Hydroxylated α,β-Unsaturated Nitriles: Stereoselective Synthesis

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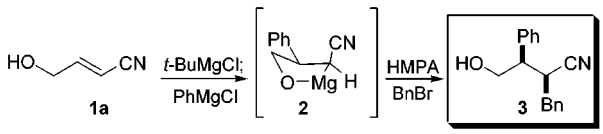
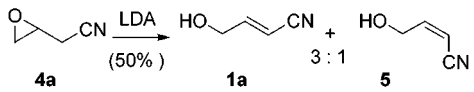
α,β-Unsaturated nitriles are versatile synthetic intermediates[1] that are readily transformed into an array of carbocycles[2] and heterocycles.[3] α,β-Unsaturated nitriles are particularly valuable as precursors to substituted nitriles by conjugate additions[4] and have featured as intermediates in several natural product syntheses.[5] Usually the α,β-unsaturated nitrile acts as a key precursor of an unsaturated carbonyl compound although the increasing isolation of bioactive nitrile-containing natural products[6] has recently reversed this trend.

α,β-Unsaturated nitriles can be synthesized from a variety of precursors[7] although fewer methods exist for accessing hydroxylated unsaturated nitriles. γ-Hydroxy unsaturated nitriles have been synthesized by cyanide or acetonitrile additions to vinyl iodides,[8] aldehydes,[9] ketones,[10] or chloroketones[11] and in some instances from nitrile precursors.[12] In contrast to these γ-hydroxy unsaturated nitriles syntheses, there is no one method for synthesizing unsaturated nitriles with hydroxylation at carbons successively removed from the unsaturated nitrile moiety.[13] Gram quantities of a range of hydroxylated unsaturated nitriles were required from readily available precursors, for expanding a key chelation-controlled conjugate addition−alkylation reaction (Scheme 1).[14]

Scheme 1



Numerous β,γ-unsaturated nitriles are commercially available suggesting an expedient synthesis of hydroxy unsaturated nitriles by sequential epoxidation and base-induced ring opening. The strategy is based on the pioneering ring opening of **4a** (eq 1)[15] and a related ring opening of epoxy nitriles generated in situ from the corresponding chloroketones.[11] The intention was to synthesize γ-hydroxynitriles from commercially available β,γ-unsaturated nitriles, complementing the substitution available via chloroketones, and to generalize the concept to the ring opening of tetrahydrofuranyl- and tetrahydropyranyl- acetonitriles.



Optimizing the synthesis of **1a** provided critical insight for preparing an array of hydroxylated unsaturated nitriles. Nitrile **1a** is highly water soluble and prone to both *E*:*Z* isomerization and polymerization. Ring opening of the epoxide is extremely facile, producing exclusively the *E*-nitrile in less than 5 min at −78 °C while prolonged exposure of **1a** to the reaction conditions causes considerable polymerization. Prompt addition of acetic acid (4 equiv) circumvents polymerization and allows a non-aqueous workup of water-soluble **1a**. However, the excess acetic acid must be removed prior to concentrating the crude product since extensive *E*:*Z* isomerization otherwise occurs. The most effective workup is to dilute the reaction mixture with EtOAc immediately after adding acetic acid, followed by a small volume of saturated, aqueous NaCl. Filtration of the resulting precipitate through silica gel, removal of the solvent, and chromatography provides gram-quantities of **1a** as a single stereoisomer.

