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Synthesis of a new chiral oxazolidinone auxiliary based on D-xylose and its application to the Staudinger reaction

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Abstract

The synthesis of a new chiral oxazolidinone auxiliary based on D-xylose is described which is employed in diastereoselective Staudinger-type β-lactam syntheses. Using 2-chloro-1-methylpyridinium iodide as the dehydrating reagent, the reaction of auxiliary tethered acetic acid with acyclic or cyclic imines gave the desired β-lactams in good yields with excellent *cis*- or *trans*-selectivity depending on the geometry of the imine. X-Ray structure determination of one of the obtained compounds corroborated the absolute configuration for all *cis* products.

1. Introduction

The β-lactam structure is a fundamental skeleton in penicillins, cephalosporins and related antibiotics,[1] and the construction of naturally occurring or unnatural β-lactams has been widely investigated during the past decades.[2] Research in this field is important for two reasons: first, because of the need for new derivatives with different biological properties displaying a higher and broader antibiotic activity, and, second, because some bacteria become multi-resistant towards presently applied antibiotics, so that new compounds are required.[3] Among various methods for the construction of β-lactams, the Staudinger reaction between ketenes and imines is one of the most efficient methods.[4] Utilization of cyclic imines possessing *cis* geometry in this reaction results in the formation of *trans*-β-lactams, whereas acyclic imines possessing *trans* geometry typically have a propensity towards the formation of *cis*-β-lactams. The latter method in particular provides a useful and economical access to β-lactams, mainly due to the ready availability of ketenes generated by dehydrohalogenation of their corresponding acid chlorides or obtained from activated carboxylic acids by using a tertiary organic base. In the middle eighties Evans and

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Sjogren introduced diastereoselectivity to the ketene–imine reaction by attaching a chiral oxazolidinone auxiliary to the ketene.[5] They generated an aminoketene in situ at low temperature (−78°C) from the oxazolidinylacetic acid chloride and triethylamine, which, upon treatment with a Schiff base, provided 3-amino β-lactams in good yields and excellent diastereoselectivity, typically >95:<5 dr.

A number of chiral auxiliaries containing oxazolidinone structure elements developed so far were derived from naturally occurring compounds such as terpenes[6] and carbohydrates.[7] A simple method to introduce the oxazolidinone moiety into free aldoses or ketoses in one step was found in our laboratory in co-operation with Hungarian colleagues.[8] For example, the reaction of inexpensive D-xylose with potassium cyanate in buffered aqueous solution led to the 1,2-annulated cyclic carbamate **1** (Fig. 1). Its isopropylidene- and benzylidene-protected derivatives **2** and **3** were successfully applied as chiral auxiliaries in a number of different diastereoselective reactions[9] or as CDAs for the resolution of carboxylic and sulphonic acids.[10] For the construction of β-lactams following the Evans procedure the acetal-protected compounds **2** and **3** are not suitable because of their lability towards acidic conditions. Therefore, we were looking for a chiral auxiliary based on D-xylose which could be applied for this reaction sequence.

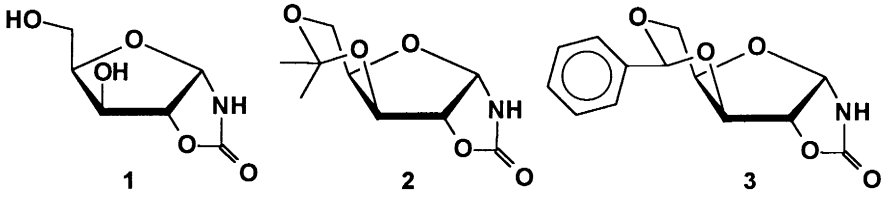
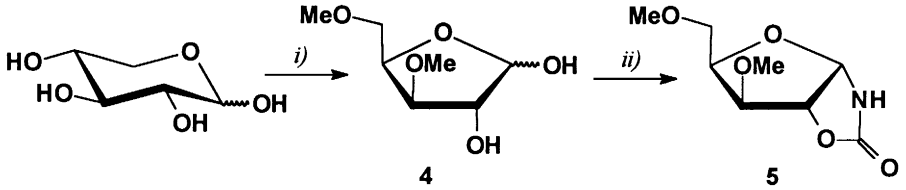


Fig. 1. 1-*N*,2-*O*-Carbonyl-α-D-xylofuranosylamine **1** and its acetal-protected derivatives **2** and **3**

2. Results and discussion

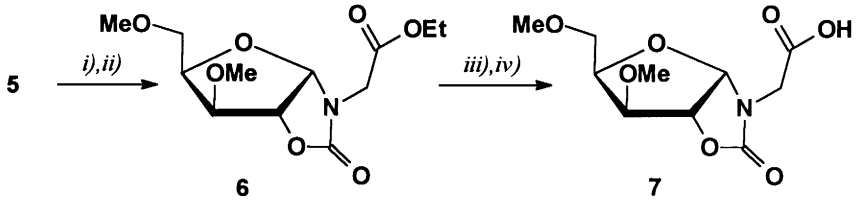
For the protection of the free hydroxyl groups alkyl ethers, especially methyl ethers, seemed to be most effective because of their high stability against a multitude of reagents. But in the reaction of **1** with methyl iodide in the usual manner, *O*-alkylation competed with the substitution at heterocyclic nitrogen. For this reason we followed another strategy which was developed by our group.[11] First the protection of the hydroxyl functions, and then introducing the heterocyclic structure. Starting from D-xylose we prepared 3,5-di-*O*-methyl-D-xylofuranose **4** in a four-step synthesis according to the literature[12] in 70% overall yield. Using the potassium cyanate methodology we were then able to synthesize 1-*N*,2-*O*-carbonyl-3,5-di-*O*-methyl-α-D-xylofuranosylamine **5** from **4** in 78% yield (Scheme 1).



