Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supporting Information

Talaronoids A−D: Four Diterpenoids with an unprecedented Tricyclic 5/8/6 Ring System from the Fungus *Talaromyces stipitatus*

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Content

Detailed computational procedures:

ECD calculation for compound 1:

The conformations of **1** generated by BALLOON[1,2] were subjected to semiempirical PM3 quantum mechanical geometry optimizations using the Gaussian 09 program.[3] Duplicate conformations were identified and removed when the root-mean-square (RMS) distance was less than 0.5 Å for any two geometry-optimized conformations. The remaining conformations were further optimized at the B3LYP/6-31G(d) level in MeOH with the IEFPCM solvation model using Gaussian 09, and the duplicate conformations emerging after these calculations were removed according to the same RMS criteria above. The harmonic vibrational frequencies were calculated to confirm the stability of the final conformers. The electronic circular dichroism (ECD) spectrum were calculated for each conformer using the TDDFT methodology at the B3LYP/6-311++G(d,p)//B3LYP/6-31G(d) level with MeOH as solvent by the IEFPCM solvation model implemented in Gaussian 09 program. The ECD spectra for each conformer were simulated using a Gaussian function with a bandwidth σ of 0.45 eV. The spectra were combined after Boltzmann weighting according to their population contributions and UV correction was applied.[4]

(1) And, M. J. V.; Johnson, M. S., Generating Conformer Ensembles Using a Multiobjective Genetic Algorithm. *J. Chem. Inf. Model.* **2007,** *47*, 2462-2474.

(2) Puranen, J. S.; Vainio, M. J.; Johnson, M. S., Accurate conformation-dependent molecular electrostatic potentials for high-throughput in silico drug discovery. *J. Comput. Chem.* **2010,** *31*, 1722-1732.

(3) Frisch MJT, G. W. S., H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.;

Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. *J.*, **2009**, Gaussian 09, Revision D 01, Gaussian, Inc, Wallingford, CT.

(4) Zhu, H. J., Organic Stereochemistry: Experimental and Computational Methods. Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim: Germany, **2015**.

Table S1. Important thermodynamic parameters (a.u.) and Boltzmann distribution of the optimized compound **3** at B3LYP/6-31G(d) level in methanol.

Conformation	**Internal Energy**	**Ratio**
1-A-a	-1006.79	90.49%
1-A-b	-1006.79	7.84%
1-A-c	-1006.79	1.62%

Table S2. Optimized coordinates of compound **1** at B3LYP/6-31G(d) level in methanol

1-A-a				**1**-A-b			
C1	2.243	1.061	-0.038	C1	-2.368	-0.733	-0.337
C2	-0.977	2.056	1.19	C2	0.829	-2.291	0.222
C3	1.29	0.718	0.845	C3	-1.349	-0.799	0.537
C4	-1.821	1.488	0.309	C4	1.68	-1.482	-0.427
C5	0.483	1.818	1.517	C5	-0.599	-2.113	0.693
C6	3.245	-1.233	-0.004	C6	-3.2	1.418	0.631
C7	1.833	-1.702	0.36	C7	-1.741	1.649	1.033
C8	-2.489	-0.039	-1.69	C8	2.351	0.641	-1.798
C9	-0.428	-1.108	1.377	C9	0.519	0.615	1.584

C10	-1.439	0.333	-0.617	C10	1.341	-0.054	-0.852
C11	-1.242	-1.055	0.082	C11	1.256	1.005	0.299
C12	-2.67	-1.675	0.174	C12	2.712	1.523	0.499
C13	-3.424	-1.099	-1.056	C13	3.384	1.371	-0.904
C14	3.229	0.134	-0.722	C14	-3.324	0.424	-0.544
C15	1.082	-0.73	1.304	C15	-1.015	0.358	1.487
C16	-3.422	-1.423	1.489	C16	3.522	0.833	1.607
C17	2.855	-0.018	-2.216	C17	-3.038	1.111	-1.899
C18	1.648	-0.886	2.741	C18	-1.495	-0.011	2.917
C19	-3.196	2.123	0.195	C19	3.041	-2.042	-0.834
C20	4.618	0.795	-0.619	C20	-4.782	-0.106	-0.556
O1	-3.728	-2.177	-1.955	O1	3.846	2.601	-1.47
O2	-3.329	2.942	-0.98	O2	3.375	-3.305	-0.267
O3	5.595	-0.056	-1.218	O3	-5.084	-0.991	-1.634
H1	2.344	2.116	-0.301	H1	-2.543	-1.601	-0.976
H2	-1.38	2.878	1.784	H2	1.193	-3.298	0.427
H3	0.541	1.686	2.609	H3	-0.618	-2.404	1.756
H4	0.996	2.775	1.337	H4	-1.188	-2.897	0.193
H5	3.855	-1.151	0.905	H5	-3.763	1.032	1.491
H6	3.737	-1.98	-0.637	H6	-3.669	2.373	0.359
H7	1.262	-1.832	-0.566	H7	-1.215	2.09	0.179
H8	1.875	-2.692	0.832	H8	-1.686	2.389	1.842
H9	-1.969	-0.528	-2.523	H9	1.807	1.403	-2.372
H10	-3.023	0.825	-2.091	H10	2.823	-0.018	-2.532
H11	-0.907	-0.481	2.137	H11	0.996	-0.268	2.026
H12	-0.478	-2.137	1.763	H12	0.657	1.427	2.313

H13	-0.501	0.607	-1.107	H13	0.365	-0.098	-1.344
H14	-0.722	-1.661	-0.671	H14	0.717	1.847	-0.153
H15	-2.599	-2.761	0.037	H15	2.682	2.594	0.741
H16	-4.369	-0.638	-0.733	H16	4.3	0.778	-0.811
H17	-4.433	-1.843	1.431	H17	3.088	1.012	2.596
H18	-2.916	-1.896	2.338	H18	3.579	-0.252	1.465
H19	-3.518	-0.355	1.716	H19	4.548	1.22	1.62
H20	1.904	-0.546	-2.335	H20	-3.121	0.393	-2.721
H21	3.632	-0.575	-2.75	H21	-2.031	1.54	-1.924
H22	2.752	0.965	-2.693	H22	-3.759	1.918	-2.081
H23	2.715	-0.646	2.783	H23	-2.573	-0.202	2.943
H24	1.517	-1.919	3.087	H24	-1.277	0.809	3.612
H25	1.132	-0.234	3.454	H25	-0.99	-0.906	3.296
H26	-3.993	1.38	0.107	H26	3.065	-2.205	-1.919
H27	-3.402	2.719	1.095	H27	3.834	-1.314	-0.615
H28	4.596	1.774	-1.124	H28	-5.005	-0.584	0.409
H29	4.855	0.972	0.441	H29	-5.464	0.744	-0.673
H30	-4.181	-1.79	-2.722	H30	3.071	3.176	-1.585
H31	-2.583	3.564	-0.965	H31	3.403	-3.187	0.697
H32	6.455	0.383	-1.13	H32	-4.676	-1.848	-1.434

1-A-c							
C1	-1.907	-0.582	-1.084	H6	-1.955	1.391	1.121
C2	1.468	-2.111	-1.004	H7	-1.912	-0.486	2.774
C3	-0.946	-1.274	-0.448	H8	-2.83	-1.494	1.668

C4	2.227	-1.022	-0.812	H9	3.672	1.29	-0.697
C5	-0.027	-2.182	-1.255	H10	2.755	1.836	-2.088
C6	-2.659	0.556	1.027	H11	1.319	-0.914	1.666
C7	-2.085	-0.688	1.709	H12	0.192	0.183	2.434
C8	2.665	1.552	-1.032	H13	0.933	0.42	-1.639
C9	0.446	-0.283	1.472	H14	-0.091	1.257	0.093
C10	1.648	0.391	-0.812	H15	0.907	2.704	1.59
C11	0.831	0.824	0.483	H16	2.971	3.427	0.072
C12	1.61	2.025	1.089	H17	3.469	0.995	1.668
C13	2.165	2.717	-0.165	H18	2.304	1.184	2.98
C14	-2.965	0.311	-0.468	H19	3.239	2.577	2.422
C15	-0.769	-1.208	1.072	H20	-3.819	2.287	-0.824
C16	2.718	1.671	2.091	H21	-3.232	1.491	-2.293
C17	-3.024	1.652	-1.228	H22	-2.073	2.191	-1.148
C18	-0.511	-2.613	1.664	H23	-0.433	-2.547	2.757
C19	3.717	-1.185	-0.591	H24	0.422	-3.047	1.292
C20	-4.327	-0.419	-0.643	H25	-1.33	-3.303	1.429
O1	1.073	3.417	-0.78	H26	4.015	-0.659	0.332
O2	4.081	-2.559	-0.506	H27	4.265	-0.697	-1.413
O3	-5.466	0.353	-0.261	H28	-4.309	-1.375	-0.1
H1	-1.969	-0.671	-2.171	H29	-4.474	-0.648	-1.704
H2	1.975	-3.072	-1.001	H30	1.383	3.735	-1.643
H3	-0.227	-2.011	-2.323	H31	5.048	-2.592	-0.451
H4	-0.329	-3.223	-1.071	H32	-5.471	0.412	0.707
H5	-3.568	0.887	1.548				

The Molecular docking assays

The crystal structures of soman-aged BChE (PDB ID: 4b0p) were obtained from the protein data bank for docking simulations. Before docking, protein should be prepared with removing the water and other co-crystallized small molecules and adding hydrogens. Then the cleaning protein were prepared in the module Prepare Protein. For ligands, potentials were assigned using CHARMm force field and energy minimized. Then prepared with the module Prepare Ligands. The binding pocket of the protein was defined based on the volume occupied by the known ligand pose already in the active site. During the docking process top 10 conformations were saved for each ligand based on Cdocker score value using the smart minimize method through CDOCKER methods. The best-scoring pose as judged by the Cdocker Interaction energy score was chosen to visual analysis using PyMOL software.

Table S3. The inhibitory value and docking score of compounds **1**-**4**with BChE.

Compound	IC_{50} (μM) [a]	Docking Score [b]
1	14.71 ± 1.07	37.29
2	26.47 ± 0.35	31.43
3	31.51 ± 0.28	28.64
4	11.37 ± 0.85	32.88
Rivastigmine	4.88 ± 0.11	

[a] IC_{50} value of compounds against BChE.

[b] The score of Cdocker interaction energy.

