Stereoselective Transacetalization of 1,1,3,3-Tetramethoxypropane and *N*-Benzoylaminodiols

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The transacetalization of 1,1,3,3-tetramethoxypropane and an *N*-benzoylaminodiol provided stereoselectively the corresponding 2,5-disubstituted-1,3-dioxanes. The stereochemistry of the rings formed in the transacetalization depended on the structure of the amino diol, and the ratio of the products depended on the reaction conditions, as expected. This kind of stereoselective transacetalization not only gives a series of useful building blocks but also generates interesting 1,3-dioxanes which target protein kinase C.

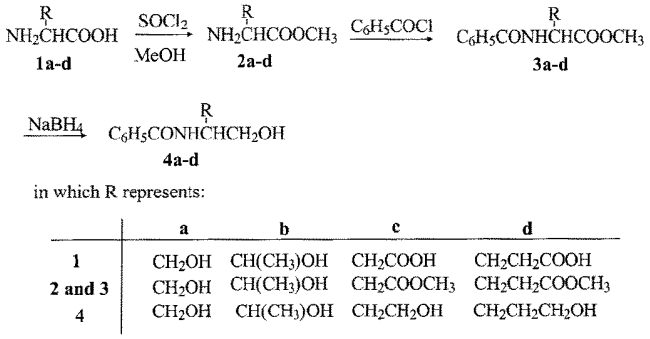
Introduction

In our previous work we demonstrated that the selective hydrolysis or transacetalization of 1,1,3,3-tetramethoxypropane and its analogues proved to be very general techniques by which a series of substituted-1,3-dioxanes was formed. The results also showed that the stereoselectivity of the transacetalization may be worth further investigation.[1] It was noticed that substituted-1,3-dioxane derivatives may be useful for the inhibition of protein kinase C and treatment of conditions related to or affected by inhibition of protein kinase C, particularly cancer tumors, inflammatory disease, reperfusion injury, and cardiac dysfunction related to reperfusion injury.[2] On the basis of the importance of substituted-1,3-dioxanes and their related stereochemistry, we report in this paper the stereoselective transacetalization of 1,1,3,3-tetramethoxypropane and amino diols as well as other related stereoselective reactions.

Results and Discussion

In the presence of thionyl chloride and methanol, L-amino acids were converted into the corresponding methyl esters **2**. The esters **2** were acylated with benzoyl chloride to afford the *N*-benzoyl-L-amino acid methyl esters. With sodium borohydride as the reducing agent compounds of type **3** were smoothly reduced to the desired *N*-benzoylaminodiols **4**, in which **4b**−**4d** are enantiomerically pure (Scheme 1).

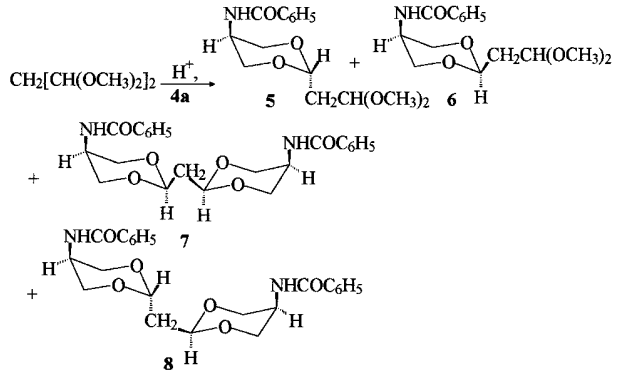
With hydrochloric acid as the catalyst, 1,1,3,3-tetramethoxypropane was treated with the aminodiols **4** to give the corresponding substituted 1,3-dioxane derivatives. In the reaction of 1,1,3,3-tetramethoxypropane and **4a** two pairs of isomers **5/6** and **7/8** were obtained. On the basis of NOE experiments **5** was assigned as *trans*-monocyclic, **6** as *cis*-monocyclic, **7** as *cis*-*cis*-dicyclic and **8** as *trans*-*cis*-dicyclic. *cis*-Monocyclic **6** and *trans*-*cis*-dicyclic **8** were the main



	a	b	c	d
1	CH_2OH	$CH(CH_3)OH$	CH_2COOH	CH_2CH_2COOH
2 and 3	CH_2OH	$CH(CH_3)OH$	CH_2COOCH_3	$CH_2CH_2COOCH_3$
4	CH_2OH	$CH(CH_3)OH$	CH_2CH_2OH	$CH_2CH_2CH_2OH$

Scheme 1. Preparation of *N*-benzoylamino-diols from L-amino acids by esterification (98%), amidation (81%), and reduction (97%)

products. At 40 °C with concentrated hydrochloric acid as the catalyst the ratio of **5**:**6**:**7**:**8** was 1.9:6.3:1.0:3.3 (Scheme 2, Table 1).



Scheme 2. The transacetalization of 1,1,3,3-tetramethoxypropane and **4a** provided two pairs of isomers **5/6** and **7/8** with *cis*-monocyclic compound **6** and *trans*-*cis*-dicyclic compound **8** as the main products

The data in Table 1 show that with concentrated hydrochloric acid as the catalyst at 80 °C, none of the desired products were obtained owing to degradation; at 60 °C the dicyclic compounds were the predominant products, and at 20 °C the monocyclic compounds were the major products; Among the catalysts used only trifluoroacetic acid (TFA)

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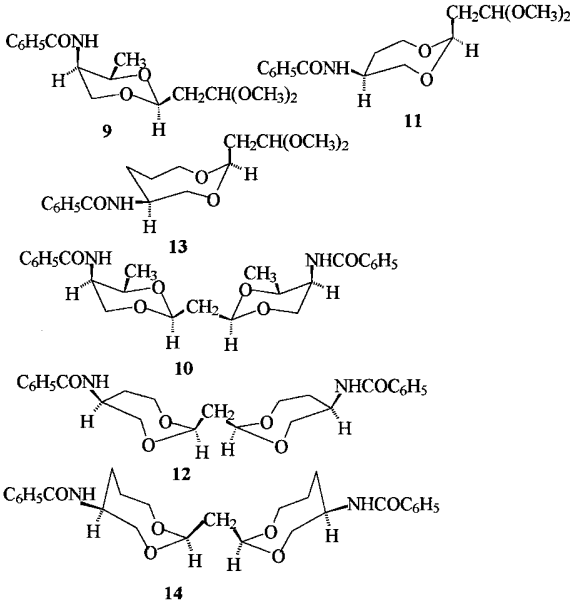
Table 1. Effect of reaction conditions on the mol ratio of the products from **4a**,**b**

Temp. (°C)	Time (h)	Cat.	Mol ratio of the products from **4a** and **4b**
80	2	HCl	**5** (0.0) **6** (0.0) **7** (0.0) **8** (0.0) **9** (0.0) **10** (0.0)
60	8	HCl	**5** (1.0) **6** (2.6) **7** (2.2) **8** (6.6) **9** (1.0) **10** (1.4)
40	12	HCl	**5** (1.9) **6** (6.3) **7** (1.0) **8** (3.3) **9** (1.3) **10** (1.0)
20	24	HCl	**5** (5.2) **6** (8.6) **7** (1.0) **8** (2.3) **9** (3.1) **10** (1.0)
40	12	TsOH	**5** (2.5) **6** (9.7) **7** (1.0) **8** (2.5) **9** (1.2) **10** (1.0)
40	24	H_3PO_4	**5** (1.4) **6** (4.4) **7** (1.0) **8** (2.6) **9** (1.1) **10** (1.0)
40	36	TFA	**5** (1.0) **6** (2.4) **7** (2.6) **8** (8.3) **9** (1.0) **10** (3.0)
40	8	H_2SO_4	**5** (2.9) **6** (4.2) **7** (1.0) **8** (1.8) **9** (1.7) **10** (1.0)
40	12	PPTS	**5** (1.6) **6** (4.4) **7** (1.0) **8** (2.7) **9** (2.3) **10** (1.0)

favored formation of dicyclic products, all the other catalysts favored monocyclic formation. In particular, with concentrated hydrochloric acid as the catalyst at 20 °C, the molar ratio of monocyclic and dicyclic products reached 4.0:1.0. These results enable us to control the reaction selectivity by changing the experimental conditions.

Under the same reaction conditions as mentioned in Scheme 2 the reaction of 1,1,3,3-tetramethoxypropane and **4b**, **4c,** or **4d** provided in each case only two products, one was the monocyclic acetal and the other was the dicyclic acetal (Scheme 3).



