Recognition and Organocatalysis with a Synthetic Cavitand Receptor

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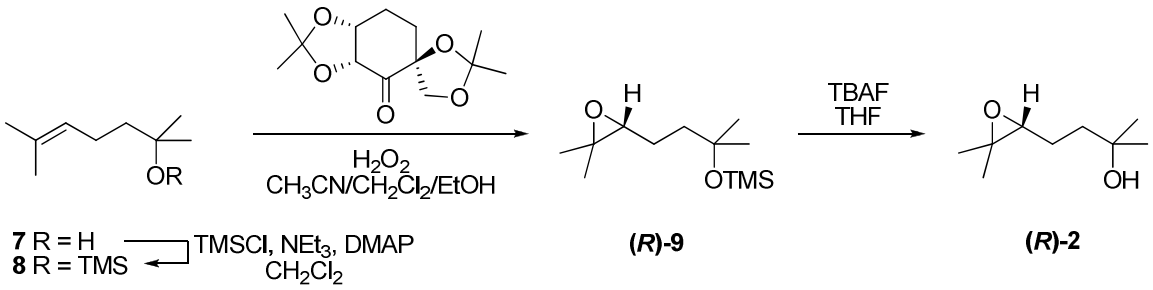
Supporting Information

Contents:

I. General Experimentals

^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature at 600 MHz and 150 MHz, respectively, using a Bruker DRX 600 spectrometer equipped with a QNP 5mm probe. The NMR data are reported as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. High resolution mass spectra were acquired on a single-quadrupole Perkin-Elmer API-100 Sciex Mass Spectrometer or a Hewlett-Packard Series 1100 LC-MS. All reactions were carried out under an atmosphere of nitrogen in glassware that had been flame-dried under vacuum (~0.05 mmHg). Unless otherwise noted, all reagents were commercially obtained and used as recieved. THF and CH_2Cl_2 were dried by filtration through alumina according to the method of Grubbs *et al.*[1] Chloroform-*d* and mesitylene-d_{12} were purchased from Cambridge Isotope Laboratories, Inc. and basified prior to use by passage through a short plug of 50-200 micron activated basic aluminum oxide. Reaction progress during the preparation of all compounds was monitored using thin layer chromatography using Merck 60 F_{254} 0.25 μm silica gel plates. Column chromatography was performed using Silicycle R10030B 60 Å 230-400 mesh silica gel.

II. Synthesis of Enantioenriched 2.



2,6-Dimethyl-6-(trimethylsiloxy)-2-heptene, 8.

2,6-Dimethyl-5-hepten-2-ol (1.13 g, 7.94 mmol) and 4-dimethylaminopyridine (97 mg, 0.794 mmol, 0.10 eq.) were weighed in a 100 mL round bottom flask and dissolved in 32 mL of dry CH_2Cl_2 under argon. Triethylamine (3.32 mL, 23.8 mmol, 3.0 eq.) was added followed by dropwise addition of chlorotrimethylsilane (2.01 mL, 15.9 mmol, 2.0 eq.) and the mixture was stirred at room temperature for 16 h. The reaction was quenched by addition of water and the phases separated. The aqueous phase was further extracted twice with CH_2Cl_2 and the combined organic phases were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to yield 1.70 g (quantitative) of a clear colorless oil. The product was used in next step without further purification. ^{1}H NMR δ 5.09 (m, 1H), 2.00 (m, 2H), 1.65 (s, 3H), 1.59 (s, 3H), 1.42 (m, 2H), 1.19 (s, 6H), 0.08 (s, 9H) ppm. ^{13}C NMR δ 131.1 (Cq), 125.1 (CH), 74.0 (Cq), 44.9 (CH_2), 30.0 (CH_3), 25.9 (CH_3), 23.3 (CH_2), 17.7 (CH_3), 2.8 (CH_3) ppm. HRMS (ESI-TOF) *m/z* calcd. for $C_{12}H_{26}NaOSi^+$ ([M+Na]$^+$) 237.1645; found 237.1653.

(*R*)-2,3-Epoxy-2,6-dimethyl-6-(trimethylsiloxy)-heptane, (*R*)-9.

To a solution of alkene **8** (570 mg, 2.66 mmol) in CH_3CN/CH_2Cl_2/EtOH (1:2:1, 15 mL) and a buffer solution (15 mL, 2M K_2CO_3, 0.4 mM EDTA) at – 5 °C was added Shi's epoxidation diketal catalyst (206 mg, 0.797 mmol, 0.30 eq.). Hydrogen peroxide (4.5 mL, 10%, prepared by dilution of 30% solution) was added via a syringe pump over 10 h. The reaction was quenched by addition of Na_2SO_3 and extracted with diethyl ether. The combined organic extracts were washed with water and brine. Purification by flash chromatography (SiO_2, hexanes/AcOEt 95:5) provided the epoxide (477 mg, 78%, 85:15 ee) as a clear oil. ^{1}H NMR δ 2.70 (dd, J = 6.1, 6.1 Hz, 1H), 1.65-1.44 (m, 4H), 1.29 (s, 3H), 1.26 (s, 3H), 1.21 (s, 3H), 1.20 (s, 3H), 0.08 (s, 9H) ppm. ^{13}C NMR δ 73.6 (Cq), 64.8 (CH), 58.5 (Cq), 41.3 (CH_2), 30.1 (CH_3), 29.8 (CH_3), 25.1 (CH_3), 24.2 (CH_2), 18.8 (CH_3), 2.7 (CH_3) ppm. HRMS (ESI-TOF) *m/z* calcd. for $C_{12}H_{26}NaO_2Si^+$ ([M+Na]$^+$) 253.1594; found 253.1600.