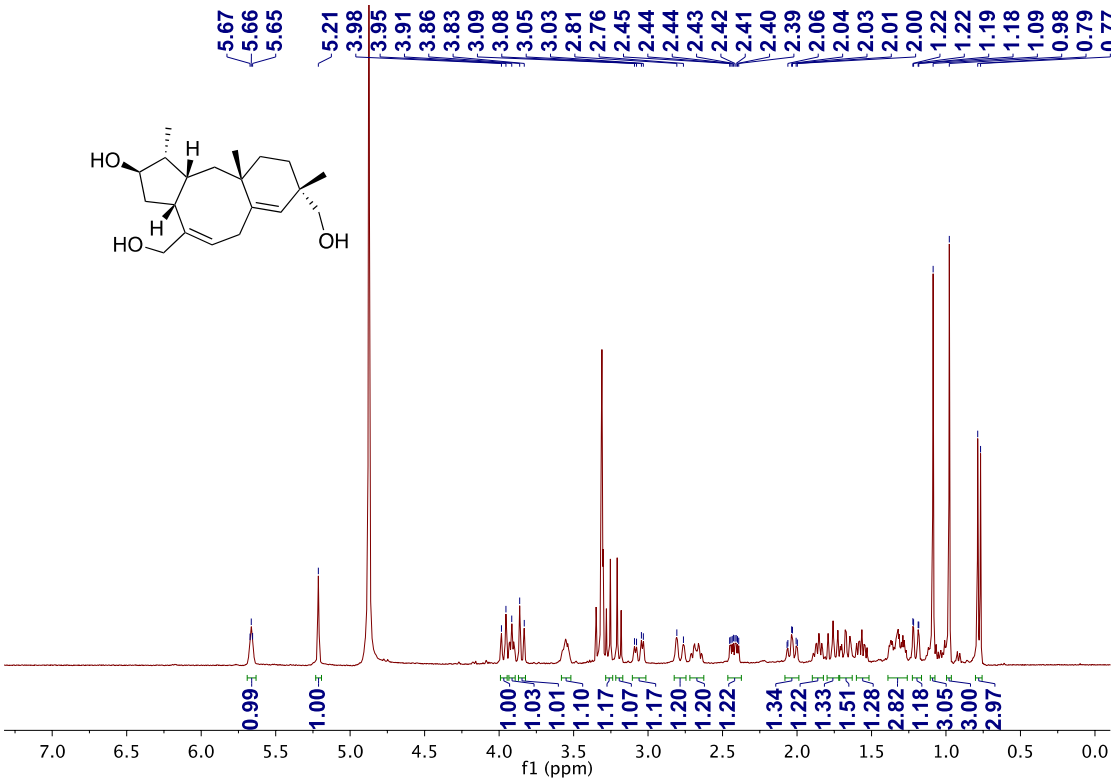

Figure S1. ^{1}H NMR spectrum of talaronid A (**1**) in CD_3OD

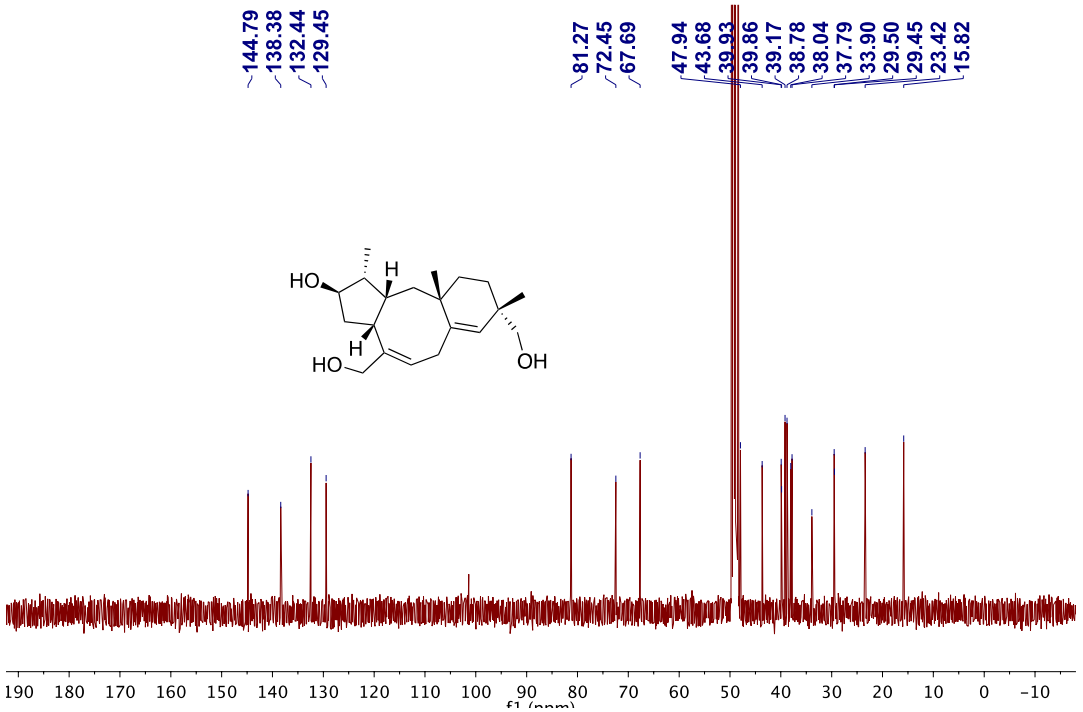

Figure S2. ^{13}C NMR spectrum of talaronid A (**1**) in CD_3OD

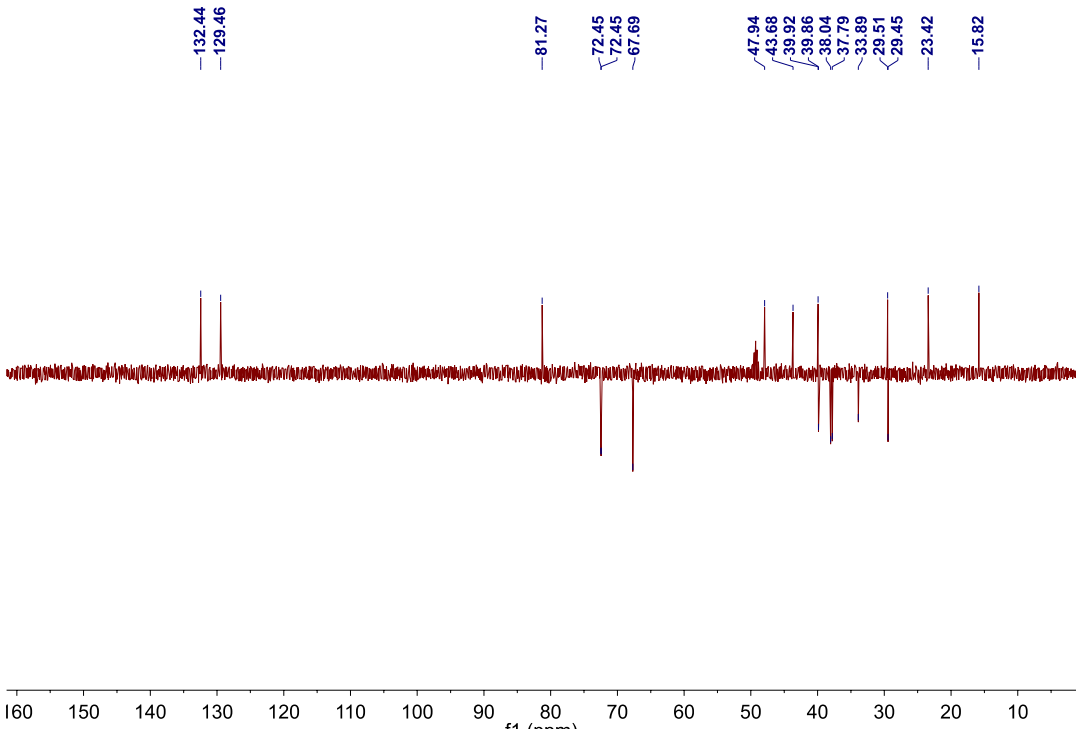

Figure S3. DEPT spectrum of talaronid A (**1**) in CD_3OD

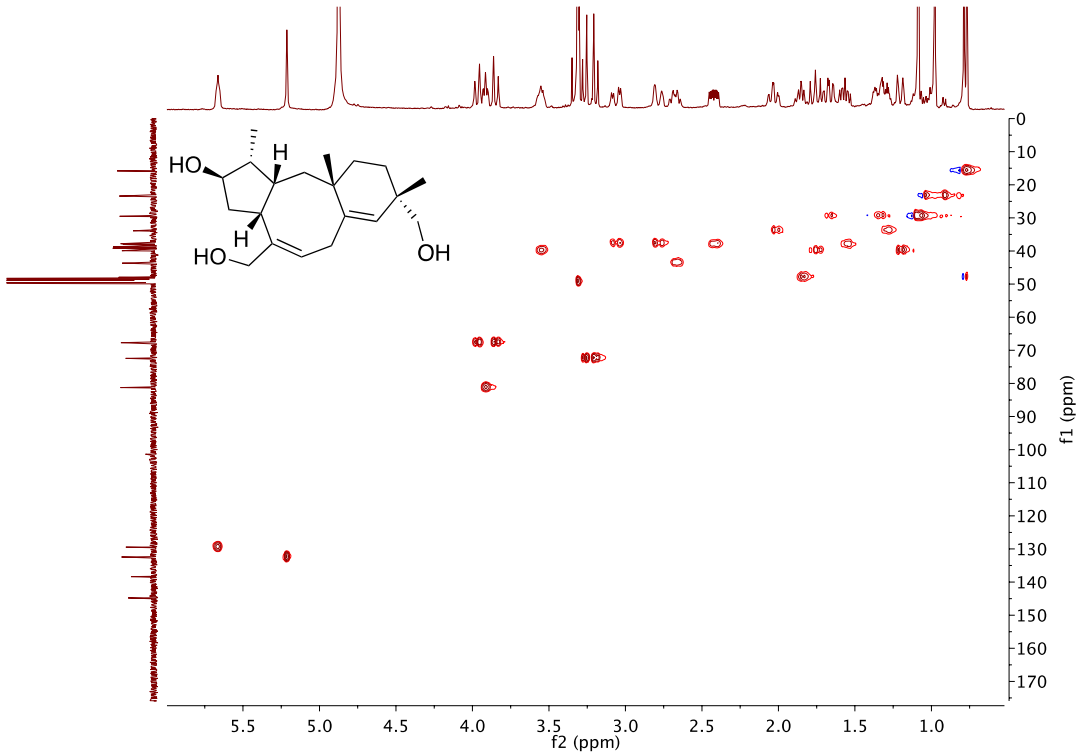

Figure S4. HSQC spectrum of talaronid A (**1**) in CD_3OD

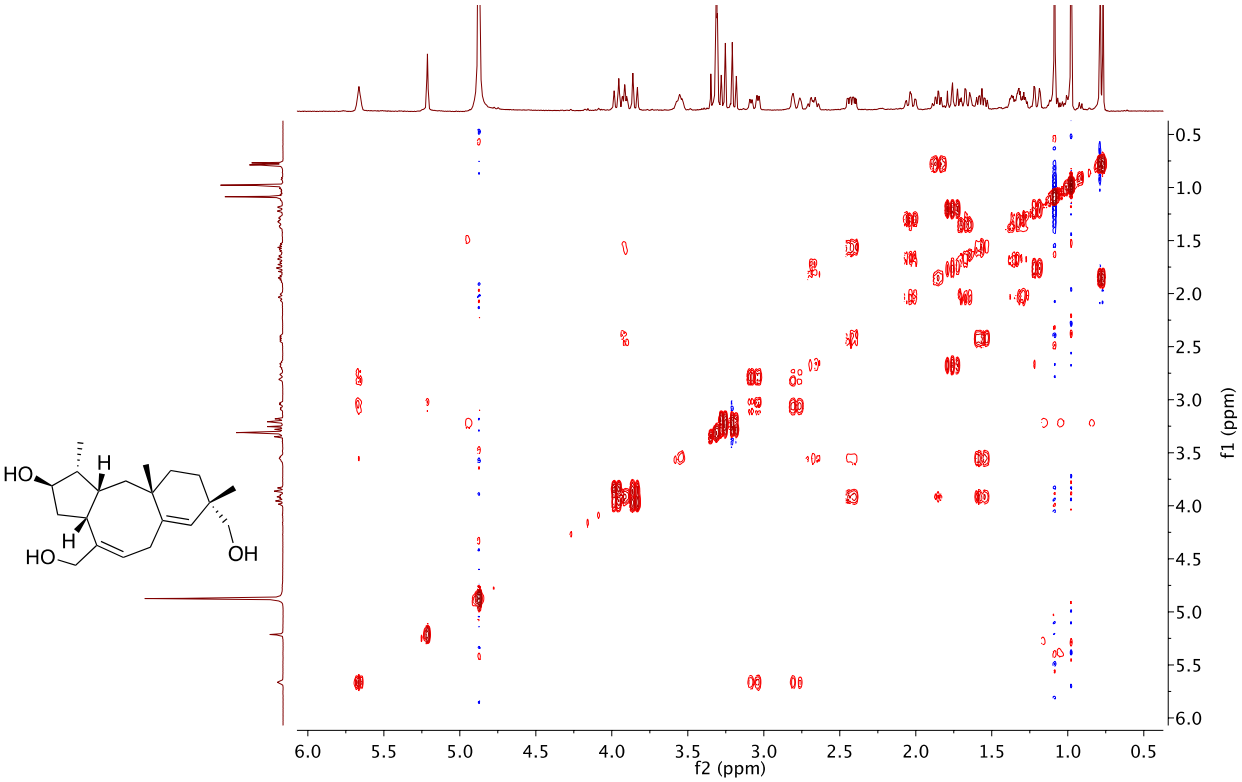

Figure S5 ^{1}H-^{1}H COSY spectrum of talaronid A (**1**) in CD_3OD

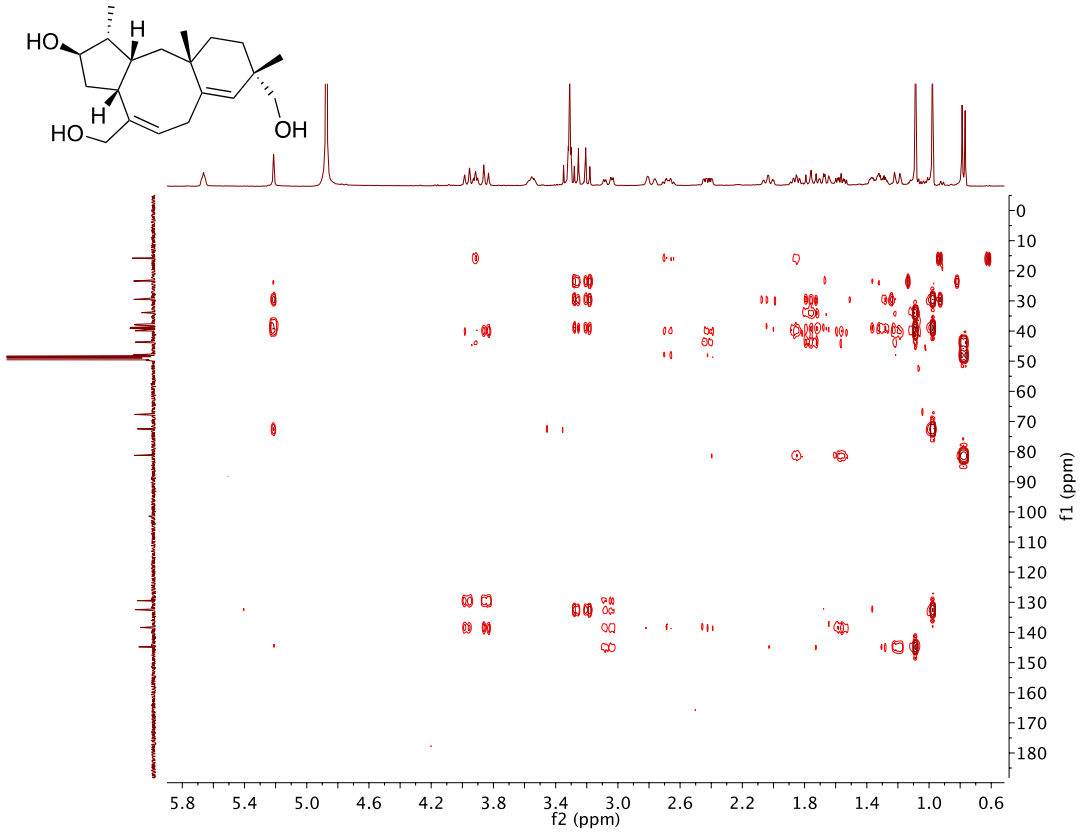

Figure S6. HMBC spectrum of talaronid A (**1**) in CD_3OD

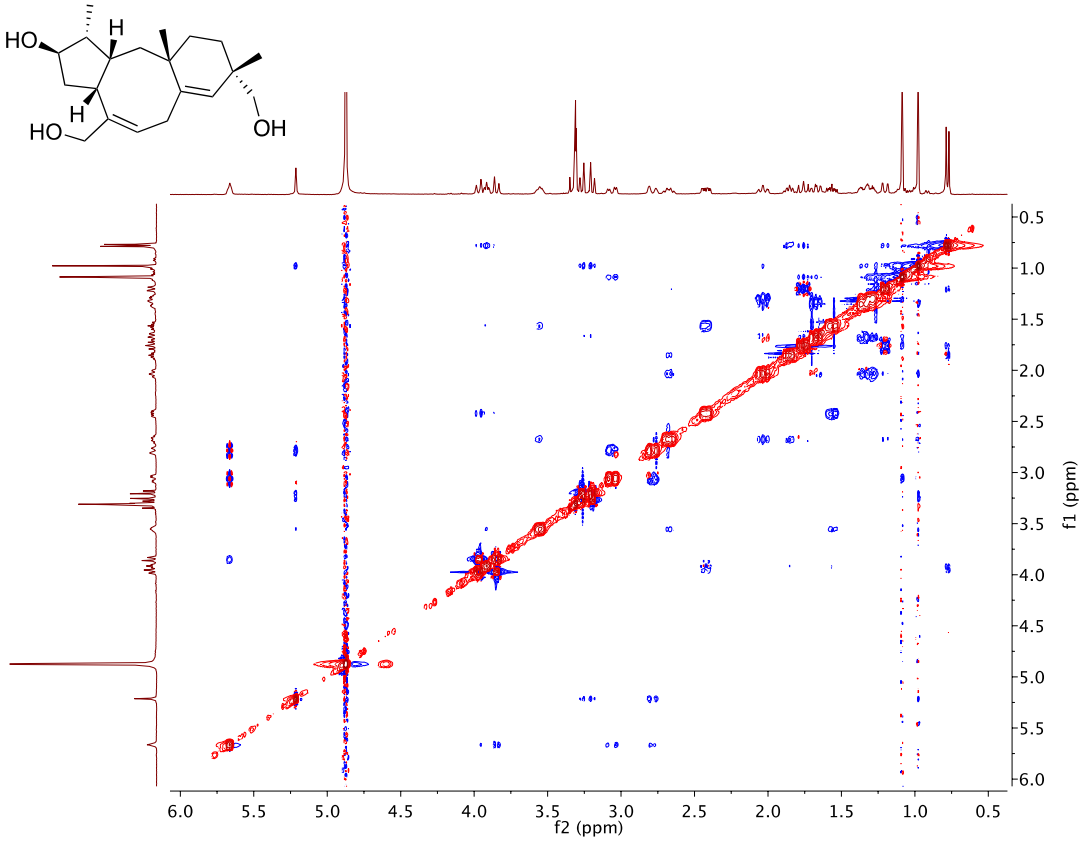

Figure S7. NOESY spectrum of talaronid A (**1**) in CD_3OD

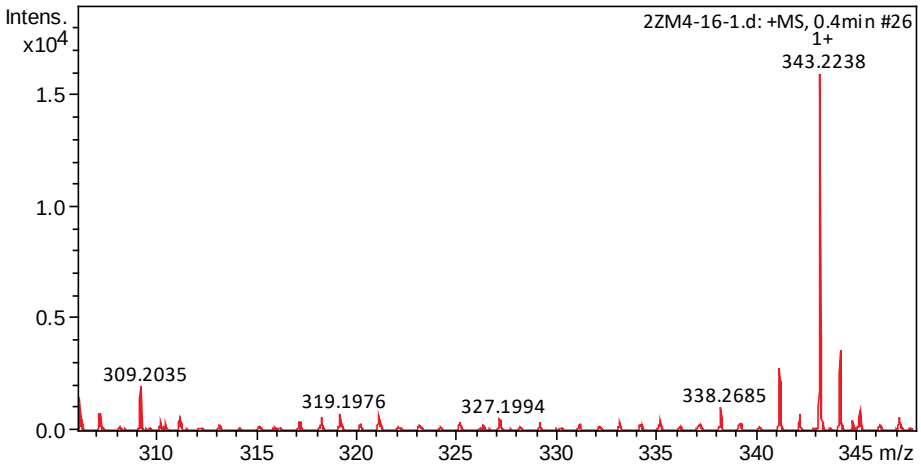

Figure S8. (+) ESI-MS spectrum of talaronid A (**1**)

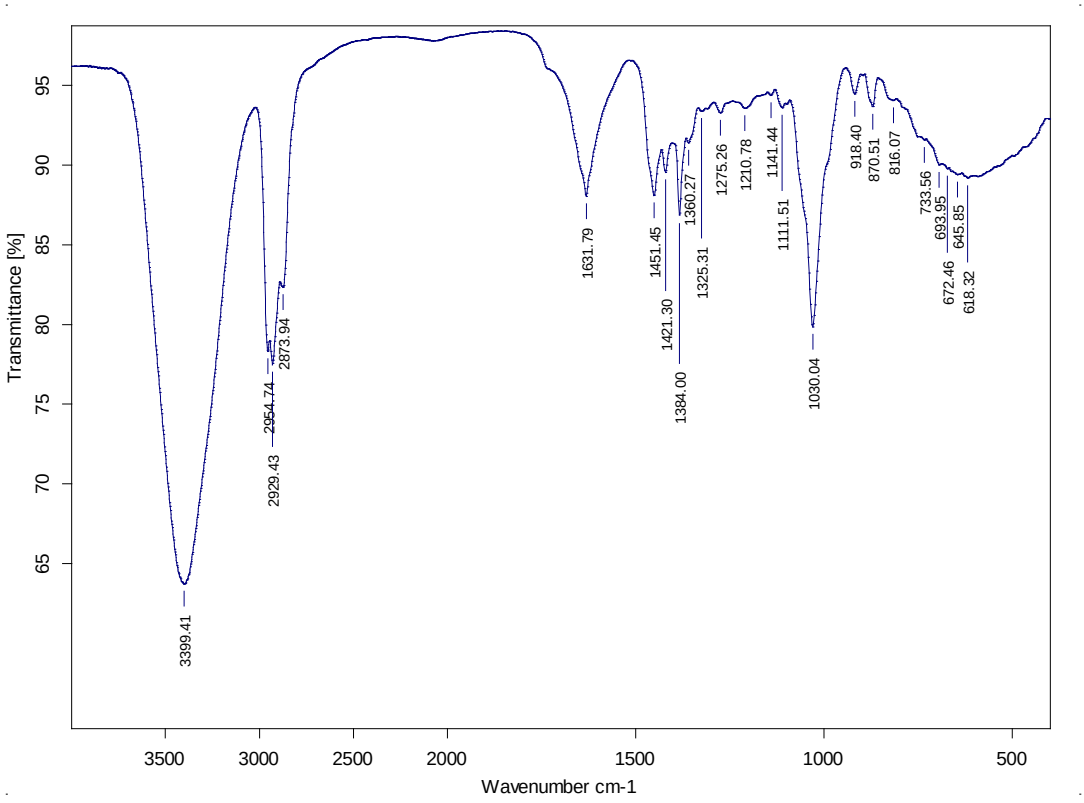

Figure S9. IR spectrum of talaronid A (**1**)

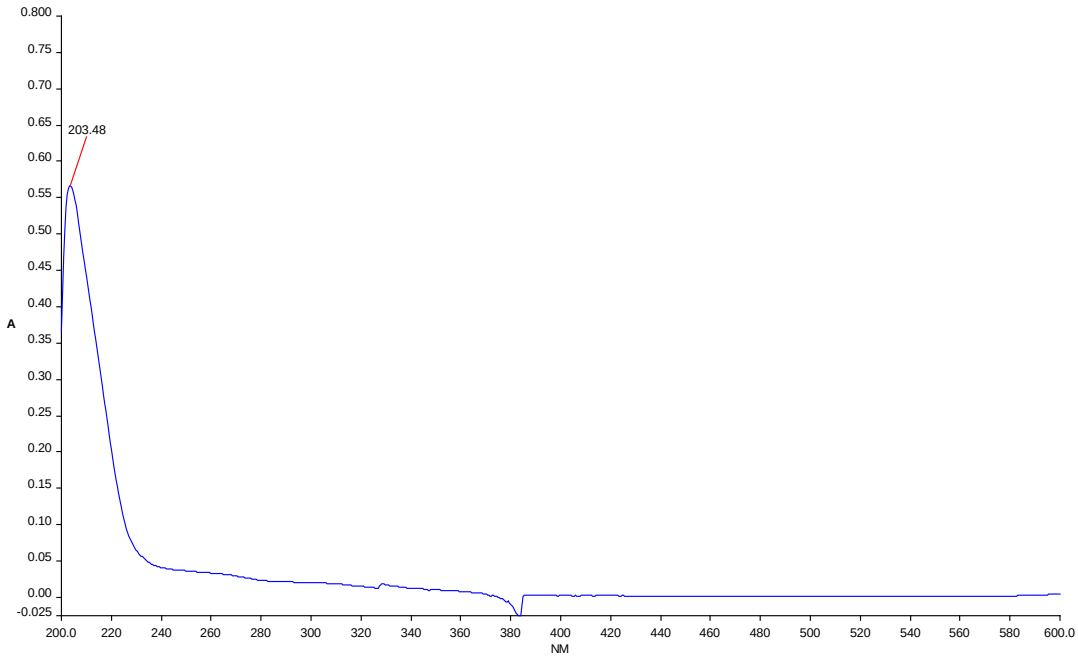

Figure S10. UV spectrum of talaronid A (**1**)

