Regioselective transformation of 6/5-fused bicyclic isoxazolidines to second-generation cyclic aldonitrones

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Abstract

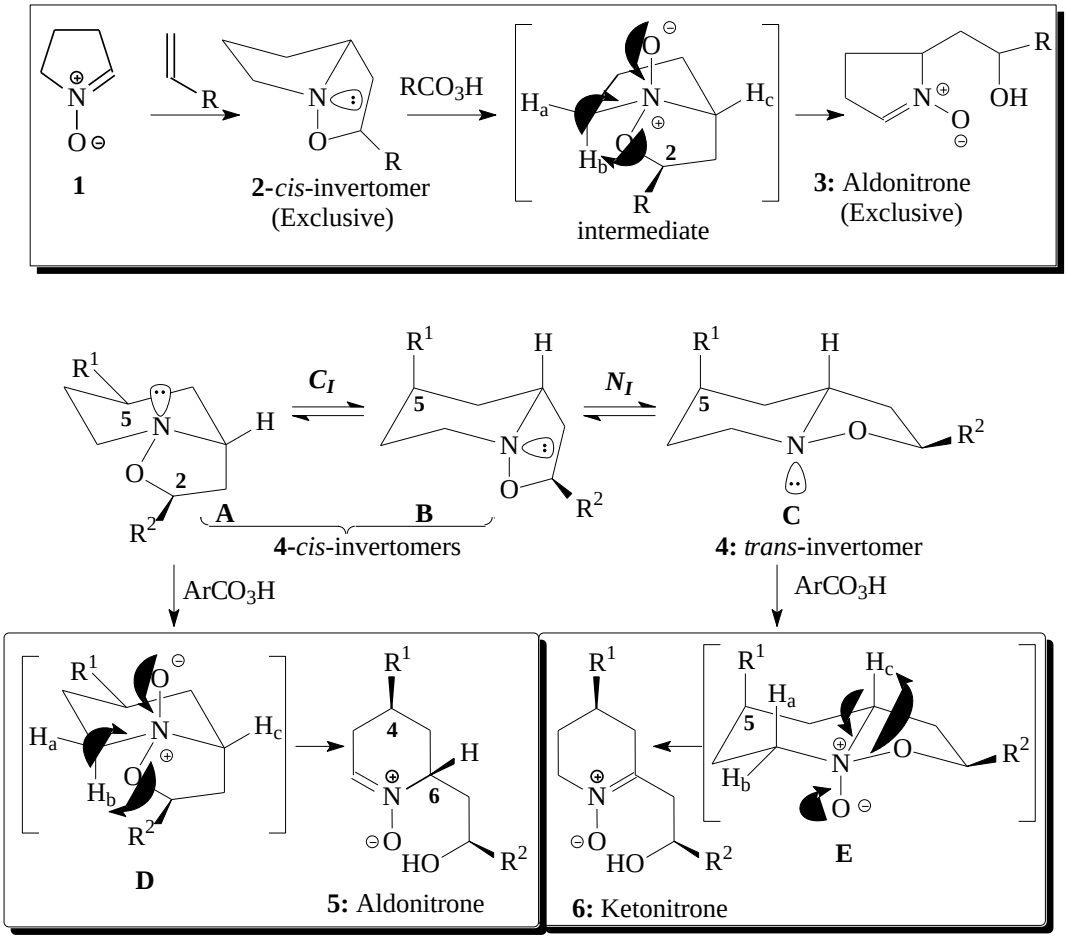
The cycloaddition reactions of 4-(2-hydroxy-2-propyl)-3,4,5,6-tetrahydropyridine 1-oxide with mono- and di-substituted alkenes have been found to be highly stereo- as well as face-selective. In solution, the 6/5 fused bicyclic cycloadducts remain solely as the *cis*-fused invertomers in order to accommodate the bulky tertiary substituent 2-hydroxy-2-propyl in the equatorial orientation. The cycloadducts, upon peracid oxidation, leads to the exclusive formation of synthetically important second-generation cyclic aldonitrones. The stereo- and face-selectivity of the cycloaddition reactions of these second-generation nitrones bearing substituents at C(4) and C(6) have been briefly examined. One interesting finding was that treatment of the first generation nitrone i.e., 4-(2-hydroxy-2-propyl)-3,4,5,6-tetrahydropyridine 1-oxide, with mercury(II) oxide afforded a novel bicyclic nitrone, 1-oxa-5,6-dehydro-6-aza-bicyclo[3,2,1]heptane 6-oxide.

Keywords: Cyclic nitrones, nitrone cycloaddition, stereoselectivity, face selectivity, peracid oxidation, conformational analysis

Introduction

The efficacy of 1,3-dipolar cycloaddition reaction of cyclic nitrones lies on the remarkable selectivity in the incorporation of multiple stereocenters in a single step.[1-3] The pyrrolidine- and piperidine-based alkaloids, which are widespread in nature, can be accessed through the cycloaddition reaction of the parent five- **1** and six-membered cyclic nitrones,[4] or the second-generation aldonitrones **3** and **5**, respectively (Scheme 1).[5] The five-membered aldonitrones **3** can be accessed regiospecifically by peracid-induced ring opening of the bicyclic isoxzolidines **2** (nitrone **1** - alkene cycloaddition products). It has been suggested that the orientation of the nitrogen lone pair in **2** dictates the formation of the N-oxide intermediate on the β-face of the nitrone; the subsequent ring opening leads the C(2)-O^- to abstract the nearby H_b immediately, thereby

leading to the exclusive formation of the aldonitrones **3**.[6] However, the proper utilization of the second-generation six-membered aldonitrones **5** has been severely hampered by the lack of selectivity[7] for the oxidation process in 6/5-fused isoxazolidines **4a,b** (R^1=H) (Table in Scheme 1), where the synthetically less important ketonitrones **6a,b** are obtained as the major products.



4	% Composition of invertomers *(cis/trans)*	% Composition of nitrones *(aldo-**5**/keto-**6**)*
a, $R^1 = R^2 = H$	24:76	23:77
b, $R^1 = H$; $R^2 = Ph$	22:78	35:65
c, $R^1 = CO_2Bu$; $R^2 = Ph$	55:45	52:48
d, $R^1 = CH_2OAc$; $R^2 = Ph$	88:12	82:18

Scheme 1

While the geometric compulsion makes sure that the 5/5-ring system in **2** remains *cis*-fused, its corresponding 6/5 ring system in cycloadducts **4** exists in three different conformations/configurations: the *cis* pair **A** and **B,** in rapid equilibrium by chair inversion (**C_I**), and its *trans* invertomer **C**, in a relatively slow equilibrium with *cis* invertomer **B** by nitrogen inversion process (**N_I**). It has been suggested that the higher activation barrier to nitrogen inversion ($\Delta G^{\#}$, ~70 kJ/mol)[7b] than the oxidation process does not permit the Curtin-Hammett principle[8] to apply; as such the invertomer ratio reflects the ratio of the products keto- and aldo-nitrones. While the *cis* invertomer leads to aldonitrones **5** *via* intermediate **D**, the *trans* invertomer affords the synthetically less important ketonitrones **6** via **E**. As evident from the Table included in the Scheme 1, the cycloadduct **4a** having a *cis/trans* invertomer ratio of 24:76 afforded the alod-**5**/keto-**6** nitrones in an almost identical ratio of 23:77.[9] Likewise, **4b** having a *cis/trans* invertomer ratio of 22:78 affords the aldo-**5**/keto-**6** nitrones in a similar ratio of 35:65.[7b]

