Full Paper

Synthesis of New Chiral Amines with a Cyclic 1,2-Diacetal Skeleton Derived from (2*R*, 3*R*)-(+)-Tartaric Acid

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Abstract: The syntheses of new chiral cyclic 1,2-diacetals from (2*R*, 3*R*)-(+)-tartaric acid are described. C_2-symmetrical diamines were prepared via direct amidation of the tartrate or from the corresponding bismesylate via reaction with sodium azide. For C_1-symmetrical compounds, the Appel reaction was used to form the key intermediate, a monochlorocarbinol, from the diol. Some of the new chiral compounds, produced in good to high yields, may be potentially useful as asymmetric organocatalysts or as nitrogen and sulfur chelating ligands for asymmetric metal catalyzed reactions. Thus, a bis-N-methyl-methanamine derivative, used in substoichiometric amounts, was found to catalyze the enantioselective addition of cyclohexanone to (E)-β-nitrostyrene with high diastereoselectivity (syn / anti = 92:8), albeit giving moderate optical purity (syn: 30 %).

Keywords: Chiral amines, 1,2-diacetals, organocatalysts, asymmetric Michael additions, chiral ligands

Introduction

Chiral amines are important organic compounds. The amine functionality is present in many natural products and due to its interesting physiological activity it is an extremely important pharmacophore in many biologically active compounds [1]. Chiral amines chelated to metals are also used in medicines (e.g. cisplatin), they are used as chiral auxiliaries in stereoselective synthesis and as metal ligands in catalytic asymmetric synthesis [2]. We are interested in using inexpensive and readily

available biomass-derived materials as chiral sources for the synthesis of, amongst other things, chiral ligands and catalysts. Tartaric acid is an example of such a synthon, and we have recently developed novel oxazoline carbinols **A** [3] and bis(oxazolines) **B** [4] based on this starting material and applied them in enantioselective metal-catalyzed processes. They are chiral 1,2-diacetals with a 1,4-dioxane ring, and only recently have compounds with this basic skeleton emerged as efficient ligands for enantioselective catalysis [5]. So far, there has been only one report of a diamine with a 1,4-dioxane skeleton [6], a dimethanamine, which was used as a mixed diamine-diphosphine-RuCl₂ catalyst in the asymmetric hydrogenation of isobutyrophenone [6c,d]. Traditional uses of tartaric acid in catalysis have been as simple esters or as 1,3-dioxolane derivatives. As diamines they catalyze, for instance, the dihydroxylation of *trans*-stilbene, i.e. compound **C** complexed to osmium [7], the addition of cyclohexanone to (E)-nitrostyrene, i.e. compound **D** as a lithium amide [8], and asymmetric phase transfer alkylations and Michael addition reactions to acrylates, i.e. compound **E** [9] (Figure 1).

Figure 1

A: X = CR'R"(OH)
B: X = oxazoline
C
D
E
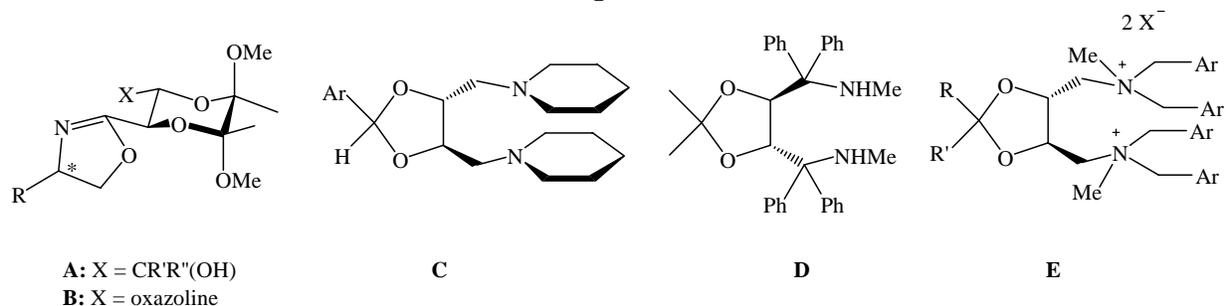
Asymmetric organocatalysis, which is the use of simple, low molecular weight molecules to catalyze organic reactions, is an area of research which has been gaining momentum since 2001 and has been the subject of some recent reviews [10]. The vast majority of these reactions are amine-based [10a], proceeding either via the formation of an enamine or imonium ions. The use of chiral Brønsted bases, inactive on their own but activated by addition of an acid, is another area where there are already a few exciting developments [11] with protonated diamine-type catalysts, such as in the asymmetric direct aldol reaction [12], in the Michael addition of aldehydes or ketones to β-nitrostyrene [13], in aza-Henry reactions [14] and others.

Considering all the new prospective applications in catalysis and the fact that the chemistry of 1,2-diacetals is still relatively unexplored, we decided to build-up a library of amines derived from tartaric acid with a 1,2-diacetal skeleton and various substitution patterns. The methods developed for their syntheses, as well as an application in the Michael addition of cyclohexanone to β-nitrostyrene catalysed by one of the new diamines and *p*-toluenesulfonic acid are presented.

Results and Discussion

Synthesis of amines

(2R, 3R)-(+)-Tartaric acid was used as the starting material for all amines, but in practice either one of the enantiomers of tartaric acid could have been used. Enantiomeric amine pairs would be useful in catalytic applications, since configuration matches or mismatched effects could be investigated. The

acid was converted by a known procedure into cyclic bisacetal ester **1** [15], from which all the ligands were synthesized.To prepare a C_2-symmetrical tosylated diamine, a diazide was chosen as intermediate (Scheme 1). Precursors **2** [16] and **3** [5d] have been described before. Compounds **4** and **5** have been described too [6], but procedures for their syntheses and characterization data have not been published. The displacement of mesylate groups with excess NaN_3 in DMF gave **4** as a single product in high yield (84 %). Catalytic reduction [17] of the diazide with hydrogen in the presence of Pd-C proceeded smoothly to give the diamine as the only product, also in high yield (87 %). Dimethanamine **5** could itself be a useful ligand for other metal catalyzed reactions, as well as a useful intermediate for the synthesis of other nitrogen chelating ligands. Finally, tosylation [18] with p-toluenesulfonyl chloride gave the desired sulfonamide in good yield (72 %). Tosylated diamine **6**, to our knowledge, has not been described before.

Scheme 1.
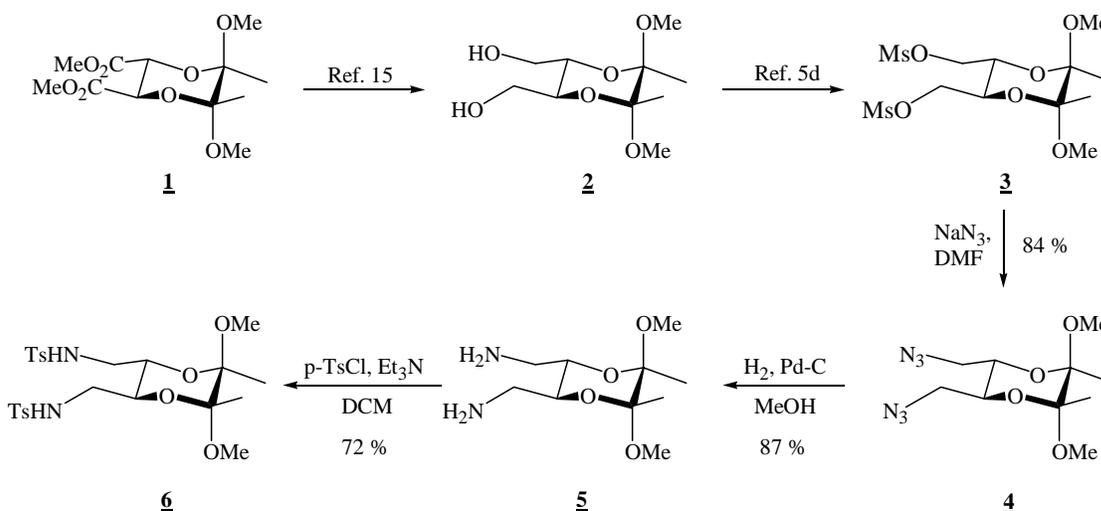
For the synthesis of N-phenyl, N-benzyl, and N-methyl diamines a shorter route, which gives secondary amines unambiguously, was chosen (Scheme 2, Table 1). Amidation of diester **1** could be carried out neat to give **7** and **8** in high yields (84 % and 63 %, respectively) or, due to the high basicity of amines, in alcoholic solvent in an autoclave, to give **9** in an almost quantitative yield after chromatography (96 %). Amide reduction with $LiAlH_4$ was a facile process in the case of the N-phenyl amide **7** and N-benzyl amide **8**, with the amine being produced in good yields (71 % and 97 %, respectively) in refluxing THF in a short period. The reduction of methylamide **9**, however, required a long period of reflux and a large excess of $LiAlH_4$ to go to completion, and highly basic diamine **12** was produced in moderate yield (39 %). Compounds **7** to **12** have not been described before.
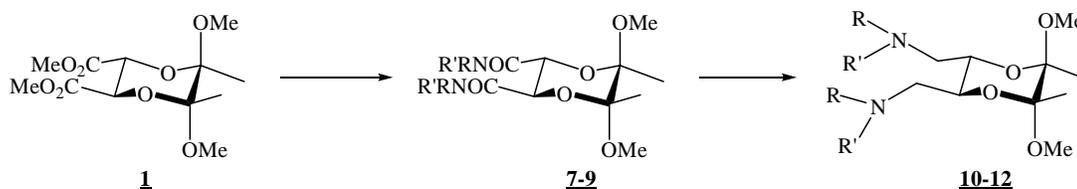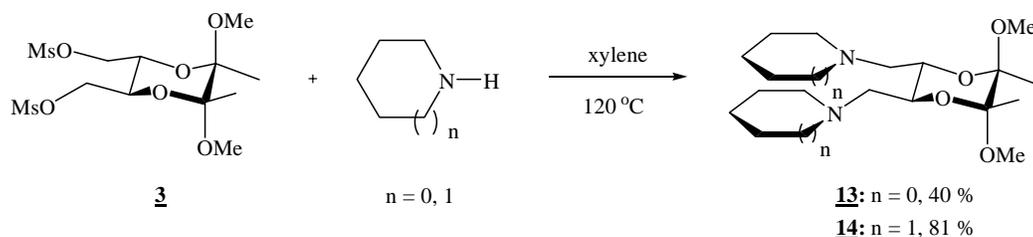
Scheme 2

Table 1

Amide	R	R,	Conditions	Yield (%)	Amine	Conditions	Yield (%)
7	Ph	H	PhNH$_2$, neat, 120 °C	84	**10**	LiAlH$_4$, THF, Δ	71
8	PhCH$_2$	H	PhCH$_2$NH$_2$, neat, 120 °C	63	**11**	LiAlH$_4$, THF, Δ	97
9	Me	H	MeNH$_2$, EtOH, 120 °C, "autoclave"	96	**12**	LiAlH$_4$, THF, Δ	39

Pyrrolidine and piperidine derivatives, analogues of diamine **C**, were also synthesized, but they could not be prepared via the amide. When reacted neat, the reaction never went to completion, even under presssure. When a polar solvent such as an alcohol was used, the steric bulk of the amine slowed down the reaction enough for esterification to compete, and two or more products were isolated. In toluene, there was no reaction. Amines **13** and **14** could finally be prepared in a three-step sequence via the mesylate, when this compound was heated in xylene with a large excess of cyclic amine (Scheme 3).