(*R*)-5,6-Epoxy-2,6-dimethyl-2-heptanol, (*R*)-2.

Epoxyether **(*R*)-9** (424 mg, 1.84 mmol) was dissolved in THF (4 mL) and the solution was cooled to 0 °C. A 1.0 M TBAF solution in THF (2.2 mL, 1.2 mmol) was added dropwise and the mixture stirred until TLC

analysis showed disappearance of the starting material (PMA stain). Water and Et_2O were added and the phases were separated. The aqueous phase was further extracted with Et_2O and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting yellowish oil was purified by Kugelrhor distillation (1 mmHg, careful must be taken not to heat over 40 °C to prevent cyclisation) to obtain 281 mg (97%) of a clear colorless oil. Spectroscopic data was consistent with that reported for *rac*-**2**.

Determination of er for (*R*)-9 by ^{1}H NMR.[2]

Samples for NMR were prepared by dissolving 5 mg (0.0217 mmol) of racemic or enantioenriched epoxyether **9** and 8 mg (0.00895 mmol) of the lanthanide shift reagent europium tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate] ($Eu(tfc)_3$) in 0.75 mL of $CDCl_3$. Samples were let to equilibrate for 30 min. at room temperature and then ^{1}H NMR spectra were recorded at 273 K. The enantiomeric ratio was determined by integration of the methyl resonances around 1.2 ppm. The absolute configuration of **9** and **2** was assigned by comparison to structurally analogue epoxides obtained by the same methodology.[3]

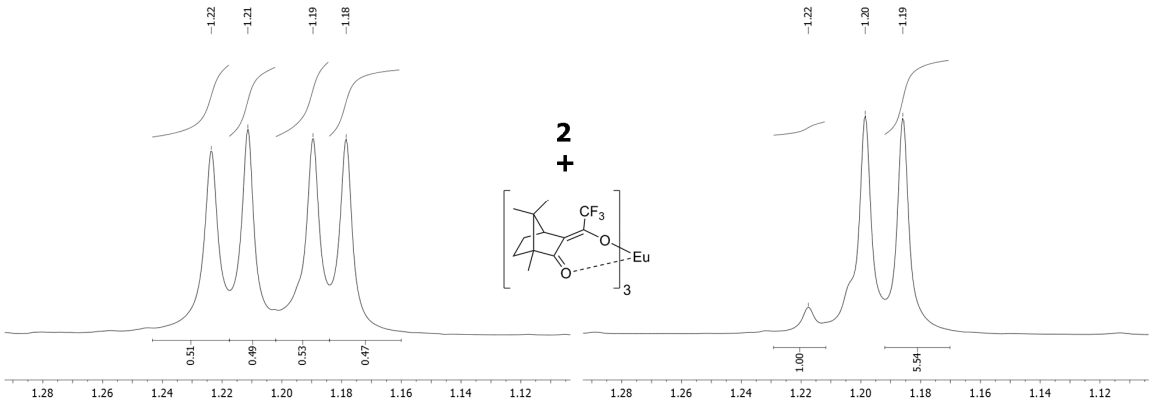


Figure S1. Expansions of the ^{1}H NMR ($CDCl_3$, 273K) spectra of **rac-2** and **(*R*)-2** in the presence of the lanthanide shift reagent $Eu(tfc)_3$.