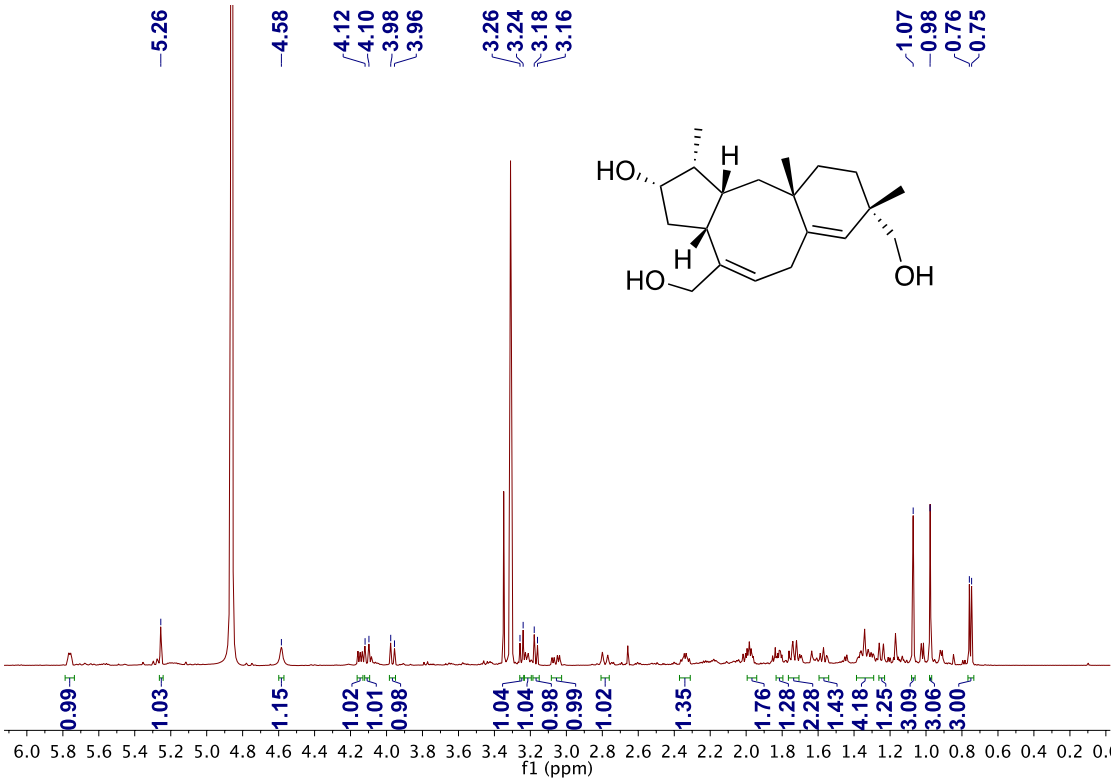

Figure S11. ^{1}H NMR spectrum of talaronid B (**2**) in CD_3OD

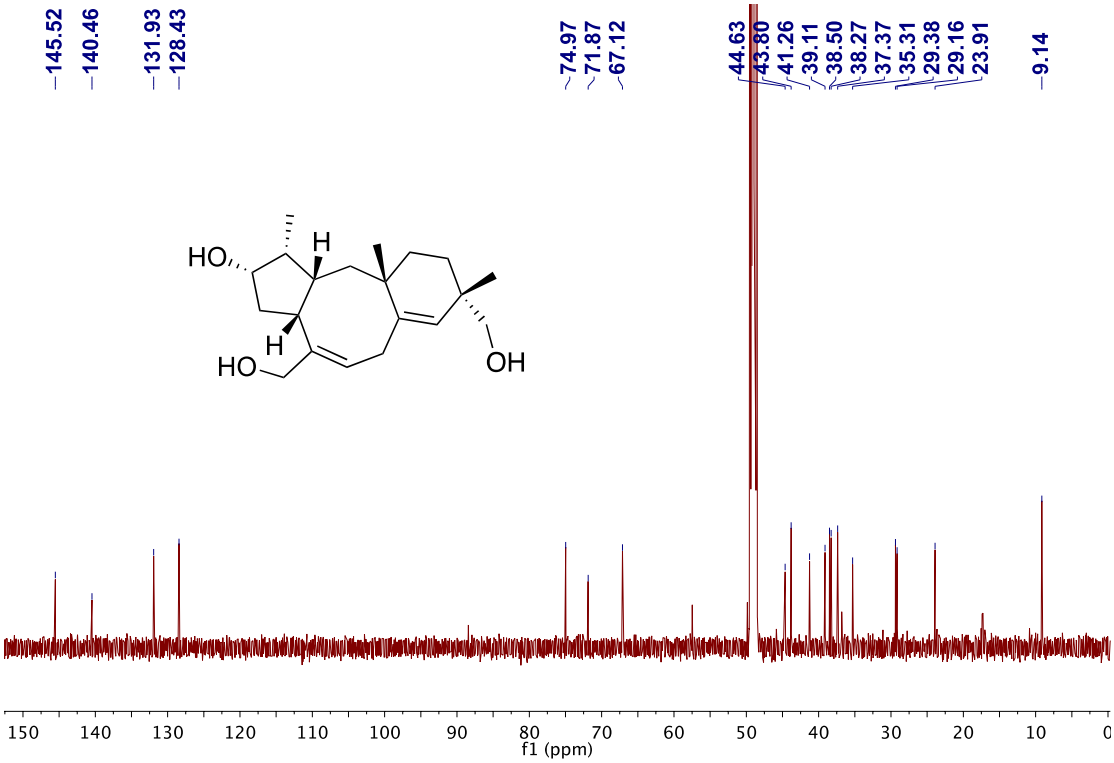

Figure S12. ^{13}C NMR spectrum of talaronid B (**2**) in CD_3OD

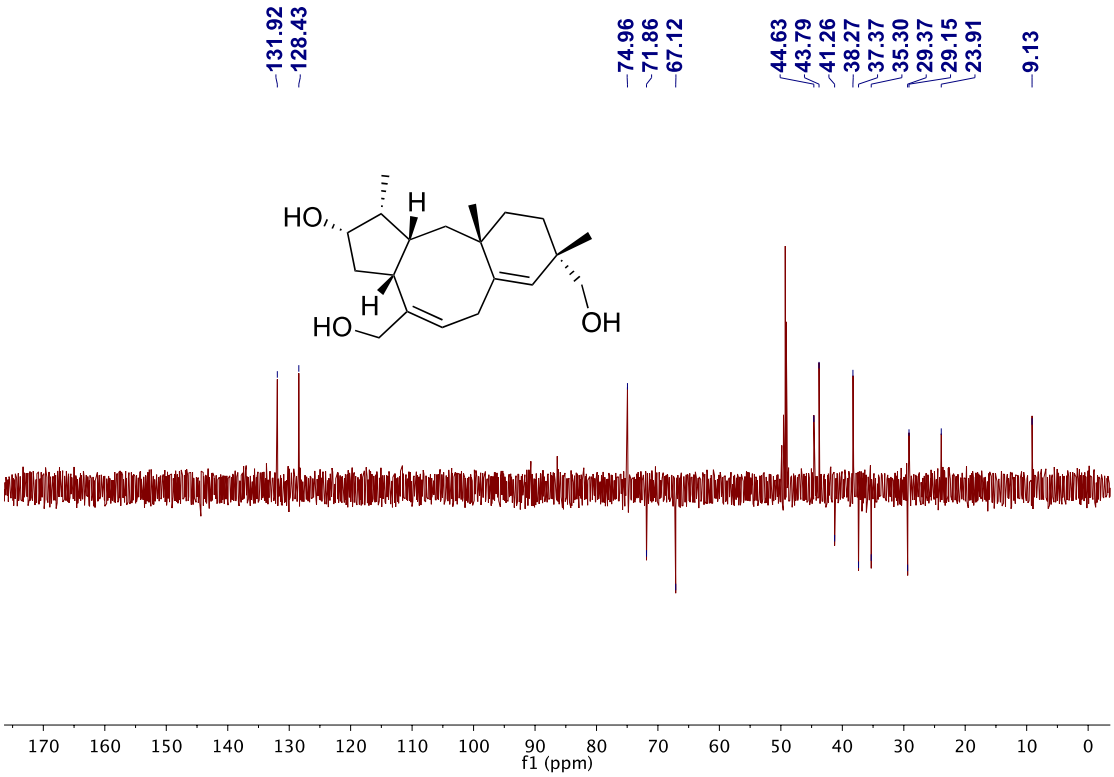

Figure S13. DEPT spectrum of talaronid B (**2**) in CD_3OD

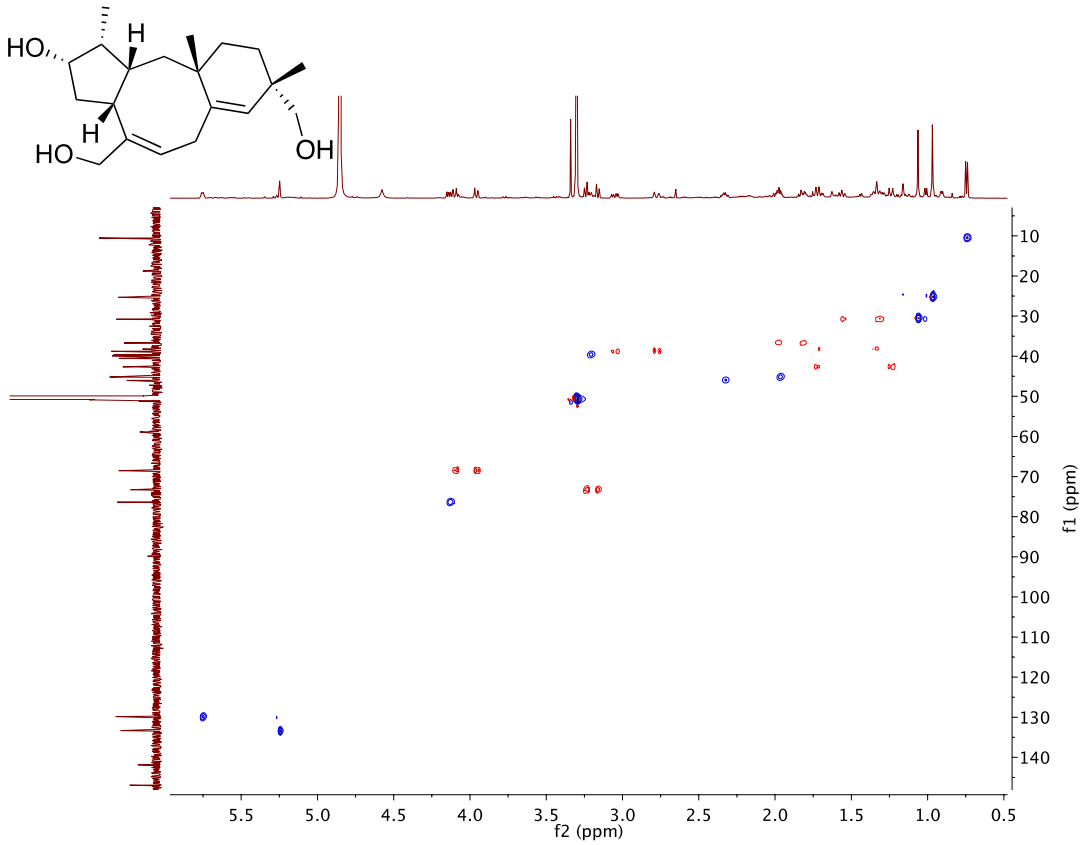

Figure S14. HSQC spectrum of talaronid B (**2**) in CD_3OD

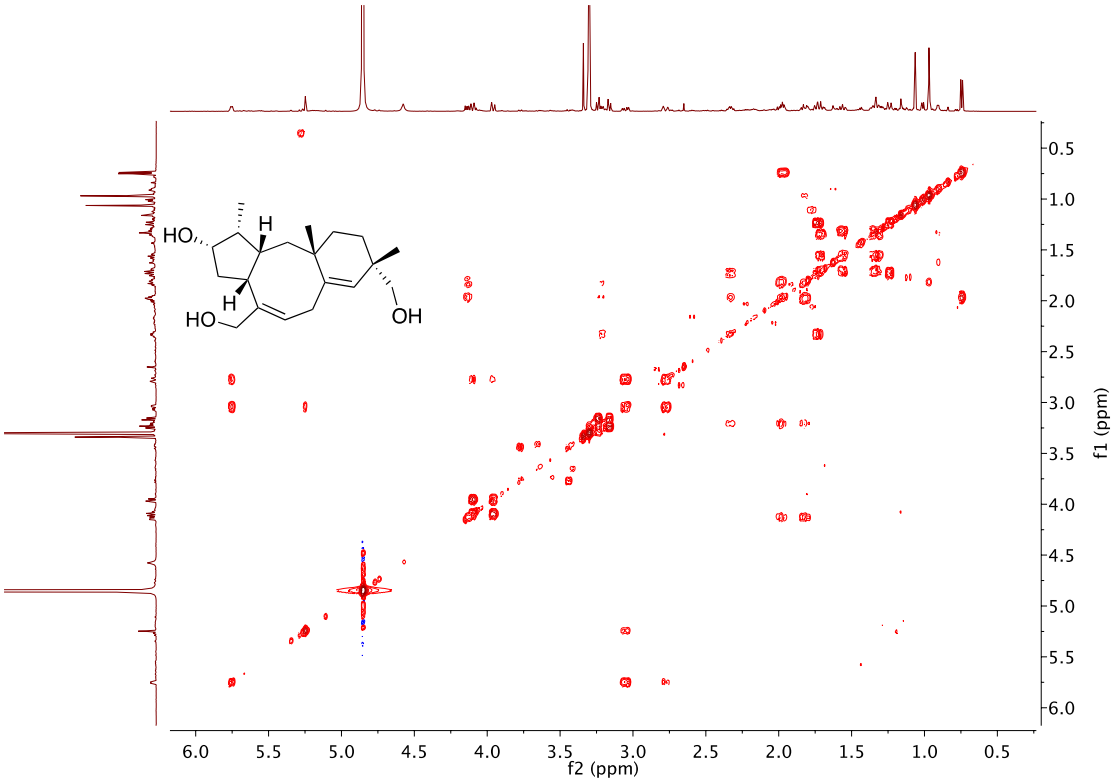

Figure S15 ^{1}H-^{1}H COSY spectrum of talaronid B (**2**) in CD_3OD

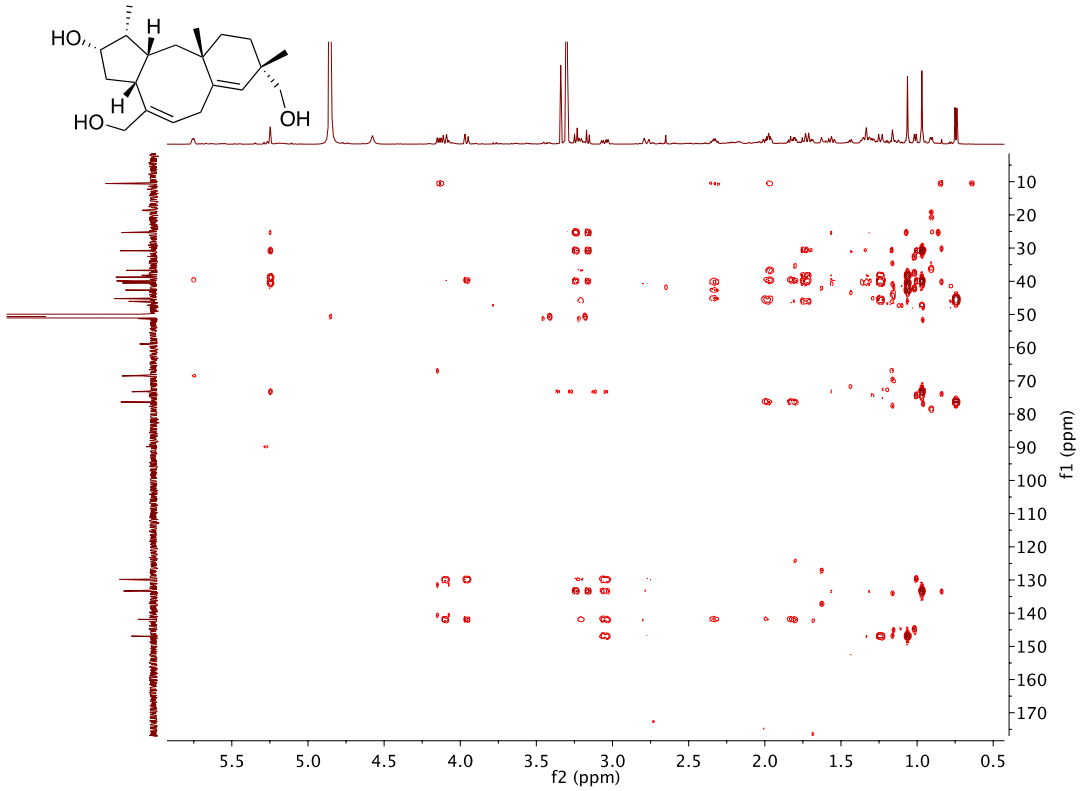

Figure S16. HMBC spectrum of talaronid B (**2**) in CD_3OD

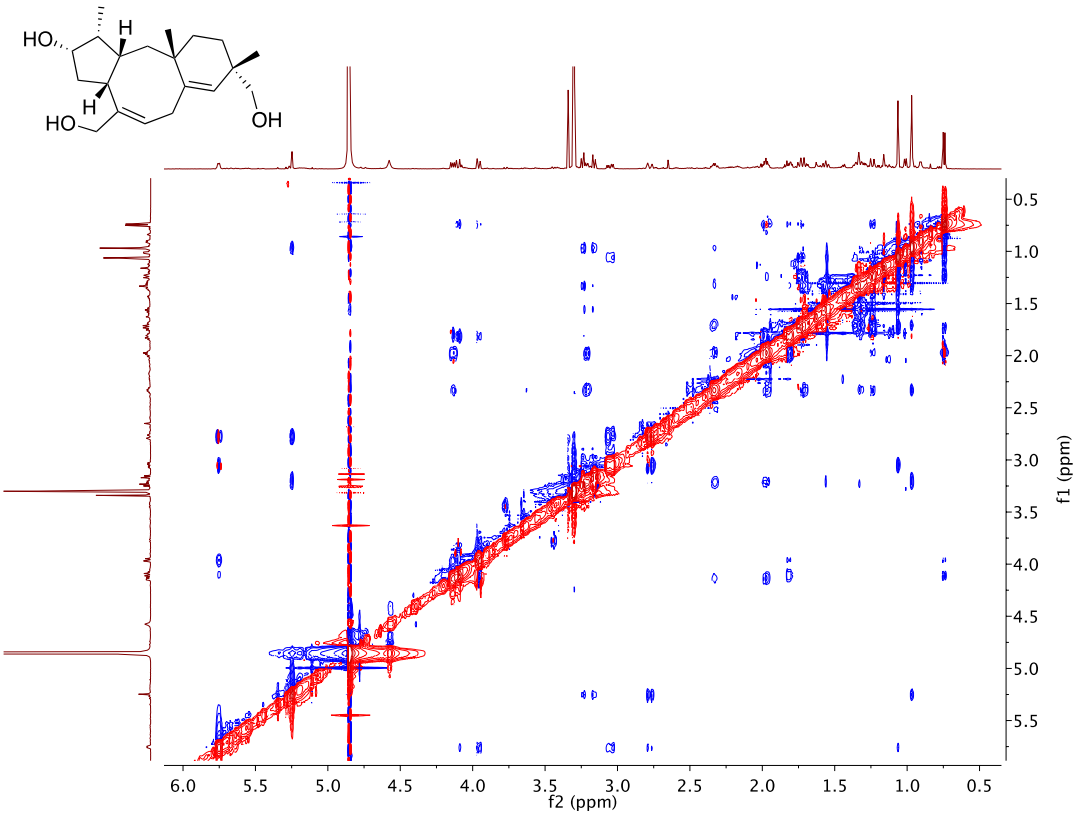

Figure S17. NOESY spectrum of talaronid B (**2**) in CD_3OD

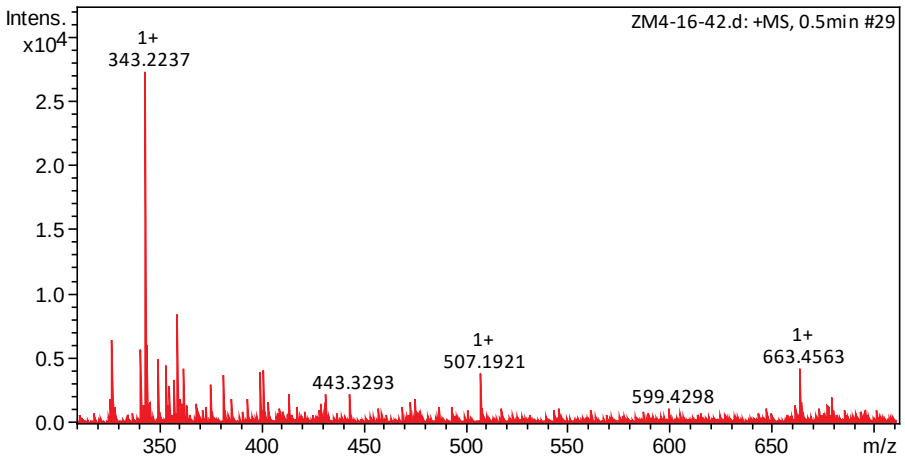

Figure S18. (+) ESI-MS spectrum of talaronid B (**2**)

