Pergamon

Tetrahedron 54 (1998) 10733–10752

TETRAHEDRON

Diastereoselective 1,3-Dipolar Cycloadditions with Enantiopure Azomethine Ylids

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Received 18 May 1998; accepted 29 June 1998

Abstract

Secondary amines **2a-c**, based on (4*S*,5*S*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-ylamine (**1**), were heated with a variety of aromatic aldehydes in chlorobenzene under reflux. The *in situ* generated 1,3-dipols were trapped with fumaric acid ester, fumaric acid nitrile or *N*-phenylmaleimide, respectively, that were present in excess in the reaction mixture. The cycloadducts **4a-e**, **5a-f** were formed in 78-91% and 67-100% yield as mixture of *exo*/*endo*-isomers (*endo*:*exo* = 30-65:70-35). These isomers were formed as diastereomerically pure compounds (*de* ≥ 96%).

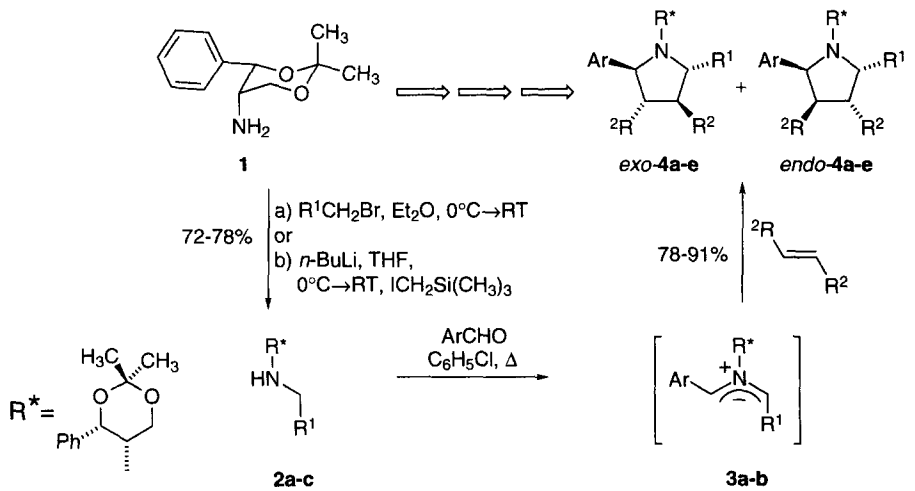
Introduction

The 1,3-dipolar [4πs + 2πs] cycloaddition reactions are among the most efficient methods for the preparation of five-membered heterocycles[1]. Since 1985, interest in the asymmetric synthesis of substituted pyrrolidine derivatives has dramatically increased and has led to the development of cycloaddition procedures in which the chirality information resides in one of the two reaction partners. The stereoselective synthesis of 2,5-disubstituted pyrrolidines utilizing 1,3-dipolar cycloadditions as key reaction step has recently been reviewed by Figadere et al.[2]. The very recent publication of Risch et al.[3] on this topic prompted us to disclose our related results on highly diastereoselective 1,3-dipolar cycloaddition reactions leading to 2,3,4,5-tetra-substituted pyrrolidines by a simple one-pot reaction, employing chiral ester-stabilized azomethine ylids.

0040-4020/98/$ - see front matter
PII: S0040-4020(98)00638-3

Results and Discussion

The formation of stabilized azomethine ylids by heating secondary α-amino esters and aldehydes, usually in toluene, is a commonly used and well established method[4]. Thus, the secondary amines **2a-b** were prepared by reacting (4*S*,5*S*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-ylamine (**1**) with methyl bromoacetate or benzyl-bromide in good yields (72-78%), as is depicted in Scheme 1[5]. Alternatively, deprotonation of **1** with *n*-butyllithium in THF at 0°C and subsequent alkylation with trimethylsilylmethyl iodide formed the secondary amine **2c**. The amines **2a-b** were then treated with a variety of aromatic aldehydes by heating the two components in chlorobenzene under reflux in the presence of excess dipolarophile, e.g. fumaric acid ester or fumaric acid nitrile. The 1,3-dipole was formed *in situ* and trapped with the dipolarophiles, furnishing the desired cycloadducts **4a-e** in 78-91% yield.



Scheme 1. Diastereoselective 1,3-dipolar cycloadditions

The cycloadducts were isolated as mixture of *exo*/*endo*-isomers (*endo*:*exo* = 30-65:70-35) with the *endo*-isomer usually favored. The *exo* and the *endo*-isomers were formed as diastereomerically pure compounds, respectively, as was determined by ^{1}H NMR spectroscopy as well as analytical HPLC (Table 1). They can easily be separated by column chromatography or preparative HPLC. When **2b** (R^1 = Ph) was employed in the reaction sequence, a higher *exo*-selectivity (*exo*:*endo* = 65:35) was determined by ^{1}H NMR spectroscopy.

Table 1. Diastereoselective synthesis of polysubstituted pyrrolidines **4**

2	4	R^1	R^2	Ar	*exo*:*endo*[a] [%]	*de*[b] [%]	yield [%]	*exo*-**4** $[a]_D$[c]	*endo*-**4** $[a]_D$[c]
a	**a**	CO_2CH_3	CO_2CH_3	C_6H_5	43:57	≥96	86	+59.0	+ 55.9
a	**b**	CO_2CH_3	CN	C_6H_5	30:70	≥96	91	+44.4	+127.4
a	**c**	CO_2CH_3	CO_2CH_3	*p*-FC_6H_4	42:58	≥96	83	+64.4	+ 65.3
a	**d**	CO_2CH_3	CN	*p*-FC_6H_4	31:69	≥96	78	+51.9	+120.5
b	**e**	C_6H_5	CO_2CH_3	C_6H_5	65:35	≥96	83	+60.4	+ 67.0

[a] Determined by analytical HPLC or ^1H NMR spectroscopy. All diastereomers could be separated by column chromatography or preparative HPLC. - [b] Determined by ^1H NMR spectroscopy. Only one diastereomer of the *endo* (*S*',*S*',*S*,*S*,*S*,*S*) and *exo* (*S*',*S*',*S*,*R*,*R*,*S*) isomer was detected, respectively. - [c] Measured in $CHCl_3$ at room temperature (see experimental).

The relative configurations and the assignments of the *exo*/*endo*-isomers are based on extensive ^1H NMR spectroscopic investigations (e.g. NOE) on compound **4a** (Figure 1). The assignments of the *exo*-isomer are based on the following observations: The *trans*-configuration of H_3 and H_2 can be deduced from 8.5% signal enhancement upon irradiation on H_3. The saturation of H_4 caused a comparable 7.7% enhancement on H_3, and a similar effect was observed with H_5, inducing 5.9% NOE on H_4. Based on these experiments, the all-*trans*-configuration of the *exo*-cycloadduct is evident. The relative configuration referring to the auxiliary was deduced from the fact that a saturation of H_{eq} of the chiral template caused a 30.1% signal enhancement on H_2. Thus, the configuration of the *exo*-isomer was unambiguously determined to (4'*S*,5'*S*,2*S*,3*S*,4*S*,5*S*)-**4a**. For the *endo*-**4a** isomer, four major effects are noteworthy. Irradiation of H_2 induces a 24.4% signal enhancement on H_3, referring to a *cis*-configuration, and the irradiation of H_5 causes 40.2% NOE on H_4, revealing a *cis*-configuration, too. Due to the fact that no NOE effect is being observed between H_3 and H_4 a *trans*-configuration has to be assumed. Thus, based on the known configuration of the auxiliary and the NOE effect between H_{eq} and H_2 (39.0%), the configuration for the *endo*-cycloadduct was determined to (4'*S*,5'*S*,2*S*,3*R*,4*R*,5*S*). The configurations of the other cycloadducts **4b-e** are based on the assumption that the same relative topicity is present in these cases, too.

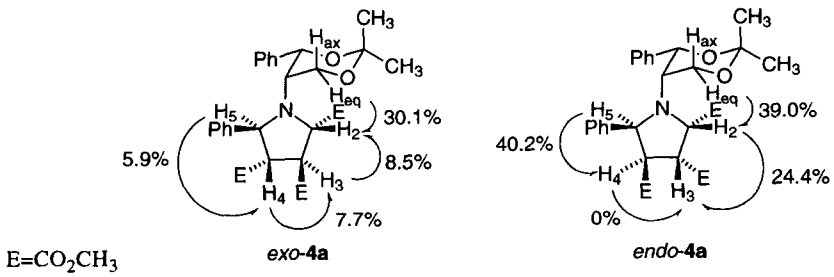
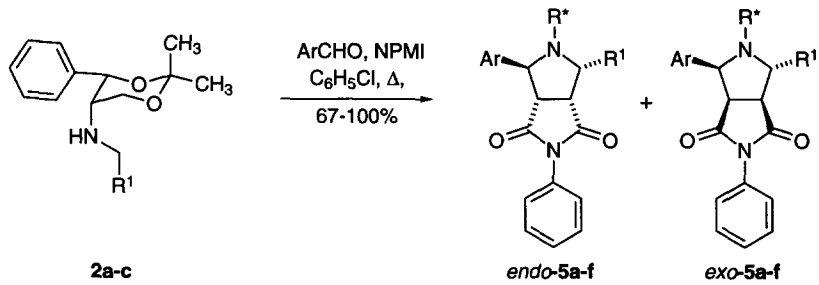


Figure 1. Determination of configurations of cycloadducts **4** by NOE experiments

Following a similar protocol, the amines **2a-c** were then treated with different aromatic aldehydes in the presence of excess *N*-phenylmaleimide (NPMI) (Scheme 2), forming the cycloadducts **5a-f** in good to excellent yields (Table 2).



Scheme 2. Diastereoselctive cycloadditions utilising NPMI

As is evident from ^{1}H NMR spectroscopy, the cycloadducts were isolated as mixtures of *endo*/*exo*-isomers (*endo*:*exo* = 61-66:39-34). The *endo*/*exo*-isomers **5a-f**, respectively, were formed as diastereomerically pure compounds and were isolated by column chromatography, by HPLC or by crystallization. Under the reaction conditions applied, the secondary amine **2c** underwent a desilylation reaction forming a 1,3-dipol that was trapped by NPMI to give **5f** [6]. In this case the assignment for the *exo*/*endo*-isomers is reversed due to the missing substituent in position 5 of the pyrrolidine formed.

Table 2. Diastereoselective synthesis of pyrrolidines **5**

2	**5**	R^1	Ar	*endo*:*exo*[a] [%]	*de*[b] [%]	yield [%]	*exo*-**5** $[\alpha]_D$[c]	*endo*-**5** $[\alpha]_D$[c]
a	**a**	CO_2CH_3	*p*-FC_6H_4	63:37	≥96	100	− 69.0	+30.7
a	**b**	CO_2CH_3	C_6H_5	66:34[d]	≥96	100	− 66.1	+15.1[e]
a	**c**	CO_2CH_3	*p*-BrC_6H_4	61:39	≥96	100	−121.2	+32.3
a	**d**	CO_2CH_3	*p*-$CH_3OC_6H_4$	62:38	≥96	100	− 86.4	+ 7.1
b	**e**	C_6H_5	C_6H_5	-	≥96	75	+21.9	
c	**f**	H[f]	C_6H_5	53:47[d,g]	≥96	67	− 85.2	+17.7[h]

[a] Determined by analytical HPLC or ^{1}H NMR spectroscopy. All diastereomers could be separated by column chromatography or preparative HPLC. - [b] Determined by ^{1}H NMR spectroscopy. Only one diastereomer of the *endo* and *exo*-isomer was detected, respectively. - [c] Measured in $CHCl_3$ at room temperature (see experimental). [d] Separation of the *exo*/*endo*-isomers by crystallization. - [e] Complete separation of the *exo*/*endo*-isomers failed, 13% of the *exo*-isomer were present. - [f] R^1 = H is formed by desilylation of R^1 = $Si(CH_3)_3$. - [g] Due to the missing substituent in the 5 position of the formed pyrrolidine, the *exo*/*endo*-assignment is reverse. - [h] Complete separation of the *exo*/*endo*-isomers failed, 18% of the *exo*- isomer were present.