Scheme 1. Synthesis of **5**. Reagents and conditions: (i) four steps, 70%; (ii) KOCN, NH_4Cl, H_2O, 60°C, 6 h, 78%

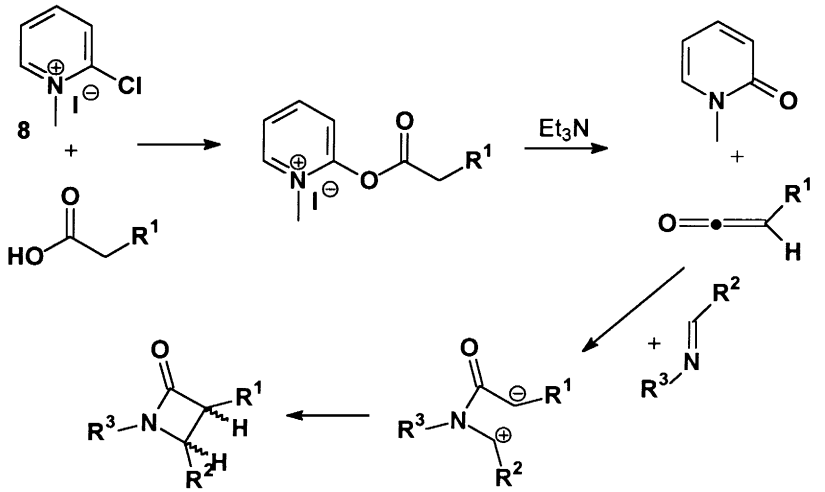
Adopting the Evans procedure the *N*-alkylation of **5** with ethyl bromoacetate gave **6** in 75% yield as depicted in Scheme 2. The corresponding acid **7** was synthesized in 83% yield by treatment of **6** with $LiOH \cdot H_2O$ and subsequent acidification with 1 M HCl. This last step is the reason why acetal-protective groups are absolutely inapplicable. The transformation of the carboxylic acid to the acid chloride with

oxalyl chloride and catalytic amounts of DMF is also possible, but isolation and purification proved difficult. This fact is in agreement with observations from other groups,[5] who generally used only the crude acid chlorides in all subsequent cycloadditions with imines. We also tried to avoid these compounds as starting materials because of their poor stability.



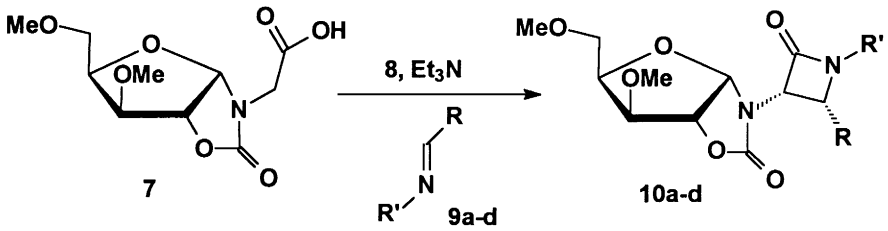
Scheme 2. Synthesis of ketene precursor **7**. Reagents and conditions: (i) NaH, DMF, 25°C, 20 min; (ii) $BrCH_2COOEt$, 30 min; (iii) $LiOH \cdot H_2O$, MeOH:H_2O, 4:1, 25°C, 2 h; (iv) 1 M HCl, pH 1

Thus, we were looking for a method to generate ketenes from carboxylic acids under moderate conditions. Among various other dehydrating agents we turned our attention to Mukaiyama's reagent **8** (2-chloro-1-methylpyridinium iodide).[13] This reagent (Scheme 3) has been applied to the generation of ketenes from carboxylic acids,[14] and applications to the Staudinger reaction have already been reported.[14,15] Even though this reaction has been known for over 90 years the mechanism remains obscure. The most popular explanation implies that the generated ketene and the imine form a zwitterionic intermediate which then furnishes the cyclized product. Additionally, the reaction has the advantage that only two products, the desired β-lactam and 1-methyl-2-pyridone, are observed.



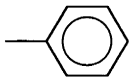
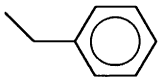
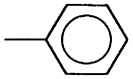
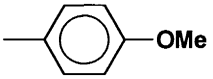
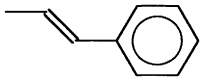
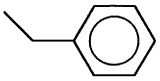
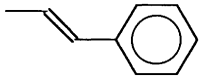
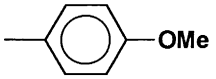
Scheme 3. Mukaiyama's reagent (2-chloro-1-methylpyridinium iodide) **8** as dehydrating reagent for the formation of ketenes

Using **8** and different acyclic imines we were able to synthesize the β-lactams **10a**–**d** at moderate temperature in good yields and excellent stereoselectivity (Scheme 4, Table 1). Best results were found when triethylamine and the imine were subsequently added at 0°C to a solution (suspension) of the acid **7** and **8** in dichloromethane, followed by stirring at room temperature until the reaction reached completion. For all compounds, we found a ratio of >99:1 of the two possible diastereomeric *cis* products. As expected, no *trans*-configured product could be observed. The configuration of the *cis*-isomer was assigned by analysis of the coupling constants ($J \approx 5$ Hz) between the respective protons, which is in agreement with results reported in the literature.[5]



Scheme 4. β-Lactam formation

Table 1
Yields and diastereomeric ratios of **10a**–**d**

compound	R	R'	yield [%][a]	dr[b]
10a			67	>99:1
10b			69	>99:1
10c			71	>99:1
10d			58	>99:1

[a] After column chromatography.