Scheme 3

3   n = 0, 1   **13:** n = 0, 40 %
                                                      14: n = 1, 81 %

For C$_1$-symmetrical ligands a monochloride was used as key intermediate, a strategy already used by Seebach and co-workers [19] in the synthesis of TADDOLates. N,N- and N,S-chelating ligands were prepared in this fashion as indicated in Scheme 4. Monochloride **15**, prepared by the Appel reaction [20], had to be chromatographed quickly, like its TADDOL derivative analogue, otherwise product recovery was low. It could be thus be obtained in 46 % yield. Azido alcohol **16** was then prepared by displacement of chloride ion with excess sodium azide in high yield (84 %). Like the diazide, **16** could be reduced by catalytic hydrogenation in the presence of palladium on charcoal to give the amino alcohol in almost quantitative yield (96 %). Amino alcohols have many applications in synthesis and catalysis and hence **17** could also be a useful endproduct.

Amino alcohol **17** was tosylated in the presence of excess *p*-tosyl chloride in pyridine to give in good yield (64 %) ditosylated **18**, which was used as an intermediate in the synthesis of three different compounds. Reaction of **18** with aniline in the presence of an inorganic base (NaHCO$_3$) gave a single product, the tosyl aryl amine 19, in high yield (94 %), but excess reagent and heating for several hours was necessary. The preparation of the sulfur-containing analogue was then attempted. Initially sodium thiophenolate was used as nucleophile under reaction conditions similar to those used by others in the preparation of a C$_2$-symmetrical dithioether ligand from the ditosylate [21]. However, instead of the desired product, the bicyclic system **20** was obtained, formed by cyclisation to a pyrrolidine ring. There has been a report of the synthesis of a related compound in the TADDOL series, when (4*R*, 5*S*)-

5-[amino(diphenyl)methyl]-2,2-dimethyl-α,α-diphenyl-1,3-dioxolan-4-methanol was mixed with tosyl chloride and N,N-dimethyl-4-aminopyridine in pyridine at 80 ^{0}C [19a].

In cyclic 1,2-diacetals the 2,3-butane diacetal group (BDA) can be easily removed, and indeed BDA is often used as a protecting group for diols, particularly in carbohydrate chemistry. Taking advantage of this capability of BDA to act as a protecting group, the synthesis of **20** could provide a route to the synthesis of chiral 3,4-disubstituted pyrrolidines, which are valuable basic units in the synthesis of biologically important systems: azabicyclics, metalloproteinase inhibitors and many natural products and pharmaceuticals [22]. This reaction is being further explored by us.

Scheme 4
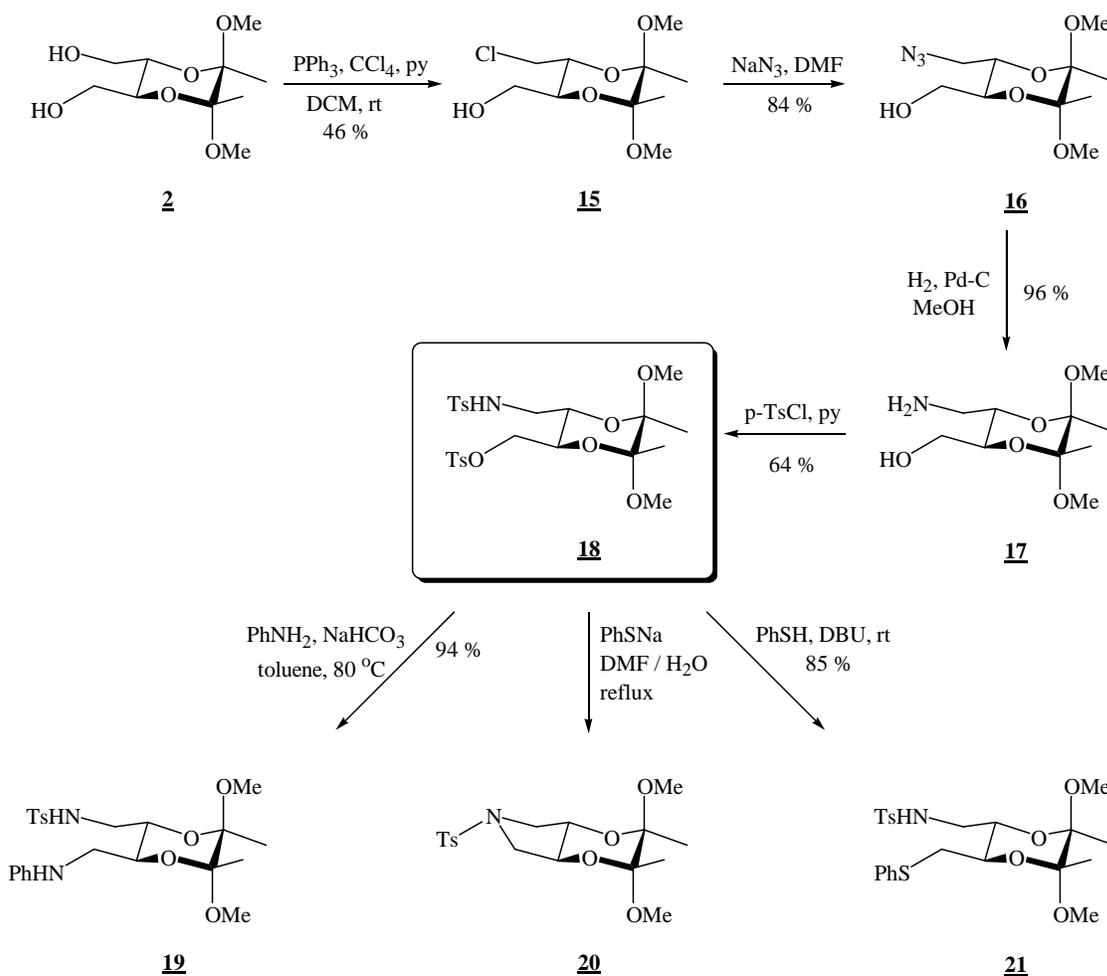
The desired N,S-ligand could be prepared afterwards with different reagents. When less basic thiophenol was used as nucleophile, **21** was obtained in good yield (85 %) when the reaction was carried out at room temperature in toluene, in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) [23]. Compounds **15–21** have not been described before.

The preparation of a thiazoline ligand was attempted next (Scheme 5). Monochloride **15** was also used to establish the difference between the two chelating groups in this case. Alcohol tosylation was carried out under standard conditions, to give **22** in high yield (72 %). The difference in reactivity between the tosyl and chloride groups was used to give preferentially monochlorosulfide **23** in good

yield (60 %) upon reaction with mercaptothiazoline [24], and **23** could be converted into the desired product by reaction with phenylsulfide in the presence of DBU at room temperature. The mercapto-thiazoline derivative **24** was obtained in 88 % yield. Compounds **22-24** have not been described before.

Scheme 5.
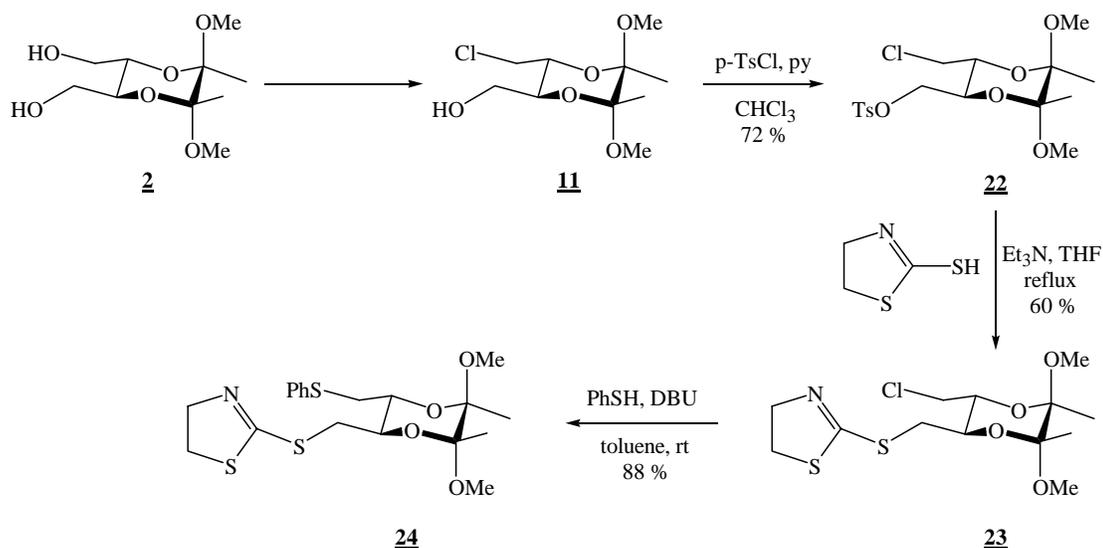
Catalysis

Since several low-molecular weight amines and diamines have already been shown to catalyze many organic transformations [9], we decided to investigate the potential of our new chiral amines as organocatalysts. For this purpose we chose the Michael addition of cyclohexanone to (E)-β-nitrostyrene [25] and reaction conditions similar to those used by Ishii *et al* [13a]. It was found that when diamine **12** was combined with enough *p*-toluenesulfonic acid to protonate one amine function per molecule and in the presence of a large excess of ketone, all the nitrostyrene had reacted after 6 days at room temperature in chloroform (Scheme 6).

