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Peracid-induced ring opening of some hexahydro-2*H*-isoxazolo[2,3-*a*]pyridines to second-generation cyclic aldonitrones

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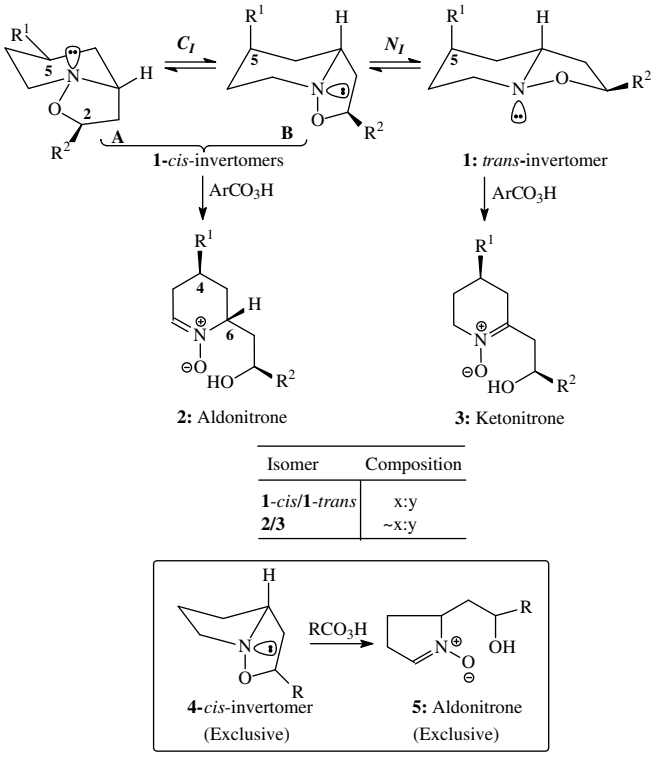
ABSTRACT

A study of the stereo- and face selectivity of the cycloaddition reactions of several mono- and di-substituted alkenes with 4-hydroxymethyl-3,4,5,6-tetrahydropyridine 1-oxide has been carried out. The addition reactions have displayed a very high degree of face selectivity in the range 13-48:1. Use of dimethyl methylenemalonate as a protective group in nitrone cycloaddition reactions has been demonstrated. The invertomeric analysis revealed that the bicyclic cycloadducts remain predominantly as the cis-fused isomer, which leads to the formation of synthetically important second-generation cyclic aldonitrones via peracid oxidation. One interesting finding was that treatment of the cycloadducts with two equivalents of peracid afforded the cyclic *N*-hydroxy lactams, presumably via further oxidation of the aldonitrones. The piperidine ring has been elaborated by cycloaddition reaction of the second-generation nitrones with several alkenes, which in most cases gave the cycloadducts in a stereoselective manner.

1. Introduction

1,3-Dipolar cycloaddition reaction of nitrones with alkenes has become an important tool in the synthesis of natural products.[1] The efficacy of these additions lies on the remarkable selectivity in the incorporation of multiple stereocenters in a single step.[1,2] The cyclic nitrones have been shown to exhibit greater stereoselectivity and reactivity compared to their acyclic counterparts as a result of the former existing in the *E* form.[3,4] The pyrrolidine- and piperidine-based alkaloids, which are widespread in nature, can be accessed through the cycloaddition reaction of five- and six-membered cyclic nitrones, respectively.[1] Nitrones generated by peracid-induced ring opening of the cycloaddition products derived from cyclic nitrones marked the beginning of the utilization of the second-generation of cyclic nitrones (Scheme 1).[5] However, the proper utilization of these second-generation nitrones has been hampered by the lack of selectivity[6] in the oxidation process in the 6/5-fused isoxazolidines **1** (R^1=H), where the major or sole trans invertomer leads to the synthetically less important ketonitrone **3** either as the major or sole product. Orientation of the nitrogen lone pair and the trans/cis invertomer ratio dictate the regiochemical outcome of the oxidation process. The higher activation barrier to nitrogen inversion ($\Delta G^{\#}$, ~70 kJ/mol)[6b] than the oxidation process does not permit the Curtin-Hammett principle[7] to apply; as such the *trans* and *cis*



Scheme 1.

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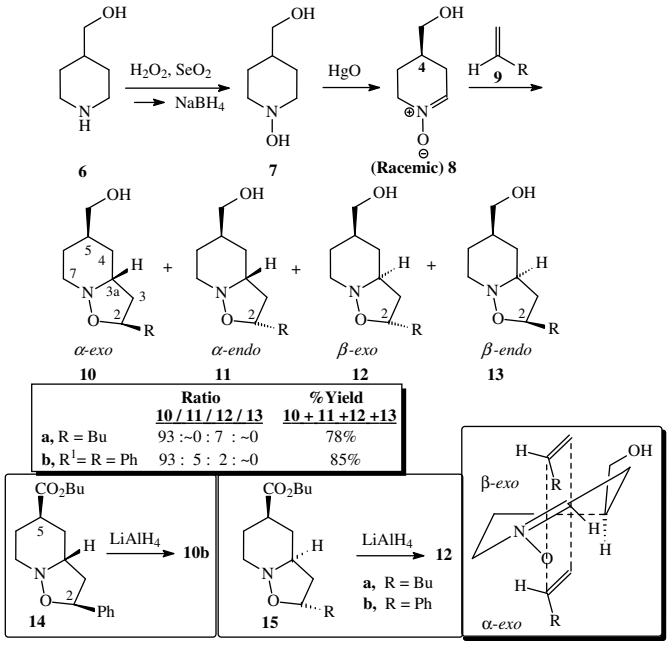
invertomers in a ratio of *x*:*y* afford the keto- and aldo-nitrones, respectively, in a similar ratio. However, the corresponding 5/5-fused isoxazolidines **4**, which exist only as the cis invertomers, give aldonitrones **5** exclusively (Scheme 1).[8]

Note that the 6/5-fused isoxazolidines **1** (R^1=H) remain in the trans-form as the major or sole invertomer (Scheme 1). In our continuing efforts to generate the synthetically important aldonitrones **2** in greater proportions, we realized that the proportion of the cis invertomer has to be increased at the expense of its trans counterpart. Attachment of an ester functionality (R^1=CO_2R) via its sp^2 hybridized carbon at C(5) in **1** did bring about a moderate change in the composition favoring the cis invertomer **A** as a result of the equatorially oriented CO_2R group.[9] We anticipated that a C(5) substituent attached through a sp^3 hybridized carbon (having a larger steric size than its sp^2 counterpart) would motivate the ring further in the direction of the cis invertomer **A**. Hence we report, for the first time, the face- and stereoselectivity of cycloaddition of a new cyclic nitrone **8** (Scheme 2) having a hydroxymethyl substituent at C(4) with various alkenes. The invertomer analysis and peracid-induced ring opening of the resultant cycloadducts may lead to the second-generation cyclic aldonitrones (Scheme 1) more selectively. The study would give an opportunity to examine the face selectivity associated with cycloaddition of the second-generation nitrones 4,6-disubstitued-3,4,5,6-tetrahydropyridine 1-oxides **2**.



Scheme 2.

2. Results and discussion

The synthesis of nitrone **8** is outlined in Scheme 2. It was presumed at the outset that preparation of the nitrone by direct oxidation of the secondary amine **9** will be a trivial matter. However, we were unable to obtain the nitrone by the procedure of Murahashi et al.[10] using hydrogen peroxide oxidation mediated by selenium dioxide either in acetone or methanol. The oxidation process gave a complicated mixture of products (presumably a mixture of **7**, **8**, and other products), which upon treatment with $NaBH_4$ afforded the hydroxylamine **7**. The required nitrone **8** was then prepared by mercury(II) oxide oxidation of **7** (Scheme 2).

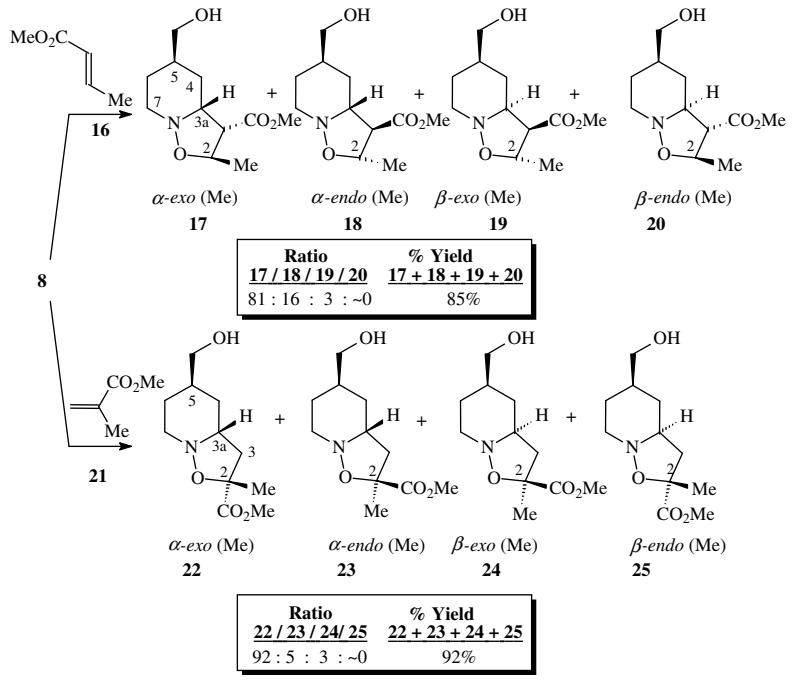
Next, we pursued the addition reaction of nitrone **8** with various alkenes. The addition of monosubstituted alkene 1-hexene (**9a**) was found to be stereo-, as well as highly faceselective; a mixture of diasteromers **10a** and **12a** was obtained in a ~13:1 ratio. The configuration of the major adduct **10a** was based on the sterically favorable *exo* approach (Scheme 2) of the Bu group from the less hindered face (i.e., α face) of the nitrone, while the β-*exo* approach of the alkene afforded the adduct **12a**. We are unable to detect the formation of the stereoisomers **11a** and **13a** arising from the α-*endo* and β-*endo* mode of approach, respectively, by the alkene. Likewise, the addition reaction with styrene (**9b**) led to the formation of the cycloadducts **10b**–**13b** in a ratio of 93:5:2:~0, thereby ascertaining again the highly face selective (98:2) nature of the cycloadditions. Such a high selectivity is surprising since the C(4)-CH_2OH group imparting the facial difference is positioned at the furthest point from the nitrone functionality in **8**. The face selectivitiy of the nitrone **8** was found to be better than a nitrone containing C(4)-CO_2Bu group (attached to the ring through a sp^2 carbon).[9] In order to confirm the stereochemistry of the cycloadducts, the compounds **14**, **15a**, and **15b** having known configurations,[9] were converted into **10b**, **12a**, and **12b**, respectively (Scheme 2).

The addition of disubstituted alkenes methyl crotonate (**16**) and methyl methacrylate (**21**) to the nitrone **8** also demonstrated very high face selectivity (97:3) in each case (Scheme 3). In both cases, the major adducts (i.e., **17** and **22**) were obtained via α-*exo* (Me) approach. The stereochemistry is based on the precedent in the lietrature[9,11]—the major adducts were obtained via an *endo*-oriented methoxycarbonyl group in the transition state as a result of a favorable secondary orbital interaction.

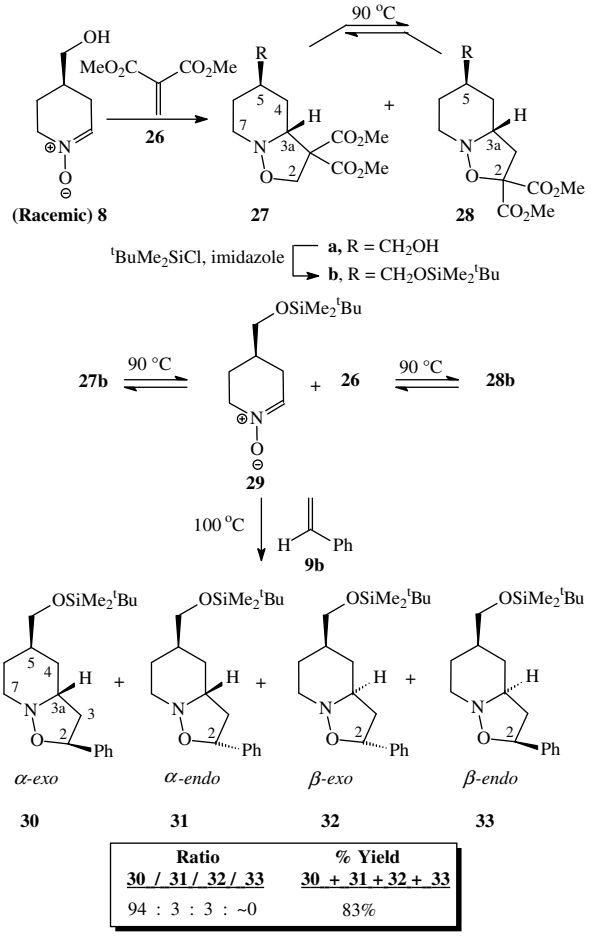
In order to study the effect of increasing the steric bulk of the C(4) substituent in nitrone **8**, the nitrone was first protected by reacting with dimethyl methylenemalonate (**26**) to give a regioisomeric mixture of **27a** and **28**a, which upon silylation afforded **27b** and **28b** (Scheme 4). Similar electronic controlled reversal in the regioselections is known[3d] in the addition reaction of the highly electron deficient alkene **26**. The nitrone functionality is protected in the sense that the cycloadducts derived from the highly electron deficient alkene readily undergo cycloreversion to the starting reactants.[3d] Thus upon thermolysis at 90 °C, either **27b** or **28b** was changed to a mixture of **27b** and **28b** in an equilibrium ratio of 3:1. When the thermolysis was carried out in the presence of styrene, the intervening nitrone **29** was trapped by undergoing stereoselctive cycloaddition to give a mixture of adducts **30**–**33** in a ratio of 94:3:3:0. The exercise has thus demonstrated a suitable way to protect a nitrone functionality and also paved the way to examine the effect of changing the substituent C(4)-CH_2OH in **8** to C(4)-$CH_2OSi^tBuMe_2$ in **29** on the stereoselection and composition of nitrogen invertomers of the cycloadducts (vide infra).