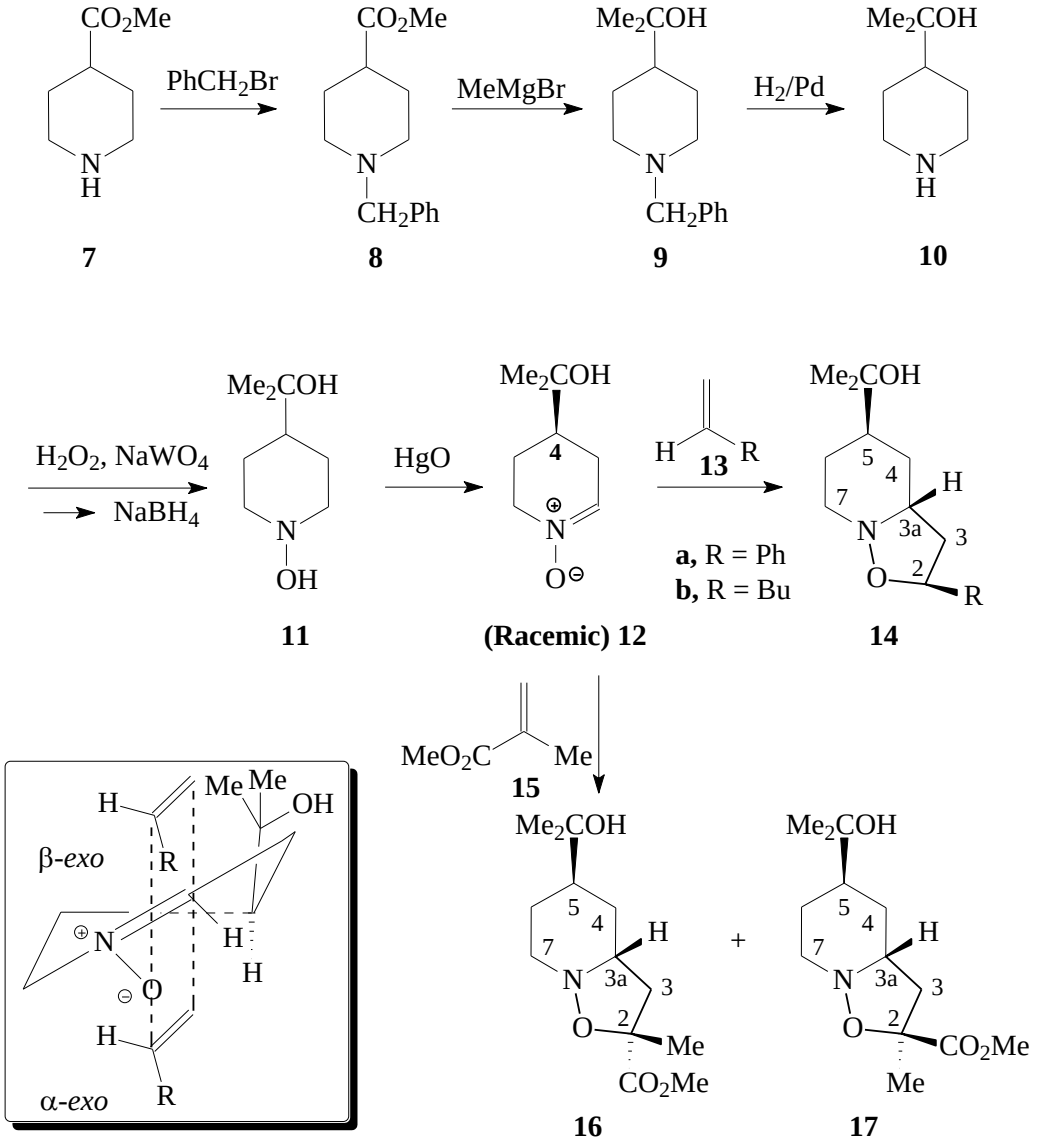
Note that the placement of a substituent R^1 at C(5) in cycloadducts **4** would favour the *cis* invertomer **A** at the expense of **B** and the *trans* invertomer **C**, both of which places the C(5)R^1 in the unfavourable axial orientation. Exploring this idea, greater percentages of the aldonitrones **5** are obtained from peracid-induced oxidation of the isoxazolidines **4c** and **4d**.[10,11] In our continuing endeavor to obtain the aldonitrones **5** regiospecifically, we intended to place at C(5) in **4** a very bulky substituent that would ascertain the exclusive presence of the invertomer **A** and exclude the C(5) axially-oriented R^1 in *cis* **B** and *trans* invertomer **C**. The current work describes our attempt to test the above proposition and confirm the mechanism of the peracid oxidation process.

Results and Discussion

The synthesis of nitrone **12**, having a bulky CMe_2OH at C(4) is outlined in Scheme 2. Amine **10** upon hydrogen peroxide oxidation in the presence of sodium tungstate[12] in water afforded a mixture of nitrone **12** and hydroxylamine **11** which upon treatment with $NaBH_4$ afforded the hydroxylamine **11** in pure form. The required nitrone **12** was then prepared by mercury(II) oxide oxidation of **11**.

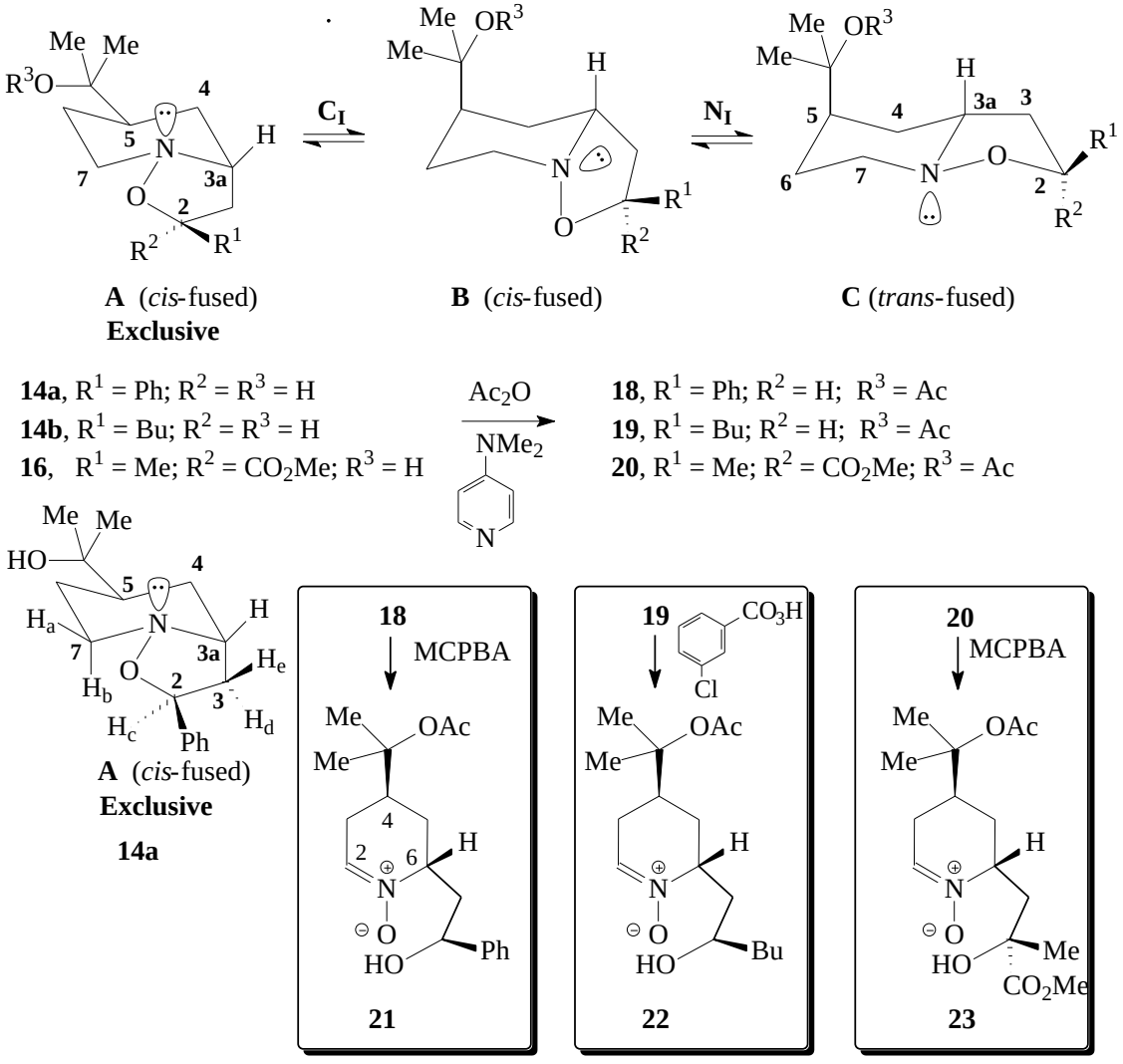
Next, we pursued the addition reaction of nitrone **12** with various alkenes. The addition of monosubstituted alkene styrene **13a** was found to be stereo-, as well as face-selective; a single adduct **14a** was obtained in 80% yield. The ^{1}H NMR analysis of the crude as well as purified product failed to reveal the presence of any minor isomer. Likewise, the addition reaction of 1-hexene **13b** also afforded a single isomer **14b**. The configuration of the adduct **14a** and **14b** was based on the sterically favourable *exo* approach (Scheme 2) of the Ph and Bu groups from the less hindered face (i.e. α face) of the nitrone.[11] Such a high selectivity is surprising since the C(4)-CMe_2OH group, imparting the facial difference, is positioned at the furthest point from the nitrone functionality in **12**, yet a surprisingly high selectivity in the addition reactions were observed.

