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# Cycloaddition of 5-Substituted 1- Pyrroline 1-oxide and Conversion of the Nitrone Cycloadducts into *cis*-and *trans*- 2,5- Disubstituted Pyrrolidines

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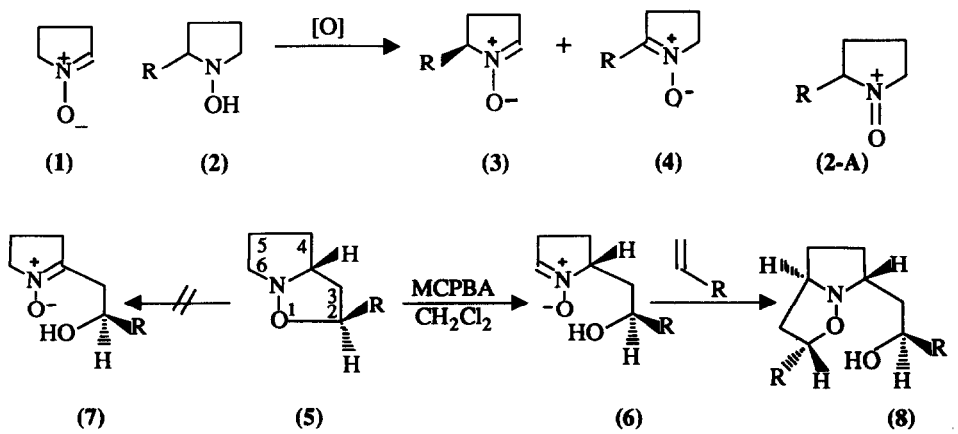
***Abstract:*** A study of the regiochemical behaviour of the oxidation of 2-substituted-1-hydroxypyrrolidines (2) leading to aldo- and kito-nitrones has been carried out. The mechanism of the peracid induced ring opening reaction of isoxazolidines (5) is now firmly established. Second cycloaddition reaction of 5-substituted 1- pyrroline 1-oxide (6) provides an efficient and stereoselective entry into the *trans*- (24) as well as *cis*-2,5- disubstituted pyrrolidines (28).

## INTRODUCTION

Among cyclic nitrones, 1-pyrroline 1-oxide (1) has emerged as one of the most important 1,3-dipoles, since its addition reactions[1] incorporate and elaborate the pyrrolidine moiety which is widespread in nature. While the nitrone (1) is readily generated by oxidation of symmetrical *N*-hydroxypyrrolidine, progress in the synthetic applications of the 5-substituted nitrones (3) was hampered because of the lack of regiochemical control in the oxidation of unsymmetrical hydroxylamines (3).[2] Successful efforts to prepare the 5-substitued nitrone (6) regioselectively were limited to a few cases of peracid induced oxidation of isoxazolidines[3] (5), obtained by the nitrone (1) - alkene cycloaddition reactions, and electrophile-mediated cyclisation of allenic oximes.[4]




(1) (2) (3) (4) (2-A)

(7) (5) (6) (8)

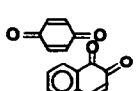
**Scheme 1**

Here, we report in detail, the effects of various oxidants on the regiochemistry of oxidation of the substituted N-hydroxypyrrolidine (2). The second cycloaddition involving the less substituted nitrone (6) provides an excellent stereoselective route to *trans* -2, 5-dialkyl-pyrrolidines[5] via the cycloadducts (8) (Scheme 1). Despite the importance of this reaction sequence, the peracid induced ring opening is limited only to a few cases of the cycloadduct (5) having monosubstitution at C-2. In our continuing efforts[6] to deduce the mechanism of peracid induced ring opening of the isoxazolidines (5) we undertook a systematic study involving the treatment of a series of 2-mono-, 2,2-, 2,6-di- and 2,2,6-tri-substituted isoxazolidines (5) with m-chlorobenzoic acid (MCPBA) in different solvents. Our interest in alkaloids having *cis*-2,5-disubstituted pyrrolidine moiety also led us to explore the possibility of converting the *trans* cycloadducts (8) to *cis*- 2,5-disubstituted pyrrolidines.

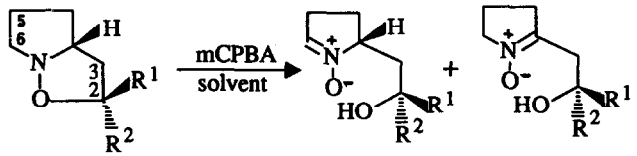
## RESULTS AND DISCUSSIONS

The regiochemistries of the oxidation of unsymmetrical hydroxylamines (2) with different oxidants (Scheme 1) are given in Table 1. While we were interested in the selective formation of the less substituted aldonitrones 3 for possible utilization in the synthesis of natural products, the ketonitrones (4) are formed as the major regioisomers under various reaction conditions. It is commonly believed that the HgO oxidation process involves the intermediacy of nitroxonium ion intermediate 2-A which then tautomerizes to give the nitrones (3) and (4) (Scheme 1). In presence of a bulky base like triethylamine we anticipated the base catalyzed tautomerization to give the less substituted nitrone (3) as the kinetically controlled product. Contrary to our expectation the more substituted nitrone (4) was the major product. The effect of changing the oxidant from HgO to benzoquinone and napthoquinone resulted only in slight increase in the proportion of the nitrone (3).

**Table 1. Regiochemistry of the oxidation of the hydroxylamines (2)**

| Hydroxylamine (2) | Oxidant | Solvent | % composition of nitrones (3) | (4) |
|---|---|---|---|---|
| a, R=$CH_2Ph$ | | $CH_2Cl_2$ | 35 | 65 |
| a | HgO | $CH_2Cl_2$/$Et_3N$ | 20 | 80 |
| | | t-Butanol | 25 | 75 |
| a |  | $CDCl_3$ | 35 | 65 |
| a | | $CDCl_3$ | 40 | 60 |
| a | | $CDCl_3$ | 35 | 65 |
| b, R=$CH_3$ | HgO | $CH_2Cl_2$ | 25 | 75 |

In an effort to prepare either the aldonitrone (**6**) or the ketonitrone (**7**) in a regioselective manner, we treated a series of nitrone cycloaddition products (**5**) with MCPBA in different solvents (scheme 2). The regiochemical details of the peracid reaction are included in Table 2. As is evident from the Table 2, all of the 2-mono- and 2,2- di-substituted adducts (**5**) underwent ring opening raction in dichloromethane resulting in the exclusive formation of the less substituted nitrone (**6**). There is a dramatic change in the product ratio as the solvent is switched from aprotic to protic. For instance, the styrene adduct (**5a**) in methanol afforded the nitrones (**6a**) and (**7a**) in a respective ratio of 20 : 80. Complete reversal in the regioselection occurred in water or acetic acid solvent affording the more substituted nitrone (**7a**) as the sole regioisomer. Similar reversal in regioselection was observed in the ring opening reaction of the monosubstituted adduct (**5c**). However, in case




(**5**) (**6**) (**7**)

**a**, $R^1$ = Ph; $R^2$ = H
**b**, $R^1$ = $CH_2OH$; $R^2$ = H
**c**, $R^1$ = $CH_2OSi^tBuMe_2$; $R^2$ = H
**d**, $R^1$ = $CH_2CH_2CH_2OH$; $R^2$ = H
**e**, $R^1$ = $CH_3$; $R^2$ = $CO_2Me$
**f**, $R^1$ = $CH_3$; $R^2$ = $CH_2OH$
**g**, $R^1$ = $CH_3$; $R^2$ = $CH_2OSi^tBuMe_2$
**h**, $R^1$ = $^nBu$; $R^2$ = H