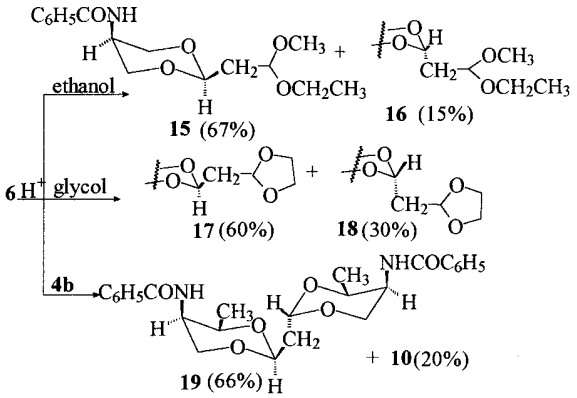
Scheme 3. Mono- and bicyclic products from the transacetalization of **4b** (**9**/**10**), **4c** (**11**/**12**), and **4d** (**13**/**14**); the configurations come from NMR-spectroscopic data the conformations from ad hoc assignments

The transacetalization of 1,1,3,3-tetramethoxypropane and **4a** was highly stereoselective, the *cis*-monocyclic compound **6** and *trans*-*cis*-dicyclic compound **8** were always the favored products. The transacetalization of 1,1,3,3-tetramethoxypropane and **4b** resulted only in the *cis*-monocyclic compound **9** and the *cis*-*cis*-dicyclic compound **10** also showing stereospecificity. It has been suggested that in 5-alkyl-substituted 1,3-dioxanes, the 5-substituent has a much smaller preference for the equatorial position than in cyclohexane derivatives.[3] With certain non-alkyl substituents (e.g. F, NO_2, $SOCH_3$, and NMe_3, etc.) the axial position is actually preferred.[4] In the chair conformation of both **5** and **6** the 5-*N*-benzoylamino group takes the axial position − the former has 2,5-diaxial substituents and the latter has 2-equatorial-5-axial substituents. The higher thermodynamic stability of **6** may be responsible for its preferential formation in the transacetalization. Establishment of the relationships between the monocyclic and dicyclic products in the transacetalization of 1,1,3,3-tetramethoxypropane and **4a**, led to treatment of **5** and **6** with **4a**. In the presence of concentrated hydrochloric acid at 20 °C, **5** was only converted into **8** and **6** was only converted into **7**. From these stereospecific conversions and the configurations of **9** and **10** we concluded that, in spite of the stereochemistry of the ring in monocyclic *N*-[2-(2,2-dimethoxyethyl)-1,3-dioxan-5-yl]benzamides, the newly formed ring in the dicyclic products always has a 2,5-*cis*-configuration, and the second transacetalization must be stereospecific.

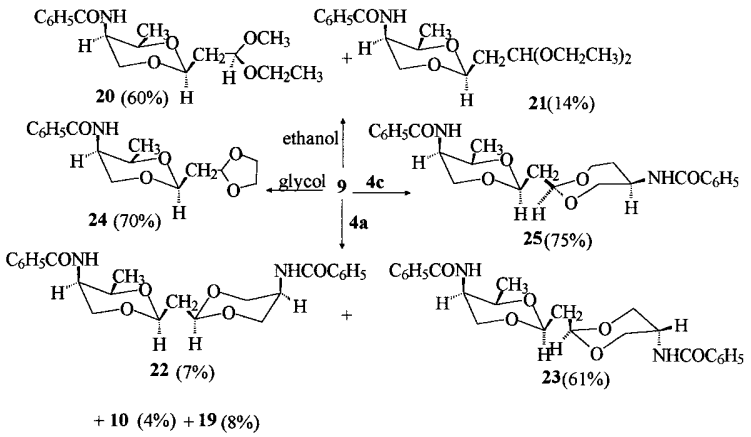
With the monocyclics **6**, **9** and alcohols as the starting materials a series of further transacetalizations was investigated. The results are summarized in Table 2, Scheme 4, and Scheme 5 (see yields in brackets). It was noticed that in the transacetalizations of **6** some kinetically controlled products **16**, **18**, and **19** were also formed. At 20 °C with concentrated hydrochloric acid as the catalyst, **8** can be converted into **7**, **16** can be converted into **15**, **19** can be converted into **10**, **18** can be converted into **17**, and **23** can be converted into **22**. With these conversions **8**, **16**, **19**, **18,** and **23** were confirmed to be the kinetically controlled products,

Table 2. Products and yields in the transacetalization of **6** and **9**

Acetal	Alcohol	Catalyst	Temp (°C)	Time (h)	Products (yield %)
6	C_2H_5OH	HCl	20	10	**15** (67), **16** (15)
6	**4b**	HCl	20	10	**10** (20), **19** (66)
6	glycol	HCl	20	10	**17** (60), **18** (30)
9	glycol	HCl	65	2	**24** (70)
9	**4c**	TsOH	50	12	**25** (74)
9	C_2H_5OH	HCl	20	24	**20** (60), **21** (14)
9	**4a**	HCl	20	24	**22** (7), **23** (61), **10** (4), **19** (8)



Scheme 4. Products obtained from the reaction of **6** with ethanol, glycol, and **4b** at 20 °C with conc. HCl as catalyst



Scheme 5. Products obtained from the reaction of **9** with ethanol, glycol, **4a**, and **4c**

and **7**, **15**, **10**, **17**, and **22** to be the thermodynamically stable products.

Experimental Section

All reactions were carried out under nitrogen (1 bar). ^{1}H NMR spectra were recorded at 300 MHz on a VXR-300 instrument or at 500 MHz on an ARX-500 instrument in $CDCl_3$ with tetramethylsilane as internal standard. − IR spectra were recorded with a Perkin-Elmer 983 instrument and mass spectra with a ZAB-MS (70 eV) spectrometer. Chromatography was performed with Qingdao silica gel H. Optical rotations were determined on a Schmidt and Haensch Polartronic D instrument at 20 °C.

General Procedure for *N*-Benzoylaminodiols 4a−d: L-Ser, L-Thr, L-Asp, or L-Glu were esterified to **2a−d** by methanol[5] in 98% yield and benzoylated to **3a−d** by benzoyl chloride[6] in 81% yield.

A solution of **3a−d** (4.5 mmol) in THF (10 mL) was slowly added to a suspension of sodium borohydride (5.6 mmol) in THF (10 mL). The reaction mixture was stirred at room temperature for 24 h until TLC ($CHCl_3$/CH_3OH, 30:1) indicated complete disappearance of **3a−d**. The reaction mixture was adjusted to pH 7 with hydrochloric acid (3%). After evaporation, the residue was dissolved in 50 mL of chloroform and washed with water (3 × 30 mL). The chloroform phase was dried with Na_2SO_4. After filtration and evaporation **4a−d** were obtained as colorless crystals in 97% yield.

***N*-[2-Hydroxy-1-(hydroxymethyl)ethyl]benzamide (4a):** M.p. 69−70 °C. − IR (KBr): $\tilde{\nu}$ = 3450 cm^{-1} (OH), 3340 (NH), 3030 (aromatic C=CH), 3000, 2960 and 2830 (CH and CH_2), 1635 (C=O), 1600, 1570, 1501 and 1450 (aromatic C=C), 720 and 660 (monosubstituted phenyl). − ^{1}H NMR ([D$_6$]DMSO): δ = 3.51 (d, *J* = 5.7 Hz, 4 H, *CH*$_2$OH), 3.97 (m, *J* = 6.0 Hz, 1 H, NH*CH*CH$_2$OH), 4.66 (broad, 2 H, *OH*), 7.45 (t, *J* = 7.2 Hz, 2 H, aromatic H), 7.52 (t, *J* = 7.2 Hz, 1 H, aromatic H), 7.86 (d, *J* = 8.1 Hz, 2 H, aromatic H), 7.97 (d, *J* = 7.5 Hz, 1 H, *NH*). − FAB-MS: *m*/*z* (%) = 196 [M + H]$^+$. − $C_{10}H_{13}NO_3$ (195.1): calcd. C 61.53, H 6.71, N 7.17; found C 61.57, H 6.75, N 7.20.

(1*S*,2*R*)-*N*-[2-Hydroxy-1-(hydroxymethyl)propyl]benzamide (4b): M.p. 75−77 °C. − IR (KBr): $\tilde{\nu}$ = 3455 cm^{-1} (OH), 3360 (NH), 3035 (aromatic C=CH), 3005, 2968 and 2860 (CH CH$_2$ and CH_3), 1645 (C=O), 1609, 1590, 1500 and 1480 (aromatic C=C), 715 and 650 (monosubstituted phenyl). − ^{1}H NMR([D$_6$]DMSO): δ = 1.20 (d, *J* = 6.9 Hz, 3 H, *CH*$_3$), 3.51 (s, 2 H, OH), 3.83 (d, *J* = 6.4 Hz, 2 H, *CH*$_2$OH), 3.98 (m, *J* = 6.3 Hz, 1 H,CH$_3$*CH*OH), 4.22 (q, *J* = 6.0 Hz, 1 H, NH*CH*), 7.06 (d, *J* = 8.1 Hz, 1 H,*NH*), 7.36 (t, *J* = 7.5 Hz, 2 H, aromatic H), 7.47 (t, *J* = 7.4 Hz,1 H, aromatic H), 7.76 (d, *J* = 8.1 Hz, 2 H, aromatic H). − FAB-MS: *m*/*z* (%) = 210 [M + H]$^+$. − $[\alpha]_D^{20}$ = −30.0 (*c* = 0.02, in MeOH). − $C_{11}H_{15}NO_3$ (209.3): calcd. C 63.13, H 7.23, N 6.70; found C 63.16, H 7.25, N 6.74.

(1*S*)-*N*-[3-Hydroxy-1-(hydroxymethyl)propyl]benzamide (4c): M.p. 80−81 °C. − IR (KBr): $\tilde{\nu}$ = 3416 cm^{-1} (OH), 3350 (NH), 3021 (aromatic C=CH), 3001, 2960 and 2835 (CH and CH_2), 1636 (C=O), 1605, 1587, 1504 and 1460 (aromatic C=C), 718 and 653 (monosubstituted phenyl). − ^{1}H NMR ([D$_6$]DMSO): δ = 1.63 (dt, *J* = 5.4 Hz, *J* = 3.3 Hz, 1 H, NHCH*CH*$_2$CH$_2$OH), 1.78 (dt, *J* = 4.5 Hz, *J* = 2.7 Hz, 1 H, NHCH*CH*$_2$CH$_2$OH), 3.42 (t, *J* = 3.3 Hz, 1 H, NHCH*CH*$_2$CH$_2$OH), 3.47 (t, *J* = 3.9 Hz, 1 H, NHCH*CH*$_2$CH$_2$OH), 3.49 (s, 2 H, OH), 4.04 (dq, *J* = 3.0 Hz, *J* = 2.7 Hz, 1 H, NH*CH*CH$_2$CH$_2$OH), 4.46 (t, *J* = 3.3 Hz, 1 H, NHCH*CH*$_2$OH), 4.73 (t, *J* = 3.3 Hz, 1 H, NHCH*CH*$_2$OH), 7.45 (t, *J* = 4.5 Hz, 2 H, aromatic H), 7.52 (t, *J* = 4.2 Hz, 1 H, aromatic H), 7.85 (d, *J* = 4.5 Hz, 2 H, aromatic H), 8.08 (d, *J* = 5.1 Hz, 1 H, NH). − FAB-MS: *m*/*z* (%) = 210 [M + H]$^+$. − $[\alpha]_D^{20}$ = −26.0 (*c* = 0.02, in MeOH). − $C_{11}H_{15}NO_3$ (209.3): calcd. C 63.13, H 7.23, N 6.70; found C 63.25, H 7.35, N 6.53.

