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Stereoselective sodium borohydride reduction, catalyzed by manganese(II) chloride, of γ-oxo-α-amino acids. A practical approach to *syn*-γ-hydroxy-α-amino acids

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Abstract

A highly stereoselective reduction of γ-oxo-α-amino acids by sodium borohydride in the presence of a catalytic amount of manganese(II) chloride gives *syn*-γ-hydroxy-α-amino acids. Enantiomerically pure *syn*-(2*S*,4*R*,1′*S*)-4-aryl-4-hydroxy-2-(1′-phenylethylamino)butanoic acids form stable gels in methanol. © 2000 Elsevier Science Ltd. All rights reserved.

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4-Hydroxylated α-amino acids and their lactones are relatively common building blocks of a vast array of bioactive compounds such as nikkomycins,[1] cymbimycins,[2] and funebrine,[3] that have been isolated from natural materials.[4] The widespread occurrence of this structural unit has led to the development of a number of stereoselective syntheses, such as the isoxazoline route,[5,6] enzymatic methods,[7,8] and photolysis of chiral chromium complexes.[9]

The wide scale of readily accessible enantiomerically pure γ-aryl-γ-oxo-α-amino acids[10–12] has allowed their usage as starting materials in the preparation of substituted γ-aryl-γ-hydroxy-α-amino acid derivatives. The effect of an existing stereogenic center on the diastereoselectivity of the reduction has been extensively studied. The reduction of esters[13,14] or amides[15] using hydride reagents proceeds with low selectivity. Jackson[16] obtained the best results by using the $Et_3SiH:Et_2O·BF_3$ system (9:1 in favor of a *cis*-lactone). Little attention has been paid so far to a direct reduction of γ-oxo-α-amino acids. The straightforward access[17] to both enantiomers of these acids by conjugate addition of chiral amines to β-aroylacrylic acids makes this approach attractive.

In our previous paper[18] we published the reduction, using $NaBH_4$ at low temperature, of some 4-aryl-4-oxo-α-amino acids with a d.r. of up to 11:1. Here we describe the application of $MnCl_2·4H_2O$ as a catalyst of such reductions, a process that allowed us to reach a d.r. of up to 97:3 with *syn*-γ-hydroxy-α-amino acids being the major products (Scheme 1).

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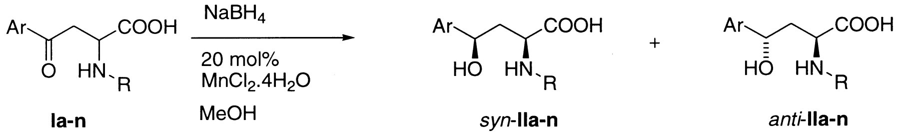
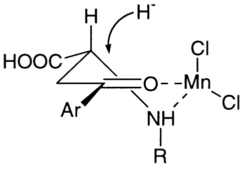


IIa,b,d,e,n	R = Bn	Ar = C_6H_5, 4-MeOC_6H_4, 3-Me-4-MeOC_6H_3, 2-thienyl, methyl
IIc,f	R = 2-furylmethyl	Ar = 4-MeOC_6H_4, 5-Me-2-thienyl
IIg,i,k,l	R = (*S*)-1′-phenylethyl	Ar = C_6H_5, 4-MeOC_6H_4, 4-MeC_6H_4, 3-Me-4-MeOC_6H_3
IIh,j,m	R = (±)-1′-phenylethyl	Ar = C_6H_5, 4-MeOC_6H_4, 3-Me-4-MeOC_6H_3

Scheme 1.

