Diastereo- and Enantioselective Synthesis of *N*-Protected 2-Amino 1,4-Diols by an Oxa Michael Addition/1,3-Dipolar Cycloaddition Protocol

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An enantioselective synthesis of *N*-protected amino diols has been accomplished by employing a diastereoselective inter- and intramolecular 1,3-dipolar cycloaddition reaction of optically active nitrile oxides as a key step. The nitro alkane starting materials were obtained by diastereoselective oxa Michael addition of (1*R*,2*S*)-(–)-*N*-formylnorephedrine (**1**) to aliphatic (*E*)-nitro alkenes **2**, **6a**, **b** (*de* = 96 – ≥ 98%). Subsequent diastereo- and regioselective cycloaddition reactions to highly substituted 4,5-isoxazolines **5a–e**, **8a**, **b** (52–81%) and reductive ring opening led – after cleavage of the auxiliary – to amino diols **13**, **14** in good overall yields (27–40%, over five steps) and with excellent diastereomeric and enantiomeric excesses (*de*,*ee* ≥ 96%).

Introduction

The dehydration of primary nitro alkanes to nitrile oxides, which are important intermediates in the synthesis of heterocycles and other highly functionalized compounds, is a practicable way for in situ generation of these reactive dipoles. The most useful method has been developed by Mukaiyama in 1960, using aromatic isocyanates in the presence of a base such as triethylamine[1]. Hassner et al. has recently reported a method of obtaining nitrile oxides using di-*tert*-butyl dicarbonate (Boc_2O) and *N*,*N*-dimethyl-4-aminopyridine (DMAP) in 1997[2]. In addition several other methods for the dehydration of nitro compounds have been described in the literature[3]. Due to their rapid dimerisation to furoxanes and other side reactions, nitrile oxides are generated in the presence of an excess of dipolarophiles[4].

Several investigations into diastereo- and enantioselective 1,3-dipolar cycloaddition reactions using chiral nitrile oxides[5] or chiral dipolarophiles[6] for the generation of isoxazolines have been described. In 1996 Ukaij et al. used an enantiomerically pure catalyst and obtained enantiomeric excesses up to 92% in the reaction of nitrile oxides and allylic alcohols[7]. In most cases the cycloaddition products are precursors to 3-amino alcohols, which are obtainable by reductive opening of the corresponding heterocycles.

The cycloaddition reactions of chiral nitrile oxides to achiral dipolarophiles generally result in a low degree of stereoselection due to the linearity of the dipole, the lack of any preorientation in the transition state, and the long distance between existing and forming stereogenic centers. To our knowledge, diastereomeric ratios of less than 75:25 have been observed in these cases[8], therefore most of the efforts towards a stereocontrolled synthesis of 4,5-isoxazolines have been based on reactions between chiral dipolarophiles and achiral dipoles. These reactions result in very good up to complete control of stereochemistry, comparable to intramolecular[9] reactions which have found a widespread application in organic synthesis[10].

We now wish to report the addition reaction of the enantiomerically pure sodium alkoxide derived from (1*R*,2*S*)-(−)-*N*-formylnorephedrine (**1**) to (*E*)-nitro alkenes **2**, **6a**, **b** leading to nitro alkanes which can be used as precursors to chiral nitrile oxides[11]. We performed the inter- and intramolecular 1,3-dipolar cycloaddition reaction of these chiral nitrile oxides to different dipolarophiles with diastereomeric ratios up to 86:14 for the intermolecular cycloaddition reaction, and up to complete stereoselection in the intramolecular case. The synthetic strategy towards enantiomerically pure amino diols was carried out in two selected examples, in order to show a possible general method for the removal of auxiliary.

Results and Discussion

Intermolecular Cycloaddition Reactions

We have recently reported the protocol for the highly diastereoselective oxa Michael addition reaction of enantiopure alkoxides to (*E*)-nitro alkenes (*de* ≥ 96%)[11]. We chose the addition reaction of (1*R*,2*S*)-(−)-*N*-formylnorephedrine (**1**) to (*E*)-3-methylnitrobut-1-ene (**2**) in order to generate the nitro ether **3** for intermolecular cycloaddition reactions. By using Mukaiyama's method[1] of adding phenyl isocyanate and triethylamine to a solution of the primary nitro alkane **3** and the dipolarophile **4a**−**e** in acetonitrile, it was possible to obtain moderate to good chemical yields (52−81%) of several different isoxazolines **5a**−**e**. The ratio of diastereomers varied from 50:50, in the case of *tert*-butyl acrylate (**4a**), up to 86:10:2:2 in the case of norbornene (**4e**),

  1434−193X/98/0909−1793 $ 17.50+.50/0

with the *exo* cycloadducts as major diastereomers (cf. Scheme 1). This nearly exclusive (96:4) *exo* face attack of norbornene is well known in the literature[4a]. In the cases of nonsymmetrical dipolarophiles – *tert*-butyl acrylate (**4a**) and 2,3-dihydrofurane (**4d**) – only one regioisomer was isolated, which is in accordance with other examples found in the literature[4a].

Scheme 1. Intermolecular cycloaddition reactions

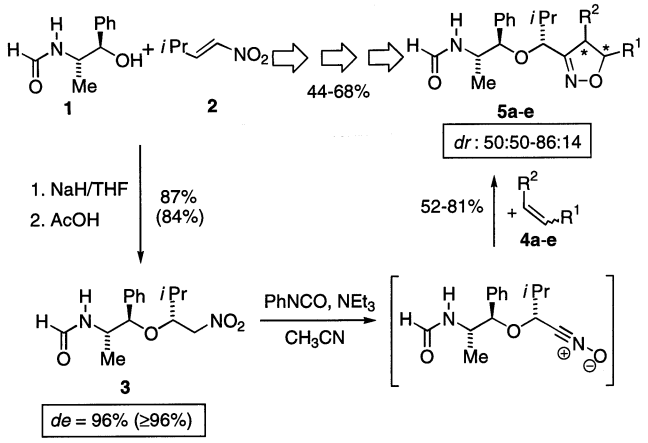


Table 1. Yields and diastereomeric ratios of the intermolecular 1,3-cycloaddition reactions of nitro compound **2** with dipolarophiles **4a–e**

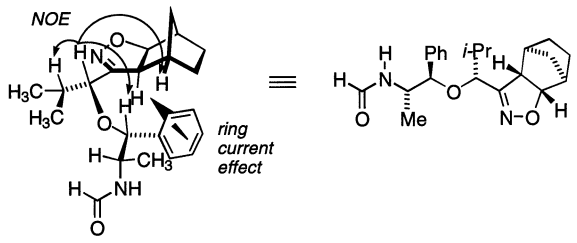
Compound	R^1	R^2	Yield [%]	Ratio of diastereomers[a]
5a	CO_2tBu	H	78	50:50
5b	CO_2Me	CO_2Me	57	75:25 (95:5)
5c	CO_2iPr	CO_2iPr	68	74:26 (90:10)
5d			52	72:28 (≥ 98:2)
5e			81	86:10:2:2 (≥ 98:2)

[a] Values in parentheses obtained after separation of the diastereomers by column chromatography.

It was possible to separate the different diastereomers partially or completely to obtain the major diastereomers with diastereomeric excesses of 80% up to ≥ 96%. Using only *tert*-butyl acrylate (**4a**) as dipolarophile, both diastereomers were obtained as an inseparable 1:1 mixture. The different steric hindrance in the case of dimethyl (**4b**) and diisopropyl fumarate (**4c**) seems not to be important for the diastereomeric ratio of the addition reaction, however with the smaller alkoxy group (**4b**) it was possible to obtain a better diastereomeric excess after chromatography (cf. Table 1).

We were able to determine the relative and therefore the absolute configuration of the enantio- and diastereomerically pure cycloaddition adduct **5e** by NMR-spectroscopic investigations[11][12]. Comparing the NMR spectra of the major and the minor *exo* diastereomer and using NOE measurements and ring-current effects of the aromatic ring, we obtained the conformation and configuration of compound **5e**, as shown in Figure 1.

Figure 1. Determination of the relative and therefore absolute configuration of **5e** by NMR studies (ring-current effects and NOE measurements)



It should be mentioned that the determination of the relative and absolute configuration of this compound was possible using NMR investigations, based on the defined favoured conformation of *N*-formylnorephdrine (**1**) in solution. We made use of this method in our previous work on the oxa Michael addition of **1** to (*E*)-nitro alkenes[11]. Nevertheless the linearity of the nitrile oxide and no stabilizing influence of hetereoatoms and either attractive or repulsive interactions made the proposal of a suitable transition state difficult. It should only be expected that the *exo* products are more favoured than the *endo* products, preferring the attack to the less hindered face of norbornene.

Intramolecular Cycloaddition Reactions

The second part of this work concerned the synthesis of nitro alkenes **6a** and **6b** bearing an additional double bond in the aliphatic side chain. This double bond in a distance of 5 or 6 atoms to the nitro group allows an intramolecular 1,3-dipolar cycloaddition reaction after the oxa Michael addition of (1*R*,2*S*)-(–)-*N*-formylnorephedrine (**1**) (Scheme 2). This application of intramolecular cycloaddition is well known in the literature. We employed the in situ generation of the nitrile oxide which was described by Hassner et al.[2][9a], using di-*tert*-butyl dicarbonate (Boc_2O) and catalytic amounts of DMAP, since Mukaiyama's method failed in this case.

Scheme 2. Intramolecular cycloaddition reactions

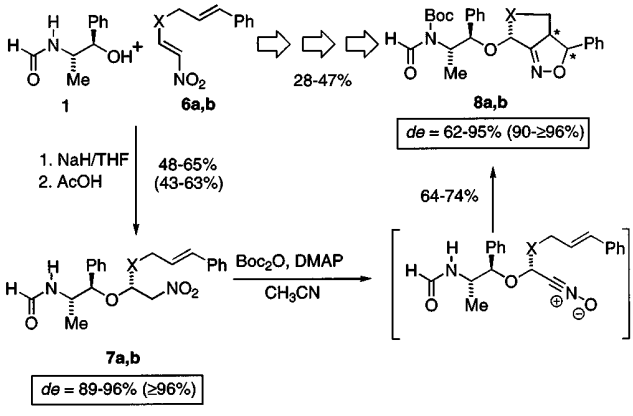


Table 2. Yields and diastereomeric excesses of the intramolecular 1,3-cycloaddition reactions of **7a** and **7b**

Compound	X	Yield [%]	*de* [%][a]
8a	$-CH_2-$	62	62 (90)
8b	$-CH_2O-$	74	95 ($\geq$ 98)

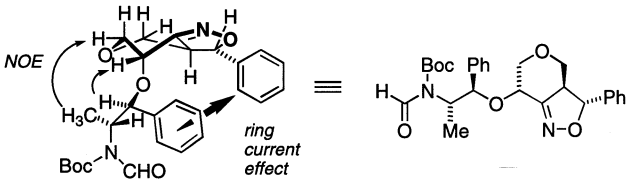
[a] Values in parentheses obtained after separation of the diastereomers by column chromatography.

The cycloaddition products were obtained in good chemical yields (62−74%) and the results, with respect to the diastereomeric excesses, were found to be better than in the case of the intermolecular reactions (*de* = 62−95%).

It was observed that the formation of the six-membered ring attached to the isoxazoline **8b** proceeded with a higher stereochemical control (*de* = 95%) than the formation of the five-membered carbocycle **8a** (*de* = 62%). This stepwise procedure − isolation of the Michael addition product followed by the cycloaddition reaction − is not as stereospecific as the consecutive protocol via intermediate silylnitronates − without protonation of the nitronates to obtain the nitro alkanes − developed by Hassner[9a]. Unfortunately trapping with silylating reagents led, in our case, to a partial ether cleavage, i.e. to retro Michael addition. In spite of this, a diastereomeric excess of 95% for **8b** in the formation of a six-membered ring system was achieved (Table 2).

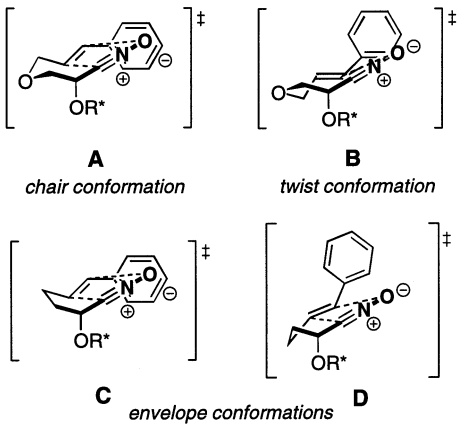
We were able to determine the relative and therefore the absolute configuration of the enantio- and diastereomerically pure cycloaddition adduct **8b** by NMR-spectroscopic investigations[11][12]. Figure 2 indicates that the favoured conformation for the six-membered ring is a chair conformation with the axial auxiliary group and an equatorially fused five-membered heterocycle. This is confirmed by NOEs, coupling constants, and the ring-current effect of the phenyl group of the auxiliary on the protons of the other aromatic ring (Figure 2).

Figure 2. Determination of the relative and therefore absolute configuration of **8b** by NMR studies (ring-current effects and NOE measurements)



In order to explain the overall stereochemical outcome, a possible model for the transition state is shown in Figure 3. The first two transition states **A** and **B** describe the generation of **8b** and **C** and **D** the generation of the five-membered carbocycle of **8a**. These postulated transition states may help to rationalize why the reaction of compound **7b** is more stereoselective than **7a**. The relative energetic difference between the chair and the twist conformation in a six-membered ring (**7b**) is larger than that between the envelope conformations in the five-membered ring system in **7a**.

Figure 3. Postulated transition states **A**−**D** for the intramolecular 1,3-cycloaddition reaction **7a** and **b** leading to the relative configurations



Conversions to Amino Diols

In order to show a general method for the synthesis of diastereo- and enantiomerically pure amino diols, removal of the auxiliary was attempted in two cases. As reported for the synthesis of vicinal amino alcohols by oxa Michael addition, the cleavage of the auxiliary could be achieved by reduction with sodium in liquid ammonia[11]. To avoid side reactions with the isoxazoline, it was necessary to cleave the N−O bond first. This reaction has been well examined by Jäger et al. with respect to the control of the relative stereochemistry. Creating a new stereogenic centre by reduction of the C−N double bond, $LiAlH_4$ in diethyl ether provided the best results in diastereoselectivity due to a postulated coordination of Li−Al−H to O−N=C in the isoxazoline[13].

It was possible to carry out this diastereoselective reduction step to obtain only one stereoisomer (*de*,*ee* $\geq$ 96%) for both examples. The stereochemical information of the existing stereogenic centres allow a very good differentiation between the diastereotopic faces of the isoxazolines **5e** and **8b**.

