Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supporting Information for

Conformational isomerism in cyclic peptoids and its specification

Assunta D'Amato, Rosaria Schettini, Giorgio Della Sala, Chiara Costabile,

Consiglia Tedesco, Irene Izzo, Francesco De Riccardis*

Department of Chemistry and Biology "A. Zambelli", University of Salerno, Via Giovanni Paolo II, 132, Fisciano (SA), 84084, Italy

Table of contents

List of abbreviations

ACN: acetonitrile

DCM: dichloromethane

DIC*: N,N′*-diisopropylcarbodiimide

DIPEA: *N,N*-diisopropylethylamine

DMF: dimethylformamide

ESI: electrospray ionisation

HATU: *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate

HFIP: hexafluoroisopropanol

HRMS: high resolution mass spectrometry

RP HPLC: reversed-phase high-performance liquid chromatography

TCDE: tetrachlorodideuteroethane

TFA: trifluoroacetic acid

1.0 Synthesis of known cyclopeptoids 4, 9 and 13

The synthesis of cyclopeptoids **4**,[1] **9**,[2] and **13**[3] was performed according the general oligomerization/cyclization procedure reported in Ref. 3.

1.1 General procedure for the solid-phase synthesis of linear precursors of cyclopeptoids 4, 9 and 13

The 2-chlorotrityl chloride resin (α-dichlorobenzhydryl-polystyrene cross-linked with 1% DVB; 100–200 mesh; 1.63 mmol g^{-1}, 0.400 g, 0.652 mmol) was swelled in dry DCM (4 mL) for 45 min and washed twice with dry DCM (4 mL). The first submonomer was attached onto the resin by adding bromoacetic acid (0.136 g, 0.978 mmol) in dry DCM (4 mL) and DIPEA (567 μL, 3.26 mmol) on a shaker platform for 60 min at room temperature, followed by washing with DCM (3 × 1 min) and then again with DMF (3 × 1 min). A solution of the chosen amine (benzylamine or isopropylamine, 1.6 M in dry DMF, 4 mL) was added to the bromoacetylated resin. The mixture was left on a shaker platform for 30 min at room temperature, then the resin was washed with DMF (3 × 1 min), DCM (3 × 1 min) and then again with DMF (3 × 1 min). Subsequent bromoacetylation reactions were accomplished by reacting the aminated oligomer with a solution of bromoacetic acid (0.910 g, 6.52 mmol) and DIC (1.11 mL, 7.17 mmol) in dry DMF (4 mL) for 40 min at room temperature. The filtrated resin was washed with DMF (4 × 1 min), DCM (4 × 1 min), DMF (4 × 1 min) and treated again with the proper amine under the same conditions reported above. This cycle of reactions was iterated until the target oligomer obtained. The cleavage was performed treating the resin, previously washed with CH_2Cl_2 (3 × 1 min), twice with a solution of HFIP in CH_2Cl_2 (20% v/v, 4.0 mL each time) on a shaker platform at room temperature for 30 min and 5 min, respectively. The resin was then filtered away and the combined filtrates were concentrated *in vacuo*. 2 mg of the final products were dissolved in 200 μL of acetonitrile (0.1% TFA) and 200 μL of HPLC grade water (0.1% TFA) and analyzed by RP-HPLC; purity >95%; conditions: 5 → 100% A in 30 min for the all oligomers [(A, 0.1% TFA in acetonitrile, B, 0.1% TFA in water); flow: 1.0 mL min^{-1}, 220 nm]. The linear oligomers (isolated as amorphous solids) were subjected to ESI mass spectrometry and, subsequently, to the cyclization reactions without further purification.

H-[*N*pe]$_3$-OH (linear precursor of **4**): white amorphous solid, 0.180 g, quantitative; t_R: 6.6 min. ES-MS *m/z*; 460.2

H-[*N*pe]$_4$-OH (linear precursor of **9**): white amorphous solid, 0.250 g, quantitative; t_R: 8.2 min. ES-MS *m/z*; 607.3

H-[*N*Phe-*N*Val]$_3$-OH (linear precursor of **13**): white amorphous solid, 0.453 g, 92%; t_R: 10.0 min. ES-MS *m/z*; 757.2.

1.2 General procedure for the high dilution cyclization

The previously synthesised linear peptoids (0.150 mmol), once co-evaporated three times with toluene, were dissolved under nitrogen in dry DMF (5.0 mL). The mixture was added dropwise to a stirred solution of HATU (0.171 g, 0.450 mmol) and DIPEA (105 µL, 0.600 mmol) in dry DMF (45.0 mL) by a syringe pump in 6 h, at room temperature in anhydrous atmosphere. After 18 h the resulting mixture was concentrated *in vacuo*, diluted with DCM (30 mL), washed with a solution of HCl (1.0 M, 15 mL). The mixture was extracted with DCM (2 × 30.0 mL) and the combined organic phases were washed with water (30.0 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude cyclic peptoid **4** was purified on flash silica gel; conditions: 80% – 50% A (A: petroleum ether; B: ethyl acetate). Peptoids **9** and **13** were dissolved or suspended in hot ACN and precipitated by slowly cooling the solutions.

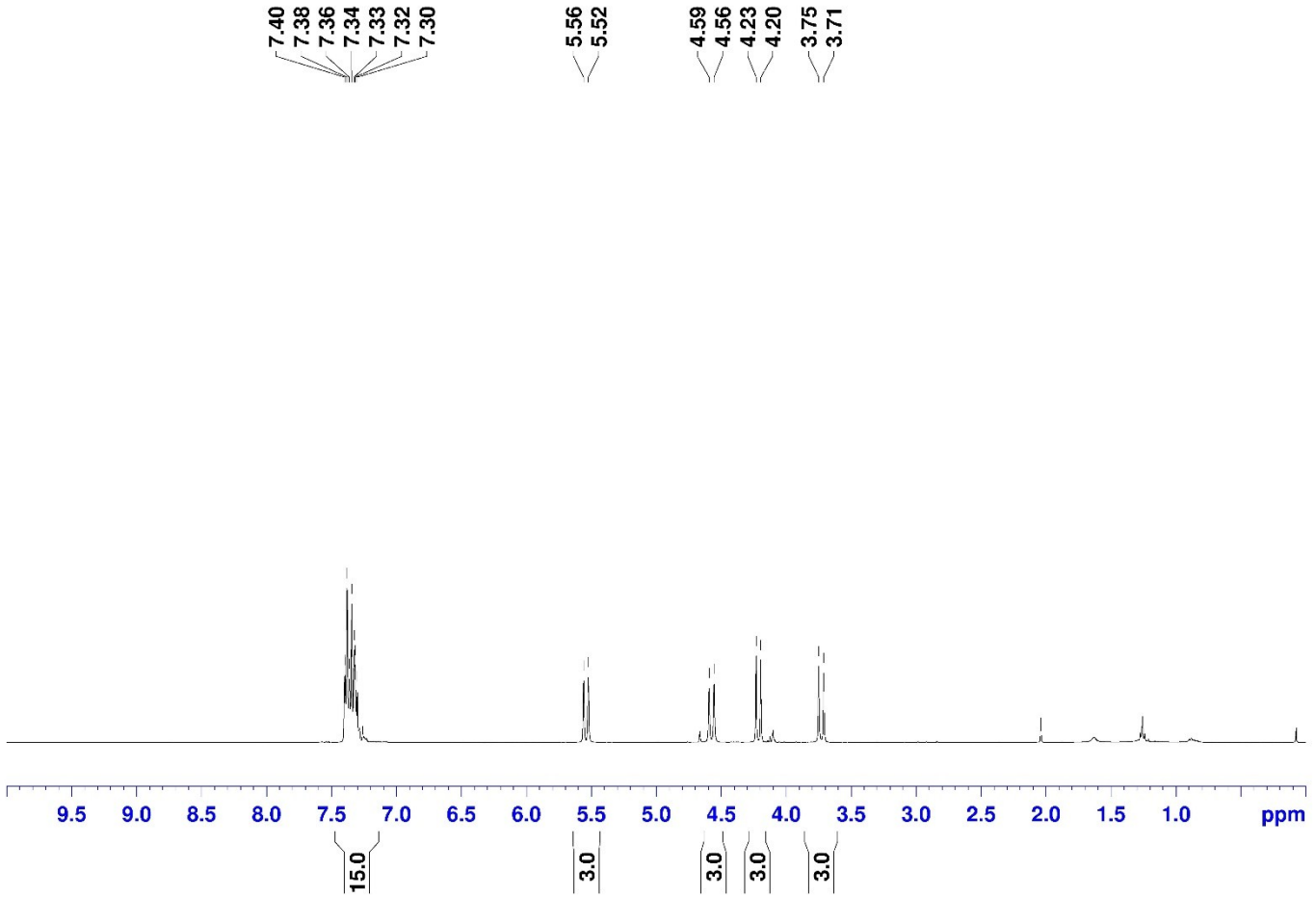
4: white amorphous solid, 0.034 g, 35%; t_R: 9.0 min. ES-MS *m/z*; 442.2.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40-7.30 (15H, *m*), 5.54 (3H, *d*, *J* 14.4 Hz), 4.58 (3H, *d*, *J* 15.5 Hz), 4.21 (3H, *d*, *J* 14.4 Hz), 3.73 (3H, *d*, *J* 15.5 Hz);

