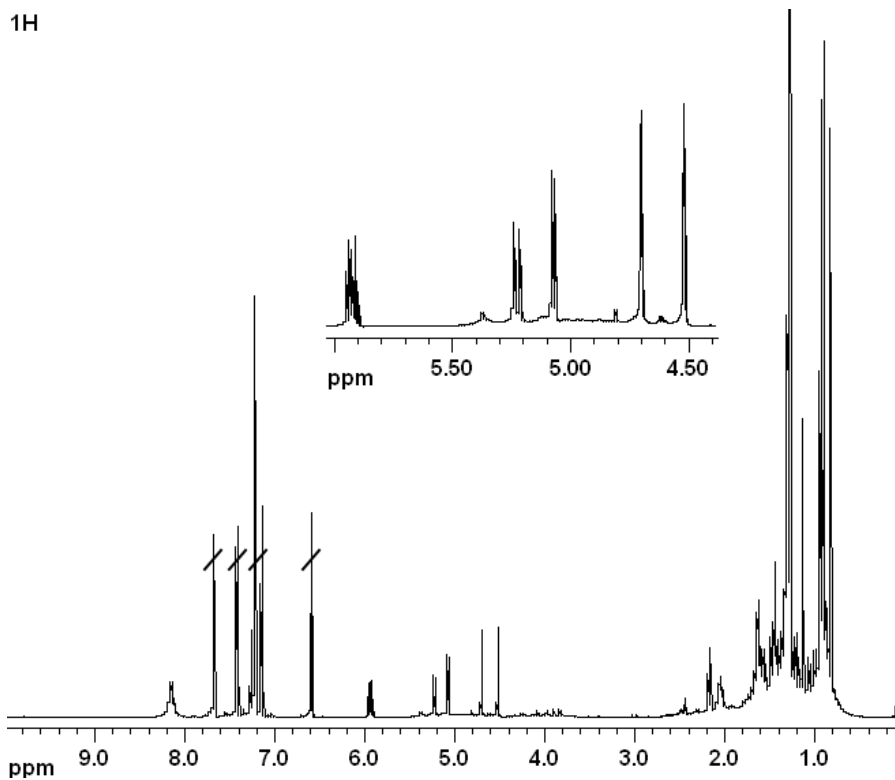


Figure S8: ¹H Spectrum of *syn*-manool **10**.

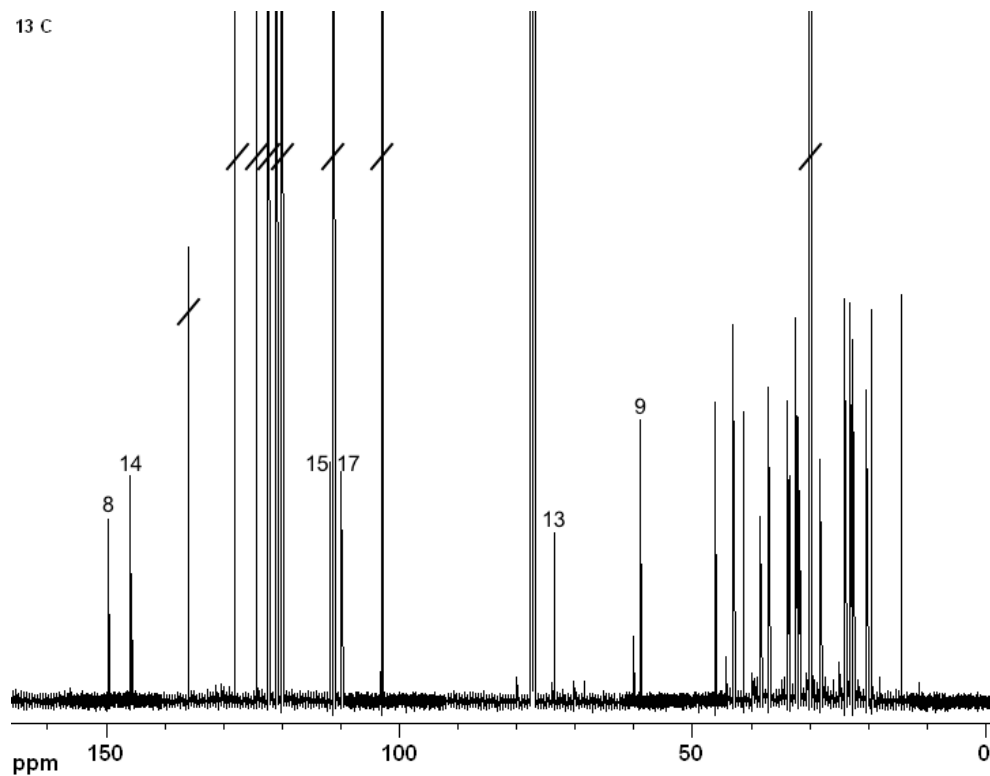


Figure S9: ¹³C Spectrum of *syn*-manool **10**.

