Supporting Information:

Development of the QM/MM(ABEEM) Method Combined with Polarizable Force Field to Investigate the Excision Reaction Mechanism of Damaged Thymine

Cui Liu*, He Jiang, Yue Li, Bing Xue, Yu-Ying Yao, Zhong-zhi Yang*

School of Chemistry and Chemical Engineering, Liaoning Normal University, Dalian, 116029, People's Republic of China

Corresponding authors E-mail address:

liuc@lnnu.edu.cn (Cui Liu)

zzyang@ lnnu.edu.cn (Zhong-zhi Yang)

Tel: +86 411-82159607

Index

page

1. The labels of (5R,6S)-Tg and (5R,6S)-TgH in ABEEM PFF, structures and the charge transfers of RC, TS and PC of protonated bases in the mono- and di-functional reaction pathways.

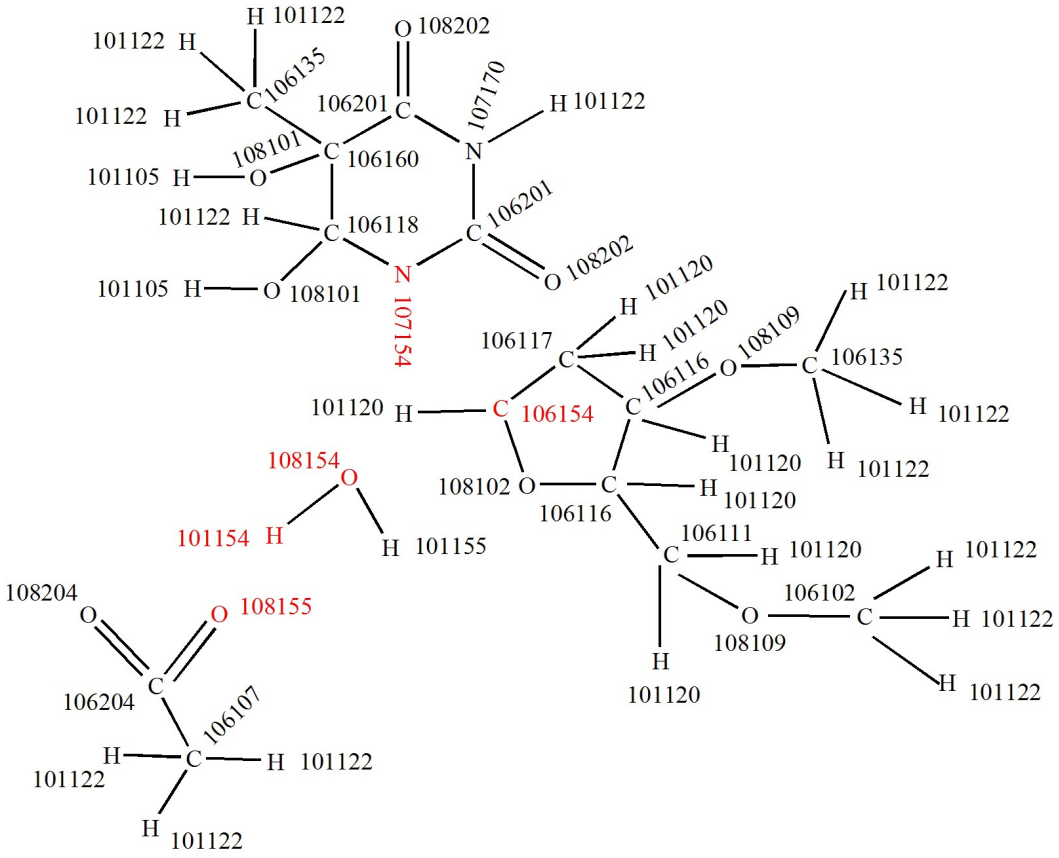

Figure S1. The labels of each atomic site of (5R,6S)-Tg in ABEEM PFF

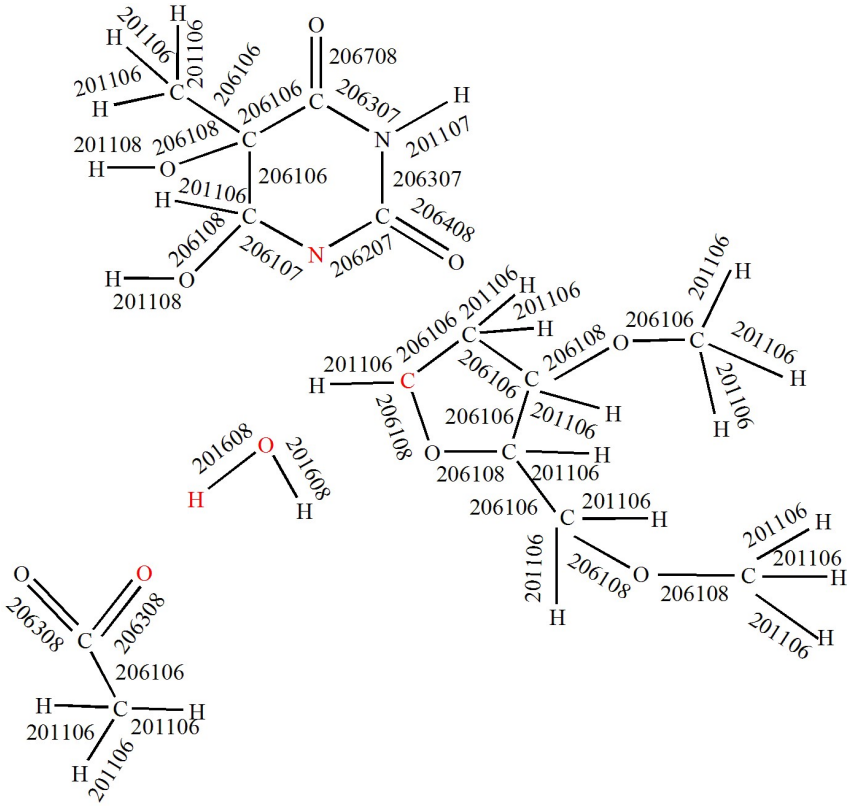

Figure S2. The labels of σ bond site of (5R,6S)-Tg in ABEEM PFF

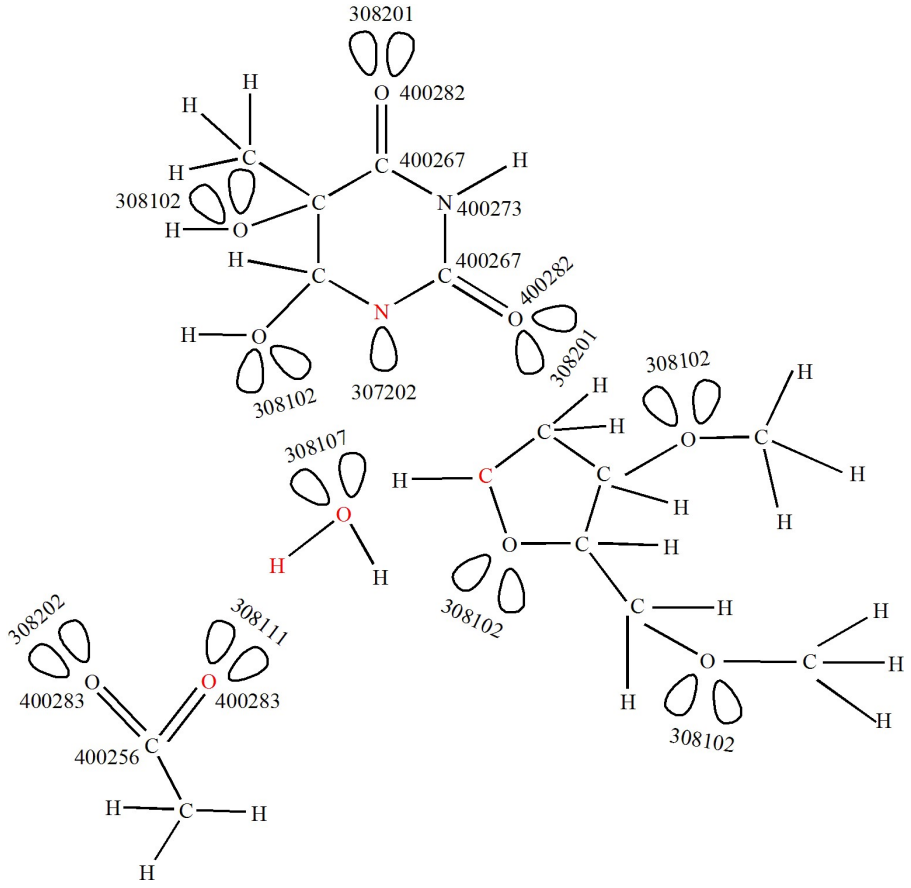

Figure S3. The labels of lone pair electronic, π bond site of (5R,6S)-Tg in ABEEM PFF

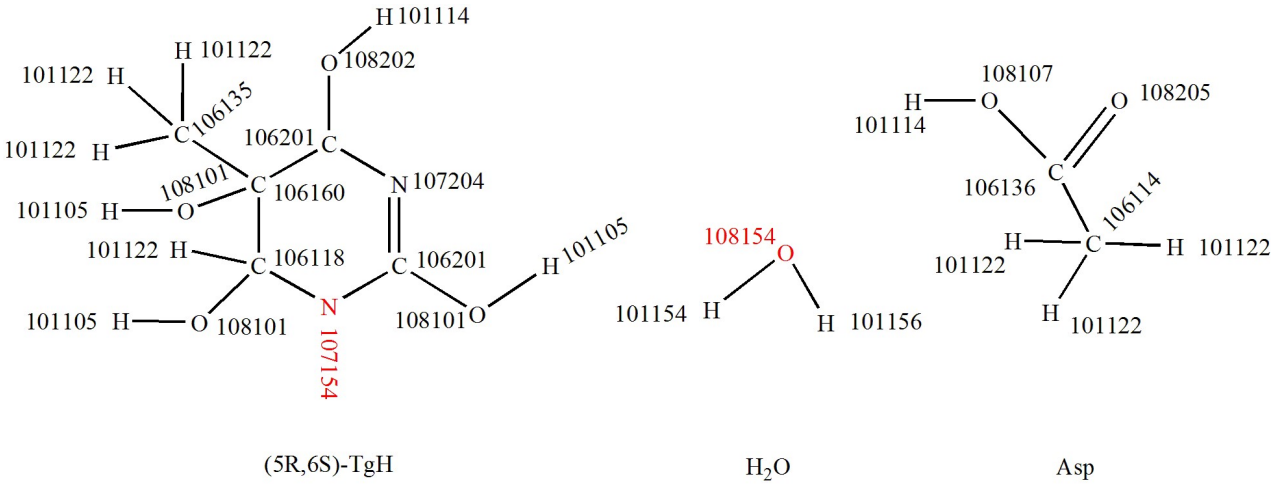

Figure S4. The labels of each atomic site of (5R,6S)-TgH in ABEEM PFF

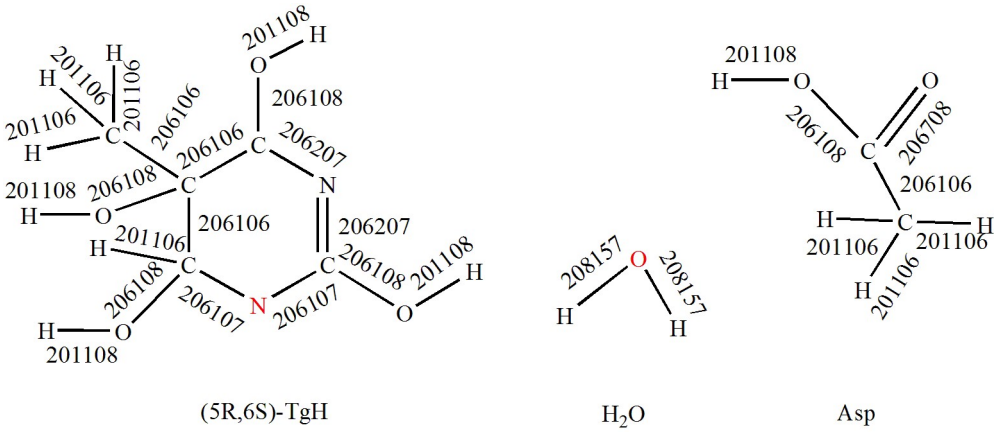

Figure S5. The labels of σ bond site of (5R,6S)-TgH in ABEEM PFF

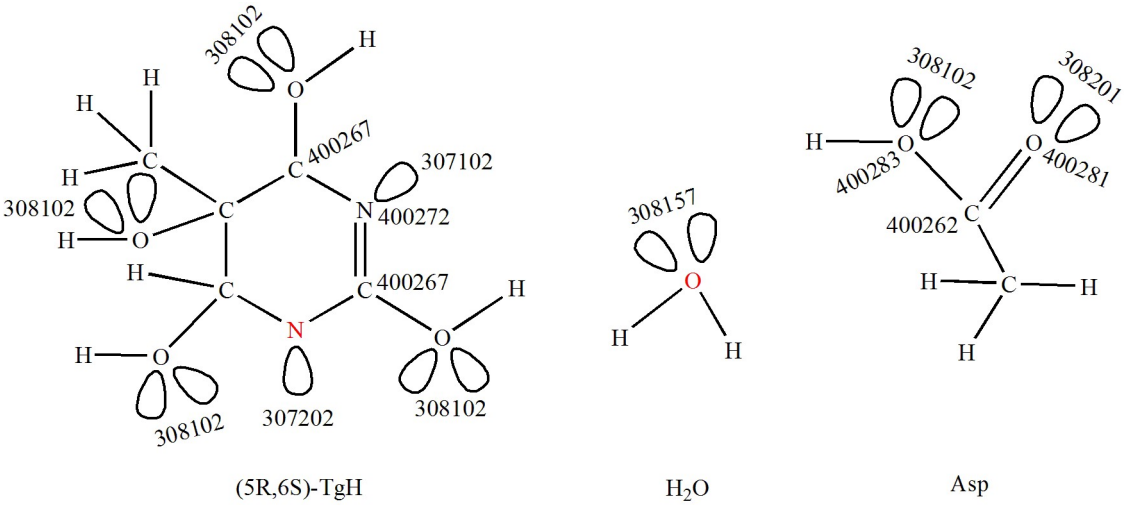

Figure S6. The labels of lone pair electronic, π bond site of (5R,6S)-TgH in ABEEM PFF

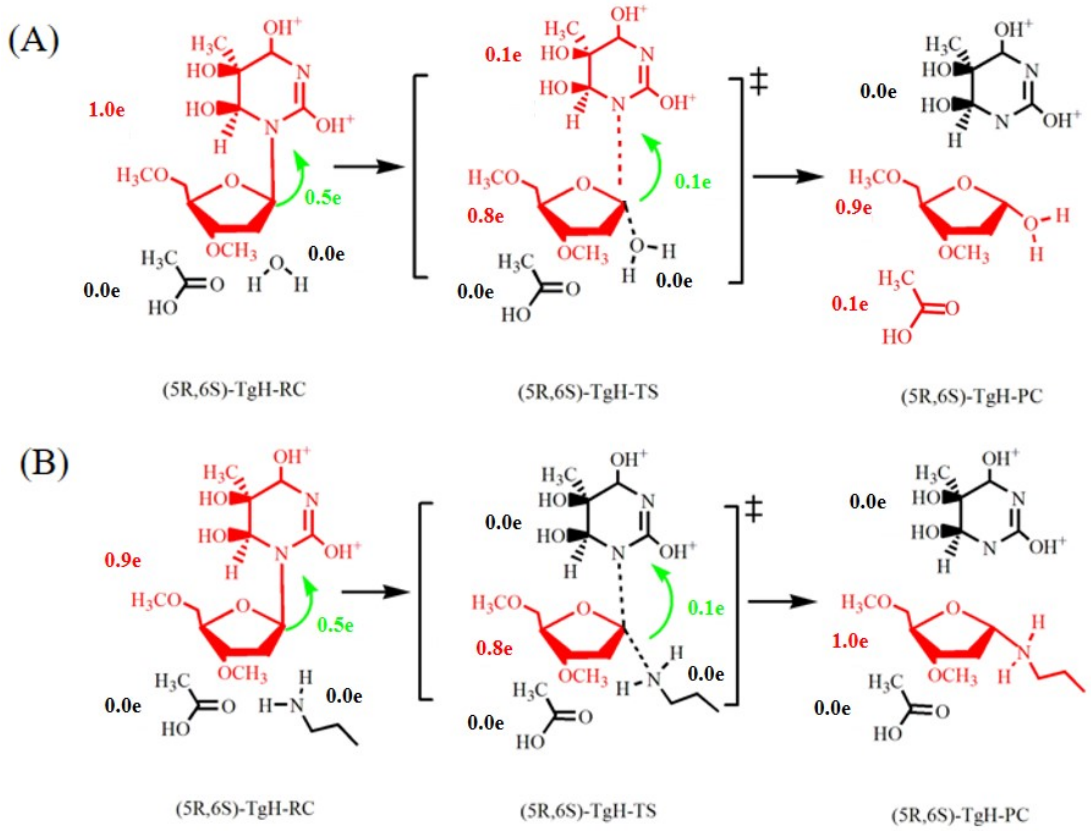

Figure S7. Schemes of the charge transfer among bases, pentoses, nucleophiles and catalytic residues during the excision of (5R,6S)-TgH under the (A) monofunctional and (B) difunctional reaction pathways.

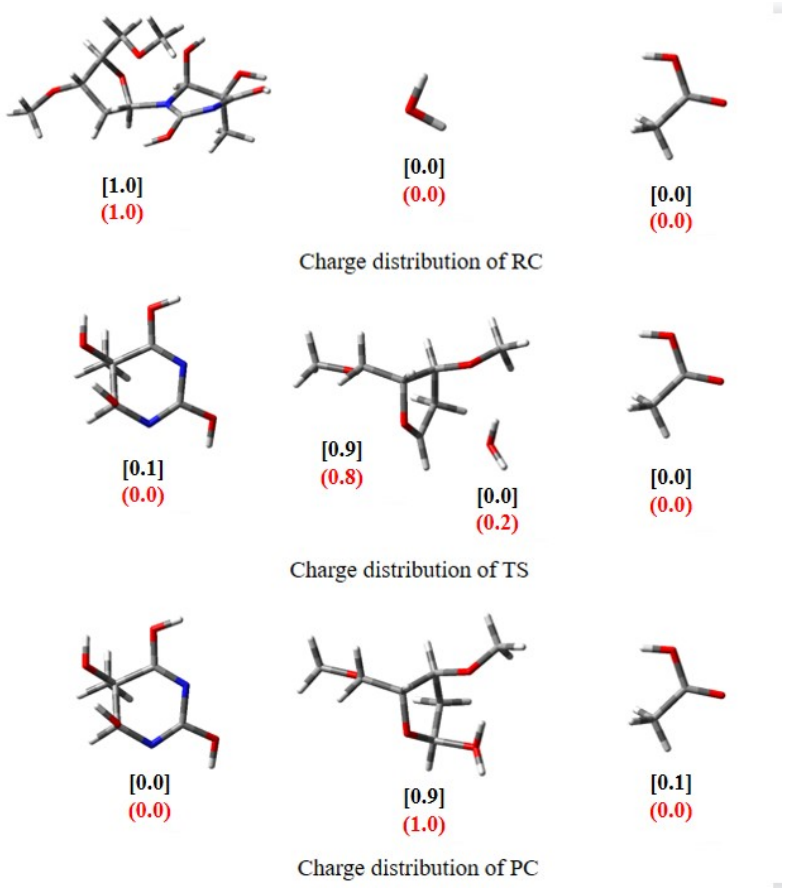

Figure S8. Schemes of the charge on each part of the RC, TS and PC calculated by ab initio (black font) and ABEEM PFF (red font) under the monofunctional pathway.

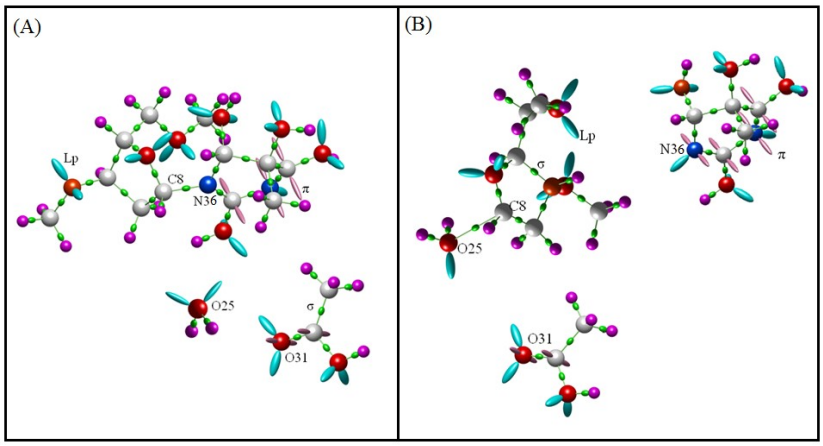

Figure S9. The sites of each part in the process from the (A) RC to (B) PC of (5R,6S)-TgH under the monofunctional reaction pathway in the ABEEM PFF. The numbers are Gaussian label.

