Pergamon

TETRAHEDRON

Tetrahedron 58 (2002) 2641–2646

Two directional electroorganic synthesis—electrochemical oxidation and application of a C_2-symmetric building block

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Received 29 October 2001; revised 23 January 2002; accepted 31 January 2002

Abstract—The C_2-symmetric building block 1,2:5,6-di-*N*,*O*-carbonyl-1,6-diamino-3,4-*O*-isopropylidene-D-mannitol can be synthesized from D-mannitol in four steps using a nucleophilic substitution with cyanate and a subsequent cyclization in the final key step. The direct electrochemical oxidation of the resulting dioxazolidinone at 40 mA/cm^2 in methanol at graphite electrodes with sodium benzene sulfonate as supporting electrolyte leads to the dimethoxylated product, which can be used in various diastereoselective amidoalkylation reactions. In all cases di-*trans*-stereoselectivity is observed. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

The concept of two directional synthesis introduced by Schreiber is a very efficient strategy to generate enantiomerically pure compounds with a large number of clearly defined stereogenic centers.[1] Although limited to a group of starting compounds with special symmetric properties e.g. C_2- and C_S-symmetric compounds this concept has been applied extensively to the synthesis of chiral compounds and natural products.[2]

On the other hand the electrochemical generation of stable *N*,*O*-acetales by the direct oxidation of cyclic carbamates or amides and their conversion with various C-nucleophiles to α-substituted compounds in amidoalkylation reactions has proven to be an effective and flexible sequence in the synthesis of various chiral mono- and bicyclic nitrogen containing products.[3,4]

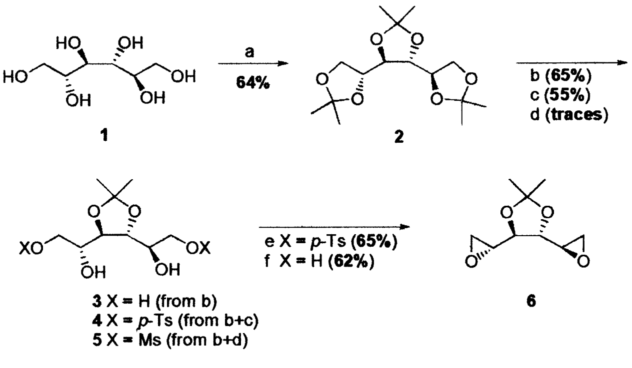
To the best of our knowledge a combination of these two concepts has not been adapted in synthetic organic chemistry so far. In this paper, we report a combination of two directional and electroorganic synthesis by the synthesis of a C_2-symmetric bis-oxazolidinone, its electrochemical oxidation and the use of the resulting bis-α-methoxylated bis-oxazolidinone in *N*-acyliminium ion coupling reactions.

2. Results and discussion

2.1. Synthesis and electrochemical oxidation of 1,2:5,6-di-*N*,*O*-carbonyl-1,6-diamino-3,4-*O*-isopropylidene-D-mannitol (7)

To study the preparation of the C_2-symmetric building block the synthesis of compounds **4–6** was envisioned starting from D-mannitol. In order to do that commercially available D-mannitol (**1**) was transformed to the 1,6-di-*O*-*p*-toluenesulfonylated protected derivative **4** using a known three-step procedure (Scheme 1).[5] In a similar fashion we tried to synthesize the 1,6-di-methanesulfonylated derivative **5**. But only traces of the desired product could be isolated along with large amounts of the 1,2,6-trimethanesulfonylated compound.

Under basic conditions the bis-epoxy derivative **6** could be



Scheme 1. Synthesis of the bis-oxazolidinone precursors **4–6**. (a) Acetone, H_2SO_4; (b) 70% AcOH; (c) *p*-Ts-Cl, pyridine; (d) Ms-Cl, pyridine; (e) K_2CO_3, MeOH; (f) (1) $CH_3C(OCH_3)_3$, PPTS; (2) AcBr; (3) K_2CO_3.

Keywords: electrochemical oxidation; amidoalkylation reactions; two directional synthesis; stereoselective synthesis.

