CHEMISTRY
A EUROPEAN JOURNAL

Supporting Information

Origin of Diastereocontrol in the Oxy-Michael Reactions of δ-Lactol Anions: A Computational and Experimental Study

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Energy breakdown for all species in the study

All energies are at the MP2/6-31++G**//B3LYP/6-31+G* level. ZPE and thermochemical energies are determined by frequency analysis at the B3LYP/6-31+G* level. Performing the single point calculations at the B3LYP/6-31++G** level reproduces the MP2 energy differences to within ±0.5 kcal•mol^{-1}.

Species	gas energy / Eh	solution energy / Eh	ZPE / kcal•mol^{-1}	imag. freq. / cm^{-1}	thermochem energy / kcal•mol^{-1}	total G / kcal•mol^{-1}
Ground state anions						
3	-384.544894	-384.651373	101.276	-	-11.800	-241279.26
4	-384.549377	-384.648748	101.568	-	-11.727	-241277.25
5	-384.542550	-384.640235	101.718	-	-11.691	-241271.72
6	-384.537399	-384.645441	101.718	-	-11.691	-241274.99
7	-384.530914	-384.632032	102.993	-	-12.607	-241266.21
Ring opening TS						
8	-384.529599	-384.625588	99.040	74.1	-12.445	-241265.96
9	-384.529973	-384.625359	99.221	81.8	-11.955	-241265.15
Reagents						
MeCl	-499.377291	-499.381359	23.365	-	-8.624	-313347.06
nitropropene	-321.509469	-321.519508	50.941	-	-11.585	-201714.13
Alkylation TS						
10	-883.922321	-884.004401	124.490	408.6	-13.928	-554602.20
11	-883.926572	-884.003784	127.625	412.2	-13.896	-554598.65
12	-883.918943	-884.002352	124.896	360.8	-13.993	-554600.57
13	-883.919655	-883.996143	126.475	398.3	-13.819	-554594.92
14	-883.913117	-883.997565	126.704	421.9	-13.395	-554595.16
15	-883.919699	-884.003032	125.219	425.8	-14.290	-554600.97
Conjugate addition TS						
17	-706.060279	-706.144139	152.487	194.0	-14.811	-442967.77
18	-706.067217	-706.142538	152.412	137.4	-14.340	-442966.37
20	-706.059398	-706.137334	152.633	117.2	-14.324	-442962.87

Cartesian coordinates for all species in the study

All structures here are optimised at the B3LYP/6-31+G* level using a THF continuum solvent model as stated in the main text.

Species discussed in this study

Diequatorial lactolate conformer 3

atom	x	y	z
C1	-2.080944	1.273389	0.738359
C2	-2.719956	2.654792	0.571573
C3	-4.25171	2.542524	0.556336
C4	-4.723578	1.483574	-0.451386
O5	-4.079549	0.23778	-0.20501
C6	-2.584281	0.285721	-0.327608
C7	-6.229542	1.245303	-0.403915
O8	-2.089038	-0.93611	-0.238074
H9	-0.987667	1.331768	0.657926
H10	-2.313463	0.8466	1.724149
H11	-2.388565	3.340171	1.362118
H12	-2.378557	3.086973	-0.381262
H13	-4.610311	2.252613	1.55513
H14	-4.708683	3.510755	0.310886
H15	-4.448804	1.824598	-1.468031
H16	-2.430347	0.759504	-1.3343
H17	-6.51895	0.461074	-1.112958
H18	-6.537154	0.925749	0.599838
H19	-6.777061	2.160688	-0.659218

Axial methyl, equatorial alkoxide lactolate conformer 4

atom	x	y	z
C1	8.998886	0.50621	-1.694637
C2	7.857368	-0.288757	-1.044197
C3	7.83562	-0.037881	0.4661
C4	9.187056	-0.379723	1.112175
O5	10.229766	0.452148	0.414351
C6	10.354118	0.272195	-0.999768
H7	9.085988	0.269976	-2.763455
H8	8.765583	1.577716	-1.619496
H9	6.896723	-0.018369	-1.501063
H10	7.994998	-1.364624	-1.224552
H11	7.614784	1.016529	0.685831
H12	7.062639	-0.643079	0.957762
H13	9.44282	-1.430591	0.834193
C14	11.030729	-1.062931	-1.349059
H15	11.971601	-1.150606	-0.792441
H16	10.41341	-1.93192	-1.100465
H17	11.262294	-1.104444	-2.420513
O18	9.262207	-0.15534	2.414425
H19	11.039056	1.070309	-1.317209