The relative and absolute configurations of the cycloadducts **5** were determinded by two independent methods. Firstly, extensive NMR measurements (e.g. NOE) were used to determine the configurations as (4'*S*,5'*S*,1*S*,3*S*,3a*S*,6a*R*) for *endo*-**5b** (major diastereomer) and (4'*S*,5'*S*,1*S*,3*S*,3a*R*,6a*S*) for *exo*-**5b** (minor diastereomer) as is depicted in Figure 2.

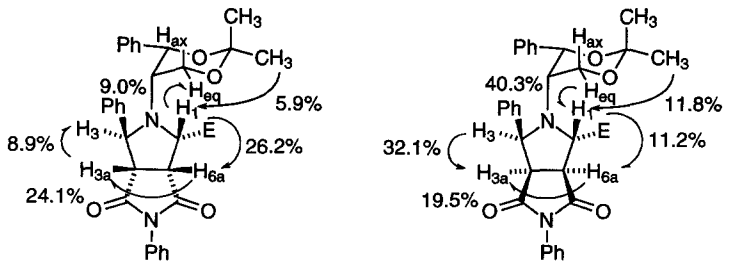


Figure 2. Observed NOE effects on **5d**

Secondly, an X-ray crystal structure analysis was carried out on the minor diastereomer **5d**. The X-ray structure revealed that the substituents at C-1 and C-3 are *trans* to each other and the orientation of the substituents at C-3a and C-6a is *cis* (Figure 3). The relative configuration of the *exo*-diastereomer referring to the auxiliary was identical with that determined by the NOE experiments, proving that both methods can be applied independently.

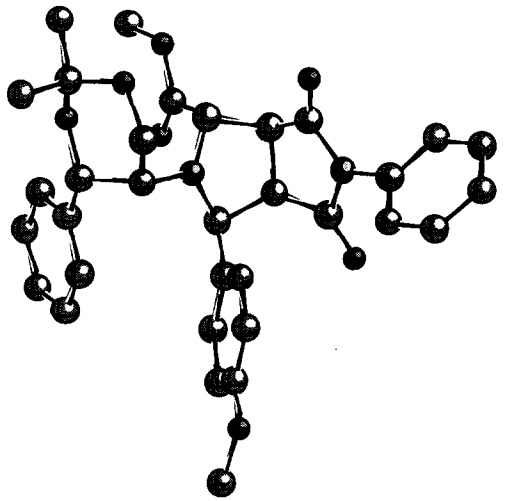
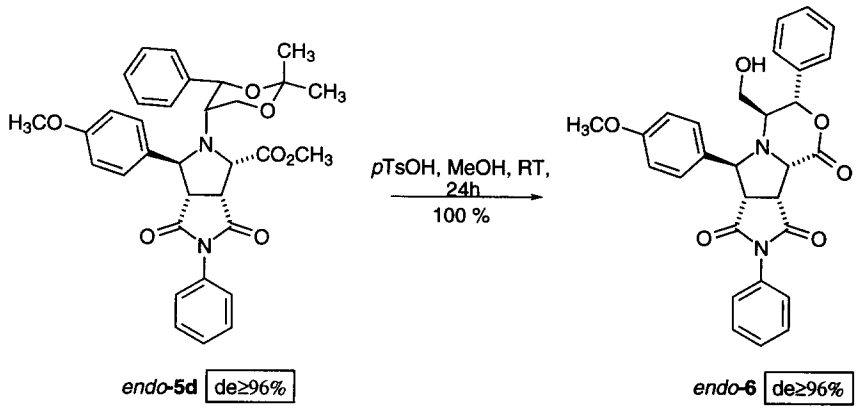


Figure 3. Structure of *exo*-**5d** in the crystal

Upon treatment of *endo*-**5d** with *p*-toluenesulfonic acid in methanol the diastereomerically pure lactone **6** is formed in quantitative yield (Scheme 3). The structure was confirmed by NOE experiments and revealed that the oxazine moiety was formed by chemoselective cyclization of the secondary alcohol function. The *exo*-isomer can similarly be transformed to the corresponding heterocycle.



endo-**5d** de≥96% *endo*-**6** de≥96%

Scheme 3. Chemoselective intramolecular lactonization

Conclusion

In conclusion, the diastereoselective 1,3-dipolar cycloaddition reaction of stabilized chiral azomethine ylids with different dipolarophiles offers an efficient entry to a variety of highly functionalized diastereomerically pure pyrrolidines. Pure *exo* and *endo*-isomers can be isolated after separation by crystallization, column chromatography or HPLC. In addition, the *exo* and *endo*-isomer of **5d** can readily be transformed into the diastereomerically pure tricyclic lactones **6** by simple acid treatment.

Experimental

General. All reactions were carried out using standard Schlenk techniques. Solvents were dried and purified by conventional methods prior to use. Chlorobenzene was freshly distilled from calciumhydride under argon. Reagents were purchased from common commercial suppliers and were used from freshly opened containers unless otherwise stated. The secondary amines were synthesized according to literature procedures[5].

Apparatus. Melting points are uncorrected and were measured on a Dr. Tottoli apparatus (Büchi 510). Optical rotations: Perkin-Elmer P 241 polarimeter; solvents of Merck UVASOL quality. - IR spectra: Perkin-Elmer FT 1750 or Perkin-Elmer PE 1760. - ^{1}H NMR spectra (300 MHz, 500 MHz) and ^{13}C NMR spectra (75 MHz, 125 MHz): Varian VXR 300, Varian Unity 500, Gemini 300 (d in ppm, solvent: $CDCl_3$, TMS as internal standard). - Mass spectra: Varian MAT 212 (EI 70 eV), Finnigan SSQ 7000 (EI 70 eV). - Microanalyses: Heraeus CHN-

O-RAPID. - Analytical HPLC: Hewlett-Packard HPLC 1050, UV detection, ChiralcelOD, (*S*,*S*)-Whelk-O1 ; Preparative HPLC: Gilson Abimed; Merck.LiCrosorb®-column (25 cm x 25 mm, silica 60, particle size 0.007 mm), UV detection.

General procedure for the preparation of the secondary amines **2**:
(4*S*,5*S*)-(+)-(2,2-Dimethyl-4-phenyl-1,3-dioxan-5-yl)-amine **1** (1 eq) was dissolved in diethyl ether (10 ml/ mmol), cooled to 0°C and triethylamine (1 eq) were added. Then, 1 eq of methyl bromoacetate or benzyl bromide was added dropwise. Stirring was continued for 24h at room temperature, and water (50 ml/ 50ml ether) was added to the reaction mixture. The organic layer was separated and was dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the product **2** was purified by column chromatography (silica gel; petroleum ether:diethyl ether).

General procedure for the preparation of **4** *and* **5** *by 1,3-dipolar cycloadditions*:
A Schlenk flask was charged with 7 eq dipolarophile, 10 eq aldehyde and 200 ml of chlorobenzene. The flask was heated to 150°C, and the amine **2**, dissolved in chlorobenzene (2 ml), was added dropwise. The mixture was refluxed for 2-7 d until the completion of the reaction was indicated by tlc control. After cooling to room temperature, the solvent was removed under reduced pressure. The cycloadducts were separated and were purified by column chromatography (silica gel; petroleum ether:diethyl ether).

Methyl(4S,5S)-(+)-2-[(2,2-Dimethyl-4-phenyl-1,3-dioxan-5-yl)amino]acetate (**2a**): 9.68 g (46.7 mmol) (4*S*,5*S*)-(+)-(2,2-Dimethyl-4-phenyl-1,3-dioxan-5-yl)-amine (**1**), 4.73 g (46.7 mmol) of triethylamine and 7.14 g (46.7 mmol) of methyl bromoacetate were reacted for 24h according to the general procedure yielding 9.8 g (75%) of **2a** as a yellow oil after column chromatography (silica gel; petroleum ether:diethyl ether 1:2). - $[\alpha]_D^{25}$ = +63.1 (1.04, $CHCl_3$); - IR (film): $\tilde{\nu}$ = 3351 cm^{-1}, 3063, 3029, 2992, 2950, 2871, 1743, 1499, 1451, 1437, 1381, 1314, 1268, 1237, 1199, 1170, 1155, 1128, 1095, 1076, 1030, 1003, 955, 847, 764, 739, 701. - ^1H NMR: δ = 1.54 (s, 3H, CH_{3eq}), 1.55 (s, 3H, CH_{3ax}), 2.11 (s, 1H, NH), 2.73 (q, *J* = 2.0 Hz, 1H, NCH), 3.12 (s, 2H, NCH_2), 3.58 (s, 3H, OCH_3), 3.98 (dd, *J* = 12.1 Hz, 2.0 Hz, 1H, OC***H***$_{eq}$), 4.16 (dd, *J* = 12.1 Hz, 2.0 Hz, 1H, OC***H***$_{ax}$), 5.13 (d, *J* = 2.0 Hz, 1H, OCH), 7.32 (m, 5H, arom.). - ^{13}C NMR: δ = 18.8 (CH_{3eq}), 29.5 (CH_{3ax}), 48.9 (NCH_2), 51.5 (NCH), 54.7 (OCH_3), 63.7 (OCH_2), 73.3 (OCH), 99.2 (C), 125.8, 127.4, 128.3 (CH arom.), 139.2 (C arom.), 172.7 (C=O). - MS (70eV); *m/z* (%) = 279 (3) [M^+], 264 (3) [M^+–CH_3], 220 (4) [M^+–$COOCH_3$], 115 (100), 77 (6) [M^+–C_6H_5]. - $C_{15}H_{21}NO_4$ (279.3): Calcd. C 64.50, H 7.58, N 5.01; found C 64.63, H 7.66, N 5.20.

