Pergamon

Tetrahedron 54 (1998) 14549–14564

TETRAHEDRON

Asymmetric reactions of α-ketoacid-derived hemiacetals: Stereoselective synthesis of α-hydroxy acids

Sunil V. Pansare* and R. Gnana Ravi

Division of Organic Chemistry (Synthesis), National Chemical Laboratory, Pune 411008, India

Received 22 July 1998; revised 15 September 1998; accepted 1 October 1998

Abstract

N-Acylation of prolinol with α-ketoacid chlorides results in concomitant hemiacetalization of the α-keto amide by the prolinol hydroxyl group. (*R*) or (*S*) α-hydroxy acids are obtained with good enantiomeric excess by stereodivergent reduction of these hemiacetals. Reaction with Grignard reagents at ambient temperature furnishes (*R*) α-alkyl mandelic acids with good stereoselectivity.

Keywords: Asymmetric reactions; reduction; Grignard reactions, hydroxy acids

Enantiomerically pure α-hydroxy acids are of interest due to their utility as building blocks for the asymmetric synthesis of natural products and biologically active molecules[1,2]. The stereoselective synthesis of α-hydroxy acids has therefore attracted considerable interest and several efficient methods have been developed[3] of which the diastereoselective reduction of chiral α-keto esters[4] and amides[5] has been most actively investigated. This study describes the utility of chiral hemiacetals of α-keto acids[6,7] as precursors of α-hydroxy acids and elaborates the unique opportunities for diastereoselective manipulation of the hemiacetal moiety[6].

The objective of the present study was to develop an efficient synthesis of both enantiomers of α-hydroxy acids from a common precursor. Practically all of the reported reductive approaches to α-hydroxy acids rely on selective shielding of one face of the prochiral carbonyl group in the keto-acid derivative, followed by a diastereoselective external delivery of hydride[8]. We decided to investigate the possibility of carrying out intramolecular reductions of appropriately functionalized chiral α-keto acid derivatives. Specifically, we chose to examine the utility of a pendant hydroxyl group in the auxiliary portion of a chiral α-keto amide. Such amides should be readily available by *N*-acylation of amino alcohols. Although the utility of a free hydroxyl group as a directing group is well documented[9], the use of a hydroxymethyl group as a sterically shielding functionality[10] is relatively less explored. We

0040-4020/98/$ - see front matter
PII: S0040-4020(98)00914-4

hoped to explore this functional duality for a stereodivergent reduction of α-keto amides. The postulate is summarized in Figure 1.

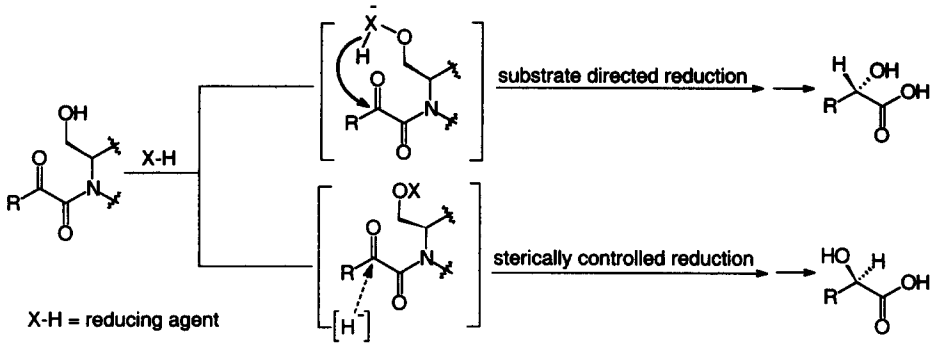
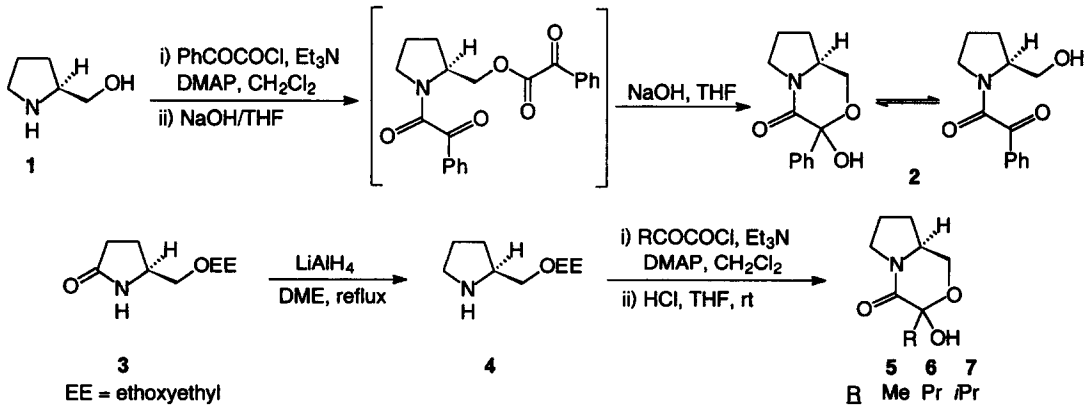


Figure 1. Stereodivergent reduction of α-ketoamides with a pendant hydroxyl group

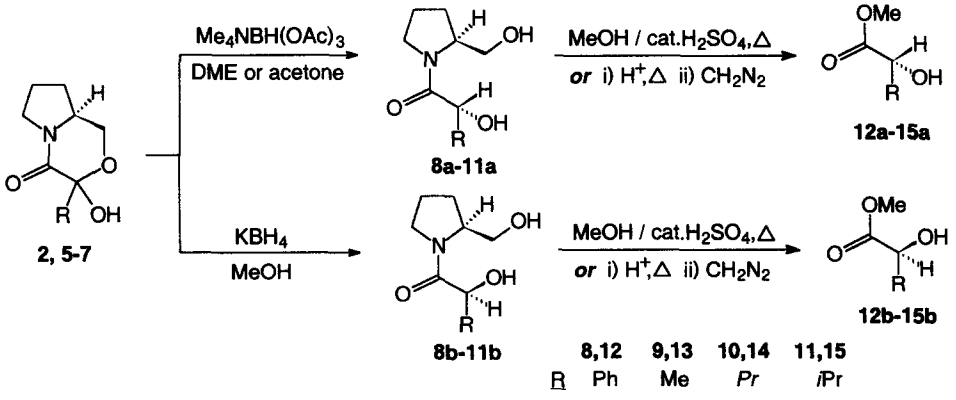
(*S*)-2-Hydroxymethyl pyrrolidine ((*S*) prolinol) **1** [11] was chosen as an auxiliary in the present study. Acylation of (*S*) prolinol with benzoylformyl chloride followed by selective ester hydrolysis in the resulting intermediate amido ester gave the keto amide **2** that exists as a 3:1 mixture of the hemiacetal/ ketoalcohol (Scheme 1). Acylation of **1** with aliphatic α-keto acid chlorides led to complex mixtures and protection of the hydroxyl group was necessary. Protection of **1** with ethylvinyl ether gave *O*-ethoxyethyl-(*S*)-prolinol **4** in low yield (10-15%). Alternatively, **4** could be readily prepared by LAH reduction of (*S*)-*O*-ethoxyethyl-5-hydroxymethyl-2-pyrrolidinone **3**[12] (prepared from commercially available (*S*)-5-hydroxymethyl-2-pyrrolidinone and ethylvinyl ether according to the literature procedure [12]). The *O*-protected prolinol **4** was readily *N*-acylated by reaction with α-keto acid chlorides or by DCC coupling with α-keto acids to furnish the *O*-protected keto amides. Acid catalyzed deprotection of the hydroxyl group provided the requisite keto amides **5-7** as single diastereomers (Scheme 1). ^{13}C and ^{1}H NMR spectroscopy indicate that **5-7** exist in the hemiacetal form in solution. The stereochemistry at the hemiacetal carbon was not determined in this study. Hemiacetal **2** was also prepared by acylation of **4** but in lower yield.



Scheme 1

Preliminary studies were conducted with **2** and **5** as substrates. The possibility of using the free hydroxyl group as a directing group in conjunction with any chelation control elements that the system may have to offer was investigated using borohydride reducing agents. A variety of reducing agents such as $LiBH_4$, $NaBH_4$, KBH_4, $Zn(BH_4)_2$, $Mg(BH_4)_2$, Me_4NBH_4 and $Me_4NBH(OAc)_3$ in different solvents such as alcohols (ROH), DME, THF, CH_3CN and acetone were investigated.