The presence of –N–O– moiety in an organic molecule has a distinctive place in conformational analysis;[12–14] 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.[15] Orientation of the nitrogen lone pair with respect to the bridgehead hydrogen and the trans-/cis-fused invertomer ratio dictates the regiochemical outcome of the peracid oxidation process leading to the second-generation nitrones (vide supra) (Scheme 1). Therefore, the proper utilization of these second-generation nitrones requires prior information on the stereochemistry of the ring fusion. We have examined the conformational aspects as well as composition of the nitrogen invertomers by NMR spectroscopy. The ^{13}C chemical shifts in $CDCl_3$ were assigned on the basis of DEPT experiment results, general chemical shifts arguments, and consideration of substituent effects, and are given in Table 1. At ambient temperature, the ^1H and ^{13}C NMR spectra of these compounds show well separated signals for the two invertomers in $CDCl_3$. Integration of the relevant peaks gives the population trends in these systems (Table 1, 3rd column).

For the 6/5-fused carbocyclic compound **34**, the ΔG° value of 2.09 kJ/mol at 25 °C favors the trans- over the cis-fused isomer



Scheme 3.



Scheme 4.

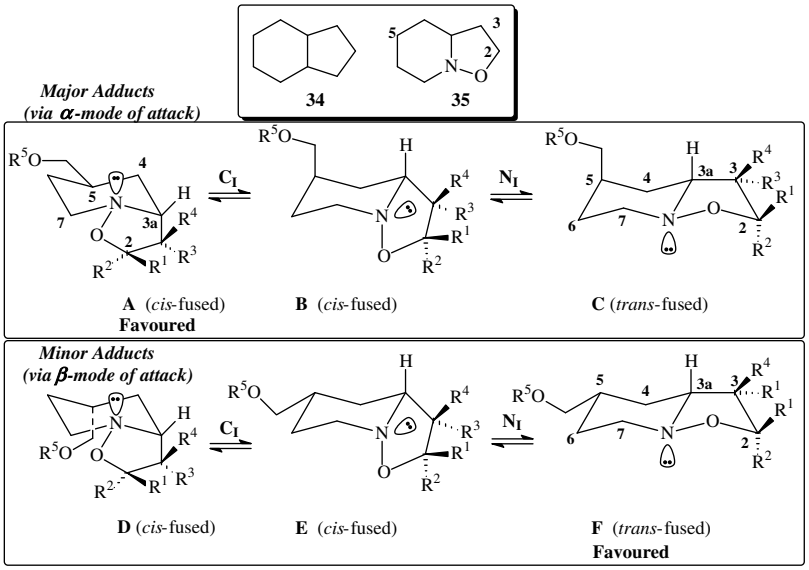
(Scheme 5).[16] Both **35** (the heterocyclic counterpart of **34**) and its derivatives having substituents at the 2-, 3-, and an ester group at the 5- position are also reported to favor, in most cases, the trans invertomers.[6c,15,16] The currently prepared major isoxazolidines, obtained by α-mode of attack, can, in principle, exist in three different chair conformations: the cis-fused pair **A** and **B** and the trans isomer **C** (Scheme 5). While the cis pair is in rapid equilibrium by chair inversion ($\mathbf{C_I}$), one of the cis conformers **B** is converted into the trans invertomer **C** by a relatively slow nitrogen inversion process ($\mathbf{N_I}$). The NMR spectra, both ^{1}H and ^{13}C, for some of the compounds show peaks due to two distinct isomers, a major and a minor invertomer. With respect to the six-membered ring, both cis-fused **A** and trans-fused **C** have one axial substituent at C(3a) and C(5), respectively, while cis-fused **B** has two energetically destabilizing axial substituents at C(5) and *N*. As such the major cycloadducts, obtained by an α-mode of attack, are expected to remain as **A** and/or **C**. For the reasons discussed above, the minor isoxazolidines, obtained by β-mode of attack, should have an overwhelming preference for the trans-fused invertomer **F** since it is free of any destabilizing axial group. The conformer **D** having two axial substituents is anticipated to be the least favored. Note that our objective is to have the isoxazolidines exist as the cis-fused invertomer in order to get the desired second-generation aldonitrones via peracid oxidation (vide supra). While this may not be achieved in the case of the trans-fused invertomer **F**, the overwhelmingly predominant cycloaddition products (via an α-mode of attack), are, however, expected to be in the desired cis-form **A**.

Isoxazolidine **14** (Scheme 2) has been shown to exist in a *cis*-**A**/*trans*-**C** ratio of 55:45 (Scheme 5).[17] A comparison between compound **14** and **10b** (Scheme 2), both having a phenyl group at C(2), may be helpful in identifying the stereochemistry of the ring fusion in the latter. Since the axially disposed CH_2OH substituent at C(5) of **10b**, being larger in size than the ester substituent in **14**, is expected to destabilize its *trans* **10**-**C** as well as *cis* **10**-**B** conformers; the relative proportion of *cis*-**10b**-**A** is anticipated to increase compared to that of compound **14** (Scheme 5). As evident from Table 1, this is indeed the case; the *cis*-**A** isomer becomes the overwhelmingly major invertomer for all the cycloadducts obtained via α-mode of attack, except **27b** (Scheme 4), which would be destabilized in *cis*-**A** as a result of

Table 1
^{13}C NMR chemical shifts of compounds studied in $CDCl_3$ at +25 °C

Compound	% Invertomer[a]		C-2	C-3	C-3a	C-4	C-5	C-6	C-7
via α-mode									
10a	*cis*-**A**	88	77.3	35.4	59.4	28.1	32.5	27.6	49.1
	trans-**C**	12	76.1	40.1	61.2	30.1	34.0	25.6	50.7
10b	*cis*-**A**	90	78.9	38.8	59.9	28.3	32.6	27.6	49.4
	trans-**C**	10	77.7	43.2	61.7	30.1	34.0	25.7	51.1
11b	*cis*-**A**	84	81.7	38.3	60.7	28.4	33.0	27.7	51.9
	trans-**C**	16	78.9	44.2	62.5	29.8	33.9	25.7	51.3
17	*trans*-**C**	65	75.2	57.1	62.9	27.1	33.6	25.2	51.3
	cis-**A**	35	75.7	56.7	62.4	26.5	32.7	26.0	48.6
18	*cis*-**A**	Solo	80.2	54.4	64.0	27.4	32.9	27.2	52.3
22	*cis*-**A**	80	84.3	39.6	59.9	27.9	32.6	27.5	50.2
	trans-**C**	20	80.0	44.9	61.6	29.5	33.7	25.3	51.2
27b	*trans*-**C**	Solo	71.8	67.0	71.6	29.3	38.3	27.3	54.5
28b	*cis*-**A**	84	87.0	38.1	60.3	27.7	32.7	27.6	50.9
	trans-**C**	16	83.3	42.7	61.7	29.7	33.3	25.3	51.4
30	*cis*-**A**	84	78.8	38.9	60.0	28.3	32.7	27.7	49.5
	trans-**C**	16	77.7	43.3	61.9	30.2	33.8	25.6	51.2
36a	*cis*-**A**	83	77.3	35.3	59.1	28.3	29.5	27.6	48.8
	trans-**C**	17	76.1	40.0	61.0	30.4	30.5	25.8	50.7
36b	*cis*-**A**	88	78.8	38.8	59.7	28.3	29.6	27.6	49.1
	trans-**C**	12	77.7	43.1	61.6	30.5	30.5	25.9	50.9
via β-mode									
12a	*trans*-**F**	Solo	76.6	39.8	65.7	32.1	38.7	27.9	53.9
12b	*trans*-**F**	Solo	78.2	42.8	66.2	32.1	38.6	27.9	54.0
24	*trans*-**F**	Solo	80.5	44.6	66.1	31.6	38.4	27.5	54.1

[a] Refers to invertomer **A**, **C** or **F** in Scheme 5.



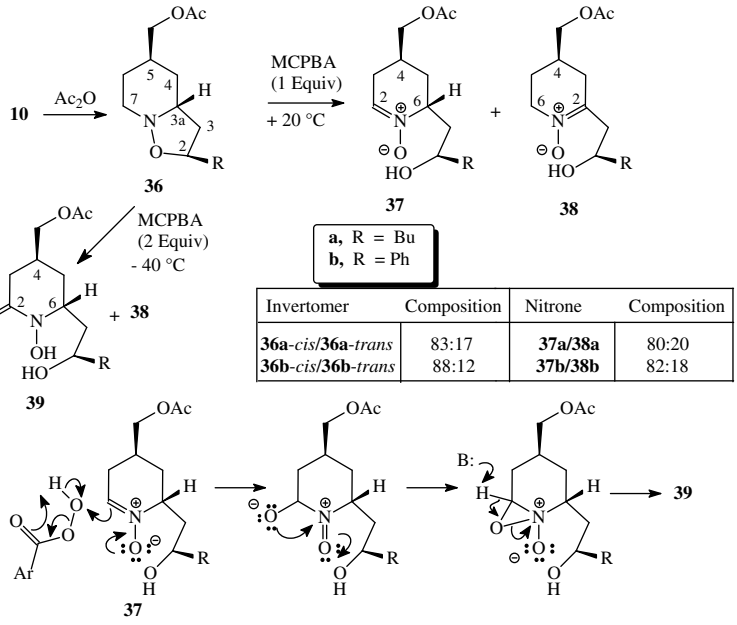
Scheme 5.

placement of an axially oriented tertiary substituent (akin to a *t*-butyl group) at C_{3a}. The correctness of the assignment of the configuration is based on the rationale detailed in the subsequent discussion.

The C(2)H of the cis invertomers of 6/5-fused isoxazolidines is known to appear at higher frequency compared to its trans invertomers.[17,18] This is indeed found to be the case for the current compounds in $CDCl_3$; the C(2)H of the *cis*-**A** invertomers invariably appeared at higher frequency compared to their *trans*-**C** isomers (Scheme 5). The axially disposed C(3a)H of *trans*-**C**, as expected, appeared at lower frequency in comparison to the corresponding equatorially disposed proton of *cis*-**A** (See Experimental). The axial substituent at C(3a) of the cis conformer **A** will have γ–*gauche* interactions with C(5) and C(7) and as such these carbon signals are expected[19] to be shielded in comparison to the *trans*-**C** as is evident from table. In *cis*-**A** all the carbons appeared at lower frequency except C-2 and C-6.

Where only one invertomer is observed as in the cases of **12a**, **12b**, **24**, **27b** (the minor products obtained via β-mode of attack), the C(2), C(3), C(3a), and C(7) chemical shifts match those of the *trans*-**C** invertomers, and we can therefore conclude that these compounds exist almost exclusively in the *trans*-**F** conformation (Scheme 5) (Table 1). The presence of 1,3-diaxial interaction excludes the participation of conformer *cis*-**D** in the equilibration process (Scheme 5). In the absence of **D**⇌**E** equilibration, the stabilization arising out of entropy gain will be lost, as such the all equatorial trans invertomer **F** is expected to be overwhelmingly favored over *cis*-**E**.