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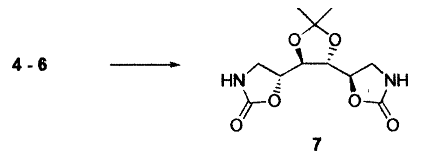
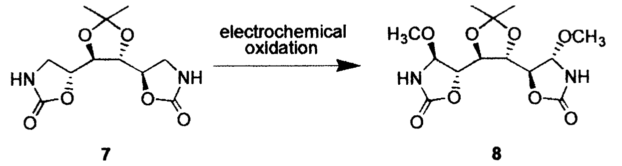
PII: S0040-4020(02)00147-3

Table 1. Synthesis of the bis-oxazolidinone **7** starting from **4** and **6**



Compound	Conditions	Yield (%)
4	KOCN, DMF, 120°C	59
6	KOCN, DMF, 120°C	14



Scheme 2. Electrochemical oxidation of **7**.

synthesized starting from **4** by an intramolecular substitution in 65% yield.[5] As an alternative to such a two-step-procedure a one-pot-synthesis starting from **3** also led to **6** in 62% yield by applying a procedure recently published by Lohray.[6] Compounds **4** and **6** were tested as precursors for the synthesis of bis-oxazolidinone **7** (Table 1). Starting from **4** the product was successfully obtained by the reaction with potassium cyanate in DMF at 120°C in a good yield of 59% for such a two-step process.[7] In contrast to that the treatment of the bis-epoxy derivative **6** with cyanate under similar conditions resulted in only minor amounts of the bis-oxazolidinone. This is in an interesting contrast to many examples in the literature where such epoxydes reacted in high yields to oxazolidinone derivatives.[8]

To study the usefulness of **7** in the electrochemical oxidation process a screening was carried out using an undivided cell (10 ml) with a graphite anode and a graphite cathode. The electrolyses were carried out in methanol p.a. until the consumption of 10 F/mol of charge on a one millimolar scale. To optimize this reaction we studied the influence of the supporting electrolyte, the current density and the concentration of the starting material on the yield of the α-bis-methoxylated product. In all cases only the C_2-symmetric di-*trans*-diastereomer was obtained after flash chromatography (Scheme 2).

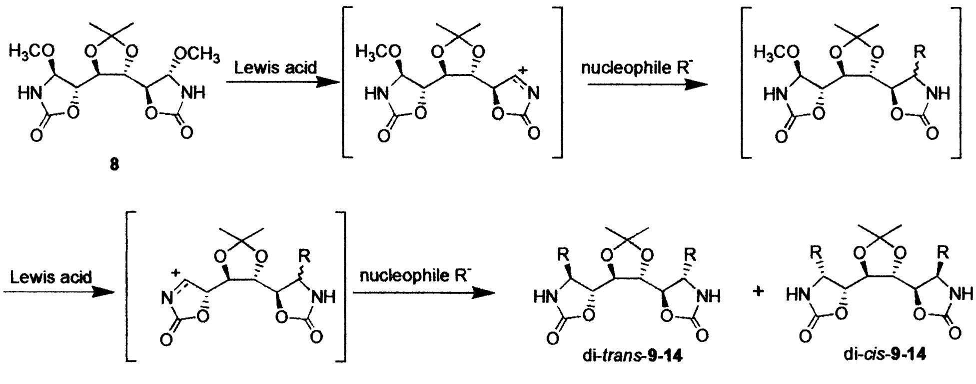
The results of the screening experiments are presented in Table 2. The product yields were highly influenced by the kind of supporting electrolyte applied (Table 2, No. 1–4). Only in the case of sodium benzene sulfonate substantial quantities of product were detected and isolated. In all other experiments no or only minor amounts of product were generated. Here starting material can be recovered in larger quantities. This behavior is in accordance with results previously reported for the electrochemical oxidation of a chiral 2-oxazolidinone.[9]

Competition between adduct and solvent oxidation explains the effect of the current density on the product yield (Table 2, No. 4–8). At higher currents (50–60 mA/cm^2) methanol oxidation to formaldehyde dimethyl acetal is favored and so product yields decrease drastically. The best conditions

Table 2. Results of the electrochemical oxidation of **7** (concentration of supporting electrolyte: 0.2 mol/l)