III. Complete NMR Assignment of 2 in Mesitylene-d_{12}.

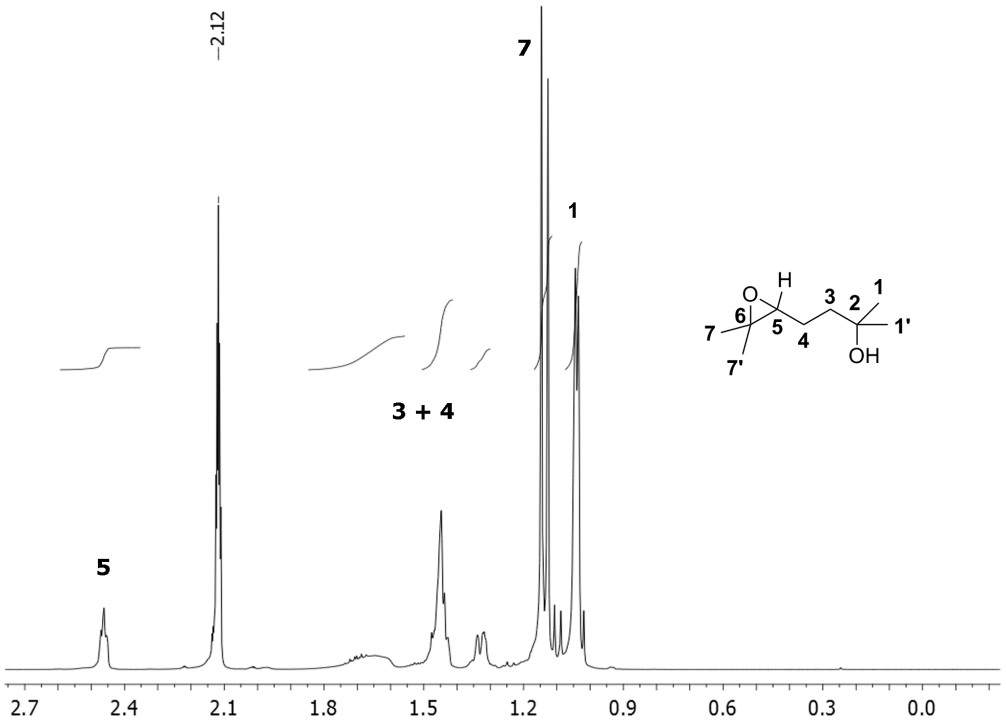


Figure S2. Expansion of the ^{1}H NMR spectrum of **2** in mesitylene-d_{12}.

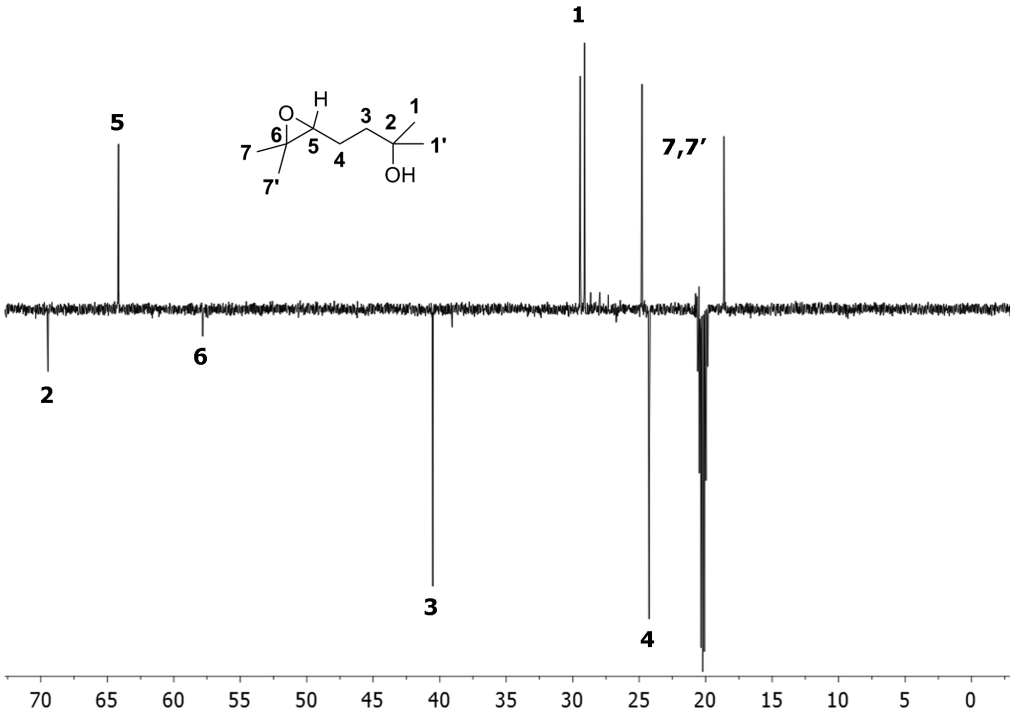


Figure S3. Expansion of the ^{13}C APT NMR spectrum of **2** in mesitylene-d_{12}.

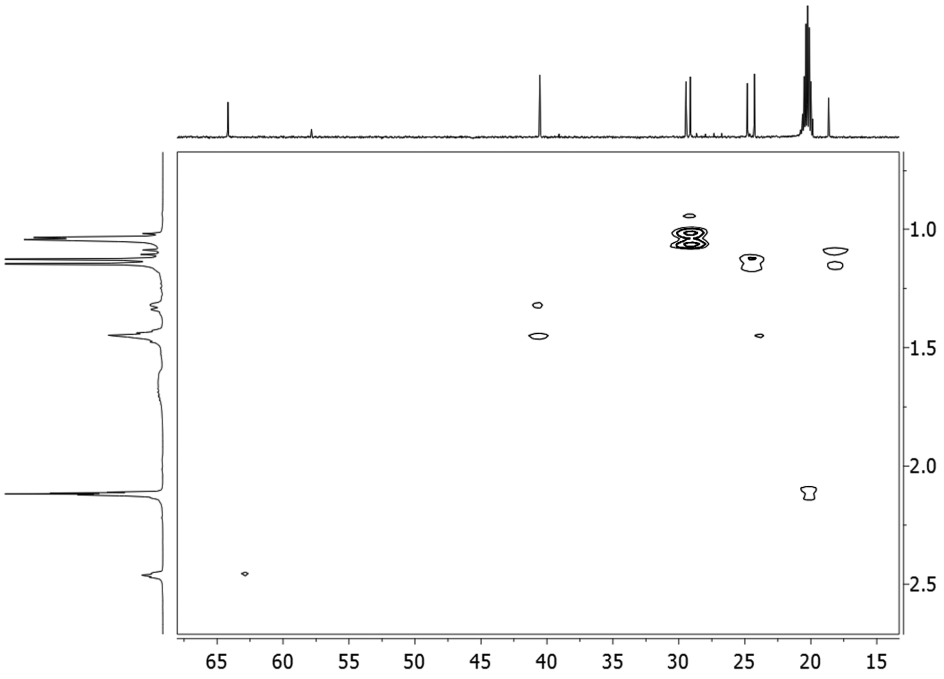


Figure S4. Expansion of the ^{1}H-^{13}C HMQC spectrum of **2** in mesitylene-d_{12}