The optimized ring-opening efficiently provides an array of hydroxylated α,β-unsaturated nitriles from the corresponding nitriles (Table 1). The nitrile precursors were synthesized in high yield by epoxidation of commercially available nitriles with *m*-CPBA, while the

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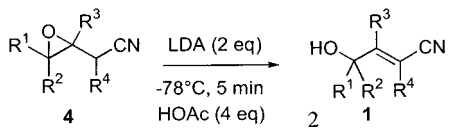
Table 1. Synthesis of Hydroxylated α,β-Unsaturated Nitriles



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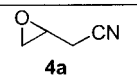
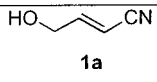
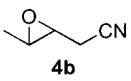
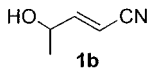
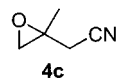
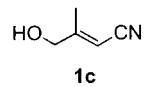
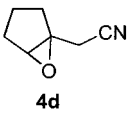
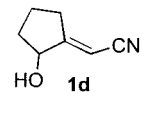
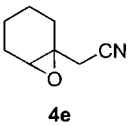
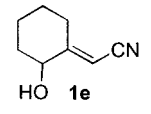
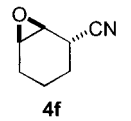
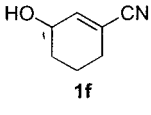
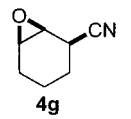
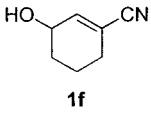
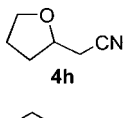
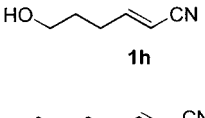
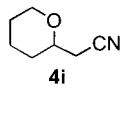
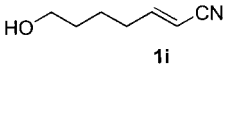
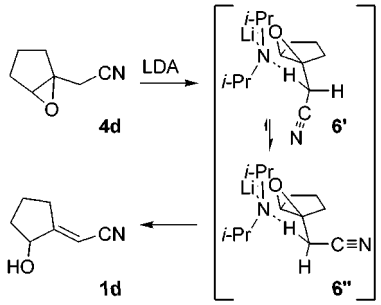
Entry	Nitrile	Unsaturated Nitrile	Yield
1	 **4a**	 **1a**	83
2	 **4b**	 **1b**	79
3	 **4c**	 **1c**	73
4	 **4d**	 **1d**	60
5	 **4e**	 **1e**	94
6	 **4f**	 **1f**	90
7	 **4g**	 **1f**	88
8	 **4h**	 **1h**	67
9	 **4i**	 **1i**	76

tetrahydrofuranyl and tetrahydropyranyl nitriles **4h**[16] and **4i** were synthesized from the corresponding alcohols by conversion to the tosylate and displacement with NaCN. The presence of molecular sieves was found to be particularly beneficial for the large-scale cyanide displacement,[17] possibly through cyanide absorption,[18] providing a very reliable synthesis of **4h** and **4i**. Ring opening of substituted epoxides is equally efficient for synthesizing di- and trisubstituted unsaturated nitriles (Table 1, entries 1−2 and 8−9, and 3−7, respectively) from both acyclic and cyclic nitriles (Table 1, entries 1−3 and 4−9, respectively). Efficient opening of the furan **4h** and the pyran **4i** (Table 1, entries 8−9) demonstrates that

Scheme 2



formation of the unsaturated nitrile is favored even when the ring-opening is not facilitated by the relief of ring strain.

Particularly significant is the exclusive formation of *E*-unsaturated nitriles. The stereoselectivity is readily assigned from diagnostic coupling and chemical shift signatures[19] while the stereochemical assignment for **1d** was secured through an X-ray analysis[20] of the corresponding *p*-nitrobenzoate. Mechanistically the *E*-stereoselectivity results from complexation between the lithium amide base and the epoxide oxygen that triggers a *syn*-elimination from a cyclic, six-membered transition state (Scheme 2).[21] The exclusive formation of **1d** likely reflects a preferential *syn*-elimination from transition state **6″** where the nitrile π-electrons are aligned for delocalization into the developing π-bond. Comparative ring-opening of **4d** with LiHMDS generates a 1:1 ratio of cis:trans isomers, confirming that chelation, and not dipole interactions, control the stereoselectivity. The influence of chelation is further evident in the *rapid* ring opening of **4f** (<5 min at −78 °C, Table 1, entry 6) compared with the slower ring opening of **4g** (30 min at −78 °C, Table 1, entry 7) where intramolecular chelation is geometrically precluded.[22]