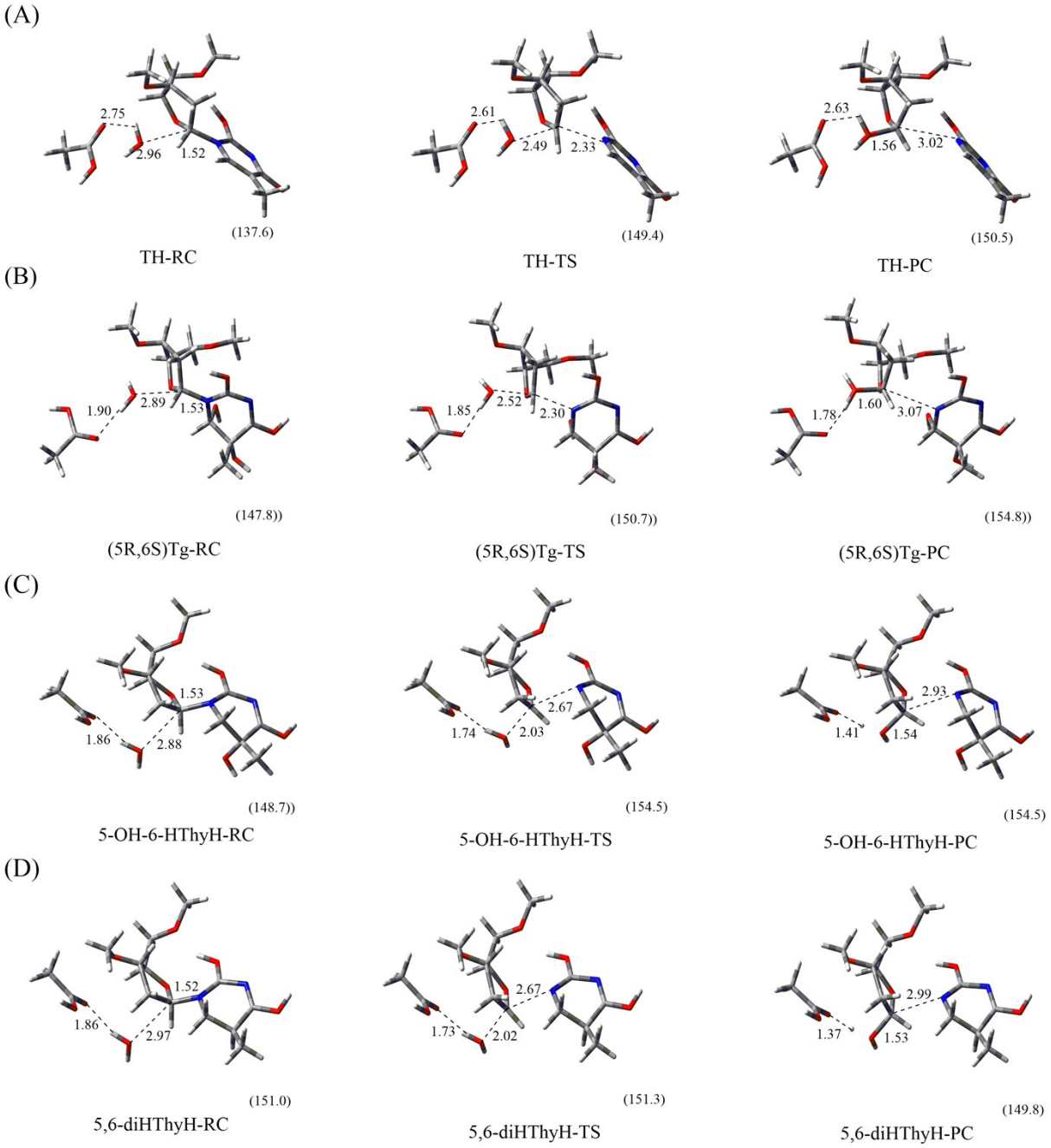

Figure S10. The structures of RC, TS and PC of protonated thymine and its damaged derivatives under the monofunctional pathway (Asp-H_2O). These numbers denote C1'-N1 glycosidic bond length, C1'-O23 nucleophilic distance, O29-H24 the distance of nucleophile and amino acid (Å), and ∠(O23-C1'-N1) reaction angles (in brackets, º) .

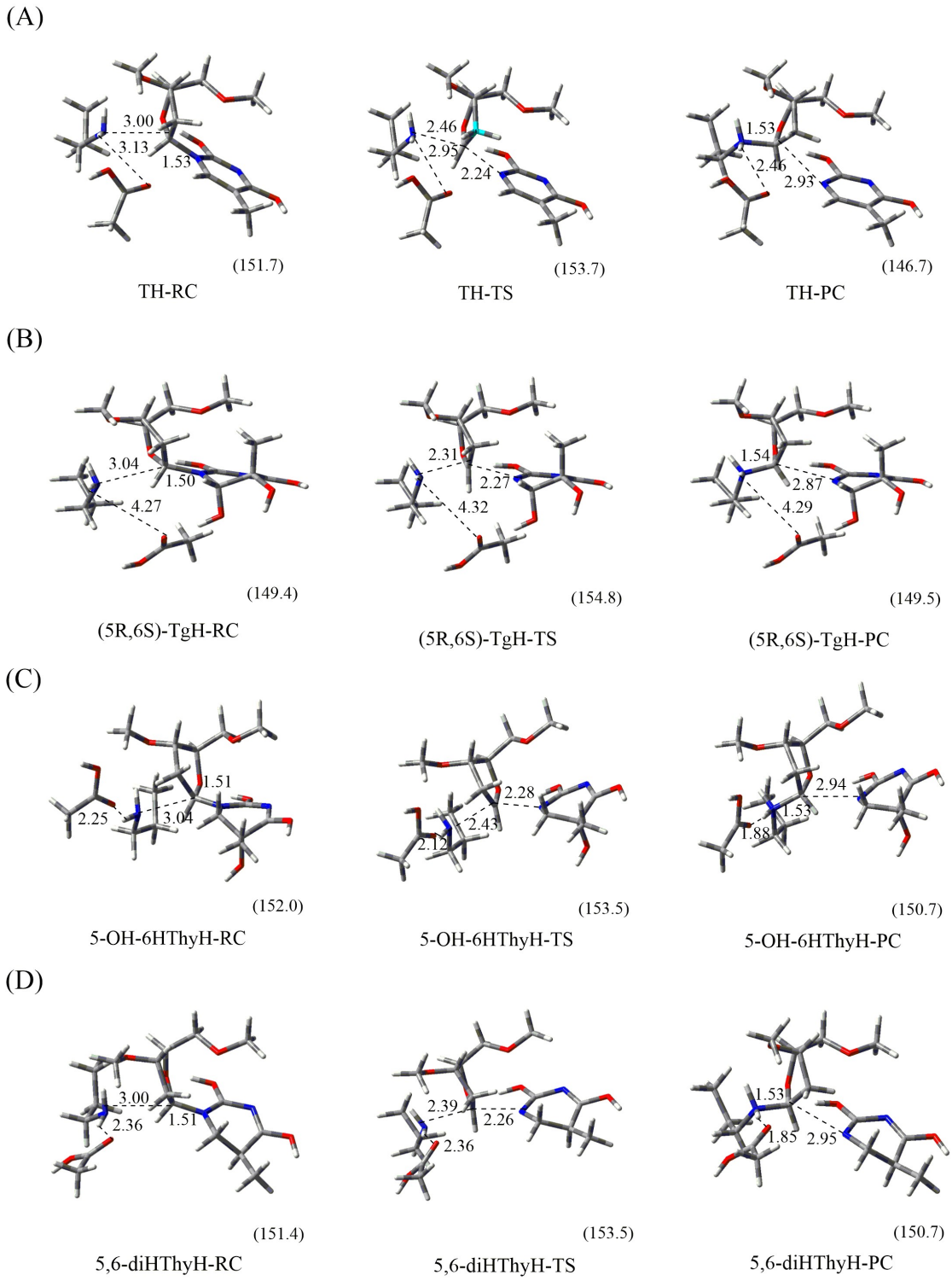

Figure S11. The structures of RC, TS and PC of protonated thymine and its damaged derivatives under the bifunctional pathway (Asp-Lys). These numbers denote C1'-N1 glycosidic bond length, N30-C1' nucleophilic distance, O29-H31 the distance of nucleophile and amino acid (Å), and ∠(N30-C1'-N1) reaction angles (in brackets, º).

2. The parameters in $\chi^*(r)$

Table S1. The parameters in $\chi^*(r)$ of C1'(106154) in (5R,6S)-TgH, which depends on variable $r_{C1'\text{-}N1}$ under the Asp-H_2O reaction pathway

Distances(Å)	Functions	Distances(Å)	Functions
$r \leq 1.56$	2.94	$1.56 < r \leq 1.68$	$2.41 + \frac{0.10}{1.00 + \exp\frac{r - 1.62}{0.01}}$
$1.68 < r \leq 2.58$	$0.48 \times r^2 - 2.47 \times r + 5.21$	$2.58 < r \leq 2.75$	$2.54 + \frac{0.01}{1.00 + \exp\frac{r - 2.72}{0.01}}$
$r > 2.75$	$2.66 - \frac{0.09}{1.00 + \exp\frac{r - 2.90}{0.02}}$		

Table S2. The parameters in $\chi^*(r)$ of N1(107145) in (5R,6S)-TgH, which depends on variable $r_{C1'\text{-}N1}$ under the Asp-H_2O reaction pathway

Distances(Å)	Functions	Distances(Å)	Functions
$r \leq 1.68$	3.70	$1.68 < r \leq 2.21$	$5.41 - \frac{3.36}{1.00 + \exp\frac{r - 1.80}{1.30}}$
$2.21 < r \leq 2.67$	$5.80 - \frac{3.75}{1.00 + \exp\frac{r - 2.44}{3.90}}$	$r > 2.67$	4.00

Table S3. The parameters in $\chi^*(r)$ of O23(108154) in (5R,6S)-TgH, which depends on variable $r_{O23\text{-}H24}$ under the Asp-H_2O reaction pathway

Distances(Å)	Functions	Distances(Å)	Functions
$r \leq 2.17$	$3.57 - \frac{0.37}{1.00 + \exp\frac{r - 1.88}{0.03}}$	$2.17 < r \leq 2.52$	$0.27 \times r + 3.54$
$r > 2.52$	3.25		

3. The charge transfer of neutral and protonated bases in mono- and di-functional reaction pathways

Table S4. The charges in RC, TS and PC under different reaction pathways excision of thymine and its damaged derivatives

Model1	Nucleobase	Pentose	Nucleophile	Asp		Nucleobase	Pentose	Nucleophile	Asp
			T					(5R,6S)-Tg	
RC	-0.25	0.22	-0.08	-0.90		-0.22	0.20	-0.06	-0.91
TS	-0.89	0.78	-0.03	-0.85		-0.93	0.74	0.03	-0.83
PC	-0.98	0.05	-	-0.07		-0.98	0.05	-	-0.07
			5,6-diHThy					5-OH-6HThy	
RC	-0.22	0.19	-0.06	-0.91		-0.21	0.19	-0.07	-0.90
TS	-0.91	0.71	0.03	-0.83		-0.88	0.72	0.00	-0.85
PC	-0.98	0.05	-	-0.07		-0.98	0.05	-	-0.07
Model2	Nucleobase	Pentose	Nucleophile	Lys		Nucleobase	Pentose	Nucleophile	Lys
			T					(5R,6S)-Tg	
RC	-0.20	0.23	-0.06	0.04		-0.19	-0.05	0.04	-0.06
TS	-0.85	0.77	0.02	0.07		-0.88	0.55	0.05	-0.08
PC	-0.75	0.02	-	0.73		-0.96	-0.09	-	0.90
			5,6-diHThy					5-OH-6HThy	
RC	-0.20	0.20	-0.07	0.03		-0.17	0.22	-0.05	0.02
TS	-0.84	0.73	0.04	0.07		-0.83	0.55	-0.01	0.04
PC	-0.43	0.01	-	0.42		-0.64	-0.12	-	0.62
Model3	Nucleobase	Pentose	Nucleophile	Asp		Nucleobase	Pentose	Nucleophile	Asp
			T					(5R,6S)-Tg	
RC	-0.28	0.23	-0.03	-0.91		-0.32	0.18	-0.02	-0.84
TS	-0.86	0.71	0.05	-0.91		-0.89	0.66	0.09	-0.86
PC	-0.98	0.40	-	-0.42		-1.01	0.46	-	-0.45
			5,6-diHThy					5-OH-6HThy	
RC	-0.22	0.18	-0.03	-0.93		-0.24	0.21	-0.02	-0.95
TS	-0.81	0.64	0.08	-0.91		-0.81	0.68	0.04	-0.91
PC	-0.97	0.40	-	-0.43		-0.97	0.47	-	-0.43
Model4	Nucleobase	Pentose	Nucleophile			Nucleobase	Pentose	Nucleophile	
			T					(5R,6S)-Tg	
RC	-0.20	0.20	0.00			-0.19	0.19	0.00	
TS	-0.84	0.73	0.11			-0.84	0.68	0.15	
PC	-0.95	0.95	-			-0.95	0.95	-	
			5,6-diHThy					5-OH-6HThy	
RC	-0.17	0.17	0.00			-0.18	0.18	0.00	
TS	-0.82	0.69	0.13			-0.77	0.70	0.08	
PC	-0.94	0.94	-			-0.96	0.96	-	

Table S5. The charges in RC, TS, and PC under different reaction pathways excision of protonated thymine and its damaged derivatives

Model5	Nucleobase	Pentose	Nucleophile	Asp	Nucleobase	Pentose	Nucleophile	Asp
			TH				(5R,6S)-TgH	
RC	0.59	0.41	-0.03	0.02	0.66	0.34	-0.03	0.03
TS	0.07	0.92	-0.01	0.02	0.12	0.86	-0.02	0.04
PC	-0.03	0.97	-	0.06	0.11	0.58	-	0.41
			5,6-diHThyH				5-OH-6HThyH	
RC	0.61	0.38	-0.03	0.03	0.60	0.39	-0.03	0.04
TS	-0.01	0.83	0.12	0.06	-0.01	0.83	0.12	0.06
PC	-0.02	0.81	-	0.21	-0.03	0.84	-	0.19
Model6	Nucleobase	Pentose	Nucleophile	Asp	Nucleobase	Pentose	Nucleophile	Asp
			TH				(5R,6S)-TgH	
RC	0.60	0.39	-0.01	0.02	0.59	0.34	0.00	0.06
TS	0.14	0.81	0.04	0.02	0.10	0.78	0.08	0.04
PC	0.00	0.98	-	0.02	-0.03	1.00	-	0.03
			5,6-diHThyH				5-OH-6HThyH	
RC	0.64	0.36	-0.01	0.02	0.64	0.36	-0.01	0.01
TS	0.14	0.78	0.05	0.02	0.13	0.80	0.04	0.02
PC	0.00	0.95	-	0.05	-0.03	0.96	-	0.04

4. The glycosidic bond lengths, the nucleophilic distances and the reaction angles of the neutral bases in the mono- and di-functional reaction pathways

Table S6. Comparison of glycosidic bond lengths of thymine and its damaged derivatives in different reaction pathways(Å)

pathway	reaction state	T	(5R,6S)-Tg	5,6-diHThy	5-OH-6HThy
	RC	1.50	1.52	1.49	1.48
Model 1	TS	2.47	2.61	2.53	2.45
	PC	3.12	3.14	3.15	3.08
	RC	1.49	1.50	1.48	1.49
Model 2	TS	2.42	2.48	2.42	2.47
	PC	3.01	3.00	3.02	3.11
	RC	1.52	1.50	1.49	1.50
Model 3	TS	2.32	2.34	2.32	2.30
	PC	2.98	2.99	3.01	2.99
	RC	1.47	1.47	1.45	1.48
Model 4	TS	2.37	2.35	2.38	2.37
	RC	2.99	2.86	3.00	3.00

Table S7. Comparison of nucleophilic distances of thymine and its damaged derivatives in different reaction pathways(Å)

pathway	reaction state	T	(5R,6S)-Tg	5,6-diHThy	5-OH-6HThy
	RC	3.04	3.21	3.12	3.04
Model 1	TS	2.25	2.15	2.08	2.13
	PC	1.43	1.45	1.45	1.43
	RC	3.08	3.06	3.09	3.04
Model 2	TS	2.19	2.10	2.10	2.34
	PC	1.42	1.43	1.41	1.42
	RC	3.00	3.04	3.05	3.02
Model 3	TS	2.28	2.21	2.21	2.29
	PC	1.50	1.52	1.50	1.58
	RC	3.02	3.05	3.06	3.02
Model 4	TS	2.23	2.12	2.18	2.31
	PC	1.54	1.55	1.54	1.55

Table S8. Comparison of reaction angles of thymine and its damaged derivatives in different reaction pathways (°)

pathway	reaction state	T	(5R,6S)-Tg	5,6-diHThy	5-OH-6HThy
Model 1	RC	161.23	154.73	157.73	158.97
	TS	158.20	158.55	158.09	158.72
	PC	157.10	160.73	154.89	153.47
Model 2	RC	152.12	160.48	149.86	147.54
	TS	151.64	151.00	154.46	142.98
	PC	148.12	146.66	150.91	134.91
Model 3	RC	152.45	149.77	146.25	153.68
	TS	153.33	154.36	155.67	152.65
	PC	147.19	150.74	153.05	150.09
Model 4	RC	147.79	146.80	145.25	158.75
	TS	151.15	155.91	149.58	148.20
	PC	143.60	152.11	142.97	139.20

5. Cartesian coordinates for the structures of RC, TS and PC of neutral bases in the mono- and di-functional reaction pathways.

Table S9. Cartesian coordinates for the optimized T structures of the monofunctional pathway (Asp-H_2O) at M06-2X/6-31+G(d)

T RC:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	-0.666219	0.713935	2.300935
C	0.748743	0.726398	2.171712
C	1.169726	0.682232	0.714822
O	0.625728	-0.504142	0.130246
C	0.609857	1.851620	-0.100094
O	1.558714	2.890943	-0.136216
C	0.301744	1.194924	-1.452042
C	-0.057386	-0.234595	-1.058925
C	-4.197745	-0.918518	-0.030139
C	-2.372549	0.586294	-0.475382
H	1.191051	-0.118722	2.716434
H	1.115334	1.658077	2.619252
H	2.265334	0.660551	0.616960
H	-0.304073	2.238695	0.382191
H	-0.467406	1.687596	-2.053516
H	1.228279	1.124947	-2.031436
C	1.089309	4.029341	-0.807050
H	1.848760	4.807079	-0.698400
H	0.934503	3.830981	-1.877913
H	0.140429	4.385912	-0.372546
C	-1.206716	-0.566633	2.558517
H	-0.958416	-0.893173	3.579840
H	-2.294128	-0.476981	2.470589
H	-0.837693	-1.309470	1.843432
O	2.741347	-0.516189	-2.208255
H	3.085511	-1.403976	-1.998191
H	3.251621	-0.024251	-1.516784
H	0.243577	-0.970676	-1.805663
C	4.743034	-0.962865	0.152638
O	4.238909	0.186611	-0.031910

Continued T RC

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	4.550666	-1.988478	-0.535629
C	5.675373	-1.078069	1.372057
H	6.170109	-2.052026	1.400979
H	6.419776	-0.275855	1.346125
H	5.085452	-0.944526	2.286294
O	-5.336668	-1.215963	0.304323
N	-3.280351	-1.905091	-0.382061
N	-1.526419	-0.435283	-0.832499
C	-4.564993	1.574168	0.261110
H	-4.031579	2.525852	0.189936
H	-4.940465	1.461372	1.283161
H	-5.438986	1.608947	-0.397093
C	-3.663686	0.433553	-0.103334
H	-3.604125	-2.865418	-0.338537
C	-1.954611	-1.755540	-0.770365
O	-1.257922	-2.713620	-1.034918
H	-1.938473	1.577165	-0.519018

T TS:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	-0.643703	0.677526	2.204701
C	0.762072	0.696535	2.157716
C	1.309034	0.704281	0.745595
O	0.983625	-0.569406	0.102954
C	0.683536	1.742462	-0.187429
O	1.441030	2.924384	-0.113614
C	0.712385	1.031628	-1.551712
C	0.681516	-0.401069	-1.128210
C	-4.369329	-0.941085	0.027605
C	-2.665434	0.618819	-0.631611
H	1.191191	-0.148135	2.716438
H	1.095699	1.627311	2.632022
H	2.404877	0.780605	0.732015
H	-0.351888	1.940172	0.123457
H	-0.122823	1.255185	-2.215661
H	1.664010	1.224867	-2.058682
C	0.881756	3.968482	-0.872020
H	1.485145	4.859263	-0.687105
H	0.901935	3.738670	-1.947016
H	-0.158684	4.163378	-0.570829