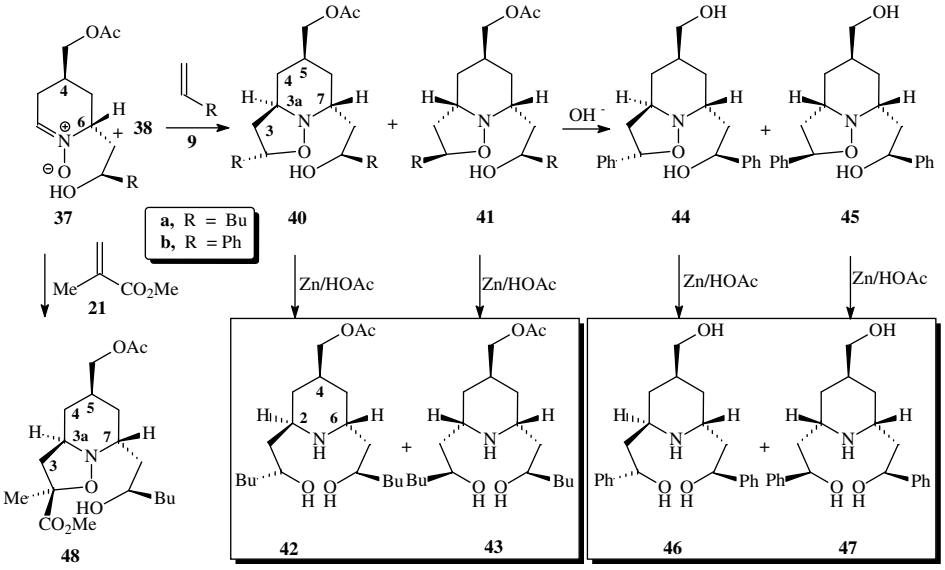
To get an idea about the magnitude of nitrogen inversion barriers in these compounds, **10b** was selected as a representative



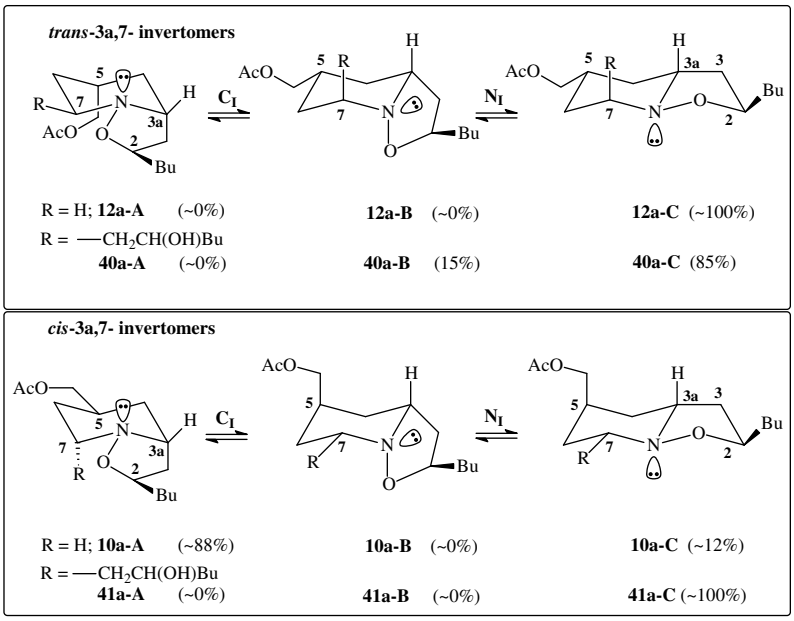
Scheme 6.

example. The nitrogen inversion barrier, $\Delta G^{\#}$, was determined to be 71.3 kJ/mol for a major to minor inversion at 35 °C in toluene-d_8. Simulations of exchange-affected proton spectra, corresponding to two non-coupled sites exchange with unequal populations, were carried out as described elsewhere.[17] For **10b** in toluene-d_6, the C(2)H signals at δ 5.42 (major, dd, J 1.7, 4.9 Hz) and 5.28 ppm (minor) in a 83:17 ratio at +30 °C were utilized. For such a high free energy of activation barrier, the extremely fast peracid oxidation process (presumably with a lower activation barrier) is not expected to follow the Curtin–Hammett principle;[7] as such the trans and cis invertomers in a ratio of *x*:*y* should afford the keto- and aldonitrones, respectively, in a similar ratio. In order to ascertain the correctness of the assignment of the configuration of the invertomers, we carried out the peracid-induced ring opening of isoxazolidines **36a** and **36b** (Scheme 6). The isoxazolidine **36a**, having the cis and trans invertomers in a 83:17 ratio, on treatment with *m*-chloroperbenzoic acid (MCPBA) gave a mixture of the aldo- (**37a**) and ketonitrone (**38a**) in a 80:20 ratio. For the corresponding ring opening reaction of the isoxazolidine **36b**, having the cis and trans invertomers in a 88:12 ratio, a mixture of the aldo- (**37b**) and ketonitrone (**38b**) in a ratio of 82:18 was obtained. It is indeed gratifying to see the ratio in favor of the synthetically more useful second-generation aldonitrones. One interesting finding was that the treatment of the isoxazolidines **36** with two equivalents of MCPBA at −40 °C afforded the *N*-hydroxyamides **39**, presumably via further oxidation of the aldonitrones with peracid as shown in Scheme 6. The formation of amide thus paves the way to obtain acyclic compounds from the cyclic piperidine system via hydrolysis of the amide functionality in **39**.

Next, we explored the cycloaddition reaction of the second-generation nitrones **37** and **38** with the alkenes **9**. Under the reaction conditions, the ketonitrones remained inactive while the aldonitrones **37** afforded the cycloadducts **40** and **41** (Scheme 7). While the aldonitrone **37a** afforded **40a** and **41a** in a 2:1 ratio, the



Scheme 7.



Scheme 8.

corresponding ratio for **40b** and **41b** was found to be 1:1.5. For the addition of 1-hexene (**9a**) 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, while styrene (**9b**) prefers to approach the nitrone from its α-face. The face selectivity is modest in these additions; however, we are unable to rationalize the difference in the face selectivity observed in the addition reactions of these two alkenes. The stereochemistry of these addition reactions was confirmed by chemical conversion into the ring opened products by cleaving the N–O bond of the cycloadducts with zinc/acetic acid. The NMR spectra of the amine **43** ($C_{20}H_{39}NO_4$), obtained from adduct **41a**, confirmed its symmetric nature; as expected the ^{13}C NMR spectrum revealed the presence of 12 carbon signals, whereas the isomeric 2,6-*trans* substituted amine **42**, obtained from adduct **40a**, displayed 18 different carbon signals as a result of its unsymmetrical nature. (In the unsymmetrical amine the signals at δ 14.1 and 22.8 ppm belonged to two carbons in each case). The nonseparable mixture of adducts **40b** and **41b** upon hydrolysis was converted into a separable mixture of compounds **44** and **45**. The N–O bond cleavage of **45** afforded the symmetrical *cis* amine **47**, while **44** led to the unsymmetricl *trans* amine **46**.

Finally, we explored the face selectivity in the cycloaddition of the aldonitrone **37a** with 1,1-disubstituted alkene, methyl methacrylate (**21**). To our surprise, the addition was found to be highly face selective; adduct **48** and a nonseparable mixture of three minor adducts were obtained in a ratio of 88:12. The stereochemistry of the adduct was based on the approach of the alkene from the β-face of the nitrone to give 2,6-*trans* substituted adduct **48**. The assignment of stereochemistry was based on the observed stereochemistry of the addition reaction of the second-generation nitrones **37** to 1-hexene and styrene. In both cases the 3a,7-*trans* substituted adducts **40a** and **44** were found to have two invertomers, whereas the 3a,7-*cis* substituted adducts **41a** and **45** gave sharp NMR signals and revealed the presence of a single invertomer in each case. The major adduct **48** in the nitrone **37a**-methyl methacrylate addition reaction was also found to have a single invertomer and as such was assigned the 3a,7-*trans* configuration. The conformational analysis revealed that while the adduct **10a** remained as a mixture of two invertomers **A** and **C** in a ratio of 88:12 (vide supra), the presence of two axial groups in **A** and **B** forces the 3a,7-*cis* substituted adduct **41a** to remain exclusively in the invertomeric form of **41a**-**C** (Scheme 8). While the adduct **12a** remained exclusively in the invertomeric form of **12a**-**C** (vide supra), the 3a,7-*cis* substituted adduct **40a** remained in the invertomeric forms of **40a**-**B** and **40a**-**C** in a ratio of 28:72 (See Experimental). The presence of **40a**-**B** in sizable proportion is justified even though it has two axial groups; the additional *gauche* interaction between C(7)R and N–O in **40a**-**C** is absent in the conformer **40a**-**B**, thereby encouraging its presence.

A systematic study of the stereochemistry associated with the cycloaddition of a C(4)-substituted and second-generation C(4),(6)-disubstituted six-membered cyclic nitrones has been carried out for the first time. The remarkable *exo*/*endo*- and face selectivity observed in our study reflects the scope inherent in these important cycloaddition reactions. The study suggests that a bulkier tertiary substituent at C(4) may freeze the invertomer exclusively in the *cis*-fused form and thus would lead to the exclusive formation of the synthetically important second-generation aldonitrones via peracid-induced ring opening of the cycloadducts.

3. Experimental

3.1. 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. ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ using TMS as internal standard on a JEOL LA 500 MHz spectrometer. Mass spectra were recorded on a GC–MS system (Agilent Technologies, 6890 N). Silica gel chromatographic separations were performed with Silica gel 100 from Fluka Chemie AG (Buchs, Switzerland). Piperidine 4-carboxylic acid, 1-hexene, styrene, methyl methacrylate, methyl crotonate, *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. 4-Piperidinemethanol (**6**) was prepared from methyl ester of piperidine 4-carboxylic acid as described.[9]

Dimethyl methylenemalonate was prepared using the literature procedure.[10]

3.2. *N*-Hydroxy-4-piperidinemethanol (7)

To a stirring solution of amine **6** (15 g, 130 mmol) with methanol (200 mL) in presence of selenium dioxide (0.7 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 8 h. Sodium borohydride (2 g, 54 mmol) was added to the above mixture and stirring continued for 2 h. After removal of the solvent, the residual mixture was taken up in saturated K_2CO_3 solution (40 mL) and extracted with CH_2Cl_2/MeOH (9:1) (4×50 mL). The combined organic layers were 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 hydroxylamine **7** as a white solid (10.2 g, 60%). *m*/*z* 131 [M^+]; mp 103–104 °C (methanol/ether), (Found: C, 54.8; H, 9.9; N, 10.6. $C_6H_{13}NO_2$ requires C, 54.94; H, 9.99; N, 10.68%.); ν_{max} (KBr) 3226, 2963, 2911, 2856, 2830, 1656, 1480, 1446, 1383, 1276, 1242, 1133, 1103, 1037, and 996 cm^{-1}; δ_H (500 MHz, 9:1 $CDCl_3/CD_3OD$, +25 °C) 3.42–3.28 (4H, m, C2-H$_a$H$_e$, C6-H$_a$H$_e$, and CH_2O), 2.50–2.44 (2H, m, C2-H$_a$H$_e$, C6-H$_a$H$_e$), 1.81–1.31 (5H, m, C3-H_2, C4-*H*, C5-H_2); δ_C (500 MHz, 9:1 $CDCl_3/CD_3OD$, +25 °C) 66.6 (2C), 58.1, 37.2, 28.2 (2C). The hydroxylamine was partially soluble in $CDCl_3$, but soluble in a $CDCl_3/CD_3OD$ mixture.

3.3. 4-Hydroxymethyl-3,4,5,6-tetrahydropyridine 1-oxide (8)

To a solution of the hydroxylamine (5.24 g, 40 mmol) in EtOH or MeOH (50 mL) was added yellow HgO (18.0 g, 84 mmol) and the mixture was stirred using a magnetic stir bar at 35 °C for 2 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 the nitrone was assumed quantitative for the percent yield calculation in the subsequent cycloaddition reactions. δ_H (500 MHz, CD_3OD, +25 °C) 7.34–7.33 (1H, m), 3.87–3.72 (2H, m, C6-H_2), 3.57–3.45 (2H, m, CH_2O), 2.66–2.56 (1H, m, C3-H$_a$H$_e$), 2.30–2.20 (1H, m, C3-H$_a$H$_e$), 2.11–2.03 (1H, m, C5-H$_a$H$_e$), 1.97–1.87 (1H, m, C4-*H*), 1.83–1.71 (1H, m, C5-H$_a$H$_e$); δ_C (500 MHz, CD_3OD, +25 °C) 143.6, 65.6, 57.7, 32.3, 29.5, 26.2. The nitrone cannot be purified further since upon concentration it undergoes dimerization and other side reactions.

3.4. Reaction of nitrone 8 with 1-hexene (9a)

A solution of nitrone (10 mmol) in EtOH (40 mL) containing 1-hexene (**9a**) (6 mL) was heated at 90 °C for 24 h under N_2 in a closed vessel. After removal of the solvent and excess alkene, the residual crude mixture of cycloadducts was separated by chromatography over silica using 95:5 ether/methanol as eluant to give **10a** containing minor amount of **12a**. Continued elution gave a pure sample of the major adduct **10a** as a colorless liquid. The minor diastereomer **12a** was obtained in the pure form after repeated chromatography of the fraction containing the mixture of **10a** and **12a**. The combined yield of the cycloadducts was found to be (1.67 g, 78%).

The C(2) of the major adduct **10a** appeared at δ 4.38 (major invertomer) and 4.02 ppm (minor invertomer). The overlapping C(2)H signal for the isomer **12a** appeared at δ 4.06 ppm. The complete ^{1}H NMR analysis of the C(2)H of crude and the separated fraction revealed the ratio of the isomers **10a**–**13a** as 93: ~0:7: ~0, respectively.

*3.4.1. Major diastereomer **10a**.* (Found: C, 67.4; H, 10.7; N, 6.5. $C_{12}H_{23}NO_2$ requires C, 67.57; H, 10.87; N, 6.57%.); ν_{max} (neat) 3352, 2954, 2925, 2858, 1455, 1379, 1260, 1100, 1037, 963, and 765 cm^{-1}. The major and minor invertomers at 25 °C were found to be in a ratio of 88:12 as determined by integration of the C(2)H at δ 4.38 (major) and 4.02 (minor) ppm.