Performing the ring-opening with a lithium amide base at low temperatures is critical for the success of the reaction. The lithium alkoxide intermediates are sufficiently covalent to suppress inter- and intramolecular additions to the unsaturated nitrile moiety that would otherwise trigger polymerization. Intermediates **7h** and **7i** are particularly prone to cyclize,[23] generating a relatively free anion (**8**) that initiates polymerization (Scheme 3). Performing the ring opening at high dilution circumvents polymerization and results in the rapid formation of unsaturated nitriles **1h** and **1i** (5 min at −78 °C) with hydroxylation 3- and 4-carbons removed from the double bond.

Hydroxy α,β-unsaturated nitriles are readily synthesized by the chelation-controlled ring opening of epoxy, tetrahydrofuranyl, and tetrahydropyranyl acetonitriles. The precursor acetonitriles are readily synthesized by epoxidation of the corresponding β,γ-unsaturated nitriles or by cyanide displacement of tetrahydrofuran- or tetrahydropyranmethanol. The ring-opening is highly ste-

(16) **4h** has been synthesized directly from the corresponding alcohol although we obtained only trace quantities of the desired nitriles using this procedure: Davis, R.; Untch, K. G. *J. Org. Chem.* **1981**, *46*, 2985.

(17) Shimizu, T.; Ohzeki, T.; Hiramoto, K.; Hori, N.; Nakata, T. *Synthesis* **1999**, 1373.

(18) Clark, J. H.; Duke, C. V. A. *J. Org. Chem.* **1985**, *50*, 1330.

(19) Ronayne, J.; Williams, D. H. *J. Chem. Soc. (C)* **1967**, 2642.

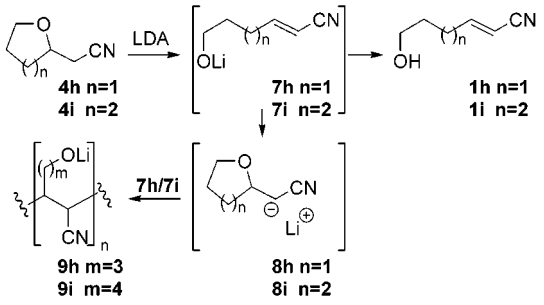
(20) The authors have deposited atomic coordinates with the Cambridge Crystallographic Data Center. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, U.K.

(21) Crandall, J. K.; Apparu, M. *Org. React.* **1983**, *29*, 345.

(22) The slower ring-opening rate for **4g** with LDA, and the lack of stereocontrol exhibited with LiHMDS and **4d**, suggest that these reactions proceed through an E_{1cB}-type transition state.

(23) Passarotti, C. M.; Valenti, M.; Ceriani, R.; Grianti, M. *Boll. Chim. Farm.* **1993**, *132*, 150.

Scheme 3



reoselective providing an efficient two-step synthesis of *trans*-α,*β*-unsaturated nitriles with hydroxylation on carbons successively removed from the double bond.

Experimental Section[24]

General Epoxidation Procedure. Solid *m*-CPBA (1.5 equiv) was added to a room temperature, CH_2Cl_2 solution (0.1−0.5 M) of the 3-alkenenitrile. The resultant solution was stirred overnight, and then saturated, aqueous $NaHSO_3$ was added to reduce the excess *m*-CPBA. The organic phase was separated, washed with saturated aqueous $NaHCO_3$ (3 × 50 mL/mmol alkenenitrile), and then dried over anhydrous Na_2SO_4 or $MgSO_4$. The dry solution was concentrated under reduced pressure to afford analytically pure epoxynitrile.

