Electronic Supplementary Information

Absolute Configurations of Naturally Occurring [5]-and [3]-Ladderanoic Acids: Isolation, Chiroptical Spectroscopy and Crystallography

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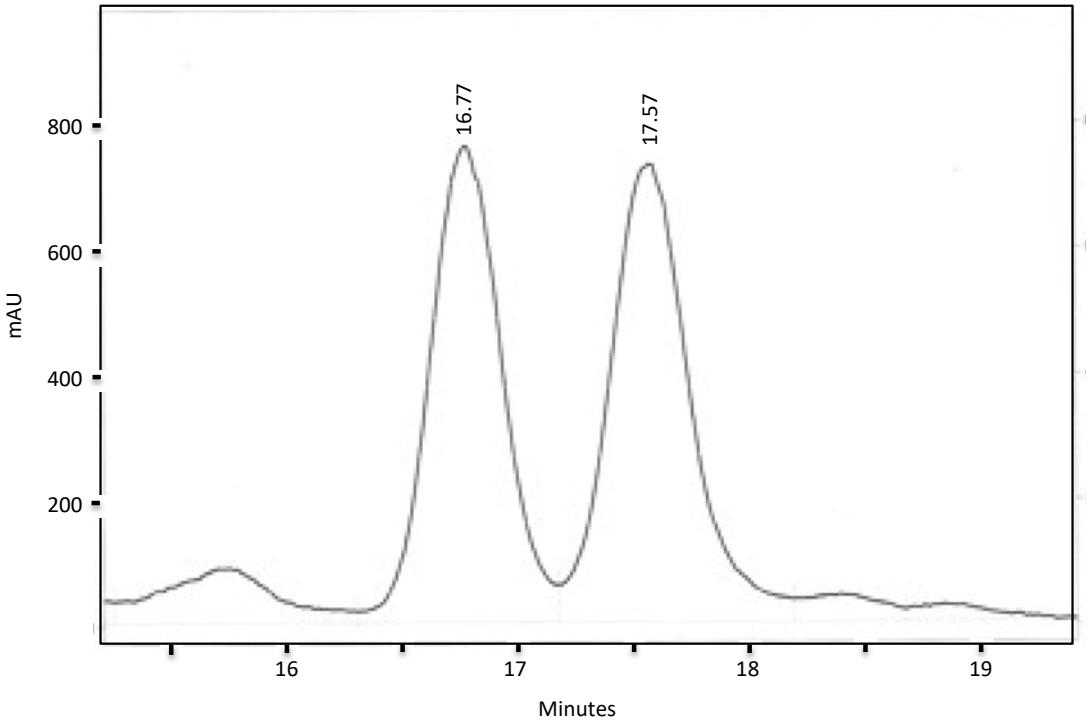


Figure S1. HPLC chromatogram of the phenacyl esters (**6a** and **7a)** of **1a** and **2a**. Conditions: Phenomenex C8 column (10 x 250 mm). Solvent A: H_2O:CH_3CN (99:1 v/v), solvent B: CH_3CN:H_2O (99:1, v/v), flow rate: 3.0 ml/min; gradient: 98.50% B to 99.50% over 5 min, hold for 20 min, return to 98.50% B over 3 min; detection at 254 nm. Retention times of phenacyl esters of **1a** and **2a**, 16.77 and 17.57 minutes, respectively.

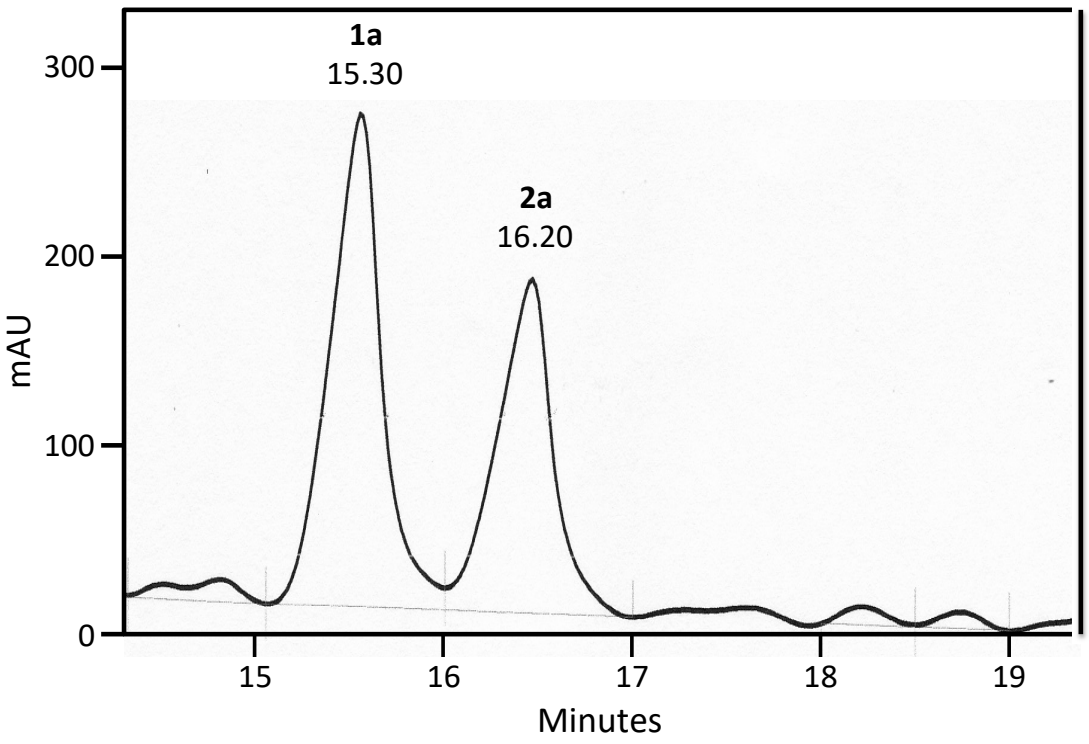


Figure S2. HPLC chromatogram of ladderanoic acids **1a** and **2a**. Conditions: Phenomenex C8 column (10 x 250 mm). Solvent A: H_2O: CH_3CN:TFA (99:1:0.1 v/v/v) , solvent B: CH_3CN:H_2O:TFA (99:1:0.1 v/v/v), flow rate: 3.0 ml/min; gradient: 90.00% B to 99.00% over 20 min, hold for 3 min, return to 90.00% B over 3 min; detection at 210 nm.

Table S1. NMR spectra of phenacyl and 4-phenylphenacyl esters of [5]-ladderanoic acid (**1a**)

	Phenacyl ester **6a**		4-Ph-phenacyl ester of **1a**		Me ester of **1a**[S1]	
	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C
1	NA	ND	NA	ND	NA	174.40
2	2.49	33.8	2.50	34.0	2.30	34.12
3	1.70	24.7	1.72	24.9	1.61	24.97
4	1.37	28.9	1.38	29.0	1.28	29.13
5	1.27	29.4	1.27	29.4	1.28	29.28
6	1.27	29.4	1.27	29.4	1.28	29.47
7	1.22	26.3	1.22	26.3	1.22	26.44
8	1.44	37.2	1.44	37.3	1.43	37.34
8'	1.46	37.2	1.44	37.3	1.48	37.34
9	2.20	39.7	2.22	39.8	2.18	39.92
10	2.35	47.1	2.36	47.2	2.35	47.29
11	2.57	48.2	2.58	48.2	2.57	48.34
12	2.63	49.3	2.63	49.3	2.63	49.47
13	2.72	41.6	2.73	41.7	2.73	41.85
14α	2.55	26.4	2.56	26.4	2.53	26.53
14β	2.04	26.4	2.04	26.4	2.04	26.53
15α	2.55	26.4	2.56	26.4	2.53	26.49
15β	2.04	26.4	2.04	26.4	2.04	26.49
16	2.72	41.6	2.73	41.7	2.73	41.85
17	2.63	49.3	2.60	49.2	2.63	49.38
18	2.60	49.0	2.58	48.2	2.60	49.21
19	2.63	38.3	2.63	38.4	2.63	38.52
20α	2.16	33.1	2.16	33.2	2.22	33.28
20β	2.00	33.1	2.01	33.2	2.00	33.28
Phenacyl						
CH_2	5.34	65.6	5.37	65.7	NA	NA
CO	ND	ND	ND	ND	NA	NA
1-C	ND	ND	ND	ND	NA	NA
2-CH	7.91	127.5	8.00	128.3	NA	NA
3-CH	7.61	133.5	7.61	127.3	NA	NA
4-CH	7.49	128.6	NA	ND	NA	NA
4-C	NA	NA	ND	ND	NA	NA
4-Phenyl						
1-C	ND	NA	ND	ND	NA	NA
2-CH	NA	NA	7.64	127.2	NA	NA
3-CH	NA	NA	7.48	128.9	NA	NA
4-CH	NA	NA	7.41	128.4	NA	NA
4-C	NA	NA	ND	ND	NA	NA

ND, Not determined; NA, Not applicable.