When **2** was subjected to reduction with $NaBH_4$ in DME at 0 °C (30 min) a 1/2.5 mixture of diastereomers (^1H NMR spectroscopy) **8a/8b** was obtained in 90% yield (Scheme 2). The configuration of the newly formed stereocenter in the major diastereomer was determined to be (*S*) by hydrolysis of the crude product (1M H_2SO_4, 90 °C, 30 min) to generate (*S*) mandelic acid in 40% enantiomeric excess. The use of $LiBH_4$ in DME reduced the selectivity (**8a/8b** = 1/1.8). Reduction with KBH_4 at 0 °C in DME was very slow and at ambient temperature (48 h) the reduction was completely unselective (**8a/8b** = 1/1). Surprisingly, the use of $Mg(BH_4)_2$ and $Zn(BH_4)_2$ further reduced the selectivity and furnished **8a** and **8b** as 1/1.5 and 1/1 mixtures respectively. Reduction with Me_4NBH_4 in DME at ambient temperature furnished a 1/3 mixture of **8a** and **8b**. The results are shown in Table 1. Interestingly, the use of MeOH was found to increase the selectivity remarkably. Thus reduction with KBH_4 in MeOH at 0 °C furnished **8a/8b** as 1/13 mixture (HPLC) which gave (*S*)(+) mandelic acid (95%, 85% ee) upon hydrolysis. However, the use of EtOH and *i*PrOH reduced the selectivity (**8a/8b** = 1/5 and 1/1 respectively). Similar results were obtained for the *N*-pyruvoyl derivative **5**. Reduction with $NaBH_4$ or $LiBH_4$ in DME proceeded with moderate stereoselection (**9a/9b** = 1/6) which improved with KBH_4/MeOH (**9a/9b** = 1/15). Methanolysis (MeOH, cat. H_2SO_4) of **9** furnished (*S*) methyl lactate **13b** (60-65%, 86% ee, Scheme 2). The results of the reagent and solvent optimization studies are summarized in Table 1.



Scheme 2

The lack of selectivity in aprotic solvents is surprising, especially with $Zn(BH_4)_2$[13], as is the increase of stereoselectivity in protic solvents. The observed solvent dependence of stereoselectivity is opposite to that seen in proline ester derived substrates[14]. The sense of asymmetric induction is, however, the same.

We next investigated triacetoxyborohydride reducing agents for which prior binding to the free hydroxyl group in **2** would be necessary for reduction of the ketone at an appreciable rate[15]. The reaction of **2** with $NaBH_4$ in AcOH, conditions known to generate $NaBH(OAc)_3$[16], was heterogeneous and extremely slow. However, changes in counterion and solvent were found to be beneficial. Thus, treatment of **2** with $Me_4NBH(OAc)_3$[15] in acetonitrile furnished **8a** and **8b** as a 3/1 mixture of diastereomers. When DME was used as solvent the selectivity increased remarkably to furnish an 18/1 mixture of **8a** and **8b.** Similar results were obtained when acetone was used as solvent (**8a** obtained as a single diastereomer by 200 MHz ^1H NMR spectroscopy). Hydrolysis of the crude product furnished (*R*)(-) mandelic acid (93%) with 90% ee. Similarly, reduction of **5** with $Me_4NBH(OAc)_3$ in acetone was also highly stereoselective (75% conversion, **9a/9b** = >50/1) at room temperature. The synthesis of authentic materials established the absolute configuration of the reduction products **8** and **9**. These reductions involving 1,4 asymmetric induction, proceed with good stereoselectivity at room temperature.

Table 1

Reduction of ketoamides **2** and **5**

Compound	Reducing agent	Solvent	Temp °C	Product	Yield%	ds a/b
2	$LiBH_4$	DME	0	8	90	1/1.8[a]
	KBH_4	*i*PrOH	0		75	1/1[a]
	KBH_4	EtOH	0		90	1/5[a]
	KBH_4	MeOH	0		90	1/13[a]
	$Mg(BH_4)_2$	THF	25		83	1/1.5[a]
	$Zn(BH_4)_2$	DME	25		65	1/1[a]
	Me_4NBH_4	DME	25		66	1/3[a]
	$Me_4NBH(OAc)_3$	DME	25		90	18/1[b]
	$Me_4NBH(OAc)_3$	acetone	28		85	19/1[a]
5	$LiBH_4$	DME	0	9	80	1/5.7[b]
	$NaBH_4$	DME	0		60	1/6[b]
	KBH_4	MeOH	0		75	1/15.7[b]
	$Me_4NBH(OAc)_3$	acetone	28		45	>50/1[b]

a: ratio determined by ^1H NMR spectroscopy b: ratio determined by HPLC

Two reducing systems thus emerged as ideal for substrates **2** and **5**, namely KBH_4 in methanol and $Me_4NBH(OAc)_3$ in acetone or DME. Substrates **6** and **7** were subjected to these conditions to generate **10a,10b** and **11a,11b** respectively (Scheme 2), with similar trends in stereoselectivity as observed for **2** and **5**. The configurational assignment was confirmed by comparing the signs of the optical rotations of the free α-hydroxy acids or esters obtained from **10** and **11** with literature values.

Removal of the (*S*)-prolinol auxiliary from the hydroxy amides **8-11** was readily achieved by acid catalyzed hydrolysis (1 M H_2SO_4, 90 °C, 1-3 h). Alternatively, a direct conversion of the hydroxy amides to the α-hydroxy esters may be achieved by refluxing methanolic solutions of the amides in the presence of a catalytic amount of H_2SO_4. These reactions probably proceed by initial acyl migration from nitrogen to oxygen[17] followed by methanolysis of the resulting ester. The crude reduction products **8a,b-11a,b** were converted to the methyl esters **12a,b-15a,b** (54-94%, Scheme 2) which were used for enantiomeric excess determinations by ^1H and/or ^{19}F NMR analysis of their MTPA esters[18]. The results are summarized in Table 2.

Table 2

Stereodivergent reduction of α-ketoamides 2,5-7

Compound	R	Reducing agent	Ester	% ee(*R*)[a]	% ee(*S*)[a]
2	Ph	$Me_4NBH(OAc)_3$	12a	90	
		KBH_4	12b		85
5	Me	$Me_4NBH(OAc)_3$	13a	95	
		KBH_4	13b		86
6	Pr	$Me_4NBH(OAc)_3$	14a	82	
		KBH_4	14b		83
7	*i*Pr	$Me_4NBH(OAc)_3$	15a	70	
		KBH_4	15b		80

a: determined by NMR analysis of MTPA esters.

Thus, both the (*R*) and the (*S*) enantiomers of α-hydroxy acids are available in greater than 80% ee from one substrate. The only exception is **15a** (70% ee) which may be due to slow reduction of **7** with $Me_4NBH(OAc)_3$ (steric effect of the isopropyl group) resulting in a competing intermolecular reduction which reduces the stereoselectivity.

Origin of stereoselection in the reduction of keto amides 2,5-7

An intriguing outcome of the study is the reagent dependence of the sense of asymmetric induction. Thus, while $Me_4NBH(OAc)_3$ in acetone or DME generates **8a-11a**, KBH_4 in methanol generates the diastereomeric **8b-11b** as the predominant isomer. This stereodivergence is probably due to a difference in the mechanism of reduction.

The reduction of **2,5,6** and **7** with $Me_4NBH(OAc)_3$ may be either intramolecular or intermolecular in nature. However, in a control experiment, the reduction of *N*-benzoylformyl pyrrolidine with $Me_4NBH(OAc)_3$ was sluggish (<10% conversion under conditions that resulted in complete reduction of **2**), indicating that the hydroxyl group in the substrate is essential for the reduction to proceed at a reasonable rate. This suggests an intramolecular process for the reduction of substrates **2,5-7** with $Me_4NBH(OAc)_3$ and, as reported earlier[15], acetone can be used as a solvent for these reductions. The intramolecular reduction pathway is in tune with previous proposals[15,19]. An alternative possibility of a non-chelation controlled intermolecular reduction may not be operative for $Me_4NBH(OAc)_3$ since reduction of **2** with Me_4NBH_4 (non chelating cation) generates **8b** as the major product.

The diastereoselectivity of the reduction with $Me_4NBH(OAc)_3$ suggests a transition state assembly as depicted in Figure 2. Assuming a coplanar *syn* amide *anti* α-dicarbonyl conformation **A'** (Figure 2), intramolecular reduction from the *Si* face of the ketone generates the α-hydroxy acid with (*R*) configuration. A *syn* amide *syn* α-dicarbonyl conformation, such as **A** (Figure 2), may be of higher energy (unfavourable steric interactions between the ketoacid portion and prolinol).