[b] Determined by 500 MHz ^{1}H NMR spectroscopy using 1D Win NMR software from Bruker.

The absolute configuration could be determined by X-ray structure analysis of **10d** (Fig. 2, Table 2).[16] Because of only small variations of the imine substituents we expect the same (3*S*,4*R*)-configuration for **10a**–**c** comparable to results by Evans.

Further experiments ought to show that utilization of cyclic imines possessing a *cis* geometry results in the formation of *trans*-β-lactams. Reacting the two 3-thiazoline derivatives **11a** and **11b**[17] with **7**, the *trans*-isopenam products **12a** and **12b** were obtained with a ratio of diastereomers of >99:1 (Scheme 5). No *cis*-isomers could actually be observed.

Yet we were not able to determine the absolute configuration of the substituents in the β-lactam ring of the major *trans*-diastereomers **12a** and **12b**.

3. Conclusions

We have shown that **5** is an excellent chiral auxiliary in the Staudinger reaction for the construction of β-lactams. Adopting the Evans methodology, the ketene precursor **7** was synthesized and employed in the reaction with imines using 2-chloro-1-methylpyridinium iodide as the dehydrating reagent. The β-lactam derivatives were obtained with excellent diastereoselectivity and in good yields. As expected, cyclic imines furnished *trans* products whereas acyclic imines possessing *trans* geometry gave *cis* products. In one case we could determine the absolute configuration by X-ray analysis. The cleavage of the β-lactam moiety from the auxiliary is currently in progress.