Table S2. NMR spectra of phenacyl and 4-phenylphenacyl esters of [3]-ladderanoic acid (**2a**)

	Phenacyl ester **7a**		4-Ph-phenacyl ester of **2a**		Diacetate of **5**[S1]	
	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C
1	NA	ND	NA	ND	3.55	70.70
2	2.49	34.0	2.48	34.0	1.58	29.85
3	1.71	24.9	1.69	24.9	1.32	25.96
4	1.37	29.1	1.27	29.1	1.28	29.90
5	1.27	29.6	1.25	29.7	1.28	29.64
6	1.31	26.9	1.29	26.8	1.28	26.86
7	1.27	29.6	1.25	29.7	1.28	29.42
8,8'	1.20	38.1	1.19	38.2	1.21	38.14
9	1.19	32.5	1.19	32.5	1.21	32.48
10α	1.75	34.2	1.75	34.2	1.75	34.22
10β	1.02	34.2	1.02	34.2	1.03	34.22
11	2.20	37.9	2.20	37.9	2.22	37.88
12	2.29	49.4	2.29	49.4	2.31	49.39
13	2.73	41.6	2.73	41.6	2.74	41.53
14α	2.49	26.1	2.48	26.1	2.51	26.17
14β	1.84	26.1	1.83	26.1	1.86	26.17
15α	2.41	25.5	2.41	25.5	2.42	25.49
15β	1.94	25.5	1.93	25.5	1.96	25.49
16	2.62	42.4	2.61	42.3	2.64	42.25
17	2.42	47.3	2.42	47.3	2.44	47.33
18	2.27	37.7	2.26	37.7	2.29	37.67
19,19'	1.50	25.6	1.49	25.6	1.50	25.50
20α	1.52	28.1	1.52	28.2	1.52	28.19
20β	1.09	28.1	1.08	28.2	1.11	28.19
Phenacyl						
CH_2	5.34	65.8	5.35	65.9	NA	NA
CO	ND	ND	ND	ND	NA	NA
1-C	ND	ND	ND	ND	NA	NA
2-CH	7.92	127.7	7.98	128.3	NA	NA
3-CH	7.61	133.8	7.72	127.3	NA	NA
4-CH	7.49	128.6	NA	NA	NA	NA
4-C	NA	NA	ND	ND	NA	NA
4-Phenyl						
1-C	NA	NA	ND	ND	NA	NA
2-CH	NA	NA	7.64	127.2	NA	NA
3-CH	NA	NA	7.48	128.9	NA	NA
4-CH	NA	NA	7.41	128.4	NA	NA
4-C	NA	NA	ND	ND	NA	NA

ND, Not determined; NA, Not applicable.

Table S3. NMR spectra of [5]-ladderanoic Acid **1a**

	5-Ladderanoic Acid **1a**		Me ester of **1a**[S1]	
	^{1}H	^{13}C	^{1}H	^{13}C
1	NA	ND	NA	174.40
2	2.37	33.3	2.30	34.12
3	1.66	24.8	1.60	24.97
4	1.29	29.7	1.28	29.13
5	1.29	29.7	1.28	29.28
6	1.29	29.7	1.28	29.47
7	1.24	26.7	1.22	26.44
8	1.48	37.5	1.43	37.34
8'	1.48	37.5	1.48	37.34
9	2.22	39.9	2.18	39.92
10	2.37	47.3	2.35	47.29
11	2.60	48.4	2.57	48.34
12	2.65	49.4	2.63	49.47
13	2.75	41.8	2.73	41.85
14α	2.58	26.6	2.53	26.53
14β	2.06	26.6	2.04	26.53
15α	2.58	26.6	2.53	26.49
15β	2.06	26.6	2.04	26.49
16	2.75	41.8	2.73	41.85
17	2.65	49.4	2.63	49.38
18	2.62	49.2	2.60	49.21
19	2.65	38.5	2.63	38.52
20α	2.18	33.3	2.22	33.28
20β	2.03	33.3	2.00	33.28

ND, Not determined; NA, Not applicable.

Table S4. NMR spectra of [3]-ladderanoic Acid **2a**

	3-Ladderanoic Acid **2a**		Diacetate of **5**[S1]	
	^{1}H	^{13}C	^{1}H	^{13}C
1		ND	3.55	70.70
2	2.38	33.5	1.58	29.85
3	1.66	24.8	1.32	25.96
4	1.29	29.7	1.28	29.90
5	1.29	29.7	1.28	29.64
6	1.30	26.9	1.28	26.86
7	1.29	29.7	1.28	29.42
8	1.22	38.2	1.21	38.14
9	1.21	32.4	1.21	32.48
10α	1.77	34.3	1.75	34.22
10β	1.04	34.3	1.03	34.22
11	2.23	37.7	2.22	37.88
12	2.32	49.4	2.31	49.39
13	2.75	41.6	2.74	41.53
14α	2.51	26.2	2.51	26.17
14β	1.87	26.2	1.86	26.17
15α	2.44	25.6	2.42	25.49
15β	1.97	25.6	1.96	25.49
16	2.65	42.2	2.64	42.25
17	2.45	47.4	2.44	47.33
18	2.29	37.7	2.29	37.67
19	1.52	25.6	1.50	25.50
20α	1.54	28.2	1.52	28.19
20β	1.11	28.2	1.11	28.19

ND, Not determined; NA, Not applicable.

Figure S3. HSQC spectrum of the 4-phenylphenacyl ester of [5]-ladderanoic acid **1a.** Red: methines; Blue: methylenes. Assignments are based on Damsté et al.[S1]

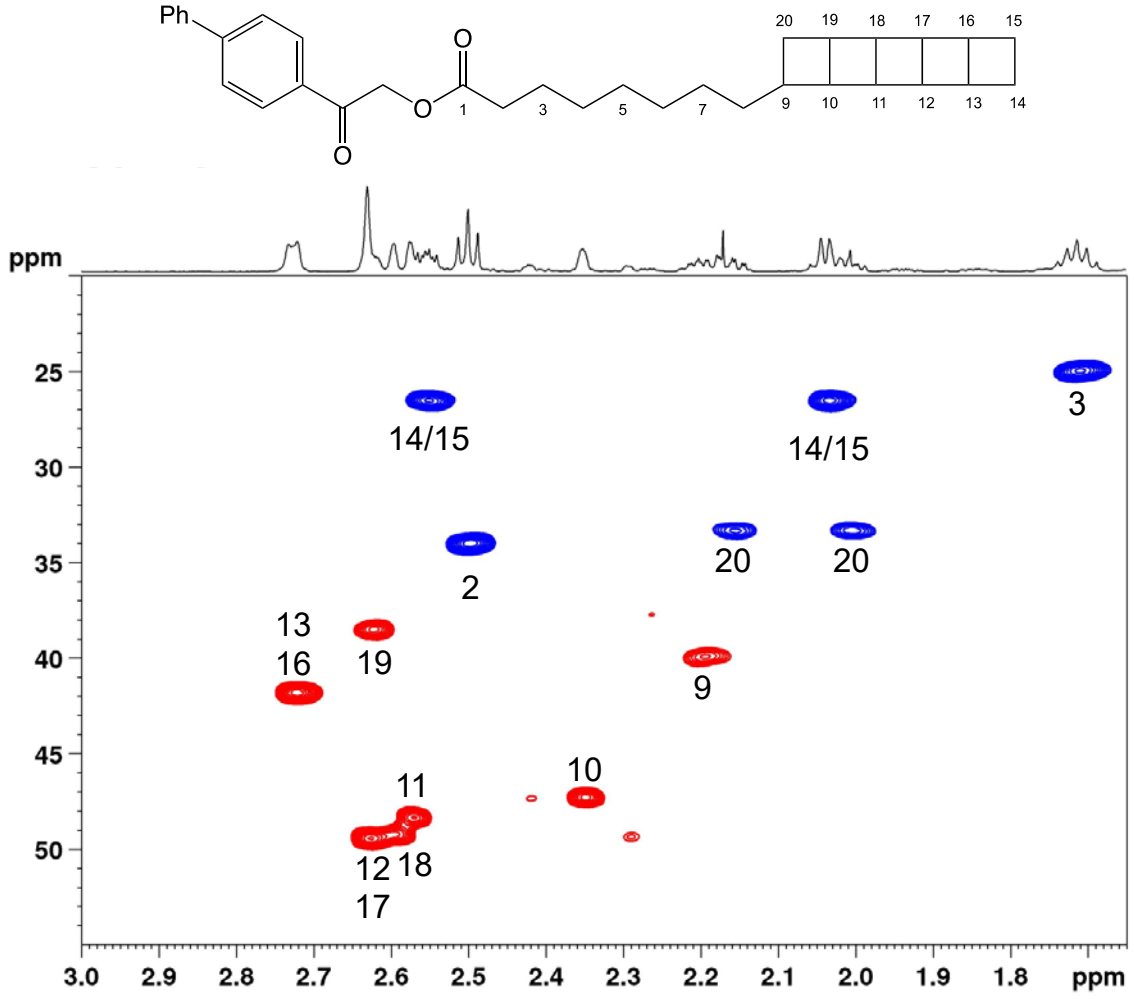


Figure S4. HSQC spectrum of the 4-phenylphenacyl ester of [3]-ladderanoic acid **2a**. Red: methines; Blue: methylenes. Assignments are based on Damsté et al.[S1]