(1*S*)-*N*-[4-Hydroxy-1-(hydroxymethyl)butyl]benzamide (4d): M.p. 92−94 °C. − IR (KBr): $\tilde{\nu}$ = 3420 cm^{-1} (OH), 3348 (NH), 3035 (aromatic C=CH), 3000, 2954 and 2840 (CH and CH_2), 1635 (C=O), 1602, 1590, 1500 and 1440 (aromatic C=C), 720 and 660 (monosubstituted phenyl). − ^{1}H NMR ([D$_6$]DMSO): δ =1.42 (q, *J* = 3.3 Hz, 2 H, NHCH*CH*$_2$CH$_2$CH$_2$OH), 1.48 (m, *J* = 4.5 Hz, 1 H, NHCHCH$_2$*CH*$_2$CH$_2$OH), 1.66 (m, *J* = 4.5 Hz, 1 H, NHCHCH$_2$*CH*$_2$CH$_2$OH), 3.37 (t, *J* = 6.6 Hz, 1 H, NHCHCH$_2$*CH*$_2$OH), 3.39 (s, 2 H, OH), 3.45 (t, *J* = 6.6 Hz, 1 H, NHCHCH$_2$CH$_2$*CH*$_2$OH), 3.94 (dq, *J* = 3.0 Hz, *J* = 2.5 Hz, 1 H, NH*CH*CH$_2$CH$_2$CH$_2$OH), 4.39 (t, *J* = 3.0 Hz, 1 H, NHCH*CH*$_2$OH), 4.69 (t, *J* = 3.3 Hz, 1 H, NHCH*CH*$_2$OH), 7.45 (t, *J* = 4.5 Hz, 2 H, aromatic H), 7.51 (t, *J* = 4.2 Hz, 1 H, aromatic H), 8.04 (d, *J* = 4.8 Hz, 2 H, aromatic H). − FAB-MS: *m*/*z* (%) = 224 [M + H]$^+$. − $[\alpha]_D^{20}$ = −21.0 (*c* = 0.02, in MeOH). − $C_{12}H_{17}NO_3$ (223.3): calcd. C 64.54, H 7.68 N 6.28; found C 64.59, H 7.72, N 6.32.

Mixed Bisacetals 5, 6 and Homo-bisacetals 7, 8: a) A mixture of *N*-[2-hydroxy-1-(hydroxymethyl)ethyl]benzamide (**4a**) (100.0 mg , 0.51 mmol), 1,1,3,3-tetramethoxypropane (84.0 mg, 0.51 mmol),

concentrated hydrochloric acid (0.2 mL), and chloroform (15 mL) was stirred at 40 °C for 12 h. When TLC ($CHCl_3/CH_3OH$ 30:1) indicated complete disappearance of **4a,** the reaction mixture was cooled to room temperature and neutralized with sodium carbonate. After filtration and evaporation, the residue was separated by chromatography ($CHCl_3/CH_3OH$, 30:1) to give **6** (20.0 mg, 13.3%) as colorless crystals, **5** (65.0 mg, 43%), as colorless crystals, **8** (50.0 mg, 23.0%) as colorless crystals, and **7** (15.0 mg, 69%) as colorless crystals.

(*trans*)-*N*-[2-(2,2-Dimethoxyethyl)-1,3-dioxan-5-yl]benzamide (**5**): M.p. 112−114 °C. − IR (KBr): $\tilde{\nu}$ = 3289 cm^{-1} (NH), 3058 (aromatic C=CH), 2966 and 2929 and 2850 (CH, CH_2 and CH_3), 1635 (C=O), 1600, 1545, and 1458 (aromatic C=C), 1402, 1386 (CH_3), 1194 and 1084 (C−O−C), 701 and 680 (monosubstituted phenyl). − ^{1}H NMR ($CDCl_3$): δ = 1.99 [t, *J* = 3.9 Hz, 2 H, $CH_2CH(OCH_3)_2$], 3.35 (s, 6 H, OCH_3), 3.48 (d, *J* = 11.7 Hz, 4 H, OCH_2CHNH), 4.44 (m, *J* = 3.0 Hz, 1 H, OCH_2CHNH), 4.57 [t, 6 H, *J* = 7.8 Hz, 1 H, $CH_2CH(OCH_3)_2$], 4.59 (t, *J* = 7.8 Hz, 1 H,−$CH_2OCHOCH_2$-), 5.67 (d, *J* = 7.8 Hz, 1 H, NH), 7.43 (t, *J* = 9.1 Hz, 2 H, aromatic H), 7.53 (d, *J* = 9.1 Hz, 1 H, aromatic H), 7.73 (d, *J* = 9.1 Hz, 2 H, aromatic H). − FAB-MS: *m*/*z* (%) = 296 (5) $[M + H]^+$, 146 (100) − $[M\ C_6H_5CONHCH_3]^+$, 105 (66) $[C_6H_5CO^+]$. − $C_{15}H_{21}NO_5$ (295.3): calcd. C 61.00, H 7.17, N 4.74; found C 61.05, H 7.20, N 4.80.

(*cis*)-*N*-[2-(2,2-Dimethoxyethyl)-1,3-dioxan-5-yl]benzamide (6): M.p. 140−142 °C. − IR (KBr): $\tilde{\nu}$ = 3267 cm^{-1} (NH), 3057 (aromatic C=CH), 2922 and 2855 (CH, CH_2 and CH_3), 1622 (C=O), 1600, 1572, 1543 and 1448 (aromatic C=C), 1382, 1365 (CH_3), 1191 and1076 (C−O−C), 720 and 698 (monosubstituted phenyl). − ^{1}H NMR ($CDCl_3$): δ = 1.99 [t, *J* = 7.9 Hz, 2 H, $CH_2CH(OCH_3)_2$], 3.34 (s, 6 H, OCH_3), 4.04 (d, *J* = 12.6 Hz, 4 H, OCH_2CHNH), 4.10 (m, *J* = 9.5 Hz, 1 H, OCH_2CHNH), 4.57 [t, 1 H, *J* = 6.3 Hz, 1 H, $CH_2CH(OCH_3)_2$], 4.74 (t, *J* = 6.3 Hz, 1 H, $CH_2OCHOCH_2$), 7.06 (d, *J* = 9.5 Hz, 1 H, $-OCH_2CHNH$), 7.46 (t, *J* = 11.1 Hz, 2 H, aromatic H), 7.53 (t, *J* = 11.1 Hz, 1 H, aromatic H), 7.83 (d, *J* = 11.1 Hz, 2 H, aromatic H), in the NOESY experiment an NOE was observed between the *NH* at the 5-position and the CH_2 at the 2-position. − FAB-MS: *m*/*z* (%) = 296 (2) $[M + H]^+$, 146 (100) $[M - C_6H_5CONHCH_3]^+$, 105 (70) $[C_6H_5CO^+]$. − $C_{15}H_{21}NO_5$ (295.34): calcd. C 61.00, H 7.17, N 4.74; found C 61.02, H 7.19, N 4.70.

***N*,*N*′-Methylenebis[(*cis*)/(*cis*)-1,3-dioxan-2,5-diyl]bisbenzamide** (**7**): M.p. 274−276 °C. − IR (KBr): $\tilde{\nu}$ = 3275 cm^{-1} (NH), 3069 (aromatic C=CH), 2948 and 2840 (CH, CH_2), 1625 (C=O), 1607, 1583, 1536 and 1449 (aromatic C=C), 1186 and 1070 (C−O−C), 735 and 690 (monosubstituted phenyl). − ^{1}H NMR ([D_6]DMSO): δ = 1.926 [t, *J* = 4.7 Hz, 2 H, $CH_2CH(OCH_2)_2$], 3.77 (d, *J* = 7.9 Hz, 2 H, $CONHCH$), 3.86 (d, *J* = 14.2 Hz, 4 H, $NHCH(CH_2O)_2$, 4.01 [q, *J* = 14.2 Hz, 8 H, $NHCH(CH_2O)_2$], 4.76 [t, *J* = 6.3 Hz, 2 H, $CH(OCH_2)_2$], 7.46 (t, *J* = 12.6 Hz, 2 H, aromatic H), 7.52 (t, *J* = 11.1 Hz, 2 H, aromatic H), 7.91 (d, *J* = 9.5 Hz, 4 H, aromatic H), 8.46 (d, *J* = 9.5 Hz, 2 H, NH). − FAB-MS: *m*/*z* (%) = 429 (15) $[M + H]^+$, 130 (100) $[M - 2 \times C_6H_5CONHCH_3]^+$, 105 (60) $[C_6H_5CO^+]$. − $C_{23}H_{26}N_2O_6$ (426.5): calcd. C 64.78 H, 6.14 N, 6.57; found C 64.70, H 6.04, N 6.60.