Scheme 6.
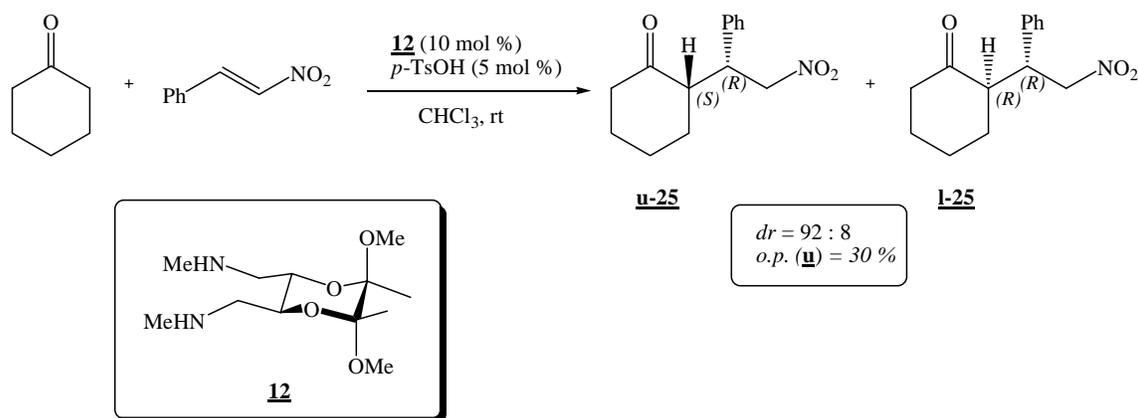
Catalytic amounts (10-12 mol %) of amine were used. The addition reaction was highly diastereoselective, with syn products forming preferentially: *dr* (syn : anti) = 92:8. The optical purity of the major product was determined after isolation, but there only moderate induction was observed: (syn) 30 %.

Conclusions

We have developed methodology to synthesize new chiral cyclic 1,2-diacetals from (*R,R*)-(+)-tartaric acid in good to high yields. To our knowledge compounds **6** to **24** have not been described before. They have C_2 or C_1 symmetry and some, which are summarized in Table 2, have potential to act as nitrogen or sulfur donor ligands in metal-catalyzed reactions or even to be organocatalysts for asymmetric transformations, as our studies on the Michael addition reaction of cyclohexanone to (E)-β-nitrostyrene have shown. Work is currently under way in our laboratory to evaluate further the potential application of these amines in asymmetric catalysis.

Table 2. Summary of chiral amines synthesized
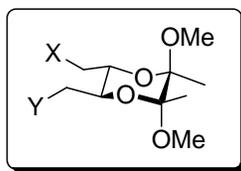
Amine	X	Y
5	NH_2	NH_2
6	NHTs	NHTs
10	NHPh	NHPh
11	NHBn	NHBn
12	NHMe	NHMe
13	Pyrrolidine	Pyrrolidine
14	Piperidine	Piperidine
17	NH_2	OH
19	NHTs	NHPh
21	NHTs	SPh
24	S-thiazoline	SPh

Experimental

General

All reactions were carried out under an atmosphere of argon. Solvents were purified by standard procedures and distilled before use. Hydrogenations were carried out on a Parr hydrogenation

apparatus. Column chromatography was carried out on Macherey-Nagel GmbH & Co silica gel (230–400 mesh) and Merck neutral alumina. Melting points were measured on a Electrothermal Melting Point apparatus. Optical rotations (0.5 dm cell, 1 mL capacity) were measured on an AA–1000 Polarimeter from Optical Activity Ltd or a Perkin-Elmer 241 MC Polarimeter. NMR spectra were obtained in CDCl$_3$ on a Bruker AR X400 NMR spectrometer. Chemical shifts are reported relative to TMS. Multiplicity assignments for ^{13}C-NMR spectra were accomplished using the DEPT sequence. Two-dimensional spectra (COSY 45, HMQC, SECSY) were recorded whenever necessary for structure elucidation. IR spectra were obtained on a Mattson Instruments Satellite FTIR spectrometer. Mass spectra were recorded at 70 eV on a Micromass GCT spectrometer, operating in the electron impact mode, and were supplied by the Mass spectrometry services of the Chemistry Department / REQUIMTE, FCT, UNL. Elemental analysis (C, H, N) were performed by the Laboratory for External Services of CQFB-Lab Associado / REQUIMTE, of the Department of Chemistry, FCT, UNL, Monte de Caparica. The following compounds were prepared according to published procedures: (2*R*, 3*R*, 5*R*, 6*R*)-5,6-dimethoxy-5,6 dimethyl[1,4]dioxane-2,3-dicarboxylic acid dimethyl ester (**1**) [15], (2*R*, 3*R*, 5*S*, 6*S*)-2,3-bis(hydroxymethyl)-5,6-dimethoxy-5,6-dimethyl[1,4]dioxane (**2**) [16], (2*R*, 3*R*, 5*S*, 6*S*)-2,3-dimethoxy-2,3-dimethyl-5,6-bis(((methanesulfonyl)oxy)methyl)[1,4]dioxane (**3**) [5d].

Amine syntheses

(2R,3R,5S,6S)-5,6-Bis(azidomethyl)-2,3-dimethoxy-2,3-dimethyl[1,4]dioxane (**4**).

Bismesylate **3** (0.984 g, 2.51 mmol), sodium azide (1.98 g, 30.5 mmol) and dry dimethylformamide (14.0 mL) were mixed. The resulting suspension was heated up to 80 °C and stirred for 2 days. The reaction mixture was cooled to room temperature, and ether and water were added. The layers were separated, and the aqueous layer was extracted twice more with ether. The combined ether extracts were then washed four times with water and dried through anhydrous sodium sulfate. Evaporation of the solvent gave a clear colourless liquid (0.604 g, 84 %), which was used in the next reaction without further purification; for elemental analysis, the product was purified by preparative chromatography on silica gel (1:4 EtOAc-hexane): [α]$^{26}_D$ = –102.7 (*c* 2.00, CHCl$_3$); ^{1}H-NMR: δ 1.33 (s, 3 H, 2 × CH$_3$), 3.21 (br d, 2 H, *J* = 12.8 Hz, CH$_2$), 3.31 (s, 3 H, OCH$_3$), 3.31–3.38 (m, 2 H, CH$_2$), 3.87–3.88 (m, 2 H, 2 × CH) ppm; ^{13}C-NMR: δ 17.3 (2 × CH$_3$), 48.1 (2 × OCH$_3$), 50.8 (2 × CH$_2$), 69.0 (2 × CH), 99.1 (2 × acetal-C) ppm; IR: $\tilde{v}$ (CHCl$_3$) 3009, 2948, 2932, 2837, 2103, 1444, 1379, 1294, 1253, 1229, 1143, 1133, 1037, 962, 909, 862, 651, 559 cm^{-1}; MS (EI) m/z (%): 271 (M$^+$-15, 0.12), 255 (0.33), 197 (46), 116 (55), 101 (99), 95 (29), 89 (23), 84 (11), 82 (30), 81 (89), 76 (99.8), 75 (96), 73 (100), 70 (11), 69 (22), 68 (44), 67 (88), 59 (36), 57 (19), 56 (20), 55 (62), 54 (95), 53 (11); Anal. Calcd for C$_{10}$H$_{18}$N$_6$O$_4$ (286.29): C 41.95, H 6.34, N 29.36; found C 41.78, H 6.32, N 29.48.

(2R,3R,5S,6S)-(5,6-Dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)dimethanamine (**5**).

Diazide **4** (0.270 g, 0.943 mmol) dissolved in dry MeOH (13.5 mL) was transferred to a hydrogenation flask and Pd on charcoal (0.034 g, 10 %, 0.032 mmol) was added. The flask was connected to a hydrogenation apparatus and the hydrogenation was performed at room temperature and

at 5 psi for 4 h. The hydrogen was then released, and the reaction mixture was filtered through Celite®. The solvent was removed under reduced pressure to give the diamine as the only product (0.191 g, 87 %). It was used as it is in the next reaction. This product deteriorated with time at room temperature, and it was kept in the refrigerator at *ca.* 7 °C; ^{1}H-NMR: δ 1.32 (s, 6 H, CH$_3$), 2.03 (s, 4 H, exchange with D$_2$O, 2 × NH$_2$), 2.79 (s, 4 H, 2 × CH$_2$), 3.28 (s, 6 H, 2 × OCH$_3$), 3.61 (s, 2 H, 2 × CH) ppm; ^{13}C-NMR: δ 17.6 (2 × CH$_3$), 42.5 (2 × CH$_2$), 47.9 (2 × OCH$_3$), 71.0 (2 × CH), 98.6 (2 × acetal-C) ppm.

(2R,3R,5S,6S)-5,6-Dimethoxy-5,6-dimethyl[1,4]dioxane-2,3-bis(methyl p-toluene sulfonamide) (**6**).

