Preparation and regioselective S_N2' reaction of novel *gem*-difluorinated vinyloxiranes with RLi

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Table 6. Preparation of α,β -unsaturated ketones **12b**, **12f**, and **12g**.

Entry	R	Time (h)	Conv. ^{a)}	Yield of 12 (%)	<i>E</i> / <i>Z</i> of 12 ^{a)}
1	2-Phenylethyl	6	>99	92: 12b	>99 / <1
2	4-NO ₂ -C ₆ H ₄	1	>99	>99: 12f	>99 / <1
3	4-Me-C ₆ H ₄	6	69	48: 12g	>99 / <1
4	4-Me-C ₆ H ₄	18	86	75: 12g	>99 / <1

a) Determined by ¹H NMR.

Scheme 7. Preparation of α,β -unsaturated ketones **12c**, **12h**, and **12i**.

Table 7. Preparation of α,β -epoxyketones **3**.

Substrate	Time (h)	Yield of 3 (%)
12b	5	85
12c	5	84
12d	5	68
12e	5	87
12f	1	49
12g	overnight	— ^{a)}
12g ^{b)}	2.5	82
12h	4	77
12i	5	77

a) The product was decomposed before the completion of the reaction. b) The reaction was conducted in DMSO and 5.0 equiv of H_2O_2 was used.

Scheme 8. Preparation of α,β -epoxyketones, **3j** and **3k**.

Reagents and conditions

- a) 1. *n*-BuLi (1.0 equiv)/THF, 0 $^\circ\text{C}$, 0.5 h 2. Acetaldehyde (1.1 equiv)/THF, -78 $^\circ\text{C}$, 5.5 h
 b) $\text{Ni}(\text{OAc})_2$ (0.4 equiv), NaBH_4 (0.4 equiv), EDA (1.0 equiv), H_2/EtOH , rt, 3 h
 c) *m*CPBA (1.2 equiv)/ CH_2Cl_2 , rt, 3.5 h
 d) PDC (0.65 equiv), Ac_2O (3.0 equiv)/ CH_2Cl_2 , reflux, 3 h

General Methods. Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. All manipulations involving air-sensitive materials were performed under argon, with such materials being exposed only to thoroughly dried and degassed solvents. Anhydrous ether, THF and CH_2Cl_2 were purchased and were used without further purification.

^1H NMR and ^{13}C NMR spectra were recorded (^1H : 300 and 500 MHz; ^{13}C : 75 MHz) in CDCl_3 unless otherwise noted. Chemical shifts were reported in parts per million (ppm) downfield from internal tetramethylsilane (Me_4Si). ^{19}F NMR spectra were recorded (282 and 470 MHz) in CDCl_3 unless otherwise noted. Chemical shifts were reported in ppm downfield from internal hexafluorobenzene (C_6F_6). Data were tabulated in the following order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sex, sextet; m, multiplet; br, broad peak), number of protons,

coupling constants (in hertz). Infrared (IR) spectra were as thin films on NaCl plates, and all spectra were reported in wave numbers (cm^{-1}). Melting points, mp, were reported without correction. Column chromatography was conducted with silica gel by using a mixture of *n*-hexane and AcOEt (v/v), and before starting separation, it is recommended to "wash" silica gel by passing AcOEt for removing the chance of decomposition of epoxy-containing products, which makes the isolation easier.

Because of the inherent instability and/or low chemical yields, **1b~e**, **1g**, **1j~l**, **6bf**, **6ib**, and **8c** were characterized only by NMR and IR, and no elemental analyses were carried out.

(E)-4-Methyl-7-phenylhept-4-en-3-one (12c): ^1H NMR δ 1.08 (3 H, m), 1.74 (3 H, s), 2.56 (2 H, m), 2.65 (2 H, dd, $J = 14.6, 7.41$ Hz), 2.78 (2 H, m), 6.64 (1 H, tq, $J = 7.14, 1.38$ Hz), 7.15-7.35 (5 H, m). ^{13}C NMR δ 8.77, 11.3, 30.3, 30.7, 34.7, 125.9, 128.0, 128.2, 137.1, 140.4, 140.7, 202.0. IR (neat) ν 700, 749, 796, 909, 984, 1040, 1092, 1162, 1250, 1340, 1375, 1419, 1454, 1473, 1496, 1641, 1670, 1874, 1943, 2346, 2937, 2977, 3027, 3062. Anal. Calcd for $\text{C}_{14}\text{H}_{18}\text{O}$: C, 83.12; H, 8.97. Found: C, 82.84; H, 9.30.