(4S,5S)-(+)-N-Benzyl-N-(2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)amine (**2b**): 9.68 g (46.7 mmol) (4*S*,5*S*)-(+)-(2,2-Dimethyl-4-phenyl-1,3-dioxan-5-yl)-amine **1**, 4.73 g (46.7 mmol) of triethylamine and 7.99 g (46.7 mmol) of benzyl bromide were reacted for 24h according to the general procedure yielding 10.0 g (72%) of **2b** as a yellow oil after column chromatography (silica gel; petroleum ether:diethyl ether 2:1). - $[\alpha]_D^{25}$ = +53.6 (0.84, $CHCl_3$); - IR ($CHCl_3$): $\tilde{\nu}$ = 3357 cm^{-1}, 3085, 3061, 3027, 2991, 2938, 2921, 2866, 1605, 1586, 1496, 1452, 1380, 1335, 1313, 1267, 1235, 1199, 1169, 1141, 1093, 1075, 1029, 1006, 954, 944, 846, 801, 743, 699, 666. - ^1H NMR: δ = 1.51 (s, 3H, CH_{3eq}), 1.53 (s, 3H, CH_{3ax}), 2.00 (s, 1H, NH), 2.52 (q, J = 2.0 Hz, 1H, NCH), 3.44 (d, J = 14.0 Hz, 1H, NCH), 3.61 (d, J = 14.0 Hz, 1H, NCH), 3.96 (dd, J = 11.8 Hz, 2.0 Hz, 1H, OCH$\boldsymbol{H}_{eq}$), 4.04 (dd, J = 12.1 Hz, 2.0 Hz, 1H, OCH$\boldsymbol{H}_{ax}$), 5.07 (d, J = 2.0 Hz, 1H, OCH), 6.93 (m, 2H, arom.), 7.13 (m, 2H, arom.), 7.32 (m, 5H, arom.). - ^{13}C NMR: δ = 18.7 (CH_{3eq}), 29.7 (CH_{3ax}), 50.7 (NCH_2), 53.6 (NCH), 63.1 (OCH_2), 73.7 (OCH), 99.1 (C), 125.9, 126.6, 127.1, 127.9, 128.0 (CH arom.), 139.9, 140.4 (C arom.). - MS (70eV); *m/z* (%) = 297 (3) [M^+], 282 (4) [M^+–CH_3], 133 (100), 91 (99) [M^+–$CH_2C_6H_5$], 77 (4) [M^+–C_6H_5]. - $C_{19}H_{23}NO_2$ (297.4): Calcd. C 76.74, H 7.80, N 4.71; found C 77.25, H 8.02, N 5.03.

(4S,5S)-(+)-(2,2-Dimethyl-4-phenyl-1,3-dioxan-5-yl)-trimethylsilylmethylamine (**2c**): 9.68 g (46.7 mmol) (4*S*,5*S*)-(+)-(2,2-Dimethyl-4-phenyl-1,3-dioxan-5-yl)amine (**1**) were dissolved in THF (250 ml) and cooled to 0°C. Then, 34 ml *n*-BuLi (1.6 M in *n*-hexane) were added dropwise. After 1h at 0°C, 10 g (46.7 mmol) of iodomethyltrimethylsilane were added. Stirring was continued for 24h at room temperature, and the reaction mixture was refluxed for another 3h. Saturated aqueous $NaHCO_3$ (100 ml) was added, the aqueous phase was extracted with diethyl ether (250 ml) and was dried over $MgSO_4$. The solvent was removed yielding 11.2 g (82%) of **2c** as a yellow oil after purification by column chromatography (silica gel; petroleum ether:diethyl ether 1:2). - $[\alpha]_D^{25}$ = +73.2 (0.85, $CHCl_3$). - IR (film): $\tilde{\nu}$ = 3349 cm^{-1}, 3092, 3029, 2992, 2781, 1607, 1499, 1423, 1380, 1268, 1247, 1198, 1168, 1141, 1089, 1075, 987, 955, 849, 763, 736, 699. - ^1H NMR: δ = 0.15 [s, 9H, $Si(CH_3)_3$], 1.26 (s, 1H, NH), 1.62 (d, J = 13.5 Hz, 1H, NCH_2) 1.65 (s, 3H, CH_{3eq}), 1.69 (s, 3H, CH_{3ax}), 2.27 (d, J = 13.5 Hz, 1H, NCH_2), 2.61 (dd, J = 4.4 Hz, 2.2 Hz, 1H, NCH), 4.17 (dd, J = 11.8 Hz, 2.2 Hz, 1H, OCH$\boldsymbol{H}_{ax}$), 4.22 (dd, J = 11.8 Hz, 1.9 Hz, 1H, OCH$\boldsymbol{H}_{eq}$), 5.25 (d, J = 2.2 Hz, 1H, OCH), 7.45 (m, 5H, arom.). - ^{13}C NMR: δ = -2.8 [$Si(CH_3)_3$], 18.8 (CH_3), 29.6 (CH_3), 37.3 (NCH_2), 58.6 (NCH), 62.2 (OCH_2), 73.9 (OCH), 99.0 (C), 126.3, 127.0, 127.8 (CH arom.), 139.9 (c arom.). - MS (70eV); *m/z* (%) = 293 (3) [M^+], 278 (6) [M^+–CH_3], 220 (8) [M^+–$Si(CH_3)_3$], 114 (100). - $C_{16}H_{27}NO_2Si$ (293.5): Calcd. C 65.48, H 9.27, N 4.77; found C 65.54, H 9.25, N 4.91.

Trimethyl(2S,3S/R,4S/R,5S)-(+)-1-[(4S′,5S′)-2′,2′-dimethyl-4′-phenyl-1′,3′-dioxan-5′-yl]-5-phenyltetrahydro-1H-2,3,4-pyrroletricarboxylate (**4a**): 1.00 g (7 mmol) dimethyl fumarate, 1.10 g (10 mmol) benzaldehyde and 0.28g (1 mmol) amine **2a** were reacted for 3d according to the general procedure yielding 0.44 g of *(2S,3S,4S,5S)*-**4a**[7] and *(2S,3R,4R,5S)*-**4a**[8] (86%) as a colourless solid after column chromatography (silica gel; petroleum ether:diethyl ether 1:1). - *exo*:*endo* = 43:57[9]. - *exo*[10]: *de* = ≥96%; $[\alpha]_D^{25}$ = +59.0 (1.02, $CHCl_3$); m.p. 112-113°C. - *endo*[10]: *de* = ≥96%; $[\alpha]_D^{25}$ = +55.9 (1.02, $CHCl_3$); m.p. 182-185°C. - IR (KBr): $\tilde{\nu}$ = 3438 cm^{-1}, 3063, 3031, 2989, 2901, 1760, 1744, 1729, 1607, 1490, 1443, 1388, 1358, 1334, 1292, 1272, 1244, 1203, 1151, 1118, 1076, 1046, 1024, 1007, 952, 937, 913, 849, 818, 752, 702, 558, 528. - ^1H NMR (*exo*): δ = 1.28 (s, 3H, CH_{3eq}), 1.38 (s, 3H, CH_{3ax}), 3.04 (m, 1H, CH_2CH), 3.31 [dd, *J* = 5.2 Hz, 3.1 Hz, 1H, NCH(Ph)C***H***], 3.43 [dd, *J* = 3.1 Hz, 1.5 Hz, 1H, $NCH(CO_2CH_3)CH$], 3.59 [s, 3H, $NCH(Ph)CH(CO_2CH_3)$], 3.60 [s, 3H, $NCH(CO_2CH_3)$], 3.66 [s, 3H, $NCH(CO_2CH_3)CH(CO_2CH_3)$], 4.09 [dd, *J* = 12.5 Hz, 1.8 Hz, 1H, $CH_{eq}H$], 4.19 [dd, *J* = 12.5 Hz, 4.0 Hz, 1H, $CH_{ax}H$], 4.45 [d, *J* = 5.2 Hz, 1H, NCH(Ph)], 4.79 [d, *J* = 1.5 Hz, 1H, $NCH(CO_2CH_3)$], 4.94 (d, *J* = 2.5 Hz, 1H, OCH), 7.15 (m, 2H, arom.), 7.25 (m, 1H, arom.), 7.28 (m, 1H, arom.), 7.31 (m, 4H, arom.), 7.34 (m, 2H, arom.); (*endo*): δ = 1.23 (s, 3H, CH_{3eq}), 1.40 (s, 3H, CH_{3ax}), 2.96 (m, 1H, CH_2CH), 3.07 [s, 3H, $NCH(Ph)CH(CO_2CH_3)$], 3.61 [s, 3H, $NCH(CO_2CH_3)CH(CO_2CH_3)$], 3.66 [s, 3H, $NCH(CO_2CH_3)$], 3.66 [dd, *J* = 12.2 Hz, 8.2 Hz, 1H, $NCH(CO_2CH_3)CH$], 3.81 [dd, *J* = 12.5 Hz, 9.5 Hz, 1H, NCH(Ph)C***H***], 4.14 [dd, *J* = 12.8 Hz, 1.2 Hz, 1H, $CH_{eq}H$], 4.22 [d, *J* = 9.5 Hz, 1H, NCH(Ph)], 4.26 (dd, *J* = 12.8 Hz, 3.4 Hz, 1H, $OCH_{ax}H$), 4.54 [d, *J* = 7.9 Hz, 1H, $NCH(CO_2CH_3)$], 4.91 (d, *J* = 1.8 Hz, 1H, OCH), 6.93 (m, 2H, arom.), 7.22 (m, 3H, arom.), 7.32 (m, 3H, arom.), 7.39 (m, 2H, arom.). - ^{13}C NMR (*exo*): δ = 19.1 (CH_{3ax}), 28.4 (CH_{3eq}), 49.3 [$NCH(CO_2CH_3)CH$], 51.4 [$NCH(CO_2CH_3)$], 52.2 [$NCH(Ph)CH(CO_2CH_3)$], 52.6 [$NCH(CO_2CH_3)CH(CO_2CH_3)$], 53.2 ($CH_2CH$), 54.6 [NCH(Ph)CH], 65.0 (CH_2), 66.2 [$NCH(CO_2CH_3)$], 67.3 [NCH(Ph)], 74.0 (OCH), 99.5 (C), 126.1, 126.8, 127.4, 127.6, 128.4 (CH arom.), 139.8, 142.6 (C arom.), 172.7, 172.8, 174.3 (C=O); (*endo*): δ = 18.8 (CH_{3ax}), 28.6 (CH_{3eq}), 47.0 [$NCH(CO_2CH_3)CH$], 50.2 [NCH(Ph)CH], 51.2 [$NCH(Ph)CH(CO_2CH_3)$], 51.6 [$NCH(CO_2CH)$], 52.2 [$NCH(CO_2CH_3)CH(CO_2CH_3)$], 54.6 ($CH_2CH$), 64.2 ($CH_2$), 65.1 [$NCH(CO_2CH_3)$], 65.7 [NCH(Ph)], 74.5 (OCH), 99.4 (C), 126.2, 127.2, 127.7, 127.8, 128.5 (CH arom.), 139.8, 140.2 (C arom.), 170.7, 170.8, 173.3 (C=O). - MS (70eV); *m/z* (%) = 511 (0.3) [M^+], 496 (3) [M^+–CH_3], 452 (8) [M^+–$COOCH_3$], 347 (100), 77 (18) [$C_6H_5^+$]. - $C_{28}H_{33}NO_8$ (511.6): Calcd. C 65.74, H 6.50, N 2.74; found C 65.42, H 6.52, N 2.65.