The addition of disubstituted alkenes methyl methacrylate **15** to the nitrone **12** also demonstrated a very high face- and stereoselectivity (Scheme 2); a nonseparable mixture of adducts **16** and **17** in a respective ratio of 95:5 was obtained. The major adduct **16** was obtained *via* α-*exo* (Me) approach. The stereochemistry is based on the precedent lietrature[2a] – the parent nitrone 3,4,5,6-tetrahydropyridine 1-oxide is known to give major and minor adducts in a ratio of 96:4 as a result of a favourable secondary orbital interaction *via* an *endo*-oriented methoxycarbonyl group in the transition state.



Scheme 2

Since the stereochemistry of the ring fusion dictates the regiochemical outcome of the peracid oxidation process leading to the second-generation nitrones (*vide supra*) (Scheme 1), we have examined the conformational aspects as well as composition of the nitrogen invertomers (if any) by NMR spectroscopy. The presence of −N−O− moiety in an organic molecule has a distinctive place in conformational analysis;[13-15] oxygen being next to nitrogen raises the barrier to nitrogen inversion to such an extent that the individual invertomers can be identified by NMR spectroscopy.[16] At ambient temperature, the ^{1}H and ^{13}C NMR spectra of these cycloadducts show sharp signals indicating the presence of a single invertomer for each of the compounds **14a**, **14b** and **16** as well as their corresponding acetate derivatives **18**-**20** obtained by reacting the former compounds with acetic anhydride in the presence of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) (Scheme 3).



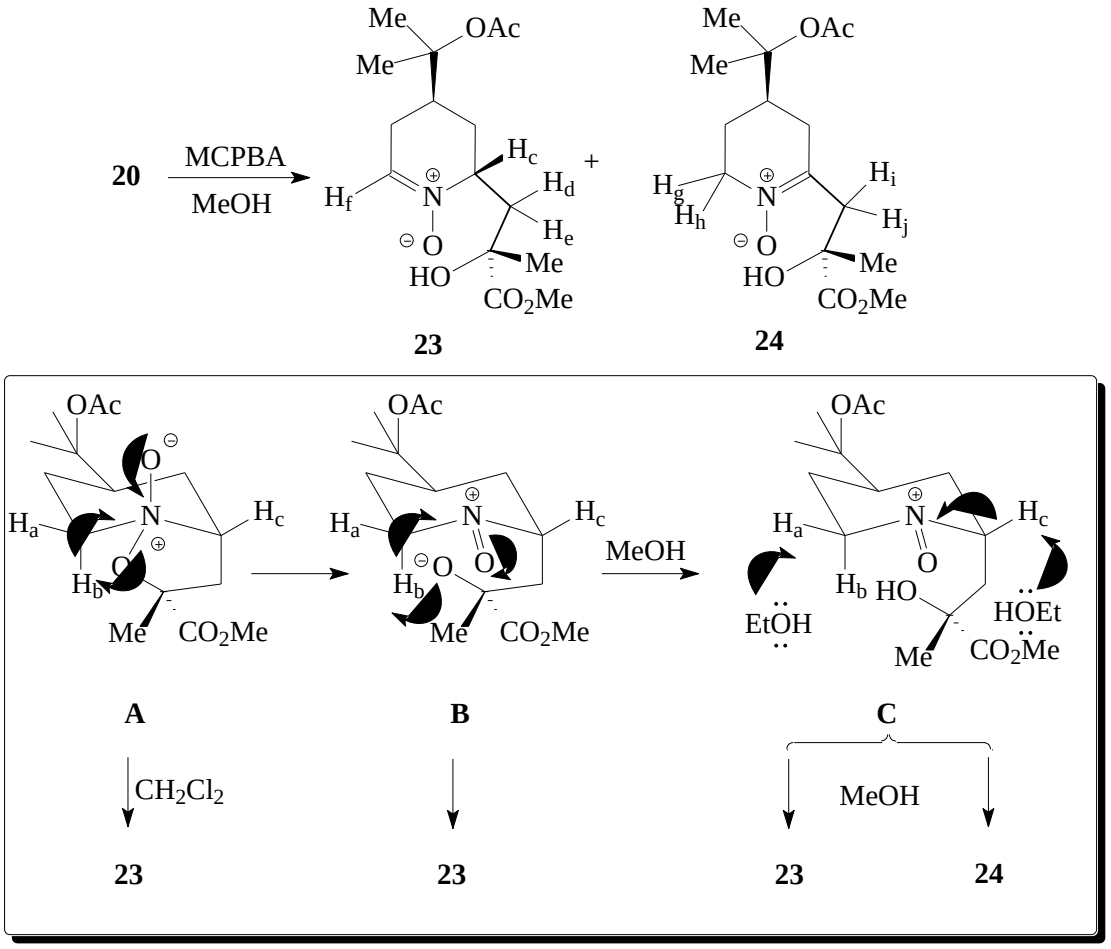
Scheme 3

With respect to the six-membered ring, both *cis*-fused **B** and *trans*-fused **C** have the bulky $CMe_2OH(Ac)$ substituent axially-oriented, while the tertiary group is equatorially oriented in *cis*-fused **A** (Scheme 3). As such the major cycloadducts **14a**, **14b** and **16a**, as well as their acetates **18-20**, are expected to remain exclusively in the invertomeric form of *cis*-fused **A**. Note that for compound **4a**, the parent 6/5 fused bicyclic isoxazolidine, a *cis/trans* ratio of 24:76 translates into a ΔG^o value (determined at -50 °C) of 2.11 kJ mol^{-1} favoring the **4a**-*trans*-fused invertomer, while for a *cis/trans* ratio of 22:78 for cycloadduct **4b**, ΔG^o value (determined at +25 °C) becomes 3.13 kJ mol^{-1} (Scheme 1). ^{t}Butyl group is well known to have a conformational enthalpy (ΔH^o) difference of 21 kJ mol^{-1}. Comparing *cis*-fused **A** of **14a** with its *trans*-fused **C**, the bulky tertiary substituent CMe_2OH (akin to a ^{t}butyl group) at C(5) is expected to destabilize the latter invertomer by an approximate ΔH^o of 21 kJ mol^{-1}, thereby implying an overall free energy (ΔG^o) advantage of about 18 kJ mol^{-1} (i.e. 21-3.13) for the *cis*-invertomer. (Note that the entropy difference (ΔS^o) between the two invertomeric forms is assumed to be zero since both the invertomers remain as *dl*-pairs and have no axis of rotation). Such an astronomical energy difference would predict the complete absence of the *trans* invertomer as far as NMR detection limit is concerned. That the stable invertomers have the configuration of *cis*-fused **A** as depicted in Scheme 3 get further credence from ^{1}H NMR spectroscopy. While the C(3a)H is equatorially oriented in *cis*-fused **A**, it is axially oriented in *trans*-fused **C**. The equatorially and axially oriented protons are known[11] to appear at the chemical shift values of δ 3.8 and 3.3 ppm, respectively; the observed chemical shifts of ~δ 3.8 for the current compounds thereby ascertain the equatorial orientation of the C(3a)H in the exclusive invertomer *cis*-fused **A**. Further credence to the conformational assignments came from NOESY experiment. Based on COSY correlation, the signals of H_a, H_b, H_c, H_d and H_e of **14a** (Scheme 3) were found to appear at δ3.25, 2.83, 5.40, 2.75, 2.03 ppm, respectively. A strong NOE peak was observed between the protons H_b and H_c as a result of their proximity, possible only in the conformer **A**.