6-Phenyl-4-(2-phenylethyl)hex-3-en-2-one (12i): ^1H NMR δ 2.00 (3 H, s), 2.23-2.30 (2 H, m), 2.59-2.67 (4 H, m), 2.69-2.77 (2 H, m), 5.92 (1 H, s), 7.00-7.20 (10 H, m). ^{13}C NMR δ 31.8, 34.0, 34.9, 35.0, 40.7, 123.7, 125.8, 126.0, 128.1, 128.2, 128.3, 128.4, 140.8, 141.6, 160.5, 197.9. IR (neat) ν 699, 748, 843, 966, 1017, 1030, 1078, 1172, 1219, 1353, 1379, 1419, 1454, 1496, 1611, 1647, 1653, 1685, 1718, 1734, 1802, 1869, 1943, 2374, 2858, 2925, 3026, 3061, 3085. Anal. Calcd for $\text{C}_{20}\text{H}_{22}\text{O}$: C, 86.29; H, 7.97. Found: C, 85.96; H, 7.70.

4-Hydroxy-6-Phenyl-4-(2-phenylethyl)hexan-2-one (13i): ^1H NMR δ 1.85-1.93 (4 H, m), 2.11 (3 H, s), 2.58-2.77 (6 H, m), 3.98 (1 H, s), 7.15-7.33 (10 H, m). ^{13}C NMR δ 30.2, 32.0, 41.0, 50.1, 73.3, 125.7, 128.2, 128.3, 141.9, 210.9. IR (neat) ν 700, 748, 938, 1030, 1062, 1092, 1165, 1362, 1411, 1454,

1473, 1496, 1603, 1700, 1869, 1943, 2346, 2371, 2865, 2936, 3001, 3025, 3061, 3084, 3482.

Anal. Calcd for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 80.83; H, 8.38.

4,5-Epoxy-4-methyl-7-phenylhept-3-one (3c): 1H NMR δ 1.00 (3 H, dd, $J = 7.42, 7.14$ Hz), 1.37 (3 H, s), 1.88 (1 H, dddd, $J = 14.3, 8.79, 7.69, 5.77$ Hz), 1.97 (1 H, ddt, $J = 14.0, 8.51, 6.31$ Hz), 2.28 (1 H, dq, $J = 18.4, 7.14$ Hz), 2.42 (1 H, dq, $J = 18.4, 7.41$ Hz), 2.75 (1 H, ddd, $J = 14.0, 8.24, 7.97$ Hz), 2.86 (1 H, ddd, $J = 14.0, 8.79, 6.32$ Hz), 3.02 (1 H, dd, $J = 6.59, 5.77$ Hz), 7.15-7.35 (5 H, m). ^{13}C NMR δ 7.45, 12.9, 28.8, 30.2, 32.5, 60.7, 63.7, 126.1, 128.2, 128.4, 140.4, 210.5. IR (neat) ν 700, 750, 805, 829, 852, 910, 938, 984, 1031, 1086, 1123, 1260, 1357, 1379, 1455, 1496, 1604, 1710, 2344, 2362, 2938, 2976, 3027, 3062. Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.84; H, 8.04.

3-Benzyl-3,4-epoxybutan-2-one (3h): 1H NMR δ 2.00 (3 H, s), 2.74 (1 H, d, $J = 4.95$ Hz), 2.91 (1 H, d, $J = 4.95$ Hz), 3.03 (1 H, d, $J = 4.84$ Hz), 3.41 (1 H, d, $J = 4.83$ Hz), 7.17-7.31 (5 H, m). ^{13}C NMR δ 24.0, 35.4, 50.0, 62.7, 126.6, 128.2, 129.7, 135.5, 207.0. IR (neat) ν 675, 703, 757, 820, 857, 878, 929, 970, 1031, 1099, 1147, 1185, 1264, 1286, 1321, 1363, 1420, 1455, 1496, 1604, 1713, 1956, 2315, 2365, 2924, 3002, 3032, 3062, 3087, 3404. Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.74; H, 7.14.

3,4-Epoxy-6-phenyl-4-(2-phenylethyl)hexan-2-one (3i): 1H NMR δ 1.80-1.87 (2 H, m), 1.91 (3 H, s), 1.94 (1 H, ddd, $J = 14.6, 9.79, 7.32$ Hz), 2.14 (1 H, ddd, $J = 14.6, 9.07, 5.77$ Hz), 2.61-2.84 (4 H, m), 3.32 (1 H, s), 7.10-7.33 (10 H, m). ^{13}C NMR δ 27.9, 30.8, 31.2, 31.4, 36.2, 64.7, 65.4, 125.9, 126.0, 128.0, 128.1, 128.3, 128.4, 140.3, 140.5, 203.2. IR (neat) ν 700, 749, 800, 865, 889, 911, 931, 958, 1031, 1081, 1159, 1188, 1242, 1356, 1412, 1454, 1496, 1584, 1603, 1721, 1773, 1803, 1870, 1950, 2346, 2862, 2931, 3002, 3026, 3061, 3085. Anal. Calcd for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.61; H, 7.89.

