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α-N-Hydroxyamino Acid Derivatives

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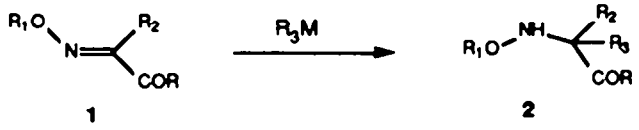
Summary: Reactions of organolithium reagents with glyoxylate derived oximes provided a direct route to α–N-hydroxyamino acids. The process required direct attachment of an ionizable group to the glyoxylate carbonyl to prevent competitive reactions. The procedure allowed for direct formation of the α–chiral center of the newly formed α–N-hydroxyamino acid derivative. Introduction of potential chiral auxiliaries on the oxime oxygen resulted in modest diastereoselection. In most instances, use of chiral glyoxylamides also gave low diastereoselectivity.

Introduction:

Because they are essential components of all living systems, the chemistry and biochemistry of amino acids have been extensively studied. However, the corresponding α-N-hydroxyamino acids (HONH-CHR-COOH) received relatively little attention until recently.[1] These unusual amino acid derivatives are now known to be important constituents of many biologically active natural products. They have also been implicated in a number of amino acid based metabolic pathways [1] Our initial interest was to synthesize α-N-hydroxyamino acids and derivatives for use during the preparation of analogs of hydroxamate containing siderophores (microbial iron chelators).[2] Although several methods for the preparation of α-N-hydroxyamino acids have been reported, most processes proceed in low yields and are complicated by the tendancy of the free acids to disproportionate.[1,3-9]

As described in our recent preliminary communication, we envisioned the preparation of α-N-alkoxyamino acids and derivatives by additions of alkyl metals to oximes of α-keto carbonyl compounds (Eq 1).[10] For R=OH and R_2=H, protected α-N-hydroxyamino acids **2** would be obtained directly from readily available glyoxylate oximes **1**. For precedent, we considered that the addition of metalated compounds to imines, oximes and hydrazones has become a useful process for syntheses of amines,[11] amino acids,[12-14] and β-lactams.[15,16] Variations of these reactions have also led to the development of asymmetric syntheses based on chiral imine derivatives.[17-19] However, two factors which often diminish the versatility of these reactions are the poor electrophilicity of the imine derivative and enolization of substrates with α-hydrogens. In some cases, these problems have been circumvented by using more activated imines[12,13,15,18] or less basic reagents.[20] Unfortunately, with oximes the same problems can be accentuated since oximes are often less electrophilic and less easily activated than the corresponding imines. α-Depro-

tonation of oximes is also facile[21] and only the use of a considerable excess of organolithium reagents produces addition products.[22] Even addition of allyl[23] or crotyl boronates[20], which proceeds smoothly with imines, requires vigorous conditions and has limited applicability with oximes. Despite these potential limitations, we found that the addition of alkyl lithium reagents to oximes of glyoxylic acid provides a direct method for the preparation of a number of O-protected α-N-hydroxyamino acids.[10] Herein we provide the details of this process and extensions of the methodology.



1 2 Eq. 1

Results:

Many variations of the substrate substituents (R, R_1, R_2) were considered to promote the conversion of **1** to **2**. Reportedly, electrophilic additions to oximes are facilitated by prior protection of the oxime oxygen.[24-27] Considering this, and with plans to eventually prepare the free α–N-hydroxyamino acids, we initially chose oxygen protecting groups (R_1 of **1**) which could easily be removed. Since the carbonyl substituent had to be compatible with strongly basic and nucleophilic reagents, yet protect the carbonyl itself from attack, we chose the free acid (R=OH). By starting with oximes of glyoxylic acid (R_2=H), we anticipated being able to prepare a number of the fundamental α-N-benzyloxyamino acids from the same substrate by simply varying the nucleophile. Table 1 summarizes our initial results. As shown, reaction of the O-benzyl oxime of glyoxylic acid (**3**) with 200 mole % of various alkyl lithium reagents at -40 to -50°C for 15-30 min followed by a quench provided the corresponding benzyl protected α-N-hydroxyamino acids **4a-e** in 63-77% isolated yields.

Table 1. Reactions of alkyl lithium reagents with the O-benzyl oxime of glyoxylic acid (**3**).