Equatorial methyl, axial alkoxide lactolate conformer 6

atom	x	y	z
C1	0.415287	3.323724	-2.743646
C2	-1.087214	3.057802	-2.891845

C3	-1.681875	2.590681	-1.554357
C4	-0.888811	1.405801	-0.985133
O5	0.489619	1.759304	-0.860553
C6	1.142899	2.078906	-2.18657
O7	1.162524	1.045357	-3.014569
C8	-1.379603	0.963925	0.389107
H9	0.867114	3.573962	-3.712116
H10	0.584797	4.177895	-2.072301
H11	-1.607506	3.953809	-3.255258
H12	-1.238077	2.275409	-3.645782
H13	-1.646071	3.41519	-0.825536
H14	-2.736529	2.305926	-1.675749
H15	-0.972965	0.559058	-1.683169
H16	2.149892	2.385318	-1.817462
H17	-0.81208	0.095811	0.744995
H18	-1.259286	1.772391	1.122059
H19	-2.440578	0.68625	0.351441

Diaxial lactolate conformer 5

atom	x	y	z
C1	7.37616	0.459562	-2.978886
C2	8.767479	0.685807	-2.372261
C3	9.021762	-0.351111	-1.275321
C4	7.948665	-0.248957	-0.169937
O5	6.599094	-0.443682	-0.843318
C6	6.267578	0.454638	-1.909574
H7	7.146581	1.216957	-3.740667
H8	7.36705	-0.518192	-3.481965
H9	9.538298	0.628939	-3.151854
H10	8.829184	1.690159	-1.937016
H11	9.016861	-1.363588	-1.705608
H12	10.001336	-0.198797	-0.804386
H13	5.368344	0.010815	-2.359082
H14	7.963874	-1.189013	0.431133
C15	5.876957	1.861187	-1.430846
H16	5.08707	1.796846	-0.674365
H17	6.721161	2.389952	-0.98514
H18	5.48754	2.443093	-2.277747
O19	8.021867	0.854553	0.554942

Lowest energy open chain conformer 7

atom	x	y	z
C1	-0.072426	-0.028057	-0.045194
C2	0.052703	-0.526712	1.407378
C3	1.481021	-0.525722	1.957714
C4	1.52943	-1.087297	3.399481
O5	1.025536	-2.359663	3.472799
C6	0.503607	-1.015012	-1.012847
O7	1.316566	-0.752485	-1.887811
C8	2.96044	-1.006313	3.970763
H9	-1.140088	0.063767	-0.304312
H10	0.399246	0.950782	-0.192422
H11	-0.58759	0.096155	2.046254
H12	-0.342437	-1.546493	1.47815
H13	2.129267	-1.15185	1.323822
H14	1.890901	0.496702	1.931616
H15	0.917551	-0.371279	4.011987

H16	0.145076	-2.058492	-0.904629
H17	2.962908	-1.412538	4.990355
H18	3.643165	-1.621091	3.367736
H19	3.351442	0.02093	4.006217

TS 8 for opening of *cis*-lactolate

atom	x	y	z
C1	1.770778	0.141338	-1.37482
C2	0.352311	-0.426222	-1.20849
C3	-0.580466	0.401946	-0.295367
C4	-1.203525	-0.480495	0.812305
O5	-0.228289	-1.016003	1.612814
C6	2.592809	0.03898	-0.12091
O7	3.429948	0.866361	0.217097
C8	-2.268834	0.300209	1.611711
H9	2.32066	-0.452434	-2.125586
H10	1.775777	1.181787	-1.722229
H11	-0.089688	-0.553052	-2.203599
H12	0.449523	-1.427416	-0.772514
H13	-0.015813	1.200333	0.210982
H14	-1.362323	0.893036	-0.894375
H15	-1.7729	-1.283466	0.268905
H16	2.429894	-0.857877	0.50035
H17	-2.672191	-0.344607	2.403095
H18	-1.821481	1.178472	2.096797
H19	-3.10619	0.639109	0.983835

TS 9 for opening of *trans*-lactolate

atom	x	y	z
C1	2.073048	-0.182493	-0.827628
C2	0.665434	-0.806827	-0.791821
C3	-0.457046	0.189977	-0.442848
C4	-1.476844	-0.416432	0.551938
O5	-0.859845	-0.827626	1.70294
C6	2.544209	0.209195	0.542919
O7	3.705102	0.112622	0.922236
C8	-2.616576	0.585446	0.829882
H9	2.82069	-0.852931	-1.268482
H10	2.060579	0.73591	-1.437855
H11	0.472579	-1.28708	-1.758683
H12	0.660924	-1.596898	-0.032292
H13	-0.036069	1.082875	0.043562
H14	-0.957437	0.536706	-1.359854
H15	-1.954493	-1.27642	0.008597
H16	1.779811	0.590448	1.240961
H17	-3.324528	0.144965	1.543307
H18	-2.208389	1.496261	1.289621
H19	-3.169015	0.869155	-0.077984