Assertion of the *cis* fusion of the ring juncture predicts that the synthesis of the desired second-generation aldonitrones regiospecifically may be achieved by the peracid oxidation process mentioned earlier. To our relief and delight, the isoxazolidines **18-20**, on treatment with *m*-chloroperbenzoic acid (MCPBA) gave the aldonitrones **21-23** exclusively and in almost quantitative yields (Scheme 3). This is the first time a series of 6/5-fused isoxazolidines have been shown to generate the synthetically important aldonitrones regiospecifically.

The peracid oxidation was also carried out in protic solvent ethanol in the hope that it will be able to intercept the intermediate **B** to obtain its protonated species **C** which would then generate both the aldo- and ketonitrones by general base catalysed abstraction of the proton H_a or H_b and H_c, respectively (Scheme 4). The oxidation of **20** with MCPBA in methanol did indeed generate two nitrones **23** and **24** in a respective ratio of 80:20. While the general base catalyzed proton abstraction would favour the formation of more substituted ketonitrone **24**, its formation as a minor isomer certifies a certain degree of concertedness as depicted in intermediate **A** as well as a competitive abstraction of proton H_b by RO^- in **B** versus the protonation leading to **C**. The nitrones are readily identified by the ^{1}H NMR spectral analysis. The nonoverlapping H_c, H_d and

H_f of aldonitrone **23** appeared at δ4.21, 2.64 (1H, dd, J 10.2, 14.3 Hz), and 7.08, respectively, while for the ketonitrone **24**, the Hg and H_h was displayed at δ 3.90, and H_i and H_j at 3.23 (d, *J* 13.6 Hz) and 2.74 (d, *J* 13.6 Hz) ppm.

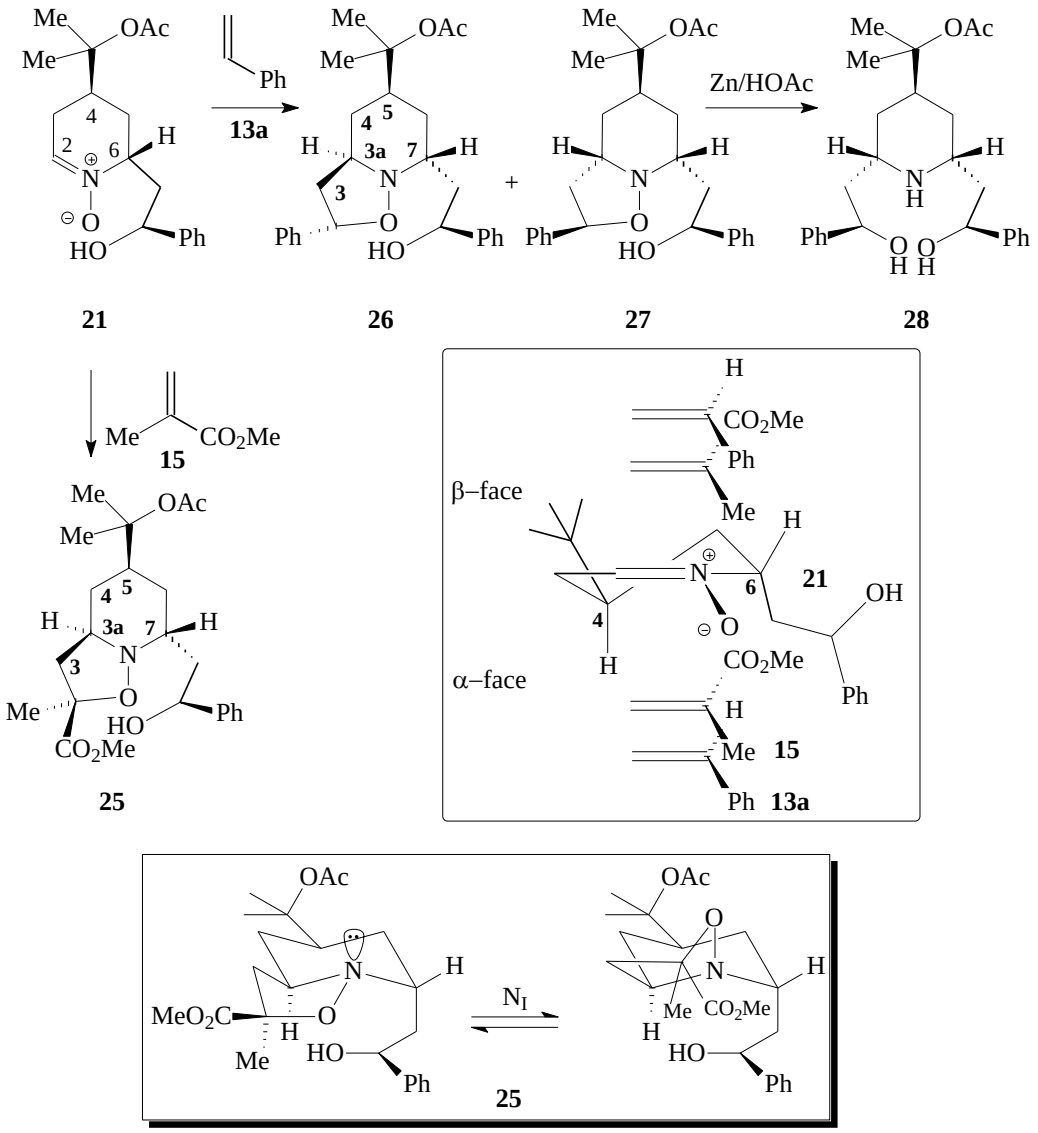


Scheme 4

Next, we explored the cycloaddition reaction of the second-generation nitrone **21** with the alkene **13**; a nonseparable mixture of three adducts in a respective ratio of 89:8:~1) was obtained in 91% yield (Scheme 5). The addition was thus found to be highly face selective. The stereochemistry of the major adduct was based on the approach of the alkene from the β-face of the nitrone to give C(3a),C(7)-*trans* substituted adduct **25**; in the α-face approach, the CO_2Me group is expected to experience severe steric crowding in the transition state. The face selectivity is thus dictated by the steric influence of the substituent at C(6) so as to force the alkene to approach from the β-face of the nitrone whereby the smaller Hs at the unsubstituted end of the alkene are in a better position to negotiate with the steric encumbrance of C(4) substituent. The adduct **25** is expected to be equilibrating between the two invertomers in both of which the bulky

tertiary substituent is placed at equatorial orientation. The ^{1}H as well as ^{13}C NMR spectra at ambient temperatures did indeed reveal broad signals.

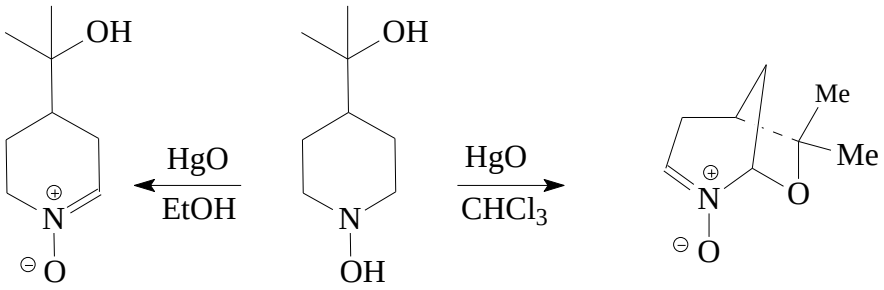
For the addition reaction of styrene **13a** with nitrone **21**, a mixture of isomers **26** and **27** was obtained in a respective ratio of 1:3; the face selectivity is thus dictated by the steric influence of the β–substituent at C(4) so as to force the alkene to a preferable approach from the α-face of the nitrone. The endo-oriented H of styrene will have very little discomfort in compare to the endo-oriented carbomethoxy as far as the steric encumbrance of the α–oriented substituent at C(6) is concerned. The stereochemical analyses thus revealed that the mono- **13a** and disubstituted **15** alkenes prefer to approach the α- and β-face of the nitrone, respectively, and the experimental findings are rationalized in terms of the transition state structures depicted in Scheme 5.

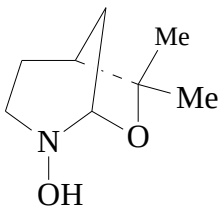


Scheme 5

The stereochemistry of the addition reaction was confirmed by chemical conversion of **27** into the ring opened product **28** by cleaving the N-O bond of the cycloadducts with zinc/acetic acid. The NMR spectra of the amine **28 (**$C_{26}H_{35}NO_4$**)**, obtained from adduct **27**, confirmed its symmetric nature; as expected the ^{13}C NMR spectrum revealed the presence of 13 carbon signals. The two benzylic protons appeared identical as displayed by a single signal at δ4.96-4.94 (2H, m); even the two phenyl rings appeared identical as displayed by three types of proton at δ7.14 (4H, d, *J* 7.3 Hz), 7.24 (4H, t, *J* 7.3 Hz), 7.14 (2H, t, *J* 7.3 Hz).