*3.4.1.1. Major invertomer of **10a**.* δ_H (500 MHz, $CDCl_3$, 25 °C) 4.42–4.34 (1H, m, C2-*H*), 3.66–3.58 (1H, m, C3a-*H*), 3.49–3.41 (2H, m, CH_2OH), 3.08 (1H, td, *J* 3.2, 10.4 Hz, C7-H$_a$H$_e$), 2.92 (1H, br, O*H*), 2.68 (1H, ddd, *J* 2.5, 10.3, 12.8 Hz, C7-H$_a$H$_e$), 2.35 (1H, dt, *J* 9.5, 11.9 Hz, C3-H$_a$H$_b$), 2.00–1.20 (12H, m, (CH_2)$_3$, C3-H$_a$H$_b$, C4-H_2, C5-*H*, C6-H_2), 0.90 (3H, t, *J* 6.8 Hz, *Me*); δ_C (500 MHz, $CDCl_3$, 25 °C) 77.3, 67.1, 59.4, 49.1, 35.4, 35.2, 32.5, 28.4, 28.1, 27.6, 22.7, 14.0.

*3.4.1.2. Minor invertomer **10a**.* Minor invertomer has the following non-overlapping signals: δ_H (500 MHz, $CDCl_3$, 25 °C) 4.07–3.97 (1H, m, C2-*H*), 3.64–3.60 (2H, m, CH_2OH), 3.33–3.27 (1H, m, C3a-*H*), 2.61–2.51 (1H, m, C7-H$_a$H$_e$), 2.04–1.94 (1H, m, C3-H$_a$H$_b$); δ_C (500 MHz, $CDCl_3$, 25 °C) 76.1, 63.2, 61.2, 50.7, 40.1, 35.0, 34.0, 30.1, 28.0, 25.6, 22.7, 14.0.

*3.4.2. Minor diastereomer **12a**.* The sharp proton and carbon signals at +25 °C or −30 °C indicated the presence of a single invertomer. Coluorless liquid (Found: C, 67.7; H, 10.9; N, 6.5. $C_{12}H_{23}NO_2$ requires C, 67.57; H, 10.87; N, 6.57%.); ν_{max} (neat) 3386, 2928, 2859, 1460, 1379, 1259, 1099, 1049, 1017, 898, and 779 cm^{-1}; δ_H (500 MHz, $CDCl_3$, +25 °C) 4.10–4.02 (1H, m, C2-*H*), 3.56–3.46 (2H, m, CH_2O), 3.51–3.43 (1H, m, C3a-*H*), 2.56–2.46 (1H, m, C7-H$_a$H$_e$), 2.30–2.20 (1H, m, C7-H$_a$H$_e$), 2.02–1.20 (13H, m, (CH_2)$_3$, C3-H_2, C4-H_2, C5-*H*, C6-H$_a$H$_e$, O*H*), 1.14 (1H, q, *J* 12.2 Hz, C6-H$_a$H$_e$), 0.90 (3H, t, *J* 6.8 Hz, *Me*); δ_C (500 MHz, $CDCl_3$, +25 °C) 76.6, 67.2, 65.7, 53.9, 39.8, 38.7, 35.0, 32.1, 28.0, 27.9, 22.7, 14.0.

3.5. Reaction of nitrone 8 with styrene (9b)

A solution of nitrone **8** (10 mmol) in EtOH (40 mL) containing styrene (4 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 of cycloadducts was separated by chromatography over silica using 95:5 ether/methanol as eluant to give **10b** containing minor amount of **12b**. Continued elution gave a pure sample of the major adduct **10b** as white crystals. Finally, a fraction containing **10b** and **11b** was obtained; repeated chromatography enriched the fraction to a ratio of 4:96 for the isomers **10b**/**11b**. The combined yield of the cycloadducts was found to be 1.98 g, 85%. The fraction containing the mixture of **10b** and **12b** was crystallized to separate the major adduct **10b**, while the mother liquor upon repeated chromatography gave the minor adduct **12b**.

A careful ^{1}H NMR ($CDCl_3$, −40 °C) analysis of the crude reaction mixture and the separated fractions revealed the presence of the isomers **10b**–**12b** in a ratio of 93:5:2: ~0, respectively. The C(2) of the major adduct **10b** appeared at δ 5.39 (major invertomer) and 5.02 ppm (minor invertomer). The corresponding proton for the isomer **11b** appeared at δ 5.23(1H, apparent t, *J* 8.5 Hz). The C(2)H signal for the isomer **12b** appeared as a dd (*J* 4.0, 9.8 Hz) at δ 5.05 ppm.

*3.5.1. Major diastereomer **10b**.* Mp 104–105 °C (ether/dichloromethane); *m*/*z* 233.1 [M^+]; (Found: C, 72.0; H, 8.1; N, 5.9. $C_{14}H_{19}NO_2$ requires C, 72.07; H, 8.21; N, 6.00%.); ν_{max} (KBr) 3406, 2925, 2844, 1450, 1380, 1308, 1253, 1090, 1052, 955, 768, 701, and 630 cm^{-1}. The major and minor invertomers at 25 °C were found to be in a ratio of 90:10 as determined by integration of the C(2)H. (The ratio becomes 93:7 at −40 °C).

*3.5.1.1. Major invertomer of **10b**.* δ_H (500 MHz, $CDCl_3$, +25 °C) 7.44–7.24 (5H, m, Ph), 5.39 (1H, dd, *J* 3.7, 9.8 Hz, C2-*H*), 3.88–3.80 (1H, m,

C3a-*H*), 3.54–3.42 (2H, m, CH_2OH), 3.26–3.18 (1H, td, *J* 3.3, 10.4 Hz, C7-H$_a$H$_e$), 2.82 (1H, ddd, *J* 2.2, 10.6, 12.8 Hz, C7-*H*$_a$H$_e$), 2.70 (1H, q, *J* 11.2 Hz, C3-*H*$_a$H$_b$), 2.50 (1H, br, O*H*), 2.05–1.60 (5H, m, C3-H$_a$*H*$_b$, C4-*H*$_2$, C5-*H*, C6-H$_a$*H*$_e$), 1.38–1.24 (1H, m, C6-*H*$_a$H$_e$); δ_C (500 MHz, $CDCl_3$, +25 °C) 142.3, 128.4 (2C), 127.6, 126.4 (2C), 78.9, 67.1, 59.9, 49.4, 38.8, 32.6, 28.3, 27.6.

3.5.1.2. Minor invertomer of ***10b****.* Minor invertomer has the following non-overlapping signals: δ_H (500 MHz, $CDCl_3$, +25 °C) δ 5.06–4.98 (1H, m, C2-*H*; at −40 °C the signal becomes a dd (*J* 4.2, 9.6 Hz)), 3.70–3.62 (2H, m, CH_2OH), 3.39–3.31 (1H, m, C3a-*H*), 2.38–2.26 (1H, m C3-*H*$_a$H$_b$); δ_C (500 MHz, $CDCl_3$, +25 °C) 141.6, 128.3 (2C), 127.7, 126.7 (2C), 77.7, 63.2, 61.7, 51.1, 43.2, 34.0, 30.1, 25.7.

3.5.2. Minor diastereomer ***11b****.* We were unable to obtain the distereomer **11b** in pure form even after repeated chromatography. Finally, a fraction containing adduct **11b** along with minor amount (~4%) of the isomer **10b** was analyzed. The proton and carbon signals at 25 °C or −40 °C indicated the presence of two invertomers for **11b** in a 84:16 ratio as indicated by the C(2)H ($CDCl_3$, −40 °C) at δ 5.28 (1H, t, *J* 8.5 Hz) and 5.10 (1H, t, *J* 8.4 Hz). The invertomer ratio becomes 80:20 at +25 °C. Colorless liquid; (Found: C, 71.9; H, 8.3; N, 6.1. $C_{14}H_{19}NO_2$ requires C, 72.07; H, 8.21; N, 6.00%.); ν_{max} (neat) 3336, 2921, 2859, 1448, 1355, 1279, 1258, 1094, 1034, 961, 756, 700, and 673 cm^{-1}.

3.5.2.1. Major invertomer of ***11b****.* δ_H (500 MHz, $CDCl_3$, 25 °C) 7.52–7.20 (5H, m, Ph), 5.24 (1H, t, *J* 8.5 Hz, C2-*H*), 3.90–3.78 (1H, m, C3a-*H*), 3.53–3.41 (2H, m, CH_2OH), 3.27 (1H, td, *J* 3.7, 11.0 Hz, C7-H$_a$*H*$_e$), 2.73 (1H, t, *J* 12.2 Hz, C7-*H*$_a$H$_e$), 2.59–2.47 (1H, m, C3-*H*$_a$H$_b$), 2.38 (1H, q, *J* 12.2 Hz, C3-H$_a$*H*$_b$), 2.09 (1H, apparent d, *J* 14.6 Hz, C6-H$_a$*H*$_e$), 1.85–1.57 (4H, m, C4-*H*$_2$, C5-*H*, O*H*), 1.31 (1H, apparent q, *J* 12.2 Hz, C6-*H*$_a$H$_e$); δ_C (500 MHz, $CDCl_3$, +25 °C) 143.2, 128.3 (2C), 127.1, 125.6 (2C), 81.7, 67.3, 60.7, 52.0, 38.3, 33.0, 28.4, 27.7.

3.5.2.2. Minor invertomer of ***11b****.* δ_C (500 MHz, $CDCl_3$, +25 °C) 143.2, 128.3 (2C), 127.1, 125.6 (2C), 78.9, 63.6, 62.5, 51.3, 44.2, 33.9, 29.8, 25.7.

3.5.3. Minor diastereomer ***12b****.* Colorless liquid; (Found: C, 71.8; H, 8.0; N, 5.8. $C_{14}H_{19}NO_2$ requires C, 72.07; H, 8.21; N, 6.00%.). The signals were sharp; the ^{1}H spectrum revealed the presence of a single invertomer. ν_{max}(neat) 3356, 2921, 2849, 1449, 1364, 1324, 1260, 1099, 1051, 1011, 948, 912, 760, 730, and 699 cm^{-1}; δ_H (500 MHz, $CDCl_3$, +25 °C) 7.47–7.23 (5H, m, Ph), 5.05 (1H, dd, *J* 4.9, 9.8 Hz, C2-*H*), 3.54 (3H, m, C3a-*H*, CH_2OH), 2.68 (1H, apparent t, *J* 9.8 Hz, C7-H$_a$*H*$_e$), 2.60–2.50 (1H, m C7-*H*$_a$H$_e$), 2.37 (1H, q, *J* 11.0 Hz, C3-*H*$_a$H$_b$), 2.23–2.15 (1H, m, C3-H$_a$*H*$_b$), 2.08 (1H, d, *J* 12.2 Hz, C4-H$_a$*H*$_e$), 2.01–1.89 (2H, m, C4-*H*$_a$H$_e$, O*H*), 1.76–1.64 (1H, m, C5-*H*), 1.48 (1H, dq, *J* 3.7, 13.4 Hz, C6-H$_a$*H*$_e$), 1.21 (1H, q, *J* 12.2 Hz, C6-*H*$_a$H$_e$); δ_C (500 MHz, $CDCl_3$, +25 °C) 141.6, 128.4 (2C), 127.8, 126.7 (2C), 78.2, 66.9, 66.2, 54.0, 42.8, 38.6, 32.1, 27.9.

3.6. Lithium aluminum hydride reduction of ester cycloadduct 14–10b

To a stirred solution of ester adduct **14** of known configuration[9] (100 mg, 0.33 mmol) in ether (15 mL) was added lithium aluminum hydride (100 mg, 2.7 mmol) at room temperature. The reaction was completed in 10 min as indicated by TLC experiment (silica, ether). To the reaction mixture were added water (0.1 mL), 10% NaOH solution (0.1 g), and water (0.4 mL). The mixture was stirred for 1 h and was then decanted and the residue was washed with CH_2Cl_2. The organic layer was dried (Na_2SO_4), concentrated, and purified by silica gel chromatography using a 95:5 CH_2Cl_2/methanol as the eluant to give **10b** as a white solid (71 mg, 92%), which is identical in every respect to that obtained by cycloaddition reaction as mentioned in Section 3.5.1.

3.7. Lithium aluminum hydride reduction of ester cycloadduct 15a–12a

A sample of adduct **15a**[9] was reduced with $LiAlH_4$ using procedure as described in Section 3.6 to give **12a** as a coluorless liquid (93% yield), which is identical in every respect to that obtained by cycloaddition reaction as mentioned in Section 3.4.2.

3.8. Lithium aluminum hydride reduction of ester cycloadduct 15b–12b

A sample of adduct **15b**[9] was reduced with $LiAlH_4$ using procedure as described in Section 3.6 to give **12b** as a colorless liquid (90% yield), which is identical in every respect to that obtained by cycloaddition reaction as mentioned in Section 3.5.3.

3.9. Reaction of nitrone 8 with methyl crotonate (16)

A solution of nitrone **8** (5.0 mmol) in EtOH (20 mL) containing methyl crotonate (**16**) (4 mL) was heated at 90 °C for 10 h under N_2 in a closed vessel. After removal of the solvent and excess alkene the residual crude mixture of cycloadducts was purified by chromatography over silica using 95:5 ether/methanol as eluant to give a nonseparable mixture of adducts **17**–**19** as a colorless liquid (0.974 g, 85%). We were unable to separate the isomers even after repeated chromatography. (Found: C, 57.5; H, 8.2; N, 6.0. $C_{11}H_{19}NO_4$ requires C, 57.63; H, 8.35; N, 6.11%.); ν_{max} (neat) 3380, 2929, 2855, 1730, 1439, 1392, 1379, 12.97, 1265, 1203, 1179, 1113, 1090, and 1029 cm^{-1}.