Continued T TS

Atoms	Coordinates (Angstroms)		
	X	Y	Z
C	-1.209731	-0.621522	2.283851
H	-1.027185	-1.052751	3.279182
H	-2.285054	-0.503935	2.129766
H	-0.806633	-1.290997	1.517502
O	2.725155	-0.826586	-2.086640
H	3.061985	-1.717887	-1.872126
H	3.308523	-0.316953	-1.444687
H	0.387633	-1.277178	-1.686249
C	4.732823	-1.032760	0.201471
O	4.208253	0.089035	-0.105967
O	4.554147	-2.114819	-0.391715
C	5.653066	-1.012249	1.426612
H	6.115007	-1.989043	1.583596
H	6.423971	-0.246492	1.295238
H	5.069337	-0.736636	2.312072
O	-5.476420	-1.304846	0.432530
N	-3.386453	-1.878508	-0.276614
N	-1.743525	-0.324175	-0.916919
C	-4.912996	1.529130	0.123553
H	-4.457249	2.505406	-0.075357
H	-5.232134	1.505173	1.172284
H	-5.822437	1.439404	-0.482548
C	-3.944331	0.424917	-0.176150
H	-3.631798	-2.854116	-0.149900
C	-2.091620	-1.625136	-0.738614
O	-1.330788	-2.579041	-0.947300
H	-2.330461	1.648911	-0.792213

T PC:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	-0.592832	0.677677	2.235668
C	0.807887	0.780040	2.206452
C	1.403822	0.797168	0.806813
O	1.294896	-0.487484	0.210092
C	0.695492	1.738687	-0.163260
O	1.248449	3.034923	-0.014548
C	0.953413	1.089914	-1.527688
C	1.217807	-0.378763	-1.196860
C	-4.418025	-0.929528	0.065402

Continued T PC

Atoms	Coordinates (Angstroms)		
	X	Y	Z
C	-2.837544	0.746051	-0.609013
H	1.271958	-0.033030	2.788796
H	1.059686	1.735273	2.683660
H	2.462656	1.099955	0.882646
H	-0.377988	1.752619	0.065394
H	0.110314	1.179228	-2.215335
H	1.856002	1.528775	-1.969912
C	0.541241	4.001189	-0.748003
H	1.002047	4.969789	-0.543246
H	0.588265	3.802274	-1.828865
H	-0.515769	4.031061	-0.445280
C	-1.091985	-0.648611	2.150739
H	-0.820227	-1.209490	3.059480
H	-2.180172	-0.565797	2.085666
H	-0.709636	-1.171515	1.270641
O	2.478616	-0.737108	-1.775583
H	2.661926	-1.669515	-1.560959
H	3.755729	-0.110699	-0.912005
H	0.443174	-1.070644	-1.529875
C	4.914361	-1.164472	0.146956
O	4.497042	0.032999	-0.251991
O	4.547705	-2.205408	-0.352377
C	5.891753	-1.077519	1.292779
H	6.324177	-2.061281	1.480660
H	6.676388	-0.348273	1.066070
H	5.360580	-0.728982	2.185565
O	-5.481948	-1.380360	0.510648
N	-3.404986	-1.788992	-0.344775
N	-1.882964	-0.114427	-1.005026
C	-5.076604	1.498192	0.332824
H	-4.691369	2.504599	0.130217
H	-5.305897	1.428026	1.404069
H	-6.029251	1.376602	-0.198619
C	-4.078109	0.461139	-0.085202
H	-3.586639	-2.782131	-0.255403
C	-2.152697	-1.437071	-0.871294
O	-1.367369	-2.351576	-1.167010
H	-2.570491	1.802909	-0.725333

Table S10. Cartesian coordinates for the optimized (5R,6S)-Tg structures of the monofunctional pathway (Asp-H_2O) at M06-2X/6-31+G(d)

(5R,6S)-Tg RC:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	-0.321714	-0.743879	2.637941
C	1.064848	-0.970920	2.415406
C	1.478409	-0.631152	0.996148
O	0.620075	-1.339408	0.095226
C	1.343348	0.844562	0.619830
O	2.536922	1.511178	0.960754
C	1.031690	0.737598	-0.872957
C	0.137850	-0.494270	-0.924448
H	1.309358	-2.018196	2.642927
H	1.618282	-0.327585	3.109326
H	2.523935	-0.922481	0.817653
H	0.511815	1.323854	1.162585
H	0.601257	1.629694	-1.321035
H	1.960164	0.470374	-1.394048
C	2.616231	2.806699	0.411813
H	3.432309	3.321512	0.925326
H	2.845719	2.756643	-0.662317
H	1.677129	3.361969	0.569668
C	-1.122564	-1.892480	2.451055
H	-0.916947	-2.639170	3.233531
H	-2.165985	-1.571634	2.545017
H	-0.960222	-2.346382	1.467718
O	2.714596	-1.617472	-2.470529
H	3.086202	-1.868107	-1.597657
H	3.225873	-0.787826	-2.604197
H	0.221481	-1.029730	-1.869668
C	4.688059	0.213179	-0.822702
O	4.223974	0.675344	-1.902356
O	4.431381	-0.907412	-0.311459
C	5.652521	1.111610	-0.032900
H	5.178971	1.359456	0.923244
H	6.574113	0.562891	0.186687
H	5.884648	2.028659	-0.580436
N	-1.347801	-0.264513	-0.720771
C	-1.866818	0.803761	0.151798
C	-3.406091	0.927920	0.091921
C	-4.134271	-0.408417	0.073904
O	-5.320135	-0.503669	0.346986

Continued (5R,6S)-Tg RC

Atoms	Coordinates (Angstroms)		
	X	Y	Z
N	-3.384362	-1.449258	-0.366862
C	-2.056943	-1.425970	-0.870925
O	-1.650791	-2.446252	-1.388263
H	-3.852031	-2.336876	-0.520902
H	-1.550892	0.615799	1.185917
O	-1.346633	2.052841	-0.196899
H	-1.743106	2.290160	-1.053329
C	-3.902904	1.795802	1.236839
H	-3.383203	2.756122	1.211041
H	-4.982771	1.945470	1.149965
H	-3.708141	1.308305	2.197693
O	-3.690298	1.524630	-1.175983
H	-4.650029	1.705836	-1.218113

(5R,6S)-Tg TS:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
C	-0.471307	-0.494722	2.554401
C	0.909035	-0.768464	2.576721
C	1.590067	-0.589585	1.237570
C	1.036710	-1.550911	0.285744
C	1.376958	0.761670	0.553524
C	2.429223	1.609742	0.951822
C	1.366253	0.394997	-0.939613
C	0.957338	-1.037621	-0.890415
H	1.097723	-1.782411	2.960640
H	1.373825	-0.050330	3.262918
H	2.666178	-0.792446	1.310075
H	0.409482	1.199618	0.836478
H	0.648804	0.966889	-1.526866
H	2.378716	0.484743	-1.354840
C	2.385819	2.862512	0.304459
H	3.138941	3.493889	0.781756
H	2.631072	2.760902	-0.761482
H	1.393477	3.324336	0.407885
C	-1.281941	-1.629643	2.301133
H	-1.186157	-2.354796	3.123685
H	-2.314820	-1.275064	2.257657
H	-1.029941	-2.113976	1.352421
C	2.748503	-1.940712	-1.765685

Continued (5R,6S)-Tg TS

Atoms	Coordinates (Angstroms)		
	X	Y	Z
H	3.371873	-1.832794	-0.986424
H	3.172562	-1.290748	-2.358949
H	0.428665	-1.624200	-1.628654
C	4.792511	0.002555	-0.568920
C	4.461383	0.299190	-1.743995
C	4.419886	-1.032170	0.065090
C	5.681054	0.976791	0.201304
H	5.060135	1.457927	0.965832
H	6.482371	0.435699	0.713005
H	6.097351	1.736788	-0.463764
N	-1.486904	-0.225825	-0.744227
C	-2.103480	0.890276	-0.095224
C	-3.626780	1.019747	-0.310166
C	-4.326117	-0.339698	-0.202898
C	-5.541921	-0.416173	-0.045272
N	-3.520376	-1.408949	-0.376826
C	-2.136721	-1.363251	-0.827675
C	-1.701448	-2.454094	-1.236102
H	-3.961775	-2.317671	-0.471571
H	-1.922091	0.863266	0.993007
C	-1.489782	2.098355	-0.521616
H	-1.695944	2.167743	-1.468960
C	-4.240698	2.017623	0.658502
H	-3.733934	2.979331	0.542658
H	-5.311295	2.128251	0.461270
H	-4.123204	1.672565	1.691571
C	-3.806585	1.451807	-1.661478
H	-4.758132	1.455963	-1.845067

(5R,6S)-Tg PC:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	-0.246406	-0.806401	2.496797
C	1.147212	-0.985355	2.440875
C	1.772410	-0.705703	1.084640
O	1.326565	-1.668406	0.137796
C	1.423375	0.655220	0.483206
O	2.432235	1.576547	0.881012
C	1.378691	0.395895	-1.027883
C	1.313590	-1.132886	-1.151239

Continued (5R,6S)-Tg PC

Atoms	Coordinates (Angstroms)		
	X	Y	Z
H	1.415475	-2.005806	2.760532
H	1.582975	-0.274973	3.154255
H	2.866385	-0.760746	1.201227
H	0.444704	1.001355	0.838335
H	0.496240	0.844628	-1.484819
H	2.295277	0.778248	-1.492012
C	2.122716	2.895668	0.489001
H	2.889703	3.549148	0.914621
H	2.133113	2.998979	-0.606121
H	1.130773	3.193651	0.858314
C	-0.996560	-1.931386	2.066683
H	-0.791186	-2.792043	2.723821
H	-2.050710	-1.656389	2.158282
H	-0.777397	-2.199356	1.029912
O	2.491214	-1.653299	-1.824009
H	3.884664	-1.316508	-0.964614
H	2.635918	-1.129329	-2.628307
H	0.420159	-1.509851	-1.655703
C	4.948972	0.267896	-0.947228
O	4.601458	0.622591	-2.058111
O	4.613536	-0.901631	-0.411000
C	5.767972	1.113073	-0.008918
H	5.074161	1.533105	0.728988
H	6.502460	0.501745	0.521517
H	6.254005	1.919331	-0.559539
N	-1.598020	-0.061849	-0.680498
C	-2.163472	0.911295	0.197242
C	-3.699415	1.047330	0.132475
C	-4.367762	-0.331794	0.111308
O	-5.571236	-0.455603	0.338494
N	-3.556377	-1.348282	-0.242769
C	-2.228166	-1.196400	-0.851479
O	-1.849331	-2.209621	-1.465535
H	-3.991245	-2.247612	-0.420978
H	-1.894646	0.707309	1.249002
O	-1.587944	2.185012	-0.070854
H	-1.749781	2.330882	-1.017168
C	-4.234809	1.886731	1.281328
H	-3.755486	2.868965	1.249182
H	-5.320966	1.993069	1.198968
H	-4.014086	1.410669	2.243096

Continued (5R,6S)-Tg PC

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	-4.011311	1.661839	-1.120948
H	-4.973228	1.619000	-1.230609

Table S11. Cartesian coordinates for the optimized 5,6-diHThy structures of the monofunctional pathway (Asp-H_2O) at M06-2X/6-31+G(d)

5,6-diHThy RC:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	-0.999348	0.153847	2.425557
C	0.410631	-0.000627	2.492869
C	1.053151	-0.126746	1.124369
O	0.441288	-1.201683	0.406390
C	0.899525	1.108640	0.236418
O	1.965376	1.991388	0.493478
C	0.864698	0.470061	-1.156308
C	0.060126	-0.792688	-0.889128
H	0.660179	-0.877573	3.106709
H	0.815556	0.891316	2.986209
H	2.130032	-0.324797	1.225645
H	-0.049565	1.629639	0.468460
H	0.462052	1.095907	-1.957182
H	1.883905	0.171034	-1.426211
C	2.060190	3.032432	-0.447319
H	2.805751	3.736919	-0.068527
H	2.393242	2.652041	-1.423334
H	1.092758	3.554805	-0.559415
C	-1.703024	-1.068869	2.540320
H	-1.552126	-1.505508	3.538860
H	-2.767463	-0.840861	2.421565
H	-1.386272	-1.789865	1.779714
O	2.782046	-2.130928	-1.604811
H	2.987104	-2.059426	-0.656038
H	3.316057	-1.370539	-1.920397
H	0.293554	-1.614447	-1.566692
C	4.466279	0.281314	-0.430760
O	4.156063	0.315717	-1.655553
O	4.138830	-0.602461	0.400721
C	5.315816	1.442139	0.108171
H	6.219742	1.050955	0.575130
H	5.581503	2.143142	-0.684357
H	4.743271	1.958262	0.880344
N	-1.412748	-0.554941	-0.922114
C	-2.068606	0.730920	-1.133186
H	-2.535827	0.754664	-2.130834
C	-3.128988	0.998741	-0.068122
C	-3.867170	2.313071	-0.294372

Continued 5,6-diHThy RC

Atoms	Coordinates (Angstroms)		
	X	Y	Z
H	-4.346759	2.326797	-1.280541
H	-4.646816	2.445872	0.459118
H	-3.168296	3.154747	-0.235909
C	-4.099379	-0.165675	-0.037058
O	-5.247585	-0.093643	0.363718
N	-3.575775	-1.349365	-0.513082
C	-2.203686	-1.643827	-0.736282
O	-1.844122	-2.806199	-0.740420
H	-4.153678	-2.175958	-0.399404
H	-2.618502	1.011530	0.907274
H	-1.326339	1.524751	-1.106153

5,6-diHThy TS:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	-1.005042	0.448951	2.371381
C	0.365231	0.183401	2.522185
C	1.102570	-0.098697	1.232749
O	0.618516	-1.331574	0.624236
C	0.934861	0.927804	0.114488
O	1.872101	1.955871	0.327284
C	1.169944	0.077907	-1.145231
C	0.726662	-1.269383	-0.662911
H	0.525363	-0.649156	3.224594
H	0.825137	1.082980	2.948457
H	2.172027	-0.231884	1.441552
H	-0.093133	1.323472	0.126726
H	0.588174	0.375706	-2.017321
H	2.241348	0.065816	-1.380908
C	1.872564	2.912195	-0.706312
H	2.558946	3.707212	-0.406515
H	2.223619	2.473710	-1.649659
H	0.867765	3.336565	-0.853518
C	-1.817295	-0.715500	2.400815
H	-1.660162	-1.262393	3.342911
H	-2.852733	-0.371335	2.363732
H	-1.610469	-1.383315	1.559043
O	2.545689	-2.325869	-0.902689
H	3.086867	-1.943422	-0.140904
H	3.070492	-1.940033	-1.623156
H	0.282245	-2.079359	-1.220982

Continued 5,6-diHThy TS

Atoms	Coordinates (Angstroms)		
	X	Y	Z
C	4.580585	-0.165606	-0.223104
O	4.368486	-0.274084	-1.456230
O	4.084549	-0.900043	0.686856
C	5.461592	0.989054	0.250011
H	5.897770	0.783736	1.230458
H	6.238371	1.211025	-0.485629
H	4.812419	1.868281	0.344054
N	-1.594263	-0.522646	-1.257889
C	-2.263963	0.726992	-1.535653
H	-2.846535	0.678625	-2.475996
C	-3.207171	1.167399	-0.411844
C	-3.907215	2.491618	-0.685207
H	-4.494692	2.434502	-1.609199
H	-4.590843	2.746659	0.128362
H	-3.169495	3.294521	-0.796097
C	-4.211933	0.051268	-0.173438
O	-5.331466	0.232276	0.293230
N	-3.743513	-1.185897	-0.508404
C	-2.357744	-1.499573	-0.816297
O	-2.026244	-2.680091	-0.598996
H	-4.304641	-1.981940	-0.225472
H	-2.609107	1.238935	0.510573
H	-1.499148	1.504126	-1.693131

5,6-diHThy PC:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	-0.908286	0.138773	2.399982
C	0.482931	0.030952	2.562651
C	1.276044	-0.127241	1.275990
O	1.003654	-1.392397	0.688670
C	0.953581	0.896364	0.189826
O	1.797439	2.022634	0.387860
C	1.215299	0.134667	-1.114712
C	1.156344	-1.342737	-0.699356
H	0.725498	-0.806396	3.237702
H	0.811901	0.964036	3.036583
H	2.345610	-0.041387	1.525052
H	-0.102537	1.195913	0.258073
H	0.454399	0.331151	-1.870173
H	2.214330	0.387179	-1.488262

Continued 5,6-diHThy PC

Atoms	Coordinates (Angstroms)		
	X	Y	Z
C	1.488506	3.080338	-0.484516
H	2.158387	3.909379	-0.243401
H	1.637706	2.790695	-1.532720
H	0.447719	3.407707	-0.355576
C	-1.579670	-1.100928	2.209649
H	-1.320047	-1.798055	3.024713
H	-2.650927	-0.881725	2.255006
H	-1.331709	-1.562325	1.248283
O	2.409268	-2.016409	-0.993365
H	3.674510	-1.291526	-0.188768
H	2.605677	-1.883589	-1.934394
H	0.332124	-1.902860	-1.149489
C	4.733647	0.261434	-0.550470
O	4.594942	0.196019	-1.756586
O	4.298665	-0.669332	0.293198
C	5.371610	1.422963	0.166799
H	6.026858	1.071116	0.967524
H	5.920674	2.044596	-0.540705
H	4.558312	2.003580	0.620949
N	-1.741923	-0.304690	-1.351160
C	-2.501337	0.922918	-1.330507
H	-3.153094	1.015440	-2.223690
C	-3.381397	1.096347	-0.087885
C	-4.186751	2.389251	-0.087387
H	-4.836777	2.437782	-0.969513
H	-4.823819	2.452977	0.798669
H	-3.515012	3.255314	-0.107726
C	-4.287343	-0.117539	0.036012
O	-5.382643	-0.094361	0.593677
N	-3.757839	-1.243818	-0.509700
C	-2.387837	-1.391331	-1.003138
O	-1.978635	-2.570310	-1.014174
H	-4.239069	-2.117421	-0.327377
H	-2.717910	1.069097	0.792488
H	-1.800347	1.772065	-1.383118

Table S12. Cartesian coordinates for the optimized 5-OH-6HThy structures of the monofunctional pathway (Asp-H_2O) at M06-2X/6-31+G(d)

5-OH-6HThy RC:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	-0.278786	0.507653	2.647717
C	1.114780	0.594030	2.375410
C	1.403156	0.601399	0.884944
O	0.802821	-0.562306	0.312464
C	0.775680	1.784251	0.146012
O	1.664316	2.876656	0.160667
C	0.494381	1.172098	-1.231785
C	0.112920	-0.262188	-0.876606
H	1.643895	-0.240918	2.854919
H	1.477404	1.531908	2.812365
H	2.489068	0.591909	0.697576
H	-0.156208	2.087684	0.655655
H	-0.259397	1.680599	-1.839509
H	1.432590	1.114879	-1.792604
C	1.119398	4.027461	-0.426819
H	1.854272	4.825764	-0.310328
H	0.919357	3.881403	-1.498205
H	0.181911	4.324696	0.070264
C	-0.736173	-0.813926	2.857071
H	-0.301467	-1.231422	3.777317
H	-1.823395	-0.758259	2.980216
H	-0.488323	-1.466111	2.013484
O	2.866069	-0.618447	-2.121251
H	3.191586	-1.496969	-1.852552
H	3.427504	-0.088167	-1.502940
H	0.418140	-0.978747	-1.636647
C	5.005179	-0.926235	0.137197
O	4.499817	0.214380	-0.090559
O	4.739149	-1.999262	-0.446933
C	6.046146	-0.965018	1.271140
H	6.812167	-0.202357	1.095485
H	5.552868	-0.716685	2.218566
H	6.508159	-1.952447	1.350498
N	-1.343021	-0.437433	-0.667467
C	-2.193618	0.637441	-0.175897
H	-1.842258	1.582434	-0.589966
C	-3.640341	0.480542	-0.617102
C	-4.534127	1.499337	0.075436

Continued 5-OH-6HThy RC

Atoms	Coordinates (Angstroms)		
	X	Y	Z
H	-5.570413	1.366672	-0.247727
H	-4.501532	1.379062	1.162709
H	-4.197670	2.507478	-0.184727
C	-4.134005	-0.939663	-0.333682
O	-5.320378	-1.222854	-0.300016
N	-3.144495	-1.867255	-0.179203
C	-1.764166	-1.719640	-0.506586
O	-1.093253	-2.724624	-0.625137
H	-3.433663	-2.837655	-0.102653
H	-2.140365	0.707303	0.920265
O	-3.670046	0.654097	-2.029898
H	-4.571486	0.476801	-2.333986