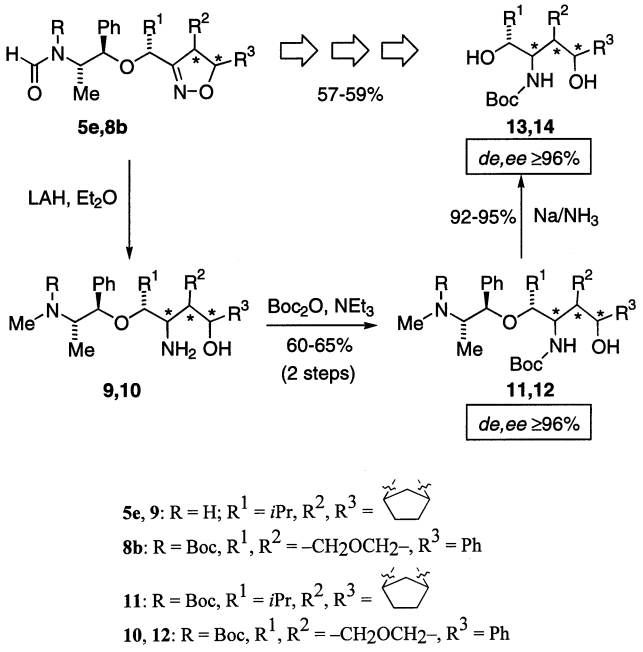
After protection of the amino function and the cleavage of the benzylic ether bond with sodium in liquid ammonia, we obtained the desired amino diols **13** and **14** in good overall yields (57−59%) and without loss of stereochemical information (Scheme 3)[11].

This conversion of isoxazolines to amino alcohols is well known and should be a practicable way to the other heterocyclic compounds as mentioned above.

Conclusion

In summary, our new method using *N*-formylnorephedrine (**1**) as oxygen nucleophile in oxa Michael addition to (*E*)-nitro alkenes **2** and **6a**, **b** has opened a way for the synthesis of primary nitro alkanes (**3**, **7a**, **b**) which are the precursors to chiral nitrile oxides. These are useful and reactive compounds for diastereoselective inter- and intramolecular 1,3-dipolar cycloaddition reactions. After cleavage of the auxiliary, this synthetic strategy led to *N*-protected enantio-

Scheme 3



merically pure amino diols **13**, **14** in good overall yields (27−40%, over five steps).

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Experimental Section

General: All solvents were dried and distilled before use. − Column chromatography: Merck silica gel 60, 0.040−0.063 mm (230−400 mesh) (flash). − Optical rotation values: Perkin-Elmer P 241, solvent UVASOL quality. − Melting points (uncorrected): Büchi 510. − IR: Perkin-Elmer FT 1750. − NMR: Varian VXR 300 and Gemini 300 (300 and 75 MHz for ^{1}H and ^{13}C, respectively), Varian Unity 500 (500 and 125 MHz for ^{1}H and ^{13}C, respectively), $CDCl_3$ as solvent, TMS as internal standard. − MS: Finnigan MAT (70 eV) and Finnigan SSQ 7000 (70 eV). − Elemental analyses (C,H,N): elementar vario EL. − High Resolution MS: Finnigan MAT, MAT 95. − The diastereomeric and enantiomeric excesses were determined by ^{1}H-NMR spectroscopy, values in parentheses obtained after separation of the diastereomers by column chromatography. The different two sets of signals in the NMR spectra − assigned as (*Z*) and (*E*) − resulted by the observable rotamers of the formyl group of the auxiliary. The NMR spectra of compound **13** and **14** show two sets of signals due to hydrogen bonding between the amino proton and the alcohol functions leading to a 5- and a 6-membered ring, respectively, resulting in a slow rotation around the C−N bond.

Products of Intermolecular 1,3-Dipolar Cycloaddition

tert-Butyl (5R/S,1′R,1″R,2″S)-(+)-3-[1′-(2″-Formylamino-1″-phenylpropoxy)-2′-methylpropyl]-4,5-dihydroisoxazol-5-carboxylate (**5a**) was obtained by dissolving (1*S*,2*R*,1′*R*)-(−)-*N*-[1-methyl-2-(2′-methyl-1′-nitromethylpropoxy)-2-phenylethyl]-formamide [(1*S*,2*R*,1′*R*)-**3**] (294 mg, 1.0 mmol) and *tert*-butyl acrylate (**4a**) (640 mg, 5.0 mmol) in acetonitrile (10 ml). To this solution triethylamine (0.2 ml) and phenyl isocyanate (357 mg, 3.0 mmol), dissolved in acetonitrile (10 ml), were added dropwise at room temp. After removing the solvent and volatile compounds under vacuum and chromatography (SiO_2; diethyl ether/pentane, 5:1), the cycloadduct was obtained as colourless oil. Yield 316 mg (78%) − Ratio of diastereomers: 1:1 − $[\alpha]_D^{24}$ = +27.7 (*c* = 1.60, $CHCl_3$) (1:1) − IR (Et_2O): $\tilde{\nu}$ = 2976 cm^{-1} (s), 2935 (s), 2875 (s), 1737 (s), 1671 (s), 1527 (s), 1496 (m), 1455 (s), 1371 (s), 1324 (m), 1303 (m), 1229 (s), 1156 (s), 1066 (s), 1002 (m), 879 (m), 842 (m), 784 (m), 746 (m), 704 (s). − ^{1}H NMR (300 MHz, $CDCl_3$): diastereomer 1: (*Z*): δ = 0.84 (d, *J* = 6.87 Hz, 3 H, C*H*$_3$CHCH$_3$), 1.16 (d, *J* = 6.52 Hz, 3 H, NCHC*H*$_3$), 1.17 (d, *J* = 6.87 Hz, 3 H, CH$_3$CHC*H*$_3$), 1.43 [s, 9 H, C(C*H*$_3$)$_3$], 1.93 (d/sept, *J* = 8.99/6.73 Hz, 1 H, CH$_3$C*H*CH$_3$), 2.58 (d/d, *J* = 17.31/11.54 Hz, 1 H, C*H*$_2$CHCO$_2$), 2.84 (d/d, *J* = 17.30/7.21 Hz, 1 H, C*H*$_2$CHCO$_2$), 4.01 (d, *J* = 9.06 Hz, 1 H, OC*H*CN), 4.23 (d/d, *J* = 11.54/7.25 Hz, 1 H, CH$_2$C*H*CO$_2$), 4.40 (d, *J* = 4.67 Hz, 1 H, C*H*C$_{ar.}$), 4.41 (d/q/d/d, *J* = 8.04/6.52/4.70/0.82 Hz, 1 H, NC*H*CH$_3$), 5.86 (br. d, 7.89 Hz, 1 H, N*H*), 7.18−7.37 (m, 5 H, C*H*$_{ar.}$), 8.00 (d, *J* = 0.80 Hz, 1 H, C*H*O); (*E*): δ = 0.83 (d, *J* = 6.87 Hz, 3 H, C*H*$_3$CHCH$_3$), 1.15 (d, *J* = 6.53 Hz, 3 H, NCHC*H*$_3$), 1.18 (d, *J* = 6.87 Hz, 3 H, CH$_3$CHC*H*$_3$), 1.42 [s, 9 H, C(C*H*$_3$)$_3$], 1.97 (d/sept, *J* = 8.99/6.73 Hz, 1 H, CH$_3$C*H*CH$_3$), 2.50 (d/d, *J* = 17.31/11.54 Hz, 1 H, C*H*$_2$CHCO$_2$), 2.81 (d/d, *J* = 17.30/7.20 Hz, 1 H, C*H*$_2$CHCO$_2$), 3.86 (d/q/d, *J* = 9.54/6.65/3.78 Hz, 1 H, NC*H*CH$_3$), 4.00 (d, *J* = 9.20 Hz, 1 H, OC*H*CN), 4.16 (d/d, *J* = 11.54/7.39 Hz, 1 H, CH$_2$C*H*CO$_2$), 4.34 (d, *J* = 3.84 Hz, 1 H, C*H*C$_{ar.}$), 5.56 (br. t, 11.54 Hz, 1 H, N*H*), 7.18−7.37 (m, 5 H, C*H*$_{ar.}$), 7.90 (d, *J* = 11.81 Hz, 1 H, C*H*O); diastereomer 2: (*Z*): δ = 0.89 (d, *J* = 6.87 Hz, 3 H, C*H*$_3$CHCH$_3$), 1.08 (d, *J* = 6.80 Hz, 3 H, CH$_3$CHC*H*$_3$), 1.11 (d, *J* = 6.66 Hz, 3 H, NCHC*H*$_3$), 1.39 [s, 9 H, C(C*H*$_3$)$_3$], 1.98 (d/sept, *J* = 8.99/6.73 Hz, 1 H, CH$_3$C*H*CH$_3$), 2.91 (d/d, *J* = 17.86/7.66 Hz, 1 H, C*H*$_2$CHCO$_2$), 3.02 (d/d, *J* = 17.44/11.26 Hz, 1 H, C*H*$_2$CHCO$_2$), 4.09 (d, *J* = 8.11 Hz, 1 H, OC*H*CN), 4.45 (d/q/d/d, *J* = 8.23/6.62/4.20/0.82 Hz, 1 H, NC*H*CH$_3$), 4.53 (d, *J* = 4.19 Hz, 1 H, C*H*C$_{ar.}$), 4.76 (d/d, *J* = 11.44/7.66 Hz, 1 H, CH$_2$C*H*CO$_2$), 5.94 (br. d, 8.17 Hz, 1 H, N*H*), 7.18−7.37 (m, 5 H, C*H*$_{ar.}$), 8.09 (d, *J* = 0.80 Hz, 1 H, C*H*O); (*E*): δ = 0.88 (d, *J* = 6.87 Hz, 3 H, C*H*$_3$CHCH$_3$), 1.12 (d, *J* = 6.86 Hz, 3 H, CH$_3$CHC*H*$_3$), 1.14 (d, *J* = 6.66 Hz, 3 H, NCHC*H*$_3$), 1.39 [s, 9 H, C(C*H*$_3$)$_3$], 1.98 (d/sept, *J* = 8.99/6.73 Hz, 1 H, CH$_3$C*H*CH$_3$), 2.80 (d/d, *J* = 18.32/7.67 Hz, 1 H, C*H*$_2$CHCO$_2$), 2.99 (d/d, *J* = 17.58/11.20 Hz, 1 H, C*H*$_2$CHCO$_2$), 3.84 (d/q/d, *J* = 9.56/6.72/4.12 Hz, 1 H, NC*H*CH$_3$), 4.04 (d, *J* = 9.14 Hz, 1 H, OC*H*CN), 4.34 (d, *J* = 4.12 Hz, 1 H, C*H*C$_{ar.}$), 4.75 (d/d, *J* = 11.58/7.80 Hz, 1 H, CH$_2$C*H*CO$_2$), 5.67 (br. t, 11.59 Hz, 1 H, N*H*), 7.18−7.37 (m, 5 H, C*H*$_{ar.}$), 7.95 (d, *J* = 11.74 Hz, 1 H, C*H*O). − ^{13}C NMR (75 MHz, $CDCl_3$): diastereomer 1: (*Z*): δ = 15.95 (*C*H$_3$CHCH$_3$), 17.87 (NCH*C*H$_3$), 19.15 (CH$_3$CH*C*H$_3$), 27.83 [C(*C*H$_3$)$_3$], 31.42 (CH$_3$*C*HCH$_3$), 38.18 (*C*H$_2$CHCO$_2$), 47.18 (N*C*HCH$_3$), 77.50 (CH$_2$*C*HCO$_2$), 78.97 (O*C*HCN), 81.96 (*C*HC$_{ar.}$), 82.32 [*C*(CH$_3$)$_3$], 127.28 (*o*-*C*H$_{ar.}$), 127.72 (*p*-*C*H$_{ar.}$), 128.32 (*m*-*C*H$_{ar.}$), 137.98 (*i*-*C*$_{ar.}$), 157.97 (*C*=N), 160.53 (*C*HO), 168.89 (*C*O$_2$); (*E*) δ = 17.87 (*C*H$_3$CHCH$_3$), 17.92 (NCH*C*H$_3$), 19.40 (CH$_3$CH*C*H$_3$), 27.83 [C(*C*H$_3$)$_3$], 31.47 (CH$_3$*C*HCH$_3$), 37.89 (*C*H$_2$CHCO$_2$), 51.20 (N*C*HCH$_3$), 77.55 (CH$_2$*C*HCO$_2$), 79.32 (O*C*HCN), 82.38 [*C*(CH$_3$)$_3$], 82.96 (*C*HC$_{ar.}$), 128.02 (*o*-*C*H$_{ar.}$), 128.32 (*m*-*C*H$_{ar.}$), 128.45 (*p*-*C*H$_{ar.}$), 136.71 (*i*-*C*$_{ar.}$), 157.86 (*C*=N), 163.87 (*C*HO), 168.69 (*C*O$_2$); diastereomer 2: (*Z*): δ = 16.36 (*C*H$_3$CHCH$_3$), 18.16 (NCH*C*H$_3$), 19.49 (CH$_3$CH*C*H$_3$), 27.88 [C(*C*H$_3$)$_3$], 31.42 (CH$_3$*C*HCH$_3$), 37.42 (*C*H$_2$CHCO$_2$), 48.11 (N*C*HCH$_3$), 77.90 (CH$_2$*C*HCO$_2$), 81.25 (O*C*HCN), 82.48 [*C*(CH$_3$)$_3$], 83.43 (*C*HC$_{ar.}$), 127.28 (*o*-*C*H$_{ar.}$), 128.05 (*p*-*C*H$_{ar.}$),

128.24 (*m*-$CH_{ar.}$), 139.06 (*i*-$C_{ar.}$), 158.15 (*C*=N), 160.40 (*C*HO), 169.18 (CO_2); (*E*): δ = 18.16 (CH_3CHCH_3), 18.25 (NCHCH_3), 19.57 (CH_3CHCH_3), 27.88 [C(CH_3)$_3$], 31.31 (CH_3CHCH_3), 37.25 (CH_2CHCO_2), 52.29 (NCHCH$_3$), 77.97 (CH_2CHCO_2), 81.33 (OCHCN), 82.53 [C(CH_3)$_3$], 84.14 ($CHC_{ar.}$), 127.63 (*o*-$CH_{ar.}$), 128.24 (*m*-$CH_{ar.}$), 128.45 (*p*-$CH_{ar.}$), 137.77 (*i*-$C_{ar.}$), 158.05 (*C*=N), 163.98 (*C*HO), 169.05 (CO_2). − MS (70 eV); *m*/*z* (%): 405 (0.5), 349 (1.3), 331 (23.1), 297 (5.9), 227 (14.3), 226 (31.9), 171 (41.6), 170 (100), 169 (8.6), 162 (34.5), 156 (14.8), 134 (28.0), 117 (11.0), 115 (6.3), 107 (7.5), 91 (9.5), 72 (14.8), 57 (33.3), 56 (8.9), 55 (34.9). − $C_{22}H_{32}N_2O_5$ (404.51): calcd. C 65.33, H 7.97, N 6.93; found C 65.71, H 8.14, N 6.62.