9: white amorphous solid, 0.115 g, 95%; t_R: 11.6 min. ES-MS *m/z*; 589.3.
^{1}H NMR (600 MHz,$CDCl_3$) δ: 7.32-7.08 (20H, *m*), 5.56 (2H, *d*, *J* 14.4 Hz), 5.41 (2H, *d*, *J* 14.9 Hz), 4.45 (2H, *d*, *J* 17.2 Hz), 4.38 (2H, *d*, *J* 17.2 Hz), 4.34 (2H, *d*, *J* 17.2 Hz), 3.74 (2H, *d*, *J* 14.4 Hz), 3.50 (2H, *d*, *J* 14.9 Hz), 3.49 (2H, *d*, *J* 17.2 Hz);

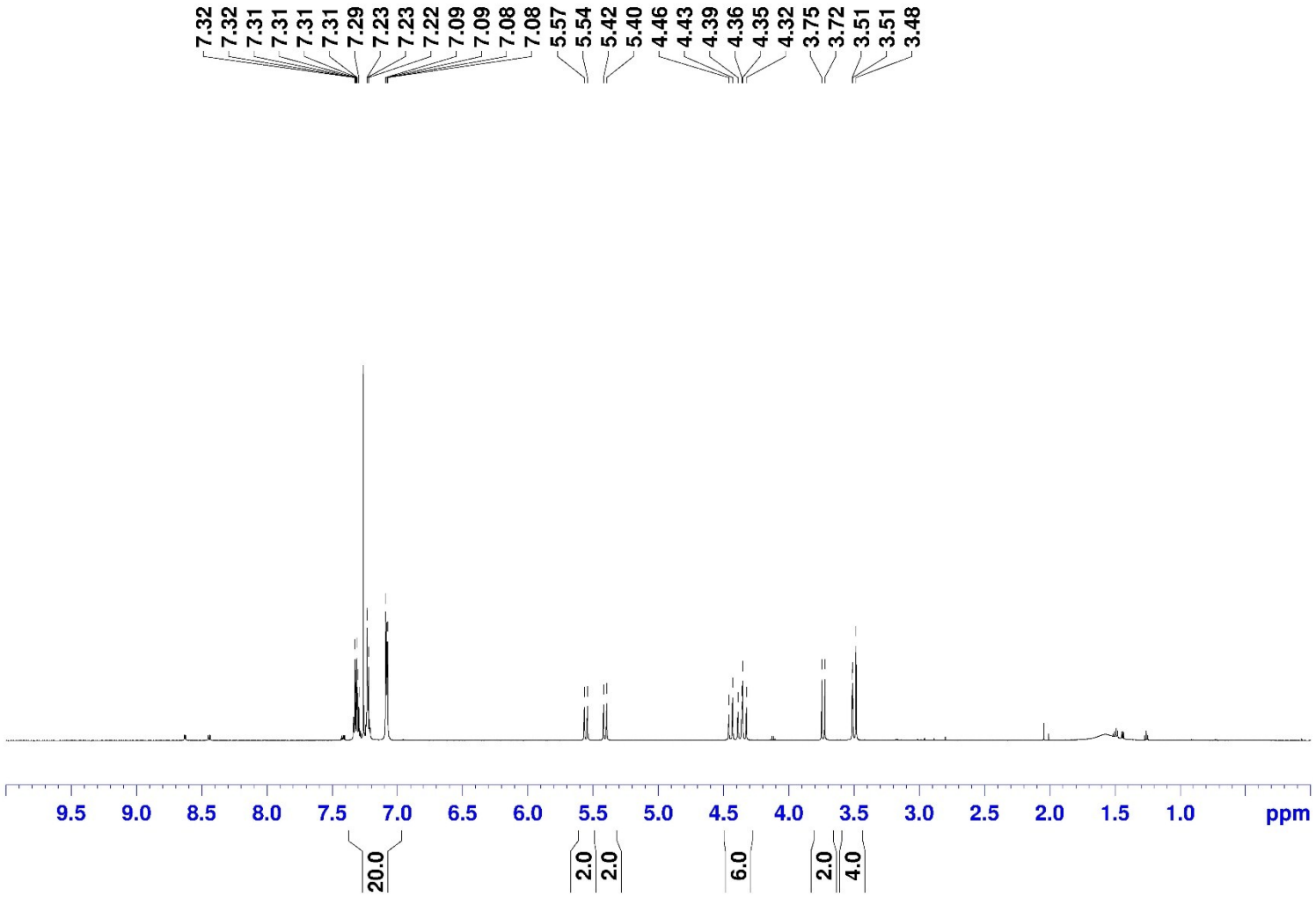
13: white amorphous solid, 0.050 g, 45%; t_R: 11.5 min. ES-MS *m/z*; 739.2.
^{1}H NMR (600 MHz,$CDCl_3$) δ: 7.39-7.11 (13H, *overlapping signals*), 6.98 (2H, t, *J* 7.5 Hz), 5.60 (1H, *d*, *J* 15 Hz), 5.37 (1H, *d*, *J* 15 Hz), 4.89 (1H, *d*, *J* 15 Hz), 4.87 (1H, *d*, *J* 7 Hz), 4.80 (1H, *d*, *J* 7 Hz), 4.69 (1H, *d*, *J* 15 Hz), 4.65 (1H, *d*, *J* 17 Hz), 4.55 (1H, *d*, *J* 17 Hz), 4.54 (1H, *d*, *J* 17 Hz), 4.34 (1H, *d*, *J* 17 Hz), 4.10 (1H, *d*, *J* 17 Hz), 3.93 (1H, *d*, *J* 17 Hz), 3.91 (1H, *d*, *J* 15 Hz), 3.86 (1H, *d*, *J* 17 Hz), 3.82 (1H, *d*, *J* 7 Hz), 3.79 (1H, *d*, *J* 15 Hz), 3.70 (1H, *d*, *J* 17 Hz), 3.59 (1H, *d*, *J* 17 Hz), 3.30 (1H, *d*, *J* 17 Hz), 3.27 (1H, *d*, *J* 17 Hz), 3.15 (1H, *d*, *J* 17 Hz), 1.43 (3H, *d*, *J* 7 Hz), 1.23 (3H, *d*, *J* 7 Hz), 1.12 (3H, *d*, *J* 7 Hz), 1.08 (3H, *d*, *J* 7 Hz), 1.01 (3H, *d*, *J* 7 Hz), 0.98 (3H, *d*, *J* 7 Hz).

The NMR data collected for **4**, **9** and **13** (^{1}H NMR, reported in this S.I., and ^{13}C NMR) were coincident with those reported in the literature Refs. 1-3).

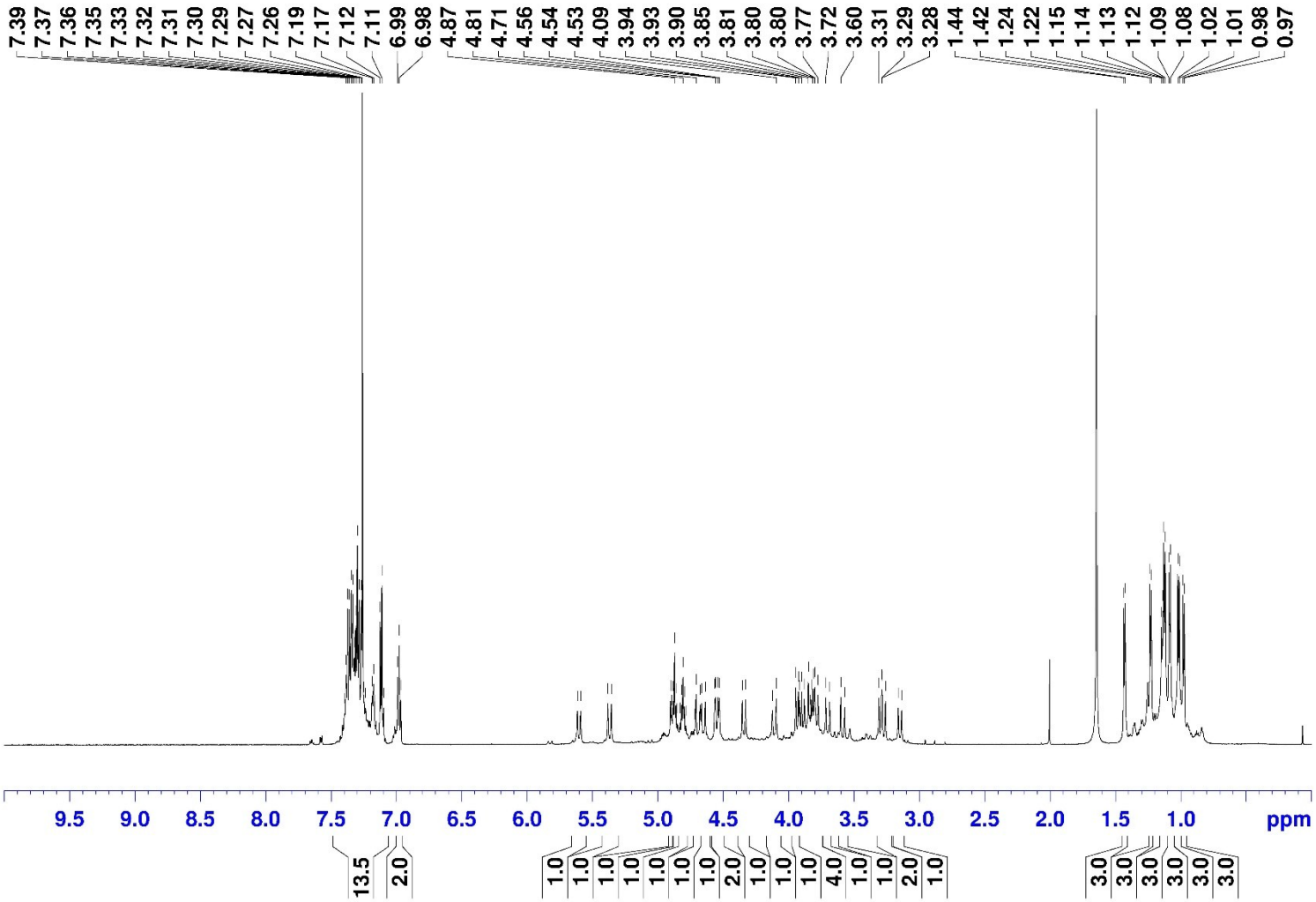
1.3 ^{1}H NMR spectra of compounds 4, 9 and 13