1,2-Epoxy-5-phenyl-pentan-3-one (3j): 1H NMR δ 2.61 (1 H, ddd, $J = 17.6, 8.18, 7.33$ Hz), 2.75 (1 H, ddd, $J = 17.6, 7.57, 7.32$ Hz), 2.76 (1 H, dd, $J = 5.74, 2.44$ Hz), 2.88-2.95 (2 H, m), 2.94 (1 H, dd, J

= 5.74, 4.64 Hz), 3.42 (1 H, dd, J = 4.64, 2.45 Hz), 7.18-7.32 (5 H, m). ^{13}C NMR δ 29.0, 38.0, 45.8, 53.3, 126.0, 128.0, 128.2, 140.3, 206.4. IR (neat) ν 670., 700, 751, 771, 862, 934, 999, 1030, 1078, 1131, 1181, 1206, 1233, 1293, 1376, 1400, 1454, 1496, 1604, 1713, 1812, 1870, 1952, 2344, 2363, 2856, 2926, 3003, 3028, 3062, 3086, 3408. Anal. Calcd for $\text{C}_{11}\text{H}_{12}\text{O}_2$: C, 74.98; H, 6.86. Found: C, 74.94; H, 7.20.

Figure 3. Calculated result of the reaction between *gem*-difluorinated vinyloxirane and MeLi.

Figure 4. Transition states structures.

Bond lengths (Å), bond orders, and partial charges by MOPAC PM3 are shown. Coordinating Me₂O molecules are omitted for clarity.

Figure 5. Energy profile for the reaction of **1** and MeLi.Energy Profile for the *re*-face Attack Energy Profile for the *si*-face Attack

ΔG (kcal/mol) at 0 °C by MOPAC PM3 was described.

2a (F0)

Total energy: -231.198705878 hartree

Number of imaginary frequency: 0

	X	Y	Z
C	0.002879	-0.012478	-0.044402
C	-0.008992	0.008117	1.292878
H	0.923984	0.031324	1.855714
C	-1.246916	0.001921	2.102516
H	-2.178970	-0.098582	1.543886
C	-1.312965	0.647020	3.429499
H	-2.268495	1.024326	3.794988
H	-0.428031	1.142315	3.830421
O	-1.216743	-0.775884	3.322422
H	-0.917871	-0.048111	-0.623888
H	0.932332	0.007543	-0.606250

1a (F2)

Total energy: -429.681497699 hartree

Number of imaginary frequency: 0

	X	Y	Z
C	0.000406	-0.023609	-0.024389
C	-0.016300	0.034390	1.301806
H	0.939109	0.075209	1.814059
C	-1.257910	0.022215	2.103544
H	-2.187834	-0.060886	1.543042
C	-1.315028	0.638501	3.442653
H	-2.266420	1.012093	3.821652
H	-0.425355	1.118275	3.851423
O	-1.228012	-0.784722	3.302282
F	-1.076290	-0.086488	-0.807807
F	1.102144	-0.016725	-0.771024

E-1m

Total energy: -508.322626824 hartree

Number of imaginary frequency: 0

	X	Y	Z
C	0.000000	0.000000	0.000000
C	0.000000	0.000000	1.331630
C	1.305323	0.000000	2.049734
C	1.489041	-0.570212	3.400586
O	1.405098	0.853936	3.214932
F	1.088570	-0.007301	-0.777390
F	-1.091143	-0.003942	-0.769889
C	2.812298	-1.120290	3.870160
C	-1.290578	0.025388	2.112197
H	2.186621	0.041977	1.411717
H	0.609301	-0.987161	3.894534
H	2.846220	-2.208152	3.731454
H	3.642698	-0.669902	3.316433
H	2.956974	-0.909515	4.936623
H	-1.234398	0.787566	2.896686
H	-1.481929	-0.940834	2.596994
H	-2.144629	0.250534	1.469617

Z-1m

Total energy: -508.318900554 hartree

Number of imaginary frequency: 0

	X	Y	Z
C	0.000000	0.000000	0.000000
C	0.000000	0.000000	1.328117
C	1.301285	0.000000	2.071384
C	2.266046	-1.120318	2.078626
O	1.389840	-0.892403	3.198781
F	1.092863	-0.048802	-0.770323
F	-1.085946	0.053238	-0.776946
C	2.086808	-2.408983	1.317878
C	-1.271353	0.085726	2.133906
H	1.694168	0.996223	2.294625

