Supporting Information

Regio- and Stereo-controlled Diels-Alder Reaction Tethered by Asp-Thr Dipeptide

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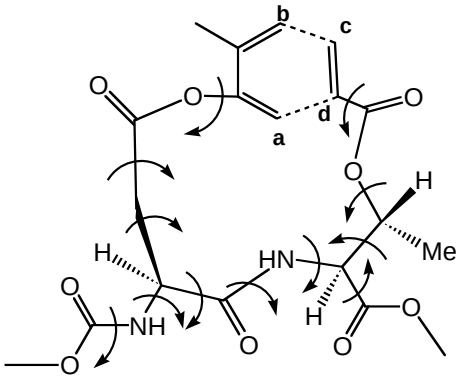
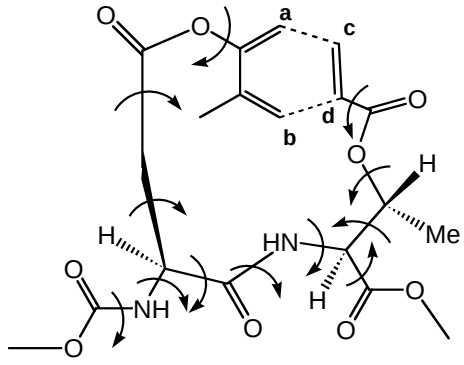
Calculation

All calculations were carried out for simplicity on a methylcarbamate derivative instead of the *t*-butoxycarbamate.

(1) MM2 transition structures were generated on a macromodel version 6.0.



regioisomers **2** and **3**



regioisomers **4** and **5**

torsional angle rotation

Regioisomers **2** and **3**	Regioisomers **4** and **5**
Monte Carlo (MCMM) : 3000 steps	Monte Carlo (MCMM) : 3000 steps
Closure distances a-d: 0.4 ~ 6.0 Å,	Closure distances a-c: 0.8 ~ 5.5 Å,
b-c: 0.8 ~ 5.5 Å	b-d: 0.4 Å ~ 6.0 Å
Force Field : MM2 TS model	Force Field : MM2 TS model
(see ref 11 in text)	

(2) The energies of the MM2 TSs were calculated by B3LYP/6-31G(d) on a Spartan. The lower energy TSs (within 30 kJ/mol from the lowest, 38 conformations for **2** and **3**, 28 conformations for **4** and **5**) were geometry optimized by PM3 and their energies were provided by a single point energy calculation using B3LYP/6-31G(d) on a Spartan.

(3) The lowest energy TSs that would produce **2a**-**5a** and **2b**-**5b** were fully optimized by B3LYP/6-31G(d) using a Gaussian 98 with an option, opt (calcall, TS, noeigentest), to provide **2A**-**5A** and **2B**-**5B** that have only one imaginary normal mode corresponding to the reaction coordinate.

(4) Energies of single point calculations based on B3LYP/6-31G(d)-optimized TSs using various theoretical models are shown below.

TS	B3LYP/6-31G(d) //PM3 (Hartrees)		Total Energy (Hartrees)	Relative Energy (kJ / mol)
2A	-1526.15044		-1526.15044	0.00
3A	-1526.14815		-1526.14815	6.02
4A	-1526.13720		-1526.13720	34.77
5A	-1526.13572		-1526.13572	38.65
2B	-1565.46390		-1565.46390	-2.05
3B	-1565.46312		-1565.46312	0.00
4B	-1565.45048		-1565.45048	33.18
5B	-1565.44903		-1565.44903	37.00

TS	B3LYP/6-31G(d) //B3LYP/6-31G(d) (Hartrees)	ZPE Correction (Hartrees)	Total Energy (Hartrees)	Relative Energy (kJ / mol)
2A	-1526.17677	0.45136	-1525.72541	0.00
3A	-1526.17730	0.45185	-1525.72545	-0.11
4A	-1526.17017	0.45276	-1525.71741	21.02
5A	-1526.16543	0.45216	-1525.71327	31.88
2B	-1565.49127	0.47927	-1565.01200	2.97
3B	-1565.49277	0.47964	-1565.01313	0.00
4B	-1565.48823	0.47939	-1565.00884	11.25
5B	-1565.47897	0.48030	-1564.99867	37.95

TS	B3LYP/6-31+G(d,p) //B3LYP/6-31G(d) (Hartrees)	ZPE Correction (Hartrees)	Total Energy (Hartrees)	Relative Energy (kJ / mol)
2A	-1526.27293	0.45136	-1525.82157	0.00
3A	-1526.27291	0.45185	-1525.82106	1.34
4A	-1526.26611	0.45276	-1525.81335	21.58
5A	-1526.26293	0.45216	-1525.81077	28.35
2B	-1565.58978	0.47927	-1565.11050	1.97
3B	-1565.59090	0.47964	-1565.11125	0.00
4B	-1565.58749	0.47939	-1565.10810	8.27
5B	-1565.57878	0.48030	-1565.09848	33.53

TS	B3LYP/6-311G(d,p) //B3LYP/6-31G(d) (Hartrees)	ZPE Correction (Hartrees)	Total Energy (Hartrees)	Relative Energy (kJ / mol)
2A	-1526.59842	0.45136	-1526.14706	0.00
3A	-1526.59825	0.45185	-1526.14640	1.74
4A	-1526.59199	0.45276	-1526.13923	20.56
5A	-1526.58731	0.45216	-1526.13515	31.27
2B	-1565.92248	0.47927	-1565.44321	1.48
3B	-1565.92341	0.47964	-1565.44377	0.00
4B	-1565.91968	0.47939	-1565.44029	9.14
5B	-1565.91058	0.48030	-1565.43028	35.42

TS	B3LYP/6-311+G(d,p) //B3LYP/6-31G(d) (Hartrees)	ZPE Correction (Hartrees)	Total Energy (Hartrees)	Relative Energy (kJ / mol)
2A	-1526.62636	0.45136	-1526.17500	0.00
3A	-1526.62616	0.45185	-1526.17431	1.81
4A	-1526.61956	0.45276	-1526.16680	21.53
5A	-1526.61639	0.45216	-1526.16423	28.26
2B	-1565.95002	0.47927	-1565.47075	1.54
3B	-1565.95098	0.47964	-1565.47133	0.00
4B	-1565.94807	0.47939	-1565.46869	6.95
5B	-1565.93921	0.48030	-1565.45891	32.62

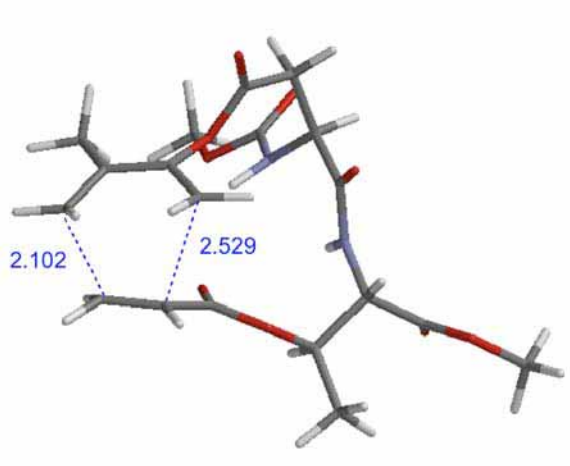
TS	MP2/6-31G(d,p) //B3LYP/6-31G(d) (Hartrees)	ZPE Correction (Hartrees)	Total Energy (Hartrees)	Relative Energy (kJ / mol)
2A	-1521.86166	0.45136	-1521.41030	0.00
3A	-1521.86138	0.45185	-1521.40953	2.02
4A	-1521.85266	0.45276	-1521.39990	27.30
5A	-1521.85125	0.45216	-1521.39909	29.44
2B	-1561.04881	0.47927	-1560.56954	-0.06
3B	-1561.04915	0.47964	-1560.56951	0.00
4B	-1561.04530	0.47939	-1560.56591	9.45
5B	-1561.03801	0.48030	-1560.55771	31.00

TS	MP2/6-31+G(d,p) //B3LYP/6-31G(d) (Hartrees)	ZPE Correction (Hartrees)	Total Energy (Hartrees)	Relative Energy (kJ / mol)
2A	-1521.96283	0.45136	-1521.51147	0.00
3A	-1521.96234	0.45185	-1521.51049	2.56
4A	-1521.95323	0.45276	-1521.50047	28.87
5A	-1521.95355	0.45216	-1521.50139	26.46
2B	-1561.15202	0.47927	-1560.67275	-0.32
3B	-1561.15227	0.47964	-1560.67263	0.00
4B	-1561.14795	0.47939	-1560.66856	10.67
5B	-1561.14210	0.48030	-1560.66180	28.42

Transition structure 2A

B3LYP/6-31G(d) optimized structure.

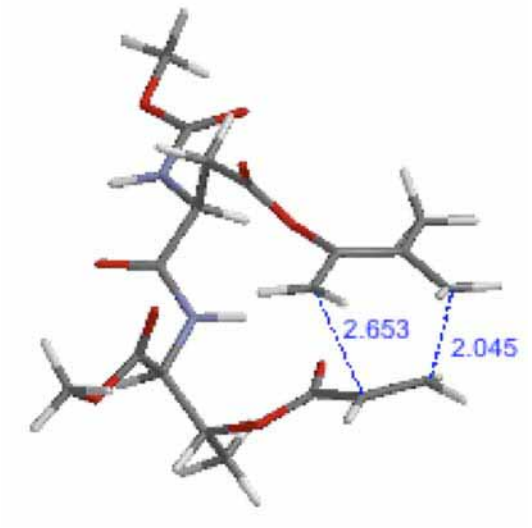
B3LYP/6-31G(d) Energy (Hartrees)	-1526.17677
ZPE corrections (Hartrees)	0.45136
Imaginary Frequency	452.7*i* cm^{-1}
B3LYP/6-31+G(d,p) Energy	-1526.27293
B3LYP/6-311G(d,p) Energy	-1526.59842
B3LYP/6-311+G(d,p) Energy	-1526.62636
MP2/6-31G(d,p) Energy	-1521.86166
MP2/6-31+G(d,p) Energy	-1521.96283



ATOM	1	C	UNK	1	-0.241	1.945	1.097	ATOM	29	H	UNK	1	-2.123	2.611	1.905
ATOM	2	C	UNK	1	0.776	0.801	1.284	ATOM	30	H	UNK	1	2.653	-0.908	1.139
ATOM	3	O	UNK	1	0.829	0.155	2.327	ATOM	31	H	UNK	1	2.063	-0.905	-1.853
ATOM	4	C	UNK	1	-1.381	1.835	2.129	ATOM	32	H	UNK	1	3.253	-3.117	-1.965
ATOM	5	C	UNK	1	-2.077	0.491	2.192	ATOM	33	H	UNK	1	4.389	-1.798	-1.640
ATOM	6	O	UNK	1	-2.609	0.013	3.159	ATOM	34	H	UNK	1	3.875	-2.873	-0.320
ATOM	7	O	UNK	1	-2.066	-0.108	0.951	ATOM	35	H	UNK	1	6.892	-0.054	1.244
ATOM	8	H	UNK	1	1.448	1.172	-0.605	ATOM	36	H	UNK	1	6.597	0.232	-0.505
ATOM	9	N	UNK	1	1.598	0.607	0.222	ATOM	37	H	UNK	1	6.196	1.502	0.677
ATOM	10	C	UNK	1	2.632	-0.405	0.171	ATOM	38	H	UNK	1	-0.363	-4.125	-0.391
ATOM	11	C	UNK	1	3.968	0.294	-0.091	ATOM	39	H	UNK	1	-2.327	-4.438	-1.864
ATOM	12	O	UNK	1	4.122	1.150	-0.937	ATOM	40	H	UNK	1	-2.170	-2.698	-2.429
ATOM	13	C	UNK	1	2.358	-1.444	-0.948	ATOM	41	H	UNK	1	-4.494	-3.205	-1.228
ATOM	14	O	UNK	1	1.272	-2.302	-0.551	ATOM	42	H	UNK	1	-3.482	-3.849	0.141
ATOM	15	C	UNK	1	3.545	-2.362	-1.230	ATOM	43	H	UNK	1	-4.971	-0.903	-1.429
ATOM	16	O	UNK	1	4.942	-0.169	0.710	ATOM	44	H	UNK	1	-4.691	0.090	0.011
ATOM	17	C	UNK	1	6.241	0.423	0.511	ATOM	45	H	UNK	1	-3.503	0.087	-1.288
ATOM	18	C	UNK	1	-0.813	-3.282	-0.903	ATOM	46	H	UNK	1	-1.888	-3.431	1.426
ATOM	19	C	UNK	1	-1.977	-3.431	-1.653	ATOM	47	H	UNK	1	-0.709	-2.087	1.892
ATOM	20	C	UNK	1	0.031	-2.103	-1.098	ATOM	48	N	UNK	1	-0.666	2.026	-0.293
ATOM	21	O	UNK	1	-0.287	-1.084	-1.694	ATOM	49	C	UNK	1	-1.112	3.216	-0.804
ATOM	22	C	UNK	1	-2.443	-1.454	0.834	ATOM	50	O	UNK	1	-1.000	4.302	-0.261
ATOM	23	C	UNK	1	-3.503	-1.709	-0.071	ATOM	51	H	UNK	1	-0.991	1.172	-0.736
ATOM	24	C	UNK	1	-3.695	-3.013	-0.516	ATOM	52	O	UNK	1	-1.685	3.017	-2.018
ATOM	25	C	UNK	1	-4.204	-0.549	-0.735	ATOM	53	C	UNK	1	-2.139	4.211	-2.670
ATOM	26	C	UNK	1	-1.588	-2.397	1.336	ATOM	54	H	UNK	1	-2.570	3.878	-3.615
ATOM	27	H	UNK	1	0.280	2.887	1.304	ATOM	55	H	UNK	1	-2.892	4.722	-2.064
ATOM	28	H	UNK	1	-0.998	2.031	3.132	ATOM	56	H	UNK	1	-1.305	4.895	-2.850

Transition structure 3A

B3LYP/6-31G(d) optimized structure.	
B3LYP/6-31G(d) Energy (Hartrees)	-1526.17730
ZPE corrections (Hartrees)	0.45185
Imaginary Frequency	437.8*i* cm^{-1}
B3LYP/6-31+G(d,p) Energy	-1526.27291
B3LYP/6-311G(d,p) Energy	-1526.59825
B3LYP/6-311+G(d,p) Energy	-1526.62616
MP2/6-31G(d,p) Energy	-1521.86138
MP2/6-31+G(d,p) Energy	-1521.96234