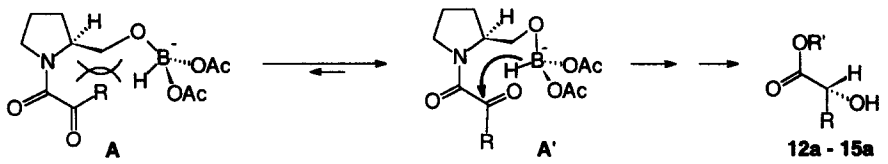


Figure 2. Intramolecular reduction of **2,5-7** with $Me_4NBH(OAc)_3$

The exact reason for the unusual solvent effect for reduction with MBH_4 reagents remains unclear at present. The low stereoselectivity for reduction of **2,5-7** with conventional borohydride reagents in aprotic solvents may presumably be due to reduction by substrate bound as well as unbound borohydride. Similarly, the reduction in alcohol solvents may be explained by invoking participation of the solvent in the reduction process. Assuming the same reactive conformer (*syn* amide *anti* α-dicarbonyl **A'**, Figure 2), and considering the known reactivity of alcohols with $NaBH_4$ (MeOH>EtOH>*i*PrOH)[20] it is plausible that reduction in methanol proceeds largely through a solvent assisted[21] mode under steric control wherein the reducing agent approaches from the less hindered *Re* face of the ketone. This results in the formation of **8b-11b** as the major diastereomer (path 'b', Figure 3). Since the rate of reaction of KBH_4 with EtOH and *i*PrOH is much slower than with MeOH it is possible that solvent assisted reduction in these alcohols is slow enough to permit intramolecular reduction involving the substrate hydroxyl group to compete effectively. This may reduce the stereoselectivity by generating substantial amounts of **8a-11a** (path 'a', Figure 3).

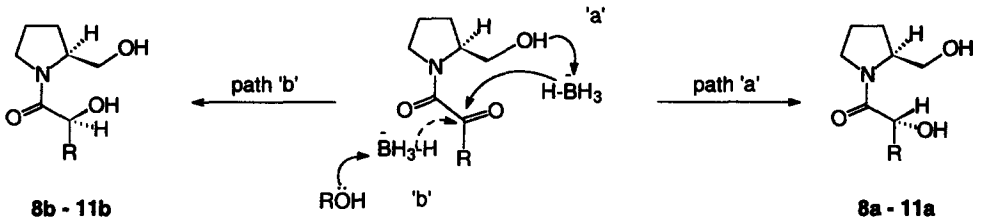


Figure 3. Competing intermolecular and intramolecular reduction of **2,5,6** and **7**

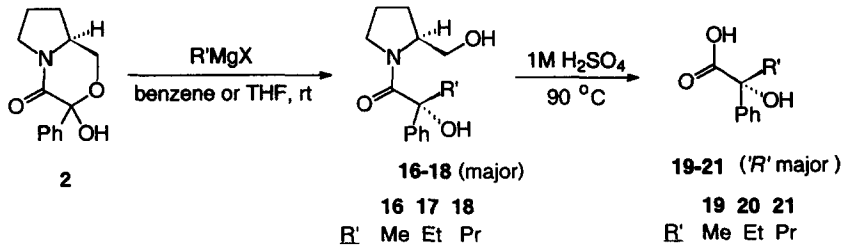
The reversal of stereochemistry with simple borohydride based reducing agents is unusual for ketoacid derived substrates and has previously been achieved only with complex reducing agents in the presence of additives such as metal salts[22] and crown ethers[23], and that too at low temperature. Also, in contrast to the present study, previous asymmetric syntheses of α-hydroxy acids employing the ketoacid reduction protocol have mainly relied on bulky reducing agents and/or low temperatures for good stereodifferentiation. The method described above therefore provides a distinct advantage in that it employs simple reducing agents at moderate reaction temperatures. It also provides both enantiomers of α-hydroxy acids with good to high enantiomeric excess from a common precursor by judicious choice of solvent and reducing agent.

Reactions of hemiacetal 2 with organometallic reagents

The synthesis of α-substituted-α-hydroxy acids[24,25] by the diastereoselective addition of organometallic reagents to the above hemiacetals was also examined. It is noteworthy that although the reactions of lactols (hydroxy aldehydes) with organometallics have been studied[26], similar reactions with hemiacetals of hydroxy ketones have not received much attention[7].

Somewhat surprisingly, reaction of hemiacetals **5-7** with a variety of organometallic reagents was unsuccessful at low temperature and led to decomposition of the hemiacetals at

ambient temperature. Hemiacetal **2** was also unreactive toward a variety of organometallic reagents at subambient temperatures. These observations are in contrast to the facile reactions of lactols with carbon nucleophiles[26]. Although the reaction of **2** with methylmagnesium iodide could not be effected in a variety of solvents, exposure to a large excess of MeMgBr (*ca.* 10 equivalents) for 8 h at room temperature generated **16**. Thus, a variety of commercial grade Grignard reagents could be added to **2** to provide the α-hydroxy amides **16-18** as a mixture of diastereomers in 65-70% yield (Scheme 3).



Scheme 3

The configuration of the newly formed stereocenter was determined by hydrolysis of the α-hydroxy amides (1M H_2SO_4, 90 °C, 2 h) to the known α-alkyl mandelic acids **19-21** [27]. In all cases the major diastereomer in **16-18** had the (*R*) configuration at the newly generated stereocenter as was evident from the sign of the specific rotation of the α-hydroxy acids obtained by hydrolysis (Scheme 3). The diastereoselectivity (82-87%) was determined from the enantiomeric excess of the α-hydroxy acids **19-21** which were analysed by chiral HPLC on a SERVA Si 100 HyproCu 5 μ chiral column (4.6 mm id x 25 cm); 1/9 acetonitrile/4mM $CuSO_4.5H_2O$ as the mobile phase; flow rate 1 ml/min; UV detection at 265 nm. The results are summarized in Table 3.

Table 3

Additions of Grignard reagents to hemiacetal **2** and hydrolysis of amides **16-18** to acids **19-21**

Compound	Yield%	% ee[a]
16	73	
17	71	
18	69	
19	62	82
20	63	87
21	68	84

a: determined by chiral HPLC.

The diastereoselectivity of the Grignard addition reactions to **2** is remarkable considering that the reactions are performed at ambient temperature and particularly when compared with results obtained on an analogous substrate[28] which has (*S*)-2-(methoxymethyl) pyrrolidine as the auxiliary (*O*-methyl analog of **2** in the open form). Addition of methylmagnesium bromide to this ketoamide at *-78 °C* proceeds with lower diastereoselectivity (ds=76/24) and with facial selectivity opposite to that observed for **2**[28]. The exact reasons for the reversal of facial selectivity with concomitant increase in diastereoselectivity in our study are unclear at present. The results may indicate a different aggregation state for **2** after deprotonation as compared with the analogous methyl ether.

In conclusion we have demonstrated that α-keto acid derived hemiacetals serve as unique precursors of α-hydroxy acids. It has been shown that the pendant hydroxyl group in the auxiliary portion of these substrates may be exploited as a useful tool in stereodivergent reductions and stereoselective addition of Grignard reagents to these substrates. The advantages of employing hemiacetals are stereodivergence in reduction by judicious choice of solvent and reducing agent as well as good stereocontrol in reduction and Grignard addition reactions at ambient temperature.

Acknowledgment: We thank Prof. Paul Harrison (McMaster University) and Prof. Naoto Chatani (Osaka University) for HRMS of some of the intermediates. Financial assistance from the Department of Science and Technology (Grant No: SP/S1/G-11/96 (in part)) and the Council of Scientific and Industrial Research (funding to RGR as a Research Associate) is gratefully acknowledged. This is NCL Communication No: 6445.

Experimental

General

General experimental methods have been described earlier[7]. All Grignard reagents, reducing agents (MBH_4) and α-keto acids used were commercial grade. $Me_4NBH(OAc)_3$ was prepared *in situ* from Me_4NBH_4 by adaptation of the literature procedure[15].

