Pergamon

Tetrahedron 55 (1999) 1087–1098

TETRAHEDRON

Nucleophilic Addition of Organometallic Reagents to *N,N*-Dimethyl- and *SAMP*-Glyoxal-Monohydrazones

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Received 12 June 1998; revised 6 November 1998; accepted 19 November 1998

Abstract: Nucleophilic addition of organometallics to *N,N*-dimethyl-glyoxal-monohydrazone occurs smoothly to give the corresponding α-hydroxy hydrazones in high yields. From these compounds, polyfunctional derivatives such as protected α-hydroxy aldehydes and α-hydroxy nitriles can be easily obtained in satisfactory to good yields. The addition to a SAMP-hydrazone proceeds with low (35% d.e.) or reasonable (60% d.e.) levels of stereoselectivity when vinylmagnesium reagents are employed.

Keywords: hydrazones; addition reactions; regiochemistry; stereoselection.

Introduction

For a long time, hydrazones have been recognized [1] as versatile starting materials for the construction of polyfunctional building blocks. Of particular interest are the recent reactions [2] involving diastereoselective additions of organometallic reagents to a C=N group using neighbouring chiral acetals or aminals as auxiliaries which lead to the formation of chiral N-protected α-amino aldehydes. In this paper we report novel methodology for the synthesis of polyfunctional compounds starting from glyoxal-monohydrazones.

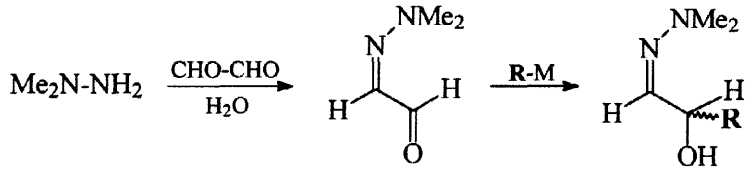
Glyoxal, a fascinating two carbon atom synthon [3], offers several advantages including its versatility and the possibility of undergoing desymmetrization through the temporary protection of one of the carbonyl functions. For instance, by simple treatment of a commercial aqueous solution (40% v/v) of glyoxal with *N,N*-dimethylhydrazine, the glyoxal-monohydrazone **1** bearing a residual reactive carbonyl function, can be obtained in high yield. Despite the easy access to this compound, it has, to the best of our knowledge, only seldom been used in synthesis for the preparation of pyrroles and pyrrolidines [4] and more recently of homochiral camphor annulated pyrrole derivatives [5].

0040-4020/99/$ - see front matter
PII: S0040-4020(98)01087-4

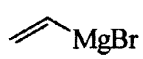
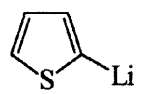
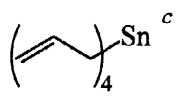
Results and discussion

Nucleophilic addition of 1 equivalent of organometallic reagent to **1** occurs smoothly and exclusively at the carbonyl function, leading in high yields to the substituted α-hydroxy hydrazones **2**. The poor electrophilicity of the C=N function towards the addition of organometallics [6], which usually requires high temperature and prolonged reaction times, or the use of non-coordinating solvents, provided suitable conditions for the observed chemoselectivity. No differences in chemical yields and selectivities could be noticed on moving from organolithium and Grignard reagents to organocuprates. The relevant results for the addition reactions are collected together in Table 1.

Table1
Synthesis and Reaction of Monohydrazone **1** with Organometallic Reagents to give **2**.



1 **2**

Entry	**R-M**[a]	T(°C)	Product	Yield, %[b]
1	MeLi	-100	**2a**	89
2	MeMgBr	-40	**2a**	89
3	*n*-BuLi	-78	**2b**	90
4	*t*-BuLi	-78	**2c**	85
5	$t\text{-Bu}_2\text{CuLi}$	-50	**2c**	85
6		25	**2d**	84
7		-50	**2e**	73
8	 [c]	40	**2f**	50

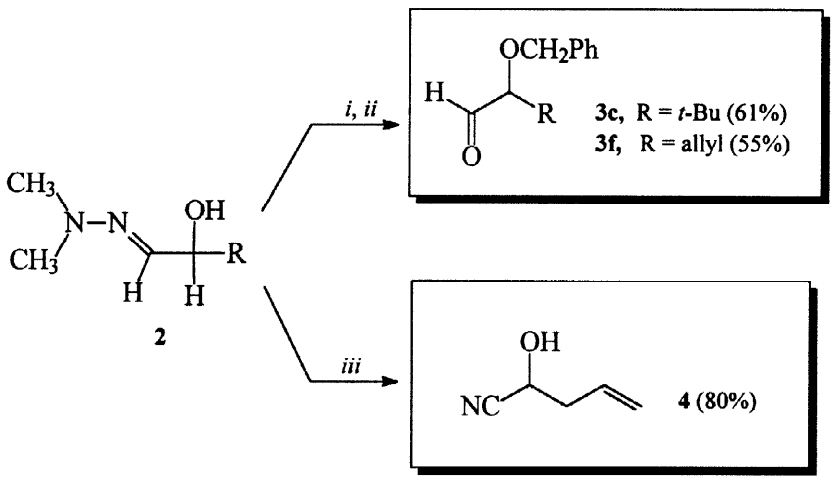
[a] Reactions in dry THF.
[b] Yields of isolated products.
[c] Performed in dry CH_2Cl_2, using $Sc(OTf)_3$.

The nucleophilic addition was equally efficient with alkyl (entries 1-5), vinyl (entry 6) and heteroaryl (entry 7) ligands thus outlining the general character of this reaction. To minimize

possible problems inherent in the preparation of lithium and copper allyl derivatives the less nucleophilic and easily-handled tetra-allyltin was used. Extensive optimization of the reaction conditions led (entry 8) to the use of catalytic amounts of $Sc(OTf)_3$ as the Lewis acid needed for promoting the allylation reaction.