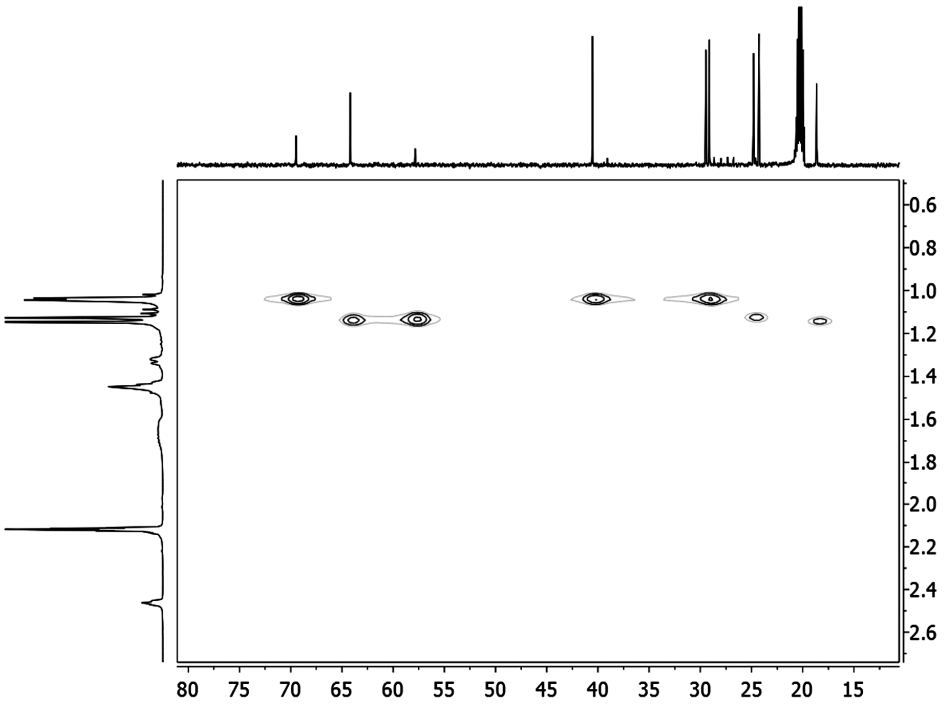


Figure S4. Expansion of the ^{1}H-^{13}C HMBC spectrum of **2** in mesitylene-d_{12}