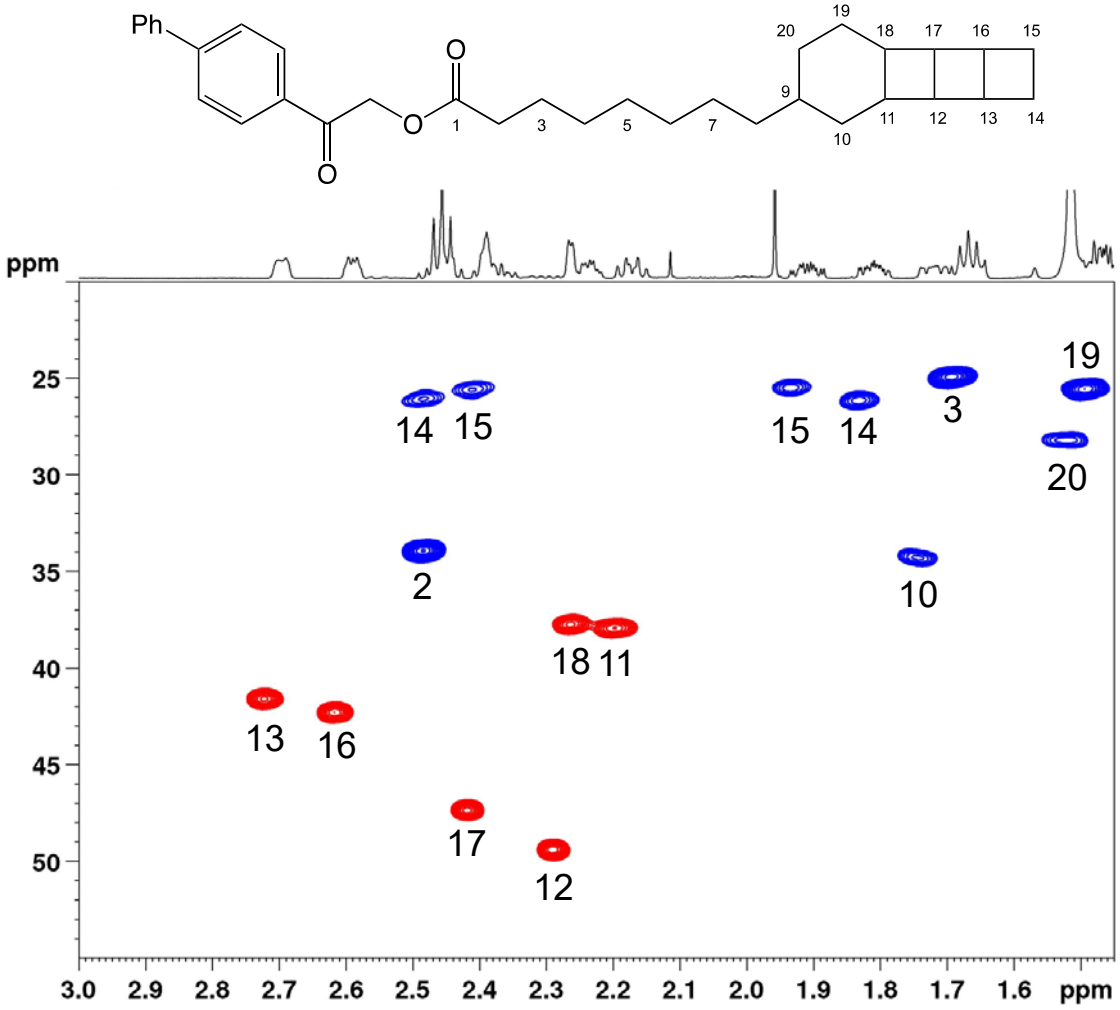


Figure S5. HSQC spectrum of [5]-ladderanoic acid **1a**. Red: methines; Blue: methylenes. Assignments are based on Damsté et al.[S1]

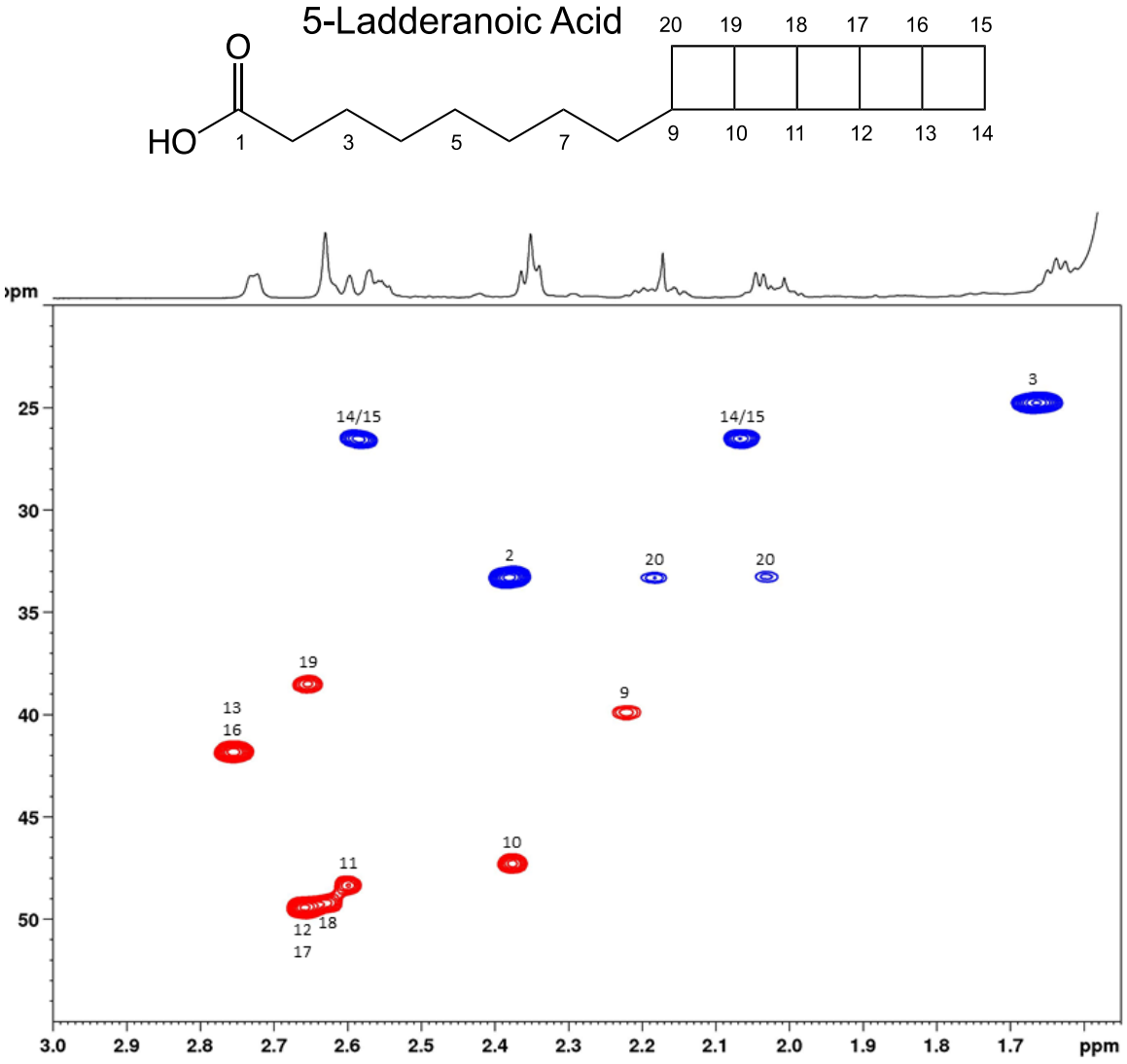
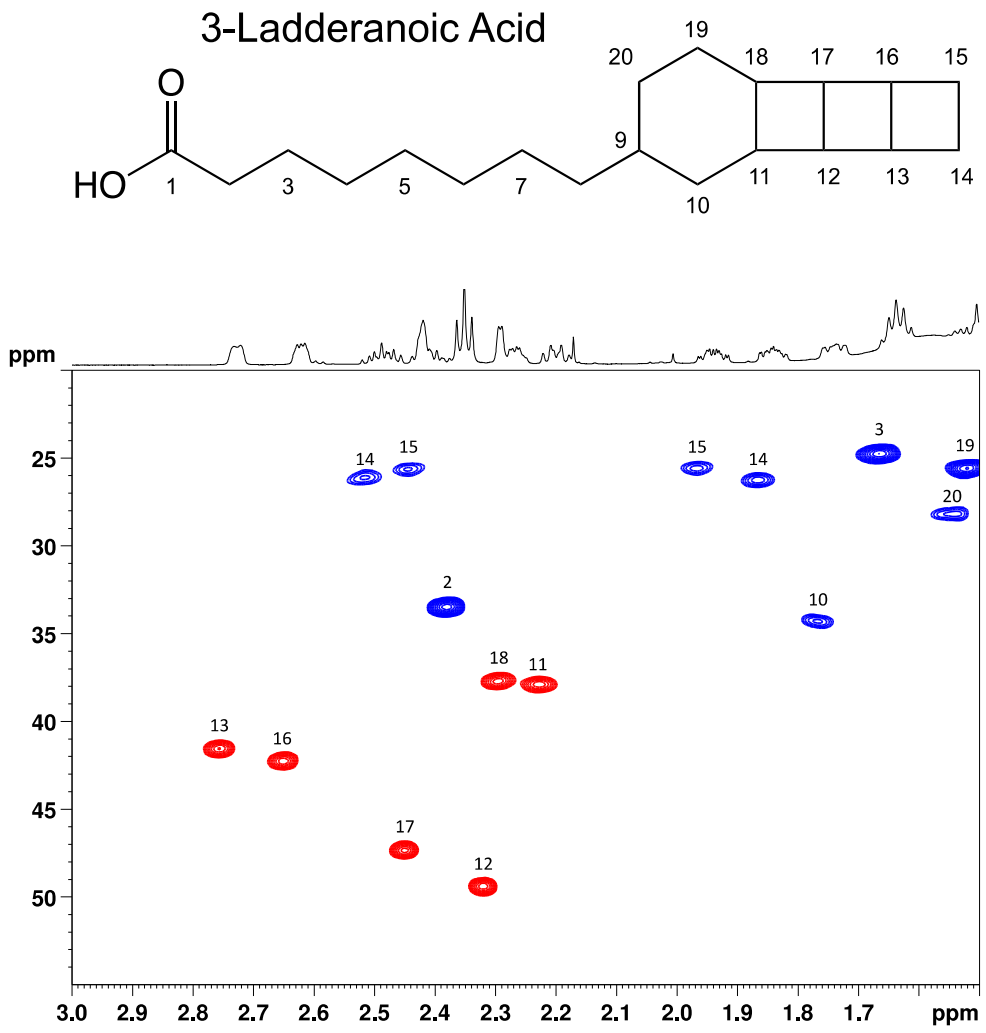


