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NITRONE 1,3-DIPOLAR CYCLOADDITIONS TO ENOL ETHERS CATALYZED BY LEWIS ACIDS. AN ACCESS TO β-AMINO ACIDS[#]

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Abstract – The stereoselectivity of nitrone cycloaddition with enol ethers (**2** and **4**) depends upon the nature of the Lewis acid. The 1,3-dipolar cycloaddition of nitrones (**1, 6** and **8**) with enol ether (**2**) under the catalysis of $AlMe_3$ and Et_2AlCl proceeded diastereoselectively; whereas nitrone substitution with TBDPS reverses the diastereoselectivity of the cycloaddition. The oxidative ring-opening of isoxazolidines (**3** and **9**) with the treatment of benzyl bromide results new β-amino acid esters (**11, 13** and **15**).

INTRODUCTION

Over the years, nitrones have become important building blocks in organic synthesis. The nitrone-olefin 1,3-dipolar cycloaddition is a powerful reaction in that it can create as many as three new contiguous stereogenic centres in a single step.[1] Based on an evaluation of the nitrone cycloaddition, it was felt that the stereochemistry of the new centres could be controlled if the reaction system were properly designed.

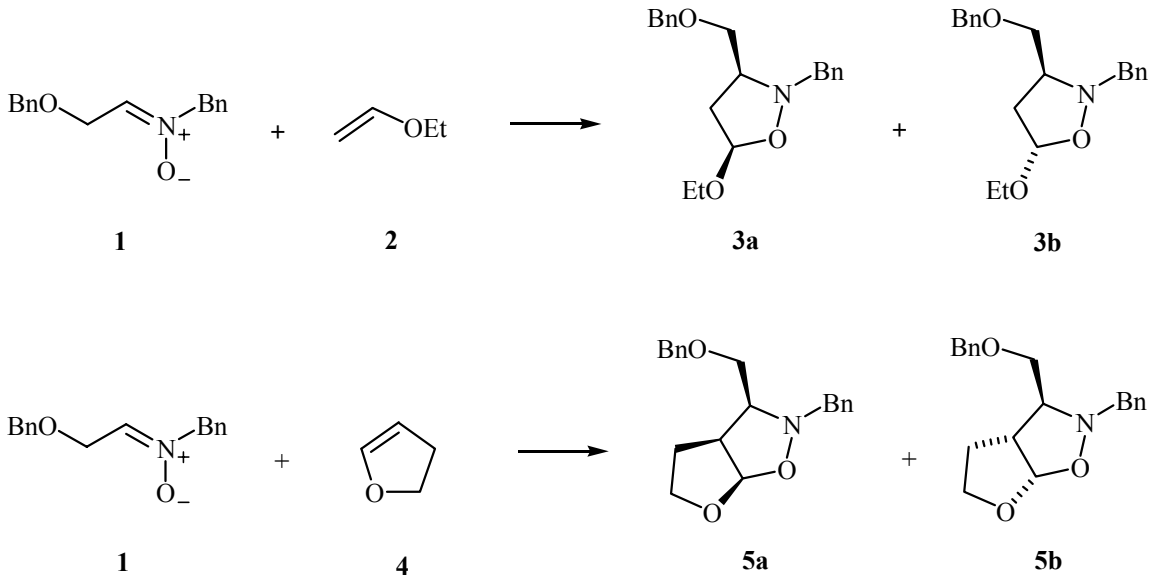
[#]*Dedicated to Professor Fritz Sauter on the occasion of his 75th birtday*

Regio- and stereoselective nitrone cycloaddition, followed by reduction of the NO bond to produce both an amino and a hydroxy function, allows the synthesis of many products of potential interest.[2-4] Lewis acids are often used as catalysts in 1,3-dipolar cycloadditions of nitrones,[5] but strong binding of nitrones to the catalyst in the cycloadditions to electron deficient alkenes is a serious problem as the dipoles have a tendency to form inactive dipole/Lewis acid complexes. Some years ago Murahashi *et al.* described a novel oxidative ring-opening reaction of isoxazolidines upon treatment with an electrophile and subsequently with a base to give β-amino acid esters.[6] β-Amino acids are fundamental compounds in the area of biology, medicine, biochemistry, material science, and synthetic organic chemistry.[7] Functionalized β-amino acids are key components of a variety of a bioactive molecules such as taxol and also as segments in peptidic natural products with various biological activities.[8] For this reason, the stereoselective synthesis of β-amino acids is of much interest these days. With our continuing efforts to utilize 1,3-dipolar cycloadditions,[9] and as extension of our recent work[5m] we report herein investigations of the effect of the addition of Lewis acid upon the stereoselectivity of cycloaddition of *N*-benzyl-2-benzyloxyethylideneamine *N*-oxide (**1**) and chiral nitrones (**6** and **8**) with enol ethers (**2** and **4**) and the further exploration of converting the isoxazolidine (**3, 9**) to new β-amino acid esters.

RESULTS AND DISCUSSION

The application of dibenzyl substituted nitrone (**1**) in a 1,3-dipolar cycloaddition strategy towards natural products is of interest because debenzylation leads to primary amino and hydroxymethyl functionalities being introduced in the molecule.[10] Therefore, firstly we examined the cycloaddition of the enol ether (**2**) with the nitrone (**1**) under various conditions (Scheme 1). The results are listed in Table 1. Nitrone (**1**) reacted very slowly with excess of enol ether (**2**) at 5°C over 14 d to give a 86 : 14 mixture of diastereomeric isoxazolidines in 43% yield, with almost 50% recovery of the starting nitrone (**1**); the 3,5-*cis*-isoxazolidine (**3a**) being the major product (Table 1, Entry 1). As shown in Table 1, the cycloaddition of the enol ether (**2**) with the nitrone (**1**) at -8°C over 20 h under $AlMe_3$ catalysis provided a 94 : 6 mixture of diastereoisomers (**3a**) and (**3b**) with the isomer (**3a**), predominant (Table 1, Entry 2). In the presence of a catalytic amount of $AlMe_3$ (0.5 and 0.2 equiv.), the reaction is slower and gave the adducts (**3a**) and (**3b**) in the same ratio as in the uncatalyzed cycloaddition (Table 1, Entries 8 and 9), with the nearly 50% recovery of the starting nitrone (**1**), indicating that stoichiometric amounts of the Lewis acid are necessary for the effective catalysis. On the other hand, when the reaction was performed in the presence of BF_3 as catalyst, a slightly lower diastereoselectivity for **3a,b** was observed (Table 1, Entry 4). However, other Lewis acids, such as $Ti(OPr\text{-}i)_2Cl_2$ and ZnI_2, were found to be efficient and

accelerate this reaction compared with the uncatalyzed cycloaddition although a considerable decrease in stereoselectivity was observed (Table 1, Entries 5-7).



Scheme 1

In the case of ZnI_2 catalyzed reaction, increasing the raction temperature to 25°C resulted in a good yield (82%) of the adducts (**3a**) and (**3b**), but the diastereoselectivity was reversed (Table 1, Entry 7). On the other hand, the use of $TiCl_4$ was found not to be efficient for this reaction and gave only an inseparable mixture of decomposition products (Table 1, Entry 3). The 1,3-dipolar cycloaddition of nitrone (**1**) to 2,3-dihydrofuran (**4**) was also carried out according to (Scheme 1) and expected regioselectivity in line with that observed in the reaction of **1** with **2** was obtained (Table 1, Entries 12-14). On the other hand reversal of the diastereoselectivity favoring 3,5-*trans* isomer (**5b**) was observed as shown in the Table 1 (Entry 14).