5-OH-6HThy TS:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	-0.128395	0.212703	2.405313
C	1.256499	0.357741	2.196523
C	1.636056	0.551434	0.743979
O	1.308186	-0.659886	0.001008
C	0.871446	1.643765	-0.001157
O	1.553971	2.862141	0.171333
C	0.846043	1.104546	-1.442834
C	0.892994	-0.370890	-1.185511
H	1.807720	-0.500463	2.609432
H	1.574050	1.260007	2.732554
H	2.716935	0.713153	0.630675
H	-0.151134	1.727797	0.391924
H	-0.041825	1.364345	-2.018944
H	1.757718	1.407136	-1.969808
C	0.855516	3.948312	-0.385474
H	1.414493	4.852757	-0.136628
H	0.783617	3.861169	-1.479152
H	-0.160564	4.020743	0.030861
C	-0.586043	-1.130269	2.346183
H	-0.206847	-1.695135	3.211096
H	-1.677719	-1.093497	2.391359
H	-0.284528	-1.624954	1.418458
O	2.908630	-0.636670	-2.267342
H	3.228066	-1.550964	-2.159776
H	3.560988	-0.179316	-1.638874

Continued 5-OH-6HThy TS

Atoms	Coordinates (Angstroms)		
	X	Y	Z
H	0.483689	-1.180932	-1.772641
C	5.016053	-0.846831	-0.082909
O	4.495426	0.271787	-0.412167
O	4.943734	-1.903996	-0.737620
C	5.715828	-0.879261	1.278491
H	6.052287	0.118922	1.569352
H	4.986859	-1.218546	2.025794
H	6.546509	-1.588348	1.272588
N	-1.561790	-0.285647	-0.695811
C	-2.425997	0.710690	-0.114140
H	-2.239770	1.680784	-0.601255
C	-3.927456	0.453413	-0.234256
C	-4.741309	1.413871	0.621519
H	-5.808797	1.194405	0.525708
H	-4.472084	1.322686	1.678699
H	-4.549983	2.439853	0.289945
C	-4.247567	-0.998716	0.139011
O	-5.379778	-1.345928	0.466031
N	-3.209297	-1.853441	-0.006018
C	-1.910352	-1.543416	-0.587379
O	-1.245942	-2.545691	-0.912014
H	-3.403955	-2.845927	0.075180
H	-2.193828	0.854378	0.957716
O	-4.284876	0.601313	-1.610353
H	-5.202215	0.301042	-1.707239

5-OH-6HThy PC:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	-0.180474	0.439344	2.563257
C	1.198399	0.692947	2.462517
C	1.725511	0.780004	1.037314
O	1.711917	-0.503379	0.432965
C	0.893176	1.667747	0.114949
O	1.351119	3.003436	0.246154
C	1.123974	1.044569	-1.264679
C	1.452755	-0.413480	-0.957901
H	1.772904	-0.070995	3.013493
H	1.368838	1.666490	2.938554
H	2.755833	1.175497	1.071112
H	-0.165464	1.596536	0.394351

Continued 5-OH-6HThy PC

Atoms	Coordinates (Angstroms)		
	X	Y	Z
H	0.251507	1.106800	-1.917766
H	1.994505	1.522608	-1.733306
C	0.519270	3.918411	-0.420056
H	0.928091	4.916028	-0.244570
H	0.493495	3.726196	-1.502731
H	-0.509046	3.872112	-0.033237
C	-0.541588	-0.927249	2.412745
H	-0.102120	-1.517528	3.231577
H	-1.631352	-0.968216	2.485237
H	-0.230346	-1.337734	1.450982
O	2.636713	-0.765188	-1.679866
H	2.851960	-1.693243	-1.477531
H	3.957011	-0.110948	-0.912863
H	0.649006	-1.116097	-1.186333
C	5.181675	-1.122805	0.109048
O	4.734597	0.059673	-0.300678
O	4.799500	-2.184562	-0.342151
C	6.206907	-0.995843	1.207556
H	6.951065	-0.239430	0.946324
H	5.701236	-0.664445	2.119927
H	6.681721	-1.960837	1.382471
N	-1.595616	-0.174560	-0.618870
C	-2.584382	0.805599	-0.250402
H	-2.325634	1.771193	-0.712943
C	-4.031607	0.513350	-0.647032
C	-5.005553	1.440496	0.069831
H	-6.030910	1.234871	-0.252588
H	-4.956774	1.300115	1.154829
H	-4.750555	2.479030	-0.168106
C	-4.383425	-0.949351	-0.356168
O	-5.554182	-1.332960	-0.368359
N	-3.321975	-1.755157	-0.155422
C	-1.924664	-1.430762	-0.493302
O	-1.203676	-2.442398	-0.615167
H	-3.506324	-2.751391	-0.097465
H	-2.576165	0.973696	0.844955
O	-4.150612	0.687099	-2.061371
H	-5.009536	0.316397	-2.318623

Table S13. Cartesian coordinates for the optimized T structures of the bifunctional pathway (Asp-Lys) at M06-2X/6-31+G(d)

T RC:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	-1.671817	1.298459	-2.206296
C	-1.218312	2.557387	-1.751723
C	0.060462	2.369803	-0.951942
O	-0.199273	1.806502	0.328414
C	1.061450	1.432161	-1.633053
O	2.358218	1.963860	-1.432017
C	0.787785	0.083039	-0.954669
C	-0.019837	0.429593	0.312190
H	-1.979531	3.018995	-1.108993
H	-1.018141	3.213070	-2.617894
H	0.518623	3.350293	-0.780518
H	0.875219	1.369636	-2.717426
H	0.195430	-0.546987	-1.624133
H	1.699247	-0.450198	-0.675791
C	3.387524	1.145678	-1.952416
H	4.310086	1.729572	-1.889790
H	3.508802	0.214915	-1.383499
H	3.190845	0.904932	-3.010252
C	-2.965515	1.357256	-2.750406
H	-2.992352	2.011005	-3.636938
H	-3.242141	0.341726	-3.043311
H	-3.681256	1.731628	-2.004515
H	0.514129	0.126075	1.212959
C	1.785996	2.059313	3.336823
H	1.842443	2.084011	4.434546
H	0.777308	1.727534	3.061790
C	2.799517	1.045490	2.801333
H	2.554344	0.047772	3.184764
H	3.802623	1.303918	3.195955
N	2.737360	0.974850	1.352293
H	3.169528	0.121030	0.986019
C	2.013898	3.458858	2.769060
H	1.860169	3.451547	1.684643
H	1.316144	4.186197	3.198317
H	3.035932	3.806623	2.973855
H	3.163358	1.777690	0.898168
C	2.877467	-2.421621	0.628648
C	3.391852	-3.869142	0.702745

Continued T RC

Atoms	Coordinates (Angstroms)		
	X	Y	Z
H	3.204999	-4.356170	-0.262274
H	4.471641	-3.883362	0.876808
H	2.869194	-4.429783	1.481951
O	1.737187	-2.195235	1.108993
O	3.634248	-1.585386	0.066728
C	-3.502083	-2.063115	-0.202611
C	-1.168027	-1.698434	0.246547
O	-4.502063	-2.720342	-0.475534
N	-3.591355	-0.683192	-0.043306
N	-1.331427	-0.330473	0.314826
C	-1.944491	-4.065924	-0.069333
H	-0.892788	-4.302101	0.115348
H	-2.231392	-4.455012	-1.052710
H	-2.559246	-4.589944	0.671063
C	-2.162733	-2.584245	0.002343
H	-4.521491	-0.282877	-0.093369
C	-2.585807	0.237704	0.253881
O	-2.881741	1.407363	0.440206
H	-0.137646	-2.023779	0.419385

T TS:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	1.385063	-2.153474	-1.496213
C	0.514758	-3.050394	-0.849085
C	-0.808439	-2.359114	-0.577848
O	-0.729648	-1.580502	0.646778
C	-1.232622	-1.355432	-1.653748
O	-2.641146	-1.436612	-1.774583
C	-0.710735	-0.026828	-1.085078
C	-0.689736	-0.306643	0.384892
H	0.951007	-3.380509	0.102781
H	0.324814	-3.922635	-1.500722
H	-1.592138	-3.102272	-0.406540
H	-0.767530	-1.585709	-2.621749
H	0.317129	0.128251	-1.421605
H	-1.316285	0.850205	-1.317227
C	-3.182273	-0.499842	-2.691097
H	-4.233776	-0.767408	-2.820737
H	-3.111396	0.531019	-2.319370
H	-2.672220	-0.576241	-3.663876

Continued T TS

Atoms	Coordinates (Angstroms)		
	X	Y	Z
C	2.684125	-2.679044	-1.645072
H	2.674373	-3.555460	-2.313896
H	3.298953	-1.892851	-2.088202
H	3.096792	-2.962065	-0.668596
H	-0.685924	0.411070	1.185428
C	-2.863246	-0.700421	2.933882
H	-3.130052	-0.434743	3.965299
H	-1.777265	-0.846719	2.912162
C	-3.248271	0.461997	2.017735
H	-2.678213	1.360541	2.279616
H	-4.316461	0.700020	2.166897
N	-2.941868	0.165595	0.623391
H	-3.010843	1.009236	0.040969
C	-3.551362	-2.007554	2.542944
H	-3.237476	-2.329078	1.542529
H	-3.301139	-2.813989	3.240240
H	-4.643433	-1.892645	2.535393
H	-3.545003	-0.553335	0.231178
C	-1.951619	3.134532	-0.456267
C	-1.781603	4.623840	-0.780715
H	-1.063773	5.095290	-0.106092
H	-1.437220	4.729002	-1.815458
H	-2.751303	5.127515	-0.711807
O	-1.245623	2.642269	0.456626
O	-2.797417	2.503620	-1.160082
C	4.262203	0.816306	0.452578
C	1.912040	1.320107	0.398846
O	5.473982	1.032141	0.338918
N	3.810190	-0.441861	0.841061
N	1.529942	0.076560	0.770080
C	3.554693	3.163193	-0.181706
H	2.647915	3.758037	-0.333967
H	4.141524	3.175478	-1.108059
H	4.168356	3.654513	0.583361
C	3.198394	1.762911	0.220204
H	4.521732	-1.132795	1.051191
C	2.482328	-0.850405	1.021268
O	2.271123	-2.017467	1.387053
H	1.078522	2.013140	0.240749

T PC:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	-1.476448	1.243683	-2.051741
C	-1.108926	2.471325	-1.464829
C	0.332991	2.416659	-0.969428
O	0.402180	1.967753	0.389603
C	1.232723	1.453812	-1.743522
O	2.563107	1.967096	-1.627117
C	1.040764	0.160512	-0.952215
C	0.977058	0.686329	0.472977
H	-1.769584	2.691440	-0.614529
H	-1.192776	3.272309	-2.221885
H	0.756203	3.428065	-0.996297
H	0.956956	1.366052	-2.801955
H	0.061541	-0.267244	-1.190384
H	1.821530	-0.585634	-1.095419
C	3.545589	1.156737	-2.243453
H	4.463616	1.748532	-2.278411
H	3.734367	0.234311	-1.679015
H	3.246946	0.900379	-3.270461
C	-2.799198	1.262891	-2.538432
H	-2.885737	1.958433	-3.390582
H	-3.034338	0.248874	-2.869472
H	-3.496291	1.558494	-1.744820
H	0.389884	0.067141	1.147671
C	1.625875	2.083949	3.104191
H	1.692438	2.000573	4.196354
H	0.566615	1.997910	2.838683
C	2.401252	0.907762	2.522626
H	2.007992	-0.052421	2.866713
H	3.459030	0.962488	2.805967
N	2.361390	0.834954	1.041371
H	2.984563	-0.048813	0.728478
C	2.165179	3.441044	2.654448
H	2.006058	3.588062	1.580899
H	1.651837	4.258110	3.171503
H	3.239444	3.530937	2.865218
H	2.778963	1.662139	0.603783
C	3.032024	-2.204534	0.799370
C	3.533273	-3.601245	0.454735
H	3.428087	-3.760795	-0.627910
H	4.599232	-3.680201	0.692643
H	2.960269	-4.363559	0.991376

Continued T PC

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	1.993336	-2.060530	1.459570
O	3.741717	-1.234109	0.339465
C	-3.789840	-2.152370	-0.365165
C	-1.584294	-1.814388	0.524230
O	-4.746054	-2.778316	-0.846946
N	-3.908305	-0.792796	-0.098138
N	-1.744885	-0.500410	0.775226
C	-2.229877	-4.141499	-0.272042
H	-1.206377	-4.395441	0.027619
H	-2.358183	-4.404369	-1.330346
H	-2.924383	-4.777715	0.292527
C	-2.497640	-2.685603	-0.029682
H	-4.805663	-0.369584	-0.306624
C	-2.931867	0.057207	0.447580
O	-3.225279	1.258264	0.582410
H	-0.599034	-2.205554	0.801796

Table S14. Cartesian coordinates for the optimized (5R,6S)-Tg structures of the bifunctional pathway (Asp-Lys) at M06-2X/6-31+G(d)

(5R,6S)-Tg RC:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	-0.845724	-2.278434	2.166468
C	0.166476	-3.125828	1.661573
C	1.290509	-2.276754	1.092913
O	0.945815	-1.729751	-0.169494
C	1.650709	-1.080255	1.977407
O	3.054611	-0.914038	1.912246
C	0.811646	0.056491	1.368509
C	0.421536	-0.445301	-0.033388
H	-0.236677	-3.757622	0.858726
H	0.552989	-3.763207	2.477367
H	2.171695	-2.908705	0.934841
H	1.367779	-1.253342	3.028250
H	-0.080652	0.210362	1.982259
H	1.374673	0.988691	1.289670
C	3.524877	0.236981	2.579982
H	4.614199	0.150362	2.620028
H	3.255704	1.163499	2.056711
H	3.134182	0.277534	3.610260
C	-2.050404	-2.958975	2.393887
H	-1.911964	-3.782254	3.111925
H	-2.759969	-2.240375	2.814625
H	-2.449499	-3.365891	1.452995
H	0.873215	0.180183	-0.806104
C	2.996441	-0.871531	-2.738170
H	3.102358	-0.840469	-3.832098
H	1.950194	-1.107634	-2.511827
C	3.330287	0.507446	-2.165066
H	2.609536	1.245349	-2.535267
H	4.328743	0.814435	-2.535976
N	3.222843	0.508522	-0.714548
H	3.125997	1.455649	-0.343668
C	3.881925	-1.971346	-2.156662
H	3.701498	-2.065075	-1.081178
H	3.671846	-2.942380	-2.615997
H	4.945672	-1.747119	-2.311551
H	4.010832	0.051853	-0.263568
C	1.456793	3.307704	0.168777
C	0.549505	4.478817	0.561714

Continued (5R,6S)-Tg RC

Atoms	Coordinates (Angstroms)		
	X	Y	Z
H	-0.496916	4.154575	0.597857
H	0.846186	4.898334	1.525306
H	0.619575	5.254926	-0.208519
O	1.102173	2.636784	-0.851276
O	2.477643	3.089550	0.853171
N	-1.063927	-0.377950	-0.256578
C	-1.516016	1.011103	-0.380524
C	-3.044133	1.137293	-0.257072
C	-3.687193	0.195619	-1.278801
O	-4.706772	0.429555	-1.895604
N	-3.037179	-1.010278	-1.361491
C	-1.790693	-1.390536	-0.800922
O	-1.508764	-2.578385	-0.841570
H	-3.486517	-1.750738	-1.888952
H	-1.063783	1.561488	0.456076
O	-1.154143	1.610636	-1.587874
H	-0.292931	2.106780	-1.424943
C	-3.553170	0.758370	1.130026
H	-3.117065	1.443541	1.863742
H	-4.641941	0.860572	1.154780
H	-3.273012	-0.265881	1.389575
O	-3.410555	2.467867	-0.492567
H	-2.890122	2.750368	-1.267433

(5R,6S)-Tg TS:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	-0.149411	-2.796189	1.733620
C	0.668472	-3.289762	0.695257
C	1.741375	-2.263485	0.358684
O	1.275219	-1.423550	-0.730627
C	2.078442	-1.283404	1.486019
O	3.460348	-0.977947	1.380554
C	1.139735	-0.106032	1.183826
C	0.944451	-0.239522	-0.297982
H	0.073801	-3.460644	-0.212212
H	1.147226	-4.230422	1.016915
H	2.645005	-2.753872	-0.013727
H	1.874295	-1.717347	2.472798
H	0.172204	-0.297464	1.652374
H	1.528220	0.871456	1.473176

Continued (5R,6S)-Tg TS

Atoms	Coordinates (Angstroms)		
	X	Y	Z
C	3.893343	0.002707	2.305234
H	4.985317	0.006585	2.265113
H	3.517557	1.003537	2.055342
H	3.573969	-0.259193	3.325332
C	-1.429465	-3.386201	1.748617
H	-1.361181	-4.462281	1.978436
H	-1.997799	-2.890154	2.538831
H	-1.928378	-3.249444	0.781988
H	0.566255	0.485595	-0.996744
C	2.709793	0.152988	-3.154786
H	2.753052	0.540487	-4.181058
H	1.717224	-0.291466	-3.023398
C	2.883658	1.326328	-2.190403
H	2.065102	2.044913	-2.307710
H	3.820381	1.857843	-2.433554
N	2.858940	0.893799	-0.795419
H	2.778110	1.705621	-0.168445
C	3.771338	-0.928824	-2.961833
H	3.677794	-1.392172	-1.972810
H	3.669721	-1.724244	-3.707606
H	4.783125	-0.510735	-3.047840
H	3.675726	0.344300	-0.536469
C	1.133469	3.234905	0.804479
C	0.185127	4.083908	1.653564
H	-0.257421	3.427637	2.410685
H	0.739833	4.866697	2.178577
H	-0.622067	4.516652	1.056993
O	0.691085	2.791886	-0.294314
O	2.271780	2.979940	1.272156
N	-1.311726	-0.469209	-0.156272
C	-1.897289	0.820398	0.084061
C	-3.421544	0.784070	0.293716
C	-4.051352	0.066131	-0.911897
O	-5.166426	0.311383	-1.341563
N	-3.269617	-0.935897	-1.410437
C	-1.943650	-1.290372	-0.981645
O	-1.524963	-2.381140	-1.409328
H	-3.667781	-1.530086	-2.128608
H	-1.451774	1.235359	1.004837
O	-1.687337	1.753086	-0.971795
H	-0.853260	2.247984	-0.778046

Continued (5R,6S)-Tg TS

Atoms	Coordinates (Angstroms)		
	X	Y	Z
C	-3.810286	0.023600	1.556903
H	-3.357208	0.513521	2.426514
H	-4.898802	0.039078	1.667699
H	-3.460934	-1.011590	1.510580
O	-3.916462	2.093191	0.419547
H	-3.454853	2.603110	-0.269954

(5R,6S)-Tg PC:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	-0.430001	-2.324409	2.463316
C	0.278278	-2.969288	1.419875
C	1.628585	-2.276396	1.176696
O	1.661162	-1.690576	-0.137598
C	1.912386	-1.101053	2.105862
O	3.330267	-0.899018	2.079670
C	1.159523	0.016261	1.388445
C	1.477005	-0.300949	-0.066108
H	-0.301447	-2.926039	0.485870
H	0.441286	-4.024113	1.699586
H	2.452558	-2.995477	1.208109
H	1.575069	-1.270499	3.133449
H	0.083408	-0.137171	1.516844
H	1.446458	1.026732	1.684833
C	3.759422	0.195325	2.866650
H	4.847048	0.121476	2.944143
H	3.493993	1.159734	2.413128
H	3.325388	0.140302	3.875394
C	-1.804147	-2.645691	2.435915
H	-1.957400	-3.713619	2.664159
H	-2.288207	-2.041691	3.208880
H	-2.232060	-2.418448	1.453207
H	0.706484	0.018224	-0.766902
C	2.983091	-0.914279	-2.652973
H	3.102034	-0.708243	-3.724275
H	2.009984	-1.398685	-2.526189
C	2.984158	0.437168	-1.949884
H	2.183767	1.089300	-2.306157
H	3.938977	0.953613	-2.100430
N	2.784608	0.349341	-0.479027
H	2.809740	1.345673	-0.069920

Continued (5R,6S)-Tg PC

Atoms	Coordinates (Angstroms)		
	X	Y	Z
C	4.096784	-1.847033	-2.178272
H	3.937188	-2.151223	-1.138154
H	4.127012	-2.761575	-2.782778
H	5.080235	-1.360438	-2.258221
H	3.524573	-0.190329	-0.016387
C	1.606965	3.187191	0.097389
C	0.913356	4.401283	0.699179
H	-0.067840	4.095850	1.082079
H	1.507009	4.836383	1.506497
H	0.737054	5.146550	-0.083281
O	1.054703	2.611869	-0.871240
O	2.698846	2.798590	0.617944
N	-1.510760	-0.467289	-0.186536
C	-1.889441	0.904738	-0.327705
C	-3.407956	1.152913	-0.364559
C	-4.005637	0.272117	-1.474712
O	-4.998742	0.576493	-2.119143
N	-3.358795	-0.915877	-1.619283
C	-2.185094	-1.351695	-0.894871
O	-1.944569	-2.572142	-0.998346
H	-3.765043	-1.601748	-2.244820
H	-1.488651	1.469294	0.532450
O	-1.396055	1.523166	-1.526598
H	-0.546873	1.967110	-1.327752
C	-4.077090	0.782427	0.953320
H	-3.649846	1.394761	1.755066
H	-5.150175	0.986599	0.883975
H	-3.916335	-0.273252	1.188358
O	-3.668226	2.516110	-0.600876
H	-3.048232	2.764213	-1.309264

