Diastereoselective Synthesis of Protected 2,3-Dihydroxynitriles from 2-Hydroxy Acids

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Abstract: The DIBAL-H reduction of dioxolanones **2** prepared from 2-hydroxy acids followed by addition of acetone cyanohydrin affords the *syn* 2,3-dihydroxynitriles in high enantiomerical purities.

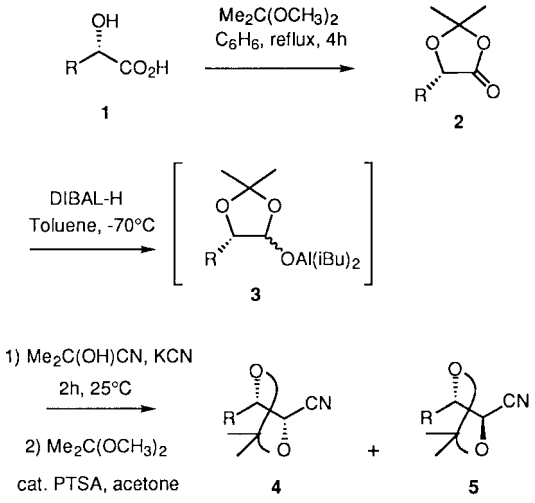
Key words: Grignard compounds, nitrile, diastereoselective reduction

Optically active cyanohydrins are an important class of compounds in organic synthesis. It is a well established source of 2-amino alcohols, which are useful chiral building blocks for biologically active compounds.[1] In recent years, a great number of procedures were developed in order to access these compounds in an optically active form.[2] In contrast, the related 2,3-dihydroxynitriles are more difficult to synthesize. The asymmetric dihydroxylation is not available in this case,[3] and they are generally prepared by cyanation of protected α-hydroxy aldehydes.[4]

We report here, the synthesis of dihydroxynitriles in good diastereoselectivity and high enantiomerical purities from 2-hydroxy acids.

Optically active 2-hydroxy acids may be easily prepared by nitrous deamination of α-amino acids.[5] Alternatively, they could be isolated in nearly quantitative yield without racemisation by aqueous lithium hydroxide hydrolysis of α-hydroxy esters.[6] When they are reacted with 2,2-dimethoxypropane, the corresponding 1,3-dioxolan-4-ones **2** are isolated in good yields. In analogy with the cyanation of 3-alkoxylactam that we have previously described,[7] we thought that it should be possible to reduce compounds **2** to lactols and to react them with an appropriate cyanation agent. In a first attempt, compound **2a** was reacted with DIBAL-H in toluene at −60 °C. After hydrolysis with 5M aqueous potassium cyanide, the 2,3-dihydroxynitrile was isolated in a 1/1 mixture of *syn*- and *anti*- isomers. Then, we isolated the hemiacetal resulting from the acid hydrolysis of the aluminium salt **3** and studied its reaction with trimethylsilylcyanide in the presence of a Lewis acid such as $TiCl_4$ or $SnCl_4$. Yields were rather disappointing; the best (49%) was obtained with zinc iodide in CH_2Cl_2 and the two diastereomers were isolated in a 67/33 ratio. By operating with tin tetrachloride in dichloromethane at −78 °C, a diastereomeric excess of 0.7 was obtained but the chemical yield was only 28%. The same result was observed after transformation of the hemiacetal hydroxyl moiety into a better leaving group such as a benzoate. Moreover, in all cases the nitriles were isolated as the free diols and not as the protected acetonide after basic hydrolysis.

We then decided to react directly on the aluminate resulting from the reduction of the dioxolanone by DIBAL-H. Using acetone cyanohydrin as a cyanating reagent, we succeeded in obtaining the dihydroxynitriles in good yields, increasing the *syn*/*anti* ratio up to 80/20. We observed also that the rate of the reaction was greatly enhanced by addition of a small amount of potassium cyanide. However, due to the excess of cyanohydrin, these dihydroxynitriles were difficult to purify. Thus, they were protected again as acetonides using 2,2-dimethoxypropane and a catalytic amount of *p*-toluenesulfonic acid



Product 2	R	4 / 5	Yield % (4 + 5)	4 ee%
a	$(CH_3)_2CH$	72 / 28	69	98
b	$(CH_3)_2CH\text{-}CH_2$	70 / 30	61[a]	99
c	C_6H_5	80 / 20	79	99
d	$C_6H_5\text{-}CH_2$	70 / 30	76	99
e	$n\text{-}C_4H_9\text{-}C{\equiv}C\text{-}CH_2$	69 / 31	74	98

[a] 4-cyano-4-isobutyl-2,2-dimethyl-1,3-dioxolane was also isolated in 20% yield.