We next investigated the catalytic effects of Lewis acids on the diastereoselectivity of the 1,3-dipolar cycloaddition of chiral sugar derived nitrones (**6** and **8**) with alkene (**2**) (Scheme 2). The results are summarized in Table 2. It should be noted that the 1,3-dipolar cycloaddition of nitrone (**6**) with enol ether (**2**) under $AlMe_3$ and Et_2AlCl catalysis proceeded diastereoselectively and gave only two diastereoisomers (**7a**) and (**7b**) with **7a** predominant, although four diastereoisomers are possible (Table 2, Entries 4 and 5). Indeed, as shown in Table 2, the cycloaddition in the absence of any Lewis acids gave a mixture of diastereoisomers (**7a-d**) constituting a considerable decrease of the stereoselectivity although **7a** was still the major adduct (Table 2, Entries 1-3). In order to study the effect of the protecting group on the reaction

stereoselectivity, the 1,3-dipolar cycloaddition of TBDPS protected nitrone (**8**) with enol ether (**2**) was examined under similar conditions (Scheme 2), and similar results, except for reversal of the diastereoselectivity, probably due to the steric effects, favoring isomer (**9b**) were obtained as shown in the Table 2 (Table 2, Entries 9-12).

Table 1 1,3-Dipolar Cycloadditions of Nitrone (**1**) with Enol Ethers (**2**) and (**4**)

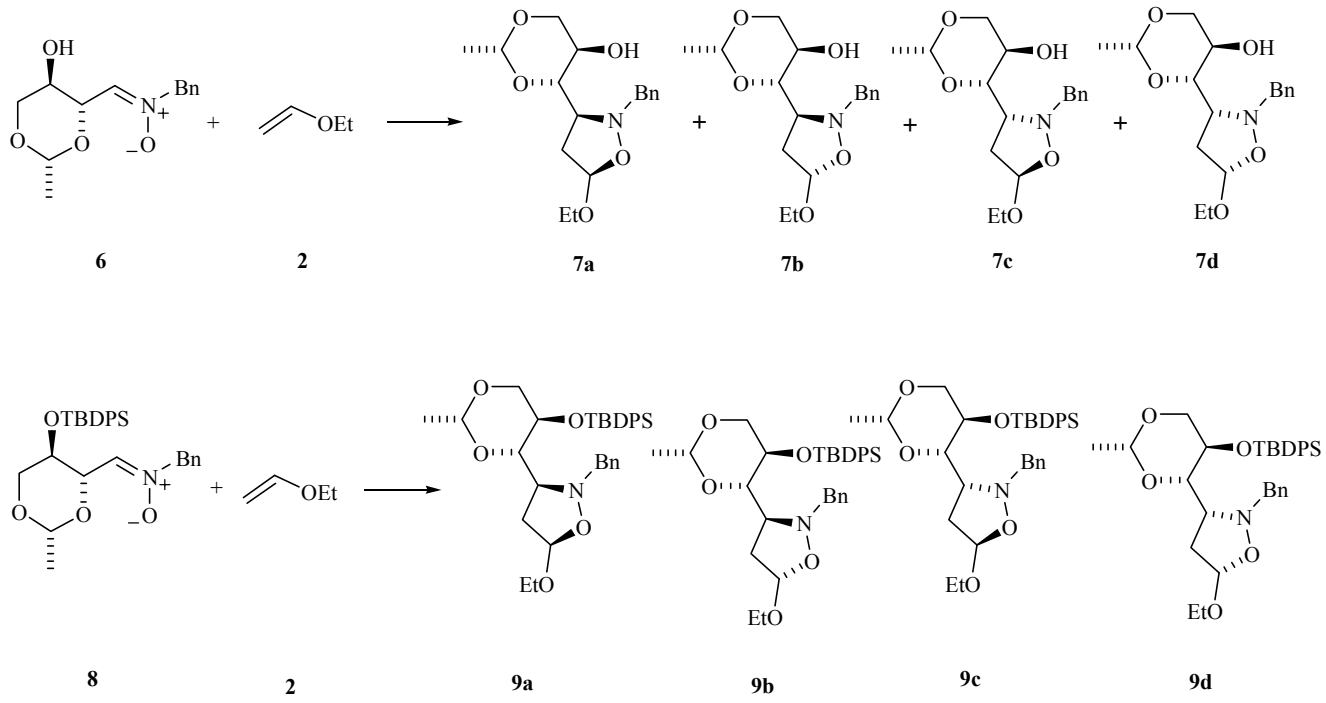
Entry	Alkene	Conditions[a]	Lewis acid (equiv.)	Yield (%)	Diastereoselectivity[b] 3,5-*cis* : 3,5-*trans*
1	**2**	5°C, 14 d	-	43[c]	86 : 14
2	**2**	-8°C 20 h	$AlMe_3$ (1)	56	94 : 6
3	**2**	-8°C 20 h	$TiCl_4$ (1)	-	-
4	**2**	-8°C, 48 h	$BF_3.OEt_2$ (1)	46	84 : 16
5	**2**	-8°C, 48 h	$Ti(OiPr)_2Cl_2$ (1)	55	53 : 47
6	**2**	-8°C, 96 h	ZnI_2 (1)	76	57 : 43
7	**2**	rt, 22 h	ZnI_2 (1)	82	40 : 60
8	**2**	5°C, 14 d	$AlMe_3$ (0.5)	50	83 : 17
9	**2**	5°C, 14 d	$AlMe_3$ (0.2)	50[c]	84 : 16
10	**2**	5°C, 4 d	AlMe-(TADDOL) (0.2)	81	78 : 22
11	**2**	5°C, 10 d	$TiCl_2$-(TADDOL) (0.2)	79	55 : 45
12	**4**	-10 to 5°C, 19 d	-	-	-
13	**4**	-10 to 5°C, 19 d	Et_2AlCl (1)	50	44 : 56
14	**4**	-10 °C, 4 d	$AlMe_3$ (1)	15	19 : 81

[a] 5 Equivalents of ethyl vinyl ether with respect to the nitrone (**1**) and CH_2Cl_2 as a solvent have been used.

[b] based on ^{13}C NMR spectrum by integration of C-5 signals

[c] conversion of nitrone (**1**)

Moreover, in this case cycloaddition in the absence of Lewis acid proceeded very slowly and gave only traces of the cycloadducts (Table 2, Entries 6-8). The enhanced reactivity in the case of $AlMe_3$ and Et_2AlCl as catalysts could be due to the increase of electron deficiency of the dipole – Lewis acid complex. However, cycloaddition in the presence of the other Lewis acids such as $ZnBr_2$, $MgBr_2$, $Mg(ClO_4)_2$ and $Ti(OiPr)_2Cl_2$ did not take place. We suppose, that with these Lewis acids an unreactive nitrone - Lewis acid – enol ether complex is formed.