Among the synthetic elaborations of compounds in Table 1, the formation of α-hydroxyaldehydes, important moieties present in a vaste array of natural products, has been investigated. Several strategies have been developed for the synthesis of this class of molecules. So far, oxidation of the corresponding enolates [7] has been widely reported as well as the one-carbon homologation strategy [8] based on the conversion of ketones into α-hydroxyaldehydes through Darzen's condensation and base-induced ring opening. Due to the presence of a chiral centre in α-hydroxy aldehydes, several enantioselective syntheses have been reported as well [9].

Exposure of the protected carbonyl function in **2** required, due to the low stability of the α-hydroxy aldehydes, protection of the OH function as a benzyl ether derivative prior to C=O deprotection. Treatment with MeI and after with HCl [10], led to formation of the expected compounds. Selected examples leading to α-hydroxy aldehydes **3c** and **3f** starting from **2c** and **2f** are reported in Scheme 1. As a further extension of the synthetic utility of α-hydroxy hydrazones **2** we studied the oxidation reaction of these compounds with magnesium monoperoxyphthalate monohydrate (MMPP). This reagent which has been successfully applied to the transformation of aldehydes into nitriles through the corresponding hydrazones [11], when applied to **2f**, led (Scheme 1) to the formation in good yield and without OH protection of 2-hydroxy-4-pentenenitrile (**4**), a useful building block for the synthesis of α-hydroxy-β-aminoacids [12] and of β-aminoalcohols [13].



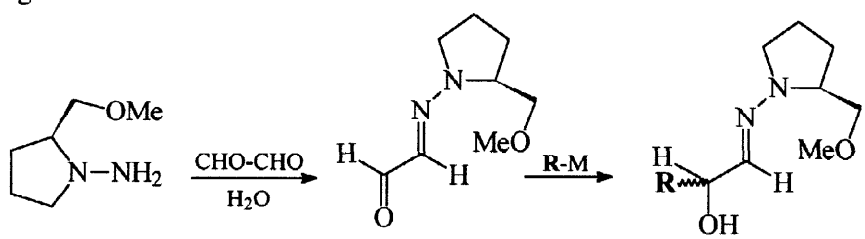
i: NaH, $PhCH_2Cl$; *ii*: CH_3I, HCl 3N; *iii*: MMPP

Scheme 1

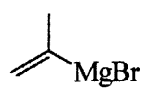
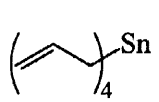
We next attempted the asymmetric version of the nucleophilic addition of organometallic reagents to glyoxal monohydrazones, starting from the SAMP-hydrazone **5** formed in high

yield in the reaction between SAMP [10, 14] and aqueous glyoxal. Addition of organometallics occurred smoothly to give the expected addition products but was disappointing (entries 1-3 in Table 2) as far as the asymmetric induction was concerned since no stereoselectivity was observed even at low temperature with organolithium and cuprate reagents. On the other hand, the use of vinyl Grignard reagents led to a sizable enhancement of the stereoselectivities with d.e. values ranging from 33% up to 60% (entries 4-6), a remarkable result taking into account the unfavourable situation due to the long distance between the chiral center and the carbonyl function.

Table 2
Synthesis and Diastereoselective Reaction of SAMP-Monohydrazone **5** with Organometallic Reagents to give **6**.



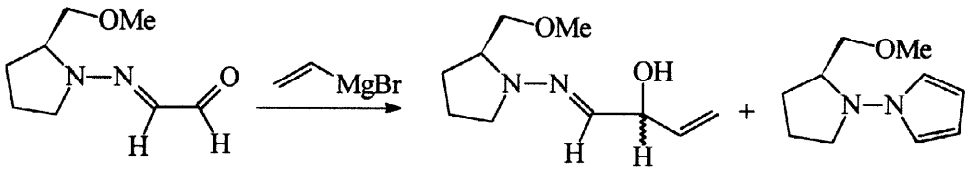
5 **6**

Entry	R-M[a]	T(°C)	Product	Yield %[b]	% d.e.[e]
1	MeLi	-100	**6a**	82	7
2	*t*-BuLi	-100	**6b**	94	0
3	*t*-Bu_2CuLi	-78	**6b**	70	0
4		25	**6c**	84	33 [d]
5		25	**6d**	88	60
6		40	**6e**	53	35

[a] Performed in dry THF.
[b] Yields of isolated products.
[c] Performed in dry CH_2Cl_2, with $Sc(OTf)_3$.
[d] Addition to the reaction mixture of an equimolar amount of $MgBr_2$ increases the d.e. value from 20% to 33%.
[e] Values evaluated by means of ^1H and ^{13}C NMR spectra.

Attempts at improving the stereoselectivity of this reaction by varying the solvent [15] failed since the decrease in the co-ordinating power of the solvent (THF > Et_2O > Toluene)

resulted unexpectedly in the formation of increasing amounts of the pyrrole derivative **7** (Scheme 2).



5

	6d	**7**
THF	100%, d.e. % = 20	—
Et_2O	50%, d.e. % = 20	50%
Toluene	—	100%

Scheme 2

Although the actual stereochemical course cannot be ascertained this trend, already observed in the diastereoselective nucleophilic addition to chiral α-ketoacetals [16], may be reasonably explained in the reaction of **5** with Grignards, by the occurrence of a rigid structure in which the magnesium metal is fixed by chelation between carbonyl oxygen and the methoxy oxygen atom.

