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Asymmetric Synthesis of Diastereomerically and Enantiomerically Pure α-Amino-γ-Nitro Carboxylic Esters via Michael Addition of the Titanated Bislactim Ether of Cyclo (-L-Val-Gly-) to Nitroolefines[1]

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Abstract - The titanated bislactim ethers of cyclo(-L-Val-Gly-) **3** and **7** were added highly diastereoselectively in a 1,4-fashion to the nitro olefines **4** yielding the nitro compounds **5**. Upon acidic hydrolysis these nitro compounds **5** afforded the α-amino-γ-nitro acid esters **12**, which can be hydrogenated to the lactames **14**. The oxazoline derivatives **17** were obtained via their nitrile oxides **15** in a subsequent dipolar (2+3)-cycloaddition. These derivatives **17** can be hydrolyzed to the oxazoline containing amino acid esters **18**.

I. Introduction

The asymmetric synthesis of α-amino-γ-nitro acids deserves special attention due to their potential biological activity and for the construction of modified oligopeptides. Moreover, the nitro group is one of the most versatile functional groups in organic synthesis and can be transformed into amino, carbonyl, nitrile oxide and many other groups.[3] Therefore, the nitro group can be called a "synthetic chameleon".[4]

Encouraged by the unexpectedly high degree of asymmetric induction which occurred during the addition of the titanated bislactim ether of cyclo(-L-Val-Gly-) towards aldehydes[5], as well as during the 1,4-addition of the lithiated bislactim ether towards α,β-unsaturates esters[6], we investigated the 1,4-addition of metalated bislactim ethers to nitro olefines. The goal was the development of a highly efficient asymmetric synthesis of the previously unknown α-amino-γ-nitro-acids[7] and of α,γ-diamino acids. α,γ-Diamino acids, such as α,γ-diamino butyric acid, are components of polymycines which are known to show antibiotic activity.[8]

Furthermore, it should be possible to transform the nitro group into a nitrile oxide group, which should be able to undergo a 1,3-dipolar cycloaddition[9] to yield isoxazoles which contain amino acids. Isoxazoles have been incorporated into antibiotics like oxacilline or cloxacilline[10] or into anti tumor drugs like acivicine.[11]

II. Results and Discussion

The lithiated bislactim ether of cyclo(-L-Val-Gly-) **2** was obtained as usual from the bislactim ether **1** and n-butyllithium.[12] Upon addition of **2** to the nitro olefines **4** the nitro adducts **5** were obtained. Yields and diastereomeric ratios are listed in Table 1. Diastereomeric ratios were determined by capillary GC MS and ^1H NMR spectroscopy. The (2R,5S)-configuration of the major diastereomer was established through the $^5J_{5H/2H}$ coupling constant. According to our previous experience, $^5J_{5H/2H}$ in the bislactim ether moiety is approximately 3.5 Hz for *trans*- and approximately 5 Hz for *cis*-disubstituted bislactim ethers. The results show clearly that the lithium reagent **2** is not suitable for diastereoselective Michael additions.

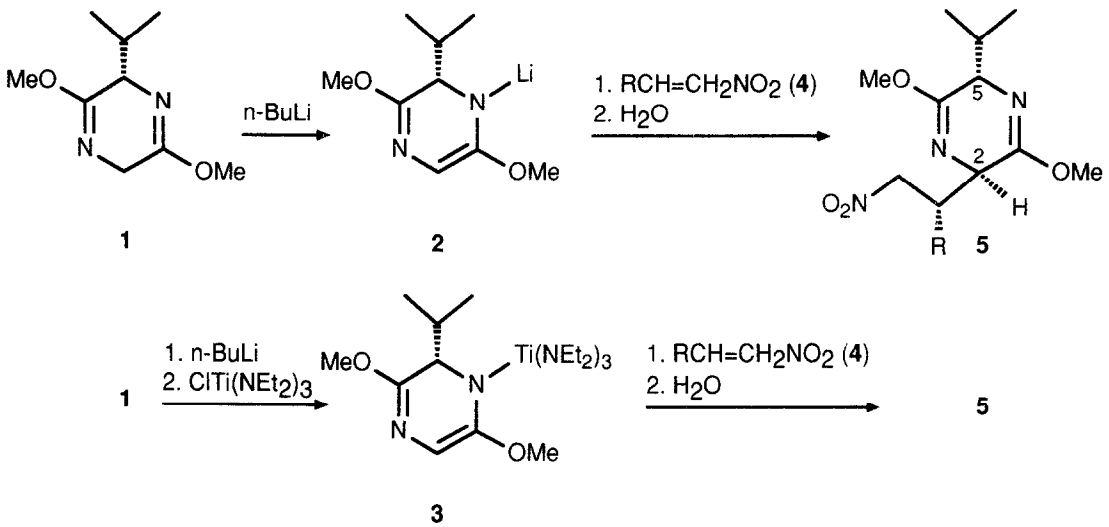
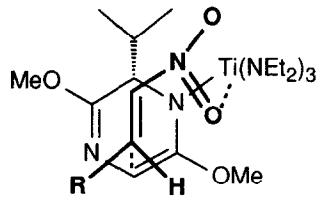


Table 1. Michael addition of the lithiated and the titanated bislactim ether **2** and **3** to nitro olefines

		via the lithiated bislactim ether 2		via the titanated bislactim ether 3	
		yield (%) of **5**	diastereomeric ratio of **5**	yield (%) of **5**	diastereomeric ratio of **5**
4,5	**R**		(2R,1'R):(2R,1'S):(2S,1'R):(2S,1'S)		(2R,1'R) : (2R,1'S)
a	H	50	65 : 35 [a]	74	[a]
b	CH_3	81	50 : 42 : 5 : 3	51	99 : 1
c	C_6H_5	78	45 : 38 : 11 : 6	57	97 : 3
d	p-CH_3-C_6H_4	44	46 : 34 : 13 : 7	63	>99 : <1
e	p-Br-C_6H_4			54	94 : 6
f	p-NO_2-C_6H_4			81	94 : 6
g	3,4-$(CH_3O)_2$-C_6H_3			67	95 : 5
h	2-$C_{10}H_7$			73	94 : 6
i	$CO_2C_2H_5$			83	64 : 36

[a] No chiral center at C-1'.

According to previous results, the titanated bislactim ether of cyclo(-L-Val-Gly-) **3** reacts highly diastereoselectively with aldehydes yielding the corresponding (2R,5S,1'S) aldol adducts as single diastereomers.[5] Consequently, the nitro olefines **4** were treated with the titanated bislactim ether **3**, which was derived from **2** and chlorotitanium tris[diethylamide].[13] The nitro compounds **5** were obtained virtually diastereomerically pure (Table 1). To establish the stereochemistry at C-1' a number of 1'-substituted bislactim ether adducts **5** were prepared in order to obtain crystals suitable for an X-ray analysis. Indeed, the nitro compounds **5d, e, g** and **h** were obtained as solids, but only the adducts **5g** and **h** were suitable for X-ray-analyses.[14] For these compounds the R-configuration at C-1' could be established. This stereochemical result is in agreement with those obtained by the Michael addition of **2** to α,β-unsaturated esters[15] and ketones.[16] In analogy to **5g** and **h** we suggest the same stereo-chemistry at C-1' for the other compounds **5**.



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In order to rationalize the stereochemical outcome of this 1,4-addition, we postulate a chelated transition state **6**. In this transition state the substituent R and the methoxy group do not hinder each other. We believe that the chelating power of the titanium stabilizes such a transition state.

Since chlorotitanium tris[diethylamide] is more difficult to prepare than other titanating agents, we prepared the titanated bislactim ether **7** from the lithiated bislactim ether **2** and the commercially available chlorotitanium tris[*iso* propoxide].[17] Addition of **7** to the nitro olefines **4** afforded after aqueous work-up the nitro compounds **5** (see Table 2). The yields of **5** from the reaction of **7** with **4** are comparable with those obtained from **3** and **4**, but the diastereoselectivities are slightly lower. Since the 1'R- and the 1'S- diastereomers are easy to separate by flash chromatography, the use of the titanated bislactim ether **7** can be recommended for the preparation of the nitro compounds **5**.