H	3.303963	-0.854752	2.293078
H	2.491416	-3.244626	1.901359
H	1.031890	-2.611489	1.114076
H	2.628100	-2.366072	0.365159
H	-1.281903	1.003135	2.737614
H	-1.331471	-0.758328	2.829936
H	-2.159716	0.083750	1.497688

1a

Free energy at 0 °C: -108.253 kcal/mol

Number of imaginary frequency: 0

	X	Y	Z
C	-1.452408	-0.858871	0.594025
C	-0.647339	0.213852	0.508316
C	0.087326	0.525620	-0.732910
C	1.579865	0.525650	-0.732910
O	0.841629	1.749985	-0.732941
F	-1.708389	-1.749985	-0.360977
F	-2.153595	-1.228226	1.664017
H	-0.526077	0.881760	1.369736
H	-0.475159	0.315994	-1.664000
H	2.149460	0.296936	-1.641495
H	2.153610	0.305573	0.175568

TS 1

Free energy at 0 °C: -142.687 kcal/mol

Number of imaginary frequency: 1 (-502.23 cm⁻¹)

	X	Y	Z
C	-1.537277	-1.256409	-0.278427
C	-0.258667	-1.762238	-0.456940
C	0.466309	-1.527405	-1.716278
C	1.954758	-1.527512	-1.716293

O	1.261398	-0.265884	-1.716309
F	-2.338608	-1.661728	0.716019
F	-2.354187	-0.914917	-1.284760
H	0.204102	-2.386307	0.321259
H	-0.099152	-1.709854	-2.652588
H	2.522369	-1.738220	-2.632889
H	2.538818	-1.773422	-0.816803
C	-1.455963	0.941879	0.538269
Li	0.490646	0.380432	0.108765
H	-1.246643	1.041336	1.612885
H	-1.163895	1.876709	0.025085
H	-2.538834	0.879883	0.437820
O	2.033615	1.028976	1.258652
C	1.824768	0.853088	2.652588
C	2.212600	2.386307	0.868088
H	1.718400	-0.233475	2.759735
H	2.692780	1.206726	3.222794
H	0.916900	1.363831	3.005173
H	2.329941	2.332993	-0.224380
H	3.120712	2.800888	1.323654
H	1.349716	3.015823	1.133148

TS 2

Free energy at 0 °C: -198.256 kcal/mol

Number of imaginary frequency: 1 (-510.24 cm⁻¹)

	X	Y	Z
C	-1.795883	-0.589249	-1.326904
C	-1.230743	0.677261	-1.461365
C	-0.418274	0.982727	-2.657500
C	1.073853	0.982712	-2.657500
O	0.336929	2.210281	-2.657516
F	-2.982330	-0.793808	-0.721268
F	-1.726913	-1.520172	-2.289673
H	-1.629913	1.532181	-0.883514
H	-0.950668	0.772461	-3.608658
H	1.658722	0.757950	-1.748352
H	1.646729	0.761246	-3.566025
C	-0.648163	-1.956345	0.128143

Li	-0.391953	0.068024	0.631393
H	-0.354477	-2.038040	1.191528
H	0.216644	-2.218582	-0.487335
H	-1.414322	-2.715347	-0.025574
O	1.462341	0.716187	1.199036
C	1.713074	2.110367	1.110321
C	2.494705	-0.081848	0.637787
O	-1.523804	0.854080	2.169571
C	-1.866592	2.227936	2.096527
C	-2.591600	0.020325	2.595078
H	0.796356	2.570297	1.513763
H	1.879105	2.440964	0.075455
H	2.577438	2.383362	1.728119
H	2.146591	-1.111191	0.804840
H	2.612885	0.113220	-0.442719
H	3.447769	0.090668	1.152100
H	-0.915131	2.715347	1.828384
H	-2.220871	2.600479	3.065674
H	-2.627396	2.419724	1.327835
H	-2.149902	-0.985916	2.586334
H	-2.913940	0.289337	3.608658
H	-3.447769	0.068390	1.908400

Int 1

Free energy at 0 °C: -251.428 kcal/mol

Number of imaginary frequency: 0

	X	Y	Z
C	-1.650818	-2.385483	-1.167465
C	-0.255890	-1.819748	-1.005127
C	0.496857	-1.610016	-2.257889
C	1.987152	-1.610000	-2.257889
O	1.309433	-0.340622	-2.257889
F	-1.649094	-3.626419	-1.763351
F	-2.420792	-1.693344	-2.069443
H	0.304200	-2.414764	-0.257965
H	-0.046906	-1.790085	-3.207474
H	2.564300	-1.818237	-3.168655
H	2.572128	-1.853409	-1.358002