Scheme

(PTSA) to give after chromatography on silica gel the pure *syn*- or *anti*-2,3-dialkoxynitriles. The *syn*- and *anti*-configurations were assigned by ^{1}H NMR according to the observation previously reported.[8] In all cases the difference of chemical shift between the two methyl groups of the acetonide is weaker for the *syn* compound ($\Delta\delta$ ppm ≤ 0.06) than for the *anti* compound ($\Delta\delta$ ppm ≥ 0.22). The enantiomerical purities were measured on the diols after transformation to the *bis* trifluoroacetate and were found in all cases to be better than 96%.

Products were purified by distillation or by medium pressure liquid chromatography on a Jobin–Yvon Modulprep (Kieselgel 60H Merck) or by flash chromatography (Kieselgel 60 Merck: 230–400 mesh, solvent: cyclohexane/EtOAc) and analyzed by VPC (BP5, 25 m capillary column) or by TLC (silica gel 60F_{254}). Optical rotations were measured on a Perkin–Elmer 141 polarimeter. NMR spectra were recorded on a Bruker AC at 200 MHz for ^{1}H and 50 MHz for ^{13}C NMR. $CDCl_3$ was used as solvent with TMS as internal standard. IR spectra were recorded on a Perkin–Elmer 599 spectrometer. Mass spectra were recorded on a NER MAG R10.10C. The enantiomeric excesses were measured by GC after derivatization of the dihydroxynitriles (CH_2Cl_2, $(CF_3CO)_2O$, 100 °C, 30 mn) on a 25m Chirasil-D-Val column (Chrompack).

Dioxolanones 2a-e; General Procedure

The hydroxy acids **1** (0.1 mol) and 2,2-dimethoxypropane (0.12 mol, 1.2 equiv) were dissolved in benzene (100 mL) and refluxed for 4h in a Dean–Stark apparatus. After elimination of the MeOH, the residual mixture was evaporated in vacuo and purified by liquid chromatography on a silica gel column (Table 1).

Protected Dihydroxynitriles 4 and 5(a-e); General Procedure

Compounds **2** (2 mmol) were dissolved in anhyd toluene (10 mL) and cooled to –70 °C. A solution of 1.5M DIBAL-H in toluene (2.2 mmol, 1.1 equiv) was slowly added and the solution was stirred for 2h at the same temperature. Acetone cyanohydrin (340 mg, 4 mmol, 2 equiv) and potassium cyanide (130 mg, 2 mmol, 1 equiv) were sequentially added and the mixture was warmed up to 25 °C under vigorous stirring. After stirring for 2 h at r.t., 1N HCl (10 mL, 10 mmol) was added and the mixture was stirred for 1 h before extracting with EtOAc. The organic layer was then dried ($MgSO_4$) and concentrated under reduced pressure. The crude mixture was dissolved in acetone (15 mL) and reacted for 16 h at 20 °C with dimethoxypropane (4 mmol, 2 equiv, 490 µl) in the presence of a catalytic amount of *p*-toluenesulfonic acid (30 mg). The acetone was then removed under reduced pressure and the residual mixture was hydrolysed with a soln of sat. $NaHCO_3$ (10 mL) and extracted with Et_2O. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give a mixture of **4** and **5** which were separated by chromatography on a silica gel column (Table 2).