$PhCH_2ON = CHCOOH$ (**3**) $\xrightarrow[(ii)\ H^+/H_2O]{(i)\ R^3Li}$ $PhCH_2ONH\text{-}CHR^3\text{-}COOH$ (**4a-e**)

Starting Material	R^3Li	Product (% yield)
3	n-BuLi	**4a** (77)
3	sec-BuLi	**4b** (63)
3	t-BuLi	**4c** (69)
3	MeLi	**4d** (73)
3	PhLi	**4e** (76)

Encouraged by these results, the O-benzyl oxime of pyruvic acid (5) was prepared and treated under similar conditions with 200 mole % of methyl lithium. The desired α-dimethyl-N-benzyloxyamino acid (6) was obtained in 67% yield (Eq 2). This result suggests that a variety of α-disubstituted-N-hydroxyamino acid derivatives should be readily accessible. However, before exploring the scope of this aspect of the methodology, we decided to further test its versatility with the glyoxylate system.

$$\underset{\mathbf{5}}{PhCH_2ON = C(CH_3)COOH} \xrightarrow[(ii)\ H^+/H_2O]{(i)\ MeLi} \underset{\mathbf{6}}{PhCH_2ONH - C(CH_3)_2-COOH} \qquad \text{Eq. 2}$$

Complexation of a variety of organometallic reagents with the oxygen of substituted oximes has presumably assisted reaction of the same reagents with substituted imines.[14] Thus, we tested the reaction of the O-benzyl oxime of glyoxylic acid (3) with vinyl Grignard and diethyl zinc. In both cases, starting material was recovered along with small amounts of benzyl alcohol. Although these results were discouraging, other organometallic reagents should be considered. As expected, reactions of sec-butyl and t-butyl lithium with methyl and t-butyl esters of glyoxylate oximes (7a,b, Eq 3) did not provide the desired amino acid esters (8). Instead, mixtures of other products from attack of the alkyl lithium at the ester carbonyl were obtained.

$$\underset{\substack{\mathbf{7a},\ R = Me\\ \mathbf{7b},\ R = t\text{-butyl}}}{PhCH_2ON = CHCOOR} \xrightarrow[(ii)\ H^+/H_2O]{(i)\ R^3Li} \underset{\mathbf{8}}{PhCH_2ONH - CHR^3-COOR} \qquad \text{Eq. 3}$$

With these limitations in mind, we considered incorporation of chiral substituents into the basic glyoxylate framework. Both of the two possible sites of chiral substitution (R_1 and R of 2) were studied. In the first instance (Table 2), chiral oxime derivatives were prepared and studied. Reaction of an O-α-phenethyl derivative (9a) with 200 mole % of n-butyl lithium produced a 1:1 mixture of the corresponding diastereomeric amino acid (10a) in 70% yield. Reaction of the same substrate with t-butyl lithium also gave a mixture of the two expected diastereomers (10b) in 69% yield, but with 30-40% de based on NMR analysis of the crude reaction mixture. Similar modest selectivity was observed upon reaction of the racemic tetrahydropyranyl (THP) oxime (9b). Treatment of the more complex oxime (9c) with 200 mole% of n-butyl lithium provided a 59% yield of the expected amino acid (10d) with 33% de.

The alternate mode of introduction of a chiral auxiliary was conversion of the glyoxylate carboxyl group to an amide by reaction with a chiral amine. The results are given in Table 3. Treatment of the (D)-phenethyl derivative (11a) with 200 mole % of n-butyl lithium gave the desired product 12a in 79% yield and 30% de. Reaction of the same substrate (11a) with t-butyl lithium provided the corresponding product 12b in the same yield (79%), but with an improvement of the

Table 2. Reactions of alkyl lithium reagents with chiral oxime derivatives of glyoxylic acids.

$$R^1ON=CHCOOH \xrightarrow[(ii)\ H^+/H_2O]{(i)\ R^3Li} R^1ONH-CHR^3-COOH$$

Starting material	R^1	R^3Li	Product (%)	de
9a	(±) CH(Me)Ph	n-BuLi	**10a** (70)	0
9a	(±) CH(Me)Ph	t-BuLi	**10b** (69)	30-40
9b	(±) THP	n-BuLi	**10c** (65)	30
9c	(R)-CHPh(CH_2OMe)	n-BuLi	**10d** (59)[a]	33