C	-2.370941	-2.461014	0.201965
Li	0.346512	0.193726	-0.458618
H	-1.828079	-3.125748	0.883804
H	-2.416168	-1.464005	0.659317
H	-3.395630	-2.839966	0.104980
O	1.435913	0.623871	1.203217
C	1.029785	-0.241226	2.255615
C	2.831940	0.601593	0.946838
O	-0.774261	1.872604	-0.592850
C	-2.161728	1.560944	-0.587967
C	-0.363373	2.637604	-1.717896
H	-0.061569	-0.115295	2.287903
H	1.286896	-1.291809	2.055817
H	1.476303	0.072586	3.207474
H	3.181732	-0.391937	0.629303
H	2.956955	1.329453	0.134674
H	3.395630	0.922287	1.831970
H	-2.463989	0.973862	-1.468033
H	-2.288528	0.965088	0.326660
H	-2.760895	2.478180	-0.529205
H	-0.588547	2.139404	-2.671783
H	0.722229	2.738831	-1.584061
H	-0.839096	3.626434	-1.701035

Int 2

Free energy at 0 °C: -249.014 kcal/mol

Number of imaginary frequency: 0

	X	Y	Z
C	-0.922394	-2.844315	-0.183228
C	-0.980072	-1.451553	-0.775803
C	-0.205994	-1.252014	-2.030380
C	1.283600	-1.252000	-2.030380
O	0.586670	0.010040	-2.030380
F	0.353333	-3.283875	0.072205
F	-1.331635	-3.813034	-1.071655
H	-2.041229	-1.167542	-0.921204
H	-0.740189	-1.438293	-2.985443
H	1.850281	-1.463089	-2.947235

H	1.870544	-1.496155	-1.130508
C	-1.778030	-2.922852	1.106522
Li	-0.143555	0.403961	-0.061340
H	-1.421158	-2.190033	1.841553
H	-2.828079	-2.700348	0.884064
H	-1.733704	-3.917664	1.566254
O	1.232040	0.661331	1.411179
C	1.419083	-0.547241	2.137268
C	2.431732	1.192596	0.866989
O	-1.226852	2.095047	0.177429
C	-2.570969	1.788589	0.521683
C	-1.100494	2.936920	-0.959534
H	0.409134	-0.789154	2.496414
H	1.799988	-1.360291	1.500229
H	2.096756	-0.389847	2.985428
H	2.936478	0.483826	0.193893
H	2.098557	2.079193	0.310379
H	3.120483	1.487061	1.668945
H	-3.097992	1.260056	-0.285889
H	-2.469528	1.138260	1.400894
H	-3.120468	2.700897	0.785492
H	-1.552872	2.498367	-1.860367
H	-0.014069	3.040359	-1.085678
H	-1.552856	3.917664	-0.764221

TS 3

Free energy at 0 °C: -250.061 kcal/mol

Number of imaginary frequency: 1 (-466.53 cm⁻¹)

	X	Y	Z
C	-1.727844	-2.340378	-1.059616
C	-0.270950	-1.949234	-0.969177
C	0.483429	-1.821762	-2.186905
C	1.964233	-1.821732	-2.186905
O	1.492371	-0.478638	-2.186905
F	-1.887390	-3.679077	-1.332397
F	-2.384796	-1.797180	-2.134705
H	0.238602	-2.474945	-0.140091
H	-0.049683	-1.901718	-3.153061

H	2.524261	-2.089035	-3.096054
H	2.537048	-2.131760	-1.296387
C	-2.468643	-1.974182	0.252075
Li	0.522888	0.084290	-0.527466
H	-1.985016	-2.451385	1.111893
H	-2.441757	-0.881729	0.403030
H	-3.518463	-2.290573	0.233124
O	1.577209	0.480881	1.176971
C	1.265182	-0.454315	2.199310
C	2.965164	0.581512	0.892838
O	-0.579193	1.768585	-0.683838
C	0.017532	2.680603	-1.595047
C	-1.960068	1.537857	-0.922867
H	0.169600	-0.412277	2.263321
H	1.593048	-1.473145	1.947006
H	1.713760	-0.149231	3.153061
H	3.388596	-0.370972	0.541992
H	3.010727	1.337800	0.097519
H	3.518463	0.925980	1.775452
H	-0.422714	3.679077	-1.479645
H	1.075089	2.695511	-1.296158
H	-0.080536	2.355331	-2.640381
H	-2.537613	2.446060	-0.711838
H	-2.221970	0.737457	-0.208389
H	-2.160721	1.200531	-1.949585

TS 4

Free energy at 0 °C: -246.400 kcal/mol

Number of imaginary frequency: 1 (-425.07 cm⁻¹)

	X	Y	Z
C	0.275223	-2.575760	0.441650
C	-0.096375	-1.519821	-0.584091
C	0.703995	-1.390381	-1.779312
C	2.183807	-1.390411	-1.779312
O	1.715302	-0.051193	-1.779327
F	0.598557	-3.776733	-0.145538
F	-0.813904	-2.955688	1.184860
H	-1.183640	-1.501862	-0.782623