A significant (> 20%) even though still modest e.e. value was finally achieved by reacting **1** with a chiral N-heterocuprate [RCuL*]Li with L* (a nontransferable ligand) = (S)-(−)-1-amino-2-(methoxymethyl)pyrrolidine and R = *t*-Bu, prepared according to Dieter [17]. Worth noting the 20% e.e. observed in this case favourably compares to the disappointing result reported in Table 2 (entry 3) in which a 1:1 diastereomeric mixture was formed by using an organocuprate and a *t*-butyl group as the nucleophilic ligand.

In conclusion it has been demonstrated that nucleophilic addition of organometallic reagents to glyoxal-monohydrazones, coupled with deprotection and/or transformation of the protected carbonyl moiety opens a new straightforward entry to a variety of polyfunctional compounds. While in the present instance the chemical yields are fully satisfactory the asymmetric version of this reaction appears not completely optimized even though type-**6** derivatives can be considered versatile chiral intermediates due to the manifold of possible chemical transformations. Efforts are currently underway to develop potentially more effective chiral ligands.

Experimental

General. All moisture sensitive reactions were performed in flame-dried glassware equipped with rubber septa under a positive pressure of dry nitrogen. Organic extracts were dried over $CaSO_4$. Preparative flash chromatographic experiments were performed using ICN Silica gel 230-400 mesh. For TLC precoated glass plates were used (Stratochrom SIF_{254}, 0.25

mm thick) and the spots were developed at 110 °C with an aqueous solution of $(NH_4)_6Mo_7O_{24}$ (2.5%) and $(NH_4)_4Ce(SO_4)_4$ (1%) in 10% H_2SO_4 or $KMnO_4$ 0.1 M/H_2SO_4 1M 1/1. Yields are for isolated compounds. Unless specified otherwise, ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in $CDCl_3$ as solvent. Chemical shifts are in ppm downfield of TMS; signal multiplicities were established by DEPT experiments. Signal assignments, if necessary, were elucidated by decoupling ^1H NMR and by 2D ^1H-^1H and ^1H-^{13}C NMR experiments. Solvents were reagent grade and were obtained dry as follows: THF was distilled from benzophenone ketyl, CH_2Cl_2 and DMF were refluxed over and distilled from CaH_2.

2-Hydroxypropanal *N,N*-dimethylhydrazone (2a). Method I. To 0.10 g (1.0 mmol) of *N,N*-dimethyl-glyoxalhydrazone (**1**) [4], dissolved in 6 mL of dry THF, under N_2 and at -100 °C, 0.80 mL (1.3 mmol) of 1.6 M solution of CH_3Li in diethyl ether were added. After 6 min, the reaction was quenched with a few drops of CH_3OH then 1 mL of brine was added. The reaction mixture was extracted with CH_2Cl_2. The organic layers were dried and evaporated to give a crude product which was purified by flash chromatography (diethyl ether), obtaining 0.10 g of **2a** (89 %) as a pale yellow oil.

Method II. The same product was obtained by treating 0.10 g (1.0 mmol) of **1** with 0.93 mL (1.3 mmol) of 1.4 M solution of MeMgBr in THF at -40 °C. Following usual workup, the title compound was obtained with identical yield. ^1H-NMR, δ: 6.55 (d, 1H, NCH, J = 3.5 Hz), 4.32 (m, 1H, C*H*OH), 3.33 (brs, 1H, OH), 2.71 (s, 6H, $N(CH_3)_2$), 1.25 (d, 3H, CH_3, J = 6.6 Hz). ^{13}C-NMR, δ: 138.5 (NCH), 67.2 (CHOH), 43.1 ($N(CH_3)_2$), 22.0 (C*C*H_3). IR (neat): ν = 3500, 2900, 1625, 1165 cm^{-1}. Anal. Calcd. for $C_5H_{12}N_2O$: C, 51.68; H, 10.42; N, 24.12. Found: C, 51.75; H, 10.49; N, 24.11.

2-Hydroxyhexanal *N,N*-dimethylhydrazone (2b). The title compound was obtained, with the same procedure used for the synthesis of **2a**, from 0.44 g (4.4 mmol) of **1** dissolved in 5 mL of dry THF, cooled at -78 °C slowly adding 2.80 mL (4.5 mmol) of 1.6 M *n*-BuLi solution in diethyl ether. After 1h the reaction workup gave a crude product which was purified by flash chromatography (diethyl ether) to give 0.63 g (90%) of **2b** as a yellow oil. ^1H-NMR: δ, 6.42 (d, 1H, NCH, J = 6.5 Hz), 4.31 (m, 1H, C*H*OH), 3.75 (brs, 1H, OH), 2.70 (s, 6H, $N(CH_3)_2$), 1.70-1.14 (m, 6H, $3CH_2$), 0.87 (t, 3H, CH_3). ^{13}C-NMR, δ: 140.2 (NCH), 73.6 (CHOH), 43.0 ($N(CH_3)_2$), 36.7 (CH_2), 27.6 (CH_2), 22.7 (CH_2), 14.1 (CH_3). IR (neat): ν = 3500, 2930, 1630, 1160 cm^{-1}. Anal. Calcd. for $C_8H_{18}N_2O$: C, 60.70; H, 11.47; N, 17.71. Found: C, 60.75; H, 11.40; N, 17.72.

2-Hydroxy-3,3-dimethylbutanal *N,N*-dimethylhydrazone (2c). Method I. The title compound was obtained with the same procedure used for the synthesis of **2a** from 0.10 g (1.0 mmol) of (**1**) and 0.71 mL (1.2 mmol) of 1.7 M *t*-BuLi solution in pentane at -78 °C. After 50 min the reaction workup gave a crude product which was purified by flash chromatography (diethyl ether) giving 0.13 g of **2c** (85%) as a yellow oil.