Diamine **5** (0.167 g, 0.714 mmol) was dissolved in dry dichloromethane (1.50 mL) and triethylamine (0.13 mL, 9.33 mmol) was added. The solution was cooled to 0 °C, and p-tosyl chloride (0.297g, 1.56 mmol) was added. After stirring for 10 min. at 0 °C, the cooling bath was removed, and the solution was stirred at room temperature for 30 min. Hydrochloric acid (1 M) was added, and the product was extracted three times with dichloromethane. The combined organic extracts were washed with water, and the solvent was removed under reduced pressure. The product was purified by chromatography on silica gel (1:1 EtOAc-hexane, adsorption from CHCl$_3$) to give a colourless crystalline solid (0.288 g, 72 %), m.p. 194-195 °C (EtOAc-hexane); [α]^{24}$_D$ = –97.7 (*c* 1.54, CHCl$_3$); ^{1}H-NMR: δ 1.14 (s, 6 H, 2 × CH$_3$), 2.38 (s, 6 H, 2 × CH$_3$ of Ts), 2.88 (d, 2 H, CH$_2$), 2.98 (d, 2 H, CH$_2$), 3.07 (s, 6 H, 2 × OCH$_3$), 3.63–3.64 (m, 2 H, 2 × CH), 4.80 (s, br, 2 H, 2 × NH), 7.27 (d, *J* = 8.0 Hz, 4 H, Ts), 7.68 (d, *J* = 8.0 Hz, 4 H, Ts) ppm; ^{13}C-NMR: δ 17.3 (2 × CH$_3$), 21.5 (2 × CH$_3$ of Ts), 43.3 (2 × CH$_2$), 48.1 (2 × OCH$_3$), 67.4 (2 × CH), 98.9 (2 × acetal-C), 127.1 (4 × CH, Ts), 129.9 (4 × CH, Ts), 136.5 (2 × Cq, Ts), 143.7 (2 × Cq, Ts) ppm; IR (KBr): $\tilde{v}$ 3294, 3272, 2985, 2946, 2900, 2892, 2834, 1599, 1455, 1438, 1386, 1327, 1169, 1154, 1129, 1092, 1050, 1030, 970, 882, 856, 816, 723, 661, 585, 551, 529 cm-1; MS (EI) m/z (%): 527 (M$^+$ - 15), 479 (70), 239 (88), 224 (73), 223 (100), 222 (92), 210 (60), 184 (63), 155 (51), 139 (28), 101 (37), 92 (20), 91 (18), 84 (22), 83 (35), 73 (21), 69 (10) 68 (88), 65 (38), 56 (25); Anal. Calcd for C$_{24}$H$_{34}$N$_2$O$_8$S$_2$ (542.66): C 53.12, H 6.32, N 5.16, S 11.82; found C 53.34, H 6.38, N 4.99, S 11.62.

(2R,3R,5S,6S)-5,6-Dimethoxy-5,6-dimethyl-N,N-diphenyl[1,4]dioxane-2,3-dicarboxamide (**7**).

Diester **1** (1.20 g, 4.10 mmol) and aniline (0.75 mL, 8.23 mmol) were mixed in a round bottom flask topped up with a reflux condenser, heated up to 140 °C, and stirred for 4 days. After cooling to room temperature, the reaction mixture was chromatographed on silica gel (3:2 ether-hexane, adsorption from CHCl$_3$) to give the product as colourless crystals (0.142 g, 84 %), m. p. 209 °C (ether-hexane); [α]^{26}$_D$ = –100.5 (*c* 2.00, CHCl$_3$); ^{1}H-NMR: δ 1.45 (s, 6 H, 2 × CH$_3$), 3.27 (s, 6 H, 2 × OCH$_3$), 4.69 (s, 2 H, 2 × CH), 7.13 (t, 1 H, *J* = 7.6 Hz, Ph), 7.34 (t, 2 H, *J* = 7.2 Hz, Ph), 7.60 (d, 2 H, *J* = 7.6 Hz, Ph), 8.27 (s, br, 2 H, 2 × NH) ppm; ^{13}C-NMR: δ 18.0 (2 × CH$_3$), 48.6 (2 × OCH$_3$), 70.9 (2 × CH), 99.8 (2 × acetal-C), 119.9 (4 × CH, Ph), 124.4 (2 × CH, Ph), 129.0 (4 × CH, Ph), 137.3 (2 × *i*-C, Ph), 166.4 (2 × CONH) ppm; IR (CHCl$_3$): $\tilde{v}$ 3469, 3389, 3366, 3329, 3198, 3136, 3081, 3000, 2947, 2836, 1687, 1600, 1531, 1499, 1445, 1377, 1312, 1142, 1115, 1045, 1034, 929, 906, 755, 693, 633, 457 cm^{-1}; MS (EI) m/z (%): 416 (M$^+$ + 2, 0.27), 415 (M$^+$ + 1, 1.55), 414 (M$^+$, 7.44), 174 (23), 146 (23), 145 (19), 116

(20), 115 (18), 101 (16), 93 (100), 92 (9), 77 (17), 73 (11); Anal. Calcd for $C_{22}H_{26}N_2O_6$ (414.46): C 63.76, H 6.32, N 6.76; found C 63.70, H 6.29, N 6.81.

(2R,3R,5S,6S)- N,N-Dibenzyl-5,6-dimethoxy-5,6-dimethyl- [1,4]dioxane-2,3-dicarboxamide (**8**).

   Diester **1** (0.34 g, 1.16 mmol) and benzylamine (0.28 mL, 2.56 mmol) were mixed in a round bottom flask topped up with a reflux condenser, heated up to 120 °C, and stirred for 21 h. After cooling to room temperature, the reaction mixture was chromatographed on silica gel (96:4 CHCl₃-acetone) to give the product as colourless crystals (0.32 g, 63 %), m. p. 120–121 °C (CHCl₃ / acetone); $[\alpha]^{16}_D = -108.6$ (*c* 0.28, CHCl₃); ¹H-NMR: δ 1.32 (s, 6 H, 2 × CH₃), 3.23 (s, 6 H, 2 × OCH₃), 4.41 (s, 2 H, 2 × CH), 4.54 (2 × dd, ABX system, 4 H, J_{AB} 14.8 Hz, 2 × CH₂), 6.70–6.82 (m, br, 2 × NH), 7.28–7.37 (m, 10 H, 2 × Ph) ppm; ¹³C-NMR: δ 17.58 (2 × CH₃), 43.1 (2 × CH₂), 48.4 (2 × OCH₃), 71.3 (2 × CH), 99.4 (2 × acetal-C), 127.4 (2 × *p*-CH, Ph), 127.9 (4 × *m*-CH, Ph), 128.7 (4 × *o*-CH, Ph), 138.1 (2 × *i*-C, Ph), 167.5 (2 × CON) ppm; IR (CHCl₃): $\tilde{v}$ 3426, 3067, 3010, 2950, 2838, 1677, 1604, 1527, 1500, 1455, 1379, 1240, 905, 700 cm⁻¹; MS (EI) m/z (%): 444 (M⁺ + 2, 0.2), 443 (M⁺ + 1, 1), 442 (M⁺, 5), 202 (24), 117 (13), 116 (30), 115 (21), 106 (100), 101 (16), 98 (11), 92 (14), 91 (76); Anal. Calcd for $C_{24}H_{30}N_2O_6$ (442.508): C 65.14, H 6.83, N 6.33; found C 65.03, H 7.07, N 6.55.

(2R,3R,5S,6S)-5,6-Dimethoxy-N,N,5,6-tetramethyl[1,4]dioxane-2,3-dicarboxamide (**9**).

   To diester **1** (1.05 g, 3.44 mmol) was added methylamine (1.3 mL *ca.* 30 % solution in ethanol, *ca.* 32.6 mmol), and the mixture was stirred at 120 °C in an autoclave for 46 h. After cooling to room temperature, the mixture was then transferred to a round-bottom flask, and the volatiles were removed under reduced pressure. After column chromatography on silica gel (7:3 acetone-CHCl₃) the product was obtained as colourless crystals (0.998 g, 96 %), m.p. 189 – 190 °C (CHCl₃ / acetone); $[\alpha]^{18}_D = -79.8$ (*c* 1.00, CHCl₃); ¹H-NMR: δ 1.34 (s, 6 H, 2 × CH₃), 2.87 (d, *J* = 4.8 Hz, 6 H, 2 × NCH₃), 3.26 (s, 6 H, 2 × OCH₃), 4.28 (s, 2 H, 2 × CH), 6.52 (s, br, 2 × NHCO) ppm; ¹³C-NMR: δ 17.5 (2 × CH₃), 25.9 (2 × NHCH₃), 48.7 (2 × OCH₃), 71.1 (2 × CH), 99.3 (2 × acetal-C), 168.0 (2 × CONH) ppm; IR (CHCl₃): $\tilde{v}$ 3442, 3008, 2949, 2838, 1679, 1537, 1458, 1416, 1378, 1144, 1115, 1074, 1037, 903, 889 cm⁻¹; MS (EI) m/z (%): 290 (M⁺, 0.07), 259 (11), 227 (30), 142 (55), 116 (100), 115 (95), 113 (98), 112 (100), 102 (74), 101 (96), 100 (14), 85 (49), 84.9 (36), 84 (91), 82.9 (47), 73 (55), 58 (90); Anal. Calcd for $C_{12}H_{22}N_2O_6$ (290.32): C 49.65, H 7.64, N 9.65; found C 49.38, H 7.86, N 9.63.

(2R,3R,5S,6S)-N,N'-[(5,6-Dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)bismethylene)]dianiline (**10**).

   To a stirred suspension of LiAlH₄ (0.119 g, 3.16 mmol) in dry tetrahydrofuran (0.78 mL) was added dropwise amide **10** (0.260 g, 0.627 mmol) in dry tetrahydrofuran (2.4 mL). The mixture was heated up and refluxed for 4.5 h, and then cooled on ice. Water (0.13 mL), KOH (10 %, 0.38 mL), and again water (0.13 mL) were added successively while the flask was swirled vigorously by hand. The resulting granular precipitate was filtered off through a sintered glass funnel. The filtrate was kept, the solid was returned to the reaction vessel, more tetrahydrofuran was added, and the mixture was refluxed for 30 min. The solids were filtered off once more, the filtrates were combined, and the

product was obtained after removal of the solvent on a rotary evaporator. Purification by chromatography on silica gel (1:3 EtOAc-hexane) gave the product as colourless crystals (0.171 g, 71 %), m.p. 104–105 °C (EtOAc- hexane); $[\alpha]^{26}_D$ = –119.8 (*c* 0.93, CHCl$_3$); ^{1}H-NMR: δ 1.25 (s, 6 H, 2 × CH$_3$), 3.12 (s, 6 H, 2 × OCH$_3$), 3.05–3.15 (m, partially overlapped, 2 H, CH$_2$N), 3.28 (d, 2 H, *J* = 13.1 Hz, CH$_2$N), 3.93–3.94 (m, 2 H, 2 × CH), 6.58 (d, 2 H, *J* = 7.9 Hz, 2 × *o*-CH, Ph), 6.67 (t, 1 H, *J* = 7.3 Hz, *p*-CH, Ph), 7.10 (t, 2 H, *J* = 7.9 Hz, 2 × *m*-CH, Ph) ppm; ^{13}C-NMR: δ 17.6 (2 × CH$_3$), 44.7 (2 × CH$_2$), 48.1 (2 × OCH$_3$), 68.1 (2 × CH), 99.0 (2 × acetal-C), 113.7 (4 × CH, Ph), 118.2 (2 × CH, Ph), 129.3 (4 × CH, Ph), 147.7 (2 × *i*-C, Ph) ppm; IR (CHCl$_3$): $\tilde{v}$ 3399, 3056, 3009, 2949, 2909, 2836, 1604, 1504, 1463, 1434, 1379, 1316, 1281, 1254, 1228, 1181, 1135, 1080, 1069, 1038, 959, 866, 732, 694, 664, 509 cm^{-1}. MS (EI) m/z (%): 388 (M$^+$ + 2, 0.4), 387 (M$^+$ + 1, 6.0), 386 (M$^+$, 80), 323 (34), 248 (36), 188 (63), 148 (71), 146 (15), 145 (98), 144 (70), 132 (18), 130 (15), 118 (17), 116 (71), 106 (100), 104 (28), 101 (43), 93 (29), 77 (58), 73 (12); Anal. Calcd for C$_{22}$H$_{30}$N$_2$O$_4$ (386.49): C 68.37, H 7.82, N 7.25; found C 68.20, H 7.92, N 7.28.