IV. Expanded NOESY Data and EXSY calculations.

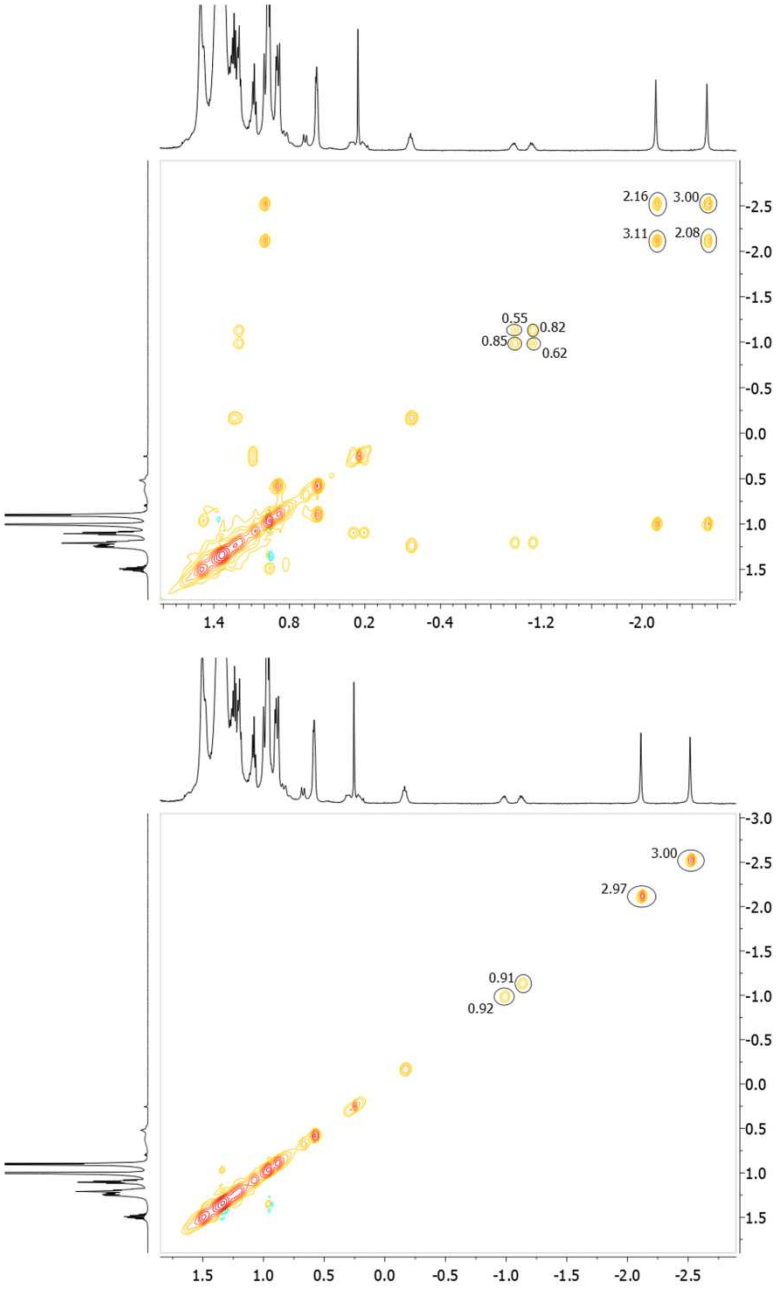


Figure S5. 2D NOESY spectra (mesitylene-d_{12}, 300K) of complex **1•6** at 350 ms (top) and 0 ms (down) mixing times, showing exchange between the free and bound guests and between the two conformers of **6** within **1** (off-diagonal peaks of the upfield methylene and methyl resonances for which integral values are shown). A 1H 1D spectrum of the free guest in mesitylene-d_{12} is shown on the vertical projection.

EXSY Calculations

Two 2D NOESY spectra were taken sequentially at 300 K, one with 350 ms mixing time and then with 0 ms mixing time (Figure S5). Spectra were recorded using the standard gradient pulsed NOESY sequence supplied with the Bruker software. Each of the 512 F1 increments was the accumulation of 32 scans. Before Fourier transformation, the FIDs were multiplied by a $\pi/2$ sine square function in both the F2 and the F1 domains. 1K _1K real data points were used, with a resolution of 1 Hz/point. The rate constant *k* for the conformational equilibrium of **6** within **1** was calculated from integral values of the bound guest's methyl resonances using the EXSYCALC program (Mestrelab Research, Santiago de Compostela). $\Delta G^{\neq}$ was obtained using the Eyring Equation:

$$k = (k_B T / h)e^{(-\Delta G\neq /RT)}$$

V. Kinetic Measurements.

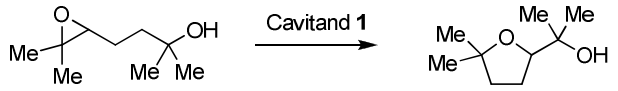
General Procedure for Catalyzing 1,5-Epoxyalcohol Cyclization Reactions Using Cavitand (1).

To a ¼ dram vial charged with cavitand **1** (2.0 mg, 9.7×10^{-4} mmol) was added the 1,5-epoxyalcohol (2.43 - 38.9 mmol) via syringe as a solution in mesitylene-d_{12} of appropriate molarity. The resultant solution was transferred by syringe from the ¼ dram vial to a 7.0 in. 5.0 mm NMR tube. The ¼ dram vial was then rinsed three times with mesitylene-d_{12} to obtain a total volume of 0.8 mL. The ^{1}H NMR spectrum was recorded at ambient temperature with a 20 ppm sweep width and a D_1 relaxation delay of 20 sec (~ 6 × T_1-relaxation time for the free 1,5-epoxyalcohol). The progress of the reaction was monitored by the disappearance of the starting epoxide proton resonance or the appearance of the ethereal proton resonance relative to the solvent residual mesitylene peak or 1,3,5-trimethoxybenzene as an internal standard.

General Procedure for Catalyzing 1,5-Epoxyalcohol Cyclization Reactions Using Acid (9).

A 7.0 in. 5.0 mm NMR tube was charged the acid as a 0.05 M solution in mesitylene-d_{12} (1.0×10^{-3} mmol). To this solution was added the 1,5-epoxyalcohol via syringe as a 0.10 M solution in mesitylene-d_{12} (0.02 mmol). The resultant mixture was diluted with 0.60 mL of mesitylene-d_{12}. The ^{1}H NMR spectrum was recorded at ambient temperature with a 20 ppm sweep width and a D_1 relaxation delay of 20 sec (~ 6 × T_1-relaxation time for the 1,5-epoxyalcohol). The progress of the reaction is monitored by the disappearance of the starting epoxide proton resonance or the appearance of the ethereal proton resonance relative to the solvent residual mesitylene peak or 1,3,5-trimethoxybenzene as an internal standard.

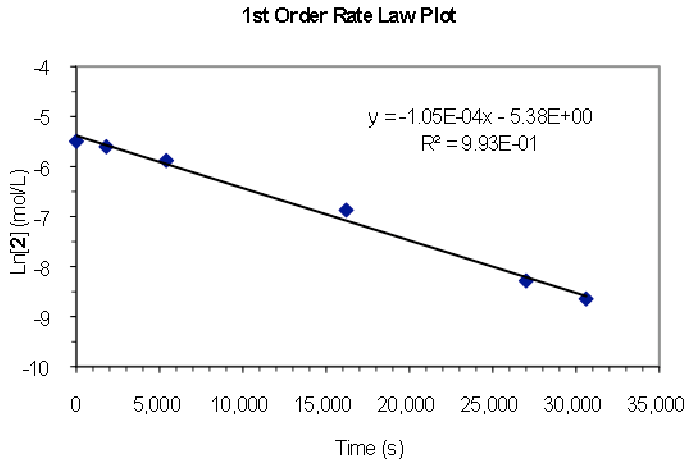
Epoxide Ring-Opening Cyclization of 2,6-Dimethyl-5,6-epoxy-2-heptanol in Cavitand 1.