TS 10 for alkylation of diequatorial lactolate with MeCl APP to C2–C3

atom	x	y	z
C1	-8.922835	-0.515735	1.681306
C2	-7.897291	0.387892	0.983687
C3	-7.828144	0.063749	-0.514091
C4	-9.215237	0.08632	-1.187996

O5	-10.105279	-0.827162	-0.428915
C6	-10.270394	-0.480327	0.946302
H7	-9.065688	-0.207974	2.726511
H8	-8.558169	-1.553952	1.692462
H9	-6.908027	0.284266	1.449367
H10	-8.193523	1.439639	1.113908
H11	-7.405336	-0.938796	-0.669059
H12	-7.178042	0.77663	-1.038026
C13	-11.026552	-0.298263	-3.70057
Cl14	-12.701737	-0.383765	-5.01102
H15	-10.882853	0.768956	-3.733309
H16	-10.37322	-0.920323	-4.289481
H17	-11.491678	-0.73007	-2.82971
H18	-9.667499	1.098074	-1.028447
O19	-9.180527	-0.281651	-2.472059
C20	-11.298163	-1.436055	1.5417
H21	-12.238688	-1.389438	0.980972
H22	-11.505228	-1.181547	2.58839
H23	-10.926758	-2.468087	1.503703
H24	-10.665918	0.551596	1.002542

TS 11 for alkylation of diequatorial lactolate with MeCl APP to C2–H

atom	x	y	z
C1	-11.124186	1.310434	1.276219
C2	-10.765943	-0.182564	1.2734
C3	-10.609076	-0.700656	-0.162739
C4	-9.620929	0.161335	-0.966962
O5	-10.101862	1.563141	-0.917133
C6	-10.145317	2.106569	0.402318
H7	-11.112676	1.709842	2.299621
H8	-12.139362	1.452021	0.877705
H9	-11.519603	-0.764818	1.819318
H10	-9.814448	-0.324252	1.80907
H11	-11.574378	-0.69408	-0.686957
H12	-10.240438	-1.734571	-0.160197
C13	-11.064367	-0.340026	-3.711023
Cl14	-12.510029	-0.483928	-5.292469
H15	-11.453	0.549849	-3.244974
H16	-10.203463	-0.247429	-4.351496
H17	-11.272092	-1.297252	-3.264883
H18	-8.654375	0.184193	-0.402457
O19	-9.433003	-0.209115	-2.239756
C20	-10.504343	3.583161	0.285943
H21	-9.771571	4.109021	-0.337519
H22	-10.519666	4.056751	1.275286
H23	-11.493429	3.703277	-0.173282
H24	-9.135886	2.0211	0.849037

TS 12 for alkylation of ax.Me, eq.alkoide lactolate with MeCl APP to C2–C3

atom	x	y	z
C1	8.86111	-0.363898	-1.473347
C2	7.697848	-0.863362	-0.606869
C3	7.661808	-0.094259	0.718855
C4	9.000987	-0.156381	1.484883
O5	10.075925	0.310835	0.534939
C6	10.195643	-0.38537	-0.7032
H7	8.952014	-0.952472	-2.395411

H8	8.658948	0.672961	-1.772985
H9	6.748349	-0.761239	-1.147673
H10	7.817893	-1.936109	-0.402653
H11	7.442455	0.966839	0.540558
H12	6.874519	-0.482016	1.377484
C13	10.992602	0.212866	3.67676
Cl14	12.747496	-0.140373	4.713088
H15	10.406716	-0.625769	4.013866
H16	10.73598	1.177852	4.082978
H17	11.351883	0.194924	2.660734
H18	9.24131	-1.238992	1.656657
C19	10.778879	-1.799858	-0.542453
H20	11.689151	-1.758021	0.063293
H21	10.085485	-2.489578	-0.053442
H22	11.037443	-2.219952	-1.521335
O23	9.023846	0.590436	2.571589
H24	10.92782	0.195437	-1.283137

TS 13 for alkylation of ax.Me, eq.alkoide lactolate with MeCl APP to C2–H

atom	x	y	z
C1	1.418455	-0.58502	1.218218
C2	0.138535	-0.628957	2.064416
C3	-1.094276	-0.469867	1.164723
C4	-1.009164	0.815543	0.326897
O5	0.255219	0.769473	-0.454284
C6	1.468718	0.652413	0.302899
H7	2.313858	-0.609849	1.853751
H8	1.450573	-1.479215	0.581001
H9	0.089691	-1.566551	2.633446
H10	0.149811	0.181959	2.807605
H11	-1.189408	-1.324957	0.480799
H12	-2.009944	-0.424737	1.768363
C13	-2.550267	-0.305646	-2.18919
Cl14	-3.176288	-1.445351	-3.894746
H15	-1.492868	-0.310326	-2.392015
H16	-3.114478	0.579603	-2.429866
H17	-2.939331	-0.973205	-1.439523
H18	-0.887039	1.669877	1.031496
O19	-2.033311	1.031358	-0.510713
C20	1.832836	1.955924	1.032259
H21	1.80674	2.795049	0.327007
H22	2.849381	1.884859	1.43996
H23	1.154554	2.189613	1.859635
H24	2.24216	0.484071	-0.457547