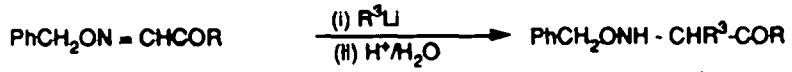
[a] Reaction time: 1hr at -40°C followed by 30min at room temperature.

diastereoselectivity to 47% de. The norephedrine derivative (**11b**) reacted smoothly with n-butyl lithium to provide the desired product (**12c**) in 54% yield, as a 1:1 mixture of diastereomers. Starting material (20%) and the corresponding ketone (**13**, 12%) were also isolated. Reaction of the O-methylnorephedrine derivative (**11c**) under identical conditions gave the desired product (**12e**) in 68% yield (33% de). Again, starting material (8%) and the same ketone (**13**, 11%) were isolated. The successful use of prolinol and related derivatives[19,28] encouraged us to prepare and study related amides **11d** and **11e**. These substrates were also expected to provide a new test of the scope of the methodology since they contain no ionizable position to protect the carbonyl group from nucleophilic attack. As might have been expected, treatment of **11d** and **11e** with n-butyl lithium gave the desired addition products in only 9% and 8% yields respectively. Small amounts (8% and 11%) of the corresponding ketone (**13**) were also obtained. The major product was benzyl alcohol which was presumably generated from direct N-O bond cleavage, a process which has precedent.[25]

With the need for direct attachment of an ionizable group to the glyoxylate carbonyl clarified, we reconsidered primary chiral amide derivatives. The valine adduct **11f** was prepared by direct coupling of the glyoxylate oxime N-hydroxysuccinimide ester with L-valine. Reaction of (**11f**) with 200 mole % of n-butyl lithium in the usual fashion gave no reaction, as expected. Use of 300 mole % of n-butyl lithium to deprotonate both the amide and acid, yet still leave 100 mole % for reaction at the oxime did provide the desired dipeptide (**12h**) in 64% isolated yield but with no diastereoselection. Finally, treatment of the same substrate with 300 mole % of t-butyl lithium provided dipeptide (**12i**) in 53% yield with 20% diastereoselection.

In conclusion, we have described a simple and general method for the preparation of α-N-hydroxyamino acid and α-N-hydroxypeptide derivatives from glyoxylate derived oximes. In most cases, the method proceeds in reasonable yields with moderate diastereoselectivity. However, the diastereoselection observed in the products suggests that further development may provide an efficient route to α-N-hydroxyamino acids, their derivatives and related peptides. Finally, the possibility of utilizing "matched" chiral auxiliaries in both the oxime oxygen and carboxyl position of the glyoxylate oxime deserves study.[29]

Table 3. Reactions of alkyl lithium reagents with chiral amide derivatives of the O-benzyl oxime of glyoxylic acid.



11a-f 12a-l

Starting material	R	R^3Li	Product (%)	de
11a	(D)-NHCH(Me)Ph	n-BuLi	12a (79)	30
11a	(D)-NHCH(Me)Ph	t-BuLi	12b (79)	47
11b	(R,S)-NHCH(Me)CH(OR')Ph			
	R' = H	n-BuLi	12c (54)[a]	0
	R' = H	t-BuLi	12d (84)[b]	0
11c	R' = Me	n-BuLi	12e (68)	33
11d	(S)-Prolinol	n-BuLi	12f (9)[a]	-
11e	(S)-O-methyl prolinol	n-BuLi	12g (8)[a]	-
11f	(S)-NHCH(iPr)COOH	n-BuLi(200 mole%)	12h (0)	-
11f		n-BuLi(300 mole%)	12h (64)	0
11f		t-BuLi(300 mole%)	12l (53)	20

[a] The ketone, $PhCH_2ON$ = CHCOnBu (13) was also isolated.

[b] Crude yield.