Methyl(2S,3S/R,4S/R,5S)-(+)-3,4-dicyano-1-[(4S′,5S′)-2′,2′-dimethyl-4′-phenyl-1′,3′-dioxan-5′-yl]-5-phenyltetrahydro-1H-2-pyrrolecarboxylate (**4b**): 0.55 g (7 mmol) fumaric

acid dinitrile, 1.06 g (10 mmol) benzaldehyde and 0.28g (1 mmol) amine reacted for 24h according to the general procedure yielding 0.41 g *(2S,3S,4S,5S)*-**4b** and *(2S,3R 4R,5S)*-**4b** (91%) as a colourless solid after column chromatography (silica gel; petroleum ether:diethyl ether 1:1). - *exo*:*endo* = 30:70[9]. - *exo*[11]: *de* = ≥96%; $[\alpha]_D^{25}$ = +44.4 (0.99, $CHCl_3$); m.p. 201-203°C. - *endo*[11]: *de* = ≥96%; $[\alpha]_D^{25}$ = +127.4 (0.98, $CHCl_3$); m.p. >200°C. - IR (KBr): $\tilde{\nu}$ = 3465 cm^{-1}, 3088, 3008, 2986, 2865, 2248, 1743, 1495, 1436, 1383, 1326, 1299, 1276, 1241, 1209, 1157, 1107, 1080, 1056, 1027, 989, 955, 918, 870, 852, 838, 813, 759, 702. - ^1H NMR (*exo*): δ = 1.44 (s, 3H, CH_{3eq}), 1.54 (s, 3H, CH_{3ax}), 3.07 [dd, *J* = 5.0 Hz, 2.4 Hz, 1H, NCH(Ph)C***H***], 3.11 (m, 1H, CH_2C***H***), 3.20 [dd, *J* = 2.4 Hz, 0.7 Hz, 1H, NCH(CO_2CH_3)C***H***], 3.64 (s, 3H, OCH_3), 4.06 (dd, *J* = 12.4 Hz, 1.3 Hz, 1H, C***H***$_{eq}$), 4.29 [d, *J* = 5.0 Hz, 1H, NCH(Ph)], 4.32 (dd, *J* = 12.4 Hz, 3.4 Hz, 1H, C***H***$_{ax}$), 5.01 (d, *J* = 1.7 Hz, 1H, OCH), 5.28 [d, *J* = 0.7 Hz, 1H, NC***H***(CO_2CH_3)], 7.11 (m, 2H, arom.), 7.17 (m, 2H, arom.), 7.39 (m, 6H, arom.); (*endo*): δ = 1.38 (s, 3H, CH_{3eq}), 1.44 (s, 3H, CH_{3ax}), 2.94 (m, 1H, CH_2C***H***), 3.36 [dd, *J* = 12.1 Hz, 7.4 Hz, 1H, NCH(CO_2CH_3)C***H***], 3.79 [dd, *J* = 12.1 Hz, 8.4 Hz, 1H, NCH(Ph)C***H***], 3.84 (s, 3H, OCH_3), 3.99 [d, *J* = 8.4 Hz, 1H, NCH(Ph)], 4.05 (dd, *J* = 13.1 Hz, 1.3 Hz, 1H, C***H***$_{eq}$), 4.29 (dd, *J* = 13.1 Hz, 3.4 Hz, 1H, C***H***$_{ax}$), 4.75 [d, *J* = 7.7 Hz, 1H, NC***H***(CO_2CH_3)], 4.95 (d, *J* = 2.0 Hz, 1H, OCH), 6.92 (m, 2H, arom.), 7.27 (m, 2H, arom.), 7.37 (m, 6H, arom.). - ^{13}C NMR (*exo*): δ = 18.7 (CH_{3ax}), 28.8 (CH_{3eq}), 36.5 [NCH(CO_2CH_3)***C***H], 41.7 [NCH(Ph)***C***H], 51.6 (OCH_3) 51.7 (CH_2***C***H), 66.1 [N***C***H(CO_2CH_3)], 66.9 (CH_2), 69.2 [NCH(Ph)], 73.3 (OCH), 100.1 (C), 117.9, 119.1 (C≡N), 125.5, 127.4, 127.9, 128.2, 129.1, 129.4 (CH arom.), 138.2, 138.9 (C arom.), 171.5 (C=O); (*endo*): δ = 18.6 (CH_{3ax}), 28.7 (CH_{3eq}), 34.2 [NCH(CO_2CH_3)***C***H], 38.0 [NCH(Ph)***C***H], 52.2 (OCH_3) 54.2 (CH_2***C***H), 63.8 [N***C***H(CO_2CH_3)], 64.5 (CH_2), 65.3 [NCH(Ph)], 74.1 (OCH), 99.8 (C), 115.1, 115.7 (C≡N), 125.9, 127.6, 127.8, 128.0, 129.0, 129.2 (CH arom.), 138.0, 139.1 (C arom.), 172.1 (C=O). - MS (70eV); *m/z* (%) = 430 (1) [M^+–CH_3], 387 (2) [M^+–CO_2CH_3], 222 (100), 77 (21) [$C_6H_5^+$]. - $C_{26}H_{27}N_3O_4$ (445.5): Calcd. C 70.10, H 6.11, N 9.43; found C 69.93, H 6.02, N 9.30.

Trimethyl(2S,3S/R,4S/R,5S)-(+)-1-[(4S′,5S′)-2′,2′-dimethyl-4′-phenyl-1′,3′-dioxan-5′-yl]-5-(4-fluorophenyl)tetrahydro-1H-2,3,4-tricarboxylate (**4c**): 1.00 g (7 mmol) dimethyl fumarate, 1.06 g (10 mmol) benzaldehyde and 0.28g (1 mmol) amine reacted for 2 d according to the general procedure yielding 0.44g *(2S,3S,4S,5S)*-**4c** and *(2S,3R,4R,5S)*-**4c** (83%) as a colourless solid after column chromatography (silica gel; petroleum ether:diethyl ether 1:1). - *exo*:*endo* = 41:56[12]. - *exo*[10]: *de*= ≥96%; $[\alpha]_D^{25}$ = +64.4 (1.10, $CHCl_3$); m.p. 49°C (dec.). - *endo*[10]: *de* = ≥96%; $[\alpha]_D^{25}$ = +65.3 (0.99, $CHCl_3$); m.p. 60°C (dec.). - IR (KBr): $\tilde{\nu}$ = 3450 cm^{-1}, 2994, 2952, 1738, 1605, 1509, 1438, 1383, 1321, 1208, 1156, 1116,

1079, 1014, 956, 847, 801, 745, 702. - ^{1}H NMR (*exo*): δ = 1.22 (s, 3H, CH_{3eq}), 1.38 (s, 3H, CH_{3ax}), 3.12 (m, 1H, CH_2CH), 3.26 [dd, *J* = 5.0 Hz, 2.8 Hz, 1H, NCH(Ar)C*H*], 3.41 [dd, *J* = 2.8, 1.4 Hz, 1H, NCH(CO_2CH_3)C*H*], 3.59 [s, 3H, NCH(Ar)CH(CO_2CH_3)], 3.61 [s, 3H, NCH(CO_2CH_3)], 3.63 [s, 3H, NCH(CO_2CH_3)CH(CO_2CH_3)], 4.10 (dd, *J* = 12.6 Hz, 1.7 Hz, 1H, CH_{eq}), 4.20 (dd *J* = 12.6 Hz, 3.8 Hz, 1H, CH_{ax},), 4.53 [d, *J* = 4.9 Hz, 1H, NCH(Ar)], 4.64 [d, *J* = 1.4 Hz, 1H, NC*H*(CO_2CH_3)], 4.94 (d, *J* = 2.5 Hz, 1H, OCH), 7.20 (m, 9H, arom.); (*endo*): δ = 1.16 (s, 3H, CH_{3eq}), 1.40 (s, 3H, CH_{3ax}), 2.95 (m, 1H, CH_2CH), 3.12 [s, 3H, NCH(Ar)CH(CO_2CH_3)], 3.59 [dd, *J* = 12.6 Hz, 7.7 Hz, 1H, NCH(CO_2CH_3)C*H*], 3.61 [s, 3H, NCH(CO_2CH_3)CH(CO_2CH_3)], 3.66 [s, 3H, NCH(CO_2CH_3)], 3.82 [dd, *J* = 12.6 Hz, 9.6 Hz, 1H, NCH(Ar)C*H*], 4.16 (dd, *J* = 12.9 Hz, 1.4 Hz, 1H, CH_{eq}), 4.27 (dd *J* = 12.9 Hz, 3.3 Hz, 1H, CH_{ax},), 4.38 [d, *J* = 7.7 Hz, 1H, NC*H*(CO_2CH_3)], 4.39 [d, *J* = 9.6 Hz, 1H, NCH(Ar)], 4.92 (d, *J* = 1.9 Hz, 1H, OCH), 6.92 (m, 4H, arom.), 7.33 (m, 5H, arom.). - ^{13}C NMR (*exo*): δ = 19.0 (CH_{3ax}), 28.3 (CH_{3eq}), 48.9 [NCH(CO_2CH_3)*C*H], 51.5 [NCH(CO_2*C*H_3)], 52.2 [NCH(Ar)CH(CO_2*C*H_3)], 52.7 [NCH(CO_2CH_3)CH(CO_2*C*H_3)], 53.6 (CH_2*C*H), 54.7 [NCH(Ar)*C*H], 64.6 (CH_2), 66.2 [N*C*H(CO_2CH_3)], 66.8 [NCH(Ar)], 73.9 (OCH), 99.5 (C), 115.0 (d, *J* = 21.2 Hz, CH arom.), 126.1, 126.9, 127.7 (CH arom.), 129.9 (d, *J* = 8.0 Hz, CH arom.), 138.6 (d, *J* = 2.9 Hz, C arom.), 139.7 (C arom.), 162.1 (d, *J* = 245.0 Hz, C arom.), 172.5, 172.6, 174.1 (C=O); (*endo*): δ = 18.7 (CH_{3ax}), 28.6 (CH_{3eq}), 46.8 [NCH(CO_2CH_3)*C*H], 50.2 [NCH(CO_2*C*H_3)], 51.3 [NCH(Ar)CH(CO_2*C*H_3)], 51.7 [NCH(CO_2CH_3)CH(CO_2*C*H_3)], 52.2 (CH_2*C*H), 54.9 [NCH(Ar)*C*H], 64.0 (CH_2), 64.4 [N*C*H(CO_2CH_3)], 65.7 [NCH(Ar)], 74.3 (OCH), 99.4 (C), 114.5 (d, *J* = 21.8 Hz, CH arom.), 126.0, 127.2, 127.9 (CH arom.), 130.1 (d, *J* = 8.0 Hz, CH arom.), 136.2 (d, *J* = 2.9 Hz, C arom.), 139.8 (C arom.), 162.3 (d, *J* = 245.6 Hz, C arom.), 170.5, 170.6, 173.3 (C=O). - MS (70eV); *m/z* (%) = 529 (2) [M$^+$], 514 (5) [M$^+$–CH_3], 470 (6) [M$^+$–$COOCH_3$], 365 (100). - $C_{28}H_{32}NO_8F$ (529.6): Calcd. C 63.51, H 6.09, N 2.65; found C 63.77, H 6.33, N 2.43.