4: ^{1}H NMR (400 MHz, $CDCl_3$)



9: ^{1}H NMR (600 MHz, $CDCl_3$)



13: ^{1}H NMR (600 MHz, $CDCl_3$)

2.0 General procedure for the Pirkle's alcohol addition to 4 and 9

To a 4.0 mM solution of cyclic peptoid **4** and **9** in $CDCl_3$ (0.5 mL), 1.0 equivalent of Pirkle's alcohol ((*R*)-1-(9-anthryl)-2,2,2-trifluoroethanol) were added. After the addition the mixture was mixed for 1 minute and the ^1H NMR spectrum was recorded. Further equivalents of Pirkle's alcohol were added in order to increase the protons resonances' splitting (as reported in Figure S1, S2).

NMR spectra were recorded on a Bruker DRX 600 (^1H at 600.13 MHz). The residual solvent peak was $CHCl_3$, set at $\delta = 7.26$. The addition of Pirkle's alcohol to **13** and the general procedure is described in the ESI of Ref. 3.

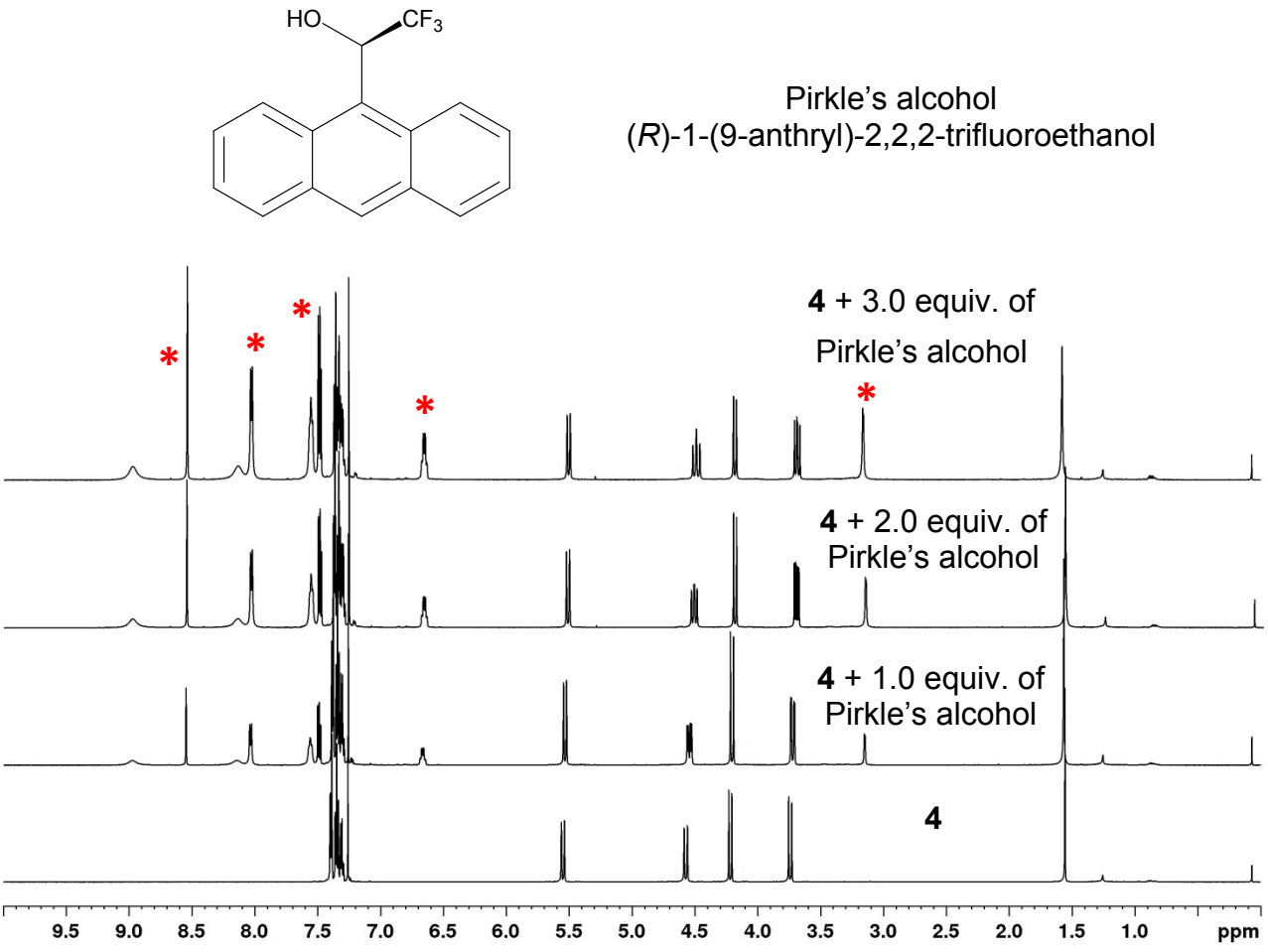


Figure S1. Quantitative step-wise addition of Pirkle's alcohol to **4**. ^1H NMR (600 MHz, $CDCl_3$, 298 K, 4.0 mM solution). Full spectra. * Indicates the Pirkle's alcohol resonances.

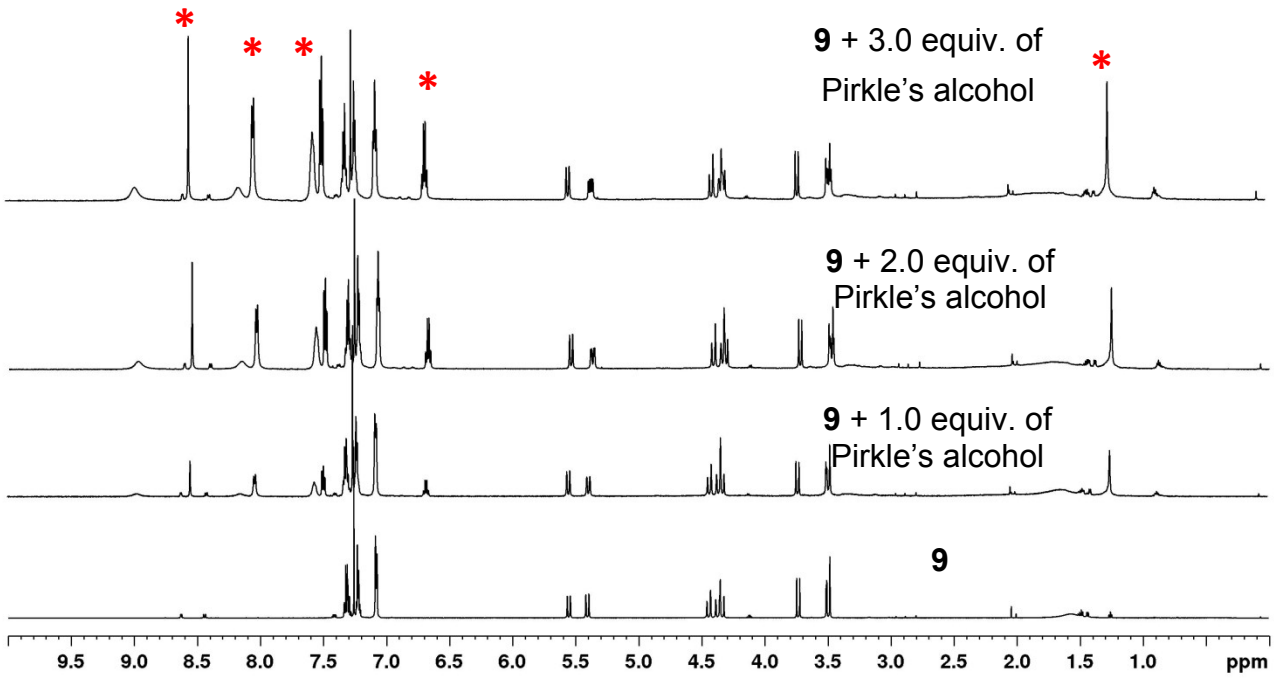


Figure S2. Quantitative step-wise addition of Pirkle's alcohol to **9**. ^{1}H NMR (600 MHz, $CDCl_3$, 298 K, 4.0 mM solution). Full spectra. * Indicates the Pirkle's alcohol resonances.

3.0 ^{1}H NMR variable temperature experiments on 4

4 was dissolved in $C_2D_2Cl_4$ (TCDE, 5.0 mM solution), then ^{1}H NMR spectra (300 MHz) were acquired at increasing temperatures. No coalescence was observed up to 120° C.