(±)-2-Oxiran-2-ylethanenitrile (4a). The general procedure was employed with 3-butenenitrile (5.0 g), adding 1/8 of the *m*-CPBA each day for a total of 8 days to provide 4.78 g (77%) of **4a** as an oil: IR (film) 2248 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 21.1, 46.1, 46.6, 115.4; MS *m*/*e* 84 (M + H). The ^1H NMR was identical to that previously reported.[15b]

(±)-2-(3-Methyloxiran-2-yl)ethanenitrile (4b). The general procedure was employed with 3-pentenenitrile (5.0 g) to provide 5.3 g (89%) of **4b**: IR (film) 2252 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (d, J = 5.2 Hz, 3H), 2.70 (t, J = 4 Hz, 2H), 2.93 (dt, J = 4.6, 2 Hz, 1H), 3.01 (dq, J = 5.2, 2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 16.7, 20.6, 53.1, 54.0, 115.9; ^{13}C NMR ($CDCl_3$) δ 16.7, 20.6, 53.1, 54.0, 115.7; MS *m*/*e* 98 (M + H).

(±)-2-(2-Methyloxiran-2-yl)ethanenitrile (4c). The general procedure was employed with 3-methyl 3-butenenitrile[25] (1.05 g) to provide 0.77 g (61%) of **4c**: IR (film) 2252 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48 (s, 3H), 2.65−2.67 (m, 2H), 2.78 (ABq, $\Delta\nu$ = 37 Hz, J = 4.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 20.5, 25.8, 52.8, 52.9, 115.9; MS *m*/*e* 98 (M + H).

(±)-2-(6-Oxabicyclo[3.1.0]hexyl)ethanenitrile (4d). The general procedure was employed with 1-cyclopenteneacetonitrile (2.00 g) to provide 1.88 g (82%) of **4d**:[26] IR (film) 2251 cm^{-1}; ^1H NMR (CS_2) δ 1.67−2.03 (m, 4H), 2.14−2.30 (m, 2H), 3.08 (ABq, $\Delta\nu$ = 22 Hz, J = 17 Hz, 2H), 3.64 (s, 1H); ^{13}C NMR (CS_2) δ 21.5, 22.2, 28.8, 30.6, 63.2, 63.3, 116.6.

(±)-2-(7-Oxabicyclo[4.1.0]heptyl)ethanenitrile (4e). The general procedure was employed with 1-cyclohexeneacetonitrile (1.21 g) to provide 1.28 g (93%) of **4e**:[27] IR (film) 2249 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17−1.55 (m, 4H), 1.79−2.06 (m, 4H), 2.65 (ABq, $\Delta\nu$ = 24.8 Hz, J = 17.1 Hz, 2H), 3.20 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 19.1, 19.6, 24.1, 26.6, 27.7, 55.8, 58.0, 116.1; MS *m*/*e* 138 (M + H).

(±)-(6*S*,1*R*,2*R*)-7-Oxabicyclo[4.1.0]heptane-2-carbonitrile (4f) and **(±)-(2*S*,6*S*,1*R*)-7-Oxabicyclo[4.1.0]heptane-2-carbonitrile (4g).** The general procedure was employed with cyclohex-2-enecarbonitrile[28] (212 mg), followed by radial chromatography (1:4 EtOAc:hexanes), to provide 104 mg of **4f** and 54 mg of **4g** (65% total) that were spectrally identical to material previously synthesized.[29]

(±)-2-Oxolan-2-ylethanenitrile (4h). An absolute ethanol solution of the tosylate[30] (3.33 g), KCN (2.0 g), and molecular seives (2 g) was vigorously refluxed for 3 days. The resulting mixture was filtered through silical gel and carefully concentrated in a rotorary evaporator, maintaining the water bath at 30 °C to prevent decomposition. Radial chromatography (CH_2Cl_2) of the crude nitrile afforded 0.93 g (64%) of **4h** that was spectrally identical to material previously synthesized.[30]