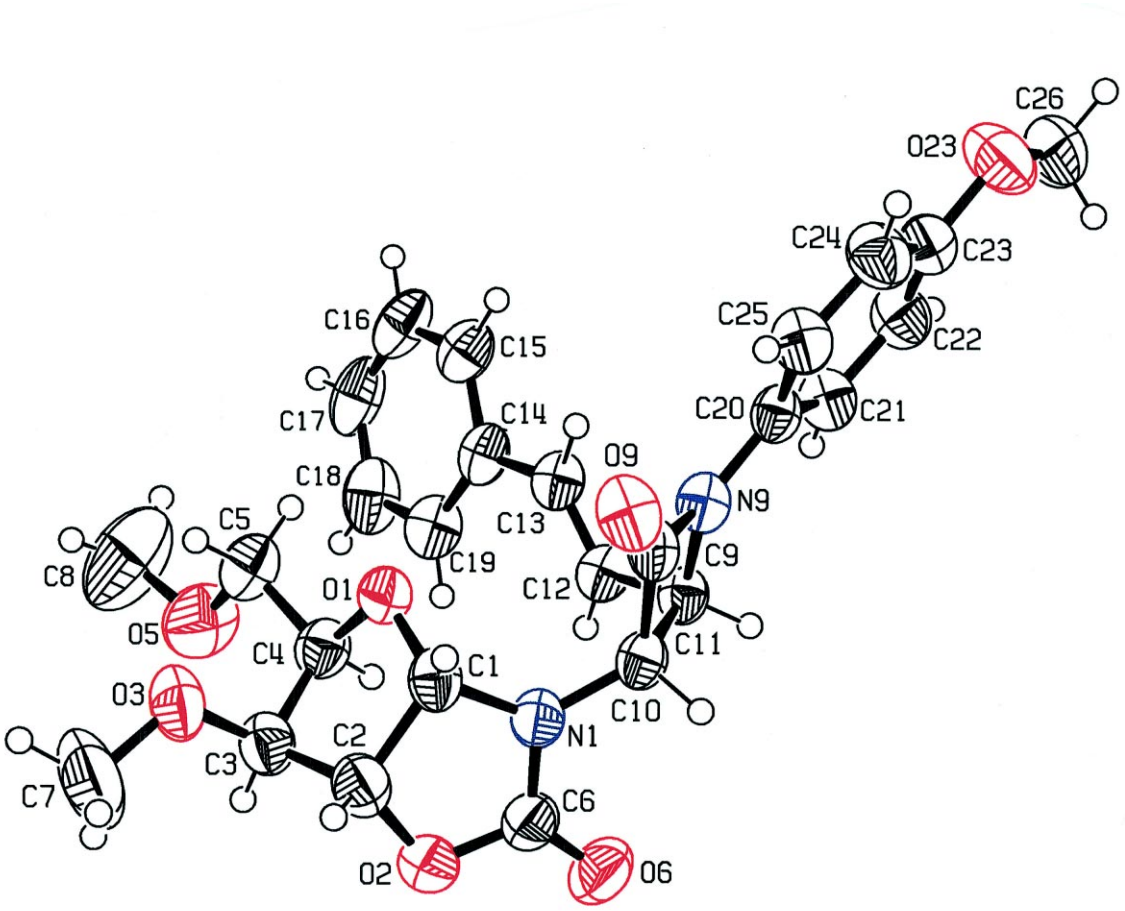


Fig. 2. ORTEP presentation of **10d**

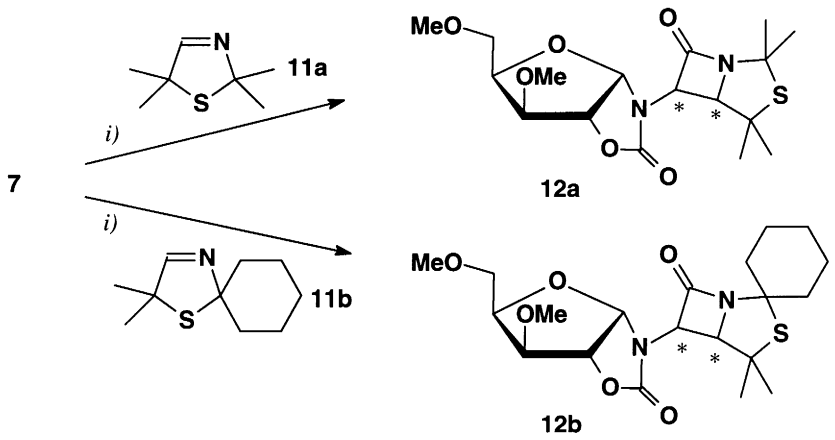
4. Experimental

All solvents were purified and dried by standard procedures. The imines and the 3,5-di-*O*-methyl-D-xylofuranose were prepared according to literature procedures. All other reagents were purchased from Aldrich or Fluka. Products were purified, if necessary, by column chromatography on silica gel 60 F_{254} (0.063–0.200 mm or 0.040–0.063 mm). Thin-layer chromatography was performed on aluminium TLC-layer silica gel 60 F_{254} from Merck. Detection was done by treatment with 10% sulphuric acid and heating with a heat-gun. NMR spectra were recorded on a Bruker Avance 500 (^{1}H NMR=500.1; ^{13}C NMR=125.8 MHz). Chemical shifts are reported on the δ-scale (ppm) relative to residual non-deuterated solvent signals in $CDCl_3$ as internal standard. Mass spectra were taken on a Finnigan MAT 212 with datasystem MSS 300 and a Finnigan MAT 95 (high resolution mass spectrometry, HR MS) using chemical ionization with *iso*-butane as reactant gas. Melting points were determined on a hot-stage microscope SM-Lux from Leitz and are not corrected. Optical rotations were measured on a Perkin–Elmer Polarimeter PE 343 in a 1 dm cell.

Table 2
Crystallographic data[a] of (3*S*,4*R*)-**10d**

Molecular Formula	$C_{26}H_{28}N_2O_7$
Formular Weight [g/mol]	480.50
Crystal Dimension [mm]	0.70 × 0.40 × 0.30
Melting Point [°C]	144
Crystal System	monoclinic
Space Group	C_2
Cell Dimensions:	
a [pm]	2865.4 (2)
b [pm]	672.2 (1), β = 106.88° (1)
c [pm]	1339.3 (1)
V [pm^3]	2468.3 (3) × 10^6
Z	4
F(000)	1016
Calculated Density D_x [g/cm^3]	1.293
μ [cm^{-1}]	0.783
λ (Cu-K_α) [pm]	154.178
2 θ Range [deg]	3.22 – 76.30
Reflexions Measured	2970
Symmetry Independent Reflexions	2819
Reflexions with (F > 2σ (F))	2659
Number of Refined Parameters	348
Ratio of Valued Reflections to Parameters	7.6
Final Residue Factors:	
R_{all}	0.0557
R_{gt}	0.0529
ωR_{ref}	0.1394
ωR_{gt}	0.1348
Flack Parameter X	0.03
Goodness of fit S	1.074
Diffractometer	Enraf-Nonius CAD4
Measurement at room temperature	

[a] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-136381. Copies of the data can be obtained free of charge from the following address: The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (+44) 1223 336033; E-mail: deposit@ccdc.cam.ac.uk].



Scheme 5. Formation of isopenam derivatives **12a** and **12b**. Reagents and conditions: (i) **8**, 0°C, Et_3N, then **11a** or **11b**, 0→25°C

4.1. 1-N,*2*-O-*Carbonyl-3,5-di*-O-*methyl*-α-D-*xylofuranosylamine* ***5***

A solution of 9 g (51 mmol) 3,5-di-*O*-methyl-D-xylofuranose **4**, 6.2 g (76 mmol) potassium cyanate and 4.1 g (76 mmol) ammonium chloride in 15 ml water was stirred for 6 h at 60°C. The mixture was extracted with dichloromethane and the organic layer was dried over Na_2SO_4. Concentration under reduced pressure and recrystallization of the residue with ethyl acetate/petroleum ether gave 8.0 g (0.51 mmol, 78%) of **5**. Mp 115°C; $[\alpha]_D^{20}=-3.7$ (*c* 1.3, acetone); ^{1}H (500.135 MHz, $CDCl_3$, δ in ppm): δ=3.387 (s, OCH_3), 3.401 (s, OCH_3), 3.599 (dd, 1H, $^2J_{5,5'}=-10.8$, H-5′), 3.637 (dd, 1H, H-5), 3.838 (d, 1H, $^3J_{3,4}$=3.2, H-3), 4.183 (m, 1H, $^3J_{4,5'}$=7.00, $^3J_{4,5}$=4.5, H-4), 4.875 (d, 1H, $^3J_{2,3}$=0, H-2), 5.715 (d, 1H, $^3J_{1,2}$=5.72, H-1), 6.692 (s, 1H, NH); ^{13}C (125.76 MHz, $CDCl_3$, δ in ppm): δ=58.06 (OCH_3), 59.18 (OCH_3), 69.81 (C-5), 77.56 (C-4), 81.26 (C-2), 83.38 (C-3), 85.87 (C-1), 157.30 (NCO); MS (CI, *iso*-butane): *m/z* (%)=204 (100) [MH^+]. Anal. calcd for $C_8H_{13}NO_5$: C 47.29, H 6.45, N 6.89. Found: C 46.61, H 6.32, N 6.43.