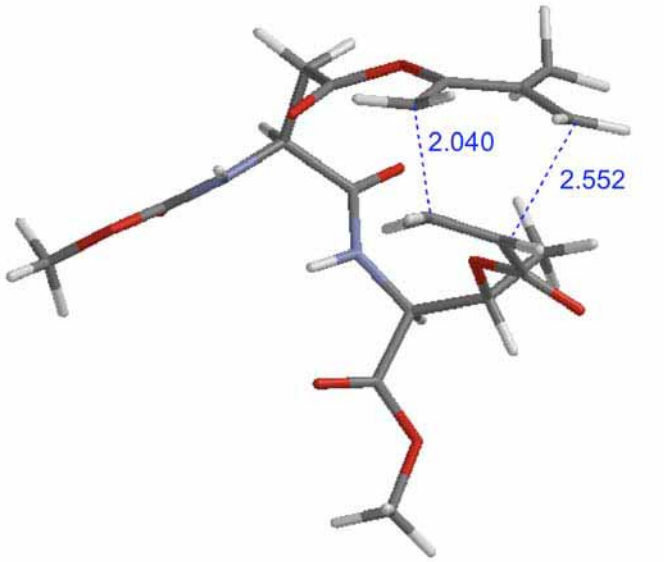


ATOM	1	C	UNK	1	0.906	-0.944	-1.725	ATOM	29	H	UNK	1	1.565	-2.695	-0.605
ATOM	2	C	UNK	1	1.697	0.048	-0.862	ATOM	30	H	UNK	1	2.507	2.235	0.401
ATOM	3	O	UNK	1	2.921	-0.038	-0.766	ATOM	31	H	UNK	1	1.266	3.528	1.999
ATOM	4	C	UNK	1	0.624	-2.256	-0.946	ATOM	32	H	UNK	1	-0.271	4.790	0.494
ATOM	5	C	UNK	1	-0.301	-2.196	0.254	ATOM	33	H	UNK	1	1.316	4.461	-0.221
ATOM	6	O	UNK	1	-0.278	-2.967	1.177	ATOM	34	H	UNK	1	-0.108	3.530	-0.743
ATOM	7	O	UNK	1	-1.228	-1.187	0.115	ATOM	35	H	UNK	1	3.976	1.656	4.468
ATOM	8	H	UNK	1	-0.050	1.012	-0.302	ATOM	36	H	UNK	1	2.422	0.775	4.644
ATOM	9	N	UNK	1	0.964	0.988	-0.219	ATOM	37	H	UNK	1	3.759	0.034	3.728
ATOM	10	C	UNK	1	1.575	1.815	0.797	ATOM	38	H	UNK	1	-4.784	1.838	2.537
ATOM	11	C	UNK	1	1.968	0.974	2.024	ATOM	39	H	UNK	1	-4.160	1.965	0.820
ATOM	12	O	UNK	1	1.559	-0.135	2.281	ATOM	40	H	UNK	1	-4.391	-0.534	2.616
ATOM	13	C	UNK	1	0.691	3.006	1.230	ATOM	41	H	UNK	1	-5.484	-0.215	1.199
ATOM	14	O	UNK	1	-0.471	2.569	1.988	ATOM	42	H	UNK	1	-4.875	-0.855	-0.987
ATOM	15	C	UNK	1	0.380	3.998	0.110	ATOM	43	H	UNK	1	-3.288	-0.146	-1.363
ATOM	16	O	UNK	1	2.835	1.656	2.795	ATOM	44	H	UNK	1	-3.447	-1.890	-1.193
ATOM	17	C	UNK	1	3.272	0.977	3.987	ATOM	45	H	UNK	1	-2.429	-0.617	3.220
ATOM	18	C	UNK	1	-2.664	1.831	2.321	ATOM	46	H	UNK	1	-0.678	-0.645	2.627
ATOM	19	C	UNK	1	-3.967	1.661	1.843	ATOM	47	N	UNK	1	1.730	-1.213	-2.889
ATOM	20	C	UNK	1	-1.597	2.099	1.375	ATOM	48	C	UNK	1	1.232	-1.835	-3.989
ATOM	21	O	UNK	1	-1.689	1.926	0.159	ATOM	49	O	UNK	1	0.064	-2.156	-4.148
ATOM	22	C	UNK	1	-2.168	-0.961	1.134	ATOM	50	H	UNK	1	2.728	-1.080	-2.778
ATOM	23	C	UNK	1	-3.504	-0.809	0.677	ATOM	51	O	UNK	1	2.218	-2.045	-4.902
ATOM	24	C	UNK	1	-4.461	-0.303	1.558	ATOM	52	C	UNK	1	1.789	-2.686	-6.109
ATOM	25	C	UNK	1	-3.801	-0.932	-0.796	ATOM	53	H	UNK	1	2.687	-2.786	-6.720
ATOM	26	C	UNK	1	-1.736	-0.653	2.392	ATOM	54	H	UNK	1	1.360	-3.670	-5.897
ATOM	27	H	UNK	1	-0.042	-0.513	-2.056	ATOM	55	H	UNK	1	1.041	-2.079	-6.627
ATOM	28	H	UNK	1	0.170	-2.953	-1.661	ATOM	56	H	UNK	1	-2.453	1.949	3.377

Transition structure 4A

B3LYP/6-31G(d) optimized structure.

B3LYP/6-31G(d) Energy (Hartrees)	-1526.17017
ZPE corrections (Hartrees)	0.45276
Imaginary Frequency	479.9*i* cm^{-1}
B3LYP/6-31+G(d,p) Energy	-1526.26611
B3LYP/6-311G(d,p) Energy	-1526.59199
B3LYP/6-311+G(d,p) Energy	-1526.61956
MP2/6-31G(d,p) Energy	-1521.85266
MP2/6-31+G(d,p) Energy	-1521.95323

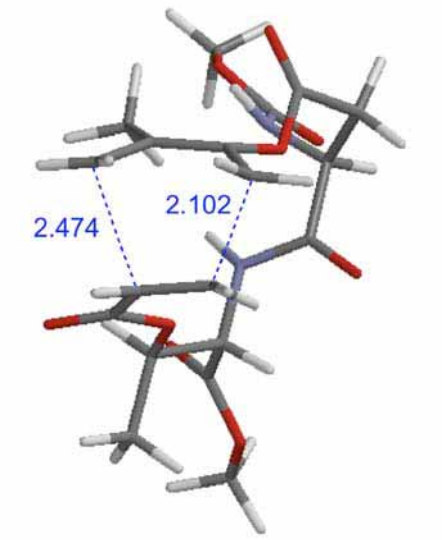


ATOM	1	C	UNK	1	-1.981	-1.478	1.112
ATOM	2	C	UNK	1	-1.100	-0.296	1.589
ATOM	3	O	UNK	1	-0.617	-0.322	2.718
ATOM	4	C	UNK	1	-1.104	-2.750	0.978
ATOM	5	C	UNK	1	-0.135	-2.623	-0.183
ATOM	6	O	UNK	1	-0.487	-2.444	-1.335
ATOM	7	O	UNK	1	1.145	-2.695	0.239
ATOM	8	H	UNK	1	-1.412	0.637	-0.197
ATOM	9	N	UNK	1	-0.898	0.682	0.677
ATOM	10	C	UNK	1	-0.245	1.953	0.937
ATOM	11	C	UNK	1	-0.756	2.919	-0.135
ATOM	12	O	UNK	1	-1.425	2.592	-1.093
ATOM	13	C	UNK	1	1.316	1.934	0.951
ATOM	14	O	UNK	1	1.726	1.020	-0.087
ATOM	15	C	UNK	1	1.916	1.570	2.305
ATOM	16	O	UNK	1	-0.367	4.176	0.120
ATOM	17	C	UNK	1	-0.769	5.164	-0.848
ATOM	18	C	UNK	1	3.197	0.377	-1.812
ATOM	19	C	UNK	1	2.204	-0.385	-2.436
ATOM	20	C	UNK	1	2.932	1.280	-0.689
ATOM	21	O	UNK	1	3.667	2.185	-0.334
ATOM	22	C	UNK	1	2.279	-2.412	-0.536
ATOM	23	C	UNK	1	3.350	-1.913	0.253
ATOM	24	C	UNK	1	4.428	-1.341	-0.382
ATOM	25	C	UNK	1	3.219	-1.864	1.759
ATOM	26	C	UNK	1	2.271	-2.360	-1.928
ATOM	27	H	UNK	1	-2.694	-1.642	1.925
ATOM	28	H	UNK	1	-0.567	-2.907	1.913
ATOM	29	H	UNK	1	-1.758	-3.608	0.787
ATOM	30	H	UNK	1	-0.564	2.336	1.915
ATOM	31	H	UNK	1	1.671	2.930	0.678
ATOM	32	H	UNK	1	3.005	1.539	2.218
ATOM	33	H	UNK	1	1.658	2.348	3.034
ATOM	34	H	UNK	1	1.530	0.622	2.679
ATOM	35	H	UNK	1	-0.364	6.108	-0.484
ATOM	36	H	UNK	1	-0.359	4.921	-1.831
ATOM	37	H	UNK	1	-1.859	5.209	-0.913
ATOM	38	H	UNK	1	4.139	0.577	-2.311
ATOM	39	H	UNK	1	2.335	-0.605	-3.493
ATOM	40	H	UNK	1	1.175	-0.229	-2.133
ATOM	41	H	UNK	1	4.694	-1.564	-1.405
ATOM	42	H	UNK	1	5.195	-0.837	0.199
ATOM	43	H	UNK	1	3.250	-2.877	2.178
ATOM	44	H	UNK	1	4.044	-1.296	2.196
ATOM	45	H	UNK	1	2.276	-1.415	2.077
ATOM	46	H	UNK	1	3.229	-2.519	-2.409
ATOM	47	H	UNK	1	1.419	-2.747	-2.468
ATOM	48	N	UNK	1	-2.737	-1.231	-0.101
ATOM	49	C	UNK	1	-4.061	-0.880	-0.043
ATOM	50	O	UNK	1	-4.672	-0.600	0.972
ATOM	51	H	UNK	1	-2.363	-1.580	-0.977
ATOM	52	O	UNK	1	-4.591	-0.878	-1.292
ATOM	53	C	UNK	1	-5.969	-0.487	-1.357
ATOM	54	H	UNK	1	-6.236	-0.544	-2.413
ATOM	55	H	UNK	1	-6.593	-1.165	-0.768
ATOM	56	H	UNK	1	-6.101	0.532	-0.984

Transition structure 5A

B3LYP/6-31G(d) optimized structure.

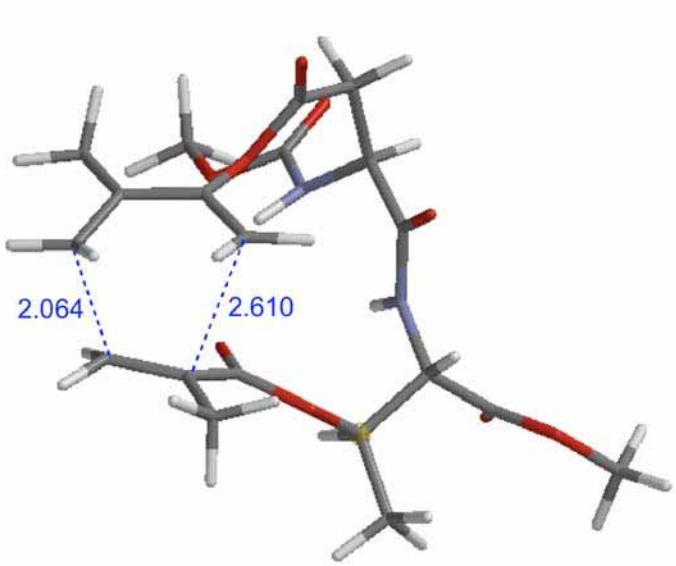
B3LYP/6-31G(d) Energy	-1526.16543 (Hartrees)
ZPE corrections	0.45216 (Hartrees)
Imaginary Frequency	478.3*i* cm^{-1}
B3LYP/6-31+G(d,p) Energy	-1526.26293
B3LYP/6-311G(d,p) Energy	-1526.58731
B3LYP/6-311+G(d,p) Energy	-1526.61639
MP2/6-31G(d,p) Energy	-1521.85125
MP2/6-31+G(d,p) Energy	-1521.95355



ATOM	1	C	UNK	1	1.725	-1.366	-1.235	ATOM	29	H	UNK	1	1.610	-3.456	-1.816
ATOM	2	C	UNK	1	0.902	-0.070	-1.433	ATOM	30	H	UNK	1	-0.054	2.233	-1.463
ATOM	3	O	UNK	1	0.443	0.194	-2.535	ATOM	31	H	UNK	1	-0.701	2.081	1.534
ATOM	4	C	UNK	1	0.943	-2.593	-1.764	ATOM	32	H	UNK	1	-2.322	3.920	1.052
ATOM	5	C	UNK	1	-0.227	-2.964	-0.872	ATOM	33	H	UNK	1	-0.660	4.473	0.817
ATOM	6	O	UNK	1	-0.256	-3.895	-0.100	ATOM	34	H	UNK	1	-1.661	4.081	-0.597
ATOM	7	O	UNK	1	-1.226	-2.059	-1.033	ATOM	35	H	UNK	1	3.511	4.506	-0.624
ATOM	8	H	UNK	1	1.341	0.505	0.476	ATOM	36	H	UNK	1	2.480	5.760	-1.393
ATOM	9	N	UNK	1	0.766	0.723	-0.330	ATOM	37	H	UNK	1	2.384	5.457	0.375
ATOM	10	C	UNK	1	0.248	2.078	-0.426	ATOM	38	H	UNK	1	-5.082	0.518	0.828
ATOM	11	C	UNK	1	1.388	3.029	-0.054	ATOM	39	H	UNK	1	-3.287	0.347	-1.670
ATOM	12	O	UNK	1	2.110	2.854	0.906	ATOM	40	H	UNK	1	-5.043	-0.171	-1.545
ATOM	13	C	UNK	1	-0.962	2.342	0.503	ATOM	41	H	UNK	1	-3.650	-1.138	2.692
ATOM	14	O	UNK	1	-2.008	1.454	0.054	ATOM	42	H	UNK	1	-4.583	-1.802	1.262
ATOM	15	C	UNK	1	-1.431	3.796	0.435	ATOM	43	H	UNK	1	-0.435	-1.025	1.321
ATOM	16	O	UNK	1	1.489	4.064	-0.901	ATOM	44	H	UNK	1	-1.347	-1.200	2.827
ATOM	17	C	UNK	1	2.540	5.006	-0.608	ATOM	45	H	UNK	1	-0.670	-2.634	2.032
ATOM	18	C	UNK	1	-4.148	0.482	0.278	ATOM	46	H	UNK	1	-3.433	-2.175	-2.177
ATOM	19	C	UNK	1	-4.101	0.015	-1.035	ATOM	47	H	UNK	1	-4.512	-2.325	-0.707
ATOM	20	C	UNK	1	-3.084	1.295	0.887	ATOM	48	N	UNK	1	2.222	-1.577	0.118
ATOM	21	O	UNK	1	-3.144	1.803	1.994	ATOM	49	C	UNK	1	3.573	-1.487	0.380
ATOM	22	C	UNK	1	-2.428	-2.117	-0.310	ATOM	50	O	UNK	1	4.404	-1.017	-0.373
ATOM	23	C	UNK	1	-2.428	-1.833	1.081	ATOM	51	H	UNK	1	1.699	-2.189	0.733
ATOM	24	C	UNK	1	-3.628	-1.498	1.668	ATOM	52	O	UNK	1	3.832	-1.977	1.615
ATOM	25	C	UNK	1	-1.145	-1.662	1.858	ATOM	53	C	UNK	1	5.206	-1.888	2.023
ATOM	26	C	UNK	1	-3.557	-2.014	-1.110	ATOM	54	H	UNK	1	5.238	-2.321	3.023
ATOM	27	H	UNK	1	2.606	-1.235	-1.872	ATOM	55	H	UNK	1	5.847	-2.452	1.340
ATOM	28	H	UNK	1	0.579	-2.340	-2.763	ATOM	56	H	UNK	1	5.534	-0.846	2.045