Experimental Section:

General Methods. Melting points were taken on a Thomas-Hoover Capillary Melting Point Apparatus and are uncorrected. Infrared spectra (IR) were recorded on a Perkin-Elmer 1420 spectrophotometer. Proton NMR spectra were obtained on Varian EM-390, Magnachem A-200, or Nicolet NB-300 spectrometers. Chemical shifts are reported in ppm relative to tetramethylsilane (δ units). Mass spectra were recorded on an AEI Scientific Apparatus MS 902, Du Pont DP 102, or Finnigan MAT Model 8430 spectrometers. Elemental analysis were performed by M-H-W Laboratories, Phoenix, AZ. All solvents were dried by standard methods.

General method for the preparation of oxime derivatives of glyoxylic acid 3 and 9a-c. Sodium acetate (0.2 mol) was added to a solution of glyoxylic acid hydrate (0.1 mol) and N-alkoxyamine hydrochloride (0.1 mol) in 150 ml of H_2O-MeOH (1:1) and the reaction was stirred overnight at room temperature. The methanol was removed in vacuum and the products were filtered off or extracted with ethyl acetate. The crystalline oximes were recrystallized from ethyl acetate / skelly B and the oily products were filtered through silica gel and washed with CH_2Cl_2 / ethyl acetate to provide pure products.

O-Benzyl oxime 3 was obtained in 94% yield: mp 77-80°C (lit[30] mp 78-80°C); ^{1}H-NMR ($CDCl_3$) δ 5.30 (s, 2H), 7.40 (s, 5H), 7.56 (s, 1H), 11.66 (s, 1H, COOH); IR (nujol) 1705, 1690, 1620 cm^{-1}; mass spectrum (CI) m/e 180 (M+1).

O-Methylbenzyl oxime 9a was obtained in 80% yield: mp 81-83°C; ^{1}H-NMR ($CDCl_3$) δ 1.63 (d, 3H, J=7 Hz), 5.40 (q, 1H, J=7 Hz), 7.33 (s, 5H), 7.53 (s, 1H), 10.56 (s, 1H); IR (nujol) 3200-

2800, 1700, 1580 cm^{-1}. Anal calcd. for $C_{10}H_{11}NO_3$: C, 62.18; H, 5.70; N, 7.25; Found: C, 62.43; H, 5.71; N, 7.23.

O-Tetrahydropyranyl oxime 9b was obtained as an oil in 29% yield; ^{1}H-NMR ($CDCl_3$) δ 1.7 (m, 6H), 3.73 (m, 2H), 5.46 (m, 1H), 7.63 (s, 1H), 10.0 (s, 1H); IR (neat) 3200-2500, 1720, 1620 cm^{-1}; mass spectrum (CI-isobutane) m/e 174 (M+1), 156 (M+1-18).

O-Methoxymethylbenzyl oxime 9c was obtained as an oil in 90% yield; $[\alpha]^{25}_D$ = -63.4 (c 2.0, CH_2Cl_2); ^{1}H-NMR ($CDCl_3$) δ 3.38 (s, 3H), 3.68 (dd, 2H, J=6 Hz), 5.43 (dd, 1H, J=6 Hz), 7.33 (s, 5H), 7.56 (s, 1H), 9.0 (broad s, 1H); IR (neat) 3300-2500, 1715, 1600 cm^{-1}; mass spectrum m/e (EI) m/e 224 (M+1). Anal calcd. for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.83; N, 6.28; Found: C, 59.21; H, 5.89; N, 6.27.

Oxime derivative of pyruvic acid 5 was prepared in two step synthesis. First, the ethyl pyruvate was transformed into the ethyl ester of O-benzyl oxime of pyruvic acid as described for 3 and subsequent ester hydrolysis provided the product in 95% yield: mp 83-85°C (lit[30] mp 83-85°C); ^{1}H-NMR ($CDCl_3$) δ 2.10 (s, 3H), 5.30 (s, 2H), 7.40 (s, 5H), 8.10 (s, br, 1H); IR (nujol) 3200-2500, 1690, 1600 cm^{-1}.

General method for the preparation of chiral amide derivatives of O-benzyl oximes of glyoxylic acid 11a-e. To a solution of amine (0.1 mol) and $NaHCO_3$ (0.1 mol) in water was added a solution of the N-hydroxysuccinimide ester of glyoxylic acid oxime 3 (0.1 mol) in ethyl acetate and the reaction mixture was stirred overnight. The ethyl acetate layer was separated, washed with 1N HCl, water, 10% $NaHCO_3$, water, brine, and dried ($MgSO_4$). The solution was filtered and the solvent was evaporated to provide the products which were either recrystallized from ethyl acetate / skelly B or purified on a silica gel column with CH_2Cl_2-ethyl acetate as the eluent.