(2R,3R,5S,6S)-(5,6-Dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)bis(N-benzylmethanamine) (**11**).

Following the reduction procedure used for the synthesis of compound **10**, diamine **11** was obtained as the only product from dicarboxamide **8** (0.205 g, 0.464 mmol) and LiAlH$_4$ (0.183 g, 5.22 mmol) in THF (2.03 ml), after 17 h reflux. Yield (0.187 g, 97 %). For analytical purposes it was purified by column chromatography on silica gel (2:1 acetone-CHCl$_3$ + 1 % Et$_3$N). A viscous liquid was obtained: $[\alpha]^{18}_D$ = –140.7 (*c* = 0.85, CHCl$_3$); ^{1}H-NMR: δ 1.29 (s, 6 H, 2 × CH$_3$), 2.64–2.72 (m, 4 H, 2 × CH$_2$), 3.27 (s, 6 H, 2 × OCH$_3$), 3.74, 3.80 (AB system, 4 H, J_{AB} = 13.1 Hz, 2 × N–CH$_2$Ph), 3.85–3.87 (m, 2 H, 2 × CH), 7.22–7.34 (m, 12 H, Ph) ppm; ^{13}C-NMR: δ 17.6 (2 × CH$_3$), 48.0 (2 × OCH$_3$), 49.7 (2 × CH$_2$), 54.0 (2 × CH$_2$Ph), 69.4 (2 × CH), 98.6 (2 × dioxane-CH), 126.9 (2 × *p*-CH, Ph), 128.1 (4 × *m*-CH, Ph), 128.3 (4 × *o*-CH, Ph), 140.1 (2 × *i*-C, Ph) ppm; IR (neat, salt plates): $\tilde{v}$ 3328, 3085, 3062, 3025, 2991, 2946, 2908, 2830, 1604, 1495, 1454, 1374, 1198, 1125, 1041, 961, 864, 739, 699 cm^{-1}. MS (EI) m/z (%): 414 (M$^+$, 0.30), 351 (3), 188 (3), 174 (3), 162 (22), 159 (9), 158 (3), 144 (8), 120 (12), 116 (13), 106 (4), 101 (7), 92 (5), 91 (100), 73 (3), 65 (5); Anal. Calcd for C$_{24}$H$_{34}$N$_2$O$_4$ (414.55): C 69.54, H 8.27, N 6.76; found C 69.31, H 8.46, N 6.73.

(2R,3R,5S,6S)-(5,6-Dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)bis(N-methylmethanamine) (**12**).

Amide **9** (0.200 g, 0.689 mmol) dissolved in dry tetrahydrofuran (10.0 mL) was added dropwise to a suspension of LiAlH$_4$ (0.290 g, 7.64 mmol) in dry tetrahydrofuran (1.0 mL). The mixture was refluxed for *ca.* 24 h, cooled, and more LiAlH$_4$ (0.43 g, 11.3 mmol) was added. The mixture was refluxed for another 24 h. The product was then hydrolysed as described for amine **10** and it was purified by preparative chromatography on neutral alumina (8:1:1 CHCl$_3$-CH$_2$Cl$_2$-MeOH). Colourless crystals were obtained (0.086 g, 39 %). It was recrystallized from diethyl ether, m. p. 53-54 °C; ^{1}H-NMR: δ 1.26 (s, 6 H, 2 × CH$_3$), 2.03 (s, 2 H, 2 × NH), 2.40 (s, 6 H, 2 × NCH$_3$), 2.54–2.64 (m, 4 H, 2 × CH$_2$), 3.24 (s, 6 H, 2 × OCH$_3$), 3.77–3.78 (m, 2 H, 2 × CH) ppm; ^{13}C-NMR: δ 17.6 (2 × CH$_3$), 36.4 (2 × NCH$_3$), 48.0 (2 × OCH$_3$), 52.3 (2 × CH$_2$), 69.2 (2 × CH), 98.6 (2 × acetal-C) ppm; IR (CHCl$_3$): $\tilde{v}$ 3338, 3005, 2949, 2855, 2837, 2804, 1670, 1462, 1451, 1378, 1236, 1219, 1137, 1122, 1039, 957,

885, 869, 817, 777, 663, 562, 423 cm^{-1}; MS (EI) m/z (%): 232 (1.3), 231 (1.5), 218.1 (38), 199.1 (50), 188 (38), 187 (41), 126 (13), 116 (93), 115 (26), 101 (88), 87 (30), 86 (100), 84 (18), 83 (87), 82 (67), 73 (42), 70 (47), 68 (72); Anal. Calcd for $C_{12}H_{26}N_2O_4$ (262.35): C 54.94, H 9.99, N 10.68; found C 54.73, H 10.00, N 10.60.

(2R,3R,5S,6S)-1,1'-[(5,6-Dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)bis(methylene)]dipyrrolidine (**13**).

    Bismesylate **3** (0.300 g, 0.765 mmol), freshly distilled pyrrolidine (0.51 mL, 6.11 mmol) and xylene (1.20 mL) were mixed and heated to 120 ^{o}C for 3 h. After cooling to room temperature, the volatiles were removed on high vacuum. The residue was dissolved in CH_2Cl_2, and the product was washed with a saturated solution of sodium chloride and three times with water. The solution was filtered through anhydrous sodium sulfate, and the solvent was removed on a rotary evaporator, to give colourless crystals (0.104 g, 40 %). For analytical purposes the product was purified by column chromatography on silica gel (2:1 acetone-CHCl$_3$ + 1 % Et$_3$N), m.p. 52–53 °C; $[\alpha]^{16}_D$ = −133.2 (*c* 0.82, CHCl$_3$); ^{1}H-NMR: δ 1.28 (s, 6 H, 2 × CH$_3$), 1.77 (s, br, 8 H, 4 × CH$_2$), 2.54–2.63 (d + s, br, 10 H, 2 × C*H*HN + 2 × CH$_2$N of pyrrolidine), 2.82 (s, br, 2 H, 2 × CH*H*N), 3.29 (s, 6 H, 2 × OCH$_3$), 3.77 (s, br, 2 H, 2 × CH) ppm; ^{13}C-NMR: δ 17.8 (2 × CH$_3$), 23.6 (4 × CH$_2$), 48.3 (2 × OCH$_3$), 54.9 (4 × CH$_2$N), 57.2 (2 × CH$_2$N), 69.8 (2 × CH), 98.4 (2 × acetal-C) ppm; IR (CHCl$_3$): $\tilde{v}$ 3000, 2963, 2912, 2881, 2832, 2808, 1461, 1375, 1353, 1221, 1209, 1178, 1162, 1141, 1122, 1104, 1084, 1073 cm^{-1}. MS (EI) m/z (%): 311 (M$^+$- OCH$_3$, 25), 126 (94), 123 (66), 108 (20), 101 (10), 84 (100); Anal. Calcd for $C_{18}H_{34}N_2O_4$ (342.48): C 63.13, H 10.01, N 8.18; found C 63.01, H 10.15, N 7.97.

(2R,3R,5S,6S)-1,1'-[(5,6-Dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)bis(methylene)]dipiperidine (**14**).

    Bismesylate **3** (0.656 g, 1.67 mmol), piperidine (1.31 mL, 13.2 mmol) and xylene (2.6 mL) were mixed, stirred 1h at room temperature, then refluxed for 2.5 h. After cooling to room temperature, the volatiles were evaporated off. The residue was dissolved in CH_2Cl_2, and the product was washed 4 × with water. The solution was filtered through anhydrous sodium sulphate, and the solvent was removed on a rotary evaporator, to give colourless crystals (0.619 g, 81 %); the product was recrystallized from hexane, m. p. 84.5–85.0 °C; $[\alpha]^{17}_D$ = −187.0 (*c* 0.37, CHCl$_3$); ^{1}H-NMR: δ 1.27 (s, 6 H, 2 × CH$_3$), 1.34–1.46 (m, 4 H, 2 × CH$_2$), 1.48–1.63 (m, 8 H, 4 × CH$_2$), 2.38–2.48 (m, 10 H, 2 × C*H*HN, 4 × CH$_2$N), 2.64 (d, 2 H, *J* = 9.64 Hz, 2 × CH*H*N), 3.28 (s, 6 H, 2 × OCH$_3$), 3.73 (s, br, 2 H, 2 × CH) ppm; ^{13}C-NMR: δ 17.8 (2 × CH$_3$), 24.3 (2 × CH$_2$), 26.1 (4 × CH$_2$), 48.1 (2 × OCH$_3$), 55.1 (4 × CH$_2$), 60.2 (2 × CH$_2$), 69.2 (2 × CH), 98.4 (2 × acetal-C) ppm; IR (CHCl$_3$): $\tilde{v}$ 3003, 2939, 2855, 2833, 2785, 1468, 1454, 1375, 1303, 1261, 1199, 1174, 1155, 1147, 1137, 1115, 1097, 1088, 1078, 1065, 1039, 991, 864, 748, 737, 663 cm^{-1}; MS (EI) m/z (%): 339 (51), 272 (35), 140 (98), 138 (16), 137 (81), 122 (41), 116 (13), 99 (8), 98.8 (16), 98 (100); Anal. Calcd for $C_{20}H_{38}N_2O_4$ (370.53): C 64.83, H 10.34, N 7.56; found C 64.66, H 10.32, N 7.63.