(±)-2-Perhydro-2*H*-pyran-2-ylethanenitrile (4i). Standard treatment[31] of tetrahydropyran-2-methanol (1.57 g) with *p*-TsCl (3.87 g) and NaOH (1.08 g) provided 3.57 g (98%) of the desired tosylate as a solid: ^1H NMR ($CDCl_3$) δ 1.18−1.84 (m, 6H), 2.43 (s, 3H), 3.30−59 (m, 2H), 3.89−4.00 (m, 1H), 3.93 (d, J = 5.0 Hz, 2H), 7.32 (d, J = 8.2 Hz, 2H), 7.78 (d, J = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.5, 22.6, 25.4, 27.5, 68.2, 72.5, 74.8, 127.9, 129.7, 133.0, 144.7. An absolute ethanol solution of the tosylate (1.9 g) KCN (1.8 g), and molecular seives (0.5 g) was vigorously refluxed for 3 days. The resulting mixture was filtered through silical gel, and carefully concentrated in a rotorary evaporator, maintaining the water bath at 30 °C to prevent decomposition. Radial chromatography (CH_2Cl_2) of the crude nitrile provided 0.618 g (70%) of **4i** as an oil: IR (film) 2238 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41−1.89 (m, 6H), 2.49 (d, J = 6.0 Hz, 2H), 3.45 (dt, J = 11, 3 Hz, 1H), 3.50−3.60 (m, 1H), 3.97−4.01 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 22.8, 24.9, 25.2, 31.0, 68.7, 72.8, 117.3.

General Ring-Opening Procedure. A THF solution of the epoxynitrile was added, by syringe, to a cold (−78 °C), THF solution (0.5−1 M) of LDA [2 equiv, prepared by the addition of a hexanes solution of BuLi (2 equiv) to a THF solution of *i*-Pr_2-NH (2 equiv) at −78 °C]. [For reactions performed with more than 2 g of an epoxynitrile the precooled (−78 °C), THF solutions were added by cannula.] After 5 min, 4 equiv of neat HOAc was added, followed by EtOAc (2−3 times the volume of THF), and then the solution was gently warmed to room temperature in a stream of hot air. The crude product was filtered through a short column of silica gel (2−5 cm pad), concentrated, and then purified by chromatography.

(2*E*)-4-Hydroxybut-2-enenitrile (1a). The general procedure was employed with **4a** (3.0 g in 30 mL of THF) followed by radial chromatography (1:1 EtOAc:hexanes) to provide 2.5 g of **1a** (83%) as an oil: ^{13}C NMR ($CDCl_3$) δ 61.4, 98.3, 117.4, 153.9. The ^1H NMR was identical to that previously reported.[9b,15b]

(2*E*)-4-Hydroxypent-2-enenitrile (1b). The general procedure was employed with **4b** (5.3 g in 50 mL of THF) followed by radial chromatography (1:0.8 EtOAc:hexanes) to provide 4.2 g of **1b** (79%) as an oil: ^{13}C NMR ($CDCl_3$) δ 21.8, 66.4, 97.4, 117.2, 158.2. The ^1H NMR was identical to that previously reported.[9b]

(2*E*)-4-Hydroxy-3-methylbut-2-enenitrile (1c). The general procedure was employed with **4c** (437.8 mg, 4.51 mmol in 5 mL of THF) followed by radial chromatography (2:3 EtOAc: hexanes) to provide 320.2 mg of **1c** (73%) as an oil: ^{13}C NMR ($CDCl_3$) δ 17.4, 64.9, 93.1, 117.1, 163.9. The ^1H NMR was identical to that previously reported.[11]