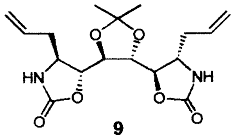
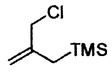
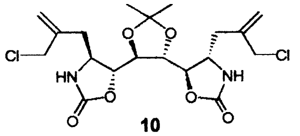
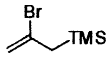
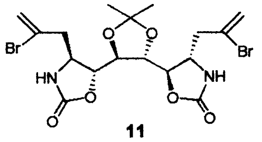
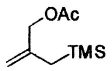
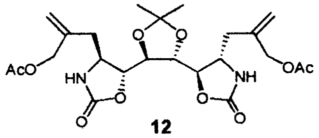
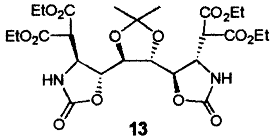
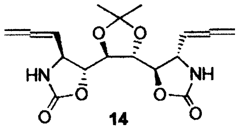
No.	Supporting electrolyte	Current density	Substrate concentration	Material yield (%)
1	Bu_4NClO_4	40	0.1	0
2	Et_4NOTs	40	0.1	9
3	$NaBF_4$	40	0.1	13
4	$PhSO_3Na$	40	0.1	46
5	$PhSO_3Na$	20	0.1	41
6	$PhSO_3Na$	30	0.1	42
7	$PhSO_3Na$	50	0.1	34
8	$PhSO_3Na$	60	0.1	29
9	$PhSO_3Na$	40	0.05	22
10	$PhSO_3Na$	40	0.15	49
11	$PhSO_3Na$	40	0.18[a]	55

[a] Saturated solution of **7**.



Scheme 3. Nucleophilic substitution of the α-bis-methoxylated dioxazolidinone **8** under the catalysis of Lewis acids.

Table 3. Nucleophilic substitution of the methoxy groups in **8** (*condititon A*: $TiCl_4$ (3 equiv.), nucleophile (4 equiv.), CH_2Cl_2, −78 °C (5 h)–rt (1 day); *condition B*: $TiCl_4$ (6.2 equiv.), NEt_3 (3.1 equiv.), nucleophile (4 equiv.), CH_2Cl_2, −78 °C (5 h)–rt (1 day); *condition C*: $BF_3{\cdot}OEt_2$ (2.2 equiv.), Ac_2O (2 equiv.), nucleophile (4 equiv.), CH_2Cl_2, −78 °C (5 h)–rt (1 day)

No.	Condition	Nucleophile	Product (major diastereomer)	Yield (%)
1	A		 **9**	59 (ds: 91% di-*trans*)
2	A		 **10**	58 (ds: 82% di-*trans*)
3	A		 **11**	53 (ds: 83% di-*trans*)
4	A		 **12**	38 (ds: 85% di-*trans*)
5	B	$CH_2(CO_2Et)_2$	 **13**	57 (ds: 88% di-*trans*)
6	C		 **14**	17[a]

[a] Only one diastereomer could be detected.

were found in a range of 20–40 mA/cm^2 with an optimal value at 40 mA/cm^2. To some extent the solvent oxidation can be suppressed by using higher concentrations of substrate (Table 2, No. 4, 9–11). This is also true in case of **7** and an optimum yield of 55% was obtained by running the electrolysis in a saturated solution of starting material even on a large scale (2 g, 7.4 mmol).

2.2. *N*-Acyliminium ion coupling reactions

N,*O*-Acetals such as the α-bis-methoxylated dioxazolidinone **8** are stable precursors of *N*-acyliminium ions. In this case **8** can undergo nucleophilic substitution of both methoxy groups by carbon nucleophiles under catalysis of Lewis acids (Scheme 3).[4a,10]

In preliminary testings we found that the use of $TiCl_4$ as a strong Lewis acid (Table 3, Method A and B) is generally necessary. Only in one case BF_3–etherate activated by the addition of acetic anhydride was used (Table 3, Method C). Here the activation is expected to be caused by an in situ transformation of the α-methoxylated into the more reactive α-acetoxylated compound.[11] Several substituted allylsilanes (Table 3, entries 1–4) were tested for their reactivity as nucleophiles. In all cases, C_2-symmetric products with good di-*trans*-stereoselectivities were obtained as main products in moderate to good material yields. This stereochemical behavior is in accordance with several amidoalkylation reactions with chiral α-methoxylated 2-oxazolidinones.[12] In case of entry 5 the titanium enolate prepared in situ from diethyl malonate in the presence of triethylamine gave predominantly the di-*trans*-product in good yield. Here the unexpected C_2-symmetric di-*cis*-product could also be isolated and characterized as the minor isomer. In case of propargyltrimethylsilane (Table 3, entry 6) the use of $TiCl_4$ as Lewis acid leads to the undesired addition of the *N*-acyliminiumion to the triple-bond. Here the modified procedure with BF_3-etherate and acetic anhydride as Lewis acid was successful resulting exclusively in the di-*trans*-product. The relatively low yield is due to the reduced nucleophilic reactivity of propargyltrimethylsilane in comparison with allyltrimethylsilanes.