TS 15 for alkylation of eq.Me, ax.alkoide lactolate with MeCl

atom	x	y	z
C1	0.640844	3.11692	-3.271845
C2	-0.830436	3.334337	-2.897403
C3	-0.969621	3.54444	-1.38256
C4	-0.270156	2.41959	-0.606261
O5	1.096729	2.306567	-1.013121
C6	1.264286	1.955292	-2.462149
O7	0.777836	0.750604	-2.774442
C8	-0.287934	2.64493	0.901152
H9	0.742284	2.891954	-4.340847
H10	1.212266	4.036383	-3.07621

H11	-1.247664	4.18968	-3.445636
H12	-1.411808	2.4531	-3.19539
H13	-0.514782	4.505574	-1.096912
H14	-2.028994	3.586455	-1.09212
H15	-0.778821	1.47152	-0.832029
H16	2.372116	2.014528	-2.543872
H17	0.207845	1.817831	1.422539
H18	0.231287	3.576356	1.162079
H19	-1.320025	2.71172	1.267998
C20	2.212081	-0.891344	-2.281371
Cl21	3.551085	-2.473465	-1.872255
H22	2.841041	-0.344753	-2.964745
H23	1.41176	-1.482768	-2.694791
H24	2.103946	-0.51992	-1.27642

TS 14 for alkylation of diaxial lactolate with MeCl

atom	x	y	z
C1	7.36596	0.447384	-3.052757
C2	8.709167	0.741116	-2.371882
C3	8.884784	-0.183535	-1.163074
C4	7.728807	-0.016106	-0.149402
O5	6.443017	-0.258008	-0.891517
C6	6.189051	0.53138	-2.062982
H7	7.187421	1.134776	-3.891181
H8	7.395406	-0.569142	-3.471504
H9	9.534375	0.610031	-3.084455
H10	8.742527	1.78538	-2.039234
H11	8.918887	-1.229627	-1.503472
H12	9.828909	0.021357	-0.643229
H13	5.321625	0.040757	-2.525672
C14	6.657154	1.029848	2.474423
Cl15	5.679456	0.96351	4.340207
H16	5.799156	1.20331	1.846355
H17	7.307874	1.862668	2.684207
H18	7.081337	0.038267	2.499026
H19	7.710943	-0.910135	0.515128
C20	5.774541	1.972449	-1.737586
H21	4.977213	1.973857	-0.986251
H22	6.608124	2.553018	-1.338659
H23	5.394748	2.461755	-2.645038
O24	7.761938	1.133209	0.525958

TS 17 for (*R*)-selective lactolate addition to nitropropene APP to C2–C3

atom	x	y	z
C1	0.000000	0.000000	0.000000
C2	0.000000	0.000000	1.534773
C3	1.435177	0.000000	2.081886
C4	2.299384	1.121907	1.466449
O5	2.224268	0.987478	-0.009247
C6	0.905695	1.116337	-0.537814
H7	-1.020064	0.130512	-0.387363
H8	0.372835	-0.964395	-0.376091
H9	-0.556939	-0.863214	1.922677
H10	-0.526677	0.896666	1.894882
H11	1.928165	-0.956095	1.859085
H12	1.431245	0.115993	3.172894
H13	1.798793	2.100699	1.682004

O14	3.576321	1.073564	1.861256
C15	1.015493	1.121232	-2.058218
H16	1.685749	1.922703	-2.390316
H17	0.032495	1.275487	-2.519849
H18	1.421331	0.166509	-2.416501
H19	0.488895	2.087542	-0.207358
C20	4.895164	2.767401	1.610532
C21	6.111221	2.168191	1.355888
N22	6.920230	1.699787	2.367851
O23	6.626795	1.869921	3.581895
O24	7.991783	1.101062	2.048924
H25	6.491310	1.955856	0.366459
H26	4.657251	3.008134	2.637690
C27	4.200115	3.538071	0.534991
H28	4.469622	3.179145	-0.462280
H29	3.116846	3.473007	0.647091
H30	4.485178	4.598207	0.617444