2-(2-Hydroxycyclopentylidene)ethanenitrile (1d). The general procedure was employed with **4d** (117.3 mg in 1 mL of THF) followed by radial chromatography (2:3 EtOAc:hexanes) to provide 70.7 mg (60%) of **1d**[32] as an oil: IR (film) 2253, 3383 cm^{-1}; ^1H NMR (CS_2) δ 1.83−2.10 (m, 2H), 2.21−2.31 (m, 1H), 2.37−2.46 (m, 2H), 2.92−3.00 (m, 2H), 4.74−4.78 (m, 1H), 5.70 (q, J = 2 Hz, 1H); ^{13}C NMR (CS_2) δ 22.2, 31.4, 36.5, 76.3, 93.9, 117.1, 173.2; MS *m*/*e* 124 (M + H). A hexanes solution of butyllithium (1.1 equiv, 1.45 M in hexanes) was added to a cold

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(−78 °C), THF solution (2 mL) of **1d** (80.7 mg), followed after 10 min., by neat *p*-nitrobenzoyl chloride (134 mg). The resulting solution was allowed to warm to room temperature, stirred for 1 h, water was added, and the crude product was then extracted with EtOAc (3 × 10 mL) and dried ($MgSO_4$). Concentration and radial chromatography (1:4 EtOAc:hexanes) provided 101.0 mg (57%) of the *p*-nitrobenzoate as a crystalline solid whose structure was solved by X-ray diffraction (see Supporting Information): IR (KBr) 1725, 2216, 2366 cm^{-1}; ^1H NMR ($CDCl_3$) δ1.81−2.15 (m, 3H), 2.28 (sextet, J = 6 Hz, 1H), 2.66−2.89 (m, 2H), 5.59 (dd, J = 4.5, 2.7 Hz, 1H), 5.77−5.82 (m, 1H), 8.19 (d, J = 8.7 Hz, 1H), 8.30 (d, J = 8.7 Hz, 1H); ^{13}C NMR (C_6D_6) δ 21.8, 31.0, 32.6, 77.2, 96.3, 116.6, 123.9, 131.0, 135.0, 151.2, 164.2, 167.1; MS *m*/*e* 272 (M).

2-(2-Hydroxycyclohexylidene)ethanenitrile (1e). The general procedure was employed with **4e** (1.19 g in 20 mL of THF) followed by radial chromatography (2:3 EtOAc:hexanes) to provide 1.11 g of **1e** (94%) as an oil that was spectrally identical to material previously synthesized.[33]

3-Hydroxycyclohex-1-enecarbonitrile (1f). The general procedure was employed with **4f** (103.6 mg in 2 mL of THF) followed by radial chromatography (2:3 EtOAc:hexanes) to provide 93.5 mg of **1f** (90%) as an oil: ^{13}C NMR ($CDCl_3$) δ 18.6, 26.5, 30.2, 64.7, 114.3, 118.7, 146.1. The ^1H NMR was identical to that previously reported.[34] The general procedure was employed with **4g** (16.0 mg in 1 mL of THF) except that the LDA solution was allowed to react for 30 min at −78 °C. Conventional workup, followed by radial chromatography (3:2 EtOAc:hexanes), provided 14.0 mg of **1f** (88%) as an oil.

(2*E*)-6-Hydroxyhex-2-enenitrile (1h). The general procedure was employed with **4h** (22.2 mg in 10 mL of THF) and 3 equiv of LDA (prepared in 100 mL of THF) to provide, after radial chromatography (3:2 EtOAc:hexanes), 14.9 mg (67%) of **1h** as an oil spectrally identical to material previously synthesized.[13]

(2*E*)-7-Hydroxyhept-2-enenitrile (1i). The general procedure was employed with **4i** (25.4 mg, 0.190 mmol in 10 mL of THF) and 4 equiv of LDA (prepared in 100 mL of THF) to provide, after radial chromatography (3:2 EtOAc:hexanes), 19.4 mg (76%) of **1i** as an oil spectrally identical to material previously synthesized.[35]

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Supporting Information Available: ^1H NMR and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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