Dimethyl (4,5R/S,1′R,1′′R,2′′S)-(+)-3-[1′-(2′′-Formylamino-1′′-phenylpropoxy)-2′-methylpropyl]-4,5-dihydroisoxazol-4,5-dicarboxylate (**5b**) was obtained by dissolving (1*S*,2*R*,1′*R*)-(−)-*N*-[1-methyl-2-(2′-methyl-1′-nitromethylpropoxy)-2-phenylethyl]-formamide [(1*S*,2*R*,1′*R*)-**3**] (294 mg, 1.0 mmol) and dimethyl fumarate (**4b**) (721 mg, 5.0 mmol) in acetonitrile (10 ml). To this solution triethylamine (0.2 ml) and phenyl isocyanate (357 mg, 3.0 mmol), dissolved in acetonitrile (10 ml), were added dropwise at room temperature. After removing the solvent and volatile compounds under vacuum and chromatography (SiO_2; diethyl ether/pentane, 1:5), the cycloadduct was obtained as colourless solid. Yield 240 mg (57%), m.p. 79°C − *de* = 50% (*de* = 90%). − $[\alpha]_D^{24}$ = +28.0 (*c* = 0.60, $CHCl_3$) (95:5). − $[\alpha]_D^{24}$ = +66.0 (*c* = 1.02, $CHCl_3$) (2:1). − IR (KBr): $\tilde{\nu}$ = 2969 cm^{-1}(m), 2956 (m), 2887 (m), 1747 (s), 1732 (s), 1671 (s), 1647 (s), 1539 (s), 1477 (m), 1451 (s), 1387 (s), 1314 (s), 1282 (s), 1219 (s), 1181 (m), 1146 (m), 1101 (s), 1048 (s), 1029 (s), 977 (m), 828 (s), 791 (m), 749 (s), 706 (s). − ^{1}H NMR (300 MHz, $CDCl_3$): major diastereomer: (*Z*): δ = 0.84 (d, *J* = 6.86 Hz, 3 H, CH_3CHCH$_3$), 1.10 (d, *J* = 6.87 Hz, 3 H, CH$_3$CHCH_3), 1.11 (d, *J* = 6.96 Hz, 3 H, NCHCH_3), 2.34 (d/sept, *J* = 7.62/6.87 Hz, 1 H, CH$_3$C*H*CH$_3$), 3.74 (s, 3 H, OCH_3), 3.75 (d, *J* = 7.69 Hz, 1 H, CO$_2$C*H*CN), 3.78 (d, 7.56 Hz, 1 H, OC*H*CN), 3.96 (s, 3 H, OCH_3), 4.38 (d/q/d/d, *J* = 9.00/6.94/3.98/0.82 Hz, 1 H, NC*H*CH$_3$), 4.50 (d, *J* = 7.69 Hz, 1 H, C*H*CO$_2$), 4.59 (d, *J* = 4.05 Hz, 1 H, C*H*C$_{ar.}$) 5.77 (br. d, 8.79 Hz, 1 H, N*H*), 7.12−7.18 (m, 2 H, *o*-C$H_{ar.}$), 7.19−7.25 (m, 3 H, *m*,*p*-C$H_{ar.}$), 8.15 (d, *J* = 0.80 Hz, 1 H, C*H*O); (*E*): δ = 0.81 (d, *J* = 6.87 Hz, 3 H, CH_3CHCH$_3$), 1.14 (d, *J* = 6.67 Hz, 3 H, NCHCH_3), 1.21 (d, *J* = 6.87 Hz, 3 H, CH$_3$CHCH_3), 2.33 (m, Σ*J* = 33.5 Hz, 1 H, CH$_3$C*H*CH$_3$), 3.73 (d, 8.86 Hz, 1 H, OC*H*CN), 3.74 (d, *J* = 7.20 Hz, 1 H, CO$_2$C*H*CN), 3.77 (s, 3 H, OCH_3), 3.84 (d/q/d, *J* = 9.34/6.59/4.88 Hz, 1 H, NC*H*CH$_3$), 3.95 (s, 3 H, OCH_3), 4.29 (d, *J* = 4.94 Hz, 1 H, C*H*C$_{ar.}$), 4.44 (d, *J* = 8.45 Hz, 1 H, C*H*CO$_2$), 5.44 (br. t, 11.47 Hz, 1 H, N*H*), 7.04−7.08 (m, 2 H, *o*-C$H_{ar.}$), 7.19−7.25 (m, 3 H, *m*,*p*-C$H_{ar.}$), 7.90 (d, *J* = 11.81 Hz, 1 H, C*H*O); minor diastereomer: (*Z*): δ = 0.91 (d, *J* = 7.05 Hz, 3 H, CH_3CHCH$_3$), 0.98 (d, *J* = 7.05 Hz, 3 H, CH$_3$CHCH_3), 1.09 (d, *J* = 6.72 Hz, 3 H, NCHCH_3), 2.16 (sept/d, *J* = 7.05/3.69 Hz, 1 H, CH$_3$C*H*CH$_3$), 3.74 (s, 3 H, OCH_3), 3.96 (s, 3 H, OCH_3), 4.24 (d/q/d/d, *J* = 9.74/6.72/3.69/0.82 Hz, 1 H, NC*H*CH$_3$), 4.30 (d, *J* = 9.07 Hz, 1 H, CO$_2$C*H*CN), 4.32 (d, *J* = 3.68 Hz, 1 H, OC*H*CN), 4.41 (d, *J* = 9.07 Hz, 1 H, C*H*CO$_2$), 4.67 (d, *J* = 3.69 Hz, 1 H, C*H*C$_{ar.}$), 5.79 (br. d, 8.39 Hz, 1 H, N*H*), 7.12−7.18 (m, 2 H, *o*-C$H_{ar.}$), 7.19−7.40 (m, 3 H, *m*,*p*-C$H_{ar.}$), 8.15 (d, *J* = 0.82 Hz, 1 H, C*H*O); (*E*): δ = 0.91 (d, *J* = 7.05 Hz, 3 H, CH_3CHCH$_3$), 1.00 (d, *J* = 6.72 Hz, 3 H, NCHCH_3), 1.14 (d, *J* = 6.72 Hz, 3 H, CH$_3$CHCH_3), 2.15 (m, Σ*J* = 33.5 Hz, 1 H, CH$_3$C*H*CH$_3$), 3.76 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 3.98 (d/q/d, *J* = 9.07/6.72/3.08 Hz, 1 H, NC*H*CH$_3$), 4.25 (d, 3.36 Hz, 1 H, OC*H*CN), 4.27 (d, *J* = 9.06 Hz, 1 H, CO$_2$C*H*CN), 4.45 (d, *J* = 9.06 Hz, 1 H, C*H*CO$_2$), 4.52 (d, *J* = 3.02 Hz, 1 H, C*H*C$_{ar.}$), 5.45 (br. t, 11.44 Hz, 1 H, N*H*), 7.04−7.08 (m, 2 H, *o*-C$H_{ar.}$), 7.19−7.25 (m, 3 H, *m*,*p*-C$H_{ar.}$), 7.88 (d, *J* = 11.75 Hz, 1 H, C*H*O). − ^{13}C NMR (75 MHz, $CDCl_3$): major diastereomer: (*Z*): δ = 15.13 (*C*H$_3$CHCH$_3$), 18.12 (NCH*C*H$_3$), 19.27 (CH$_3$CH*C*H$_3$), 27.69 (CH$_3$*C*HCH$_3$), 32.45 (CN*C*HCO$_2$), 47.97 (N*C*HCH$_3$), 52.71, 53.34 (OCH$_3$), 65.86 (O*C*HCO$_2$), 78.52 (O*C*HCN), 83.93 (*C*HC$_{ar.}$), 127.37 (*o*-*C*H$_{ar.}$), 128.08 (*p*-*C*H$_{ar.}$), 128.16 (*m*-*C*H$_{ar.}$), 137.52 (*i*-$C_{ar.}$), 156.58 (*C*=N), 160.38 (*C*HO), 161.21, 162.70 (CO_2); (*E*): δ = 17.77 (NCH*C*H$_3$), 18.32 (*C*H$_3$CHCH$_3$), 19.44 (CH$_3$CH*C*H$_3$), 27.69 (CH$_3$*C*HCH$_3$), 32.65 (CN*C*HCO$_2$), 52.04 (N*C*HCH$_3$), 52.75, 53.34 (OCH$_3$), 63.06 (O*C*HCO$_2$), 79.30 (O*C*HCN), 86.32 (*C*HC$_{ar.}$), 127.96 (*o*-*C*H$_{ar.}$), 128.24 (*p*-*C*H$_{ar.}$), 128.51 (*m*-*C*H$_{ar.}$), 136.52 (*i*-$C_{ar.}$), 159.26 (*C*=N), 160.94, 162.78 (*C*O$_2$), 163.70 (*C*HO); minor diastereomer: (*Z*): δ = 14.16 (*C*H$_3$CHCH$_3$), 16.09 (NCH*C*H$_3$), 18.09 (CH$_3$CH*C*H$_3$), 27.64 (CH$_3$*C*HCH$_3$), 32.43 (CN*C*HCO$_2$), 49.05 (N*C*HCH$_3$), 52.82, 53.35 (OCH$_3$), 56.50 (O*C*HCO$_2$), 76.22 (O*C*HCN), 80.31 (*C*HC$_{ar.}$), 127.18 (*o*-*C*H$_{ar.}$), 128.38 (*p*-*C*H$_{ar.}$), 128.52 (*m*-*C*H$_{ar.}$), 137.30 (*i*-$C_{ar.}$), 154.12 (*C*=N), 160.42 (*C*HO), 163.78, 168.05 (CO_2); (*E*): δ = 17.34 (NCH*C*H$_3$), 17.62 (*C*H$_3$CHCH$_3$), 18.99 (CH$_3$CH*C*H$_3$), 28.04 (CH$_3$*C*HCH$_3$), 32.65 (CN*C*HCO$_2$), 52.82 (N*C*HCH$_3$), 56.05, 63.80 (OCH$_3$), 76.27 (O*C*HCO$_2$), 78.31 (O*C*HCN), 81.72 (*C*HC$_{ar.}$), 127.45 (*o*-*C*H$_{ar.}$), 127.72 (*p*-*C*H$_{ar.}$), 128.76 (*m*-*C*H$_{ar.}$), 136.18 (*i*-$C_{ar.}$), 154.65 (*C*=N), 163.97 (*C*O$_2$), 163.78 (*C*HO), 168.92 (*C*O$_2$). − MS (70 eV); *m*/*z* (%): 373 (0.7), 347 (12.3), 346 (61.4), 241 (15.5), 240 (100), 208 (27.9), 181 (9.1), 180 (88.7), 162 (14.3), 148 (7.4), 134 (24.6), 126 (26.0), 120 (18.9), 118 (5.5), 117 (12.9), 115 (8.6), 107 (8.1), 105 (8.6), 91 (13.8), 77 (8.5), 72 (12.7), 58 (8.8), 56 (10.9), 55 (26.2). − $C_{21}H_{28}N_2O_7$ (420.46): calcd. C 59.99, H 6.71, N 6.66; found C 60.31, H 6.27, N 6.61.

Diisopropyl (4,5R/S,1′R,1′′R,2′′S)-(+)-3-[1′-(2′′-Formylamino-1′′-phenylpropoxy)-2′-methylpropyl]-4,5-dihydroisoxazol-4,5-dicarboxylate (**5c**) was obtained by dissolving (1*S*,2*R*,1′*R*)-(−)-*N*-[1-methyl-2-(2′-methyl-1′-nitromethylpropoxy)-2-phenylethyl]-formamide [(1*S*,2*R*,1′*R*)-**3**] (294 mg, 1.0 mmol) and diisopropyl fumarate (**4c**) (1.0 g, 5.0 mmol) in acetonitrile (10 ml). To this solution triethylamine (0.2 ml) and phenyl isocyanate (357 mg, 3.0 mmol), dissolved in acetonitrile (10 ml), were added dropwise at room temp. After removing the solvent and volatile compounds under vacuum and chromatography (SiO_2; diethyl ether/pentane, 1:5), the cycloadduct was obtained as colourless oil. Yield 324 mg (68%) − *de* = 47% (*de* = 80%). − $[\alpha]_D^{24}$ = +44.4 (*c* = 2.33, $CHCl_3$) (9:1). − $[\alpha]_D^{24}$ = +106.1 (*c* = 1.53, $CHCl_3$) (1:1). − IR ($CHCl_3$): $\tilde{\nu}$ = 2983 cm^{-1} (s), 2937 (m), 2876 (m), 1737 (s), 1684 (s), 1608 (m), 1513 (m), 1497 (m), 1468 (m), 1455 (m), 1387 (s), 1376 (s), 1277 (s), 1222 (s), 1202 (s), 1182 (s), 1147 (m), 1105 (s), 1066 (s), 890 (m), 828 (m), 757 (s), 704 (m). − ^{1}H NMR (300 MHz, $CDCl_3$): major diastereomer: (*Z*): δ = 0.90 (d, *J* = 7.05 Hz, 3 H, CH_3CHCH$_3$), 1.03 (d, *J* = 6.87 Hz, 3 H, CH$_3$CHCH_3), 1.06 (d, *J* = 6.71 Hz, 3 H, NCHCH_3), 1.11 [d, *J* = 6.38 Hz, 3 H, OCH(CH_3)$_2$], 1.14 [d, *J* = 6.38 Hz, 3 H, OCH(CH_3)$_2$], 1.28 [d, *J* = 6.38 Hz, 6 H, OCH(CH_3)$_2$], 2.22 (d/sept, *J* = 8.06/7.05 Hz, 1 H, CH$_3$C*H*CH$_3$), 4.14 (d, *J* = 7.05 Hz, 1 H, CO$_2$C*H*CN), 4.23 (d, *J* = 8.06 Hz, 1 H, OC*H*CN), 4.50 (sept, *J* = 6.38 Hz, 1 H, CO$_2$C*H*), 4.53 (d, *J* = 3.68 Hz, 1 H, C*H*C$_{ar.}$), 4.85 (d/q/d/d, *J* = 8.73/6.71/3.69/0.82 Hz, 1 H, NC*H*CH$_3$), 5.07 (sept, *J* = 6.38 Hz, 1 H, CO$_2$C*H*), 5.14 (d, *J* = 7.05 Hz, 1 H, OC*H*CO$_2$), 5.63 (br. d, 8.73 Hz, 1 H, N*H*), 7.14−7.38 (m, 5 H, C$H_{ar.}$), 8.14 (d, *J* = 0.82 Hz, 1 H, C*H*O); (*E*): δ = 0.89 (d, *J* = 6.71 Hz, 3 H, CH_3CHCH$_3$), 1.03 (d, *J* = 6.87 Hz, 3 H, CH$_3$CHCH_3), 1.06 (d, *J* = 6.71 Hz, 3 H, NCHCH_3), 1.12 [d, *J* = 6.38 Hz, 3 H, OCH(CH_3)$_2$], 1.13 [d, *J* = 6.38 Hz, 3 H, OCH(CH_3)$_2$], 1.28 [d, *J* = 6.38 Hz, 6 H, OCH(CH_3)$_2$], 2.21 (d/sept, *J* = 9.07/7.05 Hz, 1 H, CH$_3$C*H*CH$_3$), 3.91 (m, Σ*J* = 24 Hz, 1 H, NC*H*CH$_3$), 4.08 (d, *J* = 9.07 Hz, 1 H,