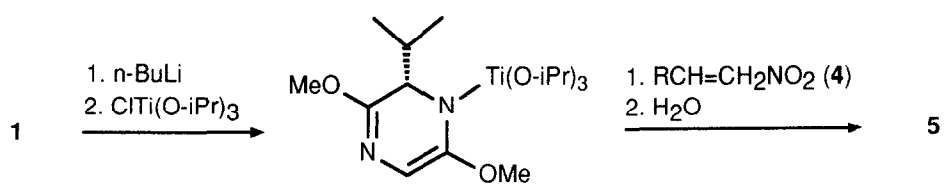

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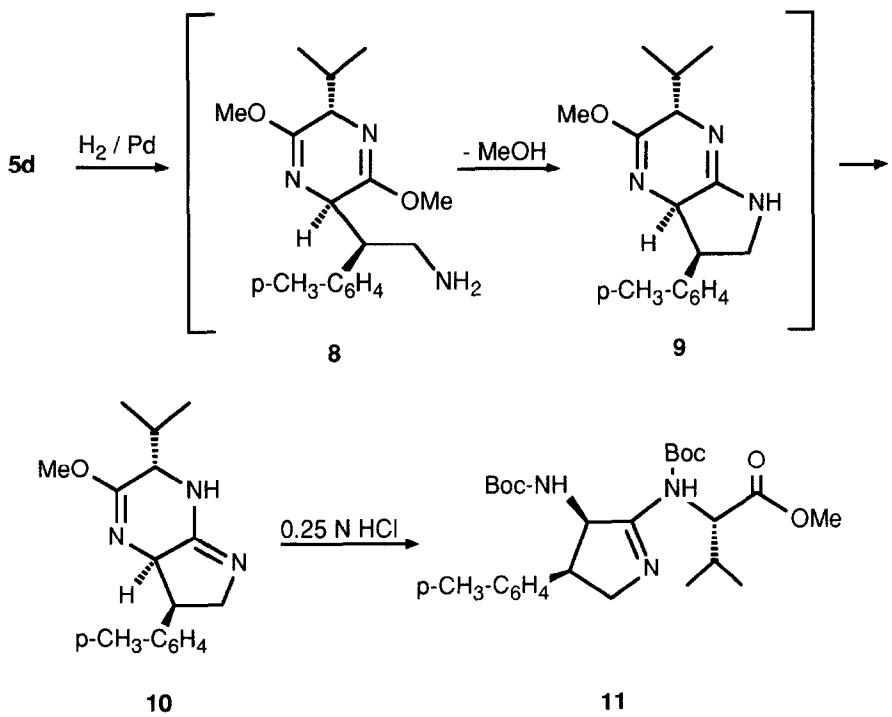
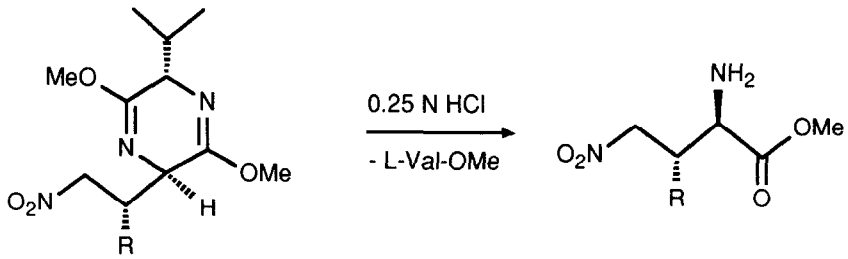
Table 2. Michael addition of the titanated bislactim ethers **3** and **7** to nitro olefines

		via the titanated bislactim ether 7		via the titanated bislactim ether 3	
4,5	**R**	yield (%) of **5**	diastereomeric ratio of **5** (2R,1'R) : (2R,1'S)	yield (%) of **5**	diastereomeric ratio of **5** (2R,1'R) : (2R,1'S)
c	C_6H_5	78	81 : 19	57	97 : 3
d	p-CH_3-C_6H_4	54	87 : 13	80	>99 : <1
e	p-Br-C_6H_4	71	83 : 17	55	94 : 6

In order to prepare the desired α,γ-diamino acids, the nitro group in **5d** was reduced by catalytical hydrogenation. The amino derivative **8** cyclized under the reaction conditions to the amidine **9**, which tautomerized to the more stable bicycle **10**. Upon acidic hydrolysis of **10** and subsequent protection of the amino group as its BOC-derivative the dipeptide analogue **11** was obtained in 52% yield.



In order to avoid the formation of **10** and to obtain the desired α,γ-diamino acids, the bislactim ether needed to be cleaved prior to reduction. The hydrolysis of the bislactim ethers **5** proceeded smoothly without any racemization to yield the α-amino acid methyl esters **12** virtually enantiomerically and diastereomerically pure (see Table 3). Under these reaction conditions a Nef-reaction[18] of the nitro group was not observed. Methyl L-valinate - the chiral auxiliary in this synthesis - could be removed easily by bulb-to-bulb distillation or by column chromatography.

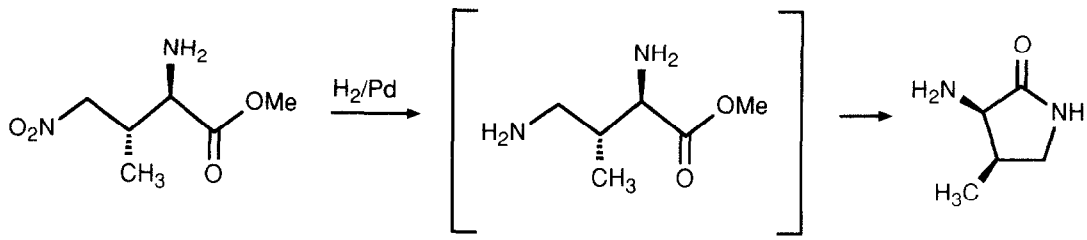


5 **12**

Table 3. α-amino-γ-nitro acid esters **12**

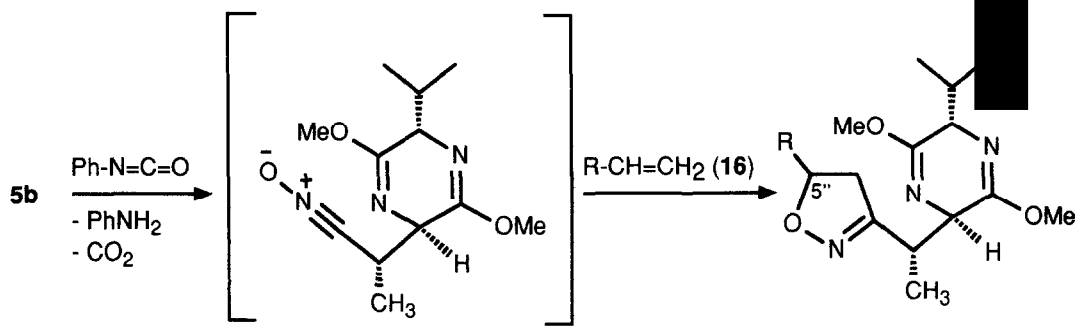
5	**12**	**R**	yield (%) of **12**
b	**a**	CH_3	78
d	**b**	p-CH_3-C_6H_4	64
e	**c**	p-Br-C_6H_4	53
h	**d**	1-$C_{10}H_7$	51

In an exemplary experiment **12a** was hydrogenated (H_2/Pd) yielding the lactam **14** via methyl 2,4-diamino-3-methyl butanoate (**13**).



12a **13** **14**

The nitro compound **5b** was converted into its nitrile oxide derivative **15** according to Mukaiyama's [redacted]ocol.[19] The in situ (2+3)-dipolar cycloaddition[9] with the olefines **16** afforded the isoxazole derivatives **17**. [redacted] cycloaddition proceeded with complete regiocontrol[20] but with a lack of stereocontrol, yielding the adduc[redacted]as 1:1-mixtures of the C-5" diastereomers.

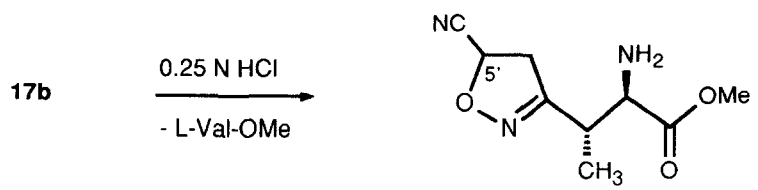


15 **17**

Table 4. Isoxazoles **17**

17	**R**	yield (%) of **17**	diastereomeric ratio at C-5" of **17**
a	OAc	70	1 : 1
b	CN	71	1 : 1
c	C_6H_5	87	1 : 1

Once again in an exemplary experiment **17b** was hydrolyzed to yield - along with L-methyl valinate - the amino acid methyl ester **18** in 62% as a 1:1-mixture of the C-5' epimers.