4.2. 1-N-*(Ethoxycarbonylmethyl)-1*-N,*2*-O-*carbonyl-3,5-di*-O-*methyl*-α-D-*xylofuranosylamine* ***6***

1-*N*,2-*O*-Carbonyl-3,5-di-*O*-methyl-α-D-xylofuranosylamine **5 (**3 g, 14.8 mmol) was dissolved under N_2 in 100 ml dry DMF. After addition of 0.65 g (16.2 mmol) sodium hydride (60% dispersion in oil) the suspension was stirred for 30 min at room temperature. Then 1.79 ml (16.2 mmol) α-bromo ethyl acetate in 10 ml DMF were added and the solution was stirred until reaction reached completion (TLC-control). The mixture was quenched cautiously with water and evaporated to dryness. The residue was extracted with dichloromethane and the organic layer was washed with water. The solution was dried over Na_2SO_4 and evaporated under reduced pressure. Purification of the crude product by column chromatography (ethyl acetate:petroleum ether, 40:60) yielded 3.22 g (11.1 mmol, 75%) of the acetate **6**. Syrup; $[\alpha]_D^{20}=+48.3$ (*c* 0.4, acetone); ^{1}H (500.135 MHz, $CDCl_3$, δ in ppm): δ=1.247 (s, 3H, ^3J=7.0, OCH_2CH_3), 3.355 (s, 3H, OCH_3), 3.409 (s, 3H, OCH_3), 3.579 (dd, 1H, $^2J_{5,5'}=-10.8$, H-5′), 3.634 (dd, 1H, H-5), 3.855 (d, 1H, $^3J_{3,4}$=3.2, H-3), 3.942 (d, 1H, $^2J=-17.8$, NC*H*′H), 4.140 (d, 1H, $^2J=-17.8$, NCH′*H*), 4.177 (q, 2H, ^3J=7.0, OCH_2CH_3), 4.198 (m, 1H, $^3J_{4,5}$=4.4, $^3J_{4,5'}$=7.0, H-4), 4.867 (d, 1H, $^3J_{2,3}$=0, H-2), 5.747 (d, 1H, $^3J_{1,2}$=5.7, H-1); ^{13}C (125.76 MHz, $CDCl_3$, δ in ppm): δ=14.04 (OCH_2CH_3), 43.05 (NCH_2), 58.06 (OCH_3), 59.21 (OCH_3), 61.63 (OCH_2CH_3), 69.59 (C-5), 77.96 (C-4), 79.13 (C-2), 83.58 (C-3), 88.78 (C-1), 156.17 (NCO), 168.19 (C=O); MS (CI, *iso*-butane): *m/z* (%)=290 (100)

[MH^+]; HRMS (*iso*-butane): calcd 290.1239. Found 290.1183. Anal. calcd for $C_{12}H_{19}NO_7$: C 49.82, H 6.62, N 4.84. Found: C 49.50, H 6.67, N 3.43.

4.3. *1*-N-*(Carboxymethyl)-1*-N,*2*-O-*carbonyl-3,5-di*-O-*methyl*-α-D-*xylofuranosylamine* ***7***

Ester **6** (3.1 g, 10.7 mmol) was dissolved in 100 ml MeOH/H_2O and 1.8 g (42.9 mmol) $LiOH \cdot H_2O$ were added. The solution was stirred for 2 h at 25°C. Then the solution's pH-factor was set down to 1 dropwise using 1 M HCl. After extraction twice with 50 ml dichloromethane, the organic layer was washed with sat. NaCl solution and dried over $MgSO_4$. Removal of the solvent gave the crude product which was finally high vacuum dried to yield 2.33 g (8.9 mmol, 83%) of the acid **7**. This product was used for the next steps without any further purifications. Mp 115°C; $[\alpha]_D^{20}$=+52.9 (*c* 1.0, acetone); ^{1}H (500.135 MHz, $CDCl_3$, δ in ppm): δ=3.373 (s, 3H, OCH_3), 3.415 (s, 3H, OCH_3), 3.608 (dd, 1H, $^2J_{5,5'}$=−10.8, H-5′), 3.665 (dd, 1H, H-5), 3.869 (d, 1H, $^3J_{3,4}$=3.2, H-3), 4.015 (d, 1H, ^2J=−19.1, NC*H*′H), 4.157 (d, 1H, ^2J=−19.1, NCH′*H*), 4.180 (m, 1H, $^3J_{4,5}$=4.4, $^3J_{4,5'}$=7.0, H-4), 4.892 (d, 1H, $^3J_{2,3}$=0, H-2), 5.749 (d, 1H, $^3J_{1,2}$=5.7, H-1), 8.423 (s, 1H, OH); ^{13}C (125.76 MHz, $CDCl_3$, δ in ppm): δ=42.87 (NCH_2), 58.05 (OCH_3), 59.18 (OCH_3), 69.64 (C-5), 77.94 (C-4), 79.27 (C-2), 83.53 (C-3), 88.90 (C-1), 156.49 (NCO), 171.59 (C=O); MS (CI, *iso*-butane): *m/z* (%)=262 (100) [MH^+]. Anal. calcd for $C_{10}H_{15}NO_7$: C 45.98, H 5.79, N 5.36. Found: C 46.60, H 5.86, N 4.72.