NMR spectra were recorded on a Bruker DRX 300 (^{1}H at 300.1 MHz). The residual solvent peak was C_2DHCl_4, set at $\delta = 5.80$.

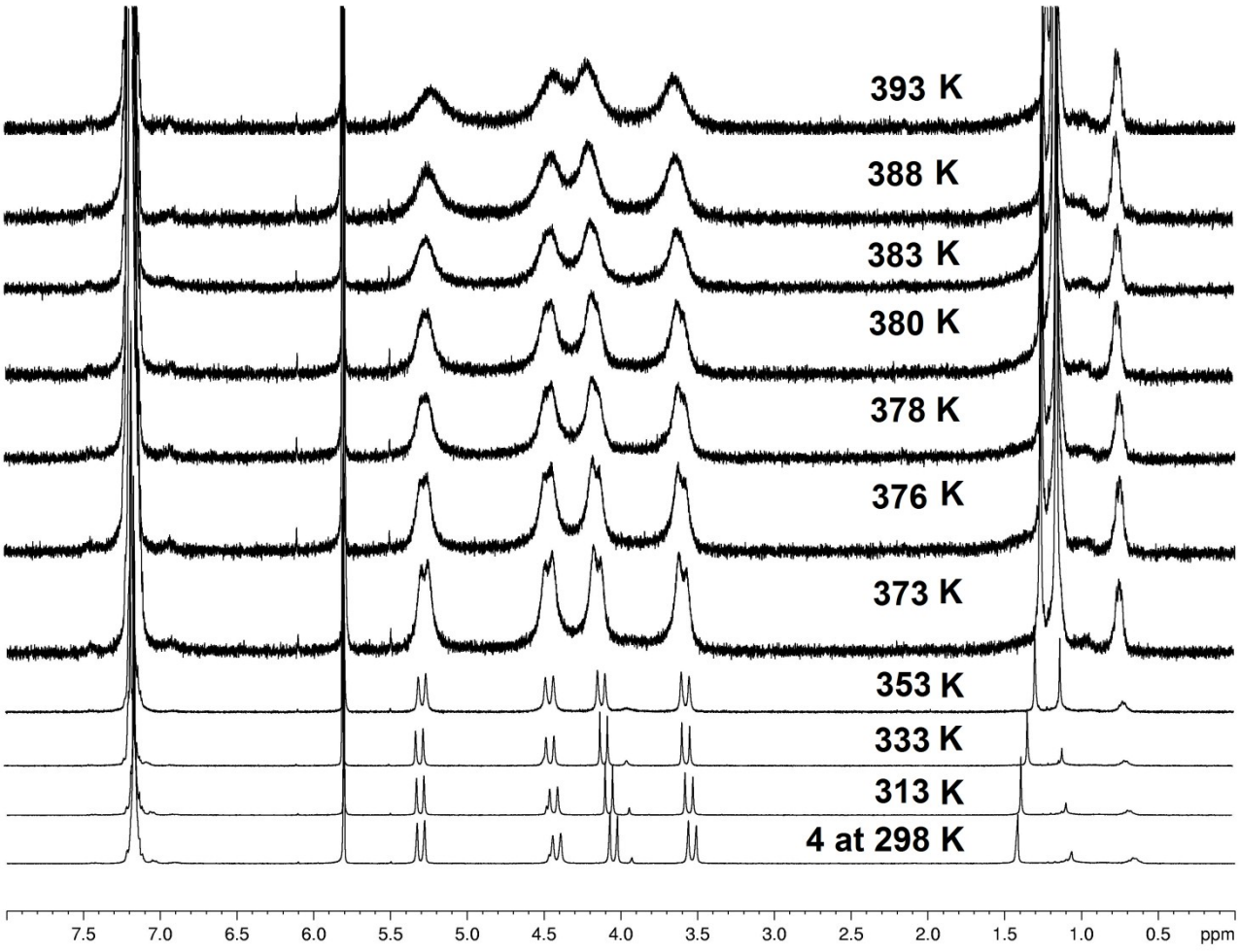


Figure S3. Variable temperature ^{1}H NMR spectra of compound **4** (300 MHz, $C_2D_2Cl_4$, 5.0 mM solution).

4.0 Computational details

The DFT calculations were performed with the Gaussian09 set of programs,[4] using the BP86 functional of Becke and Perdew.[5] The electronic configuration of the molecular systems was described with the standard triple zeta valence basis set with a polarization function of Ahlrichs and co-workers for H, C, N, O (TZVP keyword in Gaussian).[6] The geometry optimizations were performed without symmetry constraints, and the characterization of the located stationary points was performed by analytical frequency calculations.

Cartesian coordinates and gas phase internal energies of calculated structures

30

1a SCF Done: -742.194329251 A.U.

C	-0.822843	1.797975	0.141035
C	-1.556558	0.737318	0.991761
N	0.551084	1.858834	0.194601
C	1.413546	0.978542	0.993057
C	1.973748	-0.186822	0.147517
N	1.336337	-1.405840	0.193021
C	0.140308	-1.712983	0.987817
C	-1.148058	-1.610061	0.141703
N	-1.890718	-0.452721	0.198693
O	2.960390	0.021406	-0.566482
O	-1.458090	-2.563783	-0.580142
O	-1.493160	2.541960	-0.582850
C	1.809587	-2.485649	-0.683911
C	1.251945	2.804142	-0.685057
C	-3.066097	-0.321760	-0.673185
H	-2.501465	1.208964	1.297824
H	-1.028393	0.452041	1.907311
H	0.897615	0.663097	1.905044
H	2.290807	1.564548	1.303141
H	0.206319	-2.767034	1.293846
H	0.125632	-1.112323	1.902833
H	0.986925	-2.836317	-1.323044
H	2.630200	-2.094732	-1.294034
H	2.171618	-3.329740	-0.074479
H	-3.146197	-1.231389	-1.276973
H	-3.973661	-0.203329	-0.059102
H	-2.957332	0.561087	-1.318986
H	1.826722	3.521391	-0.077007
H	1.945932	2.261899	-1.342962
H	0.501779	3.339048	-1.276243

30

1b

C	-0.822843	1.797975	-0.141035
C	-1.556558	0.737318	-0.991761
N	0.551084	1.858834	-0.194601
C	1.413546	0.978542	-0.993057
C	1.973748	-0.186822	-0.147517
N	1.336337	-1.405840	-0.193021
C	0.140308	-1.712983	-0.987817
C	-1.148058	-1.610061	-0.141703
N	-1.890718	-0.452721	-0.198693
O	2.960390	0.021406	0.566482
O	-1.458090	-2.563783	0.580142
O	-1.493160	2.541960	0.582850
C	1.809587	-2.485649	0.683911
C	1.251945	2.804142	0.685057
C	-3.066097	-0.321760	0.673185
H	-2.501465	1.208964	-1.297824

H	-1.028393	0.452041	-1.907311
H	0.897615	0.663097	-1.905044
H	2.290807	1.564548	-1.303141
H	0.206319	-2.767034	-1.293846
H	0.125632	-1.112323	-1.902833
H	0.986925	-2.836317	1.323044
H	2.630200	-2.094732	1.294034
H	2.171618	-3.329740	0.074479
H	-3.146197	-1.231389	1.276973
H	-3.973661	-0.203329	0.059102
H	-2.957332	0.561087	1.318986
H	1.826722	3.521391	0.077007
H	1.945932	2.261899	1.342962
H	0.501779	3.339048	1.276243

108

8 from ref. 7

C	1.386751	-0.301402	0.299342
N	1.362122	-1.080110	-0.820677
C	0.786560	-2.411178	-0.735816
C	-0.449645	-2.573164	-1.633936
C	1.775961	1.164031	0.086127
N	-1.623597	-1.982292	-1.264084
C	-1.776128	-1.164124	-0.086019
C	-1.386892	0.301323	-0.299114
N	-1.362146	1.079881	0.820997
C	-0.786649	2.410989	0.736240
C	0.449650	2.572974	1.634238
N	1.623596	1.982203	1.264196
O	-1.044768	0.730401	-1.397631
O	0.342225	3.232863	2.662796
O	1.044753	-0.730398	1.397930
O	-0.342081	-3.232953	-2.662542
C	-1.812350	0.670240	2.146883
C	-3.288834	0.917900	2.412739
C	-2.780096	-2.180401	-2.126812
C	-3.163125	-0.969095	-2.956435
C	2.780248	2.180451	2.126690
C	3.163474	0.969268	2.956411
C	1.812380	-0.670629	-2.146585
C	3.288888	-0.918336	-2.412316
O	3.840146	0.036817	2.139440
O	-4.051578	-0.120693	1.847496
O	4.051554	0.120474	-1.847389
O	-3.839969	-0.036750	-2.139483
C	3.972789	-1.221695	2.772210
C	-5.443137	0.085222	2.009762
C	5.443139	-0.085460	-2.009440
C	-3.972467	1.221840	-2.772126
C	7.592972	3.320099	-0.495909
C	7.660204	3.000044	-1.847584
C	6.959160	1.900565	-2.337519