Transition structure 2B

B3LYP/6-31G(d) optimized structure.	
B3LYP/6-31G(d) Energy (Hartrees)	-1565.49127
ZPE corrections (Hartrees)	0.47927
Imaginary Frequency	453.2*i* cm^{-1}
B3LYP/6-31+G(d,p) Energy	-1565.58978
B3LYP/6-311G(d,p) Energy	-1565.92248
B3LYP/6-311+G(d,p) Energy	-1565.95002
MP2/6-31G(d,p) Energy	-1561.04881
MP2/6-31+G(d,p) Energy	-1561.15202

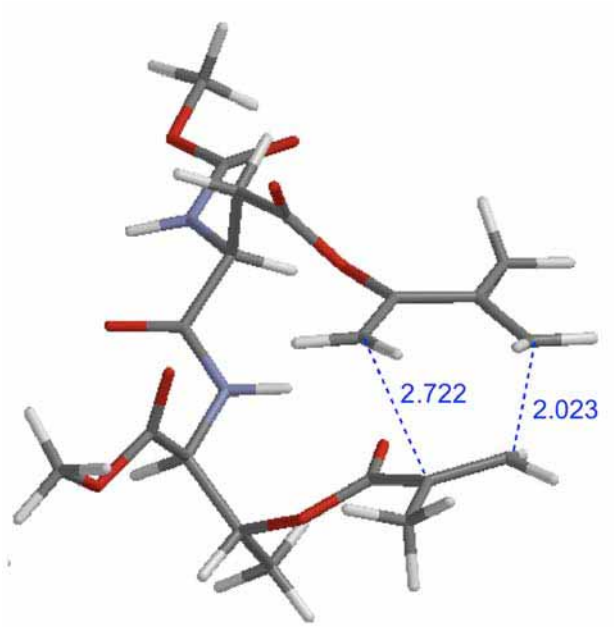


ATOM	1	C	UNK	1	-1.111	0.455	2.061
ATOM	2	C	UNK	1	-0.036	-0.586	1.688
ATOM	3	O	UNK	1	-0.270	-1.791	1.720
ATOM	4	C	UNK	1	-2.518	-0.173	2.022
ATOM	5	C	UNK	1	-2.877	-0.888	0.736
ATOM	6	O	UNK	1	-3.630	-1.819	0.630
ATOM	7	O	UNK	1	-2.250	-0.283	-0.332
ATOM	8	H	UNK	1	1.244	0.959	1.331
ATOM	9	N	UNK	1	1.166	-0.050	1.359
ATOM	10	C	UNK	1	2.326	-0.826	0.972
ATOM	11	C	UNK	1	3.465	-0.488	1.937
ATOM	12	O	UNK	1	3.754	0.643	2.264
ATOM	13	C	UNK	1	2.762	-0.512	-0.485
ATOM	14	O	UNK	1	1.853	-1.140	-1.408
ATOM	15	C	UNK	1	4.152	-1.041	-0.832
ATOM	16	O	UNK	1	4.111	-1.590	2.355
ATOM	17	C	UNK	1	5.216	-1.358	3.250
ATOM	18	C	UNK	1	0.372	-1.052	-3.229
ATOM	19	C	UNK	1	-0.365	-0.260	-4.118
ATOM	20	C	UNK	1	0.902	-0.377	-2.035
ATOM	21	O	UNK	1	0.591	0.744	-1.652
ATOM	22	C	UNK	1	-2.222	-0.929	-1.576
ATOM	23	C	UNK	1	-2.722	-0.167	-2.662
ATOM	24	C	UNK	1	-2.399	-0.570	-3.957
ATOM	25	C	UNK	1	-3.334	1.186	-2.398
ATOM	26	C	UNK	1	-1.473	-2.065	-1.685
ATOM	27	H	UNK	1	-0.930	0.758	3.099
ATOM	28	H	UNK	1	-2.623	-0.907	2.823
ATOM	29	H	UNK	1	-3.251	0.621	2.208
ATOM	30	H	UNK	1	2.063	-1.882	1.055
ATOM	31	H	UNK	1	2.714	0.571	-0.632
ATOM	32	H	UNK	1	4.356	-0.857	-1.890
ATOM	33	H	UNK	1	4.923	-0.531	-0.245
ATOM	34	H	UNK	1	4.224	-2.117	-0.647
ATOM	35	H	UNK	1	5.605	-2.346	3.493
ATOM	36	H	UNK	1	5.982	-0.750	2.761
ATOM	37	H	UNK	1	4.873	-0.844	4.151
ATOM	38	H	UNK	1	-0.367	-0.554	-5.165
ATOM	39	H	UNK	1	-0.384	0.809	-3.939
ATOM	40	H	UNK	1	-2.780	0.023	-4.786
ATOM	41	H	UNK	1	-2.299	-1.625	-4.187
ATOM	42	H	UNK	1	-3.656	1.657	-3.331
ATOM	43	H	UNK	1	-4.210	1.097	-1.744
ATOM	44	H	UNK	1	-2.630	1.860	-1.895
ATOM	45	H	UNK	1	-1.526	-2.688	-2.566
ATOM	46	H	UNK	1	-1.000	-2.489	-0.806
ATOM	47	N	UNK	1	-0.945	1.661	1.263
ATOM	48	C	UNK	1	-1.412	2.860	1.732
ATOM	49	O	UNK	1	-1.779	3.075	2.874
ATOM	50	H	UNK	1	-0.867	1.548	0.257
ATOM	51	O	UNK	1	-1.390	3.789	0.742
ATOM	52	C	UNK	1	-1.812	5.100	1.141
ATOM	53	H	UNK	1	-1.744	5.712	0.241
ATOM	54	H	UNK	1	-2.840	5.080	1.514
ATOM	55	H	UNK	1	-1.158	5.497	1.922
ATOM	56	C	UNK	1	0.927	-2.391	-3.662
ATOM	57	H	UNK	1	0.276	-2.850	-4.416
ATOM	58	H	UNK	1	1.921	-2.279	-4.117
ATOM	59	H	UNK	1	1.034	-3.090	-2.830

Transition structure <u>3B</u>

B3LYP/6-31G(d) optimized structure.

B3LYP/6-31G(d) Energy (Hartrees)	-1565.49277
ZPE corrections (Hartrees)	0.47964
Imaginary Frequency	437.0 *i* cm^{-1}
B3LYP/6-31+G(d,p) Energy	-1565.59090
B3LYP/6-311G(d,p) Energy	-1565.92341
B3LYP/6-311+G(d,p) Energy	-1565.95098
MP2/6-31G(d,p) Energy	-1561.04915
MP2/6-31+G(d,p) Energy	-1561.15227

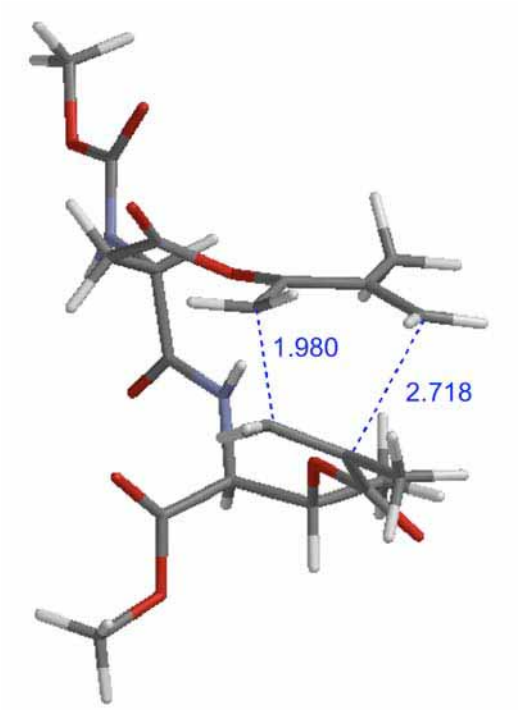


ATOM	1	C	UNK	1	2.325	0.173	0.003
ATOM	2	C	UNK	1	1.440	1.410	-0.213
ATOM	3	O	UNK	1	1.838	2.531	0.103
ATOM	4	C	UNK	1	2.209	-0.347	1.460
ATOM	5	C	UNK	1	0.880	-0.921	1.912
ATOM	6	O	UNK	1	0.497	-0.947	3.052
ATOM	7	O	UNK	1	0.200	-1.481	0.855
ATOM	8	H	UNK	1	-0.089	0.233	-0.975
ATOM	9	N	UNK	1	0.219	1.178	-0.751
ATOM	10	C	UNK	1	-0.769	2.231	-0.790
ATOM	11	C	UNK	1	-1.246	2.591	0.628
ATOM	12	O	UNK	1	-1.092	1.915	1.619
ATOM	13	C	UNK	1	-1.980	1.902	-1.692
ATOM	14	O	UNK	1	-2.824	0.865	-1.118
ATOM	15	C	UNK	1	-1.627	1.682	-3.162
ATOM	16	O	UNK	1	-1.880	3.778	0.615
ATOM	17	C	UNK	1	-2.384	4.225	1.888
ATOM	18	C	UNK	1	-3.568	-1.329	-0.712
ATOM	19	C	UNK	1	-3.476	-2.684	-1.068
ATOM	20	C	UNK	1	-2.516	-0.461	-1.228
ATOM	21	O	UNK	1	-1.465	-0.870	-1.728
ATOM	22	C	UNK	1	-1.072	-2.041	1.054
ATOM	23	C	UNK	1	-1.252	-3.312	0.443
ATOM	24	C	UNK	1	-2.548	-3.822	0.324
ATOM	25	C	UNK	1	-0.105	-3.948	-0.298
ATOM	26	C	UNK	1	-2.075	-1.272	1.563
ATOM	27	H	UNK	1	2.054	-0.630	-0.686
ATOM	28	H	UNK	1	2.953	-1.147	1.566
ATOM	29	H	UNK	1	2.473	0.448	2.162
ATOM	30	H	UNK	1	-0.306	3.137	-1.197
ATOM	31	H	UNK	1	-2.635	2.774	-1.624
ATOM	32	H	UNK	1	-2.534	1.437	-3.724
ATOM	33	H	UNK	1	-1.217	2.613	-3.570
ATOM	34	H	UNK	1	-0.903	0.881	-3.305
ATOM	35	H	UNK	1	-2.839	5.197	1.696
ATOM	36	H	UNK	1	-3.126	3.521	2.273
ATOM	37	H	UNK	1	-1.567	4.316	2.607
ATOM	38	H	UNK	1	-4.396	-3.265	-1.034
ATOM	39	H	UNK	1	-2.807	-2.938	-1.883
ATOM	40	H	UNK	1	-3.281	-3.608	1.095
ATOM	41	H	UNK	1	-2.659	-4.811	-0.114
ATOM	42	H	UNK	1	-0.370	-4.950	-0.645
ATOM	43	H	UNK	1	0.179	-3.342	-1.168
ATOM	44	H	UNK	1	0.784	-4.026	0.336
ATOM	45	H	UNK	1	-3.022	-1.711	1.842
ATOM	46	H	UNK	1	-1.888	-0.251	1.874
ATOM	47	N	UNK	1	3.684	0.595	-0.279
ATOM	48	C	UNK	1	4.689	-0.301	-0.457
ATOM	49	O	UNK	1	4.554	-1.515	-0.473
ATOM	50	H	UNK	1	3.884	1.582	-0.167
ATOM	51	O	UNK	1	5.874	0.343	-0.626
ATOM	52	C	UNK	1	6.998	-0.519	-0.836
ATOM	53	H	UNK	1	7.857	0.144	-0.944
ATOM	54	H	UNK	1	7.139	-1.190	0.016
ATOM	55	H	UNK	1	6.865	-1.120	-1.741
ATOM	56	C	UNK	1	-4.818	-0.759	-0.084
ATOM	57	H	UNK	1	-5.335	-1.525	0.506
ATOM	58	H	UNK	1	-4.606	0.092	0.568
ATOM	59	H	UNK	1	-5.525	-0.409	-0.849

Transition structure <u>4B</u>

B3LYP/6-31G(d) optimized structure.