(*S*)-2-Hydroxymethyl-*N*-benzoylfomyl pyrrolidine (2):

To a solution of benzoylformyl chloride (prepared from benzoylformic acid (0.94 g, 6.2 mmol) and oxalyl chloride (1.7 mL, 20 mmol)) in anhydrous CH_2Cl_2 (15 mL)) was added a solution of (*S*) prolinol [11](0.315 g, 3.12 mmol), triethylamine (1.8 mL, 13 mmol) and DMAP (0.64 g, 5.2 mmol) in CH_2Cl_2 (15 mL) slowly at 0 °C. The reaction mixture was stirred at ambient temperature for 6 h. The reaction mixture was diluted with CH_2Cl_2, washed with 5% HCl, saturated $NaHCO_3$ solution, brine, dried (Na_2SO_4) and concentrated to furnish 1.2 g of crude product which on purification by flash chromatography on silica gel (7/3 petroleum ether/ethyl acetate) furnished 0.6 g (52%) of (*S*) 2-hydroxymethyl-*N,O*-bisbenzoylfomyl pyrrolidine as an oil. To a solution of this product (0.6 g, 1.64 mmol) in THF (10 mL) was added 1M NaOH (1.7 mL) and the mixture was stirred for 1.5-2 h at ambient temperature. The reaction mixture was diluted with ethyl acetate and washed with brine, dried (Na_2SO_4) and concentrated to furnish 0.365 g solid which on purification by flash chromatography on silica gel (35/65 petroleum ether/ethyl acetate) furnished 0.326 g (85%) of 2 as a solid.

mp: 92-96 °C. **^{1}H NMR** (200 MHz, $CDCl_3$) **Hemiacetal:** δ 7.75-7.6 (m, 2H, Ar*H*), 7.45-7.3 (m, 3H, Ar*H*), 4.62 (br s, 1H, O*H*), 4.2-4.1 (dd, 1H, *J* = 7.5, 2.4, CH_2O), 4.05-3.30 (m, 4H, NC*H*, CH_2O, NCH_2), 2.25-1.6 (m, 3H, ring CH_2), 1.6- 1.4 (m, 1H, ring CH_2). **Visible peaks for the ketoalcohol:** δ 7.99 (dd, 2H, *J* = 7.2, 2.1, Ar*H*), 7.6-7.45 (m, 3H, Ar*H*), 4.4-4.25 (m, 1H, NC*H*). **^{13}C NMR** (50 MHz, $CDCl_3$) **Hemiacetal:** δ 167.7 (NCO), 141.0 (Ar*C ipso*), 129.6 (Ar*C*), 128.9 (Ar*C*), 128.4 (Ar*C*), 127.8 (Ar*C*), 126.1 (Ar*C*), 95.8 (PhCOH), 64.9 (*C*H_2OH), 58.3 (NCH), 45.2 (NCH_2), 25.7 (*C*H_2), 22.6 (*C*H_2). **Ketoalcohol:** δ 192 (*C*O), 167.5 (NCO), 132.4 (Ar*Cipso*), 129.8 (Ar*C*), 128.9 (Ar*C*), 128.4 (Ar*C*), 127.8 (Ar*C*), 126.1 (Ar*C*), 64.0 (*C*H_2O), 60.8 (NCH), 47.7 (N*C*H_2), 27.5 (*C*H_2), 24.1 (CH_2). **IR** ($CHCl_3$) 3300, 3020, 2860,

1660, 1620, 1450, 1345, 1220, 1070, 870, 760 cm^{-1}. **MS** (70 eV) m/z 77 (64), 85 (35), 105 (100), 128 (85), 174 (10), 202 (20), 233 (14, M^+). $[\alpha]_D$ = -70 (c 2.2, $CHCl_3$); **Analysis** for $C_{13}H_{15}NO_3$ calcd: C 66.95, H 6.48, N 6.00 , found C 66.94, H 6.70, N 6.19.

(*S*)-*O*-Ethoxyethyl-2-hydroxymethyl pyrrolidine (4):

To a suspension of LAH (1.8 g, 47.4 mmol) in anhydrous DME (40 mL) was added a solution of *O*-ethoxyethyl-(*S*)-5-hydroxymethyl-2-pyrrolidinone **3**[12](3 g, 16 mmol) in DME (10 mL) and the mixture was heated to reflux for 4 h. The mixture was cooled (ice bath), sequentially treated with water (1.8 mL), 15% NaOH (1.8 mL) and water (5 mL) and then heated to reflux for 20 min. The precipitate obtained was filtered off, heated with DME (40 mL) and the mixture was filtered. The combined filtrates were concentrated to furnish 2.4 g (87%) of **4** as a pale yellow oil (pure by ^1H NMR spectroscopy) that gradually decomposes on storage. Crude **4** was therefore used further without purification.
^1H NMR (200 MHz, $CDCl_3$) δ 4.65 (q, *J* = 5.3, 1H, OC*H*O), 3.7-3.1 (m, 5H, NC*H*, 2CH_2O), 3.05-2.70 (m, 2H, NCH_2), 2.50 (br s, 1H, N*H*), 1.9-1.6 (m, 3H, 2CH_2), 1.5-1.3 (m, 1H, CH_2), 1.26 (d, *J* = 5.3, 3H, CH_3), 1.15 (t, *J* = 7.1 3H, CH_3). **^{13}C NMR** (50 MHz, $CDCl_3$) δ 99.1 (O*C*HO), 67.9 (*C*H_2O), 60.2 (*C*H_2O), 57.3 (N*C*H), 45.7 (N*C*H_2), 27.3 (*C*H_2), 24.5 (*C*H_2), 19.1 (*C*H_3), 14.6 (*C*H_3). **Visible peaks of diastereomer:** δ 98.9 (O*C*HO), 67.3 (*C*H_2O), 60.1 (*C*H_2O). **IR** (neat) 3260, 2960, 1380, 1100, 930, 880, 810 cm^{-1}.

General procedure for preparation of 5-7 by *N*-acylation of 4:

To a suspension of the sodium salt of the α-keto acid in CH_2Cl_2 or to the neat α-keto acid was added Cl_2CHOMe at ambient temperature and the mixture was stirred for 20 minutes. The resulting suspension or solution was heated at 50-55 °C for 30 minutes after which it was cooled to ambient temperature and diluted with anhydrous CH_2Cl_2. To this was added a solution of **4**, triethylamine and DMAP in anhydrous CH_2Cl_2 dropwise with cooling (ice bath). The mixture was then stirred at ambient temperature for 6 h. The reaction mixture was diluted with CH_2Cl_2, washed with 10% aqueous citric acid, saturated sodium bicarbonate, brine and then dried over anhydrous Na_2SO_4 and concentrated to provide the crude product which was purified by flash chromatography on silica gel using petroleum ether/ethyl acetate.

Alternatively, a procedure which involves DCC coupling may also be employed. To a solution of **4** and α-keto acid in anhydrous CH_2Cl_2 was added a solution of DCC in anhydrous CH_2Cl_2 with cooling (ice bath). The mixture was then stirred at ambient temperature for 6 h. The solids that separated were filtered and the filtrate was concentrated to provide the crude product which was purified by flash chromatography on silica gel.

Deprotection of the *N*-acylated products to the hemiacetals 5-7:

The *N*-acylated product was dissolved in THF and dilute HCl was added. The mixture was stirred at ambient temperature for 3 h. The reaction mixture was diluted with ethyl acetate, washed with brine and dried over Na_2SO_4 and concentrated to give the crude product which was purified by flash chromatography on silica gel using petroleum ether/ethyl acetate. Alternatively, purification may be effected by recrystallization.

8a(*S*)-3-Methyl-3-hydroxy-4-oxo hexahydro 1*H*-pyrrolo[2,1-*c*][1,4] oxazine (5):

Reaction of pyruvoyl chloride (prepared from pyruvic acid (0.42 mL, 6.1 mmol) and Cl_2CHOMe (0.54 mL, 6.1 mmol)) and *O*-ethoxyethyl-*S*-prolinol (0.64g, 3.7 mmol) in the presence of triethylamine (1 ml, 7.4 mmol), DMAP (0.22g, 1.85 mmol) in CH_2Cl_2 (25 mL) furnished 0.69 g of crude product which on purification by flash chromatography (7/3 petroleum ether/ethyl acetate) furnished 0.5g (68%) of the *N*-acylated product as an oil. Hydrolysis of this product (0.48 g, 2 mmol) furnished 0.28 g (82%) of **5** as a solid after purification by flash chromatography on silica gel (ethyl acetate).

mp: 156-157 °C. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 4.1 (s, 1H, O*H*), 4.05-3.88 (m, 1H, CH_2O), 3.88-3.68 (m, 2H, NC*H*, CH_2O), 3.68-3.35 (m, 2H, NCH_2), 2.2-1.75 (m, 3H, CH_2), 1.65 (s, 3H, CH_3), 1.58-1.3 (m, 1H, CH_2). **^{13}C NMR** (50 MHz, $CDCl_3$) δ 168.2 (*C*O), 94.4 (*C*OH), 63.4 (*C*H_2O), 57.9 (*C*H), 44.7 (*C*H_2), 28.5 (*C*H_2), 25.5 (*C*H_3), 22.4 (*C*H_2). **IR** ($CHCl_3$) 3392, 3019, 1647, 1475, 1382, 1216, 1134, 1049, 915, 760, 668 cm^{-1}. **MS** (70 eV). m/z 55 (50), 67 (22), 61 (4), 70 (100), 83 (22), 98 (26), 111 (12), 128 (5), 154 (5), 171 (1, M$^+$). $[\alpha]_D$ = - 8.5 (c 2, CH_2Cl_2); **Analysis** for $C_8H_{13}NO_3$: Calcd: C 56.13, H 7.65, N 8.18; Found: C 55.83, H 7.83, N 8.10.

