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Intermolecular and Intramolecular Reactions of Resolved 2-Alkoxytetrahydrofuran-3-yl and 2-Alkoxytetrahydropyran-3-yl Radicals[1]

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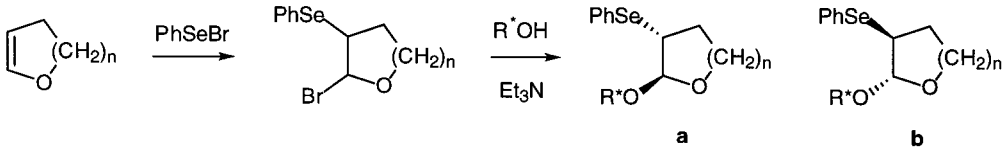
Abstract—Diastereomeric *trans*-2-alkoxy-3-phenylselenenyltetrahydrofuranyl acetals and *trans*-2-alkoxy-3-phenyl-selenenyltetrahydropyranyl acetals were prepared from dihydrofuran, dihydropyran, phenylselenenyl bromide, and the alcohols (*S*)-methyl lactate, (*S*)-methyl hexahydromandelate, and (*R*)-pantolactone. The diastereomers were chromatographically separated and were subjected to intermolecular alkylation via generation and trapping of free radicals. Observed diastereoselectivity was higher for 2-alkoxytetrahydrofuran-3-yl radicals than for 2-alkoxytetrahydropyran-3-yl radicals, and highest for acetals involving (*R*)-pantolactone. Alcohol exchanges at the anomeric carbon were highly stereocontrolled, and permitted introduction of alkenes for intramolecular trapping of free radical intermediates.

The biological significance of compounds that contain tetrahydrofuran (THF) and tetrahydropyran (THP) rings has encouraged the development of methods for the synthesis and functionalization of these heterocycles.[2] Methods that involve carbon-centered radicals are particularly compatible with the chemistry of these rings, can exhibit significant regioselectivity and diastereoselectivity, and have been widely employed.[3,4]

Table 1. Synthesis and separation of diastereomeric acetals **1**–**4**



Diastereomers	*n*	R*OH	Yields[a] (%)	α[b] (solvent)[c]
1a	1	(*S*)-methyl lactate	29	1.24 (20)
1b			35	
2a	1	(*S*)-methyl hexahydromandelate	28	1.29 (15)
2b			35	
3a	1	(*R*)-pantolactone	44	1.29 (20)
3b			26	
4a	2	(*R*)-pantolactone	31	1.20 (20)
4b			21	

[a] Isolated yields of the less polar (**a**) and more polar (**b**) diastereomers, respectively.
[b] The separation factor, α, is the ratio of the R_f values for the diastereomers on 0.25-mm silica gel 60 plates.
[c] Solvent is given as the percent of ethyl acetate in hexanes.

Keywords: selenoacetals; resolution; radicals and radical reactions; diastereoselection.
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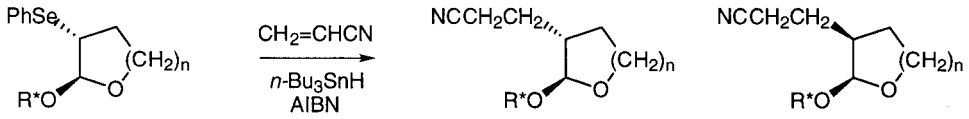


Scheme 1. Intermolecular radical trapping reactions of diastereomeric acetals **1**–**4**.

We developed a general chromatographic separation of furanoside and pyranoside acetals that incorporate enantiopure esters of α-hydroxycarboxylic acids as the alcohol component.[5] This diastereomer resolution compliments the chiron approach[2a] to THF and THP derivatives in that both enantiomers of a target can be prepared simultaneously. We are exploring the utility of this method,[6] and present herein a short survey of intermolecular and intramolecular reactions of resolved 2-alkoxytetrahydrofuran-3-yl and 2-alkoxytetrahydropyran-3-yl radicals.

Preparation of Radical Precursors for Intermolecular Reactions

Diastereomeric acetals **1**–**4** (Table 1) were prepared by reaction of dihydrofuran or dihydropyran with phenylselenenyl bromide in methylene chloride, followed by reaction of the intermediate bromide with an enantiopure alcohol and triethylamine. Separation of the diastereomer pairs was effected by column chromatography on silica gel eluted with ethyl acetate in hexanes. Yields were good and the separations facile (Table 1). Structures were assigned based on previous work in our laboratory.[5–7]

Intermolecular Radical Trapping Reactions

Acetals **1a**, **1b**, **2b**, **3a**, **3b**, **4a**, and **4b** were subjected to radical generation (*n*-Bu_3SnH, AIBN, benzene, reflux) and trapping using acrylonitrile as the radical trapping agent (Scheme 1 and Table 2). Isolated yields of the corresponding acrylonitrile adducts ranged from 60 to 82%. Diastereoselectivities were lower for THF acetals **1a**, **1b**, and **2b** that incorporate the (*S*)-methyl lactate and (*S*)-methyl hexahydromandelate auxiliaries than for acetals **3a** and **3b** that incorporate the (*R*)-pantolactone auxiliary.[8] The diastereoselectivities for THP acetals **4a** and **4b** that incorporate the (*R*)-pantolactone auxiliary were low.[9] In each case, the more polar product was predominant and could be isolated from the less polar product by column chromatography. Structures were initially assigned to the product diastereomers based on literature precedent that the *trans* products would predominate.[10] These assignments were supported by the chemical shifts for the proton at C2 and by the coupling constants between this proton and the proton at C3 (Table 3).[10–12] Radicals derived from selenoacetals **3a** and **3b** were also trapped using methyl acrylate. This produced **9a** and **11a** in 47 and 49% yields, respectively, as the only isolable monoalkylyated products.[13]