Table S4: Gene accessions.

Gene	Accession
AfCPS-PS	XP_753151
AoCPS-PS	XP_001820661
AnCPS-PS	XP_001398730
NfCPS-PS	XP_001264196
CYP503C1	XP_001398729
CYP503B4	XP_001264200
CYP58D2	XP_001820660
CYP58Dp	XP_753152
AoCPR	XP_001826472

Table S5: Primer sequences.

Gene	Purpose		Sequence
AfCPS-PS	cloning	F	<u>CACCATGATTGGCAATCCAGGAGCGT</u>
		R	GGCTCTACCACAGCGATGTGA
	PS _{inact}	F	ATTGGTTTGTTC AAGAAGCTGACTTGATGGAGAGGTCG
		R	CGACCTCTCCATCAAGTCAGCTTCTTGAAACAAACCAAT
	CPS _{inact}	F	AATGCATGTGCTGCTGCCGCTGCTACAGCCAAGGCGTTA
		R	TAACGCCTTGGCTGTAGCAGCGGCAGCAGCACATGCATT
AoCPS-PS	cloning	F	<u>CACCATGAAAGATAACCCGGTGGGCGTTC</u>
		R	ATTTGGTAGCACGACGGCGACGTAA
	PS _{inact}	F	ATTGGTATCTTTCAGGAAGCTGAACTGATGGAAAAAAG
		R	CTTTTTCCATCAGTTCAGCTTCTTGAAAGATACCAAT
	CPS _{inact}	F	AAAGCGTGCCCGGCTGCCGCTGCTACCGCAAAAGCCCTG
		R	CAGGGCTTTTGCGGTAGCAGCGGCAGCCGGGCACGCTTT
AnCPS-PS	cloning	F	<u>CACCATGACTGTTGTGAAAAAATAAAGCTGA</u>
		R	ATTCAGCCGCCAAAGTCGTCCTGA
	PS _{inact}	F	TACTCAACTATCAGGTAGCTGAGTATATGGAGTCGGTT
		R	AACCGACTCCATATACTCAGCTACCTGATAGTTGAGTAA
	CPS _{inact}	F	GGCTTTGTGCCTGCTGCCGCTGCTACTGCGCGGGCTCTT
		R	AAGAGCCCGCGCAGTAGCAGCGGCAGCAGGCACAAAGCC
NfCPS-PS	cloning	F	<u>CACCATGACCCGCCCAACGCAACC</u>
		R	GCGATATCGCCACCCGTATGTAA
	PS _{inact}	F	CTGAACTATCAGGCGGCTGAATTCATGGAAGCC
		R	GGCTTCCATGAATTCAGCCGCTGATAGTTTCAG
	CPS _{inact}	F	ATCCAGGCCGATGCAGCTGATACCGCAAAAGCC
		R	GGCTTTGCGGGTATCAGCTGCATCGGCTGGAT
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		XhoI-R	AAGCGAATGTCTGCAGCTGTAACCTCGAGTTTTT
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CYP503B4	cloning	NdeI-F	AAAAACATATGGATAACTATACGCTGCTGA
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CYP58D2	cloning	NdeI-F	AAAAACATATGGGCGTGATCAGCGTGGTTA
		XhoI-R	GGTTGGTATTGCAAGATTAACCTCGAGTTTTT
	N-term. mod.	Δ48-F	<u>CACCATGGCGAAAAAAACCAGCAGCAAAGGTAAACTGCCCGGGTCCGAAACTGGCGGC</u>
CYP58Dp	Cloning	F	ATGGATTTTATGTCTCCTGCCGAATTTT
		R	GCTTTGCCAATACTTTGGTCTGT
AoCPR	cloning	NcoI-F	AAAAACCATGGTTACCCCGCGTGGCCGCT
		NotI-R	AAATGGCAGGAAGATGTGTGGTAAGCGGCCGCAAAA
Modified CYPs	cloning	NdeI-F	AAAAACATATGGCTAAAAAAACCAG

Sequences of synthetic genes

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