8a(*S*)-3-Propyl-3-hydroxy-4-oxo hexahydro 1*H*-pyrrolo[2,1-*c*][1,4] oxazine (6):

Reaction of 2-oxopentanoyl chloride (prepared from 2-oxopentanoic acid sodium salt (0.28g, 2 mmol) and Cl_2CHOMe (0.21 mL, 2.4 mmol)) and *O*-ethoxyethyl-*S*-prolinol (0.3g, 1.73 mmol) in the presence of triethylamine (0.3 mL, 2.2 mmol), DMAP (0.05g, 0.4 mmol) in CH_2Cl_2 (8 mL) furnished 0.4 g of crude product which on purification by flash chromatography (7/3 petroleum ether/ethyl acetate) provided 0.29 g (62%) of the *N*-acylated product as an oil. Hydrolysis of this product (0.38 g, 1.4 mmol) furnished 0.245 g (87%) of **6** as a solid after purification by flash chromatography on silica gel (ethyl acetate).

mp: 115-116 °C **^{1}H NMR** (200 MHz, $CDCl_3$) δ 4.10-3.85 (m, 1H, CH_2O), 3.85-3.35 (m, 4H, CH_2O, NC*H*, NCH_2), 2.15-1.70 (m, 5H, CH_2, CH_2CH_2CHN), 1.7-1.1 (m, 3H, CH_3CH_2, ring CH_2), 0.90 (t, 3H, *J* = 7, CH_3). **^{13}C NMR** (50 MHz, $CDCl_3$) δ 168.2 (*C*O), 96.4 (*C*OH), 63.7 (*C*H_2O), 57.9 (*C*H), 44.8 (*C*H_2), 40.9 (*C*H_2), 28.5 (*C*H_2), 22.5 (*C*H_2), 16.4 (*C*H_2), 13.7 (*C*H_3). **IR** ($CHCl_3$) 3322, 2965, 1640, 1466, 1124, 1049, 757 cm^{-1}. **MS** (70 eV) m/z 70 (100), 83 (14), 98 (14), 111 (5), 128 (10), 156 (3), 181 (1), 199 (1, M$^+$); $[\alpha]_D$ = + 8.6 (c 2, $CHCl_3$); **HRMS** calcd for $C_{10}H_{17}NO_3$ 199.1208, found 199.1212.

8a(*S*)-3-(2-Propyl)-3-hydroxy-4-oxohexahydro 1*H*-pyrrolo[2,1-*c*][1,4] oxazine (7):

Reaction of 3-methyl-2-oxobutyryl chloride (prepared from 3-methyl-2-oxobutyric acid sodium salt (0.65g, 4.7 mmol) and Cl_2CHOMe (0.46 mL, 5.17 mmol)) and *O*-ethoxyethyl-*S*-prolinol (0.8g, 4.6 mmol) in the presence of triethylamine (0.72 mL, 5.2 mmol), DMAP (0.063g, 0.5 mmol) in CH_2Cl_2 (15 mL) furnished 1.2 g of crude product which on purification by flash chromatography (7/3 petroleum ether/ethyl acetate) provided 0.8 g (65%) of the *N*-acylated product as an oil. Hydrolysis of this product (0.7 g, 2.6 mmol) furnished 0.39 g (75%) of **7** as a solid after purification by flash chromatography on silica gel (ethyl acetate).

mp: 114 °C **^{1}H NMR** (200 MHz, $CDCl_3$) δ 4.08-3.9 (m, 1H, CH_2O), 3.8-3.4 (m, 4H, CH_2O, NC*H*, NCH_2), 2.34-2.14 (m, 1H, C*H*(CH_3)$_2$), 2.14-1.95 (m, 2H, CH_2CH_2), 1.95-1.70 (m, 1H,

CH_2CH_2), 1.55-1.3 (m, 1H, CH_2CH_2), 0.99 (d, 3H, J = 7, $CH(CH_3)_2$), 0.85 (d, 3H, J = 7, $CH(CH_3)_2$). **^{13}C NMR** (50 MHz, $CDCl_3$) δ 168.6 (NCO), 97.7 (COH), 63.7 (CH_2O), 57.6 (NCH), 44.6 (NCH_2), 35.2 (CH_3CHCH_3), 28.3 (CH_2), 22.3 (CH_2), 16.5 (CH_3), 14.1 (CH_3). **IR** ($CHCl_3$) 3278, 1625, 1467, 1065, 618 cm^{-1}. **MS** (70 eV) m/z 70 (100), 83 (50), 98 (47), 111 (19), 128 (16), 156 (44), 171 (2), 182 (9), 200 (1, M+1). $[\alpha]_D$ = +35.9 (c 2, $CHCl_3$); **Analysis** for $C_{10}H_{17}NO_3$ calcd: C 60.28, H 8.60, N 7.03; found C 60.28, H 9.00, N, 7.05.

General procedure for the reduction of hemiacetals 2,5-7:

a) Reduction with $Me_4NBH(OAc)_3$ in acetone or DME:

To a suspension of Me_4NBH_4 in acetone or DME was added anhydrous acetic acid dropwise with cooling (ice bath). The reaction mixture was warmed up to ambient temperature and stirred for 20 minutes at which time a clear solution of $Me_4NBH(OAc)_3$ was obtained. To this was added a solution of the substrate in acetone or DME and the mixture was stirred at ambient temperature for 24-36 h. Water was added, the solution was neutralized with solid $NaHCO_3$, and extracted with ethyl acetate. The combined extracts were dried over anhydrous Na_2SO_4 and concentrated to furnish the crude product which was purified by flash chromatography on silica gel. Alternatively, the mixture was treated with saturated aqueous NH_4Cl and then concentrated to dryness. The residue obtained was extracted with ethyl acetate, isolated and purified by flash chromatography on silica gel.

b) Reduction with KBH_4 in methanol:

To a solution of the substrate in MeOH at 0 °C was added KBH_4 and the mixture was stirred for 10 h at 0 °C. Saturated aqueous NH_4Cl was added and the product was extracted with ethyl acetate. Combined ethyl acetate extracts were dried over anhydrous Na_2SO_4 and concentrated to furnish the crude product which was purified by flash chromatography on silica gel.

(*S*)-2-Hydroxymethyl-*N*-((*R*)-2-hydroxy-2-phenyl)-acetyl pyrrolidine (8a):

Reaction of **4** (0.2 g, 0.86 mmol) and $Me_4NBH(OAc)_3$ (prepared from Me_4NBH_4 (0.765g, 8.6 mmol) and anhydrous acetic acid (1.97 mL, 34.4 mmol)) in DME (15 mL) furnished 0.24 g of crude product which on purification by flash chromatography on silica gel (3/7 petroleum ether/ethyl acetate) furnished 0.155g (77%) of **8a** as a gum.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.60-7.25 (m, 5H, ArH), 5.10 (s, 1H, PhCHOH), 4.58 (s, 1H, OH), 4.25-4.15 (m, 1H, NCH), 3.75-3.60 (m, 2H, CH_2O), 3.55-3.30 (m, 1H, NCH_2), 3.20-3.0 (m, 1H, NCH_2), 2.05-1.75 (m, 2H, CH_2CH_2), 1.75-1.50 (m, 2H, CH_2CH_2). **^{13}C NMR** (50 MHz, $CDCl_3$) δ 172.2 (NCO), 138.1 (ArCipso), 128.8 (ArC), 128.5 (ArC), 127.4 (ArC), 72.7 (PhCHOH), 65.0 (CH_2O), 61.4 (NCH), 46.7 (NCH_2), 27.4 (CH_2), 23.8 (CH_2). **IR** ($CHCl_3$) 3417, 2924, 1622, 1443, 1184, 1043, 759, 698, 617 cm^{-1}. **MS** (70 eV). m/z, 57 (22), 70 (100), 77 (41), 107 (19), 128 (55), 176 (9), 204 (4), 236 (2, M+1). **HPLC**: t_R = 17.1 min. (E.Merck Lichrospher RP-18 column (250 mm x 4 mm), MeOH/H_2O gradient elution. **Analysis for $C_{13}H_{17}NO_3$:** Calcd: C 66.36,H 7.28, N 5.95; Found: C 66.05, H 7.21, N 5.79.

Hydrolysis of **8a** (0.21 g, 0.9 mmol) furnished 0.14 g (95%) of the acid which was esterified with CH_2N_2 to give 140 mg (90%) of **12a ((*R*) enantiomer):** $[\alpha]_D$ = - 130 (c 1.1, MeOH); ee based on MTPA derivative: 90%.