2 **3**

2.5:1 Substrate to Cavitand Ratio

time (s)	% 3	% 2	[2] (mol/L)	ln[2]
0	0	1	0.004098	-5.497
1800	0.1005	0.8995	0.003687	-5.603
5400	0.3184	0.6816	0.002794	-5.880
16200	0.7468	0.2532	0.001038	-6.871
27000	0.9383	0.0617	0.000253	-8.283
30600	0.9570	0.0430	0.000176	-8.644
37800	0.9938	0.0062	0.000025	-10.580

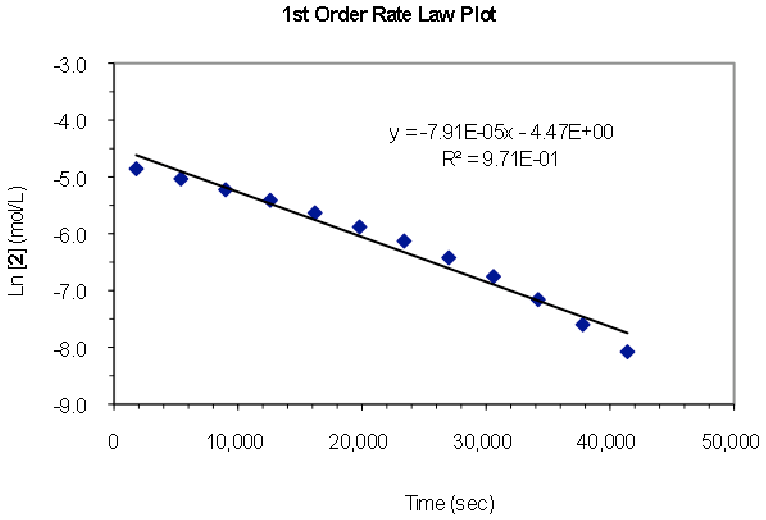


k_{obs} = 1.05×10^{-4} s^{-1}

5:1 Substrate to Cavitand Ratio

time (s)	3%	2%	[2] (mol/L)	ln[2]
0	0	1	0.0084541	-4.773
1800	0.0801	0.9199	0.007777	-4.857
5400	0.2292	0.7708	0.0065164	-5.033
9000	0.3637	0.6363	0.0053793	-5.225
12600	0.4723	0.5277	0.0044616	-5.412
16200	0.5767	0.4233	0.0035783	-5.633
19800	0.6696	0.3304	0.0027929	-5.881
23400	0.7423	0.2577	0.0021786	-6.129
27000	0.8079	0.1921	0.0016239	-6.423
30600	0.8619	0.1381	0.0011675	-6.753
34200	0.9080	0.0920	0.0007775	-7.159
37800	0.9408	0.0592	0.0005005	-7.600
41400	0.9634	0.0367	0.0003098	-8.079