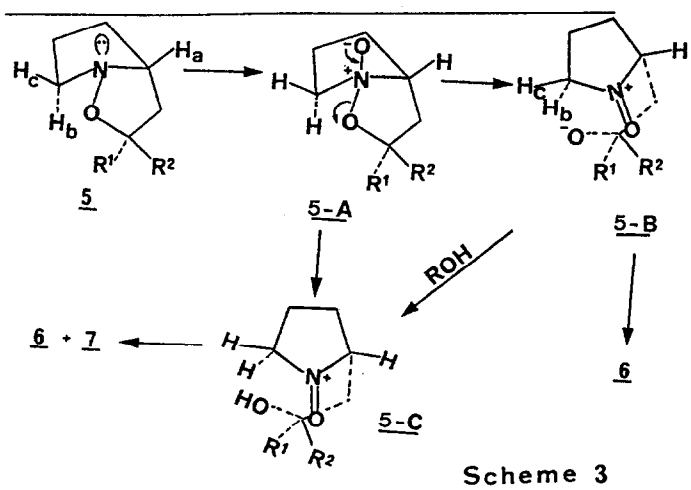
**Scheme 2**

of the adducts (**5b**) and (**5d**) having a free hydroxyl substituent as well as the 2,2-disubstituted adducts (**5e**), (**5f**) and (**5g**), the formation of the ketonitrones (**7**) in acetic acid varies in the range of 75-85 %. The nitrones (**6**) and (**7**) are readily identified by n.m.r. and i.r. spectra. The 2-H of the nitrones (**6**) and the 5-Hs of (**7**) appeared around δ 7.0 and 4.0, respectively, and the strong absorptions around 1600 and 1200 $cm^{-1}$ are indicative of the presence of nitrone functionality. Even though the peracid induced ring opening of the isoxazolidines has been known for three decades[3,5,8] a clearer picture of the mechanistic pathway of this reaction is emerging through our systematic study. The orientation of lone pair of electrons on nitrogen holds the key for a better understanding of the mechanism of peracid induced ring opening of the isoxazolidines (**5**).[6]

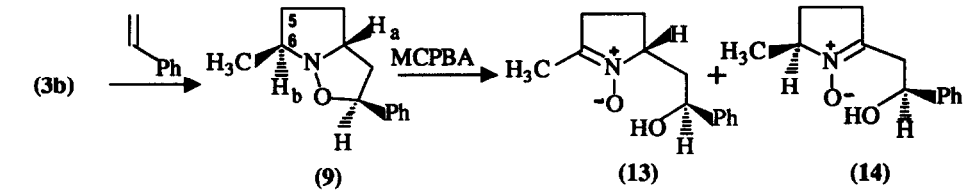
For the carbocylic counterpart of the 5-5 fused isoxazolidines (**5**), the free energy difference of approximately 25 kJ/mol favours the *cis* over the *trans* isomer. Although the presence of two heteroatoms in (**5**) somewhat decreases this energy difference, geometric constraints do not permit nitrogen inversion and lock it to remain *cis*- fused[7] as depicted in Scheme 3. The proposed mechanistic pathway[6] envisages the intermediacy of the amine oxide intermediate **5-A**, followed by nitroxonium salt **5-B**, in which the secondary or tertiary alnoxide ion finds $H_b$ in its immediate vicinity for fast kinetic deprotonation to result in the exclusive formation of the less substituted nitrone (**6**) (Scheme 3). Electrostatic attraction presumably holds the ion pair **5-B** close to each other and restricts rotation long enough to allow the selective deprotonation to occur.

Table 2 Regiochemistry of MCPBA induced ring opening of the isoxazolidines (5).

| Isoxazolidines (5) | Solvent | % composition of the nitrones (6) | (7) |
|---|---|---|---|
| | $CH_2Cl_2$ | 100 | 0 |
| a | MeOH | 20 | 80 |
| | $H_2O$ | 0 | 100 |
| | HOAc | 0 | 100 |
| | $CH_2Cl_2$ | 100 | 0 |
| b | MeOH | 50 | 50 |
| | HOAc | 15 | 85 |
| | $CH_2Cl_2$ | 100 | 0 |
| c | MeOH | 40 | 60 |
| | HOAc | O | 100 |
| | $CH_2Cl_2$ | 100 | 0 |
| d | MeOH | 50 | 50 |
| | HOAc | 15 | 85 |
| e | $CH_2Cl_2$ | 100 | 0 |
| | HOAc | 25 | 75 |
| f | $CH_2Cl_2$ | 100 | 0 |
| | HOAc | 25 | 75 |
| g | $CH_2Cl_2$ | 100 | 0 |
| | HOAc | 25 | 75 |

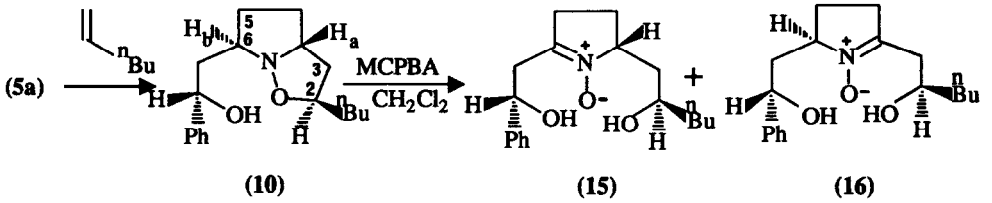



Scheme 3

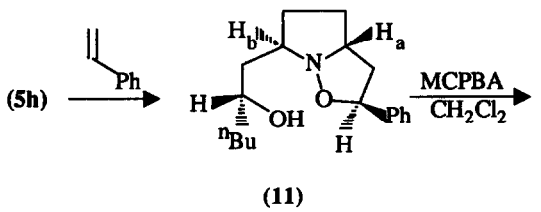



$CH_2Cl_2$ 100 : 0

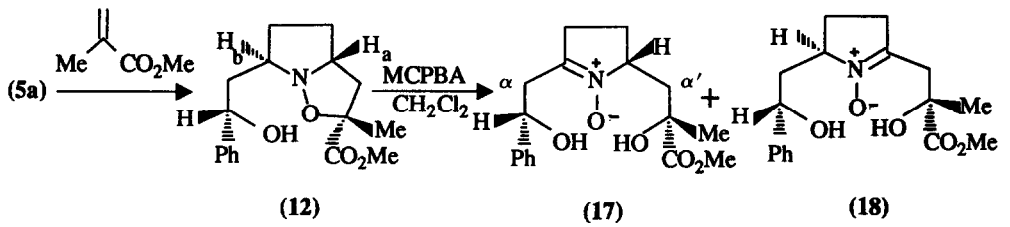
MeOH 50 : 50




100 : 0




0 : 100




100 : 0

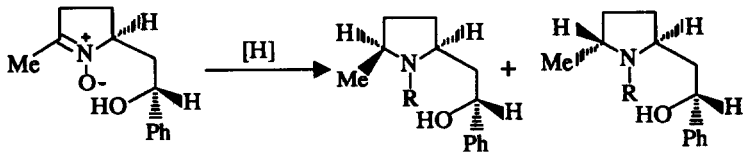
**Scheme 4**

In protic solvent hydrogen bonded **5-A** or fast proton capture by the species **5-B** leads to the interception of the protonated intermediate **5-C** which tautomerizes under thermodynamic-controlled acid-catalysed process resulting in the formation of the more substituted nitrone **(7)** as the sole or the predominant products.

At this stage, we were unable to offer any compelling evidence that would confirm the abstraction of the proton $H_b$ instead of $H_c$ in aprotic solvent. In order to substantiate the mechanism we synthesized several adducts (9) - (12) having substituents at C-6 in place of $H_c$ (Scheme 4). The cycloaddition of the nitrone (3b) with styrene afforded the adduct (9) stereoselectively by *exo* -addition of styrene onto the less hindered face of the nitrone. Likewise the addition reaction of the aldonitrone (5a) with 1-hexene and methyl methacrylate led to the exclusive formation of the adducts (10) and (12), respectively. The stereochemistry of the adduct (12) with *endo*-oriented methoxycarbonyl group is based on its ability to manifest secondary orbital interactions in the *endo* transition state.[9] Similar face- and *exo*-selectivity is enjoyed in the reaction of the nitrone (5h) with styrene leading to the formation of the sole adduct (11). This second-cycloaddition sequence involving the second-generation nitrones proceeded at 60-65°C with yields around 70 %.