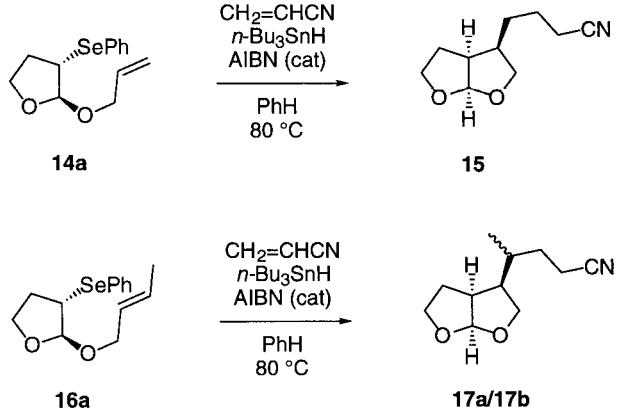
Intramolecular Radical Trapping Reactions

Treatment of acetal **1b** with a catalytic amount of *p*-toluenesulfonic acid in dichloromethane containing 10 equiv. of allyl alcohol gave, in 66% yield, a chromatographically separable 15:1 mixture of less and more polar diastereomers **14a** and **14b**.[14] Similarly, the use of *trans*-2-buten-1-ol gave a chromatographically separable 15:1 mixture of less and more polar diastereomers **16a** and **16b** in 94% yield. Assignment of the trans stereochemistry to the major products **14a** and **16a** is consistent with literature precedent[15] and participation by the 3-phenylselenenyl group.

Acetals **14a** and **16a** were subjected to radical generation (*n*-Bu_3SnH, AIBN, benzene, reflux) and trapping using acrylonitrile as the radical trapping agent (Scheme 2). Bicyclic nitrile **15** was obtained as a single diastereomer from **14a** in 45% yield, while a chromatographically inseparable 2:1 mixture of diastereomeric nitriles **17a** and **17b** was obtained in 78% yield from **16a**. Product structures were initially assigned based on literature precedent[16] and confirmed for **15** by NOE difference spectroscopy.[17]

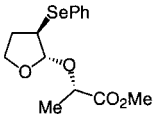
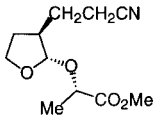
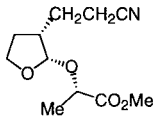
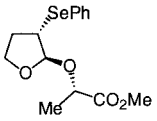
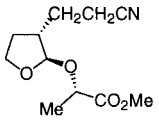
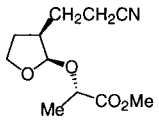
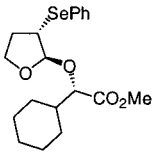
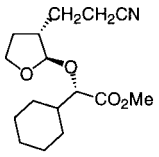
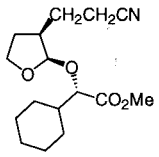
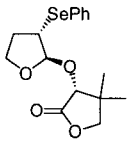
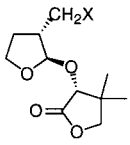
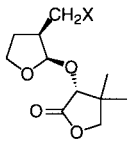
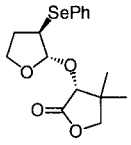
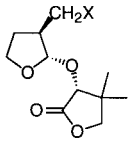
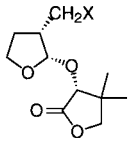
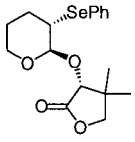
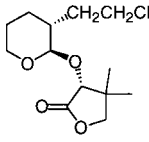
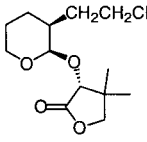
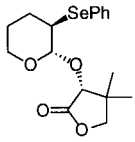
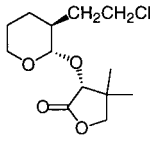
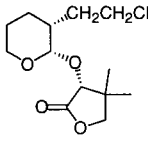
Discussion

In keeping with past observations on intermolecular trapping in cyclic systems,[3,10] *anti* attack relative to the substituent β to the radical center was generally favored. Diastereoselectivity is expected to depend on the steric bulk of the β substituent attached at the anomeric carbon. In fact, the most useful chiral auxiliary of the three alcohols examined was (*R*)-pantolactone. In the THF series, synthetically useful diastereoselectivities were obtained for intermolecular trapping of the radicals derived from **3a** and **3b**. However, diastereoselectivites were low in the THP series, even for the radicals derived from **4a** and **4b**.[9] These results were unexpected given that comparable diastereoselectivities were reported for trapping of 2-methoxytetrahydrofuran-3-yl and 2-methoxytetrahydropyran-3-yl radicals with acrylonitrile and methyl acrylate.[10]



Scheme 2. Intramolecular Radical Trapping Reactions of Acetals **14a** and **16a**.

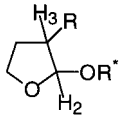
Table 2. Intermolecular radical trapping reactions of acetals **1**–**4**

Starting Material	Reaction Conditions[a]	Products	Yields,[b] %	Diastereomer Ratio	α^c (solvent)[d]
 **1a**	A	 **5a**  **5b**	**5a** 53 **5b** 15	3.5:1	1.71 (20)
 **1b**	A	 **6a**  **6b**	**6a** 57 **6b** 15	3.8:1	1.50 (20)
 **2b**	A	 **7a**  **7b**	**7a** 47 **7b** 13	3.6:1	1.33 (30)
 **3a**	A B	 **8-9a**  **8-9b**	**8a** **8b** X = CH_2CN 56 10 **9a** **9b** X = CO_2Me 47 0	5.6:1 >20:1	1.71 (20) —
 **3b**	A B	 **10-11a**  **10-11b**	**10a** **10b** X = CH_2CN 78 4 **11a** **11b** X = CO_2Me 49 0	20:1 >20:1	1.37 (40) —
 **4a**	A	 **12a**  **12b**	**12a** 43 **12b** 19	2.3:1	1.30 (35)
 **4b**	A	 **13a**  **13b**	**13a** 53 **13b** 18	2.9:1	1.36 (35)

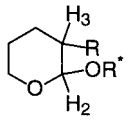
[a] Reaction conditions A, CH_2=CHCN, *n*-Bu_3SnH, AIBN, PhH, heat; B, CH_2=$CHCO_2Me$, *n*-Bu_3SnH, AIBN, PhH, heat.
[b] Isolated yields of the more polar (**a**) and less polar (**b**) diastereomers, respectively.
[c] The separation factor, α, is the ratio of the R_f values for the diastereomers on 0.25-mm silica gel 60 plates.
[d] Solvent is given as the percent of ethyl acetate in hexanes.