Amide derivative of the O-benzyl oxime 11a was obtained in 86% yield: mp 63-65°C; $[\alpha]^{25}_D$ = -68.1 (c 2.0, CH_2Cl_2); ^{1}H-NMR ($CDCl_3$) δ 1.48 (d, 3H, J=7Hz), 5.13 (s+m, 3H), 6.78 (d, br, 1H), 7.34, 7.37 (two s, 10H), 7.48 (s, 1H); IR (nujol) 3260, 1660, 1580 cm^{-1}. Anal calcd. for $C_{17}H_{18}N_2O_2$: C, 72.34; H, 6.38; N, 9.93; Found: C, 72.50; H, 6.32; N, 9.94.

Amide derivative of the O-benzyl oxime 11b was obtained in 74% yield: mp 130-131°C; $[\alpha]^{25}_D$ = +19.9 (c 2.0, CH_2Cl_2); ^{1}H-NMR ($CDCl_3$) δ 1.00 (d, 3H, J=7Hz), 3.36 (s, br, 1H), 4.33 (m, 1H), 4.82 (m, 1H), 5.16 (s, 2H), 6.72 (d, br, 1H, J=7Hz), 7.35, 7.40 (two s, 10H), 7.45 (s, 1H), IR (nujol) 3240, 1650, 1590 cm^{-1}. Anal calcd. for $C_{18}H_{20}N_2O_3$: C, 69.23; H, 6.41; N, 8.97; Found: C, 69.13; H, 6.34; N, 8.92.

Amide derivative of the O-benzyl oxime 11c was obtained as an oil in 80% yield: $[\alpha]^{25}_D$ = +36.0 (c 2.0, CH_2Cl_2); ^{1}H-NMR ($CDCl_3$) δ 1.00 (d, 3H, J=7Hz), 3.33 (s, 3H), 4.33 (m, 2H), 5.20 (s, 2H), 6.80 (d, br, 1H), 7.33, 7.40 (two s, 10H), 7.50 (s, 1H); IR (nujol) 3320, 1655, 1600 cm^{-1}. Anal calcd. for $C_{19}H_{22}N_2O_3$: C, 69.94; H, 6.75; N, 8.59; Found: C, 70.15; H, 6.71; N, 8.57.

Amide derivative of the O-benzyl oxime 11d was obtained as an oil in 69% yield: $[\alpha]^{25}_D$ = -38.0 (c 2.0, CH_2Cl_2); ^{1}H-NMR ($CDCl_3$) δ 1.87 (m, 4H), 3.66 (m, 4H), 4.30-4.43 (two m in 4:1 ratio, 1H), 5.23 (s, 2H), 7.40 (s, 5H), 7.76, 7.90 (two s in 4:1 ratio, 1H); IR (neat) 3400, 1635, 1590 cm^{-1}; mass spectrum (CI-isobutane) m/e 263 (M+1), 231 (M-31).

Amide derivative of the O-benzyl oxime 11e was obtained as an oil in 90% yield: $[\alpha]^{25}_D$ = -57.0 (c 2.0, CH_2Cl_2); ^{1}H-NMR ($CDCl_3$) δ 1.90 (m, 4H), 3.23, 3.33 (two s, 3H), 3.53 (m, 4H), 4.33 (m, 1H), 5.20 (s, 2H), 7.40 (s, 5H), 7.72, 7.87 (two s in 1:1 ratio, 1H); IR (neat) 1635, 1600 cm^{-1}; mass spectrum (EI) m/e 276 (M^+), 231 (M-45), 91.

Amide derivative of the O-benzyl oxime 11f was prepared in a manner similar to that for 11a except that the 10% $NaHCO_3$ washing during workup was ignored and the product was obtained in 30% yield: mp 95-96°C; $[\alpha]^{25}_D$ = +46.3 (c 2.0, CH_2Cl_2); ^{1}H-NMR ($CDCl_3$) δ 0.9 (d, 6H, J=7Hz), 2.23 (septet, 1H, J=7Hz), 4.63 (dd, 1H, J=3Hz; 7Hz), 5.20 (s, 2H), 7.10 (d, br, 1H, J=8Hz), 7.40 (s, 5H), 7.56 (s, 1H); IR (nujol) 3300, 3200-2500, 1710, 1630, 1585 cm^{-1}. Anal calcd. for $C_{14}H_{18}N_2O_4$: C, 60.43; H, 6.47; N, 10.07; Found: C, 60.45; H, 6.47; N, 9.97.