Table S15. Cartesian coordinates for the optimized 5,6-diHThy structures of the bifunctional pathway (Asp-Lys) at M06-2X/6-31+G(d)

5,6-diHThy RC:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	0.124514	-3.097354	1.605607
C	0.867372	-3.518828	0.480814
C	1.573454	-2.319051	-0.128200
O	0.664178	-1.502537	-0.850716
C	2.221995	-1.395307	0.907927
O	3.418079	-0.902184	0.334502
C	1.128018	-0.345454	1.162087
C	0.198221	-0.454734	-0.055293
H	0.195839	-3.944394	-0.276345
H	1.608159	-4.279685	0.786293
H	2.325742	-2.670432	-0.843249
H	2.472338	-1.936322	1.835192
H	0.584820	-0.603270	2.075176
H	1.524206	0.671239	1.239379
C	4.060013	0.085909	1.112144
H	5.039705	0.251405	0.654896
H	3.504411	1.032070	1.130901
H	4.207456	-0.267369	2.146482
C	-0.890671	-4.002852	1.957773
H	-0.464140	-4.977404	2.265233
H	-1.427595	-3.569741	2.804642
H	-1.583659	-4.147134	1.120470
H	0.240979	0.464876	-0.643909
C	1.101355	0.703983	-3.429792
H	0.627943	1.105814	-4.337259
H	0.341490	0.130543	-2.885027
C	1.575025	1.867388	-2.552706
H	0.710066	2.446836	-2.207574
H	2.195041	2.547698	-3.169714
N	2.252802	1.378450	-1.362970
H	2.254581	2.065939	-0.605072
C	2.240853	-0.241426	-3.801704
H	2.646965	-0.701987	-2.894513
H	1.899079	-1.045276	-4.463333
H	3.051252	0.297839	-4.312822
H	3.205471	1.082831	-1.549218
C	0.940153	3.304811	1.149195
C	0.444409	4.361944	2.152390

Continued 5,6-diHThy RC

Atoms	Coordinates (Angstroms)		
	X	Y	Z
H	-0.120960	5.138631	1.623880
H	-0.243949	3.884738	2.863308
H	1.276012	4.810433	2.703390
O	0.070733	2.835342	0.367308
O	2.153362	2.978928	1.204440
C	-3.772620	0.421540	-0.400442
C	-1.778948	0.541803	1.026885
O	-4.877278	0.775397	-0.772919
N	-3.419923	-0.919538	-0.394425
N	-1.230246	-0.632546	0.349055
C	-3.256083	2.582610	0.793002
H	-2.423029	3.246458	1.050512
H	-3.803721	2.304912	1.704387
H	-3.951273	3.106337	0.128290
C	-2.687018	1.347282	0.108724
H	-4.076379	-1.552711	-0.829237
C	-2.099625	-1.445764	-0.302393
O	-1.891014	-2.557586	-0.766202
H	-0.950299	1.180899	1.334930
H	-2.337471	0.215812	1.915921
H	-2.081013	1.665732	-0.753469

5,6-diHThy TS:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	-0.573496	-3.074026	-1.752157
C	-1.033104	-3.325665	-0.440937
C	-1.797065	-2.114800	0.086042
O	-0.905540	-1.281424	0.877646
C	-2.339926	-1.174551	-0.994787
O	-3.546905	-0.616335	-0.498959
C	-1.189007	-0.168904	-1.154260
C	-0.554920	-0.219100	0.202324
H	-0.186047	-3.503450	0.235425
H	-1.702055	-4.202581	-0.449244
H	-2.591397	-2.424043	0.771206
H	-2.540924	-1.709202	-1.931603
H	-0.469502	-0.566156	-1.873226
H	-1.486525	0.845189	-1.427127
C	-4.111839	0.356990	-1.357962
H	-5.10992	0.572376	-0.968299

Continued 5,6-diHThy TS

Atoms	Coordinates (Angstroms)		
	X	Y	Z
H	-3.522277	1.282786	-1.381109
H	-4.205446	-0.038963	-2.380817
C	0.628942	-3.749380	-2.054146
H	0.460084	-4.837578	-2.109457
H	0.955807	-3.389260	-3.032440
H	1.391897	-3.527979	-1.300532
H	0.114226	0.503105	0.635542
C	-1.165753	0.710541	3.371325
H	-0.792757	1.192722	4.284451
H	-0.359055	0.068421	2.998054
C	-1.480605	1.801318	2.346740
H	-0.571010	2.350658	2.078540
H	-2.179107	2.527546	2.798299
N	-2.007489	1.247232	1.103803
H	-2.049413	1.968227	0.368337
C	-2.379795	-0.155531	3.703186
H	-2.701135	-0.725425	2.824419
H	-2.150818	-0.876440	4.495013
H	-3.224749	0.460397	4.039070
H	-2.926100	0.822200	1.211736
C	-0.610405	3.257401	-1.109465
C	-0.004509	4.275905	-2.084701
H	0.648013	4.967109	-1.542162
H	0.620018	3.740376	-2.809725
H	-0.781992	4.827295	-2.618421
O	0.185853	2.687344	-0.322993
O	-1.855600	3.047819	-1.189277
C	3.893181	0.149444	0.671547
C	2.144564	0.215862	-1.080280
O	4.956990	0.520216	1.153706
N	3.464274	-1.146459	0.770590
N	1.483027	-0.948773	-0.519456
C	3.605916	2.258436	-0.687176
H	2.840651	2.928643	-1.091170
H	4.278285	1.945434	-1.495871
H	4.202217	2.796549	0.054357
C	2.920123	1.053459	-0.060974
H	3.998147	-1.765227	1.370273
C	2.174471	-1.651007	0.361702
O	1.842728	-2.735843	0.880523
H	1.387735	0.866588	-1.537437

Continued 5,6-diHThy TS

Atoms	Coordinates (Angstroms)		
	X	Y	Z
H	2.841975	-0.087323	-1.884329
H	2.198659	1.419489	0.686710

5,6-diHThy PC:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	0.574405	-3.170073	1.684735
C	0.736380	-3.237700	0.278720
C	1.759466	-2.196489	-0.201689
O	1.125601	-1.213537	-1.040972
C	2.394736	-1.374660	0.915738
O	3.626183	-0.859869	0.394106
C	1.343583	-0.282739	1.098253
C	0.951033	-0.004422	-0.344976
H	-0.220606	-3.039098	-0.223392
H	1.081142	-4.250914	0.012436
H	2.536511	-2.665353	-0.814992
H	2.586366	-1.956932	1.823039
H	0.465392	-0.718097	1.586673
H	1.684818	0.607793	1.631109
C	4.318667	-0.026293	1.301567
H	5.318304	0.129621	0.887872
H	3.826166	0.947345	1.428182
H	4.410715	-0.513368	2.283568
C	-0.642886	-3.764345	2.088630
H	-0.644163	-4.839989	1.849127
H	-0.711453	-3.641851	3.173435
H	-1.487374	-3.273071	1.593957
H	-0.071277	0.356281	-0.453919
C	1.098439	0.624102	-3.342083
H	0.693133	1.195678	-4.186700
H	0.328054	-0.092197	-3.038926
C	1.349582	1.623560	-2.217551
H	0.438341	2.151963	-1.924487
H	2.089580	2.373395	-2.524059
N	1.866834	1.016291	-0.965279
H	2.035432	1.837639	-0.228374
C	2.356293	-0.124080	-3.779928
H	2.716190	-0.783555	-2.983625
H	2.152969	-0.750396	-4.654500
H	3.160312	0.575971	-4.046447

Continued 5,6-diHThy PC

Atoms	Coordinates (Angstroms)		
	X	Y	Z
H	2.766335	0.545665	-1.109100
C	0.970541	3.266200	0.987667
C	0.730673	4.199705	2.167575
H	-0.143045	4.837948	1.979808
H	0.509101	3.583358	3.046513
H	1.611391	4.798586	2.389530
O	-0.000816	2.887672	0.311847
O	2.182842	2.889276	0.796546
C	-3.942201	0.498985	-0.547350
C	-2.189959	0.313432	1.201859
O	-4.939916	1.032415	-1.027218
N	-3.704821	-0.836761	-0.647441
N	-1.724239	-0.948749	0.665067
C	-3.347889	2.545157	0.804326
H	-2.498065	3.100852	1.212949
H	-4.063245	2.331761	1.608462
H	-3.857102	3.163455	0.060121
C	-2.843219	1.251686	0.181076
H	-4.326315	-1.379122	-1.236261
C	-2.506287	-1.539273	-0.205830
O	-2.364325	-2.672151	-0.719826
H	-1.337411	0.849394	1.646194
H	-2.916621	0.151984	2.023921
H	-2.083025	1.501583	-0.577048

Table S16. Cartesian coordinates for the optimized 5-OH-6HThy structures of the bifunctional pathway (Asp-Lys) at M06-2X/6-31+G(d)

5-OH-6HThy RC:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	-1.912756	1.411037	-1.577764
C	-1.333845	2.623479	-1.140481
C	0.034697	2.336218	-0.543564
O	-0.083157	1.735256	0.736875
C	0.876013	1.382161	-1.399211
O	2.192964	1.898656	-1.467914
C	0.741716	0.032118	-0.680942
C	0.060893	0.352205	0.661735
H	-1.969113	3.083920	-0.371497
H	-1.231396	3.315031	-1.995325
H	0.567608	3.284718	-0.404295
H	0.478247	1.319960	-2.424648
H	0.128052	-0.645317	-1.278783
H	1.713055	-0.431554	-0.496837
C	3.072882	1.077687	-2.210285
H	4.017262	1.624524	-2.284540
H	3.251884	0.110751	-1.722511
H	2.678024	0.910820	-3.226225
C	-3.266047	1.549060	-1.918511
H	-3.396453	2.248050	-2.760963
H	-3.631839	0.561149	-2.213726
H	-3.847942	1.912792	-1.058004
H	0.666787	0.019641	1.505693
C	2.785237	3.038343	2.446203
H	3.015179	3.597921	3.365027
H	1.694714	2.984706	2.343424
C	3.314211	1.608808	2.580663
H	2.855345	1.141865	3.461068
H	4.404805	1.647196	2.776435
N	2.950387	0.815375	1.420598
H	2.994568	-0.194205	1.573210
C	3.374721	3.759647	1.234844
H	3.091435	3.246022	0.309484
H	3.016093	4.793949	1.170244
H	4.471862	3.789205	1.293429
H	3.538156	1.008550	0.613291
C	2.982217	-2.472696	0.351520
C	3.218653	-3.983565	0.163235

Continued 5-OH-6HThy RC

Atoms	Coordinates (Angstroms)		
	X	Y	Z
H	3.378012	-4.460910	1.135367
H	2.318279	-4.430533	-0.275766
H	4.068804	-4.173308	-0.496757
O	2.143379	-2.151916	1.240317
O	3.616724	-1.690822	-0.398541
N	-1.260708	-0.351026	0.764730
C	-1.192802	-1.803291	0.677035
H	-1.441673	-2.241787	1.653341
C	-2.155325	-2.375645	-0.358573
C	-2.285875	-3.886704	-0.203802
H	-2.670212	-4.152311	0.786199
H	-2.978461	-4.278471	-0.954188
H	-1.300386	-4.343152	-0.339415
C	-3.529198	-1.716344	-0.202291
O	-4.513716	-2.121768	-0.804171
N	-3.564052	-0.638082	0.634463
C	-2.456901	0.237382	0.924841
O	-2.742034	1.373507	1.265509
H	-4.454014	-0.153039	0.696283
H	-0.158699	-2.093577	0.457734
O	-1.684720	-2.044426	-1.658130
H	-2.377209	-2.289147	-2.292542

5-OH-6HThy TS:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	-1.387319	-1.986746	1.282292
C	-0.393182	-2.895707	0.879521
C	0.897746	-2.137846	0.627424
O	0.885813	-1.580110	-0.711622
C	1.125055	-0.945563	1.563969
O	2.498263	-0.927929	1.914122
C	0.657686	0.247466	0.714452
C	0.799428	-0.281883	-0.676314
H	-0.697389	-3.405453	-0.045214
H	-0.216590	-3.639863	1.677560
H	1.752455	-2.821336	0.657028
H	0.521442	-1.039368	2.476152
H	-0.402339	0.436735	0.911904
H	1.234924	1.163261	0.867456
C	2.829323	0.120949	2.810791

Continued 5-OH-6HThy TS

Atoms	Coordinates (Angstroms)		
	X	Y	Z
H	3.864859	-0.051168	3.115815
H	2.745543	1.107951	2.337959
H	2.183151	0.079395	3.701118
C	-2.653024	-2.588343	1.398214
H	-2.663032	-3.324635	2.219500
H	-3.369039	-1.791424	1.616272
H	-2.931205	-3.080462	0.456849
H	0.827630	0.266403	-1.599842
C	3.933640	-1.705682	-1.904850
H	4.489149	-2.007021	-2.803196
H	2.942654	-2.169474	-1.963340
C	3.770265	-0.185768	-1.921618
H	3.223920	0.115176	-2.824315
H	4.768108	0.284502	-1.983880
N	3.010932	0.290231	-0.774169
H	2.798212	1.296662	-0.837625
C	4.663580	-2.203379	-0.656996
H	4.091768	-1.983352	0.251695
H	4.823704	-3.286784	-0.696449
H	5.646604	-1.723311	-0.561027
H	3.489414	0.124510	0.108701
C	1.923958	3.399106	0.034592
C	1.344709	4.808227	0.224646
H	1.250247	5.321749	-0.735611
H	0.342395	4.711434	0.659749
H	1.958936	5.390399	0.916745
O	1.692130	2.832422	-1.067813
O	2.546519	2.896157	1.006701
N	-1.397900	-0.061202	-1.322773
C	-1.952237	1.252332	-1.103836
H	-2.335434	1.677230	-2.048307
C	-3.091681	1.322894	-0.087647
C	-3.789364	2.675839	-0.118730
H	-4.241965	2.860521	-1.098593
H	-4.584636	2.709805	0.632476
H	-3.055126	3.460866	0.089437
C	-4.097781	0.195553	-0.342564
O	-5.201964	0.187867	0.200124
N	-3.644701	-0.796317	-1.142546
C	-2.226660	-1.070368	-1.415276
O	-1.991883	-2.260951	-1.685202

Continued 5-OH-6HThy TS

Atoms	Coordinates (Angstroms)		
	X	Y	Z
H	-4.238399	-1.615598	-1.225697
H	-1.150845	1.926656	-0.767303
O	-2.542996	1.080501	1.209658
H	-3.284725	1.000364	1.829650

5-OH-6HThy PC:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	-1.789448	1.286989	-1.669638
C	-1.216640	2.500574	-1.239632
C	0.289331	2.348475	-1.044562
O	0.608302	2.008967	0.311219
C	0.931961	1.248436	-1.888699
O	2.281951	1.663801	-2.127764
C	0.843601	0.053018	-0.942985
C	1.129852	0.705858	0.397282
H	-1.669111	2.807265	-0.284685
H	-1.397584	3.276421	-2.007817
H	0.771779	3.311016	-1.255128
H	0.418693	1.087907	-2.844759
H	-0.182720	-0.323739	-0.926689
H	1.525282	-0.768702	-1.177607
C	3.048621	0.720232	-2.851310
H	3.970080	1.228342	-3.148530
H	3.303114	-0.158861	-2.244810
H	2.510471	0.397654	-3.755391
C	-3.175150	1.408043	-1.884111
H	-3.377077	2.073443	-2.741622
H	-3.559873	0.408434	-2.104971
H	-3.669452	1.800844	-0.986701
H	0.680941	0.188888	1.246331
C	2.445326	2.334132	2.630032
H	2.767227	2.371159	3.678606
H	1.350988	2.300169	2.629470
C	2.999183	1.040994	2.042113
H	2.644940	0.157558	2.580832
H	4.096654	1.036653	2.072622
N	2.615867	0.811165	0.627960
H	3.111325	-0.133525	0.291895
C	2.923470	3.585035	1.895766
H	2.506308	3.625237	0.884140

Continued 5-OH-6HThy PC

Atoms	Coordinates (Angstroms)		
	X	Y	Z
H	2.598844	4.490263	2.416806
H	4.017689	3.612992	1.824273
H	2.962184	1.553506	0.011099
C	3.147965	-2.269687	0.573536
C	3.433691	-3.721801	0.208657
H	2.902231	-3.962301	-0.724495
H	4.503093	-3.858394	0.022188
H	3.087634	-4.398110	0.998793
O	2.367746	-2.006719	1.497967
O	3.737089	-1.391925	-0.156521
N	-1.505323	-0.253167	1.361520
C	-1.494757	-1.691780	1.238310
H	-1.851402	-2.167017	2.171849
C	-2.323598	-2.294558	0.101202
C	-2.507594	-3.796876	0.285040
H	-3.077811	-4.013314	1.195235
H	-3.050831	-4.219867	-0.565800
H	-1.522029	-4.269057	0.362008
C	-3.685900	-1.605027	0.001276
O	-4.572875	-2.055538	-0.729266
N	-3.792892	-0.467022	0.712842
C	-2.640796	0.353378	1.170619
O	-2.938135	1.560453	1.288315
H	-4.638653	0.075403	0.568062
H	-0.457297	-2.031665	1.100976
O	-1.654892	-2.040884	-1.138343
H	-2.291643	-2.226775	-1.846737

6. Cartesian coordinates for the structures of RC, TS and PC of protonated bases in the mono- and di-functional reaction pathways.

Table S17. Cartesian coordinates for the optimized TH structures of the monofunctional pathway (Asp-H_2O) at M06-2X/6-31+G(d)

TH RC:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	-0.447874	0.602458	2.958778
C	0.953300	0.382343	2.842980
C	1.285687	0.618463	1.386286
O	0.495254	-0.305883	0.615338
C	0.914267	2.036664	0.917478
O	2.012224	2.552375	0.199736
C	-0.356019	1.830266	0.074801
C	-0.279552	0.356327	-0.330900
C	-3.911175	-1.630190	-0.941074
C	-2.307156	-0.077362	-1.605130
H	1.196170	-0.646382	3.141460
H	1.504533	1.082726	3.484349
H	2.341464	0.425484	1.180963
H	0.705099	2.692588	1.774180
H	-1.244013	2.009674	0.686914
H	-0.381932	2.487135	-0.797789
C	1.947652	3.950302	-0.029933
H	2.864551	4.225477	-0.551996
H	1.085409	4.217501	-0.654270
H	1.890106	4.491038	0.923610
C	-0.943752	0.522751	4.293237
H	-0.490856	1.308756	4.905993
H	-2.022667	0.669340	4.241647
H	-0.723471	-0.460085	4.725960
O	1.943257	1.041330	-2.159585
H	2.597736	0.362406	-2.387669
H	2.316474	1.494458	-1.383718
H	0.161878	0.233298	-1.325758
C	4.541023	-1.026013	-0.946255
O	3.951837	-0.342074	-0.152087
O	4.131604	-1.011786	-2.241374

Continued TH RC

Atoms	Coordinates (Angstroms)		
	X	Y	Z
C	5.714819	-1.916731	-0.633363
H	5.950123	-1.839895	0.427058
H	5.478813	-2.957096	-0.879229
H	6.588588	-1.615359	-1.220040
O	-4.977202	-2.352137	-1.230174
N	-3.312556	-1.817558	0.214056
N	-1.642848	-0.300349	-0.423429
C	-4.266482	-0.433245	-3.168773
H	-4.362477	-1.353918	-3.750936
H	-3.781927	0.323190	-3.786551
H	-5.276762	-0.092636	-2.926942
C	-3.483910	-0.678939	-1.914977
C	-2.224860	-1.110437	0.505052
O	-1.775896	-1.242545	1.713330
H	-1.809095	0.609404	-2.287244
H	4.685141	-1.570249	-2.809636
H	-5.170462	-2.958466	-0.489842
H	-1.123328	-0.543299	2.015635

TH TS:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	0.012013	2.495919	1.249300
C	1.277453	2.021110	1.658995
C	1.834859	1.181581	0.536739
O	0.976996	-0.011542	0.391160
C	1.812491	1.850375	-0.847522
O	3.036629	1.559667	-1.486384
C	0.614204	1.185680	-1.550059
C	0.470547	-0.069511	-0.770181
C	-4.524592	-0.978113	0.298362
C	-3.006842	-0.239058	-1.311574
H	1.192986	1.426671	2.579888
H	1.966908	2.857295	1.844365
H	2.823949	0.784763	0.774011
H	1.676366	2.934378	-0.754190
H	-0.317471	1.742231	-1.387722
H	0.755209	1.006432	-2.616980
C	3.325647	2.421526	-2.581683
H	4.293597	2.112317	-2.974900
H	2.568495	2.335301	-3.370478