2.3. Configuration determination of di-*trans*-9

A colorless crystal of di-*trans*-**9** was obtained by dissolving the substance in ethyl acetate and a subsequent slow evaporation of the solvent to verify the configuration of the *N*-acyliminium ion coupling product. The X-ray crystal

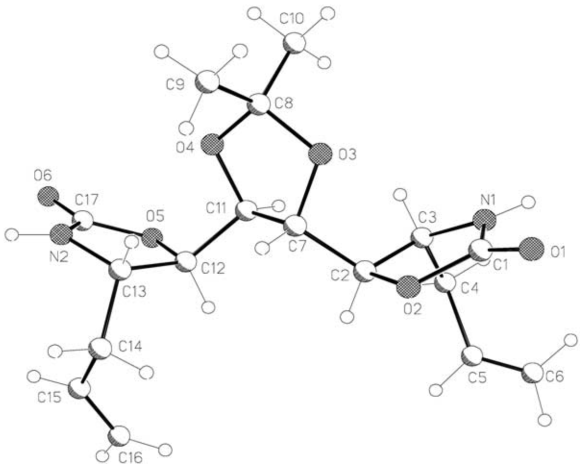


Figure 1. X-Ray crystal structure analysis of **9**.[13]

structure analysis of **9** (Fig. 1)[13] confirmed the di-*trans*-relationship between the newly introduced allylgroups and the substituents in the 5- and 5′-position of the oxazolidinone rings. Based on that the structure of the other nucleophilic substitution products could be easily determined by comparison of the ^3J(H-1,H-2) and ^3J(H-5,H-6) coupling constants. In case of **9** the value of these coupling constants is 3.7 Hz while for compounds **10–12** and **14** a similar range of $^3J=3.7–4.2$ Hz is observed. Nucleophilic substitution products with malonic acid derivatives generally have smaller coupling constants in both corresponding *cis*- and *trans*-substituted amide and oxazolidinone derivatives as shown earlier.[4b,14] Here these are $^3J=2.0$ Hz for di-*trans*-**13** and $^3J=3.0$ Hz for di-*cis*-**13**.

In conclusion, we were able to show that the concept of two directional synthesis can be applied to the field of electroorganic chemistry as an useful tool to synthesize highly functionalized oxazolidinone derivatives. The resulting compounds can be key intermediates in the synthesis of unnatural disaccharides and *C*-glycosides as well as oligoaminoalcohols with defined stereochemistry.

3. Experimental

3.1. General

All compounds are identified by microanalysis or high resolution mass spectroscopy, ^{1}H NMR, ^{13}C NMR and mass spectroscopy. Nuclear magnetic resonance (^{1}H NMR) spectra were determined in the reported solvent using a Bruker AC 400 (400 MHz) spectrometer. The same instrument was also used for the measurements of ^{13}C spectra (100.6 MHz). Chemical shifts are given in ppm downfield from tetramethylsilane. Mass spectra were obtained using A.E.I. MS-50 and MS-30 spectrometers. R_f-values were obtained using thin layer chromatography (TLC) on silica gel-coated plastic sheets (Merck silica gel F_{254}). All solvents were distilled before using. All *N*-acyliminium ion coupling reactions were carried out under an inert atmosphere of dry argon. The diastereoselectivities were determined by careful analysis of the ^{1}H NMR Spectra of the crude products or by gas chromatography (GC).

3.1.1. 1,6-Di-*O*-(*p*-toluenesulfonyl)-3,4-*O*-isopropylidene-D-mannitol (4). **4** was synthesized according to a known procedure[5] starting from D-mannitol. Selected spectroscopic data: ^{1}H NMR (CDCl$_3$) $\delta=7.77$, 7.84 (d, $J=8.4$ Hz, 4H), 7.31, 7.38 (d, $J=8.4$ Hz, 4H), 4.27, 4.33 (dd, $J=10.3$, 1.7 Hz, 2H), 4.03, 4.10 (dd, $J=10.3$, 5.8 Hz, 2H), 3.72–3.84 (m, 6H), 2.28, 2.52 (s, 6H), 1.23, 1.28 (s, 6H). ^{13}C NMR (CDCl$_3$) $\delta=145.1$, 132.5, 129.9, 128.1, 110.2, 79.0, 71.6, 71.1, 26.7, 21.7. MS (FAB) $m/z=553$ (M$^+$+Na), 531 (M$^+$+H), 515 (M$^+-$CH$_3$).