Method II. To 0.47 g (5.2 mmol) of CuCN 20 mL of dry THF were added, under N_2. The suspension was cooled to -78 °C, then 8.70 mL (10.4 mmol) of 1.2 M *t*-BuLi solution in *n*-

pentane were added dropwise. To the reaction mixture warmed to -50 °C were added, after 15 mim, 0.48 g (4.8 mmol) of **1** then, after 50 min, the reaction was quenched with 1 mL of NH_3/NH_4^+, 1 mL of NH_3 20 % and 20 mL of CH_2Cl_2. The stirring was carried out for 10 h, the organic layer was separed and the aqueous layer extracted with CH_2Cl_2. The organic extracts were collected, dried and filtered. For evaporation of the solvent 0.62 g (85%) of **2c** were obtained as a yellow oil. ^{1}H-NMR: δ, 6.69 (d, 1H, NCH, J = 3.0 Hz), 3.85 (d, 1H, C*H*OH, J = 3.0 Hz), 3.50 (brs, 1H, OH), 2.73 (s, 6H, $N(CH_3)_2$), 0.87 (s, 9H, $C(CH_3)_3$). ^{13}C-NMR, δ: 135.8 (NCH), 78.2 (CHOH), 43.4 ($N(CH_3)_2$), 35.2 ($C(CH_3)_3$)), 25.5 ($C(CH_3)_3$). IR (neat): ν = 3520, 2910, 1620, 1250, 1160 cm^{-1}. Anal. Calcd. for $C_8H_{18}N_2O$: C, 60.70; H, 11.47; N, 17.71. Found: C, 60.69; H, 11.50; N, 17.73.

2-Hydroxy-3-butenal *N,N*-dimethylhydrazone (2d). A solution of Grignard reagent, under nitrogen, was prepared from 0.31 g (13 mmol) of Mg turnings, 3 mL of dry THF and few drops of vinylbromide. This mixture was refluxed in order to start the reaction, then 1.34 mL (19 mmol) of vinylbromide dissolved in 7 mL of THF were slowly added. After addition of 4 mL of THF the reaction mixture was refluxed for 30 min, then 2 mL (2.6 mmol) of this solution were added to 0.22 g (2.2 mmol) of **1** dissolved in 4 mL of THF. After stirring at 25 °C for 15 h, the reaction mixture was quenched with 2 mL of brine, extracted with CH_2Cl_2, dried and evaporated. The crude mixture was purified by flash chromatography (diethyl ether) to give 0.24 g (86%) of **2d** as an orange oil. ^{1}H-NMR: δ, 6.39 (d, 1H, NCH, J = 4.1 Hz), 5.71 (m, 1H, *H*C=CH_2), 5.19 (d, 1H *trans*, CH=C*H*H, J = 17.1 Hz), 5.01 (d, 1H *cis*, CH=CH*H*, J = 10.2 Hz), 4.55 (m, 1H, C*H*OH), 3.90 (brs, 1H, OH), 2.63 (s, 6H, $2CH_3$). ^{13}C-NMR, δ: 138.2, 135.4 (HC= and NCH interchangeable), 115.3 (=CH_2), 72.3 (CHOH), 42.7 ($2CH_3$). IR (neat): ν = 3510, 2915, 1640, 1620, 1165 cm^{-1}. Anal. Calcd. for $C_6H_{12}N_2O$: C, 56.21; H, 9.44; N, 21.86. Found: C, 56.30; H, 9.40; N, 21.90.

2-Hydroxy-2-(2-thienyl) acetaldeide *N,N*-dimethylhydrazone (2e). 0.28 g (1.5 mmol) of thiophene dissolved in 3 mL of dry THF were cooled at -78 °C before adding 1 mL (1.6 mmol) of 1.6 M solution of *n*-BuLi [18]. To the reaction mixture, warmed to -50 °C, 0.14 g (1.4 mmol) of **1** were added. After 3 h the reaction was quenched with 1 mL of brine and extracted with CH_2Cl_2. For evaporation of the solvent 0.19 g (73%) of **2e** were obtained as a yellow oil. ^{1}H-NMR: δ, 7.20 (d, 1H, CH=), 6.94 (m, 2H, 2CH=), 6.62 (d, 1H, NCH), 5.48 (d, 1H, C*H*OH), 4.57 (brs, 1H, OH), 2.73 (s, 6H, $2CH_3$). ^{13}C-NMR, δ: 140.0 (C=) , 135.3 (NCH), 126.6 (CH=), 124.9 (CH=), 124.1 (CH=), 69.4 (CHOH), 42.7 ($2CH_3$). IR (neat): ν = 3510, 2920, 1625, 1165, 720 cm^{-1}. Anal. Calcd. for $C_8H_{12}N_2OS$: C, 52.15; H, 6.57; N, 15.22; S, 17.37. Found: C, 52.10; H, 6.60; N, 15.25; S, 17.41.

2-Hydroxy-4-pentenal *N,N*-dimethylhydrazone (2f). To 0.30 g (3 mmol) of **1** dissolved in 9 mL of CH_2Cl_2, 0.20 mL (0.75 mmol) of tetraallylstannane and 0.15 mg (0.3 mmol) of $Sc(OTf)_3$ were added. After stirring for 24 h at 40°C, the reaction mixture was evaporated and the crude product was subjected to flash chromatography (diethyl ether); 0.53 g (50%) of the title compound were obtained as an orange oil. ^{1}H-NMR: δ, 6.60 (d, 1H, NCH, J = 4.1 Hz), 5.85 (m, 1H, CH=), 5.13 (m, 2H, =CH_2), 4.28 (m, 1H, C*H*OH), 3.40 (brs, 1H, OH), 2.77 (s, 6H,

$2CH_3$), 2.36 (m, 2H, CH_2). ^{13}C-NMR, δ: 137.0 (*C*H=CH_2), 134.4 (NCH), 118.3 (*C*H_2=CH), 70.7 (CHOH), 43.5 ($2CH_3$), 41.2 (*C*H_2CH=). IR (neat): ν = 3500, 2925, 1625, 1165 cm^{-1}. Anal. Calcd. for $C_7H_{14}N_2O$: C, 59.11; H, 9.93; N, 19.71. Found: C, 59.16; H, 9.90; N, 19.75.