Figure S6. HSQC spectrum of [3]-ladderanoic acid **2a**. Red: methines; Blue: methylenes. Assignments are based on Damsté et al.[S1]



Computational studies of ladderane conformations and specific rotations

(1) Phenacyl esters

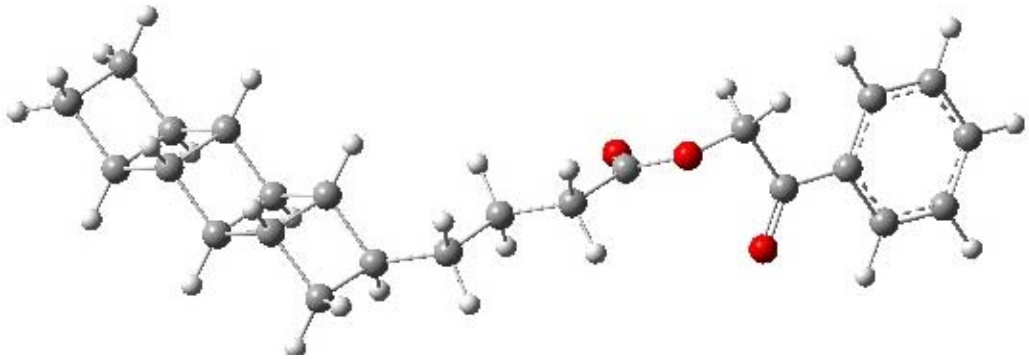
(A) Lowest energy conformers of (*S*)-6e and their specific rotations.

The specific rotations of 18 lowest energy conformers of (*S*)-**6e** predicted at B3LYP/6-311++G(2d,2p)/PCM level, with chloroform solvent represented by PCM, are shown in Table S1.

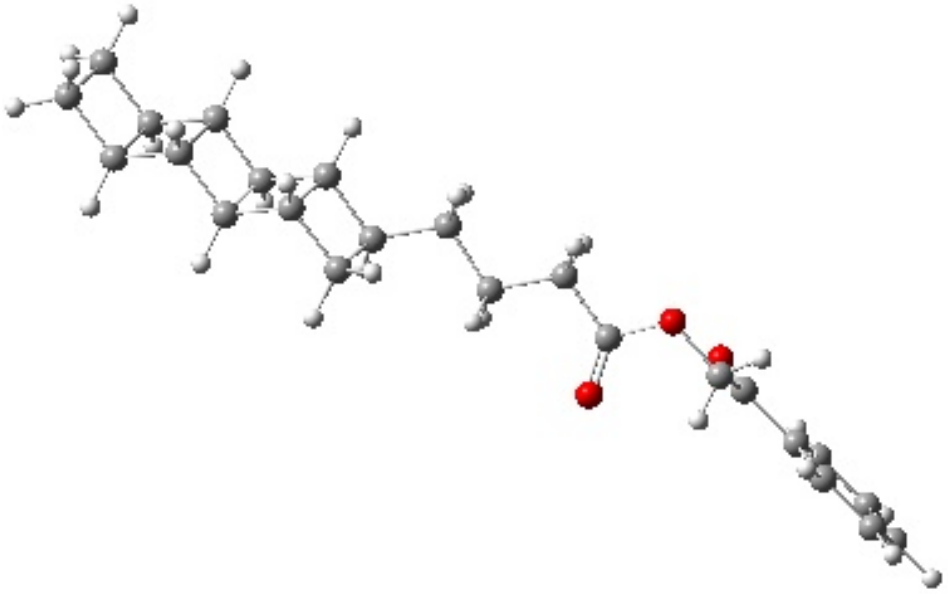
Table S5: Wavelength dependent specific rotations for 18 lowest energy conformers of (*S*)-**6e**

Conformation #	Population	Specific Rotations					
		633	589	546	436	405	365
25	0.13	-71	-83	-98	-163	-193	-238
33	0.12	83	97	115	191	226	284
29	0.08	158	185	219	373	449	594
36	0.07	-64	-75	-89	-150	-181	-242
22	0.07	-65	-76	-90	-153	-187	-258
54	0.06	34	40	48	79	94	115
42	0.06	88	103	124	218	268	370
53	0.05	-14	-16	-19	-26	-26	-11
66	0.05	51	60	72	126	155	217
48	0.05	-54	-63	-74	-119	-139	-168
62	0.05	136	160	191	335	409	555
19	0.05	30	35	41	64	72	71
242	0.03	30	35	42	72	87	115
45	0.03	49	57	67	110	129	154
37	0.03	14	17	20	41	53	79
35	0.03	-32	-37	-43	-63	-69	-68
44	0.03	36	41	48	71	78	70
26	0.02	37	44	53	99	126	194
Population weighted		22	26	31	54	66	89

The two lowest energy conformers (#25 and #33) of (*S*)-**6e,** displayed in Figure S7, have nearly the same energy but with oppositely signed specific rotations. The structural parameters of #25 are very close to those in crystal structure of phenacyl ester, **6a**.



#25



#33

Figure S7. Two lowest energy conformers, #25 and #33 of (*S*)-**6e** predicted at B3LYP/6-311++G(2d,2p)/PCM level.

(B) Specific rotations predicted for the crystalline phenacyl ester of (*R*)-**1a.**

The crystal structure of phenacyl ester of (*R*)-**1a** is compared to the lowest energy structure of **6e** with (*R*) configuration in Figure S8. The relative orientation of phenacyl group portion is quite similar in these two structures.

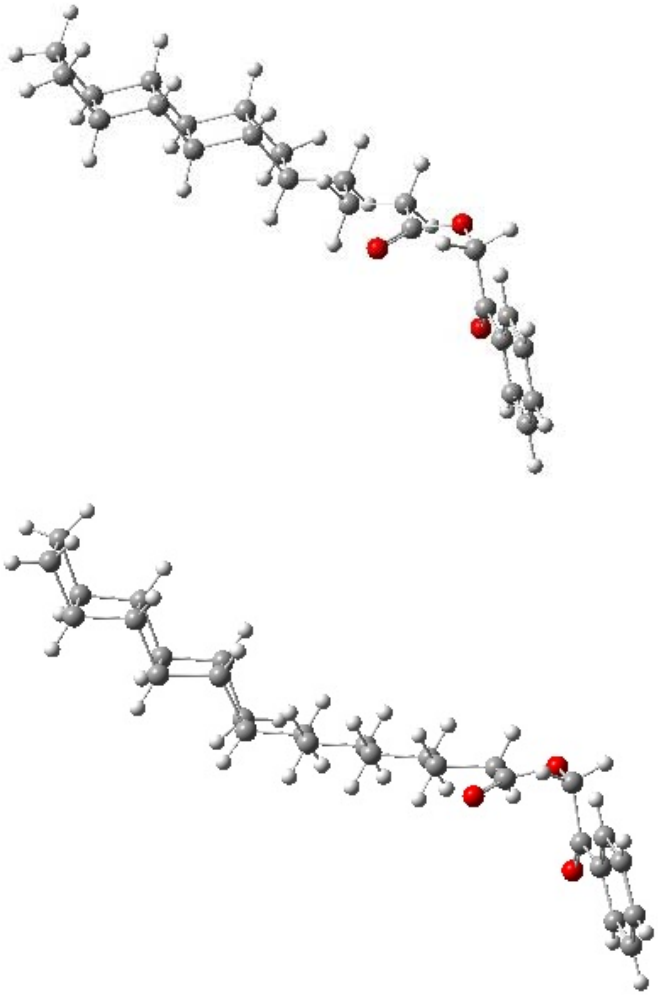


Figure S8. Comparison of conformation #25 of (*R*)-**6e** (upper) with that of crystalline phenacyl ester of (*R*)-**1a** (lower).

Wavelength dependent specific rotations calculated for the crystal structure of phenacyl ester of (*R*)-**1a**, with and without geometry optimizations, at B3LYP/6-311++G(2d,2p)/PCM level are shown in Table S6. Note that the signs of specific rotations, independent of geometry optimizations, are all positive for the (*R*) configuration, just as they are negative for the conformation #25 of (*S*)-**6e** (Table S5). Thus, crystal structure need not represent the sole structure present in the solution phase.

Table S6. Specific rotations calculated[a] for crystal structure of phenacylester **6a** at B3LYP/6-311++G(2d,2p)/PCM level

Calculation	Specific Rotations					
	633	589	545	436	405	365
1	74	87	105	185	229	320
2	51	60	71	118	141	182
3	52	60	71	118	141	183

[a] Calculation 1: crystal structure used as it is without optimization; Calculation 2: bond lengths and bond angles optimized; Calculation 3: fully optimized

(C) Lowest energy conformers of (*S*)-7e and their specific rotations.