The very idea of having a 4-hydroxymethyl substituent in the current cyclic nitrone was our desire to synthesize a nitrone with an unusual bicyclic system as shown in Scheme 6. To our surprise, while the mercury(II) oxide oxidation of **11** in protic solvent ethanol afforded cleanly the monocyclic nitrone **12**, the oxidation in aprotic solvent chloroform gave the novel bicyclic nitrone **29** in almost quantitative yield. The polar functionality of nitrone **12** is strongly solvated in ethanol; as a result, the internal aminalization of the nitrone moiety to the *N*-hydroxy compound **30** is discouraged. In an aprotic solvent, further oxidation of the intermediate **30** led to the bicyclic nitrone **29**. Work is in progress on the cycloaddition reactions of this type of nitrone(s) with the aim of constructing and elaborating the unusal bicyclic system found in a novel inhibitor of tyrosyl tRNA synthetase.[17]





30

Scheme 6

The study has confirmed the mechanism of the peracid induced ring opening of the isoxazolidine, and led to the synthetically important second-generation cyclic aldonitrones, for the first time, with a complete regioselectivity. The bulkier tertiary substituent at C(5) in the

cycloadducts has, to our advantage, frozen the invertomer exclusively in the *cis*-fused form and thus led to the observed regioselectivity. The synthesis of the novel bicyclic nitrone **29** has paved the way to study its cycloaddition reactions to incorporate and elaborate this interesting and unusal bicyclic system.

Experimental Section

General. Elemental analysis was carried out on a Perkin Elmer Elemental Analyzer Series 11 Model 2400. IR spectra were recorded on a Perkin Elmer 16F PC FTI.R spectrometer. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ at +25°C using TMS as internal standard on a JEOL LA 500 MHz spectrometer. Mass spectra were recorded on a GC/MS system (Agilent Technologies, 6890N). Silica gel chromatographic separations were performed with Silica gel 100 from Fluka Chemie AG (Buchs, Switzerland). 4-methoxycarbonylpiperidine **7**, 1-hexene, styrene, methyl methacrylate, m-chloroperbenzoic acid, from Fluka Chemie AG (Buchs, Switzerland) were used as received. All solvents were of reagent grade. Dichloromethane was passed through alumina before use. All reactions were carried out under N_2.

***N*-Benzyl-4-methoxycarbonylpiperidine (8).** To a stirring solution of amine **7** (10 g, 70 mmol) in THF (50 mL) in the presence of triethyl amine (7 g) at 0°C was added benzyl bromide (13.2 g, 70 mmol) dropwise. After stirring at room temperature overnight, the mixture was taken up in water (20 mL) and extracted with CH_2Cl_2 (4×30 mL). The combined organic layers was dried (Na_2SO_4), concentrated and the residual liquid was distilled to give amine **8** as a colorless liquid (15.3 g, 94%), $bp_{0.1\ mbarHg}$ 104 °C; (Found: C, 71.9; H, 8.2; N, 5.8. $C_{14}H_{19}NO_2$ requires C, 72.07; H, 8.21; N, 6.00%.); ν_{max} (neat) 3027, 2949, 2802, 2760, 1732, 1494, 1450, 1435, 1367, 1320, 1286, 1268, 1196, 1167, 1145, 1047, 1014, 983, 906, 738, and 699 cm^{-1}. δ_H 7.21-7.32 (5H, m), 3.67 (3H, s), 3.48 (2H, s), 2.85 (2H, apparent d, *J* 11.9 Hz), 2.29 (1H, tt, *J* 4.0, 11.0 Hz), 2.02 (2H, dt, *J* 2.3, 11.6 Hz), 1.89-1.84 (2H, m), 1.82 -1.71 (2H, m); δ_C 175.7, 138.3, 129.1 (2C), 128.1 (2C), 126.9, 63.2, 52.8 (2C), 51.5, 41.0, 28.2 (2C).

***N*-Benzyl-4-(2-hydroxy-2-propyl)piperidine (9).** To a stirring solution of amine **8** (10 g, 42 mmol) in THF (50 mL) at 0 °C was added dropwise a 3M solution of methyl magnesium bromide (30 mL, 90 mmol). The mixture was then stirred at room temperature for 6 h. After addition of a saturated solution of ammonium chloride (20 mL), the aqueous layer was extracted with CH_2Cl_2 (4×30 mL). The combined organic layers was dried (Na_2SO_4), concentrated and the residual liquid was purified by chromatography over silica using 1:1 ether/methanol mixture as eluant to give the aminoalcohol **9** as a white solid (7.3 g, 75%). Mp 75-76 °C (ether-pentane); (Found: C, 77.0; H, 10.1; N, 5.9. $C_{15}H_{23}NO$ requires C, 77.21; H, 9.93; N, 6.00%.); ν_{max} (KBr) 3366, 2961, 2939, 2861, 2802, 2760, 1452, 1368, 1342, 1269, 1218, 1137, 1090, 997, 920, 759, 739, and 700 cm^{-1}. δ_H 7.32 -7.23 (5H, m), 3.49 (2H, s), 2.97 (2H, apparent d, *J* 11.6 Hz), 1.92 (2H, dt, *J* 2.3, 11.7 Hz), 1.72 -1.66 (2H, m), 1.39 (2H, dq, *J* 3.6, 12.5 Hz), 1.32-1.24 (2H, m),

1.17 (6H, s) ; δ_C 138.0, 129.3 (2C), 128.1 (2C), 127.0, 72.4, 63.2, 54.0 (2C), 47.3, 26.9 (2C), 26.7 (2C).

4-(2-Hydroxy-2-propyl)piperidine (10). Protected aminoalcohol **9** (10 g, 42 mmol) in ethanol (50 mL) containing Pd/C (1 g) was hydrogenated at 20 °C under 50 psi pressure for 3 h. The reaction mixture was filtered over celite and washed with ethanol (2×10 mL). After removal of the solvent, the residue was crystallized from acetone to give pure aminoalcohol **10** as a white solid (4.3 g, 72%); mp 136-137°C; ν_{max} (KBr) 3387, 2970, 2856, 1643, 1632, 1537, 1470, 1426, 1380, 1307, 1276, 1254, 1172, 1117, 915 and 818 cm^{-1}. δ_H 3.23 (2H, apparent d, *J* 12.2 Hz), 2.92 (2H, br s), 2.63 (2H, t, *J* 11.7 Hz), 1.79 (2H, apparent d, *J* 12.6 Hz), 1.46-1.28 (3H, m), 1.18 (6H, s); δ_C 72.4, 47.6, 46.8 (2C), 27.7 (2C), 26.7(2C).

4-(2-Hydroxy-2-propyl)-*N*-hydroxypiperidine (11). To a stirring solution of aminoalcohol **11** (10 g, 70 mmol) in water (100 mL) in the presence of sodium tungstate (0.8 g) at 0°C under N_2 was added dropwise a 30% H_2O_2 solution (18.5 g, 163 mmol) in 15 min. The mixture was then stirred at 20°C for 2 h. Solid sodium borohydride (2 g, 54 mmol) was added in portions to the above mixture and stirring continued for 1 h. The mixture was extracted with CH_2Cl_2 (4×50 mL). The combined organic layers was dried (Na_2SO_4), concentrated and the residual liquid was purified by chromatography over silica using 70:30 ether/methanol mixture as eluant to give hydroxylamine **11** as a colorless liquid (8 g, 71%). (Found: C, 60.2; H, 10.6; N, 8.7. $C_8H_{17}NO_2$ requires C, 60.35; H, 10.76; N, 8.80%.); ν_{max} (neat) 3349, 2966, 2861, 2830, 1659, 1449, 1377, 1301, 1254, 1162, 1131, 1099, 1049, 921, 794, 733 cm^{-1}. δ_H 3.37-3.28 (2H, m), 2.47 (2H, t, *J* 10.5 Hz), 1.85-1.75 (2H, m), 1.50-1.37 (4H, m), 1.35-1.27 (1H, m), 1.17 (6H, s) ; δ_C 72.03, 58.66 (2C), 45.93, 27.13 (2C), 26.53 (2C).