With the array of cycloadducts (9) - (12) in our hands, the stage was set for probing further the pathway of the MCPBA induced ring opening reaction. It was a matter of concern whether the bulky alkoxide would act fast enough to abstract the crowded tertiary proton $H_b$ before being protonated by m-chlorobenzoic acid (which is produced in equivalent amount during the reaction). To our delight, the adducts (9), (10), (11) and (12) upon treatment with MCPBA in dichloromethane resulted in the regiospecific and quantitative formation of the nitrones (13), (15), (16) and (17), respectively, by abstraction of the proton $H_b$ (scheme 4). As expected, the ring opening reaction of (9) in methanol afforded a mixture of the nitrones (13) and (14) in a 1:1 ratio owing to the intervention of the protonated species 5-C. The adducts (10) and (11) were so chosen that each might lead to the same possible nitrones (15) and (16). However, the mechanistic pathway dictates the formation of a single regiosomer in each case (e.g. (10) ---> (15) and (11) ---> (16). The $^1H$ n.m.r. spectra readily identified the nitrones (15) and (16); the benzylic proton of the former, being closer to the nitrone functionality, appears at $\delta$ 5.12 compared to the benzylic proton of the latter ($\delta$ 4.98). Similar observations are made on several occasions (see experimental). The ring opening reaction of the adduct (12) represents an extreme case where a tert-alkoxide abstracts a tertiary hydrogen to give the nitrone (17) regiospecifically. Spectral analysis precluded the formation of the isomeric nitrone (18). The $\alpha$ and $\alpha'$ hydrogens of (17) appear at $\delta$ 2.80 and 1.80 , respectively. Irradiation of the $\alpha$ hydrogens at $\delta$ 2.80 caused the benzylic proton signals at $\delta$ 5.17 (dd, J 4.0, 7.0 Hz) to collapse into a singlet as expected.

Finally, we focussed our attention onto finding a convenient way of converting the double cycloadducts into *cis*- 2,5- disubstituted pyrrolidines. The adducts obtained by the second-cycloaddition sequence have been converted into trans-2,5- disubstituted pyrrolidines in excellent yields by hydrogenolysis of the N-O bond.[5] In our study while the adduct (9) upon treatment with zinc-aqueous acitic acid afforded the amine (22) with trans-orientation of the substituents, the nitrone (13) upon hydrogenation afforded the sole hydroxylamine (19) which on reaction with zinc and aqueous acetic acid gave the *cis* - amine (21) (Scheme 5). The *cis*-orientation of the 2,5- substituents is expected since the hydrogenation would take place from the less hindered face. Both sodium borohydride and Super-Hydride $^R$ afforded a mixture of hydroxylamines (19) and (20) in each case. The orientation of the substituents in (20) was confirmed by its conversion into the *trans* amine (22).



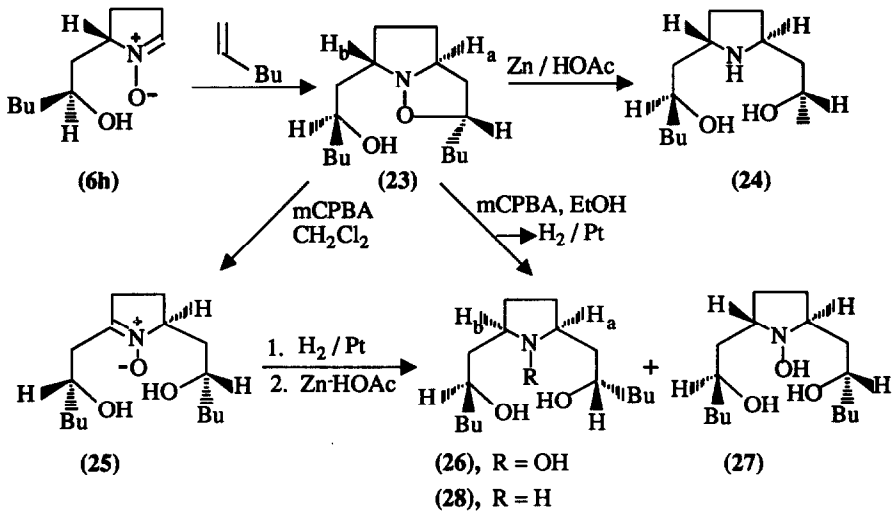

(13) (19) R = OH (20)
(21) R = H (22)

| [H] | (19) / (20) |
|---|---|
| $NaBH_4$ | 65 : 35 |
| $LiEt_3BH_4$ | 75 : 25 |
| H2 / Pt | 100 : 0 |

**Scheme 5**

To generalize this reaction sequence, we synthesized double cycloadduct (**23**) by reacting the nitrone (**6h**) with 1-hexene (Scheme 6). The adduct (**23**) on treatment with zinc and aqueous acetic acid afforded the trans-amine (**24**). The substituents were chosen judiciously so that the resulting amine (**24**) has a $C_2$ symmetry and as such the carbon NMR spectrum revealed the presence of eight well separated signals from sixteen carbons. The proton n.m.r. spectrum revealed the equivalence of the protons at 2 and 5 positions of the pyrrolidine ring (see experimental). The equivalence of the -CH-O- protons in (**24**) is also demonstrated by a single multiplet at δ 3.78. The second sequence of peracid treatment on the second cycloadduct (**23**) afforded the nitrone (**25**) which on hydrogenation afforded a single hydroxylamines (**26**). The carbon and proton n.m.r. spectra confirm the *cis* geometry of the compound (**26**) which, being unsymmetrical, has nonequivalent protons $H_a$, $H_b$,$H_c$ and $H_d$ appearing at δ 2.99, 3.20, 3.70, and 3.95. Reduction of the nitrone (**25**) with sodium borohydride, however, gave a mixture of the hydroxylamine (**26**) and (**27**) in a respective ratio of 90:10. The hydroxylamines (**26**) upon treatment with zinc and aqueous acetic acid gave the *cis*- amine (**28**). The overall yield for the three steps (**23** ---> **28**) was found to be 85%. In a separate experiment, the cycloadduct (**23**) was converted into the amine (**28**) without isolation of the intermediates (**25**) and (**26**). Thus, (**23**) upon peracid treatment in ethanol, followed by hydrogenation in ethanol-acetic acid mixture afforded the amine (**28**) in 92% yield after chromatographic purification.

The proton and carbon n.m.r. spectra again confirmed the *cis* geometry of the unsymmetrical amine (**28**). This nitrone - based approach thus provides an excellent entry to the *trans*- as well as the *cis*- 2,5- dialkyl pyrrolidines. The scope and convenience of this sequence may very well be extended to construct piperidine derivatives, an important system in geat many alkaloids. Results of the oxidation of hydroxylamines, peracid induced ring opening of several cycloadducts, and subsequent entry into the *cis*- and *trans*- 2,5- disubstituted pyrrolidines would indeed be helpful for the proper utilization of these high yielding reactions in incorporating and elaborating pyrrolidine rings.




| [H] | (26) / (27) |
|---|---|
| $NaBH_4$ | 90 : 10 |
| $H_2$ / Pt | 100 : 0 |

**Scheme 6**

## EXPERIMENTAL

All m.p.s. are uncorrected. Elemental analyses were performed on a Carlo-Erba Elemental analyser 1106. I.r. spectra were recorded on a Nicolet 5DXB F.T. IR, and are reported in wave numbers ($cm^{-1}$). $^1H$ N.M.R. were measured in $CDCl_3$ with TMS as internal standard, on a Varian XL-200 n.m.r. spectrometer or on a Bruker AC 80. $^{13}C$ n.m.r. spectra were recorded on the Bruker AC80 using $CDCl_3$ as solvent. Mass spectra were recorded on a low resultution HP5987A mass spectrometer. Silica gel chromatographic separations were performed with flash silica (Baker Chem. Co.). Reagent grade dichloromethane was washed with saturated $NaHCO_3$ solution, dried ($Na_2SO_4$), and passed through active alumina. Cycloadditions were conducted under a positive atmosphere of nitrogen. The nitrone (**1**) was prepared as before.[10] A non-separable mixture of the adducts (**5a**) and its stereoisomers in a respective ratio of 91:9 was prepared as described[9]. The major component (**5a**) was separated by crystallization at -10°C in ether-hexane mixture. The adduct (**5c**) was prepared as reported.[9] The adduct (**5c**) upon treatment with 5% aqueous HCl (10 min) followed by basification ($K_2CO_3$) and extraction ($CH_2Cl_2$) afforded (**5b**). The adducts (**5e**) - (**5g**) were also prepared using literature procedures.[9] MCPBA oxidation of several adducts in different solvents afforded the nitrones in 90-100% yields. It was difficult to purify the MCPBA oxidation products, as some decomposition occurred during chromatography and in many cases we were unable to obtain satisfactory elemental analysis and molecular ion peaks.