A careful ^{1}H NMR ($CDCl_3$, −40 °C) analysis of the crude reaction mixture and the separated fractions revealed the presence of the isomers **17**–**19** in a respective ratio of 81:16:3. The C(2) of the major adduct **17** appeared at δ 4.50 (quint, *J* 5.8 Hz, major invertomer) and 5.01 ppm (quint, *J* 6.1 Hz, minor invertomer) in a 65:35 ratio. The ratio becomes 60:40 at +25 °C. The corresponding proton of the isomers **18** and **19** appeared at δ 4.41 (qd, *J* 6.5, 8.9 Hz, single invertomer), and 4.29 (quint, *J* 6.1 Hz, single invertomer). The CO_2Me singlets of the **17** appeared at δ 3.75 (major invertomer), and 3.79 (minor invertomer) and that of **18** appeared at 3.77 ppm. The C(2)Me ($CDCl_3$, +25 °C) signal for the isomer **17**, **18**, and **19** appeared at δ 1.33 (d, *J* 6.4 Hz), 1.50 (d, *J* 6.4 Hz), and 1.44 (d, *J* 6.4 Hz), respectively.

3.9.1. Major invertomer of major diastereomer ***17****.* δ_C (500 MHz, $CDCl_3$, +25 °C) 172.1, 75.2, 64.5, 62.9, 57.1, 52.3, 51.3, 33.6, 27.1, 25.2, 19.3.

3.9.2. Minor invertomer of major diastereomer ***17****.* δ_C (500 MHz, $CDCl_3$, +25 °C) 173.6, 75.7, 66.6 (CH_2O), 62.4, 56.7, 51.8 (OMe), 48.6, 32.7, 26.5, 26.0, 19.5.

3.9.3. Minor diastereomer ***18****.* A single invertomer: δ_C (500 MHz, $CDCl_3$, +25 °C) 171.8, 80.2, 66.6 (CH_2O), 64.0, 54.4, 52.8, 52.3, 33.0, 27.4, 27.2, 22.7.

3.10. Reaction of nitrone 8 with methyl methacrylate (21)

A solution of nitrone **8** (5.0 mmol) in EtOH (20 mL) containing methyl methacrylate (**21**) (4 mL) was heated at 50 °C for 6 h under N_2 in a closed vessel. After removal of the solvent and excess alkene the residual crude mixture of cycloadducts was separated by chromatography over silica using 95:5 ether/methanol as eluant to give **24** containing minor amount **22**. Continued elution afforded **22**

along with minor amounts of **23** and **24**. The first fraction was rechoramatographed to obtain **24** as a colorless liquid. Adduct **22** was obtained from the second fraction as white crystals by crystallization. The mother liquor contained a mixture of **22**–**24**. The combined yield of the cycloadducts was found to be 1.05 g, 92%. The ^{13}C ($CDCl_3$, −40 °C) spectrum of the crude mixture revealed the presence of C(2) of the major and minor invertomers of **22** at δ 84.2 and 79.8 ppm in a 80:20 ratio. The corresponding signal for the isomer **24** appeared as a sole invertomer at 80.33, while the signals at δ 84.8 and 80.6 in a respective ratio of 65:35 were assigned to C(2) of the major and minor invertomers of **23**. The ratio, as approximated, by analysis of ^{13}C and ^{1}H of the crude as well as the separated fraction revealed the presence of **22**, **23**, and **24** in ratio of 92:5:3, respectively. We were unable to obtain a pure sample of the minor isomer **23** even after repeated chromatography.

*3.10.1. Major diastereomer **22**.* The major and minor invertomers at 25 °C were found to be in a ratio of 80:20 as determined by integration of several non-overlapping signals (the ratio remains the same at −40 °C). Mp 72–73 °C (ether/dichloromethane); *m*/*z* 229 [M^+]; (Found: C, 57.5; H, 8.3; N, 6.1. $C_{11}H_{19}NO_4$ requires C, 57.62; H, 8.35; N, 6.11%); ν_{max} (KBr) 3337, 3234, 2953, 2926, 2862, 1746, 1727, 1454, 1442, 1370, 1300, 1255, 1127, 1183, 1086, 1026, 980, 962, 770, and 631 cm^{-1}.

*3.10.1.1. Major invertomer of **22**.* δ_H (500 MHz, $CDCl_3$, +25 °C) 3.78 (3H, s, CO*Me*), 3.69–3.61 (1H, m, C3a-*H*), 3.53–3.42 (2H, m, CH_2OH), 3.16 (1H, d, *J* 7.5 Hz, C7-H$_a$H$_e$), 2.87 (1H, t, *J* 11.7 Hz, C7-H$_a$H$_e$), 2.68 (1H, t, *J* 10.0 Hz, C3-H$_a$H$_b$), 2.10–1.50 (6H, m, C3-H$_a$H$_b$, C4-H_2, C5-*H*, C6-H$_a$H$_e$, O*H*), 1.49 (3H, s, *Me*), 1.35–1.19 (1H, m, C6-H$_a$H$_e$); δ_C ($CDCl_3$, +25 °C) 175.5, 84.3, 67.1, 59.9, 52.7, 50.2, 39.6, 32.6, 27.9, 27.5, 25.7.

*3.10.1.2. Minor invertomer of **22**.* Minor invertomer has the following non-overlapping signals: δ_H (500 MHz, $CDCl_3$, +25 °C): δ 3.39–3.30 (1H, m, C3a-*H*), 2.64–2.53 (1H, m, C7-H$_a$H$_e$), 2.50–2.35 (1H, m, C7-H$_a$H$_e$), 2.18–2.07 (1H, m, C3-H$_a$H$_b$); δ_C ($CDCl_3$, +25 °C) 175.5, 80.0, 63.3, 61.6, 52.7, 51.2, 44.9, 33.7, 29.5, 25.3, 24.8.

*3.10.2. Minor diastereomer **24**.* Colorless liquid. (Found: C, 57.4; H, 8.2; N, 5.9. $C_{11}H_{19}NO_4$ requires C, 57.62; H, 8.35; N, 6.11%.). The ^{1}H spectrum revealed the presence of a single invertomer. ν_{max} (neat) 3350, 2924, 2853, 1730, 1445, 1373, 1260, 1210, 1142, 1040, and 986 cm^{-1}; δ_H (500 MHz, $CDCl_3$, +25 °C) 3.77 (3H, s, CO*Me*), 3.58–3.46 (3H, m, C3a-*H*, CH_2OH), 2.58–2.48 (1H, m, C7-H$_a$H$_e$), 2.47–2.35 (2H, m, C7-H$_a$H$_e$, O*H*), 2.20–2.12 (1H, m, C3-H$_a$H$_b$), 2.07–1.97 (1H, m, C3-H$_a$H$_b$), 1.92–1.82 (1H, m, C5-*H*), 1.73–1.60 (2H, m, C4-H$_a$H$_e$, C6-H$_a$H$_e$), 1.50 (3H, s, *Me*), 1.48–1.40 (1H, m, C4-H$_a$H$_e$), 1.16 (1H, q, *J* 11.9 Hz, C6-H$_a$H$_e$); δ_C (500 MHz, $CDCl_3$, +25 °C) 175.6, 80.5, 67.2, 66.1, 54.1, 52.6, 44.6, 38.4, 31.6, 27.5, 24.7.

3.11. Reaction of nitrone 8 with dimethyl methylenemalonate (26) and conversion of cycloadducts 27a and 28a to silylated ethers 27b and 28b

A solution of nitrone **8** (10 mmol) in methanol (40 mL) was reacted with dimethylmethylene malonate (**26**) (1.73 g, 12 mmol) at 20 °C for 1 h. After removal of the solvent by blowing a gentle stream of N_2, the residual liquid was dried under vacuum to a constant weight (3 g). Extensive decomposition happened during silica gel chromatography to separate and purify the cycloadducts **27a** and **28a**. As such, the crude products were silylated using the following procedure. To a solution of the crude adducts **27a** and **28a** (~10 mmol) in DMF (25 mL) was added imidazole (2.7 g, 40 mmol). A solution of *tert*-butyldimethylsilyl chloride (2.1 g, 14 mmol) in DMF (10 mL) was added dropwise to the above mixture at 0 °C over a period of 15 min the reaction mixture, after stirring at 0 °C for 1 h, was allowed to warm to 20 °C and stirring continued for an additional 4 h. The mixture was taken up in ether (50 ml) and washed with water (3×50 mL). The organic layer was dried over $MgSO_4$, concentrated and the residual liquid was chromatographed over silica gel using hexane/ether as the eluent to give **27b** as a white solid. Continued elution afforded a mixture of **27b** and **28b**, and finally, the isomer **28b** as a coluorless liquid. The approximate ratio of **27b** and **28b** was found to be 3:1. The overall yield for the two steps was determined to be (3.18 g, 82%).

*3.11.1. Major diastereomer **27b**.* Both the ^{1}H and ^{13}C NMR spectra in $CDCl_3$ revealed the presence of a single invertomer. Mp 45–46 °C (ether/hexane); (Found: C, 55.7; H, 8.5; N, 3.6. $C_{18}H_{33}NO_6Si$ requires C, 55.79; H, 8.58; N, 3.61%.); ν_{max} (KBr) 2953, 2927, 2855, 1741, 1460, 1435, 1257, 12.05, 1104, 1005, 836, and 776 cm^{-1}; δ_H (500 MHz, $CDCl_3$, +25 °C) 4.56 (1H, d, *J* 8.8 Hz, C2-H$_a$H$_b$), 4.21 (1H, d, *J* 8.8 Hz, C2-H$_a$H$_b$), 3.78 (3H, s, CO*Me*), 3.77 (3H, s, CO*Me*), 3.53–3.48 (1H, m, C3a-*H*), 3.47–3.42 (2H, m, CH_2OSi), 2.88 (1H, dd, *J* 2.4, 11.7 Hz, C7-H$_a$H$_e$), 2.50 (1H, ddd, *J* 2.9, 9.5, 12.3 Hz, C7-H$_a$H$_e$), 2.12 (1H, apparent d, *J* 13.1 Hz, C4-H$_a$H$_b$), 1.83 (1H, apparent d, *J* 14.0 Hz, C6-H$_a$H$_e$), 1.68–1.60 (1H, m, C5-*H*), 1.41 (1H, dq, *J* 4.0, 12.5 Hz, C4-H$_a$H$_b$), 1.03 (1H, q, *J* 11.9 Hz, C6-H$_a$H$_e$), 0.87 (9H, s, C*Me*$_3$), 0.031 (6H, s, *Me*$_2$); δ_C (500 MHz, $CDCl_3$, +25 °C) 170.2, 168.9, 71.8, 71.6, 67.0, 54.5, 53.3, 52.9, 52.8, 38.3, 29.3, 27.3, 25.9 (3C), 18.3, (-) 5.4 (2C).

*3.11.2. Minor diastereomer **28b**.* (Found: C, 55.6; H, 8.5; N, 3.5. $C_{18}H_{33}NO_6Si$ requires C, 55.79; H, 8.58; N, 3.61%.). The ^{13}C NMR spectrum revealed the presence of two invertomers in a 84:16 ratio. ν_{max} (neat) 2954, 2928, 2855, 1766, 1754, 1746, 1738, 1731, 1470, 1462, 1454, 1434, 1251, 1203, 1135, 1108, 1083, 1044, 1005, 837, and 776 cm^{-1}; δ_H (500 MHz, $CDCl_3$, +25 °C) 3.28–3.83 (10H, m, including several CO_2*Me* singlets), 2.30–2.90 (2H, m), 1.50–2.03 (5H, m), 0.87 (9H, s, C*Me*$_3$), 1.29–1.15 (1H, m, C6-H$_a$H$_e$), 0.034 (3H, s, *Me*), 0.031 (3H, s, *Me*).

*3.11.2.1. Major invertomer of **28b**.* δ_C (500 MHz, $CDCl_3$, +25 °C) 170.3, 168.9, 87.0, 67.1, 60.3, 53.3 (2C), 50.9, 38.1, 32.7, 27.7, 27.6, 25.9 (3C), 18.3, (-) 5.4 (2C).

*3.11.2.2. Minor invertomer of **28b**.* δ_C (500 MHz, $CDCl_3$, +25 °C) 170.3, 168.9, 83.3, 63.5, 61.7, 53.3, 52.7, 51.4, 42.7, 33.3, 29.5, 25.9 (3C), 25.3, 18.3, (-) 5.4 (2C).

3.12. Thermolysis of 27b in toluene-d_6

A solution of the adduct **27b** (20 mg) in toluene-d_6 was thermolyzed at 90 °C. After 30 min of heating the ratio of **27b** and **28b** became 77:23, while the ratio became72:28 after 2 h at 90 °C and thereafter remained unchanged. The CO_2Me of **27b** appeared at δ 3.29 and 3.35 ppm, while that of **28b** appeared at 3.32 and 3.39 ppm. The C(3a) proton of the **28b** appeared at δ 3.70, while the C(2) Hs appeared at 4.83 (1H, d, *J* 8.6 Hz), 4.20 (1H, *J* 8.6 Hz).