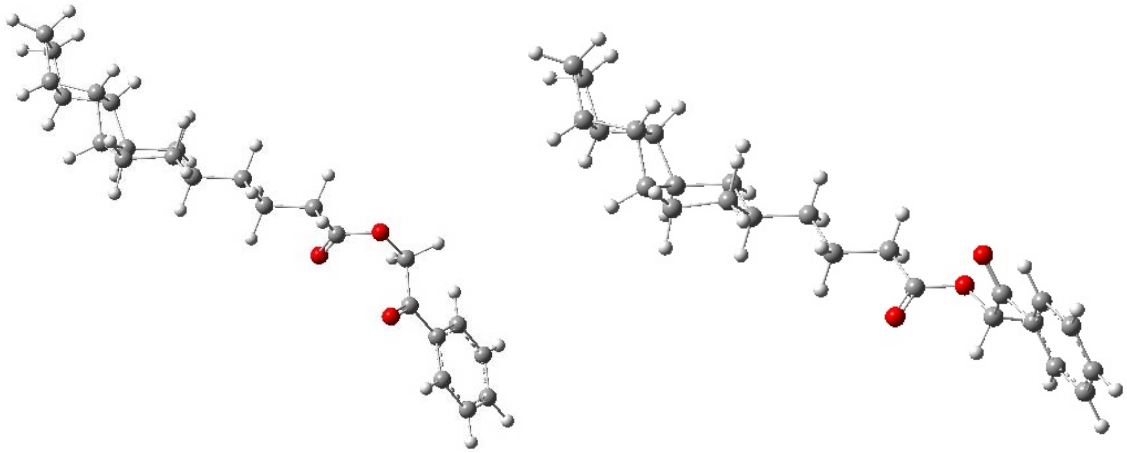
The specific rotations of 53 lowest energy conformers of (*S*)-**7e** predicted at B3LYP/6-311++G(2d,2p)/PCM level are shown in Table S7.

Table S7: Wavelength dependent specific rotations of 53 low energy conformers of (S)-**7e**

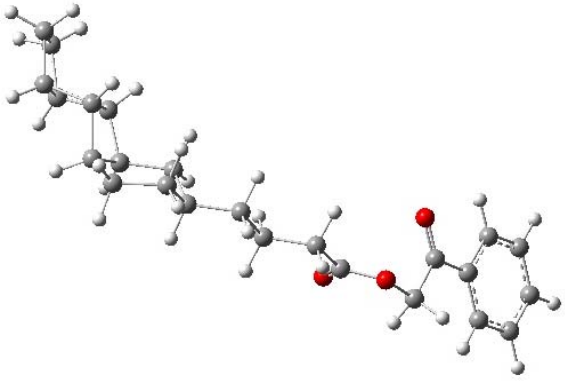
Conformer #	population	Specific Rotations						cyclohexane ring conformation
		633 nm	589 nm	546 nm	436 nm	405 nm	365 nm	
28	0.05	-163	-192	-228	-391	-474	-639	chair
38	0.05	-68	-80	-94	-157	-186	-231	chair
26	0.05	-91	-107	-127	-218	-263	-341	chair
43	0.03	19	22	27	54	72	126	boat
44	0.03	92	107	127	211	252	324	boat
45	0.03	-178	-209	-247	-419	-502	-648	chair
35	0.03	73	85	101	168	201	263	chair
98	0.03	-43	-50	-59	-98	-116	-147	boat
30	0.03	7	8	9	16	21	41	chair
376	0.02	-62	-72	-85	-141	-167	-209	boat
93	0.02	47	55	65	111	134	179	boat
13	0.02	-90	-106	-125	-209	-247	-303	chair
168	0.02	-67	-79	-95	-165	-202	-273	chair
101	0.02	-193	-228	-272	-476	-583	-800	chair
83	0.02	39	47	56	108	139	216	chair
121	0.02	-90	-107	-128	-231	-288	-412	chair
84	0.02	-45	-53	-65	-124	-160	-244	chair
61	0.02	-214	-252	-300	-521	-633	-855	chair
102	0.02	-74	-87	-103	-172	-204	-263	chair
123	0.02	34	40	48	89	112	164	chair
15	0.02	-58	-68	-81	-137	-163	-203	chair
36	0.02	-59	-69	-82	-137	-163	-214	chair
8	0.02	-56	-65	-77	-126	-148	-187	chair
25	0.02	-73	-86	-103	-182	-224	-314	chair
62	0.02	-104	-121	-143	-238	-281	-351	chair
40	0.02	155	182	215	362	431	552	boat
50	0.02	-50	-58	-69	-116	-141	-190	boat
135	0.02	4	5	5	-1	-7	-28	boat
17	0.01	46	54	64	104	120	141	boat
133	0.01	142	166	198	342	414	551	boat
92	0.01	129	153	182	322	396	552	boat
95	0.01	20	23	27	40	45	53	boat
108	0.01	113	133	157	261	309	388	boat
29	0.01	59	69	81	128	146	151	boat
94	0.01	-62	-72	-85	-142	-169	-219	boat
97	0.01	-36	-43	-52	-99	-125	-185	chair
378	0.01	-58	-68	-82	-146	-181	-258	chair
74	0.01	-85	-101	-120	-208	-252	-327	chair

65	0.01	-118	-138	-162	-267	-315	-391	chair
67	0.01	5	6	7	12	16	27	boat
66	0.01	-75	-88	-104	-178	-215	-291	chair
105	0.01	-44	-51	-61	-102	-121	-152	chair
248	0.01	-75	-88	-106	-188	-232	-324	boat
51	0.01	64	75	89	151	179	216	boat
56	0.01	-23	-27	-31	-45	-48	-42	chair
171	0.01	21	25	30	57	72	105	boat
247	0.01	48	57	68	128	163	248	boat
169	0.01	-69	-82	-98	-176	-218	-308	boat
627	0.01	55	65	79	143	179	259	boat
73	0.01	-116	-136	-163	-284	-347	-470	chair
216	0.01	-26	-31	-38	-70	-88	-130	chair
528	0.01	7	8	10	22	30	50	boat
173	0.01	-101	-119	-143	-259	-325	-476	boat
Population weighted		-36	-43	-51	-88	-106	-140	

The three lowest energy conformers of (*S*)-**7e** (#28, #38 and #26), predicted at B3LYP/6-311++G(2d,2p)/PCM level, are displayed in Figure S9. The cyclohexane ring is in chair conformation in all three structures. However, the boat conformation is also expected to be populated at room temperature, as some of the structures with the boat conformation (#43, 44, 98, 376 and 93) are within 0.5 Kcal/mol of the lowest energy chair conformer.



#28 #38



#26

Figure S9. Conformers #28, #38 and #26 of (*S*)-**7e**.

(2). Ladderanoic acids

Table S8: Conformers, energies, populations and specific rotations of (*R*)-5-ladderanoic acid, **1a**

Conformer	Relative Energy[a]	Population	Specific Rotations					
			633 nm	589 nm	546 nm	436 nm	405 nm	365 nm
1	0.00	0.046	15	17	20	32	38	46
5	0.00	0.046	-66	-77	-91	-155	-186	-244
7	0.38	0.024	-48	-56	-67	-115	-140	-186
6	0.38	0.024	-84	-98	-116	-194	-232	-302
3	0.44	0.022	-8	-10	-12	-20	-24	-33
2	0.44	0.022	19	21	25	38	43	51
70	0.81	0.012	-98	-115	-136	-230	-276	-362
76	0.84	0.011	-22	-26	-32	-56	-69	-93
58	0.84	0.011	-34	-40	-47	-81	-98	-130
59	0.84	0.011	-90	-106	-125	-212	-255	-334
22	0.85	0.011	-78	-92	-110	-191	-232	-312
74	0.85	0.011	-98	-115	-136	-229	-274	-357
283	0.87	0.011	-97	-114	-135	-228	-273	-356
45	0.87	0.011	-32	-37	-44	-75	-90	-118
30	0.87	0.011	-10	-12	-14	-25	-31	-43
46	0.88	0.010	-45	-53	-63	-106	-127	-167
68	0.88	0.010	-30	-35	-42	-72	-88	-117
41	0.89	0.010	37	43	51	84	100	127
112	0.89	0.010	-80	-94	-111	-189	-228	-299
77	0.89	0.010	-18	-21	-25	-45	-55	-75
37	0.89	0.010	75	87	102	166	196	247
16	0.89	0.010	23	28	33	58	71	97
15	0.91	0.010	-12	-14	-18	-37	-49	-74
31	0.91	0.010	56	65	76	124	146	185
29	0.92	0.010	-11	-13	-16	-28	-34	-46
9	0.92	0.010	51	60	70	111	129	160
55	0.93	0.010	-98	-115	-136	-229	-275	-358
27	0.93	0.010	20	24	28	47	56	71
69	1.17	0.006	-82	-96	-114	-193	-232	-304
11	1.18	0.006	98	114	134	217	255	320
87	1.20	0.006	-51	-60	-71	-121	-145	-191
13	1.21	0.006	-64	-75	-89	-152	-183	-241
73	1.22	0.006	12	13	15	20	22	22
78	1.23	0.006	-149	-174	-206	-345	-412	-534
66	1.25	0.006	-57	-67	-79	-133	-159	-208
60	1.25	0.006	-88	-103	-122	-205	-245	-318
14	1.25	0.006	-122	-142	-168	-282	-337	-437
33	1.25	0.006	-52	-61	-72	-119	-142	-184
62	1.26	0.005	-69	-81	-97	-165	-198	-261
85	1.26	0.005	-22	-26	-31	-55	-67	-92
25	1.28	0.005	13	15	18	27	31	36
101	1.28	0.005	-120	-140	-165	-278	-332	-431
98	1.28	0.005	-75	-88	-105	-179	-215	-284
99	1.29	0.005	-47	-55	-65	-110	-131	-171
52	1.30	0.005	-44	-52	-61	-103	-123	-161