Scheme 2

Table 2 1,3-Dipolar Cycloadditions of Nitrones (**6**) and (**8**)with Enol Ether (**2**)

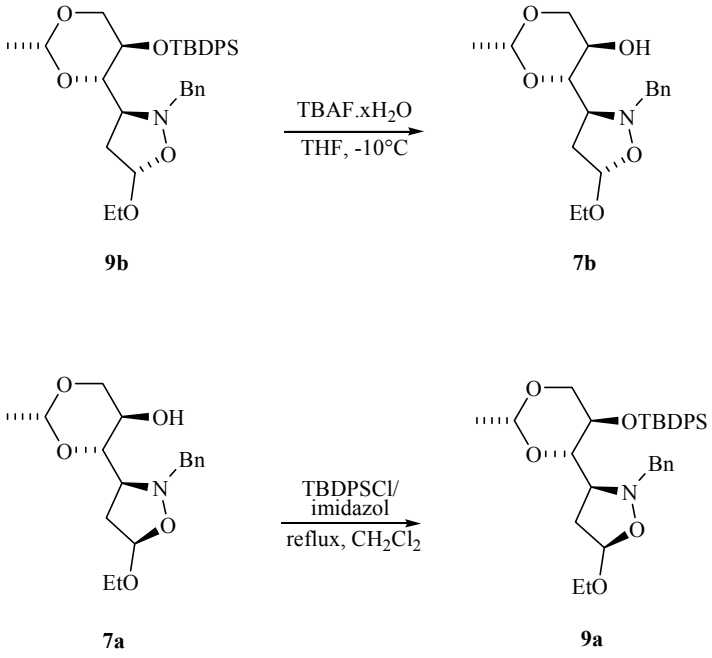
Entry	Nitrone	Conditions	Lewis acid (equiv.)	Yield (%)	Diastereoselectivity[a] **a** : **b** : **c** : **d**
1	**6**	toluene, rt, 60 d	-	80[b]	90 : 3 : 7 : -[c]
2	**6**	CH_2Cl_2, rt, 30 d	-	65	59 : 12 : 14 : 15
3	**6**	silica gel, MW, 12 min	-	75	69 : 12 : 10 : 9
4	**6**	toluene, rt, 14 d	$AlMe_3$ (0.6)	76	83 : -[c] : 17 : -[c]
5	**6**	CH_2Cl_2, 0 to 5°C, 24 h	Et_2AlCl (1)	82	90 : -[c] : 10 : -[c]
6	**8**	CH_2Cl_2, 5°C, 30 d	-	-	traces
7	**8**	CH_2Cl_2, rt, 30 d	-	-	traces
8	**8**	silica gel, MW, 35 min	-	-	-
9	**8**	CH_2Cl_2, rt, 3 d	$AlMe_3$ (1)	74	11 : 89 : -[c] : -[c]
10	**8**	CH_2Cl_2, rt, 24 h	Et_2AlCl (1)	60	10 : 90 : -[c] : -[c]
11	**8**	CH_2Cl_2, -15°C, 14 d	Et_2AlCl (1)	78	9 : 91 : -[c] : -[c]
12	**8**	CH_2Cl_2, rt, 10 d	ZnI_2 (1)	traces	15 : 85 : -[c] : -[c]

[a] based on ^{13}C NMR spectrum by integration of C-5 signals

[b] conversion of nitrone (**6**)

[c] Signals of product have not been detected in NMR spectrum of the crude reaction mixture.

Purification by flash chromatography allowed the isolation of pure adducts (**3a**), (**3b**), (**5a**), (**5b**) and (**7c**) while the chromatographic separation of isoxazolidines (**7a,b**) and (**9a,b**) was not possible. Therefore, the mixture of isoxazolidines (**7a,b**) was silylated with TBDPSCl in 58% to yield after separation the isoxazolidine (**9a**) (Scheme 3). Similarly the TBDPS substituted isoxazolidine (**9a,b**) was deprotected with TBAF in THF to afford after separation the isoxazolidine (**7b**). The structures and configurations of the synthesized isoxazolidines were determined by the analyses of their spectral data using ^{1}H NMR, ^{13}C NMR, 2D-COSY, C-H HETCOR and by the NOESY experiments. While the configuration on C-3 and C-5 was confirmed by NOE measurement of cycloadducts, relationship between stereocentres at C-3 and C-4', especially for compounds (**7a**, **7b**, **9a** and **9b**) was based on our previous results from 1,3-dipolar cycloadditions of sugar nitrones bearing free as well as a protected hydroxy group in the α-position.[9d,f-h]



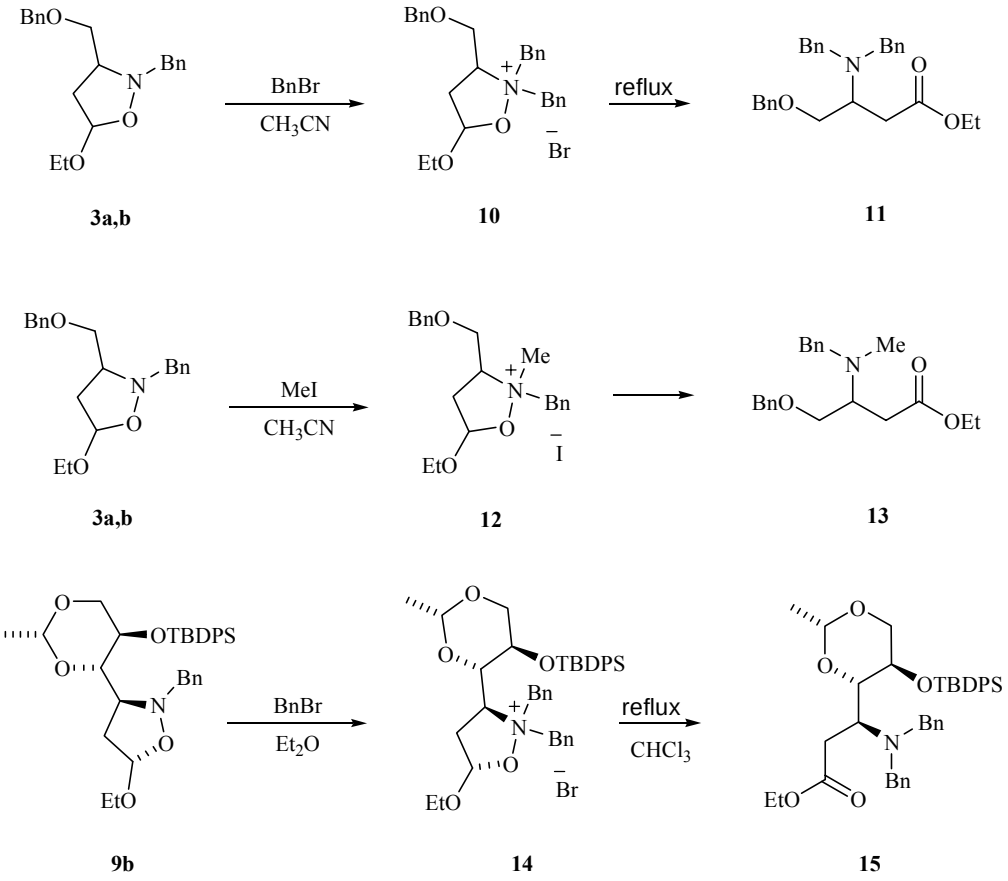
9b **7b**

7a **9a**

Scheme 3

A variety of reductive isoxazolidine ring-opening methods which generate β-amino compounds have been developed.[4a] For example, the catalytic hydrogenation with palladium[9e,g] and the treatment of the isoxazolidine with zinc[5k] are commonly used. In our case we have used the Murahashi oxidative ring-opening reaction of isoxazolidines.[6] The treatment of isoxazolidine (**3a,b**) with benzyl bromide and methyl iodide at room temperature in MeCN afforded the β-amino acid esters (**11**) and (**13**) in 67% and 54% yields, respectively. Similarly, the chiral isoxazolidine (**9b**) gave, after treatment with benzyl bromide, the chiral β-amino acid ester (**15**) in 53% yield (Scheme 4).