3.13. Thermolysis of 27b in toluene in the presence of styrene (9b)

A solution of **27b** (400 mg, 1.03 mmol), styrene (1.5 mL) in toluene (5 mL) was stirred under N_2 at 100 °C overnight. After removal of the solvent and excess alkene, residual liquid was chromatographed over silica gel using hexane/ether as the eluent to give **30** as a white solid. Continued elution afforded a mixture of **30**–**32**. The yield was found to be 83% (0.297 g). The crude mixture revealed the presence of three adducts as revealed by the presence of C(2)H of **29** at δ 5.40 (major invertomer) and 5.02 (minor invertomer), **31** at 5.23 (1H, t, *J* 8.7 Hz, major invertomer) and 5.10 (minor invertomer, overlapping), and **32** at 5.10.

In order to determine the structure and composition of **30**–**32**, a portion of the above crude adducts was hydrolyzed with 5:1 MeOH/HCl at 20 °C (10 min) to **10b**–**13b**. ^{1}H NMR ($CDCl_3$, −30 °C) analysis of the crude hydrolyzed products revealed the presence of three isomers **10b**–**12b**, hence **30**–**32**, in a ratio of 94:3:3 as indicated by integration of the C(2)H signals as described (Section 3.5).

*3.13.1. Major adduct **30**.* Mp 80–81 °C (ether/pentane); (Found: C, 68.9; H, 9.4; N, 3.9. $C_{20}H_{33}NO_2Si$ requires C, 69.11; H, 9.57; N, 4.03%.); ν_{max} (KBr) 2928, 2888, 2855, 1459, 1386, 1361, 1253, 1115, 1077, 1044, 1006, 834, 763, 703 and 661 cm^{-1}. The major and minor invertomers at 25 °C were found to be in a ratio of 86:14 as determined by integration of the C(2)H. (The ratio becomes 93:7 at −40 °C).

*3.13.1.1. Major invertomer **30**.* δ_H (500 MHz, $CDCl_3$, 25 °C) 7.37–7.25 (5H, m, Ph), 5.40 (1H, dd, *J* 3.6, 9.8 Hz, C2-*H*), 3.85–3.75 (1H, m, C3a-*H*), 3.51–3.41 (2H, m, CH_2OSi), 3.26–3.20 (1H, m, C7-H$_a$H$_e$), 2.83 (1H, ddd, *J* 2.6, 10.4, 13.1 Hz, C7-*H*$_a$H$_e$), 2.73 (1H, dt, *J* 10.0, 11.9 Hz, C3-*H*$_a$H$_b$), 1.50–2.00 (5H, m, C3-H$_a$*H*$_b$, C4-*H*$_2$, C5-*H*, C6-H$_a$*H*$_e$), 1.32–1.20 (1H, m, C6-*H*$_a$H$_e$), 0.89 (9H, s, C*Me*$_3$), 0.03 (6H, s, *Me*$_2$); δ_C (500 MHz, $CDCl_3$, 25 °C) −5.4 (2C), 18.3, 25.9 (3C), 27.7, 28.3, 32.7, 38.9, 49.5, 60.0, 67.5, 78.8, 126.4 (2C), 127.5, 128.4 (2C), 142.5.

*3.13.1.2. Minor invertomer **30**.* δ_H(500 MHz, $CDCl_3$, 25 °C). Minor invertomer has the following non-overlapping signals: δ 5.02 (1H, dd, *J* 4.3 and 9.0 Hz, C2-*H*, broad dd at 25 °C became sharp at −40 °C), 3.58–3.52 (1H, m, C3a-*H*), 3.33–3.27 (2H, m); δ_C (500 MHz, $CDCl_3$, 25 °C) 142.3, 128.4 (2C), 127.6, 126.8 (2C), 77.7, 63.8, 61.9, 51.2, 43.3, 33.8, 30.2, 25.6, 25.9 (3C), 15.0, −5.4 (2C).

3.14. Conversion 10a into its acetate 36a

The cycloadduct **10a** (1.28 g, 6.0 mmol) in CH_2Cl_2 (10 mL) was treated with acetic anhydride (3 mL) at 25 °C for overnight. After removal of the solvent and excess acetic anhydride the residual liquid was purified by chraomatography over silica gel using ether as eluant to give **36a** as a colorless liquid (1.46 g, 95%). (Found: C, 65.9; H, 9.8; N, 5.4. $C_{14}H_{25}NO_3$ requires C, 65.85; H, 9.87; N, 5.49%.); ν_{max} (neat) 2955, 2929, 2857,1742,1454, 1366, 1244, 1036, and 963 cm^{-1}. The ^{1}H NMR spectrum revealed the presence of two invertomers in a ratio of 83:17.

*3.14.1. Major invertomer of **36a**.* δ_H (500 MHz, $CDCl_3$, +25 °C) 4.43–4.37 (1H, m, C2-*H*), 3.92 (2H, ABX, *J* 6.4, 10.7 Hz, CH_2OAc), 3.60 (1H, apparent quint, *J* 5.8 Hz, C3a-*H*), 3.11 (1H, td, *J* 3.4, 10.4 Hz, C7-H$_a$H$_e$), 2.69 (1H, ddd, *J* 2.6, 10.4, 12.9 Hz, C7-*H*$_a$H$_e$), 2.33 (1H, dt, *J* 9.4, 11.9 Hz, C3-*H*$_a$H$_b$), 2.06 (3H, s, CO*Me*), 2.00–1.80 (2H, m, C3-H$_a$*H*$_b$, C5-*H*), 1.78–1.68 (2H, m, C4-H$_a$*H*$_e$, C6-H$_a$*H*$_e$), 1.63–1.53 (1H, m, C4-*H*$_a$H$_e$), 1.55–1.45 (1H, m, C6-*H*$_a$H$_e$), 1.43–1.23 (6H, m, (CH_2)$_3$Me), 0.90 (3H, t, *J* 7.0 Hz, *Me*); δ_C (500 MHz, $CDCl_3$, +25 °C) 171.0, 77.3, 68.3, 59.1, 48.8, 35.3, 35.2, 29.5, 28.3, 28.1, 27.6, 22.7, 20.9, 14.0.

*3.14.2. Minor invertomer of **36a**.* δ_H ($CDCl_3$, +25 °C) non-overlapping signals at 4.13–4.09 (2H, m, CH_2OAc), 4.06–4.01 (1H, m, C2-H), 3.32–3.26 (1H, m, C3a-H), 2.62–2.54 (1H, m), 2.03 (3H, s, CO*Me*); δ_C (500 MHz, $CDCl_3$, +25 °C) 173.8, 76.1, 65.0, 61.0, 50.7, 40.0, 34.9, 30.5, 30.4, 28.0, 25.8, 22.7, 21.1, 4.0.

3.15. Conversion 10b into its acetate 36b

The cycloadduct **10b** (1.40 g, 6.00 mmol) in toluene (10 mL) was treated with acetic anhydride (1 mL) at 70 °C for 3 h. After removal of the solvent and excess acetic anhydride the residual liquid was purified by chromatography over silica gel using 60:40 hexane/ether as eluant to give **36b** as white crystals (1.58 g, 96%). Mp 97–98 °C (hexane/ther); *m*/*z* 275 [M$^+$]; (Found: C, 69.6; H, 7.6; N, 5.0. $C_{16}H_{21}NO_3$ requires C, 69.79; H, 7.69; N, 5.09%.); ν_{max} (KBr) 3028, 2952, 2919, 2854, 1741, 1456, 1366, 1245, 1035, 946, 903, 765, 708, 670, and 644 cm^{-1}. The major and minor invertomers of **36b** at 25 °C were found to be in a ratio of 88:12 as determined by integration of the C(2)H.

*3.15.1. Major invertomer of **36b**.* δ_H (500 MHz, $CDCl_3$, 25 °C) 7.37–7.25 (5H, m, Ph), 5.41 (1H, dd, *J* 3.7, 9.8 Hz, C2-*H*), 3.95 (2H, ABX, *J* 6.1, 6.4, 10.7 Hz, CH_2OAc), 3.88–3.83 (1H, m, C3a-*H*), 3.24 (1H, td, *J* 3.4, 10.4 Hz, C7-H$_a$H$_e$), 2.84 (1H, ddd, *J* 2.5, 10.4, 12.8 Hz, C7-*H*$_a$H$_e$), 2.73 (1H, apparent q, *J* 11.6 Hz, C3-*H*$_a$H$_b$), 2.07 (3H, s, CO*Me*), 1.75–2.15 (5H, m, C3-H$_a$*H*$_b$, C4-*H*$_2$, C5-*H*, C6-H$_a$*H*$_e$), 1.40 (1H, dq, *J* 2.2, 12.2 Hz, C6-*H*$_a$H$_e$); δ_C (500 MHz, $CDCl_3$, +25 °C) 171.0, 145.2, 128.5 (2C), 127.6, 126.4 (2C), 78.8, 68.2, 59.7, 49.1, 38.8, 29.6, 28.3,27.6, 20.9.

*3.15.2. Minor invertomer of **36b**.* Minor invertomer has the following non-overlapping signals: δ_H (500 MHz, $CDCl_3$, 25 °C) 5.02 (1H, dd, *J* 3.9 and 8.8 Hz, C2-*H*), 4.14 (2H, d, *J* 7.9 Hz, CH_2OAc), 3.42–3.37 (1H, m, C3a-*H*), 2.67–2.57 (1H, m), 2.33 (1H, apparent q, *J* 10.4 Hz), 1.74–1.65 (1H, m); δ_C (500 MHz, $CDCl_3$, 25 °C) 171.0, 141.5, 128.5 (2C), 127.9, 126.7 (2C), 77.7, 64.9, 61.6, 50.9, 43.1, 30.5 (2C), 25.9, 20.9.

3.16. MCPBA oxidation of adduct 36a to nitrones 37a and 38a. Cycloaddition of 37a with 1-hexene (9a)

To a stirred solution of the cycloadduct **36a** (3.0 mmol) in dichloromethane (30 mL) at 20 °C was added MCPBA (3.0 mmol) in one portion. After 30 m at 20 °C the organic layer was washed with 5% $NaHCO_3$ solution (3×10 mL). The combined aqueous layers were re-extracted with CH_2Cl_2 (3×25 mL). The combined organic layers were dried (Na_2SO_4), concentrated to give a mixture of the aldonitrone **37a** and ketonitrone **38a** in a ratio of 80:20, respectively, as a pale yellow liquid in almost quantitative yield. A small portion of the solution was concentrated for ^{1}H NMR analysis, which revealed the aldonitrone **37a** having the following characteristic signals at δ 7.18 (1H, t, *J* 3.5 Hz, CH=N), 4.24 (1H, m, =NCH), 2.08 (3H, s), 0.90 (3H, t, *J* 7.0 Hz). The ketonitrone **38a** has the following non-overlapping signals at δ 3.00 (1H, dd, *J* 9.6, 13.1 Hz), 2.17 (3H, s).

After exchanging CH_2Cl_2 with toluene (15 mL), the above solution of nitrones was treated with 1-hexene (**9a**) (5 mL) at 75 °C for 48 h. After removal of the solvent and excess alkene, the residual mixture was separated by chraomatography over silica gel using 1:1 hexane/ether as eluant to give the minor cycloadduct **41a** as a colorless liquid (220 mg, 21%). Continued elution afforded the major isomer **40a** also as a colorless liquid (423 mg, 40%). Finally, elution with 90:10 ether/methanol afforded the unreacted ketonitrone **38a** as a colorless liquid.

*3.16.1. Major cycloadduct **40a**.* (Found: C, 67.3; H, 10.2; N, 3.8. $C_{20}H_{37}NO_4$ requires C, 67.57; H, 10.49; N, 3.94%.); ν_{max} (neat) 3440, 2918, 2850, 1743, 1467, 1451, 1427, 1371, 1254, 1121, 1039, 901, 782, and 732 cm^{-1}. The ratio of the invertomers by ^{13}C was estimated to be 85:15.

*3.16.1.1. Major invertomer of **40a**.* δ_H (500 MHz, $CDCl_3$, −40 °C) 5.48 (1H, br s, O*H*), 4.13–4.05 (1H, m, C2-*H*), 3.95–3.83 (2H, m, CH_2OAc), 3.85–3.78 (1H, m, C3a-*H*), 3.74–3.66 (1H, m, C7-CH$_2$*CH*O), 3.57–3.49 (1H. m, C7-*H*), 2.10 (3H, s, CO*Me*), 1.10–2.05 (21H, m), 0.91 (6H, two overlapping t, *J* 7.0 Hz, CH$_2$*Me*, CH$_2$*Me*); δ_C (500 MHz, $CDCl_3$, −40 °C) 171.7, 75.3, 70.0, 68.6, 54.2, 53.0, 40.9, 36.3, 35.9 (2C), 29.0, 28.6, 28.5, 28.1, 26.9, 22.8, 22.6, 21.2, 14.3, 14.2.

*3.16.1.2. Minor invertomer of **40a**.* Minor invertomer has the following non-overlapping signals: δ_C (500 MHz, $CDCl_3$, −40 °C) 76.2, 68.0, 54.5, 39.3, 36.8, 34.9, 33.5, 32.8, 32.5, 30.3, 30.0, 27.9, 22.7.