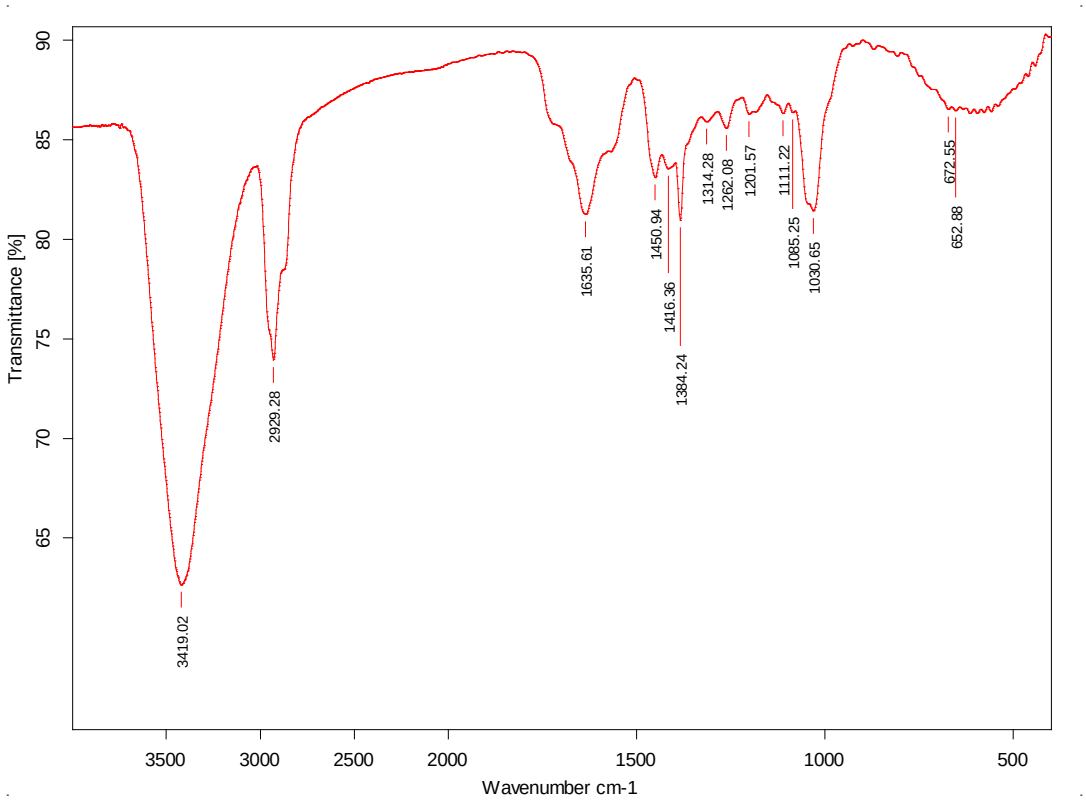

Figure S19. IR spectrum of talaronid B (**2**)

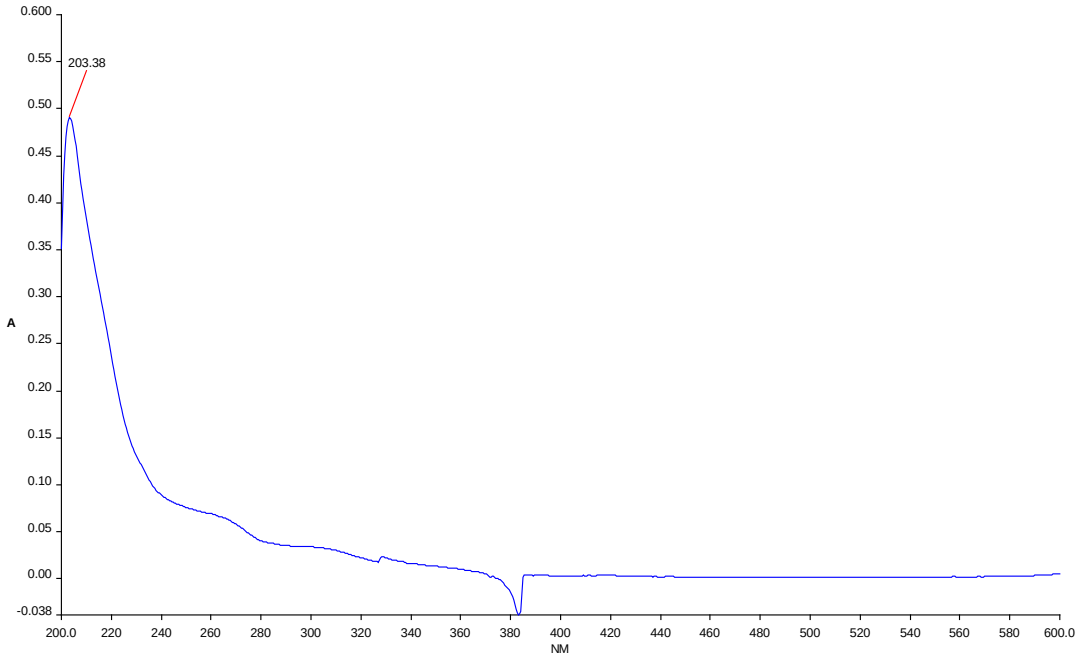

Figure S20. UV spectrum of talaronid B (**2**)