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EXPERIMENTAL

Infrared (IR) spectra were obtained using a Perkin-Elmer 298 spectrometer. NMR spectra were obtained using a Varian XL 200 or a VXR 200 spectrometer for ^1H and ^{13}C NMR. Chemical shifts are given in parts per million (δ) using tetramethylsilane as internal standard for ^1H- and ^{13}C NMR. Mass spectra were recorded on Varian MAT 731 or 311 A spectrometers. Optical rotations were measured on a Perkin Elmer Mod. 141 polarimeter. TLC analyses were performed on Polygram Sil G/UV_{254} silica gel plates. Silica gel (30-60 μm) from Baker was used for flash chromatography. Combustion analyses were carried out by the microanalytical laboratory at the University of Göttingen. The melting points are uncorrected. All reactions were carried out under a nitrogen or argon atmosphere except those involving hydrolysis. All reagents were purified and dried if necessary before use. The bislactim ether **1** was prepared as described[12] or purchased from Merck-Schuchardt.[21] Chlorotitanium tris[diethylamide] was prepared according to ref.[13]. Chlorotitanium tris[*iso* propoxide] was prepared as described[17a] or purchased from Fluka Chemie AG, Buchs, Switzerland. The nitro olefines **4a-c** and **i** were prepared according to ref. [22], [23], [24] and [25]. The nitro olefines **4d-h** were prepared in a nitro aldol condensation from nitro methane and the corresponding aldehydes according to the general procedure described in ref. [26]. The diastereomeric ratios of **5** were determined by ^{13}C NMR spectroscopical analysis of the crude compounds **5**.

Michael Addition of 3 to the Nitro Olefines 4, General Procedure: *n*-Butyllithium (2.1 ml, 3.3 mmol of a 1.58 *N* solution in hexane) was added at -78 °C to a solution of **1** (0.55 g, 3 mmol) in THF (25 ml). After the solution was stirred for 15 min, chlorotitanium tris[diethylamide][13] (1.65 g of a 60% solution in hexane, 3.3 mmol) [or chlorotitanium tris[*iso* propoxide][17] (0.86 g, 3.3 mmol)] was added and stirring continued for 1 h (formation of **3** or **7**). The solution of **3** (or **7**) was slowly added at -70°C to a precooled solution of the nitro olefines (3.6 mmol) in THF (30 ml) and stirring was continued for 12 h. Phosphate buffer (10 ml, pH 7) was added and the reaction mixture was allowed to warm up to -40 °C. H_2O (50 ml) was added, the layers were separated at room temp., the aqueous layer was extracted four times with diethyl ether (50 ml each) and the combined organic layers were dried with $MgSO_4$. After evaporation of the solvent in vacuo (40°C/20 Torr) the crude products **5** were purified by bulb-to-bulb distillation or by column chromatography.

(2R,5S)-2,5-Dihydro-5-isopropyl-3,6-dimethoxy-2(-2'-nitroethyl-1'-)-pyrazine (5a): 0.55 g (3 mmol) **1** and 0.26 g (3.6 mmol) nitro ethene (**4a**) were used. After bulb-to-bulb distillation 0.57 g (74%) **5a** were obtained. - **D.e.:** > 95% . - **B.p.:** 65°C/0.01 torr. - **IR (neat):** ν = 1690 (C=N), 1550 (NO_2), 1375 cm^{-1} (NO_2). - **^1H NMR (200 MHz,$CDCl_3$):** δ = 0.71 and 1.02 [2d; J = 8 Hz; 6H, $(CH_3)_2CH$], 2.0 - 2.4 [m; 2H; $(CH_3)_2CH$ and 1'-H], 2.6-2.8 (m; 1H; 1'-H), 3.66 and 3.72 (2s; 6H; OCH_3), 3.90 - 4.10 (m; 2H; 2-H and 5-H), 4.40 - 4.66 (m; 2H, CH_2NO_2). - **^{13}C NMR (50 MHz,$CDCl_3$):** δ = 16.98 and 19.07 [$(CH_3)_2CH$],.31.65 (C-1'), 32.22 [$(CH_3)_2CH$], 52.62 and 52.73 (OCH_3), 53.00 (C-5), 61.27 (C-2), 72.51 (CH_2NO_2), 162.32 and 164.69 (C=N). - **HRMS (70 eV):** calculated for $C_{11}H_{19}N_3O_4$ 257.1375, found 257.1375 - **$C_{11}H_{19}N_3O_4$ (257.3)** calc. C,51.35; H,7.44, found, C,51.64; H,7.58%.

(2R,5S,1'R)-2,5-Dihydro-5-isopropyl-3,6-dimethoxy-2-(-1'-methyl-2'-nitroethyl-1'-)-pyrazine (5b): 2.76 g (15 mmol) **1** and 1.57 g (18 mmol) 1-nitro propene (**4b**) were used. After bulb-to-bulb distillation 2.08 g (51%) **5b** were obtained. - **Diasteromeric ratio:** 99 : 1. - **B.p.:** 80°C/0.01 torr. - **IR (neat):** ν = 1690 (C=N), 1550 (NO_2), 1370 cm^{-1} (NO_2). - **^1H NMR (200 MHz,$CDCl_3$):** δ = 0.70 and 1.04 [2d; J = 7 Hz; 6H, $(CH_3)_2CH$], 1.13 (d, J = 7 Hz; 3H, CH_3), 2.31 [dsp, J = 3 and 7 Hz; 1H; $(CH_3)_2CH$], 2.70 - 3.25 (m; 1H; 1'-H), 3.68 and 3.73 (2s; 6H; OCH_3), 3.98 and 3.99 (2dd, J = 3.5 Hz, ^5J = 3.5 Hz; 2H; 2-H and 5-H), 4.13 (A-part of an ABX-system, J_{AB} = 11 Hz, J_{AX} = 8 Hz; 1H, CH_2NO_2), 4.34 (B-part of an ABX-system, J_{AB} = 11 Hz, J_{BX} = 6 Hz; 1H, CH_2NO_2). - **^{13}C NMR (50 MHz,$CDCl_3$):** δ = 14.25 (CH_3), 16.59 and 18.89 [$(CH_3)_2CH$], 31.88 [$(CH_3)_2CH$], 36.01 (C-1'), 52.48 and 52.57 (OCH_3), 57.79 and 60.84 (C-2 and C-5), 78.51 (CH_2NO_2), 161.42 and 164.81 (C=N). - **HRMS (70 eV):** calculated for $C_{12}H_{21}N_3O_4$ 271.1532, found 271.1532 - **$C_{12}H_{21}N_3O_4$ (271.3)** calc. C,53.12; H,7.80, found, C,52.97; H,7.77%.

(2R,5S,1'R)-2,5-Dihydro-5-isopropyl-3,6-dimethoxy-2-(-2'-nitro-1'-phenyl-ethyl-1'-)-pyrazine (5c): 0.55 g (3 mmol) **1** and 0.49 g (3.3 mmol) 1-nitro styrene (**4c**) were used. After bulb-to-bulb distillation 0.57 g (57%) **5c** were obtained. - **Diasteromeric ratio:** 97 : 3. - **B.p.:** 140°C/0.01 torr. - **IR (neat):** ν = 1690 (C=N), 1600 (C=C), 1550 (NO_2), 1370 cm^{-1} (NO_2). - **^1H NMR (200 MHz,$CDCl_3$):** δ = 0.62 and 0.94 [2d; J = 7 Hz; 6H, $(CH_3)_2CH$], 2.17 [dsp, J = 3.5 and 7 Hz; 1H; $(CH_3)_2CH$], 3.54 (dd, J = 3.5 Hz, ^5J = 3.8 Hz; 1H; 5-H), 3.73 and 3.76 (2s; 6H; OCH_3), 4.16 (X-part of an ABX-system, J_{AX} = 6 Hz, J_{BX} = 9 Hz, ^3J = 3.5 Hz; 1H; 1'-H), 4.30 (dd, J = 3.5 Hz, ^5J

= 3.8 Hz; 1H, 2-H), 4.74 (A-part of an ABX-system, J_{AB} = 12 Hz, J_{AX} = 6 Hz; 1H, CH_2NO_2), 4.85 (B-part of an ABX-system, J_{AB} = 12 Hz, J_{BX} = 9 Hz; 1H, CH_2NO_2), 7.30 - 7.37 (m; 5H, C_6H_5). - **^{13}C NMR (50 MHz,CDCl$_3$):** δ = 16.22 and 19.01 [$(CH_3)_2CH$], 31.53 [$(CH_3)_2CH$], 46.90 (C-1'), 52.72 and 52.73 (OCH_3), 58.45 and 60.57 (C-2 and C-5), 78.33 (CH_2NO_2), 127.80, 128.23, 128.44, 128.54, 137.23 (C_6H_5), 160.91 and 165.28 (C=N). - **HRMS (70 eV):** calculated for $C_{17}H_{23}N_3O_4$ 333.1689, found 333.1689 - **$C_{17}H_{23}N_3O_4$ (333.4)** calc. C,61.25; H,6.95, found, C,61.09; H,6.83%.