OC*H*CN), 4.09 (d, *J* = 7.38 Hz, 1 H, CO_2CHCN), 4.31 (d, *J* = 4.03 Hz, 1 H, $CHC_{ar.}$), 4.49 (sept, *J* = 6.38 Hz, 1 H, CO_2CH), 5.10 (sept, *J* = 6.38 Hz, 1 H, CO_2CH), 5.15 (d, *J* = 7.39 Hz, 1 H, $OCHCO_2$), 5.40 (br. t, 10.44 Hz, 1 H, N*H*), 7.14−7.38 (m, 5 H, $CH_{ar.}$), 7.92 (d, *J* = 11.78 Hz, 1 H, C*H*O); minor diastereomer: (*Z*): δ = 0.85 (d, *J* = 6.72 Hz, 3 H, CH_3CHCH_3), 1.03 (d, *J* = 6.71 Hz, 3 H, CH_3CHCH_3), 1.11 (d, *J* = 6.71 Hz, 3 H, $NCHCH_3$), 1.12 [d, *J* = 6.38 Hz, 3 H, $OCH(CH_3)_2$], 1.15 [d, *J* = 6.38 Hz, 3 H, $OCH(CH_3)_2$], 1.38 [d, *J* = 6.38 Hz, 6 H, $OCH(CH_3)_2$], 2.35 (oct, *J* = 6.71 Hz, 1 H, CH_3CHCH_3), 4.14 (d, *J* = 7.05 Hz, 1 H, CO_2CHCN), 4.37 (d/q/d/d, *J* = 9.06/6.72/3.36/0.82 Hz, 1 H, $NCHCH_3$), 4.52 (d, *J* = 7.06 Hz, 1 H, OC*H*CN), 4.61 (d, *J* = 4.03 Hz, 1 H, $CHC_{ar.}$), 5.10 (sept, *J* = 6.37 Hz, 1 H, CO_2CH), 5.15 (d, *J* = 7.05 Hz, 1 H, $OCHCO_2$), 5.25 (sept, *J* = 6.38 Hz, 1 H, CO_2CH), 5.59 (br. d, 9.40 Hz, 1 H, N*H*), 7.13−7.38 (m, 5 H, $CH_{ar.}$), 8.14 (d, *J* = 0.82 Hz, 1 H, C*H*O); (*E*): δ = 0.82 (d, *J* = 6.72 Hz, 3 H, CH_3CHCH_3), 1.05 (d, *J* = 6.71 Hz, 3 H, CH_3CHCH_3), 1.06 (d, *J* = 6.71 Hz, 3 H, $NCHCH_3$), 1.09 8d, *J* = 6.38 Hz, 3 H, $OCH(CH_3)_2$], 1.16 [d, *J* = 6.38 Hz, 3 H, $OCH(CH_3)_2$], 1.37 [d, *J* = 6.38 Hz, 6 H, $OCH(CH_3)_2$], 2.21 (d/sept, *J* = 9.07/7.05 Hz, 1 H, CH_3CHCH_3), 3.83 (m, Σ*J* = 24 Hz, 1 H, $NCHCH_3$), 4.08 (d, *J* = 9.07 Hz, 1 H, OC*H*CN), 4.14 (d, *J* = 7.05 Hz, 1 H, CO_2CHCN), 4.30 (d, *J* = 4.03 Hz, 1 H, $CHC_{ar.}$), 4.36 (sept, *J* = 6.38 Hz, 1 H, CO_2CH), 5.23 (sept, *J* = 6.38 Hz, 1 H, CO_2CH), 5.15 (d, *J* = 7.05 Hz, 1 H, $OCHCO_2$), 5.45 (br. t, 10.44 Hz, 1 H, N*H*), 7.02−7.10 (m, 2 H, *o*-$CH_{ar.}$), 7.13−7.38 (m, 3 H, $CH_{ar.}$), 7.88 (d, *J* = 12.09 Hz, 1 H, C*H*O) − ^{13}C NMR (75 MHz, $CDCl_3$): major diastereomer: (*Z*): δ = 16.23 (CH_3CHCH_3), 17.71 ($NCHCH_3$), 18.84 (CH_3CHCH_3), 21.49, 21.53, 21.61, 21.63 [$OCH(CH_3)_2$], 30.28 (CH_3CHCH_3), 45.65 ($NCHCH_3$), 57.04 ($CNCHCO_2$), 70.18, 70.21 [$OCH(CH_3)_2$], 76.75 (OCHCN), 81.15 ($OCHCO_2$), 82.06 ($CHC_{ar.}$), 126.13 (*o*-$CH_{ar.}$), 128.06 (*p*-$CH_{ar.}$), 128.25 (*m*-$CH_{ar.}$), 137.12 (*i*-$C_{ar.}$), 154.15 (*C*=N), 160.45 (*C*HO), 167.23, 168.01 (CO_2); (*E*): δ = 17.71 ($NCHCH_3$), 17.98 (CH_3CHCH_3), 18.84 (CH_3CHCH_3), 19.30, 21.49, 21.61, 21.63 [$OCH(CH_3)_2$], 30.54 (CH_3CHCH_3), 49.70 ($NCHCH_3$), 56.56 ($CNCHCO_2$), 69.96, 70.06 [$OCH(CH_3)_2$], 77.37 (OCHCN), 82.19 ($OCHCO_2$), 82.61 ($CHC_{ar.}$), 127.98 (*o*-$CH_{ar.}$), 128.11 (*p*-$CH_{ar.}$), 128.39 (*m*-$CH_{ar.}$), 136.19 (*i*-$C_{ar.}$), 155.98 (*C*=N), 163.49 (*C*HO), 166.93, 167.88 (CO_2); minor diastereomer: (*Z*): δ = 15.28 (CH_3CHCH_3), 18.24 ($NCHCH_3$), 18.43 (CH_3CHCH_3), 19.16, 21.49, 21.61, 21.63 [$OCH(CH_3)_2$], 32.48 (CH_3CHCH_3), 48.19 ($NCHCH_3$), 56.56 ($CNCHCO_2$), 70.25, 71.22 [$OCH(CH_3)_2$], 76.68 (OCHCN), 78.75 ($OCHCO_2$), 84.31 ($CHC_{ar.}$), 127.48 (*o*-$CH_{ar.}$), 128.20 (*p*-$CH_{ar.}$), 128.33 (*m*-$CH_{ar.}$), 137.68 (*i*-$C_{ar.}$), 160.18 (*C*=N), 160.40 (*C*HO), 162.39, 167.93 (CO_2); (*E*): δ = 16.23 (CH_3CHCH_3), 17.83 ($NCHCH_3$), 17.98 (CH_3CHCH_3), 19.31, 21.49, 21.61, 27.55 [$OCH(CH_3)_2$], 32.59 (CH_3CHCH_3), 52.27 ($NCHCH_3$), 58.81 ($CNCHCO_2$), 70.06, 70.18 [$OCH(CH_3)_2$], 76.04 (OCHCN), 79.33 ($OCHCO_2$), 86.44 ($CHC_{ar.}$), 127.61 (*o*-$CH_{ar.}$), 128.20 (*p*-$CH_{ar.}$), 128.58 (*m*-$CH_{ar.}$), 136.78 (*i*-$C_{ar.}$), 154.06 (*C*=N), 163.68 (*C*HO), 167.00, 167.23 (CO_2). − MS (70 eV); *m*/*z* (%): 477 (0.2), 405 (10.2), 404 (33.7), 300 (6.8), 299 (34.9), 298 (83.1), 281 (9.4), 280 (56.1), 257 (8.7), 256 (9.7), 239 (15.5), 238 (100), 215 (6.5), 214 (13.0), 196 (47.1), 194 (6.8), 178 (7.4), 168 (16.7), 163 (5.5), 162 (45.9), 152 (17.3), 150 (13.0), 140 (8.0), 134 (40.8), 124 (20.2), 118 (9.8), 117 (20.5), 115 (11.5), 110 (8.5), 107 (16.6), 106 (8.4), 105 (14.3), 98 (5.4), 91 (15.4), 82 (5.8), 79 (13.9), 77 (13.6), 73 (8.2), 72 (30.7), 56 (18.7), 55 (47.5). − $C_{25}H_{36}N_2O_7$ (476.57): calcd. C 63.01, H 7.61, N 5.89; found C 62.88, H 7.38, N 6.39.

(1S,2R,1′R,3a″S/R,6a″R/S)-(±)-N-(2-{[2′-Methyl-1′-(2″,3″,3a″,6″a-tetrahydrofuro[3″,2″-d]isoxazol-3″-yl)propyl]oxy}-1-methyl-2-phenylethyl)formamide (**5d**) was obtained by dissolving (1*S*,2*R*,1′*R*)-(−)-*N*-(1-methyl-2-{[2′-methyl-1′-(nitromethyl)-propyl]oxy}-2-phenylethyl)formamide [(1*S*,2*R*,1′*R*)-**3**] (294 mg, 1.0 mmol) and 2,3-dihydrofurane (**4d**) (357 mg, 3.0 mmol) in acetonitrile (10 ml). To this solution triethylamine (0.2 ml) and phenyl isocyanate (357 mg, 3.0 mmol), dissolved in acetonitrile (10 ml), were added dropwise at room temperature. After removing the solvent and volatile compounds under vacuum and chromatography (SiO_2; diethyl ether), the cycloadduct was obtained as colourless solid. Yield 180 mg (52%), m.p. 73°C − *de* = 44% (*de* ≥ 96%). − $[\alpha]_D^{24}$ = −73.8 (*c* = 0.83, $CHCl_3$) (≥ 98:2). − $[\alpha]_D^{24}$ = +28.3 (*c* = 0.38, $CHCl_3$) (14:86). − IR (KBr): $\tilde{\nu}$ = 2972 cm^{-1} (s), 2882 (s), 2762 (m), 2380 (m), 2188 (m), 1662 (s), 1613 (m), 1585 (m), 1511 (s), 1453 (s), 1385 (s), 1364 (s), 1330 (m) 1281 (m), 1201 (s), 1143 (m), 1119 (s), 1079 (s), 1063 (s), 1029 (s), 1013 (m), 940 (s), 785 (m). − ^{1}H NMR (500 MHz, $CDCl_3$): major diastereomer: (*Z*): δ = 0.92 (d, *J* = 6.80 Hz, 3 H, CH_3CHCH_3), 1.09 (d, *J* = 6.73 Hz, 3 H, CH_3CHCH_3), 1.14 (d, *J* = 6.60 Hz, 3 H, $NCHCH_3$), 1.81 (d/d/d/d, *J* = 12.50/12.50/8.93/7.49 Hz, 1 H, CH_2CH_2O), 2.12 (d/sept, *J* = 8.99/6.67 Hz, 1 H, CH_3CHCH_3), 2.18 (d/d, *J* = 12.39/4.57 Hz, 1 H, CH_2CH_2O), 2.94 (d/d/d, *J* = 12.47/8.93/4.81 Hz, 1 H, CH_2CH_2O), 3.60 (d/d, *J* = 8.72/6.35 Hz, 1 H, $CNCHCH_2$), 3.63 (d/d *J* = 8.24/8.24 Hz, 1 H, CH_2CH_2O), 4.03 (d, *J* = 8.93 Hz, 1 H, OC*H*CN), 4.54 (d, *J* = 3.50 Hz, 1 H, $CHC_{ar.}$), 4.56 (d/q/d/d, *J* = 9.89/6.86/3.43/0.62 Hz, 1 H, $NCHCH_3$), 5.44 (br. d, 7.35 Hz, 1 H, N*H*), 6.05 (d, *J* = 6.25 Hz, 1 H, OC*H*O), 7.26−7.29 (m, 2 H, *o*-$CH_{ar.}$), 7.30−7.40 (m, 3 H, *m*,*p*-$CH_{ar.}$), 8.13 (d, *J* = 0.62 Hz, 1 H, C*H*O); (*E*): δ = 0.92 (d, *J* = 6.80 Hz, 3 H, CH_3CHCH_3), 1.13 (d, *J* = 6.93 Hz, 3 H, CH_3CHCH_3), 1.18 (d, *J* = 6.66 Hz, 3 H, $NCHCH_3$), 1.75 (m, Σ*J* = 26.0 Hz, 1 H, CH_2CH_2O), 2.11 (d/sept, *J* = 8.99/6.67 Hz, 1 H, CH_3CHCH_3), 2.18 (m, Σ*J* = 30.5 Hz, 1 H, CH_2CH_2O), 2.78 (d/d/d, *J* = 12.43/8.99/4.80 Hz, 1 H, CH_2CH_2O), 3.60 (m, 2 H, CH_2CH_2O, $CNCHCH_2$), 3.92 (d/q/d, *J* = 10.16/6.73/3.43 Hz, 1 H, $NCHCH_3$), 3.97 (d, *J* = 8.92 Hz, 1 H, OC*H*CN), 4.40 (d, *J* = 3.43 Hz, 1 H, $CHC_{ar.}$), 5.28 (br. t, 11.50 Hz, 1 H, N*H*), 6.08 (d, *J* = 6.19 Hz, 1 H, OC*H*O), 7.24−7.26 (m, 2 H, *o*-$CH_{ar.}$), 7.30−7.40 (m, 3 H, *m*,*p*-$CH_{ar.}$), 8.03 (d, *J* = 11.81 Hz, 1 H, C*H*O); minor diastereomer: (*Z*): δ = 0.94 (d, *J* = 6.71 Hz, 3 H, CH_3CHCH_3), 1.13 (d, *J* = 6.72 Hz, 3 H, CH_3CHCH_3), 1.20 (d, *J* = 7.02 Hz, 3 H, $NCHCH_3$), 1.88 (m, Σ*J* = 32.0 Hz, 1 H, CH_2CH_2O), 1.91 (d/sept, *J* = 8.85/6.72 Hz, 1 H, CH_3CHCH_3), 2.07 (d/d, *J* = 12.39/5.46 Hz, 1 H, CH_2CH_2O), 3.20 (d/d, *J* = 8.55/6.71 Hz, 1 H, $CNCHCH_2$), 3.39 (d/d/d, *J* = 12.21/8.55/5.34 Hz, 1 H, CH_2CH_2O), 3.92 (d/d *J* = 10.06/8.24 Hz, 1 H, CH_2CH_2O), 3.97 (d, *J* = 7.63 Hz, 1 H, OC*H*CN), 4.39 (d/q/d/d, *J* = 10.22/7.02/5.19/0.80 Hz, 1 H, $NCHCH_3$), 4.44 (d, *J* = 4.89 Hz, 1 H, $CHC_{ar.}$), 5.61 (br. d, 7.80 Hz, 1 H, N*H*), 5.72 (d, *J* = 6.41 Hz, 1 H, OC*H*O), 7.18−7.26 (m, 2 H, *o*-$CH_{ar.}$), 7.26−7.38 (m, 3 H, *m*,*p*-$CH_{ar.}$), 8.07 (d, *J* = 0.82 Hz, 1 H, C*H*O); (*E*): δ = 0.84 (d, *J* = 6.71 Hz, 3 H, CH_3CHCH_3), 1.15 (d, *J* = 6.71 Hz, 3 H, CH_3CHCH_3), 1.19 (d, *J* = 6.72 Hz, 3 H, $NCHCH_3$), 1.85 (m, Σ*J* = 28.0 Hz, 1 H, CH_2CH_2O), 2.09 (m, Σ*J* = 30.5 Hz, 1 H, CH_2CH_2O), 2.32 (d/sept, *J* = 7.94/6.72 Hz, 1 H, CH_3CHCH_3), 3.15 (d/d, *J* = 8.89/4.95 Hz, 1 H, CH_2CH_2O), 3.60 (m, 2 H, CH_2CH_2O, $CNCHCH_2$), 3.88 (m, Σ*J* = 23.6 Hz, 1 H, $NCHCH_3$), 4.20 (d, *J* = 4.88 Hz, 1 H, $CHC_{ar.}$), 4.22 (d, *J* = 9.05 Hz, 1 H, OC*H*CN), 5.41 (br. t, 11.50 Hz, 1 H, N*H*), 5.62 (d, *J* = 6.41 Hz, 1 H, OC*H*O), 7.16−7.24 (m, 2 H, *o*-$CH_{ar.}$), 7.26−7.38 (m, 3 H, *m*,*p*-$CH_{ar.}$), 7.95 (d, *J* = 11.60 Hz, 1 H, C*H*O). − ^{13}C NMR (125 MHz, $CDCl_3$): major diastereomer: (*Z*): δ = 17.02 (CH_3CHCH_3), 18.29 ($NCHCH_3$), 19.20 (CH_3CHCH_3), 29.38 (CH_2CH_2O), 30.65 (CH_3CHCH_3), 45.86 ($NCHCH_3$), 51.71 ($CNCHCH_2$), 66.30 (CH_2CH_2O), 78.79 (OCHCN), 80.89 ($CHC_{ar.}$), 108.45 (OCHO), 127.33 (*o*-$CH_{ar.}$), 128.33 (*p*-$CH_{ar.}$), 128.44 (*m*-$CH_{ar.}$), 136.97 (*i*-$C_{ar.}$), 156.88 (*C*=N), 160.35 (*C*HO); (*E*): δ = 18.42 ($NCHCH_3$), 18.63 (CH_3CHCH_3), 19.69 (CH_3CHCH_3), 29.29

