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SYNTHESIS OF OPTICALLY ACTIVE (*E*)-γ-HYDROXY -α, β-UNSATURATED NITRILES

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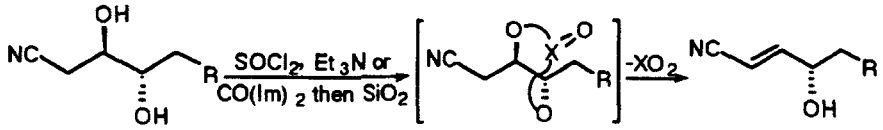
ABSTRACT : Treatment of (2*S*, 3*S*)- or (2*R*, 3*S*)-1-cyano-2, 3-alkanediols with carbonyldiimidazole or thionyl chloride resulted in one-pot preparation of (*E*, *S*)-γ-hydroxy-α, β-unsaturated nitriles based on the elimination of the cyclic carbonates or sulfites formed *in situ*.

Optically active (*E*)-γ-hydroxy-α, β-unsaturated nitrile moiety was recently prepared and functionalized to chiral synthons.[1] The synthesis of (*E*, *S*)-γ-hydroxy-α, β-unsaturated nitriles by Sharpless kinetic resolution of γ-iodoallyl alcohol followed by reaction with CuCN was known .[2] Recently, optically active (*E*, *S*)-γ-hydroxy-α, β-unsaturated nitriles were synthesized by reaction of chiral sulfoxides with aldehydes,[3] which in turn were asymmetrically amplified by lipase-mediated resolution .[4] We wish to report here a convenient and a highly enantioselective route to (*E*, *S*)-γ-hydroxy-α, β-unsaturated nitriles from (2*S*, 3*S*)- or (2*R*, 3*S*)-1-cyano-2, 3-alkanediols by elimination *via* cyclic sulfites and carbonates prepared *in situ* (Scheme 1 and 2).

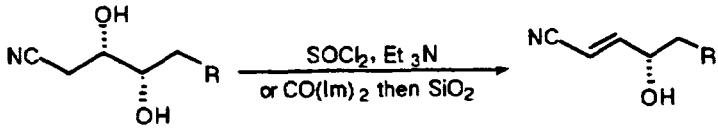
The (2*R*, 3*S*)-1-cyano-2, 3-alkanediols 1 were prepared from (2*R*, 3*S*)-2, 3-O-isopropylidenedioxyalkanols[5] by one-pot conversion[6] to nitrile (Tf_2O, pyridine, - 50 °C, then NaCN, HMPA, rt) followed by deprotection (70 % HOAc, rt). On treatment of **1a** with thionyl chloride (1.2 equiv) in the presence of 5 equiv triethylamine at 0 °C rt, (*E*)-α, β-unsaturated nitrile **4a**, $[\alpha]_D^{25}$ + 37.5 ° (*c* 2.1, $CHCl_3$) [lit.[2] $[\alpha]_D^{25}$ +36.8 ° (*c* 0.99, $CHCl_3$)], was obtained directly as the only product without formation of (*Z*)-isomer in 86 % yield (run 1, Table). The (*E*)-stereochemistry of **4a** was inferred from ^1H NMR (300 MHz) coupling constants of the two olefinic protons and capillary GLC. It is presumed that the cyclic sulfite **2a** is the intermediate in this conversion .[7] Alternatively, reaction of **1a**

Scheme 1



1a R= -$(CH_2)_3CH_3$ X=S 2a X=C 3a 4a
1b R=  2b 3b 4b
1c R=  2c 3c 4c

Scheme 2



5a R=-$(CH_2)_3CH_3$ 4a
5b R=-OCH_2Ph 4d

with carbonyldiimidazole (1.2 equiv) in dry benzene at room temperature gave the cyclic carbonate **3a**, which on exposure to silica gel afforded **4a** in 80 % overall yield (run 2). When **1a** was treated with 3 equiv carbonyldiimidazole for 12 h, **1a** was obtained directly (run 3).[8]

In these one-pot conversions, it is noteworthy that the cyclic sulfites and carbonates are good leaving groups in these β-elimination reactions. Alternatively, (2*S*, 3*S*)-1-cyano-2, 3-alkanediols **5a-b** were prepared easily from L-tartaric acid. (2*S*, 3*S*)-2, 3-O-Isopropylidenedioxyoctanol[9] derived from L-tartaric acid was converted to **5a** by conversion to nitrile followed by deprotection. Treatment of **5a** with thionyl chloride or carbonyldiimidazole afforded **4a** (runs 8 and 9). The reaction sequence was also applied to prepare **4d** (Table).