TS 18 for (*S*)-selective lactolate addition to nitropropene APP to C2–C3

atom	x	y	z
C1	-0.031576	0.058301	0.003017
C2	0.081034	0.023422	1.532489
C3	1.549513	-0.035043	1.970484
C4	2.405848	1.091866	1.345639
O5	2.207044	1.008624	-0.155203
C6	0.860685	1.167749	-0.575744
H7	-1.073718	0.218073	-0.307570
H8	0.291917	-0.906374	-0.416812
H9	-0.478019	-0.829070	1.941827
H10	-0.388711	0.927597	1.948164
H11	2.003079	-0.989869	1.671847
H12	1.630089	0.037285	3.063202
H13	1.925280	2.076459	1.599862
O14	3.696864	1.017347	1.632440
C15	0.848712	1.199242	-2.101928
H16	1.503295	1.997464	-2.471775
H17	-0.164495	1.368337	-2.486864
H18	1.219726	0.247173	-2.502932
H19	0.479011	2.138731	-0.199953
C20	5.154455	2.468471	0.972693
C21	6.103581	2.466176	1.951626
N22	7.151927	1.535805	1.968943
O23	7.326328	0.731068	1.026512
O24	7.935752	1.559573	2.954420
H25	6.108991	3.119152	2.814586
C26	4.194647	3.599745	0.817888
H27	3.246633	3.216041	0.441164
H28	4.036070	4.134639	1.761093
H29	4.595405	4.315681	0.085376
H30	5.242931	1.760322	0.159332

2nd order saddle point 20 for lactolate addition to nitropropene APP to C2–H

atom	x	y	z
C1	-0.099424	0.038325	0.035273
C2	-0.056600	0.127272	1.567333
C3	1.387334	0.043328	2.084230
C4	2.280655	1.098540	1.403404

O5	2.194056	0.852886	-0.067961
C6	0.879722	1.037638	-0.596623
H7	-1.115683	0.231462	-0.335682
H8	0.180085	-0.975362	-0.288631
H9	-0.676944	-0.659157	2.017501
H10	-0.493639	1.087098	1.883240
H11	1.801352	-0.954984	1.891528
H12	1.417334	0.208381	3.169053
H13	1.769492	2.087122	1.528258
O14	3.555976	1.179146	1.797557
C15	0.954475	0.919610	-2.115413
H16	1.644583	1.663635	-2.529892
H17	-0.034785	1.081586	-2.562093
H18	1.306954	-0.076803	-2.410562
H19	0.539768	2.059985	-0.341356
C20	5.193932	-0.177350	2.461312
C21	6.136812	0.752127	2.813150
N22	7.030995	1.283384	1.890208
O23	7.073427	0.870947	0.706869
O24	7.828540	2.177047	2.291237
H25	6.237347	1.183821	3.800541
H26	5.206468	-0.565169	1.451415
C27	4.492277	-0.960932	3.523189
H28	4.326372	-0.363886	4.425854
H29	3.537994	-1.343258	3.164251
H30	5.122133	-1.821378	3.799605

Other species relevant to this study

Chloromethane

atom	x	y	z
C1	0.000000	0.000000	1.251367
H2	-0.518700	0.898416	1.585619
H3	-0.518700	-0.898416	1.585619
Cl4	0.000000	0.000000	-0.566518
H5	1.037401	0.000000	1.585619

Nitropropene

atom	x	y	z
N1	-0.446774	1.398428	1.105461
O2	-0.485469	0.862286	2.219796
O3	-0.849966	0.839134	0.074556
H4	0.051943	3.075607	-0.072186
C5	0.544862	3.412339	2.011909
C6	0.082840	2.732468	0.954263
H7	0.513256	2.939027	2.991979
C8	1.105104	4.790568	1.924857
H9	2.139075	4.795329	2.297110
H10	1.090960	5.186697	0.905068
H11	0.537285	5.465283	2.580420

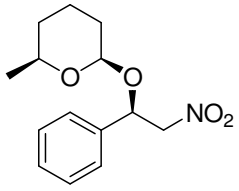
Diequatorial conformer of lactol 1

atom	x	y	z
C1	-5.683569	-14.624337	0.215835
O2	-7.069255	-14.640752	-0.132052
C3	-7.933747	-14.137601	0.912921
C4	-7.764801	-14.981508	2.181094
C5	-6.288292	-15.071595	2.598516

C6	-5.410813	-15.517767	1.417685
H7	-5.398984	-13.580630	0.436695
H8	-7.629926	-13.098646	1.126525
H9	-8.364875	-14.540186	2.987779
H10	-8.163115	-15.988404	1.990533
H11	-5.947084	-14.086944	2.950644
H12	-6.169302	-15.764214	3.440215
H13	-5.638290	-16.555094	1.136994
H14	-4.346618	-15.466232	1.677971
C15	-9.349401	-14.148643	0.353696
H16	-10.048017	-13.712458	1.077279
H17	-9.403659	-13.566437	-0.573591
H18	-9.670868	-15.175071	0.138021
O19	-4.969102	-15.095283	-0.896519
H20	-5.103958	-14.481429	-1.640554