(CH_2CH_2O), 30.72 (CH_3CHCH_3), 50.21 ($NCHCH_3$), 51.33 ($CNCHCH_2$), 66.18 (CH_2CH_2O), 79.38 ($OCHCN$), 81.85 ($CHC_{ar.}$), 108.65 ($OCHO$), 127.83 (*o*-$CH_{ar.}$), 128.62 (*m*-$CH_{ar.}$), 129.33 (*p*-$CH_{ar.}$), 135.82 (*i*-$C_{ar.}$), 156.88 ($C{=}N$), 163.59 (CHO); minor diastereomer: (*Z*): δ = 16.13 (CH_3CHCH_3), 18.74 ($NCHCH_3$), 19.23 (CH_3CHCH_3), 29.60 (CH_2CH_2O), 31.17 (CH_3CHCH_3), 48.11 ($NCHCH_3$), 51.75 ($CNCHCH_2$), 66.40 (CH_2CH_2O), 82.02 ($OCHCN$), 83.89 ($CHC_{ar.}$), 109.13 ($OCHO$), 127.68 (*o*-$CH_{ar.}$), 128.24 (*p*-$CH_{ar.}$), 128.31 (*m*-$CH_{ar.}$), 136.48 (*i*-$C_{ar.}$), 158.70 ($C{=}N$), 160.18 (CHO); (*E*): δ = 18.06 ($NCHCH_3$), 18.85 (CH_3CHCH_3), 19.44 (CH_3CHCH_3), 29.37 (CH_2CH_2O), 30.94 (CH_3CHCH_3), 51.20 ($NCHCH_3$), 52.13 ($CNCHCH_2$), 66.30 (CH_2CH_2O), 82.71 ($OCHCN$), 85.02 ($CHC_{ar.}$), 109.44 ($OCHO$), 127.83 (*o*-$CH_{ar.}$), 128.15 (*m*-$CH_{ar.}$), 128.55 (*p*-$CH_{ar.}$), 137.30 (*i*-$C_{ar.}$), 158.71 ($C{=}N$), 163.74 (CHO). − MS (70 eV); *m/z* (%): 274 (16.5), 169 (47.6), 168 (100), 162 (12.2), 154 (30.9), 134 (23.8), 118 (6.1), 117 (14.3), 115 (10.0), 107 (6.1), 105 (9.8), 95 (14.1), 91 (16.3), 79 (10.3), 77 (12.9), 72 (33.4), 70 (7.3), 68 (5.5), 56 (11.9), 55 (27.4), 54 (5.7), 53 (8.3), 51 (7.1). − $C_{19}H_{26}N_2O_4$ (346.43): calcd. C 65.88, H 7.57, N 8.09; found C 65.62, H 7.88, N 7.98.

(1S,2R,1′R,1″R/S,2″R/S,6‴R/S,7‴R/S)-(±)-N-(1-Methyl-2-{[2′-methyl-1′-(3″-oxa-4″-azatricyclo[5.2.1.0.^{2,6}]dec-4″-en-5″-yl)propyl]oxy}-2-phenylethyl)formamide (**5e**) was obtained by dissolving (1*S*,2*R*,1′*R*)-(−)-*N*-(1-methyl-2-{[2′-methyl-1′-(nitromethyl)propyl]oxy}-2-phenylethyl)formamide [(1*S*,2*R*,1′*R*)-**3**] (294 mg, 1.0 mmol) and norbornene (**4e**) (471 mg, 5.0 mmol) in acetonitrile (10 ml). To this solution triethylamine (0.2 ml) and phenyl isocyanate (357 mg, 3.0 mmol), dissolved in acetonitrile (10 ml), were added dropwise at room temp. After removing the solvent and volatile compounds under vacuum and chromatography (SiO_2; diethyl ether), the cycloadduct was obtained as colourless solid. Yield 300 mg (81%), m.p. 104°C. − *de* = 72% (*de* ≥ 96%), *exo*/*endo* 96:4. − $[\alpha]_D^{24}$ = −0.8 (*c* = 1.00, $CHCl_3$). − $[\alpha]_D^{24}$ = −0.7 (*c* = 0.67, $CHCl_3$) (≥ 98:2). − $[\alpha]_D^{24}$ = +83.7 (*c* = 0.58, $CHCl_3$) (9:91). − IR (KBr): $\tilde{\nu}$ = 2959 cm^{-1} (s), 2932 (s), 2895 (s), 2867 (s), 2755 (m), 1694 (s), 1604 (m), 1504 (s), 1454 (s), 1386 (s), 1261 (m), 1198 (s), 1138 (m), 1059 (s), 1039 (s), 996 (m), 850 (s), 811 (m), 789 (m), 778 (m), 750 (m), 708 (s). − ^{1}H NMR (500 MHz, $CDCl_3$): *exo*-major diastereomer: (*Z*): δ = 0.76 (d/quint, *J* = 10.60/1.49 Hz, 1 H, $CHCH_2CH$), 0.90 (d, *J* = 6.79 Hz, 3 H, CH_3CHCH_3), 0.95−1.13 (m, 3 H, $CHCH_2CH$, CH_2CH_2CHHCO), 1.08 (d, *J* = 6.79 Hz, 3 H, $NCHCH_3$), 1.12 (d, *J* = 6.63 Hz, 3 H, CH_3CHCH_3), 1.24−1.44 (m, 2 H, CH_2CH_2CHHCO), 2.06 (d/sept, *J* = 8.72/6.73 Hz, 1 H, CH_3CHCH_3), 2.24 (br. d, *J* = 3.97 Hz, 1 H, CH_2CHCH_2CH), 2.42 (br. d, *J* = 4.73 Hz, 1 H, $CHCH_2CHHCO$), 2.89 (br. d, *J* = 8.39 Hz, 1 H, $NCCHHCO$), 3.99 (d, *J* = 8.77 Hz, 1 H, $OCHCN$), 4.37 (d/t, *J* = 8.32/1.17 Hz, 1 H, $OCHCHCH_2$), 4.53 (d, *J* = 3.16 Hz, 1 H, $CHC_{ar.}$), 4.56 (d/q/d/d, *J* = 10.07/6.72/3.36/0.76 Hz, 1 H, $NCHCH_3$), 5.49 (br. d, *J* = 8.70 Hz, 1 H, NH), 7.22−7.38 (m, 5 H, $CH_{ar.}$), 8.15 (d, *J* = 0.77 Hz, 1 H, CHO); (*E*): δ = 0.69 (d/quint, *J* = 10.60/1.49 Hz, 1 H, $CHCH_2CH$), 0.90 (d, *J* = 6.79 Hz, 3 H, CH_3CHCH_3), 0.95−1.13 (m, 3 H, $CHCH_2CH$, CH_2CH_2CHHCO), 1.12 (d, *J* = 6.79 Hz, 3 H, $NCHCH_3$), 1.16 (d, *J* = 6.64 Hz, 3 H, CH_3CHCH_3), 1.24−1.44 (m, 2 H, CH_2CH_2CHHCO), 2.08 (d/sept, *J* = 8.72/6.80 Hz, 1 H, CH_3CHCH_3), 2.14 (br. d, *J* = 3.89 Hz, 1 H, CH_2CHCH_2CH), 2.40 (br. d, *J* = 5.12 Hz, 1 H, $CHCH_2CHHCO$), 2.87 (br. d, *J* = 7.93 Hz, 1 H, $NCCHHCO$), 3.92 (d/q/d, *J* = 10.07/6.79/3.28 Hz, 1 H, $NCHCH_3$), 3.93 (d, *J* = 9.08 Hz, 1 H, $OCHCN$), 4.37 (d, *J* = 3.43 Hz, 1 H, $CHC_{ar.}$), 4.39 (d/t, *J* = 8.92/1.30 Hz, 1 H, $OCHCHCH_2$), 5.27 (br. t, *J* = 10.60 Hz, 1 H, NH), 7.22−7.38 (m, 5 H, $CH_{ar.}$), 8.04 (d, *J* = 11.59 Hz, 1 H, CHO); *exo*-minor diastereomer: (*Z*): δ = 0.78−1.02 (m, 1 H, $CHCH_2CH$), 0.90 (d, *J* = 6.71 Hz, 3 H, CH_3CHCH_3), 1.06−1.45 (m, 5 H, $CHCH_2CH$, CH_2CH_2CHHCO), 1.16 (d, *J* = 6.71 Hz, 6 H, $NCHCH_3$, CH_3CHCH_3), 2.06 (d/sept, *J* = 8.73/6.72 Hz, 1 H, CH_3CHCH_3), 2.25 (m, Σ*J* = 8.0 Hz, 1 H, CH_2CHCH_2CH), 2.39 (m, Σ*J* = 7.5 Hz, 1 H, $CHCH_2CHHCO$), 2.51 (br. d, *J* = 8.40 Hz, 1 H, $NCCHHCO$), 3.84 (d/t, *J* = 8.39/1.17 Hz, 1 H, $OCHCHCH_2$), 3.94 (d, *J* = 9.06 Hz, 1 H, $OCHCN$), 4.40 (d/q/d/d, *J* = 8.73/6.38/5.31/0.80 Hz, 1 H, $NCHCH_3$), 4.41 (d, *J* = 5.07 Hz, 1 H, $CHC_{ar.}$), 5.59 (br. d, *J* = 7.39 Hz, 1 H, NH), 7.22−7.38 (m, 5 H, $CH_{ar.}$), 8.15 (d, *J* = 0.84 Hz, 1 H, CHO); (*E*): δ = 0.78−1.02 (m, 1 H, $CHCH_2CH$), 0.87 (d, *J* = 6.71 Hz, 3 H, CH_3CHCH_3), 1.06−1.45 (m, 5 H, $CHCH_2CH$, CH_2CH_2CHHCO), 1.16 (d, *J* = 6.71 Hz, 3 H, $NCHCH_3$), 1.18 (d, *J* = 6.72 Hz, 3 H, CH_3CHCH_3), 1.85 (m, Σ*J* = 20.0 Hz, 1 H, CH_3CHCH_3), 2.25 (m, Σ*J* = 8.0 Hz, 1 H, CH_2CHCH_2CH), 2.39 (m, Σ*J* = 7.5 Hz, 1 H, $CHCH_2CHHCO$), 2.43 (br. d, *J* = 9.40 Hz, 1 H, $NCCHHCO$), 3.71 (d/t, *J* = 8.39/1.17 Hz, 1 H, $OCHCHCH_2$), 3.85 (m, Σ*J* = 23.5 Hz, 1 H, $NCHCH_3$), 3.91 (d, *J* = 9.40 Hz, 1 H, $OCHCN$), 4.20 (d, *J* = 4.70 Hz, 1 H, $CHC_{ar.}$), 5.40 (br. t, *J* = 10.50 Hz, 1 H, NH), 7.22−7.38 (m, 5 H, $CH_{ar.}$), 7.99 (d, *J* = 12.08 Hz, 1 H, CHO). The signals of the *endo*-minor diastereomers can be observed in the ^{1}H-NMR spectrum only at: δ = 8.18 und 8.16 [d, *J* = 1.31 Hz, 1 H, CHO, (*Z*)]. Other signals are overlapped. − ^{13}C NMR (125 MHz, $CDCl_3$): *exo*-major diastereomer: (*Z*): δ = 16.74 (CH_3CHCH_3), 18.40 ($NCHCH_3$), 19.30 (CH_3CHCH_3), 22.75 ($CHCH\ CH_2CH_2$), 27.26 (CH_2CH_2CHCHO), 30.79 (CH_3CHCH_3), 32.13 ($CHCH_2CH$), 39.21 (CH_2CHCH_2CH), 42.29 ($CHCH_2CHHCO$), 46.00 ($NCHCH_3$), 56.81 ($CNCHCHCH_2$), 78.57 ($OCHCN$), 80.69 ($CHC_{ar.}$), 87.12 ($OCHCHCH_2$), 127.48 (*o*-$CH_{ar.}$), 128.00 (*p*-$CH_{ar.}$), 128.32 (*m*-$CH_{ar.}$), 137.46 (*i*-$C_{ar.}$), 157.24 ($C{=}N$), 160.51 (CHO), (*E*): δ = 18.52 ($NCHCH_3$), 18.64 (CH_3CHCH_3), 19.82 (CH_3CHCH_3), 22.72 ($CHCH\ CH_2CH_2$), 27.22 (CH_2CH_2CHCHO), 30.83 (CH_3CHCH_3), 32.12 ($CHCH_2CH$), 39.22 (CH_2CHCH_2CH), 42.18 ($CHCH_2CHHCO$), 49.99 ($NCHCH_3$), 56.41 ($CNCHCHCH_2$), 78.97 ($OCHCN$), 81.54 ($CHC_{ar.}$), 87.36 ($OCHCHCH_2$), 128.09 (*o*-$CH_{ar.}$), 128.32 (*m*-$CH_{ar.}$), 128.37 (*p*-$CH_{ar.}$), 136.19 (*i*-$C_{ar.}$), 157.23 ($C{=}N$), 163.76 (CHO); *exo*-minor diastereomer: (*Z*): δ = 16.21 (CH_3CHCH_3), 18.83 ($NCHCH_3$), 19.69 (CH_3CHCH_3), 22.50 ($CHCH\ CH_2CH_2$), 27.54 (CH_2CH_2CHCHO), 31.27 (CH_3CHCH_3), 32.55 ($CHCH_2CH$), 39.44 (CH_2CHCH_2CH), 41.88 ($CHCH_2CHCHO$), 48.01 ($NCHCH_3$), 56.62 ($CNCHCHCH_2$), 82.48 ($OCHCN$), 83.24 ($CHC_{ar.}$), 87.46 ($OCHCHCH_2$), 127.70 (*o*-$CH_{ar.}$), 127.95 (*p*-$CH_{ar.}$), 128.18 (*m*-$CH_{ar.}$), 138.85 (*i*-$C_{ar.}$), 158.37 ($C{=}N$), 160.20 (CHO); (*E*): δ = 18.02 ($NCHCH_3$), 18.89 (CH_3CHCH_3), 19.91 (CH_3CHCH_3), 22.75 ($CHCHCH_2CH_2$), 27.54 (CH_2CH_2CHCHO), 31.07 (CH_3CHCH_3), 32.55 ($CHCH_2CH$), 39.54 (CH_2CHCH_2CH), 41.76 ($CHCH_2CHCHO$), 52.08 ($NCHCH_3$), 56.21 ($CNCHCHCH_2$), 83.06 ($OCHCN$), 84.21 ($CHC_{ar.}$), 87.69 ($OCHCHCH_2$), 127.95 (*o*-$CH_{ar.}$), 128.18 (*p*-$CH_{ar.}$), 128.33 (*m*-$CH_{ar.}$), 137.64 (*i*-$C_{ar.}$), 158.37 ($C{=}N$), 163.86 (CHO). The signals of the *endo*-minor diastereomers can not be observed in the ^{13}C-NMR spectrum. − MS (70 eV); *m/z* (%): 371 (0.6), 299 (5.5), 298 (22.9), 194 (6.1), 193 (49.9), 192 (100), 178 (23.7), 162 (9.9), 134 (11.0), 117 (4.4), 91 (4.8), 72 (6.8), 67 (3.3), 55 (4.0). − $C_{22}H_{30}N_2O_3$ (370.49): calcd. C 71.32, H 8.16, N 7.56; found C 71.67, H 7.98, N 7.40.