*3.16.2. Minor cycloadduct **41a**.* The ^{1}H spectrum revealed the presence of a single invertomer. (Found: C, 67.4; H, 10.3; N, 3.8. $C_{20}H_{37}NO_4$ requires C, 67.57; H, 10.49; N, 3.94%.); ν_{max} (neat) 3430, 2954, 2927, 2858, 1742, 1466, 1451, 1433, 1370, 1237, 1036, 788, and 733 cm^{-1}; δ_H (500 MHz, $CDCl_3$, 25 °C) 3.80–4.15 (4H, m, C2-*H*, C*H*$_2$OAc, C3a-*H*), 2.98–2.90 (1H, m, C7-*H*), 2.48–2.36 (1H. m, C3-H_aH_b), 2.05 (3H, s, CO*Me*), 1.20–2.00 (21H, m), 0.90 (6H, two overlapping t, *J* 7.0 Hz, CH_2*Me*, CH_2*Me*); δ_C (500 MHz, $CDCl_3$, +25 °C) 171.1, 75.9, 68.4, 65.2, 61.0, 58.4, 40.1, 39.8, 37.4, 34.8, 31.3, 31.2, 29.9, 27.9 (2C), 22.7, 22.6, 20.9, 14.1, 14.0.

*3.16.3. Ketonitrone **38a**.* (Found: C, 61.7; H, 9.4; N, 5.2. $C_{14}H_{25}NO_4$ requires C, 61.97; H, 9.29; N, 5.16%.); ν_{max} (neat) 3366, 2955, 2929, 2858, 1738, 1446, 1367, 1245, 1193, 1150, and 1041 cm^{-1}; δ_H (500 MHz, $CDCl_3$, +25 °C) 6.13 (1H, Br O*H*), 4.05 (2H, apparent d, *J* 6.1 Hz, C*H*$_2$OAc), 3.96 (1H, m, C*H*OH), 3.96–3.84 (2H, m, C6-H_2), 3.04 (1H, dd, *J* 9.7, 12.9 Hz, C6-CH_aH$_b$CHOH), 2.73–2.57 (1H, m, C6-CH$_a$$H_b$CHOH), 2.36 (1H, apparent d, *J* 11.9 Hz, C3-H_aH_b), 2.28–2.20 (1H, m, C3-H$_a$$H_b$), 2.09 (3H, s, CO*Me*), 1.20–1.90 (9H, m), 0.91 (3H, t, *J* 6.7 Hz, *Me*); δ_C (500 MHz, $CDCl_3$, +25 °C) 170.8, 148.5, 71.8, 66.5, 57.0, 40.0, 38.4, 33.6, 30.0, 27.7, 25.7, 22.7, 20.8, 14.1.

3.17. MCPBA oxidation of adduct 36a to nitrones 37a and 38a. Cycloaddition of 37a with methyl methacrylate (21)

The mixture of nitrones **37a** and **38a** (prepared by MCPBA oxidation of **36a** (1.0 mmol) as described in Section 3.16) in CH_2Cl_2 (10 mL) was treated with methyl methacrylate (1.0 mL) and the mixture was stirred at 20 °C for overnight. The ketonitrone was unreactive under these conditions. After removal of the solvent and excess alkene, the residual liquid was separated by chromatography over silica gel using 97:3 ether/methanol as eluant to give the first fraction as a nonseparable mixture of three isomers as a colorless liquid (48 mg, 8.7%). Continued elution gave the second fraction containing the major adduct **48** as a colorless liquid (353 mg, 63%). Analysis of the first fraction revealed the presence three isomers as indicated by the ^{1}H NMR spectrum, which displayed C(2) methyl singlets at δ 1.45, 1.46, and 1.49 ppm in an approximate ratio of 1.5:1:1. The acetyl singlets appeared at 2.01, 2.02, and 2.03 ppm and the CO_2Me singlets appeared at 3.71, 3.74, and 3.75 ppm. The ratio of **48** and the combined minor isomers was thus found to be 88:12.

*3.17.1. Major adduct **48**.* (Found: C, 61.3; H, 8.9; N, 3.7. $C_{19}H_{33}NO_6$ requires C, 61.43; H, 8.95; N, 3.77%.); ν_{max} (neat) 3445, 2953, 2931, 2858, 1742, 1738, 1732, 1462, 1454, 1446, 1434, 1371, 1242, 1150, 1121, 1038, and 982 cm^{-1}. The major and minor invertomers of **48** at −40 °C were found to be in a ratio of 72:28 as determined by integration of several proton signals.

*3.17.1.1. Major invertomer of **48**.* δ_H (500 MHz, $CDCl_3$, −40 °C) 5.00 (1H, Br O*H*), 3.82 (3H, s, CO_2*Me*), 3.96–3.78 (4H, m, C*H*$_2$OAc, C7-CH$_2$C*H*O, C3a-*H*), 3.65–3.55 (1H, m, C7-*H*), 2.11 (3H, s, CO*Me*), 1.90–2.50 (5H, m), 1.50 (3H, s, C2-*Me*), 1.00–1.75 (10H, m), 0.91 (3H, t, *J* 6.7 Hz, CH_2*Me*); δ_C (500 MHz, $CDCl_3$, −40 °C) 173.8, 171.5, 80.5, 70.0, 68.3, 54.7, 53.1 (2C), 45.7, 36.6, 35.9, 32.1, 28.9, 28.4, 27.2, 25.9, 22.8, 21.2, 14.3.

*3.17.1.2. Minor invertomer of **48**.* The ^{1}H NMR (500 MHz, $CDCl_3$, −40 °C) revealed the following non-overlapping signals at: 3.79 (3H, s, CO_2*Me*), 2.89–2,82 (1H, m), 2.09 (3H, s, CO*Me*), 1.42 (3H, s, C2-*Me*); δ_C (500 MHz, $CDCl_3$, −40 °C) 175.8, 171.5, 79.8, 71.2, 68.3, 56.2, 55.5, 53.1, 44.3, 37.8, 35.9, 31.2, 30.0, 28.4, 27.8, 24.7, 22.6, 21.2, 14.3.

3.18. MCPBA oxidation of adduct 36a to lactam 39a

To a stirred solution of the cycloadduct **36a** (128 mg, 0.5 mmol) in dichloromethane (10 mL) at −40 °C was added MCPBA (1.1 mmol) in one portion. The reaction mixture was then stirred 10 min each at −40 °C, −20 °C, −0 °C, and 20 min at 20 °C. The organic layer was then washed with 5% $NaHCO_3$ solution (3×10 mL). The combined aqueous layers were re-extracted with CH_2Cl_2 (3×25 mL). The combined organic layers were dried (Na_2SO_4), concentrated and the residual mixture was purified by chromatography over silica gel using 90:10 ether/methanol as eluant to give the lactam **39a** as a liquid (110 mg, 77%). The crude spectrum revealed the presence of ketonitrone **38a** (~15%). However, the ketonitrone **38a** was not separated in this case. **39a:** *m*/*z* 288 [M$^+$+1]; (Found: C, 58.4; H, 8.6; N, 4.8. $C_{14}H_{25}NO_5$ requires C, 58.52; H, 8.77; N, 4.87%.); ν_{max} (KBr) 3380, 2954, 2930, 2870, 1743, 1642, 1632, 1468, 1454, 1416, 1371, 1315, 1246, 1046, and 731 cm^{-1}; δ_H (500 MHz, $CDCl_3$, +25 °C) 4.11–4.04 (1H, m, C6-*H*), 4.03–3.94 (2H, m, C*H*$_2$OAc), 3.92–3.84 (1H, m, C6-CH$_2$C*H*O), 2.57 (1H, dd, *J* 5.3, 17.2 Hz, C3-H$_a$$H_e$), 2.44–2.34 (1H, m, C6-CH$_a$$H_b$CHO), 2.23 (1H, dd, *J* 10.2, 17.2 Hz, C3-H_aH_e), 2.07 (3H, s, CO*Me*), 1.99–1.90 (2H, m, C6-CH_aH$_b$CHO, C4-*H*), 1.89–1.78 (1H, m, C5-H$_a$$H_e$), 1.75–1.65 (1H, m, C5-$H_aH_e$), 1.54–1.28 (6H, m, $(CH_2)_3$), 0.91 (3H, t, *J* 7.0 Hz, *Me*); δ_C (500 MHz, $CDCl_3$, +25 °C) 170.8, 163.7, 69.2, 66.6, 55.6, 41.2, 37.4, 33.6, 31.3, 28.5, 27.7, 22.6, 20.7, 14.0.

3.19. MCPBA oxidation of adduct 36b to nitrones 37b and 38b. Cycloaddition of 37b with styrene (9b) to cycloadducts 40b and 41b

To a stirred solution of the cycloadduct **36b** (3.0 mmol) was oxidized with MCPBA using procedure as described in Section 3.16 to give in dichloromethane (30 mL) at 20 °C was added MCPBA (3.0 mmol) in one portion. After 30 min at 20 °C the organic layer was washed with 5% $NaHCO_3$ solution (3×10 mL). The combined aqueous layers were re-extracted with CH_2Cl_2 (3×25 mL). The combined organic layers was dried (Na_2SO_4), concentrated to give a mixture of the aldonitrone **37b** and ketonitrone **38b** in a ratio of 82:18, respectively, as determined by ^{1}H NMR integration of several proton signals. A small portion of the solution was concentrated for ^{1}H NMR analysis, which revealed the aldonitrone **37b** having the following characteristic signals at δ 7.19 (1H, t, *J* 3.5 Hz, CH=N), 4.09 (1H, m, =NCH), 2.06 (3H, s), 3.97 (2H, d, *J* 61 Hz, CH_2O), 5.05 (1H, dd, *J* 3.6, 7.4 Hz). The NMR spectra of the ketonitrone **38b** are described later.

After exchanging the solvent CH_2Cl_2 with toluene (15 mL), the above solution of nitrones was treated with styrene (**9b**) (5 mL) at 60 °C for 48 h. After removal of the solvent and excess alkene, the residual mixture was analyzed by ^{1}H NMR analysis, which revealed the presence of two cycloadducts **40b** and **41b** as well as the unreacted ketonitrone **38b**. The **40b**/**41b** was found to be in a ratio of 40:60 as determined by integration of several proton signals at δ 3.16 (1H, m, major **41b**), 4.15 (2H, AB, CH_2O, major **41b**), 3.90 (2H, d, CH_2O, minor **40b**). The crude mixture of adducts were purified by chromatography over silica gel using 3:2 hexane/ether as eluant to give a nonseparable mixture of the cycloadducts **40b** and **41b** (in a ratio of 40:60) as a colorless liquid (830 mg, 70%). TLC analysis in several solvents revealed the nonseparability of the adducts by silica gel chromatography. The adduct mixture was not analyzed further, instead it was hydrolyzed by NaOH to a separable mixture of isomers **44** and **45** (See Section 3.20). Finally, elution with 80:20 ether/methanol afforded the unreacted ketonitrone **38b** as a white solid (122 mg, 14%).

*3.19.1. Ketonitrone **38b**.* Mp 98–99 °C (CH_2Cl_2/pentane), *m*/*z* 274 [M$^+$−*OH*]; (Found: C, 65.8; H, 7.3; N, 4.7. $C_{16}H_{21}NO_4$ requires C, 65.96; H, 7.27; N, 4.81%.); ν_{max} (KBr) 3146, 2953, 2919, 2857, 1735, 1615, 1485, 1448, 1419, 1363, 1243, 1187, 1144, 1056, 1030, 990, 915, 882, 834, 766, and 709 cm^{-1}, δ_H (500 MHz, $CDCl_3$, +25 °C) 7.30

(6H, Ph, O*H*), 5.17 (1H, dd, *J* 3.1, 8.0 Hz, PhC*H*O), 3.92–3.82 (4H, m, CH_2OAc, C6-H_2), 3.04 (1H, dd, *J* 2.2, 13.2 Hz, C2-CH_aH$_b$CHO), 2.94 (1H, dd, *J* 7.7, 13.2 Hz, C2-CH$_a$$H_b$CHO), 2.41 (1H, dd, *J* 5.5, 19.5 Hz, C3-H_aH$_b$), 2.13–2.03 (1H, m, C3-H$_a$$H_b$), 2.05 (3H, s, CO*Me*), 2.02–1.90 (1H, m, C4-*H*), 1.70 (1H, dd, *J* 9.7, 19.5 Hz, C5-H_aH$_b$),1.67–1.55 (1H, m, C5-H$_a$$H_b$); δ_C (500 MHz, $CDCl_3$, +25 °C) 170.6, 148.1, 144.3, 128.3 (2C), 127.3, 125.1 (2C), 73.7, 66.1, 56.7, 42.6, 33.9, 29.6, 25.3, 20.7.

3.20. Conversion of 40b and 41b into 44 and 45 by hydrolysis with NaOH

A solution of **40b** and **41b**, in a ratio of 40:60 (800 mg, 2.02 mmol) in methanol (5 mL) containing NaOH (100 mg, 2.5 mmol) was stirred at 20 °C for 10 min. The reaction was over as indicated by TLC experiment (silica, ether). The reaction mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers was dried (Na_2SO_4) and concentrated and the residual liquid was separated by chromatography over silica gel using ether as eluant to give **45** as a white solid (310 mg). Continued elution gave a mixture of adducts **44** and **45** (132 mg) and finally the pure adduct **44** (200 mg). The total yield of the hydrolyzed adducts was found to be 642 mg, 90%. The ratio of the hydrolyzed adducts **44** and **45** was found to be similar to the ratio of the starting acetylated adducts **40b** and **41b** as revealed by the ^{1}H NMR of the crude mixture.

*3.20.1. Minor diasteromer **44**.* Colorless liquid; *m*/*z* 353 [M$^+$]; (Found: C, 74.5; H, 7.5; N, 3.9. $C_{22}H_{27}NO_3$ requires C, 74.76; H, 7.70; N, 3.96%.); ν_{max} (neat) 3354, 3062, 3030, 2919, 1603, 1493, 1452, 1367, 1307, 1043, 952, 911, 858, 788, 700 cm^{-1}. The major and minor invertomers of **44** at −40°°C were found to be in a ratio of 87:13 as determined by integration of the benzylic proton signals.