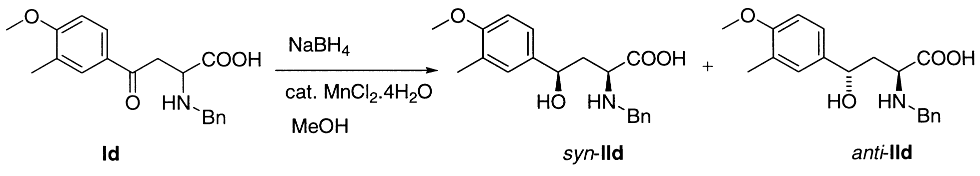
The starting γ-oxo-α-amino acids **Ia–n** were prepared by conjugate addition of benzylamine, furfurylamine or 1-phenylethylamine, respectively, to suitable β-aroyl or β-acetyl acrylic acids. The reduction was carried out in methanol. In reductions without catalyst a large excess of $NaBH_4$ had to be used because of the insolubility of the starting oxoamino acids (**Ia–m**) in the reaction media. The best results under such conditions were achieved in the case of the more soluble furfurylamino adducts **IIc,f** at low temperature; in the case of 1-phenylethylamino derivatives **Iig–m**, however, the diastereoselectivity was low and independent of the reaction temperature (d.r ~2:1).

The application of $MnCl_2$ as a chelating agent not only increased the solubility of starting materials, but also accelerated the reduction and increased the selectivity. This approach has been used recently[19] in the reduction of 2-alkyl-3-oxoesters by a 1,2-asymmetric induction process. However, metal-chelation control in 1,3-induction is not so conclusive.[20] The selective formation of the *syn*-isomer can be rationalized by a six-membered metal chelate in a similar fashion as shown in a previous report[20] on the reduction of β-aminoketones with $Zn(BH_4)_2$ (Scheme 2).



Scheme 2.

The influence of various factors on the selectivity of oxoamino acid (**Id**) reduction has been studied (Scheme 3). The most significant effects were observed when varying the amount of catalyst and the temperature (Table 1). The rate of addition of $NaBH_4$ is also very important. Thus, if it was too fast with regard to the complexation rate, $NaBH_4$ to some extent attacked the non-complexed



Scheme 3.

carbonyl group to give rise to the *anti*-isomer. A slightly diminished d.r. in the case of the much more soluble γ-oxo-α-(*N*-benzylamino)pentanoic acid **In** can also be attributed to this factor. In this case, the product was isolated as the corresponding *trans*-α-benzylaminovalerolactone hydrochloride **IIIn**.

Table 1

Effect of the reaction conditions on the stereochemical outcome of the reduction of **Id**

Entry	**Reaction conditions**				**d.r.**[a]
	$MnCl_2.4H_2O$ (mol %)	**$NaBH_4$ (equiv.)**	**Temp. (°C)**	**time**	***syn- / anti-***
1	-	4	30	5 h	3.8:1
2	-	4	-15 –20	30 h	8:1
3	-	> 2	18	1 h	4.7:1
4	5	2	18	30 min	9.7:1
5	10	> 1	18	20 min	20:1
6	20	1	18	15 min	40:1

[a] d.r. values in reaction mixture were readily determined by a reverse phase HPLC analysis on Waters Symmetry C18 $5\mu m$ column by using pH 2.5 phosphate buffer – CH_3CN = 4:1 (v/v)

Table 2

Reduction of 4-oxo-2-aminoacids (**Ia**–**n**) with $NaBH_4$/cat. $MnCl_2 \cdot 4H_2O$ in methanol[†]

Product			**$NaBH_4$**	**Temp.**	**Yield**	**d.r.**	**m.p.**
comp.	**Ar**	**R**	**(equiv.)**	**(°C)**	**(%)**	***syn-/anti-***	**(°C)**
IIa	Ph	Bn	2	20	77	>97:3	232-233
IIb	4-MeO-C_6H_4	Bn	2	18	79	96:4	214-215
IIc	4-MeO-C_6H_4	2-furylmethyl	1	20	65	>97:3	191-193
IId	3-Me-4-MeO-C_6H_3	Bn	2	20	70	>97:3	207-209
IIe	2-thienyl	Bn	2	20	76	>97:3	222-223
IIf	5-Me-2-thienyl	2-furylmethyl	2	20	60	97:3	199-200
IIg	Ph	(*S*)-1'-phenylethyl	2	2-5	80	97:3	202-203
IIh	Ph	(±)-1'-phenylethyl	2	2-5	76	>97:3	204-206
IIi	4-MeO-C_6H_4	(*S*)-1'-phenylethyl	2	2-5	63	97:3	176-178[a]
IIj	4-MeO-C_6H_4	(±)-1'-phenylethyl	2	2-5	75	>97:3	198-199
IIk	4-Me-C_6H_4	(*S*)-1'-phenylethyl	2	2-5	72	>97:3	192-193[a]
IIl	3-Me-4-MeO-C_6H_3	(*S*)-1'-phenylethyl	2	2-5	80	>97:3	199-201
IIm	3-Me-4-MeO-C_6H_3	(±)-1'-phenylethyl	2	2-5	78	97:3	190-192
IIIn	CH_3	Bn	1	2-5	66	95:5	238-240