(2R,5S,1'R)-2,5-Dihydro-5-isopropyl-3,6-dimethoxy-2-[-2'-nitro-1'-(p-methyl phenyl)-ethyl-1'-]-pyrazine (5d): 1.47 g (8 mmol) **1** and 1.43 g (8.8 mmol) 1-nitro-2-(p-methyl phenyl)-ethene (**4d**) were used. After chromatography on silica gel with diethyl ether/petroleum ether 1:10 1.75 g (63%) **5d** were obtained. - **R_f** = 0.16. - **D. e.:** >99%. - **M.p.:** 44°C. - **IR (nujol):** ν = 1690 (C=N), 1600 (C=C), 1550 (NO_2), 1370 cm^{-1} (NO_2). - **^{1}H NMR (200 MHz,CDCl$_3$):** δ = 0.62 and 0.96 [2d; J = 7 Hz; 6H, $(CH_3)_2CH$], 2.30 [dsp, J = 3.5 and 7 Hz; 1H; $(CH_3)_2CH$], 2.32 (s; 3H, CH_3), 3.55 (dd, J = 3.5 Hz, ^{5}J = 3.8 Hz; 1H; 5-H), 3.73 and 3.76 (2s; 6H; OCH_3), 4.12 (X-part of an ABX-system, J_{AX} = 6 Hz, J_{BX} = 9 Hz, ^{3}J = 3.5 Hz; 1H, 1'-H), 4.28 (dd, J = 3.5 Hz, ^{5}J = 3.8 Hz; 1H, 2-H), 4.72 (A-part of an ABX-system, J_{AB} = 12 Hz, J_{AX} = 6 Hz; 1H, CH_2NO_2), 4.82 (B-part of an ABX-system, J_{AB} = 12 Hz, J_{BX} = 9 Hz; 1H, CH_2NO_2), 7.08 - 7.28 (m; 4H, C_6H_4). - **^{13}C NMR (50 MHz,CDCl$_3$):** δ = 16.61 and 18.99 [$(CH_3)_2CH$], 21.07 (CH_3), 31.53 [$(CH_3)_2CH$], 46.44 (C-1'), 52.71 and 52.74 (OCH_3), 58.43 and 60.51 (C-2 and C-5), 76.81 (CH_2NO_2), 128.24, 129.00, 133.84, 137.29 (C_6H_4), 160.78 and 165.01 (C=N). - **$C_{18}H_{25}N_3O_4$ (347.4)** calc. C,62.23; H,7.25, found, C,62.20; H,7.21%.

(2R,5S,1'R)-2,5-Dihydro-5-isopropyl-3,6-dimethoxy-2-[-2'-nitro-1'-(p-bromo phenyl)-ethyl-1'-]-pyrazine (5e): 0.55 g (3 mmol) **1** and 0.75 g (3.3 mmol) 1-nitro-2-(p-bromo phenyl)-ethene (**4e**) were used. After chromatography on silica gel with toluene 0.67 g (54%) **5e** were obtained. - **R_f** = 0.15. - **Diastereomeric ratio:** 94 : 6. - **M.p.:** 52°C. - **IR (nujol):** ν = 1690 (C=N), 1590 (C=C), 1550 (NO_2), 1370 cm^{-1} (NO_2). - **^{1}H NMR (200 MHz,CDCl$_3$):** δ = 0.62 and 0.97 [2d; J = 7 Hz; 6H, $(CH_3)_2CH$], 2.17 [dsp, J = 3.5 and 7 Hz; 1H; $(CH_3)_2CH$], 3.65 (dd, J = 3.5 Hz, ^{5}J = 3.8 Hz; 1H; 5-H), 3.72 and 3.78 (2s; 6H; OCH_3), 4.12 (X-part of an ABX-system, J_{AX} = 5 Hz, J_{BX} = 9 Hz, ^{3}J = 3.5 Hz; 1H, 1'-H), 4.22 (dd, J = 3.5 Hz, ^{5}J = 3.8 Hz; 1H, 2-H), 4.63 (A-part of an ABX-system, J_{AB} = 12 Hz, J_{AX} = 5 Hz; 1H, CH_2NO_2), 4.75 (B-part of an ABX-system, J_{AB} = 12 Hz, J_{BX} = 9 Hz; 1H, CH_2NO_2), 7.20 - 7.50 (m; 4H, C_6H_4). - **^{13}C NMR (50 MHz,CDCl$_3$):** δ = 16.66 and 18.98 [$(CH_3)_2CH$], 31.76 [$(CH_3)_2CH$], 46.15 (C-1'), 52.79 and 52.84 (OCH_3), 58.18 and 60.75 (C-2 and C-5), 76.54 (CH_2NO_2), 121.99, 130.24, 131.38, 136.33 (C_6H_4), 160.56 and 165.41 (C=N). - **$C_{17}H_{22}BrN_3O_4$ (412.3)** calc. C,49.52; H,5.38, found, C,49.72; H,5.44%.

(2R,5S,1'R)-2,5-Dihydro-5-isopropyl-3,6-dimethoxy-2-[-2'-nitro-1'-(p-nitro phenyl)-ethyl-1'-]-pyrazine (5f): 0.55 g (3 mmol) **1** and 0.64 g (3.3 mmol) 1-nitro-2-(p-nitro phenyl)-ethene (**4f**) were used. After bulb-to-bulb distillation 0.92 g (81%) **5f** were obtained, which still were contaminated with traces of **4f**. - **Diastereomeric ratio:** 94 : 6. - **B.p.:** 160°C/0.01 torr. - **IR (neat):** ν = 1685 (C=N), 1605 (C=C), 1550 (NO_2), 1370 cm^{-1} (NO_2). - **^{1}H NMR (200 MHz,CDCl$_3$):** δ = 0.66 and 0.99 [2d; J = 7 Hz; 6H, $(CH_3)_2CH$], 2.16 [dsp, J = 3.5 and 7 Hz; 1H; $(CH_3)_2CH$], 3.73 and 3.80 (2s; 6H; OCH_3), 4.20 - 5.20 (m; 5H, 1'H, 2-H, 5-H and CH_2NO_2), 7.40 - 8.40 (m; 4H, C_6H_4). - **^{13}C NMR (50 MHz,CDCl$_3$):** δ = 16.74 and 18.97 [$(CH_3)_2CH$], 32.03 [$(CH_3)_2CH$], 46.20 (C-1'), 52.91 and 53.06 (OCH_3), 58.03 and 61.01 (C-2 and C-5), 76.12 (CH_2NO_2), 123.59, 129.57, 145.18, 147.53 (C_6H_4), 160.21 and 165.83 (C=N). - **$C_{17}H_{22}N_4O_6$ (412.3)** calc. C,53.94; H,5.86, found, C,53.22; H,5.47%.