H	0.180664	-1.443192	-2.755386
H	2.743790	-1.662415	-2.686584
H	2.745972	-1.702011	-0.878464
C	1.421082	-2.137360	1.390228
Li	0.414490	0.635681	-0.429855
H	2.325882	-1.898361	0.808304
H	1.126068	-1.237518	1.954987
H	1.678452	-2.921494	2.112686
O	1.072235	1.769440	1.149292
C	0.395950	1.349030	2.326965
C	2.487869	1.697266	1.245712
O	-0.855072	1.999985	-1.212341
C	-0.262802	2.834778	-2.195038
C	-2.164734	1.564758	-1.538406
H	-0.665512	1.476089	2.077148
H	0.609222	0.292847	2.572144
H	0.663559	1.986923	3.178329
H	2.840240	0.670410	1.426254
H	2.832230	2.054764	0.266464
H	2.857162	2.357071	2.040970
H	-0.818604	3.776749	-2.283752
H	0.747131	3.023682	-1.805679
H	-0.208954	2.348053	-3.178329
H	-2.857178	2.415451	-1.558167
H	-2.421800	0.878159	-0.720581
H	-2.202438	1.039703	-2.502365

Pro 1E

Free energy at 0 °C: -354.067 kcal/mol

Number of imaginary frequency: 0

	X	Y	Z
C	-0.878571	-0.646149	0.131210
C	-0.087036	0.433990	0.010040
C	0.650421	0.748581	-1.228973
C	2.142212	0.748581	-1.228973
O	1.405975	1.973892	-1.228973
F	-1.044373	-1.508972	-0.886673
H	0.024963	1.124069	0.855240

H	0.091537	0.539963	-2.162109
H	2.712646	0.520493	-2.137054
H	2.716309	0.528488	-0.320923
C	-1.637161	-0.989090	1.369720
H	-2.716309	-1.025757	1.168869
H	-1.336868	-1.973907	1.751846
H	-1.464767	-0.250610	2.162125

Pro 1Z

Free energy at 0 °C: -352.115 kcal/mol

Number of imaginary frequency: 0

	X	Y	Z
C	-1.105728	-0.312958	0.499435
C	0.014100	0.434174	0.516312
C	0.751800	0.756516	-0.721054
C	2.243164	0.756531	-0.721054
O	1.507767	1.981888	-0.721069
F	-1.733551	-0.595825	1.655807
H	0.414276	0.832260	1.457779
H	0.186951	0.540604	-1.655792
H	2.813644	0.528702	-1.629288
H	2.816605	0.535828	0.187500
C	-1.754089	-0.886307	-0.715866
H	-1.688248	-1.981888	-0.713852
H	-2.816620	-0.614532	-0.764313
H	-1.262802	-0.514191	-1.629120

TS 5E

Free energy at 0 °C: -233.066 kcal/mol

Number of imaginary frequency: 1 (-719.30 cm⁻¹)

	X	Y	Z
C	0.244568	-1.383743	0.507400

C	0.773788	-0.075500	0.325577
C	1.535950	0.250000	-0.892441
C	3.032532	0.249969	-0.892441
O	2.296875	1.476837	-0.892441
F	-1.438919	-1.197968	0.586945
F	0.246216	-1.896561	1.764175
H	1.003952	0.522644	1.224426
H	1.005356	0.047485	-1.848328
H	3.614151	0.037781	-1.796967
H	3.606308	0.035309	0.016449
C	0.433655	-2.448486	-0.563171
Li	-1.479279	0.592453	0.248108
H	0.073761	-2.095749	-1.539307
H	1.500198	-2.688889	-0.659851
H	-0.102646	-3.376617	-0.325623
O	-2.272461	1.787827	1.679993
C	-1.269043	2.656418	2.189331
C	-2.931488	1.021286	2.679077
O	-2.264648	1.219177	-1.515884
C	-1.496597	2.308517	-2.011734
C	-2.391556	0.143692	-2.435638
H	-0.450439	2.106200	2.676682
H	-0.900696	3.177948	1.295105
H	-1.700150	3.376602	2.896011
H	-2.233459	0.407944	3.266083
H	-3.614151	0.380386	2.105103
H	-3.499390	1.677261	3.350647
H	-1.473129	3.016800	-1.171951
H	-1.993011	2.765640	-2.876953
H	-0.474533	2.008606	-2.288345
H	-3.010803	-0.584961	-1.896300
H	-2.899490	0.472809	-3.350647
H	-1.416946	-0.298782	-2.693314