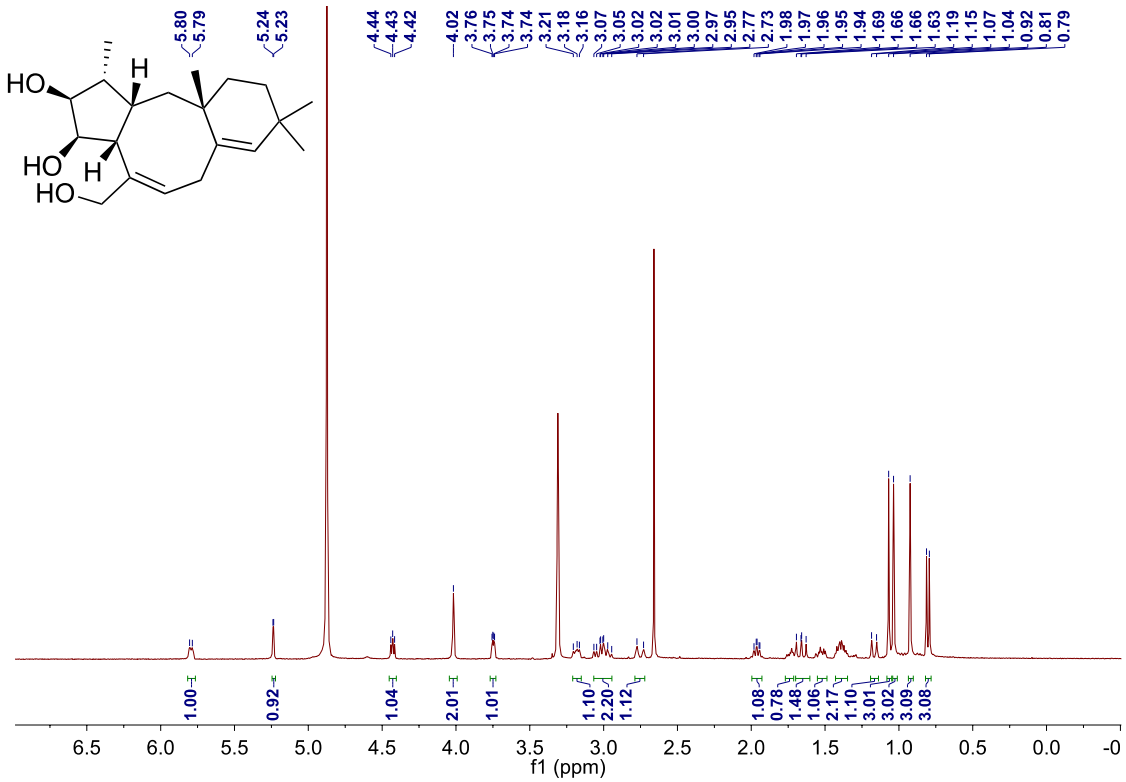

Figure S21. ^{1}H NMR spectrum of talaronid C (**3**) in CD_3OD

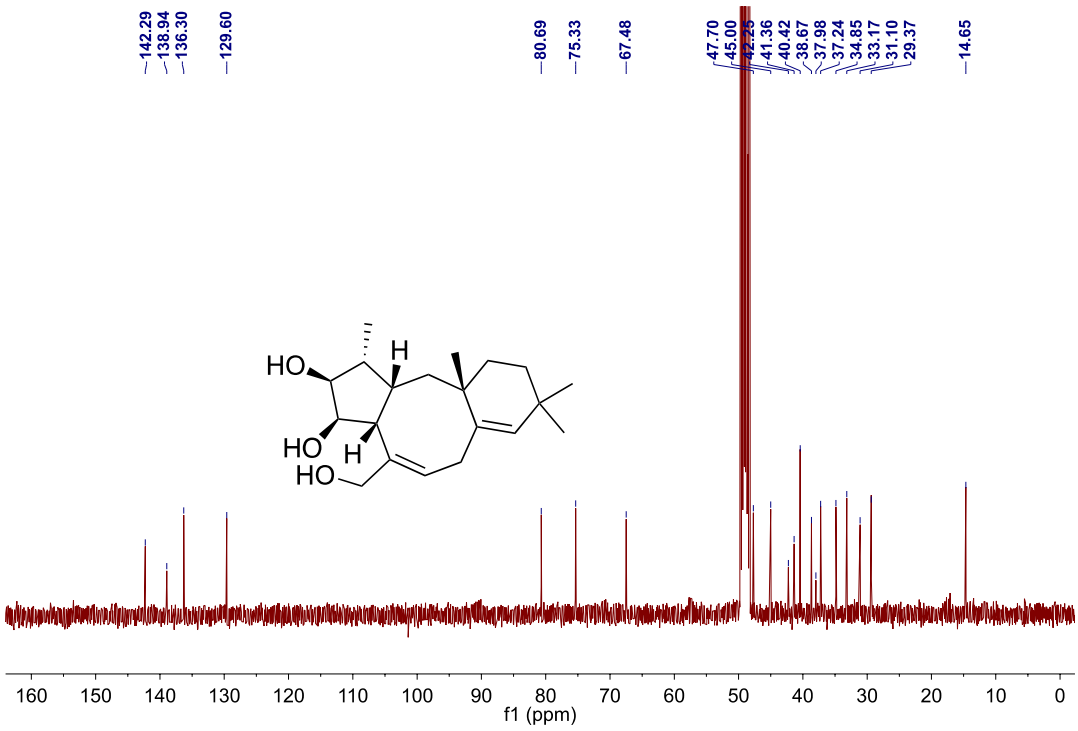

Figure S22. ^{13}C NMR spectrum of talaronid C (**3**) in CD_3OD

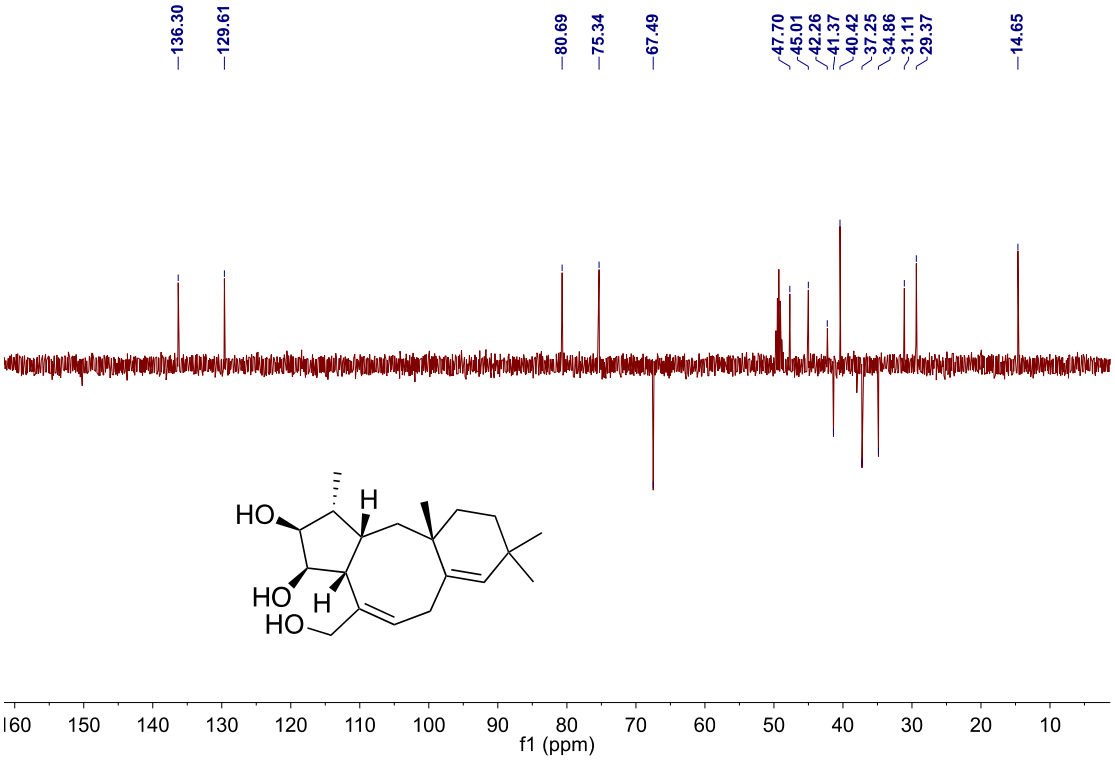

Figure S23. DEPT spectrum of talaronid C (**3**) in CD_3OD

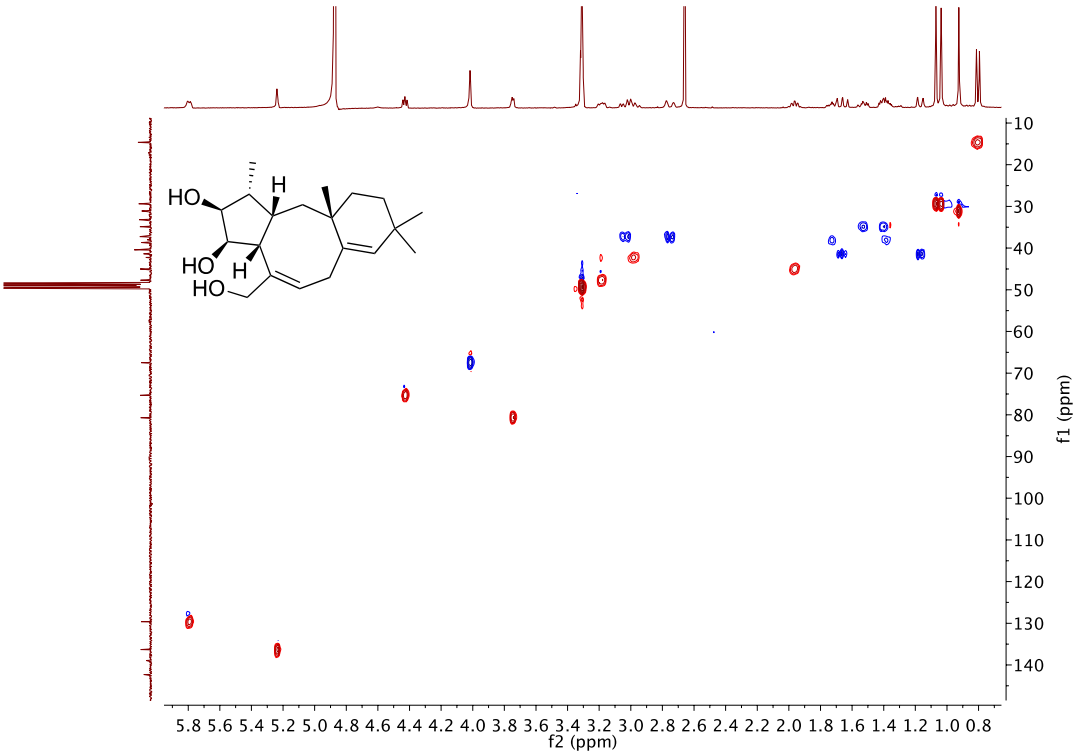

Figure S24. HSQC spectrum of talaronid C (**3**) in CD_3OD

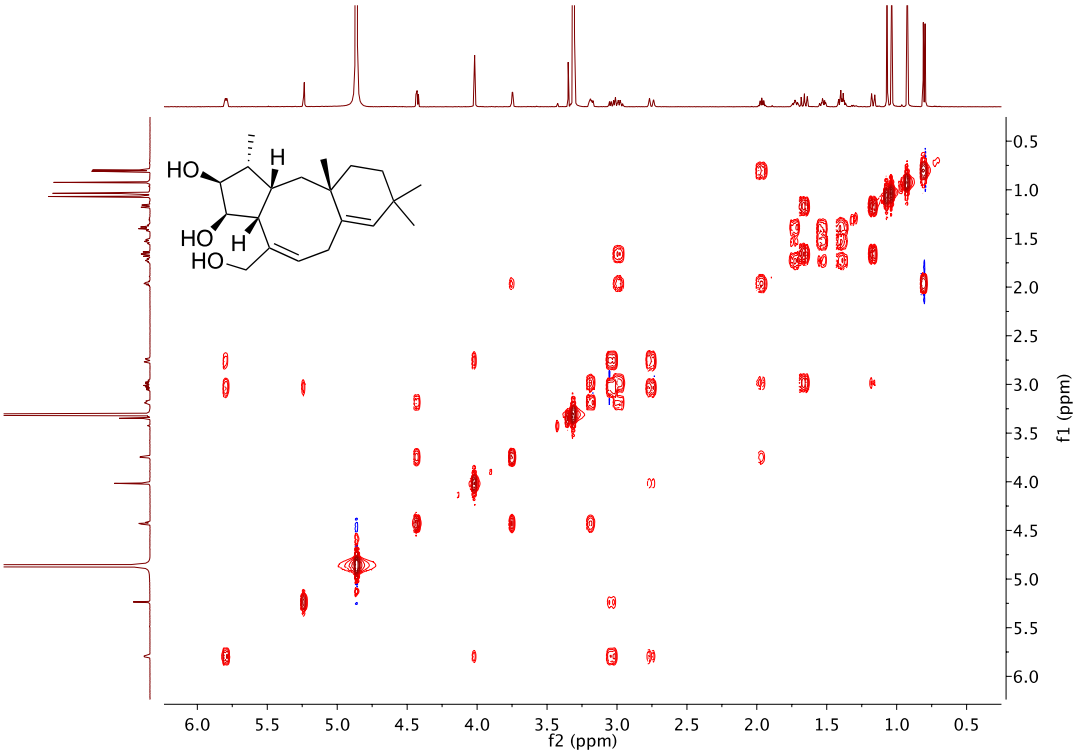

Figure S25. ^{1}H-^{1}H COSY spectrum of talaronid C (**3**) in CD_3OD

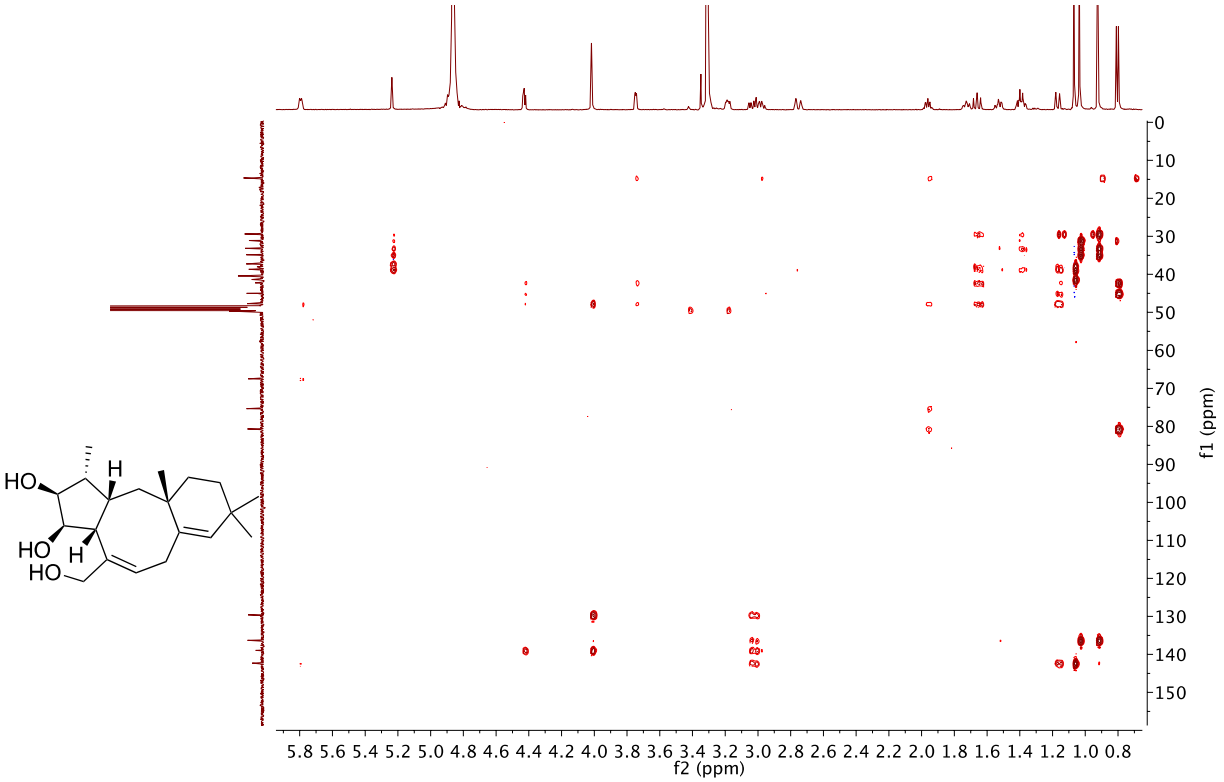

Figure S26. HMBC spectrum of talaronid C (**3**) in CD_3OD

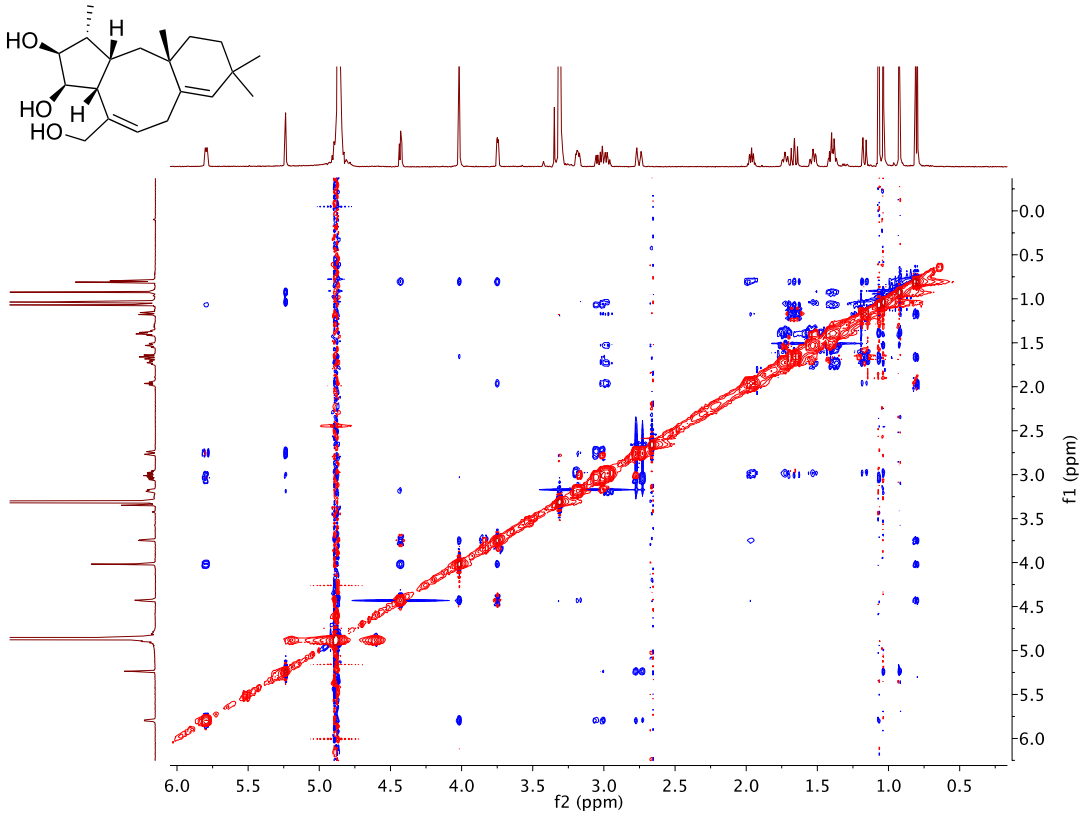

Figure S27. NOESY spectrum of talaronid C (**3**) in CD_3OD

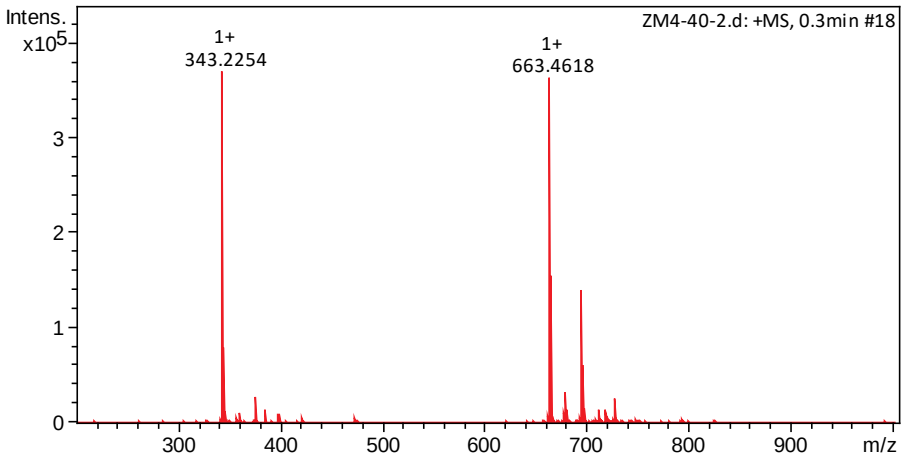

Figure S28. (+) ESI-MS spectrum of talaronid C (**3**)

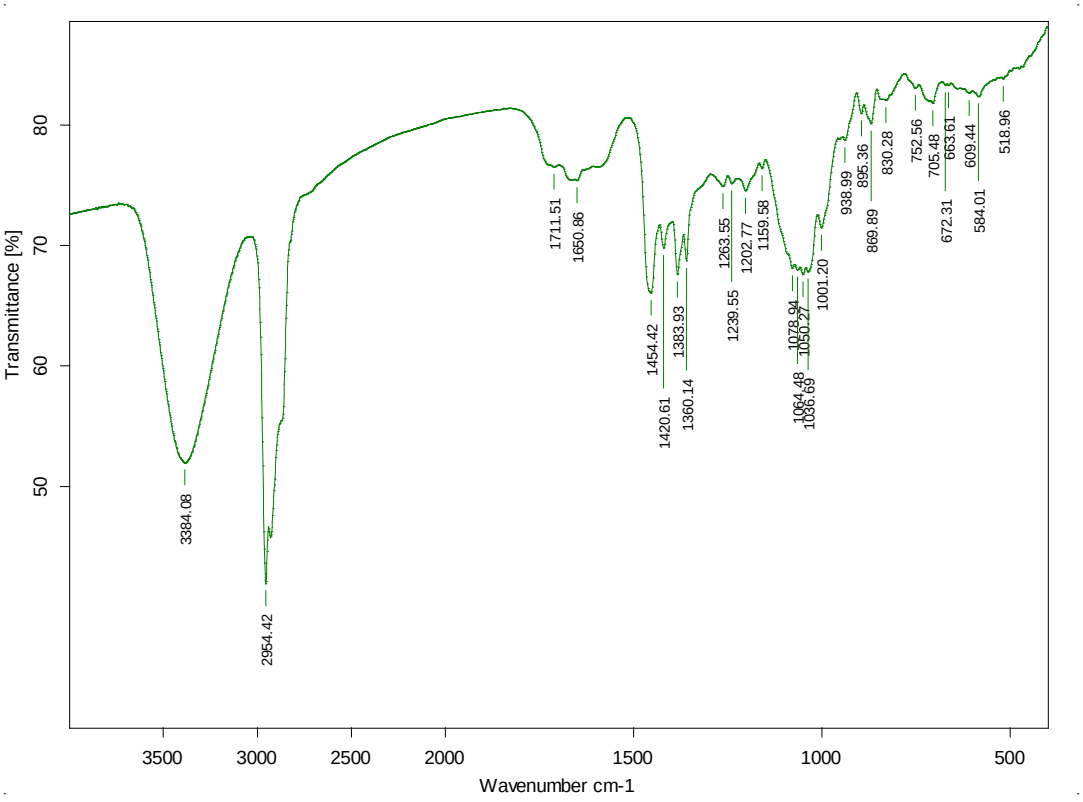

Figure S29. IR spectrum of talaronid C (**3**)