4-(2-Hydroxy-2-propyl)-3,4,5,6-tetrahydropyridine 1-oxide (12). To a solution of the hydroxylamine (4.5 g, 28.2 mmol) in EtOH (50 mL) was added yellow HgO (12.0 g, 56.4 mmol) and the mixture was stirred at 20°C for 6 h or until the oxidation was complete (as indicated by TLC experiment in ether). The mixture was then filtered through a bed of celite and $MgSO_4$. The bed was washed with liberal excess of ethanol. The formation of nitrone **12** was assumed quantitative for the percent yield calculation in the subsequent cycloaddition reactions. However, the nitrone contained minor quantities of impurities and as such its elemental analysis was not carried out. ν_{max} (neat) 3360, 2972, 2938, 1633, 1446, 1369, 1299, 1245, 1162, 1047, 950, 924, 790, 732 and 478 cm^{-1}. δ_H 7.18-7.15 (1H, m), 3.90-3.81 (2H, m), 2.55-2.48 (1H, m), 2.43-2.28 (2H, m), 2.13-2.10 (1H, m), 1.70-1.83 (2H, m), 1.25 (3H, s), 1.24 (3H, s); δ_C 137.0, 70.8, 58.2, 40.1, 27.3 (Me), 27.1, 26.9 (Me), 23.9. Assignment of the ^{13}C chemical shifts was based on DEPT experiment results.

2-Phenyl-5-(2-hydroxy-2-propyl)hexahydro-2*H*-isoxazolo[2,3-*a*]pyridine (14a). A solution of nitrone **12** (10 mmol) in EtOH (40 mL) containing styrene **13a** (5 mL) was heated at 90°C for 4 h under N_2 in a closed vessel. After removal of the solvent and excess alkene the residual crude mixture was purified by chromatography over silica using 85:15 ether/methanol as eluant to give a single adduct **14a** as a white solid (2.0 g, 80%). ^1H NMR of the crude or the separated fraction failed to reveal the presence of any other minor isomers. *m/z* 261 [M^+]; Mp 87-89°C (ether-

pentane); (Found: C, 73.3; H, 8.7; N, 5.3. $C_{16}H_{23}NO_2$ requires C, 73.53; H, 8.87; N, 5.36%.); ν_{max} (neat) 3358, 2968, 2927, 2865, 1494, 1452, 1380, 1367, 1293, 1264, 1206, 1170, 1152, 1119, 1093, 952, 921, 758, 731, and 700 cm^{-1}; δ_H 7.40-7.25 (5H, m), 5.40 (1H, dd, *J* 3.8, 9.9 Hz), 3.92-3.85 (1H, m), 3.25 (1H, td, *J* 3.4, 10.4 Hz), 2.83 (1H, ddd, J 2.5, 10.4, 12.8 Hz), 2.75 (1H, dt, *J* 10.0, 12.0 Hz), 2.05-1.70 (5H, m), 1.62-1.54 (1H, tt, *J* 3.0, 12.0 Hz), 1.52-1.42 (1H, dq, *J* 3.4, 12.8 Hz), 1.21 (3H, s), 1.20 (3H, s); δ_C 142.3, 128.4 (2C), 127.6, 126.4 (2C), 78.8 (C-Ph), 72.1 (CMe_2), 60.2, 49.9, 40.8 ($CCMe_2$), 38.8, 27.1 (Me), 27.0 (Me), 26.2, 25.8. Assignment of the ^{13}C chemical shifts was based on DEPT experiment results.

2-Butyl-5-(2-hydroxy-2-propyl)hexahydro-2*H*-isoxazolo[2,3-a]pyridine (14b). A solution of nitrone **12** (10 mmol) in EtOH (40 mL) containing 1-hexene **13b** (10 mL) was heated at 90°C for 20 h under N_2 in a closed vessel. After removal of the solvent and excess alkene the residual crude mixture was purified by chromatography over silica using 95:5 Dichloromethane/methanol as eluant to give only one adduct **14b** as a colorless liquid (1.85 g, 75%). *m/z* 241 [M^+]; mp 87-89°C (ether-pentane); (Found: C, 69.4; H, 11.1; N, 5.7. $C_{14}H_{27}NO_2$ requires C, 69.67; H, 11.27; N, 5.80%.); ν_{max} (neat) 3397, 2958, 2929, 2872, 1666, 1454, 1379, 1369, 1291, 1265, 1210, 1140, 1098, 954, 926, and 761 cm^{-1}; δ_H 4.42-4.36 (1H, m), 3.64-3.58 (1H, m), 3.11 (1H, td, *J* 3.4, 10.4 Hz), 2.68 (1H, ddd, *J* 2.5, 10.2, 12.8 Hz), 2.36 (1H, dt, *J* 9.4, 11.9 Hz), 1.97-1.20 (13H, m), 1.19 (3H, s), 1.18 (3H, s), 0.90 (3H, t, *J* 7 Hz); δ_C 77.2, 72.1, 59.7, 49.6, 40.7, 35.35, 35.26, 28.1, 27.0 (2C), 26.3, 25.7, 22.7, 14.0.

Isomers of methyl 2-methyl-5-(2-hydroxy-2-propyl)hexahydro-2*H*-isoxazolo[2,3-*a*]pyridine-2-carboxylate (16 and 17). A solution of nitrone **12** (10 mmol) in EtOH (40 mL) containing methyl methacrylate **(15)** (6 mL) was heated at 50°C for 3 h under N_2 in a closed vessel. After removal of the solvent and excess alkene the residual crude mixture was separated by chromatography over silica using 95: 5 DCM/methanol as eluant to give a nonseparable mixture of adducts **16** and **17** in a respective ratio of 95:5 as a colorless liquid (2.1 g, 83%). The presence of the minor adduct was revealed by the presence of a CO_2Me singlet at 3.75 ppm. Mp 128-129 °C (ether-pentane); (Found: C, 60.5; H, 9.1; N, 5.3. $C_{13}H_{23}NO_4$ requires C, 60.68; H, 9.01; N, 5.44%.); ν_{max} (neat) 3404, 2968, 2930, 2872, 1731, 1652, 1454, 1371, 1293, 1251, 1217, 1191, 1139, 1114, 1084, 987, 946, 920, 874, 738 and 667 cm^{-1}; δ_H 3.77 (3H, s), 3.79-3.74 (1H, m), 3.18 (1H, td, *J* 3.4,10.4 Hz), 2.90 (1H, t, *J* 12.5 Hz), 2.65 (1H, ddd, *J* 2.5, 10.7, 13.0), 2.00-1.93 (2H, m), 1.91-1.33 (1H, m), 1.79-1.71 (2H, m), 1.54 (1H, tt, *J* 3.0, 12.8 Hz), 1.50 (3H, s), 1.43-1.33 (1H, dq, J 3.4, 12.8 Hz), 1.19 (3H, s), 1.18 (3H, s); δ_C 175.6, 84.2, 72.0, 60.3 (CHN), 52.6 (CO_2Me), 50.8, 40.8 ($CHCMe_2$), 39.6, 27.0 (2C, CMe_2), 25.86 (2C), 25.75 (C-Me). Assignment of the ^{13}C chemical shifts was based on DEPT experiment results.