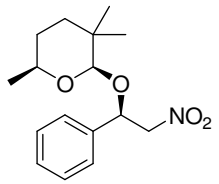
Experimental Details

General: All reactions were carried out under an atmosphere of argon, in oven-dried glassware using freshly distilled anhydrous solvents. All other solvents and reagents were used as supplied or prepared as described in previous reports.[1] Flash column chromatography was carried out using Breckland Scientific Supplies or Merck Kieselgel 60 silica gel (230-400 mesh) under pressure Infrared spectra were obtained on Perkin Elmer 983G, FTIR 1620, or Spectrum One FT-IR ATR (Attenuated Total Reflectance) spectrometers, from a thin film deposited onto the diamond ATR or on an ATI Mattison: Genesis Series FTIR spectrometer from a thin film deposited on a sodium chloride plate. Mass Spectrometric data were obtained on Micromass Platform LC-MS; Waters LCT with Agilent 1100 HPLC; Finnigan MAT 900 XLT; Bruker BIOAPEX 4.7 T FTICR; Fissions VG Trio 2000 quadrupole; or Thermo Finnigan Mat 95XP mass spectrometers, by electron ionization, chemical ionization or fast atom/ion bombardment techniques at the University Chemical Laboratory, Cambridge; the School of Chemistry, University of Manchester; or the EPSRC National Mass Spectrometry Service Centre, Swansea. ^{1}H NMR spectra were recorded in $CDCl_3$, at ambient temperature on Bruker DPX-400, Bruker DRX-500 or Bruker-DRX-600 spectrometers, at 400, 500 or 600 MHz against an internal deuterium lock; Chemical shifts (□) are given in parts per million (ppm) downfield of tetramethylsilane relative to the residual solvent signal (δ_H ($CHCl_3$) = 7.26 ppm), and coupling constants (*J*) are given in Hertz (Hz). ^{13}C NMR spectra were recorded in $CDCl_3$ at ambient temperature on the same spectrometers at 100, 125 or 150 MHz

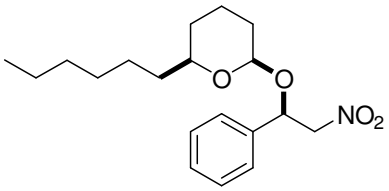


(–)-(2*R*,6*S*)-2-((*R*)-2-nitro-1-phenylethoxy)tetrahydro-6-methyl-2H-pyran (2): To a stirred solution of (*S*)-6-methyltetrahydropyran-2-ol **1** (116 mg, 1 mmol) in THF (5.5 mL) at –78 °C was added dropwise KHMDS (2 mL, 1 mmol, 0.5 M solution in toluene). The reaction mixture was stirred for 15 min at –78 °C before 18-crown-6 (0.47 mL, 2.15 M in toluene) was added dropwise. Stirring was maintained for a further 30 min at –78 °C before a solution of (E)-β-nitrostyrene (100 mg, 0.67 mmol, 1 equiv.) in THF (2 mL) was added dropwise. Stirring was maintained for a further 15 min at –78 °C. The reaction was quenched with glacial acetic acid (0.08 mL, 2 mmol) *via* syringe and the resulting mixture was allowed to warm to room temperature. Diethyl ether (15 mL) and water (15 mL) were added and the aqueous layer was separated and extracted with diethyl ether (3 × 5mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude major : minor

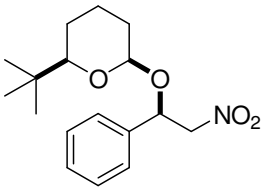
ratio of diastereoisomers was determined as 255:1 by inspection of the crude 600 MHz ^{1}H NMR spectrum. Purification by flash column chromatography eluting with 40-60 petroleum ether / diethyl ether (20 : 1) gave the title compound (180 mg, 99%) as an oil. $[\alpha]_D^{25} = -19.7$ (*c* = 1.4, $CHCl_3$); ν_{max}(film) 1557, 1379 cm^{-1}; δ_H(600 MHz) 7.41–6.98 (m, 5H), 5.42 (1H, dd, *J* 10.0, 3.5), 4.71 (1H, dd, *J* 13.0, 10.0), 4.52 (1H, dd, *J* 9.0, 2.0), 4.48 (1H, dd, *J* 13.0, 3.5), 3.45-3.38 (1H, m), 1.81-1.06 (6H, m), 1.03 (3H, d, *J* 6.0); δ_C(100 MHz) 137.7, 129.6, 128.4, 126.6, 102.9, 80.2, 77.0, 72.4, 32.0, 30.6, 22.0, 21.3; HRMS-EI (calcd for $[M]^+$) 265.1314, found 265.1300.