4.4. *General procedure for the reaction of* ***7*** *with imines* ***9a–d*** *and* ***11a,b***

To 300 mg (1.15 mmol) of **7** in 3 ml abs. dichloromethane were added 309 mg (1.21 mmol) 2-chloro-1-methylpyridinium iodide **8** and the mixture was cooled to 0°C. Under an N_2 atmosphere the mixture was treated with 0.39 ml (2.76 mmol) of freshly distilled triethylamine and then 1.38 mmol of the imine were added in one portion. The mixture was stirred for 15 min at 0°C and then at 25°C until the reaction was complete (TLC-control). The solution was quenched with 4 ml of water and extracted exhaustively with 3×10 ml dichloromethane. The combined organic layers were dried over Na_2SO_4 and evaporated to dryness. The NMR spectra from this mixture revealed the diastereomeric ratio of the β-lactams. The major product was separated by column chromatography with ethyl acetate as eluant.

4.5. *1*-N-*[*cis-*(3′*S,*4′*R*)-2′-Oxo-4′-phenyl-1′-phenyl-3′-azetidinyl]-1*-N,*2*-O-*carbonyl-3,5-di*-O-*methyl*-α-D-*xylofuranosylamine* ***10a***

Compound **7** (300 mg, 1.15 mmol) gave 336 mg (0.77 mmol, 67%) of **10a** upon treatment with 268 mg (1.38 mmol) of benzylbenzylideneamine **9a** according to the general procedure. Mp 119°C; $[\alpha]_D^{20}$=−99 (*c* 1.0, acetone); ^{1}H (500.135 MHz, $CDCl_3$, δ in ppm): δ=3.010 (m, 1H, $^3J_{4,5}$=7.0, $^3J_{4,5'}$=5.1, H-4), 3.314 (s, 3H, OCH_3), 3.331 (s, 3H, OCH_3), 3.334 (dd, 1H, $^2J_{5,5'}$=−9.5, H-5′), 3.495 (dd, 1H, H-5), 3.545 (d, 1H, $^3J_{3,4}$=3.2, H-3), 4.050 (d, 1H, ^2J=−14.6, NCH_2), 4.609 (d, 1H, ^3J=5.7, NCHPh), 4.758 (d, 1H, ^3J=5.7, NCH), 4.985 (d, 1H, ^2J=−14.6, NCH_2), 5.036 (d, 1H, $^3J_{2,3}$=0, H-2), 5.777 (d, 1H, $^3J_{1,2}$=5.7, H-1), 7.175 (dd, 2H, J=7.63, 1.90, phenyl), 7.263-7.364 (m, 8H, phenyl); ^{13}C (125.76 MHz, $CDCl_3$, δ in ppm): δ=45.40 (NCH_2), 58.06 (OCH_3), 59.20 (OCH_3), 59.87 (NCHPh), 63.43 (NCH), 68.50 (C-5), 76.75 (C-4), 80.12 (C-2), 82.42 (C-3), 86.82 (C-1), 127.58–134.54 (12 C, phenyl), 155.41 (NCO), 162.81 (C=O); MS (CI, *iso*-butane): *m/z* (%)=438.8 (100) [MH^+]. Anal. calcd for $C_{24}H_{26}N_2O_6$: C 65.74, H 5.98, N 6.39. Found: C 65.30, H 6.13, N 5.89.

4.6. 1-N-*[*cis-*(3′*S,*4′*R*)-2′-Oxo-4′-phenyl-1′-(*p*-methoxyphenyl)-3′-azetidinyl]-1*-N,*2*-O-*carbonyl-3,5-di*-O-*methyl-α*-D-*xylofuranosylamine **10b***

Compound **7** (300 mg, 1.15 mmol) gave 360 mg (0.79 mmol, 69%) of β-lactam **10b** upon treatment with 291 mg (1.38 mmol) benzylidene-(4-methoxyphenyl)-amine **9b**. Mp 61°C; $[\alpha]_D^{20}=-35$ (*c* 1.05, chloroform); ^{1}H (500.135 MHz, $CDCl_3$, δ in ppm): δ=2.779 (m, 1H, $^3J_{4,5}$=9.2, $^3J_{4,5'}$=4.9, H-4), 3.277 (s, 3H, OCH_3), 3.316 (s, 3H, OCH_3), 3.209 (dd, 1H, $^2J_{5,5'}=-9.3$, H-5′), 3.425 (dd, 1H, H-5), 3.527 (d, 1H, $^3J_{3,4}$=3.3, H-3), 3.752 (s, 3H, CH_3OPh), 4.659 (d, 1H, $^3J_{2,3}$=0, H-2), 5.259 (d, 1H, ^3J=5.5, NCHPh), 5.360 (d, 1H, ^3J=5.5, NCH), 5.869 (d, 1H, $^3J_{1,2}$=5.5, H-1), 6.802–6.834 (m, 2H, phenyl), 7.279-7.351 (m, 7H, phenyl); ^{13}C (125.76 MHz, $CDCl_3$, δ in ppm): δ=55.40 ($C_{arom}OCH_3$), 58.12 (OCH_3), 59.16 (OCH_3), 60.47 (NCHPh), 62.53 (NCH), 68.22 (C-5), 76.60 (C-4), 80.39 (C-2), 82.26 (C-3), 86.61 (C-1), 114.34 (2C, phenyl), 118.65 (2C, phenyl), 127.56-132.63 (6C, phenyl), 130.69 (NC_{arom}), 155.63 (NCO), 156.56 ($C_{arom}OCH_3$), 159.39 (C=O); MS (CI, *iso*-butane): *m/z* (%)=455 (100) [MH^+]. Anal. calcd for $C_{24}H_{26}N_2O_7$: C 63.43, H 5.77, N 6.16. Found: C 63.39, H 5.43, N 6.01.