(*S*)-2-Hydroxymethyl-*N*-((*R*)-2-hydroxy)-propanoyl pyrrolidine (9a):

Reaction of **5** (0.1g, 0.58 mmol) and $Me_4NBH(OAc)_3$ (prepared from Me_4NBH_4 (0.312g, 3.5 mmol) and anhydrous acetic acid (0.8 mL, 14 mmol)) in DME (10 mL) furnished 0.1 g of crude product which on purification by flash chromatography on silica gel (ethyl acetate) furnished 0.8 g (80%) of **9a** as a gum.

^{1}H NMR (200 MHz, $CDCl_3$) δ 4.35 (q, 1H, J = 6.5, C*H*OH), 4.25-4.1 (m, 1H, NC*H*), 3.75-3.55 (m, 2H, CH_2OH), 3.55-3.40 (m, 2H, NCH_2), 2.15-1.8 (m, 3H, CH_2), 1.8-1.6 (m, 1H, CH_2), 1.35 (d, 3H, J = 6.5, CH_3). **^{13}C NMR** (50 MHz, $CDCl_3$) δ 175.3 (*C*O), 65.9 (*C*H_2OH, *C*HOH), 61.6 (N*C*H), 47.1 (N*C*H_2), 27.8 (*C*H_2), 24.2 (*C*H_2), 20.3 (*C*H_3). **IR** ($CHCl_3$): 3366, 3020, 2926, 2394, 1626, 1436, 1128, 1098, 1038, 940, 668 cm^{-1}. **MS** (70 eV) m/z 70 (100), 128 (5), 142 (25), 174 (1, M+1). **HRMS** calcd for $C_8H_{15}NO_3$ 173.1051, found 173.1054. **HPLC**: t_R = 21.2 min. (E.Merck Lichrospher RP-18 column (250 mm x 4 mm), MeOH/H_2O gradient elution).

***(R)* Enantiomer 13a:** Methanolysis of **9a** (55 mg, 0.32 mmol) furnished 20 mg (60%) of **13a**; ee based on MTPA derivative: 95%.

(*S*)-2-Hydroxymethyl-*N*-((*R*)-2-hydroxy)-pentanoyl pyrrolidine (10a):

Reaction of **6** (0.1g, 0.50 mmol) and $Me_4NBH(OAc)_3$ (prepared from Me_4NBH_4 (0.48 g, 5.4 mmol) and anhydrous acetic acid (1.24 mL, 21.6 mmol)) in DME (15 mL) furnished 0.095 g of crude product which on purification by flash chromatography on silica gel (ethyl acetate) furnished 0.075 g (75%) of **10a** as a gum.

^{1}H NMR (200 MHz, $CDCl_3$) δ 4.3-4.05 (m, 2H, C*H*OH, NC*H*), 3.75-3.25 (m, 4H, CH_2OH, NCH_2), 2.15-1.75 (m, 3H, CH_2), 1.75-1.25 (m, 5H, CH_2), 0.9 (brt, 3H, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 174.3 (N*C*O), 69.3 (*C*HOH), 64.8 (*C*H_2OH), 60.9 (N*C*H), 46.7 (N*C*H_2), 35.9 (*C*H_2), 27.4 (*C*H_2), 23.9 (*C*$H_2CH_2CH_3$), 18.1 (CH_2*C*H_2CH_3), 13.5 (CH_2CH_2*C*H_3). **IR** (neat) 3386, 2959, 2874, 1632, 1454, 1384, 1131, 1048, 900 cm^{-1}. **MS** (70 eV) 55 (38), 70 (100), 128 (10), 158 (3), 170 (12), 183 (2), 201 (1, M$^+$). **HRMS** calcd for $C_{10}H_{20}NO_3$ (M+H) 202.1443, found 202.1428.

Hydrolysis of **10a** (0.12 g, 0.6 mmol) furnished 55 mg (79%) of the acid which was esterified with CH_2N_2 to give 50 mg (83%) of **14a ((*R*) enantiomer)** : $[\alpha]_D$ = - 11.6 (c 1.6, $CHCl_3$); ee based on MTPA derivative: 82%.

(*S*)-2-Hydroxymethyl-*N*-((*R*)-2-hydroxy-3-methyl)-butanoyl pyrrolidine (11a):

Reaction of **7** (0.08 g, 0.4 mmol), Me_4NBH_4 (0.214 g, 2.4 mmol) and anhydrous acetic acid (0.6 mL, 9.6 mmol) in DME (8 mL) furnished 0.75 g of crude product which on purification by flash chromatography on silica gel (ethyl acetate) furnished 0.06 g of **11a** as a gum.

^{1}H NMR (200 MHz, $CDCl_3$) δ 4.35-4.0 (m, 2H, C*H*OH, NC*H*), 3.7-3.2 (m, 4H, CH_2O, NCH_2), 2.2-1.55 (m, 5H, CH_2CH_2, CH_3C*H*CH_3), 1.1 (d, 3H, J = 6.3, CH_3), 0.9 (d, 3H, J = 6.3, CH_3). **^{13}C NMR** (50 MHz, $CDCl_3$) δ 174.0 (N*C*O), 74.1 (*C*HOH), 65.6 (*C*H_2OH), 61.3 (N*C*H), 46.9 (N*C*H_2), 30.9 (CH_3*C*HCH_3), 27.8 (*C*H_2), 24.1 (*C*H_2), 19.5 (*C*H_3), 15.5 (*C*H_3). **IR** (neat) 3415, 2961, 1632, 1453, 1384, 1136, 1050, 899, 844, 617 cm^{-1}. **MS** (70 eV) m/z 70 (100), 77 (17), 83 (61), 91 (24), 98 (31), 105 (23), 112 (21), 119 (18), 128 (32), 158 (26), 170 (63), 183 (5), 201 (3, M$^+$). **HRMS** calcd for $C_{10}H_{20}NO_3$ (M+H) 202.1443, found 202.1457.

Hydrolysis of **11a** (0.1 g, 0.5 mmol) furnished 35 mg (58%) of the acid which was esterified with CH_2N_2 to give 30 mg (75%) of **15a ((*R*) enantiomer)**: ee based on MTPA derivative: 70%.

(*S*)-2-Hydroxymethyl-*N*-((*S*)-2-hydroxy-2-phenyl)acetyl pyrrolidine (8b):

Reaction of **4** (0.05 g, 0.21 mmol) and KBH_4 (0.011 g, 0.21 mmol) in methanol (3 mL) furnished 0.058 g of crude product which on purification by flash chromatography on silica gel (25/75 petroleum ether/ethyl acetate) furnished 0.042 g (85%) of **8b** as a gum.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.50-7.20 (m, Ar*H*), 5.1 (s, 1H, PhC*H*OH), 4.65 (s, 1H, O*H*), 4.40-4.10 (m, 1H, NC*H*), 3.80-3.30 (m, 3H, CH_2O, NCH_2), 2.95-2.75 (m, 1H, NCH_2), 2.15-1.40 (m, 4H, CH_2). **^{13}C NMR** (50 MHz, $CDCl_3$) δ 172.3 (N*C*O), 138.5 (Ar*Cipso*), 128.6 (Ar*C*), 128.2 (Ar*C*), 127.3 (Ar*C*), 72.3 (Ph*C*HOH), 64.6 (*C*H_2O), 61.0 (N*C*H), 46.7 (N*C*H_2), 27.0 (*C*H_2), 23.8 (*C*H_2). **IR** ($CHCl_3$) 3388, 2957, 1633, 1451, 1188, 1064, 851, 762 cm^{-1}. **MS** (70 eV) m/z, 58 (81), 69 (100), 77 (51), 91 (51), 105 (25), 107 (17), 122 (8), 128 (7), 177 (3), 203 (3), 235 (4, M$^+$). **HPLC**: t_R = 15.6 min. (E. Merck Lichrospher RP-18 column (250 mm x 4 mm), MeOH/H_2O gradient elution. **Analysis for $C_{13}H_{17}NO_3$**: Calcd: C 66.36, H 7.28, N 5.95; Found: C 65.96, H 7.12, N 6.03.

Hydrolysis of **8b** (54 mg, 0.23 mmol) furnished 33 mg (94%) of the acid, 20 mg of which was esterified with CH_2N_2 to give 19 mg (87%) of **12b ((*S*) enantiomer)** : $[\alpha]_D$ = + 123 (c 0.9, MeOH); ee based on MTPA derivative: 85%.

(*S*)-2-Hydroxymethyl-*N*-((*S*)-2-hydroxy)-propanoyl pyrrolidine (9b):

Reaction of **5** (0.1 g, 0.58 mmol) and KBH_4 (0.062 g, 1.16 mmol) in methanol (6 mL) furnished 0.089 g of crude product which on purification by flash chromatography on silica gel (ethyl acetate) furnished 0.083 g (83%) of **9b** as a gum.