Products of Intramolecular 1,3-Dipolar Cycloaddition

(1S,2R,3′R/S,3′aR/S,6′R)-N-tert-Butoxycarbonyl-N-{1-methyl-2-phenyl-2-[(3′-phenyl-3′a,4′,6′,7′-tetrahydro-3H-cyclopenta[c]isoxazol-6-yl)oxy]ethyl}formamide (**8a**) was obtained by dissolving (1*S*,2*R*,1′*R*)-(−)-*N*-(1-methyl-2-{[2′-(nitromethyl)-5′-phenylpent-4′-enyl]oxy}-2-phenylethyl)formamide [(1*S*,2*R*,1′*R*)-**7a**] (191 mg, 0.5 mmol) in acetonitrile (5 ml). This solution was added

dropwise to a solution of Boc_2O (304 mg, 1.5 mmol), containig DMAP (2.5 mg) in acetonitrile (5 ml). After removing the solvent and volatile compounds under vacuum and chromatography (SiO_2; diethyl ether/pentane, 1:1), the cycloadduct was obtained as colourless solid. Yield 144 mg (62%), m.p. 46°C − *de* = 62% (*de* = 90%). − $[\alpha]_D^{24} = -1.0$ (*c* = 0.59, $CHCl_3$) (95:5). − $[\alpha]_D^{24} = +69.3$ (*c* = 0.75, $CHCl_3$) (40:60). − IR ($CHCl_3$): $\tilde{\nu}$ = 2979 cm^{-1} (s), 2938 (s), 2406 (w), 1737 (s), 1692 (s), 1632 (m), 1604 (m), 1494 (m), 1476 (m), 1456 (s), 1371 (s), 1337 (s), 1307 (s), 1233 (s), 1200 (s), 1155 (s), 1092 (s), 1069 (s), 1003 (m), 847 (s), 758 (s), 702 (s). − ^{1}H NMR (300 MHz, $CDCl_3$): major diastereomer: (*Z*): δ = 1.42 [s, 9 H, C(C*H*$_3$)$_3$], 1.50 (m, Σ*J* = 44.2 Hz, 1 H, C*H*$_2$CHCHC$_{ar.}$), 1.54 (d, *J* = 6.87 Hz, 3H NCHC*H*$_3$), 2.11 (m, Σ*J* = 21.2 Hz, 1 H, C*H*$_2$CHCHC$_{ar.}$), 2.19 (m, Σ*J* = 21.5 Hz, 1 H, OCHC*H*$_2$), 2.35 (m, Σ*J* = 44.5 Hz, 1 H, OCHC*H*$_2$), 3.33 (br. q, *J* = 9.07 Hz, 1 H, CH$_2$C*H*CHC$_{ar.}$), 4.49 (d/d, *J* = 6.04/1.92 Hz, 1 H, OC*H*CH$_2$CH$_2$), 4.67 (br. d/q, *J* = 9.34/6.87 Hz, 1 H, NC*H*CH$_3$), 4.94 (d, *J* = 9.61 Hz, 1 H, C*H*C$_{ar.}$), 5.03 (d, *J* = 10.16 Hz, 1 H, CH$_2$CHC*H*C$_{ar.}$), 6.97 (m, Σ*J* = 16.1 Hz, 2 H, *o*-C*H*$_{ar.}$), 7.25−7.35 (m, 8 H, C*H*$_{ar.}$), 8.75 (br. s, 1 H, C*H*O); (*E*): δ = 1.42 [s, 9 H, C(C*H*$_3$)$_3$], 1.50 (m, Σ*J* = 44.2 Hz, 1 H, C*H*$_2$CHCHC$_{ar.}$), 1.57 (d, *J* = 6.87 Hz, 3H NCHC*H*$_3$), 2.11 (m, Σ*J* = 21.2 Hz, 1 H, C*H*$_2$CHCHC$_{ar.}$), 2.19 (m, Σ*J* = 21.5 Hz, 1 H, OCHC*H*$_2$), 2.35 (m, Σ*J* = 44.5 Hz, 1 H, OCHC*H*$_2$), 3.33 (br. q, *J* = 9.07 Hz, 1 H, CH$_2$C*H*CHC$_{ar.}$), 4.56 (d/d, *J* = 7.97/2.47 Hz, 1 H, OC*H*CH$_2$CH$_2$), 4.65 (br. d/q, *J* = 9.60/5.22 Hz, 1 H, NC*H*CH$_3$), 4.92 (d, *J* = 9.61 Hz, 1 H, C*H*C$_{ar.}$), 5.01 (d, *J* = 10.99 Hz, 1 H, CH$_2$CHC*H*C$_{ar.}$), 6.97 (m, Σ*J* = 16.1 Hz, 2 H, *o*-C*H*$_{ar.}$), 7.25−7.35 (m, 8 H, C*H*$_{ar.}$), 8.75 (br. s, 1 H, C*H*O); minor diastereomer: (*Z*): δ = 1.38 [s, 9 H, C(C*H*$_3$)$_3$], 1.50 (m, Σ*J* = 44.2 Hz, 1 H, C*H*$_2$CHCHC$_{ar.}$), 1.58 (d, *J* = 6.71 Hz, 3H NCHC*H*$_3$), 1.94 (br. quint, *J* = 8.79 Hz, 1 H, C*H*$_2$CHCHC$_{ar.}$), 2.00 (d/d/d/d, *J* = 7.97/7.97/4.95/3.57 Hz, 1 H, OCHC*H*$_2$), 2.35 (m, Σ*J* = 56.5 Hz, 1 H, OCHC*H*$_2$), 3.56 (d/d/d, *J* = 11.27/9.34/9.07 Hz, 1 H, CH$_2$C*H*CHC$_{ar.}$), 4.39 (d/d, *J* = 7.97/3.57 Hz, 1 H, OC*H*CH$_2$CH$_2$), 4.69 (br. d/q, *J* = 9.34/6.72 Hz, 1 H, NC*H*CH$_3$), 4.92 (d, *J* = 9.62 Hz, 1 H, C*H*C$_{ar.}$), 5.32 (d, *J* = 11.81 Hz, 1 H, CH$_2$CHC*H*C$_{ar.}$), 6.97 (m, Σ*J* = 16.1 Hz, 2 H, *o*-C*H*$_{ar.}$), 7.25−7.40 (m, 8 H, C*H*$_{ar.}$), 8.83 (br. s, 1 H, C*H*O); (*E*): δ = 1.37 [s, 9 H, C(C*H*$_3$)$_3$], 1.50 (m, Σ*J* = 44.2 Hz, 1 H, C*H*$_2$CHCHC$_{ar.}$), 1.60 (d, *J* = 7.01 Hz, 3H NCHC*H*$_3$), 1.90 (quint, *J* = 9.62 Hz, 1 H, C*H*$_2$CHCHC$_{ar.}$), 2.05 (m, Σ*J* = 28.0 Hz, 1 H, OCHC*H*$_2$), 2.30 (m, Σ*J* = 40.0 Hz, 1 H, OCHC*H*$_2$), 3.56 (m, Σ*J* = 26.8 Hz, 1 H, CH$_2$C*H*CHC$_{ar.}$), 3.62 (br. d/q, *J* = 9.84/7.02 Hz, 1 H, NC*H*CH$_3$), 4.74 (d/d, *J* = 9.89/5.79 Hz, 1 H, OC*H*CH$_2$CH$_2$), 4.92 (d, *J* = 9.62 Hz, 1 H, C*H*C$_{ar.}$), 5.32 (d, *J* = 11.81 Hz, 1 H, CH$_2$CHC*H*C$_{ar.}$), 6.97 (m, Σ*J* = 16.1 Hz, 2 H, *o*-C*H*$_{ar.}$), 7.25−7.40 (m, 8 H, C*H*$_{ar.}$), 8.83 (br. s, 1 H, C*H*O). − ^{13}C NMR (75 MHz, $CDCl_3$): major diastereomer: (*Z*): δ = 15.53 (NCH*C*H$_3$), 25.34 (CHCH*C*H$_2$), 27.94 [C(*C*H$_3$)$_3$], 34.70 (OCH*C*H$_2$), 52.00 (br., N*C*HCH$_3$), 57.74 (CH*C*HCH$_2$), 72.15 (O*C*HCH$_2$), 82.49 (br., O*C*HCHCH$_3$), 84.03 [*C*(CH$_3$)$_3$], 91.03 (O*C*HCHCH$_2$), 126.58 (*o*-*C*H$_{ar.}$), 127.99 (*o*-*C*H$_{ar.}$), 128.16 (*m*-*C*H$_{ar.}$), 128.20 (*p*-*C*H$_{ar.}$), 128.22 (*p*-*C*H$_{ar.}$), 128.49 (*m*-*C*H$_{ar.}$), 139.04 (*i*-*C*$_{ar.}$), 139.21 (*i*-*C*$_{ar.}$), 151.78 (*C*N), 163.00 (br., *C*HO), 169.55 (N*C*O); (*E*): δ = 15.28 (NCH*C*H$_3$), 25.85 (CHCH*C*H$_2$), 27.87 [C(*C*H$_3$)$_3$], 34.97 (OCH*C*H$_2$), 52.00 (br., N*C*HCH$_3$), 57.74 (CH*C*HCH$_2$), 72.93 (O*C*HCH$_2$), 82.49 (br., O*C*HCHCH$_3$), 84.03 [*C*(CH$_3$)$_3$], 90.43 (O*C*HCHCH$_2$), 126.50 (*o*-*C*H$_{ar.}$), 127.43 (*o*-*C*H$_{ar.}$), 128.16 (*p*-*C*H$_{ar.}$), 128.29 (*m*-*C*H$_{ar.}$), 128.64 (*p*-*C*H$_{ar.}$), 128.69 (*m*-*C*H$_{ar.}$), 139.04 (*i*-*C*$_{ar.}$), 139.21 (*i*-*C*$_{ar.}$), 151.06 (*C*N), 163.00 (br., *C*HO), 168.73 (N*C*O); minor diastereomer: (*Z*): δ = 15.57 (NCH*C*H$_3$), 25.47 (CHCH*C*H$_2$), 27.87 [C(*C*H$_3$)$_3$], 34.95 (OCH*C*H$_2$), 52.00 (br., N*C*HCH$_3$), 59.91 (CH*C*HCH$_2$), 69.95 (O*C*HCH$_2$), 81.26 (br., O*C*HCHCH$_3$), 83.94 [*C*(CH$_3$)$_3$], 90.45 (O*C*HCHCH$_2$), 125.63 (*o*-*C*H$_{ar.}$), 126.00 (*o*-*C*H$_{ar.}$), 127.10 (*m*-*C*H$_{ar.}$), 127.90 (*p*-*C*H$_{ar.}$), 128.20 (*p*-*C*H$_{ar.}$), 128.33 (*m*-*C*H$_{ar.}$), 138.06 (*i*-*C*$_{ar.}$), 138.38 (*i*-*C*$_{ar.}$), 151.80 (*C*N), 163.37 (br., *C*HO), 171.65 (N*C*O); (*E*): δ = 12.85 (NCH*C*H$_3$), 25.47 (CHCH*C*H$_2$), 27.68 [C(*C*H$_3$)$_3$], 34.95 (OCH*C*H$_2$), 52.00 (br., N*C*HCH$_3$), 61.08 (CH*C*HCH$_2$), 71.23 (O*C*HCH$_2$), 81.26 (br., O*C*HCHCH$_3$), 83.94 [*C*(CH$_3$)$_3$], 90.41 (O*C*HCHCH$_2$), 126.50 (*o*-*C*H$_{ar.}$), 126.59 (*o*-*C*H$_{ar.}$), 128.17 (*p*-*C*H$_{ar.}$), 128.30 (*m*-*C*H$_{ar.}$), 128.33 (*p*-*C*H$_{ar.}$), 128.50 (*m*-*C*H$_{ar.}$), 137.25 (*i*-*C*$_{ar.}$), 138.06 (*i*-*C*$_{ar.}$), 150.30 (*C*N), 161.72 (br., *C*HO), 170.94 (N*C*O). − MS (70 eV); *m/z* (%): 348 (1.9), 316 (1.6), 276 (1.6), 259 (7.8), 258 (47.5), 187 (6.8), 186 (45.3), 168 (5.6), 162 (14.3), 143 (6.7), 142 (39.2), 134 (25.7), 132 (7.8), 129 (8.9), 118 (5.5), 117 (12.7), 115 (26.2), 107 (10.3), 91 (21.9), 79 (11.2), 78 (5.5), 77 (17.1), 73 (68.7), 72 (100), 55 (5.8), 51 (5.8). − $C_{27}H_{32}N_2O_5$ (464.56): calcd. C 69.81, H 6.94, N 6.03; found C 69.71, H 7.16, N 6.41.