In summary, the stereoselectivity of nitrone cycloaddition with enol ethers (**2** and **4**) depends upon the nature of the Lewis acid. The 1,3-dipolar cycloaddition of nitrones (**1, 6** and **8**) with enol ether (**2**) under the $AlMe_3$ and Et_2AlCl catalysis proceeded diastereoselectively. Substituting the nitrone with TBDPS reverses the diastereoselectivity of the cycloaddition. The oxidative ring-opening of isoxazolidines (**3** and **9b**) with the treatment of alkyl halide results in a new kind of β-amino acid esters (**11, 13** and **15**).



Scheme 4

EXPERIMENTAL

All commercially available starting materials and reagents (Fluka, Merck, Avocado or Aldrich) were used without further purification. Solvents were dried before use. Thin-layer chromatography (TLC, ALUGRAM Sil G/UV_{254} Macherey-Nagel) was used for monitoring of reaction courses; eluents are given in the text. For column chromatography the flash chromatography technique was employed using silica 60 (0.040-0.063 mm, Merck). Melting point (mp) was determined on a Kofler hot plate apparatus and is uncorrected. IR spectra were recorded on FTIR NICOLET MAGNA 750 instrument. The ^1H and ^{13}C NMR spectra of deuterochloroform solutions were obtained using Bruker DRX-400 (400 MHz)

instrument, tetramethylsilane (TMS) being the internal reference. Optical rotations [α] were measured on an IBZ Messtechnik Polar-LμP polarimeter at the sodium D line (589 nm) using a 1 dm cell with chloroform as a solvent. HRMS were performed on Finnigan MAT 8230 spectrometer (70 eV). Elemental analyses were conducted using the Thermo FlashEA 1112. Nitrones (**1, 6, 8**) were prepared from the corresponding aldehyde by the reaction with *N*-benzylhydroxylamine according to the procedures already described.[9d,f,11] The Lewis acids Et_2AlCl (1M in hexanes), $AlMe_3$ (2M in toluene), $ZnBr_2$, and ZnI_2 used for cycloadditions are commercially available reagents. The $MgBr_2.OEt_2$ and $Ti(OiPr)_2Cl_2$ were freshly prepared prior to use.

Procedure A: Uncatalyzed reaction: To the round-bottom flask equipped with magnetic stirring bar were nitrone (1 equiv.), alkene (5 equiv.) and CH_2Cl_2 added. The reaction mixture was stirred at temperature given in Tables 1 and 2. The appropriate reaction times for each reaction are listed in Tables 1 and 2. The solvent was evaporated and quantitative ^{13}C NMR spectrum of the crude reaction mixture was recorded. The reaction mixture was then purified by column chromatography. The yields of the isolated mixtures of cycloadducts for each experiment are given in Tables 1,2.

Procedure B: Reaction in the presence of catalyst: The reaction was carried out under an argon atmosphere. To a solution of appropriate nitrone, 1 equiv. of catalyst at -10°C was added. Prior to the addition of vinylether (5 equiv.), the mixture was stirred for 20 min. The temperature was kept between -10 and 0°C until complete conversion of nitrone. The reaction was quenched by addition of saturated NH_4Cl followed by CH_2Cl_2 extraction. The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on silica gel. Reaction data are listed in Tables 1 and 2.

Procedure C: Microwave mediated cycloadditions: The reactions were carried out in conventional kitchen microwave oven at the rate of 800 W. The nitrone absorbed (4.0 mmol) on silica gel (6 g) and the alkene (80 mmol) were placed into the 250 mL Erlenmayer flask, cooled to 0°C and irradiated for 15 s. The contents were then monitored by TLC. The mixture was again cooled down to 0°C and whole sequence was repeated until complete conversion of nitrone (12 min). The silica gel was then washed with 250 mL of EtOAc : Hexanes (1:1) and the solvent was removed by rotary evaporation.

***cis*-2-Benzyl-3-benzyloxymethyl-5-ethoxyisoxazolidine (3a)**

The reaction was carried out according to the procedure B, using 0.500 g (2.0 mmol) of nitrone (**1**), 1 equiv. of $AlMe_3$, 1 mL of ethyl vinyl ether (**2**) (10 mmol, 5 equiv.) and CH_2Cl_2 (10 mL) as a solvent. Flash chromatography of the residue on silicagel (30 g, 16x2.5 cm, EtOAc : Hexanes = 15 : 85) gave 0.469 g (73%) of pure diastereoisomer (**3a**). Yellow oil, R_f = 0.41 (EtOAc : Hexanes = 30 : 70), IR (film) 3337, 3063, 3030, 2976, 2898, 2865, 1605, 1585, 1496, 1454, 1371,1343, 1307, 1205, 1101, 1053, 1029 cm^{-1}; ^{1}HNMR ($CDCl_3$): δ (ppm) 7.45-7.25 (m, 10H, Ph), 5.15 (dd, 1H, *J* = 1.4, 6.1 Hz, 5-H), 4.56, 4.52

(2xd, 2x1H, *J* = 12.0 Hz, OCH_2Ph), 4.37, 3.95 (d, 1H, *J* = 14.3 Hz, NCH_2Ph), 3.74 (qd, 1H, *J* = 9.6, 7.1 Hz, OCH_2CH_3), 3.70-3.64 (m, 2H, 1'-H), 3.42 (qd, 1H, *J* = 9.6, 7.1 Hz, OCH_2CH_3), 3.18 (dddd, 1H, *J* = 7.6, 7.7, 8.0, 5.0 Hz, 3-H), 2.59 (ddd, 1H, *J* = 13.2, 8.5, 6.3 Hz, 4a-H), 2.03 (ddd, 1H, *J* = 13.2, 7.4, 1.9 Hz, 4b-H), 1.19 (t, 3H, *J* = 7.1 Hz, OCH_2CH_3); ^{13}CNMR ($CDCl_3$): δ (ppm) 138.0, 137.6, 128.9, 128.4, 128.0, 127.6, 127.6, 126.9 (6C, Ph), 100.8 (5-C), 73.3 (OCH_2Ph), 71.6 (1'-C), 63.9 (3-C), 63.4 (OCH_2CH_3), 61.9 (NCH_2Ph), 39.9 (4-C), 15.0 (OCH_2CH_3); HRMS (EI, 70 eV) calcd for $C_{20}H_{25}NO_3$ 327.1834, Found: 327.1836. Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70, N, 4.28. Found: C, 73.55; H, 7.84, N, 4.19.