TS 5Z

Free energy at 0 °C: -233.485 kcal/mol

Number of imaginary frequency: 1 (-727.13 cm⁻¹)

	X	Y	Z
C	0.247360	-1.758636	0.448822
C	0.902115	-0.501556	0.336731
C	1.660507	-0.170990	-0.882706
C	3.156235	-0.170990	-0.882706
O	2.422852	1.057816	-0.882706
F	0.401077	-2.683273	-0.526306
F	-1.364548	-1.504562	-0.004837
H	1.215286	-0.006775	1.269196
H	1.125275	-0.380432	-1.833633
H	3.737381	-0.385666	-1.786896
H	3.730957	-0.384811	0.025772
C	0.120712	-2.370941	1.840622
Li	-1.297104	0.313828	0.150024
H	1.107100	-2.709869	2.181961
H	-0.256210	-1.634369	2.564300
H	-0.555649	-3.235748	1.857742
O	-2.206894	1.158615	1.763733
C	-1.212936	1.743210	2.594650
C	-3.068176	0.257828	2.444077
O	-1.877686	1.435654	-1.427963
C	-0.979553	2.527618	-1.584732
C	-2.024643	0.643845	-2.599380
H	-0.531937	0.989304	3.017975
H	-0.667908	2.412613	1.914154
H	-1.672700	2.320511	3.406509
H	-2.518417	-0.579956	2.897583
H	-3.737381	-0.106384	1.653915
H	-3.642487	0.782166	3.217957
H	-0.961502	2.997086	-0.591415
H	-1.364960	3.235733	-2.328995
H	0.031250	2.201324	-1.872726
H	-2.705627	-0.158615	-2.286300
H	-2.475449	1.234558	-3.406525
H	-1.067444	0.222519	-2.940918

TS 6E

Free energy at 0 °C: -233.603 kcal/mol

Number of imaginary frequency: 1 (-728.52 cm⁻¹)

	X	Y	Z
C	-1.041977	1.688766	0.661194
C	0.253052	1.131119	0.425232
C	1.003677	1.480072	-0.794022
C	2.493759	1.480087	-0.794022
O	1.778046	2.714325	-0.794037
F	-1.374100	1.984665	1.941513
F	-2.113708	0.352859	0.699249
H	0.865356	0.892548	1.312622
H	0.463074	1.301422	-1.747818
H	3.071228	1.255493	-1.699112
H	3.069809	1.256256	0.112732
C	-1.685638	2.625778	-0.346970
Li	-0.861206	-0.860474	0.210220
H	-1.123000	3.568146	-0.382065
H	-1.681534	2.189758	-1.354492
H	-2.726456	2.862198	-0.089188
O	-0.448685	-2.371429	1.522110
C	-1.148422	-2.183000	2.745346
C	0.960678	-2.469955	1.677383
O	-1.231766	-1.657059	-1.586975
C	-2.309845	-2.577148	-1.634705
C	-0.089233	-2.060303	-2.323166
H	-2.191864	-2.052048	2.429153
H	-0.802170	-1.296738	3.295731
H	-1.050064	-3.072266	3.380402
H	1.399597	-1.544754	2.080154
H	1.321640	-2.652710	0.656250
H	1.223572	-3.314819	2.326370
H	-2.027954	-3.568146	-1.253983
H	-3.071243	-2.116959	-0.990128
H	-2.688492	-2.675293	-2.659988
H	0.597610	-1.208633	-2.216660
H	0.361908	-2.974304	-1.912872
H	-0.336868	-2.218033	-3.380402

TS 6Z

Free energy at 0 °C: -233.925 kcal/mol

Number of imaginary frequency: 1 (-731.88 cm⁻¹)

	X	Y	Z
C	-1.277893	1.890717	0.175568
C	0.113190	1.589645	0.084717
C	0.867828	1.921112	-1.136246
C	2.358536	1.921158	-1.136246
O	1.640320	3.155029	-1.136246
F	-2.094070	0.423294	-0.152618
F	-1.903870	2.496506	-0.855957
H	0.680237	1.613983	1.029495
H	0.323273	1.735718	-2.085968
H	2.936066	1.696000	-2.041229
H	2.935806	1.699127	-0.229965
C	-1.838242	2.290833	1.534958
Li	-0.604904	-0.615219	-0.010818
H	-1.498703	1.604813	2.322891
H	-1.487762	3.299988	1.787933
H	-2.936050	2.303116	1.549515
O	-0.242950	-1.789413	1.612717
C	-1.128006	-1.624329	2.709351
C	1.126221	-1.591766	1.943054
O	-0.399338	-1.903610	-1.572906
C	0.162857	-1.281082	-2.719589
C	-1.665009	-2.506256	-1.813370
H	-2.116776	-1.809021	2.271805
H	-1.080307	-0.611343	3.134445
H	-0.915680	-2.361389	3.493988
H	1.322083	-0.572540	2.308670
H	1.653198	-1.766785	0.994186
H	1.452820	-2.320740	2.695435
H	-0.487503	-0.496918	-3.133698
H	1.096771	-0.839996	-2.345612
H	0.377700	-2.028076	-3.494003
H	-1.937439	-2.938202	-0.840851
H	-2.420624	-1.773941	-2.133667
H	-1.578186	-3.299988	-2.566193