[a] uncrystallized crude product

[†] A typical procedure for the preparation of *syn*-**IId** is as follows: To a presonicated (1 min) stirred suspension of **Id** (655 mg, 2 mmol) and $MnCl_2 \cdot 4H_2O$ (80 mg, 0.4 mmol) in MeOH (30 ml) at 20°C $NaBH_4$ (2×74 mg, 2×2 mmol) was slowly added (during 2×10 min). The resulting solution was stirred additionally for 30 min and water (20 ml) was added. Methanol was removed under reduced pressure and the pH of the remaining solution was adjusted to 6.0 with 1N HCl. A precipitate was filtered off, washed with EtOH, ether and dried to afford 460 mg (70 %) of *syn*-**IId** (d.r. > 97:3) as a white solid. An analytical sample was obtained by recrystallization from 70 % EtOH: mp 207–209°C, ^1H NMR (0.2N $NaOD/D_2O$, 300 MHz) δ 7.30–7.42 (m, 3H, Ph), 7.22–7.27 (m, 2H, Ph), 7.11 (bs, 1H, H-2′), 7.10 (d, 1H, J = 8.1 Hz, H-6′), 6.92 (d, 1H, J = 8.1 Hz, H-5′), 4.69 (t, 1H, J = 6.9 Hz, H-4), 3.75 (d, 1H, J = 12.9 Hz, CH_2Ph), 3.48 (d, 1H, J = 12.9 Hz, CH_2Ph), 3.23 (s, 3H, OCH_3), 3.02 (t, 1H, J = 6.8 Hz, H-2), 2.17 (s, 3H, CH_3), 1.98 (t, 2H, J = 6.9 Hz, H-3). ^{13}C NMR (0.2N $NaOD/D_2O$, 75 MHz) 184.4 (C-1), 159.5 (C-4′), 141.6 (C-1Ph), 138.2 (C-1′), 131.6 (C-2′), 131.5, 131.4 (C-Ph), 130.2 (C-4Ph), 129.5 (C-3′), 127.9 (C-6′), 113.9 (C-5′), 74.7 (C-4), 63.3 (C-2), 58.5 (OCH_3), 53.9 (CH_2Ph), 43.8 (C-3), 18.3 (CH_3).

A 20 mol% of $MnCl_2{\cdot}4H_2O$ was enough to achieve high control of the diastereoselectivity in favor of the *syn*-isomer (Table 2). The stereoselectivity was independent of both the **R** and **Ar** substituents and nearly identical results were obtained using protic solvents or their aqueous mixtures. The reaction represents an inexpensive and simple approach to *N*-substituted *syn*-γ-hydroxy-α-amino acids in which the *N*-benzyl group can be removed easily by catalytic hydrogenolysis in buffered aqueous methanol.

All racemic *syn*-hydroxy amino acids have been purified by crystallization. The chiral ones (**IIg,i,k**), however, underwent extensive gelation. The gelation ability in methanol has been measured by the method of Hanabusa[21] and it was found that 7 mg/ml for **IIi** stabilized a gel for several months. Thus, *syn*-(2*S*,4*R*,1′*S*)-4-aryl-4-hydroxy-2-(1′-phenylethylamino)butanoic acids provide another example which fits the close gelation–chiral structure relationship.[22]

In summary, the highly stereoselective reduction described in conjunction with diastereoselective conjugate addition of chiral amines affords a simple and inexpensive access to the both enantiomers of a wide variety of *syn*-γ-hydroxy-α-amino acids.

Acknowledgements

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