***N*,*N*′-Methylenebis[(*cis*)/(*trans*)-1,3-dioxan-2,5-diyl]bisbenzamide** (**8**): M.p. 255−258 °C. − IR (KBr): $\tilde{\nu}$ = 3278 and 3290 cm^{-1} (NH), 3070 (aromatic C=CH), 2960 and 2850 (CH, CH_2), 1630 and 1624 (C=O), 1600, 1570, 1540 and 1450 (aromatic C=C), 1189 and 1074 (C−O−C), 730 and 695 (monosubstituted phenyl). − ^{1}H NMR ([D_6]DMSO): δ = 1.89 [t, *J* = 2.8 Hz, 2 H, $CH_2CH(OCH_2)_2$], 3.53 [d, *J* = 11.2 Hz, 1 H, $NHCH(CH_2O)_2$], 4.01 [q, *J* = 11.2 Hz, 4 H, $CH_2CH(OCH_2)_2$], 4.07 [d, *J* = 7.0 Hz, 1 H, $NHCH(CH_2O)_2$], 4.59 [t, *J* = 2.8 Hz, 1 H, $CH_2CH(OCH_2)_2$], 4.76 [t, *J* = 2.8 Hz, 1 H, $CH_2CH(OCH_2)_2$], 7.46 (t, *J* = 8.4 Hz, 2 H, aromatic H), 7.49 (t, *J* = 8.4 Hz, 2 H, aromatic H), 7.54 (t, *J* = 11.2 Hz, 2 H, aromatic H), 8.23 (d, *J* = 7.0 Hz, 2 H, aromatic H), 8.47 (d, *J* = 7.0 Hz, 2 H, aromatic H). − FAB-MS: *m*/*z* (%) = 429 (10) $[M + H]^+$, 130 (100) $[M - 2 \times C_6H_5CONHCH_3]^+$, 105 (75) $[C_6H_5CO^+]$. − $C_{23}H_{26}N_2O_6$ (426.5): calcd. C 64.78, H 6.14, N 6.57; found C 64.68, H 6.24, N 6.50.

b) Using procedure a) and changing the reaction conditions according to Table 1, compounds **5−8** were obtained in a corresponding ratio as indicated in Table 1.

Mixed Bisacetal 9 and Homo-bisacetal 10: a) A mixture of (1*S*,2*R*)-*N*-[2-hydroxy-1-(hydroxymethyl)propyl]benzamide (**4b**) (290.0 mg, 1.4 mmol), 1,1,3,3-tetramethoxypropane (227.0 mg, 1.4 mmol), concentrated hydrochloric acid (0.2 mL), and chloroform (15 mL) was stirred at 64 °C for 8 h. When TLC ($CHCl_3/CH_3OH$, 30:1) indicated complete disappearance of **4b**, the reaction mixture was cooled to room temperature and neutralized with sodium carbonate. After filtration and evaporation the residue was separated by chromatography ($CHCl_3/CH_3OH$, 30:1) to give **9** (113.0 mg, 26%) as a colorless syrup and **10** (230.0 mg, 36%) as yellow crystals.

[(2*S*,4*R*,5*R*)-*N*-2-(2,2-Dimethoxyethyl)-4-methyl-1,3-dioxan-5-yl]-benzamide (**9**). − IR (KBr): $\tilde{\nu}$ = 3439 cm^{-1} (NH), 3054 (aromatic C=CH), 2973, 2935 and 2867 (CH, CH_2, CH_3), 1657 (C=O), 1598, 1573, 1479 and 1409 (aromatic C=C), 1377 and 1358 (CH_3), 1176 and 1063 (C−O−C), 713 and 693 (monosubstituted phenyl). − ^{1}H NMR ($CDCl_3$): δ =1.21 (d, *J* = 8.0 Hz, 3 H, $OCHCH_3$), 1.99 [t, *J* = 5.0 Hz, 2 H, $CH_2CH(OCH_3)_2$], 3.34 (s, 6 H, 2×OCH_3), 3.95 (d, *J* = 10.0 Hz, 1 H, $NHCHCH_2O$), 3.98 (q, *J* = 5.0 Hz, 1 H, $NHCHCH_2O$), 4.06 [d, *J* = 15.0 Hz, 1 H, $NHCHCH_2O$], 4.10 (dt, *J* = 5.0 Hz, *J* = 1.5 Hz, 1 H, CH_3CHO), 4.60 [t, *J* = 5.0 Hz, 1 H, $CH_2CH(OCH_3)_2$], 4.77 (t, *J* = 5.0 Hz, 1 H, $CH_3CHOCHCH_2$), 6.83 (d, *J* = 10.0 Hz, 1 H, NH), 7.46 (t, *J* = 5.0 Hz, 2 H, aromatic H), 7.50 (t, *J* = 5.0 Hz, 1 H, aromatic H), 7.83 (d, *J* = 8.0 Hz, 2 H, aromatic H); in a NOESY experiment an NOE between the CH_3 at the 4-position and the CH_2 at the 2-position was observed. − FAB-MS: *m*/*z* (%) = 332 (3) $[M + Na]^+$, 309 (1) $[M^+]$, 220 (32) $[M - CH_2CH(OCH_3)_2]^+$, 192 (24) $[M - C_6H_5CON - CHCH(OCH_3)_2]^+$, 147 (70) $[M - C_6H_5CONH - OCH_3 - CH_3]$, 105 (100) $[C_6H_5CO]^+$,77 (24) $[C_6H_5]^+$. − $[\alpha]_D^{20}$ = −25.0° (*c* = 0.02, in $CHCl_3$). − $C_{16}H_{23}NO_5$ (309.4): calcd. C 62.12, H 7.49, N 4.53; found C 62.24, H 7.61, N 4.46.

***N*,*N*′-Methylenebis[(2*S*,4*R*,5*R*)/(2*R*,4*S*,5*S*)-4-methyl-1,3-dioxan-2,5-diyl]bisbenzamide (10)**: M.p. 136−138 °C. − IR (KBr): $\tilde{\nu}$ = 3548 and 3410 cm^{-1} (NH), 3063 (aromatic C=CH), 2973, 2914 and 2851 (CH, CH_2, CH_3), 1649 and 1627 (C=O), 1598, 1529, 1483 and 1418 (aromatic C=C), 1378 and 1355 (CH_3), 1183 and 1064 (C−O−C), 720 and 690 (monosubstituted phenyl). − ^{1}H NMR ($CDCl_3$): δ =1.23 (d, *J* = 6.7 Hz, 6 H, 2 × CH_3), 2.05 (t, *J* = 6.1 Hz, 4 H, $O_2CHCH_2CHO_2$), 3.96 (d, *J* = 7.2 Hz, 2 H, $NHCHCH_2O$), 4.41 (q, *J* = 7.2 Hz, 2 H, $NHCHCH_2O$×2), 4.08 (d, *J* = 12.8 Hz, 2 H, $NHCHCH_2O$), 4.12 (dt, *J* = 8.9 Hz, *J* = 1.7 Hz, 2 H, CH_3CHO × 2), 4.85 (t, *J* = 6.1 Hz, 2 H, O_2CHCH_2-CHO_2), 6.79 (t, *J* = 6.1 Hz, 2 H, NH×2), 7.46 (t, *J* = 8.9 Hz, 4 H, aromatic H), 7.53 (t, *J* = 8.3 Hz, 2 H, aromatic H), 7.82 (d, *J* = 8.3 Hz, 4 H, aromatic H); in a NOESY experiment, NOEs between the CH_3 at the 4-position and the CH_2 at the 2-position, and between the CH_3 at the 4-position and the *NH* at the 5-position were observed. − FAB-MS: *m*/*z* (%) = 455 $[M + H]^+$. − $C_{25}H_{30}N_2O_6$

(454.5): calcd. C 66.06, H 6.65, N 6.16; found C 66.26, H 6.58, N 6.27.

b). Using procedure a) and changing the reaction conditions according to Table 1 **9** and **10** were obtained in a corresponding ratio as indicated in Table 1.

Mixed Bisacetal 11 and Homo-bisacetal 12: A mixture of (1*S*)-*N*-[3-hydroxy-1-(hydroxymethyl) propyl] benzamide (**4c**) (50.0 mg, 0.24 mmol), 1,1,3,3-tetramethoxypropane (40.0 mg, 0.24 mmol), PPTS (10.0 mg), and chloroform (15.0 mL) was stirred at 40 °C for 12 h. When TLC ($CHCl_3$/CH_3OH, 30:1) indicated complete disappearance of **4c**, the reaction mixture was washed with aqueous sodium chloride (10%, 3 × 10 mL). The chloroform phase was separated and dried with Na_2SO_4. After evaporation the residue was purified by chromatography (ethyl acetate/petroleum ether, 2:1) to give **11** (11.0 mg, 15%) as colorless crystals and **12** (54.0 mg, 50%), as yellow crystals.