Continued TH TS

Atoms	Coordinates (Angstroms)		
	X	Y	Z
H	3.383032	3.461875	-2.241940
C	-0.538184	3.465384	2.143438
H	0.107716	4.349021	2.182807
H	-1.516319	3.738102	1.747718
H	-0.653508	3.038744	3.146468
O	2.097285	-1.063229	-1.882826
H	2.469525	-1.820226	-1.393722
H	2.807174	-0.394132	-1.915988
H	-0.137950	-0.931399	-1.003054
C	3.762493	-2.566175	0.846462
O	3.581964	-1.382323	0.955799
O	3.262286	-3.184441	-0.259655
C	4.499718	-3.441124	1.821868
H	4.827625	-2.839387	2.668049
H	3.849592	-4.246996	2.177168
H	5.373171	-3.891793	1.339292
O	-5.656279	-1.600854	0.625629
N	-3.777259	-0.488977	1.272977
N	-2.209773	0.267177	-0.346812
C	-5.098351	-1.442610	-2.136245
H	-5.263947	-2.513852	-1.986168
H	-4.660746	-1.293970	-3.126869
H	-6.079441	-0.958167	-2.113799
C	-4.201014	-0.882929	-1.073162
C	-2.655586	0.122767	0.900289
O	-1.918354	0.629645	1.889383
H	-2.654257	-0.114570	-2.335872
H	3.467106	-4.133239	-0.285084
H	-5.748701	-1.580231	1.594798
H	-1.198266	1.167286	1.495430

TH PC:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	-0.470710	0.698951	2.652174
C	0.904846	0.411650	2.777182
C	1.592844	0.780573	1.483221
O	1.129207	-0.108953	0.427161
C	1.274717	2.195939	0.973429
O	2.463523	2.679129	0.331677

Continued TH PC

Atoms	Coordinates (Angstroms)		
	X	Y	Z
C	0.192745	1.946862	-0.080784
C	0.672843	0.618330	-0.617230
C	-4.156936	-1.914418	-0.979697
C	-2.957050	0.037840	-1.411412
H	1.060159	-0.655727	2.992567
H	1.347879	0.999414	3.594973
H	2.674202	0.647485	1.576867
H	0.974304	2.876674	1.775947
H	-0.783059	1.776978	0.369775
H	0.121026	2.732699	-0.839480
C	2.484703	4.092233	0.132162
H	3.427949	4.325711	-0.361116
H	1.646692	4.420604	-0.494293
H	2.442439	4.600159	1.100948
C	-1.180939	0.550146	3.880264
H	-0.804789	1.263166	4.622621
H	-2.228961	0.756288	3.665620
H	-1.081078	-0.472980	4.260932
O	1.890235	0.983642	-1.528245
H	2.454252	0.189487	-1.717392
H	2.448170	1.640428	-0.987244
H	0.029639	0.036020	-1.270848
C	4.499953	-0.968551	-0.888673
O	4.163962	-0.135176	-0.083455
O	3.790011	-1.010692	-2.058459
C	5.626075	-1.949104	-0.750794
H	6.103790	-1.816418	0.223957
H	5.253633	-2.973263	-0.842515
H	6.366151	-1.779886	-1.539626
O	-5.100673	-2.796785	-1.314766
N	-3.474417	-2.126434	0.132247
N	-2.232915	-0.143296	-0.290872
C	-4.766584	-0.620408	-3.083727
H	-4.705526	-1.500517	-3.734586
H	-4.411881	0.252335	-3.642179
H	-5.825503	-0.469043	-2.842185
C	-3.953658	-0.813336	-1.839035
C	-2.542199	-1.221584	0.425844
O	-1.860431	-1.434364	1.551780
H	-2.714714	0.925114	-1.997327
H	4.082008	-1.703092	-2.674545

Continued TH PC

Atoms	Coordinates (Angstroms)		
	X	Y	Z
H	-5.125972	-3.488007	-0.629647
H	-1.268259	-0.665509	1.696942

Table S18. Cartesian coordinates for the optimized (5R,6S)-TgH structures of the monofunctional pathway (Asp-H_2O) at M06-2X/6-31+G(d)

(5R,6S)-TgH RC:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	-1.928215	2.365807	0.329202
C	-1.013972	2.620773	1.377008
C	0.357327	2.102507	0.982296
O	0.405430	0.668816	0.907279
C	0.806428	2.544435	-0.406996
O	2.213205	2.561386	-0.417715
C	0.189152	1.452263	-1.309180
C	0.059139	0.235454	-0.365840
C	-3.754804	-1.571583	0.113450
C	-2.332574	-0.315401	-1.106016
H	-1.340626	2.119317	2.295592
H	-0.947691	3.703666	1.565063
H	1.093390	2.393967	1.735760
H	0.417044	3.537428	-0.671869
H	-0.769917	1.852175	-1.634927
H	0.840091	1.208124	-2.154033
C	2.771031	3.151897	-1.581387
H	3.850963	3.170796	-1.434634
H	2.546845	2.561179	-2.477244
H	2.398751	4.175956	-1.706697
C	-3.264466	2.650107	0.693952
H	-3.374941	3.701058	0.989426
H	-3.887643	2.458262	-0.181701
H	-3.577427	2.001800	1.521083
O	2.817156	-0.079415	-1.186364
H	3.557534	-0.691439	-1.026735
H	2.966767	0.685817	-0.601072
H	0.731374	-0.578564	-0.643579
C	6.094581	-1.511109	-0.288370
O	6.295598	-0.206899	-0.011436
O	4.993960	-1.875455	-0.622845
C	7.288705	-2.420302	-0.151451
H	8.098857	-2.085845	-0.806746
H	7.655730	-2.410490	0.879750
H	7.000550	-3.434592	-0.421988
N	-1.336608	-0.384215	-0.248963
C	-1.585271	-1.066265	1.029023
C	-2.582222	-2.220167	0.821943

Continued (5R,6S)-TgH RC

Atoms	Coordinates (Angstroms)		
	X	Y	Z
N	-3.609216	-0.708845	-0.828935
H	-0.623549	-1.462506	1.373994
H	7.214260	-0.032018	0.245335
O	-2.122325	-0.135168	1.919540
H	-2.391686	-0.620145	2.719601
O	-2.912975	-2.627941	2.123009
H	-3.641356	-3.269292	2.109711
O	-4.939597	-1.982031	0.492626
H	-5.636592	-1.541552	-0.032807
O	-2.208736	0.125371	-2.332694
H	-1.293288	0.358510	-2.565730
C	-2.024233	-3.369146	-0.018766
H	-2.786258	-4.143593	-0.145907
H	-1.701949	-3.040927	-1.011299
H	-1.170232	-3.803337	0.508324

(5R,6S)-TgH TS:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	1.580165	2.423985	-0.358111
C	0.857701	2.413283	-1.564349
C	-0.544428	1.936579	-1.260103
O	-0.530502	0.489145	-0.970189
C	-1.154466	2.544358	0.003960
O	-2.540935	2.647926	-0.200513
C	-0.762377	1.518093	1.091776
C	-0.581930	0.269609	0.285386
C	4.146449	-1.218556	0.340186
C	2.528716	-0.025327	1.342305
H	1.325179	1.745227	-2.297192
H	0.791176	3.427369	-1.990115
H	-1.206134	2.045229	-2.120741
H	-0.720848	3.529812	0.215942
H	0.184909	1.833100	1.531191
H	-1.526697	1.365330	1.855616
C	-3.218465	3.369085	0.818080
H	-4.246703	3.495323	0.478650
H	-3.219369	2.817300	1.765947
H	-2.758827	4.354462	0.963078
C	2.961801	2.678492	-0.548589
H	3.113443	3.652393	-1.032029

Continued (5R,6S)-TgH TS

Atoms	Coordinates (Angstroms)		
	X	Y	Z
H	3.423196	2.690684	0.440519
H	3.411242	1.884661	-1.157783
O	-3.087963	0.006274	0.565064
H	-3.682137	-0.768174	0.495138
H	-3.466114	0.699599	0.002615
H	-0.778700	-0.743247	0.600524
C	-5.916832	-2.040849	-0.040959
O	-6.239679	-0.805621	-0.475220
O	-4.799135	-2.233485	0.374395
C	-6.993403	-3.090208	-0.117614
H	-7.873127	-2.776621	0.453267
H	-7.296683	-3.245408	-1.158022
H	-6.612042	-4.024520	0.291266
N	1.534874	-0.446152	0.637256
C	1.882399	-1.228762	-0.532931
C	3.099322	-2.133537	-0.265964
N	3.880878	-0.237542	1.118325
H	1.023595	-1.862580	-0.797238
H	-7.158115	-0.758551	-0.783573
O	2.183346	-0.338888	-1.584856
H	2.575457	-0.869582	-2.300798
O	3.494170	-2.606189	-1.532941
H	4.368770	-3.024019	-1.481262
O	5.390739	-1.541483	0.035668
H	6.006943	-0.939094	0.494722
O	2.340963	0.702549	2.439045
H	1.393483	0.734476	2.644981
C	2.787840	-3.279221	0.696090
H	3.690232	-3.869111	0.883699
H	2.407476	-2.912418	1.653758
H	2.036830	-3.927720	0.236400

(5R,6S)-TgH PC:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	-1.585345	2.226693	0.131506
C	-0.769301	2.390703	1.263896
C	0.674059	2.132902	0.877097
O	0.921099	0.699420	0.722136
C	1.067214	2.726138	-0.475199
O	2.468122	3.008174	-0.419957

Continued (5R,6S)-TgH PC

Atoms	Coordinates (Angstroms)		
	X	Y	Z
C	0.797882	1.554443	-1.425758
C	1.222845	0.399441	-0.547058
C	-4.074819	-1.605076	0.291895
C	-2.694796	-0.540093	-1.122927
H	-1.056717	1.690238	2.057062
H	-0.843821	3.422990	1.645032
H	1.342902	2.485775	1.666434
H	0.501529	3.631280	-0.717439
H	-0.277706	1.463633	-1.578858
H	1.328153	1.602437	-2.376461
C	2.917358	3.869407	-1.462808
H	3.979286	4.046645	-1.289380
H	2.776608	3.412417	-2.452231
H	2.376475	4.823132	-1.419447
C	-2.966006	2.325700	0.435374
H	-3.201048	3.317331	0.846011
H	-3.510449	2.180477	-0.499358
H	-3.250294	1.547447	1.153697
O	2.823351	0.397441	-0.732045
H	3.396368	-0.342669	-0.368026
H	3.148461	1.301461	-0.469588
H	0.962563	-0.618167	-0.818334
C	5.867412	-1.401940	-0.151265
O	6.307908	-0.140260	-0.047740
O	4.671379	-1.585319	-0.265566
C	6.903364	-2.492689	-0.111283
H	7.644872	-2.339222	-0.901319
H	7.419940	-2.477830	0.854027
H	6.420165	-3.458819	-0.247761
N	-1.577117	-0.853858	-0.579565
C	-1.682552	-1.469327	0.726622
C	-2.904491	-2.402850	0.829870
N	-3.991373	-0.739987	-0.644014
H	-0.775873	-2.061990	0.910871
H	7.270208	-0.091561	0.055676
O	-1.799071	-0.445218	1.692183
H	-2.059241	-0.877729	2.524350
O	-3.060433	-2.682263	2.205175
H	-3.940404	-3.057127	2.371597
O	-5.238915	-1.909199	0.852230
H	-5.944881	-1.388546	0.425034

Continued (5R,6S)-TgH PC

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	-2.726428	0.072419	-2.310988
H	-1.811209	0.149008	-2.624848
C	-2.730477	-3.682816	0.014166
H	-3.632343	-4.299334	0.077904
H	-2.529740	-3.463249	-1.038459
H	-1.890962	-4.248331	0.428517

Table S19. Cartesian coordinates for the optimized 5,6-diHThyH structures of the monofunctional pathway (Asp-H_2O) at M06-2X/6-31+G(d)

5,6-diHThyH RC:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	0.271596	2.926513	0.247405
C	1.443045	2.436042	0.878140
C	1.392823	0.931287	0.735275
O	0.115174	0.506758	1.246094
C	1.416363	0.431572	-0.708241
O	2.749323	0.294234	-1.131630
C	0.611307	-0.869351	-0.600360
C	-0.416769	-0.534359	0.490321
C	-4.515978	-0.137865	-0.297899
C	-2.441983	-1.297655	-0.769603
H	1.450609	2.729481	1.936029
H	2.341492	2.830879	0.384979
H	2.196861	0.451014	1.303781
H	0.896081	1.152527	-1.359881
H	0.153773	-1.187573	-1.541528
H	1.261212	-1.669102	-0.225948
C	2.858720	-0.045258	-2.500609
H	3.919789	-0.017739	-2.757020
H	2.465170	-1.052507	-2.690506
H	2.325035	0.679732	-3.129823
C	0.099684	4.336824	0.314194
H	0.907563	4.840608	-0.226706
H	-0.857122	4.561243	-0.158473
H	0.085750	4.672966	1.357350
O	1.351581	-2.301199	2.103326
H	1.351045	-2.722822	2.972668
H	2.282336	-2.078770	1.913246
H	-0.608917	-1.390070	1.148173
C	4.461581	-1.504781	0.299870
O	3.844922	-1.261425	1.310600
O	3.979662	-2.427573	-0.553188
C	5.741339	-0.814896	-0.088552
H	6.166845	-0.330190	0.789398
H	6.470420	-1.510060	-0.514280
H	5.507461	-0.046946	-0.834273
O	-5.819227	-0.112836	-0.458515
N	-3.868972	0.966377	-0.133048
N	-1.780998	-0.178366	-0.071085

Continued 5,6-diHThyH RC

Atoms	Coordinates (Angstroms)		
	X	Y	Z
C	-4.631494	-2.503422	-1.181256
H	-4.101929	-3.460004	-1.185003
H	-4.707412	-2.143605	-2.211853
H	-5.641155	-2.670007	-0.802635
C	-3.881896	-1.498435	-0.305659
C	-2.523651	0.903839	0.151616
O	-2.080028	2.009794	0.641648
H	-2.419133	-1.102538	-1.849875
H	4.582572	-2.573454	-1.298567
H	-6.133891	0.810791	-0.397934
H	-1.078844	2.111223	0.661525
H	-1.858942	-2.201381	-0.577585
H	-3.884707	-1.846131	0.738830

5,6-diHThyH TS:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	-0.118773	2.879000	0.118745
C	-1.369404	2.659210	-0.482162
C	-1.610836	1.173692	-0.557351
O	-0.576684	0.579590	-1.410370
C	-1.484635	0.389298	0.752940
O	-2.757859	0.314425	1.339840
C	-0.904135	-0.968518	0.299354
C	-0.304098	-0.615255	-1.024829
C	4.761695	-0.384941	0.023185
C	2.645220	-1.407918	0.616258
H	-1.401122	3.097210	-1.490278
H	-2.177184	3.105542	0.117601
H	-2.576352	0.964237	-1.029752
H	-0.777744	0.896180	1.424395
H	-0.131347	-1.364804	0.959133
H	-1.696447	-1.715035	0.184661
C	-2.720336	-0.219314	2.653214
H	-3.738242	-0.177238	3.045457
H	-2.373812	-1.261386	2.644884
H	-2.064822	0.377732	3.298564
C	0.213592	4.259775	0.236048
H	-0.507895	4.767192	0.886409
H	1.209597	4.307795	0.676038
H	0.224323	4.735762	-0.751516

Continued 5,6-diHThyH TS

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	-1.530102	-1.776646	-2.197764
H	-1.448533	-1.605024	-3.149682
H	-2.471218	-1.596701	-1.951585
H	0.519724	-1.110288	-1.516345
C	-4.520604	-1.245620	-0.288766
O	-3.916625	-0.902771	-1.285862
O	-4.064089	-2.301220	0.398463
C	-5.730094	-0.532992	0.239481
H	-6.162725	0.078871	-0.551411
H	-6.482640	-1.227650	0.622176
H	-5.402974	0.122916	1.054280
O	6.079302	-0.504646	0.088162
N	4.222818	0.779506	0.009911
N	2.016721	-0.166932	0.176136
C	4.728220	-2.865801	0.559019
H	4.100732	-3.760419	0.501839
H	4.960601	-2.675657	1.611572
H	5.665416	-3.068696	0.037545
C	3.993826	-1.677219	-0.055992
C	2.833206	0.797402	-0.075673
O	2.389921	1.993025	-0.447716
H	2.786749	-1.378998	1.708979
H	-4.636505	-2.524804	1.149940
H	6.467607	0.390799	0.103560
H	1.412801	2.028349	-0.364983
H	1.969503	-2.247591	0.408628
H	3.825305	-1.863166	-1.128766

5,6-diHThyH PC:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	0.253827	2.805914	0.208027
C	1.484424	2.555859	0.837666
C	1.766470	1.073824	0.756247
O	0.728422	0.377569	1.473394
C	1.743199	0.480678	-0.661775
O	3.080550	0.329076	-1.098853
C	0.980357	-0.854468	-0.513837
C	0.530881	-0.856861	0.937051
C	-4.852975	-0.123522	-0.269455
C	-2.809871	-1.233325	-0.950929

Continued 5,6-diHThyH PC

Atoms	Coordinates (Angstroms)		
	X	Y	Z
H	1.454163	2.873750	1.889952
H	2.299375	3.097808	0.332924
H	2.738453	0.862385	1.220212
H	1.206638	1.155355	-1.340741
H	0.085917	-0.877282	-1.136785
H	1.614999	-1.712985	-0.752057
C	3.172447	0.084884	-2.491432
H	4.234515	0.036752	-2.743039
H	2.687651	-0.862708	-2.762510
H	2.710638	0.898785	-3.062018
C	-0.114866	4.179568	0.225487
H	0.616520	4.775904	-0.332777
H	-1.093600	4.250361	-0.248694
H	-0.181675	4.546693	1.256682
O	1.411822	-1.864349	1.681054
H	1.238768	-1.797557	2.640461
H	2.470730	-1.707070	1.500913
H	-0.480242	-1.202325	1.136634
C	4.448940	-1.608511	0.338437
O	3.783295	-1.336449	1.335739
O	3.961665	-2.492048	-0.516289
C	5.764924	-0.956280	0.070868
H	6.246407	-0.718139	1.017354
H	6.425868	-1.571966	-0.542101
H	5.551396	-0.018700	-0.452942
O	-6.173725	-0.108197	-0.399855
N	-4.218279	0.969661	-0.055314
N	-2.097421	-0.140800	-0.301196
C	-5.012735	-2.487036	-1.180115
H	-4.470777	-3.435905	-1.239531
H	-5.178794	-2.121155	-2.198369
H	-5.987886	-2.674085	-0.726210
C	-4.204473	-1.478496	-0.368496
C	-2.834276	0.842526	0.073482
O	-2.302607	1.923766	0.639544
H	-2.905037	-1.019252	-2.028601
H	4.559761	-2.654766	-1.264588
H	-6.476588	0.812646	-0.287903
H	-1.324228	1.864555	0.603357
H	-2.215687	-2.151193	-0.863868
H	-4.097089	-1.839654	0.666823

Table S20. Cartesian coordinates for the optimized 5-OH-6HThyH structures of the monofunctional pathway (Asp-H_2O) at M06-2X/6-31+G(d)

5-OH-6HThyH RC:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	0.032642	0.174360	3.122397
C	1.284633	-0.409287	2.785434
C	1.419100	-0.313088	1.283717
O	0.265460	-0.940452	0.708715
C	1.410569	1.116253	0.742302
O	2.732415	1.593782	0.705161
C	0.737830	0.942809	-0.622208
C	-0.215512	-0.224513	-0.379228
C	-4.148959	-0.666385	-0.716159
C	-2.305545	0.785848	-1.298063
H	1.306562	-1.456504	3.114455
H	2.101644	0.141234	3.270911
H	2.324694	-0.827394	0.940695
H	0.803101	1.764131	1.394101
H	0.238006	1.845179	-0.982026
H	1.484416	0.625152	-1.358999
C	2.813654	2.946317	0.302170
H	3.855020	3.256353	0.415137
H	2.511537	3.065044	-0.747079
H	2.185284	3.585330	0.936837
C	-0.243871	0.182064	4.519530
H	0.494392	0.800204	5.041356
H	-1.238670	0.610917	4.646196
H	-0.225101	-0.838070	4.920123
O	1.630359	-1.742788	-1.994410
H	1.661214	-2.622565	-2.391718
H	2.532231	-1.559259	-1.671614
H	-0.303726	-0.887332	-1.242948
C	4.575844	0.129394	-0.924831
O	3.981581	-0.901761	-0.712855
O	4.150403	0.936171	-1.914423
C	5.762132	0.591478	-0.123388
H	6.531813	1.050180	-0.750504
H	5.412506	1.328750	0.607802
H	6.184317	-0.257962	0.412483
O	-5.319735	-1.160771	-1.044630
N	-3.777447	-0.647147	0.518602
N	-1.650555	0.225279	-0.111616