B3LYP/6-31G(d) Energy	-1565.48823 (Hartrees)
ZPE corrections	0.47939 (Hartrees)
Imaginary Frequency	448.8 *i* cm^{-1}
B3LYP/6-31+G(d,p) Energy	-1565.58749
B3LYP/6-311G(d,p) Energy	-1565.91968
B3LYP/6-311+G(d,p) Energy	-1565.94807
MP2/6-31G(d,p) Energy	-1561.04530
MP2/6-31+G(d,p) Energy	-1561.14795



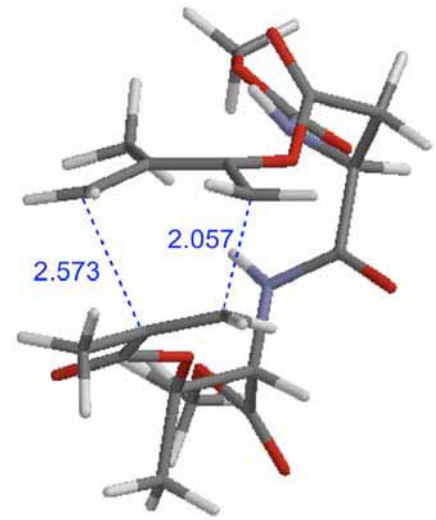
ATOM	1	C	UNK	1	-2.495	0.150	0.022
ATOM	2	C	UNK	1	-1.621	1.361	0.420
ATOM	3	O	UNK	1	-2.091	2.490	0.517
ATOM	4	C	UNK	1	-2.170	-0.371	-1.414
ATOM	5	C	UNK	1	-1.184	-1.513	-1.577
ATOM	6	O	UNK	1	-1.158	-2.259	-2.520
ATOM	7	O	UNK	1	-0.290	-1.576	-0.525
ATOM	8	H	UNK	1	0.010	0.156	0.358
ATOM	9	N	UNK	1	-0.317	1.066	0.663
ATOM	10	C	UNK	1	0.694	2.097	0.750
ATOM	11	C	UNK	1	1.051	2.606	-0.657
ATOM	12	O	UNK	1	0.697	2.091	-1.696
ATOM	13	C	UNK	1	1.946	1.539	1.462
ATOM	14	O	UNK	1	2.283	0.370	0.679
ATOM	15	C	UNK	1	1.707	1.208	2.931
ATOM	16	O	UNK	1	1.827	3.701	-0.580
ATOM	17	C	UNK	1	2.241	4.264	-1.840
ATOM	18	C	UNK	1	3.846	-1.077	-0.334
ATOM	19	C	UNK	1	3.069	-1.046	-1.507
ATOM	20	C	UNK	1	3.562	-0.132	0.752
ATOM	21	O	UNK	1	4.358	0.231	1.602
ATOM	22	C	UNK	1	0.860	-2.376	-0.531
ATOM	23	C	UNK	1	1.302	-2.726	0.775
ATOM	24	C	UNK	1	2.602	-3.123	0.953
ATOM	25	C	UNK	1	0.386	-2.521	1.961
ATOM	26	C	UNK	1	1.674	-2.443	-1.664
ATOM	27	H	UNK	1	-2.340	-0.667	0.735
ATOM	28	H	UNK	1	-3.098	-0.722	-1.867
ATOM	29	H	UNK	1	-1.797	0.452	-2.039
ATOM	30	H	UNK	1	0.296	2.939	1.321

ATOM	31	H	UNK	1	2.764	2.259	1.374
ATOM	32	H	UNK	1	2.614	0.776	3.358
ATOM	33	H	UNK	1	1.464	2.125	3.481
ATOM	34	H	UNK	1	0.878	0.506	3.051
ATOM	35	H	UNK	1	2.837	5.140	-1.585
ATOM	36	H	UNK	1	2.837	3.541	-2.402
ATOM	37	H	UNK	1	1.368	4.549	-2.432
ATOM	38	H	UNK	1	2.398	-0.204	-1.644
ATOM	39	H	UNK	1	3.574	-1.359	-2.419
ATOM	40	H	UNK	1	3.232	-3.457	0.144
ATOM	41	H	UNK	1	2.987	-3.297	1.954
ATOM	42	H	UNK	1	0.877	-2.838	2.884
ATOM	43	H	UNK	1	0.085	-1.475	2.077
ATOM	44	H	UNK	1	-0.533	-3.107	1.847
ATOM	45	H	UNK	1	2.345	-3.293	-1.716
ATOM	46	H	UNK	1	1.236	-2.179	-2.619
ATOM	47	N	UNK	1	-3.867	0.599	0.105
ATOM	48	C	UNK	1	-4.882	-0.289	0.271
ATOM	49	O	UNK	1	-4.760	-1.504	0.232
ATOM	50	H	UNK	1	-4.006	1.591	0.263
ATOM	51	O	UNK	1	-6.058	0.362	0.468
ATOM	52	C	UNK	1	-7.196	-0.494	0.627
ATOM	53	H	UNK	1	-8.046	0.176	0.763
ATOM	54	H	UNK	1	-7.340	-1.119	-0.259
ATOM	55	H	UNK	1	-7.078	-1.141	1.501
ATOM	56	C	UNK	1	5.207	-1.731	-0.305
ATOM	57	H	UNK	1	5.236	-2.610	-0.959
ATOM	58	H	UNK	1	5.983	-1.037	-0.657
ATOM	59	H	UNK	1	5.490	-2.033	0.706

Transition structure <u>5B</u>

B3LYP/6-31G(d) optimized structure.

B3LYP/6-31G(d) Energy	-1565.47897 (Hartrees)
ZPE corrections	0.48030 (Hartrees)
Imaginary Frequency	472.8*i* cm^{-1}
B3LYP/6-31+G(d,p) Energy	-1565.57878
B3LYP/6-311G(d,p) Energy	-1565.91058
B3LYP/6-311+G(d,p) Energy	-1565.93921
MP2/6-31G(d,p) Energy	-1561.03801
MP2/6-31+G(d,p) Energy	-1561.14210



ATOM	1	C	UNK	1	2.450	-1.096	0.105	
ATOM	2	C	UNK	1	1.569	-0.386	-0.952	
ATOM	3	O	UNK	1	1.535	-0.818	-2.096	
ATOM	4	C	UNK	1	2.130	-2.609	0.144	
ATOM	5	C	UNK	1	0.793	-2.892	0.803	
ATOM	6	O	UNK	1	0.640	-3.285	1.938	
ATOM	7	O	UNK	1	-0.211	-2.577	-0.051	
ATOM	8	H	UNK	1	1.108	1.066	0.402	
ATOM	9	N	UNK	1	0.895	0.721	-0.525	
ATOM	10	C	UNK	1	0.230	1.615	-1.460	
ATOM	11	C	UNK	1	0.972	2.955	-1.507	
ATOM	12	O	UNK	1	1.321	3.530	-2.510	
ATOM	13	C	UNK	1	-1.270	1.848	-1.154	
ATOM	14	O	UNK	1	-1.899	0.552	-1.264	
ATOM	15	C	UNK	1	-1.893	2.834	-2.146	
ATOM	16	O	UNK	1	1.176	3.426	-0.254	
ATOM	17	C	UNK	1	1.892	4.673	-0.170	
ATOM	18	C	UNK	1	-3.808	-0.855	-1.170	
ATOM	19	C	UNK	1	-3.086	-1.822	-1.878	
ATOM	20	C	UNK	1	-3.200	0.453	-0.842	
ATOM	21	O	UNK	1	-3.786	1.376	-0.299	
ATOM	22	C	UNK	1	-1.570	-2.661	0.297	
ATOM	23	C	UNK	1	-2.114	-1.763	1.255	
ATOM	24	C	UNK	1	-3.476	-1.590	1.273	
ATOM	25	C	UNK	1	-1.238	-0.854	2.083	
ATOM	26	C	UNK	1	-2.339	-3.306	-0.666	
ATOM	27	H	UNK	1	3.473	-0.978	-0.267	
ATOM	28	H	UNK	1	2.121	-2.965	-0.889	
ATOM	29	H	UNK	1	2.901	-3.132	0.714	
ATOM	30	H	UNK	1	0.321	1.158	-2.447	
ATOM	31	H	UNK	1	-1.398	2.211	-0.129	
ATOM	32	H	UNK	1	-2.958	2.939	-1.938	
ATOM	33	H	UNK	1	-1.428	3.821	-2.061	
ATOM	34	H	UNK	1	-1.755	2.480	-3.173	
ATOM	35	H	UNK	1	1.350	5.459	-0.702	
ATOM	36	H	UNK	1	1.956	4.902	0.894	
ATOM	37	H	UNK	1	2.889	4.568	-0.603	
ATOM	38	H	UNK	1	-2.125	-1.545	-2.297	
ATOM	39	H	UNK	1	-3.658	-2.530	-2.475	
ATOM	40	H	UNK	1	-3.919	-0.816	1.892	
ATOM	41	H	UNK	1	-4.168	-2.317	0.871	
ATOM	42	H	UNK	1	-1.843	-0.080	2.563	
ATOM	43	H	UNK	1	-0.723	-1.423	2.864	
ATOM	44	H	UNK	1	-0.483	-0.359	1.466	
ATOM	45	H	UNK	1	-1.813	-3.922	-1.389	
ATOM	46	H	UNK	1	-3.319	-3.674	-0.386	
ATOM	47	N	UNK	1	2.414	-0.506	1.439	
ATOM	48	C	UNK	1	3.494	0.210	1.908	
ATOM	49	O	UNK	1	4.408	0.631	1.226	
ATOM	50	H	UNK	1	1.857	-0.969	2.149	
ATOM	51	O	UNK	1	3.368	0.404	3.244	
ATOM	52	C	UNK	1	4.426	1.167	3.844	
ATOM	53	H	UNK	1	4.173	1.228	4.902	
ATOM	54	H	UNK	1	5.388	0.666	3.708	
ATOM	55	H	UNK	1	4.479	2.166	3.404	
ATOM	56	C	UNK	1	-5.316	-0.917	-1.071	
ATOM	57	H	UNK	1	-5.665	-1.955	-1.012	
ATOM	58	H	UNK	1	-5.688	-0.367	-0.204	
ATOM	59	H	UNK	1	-5.783	-0.469	-1.960	

Experimental Section

General Experimental

^{1}H NMR spectra were obtained on a JEOL Model EX-270 (270 MHz) or JEOL Model ECP-400 (400 MHz) in the $CDCl_3$ at 25 ℃ if not indicated. Chemical shifts are reported in (δ) units parts per million (ppm) relative to tetramethylsilane (0.0 ppm), chloroform (7.26 ppm), or benzene (7.15 ppm) as an internal standard. NMR multiplicities are reported using the following abbreviations: s; singlet, d; doublet, t; triplet, q; quartet, sept; septet, m; multiplet, br; broad, *J*; coupling constants in Hertz.

^{13}C NMR spectra were obtained on a JEOL Model EX-270 (67.8 MHz) or JEOL Model ECP-400 (100 MHz) in the $CDCl_3$ at 25 ℃ if not indicated. Chemical shifts are reported in (δ) units parts per million (ppm) relative to chloroform (77.0 ppm) as an internal standard.

^{31}P NMR spectra were obtained on a JEOL Model EX-270 (109.3 MHz) in the $CDCl_3$ at 25 ℃ if not indicated. Chemical shifts are reported in (δ) units parts per million (ppm) relative to phosphoric acid in water as an external standard (0.0 ppm).

Mass spectra were obtained on AppliedBioSystems Mariner TK3500 Biospectrometry Workstation (ESI-TOF) mass spectrometers. HRMS were calibrated with angiotensin I (SIGMA), bradykinin (SIGMA), and neurotensin (SIGMA) as an internal standard.

IR spectra were recorded on a PERKIN ELMER Model Spectrum One. Only the strongest and/or structurally important absorption are reported as all the IR date given in the units of cm^{-1}.

Optical rotations were measured with a JASCO Model P-1020 polarometer.

UV spectra were recorded on a Perkin-Elmer Lambda 40 UV/VIS spectrometer. Only the strongest and/or structurally important absorption are reported as the UV/VIS data given in units nm.

CD spectra were recorded on a JASCO J-720W circular dichroism spectrometer at 25 ℃. Only the strongest and/or structurally important absorption are reported as the CD data given in units nm.

High performance liquid chromatography (HPLC) for qualitative and quantitative analyses was performed on a Japan Analytical Industry Model RI-3H refractive index detector and on a JASCO Model UV-875 ultra violet detector.

Reversed phase HPLC for qualitative and quantitative analyses were performed on Hewlett Packard HP-1100 series system with following methods.

Method : A

Column : GL Sciences Inc, Intertsil™ - ODS-3 3 m 4.6 75 mm Column

Eluent : a gradient of 0.1% HCOOH in H_2O (A) and 0.1 % HCOOH in MeCN (B)

10% of B (0 - 1 min), 10 - 100% of B (1 - 12 min), 100% of B (12 - 15 min)

UV detection : 254 nm

Flow rate : 1.0 mL min^{-1} Temperature : 40 ℃

Method : B

Column : Waters Symmetry-C_{18}® 5 m 2.1×150 mm Column

Eluent : a gradient of 0.1% HCOOH in H_2O (A) and 0.1 % HCOOH in MeCN (B)

20 - 45% of B (0 - 40 min), 45 - 100% of B (40 - 45 min), 100% of B (45 - 50 min)

UV detection: 340 nm

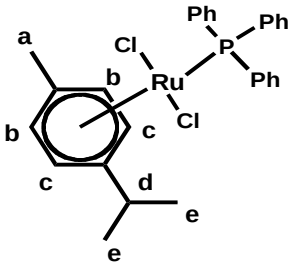
Flow rate : 0.20 mL min^{-1}

Temperature : 40 ℃

Preparation of Dichloro(η⁶-1-isopropyl-4-methyl-benzene)(triphenylphosphine) ruthenium (I)

To a suspension of di-μ-chloro-bis[chloro(η⁶-1-isopropyl-4-methyl-benzene)ruthenium [1] (1.70 g, 3.15 mmol) in dry *n*-hexane (91 mL) was added triphenylphophine (372 mg, 1.42 mmol) at room temperature under an argon atmosphere. The reaction mixture was heated to reflux. After being stirred for 4 h, an orange precipitate was observed. The crystals were filtered washed with dry *n*-hexane and dried *in vacuo* to afford 2.47 g (2.17 mmol, 69%) of dichloro(η⁶-1-isopropyl-4-methyl-benzene) (triphenylphosphine)ruthenium (**I**) as an orange powder.

^{1}H NMR (270 MHz, $CDCl_3$) δ 7.33 - 7.98 (15H, m, aromatic), 5.19 (2H, d, J = 6.3 Hz, b or c), 4.99 (2H, d, J = 6.3 Hz, b or c), 2.85 (1H, sept, J = 6.9 Hz, d), 1.87 (3H, s, a), 1.10 (6H, d, J = 6.9 Hz, e). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 134.1, 133.9, 133.8, 133.2, 129.9, 127.7, 127.6, 88.7, 86.9, 86.8, 81.0, 29.9, 21.8, 21.5, 17.4. ^{31}P NMR (109.3 MHz, $CDCl_3$) δ 24.8.



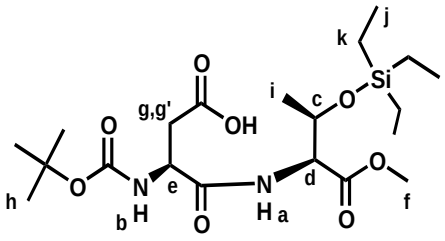
(2*S*,3*R*)- 2-[(*S*)- 3-Benzyloxycarbonyl-2-*tert*-butoxycarbonylaminopropanoylamino]-3-triethylsilyloxybutyric acid methyl ester (8)

To a stirred solution of (L)-*O*-(triethylsilyl)threonine methyl ester (**7**) in dry *N,N*-dimethylformamide and dry dichloromethane (1:4, 5.0 mL/mmol) was added 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (EDCI) (1.2 equiv.), 1-hydroxybenzotriazole (HOBt) (1.2 equiv.), dry triethylamine (2.0 equiv.) and (L)-aspartic acid derivative **6** (1.1 equiv.) at room temperature under an argon atmosphere. After being stirred for 1 h, the reaction mixture was diluted with ethyl acetate and poured into aqueous 1M HCl at 0 ℃. The aqueous layer was extracted with ethyl acetate and the combined extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to afford the corresponding dipeptide as a yellow oil.

To a suspension of $Pd(OH)_2$ (10wt%) and potassium carbonate (0.5 equiv.) in ethyl acetate (0.5 mL/mmol) was added a stirred solution of the above dipeptide in ethyl acetate (4.5 mL/mmol) at room temperature under a hydrogen atmosphere. After being stirred for 12 h, the reaction mixture was filtered

[1] Reference 16 in the text.

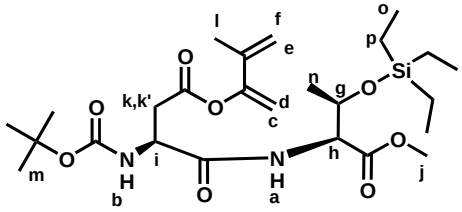
through Celite and the filtrate was poured into aqueous 1M HCl at 0 ℃. The aqueous layer was extracted with chloroform and the combined extracts were dried over $MgSO_4$, and concentrated *in vacuo*. The residue was used for the next reaction without further purification.