The synthetic utility of radical-mediated cyclization onto carbohydrate templates is well established.[18] A link between this strategy and the diastereomer resolution of simpler THF and THP acetals[5,6] was forged using **14a** and **16a**. These trans acetals, prepared from **1b** by acid-catalyzed alcohol exchange, were predominant over the *cis* diastereomers under the conditions employed.[14,19] Following radical generation, cyclization to the corresponding intermediate bicyclic radicals occurred with the expected regio- and stereochemistry. However, trapping of the bicyclic acetal radical derived from **16a** was not stereocontrolled, and led to production of diastereomers **17a** and **17b**.

Table 3. Selected ^{1}H NMR data for diastereomeric acetals **5–13**



5-11



12-13

Diastereomer	R	OR*	δ_{H2} (ppm)	$^3J_{H_2}$–H_3 (Hz)
5a	CH_2CH_2CN	(*S*)-methyl lactate	4.88	2.2
5b			5.00	4.5
6a	CH_2CH_2CN	(*S*)-methyl lactate	4.91	0.6
6b			4.99	4.3
7a	CH_2CH_2CN	(*S*)-methyl hexahydromandelate	4.81	<2
7b			4.94	4.3
8a	CH_2CH_2CN	(*R*)-pantolactone	5.30	2.3
8b			5.40	4.4
9a	$CH_2CH_2CO_2Me$	(*R*)-pantolactone	5.27	1.5
10a	CH_2CH_2CN	(*R*)-pantolactone	4.99	1.0
10b			5.10	4.1
11a	$CH_2CH_2CO_2Me$	(*R*)-pantolactone	4.94	<2
12a	CH_2CH_2CN	(*R*)-pantolactone	4.61	7.1
12b			5.20	2.8
13a	CH_2CH_2CN	(*R*)-pantolactone	4.43	4.8
13b			4.79	<2

Experimental

All reactions were performed in flame-dried glassware under argon. Hygroscopic liquids and solutions of reactive intermediates were transferred via syringe. Reaction product solutions were concentrated using a rotary evaporator at 30–40 mmHg. Dichloromethane and benzene were distilled from CaH_2. Diethyl ether and tetrahydrofuran were distilled from sodium/benzophenone ketyl. Analytical thin-layer chromatography was performed on Merck glass-backed pre-coated plates (0.25 mm, silica gel 60, F-254). Visualization of spots was effected by treatment of the plate with a 2.5% solution of *para*-anisaldehyde in ethanol containing 6% H_2SO_4 and 2% acetic acid followed by charring on a hot plate. Gravity-driven column chromatography was performed on Merck silica gel 60 (70–230 mesh). Optical rotations were measured at 589 nm. NMR spectra were recorded in $CDCl_3$ solution unless otherwise indicated. Proton and ^{13}C magnetic resonance spectra were recorded at 250.1 and 62.9 MHz, respectively, using tetramethylsilane (0 ppm) and the center line of the chloroform-*d* triplet (77.0 ppm) as internal standards. Elemental analyses were performed by Desert Analytics, Tucson, AZ.

(*R*)-Pantolactonyl 3-phenylselenenyl-3,4,5,6-tetrahydro-2*H*-pyran-2-yl ethers 4a and 4b. To a well stirred solution of Ph_2Se_2 (1.85 g, 5.94 mmol) in methylene chloride (15 mL) at 5°C was added Br_2 (306 μL, 950 mg, 5.94 mmol) dropwise. This solution was maintained at 5°C and added dropwise to a well stirred solution of dihydropyran (1.08 mL, 1.00 g, 11.9 mmol) in methylene chloride (15 mL) at −78°C. After 30 min a solution of triethylamine (1.82 mL, 1.32 g, 13.1 mmol) and (*R*)-(−)-pantolactone (1.54 g, 11.9 mmol) was added rapidly. The reaction mixture was allowed to attain room temperature and was stirred for 24 h. The reaction mixture was then diluted with methylene chloride (25 mL), washed with sat aq. $NaHCO_3$ (2×25 mL) and sat aq NaCl (25 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel 60 (275 g) eluted with 10% EtOAc/hexanes. The less polar diastereomer **4a** (1.36 g, 3.67 mmol, 31%) was obtained as colorless oil, $[\alpha]_D^{26}$=+99.4 (*c* 5.0, EtOAc); R_f 0.24 (20% EtOAc/hexanes); ^{1}H NMR δ 1.03 (3, s), 1.18 (3, s), 1.50–1.65 (1, m), 1.70–2.00 (2, m), 2.20–2.31 (1, m), 3.38–3.48 (1, m), 3.55–3.65 (1, m), 3.85–4.00 (3, m), 4.15 (1, s), 5.20 (1, d, *J*=4.4 Hz), 7.20–7.30 (3, m), 7.55–7.65 (2, m); ^{13}C NMR δ 19.2, 23.1, 23.7, 26.4, 39.9, 43.4, 62.7, 76.2, 77.4, 100.1, 127.2, 128.9, 129.5, 134.0, 174.8. The more polar diastereomer **4b** (0.914 g, 2.47 mmol, 21%) was obtained as colorless oil, $[\alpha]_D^{26}$=−50.2 (*c* 5.0, EtOAc); R_f 0.20 (20% EtOAc/hexanes); IR (neat) 3053, 2960, 1787, 1735, 1576, 1465, 1436, 1400, 1371, 1332, 1298, 1241, 1201, 1072, 1059 cm^{-1}; ^{1}H NMR δ 1.02 (3, s), 1.11 (3, s), 1.50–1.65 (1, m), 1.75–2.00 (2, m), 2.29–2.40 (1, m), 3.45–3.65 (2, m), 3.86 (1, d, *J*=8.9 Hz), 3.93 (1, d, *J*=8.9 Hz), 4.15–4.25 (1, m), 4.19 (1, s), 4.79 (1, d, *J*=3.7 Hz), 7.20–7.30 (3, m), 7.50–7.60 (2, m); ^{13}C NMR δ 19.4, 23.0, 23.4, 25.8, 41.0, 43.3, 62.4, 75.6, 79.0, 101.6, 127.5, 129.1, 134.0, 174.5. Anal. Calcd for $C_{17}H_{22}O_4Se$: C, 55.29; H, 6.00. Found: C, 55.32; H, 6.06.