General method for the alkyl metal addition to oximes. The oxime was dissolved in dry THF under nitrogen and cooled to -40°C. A solution of alkyl metal was added and the mixture was stirred at -40°C for 15-60 min. The reaction was quenched with saturated NH_4Cl, acidified with 1N HCl to pH 2, and extracted with several portions of ethyl acetate. The combined organic layers were extracted with 5% $NaHCO_3$ solution and the organic phase was discarded (this step was deleted for amide oximes). The aqueous layer was acidified to pH 2-4 with 1N HCl and extracted with several portions of ethyl acetate. The ethyl acetate extracts were combined, washed with brine, dried over $MgSO_4$, filtered, and evaporated to provide the products.

α-N-Benzyloxyamino-n-hexanoic acid (4a) was obtained in 77% yield: mp 113-115°C; ^{1}H-NMR ($CDCl_3$) δ 0.79-0.92 (m, 3H), 1.22-1.45 (m, 4H), 1.83-1.99 (m, 2H), 4.12-4.24 (t, 1H), 5.10 (s, 2H), 7.35 (s, 5H); IR (KBr) 3100-2400 (broad, weak, zwitterion form), 1580 (broad) cm^{-1}; mass spectrum (EI) m/e 237 (M^+), 178 (M-n Bu), exact mass calcd. for $C_{13}H_{19}NO_3$: 237.137. Found : 237.138. Anal. Calcd. for $C_{13}H_{19}NO_3$: C, 65.82; H, 8.02; N, 5.91; Found: C, 65.75; H, 8.10; N, 5.75.

α-N-Benzyloxyamino-γ-methylpentanoic acid (4b) was obtained in 63% yield: ^{1}H-NMR ($CDCl_3$) δ 0.81-1.77 (m, 9H), 3.59 (m, 1H), 4.65 (s, 2H), 6.60 (b, NH), 7.33 (s, 5H); IR (neat) 3640-2400 (broad), 1720 cm^{-1}; mass spectrum (EI) m/e 237 (M^+), exact mass calcd. for $C_{13}H_{19}NO_3$: 237.137. Found : 237.138.

α-N-Benzyloxyamino-β,β-dimethylbutyric acid (4c) was obtained in 69% yield: ^{1}H-NMR ($CDCl_3$ + TFA) δ 0.98 (s, 9H), 3.48 (s, 1H), 4.88 (d, 2H),7.56 (s, 5H), 8.42 (b, NH); IR (nujol) 3600-2300 (broad), 1705 cm^{-1}; mass spectrum (EI) m/e 237 (M^+), exact mass calcd. for $C_{13}H_{19}NO_3$: 237.137. Found : 237.138.

α-N-Benzyloxyamino-propionic acid (4d) was obtained in 73% yield: ^{1}H-NMR ($CDCl_3$) δ 1.58 (d, b, 3H), 4.33 (m, 1H), 5.14 (s, 2H), 7.32 (s, 5H); IR (nujol) 3140-2300 (weak, broad, zwitter- ion form), 1695 (weak), 1580 cm^{-1} ; mass spectrum (EI) m/e 195 (M^+), 150 (M - COOH -1).

α-N-Benzyloxyaminophenylacetic acid (4e) was obtained in 76% yield: ^{1}H-NMR ($CDCl_3$) δ 5.10 (s, 2H), 5.31 (s, 1H), 7.18-7.58 (m, 10H); IR (nujol) 3700-2200, 3040, 1700 cm^{-1}; mass spectrum (EI) m/e 257 (M^+), 230 (M - OH).

α-N-Benzyloxyamino-α-methylpropionoic acid (6) was obtained in 67% yield: ^{1}H-NMR ($CDCl_3$) δ 1.93 (s, 3H), 2.35 (s, 3H), 5.26 (s, 2H), 7.37 (s, 5H); IR (neat) 3380 (broad), 3140, 2940, 1695, 1610 cm^{-1}.