Methyl(2S,3S/R,4S/R,5S)-(+)-3,4-dicyano-1-[(4S′,5S′)-2′,2′-dimethyl-4′-phenyl-1′,3′-dioxan-5′-yl]-5-(4-fluorophenyl)tetrahydro-1H-2-pyrrolecarboxylate (**4d**): 0.55 g (7 mmol) fumaric acid dinitrile, 1.06 g (10 mmol) benzaldehyde and 0.28g (1 mmol) amine reacted for 15 h according to the general procedure yielding 0.36g *(2S,3S,4S,5S)*-**4d** and *(2S,3R,4R,5S)*-**4d** (78%) as a colourless solid after column chromatography (silica gel; petroleum ether:diethyl ether 1:1). - *exo*:*endo* = 31:69[9]. - *exo*[10]: *de* = ≥96%; $[\alpha]_D^{25}$ = +51.9 (0.94, $CHCl_3$); m.p. 185-187°C. - *endo*[10]: *de* = ≥96%; $[\alpha]_D^{25}$ = +120.5 (1.05, $CHCl_3$); m.p. >230°C. - IR (KBr): $\tilde{\nu}$ = 3465 cm^{-1}, 3093, 3009, 2997, 2897, 2250, 1742, 1702, 1677, 1655, 1637, 1605, 1561, 1509, 1484, 1437, 1385, 1366, 1345, 1327, 1301, 1277, 1262, 1243, 1211, 1155, 1108, 1080, 1050, 1030, 850, 840, 760, 702, 560. - ^{1}H NMR (*exo*): δ = 1.45 (s,

3H, CH_{3eq}), 1.50 (s, 3H, CH_{3ax}), 3.02 [dd, J = 4.7 Hz, 2.2 Hz, 1H, NCH(Ar)C***H***], 3.08 (m, 1H, CH_2C***H***), 3.20 [dd, J = 2.2 Hz, 0.8 Hz, 1H, NCH(CO_2CH_3)C***H***], 3.67 (s, 3H, OCH_3), 4.05 (dd, J = 12.6 Hz, 1.4 Hz, 1H, CHH_{eq}), 4.30 (d, J = 5.0 Hz, 1H, NCH(Ar)), 4.33 (dd, J = 12.6 Hz, 3.3 Hz, 1H, OCHH_{ax}), 5.01 (d, J = 1.9 Hz, 1H, OCH), 5.20 [d, J = 0.6 Hz, 1H, NC***H***(CO_2CH_3)], 7.12 (m, 6H, arom.), 7.35 (m, 3H, arom.); (*endo*): δ = 1.30 (s, 3H, CH_{3eq}), 1.43 (s, 3H, CH_{3ax}), 2.92 (m, 1H, CH_2C***H***), 3.32 [dd, J = 12.1 Hz, 7.4 Hz, 1H, NCH(CO_2CH_3)C***H***], 3.80 [dd, J = 11.5 Hz, 8.5 Hz, 1H, NCH(Ar)C***H***], 3.84 (s, 3H, OCH_3), 4.04 (dd, J = 12.9 Hz, 1.1 Hz, 1H, $OCHH_{eq}$), 4.16 [d, J = 8.8 Hz, 1H, NCH(Ar)], 4.31 (dd, J = 12.9 Hz, 3.0 Hz, 1H, CHH_{ax}), 4.63 [d, J = 7.4 Hz, 1H, NC***H***(CO_2CH_3)], 4.96 (d, J = 1.9 Hz, 1H, OCH), 6.91 (m, 2H, arom.), 7.06 (m, 2H, arom.), 7.25 (m, 2H, arom.), 7.38 (m, 3H, arom.). - ^{13}C NMR (*exo*): δ = 18.7 (CH_{3ax}), 28.8 (CH_{3eq}), 36.4 [NCH(CO_2CH_3)***C***H], 41.8 [NCH(Ar)***C***H], 51.8 (OCH_3, N***C***H(CO_2CH_3)], 66.1 (CH_2***C***H), 66.6 (CH_2), 68.3 [NCH(Ar)], 73.4 (OCH), 100.2 (C), 116.4 (d, J = 21.7 Hz, CH arom.), 117.8, 119.1 (C≡N), 125.6, 127.5, 128.0 (CH arom.), 130.0 (d, J = 8.0 Hz, CH arom.), 134.1, 138.8 (C arom.), 163.0 (d, J = 249.1 Hz, C arom.), 171.4 (C=O); (*endo*): δ = 18.6 (CH_{3ax}), 28.6 (CH_{3eq}), 34.1 [NCH(CO_2CH_3)***C***H], 38.1 [NCH(Ar)***C***H], 52.3 (OCH_3), 54.4 (CH_2***C***H), 64.2 [N***C***H(CO_2CH_3), NCH(Ar)], 64.4 (CH_2), 73.9 (OCH), 99.9 (C), 115.0, 115.7 (C≡N), 115.9 (d, J = 21.8 Hz, CH arom.), 125.8, 127.6, 128.0 (CH arom.), 129.6 (d, J = 8.0 Hz, CH arom.), 134.1, 139.1, 163.0 (d, J = 249.9 Hz, C arom.), 172.0 (C=O). - MS (70eV); *m/z* (%) = 448 (2) [M^+–CH_3], 404 (7) [M^+–CO_2CH_3], 299 (100), 77 (7) [$C_6H_5^+$]. - $C_{26}H_{26}N_3O_4F$ (463.5): Calcd. C 67.37, H 5.65, N 9.07; found C 67.32, H 5.81, N 9.05.

Dimethyl(2S,3S/R,4S/R,5S)-(+)-1-[(4S′,5S′)-2′,2′-dimethyl-4′-phenyl-1′,3′-dioxan-5′-yl]-2,5-diphenyltetrahydro-1H-3,4-pyrrolodicarboxylate (**4e**): 1.00 g (7 mmol) dimethyl fumarate, 1.06 g (10 mmol) benzaldehyde and 0.30g (1 mmol) amine reacted for 5 d according to the general procedure yielding 0.44g *(2S,3S,4S,5S)*-**4e** and *(2S,3R,4R,5S)*-**4e** (83%) as a colourless solid after column chromatography (silica gel; petroleum ether:diethyl ether 2:1). - *exo*:*endo* = 65:35[9]. - *exo*[10]: *de* = ≥96%; $[\alpha]_D^{25}$ = +60.4 (1.00, $CHCl_3$); m.p. 154-155°C. - *endo*[10]: *de* = ≥96%; $[\alpha]_D^{25}$ = +67.0 (1.06, $CHCl_3$); m.p. 142-144°C. - IR (KBr): $\tilde{\nu}$ = 3435 cm^{-1}, 3062, 3028, 2994, 2867, 1732, 1603, 1495, 1437, 1382, 1307, 1248, 1228, 1203, 1176, 1151, 1113, 1072, 953, 935, 908, 876, 852, 760, 738, 697, 622, 596, 523. - ^1H NMR (*exo*): δ = 1.26 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 2.82 (dd, J = 6.4 Hz, 3.0 Hz, 1H, CH_2C***H***), 3.62 (s, 6H, OCH_3), 3.65 [dd, J = 4.7 Hz, 2.0 Hz, 2H, C***H***(CO_2CH_3)], 4.01 (d, J = 2.7 Hz, 2H, CH_2), 4.90 (d, J =3.7 Hz, 1H, OCH), 5.05 (dd, J = 4.5 Hz, 1.0 Hz, 2H, NCH), 6.93 (m, 2H, arom.), 7.20 (m, 13H, arom.); (*endo*): δ = 1.26 (s, 1H, CH_3), 1.42 (s, 3H, CH_3), 3.12 (s, br, 1H, CH_2C***H***), 3.18 (s, 6H, OCH_3), 3.82 [dd, J = 5.8 Hz, 2.7 Hz, 2H, C***H***(CO_2CH_3)], 4.20

(dd, J = 12.9 Hz, 3.3 Hz, 1H, OCH$\boldsymbol{H}_{ax}$), 4.31 (dd, J = 12.9 Hz, 1.7 Hz, 1H, OCH$\boldsymbol{H}_{eq}$), 4.58 (s, br, 2H, NCH), 4.79 (d, J = 1.5 Hz, 1H, OCH), 7.09 (m, 2H, arom.), 7.28 (m, 13H, arom.). - ^{13}C NMR (*exo*): δ = 19.1 (CH_3), 28.4 (CH_3), 52.2 (OCH_3), 52.3, 52.4 [NCH(Ph)***C***H], 54.8 (CH_2***C***H), 64.3 (CH_2), 68.7 (NCH), 73.9 (OCH), 99.3 (C), 126.0, 126.4, 127.0, 127.5, 127.8, 128.2, 133.4 (CH arom.), 139.8, 141.3 (C arom.), 173.5 (C=O); (*endo*): δ = 18.8 (CH_3), 27.8 (CH_3), 48.9 [NCH(Ph)***C***H], 51.3 (OCH_3), 55.1 (CH_2***C***H), 63.1 (CH_2), 66.7 (NCH), 74,4 (OCH), 98.9 (C), 126.2, 127.2, 127.4, 127.7, 127.9, 128.4 (CH arom.), 140.4, 141.6 (C arom.), 170.6 (C=O). - MS (70eV); *m/z* (%) = 529 (1) [M^+], 514 (2) [M^+–CH_3], 381 (100), 77 (10) [$C_6H_5^+$]. - $C_{32}H_{35}NO_6$ (529.6): Calcd. C 72.57, H 6.66, N 2.65; found C 72.49, H 6.50, N 2.63.

Methyl(1S,3S,3aS/R,6aR/S)-2-[(4S′,5S′)-2′,2′-dimethyl-4′-phenyl-1′,3′-dioxan-5′-yl]-3-(4-fluorophenyl)-4,6-dioxo-5-phenylperhydro-pyrrolo[3,4-c]pyrrole-1-carboxylate (**5a**): 1.21 g (7 mmol) *N*-phenylmaleimide, 1.06 g (10 mmol) benzaldehyde and 0.28g (1 mmol) amine reacted for 5 d according to the general procedure yielding 0.56g *(1S,3S,3aR,6aS)*-**5a**[7] and *(1S,3S,3aS,6aR)* **5a**[8] (100%) as a colourless solid after column chromatography (silica gel; petroleum ether:diethyl ether 1:2). - *exo*:*endo* = 37:63[9]. - *exo*[10]: *de* = ≥96%; $[\alpha]_D^{25}$ = –69.0 (1.02, $CHCl_3$); m.p. >200°C. - *endo*[10]: *de* = ≥96%; $[\alpha]_D^{25}$ = +30.7 (1.03, $CHCl_3$); m.p. 102-104°C. - IR (KBr): $\tilde{\nu}$ = 3480 cm^{-1}, 3066, 2992, 2949, 2879, 1718, 1602, 1509, 1501, 1455, 1435, 1383, 1317, 1271, 1223, 1199, 1167, 1105, 1077, 1015, 954, 912, 836, 736, 699. - ^{1}H NMR (*exo*): δ = 1.43 (s, 3H, CH_{3ax}), 1.48 (s, 3H, CH_{3eq}), 3.23 (m, 1H, CH_2C***H***), 3.23 [d, J = 7.7 Hz, 1H, NCH(CO_2CH_3)C***H***], 3.48 [dd, J = 9.6 Hz, 7.8 Hz, 1H, NCH(Ar)C***H***], 3.76 (s, 3H, OCH_3), 4.01 (dd, J = 12.6 Hz, 1.0 Hz, 1H, OCH$\boldsymbol{H}_{eq}$), 4.30 (dd, J = 12.6 Hz, 3.8 Hz, 1H, OCH$\boldsymbol{H}_{ax}$), 4.57 [d, J = 9.9 Hz, 1H, NCH(Ar)], 5.02 (d, J =1.7 Hz, 1H, OCH), 5.17 [s, 1H, NC***H***(CO_2CH_3)], 6.95 (m, 6H, arom.), 7.12 (m, 2H, arom.), 7.32 (m, 6H, arom.); (*endo*): δ = 1.38 (s, 3H, CH_{3ax}), 1.42 (s, 3H, CH_{3eq}), 2.95 (m, 1H, CH_2C***H***), 3.22 [dd, J = 9.1, 3.0 Hz, 1H, NCH(Ar)C***H***], 3.61 (s, 3H, OCH_3), 3.78 [t, J = 9.3 Hz, 1H, NCH(CO_2CH_3)C***H***], 3.83 (dd, J = 12.9 Hz, 1.1 Hz, 1H, CH$\boldsymbol{H}_{eq}$), 4.12 (dd, J = 12.9 Hz, 3.6 Hz, 1H, OCH$\boldsymbol{H}_{ax}$), 4.26 [d, J = 3.3 Hz, 1H, NCH(Ar)], 4.81 [d, J = 9.3 Hz, 1H, NC***H***(CO_2CH_3)], 4.95 (d, J = 2.7 Hz, 1H, OCH), 7.07 (m, 4H, arom.), 7.19 (m, 2H, arom.), 7.35 (m, 9H, arom.). - ^{13}C NMR (*exo*): δ = 18.9 (CH_{3ax}), 28.5 (CH_{3eq}), 49.8 [NCH(Ar)***C***H], 50.4 [NCH(CO_2CH_3)***C***H], 51.6 (OCH_3), 52.0 (CH_2***C***H), 63.3 (N***C***H(CO_2CH_3)], 65.8 [NCH(Ar)], 66.0 (CH_2), 73.7 (OCH), 100.0 (C), 115.6 (d, J = 21.7 Hz, CH arom.), 125.5, 125.8, 127.2, 127.6, 128.3, 128.9, 130.1 (CH arom.), 131.6, 133.0, 139.2 (C arom.), 162.5 (d, J = 247.4 Hz, C arom.), 174.1, 174.4, 175.4 (C=O); (*endo*): δ = 18.8 (CH_{3ax}), 28.6 (CH_{3eq}), 47.9 [NCH(CO_2CH_3)***C***H], 51.8 (OCH_3), 53.2 [NCH(Ar)***C***H], 53.3 (CH_2***C***H), 63.0 (CH_2), 64.8 [N***C***H(CO_2CH_3)], 67.7 [NCH(Ar)], 74.0