***2- Benzyl-1-hydroxypyrrolidine (2a).-*** To a vigorously stirred solution of the nitrone **(1)** (10.0 mmol) in dry THF (15 $cm^3$) at 0°C was added dropwise (ca.5 min) an ether solution (50 $cm^3$) of benzylmagnesium bromide (13 mmol). The reaction mixture was stirred at 20°C for an additional 20 min and quenched with aqueous $NH_4Cl$ solution (20 $cm^3$). The aqueous layer was extracted with $CH_2Cl_2$ (4x20 $cm^3$). The combined organic layers was evaporated and 10% HCl (20 $cm^3$) was added to the residue. The acidic aqueous layer was washed with ether (2x20 $cm^3$), basified ($K_2CO_3$) and extracted with $CH_2Cl_2$ (3x20 $cm^3$). The dichloromethane layer was dried and concentrated to give **(2a)** (0.900 g, 51%) as white crystals, m.p. 67-68°C (hexane-ether) (Found: C, 74.45; H, 8.50; N, 7.85. $C_{11}H_{15}NO$ requires C, 74.54; H, 8.53; N, 7.90%); $\nu_{max.}$ (KBr) 3180, 3002, 2917, 2835, 1497, 1457, 1373, 1141, 1040, 931, 760, and 709 $cm^{-1}$; $\delta_H$ 1.70 (1 H, m), 2.00 (3 H, m), 2.80 (1 H, m), 3.05 (1 H, m): 3.24 (1 H, m), 3.37-3.65 (2 H, m ), and 7.45 (5 H, m), hydroxyl proton signal was too broad to be observed; m/z 178 ($M^+ + 1$).

***2- Methyl-1-hydroxypyrrolidine (2b).-*** The compound was prepared using procedure for the preparation of **(2a)** as described above. To the nitrone **(1)** (30 mmol) in dry THF (25 $cm^3$) was added methylmagnesium bromide (35 mmol) in ether (70 $cm^3$). The reaction mixture was quenched with $H_2O$ (30 $cm^3$) and the organic layer was separated. The aqueous layer was filtered to remove precipitated solids. The aqueous layer was then saturated with $K_2CO_3$ and extrcted with $CH_2Cl_2$ (4x20 $cm^3$). The combined organic layers was dried ($Na_2SO_4$) and evaporated to give a residual liquid which on distillation (77°C at 17 mmHg) afforded **(2b)** as colourless liquid (69%), $\nu_{max.}$ (neat) 3200, 2976, 2864, 1457, 1379, 1207, 1136, 1050, 1024, 996, and 977 $cm^{-1}$; $\delta_H$ 1.20 (3 H, d, J 6.0 Hz), 1.30-2.20 (4 H, m), 2.60-3.00 (2 H, m), and 3.25 (1 H, m), hydroxyl proton signal is too broad to be seen.

***5- and 2-Benzyl-1-Pyrroline 1-oxide (3a) and (4a).-***

**(A) HgO oxidation:**

***(i) In dichloromethane solvent:***

To a solution of the hydroxylamine **(2a)** (177 mg, 1.00 mmol) in dichloromethane (7 $cm^3$) at 0°C was added yellow HgO (650 mg, 3.00 mmol). The HgO was converted into a greyish mixture within minutes after addition. The reaction mixture was stirred for an additional 0.5 h at 0°C, filtered through a bed of $MgSO_4$ and evaporated to give a mixture of the nitrones **(3a)** and **(4a)** as a faint yellow liquid in quantitative yield, $\nu_{max.}$ (neat) 3023, 2996, 2925, 1600, 1495, 1453, 1364, 1212, 925, 751, 737, and 707 $cm^{-1}$; the following $^1H$ n.m.r. signals were attributed to the presence of the major component **(4a)**: $\delta_H$ 2.12 (2 H, m), 2.60 (2 H, m), 3.83 (2 H, s with fine splitting), 4.06 (2 H, m), and 7.25 (5 H, m). The 2-H and benzylic protons of **(3a)** appeared at $\delta$6.80 (q, J 2.0 Hz) and 3.22 (ABX, J 4.0, 7.0, 13.5 Hz), respectively. The ratio of **(3a)** and **(4a)** was determined using integration of several signals.

***(ii) In dichloromethane-triethylamine mixture:***

To a solution of the hydroxylamine **(2a)** (80 mg, 0.45 mmol) in dichloromethane (2 $cm^3$) and triethylamine (0.60 g) was added excess yellow HgO (4.5 mmol). The mixture was stirred at 20°C for 15 min. Similar work up as described above afforded a mixture of the nitrones **(3a)** and **(4a)**.

***(iii) In pyridine and t-butanol:***

The above reaction described under (ii) was conducted in pyridine and t-butanol instead of $CH_2Cl_2$ - $Et_3N$ mixture. In each case a mixture of the nitrones **(3a)** and **(4a)** were obtained.

***(B) 1,4-Benzoquinone Oxidation:*** To a solution of the hydroxylamine (**2a**) (54 mg, 0.30 mmol) in $CDCl_3$ (1 $cm^3$) at 20°C was added 1,4-benzoquinone (33 mg, 0.30 mmol). The reaction mixture turned dark blue immediately and it became colourless after 10 min. After passing through glass wool (to remove the precipitate of 1,4-hydroquinone) the $^1H$ n.m.r. spectrum was recorded and the ratio of (**3a**) and (**4a**) was determined as before.

***(C) 1,2- and 1,4- napthoquinone oxidation:***
The reaction described under (**B**) was repeated using 1,2- and 1,4- napthoquinone. The oxidation process was very slow. The n.m.r. spectra recorded after 24 h at 20°C revealed the presence of the nitrone (**3a**) and (**4a**).

***5 and 2-Methyl-1-pyrroline 1-oxide (3b) and (4b).-*** Mercury (II) oxide oxidation of the hydroxylamine (**2b**), was carried out in dichloromethane using procedure as described above, afforded a mixture of the nitrones (**3b**) and (**4b**) as a pale yellow liquid. The $^1H$ n.m.r. signals of the major isomer (**4b**) were deduced from the spectrum of the mixture : $\delta_H$ 2.05 (3 H, m), 2.15 (2 H, m), 2.72 (2 H, m), and 4.00 (2 H, m). The 2-H and 5-methyl signals for the minor isomer (**3b**) appeared at δ6.83(m) and 1.58 (d, J 6.5). The ratio of (**3b**) and (**4b**) was determined by integration of several signals.

***2-( δ-Hydroxypropyl) hexahydropyrrolo[1,2-b]isoxazole (5d).-*** A solution of the nitrone (**1**) (10.0 mmol) and 4-penten-1-ol (2.5 $cm^3$) in toluene (10 $cm^3$) was stirred at 70-75°C for 24 h. After removal of the solvent, the residual liquid was chromatographed using 3% methanol-ethyl acetate as eluant to give (**5d**) as a colourless liquid (1.33g, 78%) (Found: C,62.90; H,9.88; N,8.10. $C_9H_{17}NO_2$ requires C, 63.12; H, 10.01; N, 8.18%); $\nu_{max.}$ (neat) 3340, 2943, 2868, 1474, 1419, 1085, and 1024 $cm^{-1}$; $\delta_H$ 1.44-2.22 (10 H, m), 3.14 (2 H, t, J 5.5 Hz), 3.63 (2 H, app t), 3.79 (1 H, m), 4.34 (1 H, m), and 4.13 (1 H, br, OH); $\delta_C$ 24.3, 29.6, 30.5, 31.7, 42.4, 57.0, 62.3, 65.1 and 77.2.

***2-Butylhexahydropyrrolo[1,2-b]isoxazole (5h).-*** The reaction of the nitrone (**1**) (15.0 mmol) with 1-hexene (10 $cm^3$) in toluene (20 $cm^3$) at 85°C for 6h afforded the adduct (**6h**) as a colourless liquid (82%) after purification by chromatography using ether as the eluant, $\nu_{max.}$ (neat) 2950, 2862, 1457, 1390, 1076, and 1003 $cm^{-1}$; $\delta_H$ 0.90 (3 H, app t), 1.10-2.30 (12 H, m), 3.12 (2 H, m) and 3.40-4.30 (2 H, m); m/z 169 ($M^+$).

***General Procedures for the MCPBA Oxidation of the Cycloadducts (5) in Different Solvents.*** MCPBA oxidation of the cycloadducts (**5**) afforded nitrones (**6**) and (**7**) in almost quantitative yields.

**(A) In dichloromethane:**

To a stirred solution of the cycloadduct (**5**) (1.00 mmol) in dry dichloromethane (20 $cm^3$) at -10°C was added MCPBA (1.2 mmol, 90% purity ) in one portion. After 30 min at -10°C the dichloromethane solution was washed with 5% $NaHCO_3$ solution (3x10 $cm^3$). The combined aqueous layers were re-extracted with dichloromethane (3x20 $cm^3$). The combined organic layers were dried ($Na_2SO_4$) and evaporated with a stream of $N_2$ at 20°C to give the nitrones (**6**) and (**7**) in 90-100 % yields.