The hydroxy nitrile **4a** thus synthesized was protected with silyl group and then reduced with DIBAH to afford the unsaturated aldehyde **6**, $[\alpha]_D^{25}$ -19° (*c* 0.4, $CHCl_3$) [lit.[10, 11] -18.9° (*c* 1.67, $CHCl_3$)], which is the key chiral synthon in the synthesis[11] of (+)-coriolic acid, a self-defensive substance against the rice blast disease (Scheme 3).

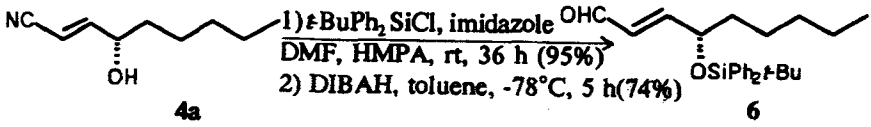
In summary, optically active (*E*)-γ-hydroxy-α, β-unsaturated nitriles were synthesized by mild and one-pot dehydration[12] of γ, β-dihydroxy nitriles.

Table Optically active (E)-γ-hydroxy-α, β-unsaturated nitriles prepared

Run	Diols	Products[a]	Reaction Conditions[b]	Yield(%)[c]
1	1a	4a	A	86
2	1a	4a	B	85
3	1a	4a	C	82
4	1b	4b	A	88
5	1b	4b	B	86
6	1c	4c	A	88
7	1c	4c	B	88
8	5a	4a	A	82
9	5a	4a	B	84
10	5b	4d	A	91
11	5b	4d	B	90

[a]The products **4a-4d** were pure by capillary GLC analysis. [b]A: $SOCl_2$ (1.2 equiv), Et_3N (5 equiv), CH_2Cl_2, rt, 1 h. B: $CO(Im)_2$ (1.2 equiv), PhH, rt, 2 h then SiO_2. C: $CO(Im)_2$ (3.0 equiv), PhH, rt,12h. [c]The yields are isolated yields.

Scheme 3



EXPERIMENTAL

(1*E*, 3*S*)-1-Cyano-1-octen-3-ol (4a): General Procedures :

Method A : To a stirred solution of the diol **1a** (500 mg, 2.92 mmol) in dry CH_2Cl_2 (50 ml) at 0 °C was added Et_3N (2.0 ml). The reaction mixture was warmed to room temperature and stirred for 1 h and then concentrated *in vacuo*. The crude product was dissolved in EtOAc (10 ml) and then filtered through Celite pad and then concentrated. The product was purified by column chromatography on silica gel using EtOAc/hexanes 1:3 as eluent to afford **4a** (385 mg, 86 %). TLC; SiO_2, EtOAc/hexanes 1:3, R_f=0.26. $[\alpha]_D^{25}$ +37.5 ° (*c* 2.1, $CHCl_3$) [lit.[2]+36.8 °

(c 0.99, $CHCl_3$)].^{1}H NMR (270 MHz, $CDCl_3$) δ 0.90 (t,3H, J=7.5Hz, CH_3), 1.20-1.78 (m, 8H, 4 CH_2), 2.12 (bs, 1H, OH), 4.18 (m, 1H, CHO), 5.73 (dd, 1H, J=15.5, 1.9 Hz, =CH), 6.82 (dd, 1H, J=15.5, 3.7 Hz, =CH). IR (neat) 3500, 2250, 1640 cm^{-1}. MS (m/e): 153 (M^+).