(*S*)-Methyl lactyl 3-phenylselenenyl-2,3,4,5-tetrahydrofuran-2-yl ethers 1a and 1b. By a similar procedure, diastereomeric acetals **1a** and **1b** were obtained as pale yellow oils in 29 and 35% yields, respectively. For the less polar diastereomer **1a**: $[\alpha]_D^{25}$=−50.4 (*c* 5.0, EtOAc); R_f 0.36 (20% EtOAc/hexanes); ^{1}H NMR δ 1.37 (3, d, *J*=7.0 Hz), 1.85–2.00 (1, m), 2.45–2.60 (1, m), 3.64 (3, s), 3.80 (1, dd, *J*=7.7 and 3.5 Hz), 3.90–4.05 (2, m), 4.31 (1, q, *J*=7.0 Hz), 5.25 (1, s), 7.25–7.31 (3, m), 7.54–7.57 (2, m); ^{13}C NMR δ 18.8, 30.5, 44.3, 51.8, 66.9, 70.1, 107.4, 127.2, 129.0, 130.0, 133.2, 174.0. For the more polar diastereomer **1b**: $[\alpha]_D^{25}$=−15.7 (*c* 6.1, EtOAc); R_f 0.29 (20% EtOAc/hexanes); IR (neat) 2986, 1747, 1269 cm^{-1}; ^{1}H NMR δ 1.30 (3, d, *J*=6.9 Hz), 1.84–2.00 (1, m), 2.50–

2.68 (1, m), 3.70 (3, s), 3.75–3.84 (1, m), 3.94 (2, t, J=7.0 Hz), 4.05 (1, q, J=6.9 Hz), 5.20 (1, s), 7.25–7.28 (3, m), 7.51–7.55 (2, m); ^{13}C NMR δ 18.2, 30.9, 44.3, 51.7, 67.2, 71.9, 108.7, 127.4, 128.0, 129.0, 133.3, 175.0. Anal. Calcd for $C_{14}H_{18}O_4Se$: C, 51.07; H, 5.51. Found: C, 50.80; H, 5.56.

(*S*)-Methyl hexahydromandelyl 3-phenylselenenyl-2,3,4,5-tetrahydrofuran-2-yl ethers 2a and 2b. By a similar procedure, diastereomeric acetals **2a** and **2b** were obtained as pale yellow oils in 28% and 35% yields, respectively. For the less polar diastereomer **2a**: $[\alpha]_D^{27}=-57.5$ (c 2.79, EtOAc); R_f 0.44 (15% EtOAc/hexanes); ^{1}H NMR δ 1.00–1.30 (6, m), 1.50–1.80 (6, m), 1.88–2.00 (1, m), 2.46–2.64 (1, m), 3.63 (3, s), 3.80–4.05 (3, m), 5.15 (1, s), 7.26–7.29 (3, m), 7.53–7.55 (2, m); ^{13}C NMR δ 25.8, 25.9, 26.0, 27.8, 29.1, 30.5, 40.5, 44.4, 51.6, 66.9, 78.0, 106.7, 127.2, 129.1, 129.8, 133.2, 177.5. For the more polar diastereomer **2b**: $[\alpha]_D^{27}=-26.9$ (c 0.91, EtOAc); R_f 0.34 (15% EtOAc/hexanes); IR (neat) 3052, 2929, 2854, 1743, 1576, 1477, 1448, 1436, 1264 cm^{-1}; ^{1}H NMR δ 0.80–2.10 (13, m), 2.50–2.65 (1, m), 3.60 (1, d, J=6.9 Hz), 3.70 (3, s), 3.70–3.95 (3, m), 5.12 (1, s), 7.25–7.29 (3, m), 7.52–756 (2, m); ^{13}C NMR δ 25.6, 25.7, 26.0, 28.3, 28.5, 31.0, 40.5, 44.1, 51.5, 67.2, 81.4, 110.8, 127.4, 129.1, 129.6, 133.2, 173.0.

(*R*)-Pantolactonyl 3-phenylselenenyl-2,3,4,5-tetrahydrofuran-2-yl ethers 3a and 3b. By a similar procedure, diastereomeric acetals **3a** and **3b** were obtained in 44 and 26% yields, respectively. The less polar diastereomer **3a** was obtained as colorless crystals, mp 74–76°C (hexanes); $[\alpha]_D^{27}=+64.1$ (c 2.5, EtOAc); R_f 0.27 (20% EtOAc/hexanes); ^{1}H NMR δ 1.05 (3, s), 1.15 (3, s), 1.90–2.05 (1, m), 2.46–2.62 (1, m), 3.81–4.09 (6, m), 5.59 (1, s), 7.25–7.35 (3, m), 7.55–7.62 (2, m); ^{13}C NMR δ 19.3, 23.2, 30.4, 40.2, 44.3, 67.5, 75.5, 78.1, 109.2, 127.6, 129.2, 129.5, 133.5, 173.0. The more polar diastereomer **3b** was obtained as a colorless oil, $[\alpha]_D^{27}=+1.4$ (c 4.8, $CHCl_3$); R_f 0.21 (20% EtOAc/hexanes); IR (CH_2Cl_2) 3054, 2986, 1789, 1250 cm^{-1}; ^{1}H NMR δ 0.91 (3, s), 1.02 (3, s), 1.82–1.98 (1, m), 2.53–2.68 (1, m), 3.80–4.25 (6, m), 5.22 (1, s), 7.26–7.30 (3, m), 7.55–7.58 (2, m); ^{13}C NMR δ 19.3, 23.2, 30.4, 40.0, 44.3, 67.5, 75.5, 78.1, 109.2, 127.6, 129.2, 129.4, 133.5, 174.8. Anal. Calcd for $C_{16}H_{20}O_4Se$: C, 54.09; H, 5.67. Found: C, 54.04; H, 5.62.