TLC R_f 0.31, 1:3 hexane-ethyl acetate. IR (neat) 3340, 2956, 2878, 2735, 2629, 1724, 1690, 1662, 1527, 1368, 1219, 1165, 1016, 847, 772, 742, 665 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 7.16 (1H, d, J = 8.6 Hz, a), 5.75 (1H, d, J = 8.6 Hz, b), 4.56 (1H, m, c), 4.41 - 4.44 (2H, m, d and e), 3.66 (3H, s, f), 3.00 (1H, dd, AB syst, J = 4.3, 17.5 Hz, g), 2.72 (1H, dd, AB syst, J = 5.6, 17.5 Hz, g'), 1.41 (9H, s, h), 1.11 (3H, d, J = 5.9 Hz, i), 0.87 (9H, t, J = 7.9 Hz, j), 0.49 (6H, q, J = 7.9 Hz, k). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 175.5, 171.4, 170.5, 155.3, 80.3, 68.4, 57.9, 52.1, 50.4, 35.5, 28.1, 20.7, 6.5, 4.6.

(2*S*,3*R*)-2-[(*S*)-2-*tert*-Butoxycarbonylamino-3-(2-methyl-1-methylene-2-propenyloxycarbonyl)propanoylamino]-3-triethylsilyloxybutyric acid methyl ester (10)

To a stirred solution of the acid derivatives in dry toluene (1.0 mL/mmol) was added 2-methyl-1-buten-3-yne (**9**) (1.2 equiv.) and dichloro(η^6-1-isopropyl-4-methyl-benzene)(triphenylphosphine)ruthenium (**I**) (0.03 equiv.) in a sealed tube at room temperature under an argon atmosphere and the reaction mixture was heated at 80 ℃. After being stirred for 24 h, the reaction mixture was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate-hexane) to afford dienol ester **10** as a yellow oil. The regioisomers were analyzed by HPLC (Lichrosorb Si60-5, 7.5×300 mm, eluted with ethyl acetate-hexane, flow rate 3.00 mL/min).



TLC R_f 0.60, 1:3 hexane-ethyl acetate. IR (neat) 3369, 2926, 1742, 1719, 1367, 1165, 1146 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 7.11 (1H, d, J = 8.9 Hz, a), 5.76 (1H, d, J = 9.2 Hz, b), 5.14 (1H, brs, c or d), 5.06 (1H, d, J = 2.0 Hz, c or d), 4.98 (1H, brs, e or f), 4.88 (1H, brs, e or f), 4.63 (1H, m, g), 4.41 - 4.47 (2H, m, h and i), 3.68 (3H, s, j), 3.20 (1H, dd, AB syst, J = 4.4, 17.2 Hz, k), 2.85 (1H, dd, AB syst, J = 5.6, 17.2 Hz, k'), 1.89 (3H, s, l), 1.43 (9H, s, m), 1.12 (3H, d, J = 6.3 Hz, n), 0.86 - 0.94 (9H, m, o), 0.44 - 0.58 (6H, m, p). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 170.9, 170.8, 170.6, 170.3, 153.3, 136.0, 114.3, 103.4, 80.3, 68.3, 65.8, 58.0, 52.1, 50.5, 35.6, 28.2, 20.9, 6.6, 5.7. MS (ESI-TOF) 553.33 $[M + H]^+$.

Removal of a Silyl Group of 10

To a stirred solution of dienol ester **10** in methanol (5 mL/mmol) was added (1*S*)-(+)-10-camphorsulfonic acid (0.03 equiv.) at room temperature. After being stirred for 20 min, the reaction mixture was diluted

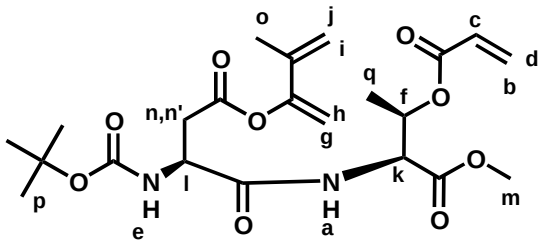
with ethyl acetate and poured into saturated aqueous $NaHCO_3$ at 0 ℃. The aqueous layer was extracted with ethyl acetate and the combined extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to afford the corresponding alcohol as a yellow oil.

General Procedure for the Acylation with Acrylic Chloride or Methacrylic Chloride

To a stirred solution of the above alcohol in dry dichloromethane (5 mL/mmol) was added *N*,*N*-diisopropylethylamine (4 equiv.) and acid chloride (2 equiv.) at 0 ℃ under an argon atmosphere. After being stirred for 1 h at room temperature, the reaction mixture was diluted with ethyl acetate and poured into saturated aqueous ammonium chloride at 0 ℃. The aqueous layer was extracted with ethyl acetate and the combined extracts were washed with aqueous 1M HCl, saturated aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to afford the precursor tethered by dipeptide as a yellow oil.

The geometrically pure precursors for the analysis of Diels-Alder reaction were obtained by preparative HPLC (Lichrosorb Si60-5, 7.5×300 mm, eluted with ethyl acetate-hexane, flow rate 3.00 mL/min).

(2*S*,3*R*)-2-[(*S*)-2-*tert*-Butoxycarbonylamino-3-(2-methyl-1-methylene-2-propenyloxycarbonyl)propanoylamino]-3-(2-propenoyloxy)butyric acid methyl ester (1a)

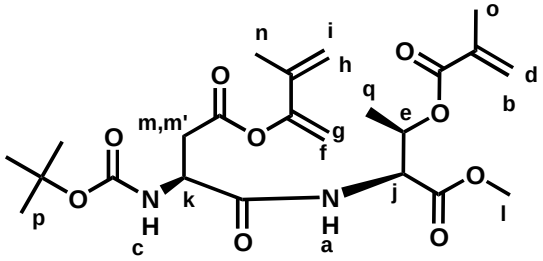


HPLC (25% ethyl acetate in hexane) Rt : 25 min. TLC R_f 0.60, 1:3 hexane-ethyl acetate. $[\alpha]^{29}_D$ +13.0 (*c* 1.01, $CHCl_3$). IR (neat) 3354, 2980, 2957, 2930, 1723, 1751, 1699, 1525, 1294, 1167 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 7.25 (1H, d, *J* = 9.9 Hz, a), 6.41 (1H, dd, *J* = 1.3, 17.5 Hz, b), 6.06 (1H, dd, *J* = 10.2, 17.5 Hz, c), 5.84 (1H, dd, *J* = 1.3, 10.2 Hz, d), 5.82 - 5.86 (1H, m, e), 5.47 (1H, dq, *J* = 2.3, 6.3 Hz, f), 5.18 (1H, brs, g or h), 5.10 (1H, d, *J* = 2.0 Hz, g or h), 5.02 (1H, brs, i or j), 4.91 (1H, brs, i or j), 4.74 (1H, dd, *J* = 2.3, 9.2 Hz, k), 4.66 (1H, m, l), 3.71 (3H, s, m), 3.21 (1H, dd, AB syst, *J* = 4.3, 17.5 Hz, n), 2.89 (1H, dd, AB syst, *J* = 6.0, 17.5 Hz, n'), 1.92 (3H, s, o), 1.47 (9H, s, p), 1.27 (3H, d, *J* = 6.3 Hz, q). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 171.1, 170.5, 169.6, 164.7, 155.5, 153.3, 135.9, 131.5, 127.8, 114.3, 103.5, 80.6, 55.7, 52.6, 50.5, 35.4, 28.2, 19.3, 16.8. MS (ESI-TOF) 469.21 $[M+H]^+$.

(2*S*,3*R*)-2-[(*S*)-2-*tert*-Butoxycarbonylamino-3-(2-methyl-1-methylene-2-propenyloxycarbonyl)propanoylamino]-3-(2-methyl-2-propenoyloxy)butyric acid methyl ester (1b)

HPLC (25% ethyl acetate in hexane) Rt : 26 min. TLC R_f 0.50, 10:1 dichloromethane-ether. $[\alpha]^{22}_D$ +16.0 (*c* 1.59, $CHCl_3$). IR (neat) 3386, 2983, 2940, 1729, 1608, 1533, 1381, 1215, 1165 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 7.20 - 7.26 (1H, m, a), 6.10 (1H, brs, b), 5.83 (1H, d, *J* = 8.6 Hz, c), 5.57 (1H, br, d), 5.46

(1H, dq, *J* = 2.3, 6.4 Hz, e), 5.18 (1H, brs, f or g), 5.10 (1H, d, J = 2.0 Hz, f or g), 5.02 (1H, brs, h or i), 4.91 (1H, brs, h or i), 4.74 (1H, dd, *J* = 2.3, 9.2 Hz, j), 4.65 - 4.72 (1H, m, k), 3.70 (3H, s, l), 3.23 (1H, dd, AB syst, *J* = 4.3, 17.5 Hz, m), 2.88 (1H, dd, AB syst, *J* = 5.9, 17.5 Hz, m'), 1.92 (3H, s, n), 1.55 (3H, s, o), 1.45 (9H, s, p), 1.27 (3H, d, *J* = 6.4 Hz, q). ^{13}C NMR (67.8 MHz, $CDCl_3$) 171.0, 169.6, 168.8, 164.7, 155.4, 138.9, 132.4, 131.6, 127.8, 117.9, 115.2, 80.8, 70.4, 55.7, 52.7, 50.4, 35.7, 28.2, 22.4, 20.4, 16.9. LCMS (ESI-TOF) (Reversed phase HPLC Analysis Method: A) Rt: 9.12 min, 482.23 $[M+H]^+$.



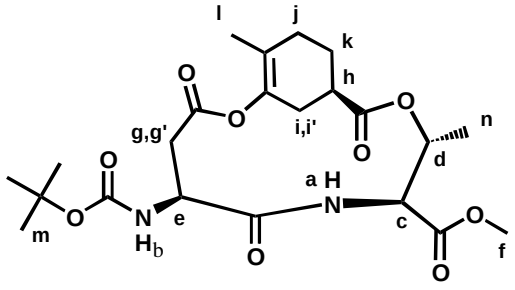
General Procedure for the Cycloaddition of 1a and 1b

To a stirred solution of **1** in dry toluene (20 mL/mmol) was added a catalytic amount of $NaHCO_3$ in a sealed tube and the mixture was heated at 150 δ under an argon atmosphere. After being stirred for 24 h, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel to afford the cycloadduct tethered by dipeptide reaction as a yellow oil.

The diastereoisomers of the products were analyzed and separated by HPLC (Lichrosorb Si60-5, 7.5 300 mm, eluted with ethyl acetate-hexane, flow rate 3.00 mL/min)

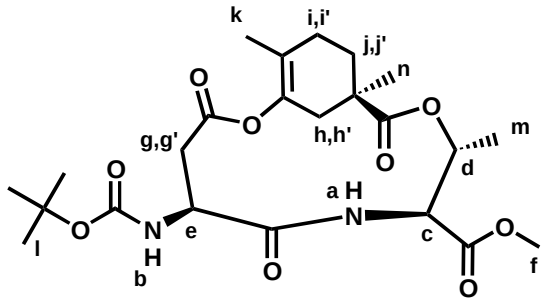
Cycloadduct 2a

HPLC (25% ethyl acetate in hexane) Rt : 34 min. TLC R_f 0.44, 1:1 ethyl acetate-hexane. $[\alpha]^{22}_D$ +20.1 (*c* 1.06, $CHCl_3$). IR (neat) 3428, 3370, 2926, 2853, 1736, 1722, 1677, 1516, 1485, 1451, 1367, 1328, 1220, 1198, 1172, 1116, 1054, 1021, 758 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$) 6.84 (1H, d, *J* = 9.6 Hz, a), 5.42 (1H, d, *J* = 9.6 Hz, b), 4.86 (1H, dd, *J* = 9.6, 10.2 Hz, c), 4.69 (1H, dq, *J* = 6.3, 10.2 Hz, d), 4.57 - 4.69 (1H, m, e), 3.77 (3H, s, f), 3.37 (1H, dd, AB syst, *J* = 4.5, 17.8 Hz, g), 2.82 (1H, br, h), 2.65 (1H, dd, AB syst, *J* = 2.6, 17.8 Hz, g'), 2.64 (1H, brd, *J* = 15.3 Hz, i), 2.42 (1H, brd, *J* = 15.3 Hz, i'), 2.00 - 2.36 (3H, m, j and k), 1.59 - 1.78 (1H, m, k), 1.59 (3H, d, *J* = 1.3 Hz, l), 1.49 (9H, s, m), 1.27 (3H, d, *J* = 6.3 Hz, n). ^{13}C NMR (67.8 MHz, $CDCl_3$) 172.7, 170.6, 169.8, 169.2, 167.6, 140.0, 119.1, 81.1, 71.9, 56.1, 52.8, 51.6, 39.3, 37.3, 30.6, 28.3, 26.4, 22.3, 17.2, 15.8. HRMS (ESI-TOF) Calcd for $[C_{22}H_{32}N_2O_9 + Na]^+$ 491.2000, Found 491.2002



Cycloadduct tethered by Asp-Thr dipeptide (metacrylate-1) 2b or 3b

Less polar diastereomer



HPLC (25% ethyl acetate in hexane) Rt : 28 min. TLC R_f 0.39, 10:1 dichloromethane-ether. $[\alpha]^{30}_D$ +50.6 (*c* 1.25, $CHCl_3$). IR (neat) 3428, 3370, 2926, 2853, 1736, 1722, 1677, 1516, 1485, 1451, 1367, 1328, 1220, 1198, 1172, 1116, 1054, 1021, 758 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 6.80 (1H, d, *J* = 9.6 Hz, a), 5.37 - 5.43 (1H, m, b), 5.39 (1H, dd, *J* = 9.6, 10.2 Hz, c), 4.64 (1H, dq, *J* = 5.9, 10.2 Hz, d), 4.50 - 4.62 (1H, m, e), 3.78 (3H, s, f), 3.49 (1H, dd, AB syst, *J* = 5.0, 18.2 Hz, g), 2.66 (1H, dd, AB syst, *J* = 2.6, 18.2 Hz, g'), 2.34 (2H, brs, h and h'), 2.01 - 2.30 (3H, m, i, i', and j), 1.4-1.8 (1H, m, j'), 1.59 (3H, s, k), 1.49 (9H, s, l), 1.26 (3H, d, *J* = 5.9 Hz, m), 1.20 (3H, s, n). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 175.0, 171.1, 170.5, 169.8, 167.3, 140.1, 118.9, 81.3, 71.6, 60.4, 56.0, 52.8, 44.3, 37.7, 37.4, 31.0, 28.2, 27.6, 25.2, 16.9, 15.7. ^1H NMR (400 MHz, **C_6D_6**) δ 6.97 (1H, d, *J* = 9.2 Hz, a), 5.54 (1H, d, *J* = 9.2 Hz, b), 5.05 (1H, dd, *J* = 9.2, 10.2 Hz, c), 4.65 (1H, m, e), 4.55 (1H, dq, *J* = 5.8, 10.2 Hz, d), 3.26 (1H, dd, AB syst, *J* = 4.8, 7.9 Hz, g), 2.97 (3H, s, f), 2.62 (1H, brd, AB syst, *J* = 5.5 Hz, h), 2.36 (1H, brd, AB syst, *J* = 5.5 Hz, h'), 2.29 (1H, brdd, AB syst, *J* = 8.2, 17.4 Hz, i), 2.19 (1H, dd, AB syst, *J* = 2.9, 7.9 Hz, g'), 2.00 (1H, brdd, *J* = 8.2, 15.5 Hz, j), 1.75 (1H, brdd, *J* = 7.3, 17.4 Hz, i'), 1.52 (3H, s, k), 1.40 (9H, s, l), 0.88 (1H, brdd, *J* = 7.3, 15.5 Hz, j'), 1.02 (3H, d, *J* = 5.8 Hz, m), 0.88 (3H, s, n). ^{13}C NMR (100 MHz, **C_6D_6**) δ 174.8, 170.9, 170.6, 170.0, 166.9, 141.2, 117.8, 77.7, 72.0, 56.3, 52.2, 51.9, 44.2, 38.1, 37.3, 31.3, 28.2, 27.8, 25.1, 17.0, 15.5. LCMS (ESI-TOF) (Reversed phase HPLC Analysis Method: A) Rt: 8.40 min, 483.26 $[M+H]^+$. HRMS (ESI-TOF) Calcd for $[C_{23}H_{34}N_2O_9 + Na]^+$ 505.2147, Found 505.2155.