Continued 5-OH-6HThyH RC

Atoms	Coordinates (Angstroms)		
	X	Y	Z
C	-4.110938	0.408409	-3.014167
H	-3.435480	0.748015	-3.803111
H	-4.701065	1.255923	-2.661542
H	-4.800958	-0.326203	-3.431328
C	-3.293254	-0.204080	-1.889912
C	-2.456654	-0.362916	0.775317
O	-2.090744	-0.718620	1.955174
H	-2.812596	1.716738	-1.019413
H	4.730548	1.705866	-2.020861
H	-5.767271	-1.498866	-0.243126
H	-1.163709	-0.426457	2.233360
H	-1.539466	1.008431	-2.044260
O	-2.518249	-1.313923	-2.305376
H	-3.040360	-1.896907	-2.879077

5-OH-6HThyH TS:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	0.463134	3.046136	-0.089185
C	1.513212	2.597316	0.734685
C	1.618125	1.096824	0.634016
O	0.421991	0.491472	1.209193
C	1.675468	0.512920	-0.782371
O	3.026066	0.405032	-1.161803
C	0.947357	-0.840741	-0.647075
C	0.179702	-0.663345	0.638353
C	-4.384103	-0.235726	0.172430
C	-2.584240	-0.806932	-1.354015
H	1.336228	2.887959	1.780298
H	2.470015	3.030086	0.406612
H	2.477218	0.750224	1.214101
H	1.117508	1.166821	-1.466045
H	0.264575	-1.049358	-1.471087
H	1.663819	-1.662884	-0.557734
C	3.185233	0.019942	-2.515748
H	4.255208	0.038708	-2.731593
H	2.794933	-0.992762	-2.687953
H	2.673744	0.721541	-3.186220
C	0.314966	4.461857	-0.078550
H	1.225641	4.938997	-0.458452
H	-0.525042	4.698480	-0.731564

Continued 5-OH-6HThyH TS

Atoms	Coordinates (Angstroms)		
	X	Y	Z
H	0.103567	4.818466	0.936495
O	1.062258	-1.925339	1.628535
H	0.767388	-1.954878	2.555332
H	2.051554	-1.741006	1.617038
H	-0.792812	-1.102398	0.842995
C	4.292950	-1.491250	0.544501
O	3.550730	-1.110991	1.433091
O	3.865858	-2.476038	-0.251775
C	5.635593	-0.892910	0.260114
H	5.805242	-0.045854	0.922147
H	6.425418	-1.637264	0.407671
H	5.663671	-0.555154	-0.781519
O	-5.620169	-0.537493	0.557803
N	-3.925486	0.946894	0.306283
N	-1.889823	0.361713	-0.841299
C	-4.433783	-2.494853	-0.987092
H	-3.786244	-3.259869	-1.425975
H	-5.080912	-2.083831	-1.766914
H	-5.077742	-2.964011	-0.237447
C	-3.573928	-1.408847	-0.363127
C	-2.591635	1.124584	-0.082378
O	-2.088119	2.234120	0.441932
H	-3.121847	-0.544988	-2.277322
H	4.528072	-2.727884	-0.916493
H	-6.032318	0.267927	0.924362
H	-1.151125	2.334489	0.157984
H	-1.856064	-1.585224	-1.614305
O	-2.792403	-1.925048	0.721152
H	-3.376807	-2.394427	1.336686

5-OH-6HThyH PC:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	0.042206	0.347574	3.058724
C	1.245852	-0.354376	2.856284
C	1.603438	-0.302728	1.388955
O	0.611758	-1.035432	0.644986
C	1.618207	1.099960	0.762522
O	2.960351	1.546633	0.713602
C	0.971180	0.908728	-0.627626
C	0.511119	-0.540216	-0.617872

Continued 5-OH-6HThyH PC

Atoms	Coordinates (Angstroms)		
	X	Y	Z
C	-4.224339	-0.864417	-0.788860
C	-2.694132	0.982889	-1.164214
H	1.141237	-1.401261	3.176015
H	2.060709	0.108877	3.433289
H	2.586646	-0.770036	1.247385
H	1.019719	1.788655	1.371844
H	0.094842	1.545473	-0.751076
H	1.681826	1.108678	-1.435203
C	3.059548	2.933151	0.440133
H	4.120737	3.191846	0.456636
H	2.637695	3.176609	-0.544871
H	2.540199	3.520609	1.206524
C	-0.390940	0.326381	4.414022
H	0.361250	0.793252	5.060552
H	-1.319341	0.895618	4.457944
H	-0.575880	-0.703362	4.742297
O	1.484298	-1.317594	-1.528043
H	1.291530	-2.272646	-1.458279
H	2.514347	-1.144815	-1.287137
H	-0.456229	-0.771768	-1.060184
C	4.498794	0.043175	-1.058848
O	3.824629	-0.952446	-0.812634
O	4.078562	0.867963	-2.005490
C	5.755604	0.349245	-0.312425
H	6.466029	0.929766	-0.904791
H	5.466911	0.922693	0.575785
H	6.215761	-0.583508	0.013803
O	-5.325520	-1.466953	-1.231637
N	-3.898997	-0.916961	0.443477
N	-2.077271	0.619552	0.098442
C	-4.199562	0.266049	-3.065380
H	-3.544779	0.795270	-3.764019
H	-5.011888	0.932790	-2.762926
H	-4.648774	-0.589659	-3.577995
C	-3.387234	-0.182077	-1.862709
C	-2.697757	-0.274562	0.776390
O	-2.234726	-0.704318	1.944277
H	-3.426643	1.788208	-1.004984
H	4.681100	1.618478	-2.137650
H	-5.760768	-1.900465	-0.473172
H	-1.377817	-0.257699	2.130782

Continued 5-OH-6HThyH PC

Atoms	Coordinates (Angstroms)		
	X	Y	Z
H	-1.929421	1.372729	-1.848519
O	-2.350113	-1.093969	-2.244872
H	-2.737889	-1.802968	-2.781334

Table S21. Cartesian coordinates for the optimized TH structures of the bifunctional pathway (Asp-Lys) at M06-2X/6-31+G(d)

TH RC:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	-2.060839	-2.183110	0.532691
C	-1.198442	-3.156108	-0.011948
C	0.207708	-2.589447	-0.022446
O	0.289584	-1.434762	-0.893793
C	0.691243	-2.084270	1.336397
O	2.068963	-2.365724	1.419911
C	0.365206	-0.578970	1.311182
C	0.166339	-0.241287	-0.172578
H	-1.511807	-3.416908	-1.034968
H	-1.213974	-4.076365	0.592202
H	0.907722	-3.327153	-0.423285
H	0.160141	-2.589152	2.156437
H	-0.544612	-0.388549	1.883590
H	1.183735	0.026878	1.707857
C	2.622777	-2.137007	2.701360
H	3.674270	-2.426738	2.644426
H	2.557188	-1.078520	2.989969
H	2.116469	-2.751902	3.458502
C	-3.428065	-2.553481	0.436113
H	-3.609790	-3.504501	0.951886
H	-4.009304	-1.764985	0.916945
H	-3.729785	-2.639755	-0.616074
H	0.906951	0.467673	-0.543980
C	3.207604	-0.438554	-2.676759
H	3.709661	-0.090328	-3.586998
H	2.164274	-0.099388	-2.734227
C	3.873137	0.213287	-1.468076
H	3.836905	1.303790	-1.578793
H	4.936076	-0.073003	-1.445993
N	3.159820	-0.131866	-0.234847
H	3.582184	0.336735	0.563339
C	3.250033	-1.965106	-2.620356
H	2.681681	-2.344924	-1.763011
H	2.816969	-2.407496	-3.522949
H	4.281386	-2.327000	-2.531992
H	3.216078	-1.131566	-0.043937
C	2.466853	3.031158	1.013877
C	2.842353	4.418557	0.558935

Continued TH RC

Atoms	Coordinates (Angstroms)		
	X	Y	Z
H	3.656283	4.364821	-0.175756
H	1.978243	4.897541	0.100455
H	3.185375	5.023578	1.407278
O	1.376623	2.532582	0.879369
O	3.447538	2.315480	1.601169
C	-3.692205	1.404322	-0.467314
C	-1.509798	1.455477	0.389044
O	-4.959772	1.785143	-0.509949
N	-3.385658	0.412136	-1.278214
N	-1.207130	0.386725	-0.399993
C	-3.096259	3.213115	1.253214
H	-2.230006	3.535885	1.830918
H	-3.888599	2.970984	1.968040
H	-3.420690	4.066008	0.650342
C	-2.745883	2.031822	0.393856
C	-2.155211	-0.063384	-1.266922
O	-1.875483	-0.977539	-2.160038
H	-0.691449	1.818527	1.005012
H	-5.136577	2.528305	0.088941
H	-0.959265	-1.318394	-2.011547
H	4.262394	2.827735	1.693805

TH TS:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	1.766343	-2.191184	-0.894450
C	0.875339	-3.142758	-0.372214
C	-0.500563	-2.517761	-0.324760
O	-0.541518	-1.485957	0.724624
C	-0.905098	-1.777789	-1.604261
O	-2.273460	-2.018935	-1.821096
C	-0.583822	-0.305105	-1.279485
C	-0.601971	-0.291982	0.216553
H	1.186566	-3.463862	0.633341
H	0.827897	-4.035446	-1.016190
H	-1.259563	-3.249949	-0.039619
H	-0.314307	-2.131538	-2.459042
H	0.420921	-0.057511	-1.630922
H	-1.297856	0.413795	-1.681420
C	-2.722538	-1.630476	-3.107387
H	-3.771140	-1.920776	-3.175454

Continued TH TS

Atoms	Coordinates (Angstroms)		
	X	Y	Z
H	-2.637984	-0.545446	-3.254673
H	-2.151129	-2.145776	-3.889933
C	3.113793	-2.643609	-0.873228
H	3.214344	-3.577902	-1.440067
H	3.718274	-1.866872	-1.343155
H	3.452526	-2.793129	0.159410
H	-0.857653	0.529848	0.862415
C	-3.101668	-0.534914	2.693972
H	-3.509294	-0.140647	3.631664
H	-2.009438	-0.452048	2.770670
C	-3.606058	0.341692	1.549601
H	-3.254837	1.371725	1.693475
H	-4.706491	0.368483	1.572152
N	-3.092042	-0.119454	0.253681
H	-3.386651	0.522400	-0.480791
C	-3.497508	-2.002233	2.540384
H	-3.018953	-2.460937	1.667296
H	-3.199899	-2.583890	3.417065
H	-4.582584	-2.106801	2.424540
H	-3.464364	-1.035457	0.007550
C	-2.246829	3.276072	-0.407113
C	-2.357054	4.731809	-0.040134
H	-3.144383	4.874654	0.707491
H	-1.407894	5.075818	0.367821
H	-2.612128	5.328592	-0.921924
O	-1.263017	2.593062	-0.258550
O	-3.352367	2.707627	-0.940518
C	4.085381	0.959018	0.453902
C	1.860160	1.508351	-0.050583
O	5.407826	1.119401	0.386584
N	3.695161	-0.095196	1.147897
N	1.443468	0.429638	0.635282
C	3.657788	3.063351	-0.939260
H	2.804967	3.615278	-1.342019
H	4.296462	2.791398	-1.788525
H	4.216161	3.755152	-0.297169
C	3.187588	1.853916	-0.181308
C	2.390617	-0.304449	1.222652
O	2.024593	-1.353159	1.962439
H	1.074034	2.109148	-0.508148
H	5.644339	1.918311	-0.109373

Continued TH TS

Atoms	Coordinates (Angstroms)		
	X	Y	Z
H	1.054611	-1.418377	1.973959
H	-4.083201	3.341219	-1.024697

TH PC:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	-1.817025	-2.073072	0.526404
C	-1.016593	-3.035925	-0.107976
C	0.437949	-2.627574	0.011715
O	0.716132	-1.499230	-0.864166
C	0.835082	-2.149838	1.410682
O	2.203614	-2.499159	1.603272
C	0.684736	-0.631532	1.298744
C	1.151558	-0.398874	-0.129053
H	-1.289169	-3.135044	-1.169866
H	-1.143580	-4.021622	0.369408
H	1.079518	-3.458486	-0.300604
H	0.209046	-2.597646	2.190820
H	-0.368290	-0.347007	1.354491
H	1.255074	-0.073996	2.046781
C	2.608304	-2.472657	2.963622
H	3.656720	-2.773058	2.990172
H	2.503651	-1.468872	3.399722
H	2.013409	-3.183049	3.552071
C	-3.201816	-2.364046	0.400206
H	-3.428039	-3.344156	0.840767
H	-3.742466	-1.586891	0.941422
H	-3.504437	-2.344846	-0.653498
H	0.790673	0.518888	-0.587704
C	2.975528	-0.664365	-2.660913
H	3.470149	-0.172850	-3.505892
H	1.903406	-0.655639	-2.874218
C	3.271415	0.194266	-1.440808
H	2.867593	1.203410	-1.549293
H	4.348825	0.265173	-1.265330
N	2.680047	-0.338202	-0.168318
H	2.973225	0.297394	0.586373
C	3.481984	-2.098220	-2.525412
H	2.941505	-2.646395	-1.745291
H	3.336868	-2.649177	-3.460439

Continued TH PC

Atoms	Coordinates (Angstroms)		
	X	Y	Z
H	4.554502	-2.122411	-2.288438
H	3.038158	-1.273393	0.079654
C	2.669706	2.943793	0.945171
C	2.854487	4.430873	1.041984
H	3.659877	4.756874	0.376216
H	1.927300	4.925870	0.757050
H	3.120154	4.716371	2.064795
O	1.663422	2.374956	0.606159
O	3.746079	2.169594	1.254992
C	-4.021904	1.380211	-0.424315
C	-1.795679	1.933797	0.055917
O	-5.350676	1.525871	-0.330024
N	-3.631880	0.399349	-1.219871
N	-1.368118	0.958033	-0.754523
C	-3.597593	3.299263	1.214254
H	-2.742231	3.801618	1.674159
H	-4.218866	2.907271	2.029554
H	-4.175298	4.068240	0.685132
C	-3.129057	2.209993	0.290977
C	-2.320536	0.229970	-1.332483
O	-1.931923	-0.785534	-2.113802
H	-1.016673	2.522093	0.541297
H	-5.579257	2.268868	0.248435
H	-0.971235	-0.899111	-1.984101
H	4.515596	2.691301	1.537437

Table S22. Cartesian coordinates for the optimized (5R,6S)-TgH structures of the bifunctional pathway (Asp-Lys) at M06-2X/6-31+G(d)

(5R,6S)-TgH RC:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	-1.249040	-2.698097	0.560394
C	-0.147358	-3.342679	-0.041287
C	1.100225	-2.512746	0.187672
O	0.995994	-1.228759	-0.471478
C	1.382285	-2.184957	1.651492
O	2.777780	-2.220574	1.832803
C	0.773548	-0.783532	1.844769
C	0.618784	-0.209605	0.426321
H	-0.323438	-3.467579	-1.121669
H	0.001622	-4.343791	0.391469
H	1.962349	-3.017485	-0.256632
H	0.903552	-2.917574	2.317265
H	-0.194887	-0.864676	2.342631
H	1.436394	-0.149894	2.438841
C	3.172703	-2.212005	3.192992
H	4.258395	-2.308488	3.206286
H	2.889033	-1.276334	3.692024
H	2.725461	-3.057625	3.730627
C	-2.476994	-3.328638	0.221368
H	-2.473028	-4.379646	0.534683
H	-3.274585	-2.801532	0.748040
H	-2.654048	-3.265654	-0.860018
H	1.275049	0.648066	0.251781
C	3.500333	0.410675	-1.922043
H	3.814151	0.976332	-2.808114
H	2.405797	0.493863	-1.854720
C	4.120062	1.048493	-0.681408
H	3.866659	2.112928	-0.648926
H	5.214720	0.978710	-0.750289
N	3.584975	0.448352	0.547627
H	4.026052	0.881204	1.356394
C	3.890379	-1.055389	-2.096741
H	3.558431	-1.661751	-1.246932
H	3.443374	-1.480476	-3.000154
H	4.977424	-1.161199	-2.180570
H	3.812723	-0.546766	0.607507
C	0.939289	2.807909	-2.182849
C	-0.242431	2.294069	-2.947793

Continued (5R,6S)-TgH RC

Atoms	Coordinates (Angstroms)		
	X	Y	Z
H	-1.116979	2.233275	-2.298595
H	-0.449828	2.937348	-3.805546
H	-0.002452	1.297015	-3.334560
O	1.033126	2.845890	-0.963843
O	1.929328	3.210496	-2.968442
N	-0.795607	0.232906	0.170706
C	-1.279573	1.330152	1.027857
C	-2.734167	1.054816	1.400290
C	-3.441993	0.763326	0.076534
O	-4.684818	1.142112	-0.010170
N	-2.901770	0.154441	-0.928291
C	-1.595404	-0.189335	-0.806770
O	-1.159114	-0.941852	-1.775039
H	-0.645458	1.347934	1.921752
O	-1.288130	2.552486	0.367492
H	-0.396782	2.758323	-0.007102
H	-4.907930	1.665145	0.789722
H	-0.208308	-1.168994	-1.597738
H	2.668461	3.519694	-2.412041
O	-3.330495	2.183246	1.989368
H	-2.934055	2.982053	1.592316
C	-2.901343	-0.126403	2.349417
H	-2.430961	0.125604	3.304552
H	-3.963498	-0.311472	2.531739
H	-2.443224	-1.031717	1.940371

(5R,6S)-TgH TS:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	-0.427919	-2.595808	-1.239356
C	0.791805	-2.489145	-1.926797
C	1.822528	-1.865782	-1.012119
O	1.511573	-0.440236	-0.812227
C	1.876790	-2.455166	0.401396
O	3.226054	-2.530058	0.787792
C	1.056822	-1.447556	1.231688
C	1.157066	-0.194860	0.420377
H	0.679098	-1.878403	-2.835848
H	1.159662	-3.481560	-2.233012
H	2.812226	-1.888575	-1.476403
H	1.418123	-3.452148	0.423509

Continued (5R,6S)-TgH TS

Atoms	Coordinates (Angstroms)		
	X	Y	Z
H	0.012225	-1.767382	1.251178
H	1.433518	-1.321366	2.243261
C	3.443079	-3.360812	1.917190
H	4.517134	-3.367302	2.102735
H	2.925259	-2.977290	2.806597
H	3.101632	-4.383532	1.716283
C	-1.486549	-2.994150	-2.103321
H	-1.266332	-3.967045	-2.560339
H	-2.387835	-3.078841	-1.494698
H	-1.647065	-2.239492	-2.882294
H	1.037486	0.834561	0.716520
C	3.483623	2.150702	-0.466795
H	3.723550	3.218473	-0.544610
H	2.437816	2.037020	-0.782462
C	3.637770	1.745577	0.998354
H	2.942894	2.321233	1.621847
H	4.657718	1.986392	1.330975
N	3.332702	0.319054	1.198088
H	3.549505	0.045835	2.163926
C	4.392375	1.372084	-1.416988
H	4.110875	0.314541	-1.476621
H	4.330617	1.775842	-2.430839
H	5.438776	1.429321	-1.097217
H	3.934503	-0.266140	0.618357
C	0.039679	3.732452	-0.064086
C	-1.181875	3.843058	-0.917141
H	-1.965235	3.182916	-0.544884
H	-1.523383	4.882983	-0.907595
H	-0.935418	3.605313	-1.956208
O	0.209223	2.921913	0.843608
O	0.968696	4.629595	-0.373169
N	-1.033897	0.154153	0.095529
C	-1.863780	0.277631	1.275648
C	-3.183041	-0.477080	1.111366
C	-3.720692	-0.123434	-0.276026
O	-5.026700	-0.105776	-0.400201
N	-2.982477	0.107781	-1.312841
C	-1.631745	0.136167	-1.050941
O	-0.915452	0.188642	-2.173358
H	-1.311887	-0.136908	2.133931
O	-2.217885	1.615810	1.527239

Continued (5R,6S)-TgH TS

Atoms	Coordinates (Angstroms)		
	X	Y	Z
H	-1.409385	2.162853	1.460023
H	-5.404645	-0.192142	0.499978
H	0.027035	0.244801	-1.934968
H	1.713008	4.508478	0.242071
O	-4.133910	-0.082788	2.072898
H	-3.982751	0.857995	2.283411
C	-2.981871	-1.986761	1.218625
H	-2.783381	-2.230653	2.265869
H	-3.881144	-2.526381	0.907704
H	-2.139849	-2.308194	0.596007

(5R,6S)-TgH PC:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	-0.980500	-2.628072	0.645597
C	0.035458	-3.293807	-0.057426
C	1.370097	-2.639737	0.233746
O	1.437791	-1.337434	-0.419513
C	1.639498	-2.357165	1.714714
O	3.039251	-2.512722	1.925522
C	1.249036	-0.884387	1.850004
C	1.708642	-0.336720	0.508262
H	-0.156612	-3.266910	-1.141811
H	0.091957	-4.351950	0.246017
H	2.173438	-3.260739	-0.177857
H	1.070004	-3.024205	2.371561
H	0.161668	-0.776542	1.875590
H	1.692520	-0.393794	2.722819
C	3.391869	-2.719957	3.287396
H	4.476094	-2.828145	3.322661
H	3.088190	-1.873591	3.917041
H	2.924808	-3.636194	3.666081
C	-2.267263	-3.118400	0.289135
H	-2.343404	-4.192059	0.504553
H	-2.999496	-2.579351	0.891626
H	-2.466145	-2.931601	-0.772883
H	1.232150	0.595259	0.195938
C	3.440614	0.258953	-1.977886
H	3.815485	1.004710	-2.687748
H	2.362296	0.176654	-2.153226
C	3.701939	0.826516	-0.590352