***trans*-2-Benzyl-3-benzyloxymethyl-5-ethoxyisoxazolidine (3b)**

The reaction was carried out according to the procedure B, using 0.500 g (2.0 mmol) of nitrone (**1**), 1 equiv.. of $TiCl_2(OiPr)_2$, 1 mL of ethyl vinyl ether (**2**) (10 mmol, 5 equiv.) and CH_2Cl_2 (10 mL) as a solvent. Flash chromatography of crude mixture on silicagel (80 g, 16x4 cm, EtOAc : Hexanes = 10 : 90) gave 0.019 g (3%) of pure diastereoisomer (**3a**), 0.170 g (27%) of mixture of both diastereoisomers (**3a,b**) and 0.170 g (27%) of pure diastereoisomer (**3b**). Yellow oil, R_f = 0.31 (EtOAc : Hexanes : CH_2Cl_2 = 5 : 75 : 20), IR (film) 3434, 3063, 3030, 2973, 2927, 2899, 2870, 1725, 1605, 1585, 1496, 1454, 1372, 1344, 1305, 1273, 1204, 1101, 1029 cm^{-1}; ^{1}HNMR ($CDCl_3$): δ (ppm) 7.45-7.27 (m, 10H, Ph), 5.18 (d, 1H, *J* = 5.2 Hz, 5-H), 4.56, 4.51 (2xd, 2x1H, *J* = 12.0 Hz, OCH_2Ph), 4.30, 4.23 (2xd, 2x1H *J* = 13.1 Hz, NCH_2Ph), 3.83 (qd, 1H, *J* = 9.6, 7.1 Hz, OCH_2CH_3), 3.66-3.59 (m, 1H, 3-H), 3.53-3.44 (m, 3H, 1-H, OCH_2CH_3), 2.50 (ddd, 1H, *J* = 12.9, 7.1, 1.4 Hz, 4a-H), 2.29 (ddd, 1H, *J* = 12.9, 7.5, 5.4 Hz, 4b-H), 1.26 (t, 3H, *J* = 7.1 Hz, OCH_2CH_3); ^{13}CNMR ($CDCl_3$): δ (ppm) 138.1, 138.0, 128.9, 128.3, 128.2, 127.5, 127.5, 127.1 (6C, Ph), 103.4 (5-C), 73.1 (OCH_2Ph), 72.4 (1'-C), 65.2 (NCH_2Ph), 63.2 (3-C), 63.0 (OCH_2CH_3), 39.7 (4-C), 15.0 (OCH_2CH_3), HRMS (EI, 70 eV) calcd for $C_{20}H_{25}NO_3$ 327.1834, Found: 327.1839. Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70, N, 4.28. Found: C, 73.63; H, 7.53, N, 4.52.

***cis*-2-Benzyl-3-benzyloxymethylhexahydrofuro[3,2-*d*]isoxazole (5a)**

***trans*-2-Benzyl-3-benzyloxymethylhexahydrofuro[3,2-*d*]isoxazole (5b)**

The reaction was carried out according to the procedure B, using 0.500 g (2.0 mmol) of nitrone (**1**), 1 equiv.. of Et_2AlCl, 0.76 mL of 2,3-dihydrofuran (**4**) (10 mmol, 5 equiv.) and CH_2Cl_2 (10 mL) as a solvent. Flash chromatography of the residue on silica gel (45 g, 20x3 cm, EtOAc : Hexanes : CH_2Cl_2 = 10 : 82 : 8) gave 0.100 g (16%) of pure diastereoisomer (**5a**), 0.098 g (15%) of mixture of both diastereoisomers (**5a,b**) and 0.123 g (19%) of **5b**. **5a:** Colorless syrup, R_f = 0.40 (EtOAc : Hexanes = 30 : 70), IR (film) 3087, 3063, 3030, 2959, 2929, 2872, 1605, 1585, 1496, 1454, 1424, 1369, 1340, 1276, 1207, 1093, 1075, 1027 cm^{-1}; ^{1}HNMR ($CDCl_3$): δ (ppm) 7.40-7.24 (m, 10H, Ph), 5.70 (d, 1H, *J* = 5.3 Hz, 1a-H), 4.56, 4.52 (2xd, 2x1H, *J* = 11.9 Hz, OCH_2Ph), 4.36 (d, 1H, *J* = 14.9 Hz, NCH_2Ph), 4.13-4.06 (m, 1H, 6a-H), 3.97

(ddd, 1H, *J* = 7.9, 7.9, 1.9 Hz, 6b-H), 3.84 (d, 1H, *J* = 14.9 Hz, NCH_2Ph), 3.69 (dd, 1H, *J* = 9.8, 5.1 Hz, 1'a-H), 3.61 (dd, 1H, *J* = 9.5, 7.0 Hz, 1'b-H), 3.22-3.16 (m, 1H, 4a-H), 3.13 (ddd, 1H, *J* = 6.9, 6.7, 5.2 Hz, 4-H), 2.04-2.00, 1.90-1.79 (2xm, 2x1H, 5-H); ^{13}CNMR ($CDCl_3$): δ (ppm) 137.6, 137.2, 128.6, 128.5, 128.1, 127.9, 127.7, 126.9 (6C, Ph), 105.0 (1a-C), 73.6 (OCH_2Ph), 69.5 (6-C), 68.6 (1'-C), 67.1 (4-C), 61.2 (NCH_2Ph), 49.6 (4a-C), 26.3 (5-C). Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12, N, 4.29. Found: C, 73.43; H, 7.50, N, 4.00. **5b:** Colorless syrup, R_f = 0.31 (EtOAc : Hexanes = 30 : 70), IR (film) 3087, 3062, 3030, 2946, 2871, 1605, 1586, 1496, 1475, 1454, 1366, 1331, 1310, 1286, 1261, 1207, 1102, 1026 cm^{-1}; ^{1}HNMR ($CDCl_3$): δ (ppm) 7.43-7.27 (m, 10H, Ph), 5.71 (d, 1H, *J* = 5.2 Hz, 1a-H), 4.58 (s, 2H, OCH_2Ph), 4.30 (d, 1H, *J* = 14.0 Hz, NCH_2Ph), 4.05-4.02 (m, 3H, H-6, NCH_2Ph), 3.69 (dd, 1H, *J* = 9.7, 6.6 Hz, 1'a-H), 3.61 (dd, 1H, *J* = 9.8, 4.6 Hz, 1'b-H), 3.00-2.92 (m, 2H, H-4, 4a-H), 2.08-1.98 (m, 1H, 5a-H), 1.91-1.87 (m, 1H, 5b-H); ^{13}CNMR ($CDCl_3$): δ (ppm) 137.7, 137.3, 128.9, 128.4, 128.1, 127.7, 127.6, 127.1 (6C, Ph), 106.2 (1a-C), 73.4 (OCH_2Ph), 70.3 (br, 1'-C), 69.2 (4-C), 67.2 (br, 6-C), 60.9 (br, NCH_2Ph), 50.8 (4a-C), 30.8 (5-C), HRMS (EI, 70 eV) calcd for $C_{20}H_{23}NO_3$ 325.1678, Found: 325.1690. Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12, N, 4.29. Found: C, 73.49; H, 7.36, N, 4.13.