3.1.2. 1,2:5,6-Di-*N*,*O*-carbonyl-1,6-diamino-3,4-*O*-isopropylidene-D-mannitol (7). 1 g of 1,6-di-*O*-(*p*-toluenesulfonyl)-3,4-*O*-isopropyliden-D-mannitol **(4)** was dissolved in 20 ml *N*,*N*-dimethylformamide and then stirred with 0.6 g KOCN at 120°C for 6 h. Then *N*,*N*-dimethylformamide was removed in vacuo and the residue was purified by flash chromatography (CH$_2$Cl$_2$/MeOH 10:1). Yield: 304 mg (59%). Mp: 245°C (white crystals). R_f: 0.31 (CH$_2$Cl$_2$/MeOH 10:1). $[\alpha]_D^{25}=-24.8°$ ($c=1$, MeOH). ^{1}H NMR (CD$_3$OD) $\delta=4.81$ (dddd, $J=8.9$, 6.2, 3.5, 1.7 Hz, 2H, CHO), 4.12 (dd, $J=3.5$, 1.7 Hz, 2H, CHO), 3.71 (dd, $J=9.1$, 8.9 Hz, 2H, CH$_2$N), 3.57 (dd, $J=9.1$, 6.2 Hz, 2H, CH$_2$N), 1.41 (s, 6H, CH$_3$). ^{13}C NMR (CD$_3$OD) $\delta=161.5$, 112.3, 79.6, 77.4, 43.0, 27.3. MS (EI) $m/z=273$ (M$^+$+H), 257 (M$^+-$CH$_3$). HRMS calculated for C$_{11}$H$_{17}$N$_2$O$_6$ (M$^+$+H) 273.1099, found 273.1090. Anal. found C 48.01, H 6.09, N 10.06. Calculated for C$_{11}$H$_{16}$N$_2$O$_6$: C 48.53, H 5.92, N 10.29.

3.2. General procedures for the electrolyses

Starting material, supporting electrolyte and solvent were placed in an undivided water-cooled beaker type glass cell of 10 ml or 100 ml volume with graphite anode and cathode of equal size. The electrolyses were performed under stirring at 15°C and constant current. After stopping the electrolysis, solvent was removed in vacuo and the crude product worked up. Preparation of the electrodes: (1) Soxlett-extraction in MeOH for 2 h (2) methanol p.a. (ultrasound 15 min). All electrolyses were performed in methanol p.a.

3.2.1. (1*S*,6*S*)-1,6-Dimethoxy-1,2:5,6-di-*N*,*O*-carbonyl-1,6-diamino-3,4-*O*-isopropylidene-D-mannitol (8). A solution of **7** (2 g, 7.4 mmol) and PhSO$_3$Na (1.44 g, 8 mmol) in 40 ml of methanol p.a. was electrolyzed at a current density of 40 mA/cm^2 at 15°C until consumption of 13.2 F/mol. The solvent was removed in vacuo. Flash chromatography (CH$_2$Cl$_2$/MeOH 15:1) afforded 1.33 g of **3** (55%). Only the di-*trans*-diastereomer was obtained. Mp: 196°C (white crystals). R_f: 0.17 (CH$_2$Cl$_2$/MeOH 15:1). ^{1}H NMR (CD$_3$OD) $\delta=4.99$ (d, $J=1.5$ Hz, 2H, CHN), 4.50 (ddd, $J=4.2$, 1.7, 1.5 Hz, 2H, CHO), 4.08 (dd, $J=4.2$, 1.7 Hz, 2H, CHO), 3.38 (s, 6H, OCH$_3$), 1.45 (s, 6H, CH$_3$). ^{13}C NMR (CD$_3$OD) $\delta=160.0$, 112.7, 85.8, 83.4, 77.9, 54.6, 27.3. MS (EI) $m/z=317$ (M$^+-$CH$_3$), 301 (M$^+-$CH$_3$O). HRMS calculated for C$_{12}$H$_{17}$N$_2$O$_8$ (M$^+-$CH$_3$) 317.0985, found 317.0990. Anal. found C 46.65, H 5.89, N 7.88. Calculated for C$_{13}$H$_{20}$N$_2$O$_8$: C 46.99, H 6.07, N 8.43.

3.3. General procedure for the *N*-acyliminium ion coupling of 8

Method A. To a solution of **8** (166 mg, 0.5 mmol) in 10 ml CH_2Cl_2 1.5 ml of a 1 M solution of $TiCl_4$ in CH_2Cl_2 (1.5 mmol) were added at −78 °C. After 15 min 4 equiv. of the nucleophile were added. The solution was stirred at −78°C for 5 h and was then allowed to warm to rt. After stirring for 1 day, the Lewis acid was hydrolyzed by adding a saturated aqueous solution of $NaHCO_3$, and the mixture was extracted three times with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography (EtOAc/cyclohexane 4:1) afforded the products.