(*S*)-Methyl lactyl 3-(2-cyano)ethyl-2,3,4,5-tetrahydrofuran-2-yl ethers 6a and 6b. Ether **1b** (200 mg, 0.60 mmol) was dissolved in dry benzene (10 mL) and acrylonitrile (278 μL, 224 mg, 4.24 mmol) and AIBN (30 mg, 0.18 mmol) were added. The reaction mixture was stirred and heated to 70–75°C and n-Bu_3SnH (484 μL, 520 mg, 1.80 mmol) in benzene (1.2 mL) was added via a syringe pump over 5.5 h. Volatiles were removed in vacuo and the residue was chromatographed on silica gel 60 (75 g) eluted with 20% EtOAc/hexanes to give products **6b** (20 mg, 0.09 mmol, 15%) and **6a** (77 mg, 0.34 mmol, 57%). For the less polar isomer **6b**: $[\alpha]_D^{27}=-31.9$ (c 0.85, EtOAc); R_f 0.15 (20% EtOAc/hexanes); ^{1}H NMR δ 1.31 (3, d, J=6.8 Hz), 1.70–2.25 (5, m), 2.30–2.40 (2, m), 3.67 (3, s), 3.70–3.95 (2, m), 4.01 (1, q, J=6.8 Hz), 4.99 (1, d, J=4.3 Hz). For the more polar isomer **6a**: $[\alpha]_D^{27}=-116.6$ (c 2.1, EtOAc); R_f 0.10 (20% EtOAc/hexanes); IR (neat) 3056, 2953, 2360, 2247, 1746 cm^{-1}; ^{1}H NMR δ 1.38 (3, d, J=6.9 Hz), 1.45–1.95 (3, m), 2.20–2.45 (4, m), 3.75 (3, s), 3.85–3.95 (2, m), 4.10 (1, q, J=6.9 Hz), 4.91 (1, d, J=0.6 Hz); ^{13}C NMR δ 15.6, 18.2, 27.9, 29.8, 44.7, 51.7, 66.8, 72.3, 107.7, 119.0, 174.0.

(*S*)-Methyl lactyl 3-(2-cyano)ethyl-2,3,4,5-tetrahydrofuran-2-yl ethers 5a and 5b. By a similar procedure, diastereomeric acetals **5a** and **5b** were obtained from **1a** in 53 and 15% yields, respectively. For the less polar isomer **5b**: $[\alpha]_D^{27}=-131.8$ (c 0.81, $CHCl_3$); R_f 0.12 (20% EtOAc/hexanes); ^{1}H NMR δ 1.37 (3, d, J=7.0 Hz), 1.60–2.33 (5, m), 2.60–2.65 (2, m), 3.73 (3, s), 3.84–4.02 (2, m), 4.35 (1, q, J=7.0 Hz), 5.00 (1, d, J=4.5 Hz). For the more polar isomer **5a**: $[\alpha]_D^{27}=+35.2$ (c 2.9, EtOAc); R_f 0.07 (20% EtOAc/hexanes); IR (neat) 3056, 2935, 2360, 2247, 1746, 1500, 1325, 1050 cm^{-1}; ^{1}H NMR δ 1.39 (3, d, J=7.0 Hz), 1.55–1.61 (1, m), 1.70–1.90 (2, m), 2.15–2.35 (2, m), 2.50 (2, t, J=7.5 Hz), 3.74 (3, s), 3.85–4.00 (2, m), 4.35 (1, q, J=7.0 Hz), 4.88 (1, d, J=2.2 Hz); ^{13}C NMR δ 15.6, 18.8, 28.2, 30.5, 44.9, 51.8, 66.8, 70.2, 106.5, 119.0, 173.0. Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 58.44; H, 7.38; N, 6.41.

(*S*)-Methyl hexahydromandelyl 3-(2-cyano)ethyl-2,3,4,5-tetrahydrofuran-2-yl ethers 7a and 7b. By a similar procedure, diastereomeric acetals **7a** and **7b** were obtained from **2b** in 47 and 13% yields, respectively. For the less polar isomer **7b**: $[\alpha]_D^{27}=+40.6$ (c 1.96, EtOAc); R_f 0.16 (30% EtOAc/hexanes); ^{1}H NMR δ 0.83–1.30 (8, m), 1.45–2.30 (8, m), 2.40–2.46 (2, m), 3.62 (1, d, J=7.2 Hz), 3.71 (3, s), 3.75–3.97 (2, m), 4.94 (1, d, J=4.3 Hz). For the more polar isomer **7a**: $[\alpha]_D^{27}=+33.9$ (c 0.38, EtOAc); R_f 0.12 (30% EtOAc/hexanes); IR (neat) 3053, 2983, 2929, 2854, 2306, 1732, 1266 cm^{-1}; ^{1}H NMR δ 0.80–1.25 (5, m), 1.45–1.92 (9, m), 2.20–2.43 (4, m), 3.63 (1, d, J=7.3 Hz), 3.71 (3, s), 3.84–3.91 (2, m), 4.81 (1, br s); ^{13}C NMR δ 15.8, 25.6, 25.7, 26.1, 28.0, 28.6, 28.7, 30.0, 40.5, 44.8, 51.5, 66.9, 82.0, 109.3, 119.2, 173.3. Anal. Calcd for $C_{16}H_{25}NO_4$: C, 65.06; H, 8.53; N, 4.74. Found: C, 65.36; H, 8.54; N, 5.00.