(*2R*,*4S*,*5R*)-4-(2-Benzyl-5-ethoxyisoxazolidin-3-yl)-2-methyl-1,3-dioxan-5-ol (7a)

The reaction was carried out according to the procedure B, using 2.0 g (8.0 mmol) of nitrone (**6**), 1 equiv. of $AlEt_2Cl$ and CH_2Cl_2 (50 mL) as a solvent. The ethyl viny ether (**2**) (0.9 mL, 9.3 mmol, 1.2 equiv.) was added during 3 h in 5 portions. Flash chromatography of the residue on silica gel (100 g, 21x4 cm, CH_2Cl_2 : EtOAc : Hexanes = 20 : 15 : 65) gave 2.113 g (82 %) of mixture of diastereoisomers (**7a**) : (**7b**) (90 : 10). Colorless syrup, $[\alpha]_D^{25}$: -73.8° (*c* 0.2, $CHCl_3$); R_f = 0.54 (CH_2Cl_2 : EtOAc : Hexanes = 30 : 20 : 50), IR (film) 3357, 3088, 3064, 3031, 2974, 2931, 2867, 1606, 1497, 1454, 1446, 1408, 1374, 1348, 1274, 1247, 1214, 1158, 1118, 1081, 1042 cm^{-1}; ^{1}HNMR ($CDCl_3$): δ (ppm) 7.38-7.31 (m, 5H, Ph), 5.35 (d, 1H, *J* = 5.5 Hz, 5-H), 5.28 (s, 1H, OH), 4.65 (q, 1H, *J* = 5.0 Hz, 2'-H), 4.09 (dd, 1H, *J* = 10.7, 5.0 Hz, 6'a-H), 4.08 (d, 1H, *J* = 13.0 Hz, NCH_2Ph), 3.98 (d, 1H, *J* = 13.1 Hz, NCH_2Ph), 3.77 (qd, 1H, *J* = 9.3, 7.1 Hz, OCH_2CH_3), 3.68 (dd, 1H, *J* = 8.2, 8.2 Hz, 4'-H), 3.52 (ddd, 1H, *J* = 9.8, 9.7, 5.5 Hz, 5'-H), 3.46 (qd, 1H, *J* = 9.5, 7.1 Hz, OCH_2CH_3), 3.39 (dd, 1H, *J* = 10.5, 10.5 Hz, 6'b-H), 3.32 (ddd, 1H, *J* = 8.2, 8.4, 2.5 Hz, 3-H), 2.47 (ddd, 1H, *J* = 13.6, 8.6, 5.6 Hz, 4a-H), 2.40 (dd, 1H, *J* = 13.6, 2.5 Hz, 4b-H), 1.29 (d, 1H, *J* = 5.1 Hz, 7'-H), 1.22 (t, 1H, *J* = 7.1 Hz, OCH_2CH_3); ^{13}CNMR ($CDCl_3$): δ (ppm) 136.0, 129.2, 128.6, 127.8 (6C, Ph), 102.7 (5-C), 98.9 (2'-C), 79.3 (4'-C), 70.0 (6'-C), 65.9 (3-C), 65.4 (5'-C), 63.4 (NCH_2Ph), 63.1 (OCH_2CH_3), 36.9 (4-C), 20.5 (7'-C), 15.1 (OCH_2CH_3). Anal. Calcd for $C_{17}H_{25}NO_5$: C, 63.14; H, 7.79, N, 4.33. Found: C, 63.41; H, 8.10, N, 4.41.

(*2R*,*4S*,*5R*)-4-(2-Benzyl-5-ethoxyisoxazolidin-3-yl)-2-methyl-1,3-dioxan-5-ol (7b)

To a solution of **9a,b** (10:90) (0.507 g, 0.9 mmol) in THF (25 mL) TBAF.xH_2O (0.307 g, 1.2 mmol, 1.3 equiv..) solution in THF (25 mL) at -10°C was added dropwise. The mixture was stirred for 3 h at this

temperature, then saturated $NaHCO_3$ was added, followed by CH_2Cl_2 extraction. The combined extracts were dried over Na_2SO_4 and the solvent was evaporated. Flash chromatography of the residue on silica gel (55 g, 24x3 cm; EtOAc : Hexanes : CH_2Cl_2 = 13 : 75 : 12) gave 0.084 g (29%) of pure diastereoisomer (**7b**) and 0.066 g (52%) of both diastereoisomers (**7a,b**). Colorless solid, mp 100-104°C (EtOAc : Hexanes); $[\alpha]_D^{25}$: +96.9° (*c* 0.1, $CHCl_3$); R_f = 0.18 (EtOAc : Hexanes : CH_2Cl_2 = 13 : 70 : 17), IR (KBr) 3204, 2988, 2988, 2978, 2868, 1452, 1409, 1155, 1138, 1122, 1110, 1085, 1060, 1052, 1037 cm^{-1}; ^{1}HNMR ($CDCl_3$): δ (ppm) 7.41-7.31 (m, 5H, Ph), 5.39 (dd, 2H, *J* = 6.5, 3.3 Hz, 5-H, OH), 4.61 (q, 1H, *J* = 5.0 Hz, 2'-H), 4.39, 4.16 (2xd, 2x1H, *J* = 12.4 Hz, NCH_2Ph), 4.05 (dd, 1H, *J* = 10.6, 5.0 Hz, 6'a-H), 3.81 (qd, 1H, *J* = 9.5, 7.1 Hz, OCH_2CH_3), 3.57-3.49 (m, 2H, OCH_2CH_3, H-3), 3.33 (dd, 1H, *J* = 10.3, 10.3 Hz, 6'b-H), 3.25 (ddd, 1H, *J* = 9.9, 8.5, 5.2 Hz, 5'-H), 3.11 (dd, 1H, *J* = 9.1, 9.1 Hz, 4'-H), 2.71 (ddd, 1H , *J* = 14.2, 6.6, 1.3 Hz, 4a-H), 2.58 (ddd, 1H, *J* = 14.3, 7.6, 3.3 Hz, 4b-H), 1.29 (d, 3H, *J* = 5.1 Hz, 7'-H), 1.26 (t, 3H, *J* = 7.1 Hz, OCH_2CH_3); ^{13}CNMR ($CDCl_3$): δ (ppm) 135.9, 129.3, 128.7, 128.0 (6C, Ph), 106.1 (5-C), 99.1 (2'-C), 79.1 (4'-C), 69.9 (6'-C), 67.3 (3-C), 66.1 (5'-C), 64.4 (OCH_2CH_3), 63.2 (NCH_2Ph), 37.9 (4-C), 20.5 (7'-C), 15.1 (OCH_2CH_3). Anal. Calcd for $C_{17}H_{25}NO_5$: C, 63.14; H, 7.79, N, 4.33. Found: C, 63.42; H, 7.66, N, 4.29.

(*2R*,*4S*,*5R*)-4-(2-Benzyl-5-ethoxyisoxazolidin-3-yl)-2-methyl-1,3-dioxan-5-ol (7c)