53	1.30	0.005	-11	-14	-16	-30	-38	-54
32	1.30	0.005	29	34	40	65	77	96
100	1.30	0.005	-10	-12	-15	-28	-36	-52
71	1.30	0.005	-77	-90	-107	-181	-217	-284
67	1.30	0.005	80	93	110	179	211	266
43	1.30	0.005	112	131	153	250	295	373
35	1.31	0.005	52	60	71	114	133	165
40	1.33	0.005	-16	-18	-22	-37	-44	-59
72	1.34	0.005	-45	-53	-63	-109	-132	-175
63	1.35	0.005	21	25	29	48	57	73
10	1.35	0.005	39	45	53	83	96	116
65	1.35	0.005	2	3	3	3	2	-1
39	1.35	0.005	30	35	42	69	82	104
146	1.36	0.005	-47	-55	-65	-108	-130	-169
64	1.37	0.005	-44	-51	-60	-101	-121	-157
34	1.39	0.004	1	1	1	2	1	0
28	1.65	0.003	74	86	100	157	182	221
196	1.67	0.003	-126	-147	-174	-291	-347	-449
130	1.68	0.003	-144	-169	-199	-334	-399	-517
221	1.68	0.003	-6	-8	-10	-24	-34	-54
137	1.68	0.003	-36	-42	-50	-80	-95	-120
237	1.68	0.003	-17	-19	-23	-36	-42	-51
83	1.69	0.003	-93	-109	-130	-224	-271	-361
153	1.69	0.003	-15	-18	-21	-35	-41	-54
188	1.70	0.003	-90	-106	-125	-211	-252	-329
228	1.70	0.003	-128	-150	-177	-293	-349	-447
165	1.71	0.003	-40	-46	-54	-87	-102	-127
155	1.71	0.003	-24	-29	-35	-64	-81	-115
86	1.72	0.003	-97	-113	-134	-221	-263	-336
236	1.72	0.003	-64	-76	-90	-158	-194	-262
210	1.72	0.003	-50	-58	-69	-111	-131	-164
179	1.72	0.003	-5	-6	-8	-18	-25	-40
192	1.72	0.003	-34	-40	-48	-84	-102	-137
195	1.72	0.002	-14	-17	-21	-39	-49	-71
219	1.72	0.002	-38	-44	-52	-84	-99	-123
170	1.73	0.002	83	97	115	192	228	295
659	1.73	0.002	74	86	102	167	197	250
148	1.73	0.002	33	39	46	75	89	113
212	1.74	0.002	-103	-122	-145	-249	-302	-402
127	1.75	0.002	-44	-52	-62	-105	-127	-166
38	1.75	0.002	74	86	100	159	185	227
96	1.75	0.002	112	130	153	247	290	364
365	1.75	0.002	-51	-60	-71	-122	-147	-195
305	1.75	0.002	-24	-28	-34	-60	-73	-100
750	1.75	0.002	-107	-125	-149	-251	-301	-392
94	1.75	0.002	13	15	17	24	25	26
122	1.75	0.002	-90	-106	-125	-211	-253	-331
143	1.76	0.002	-106	-124	-147	-246	-295	-383
181	1.76	0.002	17	20	24	44	54	76
91	1.76	0.002	-111	-129	-153	-254	-302	-389
167	1.77	0.002	-7	-9	-11	-25	-34	-53
294	1.77	0.002	-64	-75	-89	-150	-181	-237

90	1.77	0.002	62	72	85	137	160	200
763	1.77	0.002	-25	-29	-34	-57	-69	-90
336	1.77	0.002	-24	-28	-33	-58	-71	-96
197	1.77	0.002	-13	-15	-17	-25	-28	-32
180	1.78	0.002	89	104	121	194	226	279
17	1.78	0.002	-19	-22	-26	-44	-53	-69
224	1.78	0.002	-81	-95	-113	-197	-240	-323
251	1.78	0.002	55	64	75	126	150	193
361	1.78	0.002	14	16	18	27	30	34
109	1.79	0.002	-77	-90	-107	-182	-218	-286
126	1.80	0.002	-40	-47	-56	-96	-116	-153
178	1.80	0.002	-17	-20	-25	-48	-62	-92
54	1.80	0.002	46	53	63	101	118	146
231	1.80	0.002	-4	-4	-5	-11	-14	-22
75	1.80	0.002	-16	-19	-23	-43	-54	-76
114	1.80	0.002	26	30	36	58	68	86
380	1.81	0.002	27	31	37	60	71	89
299	1.82	0.002	-6	-7	-9	-15	-19	-26
26	1.82	0.002	69	80	94	156	185	238
310	1.82	0.002	-131	-154	-182	-306	-366	-477
391	1.83	0.002	34	39	46	73	85	104
164	1.83	0.002	-47	-55	-66	-113	-137	-182
169	1.84	0.002	35	41	49	85	103	139
257	1.84	0.002	-15	-18	-21	-36	-44	-58
244	1.84	0.002	27	31	36	59	70	87
84	1.85	0.002	32	37	43	67	76	90
300	1.85	0.002	-100	-117	-138	-234	-280	-366
317	1.85	0.002	-64	-76	-90	-152	-182	-238
443	1.86	0.002	-72	-85	-101	-172	-207	-274
479	1.86	0.002	-67	-78	-92	-156	-188	-246
442	1.87	0.002	-61	-72	-85	-145	-174	-229
595	1.88	0.002	-46	-54	-64	-110	-133	-176
128	1.89	0.002	5	5	6	7	6	4
892	1.89	0.002	8	10	11	19	23	28
419	1.93	0.002	17	20	23	38	44	54
93	1.97	0.002	-87	-101	-120	-199	-236	-304
Population weighted			-20	-24	-28	-49	-60	-80

[a]energies (in kcal/mol) are relative to -930.8233578 Hartrees

Figure S10: Predicted lowest energy conformer, C1 in Table S8, of (*R*)-5-ladderanoic acid. The four C atoms, starting from second C of alkyl chain and going along the edge of the ladder, make a dihedral angle of ~75°. The alkyl chain is canted with respect to the plane of the ladderane moiety, as seen in the crystal structure (see Figure 11 in the main paper).

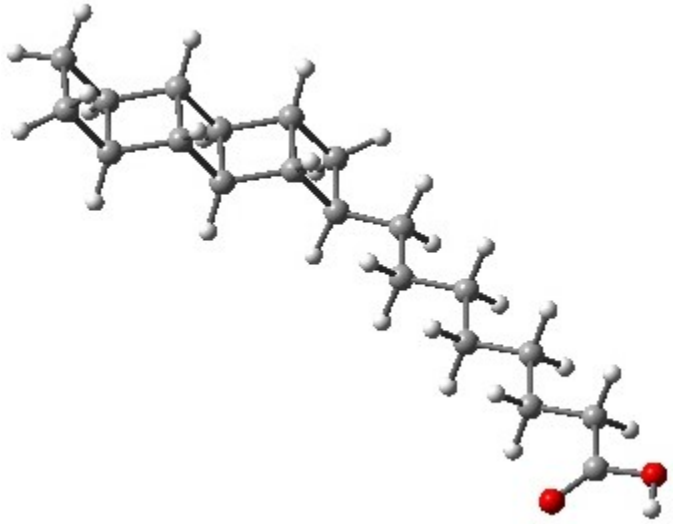


Figure S11: Predicted second lowest energy conformer, C5 in Table S8, of (*R*)-5-Ladderanoic acid. The four C atoms, starting from the second C of alkyl chain and going along the edge of the ladder, make a dihedral angle of ~180°, as seen in the crystal structure (see Figure 12 in the main paper).

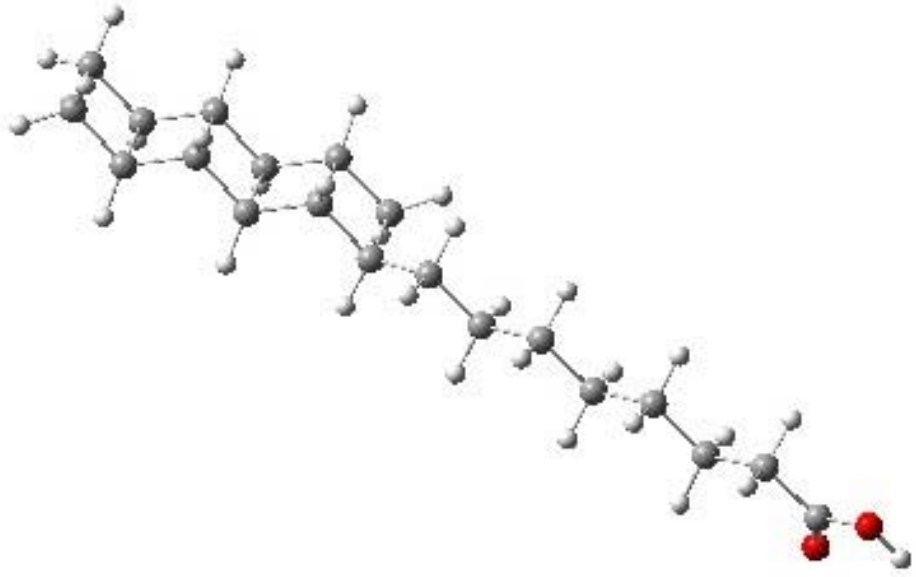


Table S9: Conformers, energies, populations, and specific rotations of (*R*)-3-ladderanoic Acid, **2a**