(OCH), 99.5 (C), 115.9 (d, J = 21.7 Hz, CH arom.), 126.3, 126.6, 127.6, 128.0, 128.7, 129.2 (CH arom.), 129,6 (d, J = 8.0 Hz, CH arom.), 137.2 (d, J = 3.5 Hz, C arom.), 139.0, 162.4 (d, J = 247.4 Hz, C arom.), 172.2, 174.9, 175.2 (C=O). - MS (70eV); *m/z* (%) = 499 (2) [M^+–CO_2CH_3], 335 (100), 77 (7) [$C_6H_5^+$]. - $C_{32}H_{31}N_2O_6F$ (558.6): Calcd. C 68.81, H 5.59, N 5.02; found C 68.41, H 5.47, N 4.93.

Methyl(1S,3S,3aS/R,6aR/S)-2-[(4S′,5S′)-2′,2′-dimethyl-4′-phenyl-1′,3′-dioxan-5′-yl]-4,6-dioxo-3,5-diphenylperhydro-pyrrolo[3,4-c]pyrrole-1-carboxylate (**5b**): 1.21 g (7 mmol) *N*-phenylmaleimide, 1.06 g (10 mmol) benzaldehyde and 0.28g (1 mmol) amine reacted for 2 d according to the general procedure yielding 0.52g *(1S,3S,3aR,6aS)*-**5b** and *(1S,3S,3aS,6aR)*-**5b** (100%) as a colourless solid after column chromatography (silica gel; petroleum ether:diethyl ether 1:2). - *exo*:*endo* = 34:66[9]. - *exo*[13]: *de* = ≥96%; $[\alpha]_D^{25}$ = –66.1 (0.67, $CHCl_3$); m.p. 212-213°C. - *endo*[13]: *de* = ≥96%; $[\alpha]_D^{25}$ = +15.1 (1.09, $CHCl_3$)[14]; m.p. 89°C (dec.).- IR (KBr): $\tilde{\nu}$ = 3479 cm^{-1}, 3063, 3030, 2991, 2881, 1725, 1599, 1500, 1455, 1434, 1382, 1320, 1271, 1239, 1200, 1167, 1105, 1076, 1028, 971, 954, 850, 731, 701, 623. - ^1H NMR (*exo*): δ = 1.44 (s, 3H, CH_{3ax}), 1.52 (s, 3H, CH_{3eq}), 3.25 [dd, J = 8.1 Hz, 0.7 Hz, 1H, NCH(CO_2CH_3)C***H***], 3.26 (m, 1H, CH_2C***H***), 3.50 [dd, J = 9.7 Hz, 8.1 Hz, 1H, NCH(Ph)C***H***], 3.76 (s, 3H, OCH_3), 4.03 (dd, J = 12.4 Hz, 1.3 Hz, 1H, OC***H***$_{eq}$), 4.30 (dd, J = 12.4 Hz, 3.7 Hz, 1H, OC***H***$_{ax}$), 4.53 [d, J = 9.7 Hz, 1H, NCH(Ph)], 5.01 (d, J = 2.4 Hz, 1H, OCH), 5.25 [s, 1H, NC***H***(CO_2CH_3)], 6.97 (m, 4H, arom.), 7.14 (m, 2H, arom.), 7.32 (m, 9H, arom.); (*endo*): δ = 1.41 (s, 6H, CH_3), 2.90 (m, 1H, CH_2C***H***), 3.25 [dd, J = 9.1 Hz, 2.7 Hz, 1H, NCH(Ph)C***H***], 3.60 (s, 3H, OCH_3), 3.78 (d, J = 13.2 Hz, 1H, OC***H***$_{eq}$), 3.82 [dd, J = 9.6 Hz, 9.1 Hz, 1H, NCH(CO_2CH_3)C***H***], 4.30 (dd, J = 13.2 Hz, 3.6 Hz, 1H, OC***H***$_{ax}$), 4.16 [d, J = 2.8 Hz, 1H, NCH(Ph)], 4.86 [d, J = 9.6 Hz, 1H, NC***H***(CO_2CH_3)], 4.92 (d, J = 2.8 Hz, 1H, OCH), 7.30 (m, 15H, arom.). - ^{13}C NMR (*exo*): δ = 18.9 (CH_{3ax}), 28.6 (CH_{3eq}), 49.8 [NCH(Ph)***C***H], 50.7 [NCH(CO_2CH_3)***C***H], 51.5 (OCH_3), 51.9 (CH_2***C***H), 63.0 [N***C***H(CO_2CH_3)], 66.2 (CH_2), 66.8 [NCH(Ph)], 73.7 (OCH), 100.0 (C), 125.6, 125.8, 126.7, 127.5, 128.1, 128.4, 128.6, 128.8 (CH arom.), 133.1, 139.3, 141.1 (C arom.), 174.2, 174.5, 178.2 (C=O); (*endo*): δ = 18.8 (CH_{3ax}), 28.7 (CH_{3eq}), 48.2 [NCH(CO_2CH_3)***C***H], 51.8 (OCH_3), 52.8 [NCH(Ph)***C***H], 53.1 (CH_2***C***H), 62.6 (CH_2), 64.6 [N***C***H(CO_2CH_3)], 69.2 [NCH(Ph)], 74.1 (OCH), 99.5 (C), 126.4, 126.7, 127.9, 128.0, 128.9, 129.1, 127.3, 128.3, 129.1 (CH arom.), 132.0, 139.1, 141.2 (C arom.), 172.0, 175.2, 175.3 (C=O). - MS (70eV); *m/z* (%) = 481 (2), 317 (100), 77 (6) [$C_6H_5^+$]. - $C_{30}H_{32}N_2O_6$ (516.6): Calcd. C 69.75, H 6.24, N 5.42; found C 69.65, H 5.94, N 5.31.

Methyl(1S,3S,3aS/R,6aR/S)-3-(bromophenyl)-2-[(4S′,5S′)-2′,2′-dimethyl-4′-phenyl-1′,3′-dioxan-5′-yl]-4,6-dioxo-5-diphenylperhydro-pyrrolo[3,4-c]pyrrole-1-carboxylate (**5c**): 1.21 g (7 mmol) *N*-phenylmaleimide, 1.85 g (10 mmol) 4-bromobenzaldehyde and 0.28g (1 mmol) amine were reacted for 4 d according to the general procedure yielding 0.62g *(1S,3S,3aR,6aS)*-**5c** and *(1S,3S,3aS,6aR)*-**5c** (100%) as a colourless solid after column chromatography (silica gel; petroleum ether:diethyl ether 1:2). - *exo*:*endo* = 39:61[9]. - *exo*[10]: *de* = ≥96%; $[\alpha]_D^{25}$ = –121.2 (0.95, $CHCl_3$); m.p. 173-175°C. - *endo*[10]: *de* = ≥96%; $[\alpha]_D^{25}$ = +32.3 (0.98, $CHCl_3$); m.p. 128-131°C. - IR (KBr): $\tilde{\nu}$ = 3428 cm^{-1}, 2988, 2953, 2870, 1743, 1719, 1599, 1500, 1455, 1384, 1315, 1267, 1234, 1200, 1183, 1100, 1080, 1010, 994, 954, 852, 831, 812, 754, 741, 694. - ^1H NMR (*exo*): δ = 1.44 (s, 3H, CH_{3ax}), 1.47 (s, 3H, CH_{3eq}), 3.23 (m, 1H, CH_2CH), 3.25 [d, *J* = 8.0 Hz, 1H, $NCH(CO_2CH_3)CH$], 3.47 [dd, *J* = 9.9 Hz, 8.0 Hz, 1H, NCH(Ar)CH], 3.77 (s, 3H, OCH_3), 4.01 (dd, *J* = 12.6 Hz, 1.1 Hz, 1H, OCH_{2eq}), 4.30 (dd, *J* = 12.6 Hz, 3.9 Hz, 1H, OCH_{2ax}), 4.53 [d, *J* = 9.6 Hz, 1H, NCH(Ar)], 5.02 (d, *J* = 2.0 Hz, 1H, OCH), 5.17 [s, 1H, $NCH(CO_2CH_3)$], 6.83 (m, 2H, arom.), 6.96 (m, 2H, arom.), 7.12 (m, 2H, arom.), 7.36 (m, 8H, arom.); (*endo*): δ = 1.37 (s, 3H, CH_{3ax}), 1.42 (s, 3H, CH_{3eq}), 2.94 (m, 1H, CH_2CH), 3.21 [dd, *J* = 9.1 Hz, 3.4 Hz, 1H, NCH(Ar)CH], 3.63 (s, 3H, OCH_3), 3.77 [dd, *J* = 9.4 Hz, 9.1 Hz, 1H, $NCH(CO_2CH_3)CH$], 3.90 (dd, *J* = 13.1 Hz, 1.1 Hz, 1H, OCH_{2eq}), 4.14 (dd, *J* = 13.1 Hz, 3.7 Hz, 1H, OCH_{2ax}), 4.27 [d, *J* = 3.4 Hz, 1H, NCH(Ar)], 4.79 [d, *J* = 9.4 Hz, 1H, $NCH(CO_2CH_3)$], 4.95 (d, *J* = 2.7 Hz, 1H, OCH), 7.00 (m, 2H, arom.), 7.20 (m, 2H, arom.), 7.40 (m, 10H, arom.). - ^{13}C NMR (*exo*): δ = 18.8 (CH_{3ax}), 28.5 (CH_{3eq}), 49.7 [NCH(Ar)CH], 50.4 [$NCH(CO_2CH_3)CH$], 51.6 (OCH_3), 52.1 (CH_2CH), 63.3 [$NCH(CO_2CH_3)$], 65.9 [NCH(Ar)], 65.9 (CH_2), 73.6 (OCH), 100.0 (C), 125.5, 125.7, 127.2, 127.6, 128.3, 129.0 (CH arom.), 122.2, 131.7, 136.5, 139.1 (C arom.), 174.0, 174.3, 175.2 (C=O); (*endo*): δ = 18.8 (CH_{3ax}), 28.6 (CH_{3eq}), 47.8 [NCH(Ar)CH], 51.9 [$NCH(COOCH_3)CH$], 53.4 (OCH_3), 63.1 (CH_2CH), 65.00 (CH_2, $NCH(CO_2CH_3)$], 67.6 [NCH(Ar)], 99.6 (C), 126.2, 126.6, 127.4, 128.0, 128.7, 129.1, 129.6, 132.1 (CH arom.), 121.9, 131.5, 138.9, 140.9 (C arom.), 172.2, 174.7, 175.1 (C=O). - MS (70eV); *m/z* (%) = 561 (2) [M^+–CO_2CH_3], 43 (100). - $C_{32}H_{31}N_2O_6Br$ (619.5): Calcd. C 62.04, H 5.04, N 4.52; found C 62.39, H 5.42, N 4.53.