[(2*R*,5*S*)-*N*-2-(2,2-Dimethoxyethyl)-1,3-dioxacycloheptan-5-yl]-benzamide (11): M.p. 67−69 °C. − IR (KBr): $\tilde{\nu}$ = 3306 cm^{-1} (NH), 3049 (aromatic C=CH), 2975, 2930 and 2860 (CH, CH_2, CH_3), 1640 (C=O), 1605, 1560, and 1450 (aromatic C=C), 1382 (CH_3), 1190 and 1085 (C−O−C), 720 and 690 (monosubstituted phenyl). − ^{1}H NMR ($CDCl_3$): δ = 1.90 (q, *J* = 4.8 Hz, 2 H, NHCH$CH_2$$CH_2$O), 1.96 [t, *J* = 3.3 Hz, 2 H, CH_2CH$(OCH_3)_2$], 3.35 (s, 6 H, OCH_3 × 2), 3.64 (dd, *J* = 6.9 Hz, *J* = 5.1 Hz, 2 H, $NHCH_2CH_2CH_2O$), 3.92 (d, *J* = 7.2 Hz, 1 H, NHCHCH_2O), 4.04 (d, *J* = 7.2 Hz, 1 H, NHCHCH_2O), 4.34 [m, 1 H, NH$CH(CH_2)_2$], 4.53 [t, *J* = 3.6 Hz, 1 H, $CH(OCH_3)_2$], 4.89 (t, *J* = 3.6 Hz, 1 H, $CH_2OCHOCH_2$), 6.89 (d, *J* = 4.2 Hz, 1 H, NH), 7.45 (t, *J* = 5.2 Hz, 2 H, aromatic H), 7.52 (d, *J* = 4.5 Hz, 1 H, aromatic H), 7.79 (d, *J* = 4.5 Hz, 2 H, aromatic H); in a NOESY experiment, an NOE between the *NH* at the 5-position and the CH_2 at the 2-position was observed. − FAB-MS: *m*/*z* (%) = 310 [M + H]$^+$. − $[\alpha]_D^{20}$= −13.0 (*c* = 0.02, in $CHCl_3$). − $C_{16}H_{23}NO_5$ (309.4): calcd. C 62.12, H 7.49, N 4.53; found C 62.10, H 7.45, N 4.51.

***N*,*N*′-Methylenebis[(2*R*,5*S*)/(2′*S*,5′*R*)-1,3-dioxacycloheptan-2,5-diyl]bisbenzamide** (**12**): M.p. 123−125 °C. − IR (KBr): $\tilde{\nu}$ = 3325 cm^{-1} (NH), 3040 (aromatic C=CH), 2975, 2916 and 2854 (CH, CH_2,CH_3), 1636 (C=O), 1600, 1554 and 1435 (aromatic C=C), 1185 and 1081 (C−O−C), 725 and 687 (monosubstituted phenyl). − ^{1}H NMR($CDCl_3$): δ = 1.95 (dt, *J* = 1.8 Hz, *J* = 1.2 Hz, 4 H,CH$CH_2$$CH_2$O), 2.35 (m, *J* = 4.2 Hz, 1 H, $O_2CHCH_2CHO_2$), 2.39 (m, *J* = 3.3 Hz, 1 H, $O_2CHCH_2CHO_2$), 3.81 (t, *J* = 4.5 Hz, 2 H, CH_2CH_2O), 3.85 (t, *J* = 4.8 Hz, 2 H, CH_2CH_2O), 3.86 (m, *J* = 3.6 Hz, 2 H, NH*CH*CH_2), 3.91 (d, *J* = 2.4 Hz, 2 H, CH_2CH_2O), 3.98 (d, *J* = 4.5 Hz, 2 H,CH_2CH_2O), 4.74 (t, *J* = 1.5 Hz, 2 H, CH_2CHO_2), 6.27 (s, 2 H, NH), 7.42 (t, *J* = 5.7 Hz, 4 H, aromatic H), 7.52 (t, *J* = 5.7 Hz, 2 H, aromatic H), 7.75 (d, *J* = 5.1 Hz, 4 H, aromatic H); in a NOESY experiment an NOE between the NH at the 5-position and the CH_2 at the 2-position was observed. − FAB-MS: *m*/*z* (%) = 455 [M + H]$^+$. − $C_{25}H_{30}N_2O_6$ (454.5): calcd. C 66.06, H 6.65, N 6.16; found C 66.26, H 6.58, N 6.27.

Mixed Bisacetal 13 and Homo-bisacetal 14: A mixture of (1*S*)-*N*-[4-hydroxy-1-(hydroxymethyl)butyl] benzamide (**4d**) (114.0 mg, 0.51 mmol), 1,1,3,3-tetramethoxypropane (84.0 mg, 0.51 mmol), concentrated hydrochloric acid (0.20 mL), and chloroform (15.0 mL) was stirred at 45 °C for 48 h. When TLC ($CHCl_3$/CH_3OH, 35:1) indicated complete disappearance of **4d**, the reaction mixture was cooled to room temperature and neutralized with sodium carbonate. After filtration and evaporation the residue was separated by chromatography ($CHCl_3$/CH_3OH, 40:1) to give **13** (23.0 mg, 14%) as a colorless powder and **14** (46.0 mg, 20%) as a colorless powder.

[(2*R*,5*S*)-*N*-2-(2,2-Dimethoxyethyl)-1,3-dioxacyclooctan-5-yl]-benzamide (**13**): M.p. 89−93 °C. − IR (KBr): $\tilde{\nu}$ = 3460 cm^{-1} (NH), 3050 (aromatic C=CH), 2950, 2890 and 2820 (CH, CH_2, CH_3), 1650 (C=O), 1605, 1590, 1506 and 1453 (aromatic C=C), 1370 (CH_3), 1195 and 1086 (C−O−C), 760 and 685 (monosubstituted phenyl). − ^{1}H NMR ($CDCl_3$): δ =1.76 (m, 4 H, NHCH$CH_2$$CH_2$$CH_2$O), 1.92 (dd, *J* = 4.8 Hz, *J* = 6.0 Hz, 2 H, $O_2CHCH_2CHO_2$), 3.31 (s, 3 H, OCH_3), 3.30 (s, 3 H, OCH_3), 3.50 (d, *J* = 7.2 Hz, 1 H, NHCHCH_2O), 3.85 (d, *J* = 7.2 Hz, 1 H, NHCHCH_2O), 4.30 (m, 1 H, $NHCHCH_2O$), 4.47 (t, *J* = 6.0 Hz, 1 H, *CH*OCH_3 (OCH_3), 4.56 (m, *J* = 4.8 Hz, 2 H, $NHCHCH_2CH_2CH_2O$), 6.63 (t, *J* = 9.3 Hz, 1 H, NH), 7.42 (t, *J* = 7.5 Hz, 2 H, aromatic H), 7.47 (t, *J* = 6.6 Hz, 1 H, aromatic H), 7.78 (d, *J* = 5.1 Hz, 2 H, aromatic H). − FAB-MS: *m*/*z* (%) = 324 [M + H]$^+$. − $[\alpha]_D^{20}$ = −10.0 (*c* = 0.02, in $CHCl_3$). − $C_{17}H_{25}NO_5$ (323.4): calcd. C 63.12, H 7.80, N 4.33; found C 63.08, H 7.84, N 4.45.

***N*,*N*′-Methylenebis[(2*R*,5*S*)/(2′*S*,5′*R*)-1,3-dioxacyclooctan-2,5-diyl]bisbenzamide** (**14**). M.p. 130−133 °C. − IR (KBr): $\tilde{\nu}$ = 3405 cm^{-1} (NH), 3040 (aromatic C=CH), 2960, 2880 and 2810 (CH, CH_2, CH_3), 1638 (C=O), 1600, 1595, 1502, 1450 (aromatic C=C), 1186 and 1080 (C−O−C), 765 and 680 (monosubstituted phenyl). − ^{1}H NMR ($CDCl_3$): δ = 1.65 (m, 4 H, NHCH$CH_2$$CH_2$$CH_2$O), 1.85 (m, 4 H, NHCH$CH_2$$CH_2$$CH_2$O), 1.96 (t, *J* = 5.1 Hz, 2 H, $O_2CHCH_2CHO_2$), 3.63 (dd, *J* = 8.4 Hz, *J* = 3.3 Hz, 4 H, $NHCHCH_2CH_2CH_2O$), 3.78 (m, 2 H, NH*CH*CH_2O), 3.82 (d, *J* = 3.0 Hz, 2 H, NHCHCH_2O), 3.86 (d, *J* = 2.7 Hz, 2 H, NHCHCH_2O), 4.49 (t, *J* = 5.1 Hz, 1 H, $O_2CHCH_2CHO_2$), 4.54 (t, *J* = 5.1 Hz, 1 H, $O_2CHCH_2CHO_2$), 6.52 (d, *J* = 6.6 Hz, 2 H, NH), 7.44 (t, *J* = 6.6 Hz, 4 H, aromatic H), 7.49 (t, *J* = 5.4 Hz, 2 H, aromatic H), 7.79 (d, *J* = 6.6 Hz, 4 H, aromatic H). − FAB-MS: *m*/*z* (%) = 483 [M + H]$^+$. − $C_{27}H_{34}N_2O_6$ (482.6): calcd. C 67.19, H 7.11, N 5.81; found C 67.28, H 7.14, N 5.90.

Transacetalization of 6 or 9 with Alcohol: A solution of **6** (50.0 mg, 0.17 mmol), ethanol (0.5 mL), concentrated hydrochloric acid (0.1 mL), and chloroform (5 mL) was stirred at room temperature for 10 h. When TLC (ethyl acetate/ petroleum ether 1:1) indicated complete disappearance of **6**, the reaction mixture was neutralized with sodium carbonate. After filtration and evaporation the residue was separated by chromatography (ethyl acetate/petroleum ether, 1:3 and 1:2) to give [(*cis*)-*N*-2-(2-ethoxyethyl-2-methoxy)-1,3-dioxan-5-yl]benzamide (**15**) (35.0 mg, 67%), as colorless crystals, and [(*trans*)-*N*-2-(2-ethoxyethyl-2-methoxy)-1,3-dioxan-5-yl]benzamide (**16**) (8.0 mg, 15%), as colorless crystals.