*3.20.1.1. Major invertomer of **44**.* δ_H (500 MHz, $CDCl_3$, −40 °C) 7.37–7.21 (10H, m, Ph, Ph), 6.75 (1H, br, O*H*), 5.12–5.06 (2H, m, C2-*H*, PhC*H*OH), 3.75–3.65 (1H, m, C3a-*H*), 3.64–3.54 (1H, m, C7-*H*), 3.50–3.40 (2H, m, CH_2OH), 2.56–2.40 (4H, m, C3-H_2, C7-CH_aH$_b$CHO, O*H*), 1.92–1.80 (1H, m, C5-H), 1.74 (1H, apparent d, *J* 14.0 Hz, C7-CH$_a$$H_b$CHO), 1.63 (1H, apparent d, *J* 13.2 Hz, C4-H$_a$$H_e$), 1.55 (1H, dt, *J* 5.2, 13.2 Hz, C6-H$_a$$H_e$), 1.22 (1H, apparent q, *J* 12.2 Hz, C4-H_aH$_e$), 1.15 (1H, apparent d, *J* 12.2 Hz, C6-H_aH$_e$); δ_C (500 MHz, $CDCl_3$, -40 °C) 144.0, 143.3, 128.5 (2C), 128.2 (2C), 127.4, 126.6, 125.4 (2C), 125.3 (2C), 76.3, 72.2, 67.4, 54.9, 53.3, 44.4, 38.7, 32.1, 28.6, 26.6.

*3.20.1.2. Minor invertomer of **44**.* Minor invertomer of **44** has the following nonoverlaping signals: δ_H (500 MHz, $CDCl_3$, −40 °C) 4.90 (1H, m, C2-*H*), 4.88–4.80 (1H, m, PhC*H*OH), 3.92–3.84 (2H, m, C3a-*H*, C7-*H*), 3.01–2.89 (2H, m, C3-H_2), 2.46–2.38 (1H, m, C7-CH_aH$_b$CHO), 2.30–2.20 (1H, m, C7-CH_aH$_b$CHO), 1.10–1.00 (1H, m, C6-H_aH$_e$); δ_C (500 MHz, $CDCl_3$, −40 °C) 73.8, 66.5, 57.0, 42.4, 33.3, 33.0.

*3.20.2. Major diasteromer **45**.* *m*/*z* 353 [M$^+$]; mp 125–126 °C (ether/pentane). (Found: C, 74.8; H, 7.8; N, 3.9. $C_{22}H_{27}NO_3$ requires C, 74.76; H, 7.70; N, 3.96%.) ν_{max} (KBr) 3280, 3181, 3029, 2906, 1485, 1452, 1380, 1306, 1242, 1206, 1037, 910, 859, 799, 760, 699, 624, and 556 cm^{-1}. The ^{1}H spectrum revealed the presence of a single invertomer. δ_H (500 MHz, $CDCl_3$, 25 °C) 7.38–22 (10H, m, Ph, Ph), 5.11 (1H, dd, *J* 2.2, 10.2 Hz, C2-*H*), 5.07 (1H, dd, *J* 4.3, 9.5 Hz, PhC*H*OH), 4.36 (1H, br s, O*H*), 3.66 (2H, d, *J* 7.3 Hz, CH_2OH), 3.15–3.05 (1H, m, C7-*H*), 2.79–2.63 (1H, m, C3-H_aH$_b$), 2.35 (1H, apparent q, *J* 10.7 Hz, C3-H$_a$$H_b$), 1.70–2.30 (8H, m), 1.65 (1H, dt, *J* 5.1, 13.0 Hz, C6-H_aH$_e$); δ_C (500 MHz, $CDCl_3$, 25 °C) 144.8, 141.4, 128.5 (2C), 128.2 (2C), 127.8, 127.0, 126.6 (2C), 125.7 (2C), 77.4, 71.3, 63.6, 61.8, 59.0, 43.0, 42.7, 34.6, 31.2, 29.6.

3.21. MCPBA oxidation of adduct 36b to lactam 39b

The cycloadduct **36b** (0.5 mmol) was oxidized with MCPBA (1.1 mmol) using procedure as described in Section 3.18. Similar work up and chromatography afforded the lactam **39b** as a white solid (115 mg, 75%). ^{1}H NMR revealed the presence of ketonitrone **38b** (~15%). Mp 96–97 °C (ether); *m*/*z* 307 [M$^+$]; (Found: C, 62.4; H, 6.7; N, 4.5. $C_{16}H_{21}NO_5$ requires C, 62.53; H, 6.89; N, 4.56%.); ν_{max} (KBr) 3136, 3025, 2942, 2922, 2883, 1740, 1622, 1492, 1454, 1418, 1365, 1342, 1243, 1225, 1181, 1123, 1085, 1045, 759, and 701 cm^{-1}; δ_H (500 MHz, $CDCl_3$, +25 °C) 7.40–7.26 (5H, m, Ph), 5.03 (1H, d, *J* 6.5 Hz, PhC*H*O), 4.12–4.00 (1H, m, C6-*H*), 3.95 (2H, d, *J* 6.1 Hz, CH_2OAc), 2.56 (1H, dd, *J* 5.0, 17.1 Hz, C3-H$_a$$H_e$), 2.38–2.24 (1H, m, C6-CH_aH$_b$CHO), 2.20 (1H, dd, *J* 10.4, 17.1 Hz, C3-H_aH$_e$), 2.20 (1H, overlapping m, C6-CH_aH$_b$CHO), 2.05 (3H, s, CO*Me*), 1.85–1.75 (2H, m, C4-H, C5-H_aH$_e$), 1.45–1.35 (1H, m, C5-H_aH$_e$); δ_C (500 MHz, $CDCl_3$, +25 °C) 170.8, 164.0, 144.2, 128.4 (2C), 127.4, 125.5 (2C), 71.51, 66.5, 55.8, 43.0, 33.6, 31.1, 28.2, 20.7.

3.22. Conversion of 40a to 42 by treatment with zinc and acetic acid

To a vigorously stirred solution of the adduct **40a** (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 **42** in almost quantitative yield as a solid. Mp 75–76 °C (ether); (Found: C, 66.9; H, 10.8; N, 3.8. $C_{20}H_{39}NO_4$ requires C, 67.19; H, 10.99; N, 3.92%.); ν_{max} (neat) 3313, 2929, 2858, 1742, 1574, 1433, 1454, 1368, 1243, 1127, 1092, 1037, and 732 cm^{-1}; δ_H (500 MHz, $CDCl_3$, +25 °C) 4.0–3.0 (3H, br, N*H*, O*H*, O*H*), 3.90 (1H, dd, BX of a ABX, *J* 6.1, 11.0 Hz, CH_aH$_b$OAc), 3.85 (1H, dd, AX of a ABX, *J* 6.4, 11.0 Hz, CH$_a$$H_b$OAc), 3.82–3.80 (2H, m, C*H*OH, C*H*OH), 3.59–3.47 (1H, m, C2-*H*), 3.21–3.08 (1H, m, C6-*H*), 2.20–2.10 (1H, m, C4-*H*), 2.08 (3H, s, CO*Me*), 1.20–1.70 (20H, m), 0.90 (6H, two overlapping triplets, *J* 7.0 Hz, *Me*, *Me*); δ_C (500 MHz, $CDCl_3$, +25 °C) 171.1, 69.8, 69.2, 68.2, 47.9, 45.6, 42.8, 37.4, 37.0, 36.2, 35.1, 34.0, 30.9, 28.3, 28.1, 22.8 (2C), 20.9, 14.1 (2C).

3.23. Conversion of 41a to 43 by treatment with zinc and acetic acid

Using procedure as described in Section 3.22, the adduct **41a** was converted into **43** as a solid in 95% yield. Mp 64–65 °C (ether); (Found: C, 66.9; H, 11.2; N, 4.0; $C_{20}H_{39}NO_4$ requires C, 67.19; H, 10.99; N, 3.92%.) ν_{max} (neat) 3351, 2928, 2858, 1742, 1645, 1632, 1573, 1555, 1452, 1370, 1246, 1128, and 1037 cm^{-1}; δ_H (500 MHz, $CDCl_3$, +25 °C) 4.18 (2H,d, *J* 7.9 Hz, CH_2OAc), 3.83–3.73 (2H, m, C*H*OH, C*H*OH), 3.06–2.94 (2H, m, C2-*H*, C6-*H*), 2.20–2.10 (1H, m, C4-*H*), 2.07 (3H, s, CO*Me*), 1.20–1.60 (23H, m), 0.90 (6H, t, *J* 6.8 Hz, *Me*, *Me*); δ_C ($CDCl_3$, +25 °C) 171.2, 68.5 (2C), 65.3, 48.5 (2C), 42.8 (2C), 37.7 (2C), 32.5 (2C), 31.5, 28.0 (2C), 22.7 (2C), 21.0, 14.1 (2C).

3.24. Conversion of 44 to 46 by treatment with zinc and acetic acid

Using procedure as described in Section 3.22, the adduct **44** was converted into **46** as a solid in 95% yield. In the work up procedure, the aqueous layer was extracted with hot $CHCl_3$ instead of CH_2Cl_2 (as a result of poor solubility of the product). Mp 146–148 °C (ether); (Found: C, 74.1; H, 8.1; N, 3.8. $C_{22}H_{29}NO_3$ requires C, 74.33; H, 8.22; N, 3.94%.); ν_{max} (KBr) 3320, 3054, 3020, 2928, 2907, 2853, 1490,

1448, 1365, 1351, 1218, 1144, 1115, 1094, 1067, 1022, 914, 881, 853, 786, 760, 749, and 701 cm^{-1}; δ_H (500 MHz, 9:1 $CDCl_3/CD_3OD$, 25 °C) 7.37–7.24 (10H, m, Ph, Ph), 4.94 (1H, dd, *J* 3.4, 8.6 Hz, PhC*H*OH), 4.98 (1H, dd, *J* 4.3, 6.1 Hz, PhC*H*OH), 3.35 (3H, a two proton d, *J* 6.1 Hz, CH_2OH, and an overlapping 1H, m, C2-H), 3.19–3.11 (1H, m, C6-H), 2.71 (4H, br, O*H*s, N*H*), 2.37 (1H, ddd, *J* 4.2, 10.4, 14.6 Hz, C2-CH_aH$_b$CHO), 1.90–1.75 (2H, m, C2-CH$_a$*H*$_b$CHO, C6-C*H*$_a$H$_b$CHO), 1.72–1.65 (2H, m, C6-CH$_a$*H*$_b$CHO, C4-*H*), 1.59–1.53 (1H, m, C5-C*H*$_a$H$_b$), 1.51–1.47 (1H, m C5-CH$_a$*H*$_b$), 1.18 (1H, dt, *J* 5.5, 12.8 Hz, C3-C*H*$_a$H$_b$), 0.83 (1H, q, *J* 12.5 Hz, C3-H$_a$*H*$_b$); δ_C (500 MHz, 9:1 $CDCl_3/CD_3OD$, 25 °C) 145.1, 144.9, 128.4 (2C), 128.4 (2C), 127.1, 127.1, 125.6 (2C), 125.6 (2C), 72.1, 70.5, 67.8, 48.2, 45.8, 45.3, 37.7, 36.2, 33.9 (2C).

3.25. Conversion of 45 to 47 by treatment with zinc and acetic acid

Using procedure as described in Section 3.22, the adduct **45** was converted into **47** as a solid in 90% yield. In the work up procedure, the aqueous layer was extracted with hot $CHCl_3$ instead of CH_2Cl_2 (as a result of poor solubility of the product). Mp 199–200 °C (ether); (Found: C, 74.2; H, 8.0; N, 3.9. $C_{22}H_{29}NO_3$ requires C, 74.33; H, 8.22; N, 3.94%.); ν_{max} (KBr) 3311, 3171, 2931, 2884, 2718, 1450, 1388, 1332, 1262, 1205, 1119, 1063, 1037, 987, 914, 878, 827, 788, 759, and 702 cm^{-1}; δ_H (500 MHz, 9:1 $CDCl_3/CD_3OD$, 25 °C) 7.38–7.32 (10H, m, Ph, Ph), 4.88 (2H, dd, *J* 4.3, 8.0 Hz, PhC*H*OH, PhC*H*OH), 4.00 (4H, br s, OHs, and NH), 3.55 (2H, d, *J* 7.6 Hz, CH_2OH), 2.95–2.82 (2H, m, C2-H, C6-H), 2.08–2.00 (1H, m, C4-*H*), 1.72–1.68 (4H, m, C3-CH_2CHO, C6-CH_2CHO,), 1.64 (2H, apparent d, *J* 13.5 Hz, C3-H$_a$*H*$_e$, C5-H$_a$*H*$_e$), 1.41 (2H, dt, *J* 5.2, 13.5 Hz, C3-*H*$_a$H$_e$, C5-*H*$_a$H$_e$); δ_C (500 MHz, 9:1 $CDCl_3/CD_3OD$, 25 °C) 144.5 (2C), 128.1 (4C), 127.0 (2C), 125.4 (4C), 70.8 (2C), 62.7, 48.1 (2C), 44.7 (2C), 34.4, 32.6 (2C).

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