Methyl(1S,3S,3aS/R,6aR/S)-2-[(4S′,5S′)-2′,2′-dimethyl-4′-phenyl-1′,3′-dioxan-5′-yl]-(3-(4-methoxyphenyl)-4,6-dioxo-5-diphenylperhydro-pyrrolo[3,4-c]pyrrole-1-carboxylate (**5d**): 1.21 g (7 mmol) *N*-phenylmaleimide, 1.36 g (10 mmol) 4-methoxybenzaldehyde and 0.28g (1 mmol) amine were reacted for 6 d according to the general procedure yielding 0.57g *(1S,3S,3aR,6aS)*-**5d** and*(1S,3S,3aS,6aR)*-**5d** (100%) as a colourless solid after column chromatography (silica gel; petroleum ether:diethyl ether 1:2). - *exo*:*endo* = 38:62[9]. -

exo[10]: *de* = ≥96%; $[\alpha]_D^{25}$ = –86.4 (1.00, $CHCl_3$); m.p. 185-186°C. - *endo*[10]: *de*= ≥96%; $[\alpha]_D^{25}$ = +7.1 (0.96, $CHCl_3$); m.p. 118-120°C. - IR (KBr): $\tilde{\nu}$ = 3474 cm^{-1}, 3063, 2992, 2950, 2850, 1718, 1611, 1512, 1501, 1458, 1381, 1318, 1302, 1270, 1248, 1199, 1169, 1103, 1078, 1031, 953, 911, 851, 832, 755, 738, 693. - ^1H NMR (*exo*): δ = 1.43 (s, 3H, CH_{3ax}), 1.54 (s, 3H, CH_{3eq}), 3.21 [d, *J* = 7.8 Hz, 1H, NCH(CO_2CH_3)C***H***], 3.26 (m, 1H, CH_2C***H***), 3.45 [dd, *J* = 9.9 Hz, 8.0 Hz, 1H, NCH(Ar)C***H***], 3.76 (s, 3H, OCH_3), 3.79 (s, 3H, *p*OC***H***$_3$Ph), 3.99 (dd, *J* = 12.4 Hz, 1.1 Hz, 1H, OCH***H***$_{eq}$), 4.32 (dd, *J* = 12.6 Hz, 3.9 Hz, 1H, OCH***H***$_{ax}$), 4.49 [d, *J* = 9.9 Hz, 1H, NCH(Ar)], 5.00 (d, *J* = 2.2 Hz, 1H, OCH), 5.26 [s, 1H, NC***H***(CO_2CH_3)], 6.85 (s, 4H, arom.), 7.01 (m, 2H, arom.), 7.13 (m, 2H, arom.), 7.30 (m, 6H, arom.); (*endo*): δ = 1.42 (s, 3H, CH_{3ax}), 1.44 (s, 3H, CH_{3eq}), 2.98 (m, 1H, CH_2C***H***), 3.23 [dd, *J* = 9.1 Hz, 2.7 Hz, 1H, NCH(Ar)C***H***], 3.58 (s, 3H, OCH_3), 3.73 (dd, *J* = 13.1 Hz, 1.4 Hz, 1H, CH***H***$_{eq}$), 3.82 (s, 3H, *p*OC***H***$_3$Ph), 3.82 [dd, *J* = 9.4 Hz, 9.1 Hz, 1H, NCH(CO_2CH_3)C***H***], 4.05 (dd, *J* = 13.1 Hz, 3.7 Hz, 1H, CH***H***$_{ax}$), 4.12 [d, *J* = 2.7 Hz, 1H, NCH(Ar)], 4.87 [d, *J* = 9.4 Hz, 1H, NC***H***(CO_2CH_3)], 4.92 (d, *J* = 2.7 Hz, 1H, OCH), 6.88 (m, 2H, arom.), 7.00 (m, 2H, arom.), 7.38 (m, 10H, arom.). - ^{13}C NMR (*exo*): δ = 18.8 (CH_{3ax}), 28.6 (CH_{3eq}), 49.8 [NCH(Ar)***C***H], 50.6 [NCH($COOCH_3$)***C***H], 51.5 (OCH_3), 55.2 (CH_2***C***H), 62.7 [N***C***H($COOCH_3$)], 66.2 [NCH(Ar)], 66.5 (CH_2), 73.7 (OCH), 99.9 (C), 113.9, 125.6, 125.8, 127.0, 127.4, 128.8 (CH arom.), 128.9, 131.7, 139.3, 159.4 (C arom.), 174.2, 174.6, 175.6 (C=O); (*endo*): δ = 18.8 (CH_{3ax}), 28.7 (CH_{3eq}), 48.3 [NCH(CO_2CH_3)***C***H], 51.7 [NCH(Ar)***C***H], 52.7 (OCH_3), 55.3 (CH_2***C***H), 62.8 (CH_2), 64.3 [N***C***H(CO_2CH_3)], 68.8 [NCH(Ar)], 74.00 (OCH), 99.5 (C), 114.4, 126.3, 126.7, 127.2, 127.9, 128.6, 129.1 (CH arom.), 132.0, 132.7, 139.1, 159.4 (C arom.), 171.9, 175.3, 175.4 (C=O). - MS (70eV); *m/z* (%) = 555 (1) [M^+–CH_3], 173 (100), 77 (19) [$C_6H_5^+$]. - $C_{33}H_{34}N_2O_7$ (570.6): Calcd. C 69.46, H 6.01, N 4.91; found C 69.25, H 5.92, N 5.01.

(3aS,4S,6S,6aR)-(+)-5-[(4S′,5S′)-2′,2′-Dimethyl-4′-phenyl-1′,3′-dioxan-5′-yl]-2,4,6-triphenylperhydropyrrolo[3,4-c]pyrrole-1,3-dione (**5e**): 1.21 g (7 mmol) *N*-phenylmaleimide, 1.06 g (10 mmol) benzaldehyde and 0.30g (1 mmol) amine reacted for 6 d according to the general procedure yielding 0.42g *(3aS,4S,6S,6aR)*-**5e** (75%) as a colourless solid after column chromatography (silica gel; diethyl ether:petroleum ether 1:2). - *de* = ≥96%; $[\alpha]_D^{25}$ = +21.9 (1.00, $CHCl_3$); m.p. 103-107°C. - IR (KBr): $\tilde{\nu}$ = 3477 cm^{-1}, 3062, 3029, 2987, 2869, 1781, 1718, 1599, 1499, 1453, 1380, 1320, 1243, 1198, 1105, 1073, 1028, 1018, 954, 914, 848, 757, 700. - ^1H NMR δ = 0.67 (s, 3H, CH_{3eq}), 1.25 (s, 3H, CH_{3ax}), 3.22 [dd, *J* = 8.8 Hz, 1.8 Hz, 1H, NCH(Ph)C***H***$_{trans}$], 3.25 (m, 1H, CH_2C***H***), 3.75 [dd, J = 9.8 Hz, 8.7 Hz, 1H, NCH(Ph)C***H***$_{cis}$], 4.07 (dd, *J* = 12.8 Hz, 4.0 Hz, 1H, OCH***H***$_{ax}$), 4.14 (dd, *J* = 12.8 Hz, 2.4 Hz, 1H, OCH***H***$_{eq}$), 4.62 [d, *J* = 9.5 Hz, br, 1H, NCH_{cis}(Ph)], 4.83 (d, *J* = 2.8 Hz, 1H, OCH), 5.02 [s, br, 1H, NCH_{trans}(Ph)], 6.52 (m, 2H, arom.), 7.05 (m, 2H, arom.), 7.30 (m, 16H, arom.). -

^{13}C NMR δ = 19.2 (CH_{3eq}), 27.5 (CH_{3ax}), 50.1 [NCH(Ph)*C*H], 54.7 (CH_2*C*H), 55.4 [NCH(Ph)*C*H], 62.4 (CH_2), 66.8 [NCH(Ph)], 68.3 [NCH(Ph)], 73.9 (OCH), 99.1 (C), 125.9, 126.3, 127.4, 127.5, 127.8, 128.0, 128.1, 128.4, 128.7 (CH arom.), 131.4, 139.6, 139.8, 145.1 (C arom.), 174.3, 176.5 (C=O). - MS (70eV); *m/z* (%) = 558 (1) [M$^+$], 543 (1) [M$^+$–CH_3], 77 (10) [$C_6H_5^+$], 44 (100). - $C_{30}H_{34}N_2O_4$ (558.7): Calcd. C 77.40, H 6.13, N 5.01; found C 77.47, H 5.91, N 4.95.