(–)-(2*R*,6*S*)-2-((*R*)-2-nitro-1-phenylethoxy)tetrahydro-3,3,6-trimethyl-2H-pyran (24a): oil; $[\alpha]_D^{25} = -15.3$ (*c* = 0.3, $CHCl_3$); ν_{max}(film) 1554, 1378, 1156, 1065 cm^{-1}; □ □(500 MHz) 7.40–7.30 (5H, m), 5.37 (1H, dd, *J* 10.0, 3.5), 4.68 (1H, dd, *J* 10.0, 13.0), 4.47 (1H, dd, *J* 13.0, 3.5), 4.42 (1H, s), 3.36 (1H, dqd, *J* 12.5, 6.0, 3.5), 1.45-1.28 (4H, m), 0.98 (3H, d, *J* 6.0), 0.96 (3H, s), 0.89 (3H, s); □ □(125 MHz) 138.1, 128.4, 128.2, 126.5, 108.6, 80.4, 77.5, 72.9, 37.4, 33.8, 29.5, 25.9, 21.1, 17.9; HRMS-ESI (calcd for $[M+NH_4]^+$) 311.1965, found 311.1969.



(+/–)-(2*R*,6*S*)-2-((*R*)-2-nitro-1-phenylethoxy)-6-hexyltetrahydro-2H-pyran (24b): oil; ν_{max}(film) 1555, 1378, 1037 cm^{-1}; δ_H(400 MHz) 7.40–7.26 (5H, m), 5.36 (1H, dd, *J* 10.0, 3.5), 4.68 (1H, dd, *J* 13.0, 10.0), 4.51-4.43 (2H, m), 3.24-3.18 (1H, m), 1.81-1.02 (16H, m), 0.87 (3H, t, *J* 7.0); δ_C(100 MHz) 137.9, 128.5, 128.4, 126.5, 103.8, 80.3, 77.9, 76.2, 35.7, 31.7, 30.9, 30.5, 29.1, 25.1, 22.6, 22.1, 14.1; HRMS-ESI (calcd for $[M+Na]^+$) 358.1994, found 358.2002.

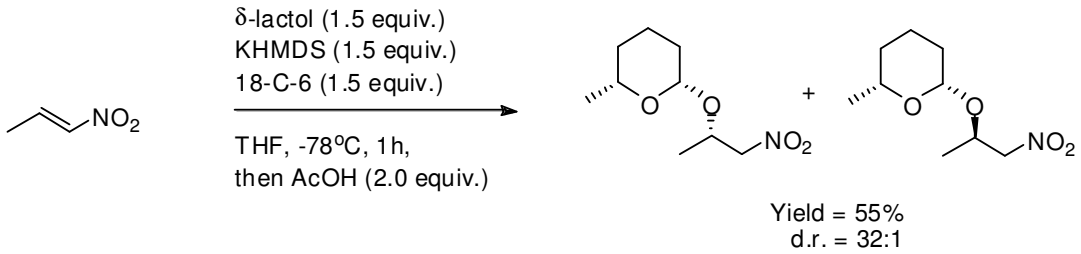


(+/–)-(2*R*,6*R*)-2-((*R*)-2-nitro-1-phenylethoxy)-6-*tert*-butyl-tetrahydro-2H-pyran (24c): oil; IR (film) ν_{max} 1555, 1378, 1139, 1037 cm^{-1}; δ_H(500 MHz) 7.42–7.28 (5H, m), 5.37 (1H, dd, *J* 10.0, 3.0), 4.64 (1H,

dd, *J* 13.0, 10.0), 4.54 (1H, dd, *J* 9.5, 2.0), 4.47 (1H, dd, *J* 13.0, 3.0), 2.88 (1H, dd, *J* 11.5, 2.0), 1.87-0.89 (6H, m), 0.63 (9H, s); δ_C(125 MHz) 138.4, 128.3, 128.1, 126.3, 104.1, 84.1, 80.5, 77.7, 33.8, 31.0, 25.7, 24.3, 22.2; HRMS-ESI (calcd for $[M+NH_4]^+$) 325.2122, found 325.2124.

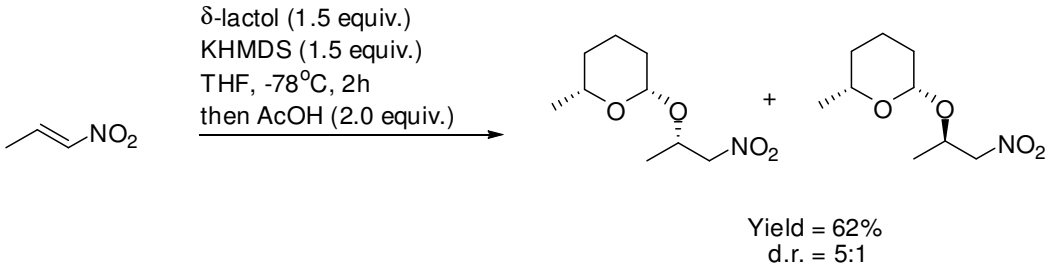
Experimental procedure for reactions with nitropropene