[(*cis*)-*N*-2-(2-Ethoxyethyl-2-methoxy)-1,3-dioxan-5-yl]benzamide (**15**): M.p. 89−91 °C. − IR (KBr): $\tilde{\nu}$ = 3302 cm^{-1} (NH), 3058 (aromatic C=CH), 2918, 2830 (CH, CH_2, CH_3), 1620 (C=O), 1594, 1492, and 1449 (aromatic C=C), 1380 and 1358 (CH_3), 1187 and 1078 (C−O−C), 730 and 697 (monosubstituted phenyl). − ^{1}H NMR ($CDCl_3$): δ =1.21 (t, *J* = 5.5 Hz, 3 H, OCH_2CH_3), 1.99 [t, *J* = 5.5 Hz, 2 H, $CH_2CH(OCH_3)OCH_2CH_3$], 3.33 (s, 3 H, OCH_3), 3.51 (q, *J* = 7.6 Hz, 1 H, OCH_2CH_3), 3.65 (q, *J* = 7.6 Hz, 1 H, OCH_2CH_3), 4.01 (d, *J* = 10.9 Hz, 2 H, NHCHCH_2O), 4.04 (d, *J* = 10.9 Hz, 2 H, NHCHCH_2O), 4.04 (m, *J* = 6.6 Hz, 1 H, NH*CH*CH_2O), 4.62 (t, *J* = 4.4 Hz, 1 H, $CH_3CHOCH_2CH_3$), 4.73 (t, *J* = 4.4 Hz, 1 H, $CH_2OCHOCH_2$), 7.06 (d, *J* = 8.7 Hz, 1 H, NH), 7.48 (t, *J* = 7.6 Hz, 3 H, aromatic H), 7.82 (d, *J* = 7.6 Hz, 2 H, aromatic H), in the NOESY experiment an NOE between the *NH* at the 5-position and the CH_2 at the 2-position was observed.

− FAB-MS: *m*/*z* (%) = 310 (3) $[M + H]^+$, 282 (100) $[M - C_2H_4]^+$. − $C_{16}H_{23}NO_5$ (309.4): calcd. C 62.10, H 7.49, N 4.53; found C 62.15, H 7.55, N 4.57.

[(*trans*)-*N*-2-(2-Ethoxyethyl-2-methoxy)-1,3-dioxan-5-yl]benzamide (**16**): M.p. 76−78 °C. − IR (KBr): $\tilde{\nu}$ = 3305 cm^{-1} (NH), 3054 (aromatic C=CH), 2920, 2830 (CH, CH_2, CH_3), 1620 (C=O), 1596, 1490, and 1450 (aromatic C=C), 1381 and 1360 (CH_3), 1187 and 1079 (C−O−C), 732 and 699 (monosubstituted phenyl). − ^{1}H NMR ($CDCl_3$): δ =1.22 (t, *J* = 6.3 Hz, 3 H, OCH_2CH_3), 2.01 (t, *J* = 6.3 Hz, 2 H, $CH_2CHOCH_2CH_3$), 3.34 (s, 3 H, OCH_3), 3.50 (q, *J* = 7.5 Hz, 1 H, $CHOCH_2CH_3$), 3.65 (q, *J* = 7.5 Hz, 1 H, $CHOCH_2CH_3$), 4.29 (d, *J* = 5.0 Hz, 2 H, $NHCHCH_2O$), 4.33 (d, *J* = 5.0 Hz, 2 H, $NHCHCH_2O$), 4.42 (m, *J* = 2.5 Hz, 1 H, $NHCHCH_2O$), 4.60 (m, *J* = 6.6 Hz, 1 H, $CH_3OCHOCH_2CH_3$), 4.68 (t, *J* = 12.5 Hz, 1 H, $CH_2OCHOCH_2$), 5.74 (d, *J* = 6.3 Hz, 1 H, NH), 7.42 (t, *J* = 6.3 Hz, 1 H, aromatic H), 7.47 (t, *J* = 6.3 Hz, 1 H, aromatic H), 7.53 (t, *J* = 7.5 Hz, 1 H, aromatic H), 7.72 (d, *J* = 8.8 Hz, 2 H, aromatic H), in the NOESY experiment an NOE between the *NH* at the 5-position and the CH_2 at the 2-position was not observed. − FAB-MS: *m*/*z* (%) = 310 (5) $[M + H]^+$, 282 (100) $[M - C_2H_4]^+$. − $C_{16}H_{23}NO_5$ (309.4): calcd. C 62.12, H 7.49, N 4.53; found C 62.16, H 7.54, N 4.57.

b) Using procedure a) with glycol (8.0 mg, 0.17 mmol) instead of ethanol, [(*cis*)-*N*-2-(1,3-dioxolan-2-yl)methyl-1,3-dioxan-5-yl]benzamide (**17)** (30.0 mg, 60%) as colorless crystals and of [(*trans*)-*N*-2-(1,3-dioxolan-2-yl)methyl-1,3-dioxan-5-yl]benzamide (**18**) (15.0 mg, 30%) as colorless crystals were obtained.

[(*cis*)-*N*-2-(1,3-Dioxolan-2-yl)methyl-1,3-dioxan-5-yl]benzamide (**17**): M.p. 118−120 °C. − IR (KBr): $\tilde{\nu}$ = 3316 cm^{-1} (NH), 3040 (aromatic C=CH), 2950 and 2840 (CH and CH_2), 1640 (C=O), 1600, 1501 and 1450 (aromatic C=C), 1460 (CH_2), 1190 and 1080 (C−O−C), 735 and 700 (monosubstituted phenyl). − ^{1}H NMR ($CDCl_3$): δ = 2.06 (t, *J* = 6.0 Hz, 2 H, $O_2CHCH_2CHO_2$), 3.87 (t, *J* = 5.8 Hz, 3 H, OCH_2CH_2O), 4.00 (t, *J* = 5.8 Hz, 2 H, OCH_2CH_2O), 4.06 (d, *J* = 8.1 Hz, 4 H, $NHCHCH_2O$), 4.08 (m, *J* = 8.1 Hz, 1 H, $NHCHCH_2O$), 4.86 (t, *J* = 6.0 Hz, 1 H, $NHCHCH_2OCHOCH_2$), 5.02 (t, *J* = 6.0 Hz, 1 H, CH_2CHOCH_2), 7.10 (d, *J* = 8.1 Hz, 1 H, NH), 7.45 (t, *J* = 7.8 Hz, 2 H, aromatic H), 7.51 (t, *J* = 7.8 Hz, 1 H, aromatic H), 7.83 (d, *J* = 6.3 Hz, 2 H, aromatic H), in the NOESY experiment an NOE between the *NH* at the 5-position and the CH_2 at the 2-position was observed. − FAB-MS: *m*/*z* (%) = 294 $[M + H]^+$. − $C_{15}H_{19}NO_5$ (293.3): calcd. C 61.42, H 6.53, N 4.78; found C 61.46, H 6.58, N 4.81.

[(*trans*)-*N*-2-(1,3-Dioxolan-2-yl)methyl-1,3-dioxan-5-yl]benzamide (**18**): M.p. 138−140 °C. − IR (KBr): $\tilde{\nu}$ = 3306 cm^{-1} (NH), 3026 (aromatic C=CH), 2955 and 2845 (CH and CH_2), 1639 (C=O), 1602, 1500 and 1450 (aromatic C=C), 1462 (CH_2), 1192 and 1078 (C−O−C), 730 and 702 (monosubstituted phenyl). − ^{1}H NMR ($CDCl_3$): δ =2.06 (t, *J* = 4.8 Hz, 2 H, $O_2CHCH_2CHOCH_2$), 3.49 (t, *J* = 10.5 Hz, 4 H, $CHOCH_2CH_2O$), 3.88 (t, *J* = 9.3 Hz, 2 H, $NHCHCH_2O$), 3.93 (t, *J* = 9.3 Hz, 2 H, $NHCHCH_2O$), 4.71 (t, *J* = 5.4 Hz, 1 H, $NHCHCH_2OCHOCH_2O$), 5.02 (t, *J* = 5.4 Hz, 1 H, $CH_2CHOCH_2CH_2O$), 7.43 (t, *J* = 6.3 Hz, 2 H, aromatic H), 7.52 (t, *J* = 7.2 Hz, 1 H, aromatic H), 7.73 (d, *J* = 6.6 Hz, 2 H, aromatic H), in the NOESY experiment an NOE between the *NH* at the 5-position and the CH_2 at the 2-position was not observed. − FAB-MS: *m*/*z* (%) = 294 $[M + H]^+$. − $C_{15}H_{19}NO_5$ (293.3): calcd. C 61.42, H 6.53, N 4.78; found C 61.45, H 6.57, N 4.82.

c) Using procedure a) with **6** (70.0 mg, 0.24 mmol) and **4b** (50.0 mg, 2.4 mmol) instead of ethanol only two bisacetals were obtained, namely, *N*,*N*′-methylenebis[(2*S*,4*R*,5*R*)/(2*R*,4*S*,5*S*)-4-methyl-1,3-dioxan-2,5-diyl]bisbenzamide (**10**) (10.0 mg, 20%) as yellow crystals, and (50.0 mg, 66%) of *N*,*N*′-methylenebis[(2*S*,4*R*,5*R*)/(2*S*,4*S*,5*S*)-4-methyl-1,3-dioxan-2,5-diyl]bisbenzamide (**19**) as yellow crystals, no desirable mixed bisacetal was found.