(2R,5S,1'R)-2,5-Dihydro-5-isopropyl-3,6-dimethoxy-2-[-2'-nitro-1'-(3,4-dimethoxy phenyl)-ethyl-1'-]-pyrazine (5g): 0.55 g (3 mmol) **1** and 0.69 g (3.3 mmol) 1-nitro-2-(3,4-dimethoxy phenyl)-ethene (**4g**) were used. After chromatography on silica gel with diethyl ether/petroleum ether 1:1 0.79 g (67%) **5g** were obtained. A sample of **5g** was recrystallized from diethyl ether/cyclohexane. - **R_f** = 0.25. - **Diastereomeric ratio:** 95 : 5. - **M.p.:** 85°C. - **IR (nujol):** ν = 1690 (C=N), 1605 (C=C), 1550 (NO_2), 1370 cm^{-1} (NO_2). - **^{1}H NMR (200 MHz,CDCl$_3$):** δ = 0.61 and 0.95 [2d; J = 7 Hz; 6H, $(CH_3)_2CH$], 2.15 [dsp, J = 3.5 and 7 Hz; 1H; $(CH_3)_2CH$], 3.58 (dd, J = 3.5 Hz, ^{5}J = 3.5 Hz; 1H; 5-H), 3.74 and 3.77 (2s; 6H; OCH_3), 3.88 (s; 6H, $C_6H_3OCH_3$), 4.10 (X-part of an ABX-system, J_{AX} = 6 Hz, J_{BX} = 9.5 Hz, ^{3}J = 3.5 Hz; 1H, 1'-H), 4.28 (dd, J = 3.5 Hz, ^{5}J = 3.5 Hz; 1H, 2-H), 4.68 (A-part of an ABX-system, J_{AB} = 13 Hz, J_{AX} = 6 Hz; 1H, CH_2NO_2), 4.77 (B-part of an ABX-system, J_{AB} = 13 Hz, J_{BX} = 9.5 Hz; 1H, CH_2NO_2), 6.80 - 6.94 (m; 3H, C_6H_3). - **^{13}C NMR (50 MHz,CDCl$_3$):** δ = 16.62 and 19.01 [$(CH_3)_2CH$], 31.53 [$(CH_3)_2CH$], 46.48 (C-1'), 52.67 and 52.71 (OCH_3), 55.75 and 55.80 ($C_6H_3OCH_3$), 58.52 and 60.58 (C-2 and C-5), 77.15 (CH_2NO_2), 111.00, 111.95, 120.59, 122.85, 129.51, 148.61 (C_6H_3), 160.84 and 165.23 (C=N). - **$C_{19}H_{27}N_3O_6$ (393.3)** calc. C,57.99; H,6.92, found, C,58.18; H,7.02%.

(2R,5S,1'R)-2,5-Dihydro-5-isopropyl-3,6-dimethoxy-2-[-2'-nitro-1'-(1-naphthyl)-ethyl-1'-]-pyrazine (5h): 0.55 g (3 mmol) **1** and 0.66 g (3.3 mmol) 1-nitro-2-(1-naphthyl)-ethene (**4h**) were used. After chromatography on silica gel with diethyl ether/petroleum ether 1:20 0.84 g (73%) **5h** were obtained. A sample of **5h** was recrystallized from hexane. - $\mathbf{R_f}$ = 0.05. - **Diastereomeric ratio:** 94 : 6. - **M.p.:** 70°C. - **IR (nujol):** ν = 1690 (C=N), 1600 (C=C), 1550 (NO_2), 1370 cm^{-1} (NO_2). - **^{1}H NMR (200 MHz,$CDCl_3$):** δ = 0.58 and 0.95 [2d; J = 7 Hz; 6H, $(CH_3)_2CH$], 2.11 [dsp, J = 3.5 and 7 Hz; 1H; $(CH_3)_2CH$], 3.63 and 3.82 (2s; 6H; OCH_3), 3.73 (dd, J = 3.5 Hz, ^{5}J = 3.8 Hz; 1H; 5-H), 4.37 (dd, J = 3.5 Hz, ^{5}J = 3.8 Hz; 1H, 2-H), 4.71 (A-part of an ABX-system, J_{AB} = 13 Hz, J_{AX} = 7 Hz; 1H, CH_2NO_2), 4.83 (B-part of an ABX-system, J_{AB} = 13 Hz, J_{BX} = 8 Hz; 1H, CH_2NO_2), 5.22 (X-part of an ABX-system, J_{AX} = 7 Hz, J_{BX} = 8 Hz, ^{3}J = 3.5 Hz; 1H, 1'-H), 7.40 - 7.90 and 8.30 -8.40 (2m; 7H, $C_{10}H_7$). - **^{13}C NMR (50 MHz,$CDCl_3$):** δ = 16.65 and 18.94 [$(CH_3)_2CH$], 31.75 [$(CH_3)_2CH$], 40.08 (C-1'), 52.54 and 52.92 (OCH_3), 57.76 and 60.74 (C-2 and C-5), 75.95 (CH_2NO_2), 122.92, 124.70, 125.06, 125.67, 126.52, 128.25, 129.06, 131.75, 133.66, 134.05 ($C_{10}H_7$), 160.96 and 164.88 (C=N). - **$C_{21}H_{25}N_3O_4$ (383.3)** calc. C,65.77; H,6.58, found, C,65.90; H,6.54%.

(2R,5S,1'R)-2,5-Dihydro-5-isopropyl-3,6-dimethoxy-2-(-2'-nitro-1'-ethyloxcarbonyl-ethyl-1'-)-pyrazine (5i): 0.55 g (3 mmol) **1** and 0.44 g (3.3 mmol) ethyl 3-nitro acrylate (**4i**) were used yielding 0.82 g (83%) of a crude mixture of **5i** and (*2R,5S,1'S*)-**5i**. After chromatography on silica gel with diethyl ether/petroleum ether 1:10 0.36 g (36%) **5i** were obtained as a single diastereomer. - $\mathbf{R_f}$ = 0.29. - **Diastereomeric ratio:** 64 : 36. - **IR (neat):** ν = 1730 (C=O), 1690 (C=N), 1550 (NO_2), 1375 cm^{-1} (NO_2). - **^{1}H NMR (200 MHz,$CDCl_3$):** δ = 0.72 and 1.02 [2d; J = 7 Hz; 6H, $(CH_3)_2CH$], 1.08 (t, J = 7 Hz; 3H, CH_2CH_3), 2.22 [dsp, J = 3 and 7 Hz; 1H; $(CH_3)_2CH$], 3.62 and 3.72 (2s; 6H; OCH_3), 3.88 (X-part of an ABX-system, J_{AX} = 4 Hz, J_{BX} = 9.5 Hz, ^{3}J = 3.5 Hz; 1H, 1'-H), 4.01 (dd, J = 3.5 Hz, ^{5}J = 3.8 Hz; 1H; 5-H), 4.13 (A-part of an ABX-system, J_{AB} = 14.5 Hz, J_{AX} = 4 Hz; 1H, CH_2NO_2), 4.25 (q, J = 7 Hz; 2H, CH_2CH_3), 4.60 (dd, J = 3.5 Hz, ^{5}J = 3.8 Hz; 1H, 2-H), 4.71 (B-part of an ABX-system, J_{AB} = 14.5 Hz, J_{BX} = 9.5 Hz; 1H, CH_2NO_2). - **^{13}C NMR (50 MHz,$CDCl_3$):** δ = 14.11 (CH_2CH_3), 16.92 and 18.98 [$(CH_3)_2CH$], 32.35 [$(CH_3)_2CH$], 45.75 (C-1'), 52.83 and 53.05 (OCH_3), 55.47 and 61.43 (C-2 and C-5), 61.62 (OCH_2CH_3), 72.01 (CH_2NO_2), 160.35 and 165.39 (C=N), 170.23 (C=O). - (*2R,5S,1'S*)-**5i**: **^{13}C NMR (50 MHz,$CDCl_3$):** δ = 14.11 (CH_2CH_3), 17.03 and 19.03 [$(CH_3)_2CH$], 32.21 [$(CH_3)_2CH$], 45.75 (C-1'), 52.70 and 52.74 (OCH_3), 55.21 and 62.80 (C-2 and C-5), 62.54 (OCH_2CH_3), 72.01 (CH_2NO_2), 160.10 and 166.33 (C=N), 167.86 (C=O). - **$C_{14}H_{23}N_3O_6$ (329.2)** calc. C,51.04; H,7.04, found, C,50.72; H,7.29%.