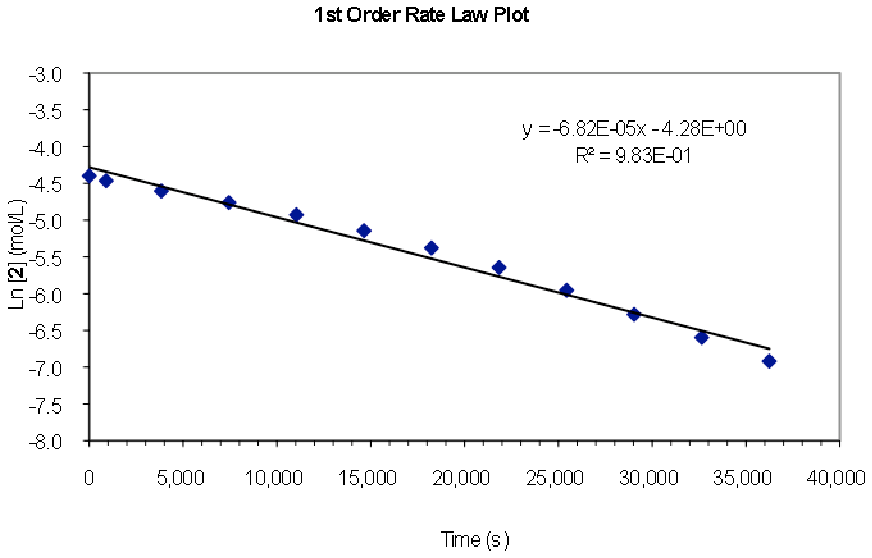
45000	0.9829	0.0171	0.0001447	-8.841



k_{obs} = 7.91×10^{-5} s^{-1}

7.5:1 Substrate to Cavitand Ratio

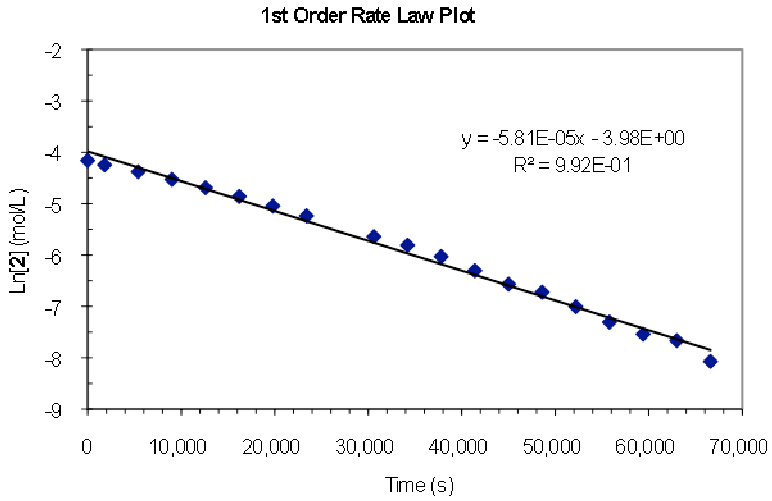
time (s)	% 3	% 2	[2] (mol/L)	ln[2]
0	0	1	0.0122821	-4.400
900	0.0632	0.9368	0.011506117	-4.465
3840	0.1846	0.8154	0.010014824	-4.604
7440	0.3034	0.6966	0.008555588	-4.761
11040	0.4102	0.5898	0.007243614	-4.928
14640	0.5247	0.4753	0.005837436	-5.143
18240	0.6244	0.3756	0.004613648	-5.379
21840	0.7120	0.2880	0.003536876	-5.645
25440	0.7887	0.2113	0.002594839	-5.954
29040	0.8479	0.1521	0.001868107	-6.283
32640	0.8889	0.1111	0.001364418	-6.597
36240	0.9195	0.0805	0.000989078	-6.919
39840	0.9455	0.0545	0.000669866	-7.308
43440	0.9607	0.0393	0.000482932	-7.636
47040	0.9771	0.0229	0.000280892	-8.178
50640	0.9790	0.0210	0.000258293	-8.261
54240	0.9837	0.0164	0.000200812	-8.513



k_{obs} = 6.82×10^{-5} s^{-1}

10:1 Substrate to Cavitand Ratio

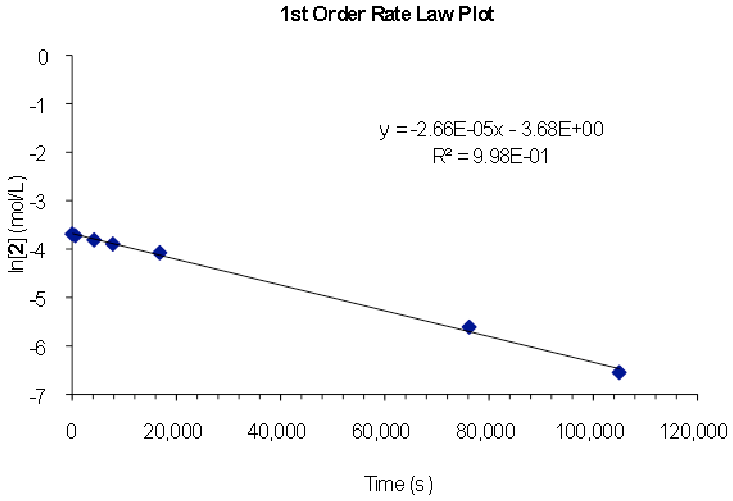
time (s)	% 3	% 2	[2] (mol/L)	ln[2]
0	0.000	1.0000	0.01563	-4.159
1800	0.082	0.9180	0.01434	-4.244
5400	0.197	0.8030	0.01255	-4.378
9000	0.309	0.6910	0.01080	-4.528
12600	0.412	0.5880	0.00919	-4.690
16200	0.504	0.4960	0.00775	-4.860
19800	0.588	0.4120	0.00644	-5.046
23400	0.660	0.3400	0.00531	-5.238
30600	0.773	0.2270	0.00355	-5.642
34200	0.808	0.1920	0.00300	-5.809
37800	0.846	0.1540	0.00241	-6.030
41400	0.883	0.1170	0.00183	-6.304
45000	0.910	0.0900	0.00141	-6.567
48600	0.923	0.0770	0.00120	-6.723
52200	0.942	0.0580	0.00091	-7.006
55800	0.957	0.0430	0.00067	-7.305
59400	0.966	0.0340	0.00053	-7.540
63000	0.970	0.0300	0.00047	-7.665
66600	0.980	0.0200	0.00031	-8.071
70200	0.987	0.0130	0.00020	-8.502