***N*,*N*′-Methylenebis[(2*S*,4*R*,5*R*)/(2*S*,4*S*,5*S*)-4-methyl-1,3-dioxan-2,5-diyl]bisbenzamide** (**19**): M.p. 167−169 °C. − IR (KBr): $\tilde{\nu}$ = 3550 and 3405 cm^{-1} (NH), 3050 (aromatic C=CH), 2976, 2905 and 2860 (CH and CH_2 and CH_3), 1650 and 1630 (C=O), 1600, 1530, 1485 and 1400 (aromatic C=C), 1370 and 1360 (CH_3), 1186 and 1060 (C−O−C), 730 and 700 (monosubstituted phenyl). − ^{1}H NMR ($CDCl_3$): δ = 1.23 (d, *J* = 6.6 Hz, 3 H, $NHCHCHCH_3$), 1.25 (d, *J* = 4.2 Hz, 3 H, $NHCHCHCH_3$), 2.06 (t, *J* = 5.7 Hz, 2 H, $O_2CHCH_2CHOCH_2$), 4.07 (m, 8 H, $CH_3CHCHCH_2$), 4.83 (t, *J* = 4.5 Hz, 1 H, $O_2CHCH_2CHO_2$), 4.84 (t, *J* = 4.5 Hz, 1 H, $O_2CHCH_2CHO_2$), 6.78 (d, *J* = 8.4 Hz, 1 H, NH),7.03 (d, *J* = 8.4 Hz, 1 H, NH),7.46 (t, *J* = 7.5 Hz, 2 H, aromatic H), 7.51 (t, *J* = 6.6 Hz, 1 H, aromatic 1 H), 7.82 (d, *J* = 7.2 Hz, 2 H, aromatic H), in the NOESY experiment the NOEs between the CH_3 at the 4-position and the CH_2 at the 2-position, and between the CH_3 at the 4-position and the *NH* at the 5-position, in one ring were observed; an NOE between the CH_3 at the 4-position and the CH_2 at the 2-position or NH at the 5-position was not observed in the other ring. − FAB-MS: *m*/*z* (%) = 455 $[M + H]^+$. − $C_{25}H_{30}N_2O_6$ (454.5): calcd. C 66.06, H 6.65, N 6.16; found C 66.01, H 6.54, N 6.28.

d). Using procedure a) with **9** (40.0 mg, 0.13 mmol) instead of **6** (50.0 mg) to give (2*S*,4*R*,5*R*)-[*N*-2-(2-ethoxy-2-methoxyethyl)-4-methyl-1,3-dioxan-5-yl]benzamide (**20**) (25.0 mg, 60%), as a colorless syrup, and of (2*S*,4*R*,5*R*)-[*N*-2-(2,2-diethoxyethyl)-4-methyl-1,3-dioxan-5-yl]benzamide (**21**) (6.0 mg, 14%), as a colorless syrup.

(2*S*,4*R*,5*R*)-[*N*-2-(2-Ethoxy-2-methoxyethyl)-4-methyl-1,3-dioxan-5-yl]benzamide (**20**): IR (KBr): $\tilde{\nu}$ = 3318 cm^{-1} (NH), 3055 (aromatic C=CH), 2972, 2922 and 2864 (CH, CH_2 and CH_3), 1659 (C=O), 1598, 1570, 1512 and 1400 (aromatic C=C),1378 and 1359 (CH_3), 1176 and 1064 (C−O−C), 713 and 693 (monosubstituted phenyl). − ^{1}H NMR ($CDCl_3$): δ =1.18 (t, *J* = 2.6 Hz, 3 H, OCH_2CH_3), 1.20 (d, *J* = 2.6 Hz, 3 H, $NHCHCHCH_3$), 1.98 (t, *J* = 2.6 Hz, 2 H, $O_2CHCH_2CHO_2$), 3.32 (s, 3 H, OCH_3), 3.53 (m, *J* = 10.2 Hz, 1 H, OCH_2CH_3), 4.03 (m, *J* = 10.2 Hz, 1 H, OCH_2CH_3), 3.94 (d, *J* = 11.5 Hz, 1 H, $NHCHCH_2O$), 4.05 (d, *J* = 11.5 Hz, 1 H, $NHCHCH_2O$), 4.05 (m, *J* = 7.7 Hz, 2 H, $NHCHCHCH_3$), 4.64 (t, *J* = 12.8 Hz, 1 H, $CH_3OCHOCHOCH_2$), 4.75 (t, *J* = 12.8 Hz, 1 H, $CH_3CHOCHOCH_2$), 6.82 (d, *J* = 19.2 Hz, 1 H, NH), 7.42 (q, *J* = 15.3 Hz, 2 H, aromatic H), 7.49 (m, *J* = 12.8 Hz, 1 H, aromatic 1 H), 7.82 (d, *J* = 15.3 Hz, 2 H, aromatic H), in the NOESY experiment the NOEs between the CH_3 at the 4-position, the NH at the 5-position and the CH_2 at the 2-position were observed. − FAB-MS: *m*/*z* (%) = 324 $[M + H]^+$. − $[\alpha]_D^{20}$ = −32.0 (*c* = 0.01, in $CHCl_3$). − $C_{17}H_{25}NO_5$ (323.4): calcd. C 63.12, H 7.80, N 4.33; found C 63.10, H 7.77, N 4.31.

(2*S*,4*R*,5*R*)-[*N*-2-(2,2-Diethoxyethyl)-4-methyl-1,3-dioxan-5-yl]-benzamide (**21**): IR (KBr): $\tilde{\nu}$ = 3445 cm^{-1} (NH), 3035 (aromatic C=CH), 2970, 2930 and 2860 (CH, CH_2 and CH_3), 1650 (C=O), 1601, 1570, 1480 and 1400 (aromatic C=C),1378 and 1360 (CH_3), 1170 and 1065 (C−O−C), 716 and 690 (monosubstituted phenyl). − ^{1}H NMR ($CDCl_3$): δ = 1.20 (t, *J* = 2.6 Hz, 6 H, OCH_2CH_3), 1.24 (d, *J* = 2.6 Hz, 3 H, $NHCHCHCH_3$), 2.00 (t, *J* = 3.9 Hz, 2 H, $O_2CHCH_2CHO_2$), 3.52 (dm, *J* = 5.2 Hz, *J* = 1.3 Hz, 2 H, OCH_2CH_3), 3.65 (m, *J* = 9.1 Hz, 2 H, OCH_2CH_3), 3.96 (d, *J* = 13.0 Hz, 1 H, $NHCHCH_2O$), 4.02 (m, *J* = 7.8 Hz, 2 H, $NHCHCHCH_3$), 4.07 (d, *J* = 13.0 Hz, 1 H, $NHCHCH_2O$), 4.71

[t, J = 2.6 Hz, 1 H, $CH(OCH_2CH_3)_2$], 4.77 (t, J = 2.6 Hz, 1 H, $O_2CHCH_2CHOCH_2CH_3$), 6.83 (d, J = 10.4 Hz, 1 H, NH), 7.47 (t, J = 10.4 Hz, 2 H, aromatic H), 7.52 (t, J = 7.8 Hz, 1 H, aromatic H), 7.84 (d, J = 7.8 Hz, 2 H, aromatic H). − FAB-MS: *m/z* (%) = 338 $[M + H]^+$. − $[\alpha]_D^{20}$= −20.0 (c = 0.02, in $CHCl_3$). − $C_{18}H_{27}NO_5$ (337.4): calcd. C 64.06, H 8.07, N 4.15; found C 64.01, H 8.04, N 4.12.

e) Using procedure a) with **9** (100.0 mg, 0.32 mmol) instead of **6**, and with **4a** (70.0 mg, 0.36 mmol) instead of ethanol, the reaction mixture was stirred for 24 h instead of 10 h. Compounds **10** (6.0 mg, 4%), **19** (12.0 mg, 8%), *N*,*N*′-methylene[(2*S*,4*R*,5*R*)-4-methyl-1,3-dioxan-2,5-diyl][(*cis*)-1,3-dioxan-2,5-diyl]bisbenzamide (**22**) (10.0 mg, 7%), as yellow crystals, and *N*,*N*′-methylene[(2*S*,4*R*,5*R*)-4-methyl-1,3-dioxan-2,5-diyl] [(*trans*)-1,3-dioxan-2,5-diyl]bisbenzamide (**23**) (87.0 mg, 61%) as yellow crystals, were obtained.

***N*,*N*′-Methylene[(2*S*,4*R*,5*R*)-4-methyl-1,3-dioxan-2,5-diyl][(*cis*)-1,3-dioxan-2,5-diyl]bisbenzamide** (**22**): M.p. 172−174°C . − IR (KBr): $\tilde{\nu}$ = 3550 and 3400 cm^{-1} (NH), 3054 (aromatic C=CH), 2970, 2905 and 2860 (CH, CH_2 and CH_3), 1650 and 1630 (C=O), 1590, 1530, 1486 and 1400 (aromatic C=C), 1376 (CH_3), 1186 and 1055 (C−O−C), 735 and 690 (monosubstituted phenyl). − ^{1}H NMR ($CDCl_3$): δ =1.22 (d, J = 6.6 Hz, 3 H, NHCHCHCH_3), 2.06 (t, J = 4.5 Hz, 2 H, $O_2CHCH_2CHO_2$), 4.00 (m, 1 H, NHCHCHCH$_3$), 4.05 (d, J = 8.7 Hz, 6 H, NHCHCH_2O), 4.10 (m, J = 8.7 Hz, 2 H, NHCHCH$_2$O), 4.83 (t, J = 4.5 Hz, 1 H, O_2CHCH$_2$CHO$_2$), 4.84 (t, J = 4.5 Hz, 1 H, O_2CHCH$_2$CHO$_2$), 6.78 (d, J = 9.9 Hz, 1 H,NH),7.03 (d, J = 8.1 Hz, 1 H, NH), 7.46 (t, J = 6.3 Hz, 4 H, aromatic H), 7.54 (t, J = 4.2 Hz, 2 H, aromatic H), 7.82 (d, J = 8.1 Hz, 2 H, aromatic H), in the NOESY experiment the NOEs between the CH_3 at the 4-position and the CH_2 at the 2-position, and between the CH_3 at the 4-position and the NH at the 5-position in the (4-methyl-1,3-dioxan-5-yl)benzamide moiety were observed, and an NOE between the CH_2 at the 2-position and the NH at the 5-position in the (1,3-dioxan-5-yl)benzamide moiety was observed. − FAB-MS: *m/z* (%) = 441 $[M + H]^+$. − $[\alpha]_D^{20}$= −20.0 (c = 0.02 in $CHCl_3$). − $C_{24}H_{28}N_2O_6$ (440.5): calcd. C 65.44, H 6.41, N 6.36; found C 65.50, H 6.60, N 6.19.