(*R*)-Pantolactonyl 3-(2-cyano)ethyl-2,3,4,5-tetrahydrofuran-2-yl ethers 8a and 8b. By a similar procedure, diastereomeric acetals **8a** and **8b** were obtained from **3a** in 56 and 10% yields, respectively. For the less polar isomer **8b**: $[\alpha]_D^{26}=+138.9$ (c 0.42, EtOAc); R_f 0.20 (40% EtOAc/hexanes); ^{1}H NMR δ 1.04 (3, s), 1.17 (3, s), 1.75–2.14 (4, m), 2.30–2.40 (1, m), 2.55–2.62 (2, m), 3.93–4.04 (4, m), 4.12 (1, s), 5.40 (1, d, J=4.4 Hz). For the more polar isomer **8a**: $[\alpha]_D^{26}=+119.2$ (c 1.46, EtOAc); R_f 0.18 (40% EtOAc/hexanes); IR (neat) 3057, 2963, 2245, 1787, 1734, 1464 cm^{-1}; ^{1}H NMR δ 1.06 (3, s), 1.17 (3, s), 1.55–1.95 (3, m), 2.20–2.28 (1, m), 2.35–2.45 (1, m), 2.52 (2, t, J=7.3 Hz), 3.88–3.98 (4, m), 4.11 (1, s), 5.30 (1, d, J=2.3 Hz); ^{13}C NMR δ 15.7, 19.4, 22.8, 28.1, 30.5, 39.9, 44.7, 67.0, 76.3, 77.9, 106.8, 119.2, 174.8. Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.56; H, 7.40; N, 5.56.

(*R*)-Pantolactonyl 3-(3-methyl propanoyl)-2,3,4,5-tetrahydrofuran-2-yl ether 9a. By a similar procedure, acetal **9a** was obtained from **3a** in 47% yield; $[\alpha]_D^{27}=+151.8$ (c

2.7, EtOAc); R_f 0.19 (30% EtOAc/hexanes); IR (neat) 3056, 2961, 1787, 1733, 1436, 1371, 1266 cm^{-1}; ^1H NMR δ 1.08 (3, s), 1.22 (3, s), 1.45–1.85 (3, m), 2.19–2.40 (4, m), 3.69 (3, s), 3.85–4.00 (4, m), 4.09 (1, s), 5.27 (1, d, J=1.5 Hz); ^{13}C NMR δ 19.4, 23.4, 27.4, 29.7, 32.3, 40.2, 44.9, 51.6, 67.1, 75.5, 78.1, 108.3, 173.5, 174.8. Anal. Calcd for $C_{14}H_{22}O_6$: C, 58.73; H, 7.74. Found: C, 58.71; H, 7.87.

(*R*)-Pantolactonyl 3-(2-cyano)ethyl-2,3,4,5-tetrahydrofuran-2-yl ethers 10a and 10b. By a similar procedure, diastereomeric acetals **10a** and **10b** were obtained from **3b** in 78 and 4% yields, respectively. For the more polar isomer **10a**: $[\alpha]_D^{27}=-82.8$ (c 2.8, EtOAc); R_f 0.16 (40% EtOAc/hexanes); ^1H NMR δ 1.09 (3, s), 1.22 (3, s), 1.48–1.95 (3, m), 2.25–2.45 (4, m), 3.88–4.10 (4, m), 4.14 (1, s), 4.99 (1, d, J=1.0 Hz); ^{13}C NMR δ 15.7, 19.4, 23.4, 27.9, 29.4, 29.6, 40.2, 44.7, 67.0, 75.7, 78.2, 107.7, 119.0, 174.7. The less polar isomer **10b**, R_f 0.22 (40% EtOAc/hexanes), was contaminated with >20% of **10a** and was not characterized.

(*R*)-Pantolactonyl 3-(3-methyl propanoyl)-2,3,4,5-tetrahydrofuran-2-yl ether 11a. By a similar procedure, acetal **11a** was obtained from **3b** in 49% yield; $[\alpha]_D^{27}=-77.1$ (c 2.65, EtOAc); R_f 0.11 (20% EtOAc/hexanes); ^1H NMR δ 1.08 (3, s), 1.22 (3, s), 1.55–1.85 (3, m), 2.25–2.35 (2, m), 2.35–2.41 (2, m), 3.69 (3, s), 3.70–4.10 (3, m), 4.10–4.25 (2, m), 4.94 (1, br s); ^{13}C NMR δ 19.4, 23.4, 27.4, 29.7, 32.3, 40.2, 44.9, 51.6, 67.1, 75.5, 78.1, 108.3, 173.3.

(*R*)-Pantolactonyl 3-(2-cyano)ethyl-3,4,5,6-tetrahydropyran-2*H*-2-yl ethers 12a and 12b. By a similar procedure, diastereomeric acetals **12a** and **12b** were obtained from **4a** in 43 and 19% yields, respectively. For the less polar isomer **12b**: $[\alpha]_D^{27}=+225$ (c 0.5, EtOAc); R_f 0.17 (35% EtOAc/hexanes); ^1H NMR δ 1.09 (3, s), 1.20 (3, s), 1.45–2.00 (7, m), 2.45–2.65 (2, m), 3.53–3.78 (2, m), 3.90 (1, d, J=8.9 Hz), 3.96 (1, d, J=8.9 Hz), 4.15 (1, s), 5.20 (1, d, J=2.8 Hz); ^{13}C NMR δ 14.1, 19.5, 23.2, 23.9, 25.1, 27.4, 38.2, 40.3, 60.0, 76.0, 76.7, 96.3, 120.2, 175.4. For the more polar isomer **12a**: $[\alpha]_D^{27}=+272$ (c 1.3, EtOAc); R_f 0.13 (35% EtOAc/hexanes); IR (CH_2Cl_2) 3056, 2245, 1788, 1733 cm^{-1}; ^1H NMR δ 1.11 (3, s), 1.21 (3, s), 1.20–1.40 (1, m), 1.50–1.75 (4, m), 1.85–2.05 (2, m), 2.39–2.68 (2, m), 3.38–3.52 (1, m), 3.90–4.05 (1, m), 3.94 (1, d, J=8.9 Hz), 4.01 (1, d, J=8.9 Hz), 4.22 (1, s), 4.61 (1, d, J=7.1 Hz); ^{13}C NMR δ 15.4, 19.5, 22.6, 24.4, 27.4, 27.6, 38.9, 40.0, 65.2, 76.2, 78.1, 103.4, 119.9, 175.4. Anal. Calcd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24. Found: C, 62.80; H, 8.03; N, 5.16.