2-Phenyl-5-(2-acetoxy-2-propyl)hexahydro-2*H*-isoxazolo[2,3-*a*]pyridine (18). Cycloadduct **14a** (1.10 g, 4.3 mmol) in toluene (20 mL) was treated with acetic anhydride (3 mL) and DMAP [4-(*N*,*N*-dimethylamino)pyridine] (0.12 g, 1 mmol) at 70 ºC for overnight. After removal of the solvent and excess acetic anhydride, the residual liquid was purified by chromatography over silica gel using 1:1 ether/hexane as eluant to give acetate **18** as a white solid (1.24 g, 95%). Mp 58-60°C (ether-pentane); (Found: C, 71.0; H, 8.1; N, 4.7. $C_{18}H_{25}NO_3$ requires C, 71.26; H, 8.31;

N, 4.62%.); ν_{max} (KBr) 2977, 2951, 2930, 2857, 1728, 1494, 1453, 1368, 1257, 1150, 1133, 1018, 949, 758, and 701 cm^{-1}; δ_H 7.37-7.25 (5H, m), 5.40 (1H, dd, *J* 3.8, 9.9 Hz), 3.93-3.80 (1H, m), 3.27 (1H, td, *J* 3.4,10.3 Hz), 2.84 (1H, ddd, *J* 2.7, 10.3, 12.8 Hz), 2.76 (1H, dt, *J* 10.1, 12.0 Hz), 2.23 (1H, tt, *J* 3.35, 12.3 Hz), 2.04 (1H, ddd, *J* 3.4, 7.6, 12.3 Hz), 1.98 (3H, s), 1.98-1.91 (1H, m), 1.88-1.91 (1H, m), 1.77-1.71 (1H, m), 1.52 (1H, dq, *J* 3.1, 12.8 Hz), 1.45 (3H, s), 1.43 (3H, s); δ_C 170.5, 142.2, 128.5 (2C), 127.6, 126.4 (2C), 84.0 (CPh), 78.9 (CMe_2CO), 60.0, 49.8, 38.8, 38.2 ($CCMe_2$), 25.8, 25.5, 23.47 (CMe), 23.44 (CMe), 22.4 $COCH_3$).

2-Butyl-5-(2-acetoxy-2-propyl)hexahydro-2*H*-isoxazolo[2,3-*a*]pyridine (19). Cycloadduct **14b** (1.30 g, 5.4 mmol) in toluene (10 mL) was treated with acetic anhydride (3 mL) and DMAP [4-(N,N-dimethylamino) pyridine] (0.12 g, 1 mmol) at 70 ºC for overnight. After removal of the solvent and excess acetic anhydride the residual liquid was purified by chromatography over silica gel using 80:20 ether-Hexanes as eluant to give the acetate **19** as a colourless liquid (1.30 g, 85%). *m/z* 283 [M^+]; (Found: C, 67.6; H, 10.2; N, 4.8. $C_{16}H_{29}NO_3$ requires C, 67.81; H, 10.31; N, 4.94%.); ν_{max} (neat) 2955, 2930, 2858, 1729, 1454, 1431, 1368, 1256, 1222, 1153, 1134, 1018, 946, and 759 cm^{-1}; δ_H 4.43-4.36 (1H, m), 3.67-3.58 (1H, m), 3.11 (1H, td, *J* 3.4,10.40 Hz), 2.68 (1H, ddd, *J* 2.7, 10.4, 12.9 Hz), 2.36 (1H, dt, *J* 9.4, 11.9 Hz), 2.16 (1H, tt, *J* 4.0, 11.9 Hz), 1.97 (3H, s), 1.90-1.76 (2H, m), 1.73-1.55 (4H, m), 1.53-1.25 (5H, m), 1.43 (3H, s), 1.41 (3H, s), 0.90 (3H, t, *J* 7.0 Hz); δ_C 170.5, 84.1, 77.3, 59.7, 49.6, 38.2, 35.34, 35.29, 28.2, 26.0, 25.5, 23.48, 23.42, 22.7, 22.4, 14.0.

Methyl 2-methyl-5-(2-acetoxy-2-propyl)hexahydro-2*H*-isoxazolo[2,3-*a*]pyridine-2-carboxylate (20). Cycloadduct **16** (1.90 g, 7.4 mmol) in toluene (10 mL) was treated with acetic anhydride (3 mL) and DMAP (0.12 g, 1 mmol) at 70 ºC for overnight. After removal of the solvent and excess acetic anhydride the residual liquid was purified by chromatography over silica gel using 80:20 ether-hexane as a eluant to give acetate **20** as a colourless liquid (1.99 g, 90%). (Found: C, 60.0; H, 8.3; N, 4.6. $C_{15}H_{25}NO_5$ requires C, 60.18; H, 8.42; N, 4.68%.); ν_{max} (neat) 2959, 2951, 1730, 1454, 1370, 1255, 1192, 1137, 1116, 1086, 1019, 988, 947, 873, 757, and 608 cm^{-1}. δ_H 3.78 (3H, s), 3.80-3.75 (1H, m), 3.18 (1H, td, *J* 3.4,10.4 Hz), 2.87 (1H, t, *J* 12.5 Hz), 2.66 (1H, ddd, *J* 2.5, 10.7, 13.0), 2.11-2.02 (1H, m), 1.96 (3H, s), 1.70-1.63 (1H, m), 1.99-1.82 (3H, m), 1.50 (3H, s), 1.43 (3H, s), 1.41 (3H, s), 1.45-1.36 (1H, m); δ_C 175.5, 170.4, 84.3, 83.8, 60.1 (CHN), 52.7(OMe), 50.6, 39.5, 38.7 ($CHCMe_2$), 25.8 (Me), 25.6, 25.4, 23.4 (Me), 23.3 (Me), 22.4 (Me). Assignment of the ^{13}C chemical shifts was based on DEPT experiment results.

4-(2-Acetoxy-2-propyl)-6-(2-hydroxy-2-phenyl-1-ethyl)-3,4,5,6-tetrahydropyridine 1-oxide (21). To a stirred solution of cycloadduct **18** (3.0 mmol) in dichloromethane (30 mL) at 20ºC was added MCPBA (3.0 mmol) in one portion. After 30 min at 20 ºC the organic layer was washed with 5% $NaHCO_3$ solution (3×10 mL). The combined aqueous layers was re-extracted with CH_2Cl_2 (3×25 mL). The combined organic layers was dried (Na_2SO_4), concentrated to give only aldonitrone **21** as a pale yellow liquid in almost quantitative yield. The crude nitrone was not purified further and its elemental analysis was not carried out. ν_{max} (neat) 3250, 2981, 2929, 1729, 1621, 1493, 1454, 1431, 1370, 1257, 1224, 1167, 1138, 1098, 1019, 914, 760, 733, and

703 cm^{-1}; δ_H 7.43-7.21 (5H, m), 7.21-7.17 (1H, m), 6.17 (1H, br s), 5.08-5.03 (1H, dd, *J* 2.7, 6.4 Hz), 4.15-4.08 (1H, m), 2.55-2.45 (1H, m), 2.42-2.30 (3H, m), 2.03-1.98 (1H, m), 1.97 (3H, s), 1.88–1.82 (1H, m), 1.72-1.67 (1H, m), 1.46 (3H, s), 1.42 (3H, s); δ_C 170.1, 143.8, 137.5, 128.3 (2C), 127.0, 125.7 (2C), 82.2, 70,2, 63.1, 44.2, 34.4, 29.9, 27.0, 23.2, 23.1, 22.2.

4-(2-Acetoxy-2-propyl)-6-(2-hydroxy-1-hexyl)-3,4,5,6-tetrahydropyridine 1-oxide (22). Using procedure as described in the preparation of **21**, cycloadduct **19** (3.0 mmol) was treated with MCPBA to generate the aldonitrone **22** as a pale yellow liquid in almost quantitative yield. The crude nitrone was not purified further and its elemental analysis was not carried out. ν_{max} (neat) 3357, 2932, 2871, 1729, 1631, 1454, 1370, 1256, 1224, 1170, 1139, 1019, 921, 788, and 732 cm^{-1}; δ_H 7.16 (1H, t, *J* 3.8 Hz), 5.02 (1H, br s), 4.33-4.22 (1H, m), 3.92-3.78 (1H, m), 2.55-2.30 (4H, m), 2.10-1.90 (2H, m), 2.00 (3H, s), 1.88-1.80 (1H, m), □□1.70-1.22 (6H, m), 1.50 (3H, s), 1.47 (3H, s)□□ 0.91 (3H, t, *J* 7.0 Hz), δ_C 170.2, 136.7, 82.4, 68.2, 63.7, 42.1, 36.5, 34.2, 29.2, 28.2, 26.9, 23.3, 23.2, 22.7, 22.3, 14.1.