C	6.192722	1.107272	-1.485085
C	6.131202	1.432872	-0.126709
C	6.824799	2.534872	0.362011
C	6.184166	-3.882549	0.210896
C	6.832868	-2.830916	0.855918
C	6.116652	-1.976039	1.687132
C	4.744605	-2.154058	1.880571
C	4.104763	-3.208716	1.229364
C	4.818328	-4.071743	0.400838
C	-7.593343	-3.319519	0.494912
C	-6.825177	-2.533978	-0.362729
C	-6.131448	-1.432250	0.126415
C	-6.192829	-1.107237	1.484937
C	-6.959258	-1.900844	2.337088
C	-7.660431	-3.000053	1.846732
C	-6.184209	3.882512	-0.210937
C	-4.818349	4.071738	-0.400691
C	-4.104658	3.208765	-1.229165
C	-4.744398	2.154134	-1.880515
C	-6.116469	1.976086	-1.687268
C	-6.832809	2.830904	-0.856101
H	0.581195	-2.613165	0.315580
H	1.497613	-3.155445	-1.103681
H	1.155277	1.558883	-0.721548
H	2.811725	1.210930	-0.256683
H	-1.155622	-1.559014	0.721771
H	-2.811954	-1.211005	0.256608
H	-0.581395	2.613117	-0.315152
H	-1.497700	3.155188	1.104249
H	-1.230563	1.243633	2.872205
H	-1.578811	-0.379917	2.326284
H	-3.451959	0.952431	3.502284
H	-3.632841	-2.476937	-1.506141
H	-2.528327	-3.004831	-2.794178
H	-3.818518	-1.286178	-3.784168
H	2.528597	3.004978	2.793977
H	3.632879	2.476902	1.505822
H	2.259728	0.519082	3.384152
H	3.819049	1.286475	3.783951
H	1.578877	0.379508	-2.326117
H	1.230602	-1.244094	-2.871859
H	3.592031	-1.893186	-2.000884
H	3.452080	-0.953242	-3.501841
H	-2.259271	-0.518864	-3.383900
H	-3.591967	1.892897	2.001658
H	4.498036	-1.097532	3.733194
H	2.976565	-1.631197	2.982465
H	-5.676513	0.236825	3.074988
H	-5.743202	0.997662	1.472779
H	5.743196	-0.997642	-1.472016
H	5.676607	-0.237539	-3.074576

H	-2.976196	1.631339	-2.982180
H	-4.497561	1.097806	-3.733210
H	8.136687	4.177177	-0.110925
H	8.254317	3.607342	-2.523276
H	7.007826	1.657453	-3.395528
H	5.532116	0.824099	0.544060
H	6.771760	2.779205	1.418826
H	6.743693	-4.555301	-0.431477
H	7.898978	-2.681690	0.716490
H	6.625127	-1.159458	2.191389
H	3.038925	-3.353014	1.378238
H	4.308498	-4.893521	-0.092610
H	-8.137165	-4.176381	0.109597
H	-6.772248	-2.777854	-1.419655
H	-5.532349	-0.823249	-0.544136
H	-7.007814	-1.658191	3.395208
H	-8.254534	-3.607598	2.522211
H	-6.743830	4.555224	0.431394
H	-4.308600	4.893496	0.092873
H	-3.038800	3.353082	-1.377876
H	-6.624862	1.159521	-2.191634
H	-7.898936	2.681655	-0.716828

108

13a from ref 3

O	0.809614	-0.825881	-0.106285
N	3.337792	0.005429	0.567729
C	3.139611	-0.598145	-0.741058
H	3.774713	-1.496929	-0.788902
H	3.503142	0.075906	-1.531177
O	-0.322119	-3.785165	-1.952529
N	1.309610	-1.382453	-2.256535
C	1.653226	-0.966914	-1.003846
O	-3.315535	-0.999875	-3.336387
N	-2.062967	-2.436349	-1.319034
C	3.649170	-0.912781	1.677877
H	2.844945	-1.664011	1.752270
H	3.621894	-0.298004	2.588946
O	-0.888367	1.683818	-1.405906
N	-3.485156	0.939661	-2.117874
C	4.995201	-1.591345	1.520555
O	0.176249	4.716781	0.808575
N	-1.461570	2.346067	0.697816
C	5.095256	-2.990493	1.497246
H	4.187521	-3.595189	1.579813
O	3.015929	1.767411	2.000235
N	1.936186	3.449666	0.052234
C	6.341803	-3.617673	1.374555
H	6.402050	-4.708267	1.358934
C	7.504111	-2.848601	1.268337
H	8.477328	-3.334830	1.171516
C	7.414853	-1.450120	1.287095

H	8.320670	-0.844134	1.210214
C	6.170760	-0.827535	1.412573
H	6.103054	0.263263	1.432405
C	-0.131852	-1.448663	-2.525545
H	-0.279489	-1.569334	-3.607990
H	-0.574698	-0.487183	-2.238834
C	-0.825910	-2.660416	-1.879432
C	2.272811	-1.616423	-3.362064
H	3.269368	-1.621517	-2.899150
C	2.069898	-2.993528	-4.008315
H	2.056605	-3.787389	-3.251012
H	2.883468	-3.183526	-4.725068
H	1.118724	-3.048909	-4.557852
C	2.229474	-0.478962	-4.396060
H	1.249889	-0.430784	-4.895652
H	2.990789	-0.644461	-5.173366
H	2.418095	0.499144	-3.928770
C	-2.581820	-1.107687	-1.029397
H	-1.787749	-0.510909	-0.559443
H	-3.379521	-1.220358	-0.276077
C	-3.158648	-0.390478	-2.275380
C	-2.913627	-3.587676	-0.996643
H	-2.406896	-4.465172	-1.425600
H	-3.879854	-3.464041	-1.513610
C	-3.137078	-3.797463	0.490268
C	-4.422526	-4.065292	0.985123
H	-5.271248	-4.082044	0.294885
C	-4.628378	-4.317650	2.346929
H	-5.635421	-4.526653	2.715287
C	-3.546440	-4.298847	3.232514
H	-3.703134	-4.498137	4.295087
C	-2.260493	-4.022500	2.749132
H	-1.410268	-4.008219	3.435330
C	-2.056747	-3.772703	1.389005
H	-1.053461	-3.558602	1.013085
C	-3.266160	1.659652	-0.872616
H	-3.717232	1.120479	-0.023473
H	-3.803136	2.617095	-0.942753
C	-1.765245	1.927296	-0.566778
C	-4.011152	1.687085	-3.291017
H	-3.944660	0.958738	-4.111317
C	-5.486697	2.060634	-3.090579
H	-6.095626	1.166077	-2.895692
H	-5.876897	2.551203	-3.995259
H	-5.625168	2.764209	-2.252852
C	-3.138095	2.900707	-3.632264
H	-3.196944	3.686230	-2.861323
H	-3.483638	3.346458	-4.577236
H	-2.085048	2.609692	-3.741099
C	-0.044473	2.341655	1.078645
H	0.392405	1.403473	0.720022

H	0.008013	2.331265	2.177592
C	0.693122	3.608774	0.615172
C	-2.414535	2.942519	1.639852
H	-3.358561	3.137028	1.109500
H	-2.013607	3.930197	1.920302
C	-2.692395	2.114426	2.886726
C	-3.114155	2.766429	4.057074
H	-3.183616	3.858047	4.070963
C	-3.438626	2.034806	5.203099
H	-3.762081	2.556806	6.106565
C	-3.338873	0.638458	5.196166
H	-3.588663	0.065888	6.092070
C	-2.906979	-0.018080	4.039303
H	-2.819861	-1.106608	4.021799
C	-2.585027	0.716753	2.892584
H	-2.227146	0.196544	2.000912
C	2.452971	2.144997	-0.333901
H	3.290266	2.304393	-1.031427
H	1.677677	1.599069	-0.893887
C	2.956760	1.298108	0.863334
C	2.743794	4.661683	-0.233731
H	2.184770	5.468120	0.261839
C	2.784566	4.964789	-1.738951
H	3.321132	4.183478	-2.302740
H	3.309973	5.915349	-1.918248
H	1.767598	5.050261	-2.147162
C	4.141927	4.566739	0.387917
H	4.080218	4.321554	1.456609
H	4.661599	5.530125	0.272721
H	4.764009	3.801045	-0.104686

108

13b SCF Done: -2413.68785715 A.U.