Method B. To a solution of **8** (166 mg, 0.5 mmol) in 10 ml CH_2Cl_2 3.3 ml of a 1 M solution of $TiCl_4$ in CH_2Cl_2 (3.3 mmol) were added at −78 °C. After 15 min 4 equiv. of the nucleophile and an additional 5 min later triethylamine (0.24 ml, 1.7 mmol) were added. The solution was stirred at −78 °C for 5 h and was then allowed to warm to rt. After stirring for 1 day, the Lewis acid was hydrolyzed by adding a saturated aqueous solution of $NaHCO_3$, and the mixture was extracted three times with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography (EtOAc/cyclohexane 4:1) affords the product.

Method C. To a solution of **8** (166 mg, 0.5 mmol) in 10 ml CH_2Cl_2 acetic anhydride (0.1 ml, 1 mmol) and BF_3–etherate (0.15 ml, 0.12 mmol) were added at −78 °C. After 15 min 4 equiv. of the nucleophile were added. The solution was stirred at −78 °C for 5 h and was then allowed to warm to rt. After stirring for 1 day, the Lewis acid was hydrolyzed by adding a saturated aqueous solution of $NaHCO_3$, and the mixture was extracted three times with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography (EtOAc/cyclohexane 4:1) affords the product.

3.3.1. (1*S*,6*S*)-1,6-Diallyl-1,2:5,6-di-*N*,*O*-carbonyl-1,6-diamino-3,4-*O*-isopropylidene-D-mannitol (9). **9** was synthesized according to method A using 0.32 ml of allyltrimethylsilane as nucleophile. Yield: 104 mg (59%, ds (di-*trans*): 91%). Mp: 162 °C (white crystals). R_f: 0.24 (EtOAc/cyclohexane 4:1). $[\alpha]_D^{25}=-34.3°$ (c=0.2, $CHCl_3$) (di-*trans*). ^1H NMR ($CDCl_3$) δ=7.08 (s, 2H, NH), 5.66 (dddd, J=14.7, 9.8, 7.1, 6.9 Hz, 2H, =CH), 5.14 (m, 4H, =CH_2), 4.26 (ptd, J=3.7, 1.2 Hz, 2H, CHO), 3.98 (dd, J=4.0, 1.2 Hz, 2H, CHO), 3.82 (ptd, J=6.4, 3.7 Hz, 2H, CHN), 2.28 (m, 4H, CH_2), 1.35 (s, 6H, CH_3). ^{13}C NMR ($CDCl_3$) δ=159.0, 131.6, 119.9, 111.2, 80.4, 78.2, 53.7, 39.9, 27.1. MS (EI) m/z=351 (M^+-H), 337 (M^+-CH_3). HRMS calculated for $C_{16}H_{21}N_2O_6$, (M^+-CH_3) 337.1400, found 337.1398. Anal. found C 57.95, H 6.84, N 7.68. Calculated for $C_{17}H_{24}N_2O_6$: C 57.94, H 6.86, N 7.95.

Crystal structure analysis of ***9***.[13] A colorless crystal of **9** with the dimensions 0.40×0.15×0.05 mm^3 was obtained by dissolving the substance in acetic acid ethyl ester. The crystal was measured on a Nonius KappaCCD diffractometer using Mo Kα-radiation (λ=0.71073 Å).Crystal data: $C_{17}H_{24}N_2O_6+0.5C_4H_8O_2$, M=396.43 g/mol, monoclinic space group $P2(1)$, a=10.9159(2), b=10.9044(3), c=17.9994(4) Å, V=2121.13(8) Å^3, Z=4, D_c=1.241 g/cm^3, F(848), μ(Mo Kα)=0.095 mm^{-1}. At 123(2) K in the range of $1.14<\theta<25.00°$ 16,583 reflections were measured with $R_I[I>2\sigma(I)]=0.0408$, wR_2 (F^2)=0.0808 and Goof=0.935. The structure was solved by direct methods and refined by full-matrix least square procedure.