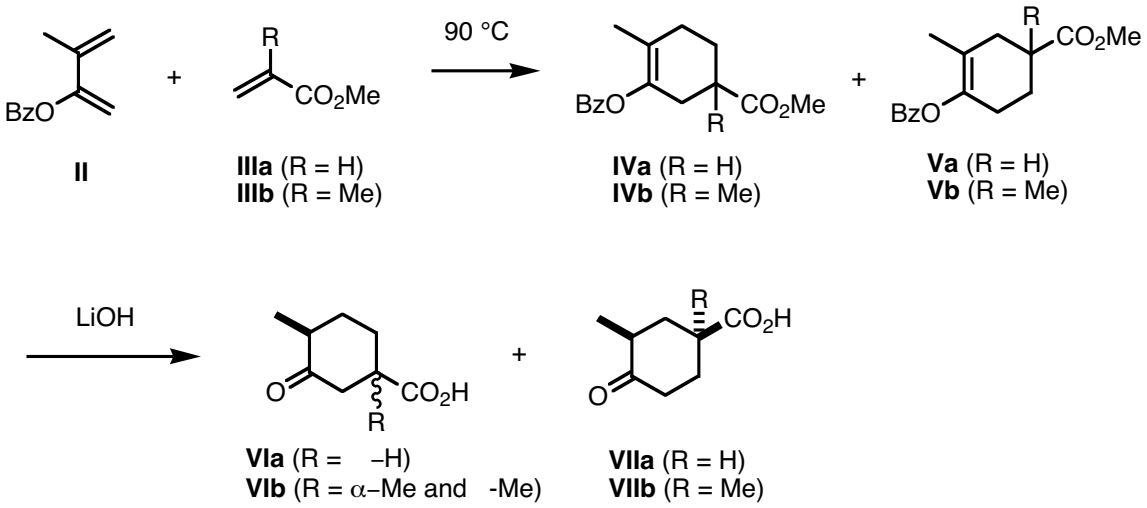
Polar diastereomer

HPLC (25% ethyl acetate in hexane) Rt : 48 min. TLC R_f 0.23, 10:1 dichloromethane-ether. $[\alpha]^{29}_D$ +1.98 (*c* 1.12, $CHCl_3$). IR (neat) 3412, 2979, 2932, 1732, 1690, 1525, 1368, 1245, 1190, 1168, 1144, 1071, 757 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 7.17 (1H, d, *J* = 6.9 Hz, a), 5.50 (1H, brs, b), 5.03 (1H, dd, *J* = 6.6, 7.3 Hz, c), 4.4 - 4.6 (2H, m, c and e), 3.75 (3H, s, f), 3.17 (1H, dd, AB syst, *J* = 2.6, 14.2 Hz, g), 2.69 (1H, dd, AB syst, *J* = 7.9, 14.2 Hz, g'), 2.44 (2H, brs, h and h'), 1.9 - 2.2 (4H, m, i, i', j, and j'), 1.55 (3H, s, k), 1.47 (9H, s, l), 1.30 (3H, d, *J* = 6.6 Hz, m), 1.28 (3H, s, n). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 174.4, 170.2, 169.7, 167.3, 155.0, 141.6, 119.4, 81.0, 72.8, 56.4, 52.9, 45.2×2, 38.8, 37.6, 32.3, 28.2, 27.8, 25.3, 17.3, 15.6. ^1H NMR (400 MHz, **C_6D_6**) δ 7.02 - 7.15 (1H, m, a), 5.64 (1H, brs, b), 4.98 (1H, brq, *J* = 6.3 Hz, d), 4.55 (1H, brs, c), 4.27 (1H, s, e), 3.11 (3H, s, f), 2.87 (1H, dd, AB syst, *J* = 2.9, 14.5 Hz, g), 2.61 (1H, d, AB syst, *J* = 5.3 Hz, h), 2.36 (1H, dd, AB syst, *J* = 2.4, 5.3 Hz, h'), 2.18 (1H, dd, AB syst, *J* = 8.2, 14.5 Hz, g'), 1.80 - 1.96 (2H, m, i), 1.61 - 1.80 (2H, m, j), 1.47 (9H, s, l), 1.35 (3H, s, k), 1.18 (3H, d, *J* = 6.3 Hz, m), 0.83 (3H, s, n). LCMS

(ESI-TOF) (Reversed phase HPLC Analysis Method: A) Rt: 8.74 min, 483.26 $[M+H]^+$. HRMS (ESI-TOF) Calcd for $[C_{21}H_{30}N_2O_9 + Na]^+$ 505.2147, Found 505.2158.

Structure Determination of Cycloadducts 2a, 2b, and 3b.

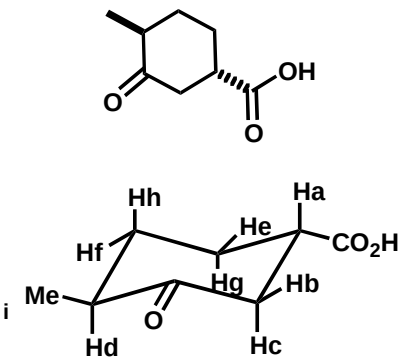
Intermolecular Diels-Alder reaction of 2-benzyloxy-3-methyl-1,3-butadine (**II**) and α,β-unsaturated ester **IIIa** and **IIIb** [toluene/cat. hydroquinone/90°C/24 h] provided a 1:1 mixture of regioisomers **IV** and **V** in 66% and 80%, respectively. Hydrolysis of the products [aq. LiOH (8.5 M)/dioxane-methanol (1:1)/rt], acidification, followed by preparative separation using HPLC afforded **VI** and **VII**, respectively. The spectral data including coupling patterns and constants of the products were good agreement with these structures. (Scheme 1)



Scheme 1.

trans -4-Methyl-3-oxocyclohexanecarboxylic acid (Vla)

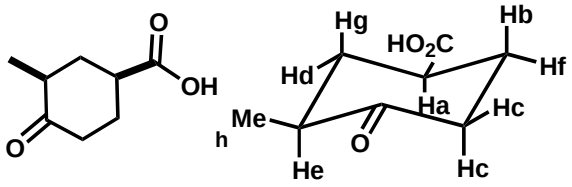
HPLC (25% ethyl acetate in hexane) Rt : 23 min. TLC R_f 0.15, 1:2 hexane-ethyl acetate. IR (solid) 3450, 3216, 2969, 2938, 2875, 2615, 1708, 1637, 1459, 1421, 1380, 1232, 1194 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 2.77 (1H, dddd, J = 4.0, 4.3, 12.5, 13.2 Hz, a), 2.66 (1H, ddd, J = 1.7, 4.3, 13.8 Hz, b), 2.52 (1H, dd, J = 12.5, 13.8 Hz, c), 2.41 (1H, m, d), 2.17 (1H, ddddd, J = 1.7, 3.0, 3.3, 4.0, 12.5 Hz, e), 2.13 (1H, dddd, J = 3.3, 3.3, 6.3, 12.5 Hz, f), 1.88 (1H, dddd, J = 3.3, 12.5, 12.5, 13.2 Hz, g), 1.42 (1H, dddd, J = 3.0, 12.5 , 12.5, 12.5 Hz, h), 1.04 (3H, d, J = 6.3 Hz, i). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 210.5, 179.2, 44.6,



44.0, 43.0, 34.0, 28.1, 14.3.

cis-3-Methyl-4-oxocyclohexanecarboxylic acid (VIIa)

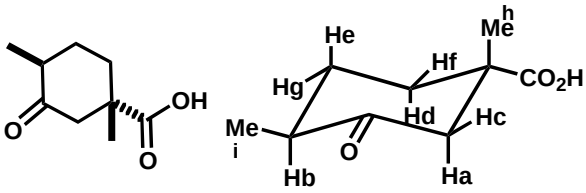
HPLC (25% ethyl acetate in hexane) Rt : 19 min. TLC R_f 0.16, 1:2 hexane-ethyl acetate. IR (solid) 3450, 3216, 2969, 2938, 2615, 1708, 1637, 1459, 1421, 1380, 1232, 1194, 1112 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 2.89 (1H, dddd, J = 3.3, 3.6, 12.2, 12.5 Hz, a), 2.18 - 2.50 (5H, m, c, d, e, and f), 1.89 (1H, dddd, J = 5.3, 12.2, 12.2, 14.5 Hz, b), 1.60 (1H, ddd, J = 12.5, 12.8, 12.8 Hz, g), 1.06 (3H, d, J = 6.3 Hz, h). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 211.1, 180.0, 43.6, 41.8, 40.1, 37.4, 29.4, 14.4.



(1*R**,4*R**)-1,4-Dimethyl-3-oxocyclohexanecarboxylic acid (VIb) and (1*R**, 4*S**)-1,4-Dimethyl-3-oxocyclohexanecarboxylic acid (VIb')

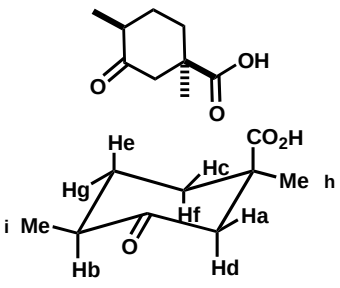
Less polar diastereomer

HPLC (25% ethyl acetate in hexane) Rt : 20 min. TLC R_f 0.41, 4:1 hexane-ethyl acetate. IR (solid) 3453, 3214, 2973, 2938, 2624, 1738, 1723, 1714, 1464, 1456, 1417, 1380, 1208, 1131, 937, 888, 856 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 2.74 (1H, d, J = 14.0 Hz, a), 2.40 (1H, m, b), 2.39 (1H, dd, J = 1.9, 14.0 Hz, c), 2.16 (1H, ddd, J = 3.9, 13.1, 14.0 Hz, d), 2.06 (1H, dddd, J = 3.9, 3.9, 3.9, 14.0 Hz, g), 1.90 (1H, ddd, J = 1.9, 3.9, 13.1 Hz, f), 1.58 (1H, dddd, J = 3.9, 14.0, 14.0, 14.0 Hz, e), 1.21 (3H, s, h), 1.06 (3H, d, J = 6.8 Hz, i). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 208.3, 181.1, 49.1, 34.9, 32.6, 30.2, 21.0, 14.2, 14.1.



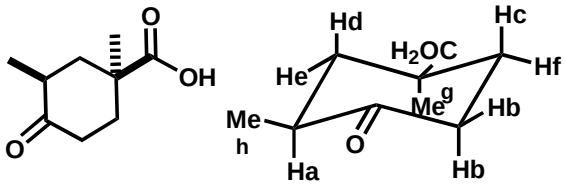
Polar diastereomer

HPLC (25% ethyl acetate in hexane) Rt : 22 min. TLC R_f 0.39, 1:1 hexane-ethyl acetate. IR (solid) 3450, 3216, 2969, 2938, 2875, 2615, 1708, 1637, 1459, 1421, 1380, 1232, 1194 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 2.78 (1H, dd, J = 2.3, 14.2 Hz, a), 2.19 - 2.30 (2H, m, b and c), 2.09 (1H, d, J = 14.2 Hz, d), 1.92 - 2.07 (1H, m, e), 1.72 (1H, ddd, J = 3.6, 13.2, 13.2 Hz, f), 1.51 (1H, ddd, J = 3.3, 3.6, 13.2, g), 1.34 (3H, s, h), 1.05 (3H, d, J =6.0 Hz, i). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 181.6, 177.2, 49.5, 47.5, 43.8, 35.2, 31.3, 26.5, 14.4.

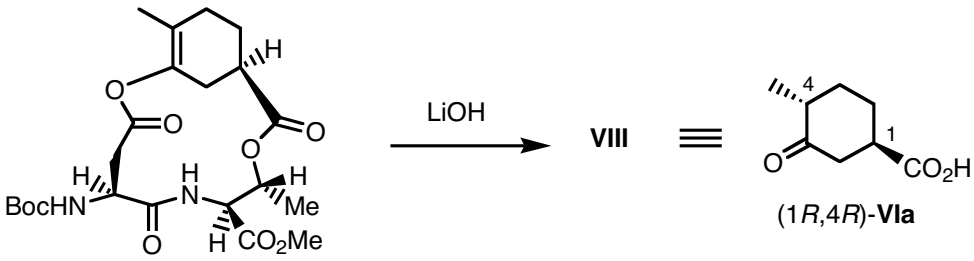


(1*R,3*R**)-1,3-Dimethyl4-oxocyclohexanecarboxylic acid (VIIb)**

HPLC (25% ethyl acetate in hexane) Rt : 16 min. TLC R_f 0.46, 1:3 hexane-ethyl acetate. IR (solid) 3450, 3216, 2969, 2938, 2875, 2615, 1708, 1637, 1459, 1421, 1380, 1232, 1194 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 2.47 - 2.65 (4H, m, a, b, b, e), 2.29 - 2.37 (1H, m, f), 1.63 (1H, ddd, J = 5.5, 12.5, 12.5 Hz, c), 1.38 (1H, dd, J = 12.9, 12.9 Hz, d), 1.34 (3H, s, g), 1.02 (3H, d, J = 6.3 Hz, h). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 212.7, 182.7, 44.3, 43.5, 41.8, 38.8, 36.0, 27.0, 14.3.