1,3-Dipolar Addition of the Nitrile Oxides 15 to the Olefines 16, Isoxazolines 17, General Procedure: To a solution of the nitro compounds **5** (3 mmol) and triethyl amine (3 drops) in benzene (2 ml) phenyl isocyanate (0.71 g, 6 mmol) and a solution of the olefines **16** (3.5 mmol) in benzene (2 ml) were added. After stirring for 1 h at room temp. the mixture was refluxed for 8 h. Solid compounds were removed by filtration and the solvent was removed in vacuo (30°C/12 Torr). The residues - the crude isoxazolines **17** - were purified by chromatography on silica gel or by bulb-to-bulb distillation.

(2R,5S,1'R,5''RS)-2,5-Dihydro-3,6-dimethoxy-5-isopropyl-2-[-1'-(-5''-acetoxyisoxazolinyl-3'')-ethyl-1'] pyrazine (17a): 0.81 g (3 mmol) **5b** and 0.30g (3.5mmol) vinyl acetate (**16a**) were used. After chromatography on silica gel with diethyl ether/hexane 1:30 0.71 g (70%) **17a** were obtained. - $\mathbf{R_f}$ = 0.06 and 0.08. - **Diasteromeric ratio:** 1:1, determined by ^{13}C NMR spectroscopy. - **IR (neat):** ν = 1750 (C=O), 1690 cm^{-1} (C=N). - **^{1}H NMR (200 MHz,$CDCl_3$):** δ = 0.70 and 1.04 [2d; J = 7 Hz; 6H, $(CH_3)_2CH$], 1.34 (d, J = 7 Hz; 3H, CH_3), 2.04 (s; 3H, $COCH_3$), 2.28 [dsp, J = 3.5 and 7 Hz; 1H; $(CH_3)_2CH$], 2.82-3.16 (m; 2H, 4''-H), 3.20 - 3.54 (m; 1H; 1'-H), 3.72 and 3.74 (2s; 6H; OCH_3), 3.96 (dd, J = 3.5 Hz, ^{5}J = 3.5 Hz; 1H; 5-H), 4.16 (dd, J = 3.5 Hz, ^{5}J = 3.5 Hz; 1H; 2-H), 6.64 (m; 1H, 5''-H). - **^{1}H NMR (200 MHz,$CDCl_3$) of the second diastereomer:** δ = 0.68 and 1.04 [2d; J = 7 Hz; 6H, $(CH_3)_2CH$], 1.36 (d, J = 7 Hz; 3H, CH_3), 2.06 (s; 3H, $COCH_3$); the other signals are covered by the signals of the first diastereomer. - **^{13}C NMR (50 MHz,$CDCl_3$):** δ = 14.11 and 14.53 (CH_3), 16.57, 16.62, 19.02 and 19.03 [$(CH_3)_2CH$], 31.63 and 31.76 [$(CH_3)_2CH$], 36.53 and 36.87 (C-1'), 42.53 and 42.70 (C-4''), 52.32, 52.42, 52.43, 52.54 , 52.57 and 52.61 (OCH_3), 58.41, 59.05, 60.63 and 60.76 (C-2 and C-5), 95.14 and 95.24 (C-5''), 160.46, 160.62, 161.22, 161.63, 164.51 and 164.62 (C-3, C-6, C-3''), 169.54 ($COOCH_3$).- **$C_{16}H_{25}N_3O_5$ (339.3)** calc. C,56.62; H,7.43, found, C,57.02; H,7.38%.

(2R,5S,1'R,5''RS)-2,5-Dihydro-3,6-dimethoxy-5-isopropyl-2-[-1'-(-5''-cyanoisoxazolinyl-3'')-ethyl-1'] pyrazine (17b): 0.81 g (3 mmol) **5b** and 0.19g (3.5mmol) acrylonitrile (**16b**) were used. After by bulb-to-bulb distillation 0.65 g (71%) **17b** were obtained. - **B.p.:** 100-110°C/0.01 Torr. - **Diasteromeric ratio:** 1:1, determined by ^{13}C NMR spectroscopy. - **IR (neat):** ν = 2260 (CN), 1690 cm^{-1} (C=N). - **^{1}H NMR (200 MHz,$CDCl_3$):** δ = 0.68 and

1.04 [2d; J = 7 Hz; 6H, $(CH_3)_2CH$], 1.28 (d, J = 7 Hz; 3H, CH_3), 2.28 [dsp, J = 3.5 and 7 Hz; 1H; $(CH_3)_2CH$], 3.10 - 3.22 (m; 1H; 1'-H), 3.24-3.42 (m; 2H, 4"-H), 3.70 and 3.72 (2s; 6H; OCH_3), 3.98 (dd, J = 3.5 Hz, ^5J = 3.5 Hz; 1H; 5-H), 4.14 (dd, J = 3.5 Hz, ^5J = 3.5 Hz; 1H; 2-H), 5.08-5.24 (m; 1H, 5"-H). - **^{1}H NMR (200 MHz,$CDCl_3$) of the second diastereomer:** δ = 0.69 and 1.06 [2d; J = 7 Hz; 6H, $(CH_3)_2CH$], 1.30 (d, J = 7 Hz; 3H, CH_3), 3.71 and 3.73 (2s; 6H; OCH_3), 4.18 (dd, J = 3.5 Hz, ^5J = 3.5 Hz; 1H; 2-H),; the other signals are covered by the signals of the first diastereomer. - **^{13}C NMR (50 MHz,$CDCl_3$):** δ = 13.51 and 14.01 (CH_3), 16.60, 16.62, 19.02 and 19.04 [$(CH_3)_2CH$], 31.78 and 31.79 [$(CH_3)_2CH$], 36.64 and 37.12 (C-1'), 42.33 and 42.35 (C-4"), 52.53, 52.60, 52.65 and 52.67 (OCH_3), 58.08, 58.62, 60.84 and 60.89 (C-2 and C-5), 65.53 and 65.75 (C-5"), 117.47 and 117.55 (CN), 160.48, 160.54, 161.22, 161.30, 165.04 and 165.13 (C-3, C-6, C-3").- **$C_{15}H_{22}N_4O_3$ (306.3)** calc. C,58.81; H,7.24, found, C,58.85; H,7.23%.

(2R,5S,1'R,5"RS)-2,5-Dihydro-3,6-dimethoxy-5-isopropyl-2-[-1'-(-5"-phenylisoxazolinyl-3")-ethyl-1'] pyrazine (17c): 0.81 g (3 mmol) **5b** and 0.37g (3.5mmol) styrene (**16c**) were used. After bulb-to-bulb distillation 0.93 g (87%) **17c** were obtained. - **B.p.:** 130-135°C/0.01 Torr. - **Diasteromeric ratio:** 1:1, determined by ^{13}C NMR spectroscopy. - **IR (neat):** ν = 1690 (C=N), 1595 cm^{-1} (C=C). - **^{1}H NMR (200 MHz,$CDCl_3$):** δ = 0.66 and 1.01 [2d; J = 7 Hz; 6H, $(CH_3)_2CH$], 1.32 (d, J = 7 Hz; 3H, CH_3), 2.24 [dsp, J = 3.5 and 7 Hz; 1H; $(CH_3)_2CH$], 2.92 (A-part of an ABX-system, J_{AB} = 17 Hz, J_{AX} = 8 Hz; 1H, 4"-H), 3.20-3.32 (m; 1H; 1'-H), 3.28 (B-part of an ABX-system, J_{AB} = 17 Hz, J_{BX} = 11 Hz; 1H, 4"-H), 3.66 and 3.70 (2s; 6H; OCH_3), 3.79 (dd, J = 3.5 Hz, ^5J = 3.5 Hz; 1H; 5-H), 4.14 (dd, J = 3.5 Hz, ^5J = 3.5 Hz; 1H; 2-H), 5.52 (X-part of an ABX-system, J_{AX} = 8 Hz, J_{BX} = 11 Hz; 1H, 5"-H), 7.26-7.42 (m; 5H, C_6H_5). - **^{13}C NMR (50 MHz,$CDCl_3$):** δ = 14.09 and 14.38 (CH_3), 16.56, 16.60, 19.00 and 19.01 [$(CH_3)_2CH$], 31.71 and 31.73 [$(CH_3)_2CH$], 36.84 and 37.42 (C-1'), 44.47 and 44.71 (C-4"), 52.36, 52.47, 52.54 and 52.59 (OCH_3), 58.30, 58.88, 60.67 and 60.69 (C-2 and C-5), 80.98 and 81.19 (C-5"), 125.54, 125.54, 125.59, 125.62, 128.59, 129.07, 141.57, 141.65 (C_6H_5), 159.53, 159.54, 161.77, 161.81, 164.53 and 164.55 (C-3, C-6, C-3").- **HRMS (70 eV):** calculated for $C_{20}H_{27}N_3O_3$ 357.2052, found 357.2052. - **$C_{20}H_{27}N_3O_3$ (357.3)** calc. C,67.19; H,7.62, found, C,66.90; H,7.58%.