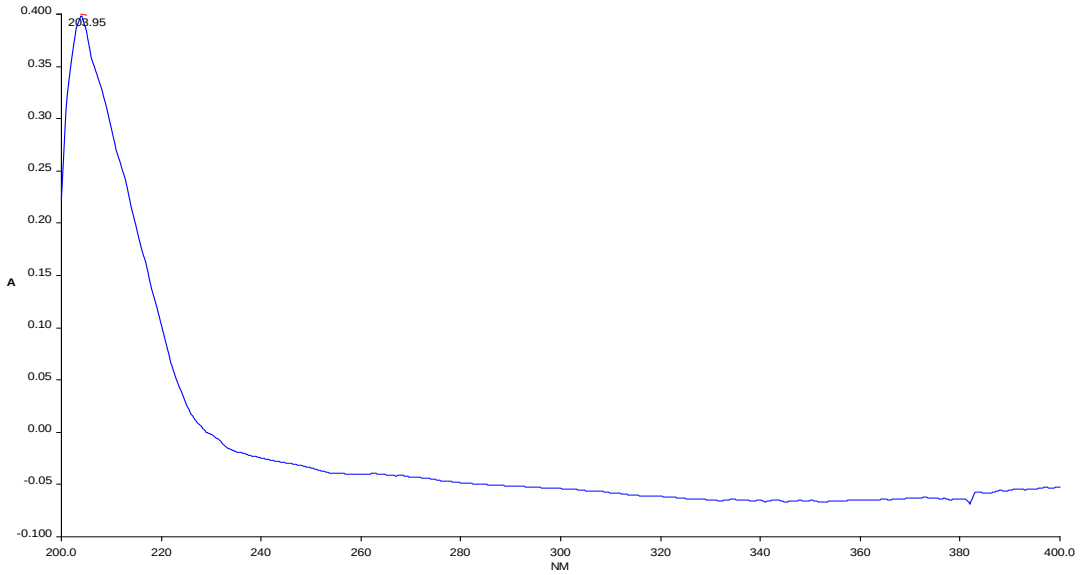

Figure S30. UV spectrum of talaronid C (**3**)