Conformer	Relative Energy[a]	Population	Specific Rotations						cyclohexane ring[b]
			633 nm	589 nm	546 nm	436 nm	405 nm	365 nm	
4	0.00	0.046	42	50	60	106	130	175	chair
1	0.03	0.044	140	164	194	329	395	516	chair
7	0.26	0.030	-73	-85	-101	-171	-205	-267	boat
5	0.34	0.026	31	37	44	81	100	138	chair
6	0.35	0.025	70	83	98	169	204	269	chair
3	0.40	0.023	105	123	146	250	302	399	chair
2	0.42	0.023	144	169	201	339	407	531	chair
18	0.47	0.021	0	0	-1	-3	-5	-10	boat
37	0.61	0.016	-49	-57	-68	-115	-138	-181	boat
8	0.63	0.016	-95	-112	-132	-222	-265	-345	boat
9	0.64	0.016	-61	-72	-85	-146	-177	-234	boat
21	0.78	0.012	-36	-43	-51	-86	-103	-134	boat
20	0.83	0.011	5	5	6	7	7	5	boat
234	0.87	0.010	35	42	51	92	114	157	chair
72	0.88	0.010	15	18	22	42	53	76	chair
48	0.90	0.010	22	26	31	58	72	99	chair
46	0.90	0.010	86	101	120	206	249	329	chair
43	0.90	0.010	106	124	148	252	303	398	chair
10	0.91	0.010	139	163	192	324	388	505	chair
402	0.92	0.010	21	25	30	56	70	97	chair
34	0.92	0.010	111	131	155	264	318	417	chair
35	0.92	0.010	170	199	236	399	478	625	chair
24	0.92	0.010	36	42	51	92	114	157	chair
62	0.93	0.010	73	86	102	176	213	282	chair
67	0.93	0.010	11	13	16	34	44	65	chair
468	0.93	0.010	74	87	104	179	217	287	chair
467	0.94	0.009	95	111	132	226	272	357	chair
27	0.94	0.009	142	167	198	336	403	527	chair
44	0.96	0.009	155	181	215	363	436	569	chair
39	0.96	0.009	176	206	244	411	492	641	chair
79	0.97	0.009	76	89	106	184	222	295	chair
124	1.01	0.008	103	121	143	244	294	386	chair
81	1.08	0.007	-52	-61	-72	-123	-148	-194	boat
82	1.10	0.007	-105	-123	-145	-245	-293	-382	boat
90	1.12	0.007	-104	-121	-144	-241	-288	-374	boat
94	1.12	0.007	-29	-34	-40	-69	-83	-109	boat
13	1.13	0.007	76	90	107	184	222	293	chair
68	1.15	0.007	-106	-124	-147	-246	-294	-381	boat
49	1.18	0.006	-84	-98	-116	-195	-233	-302	boat
87	1.19	0.006	-41	-48	-58	-99	-120	-158	boat
85	1.20	0.006	-115	-134	-159	-267	-320	-416	boat
621	1.21	0.006	-33	-39	-46	-80	-97	-128	boat
26	1.21	0.006	-3	-2	-2	6	13	28	chair
117	1.23	0.006	-26	-31	-37	-63	-77	-102	boat
11	1.25	0.006	128	150	178	301	361	471	chair
25	1.25	0.006	53	63	75	132	161	216	chair

40	1.25	0.006	126	148	175	297	357	466	chair
12	1.28	0.005	181	212	251	420	502	650	chair
194	1.28	0.005	135	158	188	318	382	499	chair
101	1.28	0.005	39	46	55	96	118	158	chair
29	1.28	0.005	128	150	179	305	367	483	chair
70	1.29	0.005	-32	-36	-42	-62	-70	-80	chair
64	1.29	0.005	29	34	41	74	91	125	chair
57	1.30	0.005	78	92	109	190	230	307	chair
102	1.30	0.005	101	119	141	240	288	377	chair
71	1.30	0.005	44	52	62	111	135	183	chair
77	1.30	0.005	117	137	162	275	330	432	chair
53	1.30	0.005	24	29	35	65	82	114	chair
55	1.31	0.005	46	54	65	112	137	182	chair
38	1.31	0.005	154	181	215	363	435	569	chair
217	1.32	0.005	-22	-26	-30	-51	-61	-80	boat
56	1.32	0.005	145	170	202	343	413	542	chair
47	1.32	0.005	59	70	84	146	178	239	chair
218	1.32	0.005	30	35	41	66	77	97	boat
73	1.32	0.005	77	91	108	184	222	292	chair
103	1.32	0.005	60	71	84	147	178	238	chair
42	1.33	0.005	220	258	305	512	612	793	chair
96	1.33	0.005	-27	-32	-38	-63	-75	-97	boat
28	1.33	0.005	151	177	210	355	425	555	chair
251	1.33	0.005	-49	-58	-68	-115	-138	-179	boat
59	1.34	0.005	117	137	163	277	333	436	chair
69	1.34	0.005	31	36	44	79	98	134	chair
111	1.34	0.005	25	29	34	53	61	74	boat
60	1.34	0.005	191	223	264	444	532	691	chair
45	1.35	0.005	102	120	143	245	295	390	chair
41	1.36	0.005	146	171	203	343	411	537	chair
229	1.37	0.005	44	51	59	96	113	142	boat
177	1.37	0.005	-3	-3	-4	-8	-11	-17	boat
237	1.38	0.004	-43	-50	-60	-102	-122	-161	boat
130	1.39	0.004	98	115	137	232	279	365	chair
131	1.39	0.004	74	87	104	179	217	287	chair
88	1.40	0.004	108	127	151	257	308	404	chair
86	1.42	0.004	81	95	113	196	238	316	chair
14	1.46	0.004	69	82	97	169	205	273	chair
15	1.46	0.004	95	111	132	224	270	353	chair
384	1.48	0.004	-64	-75	-89	-151	-180	-235	boat
52	1.50	0.004	-65	-76	-90	-152	-183	-238	boat
95	1.50	0.004	-3	-4	-5	-12	-16	-26	boat
114	1.51	0.004	-128	-149	-176	-294	-351	-453	boat
84	1.51	0.004	-71	-83	-99	-167	-200	-261	boat
127	1.51	0.004	-51	-59	-70	-117	-139	-180	boat
93	1.51	0.004	-157	-184	-217	-363	-432	-559	boat
78	1.52	0.004	-89	-104	-124	-210	-253	-332	boat
54	1.52	0.004	-116	-136	-160	-266	-316	-405	boat
76	1.53	0.003	-102	-120	-142	-238	-284	-368	boat
83	1.53	0.003	-95	-112	-133	-224	-269	-352	boat
91	1.53	0.003	-54	-63	-75	-129	-156	-206	boat
89	1.54	0.003	-98	-115	-136	-229	-274	-357	boat

110	1.54	0.003	-95	-111	-132	-224	-270	-353	boat
112	1.57	0.003	-63	-74	-88	-147	-176	-229	boat
125	1.57	0.003	-30	-35	-42	-71	-86	-113	boat
455	1.58	0.003	-39	-46	-55	-95	-115	-153	boat
265	1.58	0.003	-127	-149	-176	-294	-350	-452	boat
104	1.67	0.003	-23	-27	-32	-56	-69	-92	boat
121	1.68	0.003	67	78	92	149	175	220	boat
222	1.69	0.003	21	24	28	44	51	62	boat
239	1.70	0.003	81	94	110	177	208	260	boat
118	1.70	0.003	5	6	6	7	6	3	boat
105	1.70	0.003	-48	-56	-67	-111	-132	-171	boat
665	1.72	0.003	-14	-17	-20	-35	-43	-58	boat
1066	1.72	0.003	64	76	91	159	194	260	chair
190	1.72	0.002	-5	-6	-7	-12	-14	-19	boat
252	1.73	0.002	-86	-100	-119	-199	-238	-308	boat
312	1.74	0.002	-24	-28	-33	-59	-71	-96	boat
187	1.74	0.002	14	16	18	27	30	35	boat
149	1.74	0.002	201	235	278	464	554	717	chair
231	1.74	0.002	-21	-25	-30	-53	-65	-88	boat
320	1.74	0.002	105	124	147	250	301	394	chair
259	1.74	0.002	17	20	25	48	60	85	chair
258	1.74	0.002	-4	-4	-4	3	8	22	chair
157	1.75	0.002	151	177	209	354	425	555	chair
155	1.75	0.002	195	229	270	453	541	701	chair
273	1.75	0.002	23	28	34	63	79	111	chair
267	1.75	0.002	86	101	120	204	246	324	chair
314	1.76	0.002	70	82	99	176	216	294	chair
278	1.76	0.002	66	78	94	163	199	266	chair
308	1.76	0.002	-4	-4	-5	-10	-13	-19	boat
254	1.76	0.002	98	115	136	229	275	359	chair
152	1.76	0.002	74	87	104	182	222	297	chair
99	1.76	0.002	28	33	41	79	101	144	chair
140	1.77	0.002	114	133	158	266	318	415	chair
240	1.77	0.002	4	5	5	6	6	4	boat
246	1.77	0.002	65	77	92	162	197	265	chair
396	1.78	0.002	156	183	216	360	429	553	chair
274	1.78	0.002	-22	-24	-28	-37	-39	-38	chair
165	1.78	0.002	102	120	142	244	294	387	chair
427	1.78	0.002	2	3	5	14	20	33	chair
309	1.79	0.002	-74	-86	-102	-172	-205	-267	boat
286	1.79	0.002	183	214	254	429	514	671	chair
245	1.79	0.002	-33	-39	-46	-76	-90	-116	boat
205	1.79	0.002	30	36	43	78	96	132	chair
50	1.79	0.002	148	173	205	342	407	526	chair
408	1.79	0.002	-21	-24	-28	-41	-45	-51	chair
129	1.80	0.002	144	169	200	338	405	528	chair
292	1.80	0.002	115	134	160	271	326	428	chair
302	1.80	0.002	184	216	256	431	516	673	chair
148	1.80	0.002	157	184	218	368	440	573	chair
415	1.80	0.002	48	57	68	118	144	193	chair
313	1.81	0.002	54	63	74	118	138	173	boat
150	1.81	0.002	109	128	152	256	306	399	chair