(2R,3R,5S,6S)-3-Chloromethyl-5,6-dimethoxy-5,6-dimethyl[1,4]dioxane-2-methanol (**15**).

Bis-alcohol **2** (1.76 g, 7.45 mmol) and triphenylphosphine (3.92 g, 15.0 mmol) were dissolved in dichloromethane (13.1 mL) and pyridine (1.22 mL, 15.1 mmol) and tetrachloromethane (1.50 mL, 15.6 mmol) were added. The reaction vessel was wrapped in foil and the solution was stirred at room temperature for 23 h. The volatiles were then evaporated off under reduced pressure. The product was purified by column chromatography on silica gel (3:2 EtOAc-hexane, adsorption from DCM) to give the product as colourless needle-like crystals (0.798 g, 47 %), m.p. 100–101 °C; $[\alpha]^{19}_D$ = –188.7 (*c* 2.05, CHCl$_3$); ^{1}H-NMR: δ 1.30 (s, 3 H, CH$_3$), 1.32 (s, 3 H, CH$_3$), 2.21 (s, br, 1 H, OH), 3.25 (s, 3 H, OCH$_3$), 3.28 (s, 3 H, OCH$_3$), 3.54–3.77 (m, 5 H, 2 × CH$_2$ + 1 × dioxane-CH), 3.95–4.00 (m, 1 H, dioxane-CH) ppm; ^{13}C-NMR: δ 17.4 (2 × CH$_3$), 43.6 (CH$_2$Cl), 48.0 (2 × OCH$_3$), 62.1 (CH$_2$OH), 68.5 (dioxane-CH), 70.1 (dioxane-CH), 98.9 (acetal-C), 99.2 (acetal-C) ppm; IR (KBr): $\tilde{v}$ 3232, 3025, 3008, 2991, 2964, 2938, 2884, 2836, 1462, 1425, 1384, 1266, 1221, 1144, 1131, 1090, 1040, 966, 954, 914, 892, 872, 860, 825, 737, 651, 564, 511, 459 cm^{-1}; MS (EI) m/z (%): 225 (6), 223 (51), 193 (59), 192 (14), 191 (53), 165 (38), 151 (38), 116 (15), 113 (52), 105 (67), 101 (62), 88 (63), 76 (100), 75 (41), 73 (55), 71 (10), 70 (58), 69 (41), 57 (44); Anal. Calcd for C$_{10}$H$_{19}$ClO$_5$ (254.71): C 47.16, H 7.52; found C 46.93, H 7.49.

(2R,3R,5S,6S)-3-Azidomethyl-5,6-dimethoxy-5,6-dimethyl[1,4]dioxane-2-methanol (**16**).

Monochloride **15** (0.708 g, 2.78 mmol), sodium azide (0.704 g, 10.8 mmol) and dry dimethylformamide (14.0 mL) were mixed. The resulting suspension was stirred at 80 °C, for 88 h. After cooling to room temperature, the product was extracted as described for the bisazide. A single product was obtained, as colourless crystals (0.607 g, 84 %), used as it is in the next reaction. For analytical purposes it was purified by chromatography on silica gel (2:3 EtOAc-hexane), m.p. 71 – 72 °C (EtOAc / hexane); $[\alpha]^{27}_D$ = –134.2 (*c* 2.02, CHCl$_3$); ^{1}H-NMR: δ 1.31 (s, 3 H, CH$_3$), 1.33 (s, 3 H, CH$_3$), 1.91 (s, br, 1 H, OH), 3.26 (dd, 1 H, *J* = 3.2, 12.0 Hz, CH$_2$N$_3$), 3.39 (dd, 1 H, *J* = 6.8, 12.0 Hz, CH$_2$N$_3$), 3.60 (dd, 1 H, *J* = 5.2, 12.0 Hz, CH*H*OH), 3.69 (dd, 1 H, *J* = 3.2, 12.0 Hz, C*H*HOH), 3.75 (ddd, 1 H, *J* = 3.2, 5.2, 9.6 Hz, C*H*-CH$_2$OH), 3.97 (ddd, 1 H, *J* = 2.8, 6.8, 9.6 Hz, C*H*-CH$_2$N$_3$) ppm; ^{13}C-NMR: δ 17.4 (2 × CH$_3$), 48.0 (2 × OCH$_3$), 50.9 (CH$_2$), 62.0 (CH$_2$), 68.4 (CH), 69.5 (CH), 99.0 (2 × acetal-C) ppm; IR (CH$_2$Cl$_2$): $\tilde{v}$ 3590, 2996, 2950, 2929, 2836, 2102, 1460, 1446, 1377, 1266, 1224, 1202, 1138, 1132, 1037, 962, 861, 754, 746, 726 cm^{-1}; MS (EI) m/z (%): 172 (20), 129 (11), 116 (25), 110 (22), 101 (99), 85 (11), 84 (22), 76 (86), 75 (89), 73 (100), 70 (86), 69 (49), 68 (60), 67 (85), 59 (20), 57 (70), 56 (90), 55.0 (13), 54 (11); Anal. Calcd for C$_{10}$H$_{19}$N$_3$O$_5$ (261.28): C 45.97, H 7.33, N 16.08; found C 46.14, H 7.14, N 15.74.

(2R,3R,5S,6S)-3-Aminomethyl-5,6-dimethoxy-5,6-dimethyl[1,4]dioxane-2-methanol (**17**).

Azido alcohol **16** (0.270 g, 0.943 mmol) dissolved in dry MeOH (13.5 mL) was transferred to an hydrogenation flask and Pd on charcoal (0.034 g, 10 %, 0.032 mmol) was added. The flask was connected to a hydrogenation apparatus, and the hydrogenation was performed at room temperature and at 5 psi for 4 h. The reaction mixture was then treated as described for the diazide. A single

product was obtained (0.260 g, 96 %), used as it is in the next reaction. For analytical purposes it was crystallized from ether, m.p. 109 °C; ^{1}H-NMR: δ 1.16 (s, 6 H, 2 × CH$_3$), 2.72 (s, br, 2 H, CH$_2$N), 2.83 (s, br, 2 H, NH$_2$), 3.12 (s, 6 H, 2 × OCH$_3$), 3.47 (s, br, CH$_2$O), 3.50 (s, br, 2 × CH) ppm; ^{13}C-NMR: δ 17.3 (2 × CH$_3$), 42.5 (CH$_2$N), 47.6 (2 × OCH$_3$), 62.0 (CH$_2$OH), 70.6 (CH), 71.0 (CH), 98.4 (2 × acetal-C) ppm; IR (KBr): $\tilde{v}$ 3382, 3301, 3113, 3012, 2995, 2949, 2926, 2894, 2882, 2834, 1606, 1456, 1440, 1395, 1379, 1215, 1126, 1083, 1037, 957, 889, 858, 655, 566 cm-1; MS (EI) m/z (%): 172 (78), 116 (12), 101 (50), 87 (16), 86 (15), 75 (31), 73 (41), 70 (38), 69 (100), 68 (14), 56 (94); Anal. Calcd for C$_{10}$H$_{21}$NO$_5$ (235.28): C 51.05, H 9.00, N 5.95; found C 50.87, H 8.81, N 6.03.

(2R,3R,5S,6S)-5,6-Dimethoxy-5,6-dimethyl-3-[(p-toluenesulfonylamino)-methyl]-[1,4]-dioxan-2-yl-methyl p-toluenesulfonate (**18**).

Amino alcohol **17** (0.296 g, 1.26 mmol) was dissolved in dry chloroform (1.50 mL) and pyridine (0.49 mL, 6.06 mmol) was added. The solution was cooled to 0 °C, and p-tosyl chloride (0.604 g, 3.17 mmol) was added in portions. The resulting solution was stirred for 2.5 h at 0 °C, under argon. The reaction mixture was then partitioned between ether and water, and the ether layer washed successively with HCl (2 M) and a saturated solution of sodium bicarbonate. The solvent was evaporated off under reduced pressure, and the residue was chromatographed on silica gel (2:3 EtOAc-hexane, adsorption from CHCl$_3$), to give the product as colourless crystals (0.438 g, 64 %), m.p. 110 °C (EtOAc / hexane); $[\alpha]^{25}_D$ = –87.2 (*c* 1.00, CHCl$_3$); ^{1}H-NMR: δ 1.18 (s, 3 H, CH$_3$), 1.20 (s, 3 H, CH$_3$), 2.44 (s, 3 H, CH$_3$ of Ts), 2.46 (s, 3 H, CH$_3$ of Ts), 2.88–2.94 (m, 1 H, CH$_2$N), 2.88–2.94 (m, 1 H, CH$_2$N), 3.10 (s, 3 H, OCH$_3$), 3.12 (s, 3 H, OCH$_3$), 3.71–3.78 (m, 2 H, 2 × CH), 3.99 (dd, 1 H, *J* = 3.2, 10.8 Hz, CH$_2$O), 4.11 (dd, 1 H, *J* = 4.4, 11.2 Hz, CH$_2$O), 4.88 (t, br, 1 H, NH), 7.33 (d, 2 H, *J* = 8 Hz, aniline or Ts), 7.37 (d, 2 H, *J* = 8 Hz, aniline or Ts), 7.72 (d, 2 H, *J* = 8 Hz, aniline or Ts), 7.82 (d, 2 H, *J* = 8 Hz, aniline or Ts) ppm; ^{13}C-NMR: δ 17.2 (CH$_3$), 17.3 (CH$_3$), 21.5 (CH$_2$NTs), 21.6 (CH$_3$, Ts), 43.2 (CH$_2$NTs), 48.0 (2 × OCH$_3$), 67.1 (CH), 67.2 (CH), 68.7 (CH$_2$O), 98.9 (acetal-C), 99.0 (acetal-C), 127.0 (CH, aniline or Ts), 128.0 (CH, aniline or Ts), 129.8 (CH, aniline or Ts), 129.9 (CH, aniline or Ts), 132.6 (Cq, aniline or Ts), 136.5 (Cq, aniline or Ts), 143.6 (Cq, aniline or Ts), 145.0 (Cq, aniline or Ts) ppm; IR (KBr): $\tilde{v}$ 3368, 3031, 3009, 3000, 2951, 2930, 2837, 1599, 1495, 1456, 1414, 1402, 1375, 1337, 1307, 1291, 1212, 1190, 1177, 1162, 1137, 1095, 1036, 980, 930, 866, 815, 774, 662, 585, 553 cm^{-1}; MS (EI) m/z (%): 482 (0.16), 481 (0.45), 480 (2.66), 294 (9), 224 (22), 223 (84), 155 (97), 101 (12), 92 (17), 91 (100), 68 (74), 65 (23); Anal. Calcd for C$_{24}$H$_{33}$NO$_9$S$_2$ (543.65): C 53.02, H 6.12, N 2.58; found C 53.34, H 2.45, N 6.15.