(3aS,4S,6aR/S)-5-[(4S′,5S′)-2′,2′-Dimethyl-4′-phenyl-1′,3′-dioxan-5′-yl]-2,4-diphenylperhydro-pyrrolo[3,4-c]pyrrole-1,3-dione (**5f**): 1.21 g (7 mmol) *N*-phenylmaleimide, 1.06 g (10 mmol) benzaldehyde and 0.29g (1 mmol) amine reacted for 7 d according to the general procedure yielding 0.32 g *(3aR,4S,6aS)*-**5f** and *(3aS,4S,6aR)*-**5f** (67%) as a colourless solid after column chromatography (silica gel; petroleum ether:diethyl ether 2:1). - *exo*:*endo* = 47:53[9]. - *exo*[13]: *de* = ≥96%; $[\alpha]_D^{25}$ = –85.2 (0.99, $CHCl_3$); m.p. 208-209°C. - *endo*[13]: *de* = ≥96%[15]; $[\alpha]_D^{25}$ = +17.7 (0.97, $CHCl_3$); m.p. 77-79°C (dec.). - IR (KBr): $\tilde{\nu}$ = 3467 cm^{-1}, 3063, 3030, 2990, 2860, 1714, 1599, 1500, 1453, 1382, 1343, 1318, 1266, 1240, 1198, 1105, 1079, 1063, 1022, 953, 913, 854, 751, 702, 606, 577. - ^{1}H NMR (*exo*): δ = 1.46 (s, 3H, CH_{3ax}), 1.63 (s, 3H, CH_{3eq}), 2.92 (m, 1H, CH_2C***H***), 2.94 [dd, *J* = 9.5 Hz, 8.2 Hz, 1H, NCH(Ph)C***H***], 3.20 (dd, *J* = 8.3 Hz, 6.4 Hz, 1H, NCH_2C***H***), 3.22 [d, *J* = 9.8 Hz, 1H, NCH(Ph)], 3.74 (dd, *J* = 10.4 Hz, 6.7 Hz, 1H, NCH***H***$_{cis}$), 3.89 (dd, 1H,, *J* = 11.9, 1.5 Hz OCH***H***$_{eq}$), 4.24 (dd, *J* = 11.9 Hz, 4.0 Hz, 1H, OCH***H***$_{ax}$), 4.49 (d, J = 10.4 Hz, 1H, NCH***H***$_{trans}$), 5.10 (d, *J* = 2.8 Hz, 1H, OCH), 6.92 (m, 2H, arom.), 7.12 (m, 2H, arom.), 7.30 (m, 4H, arom.), 7.38 (m, 8H, arom.); (*endo*): δ = 1.42 (s, 3H, CH_{3ax}), 1.52 (s, 3H, CH_{3eq}), 2.85 (m, 1H, CH_2C***H***), 3.16 [dd, *J* = 8.6 Hz, 3.1 Hz, 1H, NCH(Ph)C***H***], 3.23 (dd, *J* = 12.4 Hz, 1.5 Hz, 1H, OCH***H***$_{eq}$), 3.50 (ddd, *J* = 8.6 Hz, 7.9 Hz, 4.2 Hz, 1H, NCH_2C***H***), 3.62 [d, *J* = 3.1 Hz, 1H, NC***H***(Ph)], 3.91 (dd, *J* = 12.4 Hz, 3.1 Hz, 1H, OCH***H***$_{ax}$), 3.96 (m, 2H, NCH_2), 5.03 (d, *J* = 2.7 Hz, 1H, OCH), 7.10 (m, 2H, arom.), 7.30 (m, 13H, arom.). - ^{13}C NMR (*exo*): δ = 18.9 (CH_{3ax}), 29.3 (CH_{3eq}), 45.2 (NCH_2*C*H), 49.4 (CH_2*C*H), 51.3 (NCH_2), 51.4 [NCH(Ph)*C*H], 67.6 (CH_2), 67.9 (NCH), 73.9 (OCH), 99.4 (C), 125.8, 126.0, 127.5, 128.1, 128.2, 128.3, 128.4, 128.9 (CH arom.), 132.1, 137.2, 140.4 (C arom.), 175.2, 178.6 (C=O); (*endo*): δ = 18.6 (CH_{3ax}), 29.6 (CH_{3eq}), 44.8 (NCH_2*C*H), 50.7 (NCH_2), 51.4 [NCH(Ph)*C*H], 52.3 (CH_2*C*H), 63.7 (CH_2), 69.9 (NCH), 74.5 (OCH), 99.0 (C), 125.5, 126.5, 127.3, 127.8, 128.1, 128.3, 128.4, 128.7, 128.8 (CH arom.), 131.9, 139.9, 140.5 (C arom.), 176.7, 178.0 (C=O). - MS (70eV); *m/z* (%) = 482 (2) [M$^+$], 467 (4) [M$^+$–CH_3], 318 (100), 77 (8) [$C_6H_5^+$]. - $C_{30}H_{30}N_2O_4$ (482.6): Calcd. C 74.67, H 6.27, N 5.81; found C 74.46, H 6.25, N 5.77.

(3S,4S,6S,6aR/S,9aS/R,9bS)-(–)-4-(Hydroxymethyl)-6-(4-methoxyphenyl)-3,8-diphenylperhydropyrrolo[3',4':3,4]pyrrolo[2,1-c][1,4]oxazine-1,7,9-trione (**6**): 0.33 g (0.58 mmol) Cycloadduct *exo*-**5d** were dissolved in 3 ml MeOH. Then, 0.13 g (0.70 mmol) of *p*TsOH were added. Stirring was continued for 24h at room temperature. The solvent was removed under reduced pressure and the solid was dissolved in CH_2Cl_2. Water (5ml) was added to the solution. The organic layer was separated and was dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure. No further purification of the product was necessary, yielding 0.29 g (100%) of *exo*-**6**[16] as a colourless solid. - *exo*: *de* = ≥96%; $[\alpha]_D^{25}$ = –145.4 (0.92; $CHCl_3$); m.p. 123-126°C. - IR (KBr): $\tilde{\nu}$ = 3467 cm^{-1}, 2937, 2838, 1780, 1748, 1713, 1612, 1513, 1498, 1459, 1383, 1289, 1250, 1177, 1111, 1070, 1029, 832, 802, 758, 736, 697. - ^1H NMR: δ = 2.45 (s, 1H, OH), 2.75 (m, 1H, NC***H***CH_2), 2.98 (d, *J* = 11.8 Hz, 1H, CH_2), 3.15 (dd, *J* = 12.1 Hz, 3.0 Hz, 1H, CH_2), 3.58 [dd, *J* = 9.4 Hz, 8.4 Hz, 1H, NCH(Ar)C***H***], 3.75 (s, 3H, OCH_3), 4.16 [d, *J* = 8.4 Hz, 1H, NCH(Ar)], 4.25 (d, *J* = 9.4 Hz, 1H, NCHC***H***), 4.77 (s, 1H, NCH), 5.51 (d, *J* = 10.7 Hz, 1H, OCH), 6.86 (m, 2H, arom.), 7.24 (m, 2H, arom.), 7.38 (m, 10H, arom.). - ^{13}C NMR (*exo*): δ = 46.2 (NCH***C***H), 48.7 [NCH(Ar)***C***H], 55.2 (OCH_3), 61.3 (CH_2), 61.7 (NCH), 64.1 (N***C***HCH_2), 72.5 [NCH(Ar)] , 79.6 (OCH), 113.9, 114.1, 126.0, 127.7, 128.7, 128.8, 129.2, 129.4 (CH arom.), 127.2, 131.7, 135.5, 160.1 (C arom.), 170.6, 173.9, 176.7 (C=O). - MS (70eV); *m/z* (%) = 499 (1) [M^++1], 467 (26) [M^+–CH_2OH], 391 (26)[M^+–$C_6H_4OCH_3$], 320 (100). - $C_{29}H_{26}N_2O_6$ (498.5): Calcd. C 69.869, H 5.256, N 5.619; found C 69.560, H 5.258, N 5.384. - Analogous to the shown procedure above, 0.54 g (0.95 mmol) of *endo*-**5d** were reacted with 0.22 g (1.14 mmol) *p*TsOH in MeOH, yielding 0.47 g (100%) of *endo*-**6**[16] as a colourless solid. - *endo*: *de* = ≥96%; $[\alpha]_D^{25}$ = –2.6 (0.92; $CHCl_3$); m.p. 129-132°C. - ^1H NMR: δ = 2.76 (ddd, *J* = 11.0 Hz, 2.9 Hz, 1.2 Hz, 1H, NC***H***CH_2), 2.84 (dd, *J* = 11.9 Hz, 2.9 Hz, 1H, CH_2), 2.91 (dd, *J* = 11.9 Hz, 1.2 Hz, 1H, CH_2), 3.45 [dd, *J* = 10.2 Hz, 7.5 Hz, 1H, NCH(Ar)C***H***], 3.73 (s, 3H, OCH_3), 3.86 (dd, *J* = 10.4 Hz, 7.9 Hz, 1H, NCHC***H***), 4.04 [d, *J* = 7.6 Hz, 1H, NCH(Ar)], 4.67 (d, 1H,, *J* = 7.9 Hz, NCH), 5.43 (d, *J* = 10.8 Hz, 1H, OCH), 6.86 (m, 2H, arom.), 7.33 (m, 7H, arom.), 7.40 (m, 1H, arom.), 7.47 (m, 4H, arom.). - ^{13}C NMR: δ = 44.9 (NCH***C***H), 53.3 [NCH(Ar)***C***H], 55.3 (OCH_3), 61.0 (CH_2), 61.4 (NCH), 63.7 (N***C***HCH_2), 70.9 [NCH(Ar)] , 80.0 (OCH), 114.7,

127.0, 127.7, 128.9, 129.3, 128.8, 129.4 (CH arom.), 130.8, 132.3, 135.4, 160.1 (C arom.), 169.2, 174.2, 175.6 (C=O).

*X-Ray Crystallographic Analysis Data for exo-**5d**.*

Crystal data for $C_{33}H_{34}O_7N_2$ (*exo*-**5d**), M_r = 570.65, orthorhombic, P 2_1 2_1 2_1, a = 9.990 (4), b = 16.983 (1), c = 17.854 (1) Å, V = 3029.0 Å^3, Z = 4, D_{calc} = 1.251 gcm^{-1}, λ (CuK_α) = 1.54179 Å, μ = 6.84 cm^{-1}, T = 298 K. Data were collected on a CAD4 ENRAF-NONIUS diffractometer with monochromated CuK_α radiation. Ω/2Θ scans 2081 reflections with I > 2σ(I). The structure was solved with direct methods as implemented in the XTAL3.2 package of crystallographic writing[17]. The structure was refined by the full-matrix least-squares technique (2075 observed reflections, No. of parameters refined = 380) terminating at R = 0.050, R_w = 0.037 and a residual electron density of ± 0.4 eÅ^{-3}. All the hydrogen positions were calculated and not refined. Atomic coordinates and bond length and angles have been deposited at the Cambridge Crystallographic Data Centre.

Acknowledgements.

This work was supported by the *Fonds der Chemischen Industrie* and by the *Deutsche Forschungsgemeinschaft (Leibniz prize)*. We thank the companies BASF AG, BAYER AG, Degussa AG, Höchst AG and Boehringer Mannheim AG for their donation of chemicals.

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[7] Refers to the *exo* isomer.

[8] Refers to the *endo* isomer.

[9] Determined by ^{1}H NMR spectroscopy.

[10] Complete separation of the *exo*/*endo* isomers by preparative HPLC.

[11] Separation of the *exo*/*endo* isomers by column chromatography.

[12] Determined by analytical HPLC.

[13] Separation of the *exo*/*endo* isomers by crystallization.

[14] Complete separation of the *exo*/*endo* isomers failed, 13% of the *exo* isomer were present.

[15] Complete separation of the *exo*/*endo* isomers failed, 18% of the *exo* isomer were present.

[16] (3*S*,4*S*,6*S*,6a*R*,9a*S*,9b*S*) refers to *exo*-**6** and (3*S*,4*S*,6*S*,6a*S*,9a*R*,9b*S*) to *endo*-**6**.

[17] Hall, S. R.; Flack, H. D.; Stewart, J. M.; Eds. *XTAL3.2 Reference Manual*. Universities of Western Australia, Geneva and Maryland. Lamb: Perth **1992**.