α-N-(1-Phenethyloxyamino)-n-hexanoic acid (10a) was obtained in 70% yield: ^{1}H-NMR ($CDCl_3$) δ 0.74-1.67 (m, 12H), 3.42 (t, 1H), 3.68 (t, 1H), 4.69-4.89 (m, 2H), 7.32 (s, 5H), 8.75 (b, NH); IR (neat) 3500-2300 (broad), 1640 (broad) cm^{-1}; mass spectrum (EI) m/e 251 (M$^+$), 147 (M - Ph(Me)CH), exact mass calcd. for $C_{14}H_{21}NO_3$: 251.152. Found : 251.152.

α-N-(1-Phenethyloxyamino-β,β-dimethylbutyric acid (10b) was obtained in 69% yield: ^{1}H-NMR ($CDCl_3$) δ 0.79-1.40 (m, 12H), 3.10-3.40 (two singlets for two diastereomers in 70:30 ratio, 1H), 4.63-4.88 (two q, 2H), 6.77 (b, NH), 7.28 (s, 5H); IR (neat) 3700-2300 (broad), 1710, 1450 cm^{-1}.

α-N-(2-Tetrahydropyranyloxyamino)-n-hexanoic acid (10c) was obtained in 65% yield: ^{1}H-NMR ($CDCl_3$) δ 0.80-1.98 (m, 15H), 3.37-4.10 (m, 3H), 4.60-4.88 (m, 1H), 6.99 (b, NH); IR (neat) 3700-2400 (broad), 1730, 1450 cm^{-1}.

α-N-(2-(R)-methoxy-1-phenethyloxyamino)-n-hexanoic acid (10d) was obtained as an oil in 59% yield: $[\alpha]^{25}_D$ = -49.2 (c 0.5, CH_2Cl_2); ^{1}H-NMR ($CDCl_3$) δ 0.80 (m, 3H), 1.40 (m, 4H), 1.51 (m, 2H), 3.35, 3.41 (two s in 1:2 ratio, 3H), 3.50 (m, 3H), 4.87 (three d, 1H, J=3Hz), 5.97 (s, br, 1H), 7.32 (m, 5H); IR (neat) 3440, 3250, 2500 (COOH), 1730 cm^{-1}; mass spectrum (CI-Isobutane) m/e 282 (M+1), 135 (M-46).

N-(R)-Phenethylamide of α-N-benzyloxyamino-n-hexanoic acid (12a) was obtained in 79% yield: ^{1}H-NMR ($CDCl_3$) δ 0.68-1.66 (m, 12H), 3.45 (b, 1H), 4.63 (m, 2H), 4.94-5.23 (m, 2H), 6.80 (b, NH), 7.29 (s, 10H); IR (neat) 3310 (broad), 1660 (broad), 1525 (broad) cm^{-1}; mass spectrum (CI) m/e 340 (M$^+$), 234 (M - $CH(CH_3)Ph$).

N-(R)-Phenethylamide of α-N-benzyloxyamino-β,β-dimethylbutyric acid (12b) was obtained in 79% yield: ^{1}H-NMR ($CDCl_3$) δ 0.94 (d, 3H), 1.31-1.55 (m, 9H), 3.11 (two merging singlets, 1H), 4.54, 4.66 (dd, 2H), 5.04 (t, 1H), 5.21 (t, 1H), 6.39 (b, NH), 6.56 (b, NH), 7.28 (s, 10H); IR (neat) 3300 (broad), 1650 (broad) cm^{-1}; mass spectrum (CI-Isobutane) m/e 341 (M+1).

α-N-Benzyloxyamino-n-hexanoyl-(1S,2R)-norephedrine (12c) was obtained in 54% yield: $[\alpha]^{25}_D$ = +54.4 (c 0.9, CH_2Cl_2); ^{1}H-NMR ($CDCl_3$) δ 0.85 (t, 3H, J=7Hz), 0.98 (d, 3H, J=7Hz), 1.27 (m, 4H), 1.56 (m, 2H), 3.40 (q, 1H, J=7Hz), 4.12 (s, br, 1H), 4.30 (m, 1H), 4.61 (s, 1H), 4.67 (d, 1H, J=3Hz), 4.80 (dd, 1H), 5.71 (s, br, 1H), 6.69, 6.81 (dd, 1H), 7.29 (m, 10H); IR (nujol) 3300, 3240,1640, 1560 cm^{-1}; mass spectrum (CI-Isobutane) m/e 371 (M+1), 370 (M$^+$), 264 (M-107).