***N*,*N*′-Methylene[(2*S*,4*R*,5*R*)-4-methyl-1,3-dioxan-2,5-diyl][(*trans*)-1,3-dioxan-2,5-diyl]bisbenzamide** (**23**): M.p. 183−186 °C. − IR (KBr): $\tilde{\nu}$ = 3547 and 3450 (NH), 3061 (aromatic C=CH), 2956, 2900 and 2856 (CH, CH_2 and CH_3), 1635 and 1628 (C=O), 1600, 1535, 1480 and 1415 (aromatic C=C), 1367 (CH_3), 1180 and 1060 (C−O−C), 740 and 685 (monosubstituted phenyl). − ^{1}H NMR ($CDCl_3$): δ =1.21 (d, J = 6.6 Hz, 3 H, NHCHCHCH_3), 2.06 (t, J = 5.7 Hz, 2 H, $O_2CHCH_2CHO_2$), 3.99 (d, J = 9.9 Hz, 2 H, NHCHCH_2O), 4.31 (d, J = 5.7 Hz,1 H, NHCHCH_2O), 4.34 (d, J = 4.8 Hz, 1 H, NHCHCH_2O), 4.45 (m, 1 H, NHCHCH$_2$O), 4.68 (t, J = 5.7 Hz, 1 H, O_2CHCH$_2$CHO$_2$), 4.84 (t, J = 5.4 Hz, 1 H, O_2CHCH$_2$CHO$_2$), 5.71 (d, J = 8.4 Hz, 1 H, NH), 6.79 (d, J = 9.9 Hz, 1 H, NH), 7.46 (t, J = 7.2 Hz, 4 H, aromatic H), 7.50 (t, J = 7.2 Hz, 2 H, aromatic H), 7.73 (d, J = 7.4 Hz, 2 H, aromatic H), 7.82 (d, J = 7.2 Hz, 2 H, aromatic H), in the NOESY experiment the NOEs between the CH_3 at the 4-position and the CH_2 at the 2-position, and between the CH_3 at the 4-position and the NH at the 5-position in the (4-methyl-1,3-dioxan-5-yl)benzamide moiety were only observed. − FAB-MS: *m/z* (%) = 441 $[M + H]^+$. − $[\alpha]_D^{20}$= +30.0 (c = 0.02 in $CHCl_3$). − $C_{24}H_{28}N_2O_6$ (440.5): calcd. C 65.44, H 6.41, N 6.36; found C 65.56, H 6.38, N 6.15.

f) Using procedure a) with **9** (30.0 mg, 0.10 mmol) instead of **6** (50.0 mg) and with glycol (8.0 mg, 0.17 mmol) instead of ethanol, (2*S*,4*R*,5*R*)-*N*-[2-(1,3-dioxan-2-yl)methyl-4-methyl-1,3-dioxan-5-yl]benzamide (**24**) (21.0 mg, 70%) was obtained as a colorless syrup.

(2*S*,4*R*,5*R*)-*N*-[2-(1,3-dioxolan-2-yl)methyl-4-methyl-1,3-dioxan-5-yl]benzamide (**24**): IR (KBr): $\tilde{\nu}$ = 3346 cm^{-1} (NH), 2914 and 2846 (CH, CH_2 and CH_3), 1657 (C=O), 1598, 1574, 1513 and 1416 (aromatic C=C), 1479 (CH_2), 1377 and 1360 (CH_3), 1125 and 945 (C−O−C), 713 and 664 (monosubstituted phenyl). − ^{1}H NMR ($CDCl_3$): δ = 1.24 (d, J = 6.0 Hz, 3 H, NHCHCHCH_3), 2.05 (t, J = 3.0 Hz, 2 H, $O_2CHCH_2CHO_2$), 3.86 (d, J = 3.0 Hz, 1 H, NHCHCH_2O), 3.95 (d, J = 3.0 Hz, 1 H, NHCHCH_2O), 3.98 (m, J = 6.0 Hz, 1 H, NHCHCH$_2$O), 4.11 (t, J = 15.0 Hz, 2 H, $CH_2CHOCH_2CH_2O$), 4.13 (t, J = 15.0 Hz, 2 H, CH_2CHOCH_2-CH_2O), 4.88 (t, J = 3.0 Hz, 1 H, $CH_2CHOCH_2CH_2O$), 5.04 (t, J = 3.0 Hz, 1 H, NHCHCH$_2$OCHCH$_2$), 6.85 (d, J = 15.0 Hz, 1 H, NH), 7.48 (m, J = 7.6 Hz, 3 H, aromatic H), 7.83 (d, J = 7.6 Hz, 2 H, aromatic H), in the NOESY experiment the NOEs between the CH_3 at the 4-position and the CH_2 at the 2-position, and between the CH_3 at the 4-position and the NH at the 5-position were observed. − FAB-MS: *m/z* (%) = 308 $[M + H]^+$. − $[\alpha]_D^{20}$= −16.0 (c = 0.02, in $CHCl_3$). − $C_{16}H_{21}NO_5$ (307.4): calcd. C 62.51, H 6.89, N 4.56; found C 62.54, H 6.92, N 4.59.

g) A solution of **9** (60.0 mg, 0.19 mmol), **4c** (40.0 mg, 0.52 mmol) and of toluenesulfonic acid (10.0 mg) in chloroform (10 mL) was stirred at 50°C for 12 h then TLC ($CHCl_3$/CH_3OH, 20:1) indicated complete disappearance of **9**. The reaction mixture was neutralized by sodium carbonate. After filtration and evaporation the residue was separated by chromatography to give *N*,*N*′-methylene[(2*S*,4*R*,5*R*)-4-methyl-1,3-dioxan-2,5-diyl][(2′*S*,5′*R*)-1,3-dioxacyclooctan-2,5-diyl]bisbenzamide (**25**) (65.0 mg, 74%), as colorless crystals.

***N*,*N*′-Methylene[(2*S*,4*R*,5*R*)-4-methyl-1,3-dioxan-2,5-diyl]-[(2′*S*,5′*R*)-1,3-dioxacyclooctan-2,5-diyl]bisbenzamide** (**25**): M.p. 136−138°C. − IR (KBr): $\tilde{\nu}$ = 3552 and 3450 cm^{-1} (NH), 3060 (aromatic C=CH), 2975, 2910 and 2850 (CH, CH_2 and CH_3), 1650 and 1630 (C=O), 1600, 1525, 1480 and 1400 (aromatic C=C), 1375 (CH_3), 1180 and 1062 (C−O−C), 730 and 686 (monosubstituted phenyl). − ^{1}H NMR ($CDCl_3$): δ = 1.22 (d, J = 6.6 Hz, 3 H, NHCHCHCH_3), 1.97 (m, 2 H, NHCHCH_2CH$_2$O), 2.04 (t, J = 7.5 Hz, 2 H, NHCHCH_2O), 3.74 (dq, J = 12.6 Hz, J = 3.2 Hz, 1 H, NHCHCHCH$_3$), 3.91 (d, J = 8.1 Hz, 2 H, NHCHCH_2O), 3.94 (d, J = 8.1 Hz, 2 H, NHCHCH_2O), 4.14 (d, J = 10.4 Hz, 2 H, NHCHCH$_2CH_2$O), 4.29 (m, 1 H, NHCHCH$_2$O), 4.48 (m, 1 H, NHCHCH$_2$O), 4.82 (t, J = 4.8 Hz, 1 H, O_2CHCH$_2$CHO$_2$), 4.95 (J = 9.3 Hz, 1 H, O_2CHCH$_2$CHO$_2$), 6.79 (d, J = 6.7 Hz, 1 H, NH), 6.85 (d, J = 6.7 Hz, 1 H, NH), 7.45 (t, J = 7.2 Hz, 4 H, aromatic H), 7.52 (t, J = 6.3 Hz, 2 H, aromatic H), 7.80 (d, J = 7.4 Hz, 2 H, aromatic H), 7.86 (d, J = 7.2 Hz, 2 H, aromatic H), in the NOESY experiment the NOEs between the CH_3 at the 4-position and the CH_2 at the 2-position, and between the CH_3 at the 4-position and the NH at the 5-position in (4-methyl-1,3-dioxan-5-yl)benzamide moiety and an NOE between the CH_2 at the 2-position and the NH at the 5-position in the (1,3-dioxan-5-yl)benzamide moiety were observed. − FAB-MS: *m/z* (%) = 455 $[M + H]^+$. − $[\alpha]_D^{20}$= −14.0 (c = 0.02 in $CHCl_3$). − $C_{25}H_{30}N_2O_6$ (454.5): calcd. C 66.06, H 6.65, N 6.16; found C 65.90, H 6.58, N 6.25.

Configuration Conversion of 8, 19, 18, 16, and 23: A solution of the kinetically controlled product, **8**, **19**, **18**, **16,** or **23** (0.01 mmol), concentrated hydrochloric acid (0.01 mL) and chloroform (5 mL) was stirred at 50 °C for 12 h until TLC ($CHCl_3$/CH_3OH, 30:1) indicated complete disappearance of **8**, **19**, **18**, **16,** or **23**. After neutralization, filtration, and evaporation the residue was purified, and

the thermodynamically stable product **7**, **10**, **17**, **15,** or **22** (0.0095 mmol, 95%) was obtained. Their structures were confirmed by spectroscopy data.

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