(2R,3R,5S,6S)-5,6-Dimethoxy-5,6-dimethyl-3-(N-phenylamino)methyl[1,4]dioxan-2-ylmethyl p-toluene sulfonate (**19**).

Tosyl derivative **18** (0.207 g, 0.368 mmol) was dissolved in toluene (0.76 mL) and sodium bicarbonate (0.066 g, 0.786 mmol) was added. To the resulting suspension aniline (0.17 mL, 1.87 mmol) was added, and the mixture was left stirring at 80 °C for 48 h. More toluene (0.4 mL) was added and also aniline (0.17 mL, 1.87 mmol) and the mixture was stirred at 80 °C another 24 h. The reaction mixture was then cooled to room temperature, filtered, and dried. The product (0.161 g, 94

%) was obtained after chromatography on silica gel (2:3 EtOAc-hexane), m.p. 174-175 ºC (EtOAc / hexane); $[\alpha]^{29}_D$ = –113.7 (*c* 2.01, CHCl$_3$); ^{1}H-NMR: δ 1.17 (s, 3 H, CH$_3$), 1.21 (s, 3 H, CH$_3$), 2.35 (s, 3 H, CH$_3$ of Ts), 2.88–3.02 (m, partially overlapped, 1 H, C*H*HNHSO$_2$), 2.97 (s, 3 H, OCH$_3$), 3.08 (s, 3 H, OCH$_3$), 3.00–3.18 (m, partially overlapped, 3 H, CH*H*NHSO$_2$ + 2 × H of CH$_2$NHPh), 3.68–4.00 (m, 2 H, 2 × CH), 4.94 (t, 1 H, NHSO$_2$), 6.64 (d, 2 H, *J* = 7.6 Hz, aniline), 6.71 (t, 1 H, *J* = 7.2 Hz, *p*-H, aniline), 7.13 (t, 2 H, *J* = 7.2 Hz, aniline), 7.22 (d, *J* = 7.6 Hz, 2 H, Ts), 7.65 (d, *J* = 7.6 Hz, 2 H, Ts); ^{13}C-NMR: δ 17.3 (CH$_3$), 17.4 (CH$_3$), 21.4 (CH$_3$ of Ts), 43.6 (CH$_2$NHSO$_2$), 44.5 (CH$_2$NHPh), 47.9 (OCH$_3$), 48.1 (OCH$_3$), 67.2 (CH), 68.2 (CH), 98.85 (acetal-C), 98.91 (acetal-C), 113.7 (2 × CH, aniline), 118.3 (*p*-CH, aniline), 127.0 (2 × CH, Ts), 129.2 (2 × CH, aniline), 129.8 (2 × CH, Ts), 136.6 (Cq, Ts), 143.6 (CqSO$_2$N), 147.4 (Cq, aniline) ppm; IR (KBr): $\tilde{v}$ 3369, 3060, 3016, 2990, 2947, 2904, 2876, 2852, 1605, 1505, 1463, 1393, 1378, 1335, 1260, 1253, 1237, 1208, 1184, 1164, 1135, 1076, 1050, 1034, 993, 951, 855, 816, 763, 697, 666, 655 cm^{-1}; MS (EI) m/z (%): 466 (M$^+$ + 2, 1), 465 (M$^+$ + 1, 4), 464 (M$^+$, 24), 401 (18), 223 (12), 188 (17), 187 (27), 155 (41), 145 (47), 132 (28), 116 (24), 106 (100), 101 (20), 93 (18), 91 (65), 73 (11); Anal. Calcd for C$_{23}$H$_{32}$N$_2$O$_6$S (414.46): C 59.46, H 6.94, N 6.03; found C 59.19, H 6.96, N 5.75.

(2R,3R,5S,6S)-2,3-Dimethoxy-2,3-dimethyl-6-(toluene-4-sulfonyl)-hexahydro-[1,4]dioxino[2,3-c]-pyrrole (**20**).

Tosylate **18** (0.061 g, 0.112 mmol) dissolved in dimethylformamide (0.15 mL) was added to sodium thiophenolate (0.045 g, 0.341 mmol) dissolved in H$_2$O (0.15 mL), producing an exothermic reaction. The mixture was refluxed for 16 h. It was then cooled to room temperature and ether and water were added. The layers were separated, and the aqueous phase was extracted three times more with ether. Removal of the solvent gave a crude product which was chromatographed on silica gel (4:0.2 hexane-EtOAc). Colourless crystals were obtained mp?; ^{1}H-NMR: δ 1.21 (s, 6 H, 2 × CH$_3$), 2.37 (s, 3 H, CH$_3$ of Ts), 3.02 (t, 2 H, *J* = 9.2 Hz), 3.13 (s, 3 H, 2 × OCH$_3$), 3.51 (t, 2 H, *J* = 6.8 Hz), 3.73 (t, 2 H, *J* = 6.0 Hz), 7.27 (d, 2 H, *J* = 8.0 Hz, Ts), 7.64 (d, 2 H, *J* = 8.0 Hz, Ts); MS (EI) m/z (%): 279 (0.74), 214 (39), 202 (11), 155 (70), 149 (11), 102 (32), 92 (9), 91 (100), 84 (11), 65 (20).

(2R,3R,5R,6R)-5,6-Dimethoxy-5,6-dimethyl-3-(phenylthio)methyl[1,4]dioxan-2-ylmethyl p-toluene sulfonamide (**21**).

Tosylate **18** (0.082 g, 0.151 mmol) was dissolved in toluene (0.17 mL) and thiophenol (0.020 mL, 0.195 mmol) was added. The components were mixed well. DBU (0.020 mL, 0.134 mmol) was added. The resulting solution was stirred under argon, at room temperature, overnight. Volatiles were then removed on a rotary evaporator and the remaining residue was chromatographed on silica gel plates (3:1 hexane-EtOAc) to give the product as colourless hygroscopic crystals (0.062 g, 85 %), m.p. 58-59 °C (hexane-EtOAc); $[\alpha]^{26}_D$ = –132.4 (*c* 0.79, CHCl$_3$); ^{1}H-NMR: δ 1.15 (s, 3 H, CH$_3$), 1.18 (s, 3 H, CH$_3$), 2.36 (s, 3 H, CH$_3$ of Ts), 2.79–2.86 (m, 1 H, CH$_2$N), 2.90–2.96 (m, 2 H, CH$_2$S), 3.08 (s, 3 H, OCH$_3$), 3.11 (s, 3 H, OCH$_3$), 3.03–3.19 (m, partially overlapped, 1 H, CH$_2$N), 3.63–3.71 (m, 2 H, 2 × CH), 4.84 (t, 1 H, NHSO$_2$), 7.11 (t, 1 H, *p*-H, SPh), 7.10–7.29 (m, 6 H, 4 × CH, SPh + 2 × CH, Ts), 7.65 (d, 2 H, *J* = 8.4 Hz, 2 × CH, Ts) ppm; ^{13}C-NMR: δ 17.3 (CH$_3$), 17.4 (CH$_3$), 21.5 (CH$_3$ of Ts), 35.0

(CH$_2$S), 43.7 (CH$_2$N), 48.0 (OCH$_3$), 48.1 (OCH$_3$), 68.3 (CH), 69.9 (CH), 98.9 (acetal-C), 99.1 (acetal-C), 126.3 (CH, SPh), 127.1 (2 × CH, Ts), 128.9 (2 × CH, SPh), 129.5 (2 × CH, SPh), 129.8 (2 × CH, Ts), 136.1 (Cq, SPh or Ts), 136.6 (Cq, SPh or Ts), 143.6 (C$_q$SO$_2$N) ppm; IR (CHCl$_3$): $\tilde{v}$ 3359, 3029, 3007, 2951, 2030, 2836, 1599, 1481, 1459, 1439, 1413, 1379, 1335, 1214, 1162, 1141, 1131, 1093, 1049, 1036, 1004, 961, 892, 856, 814, 778, 761, 748, 740, 691, 663, 552 cm^{-1}; MS (EI) m/z (%): 481 (M$^+$, 0.22), 333 (10), 294 (10), 224 (54), 223 (49), 184 (10), 162 (82), 155 (97), 123 (22), 110 (11), 109 (17), 101 (11), 91 (100), 68 (14), 65 (13); Anal. Calcd for C$_{23}$H$_{31}$NO$_6$S$_2$ (481.62): C 57.36, H 6.49, N 2.91; found C 57.05, H 6.50, N 2.62.

(2R,3R,5S,6S)-3-Chloromethyl-5,6-dimethoxy-5,6-dimethyl[1,4]-dioxan-2-ylmethyl-p-toluene sulfonate (**22**).