**(B) In Methanol:**

To a stirred solution of the cycloadduct (**5**) (1.00 mmol) in methanol (10 $cm^3$) at -10°C was added MCPBA (1.2 mmol). After 30 min at -5-0°C the reaction mixture was taken up in $CH_2Cl_2$ (20 $cm^3$). The rest of the procedure follows that described above under (**A**).

**(C) In water:**

To a mixture of the cycloadduct (**5**) (1.00 mmol) in water (15 $cm^3$) was added MCPBA (1.2 mmol). The heterogeneous reaction mixture was vigorously stirred for 4 h and then basified by $NaHCO_3$. The aqueous layer

was then extracted with $CH_2Cl_2$ (3x20 $cm^3$). The organic layer was dried ($Na_2SO_4$) and evaporated with a stream of $N_2$ at 20°C to give the nitrones.

**(D) in acetic acid:**

To a solution of the cycloadduct **(5)** (1.00 mmol) in acetic acid (5 $cm^3$) was added MCPBA (1.3 mmol) and the reaction mixture was stirred for 1-3 h at 20°C. Completion of the reaction was indicated by t.l.c. (silica gel, ethyl acetate). After completion the acetic acid was removed by a gentle stream of nitrogen and the residue was taken up in dichloromethane (20 $cm^3$). The rest of the work up follows that described under **(A)**.

***5- and 2- (β-Hydroxy -β - phenyl) ethyl - 1 - pyrroline 1-oxide (6a) and (7a).-*** MCPBA oxidation of the adduct **(5a)** in $CH_2Cl_2$ using procedure (A) afforded the nitrone **(6a)**. The analytical data of **(6a)** is already reported.[3a] Oxidation in $H_2O$ and acetic acid using procedure **(C)** and **(D)** gave the nitrone **(7a)** as white crystals, m.p. 113-114°C (dichloromethane-ether) (Found: C, 70.15; H, 7.33; N, 6.80. $C_{12}H_{15}NO_2$ requires C, 70.22; H, 7.37; N, 6.83%); $\nu_{max.}$ (KBr) 3146, 2976, 2928, 1625, 1495, 1451, 1373, 1324, 1225, 1200, 1160, 1055, 776, and 714 $cm^{-1}$ ; $\delta_H$ 1.75-3.00 (6 H, m), 3.95 (2 H, m), 5.13 (1 H, dd, J 4.5, 6.3 Hz), 6.25 (1 H, br, OH), and 7.30 (5 H, m). Oxidation in methanol using procedure **(B)** afforded a mixture of the nitrones **(6a)** and **(7a)**, the ratio of which was determined using benzylic proton integration at δ5.06 and 5.13, respectively.

***5- and 2- (β,γ- Dihydroxy) propyl-1-pyrroline-1-oxide (6b) and (7b).-*** MCPBA oxidation of the adduct **(5b)** in $CH_2Cl_2$ using procedure **(A)** afforded the nitrone **(6b)**. The work up procedure was modified since the nitrone **(6b)** was very soluble in water. The reaction mixture in dichloromethane was extracted with $H_2O$ (7 $cm^3$). The aqueous layer was washed with $CH_2Cl_2$ (2x10 $cm^3$). Removal of water in *vacuo* gave the nitrone **(6b)** as a pale yellow liquid, $\nu_{max.}$ (neat ) 3270, 2867, 1597, 1439, 1390, 1196, 1054, and 926 $cm^{-1}$; $\delta_H$ 1.70-3.00 (6 H, m), 3.55 (2 H, m), 3.98 (1 H, m), 4.30 (1 H, m), 5.00 (2 H, br, OHs), and 7.06 (1 H, m). The oxidation in methanol and acetic acid using procedures **(B)** and **(D)** afforded a mixture of the nitrones **(6b)** and **(7b)** in each case. The modified work up procedure as described above was followed. Thus, the $CH_2Cl_2$ solution in **(B)** and **(D)** was extracted with $H_2O$ as above. Removal of $H_2O$ in *vacuo* gave the nitrones **(6b)** and **(7b)**. The ratio of the nitrones was determined by integration of the 2-H proton of **(6b)** at δ7.06 and -$CH_2O$- protons of **(6b)** and **(7b)** at δ3.55.

***5- and 2- (γ-t-bulyldimethylsiloxy-β-hydroxy) propyl-1-pyrroline-1-oxide (6c) and (7c).*** - MCPBA oxidation of the adduct **(5c)** in $CH_2Cl_2$ using procedure **(A)** afforded the nitrone **(6c)** as a pale yellow liquid, $\nu_{max.}$ (neat) 3260, 2940, 2917, 2842, 1595, 1474, 1466, 1260, 1120, 845, and 788 $cm^{-1}$; $\delta_H$ 0.07 (6 H, s), 0.87 (9 H, s), 1.60-2.85 (6 H, m), 3.57 (2 H, m), 3.67-4.75 (3 H, m including a broad OH), and 6.95 (1 H, q, J 2.0 Hz); m/z 273 ($M^+$). Oxidation in acetic acid using procedure **(D)** gave the nitrone **(7c)** as a faint yellow liquid, $\nu_{max.}$ (neat) 3230, 2966, 2938, 2862, 1617, 1472, 1463, 1254, 1210, 1164, 1120, 1079. 837, and 776; $\delta_H$ 0.07 (6 H, s), 0.90 (9 H, s), 2.17 (2 H, m), 2.35-3.00 (4 H, m), 3.30-4.20 (5 H, .m), and 5.45 (1 H, br, OH). Oxidation in methanol afforded a mixture of the nitrones **(6c)** and **(7c)** and their ratio was estimated by iintegration of 2-H signal of **(6c)** at δ6.95 and the $CH_2O$-$SiMe_2{}^tBu$ protons of **(6c)** and **(7c)**.

***5- and 2- (βε-Dihydroxy) pentyl-1-pyrroline 1-oxide (6d) and (7d).*** - MCPBA oxidation of the adduct **(5d)** in $CH_2Cl_2$, using modified procedure **(A)** as described in the preparation of **(6b)**, **(7b)** *(vide supra)* afforded the nitrone **(6d)** as a faint yellow liquid, $\nu_{max.}$ (neat) 3280, 2898, 2830, 1596, 1448, 1198, and 1063 $cm^{-1}$; $\delta_H$ 1.40-2.90 (10 H, m), 3.64 (2 H, m), 3.95 (1 H, m), 4.30 (1 H, m), 5.00 (2 H, br, OHs), and 7.05 (1 H, m); m/z 187 ($M^+$). Oxidation in methanol and acetic acid using modified procedures **(B)** and **(D)** as described in the preparation of **(6b)**, **(7b)**, afforded a mixture of the nitrones **(6d)** and **(7d)** in each case. The ratio of the

nitrones were determined by integration of 2-H signal of (**6d**) at δ7.05 and $CH_2O$- protons of (**6d**) and (**7d**) at δ3.64 and 5-Hs of (**7d**) at 4.04. The $^1H$ n.m.r. spectrum of (**7d**) was deduced from the spectra of the mixture of the nitrones. $\delta_H$ 1.40-3.00 (10 H, m), 3.62 (2 H, m), 4.04 (3 H, m) and 5.30 (2 H, br, OHs).

***5- and 2- (β-Carbomethoxy-β-hydroxy)propyl-1-pyrroline 1-oxide (6e) and (7e).*** MCPBA oxidation of the adduct (**5e**) in $CH_2Cl_2$ afforded the nitrone (**6e**) as a pale yellow liquid, $\nu_{max.}$ (neat) 3200, 2920, 1730, 1590, 1449, 1374, 1280-1100 (br), 977, and 824 $cm^{-1}$; $\delta_H$ 1.50 ( 3 H, s), 1.70-3.00 (6 H, m), 3.80 (3 H, s), 4.30 (1 H, m), 5.85 (1 H, br, OH) and 6.95 (1 H, q, J 2.0 $H_Z$); m/z 201 ($M^+$). Oxidation in acetic acid solvent gave a mixture of the nitrones (**6e**) and (**7e**). The major component (**7e**) was separated from the minor isomer (**6e**) by crystallization. m.p.88-92°C (dichloromethane-ether) (Found: C, 53.61; H, 7.77; N, 7.00. $C_9H_{15}NO_4$ requires C, 53.72; H, 7.51; N, 6.96%); $\vartheta_{max.}$ (KBr) 3060, 2944, 2915, 1731, 1602, 1460, 1452, 1365, 1193, 1108, 1054, 965, and 822 $cm^{-1}$; $\delta_H$ 1.50 (3 H, s), 1.90-3.02 (7 H, m including a 2 H, s at δ 2.94), 3.80 (3 H, s), and 4.07 (2 H, m), m/z 201 ($M^+$).