2-(Benzyloxy)-3,3-dimethylbutanal (3c). To 0.11 g (2.6 mmol) of NaH (60%) washed with petroleum ether under N_2, 2.5 mL of dry DMF were added and, dropwise, 0.38 g (2.4 mmol) of **2c**. After 30 min 0.30 mL (2.6 mmol) of benzyl chloride were added then, after 3 h, 2 mL of water were added, extracting with CH_2Cl_2. The crude product, obtained after evaporation of the solvent, was purified by flash chromatography (petroleum-ether/diethyl ether 2:1) and 0.41 g (68%) of the O-benzyl derivative (68%) were obtained, as a white oil. ^{1}H-NMR: δ 7.32 (m, 5H, 5Ar-CH), 6.50 (d, 1H, NCH, *J* = 7.7 Hz), 4.60 (d, 1H, C*H*HPh, *J* = 12.2 Hz), 4.40 (d, 1H, CH*H*Ph, *J* = 12.2 Hz), 3.55 (d, 1H, CHO, *J* = 7.6 Hz), 2.78 (s, 6H, $N(CH_3)_2$), 0.95 (s. 9H, $C(CH_3)_3$). ^{13}C-NMR, δ: 139.4 (Ar-C), 135.8 (NCH), 128.2 (2Ar-CH), 127.6 (2Ar-CH), 127.3 (Ar-CH), 87.1 (CHO), 70.6 (CH_2O), 43.2 ($2(CH_3)N$), 34.9 (*C*$(CH_3)_3$), 26.4 ($(CH_3)_3$C).

0.41 g (1 mmol) of the benzyl derivative were refluxed with 5 mL of CH_3I [10]. After 24 h, the excess of CH_3I was evaporated and the crude ammonium salt obtained was treated with 4 mL of 3N HCl. After 12 h 10 mL of CH_2Cl_2 were added then the reaction mixture was stirred for 30 min. The organic layer was separed and washed with $NaHCO_3$ then dried and evaporated, obtaining 0.23 g of **3c** (75%). ^{1}H-NMR: δ 9.73 (d, 1H, CHO, *J* = 3.5 Hz), 7.35 (m, 5H, 5Ar-CH), 4.42 (d, 1H, C*H*H, *J* = 11.4 Hz), 4.65 (d, 1H, CH*H*, *J* = 11.5 Hz), 3.30 (d, 1H, CHO, *J* = 3.5 Hz), 1.05 (s, 9H, $C(CH_3)_3$). ^{13}C-NMR, δ: 205.3 (CHO), 137.7 (Ar-C), 128.6 (2Ar-CH), 128.2 (2Ar-CH), 128.1 (Ar-CH), 90.7 (CHO), 73.1 (CH_2O), 35.5 (*C*$(CH_3)_3$), 26.3 ($3CH_3$). IR (neat): ν = 3010, 1730, 1240 cm^{-1}. Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.68; H, 8.80. Found: C, 75.73; H, 8.83.

2-(Benzyloxy)-4-pentenal (3f). The title compound was prepared analogously to *t*-butyl derivative **3c** from 0.11 g (2.6 mmol) of NaH (60%) in 2.5 mL of dry DMF, 0.34 g (2.4 mmol) of allyl derivative **2f** and 0.30 mL (2.6 mmol) of benzyl chloride. After purification by flash chromatography (petroleum-ether/diethyl ether 2:1) 0.38 g (68%) of the benzyl derivative were obtained, as a white oil. ^{1}H-NMR: δ 7.35 (m, 5H, 5Ar-CH), 6.43 (d, 1H, NCH, *J* = 7.0 Hz), 5.90 (m, 1H, C*H*=CH_2), 5.15 (m, 2H, CH=C*H*$_2$), 4.62 (d, 1H, C*H*HPh, *J* = 12.0 Hz), 4.49 (d, 1H, CH*H*Ph, *J* = 11.9 Hz), 4.05 (m, 1H, CHO), 2.83 (s, 6H, $2CH_3$), 2.50 (m, 2H, C*H*$_2$CH=). ^{13}C-NMR, δ: 138.8 (Ar-C), 136.2, 134.3 (CHN, *C*H=CH_2 interchangeable), 128.3 (2Ar-CH), 127.8 (2Ar-CH), 127.5 (Ar-CH), 117.2 (CH_2=) 79.2 (CHO), 70.4 (*C*H_2Ph), 42.9 ($2CH_3$), 39.1 (*C*H_2CH=).

0.23 g (1 mmol) of the benzyl derivative were refluxed with 5 mL of CH_3I [10]. After 24 h the excess of CH_3I was evaporated and the crude ammonium salt was treated with 3 mL of 3N HCl. After 12 h 10 mL of CH_2Cl_2 were added then the reaction mixture was stirred for 30 min The organic layer was separed and washed with $NaHCO_3$ then dried and evaporated, obtaining 0.15 g (75%) of **3f** as a white oil. ^{1}H-NMR, δ: 9.57 (d, 1H, CHO, *J* = 3.5 Hz), 7.27 (m, 5H, Ar-CH), 5.75 (m, 1H, C*H*=CH_2), 5.08 (m, 2H, C*H*$_2$=CH), 4.58 (d, 1H, C*H*HPh, *J* = 11.8 Hz), 4.42 (d, 1H, CH*H*Ph, *J* = 11.8 Hz), 3.77 (m, 1H, CHO), 2.40 (m, 2H, C*H*$_2$CH=). ^{13}C-NMR, δ: 203.3

(CHO), 137.0 (Ar-C), 132.5 (*C*H=CH_2), 128.7 (2Ar-CH), 128.5(2Ar-CH), 128.2 (Ar-CH), 118.6 (*C*H_2=CH), 82.9 (CHO), 72.6 (*C*H_2Ph), 34.7 (*C*H_2CH=). IR (neat): ν = 3000, 1735, 1640 cm^{-1}. Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.75; H, 7.42. Found: C, 75.70; H, 7.49.