(*R*)-Pantolactonyl 3-(2-cyano)ethyl-3,4,5,6-tetrahydropyran-2*H*-2-yl ethers 13a and 13b. By a similar procedure, diastereomeric acetals **13a** and **13b** were obtained from **4b** in 53 and 18% yields, respectively. For the less polar isomer **13b**: $[\alpha]_D^{27}=-71.2$ (c 0.5, EtOAc); R_f 0.15 (35% EtOAc/hexanes); ^1H NMR δ 1.11 (3, s), 1.23 (3, s), 1.20–2.50 (8, m), 2.60–2.70 (1, m), 3.55–3.57 (1, m), 3.92 (1, d, J=8.7 Hz), 3.98 (1, d, J=8.7 Hz), 4.18–4.32 (1, m), 4.25 (1, s), 4.79 (1, br s); ^{13}C NMR δ 14.7, 19.7, 22.6, 23.7, 24.8, 27.4, 38.8, 40.6, 60.2, 75.5, 78.1, 99.7, 119.5. For the more polar isomer **13a**: $[\alpha]_D^{27}=-68.0$ (c 2.9, EtOAc); R_f 0.11 (35% EtOAc/hexanes); ^1H NMR δ 1.12 (3, s), 1.22 (3, s), 1.20–1.85 (6, m), 1.95–2.10 (1, m), 2.44 (2, t, J=7.4 Hz), 3.45–3.55 (1, m), 3.92 (1, d, J=8.9 Hz), 3.99 (1, d, J=8.9 Hz), 4.05–4.25 (1, m), 4.25 (1, s), 4.43 (1, d, J=4.8 Hz); ^{13}C NMR δ 14.9, 19.4, 22.3, 23.4, 24.3, 26.2, 38.0, 40.4, 63.4, 75.5, 78.6, 102.8, 119.3, 174.3.

Allyl 3-phenylselenenyl-2,3,4,5-tetrahydrofuran-2-yl ethers 14a and 14b. To a well stirred solution of **1b** (1.00 g, 3.03 mmol) and allyl alcohol (2.06 mL, 1.75 g, 30.3 mmol) in CH_2Cl_2 (10 mL) at room temperature was added a catalytic amount of TsOH (58 mg, 0.30 mmol). After 20 min the reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with sat aq $NaHCO_3$ (2×20 mL) and water (20 mL), dried over anhydrous $MgSO_4$, and filtered. Concentration in vacuo gave a mixture of isomers. Chromatography on silica gel 60 (100 g) eluted with 5% EtOAc/hexanes afforded 528 mg (1.86 mmol, 62%) of the trans isomer **14a** as a colorless oil, R_f 0.49 (20% EtOAc/hexanes); $[\alpha]_D^{26}=+38.3$ (c 6.5, EtOAc); IR (neat) 3070, 2977, 2891, 1644, 1578, 1448, 1435, 1358, 1104, 1021 cm^{-1}; ^1H NMR δ 1.85–2.00 (1, m), 2.44–2.60 (1, m), 3.70–3.75 (1, m), 3.85–4.02 (3, m), 4.06–4.16 (1, m), 5.15–5.25 (3, m), 5.75–5.90 (1, m), 7.25–7.30 (3, m), 7.52–7.56 (2, m); ^{13}C NMR δ 30.9, 44.5, 66.8, 68.0, 108.0, 117.0, 127.4, 129.0, 129.5, 133.5, 134.2. Also obtained were 39 mg (0.14 mmol, 4%) of **14b**, R_f 0.45 (20% EtOAc/hexanes); $[\alpha]_D^{26}=-41.5$ (c 2.6, EtOAc); ^1H NMR δ 2.15–2.40 (2, m), 3.43–3.55 (1, m), 3.75–3.85 (1, m), 3.89–4.05 (2, m), 4.08–4.20 (1, m), 5.05–5.15 (2, m), 5.26 (1, dm, J=18 Hz), 5.75–5.95 (1, m), 7.15–7.25 (3, m), 7.45–7.52 (2, m); ^{13}C NMR δ 37.7, 44.3, 66.8, 68.2, 102.8, 116.8, 127.2, 129.0, 130.4, 133.4, 134.3. Anal. Calcd for $C_{13}H_{16}O_2Se$: C, 55.13; H, 5.69. Found: C, 55.38; H, 5.74.

Crotyl 3-phenylselenenyl-2,3,4,5-tetrahydrofuran-2-yl ethers 16a and 16b. By a similar procedure, acetals **16a** and **16b** were obtained from *trans*-crotyl alcohol and **1b** in 88 and 6% yields, respectively. For the less polar isomer **16a**: $[\alpha]_D^{26}=-33.3$ (c 6.15, $CHCl_3$); R_f 0.37 (10% EtOAc/hexanes); IR (neat) 2936, 2887, 1735, 1671, 1577, 1476, 1436 cm^{-1}; ^1H NMR δ 1.67 (3, m), 1.84–1.98 (1, m), 2.43–2.60 (1, m), 3.69–3.74 (1, m), 3.84–3.87 (1, m), 3.95–4.18 (3, m), 5.15 (1, s), 5.50–5.51 (1, m), 5.62–5.65 (1, m), 7.25–7.29 (3, m), 7.52–7.55 (2, m); ^{13}C NMR δ 17.8, 31.0, 44.5, 66.7, 67.9, 107.7, 126.9, 127.4, 129.1, 129.5, 129.9, 133.5. The more polar isomer **16b**, R_f 0.31 (10% EtOAc/hexanes), was contaminated with >20% of **16a** and was not characterized. Anal. Calcd for $C_{14}H_{18}O_2Se$: C, 56.57; H, 6.10. Found: C, 56.73; H, 6.13.