^{1}H NMR (200 MHz, $CDCl_3$) δ 4.75 (br s, OH), 4.35 (q, 1H, *J* = 6.5, C*H*OH), 4.3-4.1 (m, 1H, NC*H*), 3.75-3.25 (m, 4H, NCH_2, CH_2OH), 2.2-1.75 (m, 3H, CH_2), 1.75-1.55 (m, 1H, CH_2), 1.35 (d, 3H, *J* = 6.5, CH_3). **^{13}C NMR** (50 MHz, $CDCl_3$) δ 175.5 (*C*O), 65.6 (*C*H_2OH, *C*HOH), 61.1 (N*C*H), 47.1 (N*C*H_2), 27.4 (*C*H_2), 24.4 (*C*H_2), 20.6 (*C*H_3). **IR** ($CHCl_3$) 3374, 2974, 2904, 2880, 1632, 1454, 1446, 1436, 1128, 1078, 1038 cm^{-1}. **MS** (70 eV) m/z 70 (100), 128 (4), 142 (18), 174 (1, M+1). **HRMS** calcd for $C_8H_{15}NO_3$ 173.1051, found 173.1053. **HPLC**: t_R = 20.1 min. (E. Merck Lichrospher RP-18 column (250 mm x 4 mm), MeOH/H_2O gradient elution.

Methanolysis of **9b** (80 mg, 0.46 mmol) furnished 34 mg (71%) of **13b ((*S*) enantiomer)**: ee based on MTPA derivative: 86%.

(*S*)-2-Hydroxymethyl-*N*-((*S*)-2-hydroxy)-pentanoyl pyrrolidine (10b):

Reaction of **6** (0.088 g, 0.44 mmol) and KBH_4 (0.051 g, 0.88 mmol) in methanol (4 mL) furnished 0.085 g of crude product which on purification by flash chromatography on silica gel (ethyl acetate) furnished 0.075 g (88%) of **10b** as a gum.

^{1}H NMR (200 MHz, $CDCl_3$) δ 4.3 (br s, 1H, O*H*), 4.25-4.10 (m, 1H, C*H*OH), 3.7-3.6 (m, 1H, NC*H*), 3.6-3.45 (m, 3H, CH_2OH, NCH_2), 3.35-3.20 (m, 1H, NCH_2), 2.1-1.65 (m, 4H, ringCH_2, CH_2CH_2CH$_3$), 1.6-1.3 (m, 4H, ringCH_2, CH$_2$CH_2CH$_3$), 0.88 (t, 3H, *J* = 7, CH_3). **^{13}C NMR** (200 MHz, $CDCl_3$) δ 174.5 (N*C*O), 68.9 (*C*HOH), 64.6 (*C*H_2OH), 60.4 (N*C*H), 46.8 (N*C*H_2), 36.2

(CH_2), 27.0 (CH_2), 24.1 (CH_2), 17.8 (CH_2), 13.4 (CH_3). **IR** (neat) 3409, 2959, 2366, 1625, 1459, 1385, 1045, 901 cm^{-1}. **MS** (70 eV) m/z 70 (100), 83 (12), 98 (13), 128 (13), 158 (8), 170 (34), 202 (2, M+1). **HRMS** calcd for $C_{10}H_{20}NO_3$ (M+H) 202.1443, found 202.1437.
Hydrolysis of **10b** (105 mg, 0.52 mmol) furnished 51 mg (74%) of the acid, 40 mg of which was esterified with CH_2N_2 to give 40 mg (90%) of **14b ((*S*) enantiomer):** $[\alpha]_D$ = + 10.5 (c 0.6, $CHCl_3$); ee based on MTPA derivative: 83%.

(*S*)-2-Hydroxymethyl-*N*-((*S*)-2-hydroxy-3-methyl)-butanoyl pyrrolidine (11b):

Reaction of **7** (0.06 g, 0.3 mmol) and KBH_4 (0.035 g, 0.6 mmol) in methanol (3 mL) furnished 0.07 g of crude product which on purification by flash chromatography on silica gel (ethyl acetate) furnished 0.06 g (85%) of **11b** as a gum.
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.4-4.15 (m, 1H, C*H*OH), 4.15-3.95 (m, 1H, NC*H*), 3.75-3.2 (m, 4H, CH_2O, NCH_2), 2.3-1.7 (m, 4H, CH_2CH_2), 1.7-1.5 (m, 1H, CH_3CHCH_3), 1.05 (d, 3H, *J* = 6.8, CH_3), 0.8 (d, 3H, *J* = 6.8, CH_3). **^{13}C NMR** (50 MHz, $CDCl_3$) δ 174.2 (NCO), 73.6 (CHOH), 65.0 (CH_2OH), 60.6 (NCH), 47.2 (NCH_2), 31.0 (CH_3CHCH_3), 27.1 (CH_2), 24.3 (CH_2), 19.2 (CH_3), 15.0 (CH_3). **IR** (neat): 3391, 2962, 1632, 1453, 1384, 1178, 1137, 1050, 896, 845 cm^{-1}. **MS** (70 eV) 70 (100), 128 (4), 158 (5), 170 (10), 183 (1), 202 (1, M+1). **HRMS** calcd for $C_{10}H_{20}NO_3$ 202.1443, found 202.1437.
Hydrolysis of **11b** (140 mg, 0.7 mmol) furnished 50 mg (54%) of the acid which was esterified with CH_2N_2 to give 40 mg (72%) of **15b ((*S*) enantiomer):** $[\alpha]_D$ = + 20.5 (c 0.8, $CHCl_3$); ee based on MTPA derivative: 80%.

General procedure for the reaction of 4 with Grignard reagents and hydrolysis of amides 16-18 to acids 19-21:

To a solution of the hemiacetal **2** in anhydrous benzene or THF was added the Grignard reagent with cooling (ice/water bath) and the mixture was stirred for 8 h. at ambient temperature. Saturated aqueous NH_4Cl was added and the mixture was diluted with water and extracted with ethyl acetate. The combined ethyl acetate extracts were dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by flash chromatography on silica gel using petroleum ether/ethyl acetate. Acid hydrolysis (1M H_2SO_4, 90 °C) of the crude hydroxy amides **16-18** furnished the hydroxy acids **19-21** which were analyzed for enantiomeric excess by chiral HPLC.

(*S*)-2-Hydroxymethyl-*N*-((*R*)-2-hydroxy-2-phenyl)propanoylpyrrolidine (16):

Reaction of **2** (0.15 g, 0.64 mmol) and MeMgBr (4.6 mL of 1.4 M solution in 75% toluene and 25% THF, 6.4 mmol), in benzene 4 mL afforded 0.17 g of a gum which on purification by flash chromatography on silica gel (3/7petroleum ether/ethyl acetate) furnished 0.115 g (73%) of **16** as a solid.
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.45-7.20 (m, 5H, Ar*H*), 5.05 (br s, 1H, O*H*), 4.75-4.3 (br, O*H*), 4.4-4.2 (m, 1H, NC*H*), 3.75-3.55 (m, 2H, CH_2O), 3.25-3.10 (m, 1H, NCH_2), 3.0-2.85 (m, 1H, NCH_2), 2.05-1.9 (m, 1H, CH_2), 1.8 (s, 3H, CH_3), 1.75-1.25 (m, 3H, CH_2) **^{13}C NMR** (75 MHz, $CDCl_3$) δ 175.5 (NCO), 142.3 (Ar ipso), 128.6 (Ar), 127.8 (Ar), 125.3 (Ar), 75.4 (COH), 66.3 (CH_2OH), 62.2 (NCH), 48.1 (NCH_2), 27.3 (CH_2), 25.0 (CH_3), 24.6 (CH_2). **IR** (nujol)

2922, 1610, 1455, 1034, 732 cm^{-1}. **MS** (70 eV) /z 70 (74), 77 (18), 84 (100), 105 (22), 121 (94), 128 (38), 190 (52), 218 (7), 232 (2), 250 (3, M+1). **HRMS (FAB+)** calcd for $C_{14}H_{20}NO_3$ (M+H) 250.1444, found 250.1445.
Hydrolysis of **16** (0.16 g, 0.64 mmol) afforded 0.07 g (62%) of the hydroxy acid **19.** $[\alpha]_D$ = -27 (c 1.35, EtOH), (Lit[27]. $[\alpha]_D$ = + 36.3 (c 2.7, EtOH) for (*S*) enantiomer). Enantiomeric excess = 82%; **HPLC**: t_R = 25.3 min (major, (*R*) enantiomer), 22.5 (minor, (*S*) enantiomer).