Pro 2E

Free energy at 0 °C: -68.894 kcal/mol

Number of imaginary frequency: 0

	X	Y	Z
C	-3.238281	-3.098602	0.174194
C	-1.722488	-3.063766	0.138200
C	-1.012802	-1.935989	0.143800
C	0.498627	-1.935989	0.143800
O	1.016998	-0.687057	0.143800
F	-3.730682	-4.069244	-0.653992
F	-3.815033	-1.980286	-0.359375
H	-1.239349	-4.047485	0.124893
H	-1.501587	-0.945160	0.145966
H	0.857086	-2.493439	-0.750168
H	0.857529	-2.492432	1.037735
C	-3.713882	-3.322083	1.628036
Li	1.566620	0.878723	0.033005
H	-3.296402	-4.254745	2.024246
H	-3.377945	-2.497910	2.267548
H	-4.806824	-3.382462	1.694183
O	2.587097	1.276398	-1.761566
C	2.031708	0.569717	-2.857834
C	3.065079	2.564117	-2.097992
O	2.923904	1.444900	1.565216
C	4.072800	0.625168	1.401733
C	2.240417	1.223100	2.791077
H	2.782318	0.412003	-3.642900
H	1.726303	-0.392334	-2.421692
H	1.164993	1.092224	-3.284424
H	3.488937	2.938049	-1.158310
H	3.843979	2.512329	-2.869385
H	2.257904	3.226120	-2.440948
H	3.827316	-0.446991	1.389221
H	4.476364	0.937836	0.430542
H	4.806824	0.823624	2.193375
H	1.885712	0.187164	2.895996
H	1.390717	1.915527	2.742844
H	2.884064	1.478317	3.642883
O	-0.016479	2.262680	0.176071
C	-1.267990	1.840088	-0.336533
C	0.231537	3.643661	-0.004410
H	-1.338165	1.995712	-1.421021

H	-1.303467	0.761993	-0.100082
H	-2.093323	2.365067	0.160675
H	0.273010	3.919388	-1.067413
H	1.210678	3.798218	0.465424
H	-0.529037	4.254730	0.498169

Pro 2Z

Free energy at 0 °C: -68.888 kcal/mol

Number of imaginary frequency: 0

	X	Y	Z
C	-2.344986	-3.827240	0.617142
C	-2.852463	-2.420593	0.350388
C	-2.072952	-1.355331	0.158203
C	-0.564087	-1.355331	0.158203
O	-0.043716	-0.106537	0.158173
F	-1.491592	-4.264511	-0.356827
F	-3.354965	-4.744141	0.507477
H	-3.944229	-2.322266	0.328842
H	-2.549362	-0.378082	-0.012924
H	-0.211502	-1.911850	-0.737930
H	-0.204880	-1.921341	1.054291
C	-1.685135	-3.910797	2.012054
Li	0.706497	1.375992	0.046844
H	-0.841873	-3.202500	2.062775
H	-2.405594	-3.647049	2.792969
H	-1.304352	-4.916656	2.222885
O	2.065155	1.392136	-1.620285
C	3.203094	0.643417	-1.220108
C	1.380905	0.823776	-2.727936
O	1.841843	1.954681	1.706100
C	1.452087	1.271454	2.885437
C	2.189529	3.308868	1.922180
H	3.944229	0.601959	-2.028793
H	3.605743	1.213226	-0.373520
H	2.945709	-0.379120	-0.908264
H	0.550934	1.519516	-2.904251
H	2.034210	0.788986	-3.609314
H	0.995438	-0.184479	-2.513245

H	1.214706	0.257477	2.534195
H	2.276900	1.243042	3.609300
H	0.572220	1.730469	3.355850
H	2.422775	3.682663	0.917862
H	3.071960	3.386749	2.569809
H	1.365982	3.886444	2.361267
O	-0.574722	3.053391	-0.135071
C	-1.936432	2.658691	-0.098221
C	-0.283096	3.995560	-1.151016
H	-2.259033	2.190567	-1.038100
H	-1.974503	1.928238	0.721573
H	-2.583771	3.517197	0.122894
H	-0.470154	3.593628	-2.156219
H	0.786072	4.200150	-1.015167
H	-0.863785	4.916641	-1.014648