Method B : To a stirred solution of the diol **1a** (500 mg, 2.92 mmol) in dry benzene (5.0 ml) was added carbonyldiimidazole (570 mg, 3.50 mmol) in dry benzene (5.0 ml) at room temperature. The reaction mixture was stirred at room temperature for 2 h . The mixture was washed with H_2O (10 ml) and then brine (10 ml). The organic layer was dried over anhydrous $MgSO_4$ and then concentrated *in vacuo* . The crude product (TLC; SiO_2, ether, R_f=0.65) was passed through a short pad of silica gel and then concentrated. The crude product (TLC; SiO_2, ether, R_f=0.93) was separated by column chromatography using EtOAc/hexanes 1:3 as eluent to afford **4a** (381 mg, 85 %).

(1*E*, 3*S*, 5*Z*)-1-Cyano-1,5-octadien-3-ol (4b)

TLC; SiO_2, EtOAc/hexanes 1:3, R_f=0.24. $[\alpha]_D^{25}$ -8.24 ° (c 0.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (t, 3H, J=7.5 Hz, CH_3), 2.04 (m, 2H, CH_2), 2.36 (m, 2H, CH_2), 4.33 (m, 1H, CHO), 5.30-5.40 (m, 1H, =CH), 5.68 (m, 1H, =CH), 5.70 (dd, 1H, J=15.5, 2.0 Hz, =CH), 6.70 (dd, 1H, J=15.5, 3.8 Hz, =CH). IR (neat) 3450, 2250, 1640 cm^{-1}. MS (m/e): 151 (M^+).

(1*E*, 3*S*, 5*Z*)-1-Cyano-1,5-undecadien-3-ol (4c)

TLC; SiO_2, EtOAc/hexanes 1:3, R_f=0.30. $[\alpha]_D^{25}$ -1.57 ° (c 3.0, $CHCl_3$). ^{1}H NMR (80 MHz, $CDCl_3$) δ 0.91 (t, 3H, J=7.5 Hz, CH_3), 1.27 (m, 6H, 3 CH_2), 2.05 (m, 2H, CH_2), 2.37 (m, 2H, CH_2), 4.23 (m, 1H, CHO), 5.45 (m, 2H, CH=CH), 5.70 (dd, 1H, J=15.5, 1.9 Hz, =CH), 6.76 (dd, 1H, J=15.5, 3.9 Hz, =CH). IR (neat) 3450, 2250, 1640 cm^{-1}. MS (m/e): 192 (M^+).

(1*E*, 3*S*)-4-Benzyloxy-1-cyano-1-buten-3-ol (4d)

TLC; SiO_2, EtOAc/hexanes 1:3, R_f=0.14, $[\alpha]_D^{25}$ +34.1 °(c 2.1, $CHCl_3$). ^{1}H NMR (80 MHz, $CDCl_3$) δ 3.37-3.67 (m, 2H, OCH_2), 4.35 (m, 1H, CHO), 4.50 (s, 2H, $PhCH_2O$), 5.75 (dd,1H, J=15.5, 3.8 Hz, =CH), 6.72(dd,1H, J=15.5, 2.0 Hz, =CH), 7.38 (s, 5H, Ar). IR (neat) 3450, 2250, 1640 cm^{-1}. MS (m/e): 193 (M^+), 91 (base peak).

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7. Treatment of **1a** with thionyl chloride (1.2 equiv) in the presence of 2 equiv triethylamine at 0 °C for 10 min provided the cyclic sulfite **2a**, which on exposure to 2 equiv LDA in THF at -78 °C for 30 min afforded **4a** in 80 % overall yield.
8. When the compound **1a** was treated with 3 equiv NaH and excess dimethyl carbonate, **4a** was obtained directly.
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12. Dehydrations are normally carried out in two steps by first activating as acetate or sulfonate of the hydroxyl and then effecting elimination with base. In the case of β-hydroxy lactone, one-pot dehydration by treatment with mesyl chloride in the presence of triethylamine is known, see : (a) J. E. Worbel and B. Ganem, *J. Org. Chem.*, **48**, 3761 (1983). (b) S. Takano, M. Morimoto, and K. Ogasawara, *Synthesis*, 834 (1984).

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