Hydrolysis of the Bislactim Ethers 5 and 17, Methyl α-Amino-γ-Nitro Butanoates 12 and Methyl α-Amino Butanoate 18, General Procedure: To a stirred suspension of **5** (4 mmol) in hydrochloric acid (0.25 *N*, 32 ml, 8 mmol) THF was added until the mixture became homogeneous and stirring was continued at room temp. for 1d - 6d. Volatiles were removed in vacuo (25°C/10 torr) and the aqueous solution was extracted with diethyl ether (25 ml) in order to remove undesired non basic organic materials. Diethyl ether (25 ml) was added to the aqueous layer and the mixture was brought to pH 8-10 with conc. ammonia under stirring. The layers were separated and the aqueous layer was extracted twice with diethyl ether (25 ml each). The combined ethereal layers were dried with $MgSO_4$ and the solvent was evaporated in vacuo (0°C/ 10 torr). Methyl *L*-valinate was removed in vacuo (30°C/0.01 torr) and the residues - the crude amino acid esters **12** - were purified by chromatography or bulb-to-bulb distillation.

Methyl α-amino-β-methyl-γ-nitro butanoate (12a): 1.08 g (4 mmol) **5b** were used and stirring was continued for 1 d. After bulb-to-bulb distillation 0.55 g (78%) **12a** were obtained. - **B.p.:** 60°C/0.01 torr. - - **D.e.** and **e.e.:** >95%. - **$[\alpha]^{20}_D$** = -40.7° (c=2.0, EtOH). - **IR (neat):** ν = 3380 and 3340 (NH_2), 1730 (C=O), 1550 (NO_2), 1370 cm^{-1} (NO_2). - **^{1}H NMR (200 MHz,$CDCl_3$):** δ = 1.06 (d; J = 6.5 Hz; 3H, CH_3), 2.66 (br. s; 2H, NH_2), 2.40 - 3.10 (m; 1H, $CHCH_3$), 3.42 (d, J = 6.5 Hz; 1H, $CHNH_2$), 3.76 (s; 3H; OCH_3), 4.31 (A-part of an ABX-system, J_{AB} = 12 Hz, J_{AX} = 8 Hz; 1H, CH_2NO_2), 4.64 (B-part of an ABX-system, J_{AB} = 12 Hz, J_{BX} = 6.5 Hz; 1H, CH_2NO_2). - **^{13}C NMR (50 MHz,$CDCl_3$):** δ = 14.59 (CH_3), 36.63 ($CHCH_3$), 52.25 (OCH_3), 57.02 ($CHNH_2$), 78.25 (CH_2NO_2), 174.54 ($COOCH_3$). - **$C_6H_{12}N_2O_4$ (176.1)** calc. C,40.89; H,6.87, found, C,41.06; H,6.89%.

Methyl α-amino-β-(p-methyl phenyl)-γ-nitro butanoate (12b): 0.52 g (1.5 mmol) **5d** were used and stirring was continued for 4 d. After chromatography on silica gel with diethyl ether 0.24 g (64%) **12b** were obtained. - **R_f** = 0.24. - **M.p.:** 52°C. - - **D.e.** and **e.e.:** >95%. - **$[\alpha]^{20}_D$** = -8.2° (c=1.0, EtOH). - **IR (nujol):** ν = 3370 (NH_2), 1730 (C=O), 1540 (NO_2), 1370 cm^{-1} (NO_2). - **^{1}H NMR (200 MHz,$CDCl_3$):** δ = 1.63 (br. s; 2H, NH_2), 2.32 (s; 3H, CH_3), 3.59 (s; 3H; OCH_3), 3.69 (d, J = 7.5 Hz; 1H, $CHNH_2$), 3.81 (X-part of an ABX-system, J_{AX} = 8.5 Hz, J_{BX} = 5.5 Hz, ^3J = 7.5 Hz; 1H, $CHCH_2NO_2$), 4.78 (A-part of an ABX-system, J_{AB} = 13 Hz, J_{AX} = 8.5 Hz; 1H, CH_2NO_2), 5.05 (B-part of an ABX-system, J_{AB} = 13 Hz, J_{BX} = 5.5 Hz; 1H, CH_2NO_2), 7.12 - 7.15 (m; 4H, C_6H_4). - **$C_{12}H_{16}N_2O_4$ (252.2)** calc. C,57.13; H,6.39, found, C,57.32; H,6.43%.

Methyl α-amino-β-(p-bromo phenyl)-γ-nitro butanoate (12c): 0.62 g (1.5 mmol) **5e** were used and stirring was continued for 5 d. After chromatography on silica gel with diethyl ether 0.25 g (53%) **12c** were obtained. - $\mathbf{R_f}$ = 0.21. - **M.p.:** 58°C. - - **D.e.** and **e.e.:** >95%. - $\mathbf{[\alpha]^{20}_D}$ = -7.4° (c=1.0, EtOH). - **IR (nujol):** ν = 3350 and 3270 (NH_2), 1730 (C=O), 1540 (NO_2), 1370 cm^{-1} (NO_2). - **^{1}H NMR (200 MHz,$CDCl_3$):** δ = 1.66 (br. s; 2H, NH_2), 3.60 (s; 3H; OCH_3), 3.65 (d, J = 7.5 Hz; 1H, C*H*NH_2), 3.81 (X-part of an ABX-system, J_{AX} = 8.5 Hz, J_{BX} = 5.5 Hz, ^{3}J = 7.5 Hz; 1H, C*H*CH_2NO_2), 4.75 (A-part of an ABX-system, J_{AB} = 13 Hz, J_{AX} = 8.5 Hz; 1H, CH_2NO_2), 5.06 (B-part of an ABX-system, J_{AB} = 13 Hz, J_{BX} = 5.5 Hz; 1H, CH_2NO_2), 7.12 - 7.52 (m; 4H, C_6H_4). **^{13}C NMR (50 MHz,$CDCl_3$):** δ = 47.14 (*C*HCH_2NO_2), 52.27 (OCH_3), 57.52 ($CHNH_2$), 76.82 (CH_2NO_2), 122.27, 129.69, 132.06, 135.55 (C_6H_4), 173.69 (*C*$OOCH_3$). - **$C_{11}H_{13}BrN_2O_4$ (317.1)** calc. C,41.65; H,4.13, found, C,41.86; H,4.22%.

Methyl α-amino-β-(1- naphthyl)-γ-nitro butanoate (12d): 0.57 g (1.5 mmol) **5h** were used and stirring was continued for 6 d. After chromatography on silica gel with diethyl ether 0.22 g (51%) **12d** were obtained. - $\mathbf{R_f}$ = 0.31. - - **D.e.** and **e.e.:** >95%. - $\mathbf{[\alpha]^{20}_D}$ = -9.1° (c=1.0, EtOH). - **IR (neat):** ν = 3370 and 3320 (NH_2), 1730 (C=O), 1540 (NO_2), 1370 cm^{-1} (NO_2). - **^{1}H NMR (200 MHz,$CDCl_3$):** δ = 1.62 (br. s; 2H, NH_2), 3.58 (s; 3H; OCH_3), 3.95 (d, J = 5.5 Hz; 1H, C*H*NH_2), 4.86 - 5.18 (m; 3H, C*H*CH_2NO_2), 7.38 - 8.26 (m; 7H, $C_{10}H_7$). **^{13}C NMR (50 MHz,$CDCl_3$):** δ = 41.02 (*C*HCH_2NO_2), 52.34 (OCH_3), 57.21 ($CHNH_2$), 76.11 (CH_2NO_2), 122.47, 124.13, 125.14, 126.00, 126.86, 128.64, 129.13, 131.18, 131.82, 134.09 ($C_{10}H_7$), 173.73 (*C*$OOCH_3$). - **$C_{15}H_{16}N_2O_4$ (288.3)** calc. C,62.49; H,5.59, found, C,62.46; H,5.74%.