4-(2-Acetoxy-2-propyl)-6-(2-hydroxy-2-carbomethoxy-1-propyl)-3,4,5,6-tetrahydropyridine 1-oxide (23). Using procedure as described in the preparation of **21**, cycloadduct 20 (3.0 mmol) was treated with MCPBA to generate aldonitrone 23 as a pale yellow liquid in almost quantitative yield. The crude nitrone was not purified further and its elemental analysis was not carried out. ν_{max} (neat) 3438, 2981 1728, 1713, 1644, 1631, 1554, 1537, 1516, 1452, 1371, 1256, 1137, 1020, 918, 732, 645 and 611 cm^{-1}. δ_H 7.09-7.06 (1H, m), 6.46 (1H, br s), 4.24-4.18 (1H, m), 3.75 (3H, s), 2.64 (1H, dd, J 10.2, 14.3 Hz), 2.58-2.25 (3H, m), 1.99 (3H, s), 2.02-1.77 (2H, m), 1.51 (3H, s), 1.50 (3H, s), 1.48 (3H, s), 1.54-1.37 (1H, m); δ_C 176.2, 170.0, 137.5, 82.1, 73.2, 62.4, 52.4, 43.6, 34.7, 28.9, 26.8, 26.7, 23.2 (2C), 22.2.

Reaction of nitrone 21 with methymethacrylate (15). Nitrone **21** [prepared by MCPBA oxidation of adduct **18** (1.0 mmol)] in CH_2Cl_2 (10 mL) was treated with methyl methacrylate **(15)** (1.0 mL) and the mixture was stirred at 45ºC for overnight. After removal of the solvent and excess alkene, the residual liquid was purified by chromatography over silica gel using 9:1 ether/hexane as eluant to give a nonseparable mixture of three adducts (as indicated by the presence of three CO_2Me singlets at δ3.77, 3.80 and 3.84 ppm in a respective ratio of 89:8:~1 as a colourless liquid (380 mg, 91%). The major adduct was assigned the stereochemistry of **25**. (Found: C, 65.6; H, 7.7; N, 3.2. $C_{23}H_{33}NO_6$ requires C, 65.85; H, 7.93; N, 3.34%.); ν_{max} (neat) 3475, 2982, 2951, 2872, 1728, 1653, 1448, 1368, 1254, 1215, 1125, 1057, 1020, 936, 754, 700, 609 cm^{-1}; δ_H 7.40-7.23 (5H, m), 5.00 (1H, m), 3.77 (3H, s), 3.77-3.70 (2H, m), 2.43-2.20 (4H, m), 1.95 (3H, s), 1.98-1.22 (6H, m), 1.56 (3H, s), 1.37 (3H, s), 1.35 (3H, s); δ_C 174.2, 170.3, 144.6, 128.3 (2C),126.9, 125.5 (2C), 84.1, 80.3, 72.6, 56.0, 54.8, 52.6, 46.2, 38.4 (2C), 27.5, 25.4 (2C), 23.14, 23.06, 22.4.

Reaction of nitrone 21 with styrene 13a. Nitrone **21** [prepared by MCPBA oxidation of adduct **18** (2.0 mmol)] in CH_2Cl_2 (10 mL) was treated with styrene (2.0 mL) and the mixture was stirred at 45ºC for overnight. After removal of the solvent and excess alkene, the residual liquid was separated by chromatography over silica gel using 7:1 ether/hexane as eluant to give the minor isomer **26** as a colorless liquid (90 mg). Continued elution gave a mixture of **26** and **27**. Finally,

the major adduct **27** was eluted as a colorless liquid. The total isolated yield was 82% and respective ratio of **26** and **27** was found to be 1:3.

Minor diastereomer 26. (Found: C, 77.4; H, 7.7; N, 3.2. $C_{26}H_{33}NO_4$ requires C, 73.73; H, 7.85; N, 3.31%.); ν_{max} (neat) 3446, 3027, 2947, 2880, 1725, 1656, 1493, 1454, 1369, 1258, 1221, 1132, 1055, 1020, 946, 913, 759, 733 and 701 cm^{-1}; δ_H 7.40-7.20 (10H, m), 5.13-5.09 (1H, m), 5.06-5.02 (1H, m), 3..72-3.60 (2H, m), 2.50- 2.28 (5H, m), 1.98 (3H, s), 1.75-1.22 (5H, m), 1.41 (3H, s), 1.38 (3H, s); δ_C 170.4, 144.6, 141.7, 128.5 (2C), 128.2 (2C), 127.4, 126.8, 125.6 (4C), 84.2, 76.5, 72.3, 56.3, 54.4, 44.6, 39.6, 38.4, 27.3, 25.2, 23.1 (2C), 22.4.

Major distereomer 27. (Found: C, 73.4; H, 7.6; N, 3.2. $C_{26}H_{33}NO_4$ requires C, 73.73; H, 7.85; N, 3.31%.); ν_{max} (neat) 3429, 3064, 3026, 2945, 1726, 1451, 1367, 1253, 1136, 1018, 782, 753, and 698 cm^{-1}; δ_H 7.40-7.20 (10H, m), 5.20-5.05 (2H, m), 4.60 (1H, br s), 3.41-3.32 (1H, m), 3.10-3.00 (1H, m), 2.50-1.40 (9H, m), 1.96 (3H, s), 1.52 (6H, s); δ_C 170.1, 144.7, 141.8, 128.4 (2C), 128.2 (2C), 127.8, 126.9, 126.4 (2C), 125.7 (2C), 84.3, 78.6, 71.5, 61.3, 59.2, 43.9, 43.6, 40.3, 29.7, 29.3, 24.8, 24.2, 22.6.

Conversion of 27 to 28 by treatment with zinc and acetic acid. To a vigorously stirred solution of adduct **27** (0.3 mmol) in acetic acid (2 mL) and water (2 mL) at 60 °C was added Zn (0.85 g) in two portions (ca. 5 min). The reaction mixture was stirred at 60°C for a total 30 min. The reaction mixture was decanted and the residual solid was washed with water (10 mL) and CH_2Cl_2 (20 mL). After basification (K_2CO_3), the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The organic layer was dried (Na_2SO_4), concentrated to give the amine **28** in almost quantitative yield. Mp. 134-137 °C; (Found: C, 73.1; H, 8.0; N, 3.2. $C_{26}H_{35}NO_4$ requires C, 73.38; H, 8.29; N, 3.29%.); ν_{max} (KBr) 3410, 3297, 3126, 3066, 2978, 2858, 2844, 1735, 1638, 1550, 1425, 1372, 1330, 1249, 1216, 1108, 1059, 1013, 923, 752, 703, and 649 cm^{-1}; δ_H 7.45 (4H, d, *J* 7.3 Hz), 7.32 (4H, t, *J* 7.3 Hz), 7.22 (2H, t, *J* 7.3 Hz), 6.25-4.25 2H, br, OH), 5.19 (2H, t, *J* 4.0 Hz), 3.28 (2H, t, *J* 10.7 Hz), 2.47 (2H, ddd, J 4.1, 10.1, 14.7 Hz), 1.98 (3H, s), 1.90-1.70 (7 H, m), 1.55-1.45 (1H, m), 1.34 (6H, s) ; δ_C 169.9, 143.4 (2C), 128.6 (4C), 127.2 (2C), 125.6 (4C), 84.0, 69.8 (2C), 49.4 (2C), 41.0 (2C), 40.6, 29.1 (2C), 24.5 (2C), 21.8.

1-Oxa-5,6-dehydro-6-aza-bicyclo[3,2,1]heptane 6-oxide (29). To a solution of hydroxylamine 11 (0.796 g, 5.0 mmol) in dry $CHCl_3$ (50 mL) was added yellow HgO (4.3 g, 20 mmol) and the mixture was stirred using a magnetic stir bar at 20°C for overnight or until the oxidation was complete (as indicated by TLC experiment in ether). The mixture was then filtered through a bed of celite and $MgSO_4$. After removal of the solvent, the bicyclic nitrone 29 was obtained as a solid in almost quantitative yield. Mp 87-89°C (ether); **(**Found: C, 61.7; H, 8.3; N, 8.9. $C_8H_{13}NO_2$ requires C, 61.91; H, 8.44; N, 9.03%.); ν_{max} (KBr) 3296, 2972, 2937, 1642, 1605, 1451, 1369, 1303, 1195, 1176, 1142, 1117, 1088, 1059, 1032, 963 and 899 cm^{-1}; δ_H 6.82-6.79 (1H, m), 5.18 (1H, d, *J* 3.5 Hz), 2.66-2.48 (3H, m), 2.40-2.36 (1H, m), 2.21 (1H, d, *J* 12.3 Hz), 1.38 (3H, s), 1.30 (3H, s) ; δ_C 130.2, 98.0, 85.3, 38.2, 34.5, 28.9, 28.6, 24.6.

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