4.7. 1-N-*[*cis-*(3′*S,*4′*R*)-2′-Oxo-4′-(2-phenylethenyl)-1′-(phenylmethyl)-3′-azetidinyl]-1*-N,*2*-O-*carbonyl-3,5-di*-O-*methyl-α*-D-*xylofuranosylamine **10c***

Reaction of 300 mg (1.15 mmol) of **7** with 305 mg (1.38 mmol) benzyl-((*E*)-3-phenylallylidene)amine **9c**, according to the general procedure, gave 380 mg (0.82 mmol, 71%) of **10c**. Mp 161°C; $[\alpha]_D^{20}=-60$ (*c* 1.03, chloroform); ^{1}H (500.135 MHz, $CDCl_3$, δ in ppm): δ=3.329 (s, 3H, OCH_3), 3.386 (s, 3H, OCH_3), 3.528 (dd, 1H, $^2J_{5,5'}=-9.9$, H-5′), 3.642 (dd, 1H, H-5), 3.793 (d, 1H, $^3J_{3,4}$=3.3, H-3), 4.041 (m, 1H, $^3J_{4,5}$=5.5, $^3J_{4,5'}$=6.0, H-4), 4.216 (d, 1H, $^2J=-15.4$, NCH_2), 4.317 (dd, 1H, ^3J=4.9, 8.8, C*H*CHCHPh), 4.606 (d, 1H, $^2J=-15.4$, NCH_2), 4.829 (d, 1H, $^3J_{2,3}$=0, H-2), 5.064 (d, 1H, ^3J=4.9, NCH), 6.007 (d, 1H, $^3J_{1,2}$=5.5, H-1), 6.139 (dd, 1H, ^3J=8.8, 15.9, CHC*H*CHPh) 6.538 (d, 1H, ^3J=15.9, CHCHC*H*Ph), 7.235–7.363 (m, 10H, phenyl); ^{13}C (125.76 MHz, $CDCl_3$, δ in ppm): δ=45.08 (NCH_2), 58.12 (OCH_3), 59.14 (OCH_3), 60.31 (*C*HCHCHPh), 62.90 (NCH), 69.21 (C-5), 77.70 (C-4), 79.92 (C-2), 82.84 (C-3), 87.41 (C-1), 122.70 (CH*C*HCHPh) 126.88–135.71 (12C, phenyl), 137.43 (CHCH*C*HPh), 155.76 (NCO), 162.65 (C=O); MS (CI, *iso*-butane): *m/z* (%)=465 (100) [MH^+]. Anal. calcd for $C_{26}H_{28}N_2O_6$: C 67.23, H 6.08, N 6.03. Found: C 67.00, H 6.14, N 5.90.

4.8. 1-N-*[*cis-*(3′*S,*4′*R*)-[2′-Oxo-4′-(2-phenylethenyl)-1′-(*p*-methoxyphenyl)-3′-azetidinyl]-1*-N,*2*-O-*carbonyl-3,5-di*-O-*methyl-α*-D-*xylofuranosylamine **10d***

Treatment of 300 mg (1.15 mmol) of **7** with 328 mg (1.38 mmol) of (4-methoxyphenyl)-((*E*)-3-phenylallylidene)amine **9d** gave 318 mg (0.66 mmol, 58%) of **10d**. Mp 144°C; $[\alpha]_D^{20}=-82.2$ (*c* 1.2, chloroform); ^{1}H (500.135 MHz, $CDCl_3$, δ in ppm): δ=3.266 (s, 3H, OCH_3), 3.388 (s, 3H, OCH_3), 3.462 (dd, 1H, $^2J_{5,5'}=-9.9$, H-5′), 3.598 (dd, 1H, H-5), 3.757 (s, 3H, CH_3OPh), 3.800 (d, 1H, $^3J_{3,4}$=3.3, H-3), 4.032 (m, 1H, $^3J_{4,5}$=5.5, $^3J_{4,5'}$=6.0, H-4), 4.858 (d, 1H, $^3J_{2,3}$=0, H-2), 4.882 (dd, 1H, ^3J=4.9, 8.8, C*H*CHCHPh), 5.225 (d, 1H, ^3J=4.9, NCH), 6.049 (d, 1H, $^3J_{1,2}$=5.5, H-1), 6.356 (dd, 1H, ^3J=8.8, 15.9, CHC*H*CHPh) 6.825 (d, 1H, ^3J=15.9, CHCHC*H*Ph), 6.822–6.854 (m, 2H, phenyl), 7.248–7.482 (m, 7H, phenyl); ^{13}C (125.76 MHz, $CDCl_3$, δ in ppm): δ=55.43 ($C_{arom}OCH_3$), 58.19 (OCH_3), 59.10 (OCH_3), 60.52 (*C*HCHCHPh), 62.24 (NCH), 69.01 (C-5), 77.71 (C-4), 80.17 (C-2), 82.77 (C-3), 87.29 (C-1), 114.33 (2C, phenyl), 118.62 (2C, phenyl), 122.98 (CH*C*HCHPh) 126.96–135.55 (6C, phenyl), 131.09 (NC_{arom}), 137.37 (CHCH*C*HPh), 155.91 (NCO), 156.57 ($C_{arom}OCH_3$), 159.57 (C=O); MS (CI, *iso*-

butane): *m/z* (%)=481 (100) [MH^+]. Anal. calcd for $C_{26}H_{28}N_2O_7$: C 64.99, H 5.87, N 5.83. Found: C 65.05, H 5.98, N 5.80.