O	1.239553	0.423580	0.099849
N	3.153629	-1.452012	-0.367950
C	2.984325	-0.988417	0.999824
H	3.963208	-0.621103	1.344481
H	2.719475	-1.824637	1.665960
O	1.758343	3.624342	1.877984
N	1.667701	0.711130	2.308287
C	1.905209	0.122829	1.103876
O	-2.419245	2.999926	2.203050
N	-0.173248	3.353068	0.670614
C	4.127619	-0.702875	-1.186456
H	3.830565	0.359502	-1.214386
H	4.028515	-1.101913	-2.205857
N	-3.545159	1.672479	0.705901
C	5.549092	-0.839852	-0.681356
O	-1.824566	-3.540030	-2.175307
C	6.295905	0.294447	-0.328434
H	5.837006	1.284536	-0.403854
O	2.264461	-2.455422	-2.229274

N	0.075129	-3.549055	-0.891894
C	7.620584	0.172120	0.110480
H	8.188362	1.065819	0.379047
C	8.211841	-1.090769	0.205942
H	9.244585	-1.189241	0.547420
C	7.473692	-2.230391	-0.140906
H	7.933250	-3.219379	-0.075347
C	6.154130	-2.105238	-0.581775
H	5.583204	-2.994984	-0.859760
C	0.515537	1.624855	2.338354
H	0.329674	1.916501	3.380109
H	-0.372850	1.090044	1.984335
C	0.768772	2.946251	1.582561
C	2.398332	0.405449	3.564320
H	3.235765	-0.244502	3.274772
C	2.992497	1.669954	4.198223
H	3.607343	2.222960	3.476903
H	3.611453	1.389253	5.064077
H	2.208185	2.356066	4.549526
C	1.510968	-0.376136	4.547175
H	0.653433	0.228197	4.880326
H	2.089863	-0.649356	5.442003
H	1.123242	-1.300564	4.092994
C	-1.238011	2.498519	0.162410
H	-0.826383	1.497109	-0.028309
H	-1.538475	2.881552	-0.825368
C	-2.452701	2.428217	1.108654
C	-0.147013	4.747538	0.208033
H	0.666042	5.233023	0.768163
H	-1.095217	5.230138	0.501697
C	0.075780	4.911562	-1.284135
C	-0.642254	5.884861	-1.995786
H	-1.390586	6.489501	-1.474616
C	-0.411504	6.089779	-3.360561
H	-0.980865	6.850372	-3.899933
C	0.536745	5.313285	-4.033753
H	0.712768	5.463796	-5.101101
C	1.250306	4.332878	-3.333924
H	1.984678	3.715259	-3.855934
C	1.023696	4.134734	-1.969116
H	1.573833	3.361415	-1.428014
C	-3.747116	1.141965	-0.660330
C	-4.788953	1.825373	1.527208
H	-4.446127	2.387302	2.406041
C	-5.844274	2.669814	0.795815
H	-5.424327	3.632156	0.467760
H	-6.681371	2.881866	1.477655
H	-6.259535	2.151921	-0.082697
C	-5.348204	0.481621	2.000285
H	-5.667104	-0.169021	1.171312
H	-6.231344	0.657387	2.633172

H	-4.609555	-0.065885	2.603150
C	-0.949315	-2.913273	-1.572301
C	1.097919	-2.843571	-0.135984
C	-0.961809	-1.380573	-1.584559
H	1.558350	-3.559263	0.564615
H	0.641742	-2.057755	0.482049
C	2.214506	-2.227509	-1.022938
C	0.135002	-5.033659	-0.953852
H	-0.618950	-5.290136	-1.711079
C	-0.297000	-5.653089	0.383604
H	0.396307	-5.392319	1.201159
H	-0.309773	-6.750937	0.305376
H	-1.306822	-5.318437	0.661440
C	1.503166	-5.540788	-1.422583
H	1.798083	-5.060432	-2.364334
H	1.453959	-6.629363	-1.576341
H	2.294850	-5.353366	-0.678182
N	-2.148748	-0.805275	-0.909292
H	-0.058117	-0.918041	-1.163423
H	-1.013298	-1.077117	-2.638965
C	-2.602167	0.399145	-1.396164
H	-4.605811	0.454971	-0.600467
H	-4.019867	1.950222	-1.356410
C	-2.670996	-1.432552	0.306662
H	-2.909518	-0.640671	1.035101
C	-3.893077	-2.333774	0.140985
H	-1.852897	-2.020568	0.753476
O	-2.163812	0.891998	-2.439659
C	-4.377066	-3.010788	1.273330
C	-5.512676	-3.820687	1.191403
C	-6.183019	-3.964125	-0.029617
C	-5.701706	-3.299761	-1.161372
C	-4.562440	-2.490116	-1.078186
H	-3.860166	-2.901965	2.232226
H	-5.874291	-4.341752	2.080968
H	-7.070129	-4.597537	-0.098356
H	-6.206117	-3.420414	-2.122690
H	-4.167184	-2.011204	-1.975056

70

[33a·Na]$^{+}$ from ref 39

C	4.441329	-1.429302	1.227229
C	3.549217	-2.512621	1.136576
C	2.800158	-2.724894	-0.038451
C	2.961180	-1.826217	-1.113550
C	3.831805	-0.725063	-1.027919
C	4.581441	-0.537279	0.152967
C	3.946316	0.237358	-2.201008
N	3.742086	1.655312	-1.839702
C	2.495164	2.020557	-1.416395
C	4.856836	2.601620	-1.945598
C	2.294523	3.494985	-1.023087

C	-2.791892	-2.442402	3.090704
C	-3.388074	-1.232164	2.694843
C	-3.560016	-0.933916	1.328225
C	-3.116662	-1.870554	0.371448
C	-2.495847	-3.073307	0.752543
C	-2.345291	-3.358785	2.126298
C	-1.999113	-4.036862	-0.315613
N	-0.584895	-4.434829	-0.156647
C	0.361539	-3.463032	-0.323156
C	-0.249716	-5.825328	0.164173
C	1.831134	-3.882169	-0.141917
C	-0.162159	4.462847	1.757778
C	1.036923	4.226981	1.061996
C	1.011046	3.764362	-0.269160
C	-0.239099	3.539811	-0.882485
C	-1.445552	3.748186	-0.190819
C	-1.397952	4.221898	1.137739
C	-2.770273	3.458878	-0.882639
N	-3.669767	2.572408	-0.116076
C	-3.262161	1.282154	0.075032
C	-4.936157	3.095164	0.404946
O	-2.191222	0.872935	-0.415023
C	-4.192712	0.369735	0.893404
O	1.565636	1.190404	-1.377172
O	0.034444	-2.299357	-0.629316
H	5.031213	-1.281771	2.145428
H	3.438622	-3.202369	1.989421
H	2.377643	-1.976768	-2.036140
H	5.279354	0.311606	0.237671
H	3.205011	-0.045214	-2.977610
H	4.952459	0.166048	-2.661686
H	4.560604	3.524886	-2.482960
H	5.673396	2.130753	-2.523461
H	5.264816	2.890305	-0.951908
H	2.320017	4.090913	-1.965612
H	3.162606	3.846244	-0.428593
H	-2.676586	-2.671268	4.161716
H	-3.725310	-0.512649	3.459011
H	-3.240173	-1.648147	-0.700674
H	-1.873439	-4.301533	2.447948
H	-2.130256	-3.571529	-1.314990
H	-2.598330	-4.969979	-0.304244
H	-1.151866	-6.450633	0.033590
H	0.100288	-5.946360	1.212778
H	0.532246	-6.224848	-0.512792
H	2.096804	-4.529369	-1.010671
H	1.926401	-4.534407	0.750284
H	-0.129799	4.838194	2.792597
H	2.003107	4.409095	1.560487
H	-0.273599	3.174123	-1.921503
H	-2.331087	4.403976	1.695092

H	-3.326111	4.401407	-1.063761
H	-2.570021	2.997630	-1.872309
H	-5.782606	2.415456	0.180871
H	-4.906173	3.266400	1.503596
H	-5.152003	4.063183	-0.083541
H	-4.568784	0.919916	1.780168
H	-5.092634	0.169969	0.265343
Na	-0.152929	-0.056786	-0.627896

48

37a SCF Done: -1128.20296369 A.U.

N	1.709584	-1.857868	0.068003
C	2.512336	-0.878614	0.831907
C	2.912793	0.345246	-0.038422
N	2.132775	1.469238	-0.000619
C	0.878321	1.731310	0.736353
C	-0.347268	1.443706	-0.179258
N	-0.898693	0.185166	-0.169797
C	-0.516268	-0.920776	0.713999
C	0.350644	-1.968660	-0.008834
C	3.756453	-1.705526	1.217106
C	3.970747	-2.645783	0.014321
C	2.554030	-2.924128	-0.523932
C	2.601506	2.684674	-0.711899
C	1.724246	3.832027	-0.166774
C	0.990768	3.235021	1.053268
H	2.148055	-3.896789	-0.206180
H	2.498603	-2.889819	-1.621743
H	4.483380	-3.574711	0.300573
H	4.574192	-2.131276	-0.743103
H	3.524610	-2.278346	2.129023
H	4.627918	-1.068434	1.413373
H	1.963486	-0.556409	1.726759
O	3.937093	0.312326	-0.731137
H	3.673203	2.808233	-0.498279
H	2.498174	2.554254	-1.799299
H	2.331423	4.705561	0.108847
H	0.989888	4.140207	-0.919418
H	1.591171	3.350352	1.969219
H	0.007680	3.693392	1.219350
H	0.848506	1.140399	1.659357
O	-0.771724	2.334516	-0.924973
C	-1.969416	-0.128987	-1.148869
H	-1.708116	-1.081405	-1.633539
C	-3.338931	-0.225633	-0.506683
H	-1.945890	0.674837	-1.895454
C	-3.991122	0.931757	-0.045181
C	-5.255857	0.845712	0.542396
C	-5.886994	-0.398185	0.677210
C	-5.246691	-1.554012	0.220400
C	-3.978747	-1.467324	-0.368499
H	-3.501557	1.902105	-0.161934

H	-5.756743	1.752670	0.889195
H	-6.877561	-0.463391	1.133010
H	-5.734102	-2.526670	0.319335
H	-3.477511	-2.370484	-0.727649
H	-0.049209	-0.535932	1.626252
H	-1.437413	-1.442585	1.014093
O	-0.190514	-2.880901	-0.648459

48

37b SCF Done: -1128.20118696 A.U.