Hydrolysis of the Diels-Alder product **2a** (single isomer) [aq. LiOH (8.5 M)/dioxane-methanol (1:1)/rt/ 24 h], followed by acidification provided the acid **VIII** in 70% yield (Scheme 2). The ^1H NMR spectra and the retention time of HPLC analysis (Rt = 23 min) of **VIII** were identical with those of **VIa**. The CD spectra of **VIII** shown in Figure 1 exhibited a positive Cotton effect. The absolute configuration of **VIII** was determined to be (1*R*,4*R*).



2a

Scheme 2

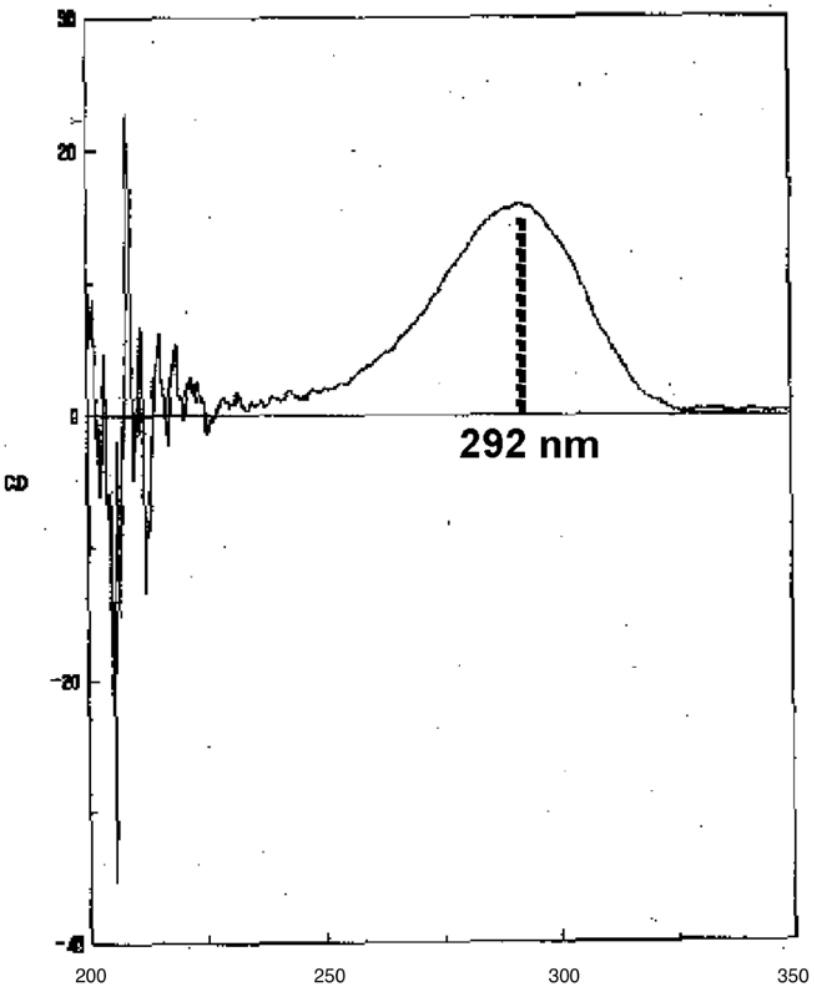
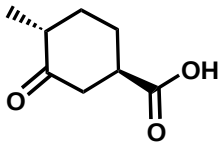


Figure 1. The CD spectra of **VIII**

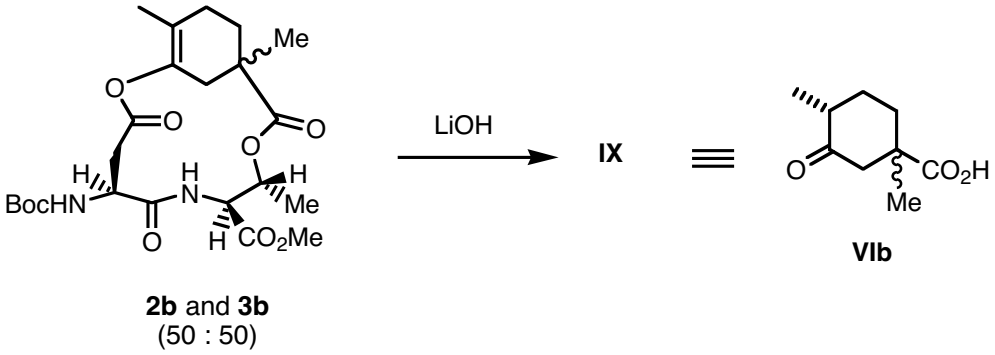
(1*R*, 4*R*)-4-Methyl-3-oxocyclohexanecarboxylic acid (VIa)

HPLC Rt. 23 min, Chiral HPLC (2% 2-propanol in hexane) Rt : 43 min.

CD (EtOH, c = 0.20 M) $_{ext}$ 292.20 nm ($\Delta\varepsilon$ +16). UV : λ_{max} 212.20 nm.



Hydrolysis of the Diels-Alder products **2b** and **3b** (1:1 mixture) [aq. LiOH (8.5 M) / dioxane-methanol (1:1) / rt / 24 h], followed by acidification provided the acids **IX** in quantitative yield (Scheme 3). The ^{1}H NMR spectra and the retention time of HPLC analysis of **IX** (Rt = 20 and 22 min) were not identical with that of **VIIb** but identical with those of **VIb** and **VIb'**.



2b and **3b**
(50 : 50)

Scheme 3

Confirmation of No Epimerization of the Peptide Moieties

The Diels-Alder products were hydrolyzed with 6 M HCl (90°C for 6 h) and then the amino acids obtained were converted to Marfey's derivatives **X** and **XI**. Retention time of the authentic samples, (L)- and (D)- aspartic acid and threonine derivatives are shown below. The retention time of **X** and **XI** were identical to those of (L)-aspartic acid and (L)-threonine derivatives, respectively. Therefore, it is concluded that no epimerization of the peptide moieties occurred during the macrocyclic Diels-Alder reaction.

General Procedure of Marfey's Method[2]

To a solution of amino acid in water (50 μL) was sequentially added aqueous 1 M $NaHCO_3$ (50 μL) 1% solution of 1-fluoro-2,4-dinitrophenyl-5-L-alanneamide (L-FDAA) in acetone. The reaction mixture was incubated at 37 δ. After being stirred for 1 h, the reaction mixture was quenched with aqueous 1M HCl (50 μL) and diluted with methanol (750 μL). This solution (1.0 μL) was analyzed by HPLC-MS.

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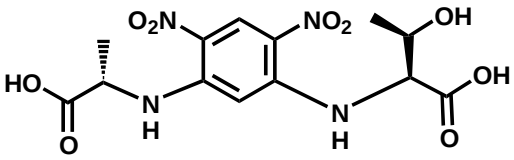
[2] Fujita, K.; Ikai, Y.; Oka, H.; Suzuki, M.; Harada, K. *Anal. Chem.* **1997**, *69*, 5146.

α-[*N*-(L-FDAA)]-L-threonine

Reversed phase HPLC Analysis Method : B

Rt : 13.2 min.

MS (ESI-TOF) 372.20 $[M + H]^+$

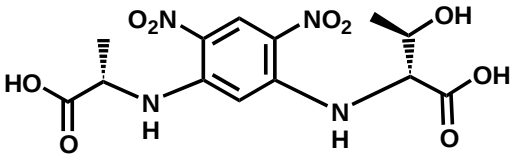


α-[*N*-(L-FDAA)]-D-threonine

Reversed phase HPLC Analysis Method : B

Rt : 17.8 min.

MS (ESI-TOF) 372.20 $[M + H]^+$.

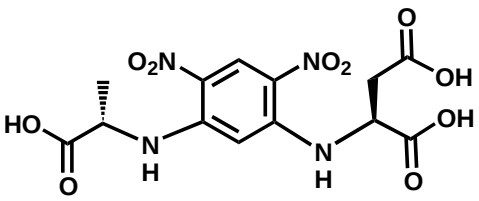


α-[*N*-(L-FDAA)]-L-aspartic acid

Reversed phase HPLC Analysis Method : B

Rt : 14.4 min.

MS (ESI-TOF) 386.19 $[M + H]^+$.

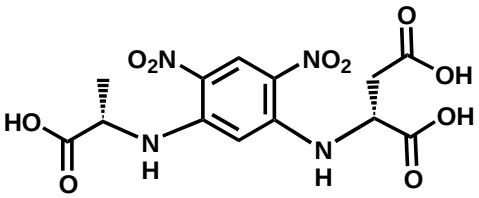


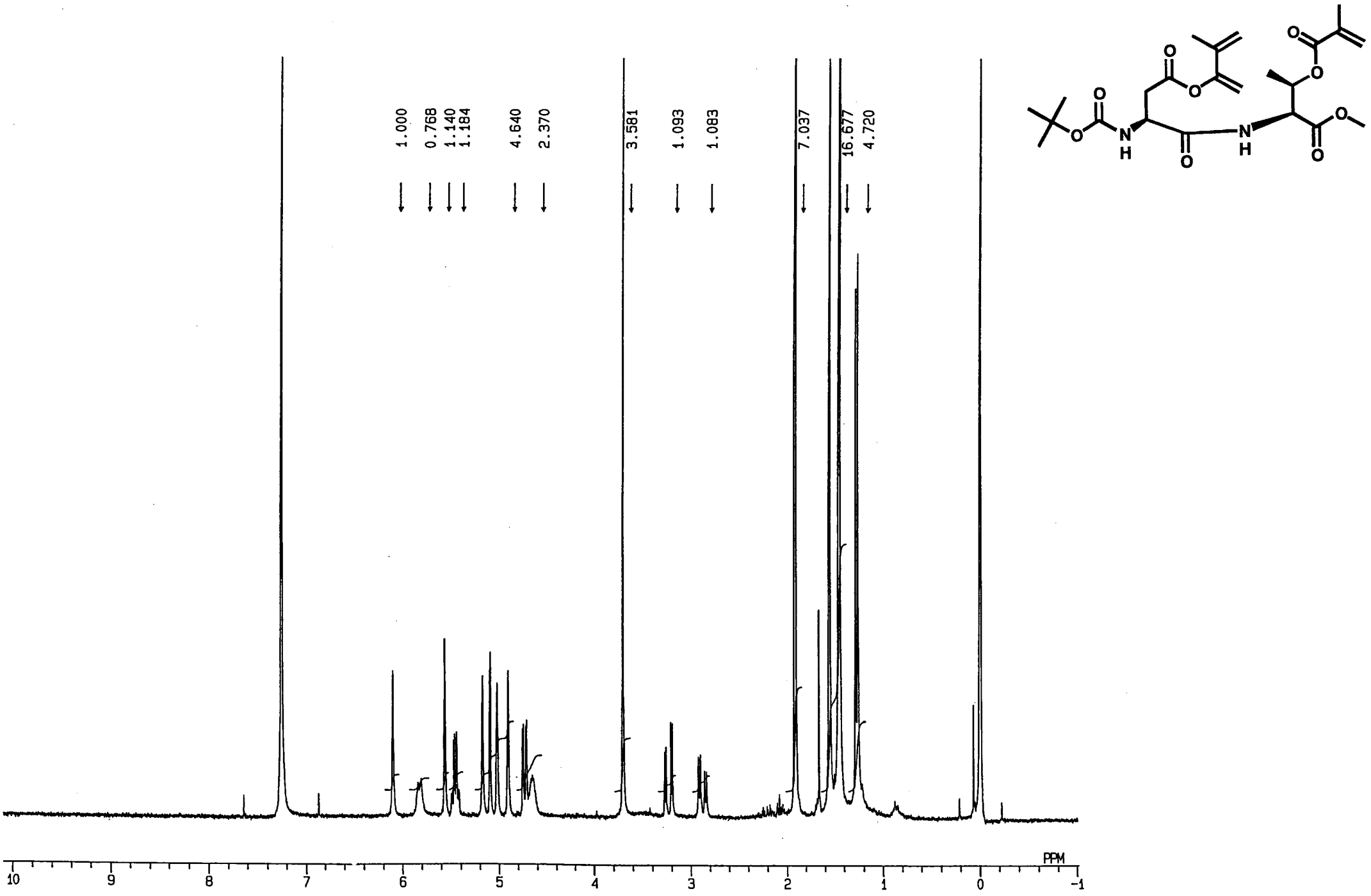
α-[*N*-(L-FDAA)]-D-aspartic acid

Reversed phase HPLC Analysis Method : B

Rt : 16.0 min.

MS (ESI-TOF) 386.19 $[M + H]^+$.