(*S*)-2-Hydroxymethyl-*N*-((*R*)-2-hydroxy-2-phenyl)-butanoylpyrrolidine (17):

Reaction of **2** (0.16 g, 0.69 mmol) and EtMgCl (3.4 mL of 2 M solution in THF, 6.8 mmol), in benzene (6 mL) afforded 0.18 g of a gum which on purification by flash chromatography on silica gel (1/1petroleum ether/ethyl acetate) furnished 0.128 g (71%) of **17** as a gum.
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.55-7.20 (m, 5H, Ar*H*), 5.10 (s, 1H, O*H*), 4.50-4.20 (m, 1H, NC*H*), 3.85-3.45 (m, 2H, CH_2O), 3.25-2.85 (m, 2H, NCH_2), 2.45-2.10 (m, 2H, CH_2), 2.10-1.80 (m, 1H, CH_2) 1.80-1.15 (m, 3H, CH_2), 1.00 (t, 3H, J = 7.1, CH_3) **^{13}C NMR** (50 MHz, $CDCl_3$) δ 174.2 (N*C*O), 141.9 (Ar*Cipso*), 128.4 (Ar*C*), 127.6 (Ar*C*), 125.5 (Ar*C*), 78.0 (Ph*C*OH), 65.7 (CH_2O), 61.9 (N*C*H), 47.6 (NCH_2), 28.7 (CCH_2), 26.9 (CH_2), 24.4 (CH_2), 7.5 (CH_3) **IR** (Neat) 3368, 2879, 1605, 1048, 950, 853 cm^{-1}. **MS** (70 eV) m/z 70 (100), 77 (18), 105 (23), 128 (18), 135 (81), 170 (8), 186 (1), 204 (130), 232 (1), 246 (1), 264 (1, M+1). **HRMS (FAB+)** calcd for $C_{15}H_{22}NO_3$ (M+H) 264.1600, found 264.1603.
Hydrolysis of **17** (0.16 g, 0.6 mmol) afforded 0.072 g (63%) of the hydroxy acid **20** as a solid. $[\alpha]_D$ = - 24.6 (c 1.27, EtOH) (Lit[27]. $[\alpha]_D$ = + 33.3 (c 0.87, EtOH) for (*S*) enantiomer). Enantiomeric excess = 87%; **HPLC**: t_R = 24.2 min (major, (*R*) enantiomer), 21.1 (minor, (*S*) enantiomer).

(*S*)-2-Hydroxymethyl-*N*-((*R*)-2-hydroxy-2-phenyl)pentanoylpyrrolidine (18):

Reaction of **2** (0.15 g, 0.64 mmol) and nPrMgBr (3.2 mL of 2 M solution in THF, 6.4 mmol), in benzene (6 mL) afforded 0.16 g of a gum which on purification by flash chromatography on silica gel (1/1petroleum ether/ethyl acetate) furnished 0.115 g (69%) of **18** as a gum.
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.50-7.15 (m, 5H, Ar*H*), 5.10 (s, 1H, O*H*), 4.6-4.1 (br, O*H*), 4.50-4.20 (m, 1H, NC*H*), 3.85-3.45 (m, 2H, CH_2O), 3.25-3.05 (m, 1H, NCH_2), 3.05-2.8 (m, 1H, NCH_2), 2.40-1.80 (m, 3H, ring CH_2, alkyl CH_2), 1.80-1.10 (m, 5H, ring CH_2, alkyl CH_2), 1.00 (t, 3H, J = 6.8, CH_3) **^{13}C NMR** (75 MHz, $CDCl_3$): δ 174.4 (N*C*O), 141.9 (Ar*Cipso*), 128.4 (Ar*C*), 127.6 (Ar*C*), 125.4 (Ar*C*), 77.6 (Ph*C*OH), 65.8 (CH_2O), 62.0 (N*C*H), 47.6 (NCH_2), 38.2 (CCH_2), 26.9 (CH_2), 24.4 (CH_2), 16.5 (CH_2), 14.3 (CH_3) **IR** ($CHCl_3$): 3377, 2964, 2875, 1611, 1433, 1366, 1216, 1050, 757 cm^{-1}. **MS** (70 eV): m/z 70 (100), 77 (36), 83 (30), 105 (26), 128 (18), 149 (98), 218 (35), 234 (1), 246 (1), 260 (5), 278 (7, M+1). **HRMS** calcd for $C_{16}H_{23}NO_3$ 277.1678, found 277.1674.
Hydrolysis of **18** (0.2 g, 0.72 mmol) afforded 0.1 g (68%) of the hydroxy acid **21.** $[\alpha]_D$ = -17.6 (c 2, EtOH), (Lit[27]. $[\alpha]_D$ = + 21.6 (c 2.5, EtOH) for (*S*) enantiomer). Enantiomeric excess = 84%; **HPLC**: t_R = 24.2 min (major, (*R*) enantiomer), 21.7 (minor, (*S*) enantiomer).

References

[1] Hanessian, S. Total Synthesis of Natural Products: The Chiron Approach; Pergamon Press: New York, 1983, Chapter 2.
[2] Seuring, B.; Seebach, D. Helv. Chim. Acta 1977;60:1175.
[3] For leading references see: Aller, E.; Brown, D. S.; Cox, G. G.; Miller, D. J.; Moody, C. J. J. Org. Chem. 1995;60:4449.
[4] For leading references, see: Xiang, Y.B.; Snow, K.; Belly, M. J. Org. Chem. 1993;58:993.
[5] For leading references, see: Byun, I. S.; Kim, Y. H. Syn. Comm. 1995;25:1963.
[6] Pansare, S. V.; Ravi, R. G. Tetrahedron Lett. 1995;36:5959.
[7] Pansare, S. V.; Ravi, R. G.; Jain, R. P. J. Org. Chem. 1998;63:4120.
[8] Meyers, A. I.; Brown, J. D. J. Am. Chem. Soc. 1987;109:3155. This study is the sole example of an intramolecular reduction of an α-keto ester in an NADH mimicking system.
[9] For a review on substrate directable organic reactions see: Hoveyda, A. H.; Evans, D. A..; Fu, G. C. Chem. Rev. 1993;93:1307.
[10] Gallagher, T.; Miles, G. M.; Sankara Subramanian, R.; Hadley, M. S. J. Chem. Soc., Chem. Commun. 1992;166.
[11] Enders, D.; Fey, P.; Kipphardt, H. Org. Syn. 1987;65:173.
[12] Saijo, S.; Wada, M.; Himizu, J. -I.; Ishida, A. Chem. Pharm. Bull. 1980; 28:1449.
[13] For chelation controlled reduction of α-hydroxy ketones with $Zn(BH_4)_2$, see: Nakata, T.; Tanaka, T.; Oishi, T. Tetrahedron Lett. 1983;24:2653.
[14] Soai, K.; Komiya, K.; Shigematsu, Y.; Hasegawa, H.; Ogasawara, K. J. Chem. Soc. Chem. Commun. 1982;1282.
[15] Evans, D. A.; Chapman, K. T.; Carriera, E. M. J. Am. Chem. Soc. 1988;110:3560.
[16] Gribble, G. W.; Ferguson, D. C. J. Chem. Soc. Chem. Commun. 1975;536.
[17] Evans, D. A.; Takacs, J. M. Tetrahedron Lett. 1980;21:4233.
[18] Dale, J. A.; Dull, D. L.; Mosher, H. S. J. Org. Chem. 1969;34:2543.
[19] Eight membered transition structures have been invoked earlier in reduction with sodium cyanaborohydride, see: Takano, S.; Otaki, S.; Ogasawara, K. J. Chem. Commun. 1983;1172.
[20] Brown, H. C.; Mead, E. J.; Subba Rao, B. C. J. Am. Chem. Soc. 1955;77:6209.
[21] Wigfield, D. C. Tetrahedron, 1979;35:449.
[22] Soai, K,; Isoda, T.; Hasegawa, H.; Ishizaki, M. Chem. Lett. 1986;1897.
[23] Akiyama, T.; Nishimoto, H.; Ozaki, S. Tetrahedron Lett. 1991;32:1335.
[24] Synthesis from chiral α-keto esters: Esser, P.; Buschmann, H.; Meyer-Stork, M.; Scharf, H-D. Angew. Chem. Int. Ed. Engl. 1992;31:1190 and references therein.
[25] Synthesis from chiral α-keto amides: Kim, Y. H.; Byun, I. S.; Choi, J. Y. Tetrahedron: Asymmetry 1995;6:1025 and references therein.
[26] Tomooka, K.; Okinaga, T.; Suzuki, K.; Tsuchihashi, G. Tetrahedron Lett. 1989;30:1563 and references therein.
[27] Meyers, A. I.; Slade, J. J. Org. Chem. 1980;45:2912.
[28] Fujisawa, T.; Ukaji, Y.; Funabora, M.; Yamashita, M.; Sato, T. Bull. Chem. Soc. Jpn. 1990;63:1894.