k_{obs} = 5.81×10^{-5} s^{-1}

20:1 Substrate to Cavitand Ratio

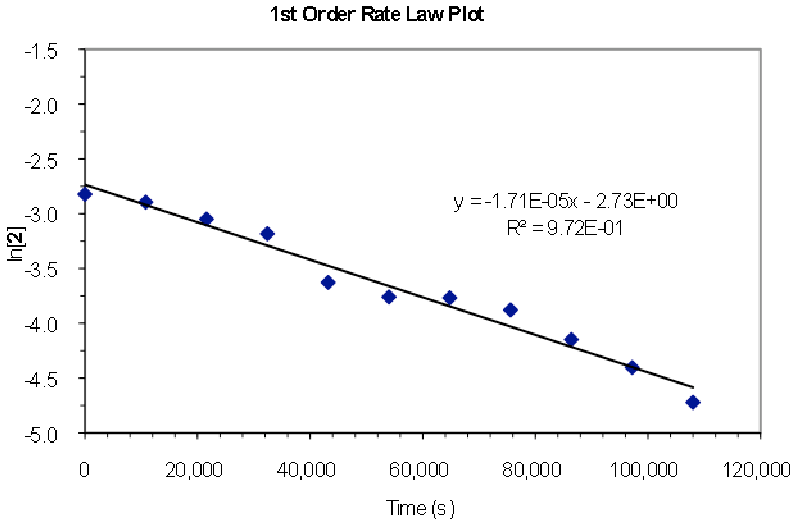
Time (s)	% 3	% 2	[2] (mol/L)	ln[2]
0	0	1.0000	0.02500	-3.689
600	0.0341	0.9659	0.02415	-3.724
4200	0.1150	0.8850	0.02212	-3.811
7800	0.1867	0.8134	0.02033	-3.895
16800	0.3207	0.6793	0.01698	-4.076
76200	0.8534	0.1467	0.00367	-5.609
105000	0.9426	0.0574	0.00143	-6.547



k_{obs} = 2.66×10^{-5} s^{-1}

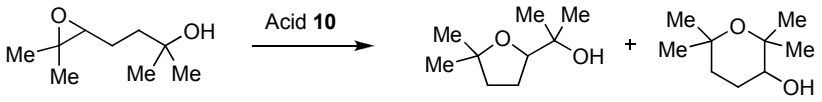
40:1 Substrate to Cavitand Ratio

Time (s)	% **3**	% **2**	[**2**] (mol/L)]	ln[**2**]
0	0	1	0.05945	-2.823
10800	0.0699	0.9301	0.05529	-2.895
21600	0.2029	0.7971	0.04739	-3.049
32400	0.3026	0.6974	0.04146	-3.183
43200	0.5528	0.4472	0.02659	-3.627
54000	0.6084	0.3916	0.02328	-3.760
64800	0.6115	0.3885	0.02310	-3.768
75600	0.6520	0.3480	0.02069	-3.878
86400	0.7344	0.2656	0.01579	-4.148
97200	0.7942	0.2058	0.01224	-4.403
108000	0.8503	0.1498	0.00890	-4.721



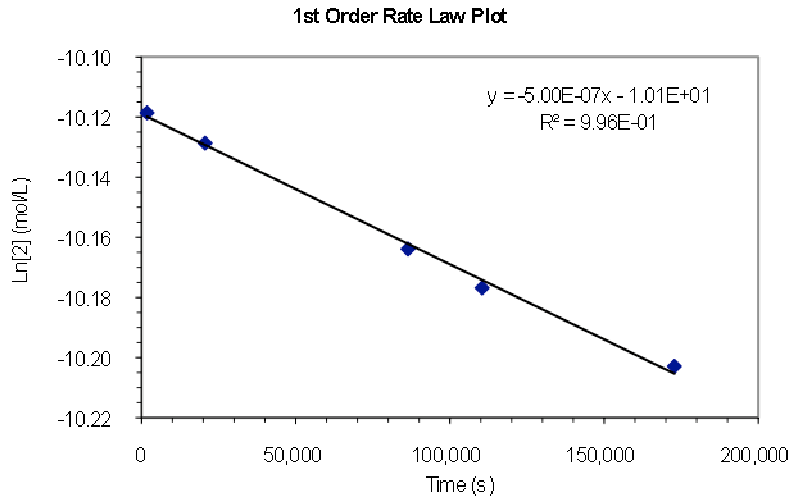
k_{obs} = 1.71×10^{-5} s^{-1}

Epoxide Ring-Opening Cyclization of 2,6-Dimethyl-5,6-epoxy-2-heptanol using Acid 10.



2 **3** **11**

Time (sec)	**% 3+11**	**% 2**	**[2] (mol/L)**	**Ln[2]**
1800	0	1	4.032E-05	-10.1186
20592	0.01004	0.9900	3.992E-05	-10.1287
86400	0.04428	0.9557	3.854E-05	-10.1639
110412	0.05656	0.9434	3.804E-05	-10.1768
172800	0.08085	0.9192	3.706E-05	-10.2029



k_{obs} = 5.00×10^{-7} s^{-1}

VI. References

[1]Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-1520.

[2] Kime, K. A.; Sievers, R. E. *Aldrichimica Acta* **1977**, *10*, 54–62.

[3] a) Neighbors, J. D.; Mente, N. R., Boss, D. K.; Zehnder, D. W., II; wiemer, D. F. *Tetrahedron Lett.* **2008**, *49*, 516–519. b) Morimoto, Y.; Yata, H.; Nishikawa, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 6481–6484. c) Frohn, M; Shi, Y. *Synthesis* **2000**, *14*, 1979–2000.