2-Hydroxy-4-pentenenitrile (4). To a solution of 1.24 g (2.5 mmol) of magnesium monoperoxyphthalate hexahydrate (MMPP) dissolved in 8 mL of CH_3OH at 0 °C, 0.14 g (1 mmol) of allylalcohol **2f** [11b], dissolved in 1 mL of CH_3OH, were added dropwise. After 5 min, the solvent was evaporated and the residue was extracted with CH_2Cl_2. The organic layer, washed with brine and dried, was evaporated to give a crude product which was purified by flash chromatography (diethyl ether), obtaining 0.59 g (60%) of **4**, as a white oil. ^{1}H-NMR, δ: 5.85 (m, 1H, C*H*=CH_2), 5.50 (brs, 1H, OH), 5.20 (m, 2H, CH_2=CH), 4.52 (t, 1H, C*H*OH, *J* = 6.4 Hz), 2.55 (m, 2H, CH_2CH=). ^{13}C-NMR, δ: 133.9 (*C*H=CH_2), 121.1 (CN), 118.8 (CH=CH_2), 61.1 (CHOH), 40.0 (*C*H_2CH). IR (neat): ν = 3510, 2920, 2250, 1630 cm^{-1}. Anal. Calcd. for C_5H_7NO: C, 61.82; H, 7.27; N, 14.43. Found: C, 61.78; H, 7.30; N, 14.45.

2-{[(2S)-2-(Methoxymethyl)tetrahydro-1H-pyrrol-1-yl]imino}acetaldeide (5). To 2.76 g of glyoxal 40% aqueous solution diluted with 6 mL of H_2O, 0.51 mL (3.8 mmol) of (–)-(S)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) were added dropwise. The reaction mixture was stirred for 50 min and by extraction with CH_2Cl_2 0.63 g (97%) of the title compound were obtained as a orange oil and used, without any further purification, for the next reaction. An analytical sample was purified by flash chromatography (SiO_2; petroleum ether/Et_2O/MeOH - 5/5/0.1). ^{1}H-NMR, δ: 9.23 (d, 1H, CHO, *J* = 7.7 Hz), 6.51 (d, 1H, HC=N, *J* = 7.7 Hz), 3.78 (m, 1H, NCH), 3.46 (m, 2H, CH_2O), 3.22 (s, 3H, CH_3), 3.13 (m, 2H, CH_2N), 1.93 (m, 4H, $2CH_2$). ^{13}C-NMR, δ: 190.9 (C=O), 130.3 (C=N), 73.1 (CH_2O), 63.0 (CHN), 59.2 (CH_3), 49.4 (CH_2N), 26.6 (CH_2), 22.9 (CH_2). $[\alpha]_D^{25}$ = –103.9 (c = 1.08, $CHCl_3$). IR (neat): ν = 2920, 1670, 1135 cm^{-1}. Anal. Calcd. for $C_8H_{14}N_2O_2$: C, 56.44; H, 8.29; N, 16.46. Found: C, 56.49; H, 8.25; N, 16.43.

2-{[(2S)-2-(Methoxymethyl)tetrahydro-1H-pyrrol-1-yl]imino}acetaldeide (6a). The reaction was carried out, analogously to **2a**, at -100°C from 0.19 g (1.1 mmol) of **5** in 4 mL of dry THF and 0.75 mL (1.2 mmol) of 1.6 M CH_3Li. After 90 min the reaction mixture was treated with 0.5 mL of CH_3OH then with 1 mL of brine and extracted with CH_2Cl_2. By evaporation of the solvent 0.15 g (82%) of **6a** were obtained as a yellow oil. The presence of a diastereomeric excess of 7% is evaluated from ^{1}H-NMR, particularly from related integral values of CH_3, OCH_3 groups and also of the CH=N integrals recorded after irradiation at δ = 4.45; for these groups we report in brackets the chemical shifts of the minor isomer. When possible also for ^{13}C-NMR couples of values for the two diastereoisomers are indicated. ^{1}H-NMR (C_6D_6), δ: 6.49 (d, 1H, NCH, *J* = 3.6 Hz), [6.46 (d, 1H, NCH, *J* = 3.7 Hz)], 4.45 (m, 1H, C*H*OH), 3.59-3.17 (m, 4H, C*HCH*$_2$O and OH), 3.14 (s, 3H, OCH_3), [3.13 (s, 3H, OCH_3)], 2.99 (m, 1H, NC*H*H), 2.46 (m, 1H, NCH*H*), 1.70 (m, 4H, $2CH_2$), 1.32 (d, 3H, CH_3, *J* = 6.6 Hz), [1.31 (d, 3H, CH_3, *J* = 6.6 Hz)]. ^{13}C-NMR (C_6D_6), δ: 138.2/138.1 (NCH), 70.0/67.9 (CHOH), 63.8 (*C*HCH$_2$O), 59.3/59.2 (OCH_3), 50.1 (NCH_2), 22.7(CH_2), 22.9 (CH_2), 22.8 (CH_3). IR

(**neat**): ν = 3550, 2900, 1620, 1135 cm^{-1}. Anal. Calcd. for $C_9H_{18}N_2O_2$: C, 58.02; H, 9.75; N, 15.05. Found: C, 58.10; H, 9.78; N, 15.03.