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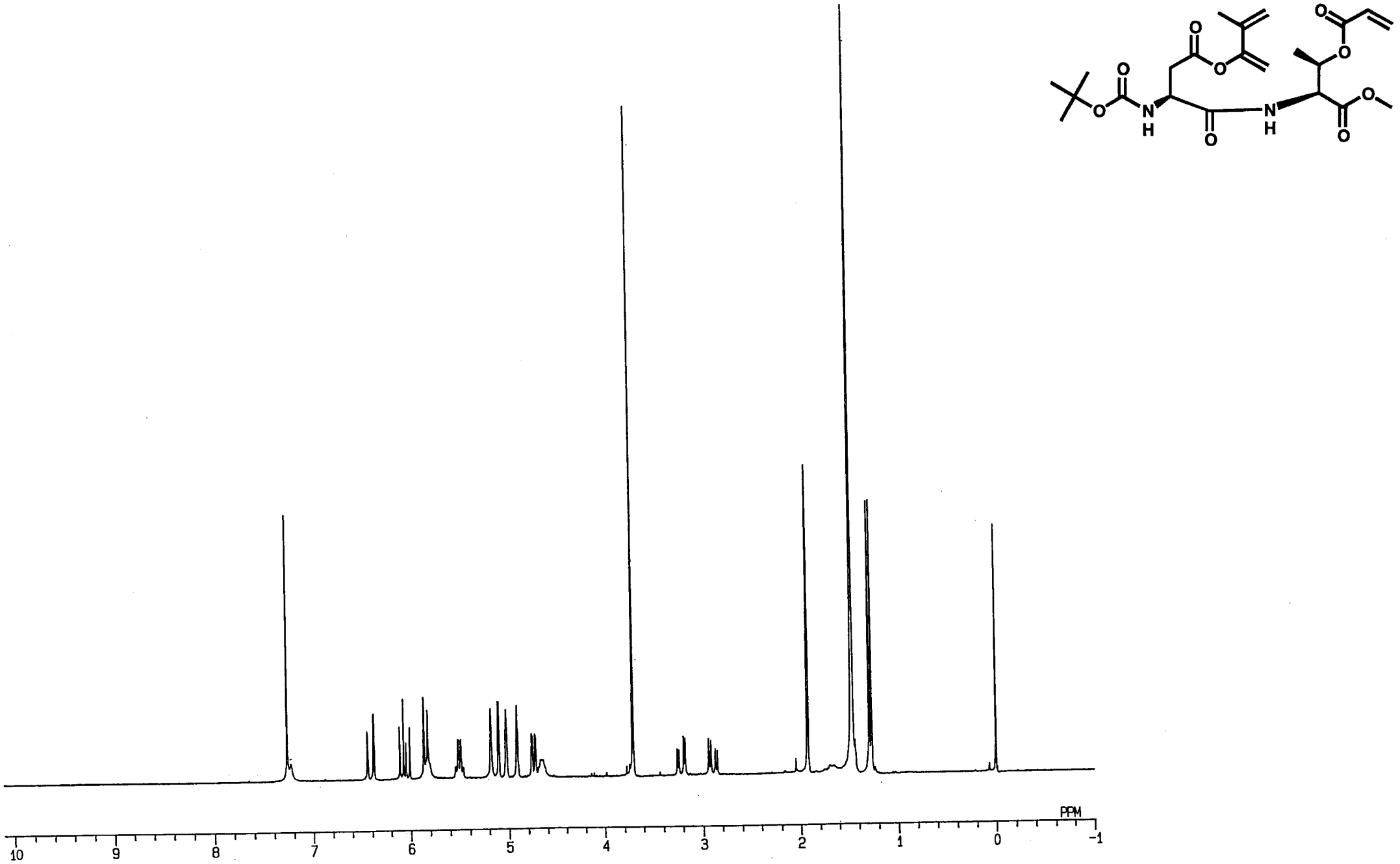
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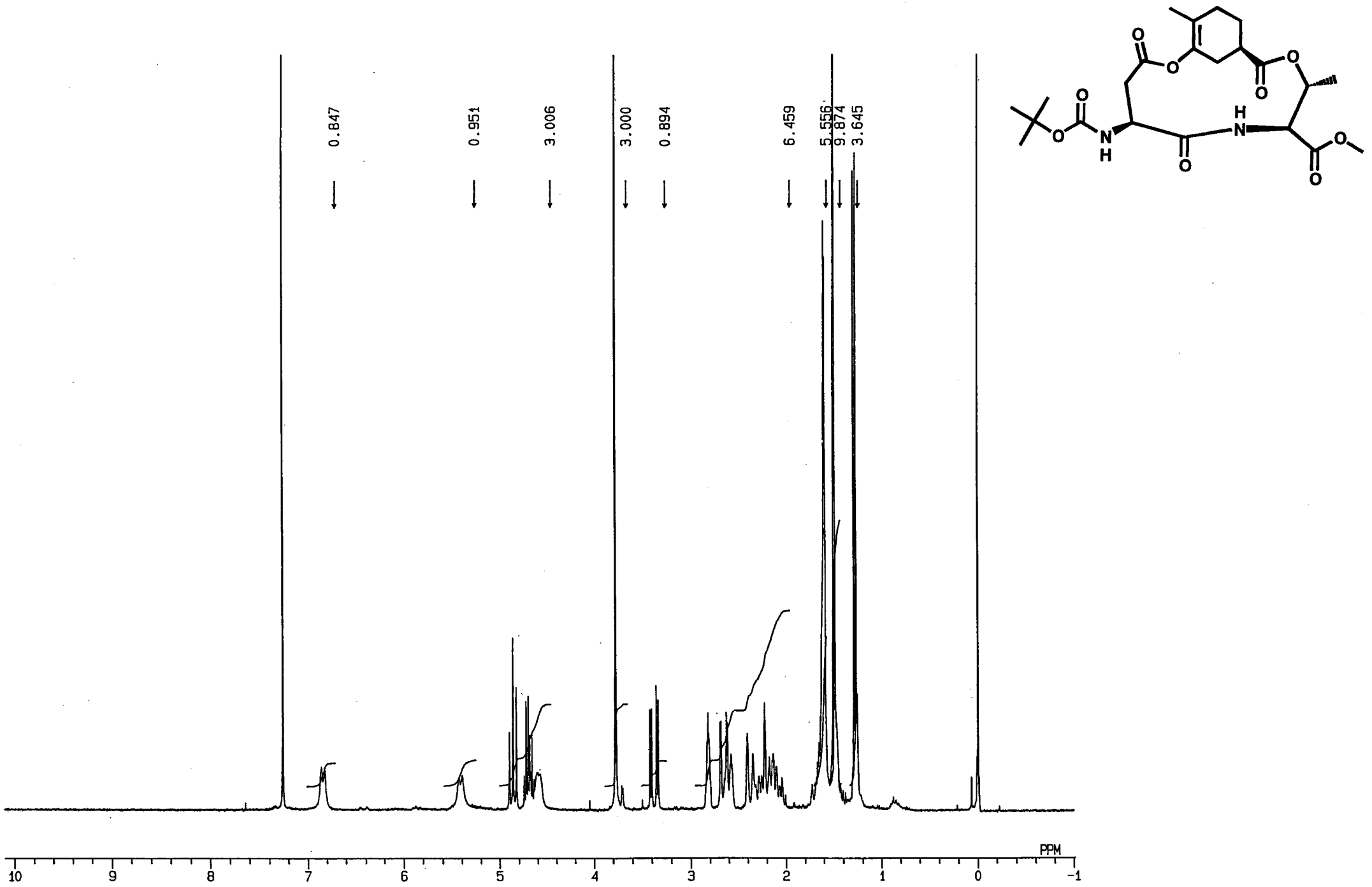
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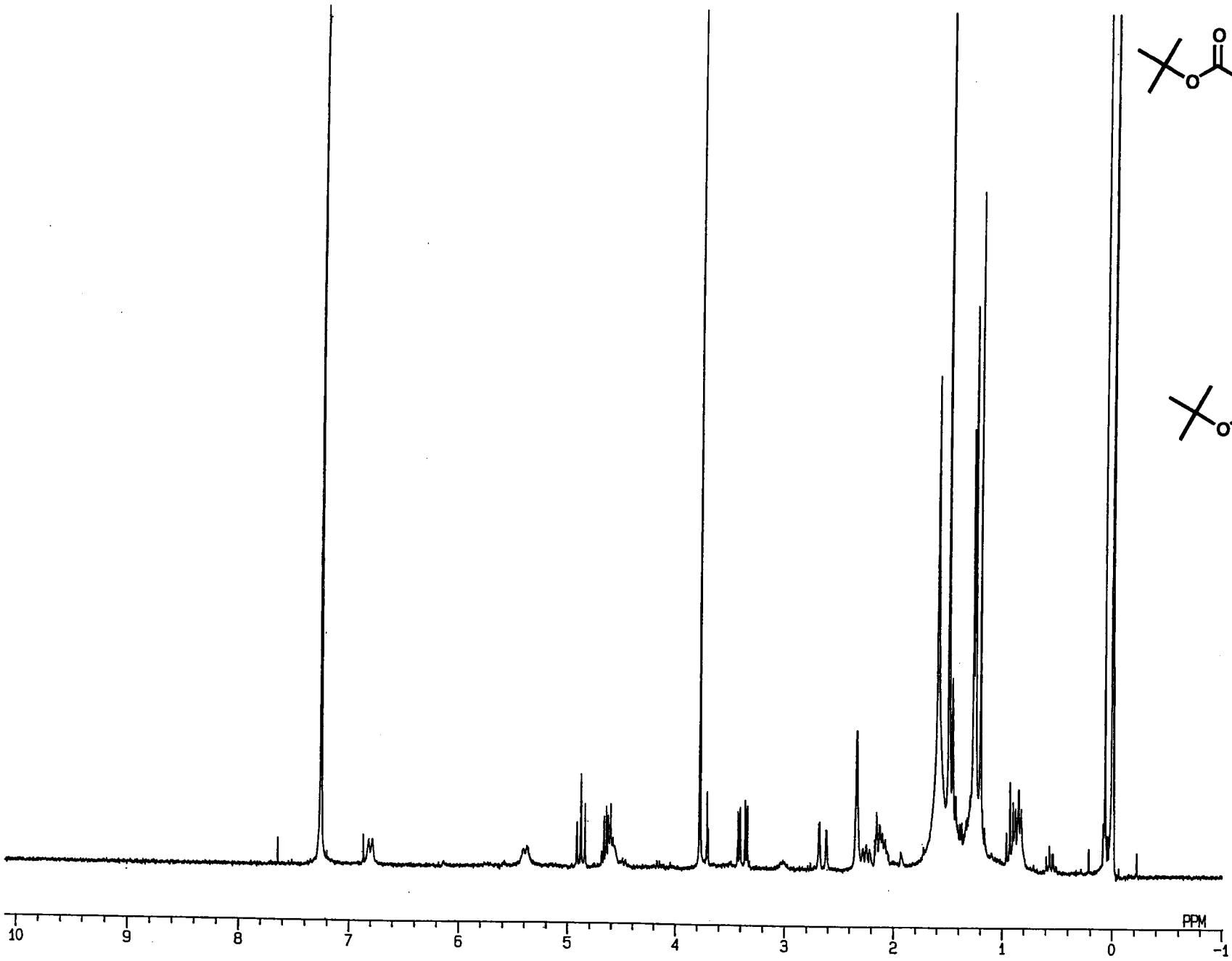

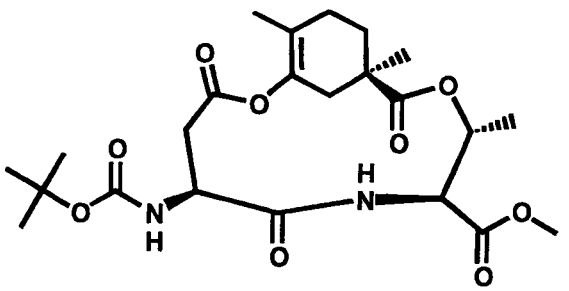

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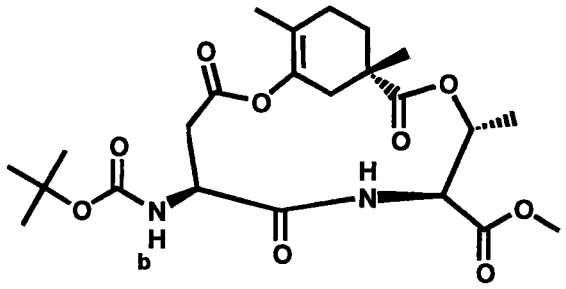
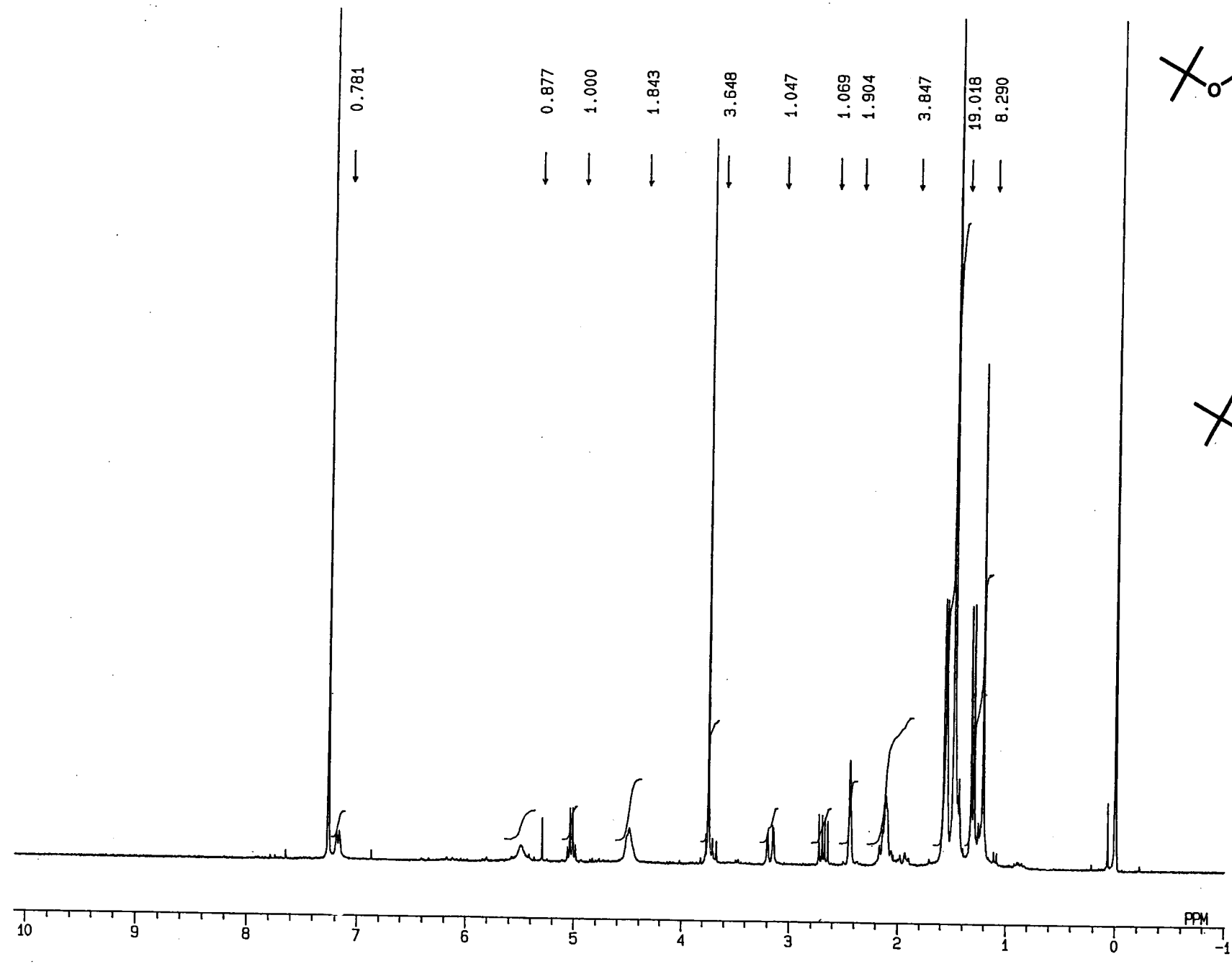
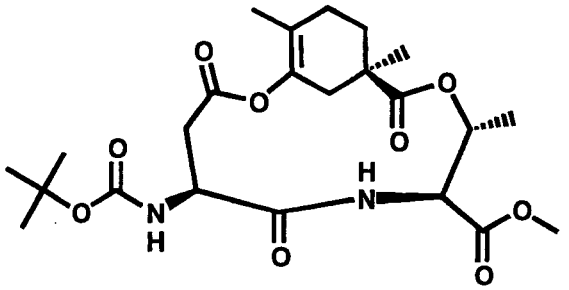
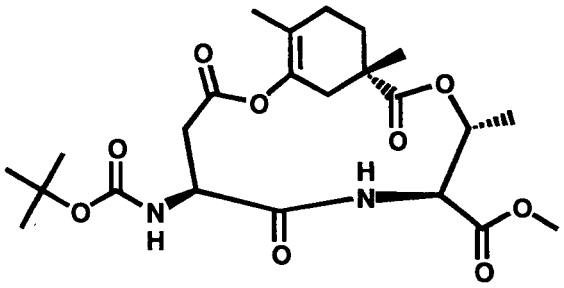


Less polor stereoisomer





or



Polor stereoisomer