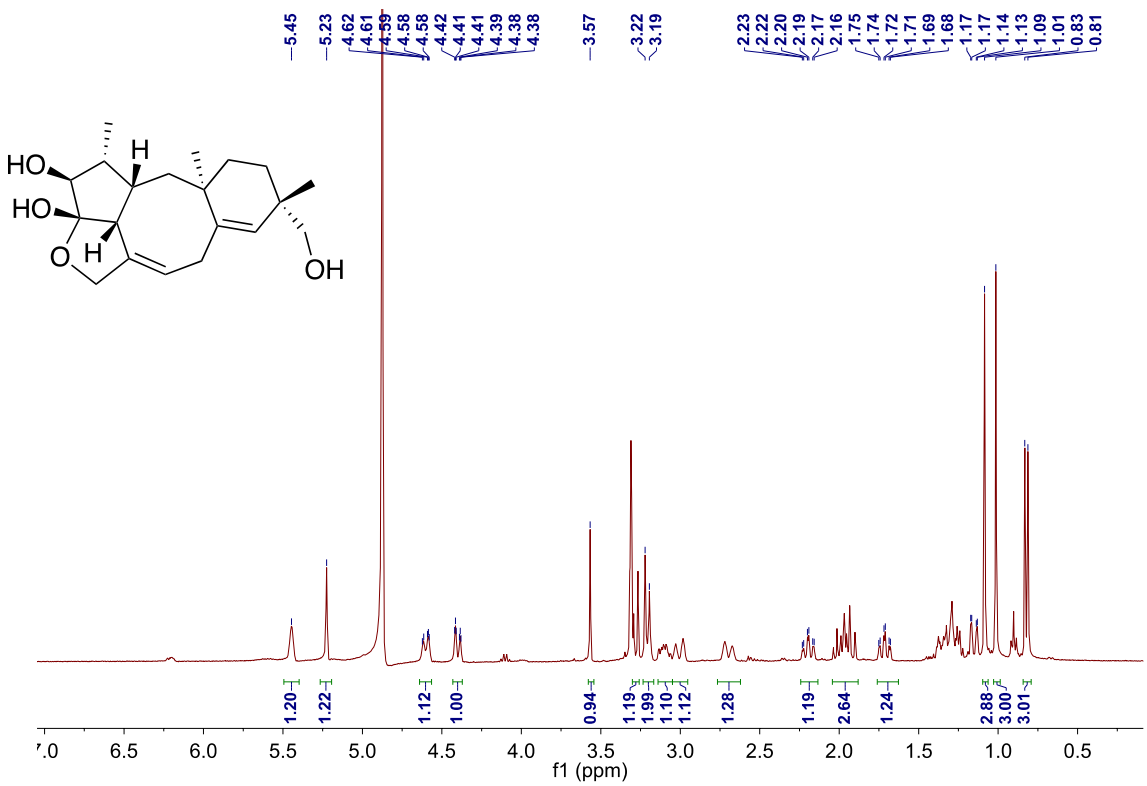

Figure S31. ^{1}H NMR spectrum of talaronid D (**4**) in CD_3OD

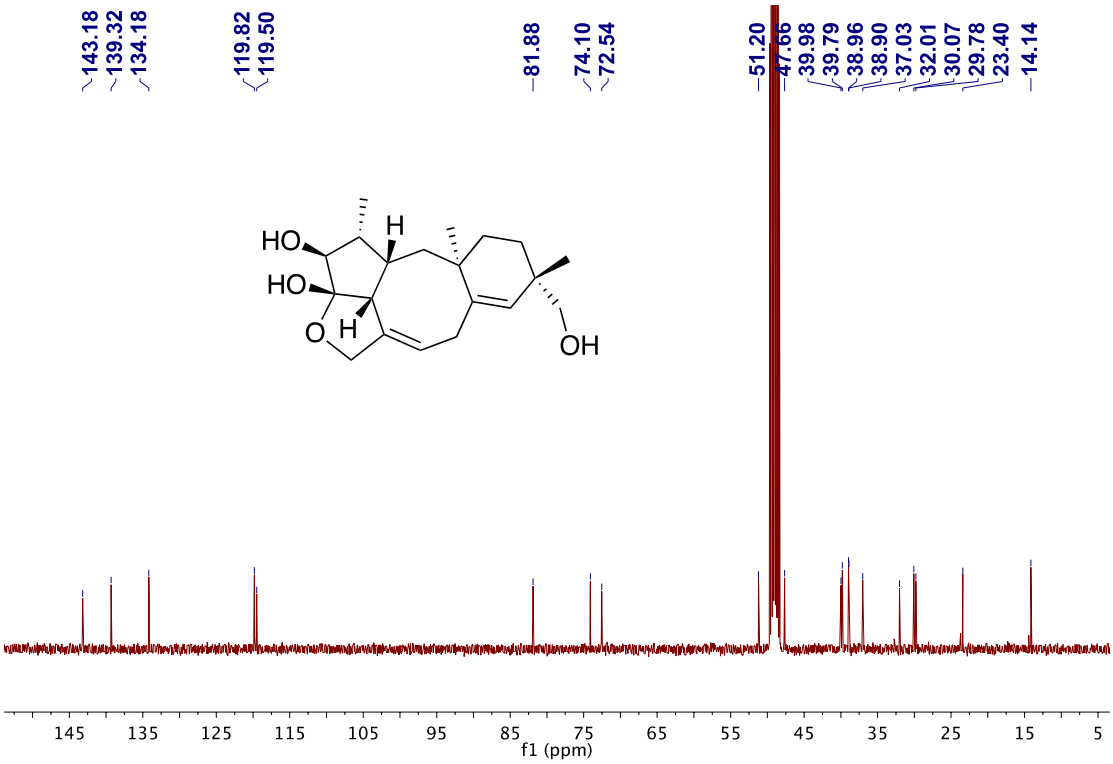

Figure S32. ^{13}C NMR spectrum of talaronid C (**3**) in CD_3OD

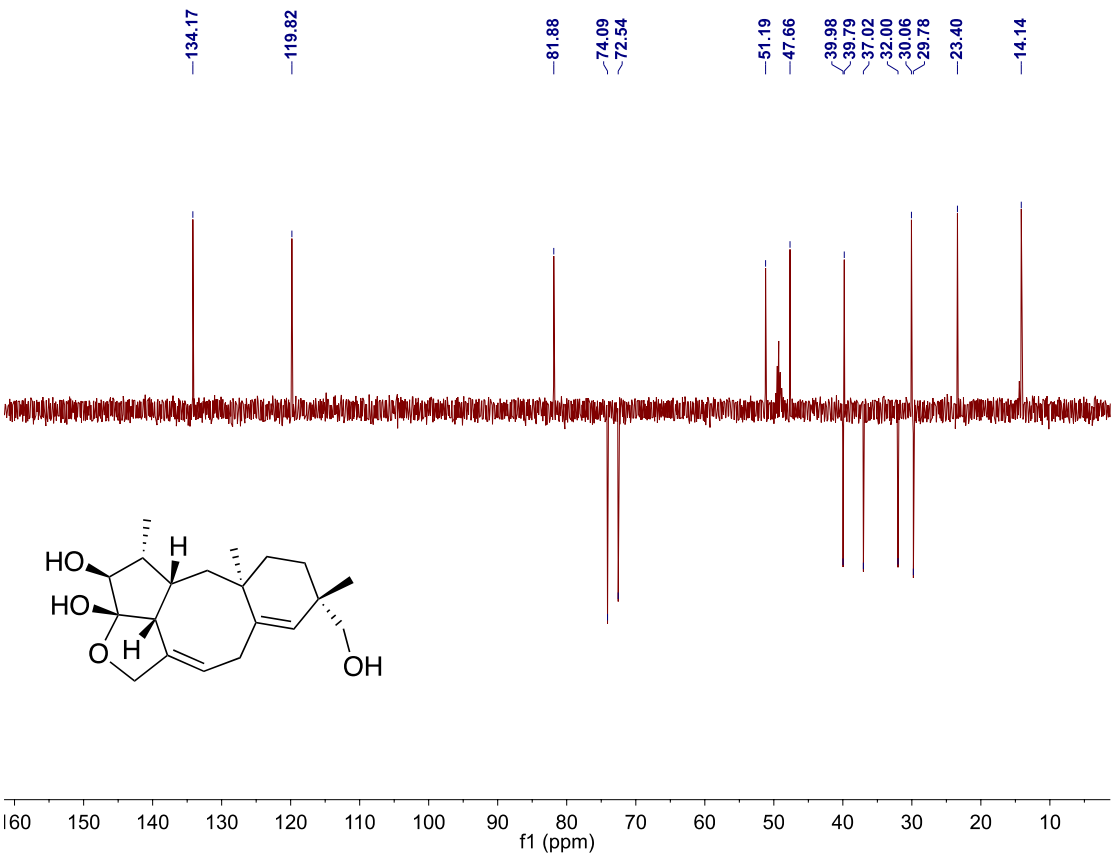

Figure S33. DEPT spectrum of talaronid D (**4**) in CD_3OD

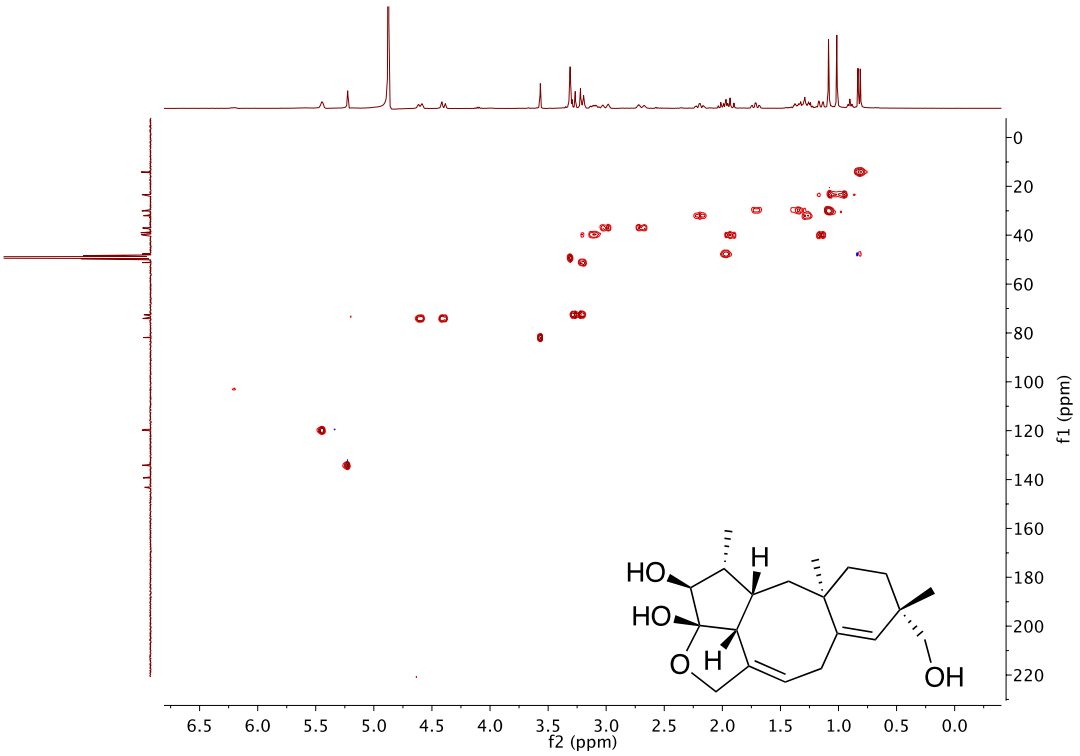

Figure S34. HSQC spectrum of talaronid D (**4**) in CD_3OD

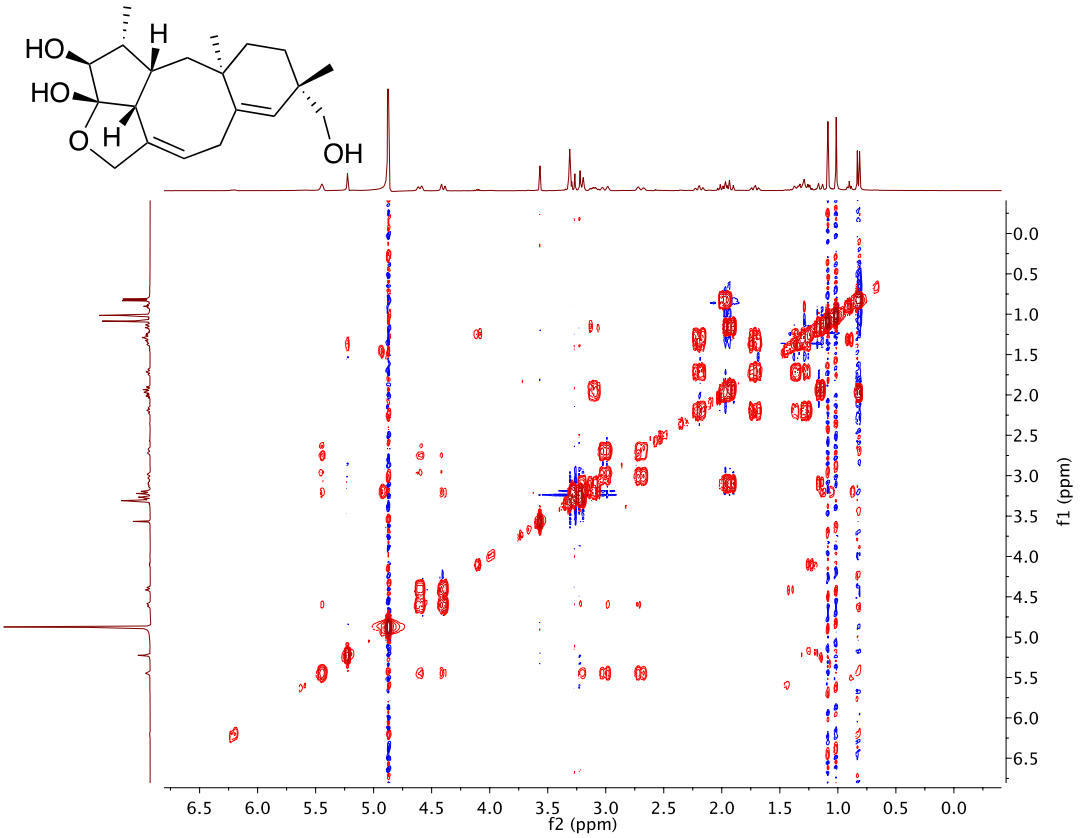

Figure S35. ^{1}H-^{1}H COSY spectrum of talaronid D (**4**) in CD_3OD