Methyl α-amino-β-(5'-cyanoisoxazolinyl-3') butanoate (18): 0.61 g (2 mmol) **17b** were used and stirring was continued for 2 d. After bulb-to-bulb distillation 0.26 g (62%) **18** were obtained. - **B.p.:** 110-115°C/0.01 torr. - **Diasteromeric ratio:** 1:1, determined by ^{13}C NMR spectroscopy. - **IR (neat):** ν = 3380 (NH_2), 2260 (CN), 1730 (C=O), 1690 cm^{-1} (C=N). - **^{1}H NMR (200 MHz,$CDCl_3$):** δ = 1.18 (d; J = 7 Hz; 3H, CH_3), 1.68 (br. s; 2H, NH_2), 2.90 (dq, J = 7 and 6.5 Hz; 1H, 3-H), 3.10 - 3.44 (m; 2H, 4'-CH_2), 3.34 (d, J = 6.5 Hz; 1H, 2-H), 3.62 (s; 3H; OCH_3), 4.80-5.16 (m; 1H, 5'-H). - **^{13}C NMR (50 MHz,$CDCl_3$):** δ = 14.85 and 15.06 (CH_3), 36.74 and 36.80 (C-3), 41.96 and 42.00 (C-4'), 52.36 and 52.47 (OCH_3), 57.49 and 57.73 (C-2), 65.69 and 65.74 (C-5'), 117.38 and 117.41 (CN), 160.41 and 160.47 (C-3'), 174.08 and 174.13 (*C*$OOCH_3$). - **$C_6H_{12}N_2O_4$ (211.2)** calc. C,51.17; H,6.21, found, C,51.48; H,6.41%.

Hydrogenation of the Bislactim Ether Adduct 5d, (1R,4S,9R)-2,5,7-Triaza-4-isopropyl-3-methoxy-9-(p-methyl phenyl)-bicyclo-[4.3.0]-nona-2,6-diene (10): A suspension of 1.5 g (4.3 mmol) **5d**, 0.20 g palladium (10%, on charcoal) and 1.4 g ammonium formiate in methanol (10 ml) was stirred under a hydrogen atmosphere for 1 h at room temp. . The suspension was filtered through celite and the celite was washed with methanol (10 ml). The methanol was removed in vacuo and the residue was dissolved in H_2O (10 ml) and CH_2Cl_2 (20 ml). The layers were separated and the aqueous layer was extracted twice with CH_2Cl_2 (20 ml each). The combined organic layers were dried with $MgSO_4$, the solvent was removed in vacuo and the residue purified by column filtration on silica gel (10 g) first with diethyl ether and then with methanol. 0.91 g (74%) **10** were obtained. - **D.e.:** >99%. - **M.p.:** 62°C. - **IR (nujol):** ν = 3300-3100 (NH), 1700 (C=N), 1650 (C=N), 1600 cm^{-1} (C=C). - **^{1}H NMR (200 MHz,$CDCl_3$):** δ = 0.89 and 1.01 [2d; J = 7 Hz; 6H, $(CH_3)_2CH$], 1.90 - 2.30 [m; 1H; $(CH_3)_2CH$], 2.22 (s; 3H, CH_3), 3.42 (s; 3H; OCH_3), 3.66 - 3.96 (m; 3H, 1-H and 8-H), 4.40 (X-part of an ABX-system, J_{AX} = 6 Hz, J_{BX} = 6 Hz, ^{3}J = 1 Hz; 1H, 9-H), 4.84 (d, J = 7.5 Hz; 1H, 4-H), 6.80 - 7.00 (m; 4H, C_6H_4), 8.01 (br. s; 1H, NH). - **^{13}C NMR (50 MHz,$CDCl_3$):** δ = 17.26 and 18.96 [$(CH_3)_2CH$], 20.91 (CH_3), 33.36 [$(CH_3)_2CH$], 43.51 (C-9), 52.90 (OCH_3), 57.02 and 58.76 (C-1 and C-5), 62.09 (C-8), 127.57, 128.98, 135.83, 136.30 (C_6H_4), 146.69 (C-6), 164.21 (C-3). - **$C_{17}H_{23}N_3O$ (285.2)** calc. C,71.53; H,8.13, found, C,71.25; H,8.02%.

Hydrolysis of the 2,5,7-Triazabicyclo-[4.3.0]-nona-2,6-diene 10, (3R,4R)-3-(N-t-Butoxycarbonylamino)-4-(p-methyl phenyl)-2-[N-(methyl L-N-t-butoxycarbonyl valinate]-1-pyrroline(11): To a solution of 0.40 g (1.4 mmol) **10** in THF (10 ml) 1 *N* HCl (10 ml) was added and stirring was contiued for 36 h. The solvent was removed in vacuo (50°C/12 Torr) and the crude amino acid hydrochloride dried in vacuo (30°C/0.1 Torr) for 2 d. The residue was dissolved in methylene chloride (10 ml), 1.30 g (6 mmol) di-*t*-butyl dicarbonate were added and the mixture cooled down to 0°C. 0.60 g (6 mmol) Triethyl amine were slowly added and stirring was continued for 45 min at room temp. . The solution was extracted twice with H_2O (5 ml each) and the aqueous layer was reextracted twice with methylene chloride (15 ml each). The combined organic layers were dried over $MgSO_4$, the solvent was removed in vacuo (20°C/12 Torr) and the residue purified by chromatography. 0.37 g (52%) **11** were obtained. - $\mathbf{R_f}$ = 0.23 (ether). - **M.p.:** 63°C. - **IR (nujol):** ν = 3400 (NH), 1750-1700 (C=O), 1690 (C=N), 1600 cm^{-1} (C=C). -

^{1}H NMR (200 MHz,$CDCl_3$): δ = 1.11 and 1.22 [2d; J = 7 Hz; 6H, $(CH_3)_2CH$], 1.26 and 1.44 [2s; 18H, $(CH_3)_3C$], 2.34 (s; 3H, CH_3), 2.45 - 2.70 [m; 1H; $(CH_3)_2CH$], 3.60 (s; 3H; OCH_3), 3.93 - 4.14 (m; 2H, 5-H), 4.43 (X-part of an ABX-system, J_{AX} = 6 Hz, J_{BX} = 8 Hz, ^3J = 2 Hz; 1H, 4-H), 4.70 (dd, J = 7 and 9 Hz; 1H, $CHCOOCH_3$), 5.27 (d, J = 9 Hz; 1H, NH), 5.50-5.70 (m; 1H, 3-H), 6.96 - 7.16 (m; 4H, C_6H_4). - **^{13}C NMR (50 MHz,$CDCl_3$):** δ = 19.41 and 21.06 [$(CH_3)_2CH$], 22.04 (CH_3), 27.68 and 28.10 [$(CH_3)_3C$], 28.10 [$(CH_3)_2CH$], 40.90 (C-4), 52.04 (OCH_3), 55.94 (C-3), 61.84 ($CHCOOCH_3$), 65.02 (C-5), 79.48 and 83.69 [$(CH_3)_3CO$], 127.88, 129.23, 134.64, 137.25 (C_6H_4), 139.65 (C-2), 151.28 and 154.50 (N-C=O), 171.70 ($COOCH_3$). - **$C_{27}H_{41}N_3O_6$ (503.4)** calc. C,64.37; H,8.21, found, C,64.68; H,8.32%.

Hydrogenation of the Amino Acid Ester 12a, (3R,4R),-3-Amino-4-methyl-pyrrolidone-(2) (14): A suspension of 0.26 g (1.5 mmol) **12a** and 0.10 g palladium (10%, on charcoal) in methanol (10 ml) was stirred under a hydrogen atmosphere for 3 h at room temp. . The suspension was filtered through celite and the celite was washed with methanol (10 ml). The methanol was removed in vacuo and the residue was recrystallized from diethyl ether/ethanol. 79 mg (46%) **14** were obtained as a white hygroscopic solid. - **D.e.:** >99%. - **IR (NaCl):** ν = 1695 cm^{-1} (C=O). - **^{1}H NMR (200 MHz,D_2O):** δ = 1.02 (d, J = 7 Hz; 3H, CH_3), 1.80 - 2.40 (m; 1H, 4-H), 3.20 - 3.50 (m; 2H, 5-H), 3.52 (d, J = 7 Hz; 1H, 3-H). - **HRMS (70 eV):** calculated for $C_5H_{10}N_2O$ 114.0793, found 114.0793.

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