2-{[(2S)-2-(Methoxymethyl)tetrahydro-1H-pyrrol-1-yl]imino}-3,3-dimethyl-2-butanol (6b). Method I. **6b** Was prepared from 0.14 g (0.8 mmol) of **5** dissolved in 4 mL of dry THF and 1.7 mL (1 mmol) of 1.7 M *t*-BuLi in pentane at -100 °C using the same procedure employed for the synthesis of **6a**, obtaining 0.17 g (94%) of the title compound as a yellow oil. The ratio between the diastereoisomers was approximately 1:1 and was extimated from intensity of the corresponding carbon in the two isomers using conditions suitable for integrability of ^{13}C-NMR spectrum.

Method I. 0.15 g (1.7 mmol) of CuCN were added, under N_2, to 4 mL of THF. To the suspension, cooled to -78 °C 2 mL (3.4 mmol) of a 1.7 M solution of *t*-BuLi were added. The temperature was maintained at - 50 °C for 15 min then to the solution cooled at -78 °C 0.14 g (0.8 mmol) of **5** were added. After 90 min the reaction was quenched with 1 mL of NH_3/NH_4^+, 1 mL of 20 % NH_3 and the mixture extracted with CH_2Cl_2. By evaporation of the solvent 0.13 g (70%) of **6b** were obtained, as a yellow oil. ^1H-NMR, δ: 6.65 (d, 1H, NCH, *J* = 2.9 Hz), 3.79 (d, 1H, C*H*OH, *J* = 2.9 Hz), 3.40 (m, 5H, C*H*C*H*$_2$O, OH, NC*H*H), 3.30 (s, 3H, OCH_3), 2.73 (m, 1H, NCH*H*), 1.85 (m, 4H, $2CH_2$), 0.85 (s, 9H, $C(CH_3)_3$). ^{13}C-NMR, δ: 136.0/135.8 (NCH), 78.6/78.5 (CHOH), 75.0/74.9 (OCH_2), 59.6/59.6 (OCH_3), 51.0/50.7 (NCH_2), 36.0/35.6 ($C(CH_3)_3$), 27.1/27.1 (CH_2), 25.9/25.9 ($3CH_3$), 22.5/22.5 (CH_2). IR (neat): ν = 3500, 2940, 1625, 1250, 1135 cm^{-1}. Anal. Calcd. for $C_{12}H_{24}N_2O_2$: C, 63.11; H, 10.60; N, 12.27. Found: C, 63.18; H, 10.52; N, 12.30.

2-{[(2S)-2-(Methoxymethyl)tetrahydro-1H-pyrrol-1-yl]imino}-3-buten-2-ol (6c). To 1.2 mL (1.2 mmol) of a 1.0 M solution of vinylmagnesium bromide in THF 0.17 g (1.0 mmol) of **5** were added, under N_2 at 25 °C. After 15 h the reaction mixture, treated as described for **6a**, gave 0.17 g (84 %) of **6c** as an orange oil. The diastereomeric excess of 20% was evaluated by ^1H-NMR spectrum from the related intensities of OCH_3 groups, of CH=N after irradiation at δ 4.90 and also of C*H*OH after irradiation at δ 6.44. Addition to the reaction mixture of an equimolar amount of $MgBr_2$ increases the d.e. value from 20% to 33%. For ^1H-NMR spectrum some significative chemical shifts of the minor isomer are reported in brackets. ^1H-NMR (C_6D_6), δ: 6.45 [6.42] (d, 1H, NCH, *J* = 4.5 Hz), 6.02 (m, 1H, =CH), 5.47 (d, 1H, =C*H*H, *J* = 17.2 Hz, *J* = 1.6 Hz), 5.15 (d, 1H, =CH*H*, *J* = 10.2 Hz, *J* = 1.6 Hz), 4.90 (m, 1H, C*H*OH), 3.90 (brs, 1H, OH), 3.53 (m, 2H, CH_2O), 3.33 (m, 1H, C*H*CH_2O), 3.17 [3.16] (s, 3H, OCH_3), 2.98 (m, 1H, NC*H*H), 2.50 (m, 1H, NCH*H*), 1.70 (m, 2H, CH_2), 1.48 (m, 2H, CH_2). ^{13}C-NMR (C_6D_6), δ: 139.5 (CH=), 134.5/134.4 (NCH), 114.4 (=CH_2), 74.9 (CH_2O), 72.9/72.8 (CHOH), 63.0 (*C*HCH_2O), 58.6 (OCH_3), 49.3 (NCH_2), 27.0 (CH_2), 22.1 (CH_2). IR (neat): ν = 3500, 2930, 1640, 1620, 1130 cm^{-1}. Anal. Calcd. for $C_{10}H_{18}N_2O_2$: C, 60.56; H, 9.16; N, 14.13. Found: C, 60.61; H, 9.12; N, 14.10.