4.9. 1-N-*[5′,6′*-trans-*2′,2′,4′,4′-Tetramethyl-1′-aza-3′-thio-bicyclo[3.2.0]-heptan-7′-onyl]-1*-N,*2*-O-*carbonyl-3,5-di*-O-*methyl-α*-D-*xylofuranosylamine* ***12a***

Reaction of 300 mg (1.15 mmol) of **7** with 200 mg (1.38 mmol) 2,2,5,5-tetramethyl-3-thiazoline **11a**, according to the general procedure, gave 162 mg (0.42 mmol, 36%) of **12a**. Mp 117°C; $[\alpha]_D^{20}$=+50.4 (*c* 0.5, chloroform); ^{1}H (500.135 MHz, $CDCl_3$, δ in ppm): δ=1.477, 1.538, 1.604, 1.919 (4×s, 12H, 4×CH_3), 3.374 (s, 3H, OCH_3), 3.419 (s, 3H, OCH_3), 3.577 (dd, 1H, $^2J_{5,5'}$=−10.4, H-5′), 3.688 (dd, 1H, H-5), 3.859 (d, 1H, $^3J_{3,4}$=3.3, H-3), 4.023 (d, 1H, ^3J=1.7, NCH), 4.064 (m, 1H, $^3J_{4,5}$=5.5, $^3J_{4,5'}$=6.0, H-4), 4.726 (d, 1H, ^3J=1.7, NCH), 4.843 (d, 1H, $^3J_{2,3}$=0, H-2), 5.795 (d, 1H, $^3J_{1,2}$=5.5, H-1); ^{13}C (125.76 MHz, $CDCl_3$, δ in ppm): δ=2×27.21, 28.78, 32.31 (4×CH_3), 54.90 (C(CH_3)$_2$), 56.67 (NCHCH), 58.19 (OCH_3), 59.23 (OCH_3), 69.27 (C-5), 69.62 (C(CH_3)$_2$), 72.18 (N*C*HC=O), 78.35 (C-4), 79.43 (C-2), 83.07 (C-3), 87.56 (C-1), 155.35 (NCO), 160.69 (C=O); MS (CI, *iso*-butane): *m/z* (%)=387 (100) [MH^+]. Anal. calcd for $C_{17}H_{26}N_2O_6S$: C 52.83, H 6.78, N 7.25, S 8.30. Found: C 52.69, H 6.80, N 7.01, S 8.11.

4.10. 1-N-*(5′,6′*-trans-*2′,2′-Pentamethylene-4′,4′-dimethyl-1′-aza-3′-bicyclo[3.2.0]heptan-7′-onyl)-1*-N,*2*-O-*carbonyl-3,5-di*-O-*methyl-α*-D-*xylofuranosylamine* ***12b***

Treatment of 250 mg (0.96 mmol) of **7** with 211 mg (1.15 mmol) 2,2-dimethyl-1-thia-4-azaspiro[4.5]dec-3-ene **11b**, according to the general procedure, gave 260 mg (0.61 mmol, 63%) of **12b**. Mp 90°C; $[\alpha]_D^{20}$=+45 (*c* 0.5, chloroform); ^{1}H (500.135 MHz, $CDCl_3$, δ in ppm): δ=1.228–2.009 (m, 16H, 5×CH_2, 2×CH_3), 3.365 (s, 3H, OCH_3), 3.418 (s, 3H, OCH_3), 3.563 (dd, 1H, $^2J_{5,5'}$=−10.4, H-5′), 3.684 (dd, 1H, H-5), 3.856 (d, 1H, $^3J_{3,4}$=3.3, H-3), 4.012 (d, 1H, ^3J=1.6, NCH), 4.055 (m, 1H, $^3J_{4,5}$=4.9, $^3J_{4,5'}$=6.0, H-4), 4.709 (d, 1H, ^3J=1.6, NCH), 4.835 (d, 1H, $^3J_{2,3}$=0, H-2), 5.801 (d, 1H, $^3J_{1,2}$=5.5, H-1); ^{13}C (125.76 MHz, $CDCl_3$, δ in ppm): δ=53.21 (*C*(CH_3)$_2$), 56.18 (NCHCH), 58.19 (OCH_3), 59.23 (OCH_3), 69.26 (C-5), 71.60 (N*C*HC=O), 78.34 (C-4), 79.42 (C-2), 83.08 (C-3), 87.56 (C-1), 155.38 (NCO), 160.62 (C=O); MS (CI, *iso*-butane): *m/z* (%)=427 (100) [MH^+]. Anal. calcd for $C_{20}H_{30}N_2O_6S$: C 56.32, H 7.09, N 6.57, S 7.52. Found: C 55.93, H 6.83, N 6.44, S 7.16.

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