3.3.2. (1*S*,6*S*)-1,6-Di-(2-chloromethyl-2-propenyl)-1,2:5,6-di-*N*,*O*-carbonyl-1,6-diamino-3,4-*O*-isopropylidene-D-mannitol (10). **10** was synthesized according to method A using 0.36 ml of 2-chloromethyl-allyltrimethylsilane as nucleophile. Yield: 131 mg (58%, ds (di-*trans*): 82%). Mp: 127°C (white crystals). R_f: 0.29 (EtOAc/cyclohexane 4:1). $[\alpha]_D^{25}=-48.9°$ (c=0.2, $CHCl_3$) (di-*trans*). ^1H NMR ($CDCl_3$) δ=7.44 (s, 2H, NH), 5.28, 5.08 (2s, 4H, =CH_2), 4.28 (ptd, J=3.7, 1.3 Hz, 2H, CHO), 4.02 (m, 8H, CH_2, CHO, CHN), 2.42 (m, 4H, CH_2), 1.33 (s, 6H, CH_3). ^{13}C NMR ($CDCl_3$) δ=159.0, 139.7, 118.5, 111.4, 80.6, 77.9, 52.4, 47.8, 39.4, 27.1. MS (EI) m/z=433 (M^+-CH_3), 359 ($M^+-C_4H_6Cl$). HRMS calculated for $C_{18}H_{23}Cl_2N_2O_6$ (M^+-CH_3) 433.0933, found 433.0929. Anal. found C 50.81, H 5.98, N 5.71. Calculated for $C_{19}H_{26}Cl_2N_2O_6$: C 50.79, H 5.83, N 6.23.

3.3.3. (1*S*,6*S*)-1,6-Di-(2-bromoallyl)-1,2:5,6-di-*N*,*O*-carbonyl-1,6-diamino-3,4-*O*-isopropylidene-D-mannitol (11). **11** was synthesized according to method A using 0.34 ml of 2-bromoallyl-trimethylsilane as nucleophile. Yield: 136 mg (53%, ds (di-*trans*): 83%). Mp: 88°C (yellow crystals). R_f: 0.29 (EtOAc/cyclohexane 4:1). $[\alpha]_D^{25}=-35.9°$ (c=0.18, $CHCl_3$) (di-*trans*). ^1H NMR (CD_2Cl_2) δ=6.78 (s, 2H, NH), 5.72 (d, J=2.0 Hz, 2H, =CH_2), 5.53 (d, J=2.0 Hz, 2H, =CH_2), 4.29 (ptd, J=3.7, 1.5 Hz, 2H, CHO), 4.07 (ptd, J=6.4, 3.7 Hz, 2H, CHN), 4.02 (dd, J=4.1, 1.5 Hz, 2H, CHO), 2.67 (dd, J=14.4, 7.2 Hz, 2H, CH_2), 2.63 (dd, J=14.4, 6.4 Hz, 2H, CH_2), 1.34 (s, 6H, CH_3). ^{13}C NMR ($CDCl_3$) δ=158.4, 127.1, 121.2, 111.4, 79.9, 78.1, 52.6, 47.2, 27.0. MS (EI) m/z=509 (M^++H), 494 (M^+-CH_3), 389 ($M^+-C_3H_4Br$). HRMS calculated for $C_{14}H_{18}BrN_2O_6$ ($M^+-C_3H_4Br$) 389.0348, found 389.0346. Anal. found C 39.97, H 4.47, N 5.25. Calculated for $C_{17}H_{22}Br_2N_2O_6$: C 40.02, H 4.35, N 5.49.

3.3.4. (1*S*,6*S*)-1,6-Di-(2-acetoxymethyl-2-propenyl)-1,2:5,6-di-*N*,*O*-carbonyl-1,6-diamino-3,4-*O*-isopropylidene-D-mannitol (12). **12** was synthesized according to method A using 0.26 ml of 2-acetoxymethyl–allyltrimethylsilane as nucleophile. Yield: 76 mg (38%, ds (di-*trans*): 85%). Colorless oil. R_f: 0.16 (EtOAc/cyclohexane 4:1). ^1H NMR (CD_2Cl_2) δ=6.78 (s, 2H, NH), 5.14, 5.03 (2s, 4H, =CH_2), 4.48 (d, J=14.5 Hz, 2H, CH_2), 4.42 (d, J=14.5 Hz, 2H, CH_2) 4.25 (ptd, J=3.8, 1.5 Hz, 2H, CHO), 4.01 (dd, J=4.2, 1.5 Hz, 2H, CHO), 3.94 (ptd, J=6.9, 3.8 Hz, 2H, CHN), 2.29 (m, 4H, CH_2), 2.0 (s, 6H, CH_3), 1.35 (s, 6H, CH_3). ^{13}C NMR ($CDCl_3$) δ=170.7, 158.9, 138.4, 117.1, 111.2, 82.1, 80.5, 66.6, 52.6, 39.7, 27.0, 20.9. MS (EI) m/z=496 (M^+), 481 (M^+-CH_3), 383 ($M^+-C_6H_9O_2$). HRMS calculated for $C_{23}H_{32}N_2O_{10}$ (M^+) 496.2057, found 496.2061.