2-{[(2S)-2-(Methoxymethyl)tetrahydro-1H-pyrrol-1-yl]imino}-3-methyl-3-buten-2-ol (6d). To 0.04 g (1.6 mmol) of Mg turnings in 0.3 mL of dry THF, under N_2, 0.15 mL (1.7 mmol) of 2-bromopropene were added. The mixture was refluxed for 3 h, then 0.17 g (1.0 mmol) of **5**

were added dropwise. After 15 h at 25 °C the reaction was quenched with 2 mL of brine and extracted with CH_2Cl_2. For evaporation of the solvent 0.18 g (88%) of **6d** were obtained as an orange oil. By means of ^{13}C-^1H 2D NMR carbons and protons were correlated, then the diastereomeric excess of 60% was calculated by integral values of OCH_3 groups and of N=CH after irradiation at 4.81 δ. For the ^1H-NMR spectra some interesting values of chemicals shifts of the minor isomer are reported in brackets. In the ^{13}C-NMR spectrum the chemical shifts of the major isomer are reported. ^1H-NMR (C_6D_6), δ: 6.35 (m, 1H, NCH), 5.19 (m, 1H, =C*H*H), 4.90 (m, 1H, CH*H*), 4.81 (m, 1H, C*H*OH), 3.77-3.22 (m, 3H, C*H*C*H*$_2$O), 3.45 (brs, 1H, OH), 3.13 [3.16] (s, 3H, OCH_3), 2.87 (m, 1H, NC*H*H), 2.41 (m, 1H, NCH*H*), 1.79 (s, 3H, CH_3), 1.64 (m, 4H, $2CH_2$). ^{13}C-NMR (C_6D_6), δ: 147.2 (C=), 135.7 (N=CH), 113.0 (=CH_2), 76.3 (CHOH), 75.8 (CH_2O), 63.9 (*C*HCH$_2$O), 59.6 (OCH_3), 50.3 (NCH_2), 49.7 (CH_3), 27.9 (CH_2), 23.0 (CH_2). IR (neat): ν = 3550, 2920, 1650, 1620, 1135 cm^{-1}. Anal. Calcd. for $C_{11}H_{20}N_2O_2$: C, 62.22; H, 9.50; N, 13.20. Found: C, 62.27; H, 9.44; N, 13.26.

2-{[(2S)-2-(Methoxymethyl)tetrahydro-1H-pyrrol-1-yl]imino}-4-penten-2-ol (6e). To 0.51 g (3 mmol) of **5** dissolved in 9 mL of CH_2Cl_2, 0.20 mL (0.75 mmol) of tetraallyltin and 0.15 g (0.3 mmol) of scandium trifluoromethanesulfonate were added. The reaction mixture, warmed to 40 °C for 24 h, was quenched with 2 mL of brine and extracted with CH_2Cl_2. By evaporation of the solvent 0.34 g (53 %) of the title compound were obtained as an orange oil. The 35% diastereomeric excess was evaluated by ^1H-NMR, analyzing the integrals of OCH_3 groups, the value of chemical shift of the minor isomer is reported in brackets. By means of ^{13}C-^1H 2D NMR carbons of the two different diastereoisomers were attributed then the related ratio was evaluated from ^{13}C-NMR recorded in conditions suitable for integration. ^1H-NMR (C_6D_6), δ: 6.50 (m, 1H, HC=N), 6.30 (m, 1H, C*H*=CH_2), 5.15 (m, 2H, C*H*$_2$=CH), 4.45 (m, 1H, C*H*OH, irradiating at δ 2.52 was obtained a doublet, J = 4.0 Hz), 3.53 (m, 2H, CH_2O), 3.33 (m, 1H, C*H*CH$_2$O), [3.20], 3.18 (s, 3H, OCH_3), 3.10 (m, 1H, NC*H*H), 2.80 (m, 1H, NCH*H*), 2.52 (m, 2H, C*H*$_2$CH=), 1.80 (m, 2H, CH_2), 1.60 (m, 2H, CH_2). ^{13}C-NMR (C_6D_6), δ: 137.0/135.9 (CH=CH_2), 135.4 (HC=N), 117.8 (*C*H$_2$=CH), 75.8 (CH_2O), 71.8/71.6 (CHOH), 63.9 (*C*HCH$_2$O), 59.5 (OCH_3), 50.3/49.7 (NCH_2), 42.0 (*C*H$_2$CH=), 27.9 (CH_2), 23.0 (CH_2). IR (neat): ν = 3500, 2920, 1645, 1625, 1130 cm^{-1}. Anal. Calcd. for $C_{11}H_{20}N_2O_2$: C, 62.22; H, 9.50; N, 13.20. Found: C, 62.15; H, 9.40; N, 13.23.

Methyl [(2S)-1-(1H-pyrrol-1-yl)tetrahydro-1H-pyrrol-2-yl] methyl ether (7). To 1 mL of a 1M solution in THF of vinylmagnesium bromide, diluted with 10 mL of toluene under N_2, 0.12 g (0.7 mmol) of **5** dissolved in 1 mL of toluene were added dropwise. After 15 h the reaction mixture was quenched with brine and extracted with CH_2Cl_2. By evaporation of the solvent 0.11 g (88 %) of the title compound were obtained, as a brown oil. ^1H-NMR, δ: 6.81 (m, 2H, 2NCH=, J = 2.3 Hz), 6.02 (m, 2H, 2CH=), 3.50 (m, 2H, CH_2O), 3.30 (m, 1H, C*H*CH$_2$O), 3.20 (s, 3H, OCH_3), 3.05 (m, 2H, CH_2N), 1.83 (m, 4H, $2CH_2$). ^{13}C-NMR, δ: 118.0 (2NCH=), 106.1 (2CH=), 73.4 (CH_2O), 63.0 (*C*HCH$_2$O), 59.3 (OCH_3), 56.7 (NCH_2), 26.1 (CH_2), 21.3 (CH_2). IR (neat): ν = 3120, 2950, 1580, 1130 cm^{-1}. Anal. Calcd. for $C_{10}H_{16}N_2O$: C, 66.62; H, 8.95; N, 15.55. Found: C, 66.60; H, 8.91; N, 15.60.

Acknowledgements

The financial support of the University of Bologna (*Funds for Selected Research Topics, A.A.1997-99*) is gratefully acknowledged.

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