Selective oxy-Michael reaction



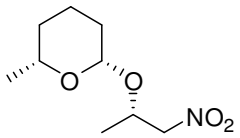
To a stirred solution of (*S*)-6-methyltetrahydropyran-2-ol (199 mg, 1.5 equiv.) in dry THF (16 mL) at –78 °C was added KHMDS (3.43 mL, 1.5 equiv., 0.5 M solution in toluene) dropwise. The reaction mixture was then stirred for 15 min at –78 °C before of 18-crown-6 (0.85 mL, 1.5 equiv., 2.03 M solution in toluene) was added dropwise. Stirring was maintained for a further 30 min at –78 °C before a solution of nitropropene (100 mg, 1.0 equiv.) in dry THF was added dropwise. Stirring was maintained for a further 2 h at –78 °C. The reaction was then quenched by adding glacial acetic acid (0.132 mL, 2.0 equiv.) dropwise *via* syringe. The resulting mixture was allowed to slowly warm to room temperature and partitioned between diethyl ether and water. The aqueous layer was separated and extracted three times with diethyl ether. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification was performed by flash column chromatography on silica (Light petroleum ether : diethyl ether, 3 : 1) affording a inseparable mixture of diastereomers (128 mg, 55%) as a colourless oil. A small amount of each diastereomer was isolated for characterisation.

Unselective oxy-Michael reaction

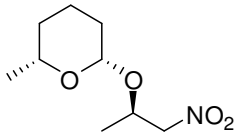


To a stirred solution of (*S*)-6-methyltetrahydropyran-2-ol (199 mg, 1.5 equiv.) in dry THF (16 mL) at –78 °C was added KHMDS (3.43 mL, 1.5 equiv., 0.5 M solution in toluene) dropwise. The reaction mixture was then stirred for 30 min at –78 °C before a solution of nitropropene (100 mg, 1.0 equiv.) in dry THF was added dropwise. Stirring was maintained for a further 2 h at –78 °C. The reaction was then quenched by adding glacial acetic acid (0.132 mL, 2.0 equiv.) dropwise *via* syringe. The resulting mixture

was allowed to slowly warm to room temperature and partitioned between diethyl ether and water. The aqueous layer was separated and extracted three times with diethyl ether. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification was performed by flash column chromatography on silica (Light petroleum ether : diethyl ether, 3 : 1) affording a inseparable mixture of diastereomers (144 mg, 62%) as a colourless oil.



(2*R*,6*S*)-2-methyl-6-((*S*)-1-nitropropan-2-yloxy)tetrahydro-2H-pyran **((β*S*)-22)** $[\alpha]_D^{26}$ -46.15° (*c* 0.35, $CHCl_3$); IR (neat) 2935, 2861, 1555, 1458, 1384, 1162, 1068, 1035, 996 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) 4.33 (1H, dd, *J* 9.3, 2.1), 4.27 (1H, dqd, *J* 9.7, 6.5, 3.3), 3.84 (1H, dd, *J* 12.8, 9.3), 3.36 (1H, dd, *J* 12.8, 3.3), 3.10 (1H, dqd, *J* 12.4, 6.2, 1.9), 1.53 (1H, m, CH_2), 1.37-1.23 (2H, m), 1.06 (3H, d, *J* 6.2), 1.03 (1H, m), 1.00 (1H, m), 0.96 (3H, d, *J* 6.4), 0.85 (1H, m); ^{13}C NMR (125 MHz, C_6D_6) δ 103.4, 80.0, 72.1, 71.9, 32.5, 31.2, 22.2, 21.8, 19.5; HRMS calcd for $C_9H_{17}O_4NNa$ ($M+Na^+$) 226.1050, found 226.1054.



(2*R*,6*S*)-2-methyl-6-((*R*)-1-nitropropan-2-yloxy)tetrahydro-2H-pyran **((β*R*)-22)** $[\alpha]_D^{26}$ -73.55° (*c* 0.39, $CHCl_3$); IR (neat) 2930, 1555, 1459, 1380, 1162, 1068, 1035 cm^{-1} ; ^1H NMR (500 MHz, C_6D_6) 4.35 (2H, m), 4.18 (1H, d, *J* 9.4), 3.65 (1H, t, *J* 7.3), 3.14 (1H, qd, *J* 12.0), 1.51 (1H, d, *J* 12.1 Hz), 1.36 (2H, m), 1.13 (3H, d, *J* 6.1 Hz), 1.07 (4H, m), 0.88 (3H, d, *J* 6.1 Hz); ^{13}C NMR (125 MHz, C_6D_6) δ 101.4, 80.7, 72.1, 70.8, 32.4, 31.2, 22.3, 21.6, 18.2; HRMS calcd for $C_9H_{17}O_4NNa$ ($M+Na^+$) 226.1050, found 226.1041.