α-N-Benzyloxyamino-β,β-dimethylbutyryl-(1S,2R)-norephedrine (12d) was obtained in 84% yield: ^{1}H-NMR ($CDCl_3$) δ 0.92-1.04 (m, 9H), 1.16 (s, 3H), 3.04-3.08 (d, J=13.5 Hz, 1H), 3.88 (b, OH), 4.20-4.40 (m, 1H), 4.54-4.72 (m, 2H), 4.77-4.87 (m, 1H), 6.38 (d, NH), 6.62 (d, NH), 7.26 (m, 10H); IR (neat) 3600-3100 (broad), 1640, 1520 cm^{-1}; mass spectrum (FAB - Glycerol matrix) m/e 371 (M+1), 185.

α-N-Benzyloxyamino-n-hexanoyl-(1S,2R)-O-methylnorephedrine (12e) was obtained in 68% yield: $[\alpha]^{25}_D$ = +29.0 (c 0.5, CH_2Cl_2); ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.03 (d, 3H,

J=7Hz), 1.31 (m, 4H), 1.60 (m, 2H), 3.28 (two s in 2:1 ratio, 3H), 3.44 (q, 1H), 4.25 (m, 0.5H) 4.33, 4 37 (two d, 0 5H, J=7Hz in 1:2 ratio) 4 70, 4.75 (two d in 1:2 ratio, J=11Hz), 5.79 (s, br, 1H), 6.80, 6.87 (two d in 1:2 ratio, 1H), 7.32 (m, 10H); IR (neat) 3300 with shoulder at 3400, 1650 cm^{-1}; mass spectrum (CI-Isobutane) m/e 385 (M+1), 384 (M^+), 353 (M-32), 283 (M-122).

α-N-Benzyloxyamino-n-hexanoyl-(L)-valine (12h) was obtained in 64% yield: $[\alpha]^{25}_D$ = -4.8 (c 0.5, CH_2Cl_2); ^{1}H-NMR ($CDCl_3$) δ 0.82 (m, 9H), 1.35 (m, 4H), 1.65 (m, 2H), 2.24 (m, 1H), 2.89 and 3.52 (two t in 1:1 ratio, 1H, J=7Hz), 4.50, 4.60 (two dd, 1H), 4.68 (s, 1H), 4.75 (d, 1H), 7.33 (m, 5H), 7.67 (s, br, 2H); IR (nujol) 3310, 3280, 1650 with shoulder at 1680 cm^{-1}; mass spectrum (CI-Isobutane) m/e 337 (M+1), 319, 231.

α-N-Benzyloxyamino-β,β-dimethylbutyryl-(L)-valine (12i) was obtained in 53% yield: ^{1}H-NMR ($CDCl_3$) δ 0.90-1.07 (m, 12H), 1.33 (s, 3H), 2.19-2.36 (m, 1H), 3.22 (s, 1H), 4.47-4.55 (m, 1H), 4.63-4.78 (m, 2H), 6.93 (m, 1H, NH), 7.27-7.39 (m, 5H), 9.03 (b, COOH); IR (neat) 3550-2300 (broad), 1710, 1680 (broad), 1520 (broad) cm^{-1}; mass spectrum (FAB - Glycerol matrix) m/e 336 (M^+), 337 (M+1), 185.

n-Butyl-(N-benzyloxyimine)methyl ketone (13): ^{1}H-NMR ($CDCl_3$) δ 0.90 (t, 3H, J=7 Hz), 1.31 (septet, 2H, J=7 Hz), 1.58 (quintet, 2H, J=7 Hz), 2.74 (t, 2H, J=7 Hz), 5.24 (s, 2H), 7.37 (s, 5H), 7.47 (s, 1H); IR (neat) 1690, 1590 cm^{-1}. Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.23; H, 7.76; N, 6.39; Found: C, 71.17; H, 7.80; N, 6.27.

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