The diastereoisomer (**7c**) was isolated following procedure B using 1 g (8.0 mmol) of nitrone (**6**), 4 mL (41.8 mmol, 10.4 equiv.) of ethyl vinyl ether (**2**), 0.4 mL of $AlMe_3$ (0.8 mmol, 0.2 equiv.) as catalyst and toluene as a solvent. Flash chromatography of the crude mixture on silica gel (30 g, 20x3 cm, EtOAc : Hexanes = 25 : 75) gave 0.846 g (66%) of mixture of diastereoisomers (**7a-c**) and 0.038 g (3%) of pure diastereoisomer (**7c**). Colorless syrup, $[\alpha]_D^{25}$: -41.4° (*c* 0.06, $CHCl_3$); R_f = 0.38 (EtOAc : Hexanes = 50 : 50), IR (film) 3427, 3088, 3064, 3031, 2971, 2924, 2855, 2794, 1668, 1605, 1497, 1455, 1408, 1372, 1343, 1301, 1231, 1204, 1153, 1138, 1087, 1040 cm^{-1}; ^{1}HNMR ($CDCl_3$): δ (ppm) 7.38-7.30 (m, 5H, Ph), 5.28 (d, 1H, *J* = 5.3 Hz, 5-H), 4.59 (q, 2H, *J* = 5.0 Hz, 2'-H, OH), 4.35, 4.18 (2xd, 2x1H, *J* = 12.7 Hz, NCH_2Ph), 4.13 (dd, 1H, *J* = 10.8, 5.4 Hz, 6'a-H), 3.84 (qd, 1H, *J* = 9.4, 7.1 Hz, OCH_2CH_3), 3.79 (ddd, 1H, *J* = 7.7, 7.5, 5.3 Hz, 3-H), 3.70 (ddd, 1H, *J* = 9.5, 9.5, 5.4 Hz, 5'-H), 3.52 (qd, 1H, *J* = 9.4, 7.0 Hz, OCH_2CH_3), 3.38 (dd, 1H, *J* = 9.1, 5.0 Hz, 4'-H), 3.34 (dd, 1H, *J* = 10.7, 10.4 Hz, 6'b-H), 2.61 (ddd, 1H, *J* = 13.4, 7.4, 5.4 Hz, 4a-H), 2.50 (dd, 1H, *J* = 13.6, 8.1 Hz, 4b-H), 1.28 (d, 3H, *J* = 5.7 Hz, 7'-H), 1.27 (t, 1H, *J* = 7.5 Hz, OCH_2CH_3); ^{13}CNMR ($CDCl_3$): δ (ppm) 136.7, 129.1, 128.6, 127.8 (6C, Ph), 104.6 (5-C), 99.0 (2'-C), 79.2 (4'-C), 70.0 (6'-C), 65.6 (3-C), 65.4 (NCH_2Ph), 63.4 (OCH_2CH_3), 61.7 (5'-C), 37.1 (4-C), 20.4 (7'-C), 15.0 (OCH_2CH_3), HRMS (EI, 70 eV) calcd for $C_{17}H_{25}NO_5$ 323.1733, Found: 323.1723. Anal. Calcd for $C_{17}H_{25}NO_5$: C, 63.14; H, 7.79, N, 4.33. Found: C, 62.98; H, 7.55, N, 4.47.

(*2R*,*4S*,*5R*)-4-(2-Benzyl-5-ethoxyisoxazolidin-3-yl)-2-methyl-1,3-dioxanyl-5-*tert*-butyldiphenylsilanol (9a,b)

The reaction was carried out according to procedure B, using 0.690 g (1.4 mmol) of nitrone (**8**), 1 equiv.. of $AlMe_3$, 0.7 mL of ethyl vinyl ether (**2**) (7.0 mmol, 1.2 equiv.) and CH_2Cl_2 (10 mL) as solvent at rt. Flash chromatography of the residue on silicagel (90 g, 18x4 cm, EtOAc : Hexanes = 20 : 80) gave 0.580 g (73 %) of mixture of diastereoisomers (**9a,b**) (colorless oil).

(*2R*,*4S*,*5R*)-4-(2-Benzyl-5-ethoxyisoxazolidin-3-yl)-2-methyl-1,3-dioxanyl-5-*tert*-butyldiphenylsilanol (9a)

To a solution of mixture of cycloadducts (**7a,b**) (**7a : 7b** (90:10), 0.106 g, 0.33 mmol) and imidazol (0.022 g, 0.33 mmol, 1 equiv.) in CH_2Cl_2 (0.5 mL), TBDPSCl (0.090 g, 0.33 mmol, 1 equiv.) was added, and the resulting suspension was heated at 40°C in 5 days. The mixture was poured into water, neutralised with 1N HCl and extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel (22 g, 11.5x2.5 cm, EtOAc : Hexanes = 15 : 85) to obtain 0.092 g (58%) of pure **9a**. Starting material (**7a,b**) (0.046 g, 43%) was recovered. Colorless syrup, $[\alpha]_D^{25}$: -79.0° (*c* 0.2, $CHCl_3$); R_f = 0.54 (EtOAc : Hexanes 50 : 50), IR (film) 3070, 3029, 2963, 2931, 2859, 1606, 1589, 1496, 1472, 1455, 1428, 1411, 1391, 1372, 1347, 1309, 1282, 1234, 1210, 1157, 1113, 1029,1007 cm^{-1}; ^{1}HNMR ($CDCl_3$): δ (ppm) 7.72-7.26 (m, 15H, Ph), 4.91 (dd, 1H, *J* = 6.5, 3.3 Hz, 5-H), 4.61 (q, 1H, *J* = 4.9 Hz, 2'-H), 4.22 (d, 1H, *J* = 14.2 Hz, NCH_2Ph), 3.95 (dd, 1H, *J* = 10.3, 4.5 Hz, 6'e-H), 3.85 (d, 1H, *J* = 14.1 Hz, NCH_2Ph), 3.72 (qd, 1H, *J* = 9.4, 7.2 Hz, OCH_2CH_3), 3.61-3.57 (m, 5H, 4'-H), 3.51 (ddd, 1H, *J* = 9.1, 8.8, 4.6 Hz, 5'-H), 3.43 (dd, 1H, *J* = 10.9, 10.2 Hz, 6'a-H), 3.38 (qd, 1H, *J* = 9.7, 7.2 Hz, OCH_2CH_3), 3.10 (br, 1H, 3-H), 2.32 (ddd, 1H , *J* = 13.1, 10.2, 3.3 Hz, 4a-H), 1.54 (ddd, 1H, *J* = 13.1, 7.7, 6.6 Hz, 4b-H), 1.31 (d, 1H, *J* = 5.0 Hz, 7'-H), 1.16 ("t", 1H, *J* = 7.1 Hz, OCH_2CH_3), 1.10 (s, 9H, $SiC(CH_3)_3$); ^{13}CNMR ($CDCl_3$): δ (ppm) 136.9, 135.9, 135.8, 133.2, 132.6, 130.2, 130.1, 129.3, 128.0, 127.9, 127.7, 127.0 (18C, Ph), 100.7 (br, 5-C), 98.6 (2'-C), 77.6 (4'-C), 71.1 (6'-C), 65.3 (br, 3-C), 65.0 (5'-C), 63.6 (OCH_2CH_3), 60.6 (br, NCH_2Ph), 35.1 (br, 4-C), 27.0 ($SiC(CH_3)_3$), 20.3 (7'-C), 19.2 ($SiC(CH_3)_3$), 14.9 (OCH_2CH_3). Anal. Calcd for $C_{33}H_{43}NO_5Si$: C, 70.55; H, 7.71, N, 2.49. Found: C, 70.33; H, 7.58, N, 2.73.

Ethyl 4-benzyloxy-3-dibenzylaminobutanoate (11)

A solution of a mixture of diastereoisomers (**3a,b**) (80:20) (0.153 g, 0.47 mmol) and 0.160 g BnBr (0.94 mmol, 2 equiv.) was stirred in MeCN (3 mL) for 4 d at rt and than refluxed in $CHCl_3$ for 24 h. The solvent was evaporated and the flash chromatography of residue on silica gel (18 g, 8x3 cm; EtOAc : Hexanes : CH_2Cl_2 = 40 : 10 : 50) gave 0.132 g (67 %) of pure diastereoisomer (**11**). Yellowish oil, R_f = 0.56 (EtOAc : Hexanes = 30 : 70), IR (film) 3437 br, 3085, 3062, 3028, 2979, 2930, 2857, 2804, 1732, 1666 w, 1602 w, 1585 w, 1495, 1476, 1454, 1366, 1301, 1251, 1205, 1182, 1113, 1072, 1029 cm^{-1}; ^{1}HNMR ($CDCl_3$): δ (ppm) 7.43-7.28 (m, 15H, Ph), 4.55 (s, 2H, OCH_2Ph), 4.19 (qd, 1H, *J* = 10.8, 7.2, Hz,