Continued (5R,6S)-TgH PC

Atoms	Coordinates (Angstroms)		
	X	Y	Z
H	3.179033	1.775045	-0.436265
H	4.773102	0.973301	-0.423768
N	3.225594	-0.082709	0.512118
H	3.475963	0.337130	1.413213
C	4.130547	-1.080366	-2.227470
H	3.707012	-1.880654	-1.610287
H	4.004222	-1.385376	-3.268175
H	5.205991	-1.018024	-2.029513
H	3.698111	-0.998808	0.504539
C	0.832491	2.852216	-2.164124
C	-0.398803	2.328881	-2.837546
H	-1.270912	2.505303	-2.206082
H	-0.525015	2.786354	-3.819291
H	-0.294755	1.245593	-2.971489
O	1.014333	2.925985	-0.958724
O	1.780289	3.227779	-3.029802
N	-0.953838	0.621267	0.052873
C	-1.547537	1.604190	0.926796
C	-2.990156	1.253283	1.293146
C	-3.686317	0.800230	0.010167
O	-4.970848	1.073809	-0.074276
N	-3.107538	0.151889	-0.935273
C	-1.741687	0.012041	-0.763192
O	-1.212405	-0.853407	-1.636734
H	-0.953084	1.651329	1.852414
O	-1.584374	2.880651	0.323044
H	-0.683339	3.080651	0.003122
H	-5.205340	1.650212	0.681580
H	-0.272941	-0.953762	-1.382809
H	2.519491	3.617670	-2.529156
O	-3.684764	2.358464	1.829257
H	-3.318835	3.164107	1.419188
C	-3.032552	0.122736	2.317730
H	-2.629552	0.497588	3.262999
H	-4.061246	-0.207994	2.487797
H	-2.432548	-0.727217	1.977783

Table S23. Cartesian coordinates for the optimized 5,6-diHThyH structures of the bifunctional pathway (Asp-Lys) at M06-2X/6-31+G(d)

5,6-diHThyH RC:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	-2.099199	-2.157310	0.824525
C	-1.152324	-3.110203	0.396294
C	0.178617	-2.414840	0.185109
O	0.089853	-1.435274	-0.875382
C	0.682193	-1.631668	1.395795
O	2.080484	-1.781918	1.437148
C	0.223098	-0.183771	1.129562
C	-0.129872	-0.144039	-0.366376
H	-1.485657	-3.583800	-0.540199
H	-1.028377	-3.903085	1.149405
H	0.930780	-3.142783	-0.131223
H	0.241651	-2.017463	2.326641
H	-0.640726	0.042013	1.757039
H	1.021853	0.529245	1.344780
C	2.672021	-1.278801	2.623788
H	3.732544	-1.529757	2.572169
H	2.562755	-0.190017	2.700347
H	2.228533	-1.759679	3.506385
C	-3.406766	-2.701512	0.921652
H	-3.427352	-3.538610	1.629768
H	-4.061675	-1.906690	1.280659
H	-3.755855	-3.040048	-0.061719
H	0.513893	0.540972	-0.924126
C	3.004399	-0.641957	-2.990664
H	3.531875	-0.506504	-3.942048
H	1.952125	-0.382511	-3.166321
C	3.582488	0.325411	-1.961703
H	3.520986	1.348531	-2.345698
H	4.651181	0.100215	-1.816603
N	2.819154	0.274632	-0.711164
H	3.176791	0.968721	-0.058450
C	3.108648	-2.100963	-2.551335
H	2.539255	-2.278755	-1.632373
H	2.718906	-2.778010	-3.317844
H	4.151776	-2.377083	-2.360134
H	2.942912	-0.626408	-0.251583
C	3.840228	2.793495	1.795370
C	4.409984	3.776040	2.786073

Continued 5,6-diHThyH RC

Atoms	Coordinates (Angstroms)		
	X	Y	Z
H	4.436315	4.781173	2.352659
H	3.791570	3.784589	3.682334
H	5.433228	3.494050	3.055251
O	2.854343	2.121866	1.974232
O	4.500935	2.673000	0.623001
C	-4.157049	1.055588	-0.898031
C	-2.020548	1.444795	0.156484
O	-5.451735	1.281788	-0.819436
N	-3.796200	-0.127709	-1.249343
N	-1.563611	0.273278	-0.594018
C	-3.716553	3.312241	0.230715
H	-2.914075	4.011973	0.479840
H	-4.163303	2.970112	1.170872
H	-4.458978	3.888438	-0.332635
C	-3.155060	2.148064	-0.583715
C	-2.463374	-0.405601	-1.283617
O	-2.153626	-1.407851	-2.052308
H	-2.362443	1.131181	1.152887
H	-5.647764	2.195267	-0.554817
H	-1.194212	-1.629960	-1.924927
H	5.283215	3.245208	0.582042
H	-1.167300	2.118332	0.280691
H	-2.775463	2.517919	-1.547375

5,6-diHThyH TS:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	2.033433	-1.566701	-1.568658
C	1.321324	-2.720990	-1.203545
C	-0.069234	-2.311357	-0.771434
O	-0.008897	-1.618203	0.525566
C	-0.761596	-1.318078	-1.711322
O	-2.117769	-1.682409	-1.790975
C	-0.519154	0.044199	-1.027438
C	-0.281290	-0.349728	0.398640
H	1.832752	-3.255557	-0.388922
H	1.225463	-3.410656	-2.057784
H	-0.698760	-3.188169	-0.601106
H	-0.301416	-1.341403	-2.707971
H	0.395388	0.483817	-1.431378
H	-1.349315	0.746659	-1.124842

Continued 5,6-diHThyH TS

Atoms	Coordinates (Angstroms)		
	X	Y	Z
C	-2.836546	-0.979739	-2.792167
H	-3.850704	-1.380325	-2.784659
H	-2.871050	0.096366	-2.582806
H	-2.386945	-1.149620	-3.779023
C	3.380875	-1.855020	-1.917088
H	3.418413	-2.532770	-2.779377
H	3.854442	-0.906891	-2.172678
H	3.910691	-2.298879	-1.065525
H	-0.466257	0.216408	1.296260
C	-2.283802	-1.661919	2.984227
H	-2.587731	-1.622611	4.036294
H	-1.206179	-1.450269	2.961819
C	-3.038352	-0.572247	2.224732
H	-2.799807	0.412590	2.643903
H	-4.121544	-0.717352	2.354573
N	-2.659950	-0.557949	0.806448
H	-3.131664	0.202870	0.317187
C	-2.539905	-3.061325	2.427434
H	-2.166272	-3.160805	1.401497
H	-2.040299	-3.824152	3.030843
H	-3.611478	-3.291653	2.419433
H	-2.945859	-1.416322	0.338638
C	-4.269706	2.521748	-0.406095
C	-4.989145	3.727925	-0.948429
H	-4.981808	4.539643	-0.212442
H	-4.496843	4.060939	-1.861194
H	-6.031584	3.479431	-1.170743
O	-3.311563	1.998697	-0.922330
O	-4.743845	1.998088	0.743702
C	4.345271	1.336452	0.512225
C	1.991462	1.833236	0.201502
O	5.589982	1.675460	0.208017
N	4.086601	0.080188	0.586893
N	1.732466	0.495944	0.708183
C	3.631342	3.768190	0.154828
H	2.793052	4.454307	0.304937
H	3.812840	3.697234	-0.923415
H	4.498386	4.238375	0.632215
C	3.298478	2.406001	0.759349
C	2.777312	-0.244911	0.878868
O	2.674614	-1.482117	1.358174

Continued 5,6-diHThyH TS

Atoms	Coordinates (Angstroms)		
	X	Y	Z
H	2.055100	1.814266	-0.900142
H	5.699090	2.638379	0.171803
H	1.735118	-1.682847	1.514278
H	-5.519381	2.480018	1.071761
H	1.154311	2.485059	0.473129
H	3.194394	2.499494	1.851086

5,6-diHThyH PC:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	-1.842044	-2.057119	0.777479
C	-0.974268	-3.006012	0.214878
C	0.436435	-2.452651	0.204030
O	0.582343	-1.441573	-0.834243
C	0.832993	-1.749478	1.504418
O	2.227336	-1.973367	1.691531
C	0.553229	-0.281142	1.179914
C	0.980653	-0.225187	-0.276165
H	-1.283440	-3.263301	-0.809429
H	-0.975869	-3.932110	0.813457
H	1.143036	-3.258966	-0.019160
H	0.265202	-2.121257	2.365048
H	-0.523844	-0.098746	1.203001
H	1.072533	0.428239	1.828217
C	2.699547	-1.589503	2.974348
H	3.751294	-1.874465	3.020990
H	2.607755	-0.507573	3.132002
H	2.147285	-2.120497	3.758625
C	-3.192215	-2.497533	0.759664
H	-3.294573	-3.440280	1.314248
H	-3.788393	-1.721858	1.241347
H	-3.541285	-2.624429	-0.271906
H	0.545237	0.593403	-0.850980
C	2.753317	-0.729056	-2.802320
H	3.200650	-0.333820	-3.721077
H	1.677223	-0.800221	-2.981461
C	3.034292	0.298477	-1.714049
H	2.584718	1.269437	-1.946250
H	4.111220	0.446098	-1.577675
N	2.498428	-0.096231	-0.371529
H	2.786883	0.614280	0.329272

Continued 5,6-diHThyH PC

Atoms	Coordinates (Angstroms)		
	X	Y	Z
C	3.334698	-2.106677	-2.493466
H	2.835975	-2.575285	-1.636916
H	3.204121	-2.781538	-3.345923
H	4.410296	-2.045956	-2.280396
H	2.900706	-0.983928	-0.036629
C	3.908537	2.634657	1.589262
C	4.257512	3.675242	2.614489
H	4.157241	4.677538	2.185926
H	3.591186	3.578165	3.469898
H	5.293564	3.545916	2.944284
O	3.031985	1.805945	1.717458
O	4.621527	2.622313	0.450609
C	-4.457086	1.040136	-0.859618
C	-2.291494	1.895280	-0.168489
O	-5.774761	1.054604	-0.664159
N	-3.930634	-0.079002	-1.188710
N	-1.709311	0.806810	-0.928937
C	-4.311284	3.367735	0.205719
H	-3.620283	4.202638	0.354996
H	-4.547538	2.952851	1.192088
H	-5.222325	3.798698	-0.225026
C	-3.661717	2.321052	-0.697657
C	-2.548168	-0.062059	-1.357714
O	-2.122167	-1.140466	-2.027674
H	-2.397288	1.592376	0.888954
H	-6.083104	1.939408	-0.417238
H	-1.148524	-1.154346	-1.949446
H	5.302774	3.314366	0.433688
H	-1.611756	2.753096	-0.189953
H	-3.528753	2.735621	-1.708673

Table S24. Cartesian coordinates for the optimized 5-OH-6HThyH structures of the bifunctional pathway (Asp-Lys) at M06-2X/6-31+G(d)

5-OH-6HThyH RC:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	-1.762900	-2.245253	0.871325
C	-0.845576	-3.157701	0.310535
C	0.438791	-2.421948	-0.019959
O	0.227450	-1.433386	-1.054491
C	1.029946	-1.640743	1.151820
O	2.430688	-1.756608	1.080389
C	0.526676	-0.198063	0.942785
C	0.021272	-0.156104	-0.509589
H	-1.268417	-3.614694	-0.597919
H	-0.619466	-3.967907	1.021245
H	1.174500	-3.126345	-0.415928
H	0.675064	-2.045367	2.110410
H	-0.270426	0.016547	1.655811
H	1.337814	0.522298	1.080658
C	3.088167	-1.297297	2.249857
H	4.158648	-1.430234	2.077582
H	2.879841	-0.237032	2.440875
H	2.783566	-1.895208	3.120970
C	-3.033536	-2.832836	1.106256
H	-2.946379	-3.684517	1.792400
H	-3.665417	-2.066405	1.557235
H	-3.484804	-3.162829	0.161554
H	0.574661	0.557047	-1.125650
C	2.970052	-0.893560	-3.244455
H	3.361563	-0.865949	-4.268205
H	1.886144	-0.731586	-3.307311
C	3.585442	0.253598	-2.448635
H	3.423452	1.197004	-2.985166
H	4.676246	0.102345	-2.385173
N	2.950775	0.374448	-1.129488
H	3.328961	1.171006	-0.618693
C	3.256631	-2.260550	-2.626333
H	2.893298	-2.318962	-1.596151
H	2.778495	-3.060984	-3.195261
H	4.333030	-2.462849	-2.606953
H	3.156858	-0.444645	-0.560812
C	3.659921	2.556310	2.381809
C	4.740815	3.606784	2.363567

Continued 5-OH-6HThyH RC

Atoms	Coordinates (Angstroms)		
	X	Y	Z
H	5.676607	3.191645	2.751038
H	4.896309	3.947419	1.340820
H	4.459799	4.457927	2.991160
O	3.100813	2.124119	1.403625
O	3.311981	2.074110	3.593568
C	-4.092000	0.889897	-0.570923
C	-1.847160	1.380206	0.203471
O	-5.371747	1.061857	-0.319477
N	-3.718686	-0.267529	-0.973179
N	-1.442457	0.211606	-0.570671
C	-3.596394	3.153973	0.514786
H	-2.795286	3.880847	0.686819
H	-3.917632	2.777821	1.491107
H	-4.420110	3.697943	0.040068
C	-3.093552	2.038571	-0.394624
C	-2.387015	-0.486456	-1.172142
O	-2.133945	-1.466439	-1.987518
H	-2.048558	1.088012	1.242864
H	-5.582151	1.982638	-0.094950
H	-1.158843	-1.646355	-1.987419
H	3.827854	2.483059	4.305964
H	-1.013220	2.091540	0.200528
O	-2.871109	2.481802	-1.716160
H	-2.334488	3.290885	-1.713996

5-OH-6HThyH TS:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	1.486294	-1.408339	-2.014224
C	0.744995	-2.573214	-1.760937
C	-0.528636	-2.193859	-1.039044
O	-0.226024	-1.798664	0.346775
C	-1.270267	-0.988904	-1.625291
O	-2.647267	-1.265043	-1.555105
C	-0.831175	0.180439	-0.717968
C	-0.403130	-0.526734	0.528765
H	1.326783	-3.286206	-1.156990
H	0.464426	-3.072539	-2.702690
H	-1.194517	-3.055581	-0.954485
H	-0.968214	-0.814331	-2.665991
H	0.034897	0.677603	-1.159738

Continued 5-OH-6HThyH TS

Atoms	Coordinates (Angstroms)		
	X	Y	Z
H	-1.622170	0.909850	-0.522561
C	-3.442416	-0.349112	-2.293220
H	-4.475709	-0.683050	-2.191198
H	-3.344445	0.672150	-1.906670
H	-3.159644	-0.366149	-3.353807
C	2.733950	-1.691252	-2.633756
H	2.579773	-2.210402	-3.588453
H	3.224808	-0.734520	-2.813285
H	3.362871	-2.299241	-1.972720
H	-0.378736	-0.161233	1.539911
C	-2.267460	-2.523303	2.868456
H	-2.429194	-2.856698	3.899802
H	-1.184439	-2.395653	2.744613
C	-2.960777	-1.176506	2.686217
H	-2.560877	-0.454507	3.407041
H	-4.033904	-1.288119	2.904285
N	-2.733287	-0.635348	1.337679
H	-3.146744	0.292487	1.247612
C	-2.777927	-3.590942	1.902709
H	-2.582139	-3.323101	0.857715
H	-2.296210	-4.555167	2.088197
H	-3.859373	-3.732250	2.011539
H	-3.180772	-1.214206	0.626920
C	-4.029309	3.004447	-0.310181
C	-5.069585	3.870532	0.349976
H	-6.052819	3.675866	-0.091303
H	-5.105033	3.650210	1.415706
H	-4.835357	4.929786	0.204587
O	-3.379185	2.151615	0.247781
O	-3.827626	3.201722	-1.627218
C	4.362335	0.867850	0.178406
C	2.029679	1.544827	0.389900
O	5.573053	1.195305	-0.246881
N	4.002760	-0.352785	0.057138
N	1.735913	0.148711	0.636821
C	3.778823	3.353563	0.328264
H	3.013506	4.045896	0.696479
H	3.802231	3.432408	-0.763222
H	4.734298	3.695946	0.740897
C	3.455463	1.937724	0.795873
C	2.725564	-0.660094	0.488598

Continued 5-OH-6HThyH TS

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	2.593131	-1.964822	0.719002
H	1.894622	1.779136	-0.679191
H	5.787841	2.117776	-0.038270
H	1.687298	-2.141053	1.026163
H	-4.394140	3.906689	-1.979186
H	1.319784	2.165100	0.953464
O	3.666835	1.791362	2.187774
H	3.119154	2.431187	2.669522

5-OH-6HThyH PC:

Atoms	Coordinates (Angstroms)		
	X	Y	Z
O	-1.509015	-2.136797	0.826284
C	-0.690004	-3.077169	0.181789
C	0.706484	-2.507958	0.029984
O	0.742350	-1.502893	-1.023292
C	1.218995	-1.791865	1.281912
O	2.627780	-1.998080	1.333781
C	0.892482	-0.327880	0.981672
C	1.168578	-0.278646	-0.512300
H	-1.097104	-3.340874	-0.806164
H	-0.621540	-4.001752	0.779281
H	1.395774	-3.309903	-0.255188
H	0.742864	-2.165855	2.195435
H	-0.179187	-0.153045	1.117399
H	1.476709	0.387018	1.563581
C	3.213255	-1.612735	2.569159
H	4.271909	-1.868886	2.509435
H	3.105187	-0.536817	2.751298
H	2.754703	-2.169229	3.395281
C	-2.843307	-2.603002	0.965137
H	-2.867095	-3.523136	1.564372
H	-3.404989	-1.819336	1.474489
H	-3.293332	-2.782393	-0.018328
H	0.672611	0.530551	-1.048189
C	2.805974	-0.961611	-3.135049
H	3.200344	-0.634365	-4.103117
H	1.728363	-1.087909	-3.259175
C	3.091560	0.171214	-2.158330
H	2.570363	1.091591	-2.440175
H	4.165720	0.384534	-2.111182

Continued 5-OH-6HThyH PC

Atoms	Coordinates (Angstroms)		
	X	Y	Z
N	2.671949	-0.130968	-0.750971
H	3.000352	0.625522	-0.129249
C	3.455360	-2.281578	-2.728316
H	3.013855	-2.689344	-1.812180
H	3.317509	-3.033296	-3.508330
H	4.533281	-2.164526	-2.568836
H	3.119336	-0.987287	-0.388133
C	3.728594	2.463334	2.211317
C	4.620321	3.670512	2.316934
H	5.502256	3.431893	2.920791
H	4.938538	3.976030	1.321495
H	4.089757	4.497140	2.800177
O	3.459736	1.898519	1.173197
O	3.208170	1.987362	3.352279
C	-4.327117	0.911947	-0.561878
C	-2.091751	1.764820	-0.077853
O	-5.621486	0.936963	-0.257031
N	-3.829480	-0.199816	-0.943052
N	-1.587732	0.669353	-0.873298
C	-4.057136	3.184792	0.581261
H	-3.343210	4.004891	0.717741
H	-4.215982	2.711728	1.555480
H	-4.993871	3.638416	0.238986
C	-3.509199	2.202185	-0.450724
C	-2.467243	-0.189140	-1.231922
O	-2.109957	-1.264624	-1.943135
H	-2.081177	1.487789	0.990501
H	-5.921034	1.839600	-0.070229
H	-1.135264	-1.256202	-1.989957
H	3.487492	2.502601	4.124075
H	-1.423865	2.630516	-0.187142
O	-3.565479	2.747755	-1.758684
H	-2.969188	3.510971	-1.816180

6. The linear correlation of charge distribution at each stationary point calculated by ABEEM method and QM

Table S25. The linear correlation of charge distribution at each stationary point calculated by ABEEM method and QM on the monofunctional reaction pathway

Local conservation conditions 1		Local conservation conditions 2		Local conservation conditions 3	
Reaction steps	R	Reaction steps	R	Reaction steps	R
1	0.96	51	0.97	66	0.97
4	0.96	54	0.97	69	0.97
7	0.96	57	0.97	72	0.97
10	0.96	60	0.96	75	0.97
13	0.96	63	0.96	78	0.97
16	0.96	-	-	81	0.97
19	0.96	-	-	84	0.97
22	0.96	-	-	87	0.97
25	0.96	-	-	90	0.97
28	0.97	-	-	93	0.97
31	0.97	-	-	96	0.97
34	0.97	-	-	98	0.97
37	0.97	-	-	100	0.97
40	0.97	-	-	-	-
43	0.97	-	-	-	-
46	0.97	-	-	-	-
48	0.97	-	-	-	-