N	1.907960	-1.681761	0.063524
C	2.478229	-0.446555	0.658812
C	2.651860	0.630203	-0.433203
N	1.778726	1.684438	-0.404386
C	0.858323	2.064882	0.690686
C	-0.341682	1.165822	1.118884
N	-0.669596	-0.020897	0.514340
C	-0.174405	-0.559102	-0.756838
C	0.721724	-1.810499	-0.605770
C	3.837935	-0.919044	1.227566
C	4.205071	-2.147471	0.377187
C	2.852353	-2.818661	0.120392
C	1.778728	2.665005	-1.512450
C	0.490937	3.459630	-1.273085
C	0.375174	3.476690	0.258709
O	3.482434	0.498275	-1.338163
H	1.818824	2.135954	-2.475166
H	2.677249	3.302817	-1.451328
H	0.534726	4.466553	-1.709842
H	-0.369678	2.936611	-1.720014
H	1.055964	4.232386	0.679726
H	-0.631592	3.684590	0.639702
H	1.420727	2.151926	1.633895
O	-0.945060	1.571908	2.121315
C	-1.723215	-0.851398	1.155768
H	-1.039907	-0.894896	-1.346363
H	0.332525	0.222200	-1.329819
O	0.360039	-2.888385	-1.092631
H	-1.775366	-0.539211	2.206191
C	-3.078098	-0.715068	0.489457
H	-1.384618	-1.898041	1.108853
C	-3.869532	0.424667	0.718540
C	-5.116331	0.555160	0.100974
C	-5.588842	-0.449943	-0.753103
C	-4.809512	-1.587537	-0.984276
C	-3.560538	-1.719599	-0.364520
H	-3.498394	1.202013	1.390905
H	-5.726473	1.441253	0.291525
H	-6.564751	-0.347401	-1.233059
H	-5.172951	-2.376692	-1.646384
H	-2.953420	-2.611775	-0.543102
H	2.565478	-3.501540	0.939615

H	2.797093	-3.382157	-0.819913
H	4.912278	-2.817069	0.886516
H	4.648286	-1.818658	-0.572782
H	3.704696	-1.203090	2.283131
H	4.594638	-0.124822	1.178299
H	1.826669	-0.090876	1.468517

189

45 from ref 50a

N	5.350000	-0.153000	-0.004000
C	6.177000	0.251000	1.159000
H	7.183000	0.371000	0.755000
C	6.292000	-0.891000	2.170000
C	6.753000	-2.155000	1.739000
H	7.028000	-2.336000	0.710000
C	6.869000	-3.220000	2.648000
H	7.213000	-4.187000	2.308000
C	6.543000	-3.034000	4.001000
H	6.637000	-3.854000	4.700000
C	6.105000	-1.776000	4.446000
H	5.864000	-1.632000	5.490000
C	5.974000	-0.712000	3.536000
H	5.630000	0.235000	3.923000
C	5.767000	1.635000	1.691000
H	4.779000	1.595000	2.152000
H	5.747000	2.351000	0.869000
H	6.496000	1.974000	2.427000
C	3.941000	-0.458000	0.332000
H	3.775000	-1.483000	0.009000
H	3.725000	-0.382000	1.398000
C	3.033000	0.496000	-0.448000
O	3.588000	1.443000	-1.006000
H	5.340000	0.602000	-0.682000
H	5.763000	-0.968000	-0.435000
N	1.696000	0.285000	-0.478000
C	0.792000	1.244000	-1.140000
H	1.346000	2.158000	-1.362000
C	-0.305000	1.710000	-0.179000
C	0.068000	2.308000	1.042000
H	1.112000	2.422000	1.293000
C	-0.909000	2.754000	1.949000
H	-0.612000	3.200000	2.888000
C	-2.272000	2.625000	1.633000
H	-3.025000	2.972000	2.327000
C	-2.654000	2.046000	0.411000
H	-3.702000	1.951000	0.164000
C	-1.677000	1.588000	-0.491000
H	-2.006000	1.145000	-1.418000
C	0.352000	0.681000	-2.501000
H	-0.264000	-0.208000	-2.364000
H	1.231000	0.417000	-3.090000
H	-0.216000	1.436000	-3.045000

C	1.073000	-0.908000	0.127000
H	1.384000	-0.943000	1.166000
H	-0.012000	-0.811000	0.122000
C	1.414000	-2.230000	-0.594000
O	1.947000	-2.169000	-1.703000
N	1.134000	-3.409000	0.012000
C	1.316000	-4.691000	-0.697000
H	1.419000	-4.491000	-1.764000
C	0.048000	-5.546000	-0.612000
C	-1.190000	-4.974000	-0.971000
H	-1.241000	-3.940000	-1.281000
C	-2.373000	-5.732000	-0.921000
H	-3.317000	-5.277000	-1.185000
C	-2.328000	-7.080000	-0.527000
H	-3.237000	-7.664000	-0.489000
C	-1.099000	-7.664000	-0.179000
H	-1.062000	-8.702000	0.121000
C	0.084000	-6.903000	-0.220000
H	1.009000	-7.387000	0.053000
C	2.638000	-5.340000	-0.255000
H	2.582000	-5.647000	0.790000
H	3.456000	-4.628000	-0.374000
H	2.848000	-6.210000	-0.878000
C	0.747000	-3.495000	1.433000
H	-0.134000	-2.874000	1.567000
H	0.464000	-4.516000	1.690000
C	1.869000	-3.069000	2.407000
O	3.011000	-2.923000	1.962000
N	1.578000	-2.865000	3.714000
C	2.637000	-2.546000	4.689000
H	3.603000	-2.767000	4.236000
C	2.584000	-3.500000	5.885000
C	2.637000	-4.889000	5.650000
H	2.695000	-5.264000	4.638000
C	2.607000	-5.800000	6.721000
H	2.637000	-6.862000	6.527000
C	2.538000	-5.327000	8.042000
H	2.515000	-6.026000	8.867000
C	2.492000	-3.944000	8.288000
H	2.441000	-3.580000	9.304000
C	2.513000	-3.034000	7.216000
H	2.473000	-1.980000	7.441000
C	2.638000	-1.037000	4.983000
H	1.715000	-0.745000	5.485000
H	2.730000	-0.481000	4.049000
H	3.488000	-0.786000	5.618000
C	0.193000	-2.860000	4.220000
H	-0.261000	-3.801000	3.927000
H	0.189000	-2.826000	5.309000
C	-0.651000	-1.665000	3.719000
O	-0.065000	-0.713000	3.200000

N	-1.997000	-1.689000	3.870000
C	-2.834000	-0.552000	3.445000
H	-2.189000	0.302000	3.236000
C	-3.711000	-0.066000	4.600000
C	-3.088000	0.364000	5.789000
H	-2.011000	0.330000	5.876000
C	-3.854000	0.828000	6.873000
H	-3.366000	1.146000	7.783000
C	-5.255000	0.879000	6.772000
H	-5.846000	1.237000	7.603000
C	-5.885000	0.460000	5.588000
H	-6.962000	0.503000	5.507000
C	-5.119000	-0.014000	4.507000
H	-5.634000	-0.329000	3.613000
C	-3.531000	-0.885000	2.116000
H	-4.226000	-1.715000	2.245000
H	-2.785000	-1.156000	1.368000
H	-4.081000	-0.014000	1.761000
C	-2.709000	-2.868000	4.397000
H	-2.264000	-3.112000	5.356000
H	-3.755000	-2.626000	4.582000
C	-2.684000	-4.093000	3.454000
O	-2.354000	-3.917000	2.280000
N	-3.025000	-5.313000	3.935000
C	-3.005000	-6.505000	3.065000
H	-2.965000	-6.181000	2.025000
C	-4.334000	-7.254000	3.150000
C	-5.506000	-6.596000	2.726000
H	-5.448000	-5.590000	2.336000
C	-6.756000	-7.235000	2.813000
H	-7.649000	-6.720000	2.490000
C	-6.842000	-8.541000	3.324000
H	-7.802000	-9.033000	3.392000
C	-5.679000	-9.206000	3.747000
H	-5.745000	-10.210000	4.143000
C	-4.429000	-8.566000	3.663000
H	-3.555000	-9.098000	4.007000
C	-1.719000	-7.312000	3.303000
H	-1.690000	-7.698000	4.322000
H	-0.850000	-6.674000	3.136000
H	-1.676000	-8.149000	2.605000
C	-3.327000	-5.544000	5.361000
H	-4.104000	-4.844000	5.653000
H	-3.731000	-6.545000	5.504000
C	-2.098000	-5.414000	6.292000
O	-0.979000	-5.398000	5.778000
N	-2.281000	-5.325000	7.632000
C	-1.126000	-5.195000	8.543000
H	-0.212000	-5.407000	7.989000
C	-1.157000	-6.289000	9.606000
C	-0.795000	-7.599000	9.234000

H	-0.500000	-7.806000	8.215000
C	-0.816000	-8.640000	10.178000
H	-0.537000	-9.642000	9.884000
C	-1.195000	-8.377000	11.505000
H	-1.210000	-9.176000	12.233000
C	-1.551000	-7.071000	11.887000
H	-1.842000	-6.869000	12.908000
C	-1.532000	-6.030000	10.942000
H	-1.815000	-5.038000	11.260000
C	-0.977000	-3.745000	9.029000
H	-1.857000	-3.429000	9.588000
H	-0.843000	-3.085000	8.171000
H	-0.101000	-3.663000	9.673000
C	-3.621000	-5.219000	8.243000
H	-4.222000	-6.051000	7.883000
H	-3.552000	-5.316000	9.325000
C	-4.334000	-3.881000	7.947000
O	-3.674000	-2.968000	7.450000
N	-5.647000	-3.742000	8.251000
C	-6.355000	-2.481000	7.946000
H	-5.627000	-1.726000	7.650000
C	-6.976000	-1.888000	9.206000
C	-6.134000	-1.233000	10.126000
H	-5.074000	-1.159000	9.927000
C	-6.663000	-0.672000	11.302000
H	-6.011000	-0.170000	12.003000
C	-8.041000	-0.760000	11.564000
H	-8.449000	-0.328000	12.467000
C	-8.890000	-1.406000	10.648000
H	-9.950000	-1.471000	10.850000
C	-8.361000	-1.968000	9.472000
H	-9.033000	-2.461000	8.787000
C	-7.269000	-2.652000	6.721000
H	-8.051000	-3.385000	6.918000
H	-6.676000	-2.985000	5.868000
H	-7.732000	-1.697000	6.475000
C	-6.470000	-4.850000	8.779000
H	-5.928000	-5.362000	9.574000
H	-7.383000	-4.457000	9.225000
C	-6.877000	-5.877000	7.713000
O	-6.356000	-5.881000	6.600000
N	-7.734000	-6.825000	8.088000
H	-7.998000	-7.535000	7.422000
H	-8.121000	-6.826000	9.020000

4.0 HPLC Chromatograms

HPLC: JASCO LC-NET II/ADC model with a JASCO PU-2089 Plus Pump and a UV detector JASCO MD-2010, set at 220 nm.