4-(3-Cyano)propyl-2,8-dioxabicyclo[3.3.0]octane 15. Selenoacetal **14a** (200 mg, 0.70 mmol) was dissolved in dry benzene (10 mL) and acrylonitrile (0.292 mL, 235 mg, 4.43 mmol) and AIBN (30 mg, 0.21 mmol) were added. The reaction mixture was stirred and heated to 70–75°C and *n*-Bu_3SnH (508 μL, 550 mg, 1.89 mmol) in benzene (1.2 mL) was added via syringe pump over 4.5 h. Volatiles were then removed in vacuo and the residue was chromatographed on silica gel 60 (90 g) eluted with 40% EtOAc/hexanes to afford 67 mg (0.30 mmol, 45%) of **15** as a colorless oil, R_f 0.05 (30% ether/hexanes); $[\alpha]_D^{25}=-11.9$ (c 3.39, EtOAc); IR (neat) 3058, 2869, 2245, 1596, 1458, 1423, 1404,

1376 cm^{-1}; ^1H NMR δ 1.35–1.70 (4, m), 1.70–1.85 (2, m), 2.15–2.40 (3, m), 2.65–2.80 (1, m), 3.30–3.41 (1, m), 3.75–3.90 (3, m), 5.73 (1, d, J=4.9 Hz); ^{13}C NMR δ 17.2, 24.2, 24.6, 26.5, 41.4, 45.0, 68.9, 71.9, 109.5, 119.1. Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.46; H, 8.44; N, 7.69.

4-(3-Cyano-1-methyl)propyl-2,8-dioxabicyclo[3.3.0]octanes 17a and 17b. By a similar procedure, an inseparable 2:1 mixture of nitriles **17a** and **17b** was obtained from **16a** and acrylonitrile in 78% yield. R_f 0.07 (30% ether/hexanes); IR (neat) 2955, 2243, 1730, 1637, 1451, 1425, 1391 cm^{-1}; ^1H NMR δ 0.96–1.10 (3, m), 1.25–2.15 (6, m), 2.30–2.50 (2, m), 2.80–2.90 (1, m), 3.50–3.61 (1, m), 3.82–4.13 (3, m), 5.69–5.74 (1, m); ^{13}C NMR δ 13.4, 14.4, 14.5, 17.2, 17.3, 24.4, 24.5, 30.7, 31.2, 31.5, 44.4, 44.8, 48.3, 48.6, 68.6, 68.7, 70.7, 71.2, 109.3, 109.6, 119.2, 119.3. Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.48; H, 8.71; N, 7.38.

Acknowledgements

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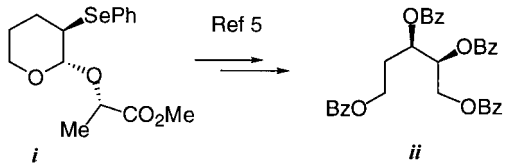
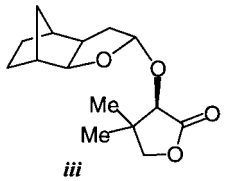
7. We have assumed that all less polar THF and THP diastereomers derived from a particular α-hydroxyester enantiomer have related configurations at the acetal carbon, and all more polar diastereomers have the opposite configuration. Thus far this has proved to be the case. The less polar diastereomer *i* was converted to known tetrabenzoate *ii*; see Ref. 5. The structure of more polar diastereomer *iii* was established by X-ray crystallography (J. Fryling, unpublished results).



i *ii*



iii

8. Use of (*S*)-methyl mandelate as the chiral auxiliary gave products derived from intramolecular abstraction of the benzylic hydrogen.

9. Diastereomer ratios for product THP acetals having (*S*)-methyl lactate or (*S*)-methyl hexahydromandelate as the chiral auxiliary were approximately 1:1; see Ref. 1.

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12. The proton at the anomeric carbon of the cis isomer should be upfield from this proton of the trans isomer and should exhibit a larger coupling with the adjacent proton; see: Descotes, G.; Sinou, D.; Martin, J.-C. *Bull. Soc. Chim. Fr.* **1970**, 3730–3737.

13. Greater diastereoselectivity for the methyl acrylate trap is consistent with the literature; see Ref. 10.

14. The predominance of **14a** over **14b** reflects kinetic control of this exchange reaction at short reaction times. Use of long reaction times resulted in equilibration to approximately a 1:1 mixture of **14a** and **14b**.

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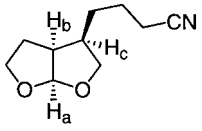
17. For compound **15**, irradiation of proton H_a increased the intensities of protons H_b and H_c by 3.3 and 1.2%, respectively. Irradiation of H_b increased the intensities of protons H_a and H_c by 3.7 and 2.8%, respectively.



15

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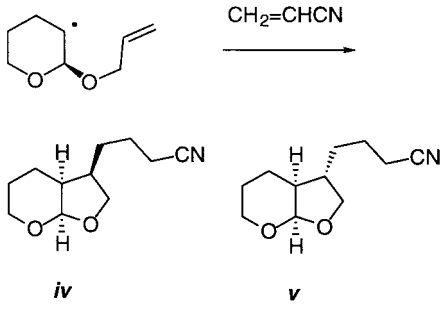
19. Treatment of acetal **6a** with TsOH in CH_2Cl_2 containing 10 equiv. of allyl alcohol gave, in 88% yield, a chromatographically inseparable 10:1 mixture of the corresponding diastereomeric allyl pyranosides. Radical generation, cyclization, and trapping with acrylonitrile afforded a 5:1 mixture of acetals *iv* and *v* (see Ref. 1).



iv ***v***