Table 1 Dioxolanones **2** Prepared

Products **2**	Yield (%)	$[\alpha]_D^{20}$ (*c*, $CHCl_3$)	^{1}H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$) δ	MS m/z (%)
(*S*)-**2a**	75	– 8.2 (3.58)[a] Lit: – 15.4 (neat)	0.98 (d, 3 H, *J* = 6.8, CH_3), 1.04 (d, 3 H, *J* = 6.8, CH_3), 1.54 and 1.60 (s, 3 H, CH_3), 2.15 (m, 1 H, CH), 4.25 (d, 1 H, *J* = 3.8, CH-O)	16.3 (CH_3), 18.3 (CH_3), 25.8 (CH_2), 26.6 (CH_3), 29.9 (CH_3), 78.4 (CH) 110.0 (C), 172.5 (C=O)	158 (0.5), 149 (39), 104 (15), 91 (33), 86 (29), 65 (41), 57 (62), 43 (100)
(*S*)-**2b**	89	– 9.0 (5.54) Lit[9]: – 9.9 (neat)	0.94 (d, 3 H, *J* = 6.8, CH_3), 0.95 (d, 3 H, *J* = 6.9, CH_3), 1.56 (s, 3 H), 1.62 (s, 34) 1.5–1.9 (m, 3 H, CH and CH_2), 4.38 (dd, 1 H, *J* = 4.1, 9.0, CH-O),	21.8 (CH_3), 23.0 (CH_3), 25.0 (CH_3), 25.8 (CH_3) 27.5 (CH), 40.8 (CH_2) 72.8 (CH), 110.5 (C), 173.9 (C=O)	172 (0.5), 157 (6), 128 (10), 114 (9), 85 (43), 43 (100)
(S)-**2c**	83	+ 56.2 (2.11)[b] Lit[9]: + 41 (2.0, CCl_4)	1.67 (s, 3 H, CH_3), 1.72 (s, 3 H, CH_3) 5.41 (s, 1 H, CH), 7.3–7.5 (m, 5 H, C_6H_5)	26.1 (CH_3), 27.2 (CH_3), 75.9 (CH), 110.9 (C), 126.5(CH), 128.7 (CH), 128.9 (CH), 132.5 (C), 171.4 (C=O)	192 (2), 177 (2) 148 (96), 133 (20), 105 (52), 90 (100), 77 (54), 43 (86)
(*S*)-**2d**	89	–53.3 (0.82) Lit[10]: – 51.7 (0.97, $CHCl_3$)	1.37 (s, 3 H, CH_3), 1.51 (s, 3 H, CH_3), 3.04 (dd, 1 H, *J* = 14.5, 6.4, CH_2), 4.66 (dd, 1 H, *J* = 6.4, 4.2, CH-O), 7.2–7.4 (m, 5 H, Ph)	126.0 (CH_3), 26.8 (CH_3), 37.5 (CH_2), 74.9 (CH), 110.7 (C), 126.9 (CH), 128.3 (CH), 129.7 (CH), 135.7 (C), 172.3 (C=O)	206 (11), 148 (10), 104 (6), 91 (100), 43 (43)
(*R*)-**2e**	83	– 16.4 (2.56)[a]	0.92 (d, 3 H, *J* = 6.7, CH_3), 1.40 (m, 4 H, CH_2), 1.57 and 1.67 (s, 3H, CH_3), 2.13 (m, 2 H, CH_2), 2.71 (m, 2 H, CH_2), 4.50 (t, 1 H, *J* = 2.4, CH-O)	13.4 (CH_3), 18.2 (CH_2), 21.7 and 22.4 (CH_2), 26.2 and 26.9 (CH_3), 30.7 (CH), 73.3 (CH-O), 73.6 (C≡C), 83.2 (C≡C), 171.6 (C=O)	210 (5), 109 (12), 73 (25), 43 (100)