3.3.5. (1*S*,6*S*)-1,6-Di-(di(ethoxycarbonyl)methyl)-1,2:5,6-di-*N*,*O*-carbonyl-1,6-diamino-3,4-*O*-isopropylidene-D-mannitol (13). **13** was synthesized according to method B using 0.3 ml of malonic acid diethylester as nucleophile. Yield: 171 mg (57% ds (di-*trans*): 88%). Mp: 144°C (white crystals, di-*trans*), yellow oil (di-*cis*). R_f: 0.39 (di-*trans*), 0.25 (di-*cis*) (EtOAc/cyclohexane 4:1). $[\alpha]_D^{25}=-40{,}1°$ (c=0.22, $CHCl_3$) (di-*trans*). ^1H NMR ($CDCl_3$), di-*trans*, δ=6.49 (s, 2H, NH), 4.54 (m, 2H, CHO), 4.31 (dd, J=7.4, 2.0 Hz, 2H, CHN), 4.18, 4.17 (2q, J=7.1 Hz, 8H, CH_2), 4.13 (dd, J=3.6, 1.6 Hz, 2H, CHO), 3.53 (d, J=7.4 Hz, 2H, CH), 1.34 (s, 6H, CH_3), 1.21, 1.20 (2t, J=7.1 Hz, 12H, CH_3); di-*cis*, δ=6.71 (s, 2H, NH), 4.56 (m, 2H, CHO), 4.32 (dd, J=7.4, 3.0 Hz, 2H, CHN), 4.19, 4.18 (2q, J=7.1 Hz, 8H, CH_2), 4.15 (m, 2H, CHO), 3.54 (d, J=7.4 Hz, 2H, CH), 1.34 (s, 6H, CH_3), 1.22, 1.21 (2t, J=7.1 Hz, 12H, CH_3). ^{13}C NMR ($CDCl_3$), di-*trans*, δ=166.6, 166.5, 157.6, 111.0, 78.5, 78.0, 62.5, 62.4, 56.0, 53.3, 26.9, 14.0, 13.9; di-*cis*, δ=166.6, 166.5, 157.8, 111.0, 78.5, 78.0, 62.5, 62.3, 56.0, 53.4, 26.9, 14.0, 13.9. MS (EI) m/z=573 (M^+-CH_3), 543 ($M^+-C_2H_5O$). HRMS calculated for $C_{24}H_{33}N_2O_{14}$ (M^+-CH_3) 573.1944, found 573.1931. Anal. found C 50.87, H 6.15, N 4.63. Calculated for $C_{25}H_{36}N_2O_{14}$: C 51.02, H 6.16, N 4.76.

3.3.6. (1*S*,6*S*)-1,6-Di-allenyl-1,2:5,6-di-*N*,*O*-carbonyl-1,6-diamino-3,4-*O*-isopropylidene-D-mannitol (14). 14 was synthesized according to method C using 0.3 ml of propargyltrimethylsilane as nucleophile. Yield: 30 mg (17%). Yellow oil. R_f: 0.29 (EtOAc/cyclohexane 4:1). ^1H NMR ($CDCl_3$) δ=6.41 (s, 2H, NH), 5.19 (ptd, J=6.6, 6.4 Hz, 2H, =CH), 4.92 (dd, J=6.4, 1.8 Hz, 2H, $=CH_2$), 4.91 (dd, J=6.6, 1.8 Hz, 2H, $=CH_2$), 4.42 (ptd, J=4.2, 1.4 Hz, 2H, CHO), 4.30 (dd, J=6.4, 4.2 Hz, 2H, CHN), 4.06 (dd, J=3.8, 1.4 Hz, 2H, CHO), 1.38 (s, 6H, CH_3). ^{13}C NMR ($CDCl_3$) δ=207.8, 158.1, 111.4, 91.1, 81.4, 79.5, 77.7, 52.9, 27.1. MS (EI) m/z=348 (M^+), 333 (M^+-CH_3), 309 ($M^+-C_3H_3$). HRMS calculated for $C_{17}H_{20}N_2O_6$ (M^+) 348.1321, found 348.1320.

Acknowledgements

M. Z. is thankful for the financial support by the Deutsche Forschungsgemeinschaft (Ste 227/21-3).

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