OCH_2CH_3), 4.05 (qd, 1H, *J* = 10.8, 7.1 Hz, OCH_2CH_3), 3.80 (d, 2H, *J* = 13.7 Hz, NCH_2Ph), 3.75 (dd, 1H, *J* = 9.6, 5.5 Hz, 3a-H), 3.72 (d, 2H, *J* = 13.9 Hz, NCH_2Ph), 3.64 (dd, 1H, *J* = 9.6, 5.8 Hz, 3b-H), 3.60-3.53 (m, 1H, 2-H), 2.72 (dd, 1H, *J* = 14.3, 7.7 Hz, 1a-H), 2.58 (dd, 1H, *J* = 14.4, 6.5 Hz, 1b-H), 1.24 (t, 3H, *J* = 7.2 Hz, OCH_2CH_3); ^{13}CNMR ($CDCl_3$): δ (ppm) 172.3 ($COOCH_2CH_3$), 139.9, 138.3, 128.8, 128.3, 128.0, 127.5, 127.4, 126.8 (18C, Ph), 73.0 (OCH_2Ph), 70.1 (3-C), 60.3 (OCH_2CH_3), 55.0 (2-C), 54.3 (2C, NCH_2Ph), 34.5 (1-C), 14.0 ($COOCH_2CH_3$). Anal. Calcd for $C_{27}H_{31}NO_3$: C, 77.67; H, 7.48, N, 3.35. Found: C, 77.49; H, 7.26, N, 3.57.

Ethyl 3-(*N*-benzyl-*N*-methylamino)-4-benzyloxybutanoate (13)

A solution of a mixture of diastereoisomers (**3a,b**) (80:20) (0.141 g, 0.43 mmol) and MeI (0.488 g, 3.4 mmol, 8 equiv.) was stirred in CH_3CN (3 mL) for 3 days at rt. The solvent was evaporated, the residue was dissolved in CH_2Cl_2 and extracted with aqueous $NaHCO_3$. The aqueous extract was extracted with CH_2Cl_2, the combined organic extracts dried over Na_2SO_4 and the solvent was evaporated. Flash chromatography of the residue on silica gel (12 g, 12x2 cm; EtOAc : Hexanes = 50 : 50) gave 0.110 g (54%) of **13**. Yellow syrup, R_f = 0.63 (EtOAc : Hexanes = 50 : 50), IR (film) 3086, 3063, 3029, 2976, 2930, 2857, 2795, 1732, 1603, 1495, 1454, 1368, 1301, 1261, 1207, 1177, 1114, 1101, 1075, 1028 cm^{-1}; ^{1}HNMR ($CDCl_3$): δ (ppm) 7.39-7.32 (m, 10H, Ph), 4.56 (s, 2H, OCH_2Ph), 4.27-4.10 (m, 2H, OCH_2CH_3), 3.73 (d, 1H, *J* = 13.4 Hz, NCH_2Ph), 3.72 (dd, 1H, *J* = 8.4, 4.9 Hz, 3a -H), 3.69 (d, 1H, *J* = 13.6 Hz, NCH_2Ph), 3.58 (dd, 1H, *J* = 8.5, 5.8 Hz, 3b -H), 3.58-3.51 (m, 1H, 2-H), 2.63 (dd, 1H, *J* = 14.7, 7.4 Hz, 1a -H), 2.55 (dd, 1H, *J* = 14.7, 6.5 Hz, 1b -H), 2.27 (s, 3H, NCH_3), 1.26 (t, 3H, *J* = 7.1 Hz, OCH_2CH_3); ^{13}CNMR ($CDCl_3$): δ (ppm) 172.5 ($COOCH_2CH_3$), 139.8, 138.3, 128.5, 128.2, 128.0, 127.5, 127.4, 126.7 (12C, Ph), 73.1 (OCH_2Ph), 69.9 (C-3), 60.2 (OCH_2CH_3), 59.7 (C-2), 58.5 (NCH_2Ph), 37.3 (NCH_3), 34.3 (1-C), 14.1 ($COOCH_2CH_3$). Anal. Calcd for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97, N, 4.10. Found: C, 73.74; H, 7.59, N, 4.35.

(*2R,4S,5R*)-Ethyl 3-[5-*tert*-butyldiphenylsilanyloxy-2-methyl[1,3]dioxan-4-yl]-3-dibenzylamino-propionate (15)

A solution of isoxazolidines (**9a,b**) (10:90) (0.100 g, 0.18 mmol) and BnBr (0.031 g 0.18 mmol, 1 equiv.) was refluxed for 24 h in Et_2O (2 mL). The solvent was evaporated, the residue was dissolved in $CHCl_3$ (3 mL), and the mixture was refluxed for 2 days. The solvent was evaporated and flash chromatography of the residue on silica gel was carried out (10 g, 11x2 cm; $CHCl_3$: EtOAc : Hexanes = 1 : 10 : 90) to give 0.061 g (53 %) of **15**. Yellowish oil, $[\alpha]_D^{25}$: -12.2° (*c* 0.05, $CHCl_3$); R_f = 0.41 (EtOAc : Hexanes : $CHCl_3$ = 10 : 90 : 1), IR (film) 3068, 3027, 2959, 2931, 2858, 2805, 1736, 1603, 1589, 1494, 1471, 1454, 1428, 1408, 1368, 1276, 1191, 1154, 1113, 1054, 1029 cm^{-1}; ^{1}HNMR ($CDCl_3$): δ (ppm) 7.68-7.17 (m, 20H, Ph), 4.72 (q, 1H, *J* = 5.0, 2'-H), 4.32 (qd, 1H, *J* = 10.8, 7.2 Hz, OCH_2CH_3), 4.12-4.03 (m, 2H, H-4', OCH_2CH_3),

4.04 (d, 2H, *J* = 14.4 Hz, NCH_2Ph), 3.94 ("dd", 1H, *J* = 11.7, 2.9 Hz, 3-H), 3.65 (d, 2H, *J* = 14.4 Hz, NCH_2Ph), 3.61 (dd, 1H, *J* = 9.7, 4.0 Hz, H-6'e), 3.45 (ddd, 1H, *J* = 9.6, 9.0, 4.3 Hz, 5'-H), 3.39 (dd, 1H, *J* = 9.7 Hz, 6'a-H), 2.86 (dd, 1H, *J* = 14.4, 11.8 Hz, 2a-H), 2.30 (dd, 1H, *J* = 14.4, 3.2 Hz, 2b-H), 1.24 (dd, 3H, *J* = 7.2, 7.0 Hz, OCH_2CH_3), 1.23 (d, 3H, *J* = 5.2 Hz, 7'-H), 0.84 (s, 9H, $SiC(CH_3)_3$); ^{13}CNMR ($CDCl_3$): δ (ppm) 172.7 ($COOCH_2CH_3$), 140.3, 135.9, 135.6, 128.7, 128.0, 127.9, 127.5, 126.6 (24C, Ph), 98.3 (2'-C), 80.1 (4'-C), 71.3 (6'-C), 64.4 (5'-C), 60.3 (OCH_2CH_3), 54.9 (3-C), 54.7 (NCH_2Ph), 32.5 (C-2), 26.7 ($SiC(CH_3)_3$), 20.6 (7'-C), 19.0 ($SiC(CH_3)_3$), 14.1 (OCH_2CH_3). Anal. Calcd for $C_{40}H_{49}NO_5Si$: C, 73.70; H, 7.58, N, 2.15. Found: C, 74.02; H, 7.31, N, 2.51.

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