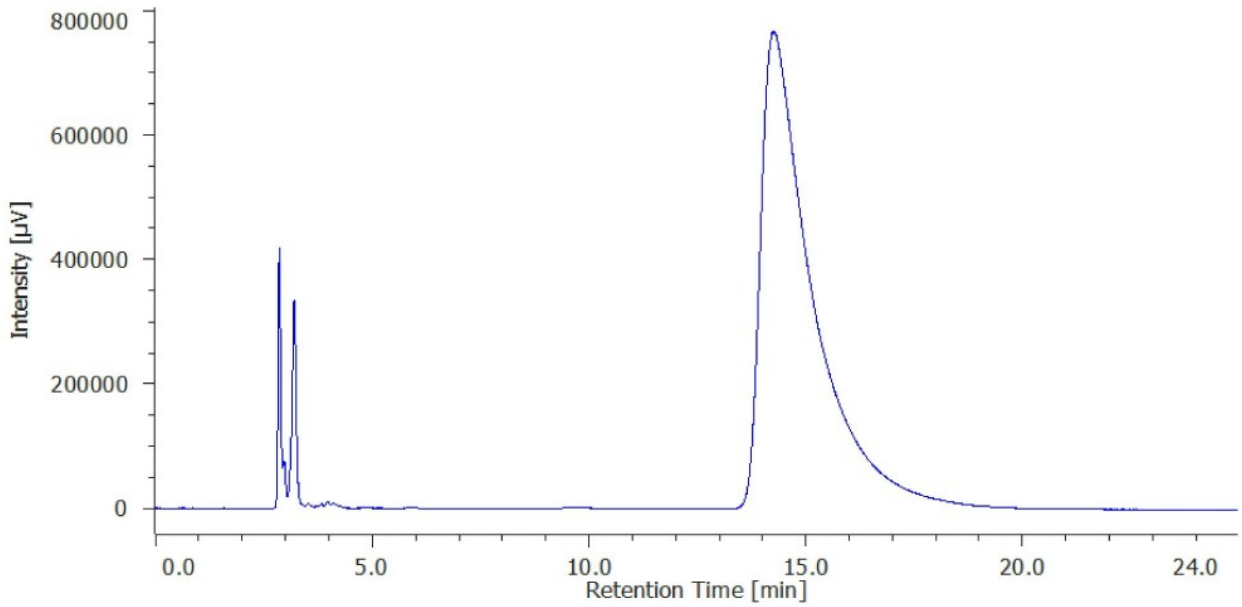


Figure S4. HPLC analysis of **4.** Elution conditions: 85:15 hexane:isopropanol; 1.0 mg/mL; flow: 1.0 mL min^{-1}, 220 nm. CHIRALPAK® AD chromatographic column (0.46 x 25 cm).

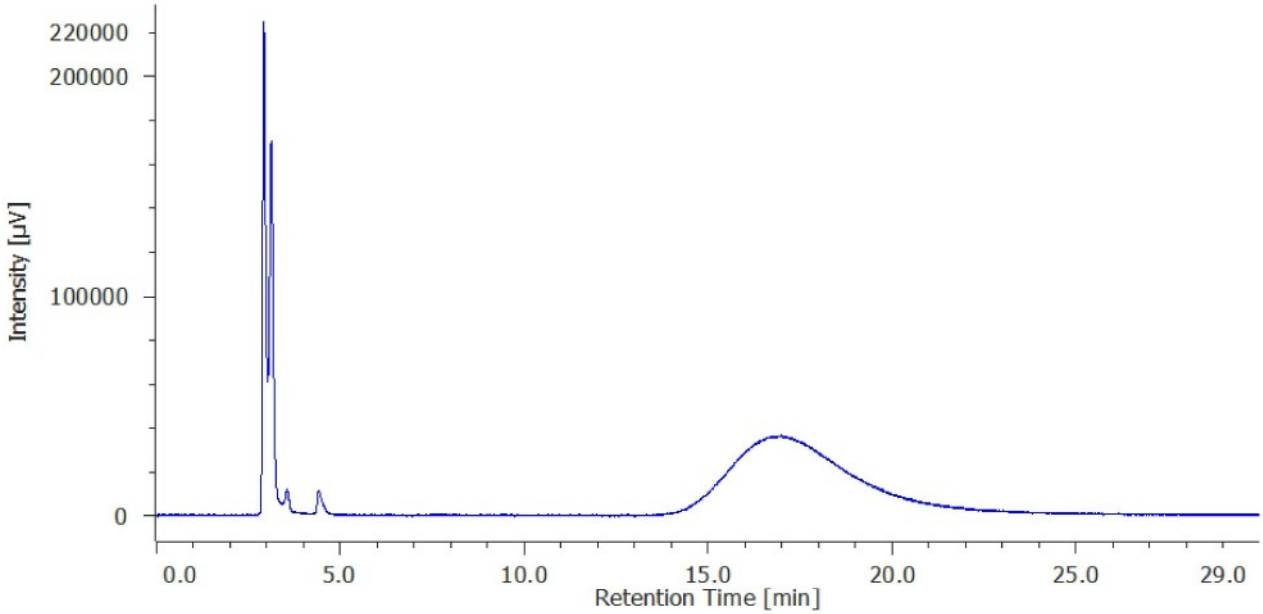


Figure S5. HPLC analysis of **13.** Elution conditions: 75:25 hexane:isopropanol; 1.0 mg/mL; flow: 1.0 mL min^{-1}, 220 nm. CHIRALPAK® AD chromatographic column (0.46 x 25 cm).

The conditions of enantioseparation were varied increasing or decreasing the percentage of isopropanol ±5%, varying the flux to 0.5 mL/min and changing the chromatographic column (CHIRALPAK® AS-H (0.46 x 25 cm), CHIRALPAK® AD-H (0.46 x 25 cm), CHIRALCEL® OD-H (0.46 x 25 cm)).

5.0 References

1) Culf, A. S.; Čuperlović-Culf, M.; Léger, D. A.; Decken, A. *Org. Lett.* **2014**, *16*, 2780–2783.
2) Tedesco, C.; Erra, L.; Izzo, I.; De Riccardis, F. *Cryst. Eng. Comm.* **2014**, *16*, 3667–3687 and Ref. 1.
3) D'Amato, A.; Volpe, R.; Vaccaro, M. C.; Terracciano, S.; Bruno, I.; Tosolini, M.; Tedesco, C.; Pierri, G.; Tecilla, P.; Costabile, C.; Della Sala, G.; Izzo, I.; De Riccardis, F. *J. Org. Chem.* **2017**, *82*, 8848–8863.
4) Gaussian 09, Revision A.02, Frisch, M. J.; Trucks, G. W.; Schlegel, 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.; N. Kudin, K.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; 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, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian, Inc., Wallingford CT, **2009**.
5) a) Becke, A. *Phys. Rev. A* **1988**, *38*, 3098– 3100. b) Perdew, J. P. *Phys. Rev. B* **1986**, *33*, 8822– 8824. c) Perdew, J. P. *Phys. Rev. B* **1986**, *34*, 7406– 7406.
6) Schaefer, A.; Horn, H.; Ahlrichs, R. *J. Chem. Phys.* **1994**, *100*, 5829– 5835.
7) Maulucci, N.; Izzo, I.; Bifulco, G.; Aliberti, A.; De Cola, C.; Comegna, D.; Gaeta, C.; Napolitano, A.; Pizza, C.; Tedesco, C.; Flot, D.; De Riccardis, F. *Chem. Commun.* **2008**, 3927–3929.
8) Meli, A.; Gambaro, S.; Costabile, C.; Talotta, C.; Della Sala, G.; Tecilla, P.; Milano, D.; Tosolini, M.; Izzo, I.; De Riccardis, F. *Org. Biomol. Chem.* **2016**, *14*, 9055–9062.
9) Armand, P.; Kirshenbaum, K.; Falicov, A.; Dunbrack, R. L. Jr.; Dill, K. A.; Zuckermann R. N.; Cohen, F. E. *Fold. Des.* **1997**, *2*, 369–375.