(1S,2R,3′R,3a′S,7′S)-(−)-N-tert-Butoxycarbonyl-N-{[1-methyl-2-phenyl-2-(3′-phenyl-3′a,4′,6′,7′-tetrahydro-3H-pyrano-[4,3-c]isoxazol-7′-yl)oxy]ethyl}formamide (**8b**) was obtained by dissolving (1*S*,2*R*,1′*S*)-(−)-*N*-{1-methyl-2-[(2′-nitro-1′-{[(3′-phenylallyl)oxy]methyl}ethyl)oxy]-2-phenylethyl}formamide [(1*S*,2*R*,1′*S*)-**7b**] (398 mg, 1.0 mmol) in acetonitrile (10 ml). This solution was added dropwise to a solution of Boc_2O (608 mg, 3.0 mmol), containig DMAP (5.0 mg) in acetonitrile (10 ml). After removing the solvent and volatile compounds under vacuum and chromatography (SiO_2; diethyl ether/pentane, 1:1), the cycloadduct was obtained as colourless solid. Yield 355 mg (74%), m.p. 150°C. − *de* = 95% (*de* ≥ 96%). − $[\alpha]_D^{24} = -59.9$ (*c* = 1.41, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 2979 cm^{-1} (s), 2931 (s), 2853 (m), 1737 (s), 1692 (s), 1632 (m), 1604 (m), 1454 (s), 1373 (s), 1307 (m), 1224 (s), 1199 (m), 1156 (s), 1138 (s), 1102 (s), 1052 (s), 990 (m), 940 (m), 912 (m), 870 (m), 852 (m), 754 (s), 701 (s). − ^{1}H NMR (500 MHz, $CDCl_3$): (*Z*): δ = 1.42 [s, 9 H, C(C*H*$_3$)$_3$], 1.56 (d, *J* = 6.71 Hz, 3 H, NCHC*H*$_3$), 3.01 (d/d/d, *J* = 10.60/10.38/6.94 Hz, 1 H, CH$_2$C*H*CHC$_{ar.}$), 3.32 (d/d, *J* = 10.83/10.76 Hz, 1 H, C*H*$_2$CHCHC$_{ar.}$), 3.47 (d/d, *J* = 12.44/1.99 Hz, 1 H, OCHC*H*$_2$O), 4.23 (d/d, *J* = 10.60/6.95 Hz, 1 H, C*H*$_2$CHCHC$_{ar.}$), 4.40 (d/d, *J* = 12.44/1.15 Hz, 1 H, OCHC*H*$_2$O), 4.43 (t, *J* = 1.68 Hz, 1 H, OC*H*-CH$_2$O), 4.70 (br. pent, *J* = 8.25 Hz, 1 H, NC*H*CH$_3$), 4.84 (d, *J* = 9.76 Hz, 1 H, CH$_2$CHC*H*C$_{ar.}$), 5.00 (d, *J* = 9.61 Hz, 1 H, CH$_3$CHC*H*C$_{ar.}$), 6.73 (m, Σ*J* = 9.69 Hz, 2 H, *o*-C*H*$_{ar.}$), 7.19−7.36 (m, 8 H, C*H*$_{ar.}$), 8.73 (br. s, 1 H, C*H*O); (*E*): δ = 1.42 [s, 9 H, C(C*H*$_3$)$_3$], 1.56 (d, *J* = 6.71 Hz, 3 H, NCHC*H*$_3$), 3.15 (d/d/d, *J* = 10.98/9.92/7.09 Hz, 1 H, CH$_2$C*H*CHC$_{ar.}$), 3.36 (d/d, *J* = 10.76/10.76 Hz, 1 H, C*H*$_2$CHCHC$_{ar.}$), 3.53 (d/d, *J* = 12.66 Hz/*J* = 1.73 Hz, 1 H, OCHC*H*$_2$O), 3.82 (br. quint, *J* = 6.71 Hz, 1 H, NC*H*CH$_3$), 4.26 (d/d, *J* = 10.68/6.86 Hz, 1 H, C*H*$_2$CHCHC$_{ar.}$), 4.46 (d/d, *J* = 12.67/1.07 Hz, 1 H, OCHC*H*$_2$O), 4.54 (t, *J* = 1.35 Hz, 1 H, OC*H*CH$_2$O), 4.64 (d, *J* = 5.34 Hz, 1 H, CH$_3$CHC*H*C$_{ar.}$), 4.88 (d, *J* = 9.92 Hz, 1 H, CH$_2$CHC*H*C$_{ar.}$), 6.73 (m, Σ*J* = 9.69 Hz, 2 H, *o*-C*H*$_{ar.}$), 7.19−7.36 (m, 8 H, C*H*$_{ar.}$), 8.73 (br. s, 1 H, C*H*O). − ^{13}C NMR (125 MHz, $CDCl_3$): (*Z*): δ = 15.44 (NCH*C*H$_3$), 27.93 [C(*C*H$_3$)$_3$], 52.00 (br., N*C*HCH$_3$), 52.08 (CH*C*HCH$_2$O), 71.74 (O*C*HCH$_2$O), 72.26 (CHCH*C*H$_2$O), 72.38 (OCH*C*H$_2$O), 83.04 (br., O*C*HCHCH$_3$), 83.99 [*C*(CH$_3$)$_3$], 84.61 (*C*HCHCH$_2$O), 126.36 (*o*-*C*H$_{ar.}$), 127.75 (*o*-*C*H$_{ar.}$), 128.10 (*p*-*C*H$_{ar.}$), 128.16 (*m*-*C*H$_{ar.}$), 128.30 (*p*-*C*H$_{ar.}$), 128.50 (*m*-*C*H$_{ar.}$), 138.50 (*i*-*C*$_{ar.}$), 138.89 (*i*-*C*$_{ar.}$), 151.70 (N*C*O), 155.81 (*C*N), 162.90 (br., *C*HO); (*E*): δ = 16.70 (NCH*C*H$_3$), 27.93 [C(*C*H$_3$)$_3$], 52.00 (br., N*C*HCH$_3$), 52.20 (CH*C*HCH$_2$O), 71.74 (O*C*HCH$_2$O), 71.99 (CHCH*C*H$_2$O), 72.21 (OCH*C*H$_2$O), 82.18 [*C*(CH$_3$)$_3$], 83.04 (br., O*C*HCHCH$_3$), 84.77 (*C*HCHCH$_2$O), 126.36 (*o*-*C*H$_{ar.}$), 127.34 (*p*-*C*H$_{ar.}$), 127.75 (*o*-*C*H$_{ar.}$), 128.16 (*m*-*C*H$_{ar.}$), 128.44 (*p*-*C*H$_{ar.}$), 128.63

(*m*-$CH_{ar.}$), 137.10 (*i*-$C_{ar.}$), 138.40 (*i*-$C_{ar.}$), 151.70 (N*C*O), 155.21 (*C*N), 162.90 (br., *C*HO). − MS (70 eV); *m*/*z* (%): 308 (10.9), 275 (5.0), 274 (29.9), 204 (13.3), 203 (100), 202 (96.5), 141 (12.9), 134 (18.9), 118 (6.7), 117 (25.7), 116 (7.5), 115 (30.3), 107 (11.0), 106 (12.1), 105 (34.0), 96 (39.1), 91 (34.6), 79 (9.1), 78 (7.5), 77 (26.2), 54 (5.8), 51 (14.1), 50 (5.9). − CI (isobutane, 4000 mTorr); *m*/*z* (%): 437 (6.4), 419 (7.2), 382 (24.0), 381 (100), 277 (17.7), 164 (8.0), 162 (20.8), 107 (59.9). − $C_{27}H_{32}N_2O_6$ (480.56): calcd. C 67.48, H 6.71, N 5.83; found C 67.25, H 6.70, N 5.57.

Reductive Ring Opening Reactions and Protection of Amino Function

(1S,2R,3R,4R,1′R/S,2′R,1″R,2″S)-(−)-3-{1′-[(tert-Butoxycarbonyl)amino]-2′-({2″-[(tert-butoxycarbonyl)(methyl)amino]-1″-phenylpropyl}oxy)-3′-methylbutyl}bicyclo[2.2.1]heptan-2-ol (**11**): $LiAlH_4$ (25 mg, 0.625 mmol), dissolved in abs. diethyl ether (40 ml), and the isoxazoline **5e** (110 mg, 0.30 mmol), dissolved in abs. diethyl ether (20 ml), were added dropwise at −30°C, then the reaction mixture was allowed to warm up to room temperature. The reaction was monitored by TLC and quenched by adding H_2O (1 ml/g $LiAlH_4$), NaOH (aq, 20%) (0.75 ml/g $LiAlH_4$) and H_2O (3.5 ml/g $LiAlH_4$). The crystalline Al_2O_3 was filtered of and washed with diethyl ether and CH_2Cl_2. After separation of the phases, the organic layer was dried and the solvent was removed under vacuum. The crude product **9** was dissolved in methanol, and triethylamine (2 ml) and Boc_2O (0.30 mmol) were added. The solvent and excess of reagents were removed under vacuum to stop the reaction and after flash-chromatography (SiO_2; diethyl ether), the product was obtained as colourless solid. Yield 109 mg (65%), m.p. 130°C − *ee*, *de* ≥ 96%. − $[\alpha]_D^{24} = -42.9$ (*c* = 1.13, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3262 cm^{-1} (s), 2980 (s), 2960 (s), 2939 (m), 2904 (m), 2879 (m), 1698 (s), 1672 (s), 1569 (s), 1509 (m), 1479 (m), 1455 (s), 1428 (m), 1392 (s), 1367 (s), 1329 (s), 1319 (s), 1301 (m), 1287 (s), 1256 (s), 1184 (s), 1149 (s), 1139 (s), 1078 (s), 1052 (s), 1037 (s), 1029 (s), 995 (m), 872 (m). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (m, Σ*J* = 15.4 Hz, 1 H, CHCH_2CH), 1.04 (d, *J* = 6.59 Hz, 6 H, CH_3CHCH_3), 1.24 (d, *J* = 6.79 Hz, 3 H, NCHCH_3), 1.40−1.60 (m, 2 H, CH_2CH_2CH), 1.35 [s, 9 H, C(CH_3)$_3$], 1.40 [s, 9 H, C(CH_3)$_3$], 1.58 (d/sept, *J* = 10.17/6.65 Hz, 1 H, CH_3C*H*CH_3), 2.02 (s, 3 H, NCH_3), 2.20 (br. s, 1 H, O*H*), 2.49 (m, Σ*J* = 17.5 Hz, 2 H, CHCH_2CH_2CH), 2.57 (m, Σ*J* = 17.5 Hz, 2 H, C*H*CH_2CH_2 C*H*), 2.90 (m, Σ*J* = 10.98 Hz, 1 H, CHCH_2CH), 3.64 (d, *J* = 5.49 Hz, 1 H, C*H*), 3.71 (d, *J* = 6.32 Hz, 1 H, C*H*$C_{ar.}$), 3.80 (m, Σ*J* = 18.55 Hz, 1 H, NC*H*CH_3), 3.88 (d/d, *J* = 9.89/6.32 Hz, 1 H, OCHC*H*NHBoc), 3.92 (d/d *J* = 6.32/5.77 Hz, 1 H, C*H*OH), 4.13 [d/d *J* 9.61/6.57 Hz, 1 H, OC*H*CH$(CH_3)_2$], 4.50 (br. s, 1 H, N*H*), 7.29−7.39 (m, 5 H, C$H_{ar.}$). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.86 (*C*H_3CHCH_3), 19.10 (NCH*C*H_3), 19.48 (CH_3CH*C*H_3), 19.77 (*C*H), 24.71 (*C*H_2), 28.23 [C(*C*H_3)$_3$], 28.36 [C(*C*H_3)$_3$], 29.61 (*C*H_2), 30.20 (CH_3*C*HCH_3), 33.42 (*C*H_2), 38.32 (CHCH_2*C*H), 43.75 (*C*HCH_2CH), 48.26 (N*C*H_3), 50.72 (N*C*HCH_3), 50.90 (N*C*H$(CH_2)_2$), 77.96 (O*C*HCHN), 79.10 (O*C*$(CH_3)_3$], 79.20 (O*C*$(CH_3)_3$], 83.40 (O*C*HC$H_{ar.}$), 84.13 (O*C*HCH), 128.38 (*o*-*C*$H_{ar.}$), 128.60 (*m*-*C*$H_{ar.}$), 128.86 (*p*-*C*$H_{ar.}$), 138.48 (*i*-$C_{ar.}$), 155.04 (*C*O), 155.66 (*C*O). − MS (70 eV); *m*/*z* (%): 560 (0.2), 487 (0.2), 459 (0.2), 429 (0.9), 403 (6.2), 402 (13.1), 346 (11.5), 248 (12.2), 241 (10.4), 240 (56.6), 196 (10.7), 193 (15.4), 192 (100), 184 (34.9), 179 (7.0), 158 (29.7), 148 (22.9), 140 (34.4), 118 (5.6), 117 (5.3), 102 (36.2), 58 (10.9), 57 (19.7). − $C_{32}H_{52}N_2O_6$ (560.77): calcd. C 68.54, H 9.35, N 5.00; found C 68.49, H 8.86, N 4.95.