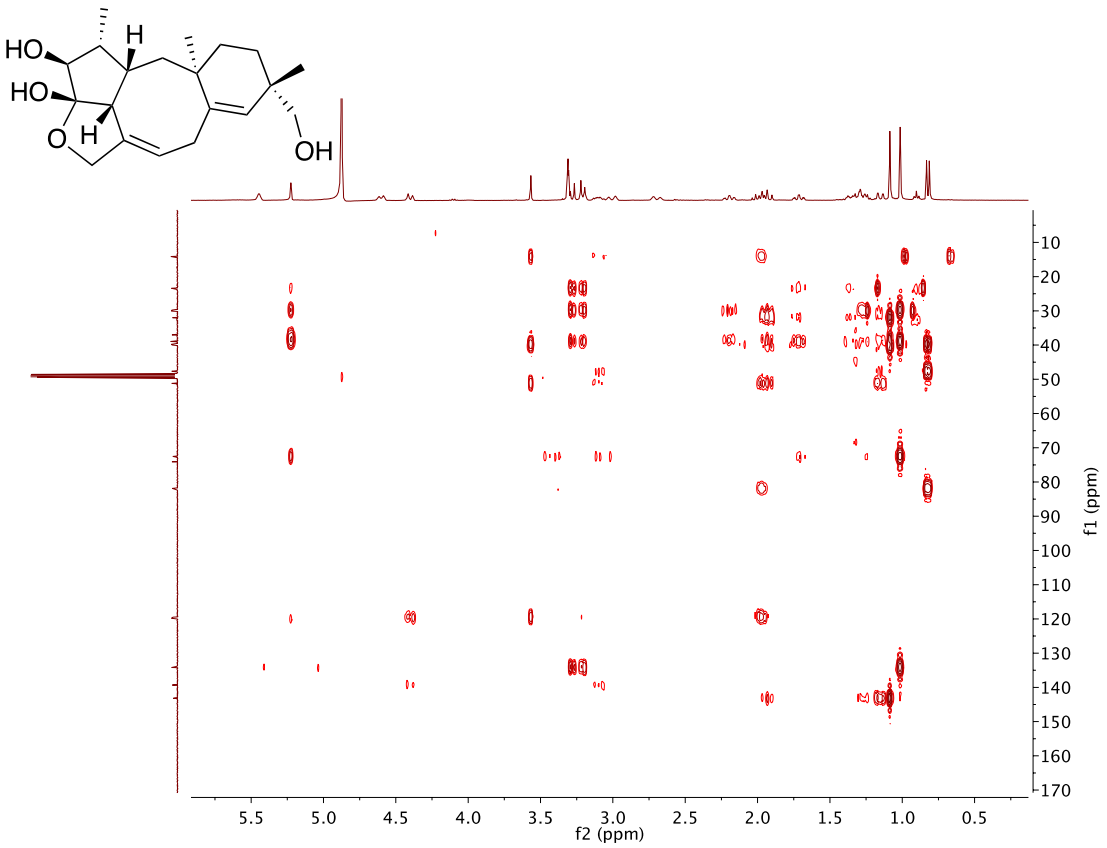

Figure S36. HMBC spectrum of talaronid D (**4**) in CD_3OD

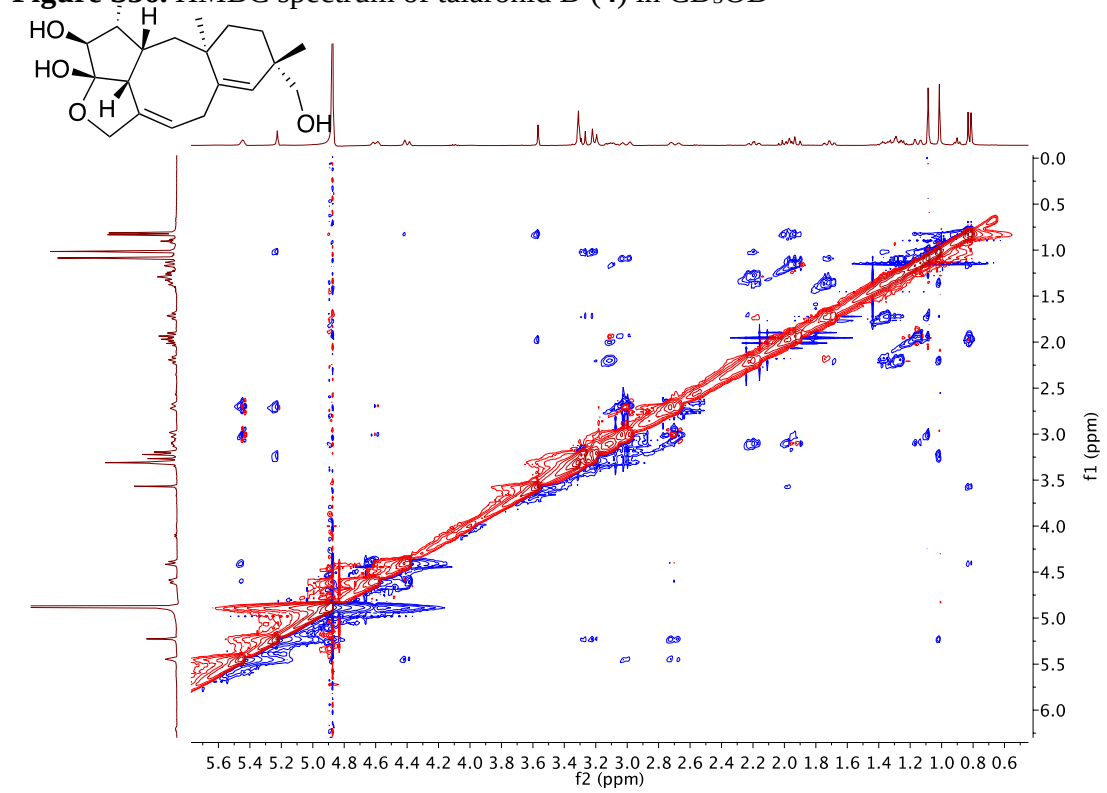

Figure S37. NOESY spectrum of talaronid D (**4**) in CD_3OD

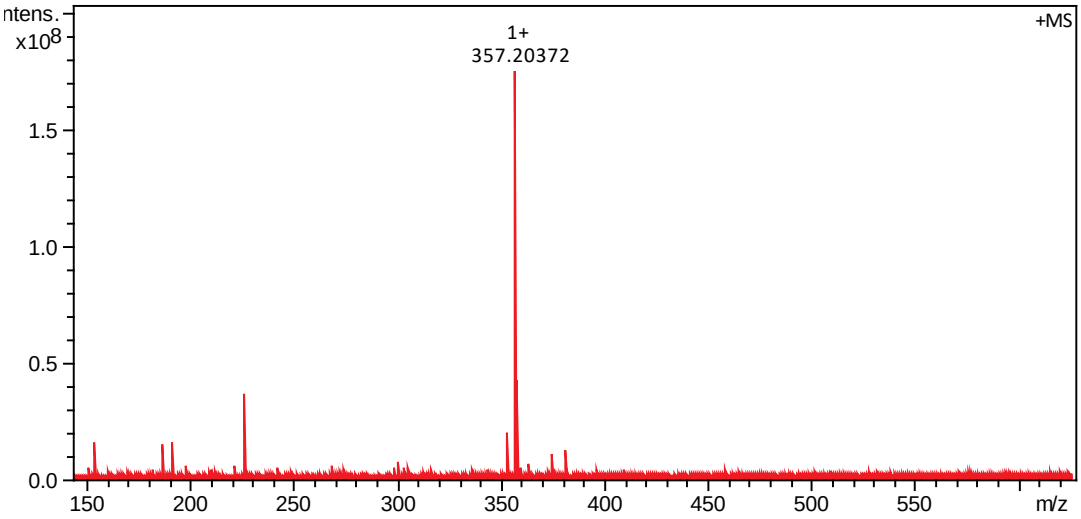

Figure S38. (+) ESI-MS spectrum of talaronid D (**4**)

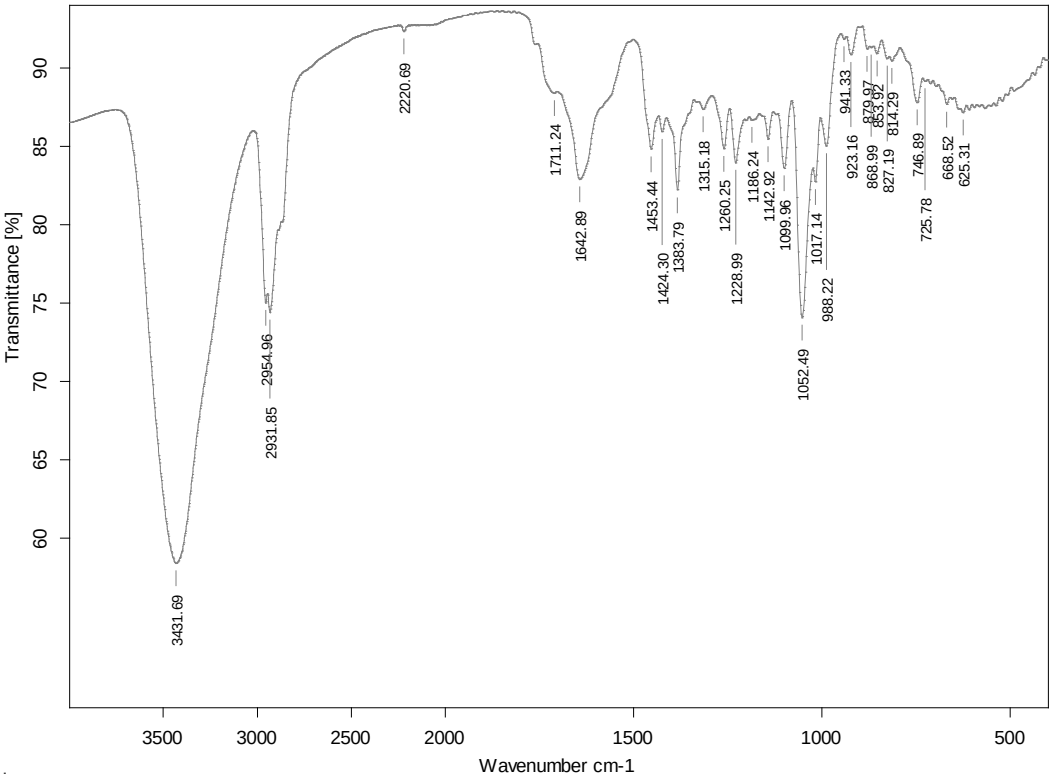

Figure S39. IR spectrum of talaronid D (**4**)

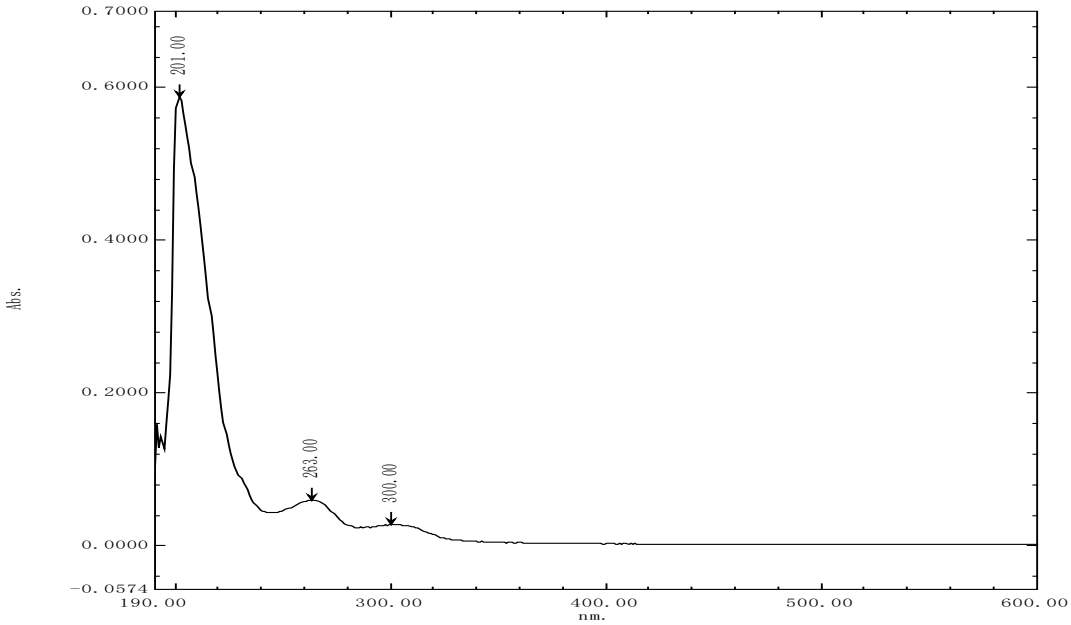

Figure S40. UV spectrum of talaronid D (**4**)