[a] MeOH
[b] CCl_4

Table 2 *syn*-Protected Dihydroxynitriles **4** Prepared

Products[b] **4**	$[\alpha]_D^{20}$ (*c*, $CHCl_3$)	ee (%)	^1H NMR ($CDCl_3$/TMS) δ, *J*(Hz)	^{13}C NMR ($CDCl_3$) δ	MS m/z (%)
(*2S*,*3S*)-**4a**	–4.1 (1.83)[a]	96	1.00 (d, 3 H, *J* = 6.8, CH_3), 1.02 (d, 3 H, *J* = 6.8, CH_3), 1.46 and 1.50 (s, 3 H, CH_3), 1.88 (sext, 1 H, *J* = 6.8, CH), 4.13 (dd, 1 H, *J* = 6.8, 6.8, CH-O), 4.34 (d, 1 H, *J* = 6.6, CH-O)	17.8 (CH_3), 18.3 (CH_3), 24.6 (CH_3), 26.4 (CH), 31.2 (CH_3), 65.7 (CH), 85.2 (CH), 112.2(C), 118.3 (CN)	169 (1), 154 (39), 126 (15), 97 (34), 94 (89), 67 (30), 54 (30), 43 (100)
(*2S*,*3S*)-**4b**	–8.4 (3.81)	98	0.96 (d, 3 H, *J* = 6.6, CH_3), 0.98 (d, 3 H, *J* = 6.4, CH_3), 1.5–1.9 (m, 3 H, CH and CH_2) 1.45 and 1.47 (s, 3 H, CH_3), 4.19 (d, 1 H, *J* = 6.8, CH-O), 4.39 (m, 1 H, CH-O),	22.2 (CH_3), 23.0 (CH_3), 25.1 (CH_3), 25.3 (CH_3), 27.0 (CH), 41.8 (CH_2), 68.1 (CH), 78.9 (CH), 112.3 (C), 117.8 (CN)	183 (1), 168 (63), 126 (19), 108 (38), 99 (27), 97 (43), 81 (49), 68 (16), 54 (29), 43 (100)
(*2S*,*3S*)-**4c**	–30.4 (6.74)	99	1.63 and 1.64 (s, 3 H, CH_3), 4.41 (d, 1 H, *J* = 7.4, CH-O), 5.34 (d, 1 H, *J* = 7.4, CH-O), 7.4–7.5 (m, 5 H, C_6H_5)	25.2 (CH_3), 26.7 (CH_3), 70.3 (CH), 113.2 (C) 117.3 (CN), 126.1 (CH), 129.1 (CH), 129.4 (CH), 132.5 (C)	203 (18), 188 (7), 177 (5), 163 (6), 91 (18), 77 (26), 54 (57), 43 (100)
(*2S*,*3S*)-**4d**	–21.9 (4.85)	99	1.48 and 1.51 (s, 3 H, CH_3), 2.95 (dd, 1 H, *J* = 6.1, 14.1, C<u>H</u>H), 3.07 (dd, 1 H, *J* = 4.3, 14.1, CH<u>H</u>), 4.35 (d, 1 H, *J* = 6.4, CH-O), 4.65 (q, 1 H, *J* = 6.3, CH-O), 7.2–7.4 (m, 5 H, C_6H_5)	25.2 (CH_3), 27.0 (CH_3), 38.9 (CH_2), 66.9 (CH), 80.7 (CH), 112.9 (C), 117.7 (CN), 127.4 (CH), 127.4 (CH), 128.9 (CH), 129.4 (CH), 135.4 (C)	217 (3), 202 (15), 159 (14), 91 (35), 68 (13), 77 (9), 43 (100)
(*2R*,*3R*)-**4e**	8.5 (1.79)	98	0.91 (t, 3 H, *J* = 7.0, CH_3), 1.46 (s, 3 H, CH_3), 1.51–1.54 (m, 4 H, CH_2), 1.57 (s, 3 H, CH_3), 2.1–2.2 (m, 2 H, CH_2), 2.5–2.7 (m, 2 H, CH_2) 4.33 (dt, 1 H, *J* = 5.2, 8.4, CH-O), 4.88 (d, 1 H, *J* = 5.2, CH-O)	13.4 (CH_3), 18.2 (CH_2), 21.8 (CH_2), 23.3 (CH_3), 25.1 (CH_3), 26.7 (CH_2), 29.8 (CH_2), 30.6 (CH_3), 67.1 (CH), 72.7 (C≡C), 78.5 (CH), 84.4 (C≡C), 113.1 (C), 117.8 (CN)	221 (5), 206 (17), 164 (3), 126 (82), 68 (18), 43 (100)

[a] MeOH
[b] For new compounds satisfactory microanalyses were obtained : C ± 0.3, H ± 0.21

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