386	1.81	0.002	28	33	40	72	88	121	chair
115	1.81	0.002	157	184	218	369	442	577	chair
409	1.83	0.002	-64	-75	-89	-151	-181	-236	boat
167	1.84	0.002	7	9	12	27	36	55	chair
445	1.84	0.002	75	88	105	181	219	291	chair
651	1.85	0.002	40	47	57	101	124	168	chair
279	1.86	0.002	104	122	145	246	295	387	chair
678	1.87	0.002	146	171	202	342	411	537	chair
584	1.88	0.002	57	67	80	139	169	225	chair
385	1.88	0.002	115	135	160	270	323	421	chair
525	1.89	0.002	103	121	144	247	297	391	chair
281	1.89	0.002	77	91	108	187	227	303	chair
691	1.89	0.002	76	89	106	181	219	289	chair
433	1.89	0.002	67	79	95	165	200	266	chair
501	1.90	0.002	143	168	199	338	406	532	chair
476	1.91	0.002	74	87	103	178	216	287	chair
682	1.91	0.002	36	43	51	91	111	149	chair
1455	1.92	0.002	123	145	172	292	351	460	chair
477	1.92	0.002	143	167	198	335	402	524	chair
627	1.93	0.002	106	124	147	251	302	397	chair
513	1.95	0.002	45	53	64	113	139	187	chair
297	1.95	0.002	-103	-120	-142	-239	-286	-372	boat
298	1.96	0.002	-129	-150	-177	-295	-351	-452	boat
996	1.96	0.002	44	52	63	109	133	178	chair
285	1.97	0.002	-21	-26	-31	-58	-73	-103	boat
300	1.98	0.002	-32	-38	-45	-76	-92	-120	boat
426	1.99	0.002	-140	-164	-193	-320	-380	-488	boat
416	1.99	0.002	-53	-62	-73	-123	-147	-190	boat
180	1.99	0.002	104	122	145	247	298	391	chair
756	2.00	0.002	109	128	152	258	311	408	chair
population weighted			41	49	58	99	120	158	

[a]energies (in kcal/mol) are relative to -932.09477157 Hartrees

[b]alkyl chain is in equatorial position; sum of populations of chair equatorial conformations is 0.658 and of boat equatorial conformations is 0.342.

Figure S12: Predicted lowest energy conformer, C4 in Table S9, of (*R*)-3-ladderanoic acid. The four C atoms, starting from the second C of alkyl chain and going along the edge of the ladder, make a dihedral angle of ~170°. Cyclohexane ring is in chair conformation.

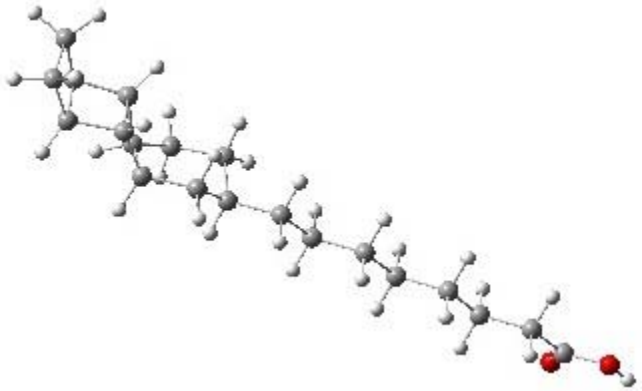


Figure S13: Predicted lowest energy conformer, C1 in Table S9, of (*R*)-3-ladderanoic acid. The four C atoms, starting from the second C of alkyl chain and going along the edge of the ladder, make a dihedral angle of ~70°. Cyclohexane ring is in chair conformation.

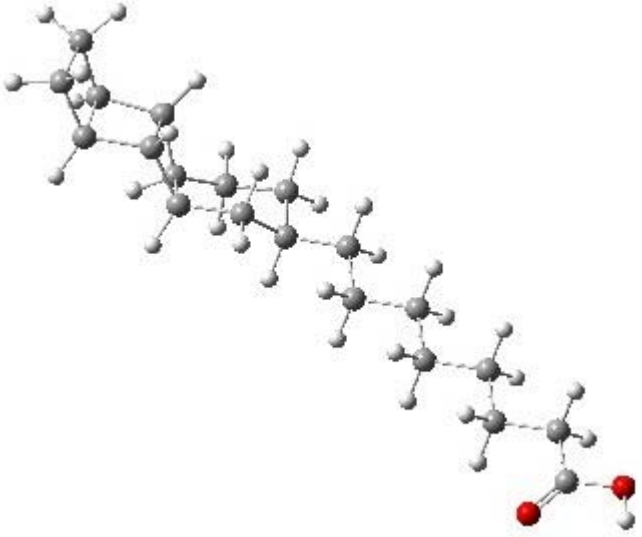


Table S10: Experimental specific rotations for **1a**, **2a**, **6a** and **7a** in chloroform

	1a[1]		**2a**[2]		**6a**[3]		**7a**[4]	
λ(nm)	[α]	error (±)	[α]	error (±)	[α]	error (±)	[α]	error (±)
365	-38	4	43	5	-7	1	35	6
405	-29	3	31	3	-5	1	25	5
436	-24	3	26	3	-4	1	19	5
546	-14	2	13	2	-2	1	8	4
589	-12	2	10	1	-2	1	7	4
633	-10	2	8	1	-2	1	3	4

[1]3.5 mg/mL ; [2]4.5 mg/mL ; [3]6.1 mg/mL; [4]1.1 mg/mL

X-Ray Crystallographic Data

Table S11. Phenacyl ester **6a** of [5]-ladderanoic acid **1a**.

Identification code	CCDC 1552002	
Empirical formula	$C_{28}H_{36}O_3$	
Formula weight	420.57	
Temperature	100 K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 5.3774(3) Å	α = 90°
	b = 14.7492(6) Å	β= 90.817(5)°
	c = 43.061(2) Å	γ = 90°
Volume	3414.9(3) $Å^3$	
Z	6	
Density (calculated)	1.227 Mg/m^3	
Absorption coefficient	0.607 mm^{-1}	
F(000)	1554.000	
Crystal size	0.194 x 0.061 x 0.009 mm^3	
Theta range for data collection	3.167 to 66.581°.	
Index ranges	-4<=h<=6, -17<=k<=17, -51<=l<=50	
Reflections collected	34221	
Independent reflections	11658 [R(int) = 0.0463]	
Completeness to theta = 66.581°	99.37 %	
Absorption correction	Gaussian	
Max. and min. transmission	1.000 and 0.760	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	11658 / 1 / 838	
Goodness-of-fit on F^2	1.046	
Final R indices [I>2sigma(I)]	R1 = 0.0646, wR2 = 0.1690	
R indices (all data)	R1 = 0.0767, wR2 = 0.1800	
Absolute structure parameter (Flack)	0.04(15)	
Absolute structure parameter (Hooft)	0.01(12)	
Largest diff. peak and hole	0.344 and -0.272 $e/Å^{-3}$	

Table S12. [5]-Ladderanoic acid **1a**.

Identification code	CCDC 1552003	
Empirical formula	$C_{20}H_{30}O_2$	
Formula weight	302.44	
Temperature	100 K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	C_2	
Unit cell dimensions	a = 64.164(2) Å	α = 90°
	b = 4.8171(2) Å	β= 90.556(3)°
	c = 10.9786(4) Å	γ = 90°
Volume	3393.2(2) $Å^3$	
Z	8	
Density (calculated)	1.184 Mg/m^3	
Absorption coefficient	0.572 mm^{-1}	
F(000)	1328	
Crystal size	0.259 x 0.068 x 0.012 mm^3	
Theta range for data collection	4.027 to 66.600°.	
Index ranges	-76<=h<=76, -5<=k<=5, -10<=l<=13	
Reflections collected	16132	
Independent reflections	5530 [R(int) = 0.0444]	
Completeness to theta = 66.600°	99.2 %	
Absorption correction	Gaussian	
Max. and min. transmission	1.000 and 0.785	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5530 / 1 / 399	
Goodness-of-fit on F^2	1.020	
Final R indices [I>2sigma(I)]	R1 = 0.0484, wR2 = 0.1284	
R indices (all data)	R1 = 0.0600, wR2 = 0.1383	
Absolute structure parameter (Flack)	-0.1(2)	
Absolute structure parameter (Hooft)	-0.03(18)	
Largest diff. peak and hole	0.213 and -0.216 $e/Å^{-3}$	

Table S13. [3]-Ladderanoic acid **2a**.

Identification code	1555318	
Empirical formula	$C_{20}H_{32}O_2$	
Formula weight	304.45	
Temperature	100.0(3) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	$C2_1$	
Unit cell dimensions	a = 36.457(2) Å	α = 90°
	b = 4.8860(3) Å	β = 105.385(5)°
	c = 20.2686(9) Å	γ = 90°
Volume	3481.0(3) $Å^3$	
Z	8	
Density (calculated)	1.162 Mg/m^3	
Absorption coefficient	0.558 mm^{-1}	
F(000)	1344	
Crystal size	0.137 x 0.025 x 0.02 mm^3	
Theta range for data collection	3.803 to 68.394°.	
Index ranges	-42<=h<=38, -5<=k<=5, -24<=l<=23	
Reflections collected	17577	
Independent reflections	6145 [R(int) = 0.0476]	
Completeness to theta = 67.684°	99.2 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.88685	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6145 / 1 / 409	
Goodness-of-fit on F^2	1.029	
Final R indices [I>2sigma(I)]	R1 = 0.0555, wR2 = 0.1152	
R indices (all data)	R1 = 0.0898, wR2 = 0.1324	
Absolute structure parameter (Flack)	0.0(3)	
Absolute structure parameter (Hooft)	-0.2(2)	
Largest diff. peak and hole	0.156 and -0.144 $e/Å^{-3}$	

Reference

(1) Damsté, J. S. S.; Strous, M.; Rijpstra, W. I. C.; Hopmans, E. C.; Geenevasen, J. A. J.; van Duin, A. C. T.; van Niftrik, L. A.; Jetten, M. S. M. *Nature* **2002**, *419*, 708-712.