   Monochloride **15** (0.541 g, 2.13 mmol) was dissolved in chloroform (2.18 mL) and pyridine was added (0.35 mL, 4.33 mmol). The solution was cooled to 0 °C, and p-tosyl chloride (0.623 g, 3.27 mmol) was added in portions. The mixture was then stirred for 2 h at 0 °C (ice bath), and then it was poured into a 1:1 ether / water mixture. Afterwards it was washed successively with 2 M HCl, a saturated solution of NaHCO$_3$, and H$_2$O. The solvent was removed under reduced pressure to give a white solid, which was purified by column chromatography on silica gel (1.5:8.5 EtOAc-hexane, adsorption from CHCl$_3$). Colourless crystals were obtained (0.626 g, 72 %), m.p. 74-75 °C (EtOAc-hexane); [α]^{16}$_D$ = –20.5 (c 2.01, CHCl$_3$); ^{1}H-NMR: δ 1.21 (s, 3 H, CH$_3$), 1.28 (s, 3 H, CH$_3$), 2.46 (s, 3 H, CH$_3$ of Ts), 3.18 (s, 3 H, OCH$_3$), 3.24 (s, 3 H, OCH$_3$), 3.49–3.57 (m, 2 H, CH$_2$Cl), 3.83–3.90 (m, 2 H, 2 × CH), 4.02–4.06 (m, 2 H, CH$_2$OSO$_2$), 7.36 (d, 2 H, J = 8.0 Hz, Ts), 7.81 (d, 2 H, J = 8.0 Hz, Ts) ppm. ^{13}C-NMR: δ 17.2 (CH$_3$), 17.3 (CH$_3$), 21.6 (CH$_3$ of Ts), 43.2 (CH$_2$Cl), 48.0 (2 × OCH$_3$), 67.8 (CH), 68.8 (CH), 68.9 (CH$_2$OSO$_2$), 99.1 (acetal-C), 99.2 (acetal-C), 128.0 (2 × CH, Ts), 129.9 (2 × CH, Ts), 132.7 (Cq – CH$_3$), 145.0 (Cq – SO$_2$–O) ppm. IR (KBr): $\tilde{v}$ 3019, 2993, 2951, 2909, 2838, 1597, 1455, 1370, 1353, 1190, 1170, 1127, 1097, 1037, 982, 931, 881, 859, 847, 819, 704, 680, 665, 619, 573, 556, 535, 504, 463 cm^{-1}; MS (EI) m/z (%): 380 (0.13), 379 (M$^+$ + 2 – OMe, 0.97), 225 (17), 155 (100), 91 (45), 88 (18), 73 (10); Anal. Calcd for C$_{17}$H$_{25}$ClO$_7$S (408.89): C 49.94, H 6.16, S 7.84; found C 50.23, H 6.15, S 7.47.

(2R,3R,5R,6R)-2-(5,6-Dimethoxy-5,6-dimethyl-3-chloro[1,4]dioxan-2-ylmethylthio)-4,5-dihydro-thiazole (**23**).

   Monotosylate **22** (0.330 g, 0.807 mmol) and 2-mercapto-2-thiazoline (0.100 g, 0.839 mmol) were dissolved in dry tetrahydrofuran. Triethylamine (0.220 mL, 1.58 mmol) was added, and the solution was refluxed for 20 h. After cooling to room temperature, the volatiles were removed on a rotary evaporator. The product was isolated by chromatography on silica gel (1:3 hexane-EtOAc). 0.172 g (60 % yield) of a clear colourless liquid were obtained, [α]^{26}$_D$ = –123.3 (c 1.00, CHCl$_3$); ^{1}H-NMR: δ 1.23 (s, 3 H, CH$_3$), 1.25 (s, 3 H, CH$_3$), 3.01 (dd, 1 H, J = 8.6, 13.6 Hz, CH$_2$S), 3.19 (s, 3 H, OCH$_3$), 3.22 (s, 3 H, OCH$_3$), 3.33 (t, J = 8.0 Hz, 2 H, SCH$_2$ of thiazoline), 3.43 (dd, 1 H, J = 2.9, 13.6 Hz, CH$_2$S), 3.45 (dd, 1 H, J = 7.2, 11.9 Hz, CH$_2$Cl), 3.65 (dd, 1 H, J = 2.8, 12.0 Hz, CH$_2$Cl), 3.74 (td, 1 H, J = 2.8, 7.2 Hz, CH), 3.83 (td, 1 H, J = 2.9, 8.7 Hz, CH), 4.11 (td, 3 H, J = 3.0, 8.0 Hz, NCH$_2$ of

thiazoline) ppm; ^{13}C-NMR: δ 17.3 (CH$_3$), 33.5 (CH$_2$S), 35.7 (SCH$_2$), 43.7 (CH$_2$Cl), 47.95 (OCH$_3$), 47.98 (OCH$_3$), 63.8 (CH$_2$N), 68.8 (CH), 71.4 (CH), 99.0 (2 × acetal-C), 165.2 (C=N) ppm; IR (KBr): $\tilde{v}$ 3031, 3010, 2953, 2909, 2837, 1599, 1456, 1433, 1211, 1190, 1177, 1141, 1122, 1097, 1036, 985, 925, 859, 815, 780, 758, 744, 663, 555 cm^{-1}; MS (EI) m/z (%): 324 (36), 292 (13), 224 (16), 206 (9.8), 208 (3.4), 174 (27), 173 (64), 172 (100), 170 (12), 119 (14), 116 (11), 101 (44), 91 (18), 89 (17), 85 (48), 83 (67), 75 (69), 73 (48), 72 (10), 60 (22), 59 (17), 53 (24); Anal. Calcd for C$_{13}$H$_{22}$ClNO$_4$S$_2$ (355.90): C 43.87, H 6.23, N 3.94, S 18.02; found C 44.14, H 6.02, N 3.75, S 17.84.

(2R,3R,5R,6R)-2-(5,6-Dimethoxy-5,6-dimethyl-3-phenylthiomethyl[1,4]dioxan-2-ylmethylthio)-4,5-dihydrothiazole (**24**).

Monochloride **23** (0.045 g, 0.126 mmol) was dissolved in dry toluene (0.26 mL); thiophenol (0.030 mL, 0.292 mmol) was added and the mixture was well stirred; finally 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.030 mL, 0.201 mmol) was added. The solution was then stirred at room temperature for 22 h. The solvent was evaporated off, and the product was isolated by chromatography on silica gel (1:9 EtOAc-CH$_2$Cl$_2$). Colourless hygroscopic crystals were obtained (0.048 g, 88 %), m.p. 58–59 °C (EtOAc-CH$_2$Cl$_2$); [α]^{27}$_D$ = –179.7 (c 0.61, CHCl$_3$); ^{1}H-NMR: δ 1.21 (s, 6 H, 2 × CH$_3$), 2.94–3.01 (m, 2 H, C*H*HSPh + C*H*HS-thiazoline), 3.12 (s, 3 H, OCH$_3$), 3.14 (dd, 1 H, J = 3.6, 13.6 Hz, CH$_2$S), 3.20 (s, 3 H, OCH$_3$), 3.32 (t, 2 H, J = 8.0 Hz, SCH$_2$ of thiazoline), 3.55 (dd, 1 H, J = 2.0, 13.6 Hz), 3.71 (td, 1 H, J = 3.6, 9.6 Hz, CH), 3.82 (td, 1 H, J = 2.8, 9.2 Hz, CH), 4.10 (t, 2 H, J = 8.0 Hz, NCH$_2$), 7.10 (t, 1 H, J = 7.2 Hz, Ph), 7.20 (t, 2 H, J = 7.6 Hz, Ph), 7.32 (d, 2 H, J = 7.6 Hz, Ph) ppm; ^{13}C-NMR: δ 17.4 (2 × CH$_3$), 34.1 (CH$_2$), 35.3 (CH$_2$), 35.4 (CH$_2$ of thiazoline), 48.0 (OCH$_3$), 48.1 (OCH$_3$), 63.1 (NCH$_2$ of thiazoline), 70.4 (CH), 70.5 (CH), 99.1 (2 × acetal-C), 126.1 (p-CH, Ph), 128.9 (2 × CH, Ph), 129.6 (2 × CH, Ph), 136.4 (i-C, Ph), 167.6 (SC=N) ppm; IR (CHCl$_3$): $\tilde{v}$ 3077, 3062, 3007, 2951, 2854, 2836, 1569, 1481, 1460, 1439, 1378, 1306, 1234, 1212, 1161, 1138, 1122, 1091, 1036, 1018, 997, 968, 943, 922, 890, 857, 776, 764, 754, 738, 692, 665, 647, 565, 535 cm^{-1}; MS(EI) m/z (%): 431 (M$^+$ + 2, 0.21), 430 (M$^+$ + 1, 0.32), 429 (M$^+$, 2.8), 172 (100), 162 (20), 110 (9), 101 (13), 85 (14); Anal. Calcd for C$_{19}$H$_{27}$NO$_4$S$_3$.H$_2$O (438.62): C 52.03, H 6.44, N 3.19; found C 51.99, H 6.34, N 3.47.

Catalysis

u- and l-2-(1-Phenyl-2-nitroethyl)cyclohexanone (**u-** and **l-25**).

trans-β-Nitrostyrene (0.046 g, 0.308 mmol) and diamine **12** (0.012 g, 0.046 mmol) were dissolved in dry CHCl$_3$ (2.5 ml) and cyclohexanone (0.6 ml, 6.11 mmol) was added. Finally, *p*-toluenesulfonic acid monohydrate (0.008 g, 0.042 mmol) was added, and the resulting solution was stirred at room temperature, under argon, for 6 days. The reaction was quenched with HCl (1 M), water was added, and the product was extracted with dichloromethane, and filtered through anhydrous sodium sulfate. The volatiles were evaporated off on a rotary evaporator. The ratio of diastereoisomeric products, based on integral ratios in the ^{1}H-NMR spectrum of the crude product was **u-25:l-25** = 92:8. The major diastereoisomer was isolated by preparative TLC (1:4 Et$_2$O-pentane) as a white solid (0.049 g, 64 %). It was assigned the (2*S*,1'*R*) configuration, based on literature ^{1}H-NMR data [7a] and its optical

rotation sign. The enantiomeric excess was determined by optical rotation to be 30 %, relative to the literature value [24]: (2*S*,1'*R*)-**25**: $[\alpha]^{20}_D = -8.22$ (*c* 1.01, CHCl$_3$), lit. $[\alpha]^{rt}_D = -28.0$ (CHCl$_3$); ^{1}H-NMR: δ 1.18–1.28 (m, 1 H), 1.51–1.80 (m, 4 H), 2.05–2.10 (m, 1 H), 2.34–2.49 (m, 2 H), 2.69 (td, 1 H, *J* = 11.6 Hz, CHCO), 3.76 (td, 1 H, *J* = 4.4, 10.0 Hz, C*H*Ph), 4.63 (dd, *J* = 9.6, 12.0 Hz, 1 H, C*H*HNO$_2$), 4.94 (dd, 1 H, *J* = 4.4, 12.4 Hz, CH*H*NO$_2$), 7.16–7.33 (m, 5 H, Ph) ppm; l-**25**: ^{1}H-NMR: δ 3.99–4.04 (m, CHPh), 4.80–5.03 (m, partially overlapped, CH$_2$NO$_2$).

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Sample availability: A sample of ditosylated bisamine **6** is available from MDPI.