***5- and 2- (β,γ-Dihydroxy-β-methyl)propyl-1-pyrroline 1-oxide (6f) and (7f).***- MCPBA oxidation of the adduct (**5f**), using the modified procedure as described in the preparation of (**6b**) and (**7b**), afforded the nitrone (**6f**) in $CH_2Cl_2$ and a mixture of the nitrones (**6f**) and (**7f**) in methanol and acetic acid. Nitrone (**6f**): faint yellow liquid, $\nu_{max.}$ (neat) 3500-3000 (very broad), 2850, 1595, 1462, 1330, 1200 (br), 1122, and 918 $cm^{-1}$; $\delta_H$ 1.21 (3 H, s), 1.67 (1 H, m ), 1.98 (1 H, m), 2.33–2.80 (4 H, m), 3.43 (2 H, AB, J 10.0 Hz), 4.43 (1 H, m), 4.70 (2 H, br, OHs) and 6.98 (1 H, q, J 2.0 Hz). The methyl, $CH_2O$-, and 5-H protons of the nitrone (**7f**) appeared at δ1.23 (s), 3.35 (s) and 4.06 (m), respectively. From the spectrum of the mixture of nitrones the $^1H$ signals of the nitrone (**7f**) were deduced as follows: $\delta_H$ 1.23 (3 H, s), 2.06-2.98 (6 H, m), 3.35 (2 H, s), 4.06 (2 H, m), and 5.36 ( 2 H, br, OHs).

***5- and 2- (γ-t-Butyldimethylsiloxy-β-hydroxy-β-methyl) propyl-1-pyrroline 1-oxide (6g) and (7g).*** - MCPBA oxidation of the adduct (**5g**) in $CH_2Cl_2$ and acetic acid afforded (**6g**) and (**7g**), respectively. Oxidation in methanol gave a mixture of the nitrones. Nitrone (**6g**): pale yellow liquid, $\nu_{max.}$ (neat) 3180, 2983, 2910, 2845, 1595, 1470, 1389, 1260, 1198, 920, 847, and 785 $cm^{-1}$; $\delta_H$ 0.06 (6 H, s), 0.90 (9 H, s), 1.22 (3 H, s), 1.55-2.85 (6 H, m), 3.40 (2 H, s), 4.33 (1 H, m), 5.95 (1 H, br, 0H), and 7.00 (1 H, q, J 2.0 Hz). Nitrone (**7g**): pale yellow liquid, $\nu_{max.}$ (neat) 3180, 2930, 2907, 2832, 1615, 1475, 1466, 1367, 1260, 1202, 1102, 858, 790, and 745 $cm^{-1}$; $\delta_H$ 0.06 (6 H, s), 0.90 (9 H, s) 1.29 (3 H, s), 1.90-3.15 (6 H, m), 3.50 (2 H, s), 4.15 (2 H, m) and 5.90 (1 H, m).

***(2S*, 3aR*, 6S*) -6-Methyl-2-phenylhexahydropyrrolo[1,2-b]isoxazole (9).*** A solution of a mixture of the nitrones (**3b**) and (**4b**) (prepared by HgO oxidation of (**2b**) (20.0 m mol) and styrene (5 $cm^3$) in toluene (10 $cm^3$) was heated to 55-60°C for 48 h. After removal of the excess alkene and solvent, the residual liquid was chromatographed using 1:1 hexane-ethyl acetate as the eluant to give the adduct (**9**) as a colourless liquid (66% based on the amount of the nitrone (**3b**); (Found: C, 76.72; H, 8.33; N, 6.80. $C_{13}H_{17}NO$ requires C, 76.81; H, 8.43; and N, 6.89); $\nu_{max.}$ (neat) 2938, 2838, 1458, 1383, 1314, 1200, 1120, 1030, 920, 766, and 708 $cm^{-1}$; $\delta_H$ 1.26 (3 H, d, J 7.0 Hz), 1.32-1.76 (2 H, m), 1.94-2.44 (4 H, m), 3.28 (1 H, m), 4.00 (1 H, dq, J 4.0, 7.0 Hz), 5.06 (1 H, dd, J 6.5, 9.0 Hz), and 7.40 (5 H, m).

***(βS*, 2R*, 3aR*, 6R*)-2-Butyl -6- (β-hydroxy-β-phenyl)ethylhexahydropyrrolo[1,2-b] isoxazole (10).*** - The nitrone (**6a**), prepared from (**5a**) (400 mg, 2.12 m mol) by MCPBA oxidation in $CH_2Cl_2$, was heated with 1-hexene (5 $cm^3$) in toluene (15 $cm^3$) at 60-65°C for 48 h. Removal of the solvent and excess alkene followed by chromatography using ether as eluant afforded the single adduct (**10**) as a colourless liquid (69%) (The n.m.r. spectra for the crude as well as the purified product failed to detect the presence of any other isomers)

(Found: C, 74.55; H, 9.30; N, 4.73. $C_{18}H_{27}NO_2$ requires C, 74.70; H, 9.40; and N, 4.84 %); $\nu_{max.}$ (neat) 3300, 2958, 2934, 2871, 1452, 1061, 760 and 701 $cm^{-1}$; $\delta_H$ 0.90 (3 H, app t), 1.00-2.30 (14 H, m), 3.30 (1 H, m), 3.65-4.30 (2 H, m), 4.50 (1 H, br, OH), 5.08 (1 H, dd, J 4.0, 9.0 Hz), and 7.35, (5 H, m).

***(βR*, 2S*, 3aR*, 6R*) -6- (β-hydroxy)hexyl-2-Phenylhexahydropyrrolo [1,2-b] isoxazole (11).*** The nitrone (**6h**), prepared from the adduct (**5h**) (240 mg, 1.42 m mol) by MCPBA oxidation in $CH_2Cl_2$, was heated with styrene (3 $cm^3$) in toluene (10 $cm^3$) at 60-65°C for 48 h. The $^1H$ n.m.r. of the crude reaction mixture revealed the formation of a single isomer (**11**). Chromatography using ether as the eluant afforded (**11**) (270 mg, 66%) as colourless needles, m.p. 62-63°C (ether-hexane) (Found: C, 74.54; H, 9.57; N, 5.00. $C_{18}H_{27}NO_2$ requires C, 74.70; H, 9.40; and N, 4.84 %); $\nu_{max.}$ (KBr) 3180, 2960, 2938, 2862, 1455, 1136, 1091, 1011, 906, 759, and 703 $cm^{-1}$; $\delta_H$ 0.88 (3 H, app t), 1.10 - 2.44 (14 H, m), 3.50 (1 H, m), 4.00 (3 H, m including an 'OH'), 5.06 (1 H, dd, J 5.5, 9.0 Hz), and 7.40 (5 H, m).

***(βS*, 2R*, 3aR*, 6R*) - 2-Carbomethoxy-2-methyl - 6 - (β-hydroxy- β-phenyl)ethylhexahydropyrrolo [1,2-b] isoxazole (12).*** Methyl methacrylate (2 $cm^3$) was added to the nitrone (**6a**) in $CH_2Cl_2$ (3 $cm^3$) [prepared by MCPBA oxidation of the adduct (**5a**) (260 mg, 1.37 mmol) in $CH_2Cl_2$]. The reaction mixture was stirred at 35-40°C for 48 h. $^1H$ n.m.r. spectra of the crude reaction mixture as well as the purified adduct (chromatography, ether) indicated the presence of a single isomer (**12**) (336 mg, 80%), colourless liquid, (Found: C, 66.68; H,7.43; N, 4.57, $C_{17}H_{23}NO_4$ requires C, 66.86; H, 7.59; and N, 4.59%); $\nu_{max.}$ (neat) 3495, 3316, 2966, 1733, 1452, 1298, 1261, 1198, 1122, 760, and 702 $cm^{-1}$; $\delta_H$, 1.53 (3 H, s), 1.40-2.60 (8 H, m), 3.50 (1 H, m), 3.80 (3 H, s), 4.00 (1 H, s), 4.70 (1 H, br, OH), 5.17 (1 H, dd, J 4.0, 9.5 Hz), and 7.35 (5 H, m).