(1R,3′R,4′S,5′S,1″R,2″S)-(−)-1-{4′-[(tert-butoxycarbonyl)amino]-5′-({2″-[(tert-butoxycarbonyl)(methyl)amino]-1″-phenylpropyl}oxy)tetrahydro-2H-3′-pyranyl}-1-(phenyl)methanol (**12**): $LiAlH_4$ (17 mg, 0.425 mmol) was dissolved in abs. diethyl ether (40 ml) and the isoxazoline **8b** (100 mg, 0.21 mmol), dissolved in abs. diethyl ether (20 ml), was added dropwise at −30°C, then the reaction mixture was allowed to warm up to room temperature. The reaction was monitored by TLC and quenched by adding H_2O (1 ml/g $LiAlH_4$), NaOH (aq, 20%) (0.75 ml/g $LiAlH_4$) and H_2O (3.5 ml/g $LiAlH_4$). The crystalline Al_2O_3 was filtered off and washed with diethyl ether and CH_2Cl_2. After separation of the phases, the organic layer was dried and the solvent was removed under vacuum. The crude product **10** was dissolved in methanol and triethylamine (2 ml) and Boc_2O (0.30 mmol) were added. The solvent and excess of reagents were removed under vacuum to stop the reaction and after flash chromatography (SiO_2; diethyl ether), the product was obtained as colourless solid. Yield 72 mg (60%), m.p. 73°C − *ee*, *de* ≥ 96%. − $[\alpha]_D^{24} = -12.7$ (*c* = 0.98, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3414 cm^{-1} (s),2978 (s), 2933 (s), 1696 (s), 1604 (m), 1508 (s), 1455 (s), 1385 (s), 1367 (s), 1347 (s), 1330 (s), 1250 (s), 1170 (s), 1103 (s), 1054 (s), 919 (m), 867 (m), 764 (m), 743 (m), 703 (s). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (d/d/d, *J* = 12.42/6.71/5.71 Hz, 1 H, C*H*), 1.10 (d, *J* = 6.72 Hz, 3H NCHCH_3), 1.33 [s, 9 H, C(CH_3)$_3$], 1.41 [s, 9 H, C(CH_3)$_3$], 1.65 (s, 3 H, NCH_3), 2.64 (m, Σ*J* = 21.5 Hz, 1 H, OCHCH_2), 2.68 (br. m, Σ*J* = 20.5 Hz, 1 H, OCHCH_2), 3.23 (br. s, 1 H, O*H*), 3.75 (br. m, Σ*J* = 28.2 Hz, 1 H, OCHC*H*NHBoc), 3.90 (br. m, Σ*J* = 22.2 Hz, 1 H, CH_2O), 4.07 (br. d, *J* = 13.09 Hz, 1 H, OCH_2), 4.41 (br. d/d, *J* = 12.09/5.39 Hz, 1 H, OC*H*CH_2), 4.52 (br. s, 1 H, N*H*) 4.68 (br. m, Σ*J* = 32.8 Hz, 1 H, NC*H*CH_3), 4.94 (br. d, *J* = 8.39 Hz, 1 H, C*H*C$_{ar.}$), 5.06 (br. d, *J* = 9.74 Hz, 1 H, CH_2CHC*H*C$_{ar.}$), 7.22−7.38 (m, 10 H, C$H_{ar.}$). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.36 (NCH*C*H_3), 28.32 [C(*C*H_3)$_3$], 28.36 (*C*H), 28.40 [C(*C*H_3)$_3$], 42.65 (N*C*H_3), 51.50 (N*C*HCH_3), 52.45 (BocHN*C*H), 73.11 (O*C*H_2), 79.10 (O*C*H_2), 79.91 (O*C*H), 80.33 (O*C*$(CH_3)_3$], 80.96 (O*C*H), 81.65 (O*C*HC$H_{ar.}$), 84.69 (O*C*$(CH_3)_3$], 127.06 (*o*-*C*$H_{ar.}$), 127.19 (*o*-*C*$H_{ar.}$), 127.81 (*m*-*C*$H_{ar.}$), 128.36 (*m*-*C*$H_{ar.}$), 128.42 (*p*-*C*$H_{ar.}$), 128.62 (*p*-*C*$H_{ar.}$), 138.65 (*i*-$C_{ar.}$), 141.90 (*i*-$C_{ar.}$), 155.44 (*C*O), 155.66 (*C*O). − MS (70 eV); *m*/*z* (%): 571 (0.4), 557 (0.5), 441 (0.5), 429 (3.9), 413 (22.2), 412 (43.4), 357 (10.3), 356 (31.8), 339 (33.4), 338 (100), 312 (11.1), 295 (11.9), 294 (46.0), 251 (13.1), 250 (51.2), 233 (23.5), 232 (19.4), 192 (10.4), 188 (14.6), 178 (11.1), 172 (22.2), 158 (45.5), 148 (7.5), 144 (18.6), 134 (11.4), 118 (12.5), 117 (42.3), 115 (7.9), 107 (18.1), 105 (18.1), 105 (15.4), 102 (61.3), 100 (16.4), 91 (9.9), 88 (10.4), 79 (11.3), 58 (35.2), 57 (85.6), 56 (12.9). − $C_{32}H_{46}N_2O_7$ (570.73): calcd. C 67.34, H 8.12, N 4.91; found C 67.58, H 7.81, N 4.50.

Synthesis of N-Boc-Protected 2-Amino 1,4-Diols

(1S,2R,3R,4R,1′R/S,2′R)-(+)-3-{1′-[(tert-Butoxycarbonyl)amino]-2′-hydroxy-3′-methylbutyl}-bicyclo[2.2.1]heptan-2-ol (**13**): Alcohol **11** (90 mg, 0.16 mmol) was dissolved in abs. THF (10 ml) and added dropwise to liquid ammonia (25 ml), containing sodium (9.5 mg, 0.4 mmol), at −78°C. Quenching of the reaction by adding NH_4Cl until the solution was colourless and removing of the ammonia was followed by flash chromatography (SiO_2; diethyl ether). The product was obtained as colourless solid. Yield 46 mg (92%), m.p. 140°C − *ee*, *de* ≥ 96%. − $[\alpha]_D^{24} = +28.9$ (*c* = 0.45, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3262 (s), 2963 cm^{-1} (s), 2909 (m), 2877 (m), 1692 (s), 1547 (s), 1473 (m), 1457 (m), 1391 (s), 1367 (s), 1340 (s), 1304 (m), 1272 (m), 1253 (s), 1174 (s), 1143 (m), 1078 (m), 1046 (m), 1016 (s), 998 (s), 744 (m), 734 (m), 613 (m). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 6.71 Hz, 3 H, CH_3CHCH_3), 0.97 (d, *J* = 6.71 Hz, 3 H, CH_3CHCH_3), 1.02−1.11 (m, 3 H, CH_2CH_2,CHCH_2CH), 1.44 [s, 9 H, C(CH_3)$_3$], 1.49 (br. m, Σ*J* = 25.4 Hz, 2 H, CH_2CH_2), 1.70 (br. t, *J* = 7.33 Hz, 1 H, CH_2), 1.73 (br. d, Σ*J* = 11.30 Hz, 1 H, C*H*), 1.85 [sept/d, *J* = 6.71/3.05, 1 H, C*H*$(CH_3)_2$], 2.19 (br. m, Σ*J* = 10.4 Hz, 2 H, C*H*,

HNCHC*H*CHOH), 2.89 (br. s, 1 H, O*H*), 3.21 (br. m, Σ*J* = 32.5 Hz, 2 H, C*H*O*H*), 3.84 (br. d, *J* = 6.41 Hz, 1 H, C*H*OH), 3.91 (br. t, *J* = 8.24 Hz, 1 H, C*H*NH), 4.53 (br. d, *J* = 10.38 Hz, 1 H, N*H*); δ = 0.87 (d, *J* = 6.41 Hz, 3 H, C*H*$_3$CHCH$_3$), 0.98 (d, *J* = 6.41 Hz, 3 H, CH$_3$CHC*H*$_3$), 1.05−1.13 (m, 3 H, CH$_2$C*H*$_2$,CHC*H*$_2$CH), 1.48 [s, 9 H, C(C*H*$_3$)$_3$], 1.49 (br. m, Σ*J* = 25.4 Hz, 2 H, C*H*$_2$CH$_2$), 1.72 (br. m, Σ*J* = 32.5 Hz, 1 H, C*H*$_2$), 1.78 (br. d, *J* = 9.16 Hz, 1 H, C*H*), 1.99 [d/sept, *J* = 7.02/6.41, 1 H, C*H*(CH$_3$)$_2$], 2.22 (br. s, 1 H, C*H*), 2.27 (br. s, 1 H, HNCHC*H*CHOH), 2.94 (br. s, 1 H, O*H*), 3.12 (br. m, Σ*J* = 32.5 Hz, 2 H, C*H*O*H*), 3.86 (br. d, *J* = 6.41 Hz, 1 H, C*H*OH), 3.93 (br. t, *J* = 8.24 Hz, 1 H, C*H*NH), 4.05 (br. d, *J* = 10.98 Hz, 1 H, N*H*). − ^{13}C NMR (125 MHz, CDCl$_3$): δ = 15.59 (*C*H$_3$CHCH$_3$), 20.08 (CH$_3$CH*C*H$_3$), 24.45 (*C*H$_2$), 28.41 [C(*C*H$_3$)$_3$], 29.58 (*C*H$_2$), 30.39 (CH$_3$*C*HCH$_3$), 33.25 (*C*H$_2$), 38.35 (CHCH$_2$*C*H), 44.50 (*C*HCH$_2$CH), 49.54 (N*C*H), 51.85 (*C*H(CH$_3$)$_2$), 77.59 (O*C*HCHN), 79.43 (O*C*(CH$_3$)$_3$], 80.59 [O*C*HCH(CH$_3$)$_2$], 155.81 (*C*O); δ = 14.16 (*C*H$_3$CHCH$_3$), 20.55 (CH$_3$CH*C*H$_3$), 24.48 (*C*H$_2$), 28.41 [C(*C*H$_3$)$_3$], 29.39 (*C*H$_2$), 30.39 (CH$_3$*C*HCH$_3$), 32.97 (*C*H$_2$), 38.55 (CHCH$_2$*C*H), 44.55 (*C*HCH$_2$CH), 50.90 (N*C*H), 54.11 (*C*H(CH$_3$)$_2$), 77.59 (O*C*HCHN), 79.43 (O*C*(CH$_3$)$_3$], 79.99 [O*C*HCH(CH$_3$)$_2$], 155.23 (*C*O). − MS (70 eV); *m*/*z* (%): 314 (0.1), 258 (0.3), 240 (17.0), 196 (11.2), 185 (16.7), 184 (73.1), 178 (11.7), 167 (8.7), 152 (7.3), 141 (10.7), 140 (100), 122 (27.9), 113 (5.1), 95 (9.4), 81 (6.1), 80 (17.6), 19 (12.3), 73 (5.4), 57 (55.6), 55 (10.3). − CI (*iso*-butane, 2500 mTorr); *m*/*z* (%): 315 (14.5), 314 (100), 313 (1.0), 295 (4.3), 259 (10.6), 258 (89.7), 240 (8.7). − M^+ = $C_{17}H_{31}NO_4$ (313.44). − HR MS: $C_{13}H_{22}NO_3$ [M^+ − C_4H_9O]: calcd. 240.159968; found 240.160052.

(3S,4S,5R,1′R)-(−)-4-[(tert-Butoxycarbonyl)amino]-5-[1′-hydroxy-1′-phenylmethyl]tetrahydro-2H-3-pyranol (**14**): Alcohol **12** (50 mg, 0.088 mmol) was dissolved in abs. THF (10 ml) and added dropwise to liquid ammonia (25 ml), containing sodium (5.0 mg, 0.22 mmol), at −78°C. Quenching of the reaction by adding NH_4Cl until the solution was colourless and removing of the ammonia was followed by flash chromatography (SiO_2; diethyl ether). The product was obtained as colourless solid. Yield 27 mg (95%), m.p. 78°C − *ee*, *de* ≥ 96% . − $[\alpha]_D^{24}$ = − 16.3 (*c* = 0.54, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3373 cm^{-1} (s), 3065 (m), 2964 (s), 2918 (s), 2851 (s), 1684 (s), 1605 (m), 1516 (s), 1456 (s), 1386 (s), 1369 (s), 1343 (m), 1252 (s), 1169 (s), 1122 (s), 1089 (s), 1055 (s), 1010 (s), 957 (m), 863 (m), 737 (s), 702 (s), 614 (m). − ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.47 [s, 9 H, C(C*H*$_3$)$_3$], 2.08 (br. d/d/d/d, *J* = 15.11/10.71/7.41/4.70 Hz, 1 H, HNCHC*H*CH$_2$O), 2.22 (br. s, 1 H, O*H*), 2.30 (d/d, *J* = 14.10/10.44 Hz, 1 H, C*H*$_2$O), 2.60 (d/d, *J* = 13.09/10.07 Hz, 1 H, C*H*$_2$O), 2.67 (d/d, *J* = 13.09/5.70 Hz, 1 H, C*H*$_2$O), 2.89 (d/d, *J* = 14.10/10.44 Hz, 1 H, C*H*$_2$O), 3.52 (br. d/d/d, *J* = 12.42/9.40/7.41 Hz, 1 H, C*H*NH), 3.73 (br. d/d, *J* = 11.42/4.70 Hz, 1 H, C*H*OH), 3.79 (br. s, 1 H, O*H*), 3.97 (br. d/d, *J* = 12.42/1.10 Hz, 1 H, C*H*OH), 5.10 (br. d, *J* = 9.40 Hz, 1 H, N*H*), 7.11−7.32 (m, 5 H, C*H*$_{ar.}$); δ = 1.46 [s, 9 H, C(C*H*$_3$)$_3$], 1.74 (br. m, Σ*J* = 36.3 Hz, 1 H, HNCHC*H*CH$_2$O), 2.22 (br. s, 1 H, O*H*), 2.35 (m, 1 H, C*H*$_2$O), 2.40 (d/d/d, *J* = 8.73/5.71/4.37 Hz, 1 H, C*H*$_2$O), 2.58 (br. m, Σ*J* = 28.6 Hz, 1 H, C*H*$_2$O), 2.80 (m, Σ*J* = 32.4 Hz, 1 H, C*H*$_2$O), 3.48 (br. d, *J* = 9.15 Hz, 1 H, C*H*NH), 3.75 (br. m, 1 H, C*H*OH), 3.79 (br. s, 1 H, O*H*), 3.94 (br. m, 1 H, C*H*OH), 4.88 (br. s, 1 H, N*H*), 7.11−7.32 (m, 5 H, C*H*$_{ar.}$). − ^{13}C NMR (75 MHz, CDCl$_3$): δ = 28.35 [C(*C*H$_3$)$_3$], 39.22 (CH*C*HCH$_2$), 54.39 (N*C*H), 63.90 (O*C*H$_2$CH), 68.13 (HO*C*HC$_{ar.}$), 68.29 (HO*C*HCH$_2$), 71.94 (HOCH*C*H$_2$O), 79.98 (O*C*(CH$_3$)$_3$], 126.35 (*p*-*C*H$_{ar.}$), 128.51 (*o*-*C*H$_{ar.}$), 129.08 (*m*-*C*H$_{ar.}$), 139.79 (*iC*$_{ar.}$), 156.42 (*C*O); δ = 28.38 [C(*C*H$_3$)$_3$], 35.11 (CH*C*HCH$_2$), 55.15 (N*C*H), 63.90 (O*C*H$_2$CH), 67.35 (HO*C*HC$_{ar.}$), 70.70 (HO*C*HCH$_2$), 71.34 (HOCH*C*H$_2$O), 80.35 (O*C*(CH$_3$)$_3$], 126.27 (*p*-*C*H$_{ar.}$), 128.60 (*o*-*C*H$_{ar.}$), 128.79 (*m*-*C*H$_{ar.}$), 139.79 (*iC*$_{ar.}$), 156.81 (*C*O). − MS (70 eV); *m*/*z* (%): 307 (0.8), 252 (10.4), 251(78.8), 208 (8.4), 207 (30.2), 191 (5.7), 190 (36.9), 173 (7.2), 172 (8.4), 147 (13.5), 146 (11.3), 133 (16.0), 132 (33.6), 129 (49.8), 118 (12.6), 117 (60.1), 116 (22.3), 114 (14.4), 111 (9.8), 108 (7.3), 105 (13.2), 100 (12.4), 97 (11.3), 91 (49.0), 85 (9.5), 73 (24.5), 71 (11.0), 70 (11.4), 69 (12.6), 61 (25.5), 57 (100), 45 (24.5). − CI (*iso*-butane, 2500 mTorr); *m*/*z* (%): 309 (8.1), 308 (53.0), 253 (11.5), 251 (100). − M^+ = $C_{17}H_{25}NO_5$ (323.39). − HR MS: $C_{13}H_{17}NO_4$ [M^+ − C_4H_8O]: calcd. 251.115758; found 251.115546.

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