***5- and 2- (β-Hydroxy-β-phenyl)ethyl-2- and - 5-methyl-1- pyrroline 1-oxide (13) and (14).-*** MCPBA oxidation of the adduct (**9**) in $CH_2Cl_2$ afforded the nitrone (**13**) as pale yellow liquid; $\nu_{max.}$ (neat) 3200, 2890, 1620, 1496, 1455, 1203, 1068, and 925 $cm^{-1}$; $\delta_H$ 1.76 (1 H, m), 2.06, (3 H, m), 2.16 (2 H, m), 2.36-2.80 (3 H, m), 4.10 (1 H, m), 5.06 (1 H, dd, J 3.8, 5.5 Hz), 6.20 (1 H, br, OH), and 7.40 (5 H, m); m/z 219 ($M^+$). Oxidation in methanol afforded a mixture of the nitrones (**13**) and (**14**). The 5-$CH_3$ and benzylic H of (**14**) appeared at δ 1.40 (d, J 6.0 Hz) and 5.16 (dd, J 3.3, 6.5 Hz), respectively.

***(βS*, β 'R*, 5R*) 5- (β'-Hydroxy)hexyl-2-(β-hydroxy-β-phenyl)ethyl-1-pyrroline 1-oxide (15).-*** MCPBA oxidation of the adduct (**10**) in $CH_2Cl_2$ afforded the nitrone (**15**) as a pale yellow liquid, $\nu_{max.}$ (neat) 3300, 2956, 2930, 2858, 1609, 1455, 1196, 1056, 911, 755, 733, and 702 $cm^{-1}$; $\delta_H$ 0.90 (3 H, app t), 1.00-3.10 (14 H, m), 3.85 (1 H, m), 4.27 (1 H, m), 5.12 (1 H, dd, J 4.0, 7.0 Hz), 5.65 (2 H, br, OHs), and 7.30 (5 H, m).

***(βS*, β'S*, 5R*) 2-(β-Hydroxy)hexyl-5-(β'-hydroxy-β'-phenyl)ethyl-1-pyrroline 1-oxide (16).-*** MCPBA oxidation of the adduct (**11**) in $CH_2Cl_2$ gave the nitrone (**16**) as a pale yellow liquid, $\nu_{max.}$ (neat) 3300, 2955, 2930, 2860, 1605, 1454, 1204, 1061, 911, 756, 732, and 702 $cm^{-1}$; $\delta_H$ 0.90 (3 H, app t), 1.00-3.00 (14 H, m), 3.65-4.44 (2 H, m), 4.98 (1 H, dd, J 4.0, 6.0 Hz), 5.65 (2 H, br, OH), and 7.30 (5 H, m).

***(βS*, β'R*, 5R*) 5-(β'-Carbomethoxy-β'-hydroxy)propyl-2-(β hydroxy-β-phenyl)ethyl -1-pyrroline 1-oxide (17).*** - MCPBA oxidation of the adduct (**12**) in $CH_2Cl_2$ afforded the nitrone (**17**) as a pale yellow oil, $\nu_{max.}$ (neat) 3270, 2957, 2919, 1735, 1616, 1455, 1436, 1373, 1197, 1116, 1059, 756, and 703 $cm^{-1}$, $\delta_H$ 1.48(3 H, s), 1.58-3.17 (8 H. m), 4.00 (3 H, s), 4.25 (1 H, m), 5.15 (1 H, dd, J 4.0, 7.3 Hz), 5.40 (2 H, br, OH), and 7.35 (5 H, m). Irradiation at δ2.85 reduces the dd at δ5.15 to a singlet.

***(βR*, 2S*, 5S*) - 1-Hydroxy-5 - Methyl - 2-(β-hydroxy-β-phenyl)ethylpyrrolidine (19) and its trans isomer (20).*** - Usual reduction of the nitrone (**13**) (1.00 mmol) with excess $NaBH_4$ (200 mg) in ethanol (5 $cm^3$) at 20°C for 1 h afforded a mixture of the hydroxylamines (**19**) and (**20**). After removal of ethanol the reaction mixture was taken up in saturated $K_2CO_3$ solution (20 $cm^3$) and extracted with $CH_2Cl_2$ (3x20 $cm^3$). The organic layer was dried ($Na_2SO_4$), evaporated and the residue was chromatographed using ether as the eluant. The first component eluted was the compound (**19**) (108 mg), which was obtained as white crystals, m.p. 106-107°C (dichloromethane - ether) (Found : C, 70.40; H, 8.57; N, 6.20, $C_{13}H_{19}NO_2$ requires C, 70.55; H, 8.65; and N, 6.33%); $\nu_{max.}$ (KBr) 3306, 2966, 2938, 1454, 1072, 1054, 1045, 758, and 700 $cm^{-1}$; $\delta_H$ (55°C) 1.20 (3 H, d, J 6.5 Hz), 1.30 - 2.28 (6 H, m), 2.85 (1 H, m), 3.12 (1 H, m), 5.09 (1 H, dd, J 3.5, 10.0 Hz and a 2 H, br, OH underneath), and 7.35 (5 H, m). Continued elution afforded (**20**) as a white crystals (58 mg), m.p. 125 – 127 °C (dichloromethane – ether) (Found: C, 70.35; H, 8.53; N, 6.27. $C_{13}H_{19}NO_2$ requires C, 70.55; H, 8.65; and N, 6.33 %); $\nu_{max.}$ (KBr) 3335, 2966, 2938, 1456, 1405, 1381, 1204, 1062, 1033, 975, 764, and 698 $cm^{-1}$; δH (55 °C) 1.15 (3 H, d, J 6.5 Hz), 1.53 (2 H, m), 1.78 - 2.12 (4 H, m), 3.42 (2 H, m), 5.02 (1 H, dd, J 5.0, 8.0 Hz), 5.40 (2 H, br 0Hs) and 7.35 (5 H, m). Total isolated yield for the reaction was 75%.

Reduction of the nitrone (**13**) (0.50 mmol) was carried out with Super Hydride $^R$ ($LiEt_3BH$) (4 $cm^3$ of 1 M solution in THF) at 20°C for 30 min. The reaction mixture was quenched with 10% HCl solution (10 $cm^3$). The aqueous layer was washed with ether ( 3x10 $cm^3$), basified ($K_2CO_3$) and extracted with $CH_2Cl_2$ 3(x15 $cm^3$). The$CH_2Cl_2$ layer was dried ($Na_2SO_4$), evaporated and purified by chromatographic separation to give (**19**) and (**20**) in 83% yield.

Hydrogenation of the nitrone (**13**) (0.50 mmol) in ethanol (5 $cm^3$) using $PtO_2$ (15 mg) was carried out at 20 °C for 1 h under a positive pressure of hydrogen. T.l.c. (silica gel, ethyl acetate) analysis revealed the presence of a single new compound (**19**) along with the unreacted nitrone (**13**). Further hydrogenation was discontinued, because of complication arising out of hydrogenolysis of the N-O and C-O bonds. Chromatographic purification afforded the compound (**19**) (50%).

***(βR*, 2S*, 5S*) - 5 -Methyl - 2-(β-hydroxy-β-phenyl)ethylpyrrolidine (21):*** To a vigorously stirred solution of the hydroxylamine (**19**) (0.50 mmol) in acetic acid (2 $cm^3$) and water (2 $cm^3$) at 60 °C was added Zn (0.85g) in two portions (ca. 5 min). The reaction mixture was stirred at 60-65 °C for a total of 30 min. The reaction mixture was decanted and the residual solid was washed with water (20 $cm^3$). After basification the aqueous layer was carefully extracted (in order to avoid emulsion) with $CH_2Cl_2$ (3x20 $cm^3$). The organic layer was dried ($Na_2SO_4$), evaporated and purified by chromatography (2 % methanol (saturated with $NH_3$)-ether) to give the amine (**21**) (80 %) as a colourless liquid, (Found: C, 75.87; H, 9.25; N, 6.73. $C_{13}H_{19}NO$ requires C, 76.05; H, 9.33; and N, 6.82 %); $\nu_{max.}$ (neat) 3210, 2949, 2836, 1532, 1451, 1406, 1340, 1064, 756 and 701 $cm^{-1}$; $\delta_H$ 1.20 (3 H, d, J 6.0 Hz), 1.30-2.10 (8 H, m), 3.20 (1 H, m), 3.50 (1 H, m), 5.10 (1 H, dd, J 3.5, 9.0 Hz), and 7.40 (5 H, m).

***(βR*, 2S*, 5R*) - 5 Methyl - 2-(β-hydroxy-β-phenyl)ethylpyrrolidine (22)*** .- The N-O bond cleavage of the adduct (**9**) or the hydroxylamine (**20**) by Zn in aquous acetic acid using procedure as described above for the preparation of the amine (**21**) afforded the *trans*-amine (**22**) as a pale yellow liquid in almost quantitative yield, m.p. 77-80°C (hexane-ether) $\nu_{max.}$ (KBr) 3235, 2976, 1506, 1452, 1348, 1059, 756 and 700 $cm^{-1}$; $\delta_H$ 1.17 (3 H, d. J 6.5 Hz), 1.36-2.10 (6 H, m), 3.24 (1 H, m), 3.42 (1 H, m), 3.70 (2 H, br), 5.06 (1 H, dd, J 3.5, 5.5 Hz), and 7.35 (5 H, m).

***(βS*, 2S*, 3aS*, 6S*)-2-Butyl-6-(β-hydroxy)hexylhexahydropyrrolo[1,2-b]isoxazole (23).***- MCPBA oxidation of the adduct (**5h**) (1.91g, 11.3 mmol) in $CH_2Cl_2$ afforded the nitrone (**6h**) as a faint yellow oil which was heated with 1-hexene (7 $cm^3$) in toluene (40 $cm^3$) at 65-70°C for 48 h. Removal of the excess alkene and solvent, followed by chromatography using 2:1 ether-hexane as the eluant gave the adduct (**23**) as white

crystals (2.17 g, 71%), m.p. 43-44°C (hexane-ether) Found: C, 71.20; H, 11.53; N, 5.17. $C_{16}H_{31}NO_2$ requires C, 71.32; H, 11.60; and N, 5.20%); $\nu_{max.}$ (K Br) 3353, 3274, 2957, 2938, 2862, 1468, 1371, 1123, 1086, 1057, 1002, and 653 $cm^{-1}$; $\delta_H$ 0.90 (6 H, app t), 1.10-2.10 (20 H, m), 3.32 (1 H, m), 3.80 (1 H, m), 4.00 (2 H, m), and 4.48 (1 H, br, OH); $\delta_C$ 13.9, 14.1, 22.8, 22.9, 28.1, 28.7, 29.5, 31.1, 32.7, 37.4, 40.0, 42.1, 64.1, 64.6. 69.2, and 75.6; m/z 269 ($M^+$).

***(βS*, β'S*, 2S*, 5S*) - 2-(β-Hydroxyhexyl)-5-(β'-hydroxyhexyl)pyrrolidine ( 24).-*** The N-O bond cleavage of the adduct (**23**) by Zn in aqueous acetic acid using procedure as described *(vide supra)* afforded the amine (**24**) as white crystals in almost quantitative yield; m.p. 87-89 °C (hexane) (Found: C, 70.63; H, 12.05; N, 4.97. $C_{16}H_{33}NO_2$ requires C, 70.80; H, 12.26; N, 5.16%); $\nu_{max.}$ (KBr) 3350, 3255, 2967, 2920, 2864, 1465, 1344, 1134, 1066, 1029, 893, and 859 $cm^{-1}$; $\delta_H$ 0.88 (6 H, app t), 1.10-2.10 (20 H, m), 3.50 (2 H, m), 3.78 (2 H, m), and 4.10 (3 H, br), $\delta_C$ 14.0, 22.8, 28.1, 32.5, 37.5, 41.2, 55.4, and 69.7.

***(βS*, β'S*, 5S*) 2-(β-Hydroxy)hexyl-5-(β'-hydroxy)hexyl-1-pyrroline 1-oxide (25).-*** MCPBA oxidation of the adduct (**23**) in $CH_2Cl_2$ afforded the nitrone (**25**) as a pale yellow oil, $\nu_{max.}$ (neat ) 3334, 2957, 2928, 2862, 1608, 1466, 1458, 1377, 1204, 1164, 1127, 1080, 1051, and 1045 $cm^{-1}$; $\delta_H$ 0.90 (6 H, app t), 1.00-1.73 (12 H, m), 1.76-2.90 (8 H, m), 3.86 (1 H, m), 4.00 (1 H, m), 4.40 (1 H, m), and 5.03 (2 H, br, OH).

***(βS*, β'S*, 2R*, 5S*)-1-Hydroxy - 2-(β-hydroxyhexyl)-5-(β'-hydroxyhexyl)pyrrolidine (26) and its isomer (27).-*** $NaBH_4$ reduction of the nitrone (**25**), using procedure *(vide supra)* as described in the preparation of (**19**) and (**20**), afforded a mixture of the hydroxylamine (**26**) and (**27**) in almost quantitative yield. The major isomer (**26**) was separated as white crystals by crystallization, m.p. 99-100°C ($CH_2Cl_2$ - ether - hexane) (Found; C, 66.76; H, 11.78; N, 4.86. $C_{16}H_{33}NO_3$ requires C, 66.85; H, 11.57; and N, 4.87%); $\nu_{max.}$ (KBr) 3325, 2966, 2938, 2862, 1453, 1416, 1375, 1326, 1127, 1065, and 838 $cm^{-1}$; $\delta_H$ (55°C) 0.90 (6 H, app t), 1.15-2.15 (20 H, m), 2.99 (1 H, m), 3.20 (1 H, m), 3.70 (1 H, m), 3.95 (1 H, m), and 5.60 (3 H, br, OH); $\delta_C$ 14.0, 14.0, 22.8, 22.8, 24.8, 27.7, 27.9, 27.9, 37.2, 37.5, 38.1, 42.4, 66.4, 67.4, 69.2, and 71.1; m/z 287 ($M^+$). The signals at δ3.48 (m) and 3.80 (m) were assigned to the minor hydroxylamine (**27**). The ratio of (**26**) and (**27**) was found to be 90:10, respectively. Hydrogenation of the nitrone (**25**) afforded the hydroxylamine (**26**) as the sole isomer.

***(βS*, β'S*, 2R*, 5S*) - 2-(β-Hydroxyhexyl)-5-(β'-hydroxyhexyl)pyrrolidine (28).-*** The adduct (**23**) (100 mg) on MCPBA oxidation in $CH_2Cl_2$, hydrogenation (1 atm, 20 mg $PtO_2$) in ethanol (5 $cm^3$) for 3 h, hydrogenolysis by Zn (850 mg) - HOAc (2 $cm^3$), $H_2O$ (2 $cm^3$) (1 h, 75°C), as described *(vide supra)*, followed by chromatographic purification using 2% methanol saturated with $NH_3$-ether afforded the amine (**28**) (86 mg, 85%) as a semisolid, m.p. 35-37°C; (Found: C, 70.53; H, 11.98; N, 5.05. $C_{16}H_{33}NO_2$ requires, C, 70.80; H, 12.26; N, 5.16%); $\nu_{max.}$ (neat) 3306, 3240, 2957, 2938, 2853, 1467, 1458,1417, 1376, 1343, 1126, 1077, and 1043 $cm^{-1}$; $\delta_H$ 0.88 (6 H, app t), 1.20-1.80 (18 H, m), 1.92 (2 H, m), 3.30 (1 H, m), 3.49 (1 H, m), 3.68 (1 H, m), 3.84 (1 H, m), and 4.22 (3 H, m); $\delta_C$14.0, 14.0, 22.8, 22.8, 27.8, 27.9, 30.1, 32.4, 37.9, 38.0, 42.0, 43.4, 56.5, 58.3, 69.3, and 71.7.

In another experiment, the adduct (**23**) (100 mg) in ethanol (5 $cm^3$) was treated with 1.1 equivalent MCPBA at 0°C for 30 min to give the nitrone (**25**). To the resulting reaction mixture was added HOAc (0.5 $cm^3$) and $PtO_2$ (20 mg) and the mixture hydrogenated under a positive pressure of $H_2$ for 48 h at 20°C. The reaction mixture was diluted with $H_2O$ (15 $cm^3$), basified ($K_2CO_3$), and extracted with $CH_2Cl_2$ (3x15 $cm^3$). The organic layer was dried ($Na_2SO_4$), evaporated, and chromatographed as above to give the amine (**28**) (93 mg, 92%).

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