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[2 + 2] Cycloadditions of Methylene *exo*-Glycals: Synthesis of Glycopyranosylidene-Spiro-Azetidine-2-ones (β-Lactams) and Cyclobutanones

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[2 + 2] Cycloadditions of methylene *exo*-glycal derivatives with chlorosulfonyl isocyanate and dichloroketene were studied in detail, investigating the effect of the carbohydrate moiety, protecting groups as well as reaction temperature on the yields of the transformations. These reactions gave new anomeric spiro-β-lactam and spiro-cyclobutanone derivatives, whose structure was established by 1D and 2D NMR and MS experiments. The transformation of spiro-cyclobutanone into spiro-γ-lactone was also demonstrated.

Introduction

Glycomimetics are "carbohydrate mimetic" compounds that have a structural and functional similarity to a natural glycan but with more favorable chemical properties, greater stability against various enzymes, better drug-like properties and at least equal or sometimes better affinity and selectivity for the respective protein target.[1] Among glycomimetics the anomeric spirocycles represent a special class, such compounds are characterized by various biological activities.[2]

There are several examples in the literature for the synthesis of anomeric spirocyclic derivatives prepared by cycloadditions of methylene *exo*-glycals (further on mentioned as *exo*-glycals.) A regio- and stereoselective synthesis of 4′-thiaspiroacetals was achieved by the inverse electron-demand hetero Diels-Alder reaction of *exo*-glycals and 3-thioxopentane-2,4-dione.[3] Spiro-isoxazolines[4] and -isoxazolidines[4a,5] were obtained from *exo*-glycals with nitrile oxides and nitrones, respectively, as 1,3-dipoles. For the synthesis of *C*-glycosylamino acids, anomeric spiro-oxazines were prepared by hetero Diels-Alder reactions of furanoid and pyranoid *exo*-glycals and ethyl-2-nitrosoacrylate.[6] The synthesis of *C*-glycosyl quinolines was elaborated by the Povarov reaction of *exo*-glycals and aromatic Schiff bases.[7]

[2 + 2] type cycloaddition reactions of *exo*-glycals have not been published yet in the literature, though such transformations were studied with *endo*-glycals, which are briefly summarized here.

In general, [2 + 2] type cycloadditions between sulfonyl or acyl isocyanates and activated olefines (vinyl ethers or acetates, enamines) give β-lactams (azetidine-2-ones).[8] Chmielewski and co-workers studied in detail the cycloaddition of *endo*-glycals with sulfonyl and acyl isocyanates to get sugar annulated β-lactams,[9] and concluded that at high pressure *O*-peracylated glycals reacted with tosyl isocyanates stereoselectively. These transformations showed high sensitivity to the applied reaction conditions and, in addition, retro-cycloaddition or opening of the β-lactam ring were also observed.[10] Chlorosulfonyl isocyanate (CSI) had several advantages over other isocyanates, as it reacted easier and faster with simple, non-activated alkenes, and the cleavage of the chlorosulfonyl group could be performed under mild conditions.[11]

Another [2 + 2] type cycloaddition between ketenes and alkenes gives cyclobutanone derivatives.[12] The reactions with the ketene itself ($H_2C{=}C{=}O$) result in very low yields, but electron-withdrawing groups on the ketene (e.g. Hlg–, RO–, RS–, R(CO)–) promote the reaction. Although several halogenated ketenes are known, the synthetic application of dichloroketene is the most common, which can be formed in situ from dichloroacetyl chloride or trichloroacetyl chloride.[13] The dichlorocyclobutanone ring formed by cycloaddition is readily dehalogenated reductively or under radical conditions, but the (di)halocyclobutanones can also be very useful synthetic intermediates, since halogens can easily be replaced by nucleophiles and can be converted further in ring-expansion or ring-contraction reactions.[14]

Cycloadditions of *endo*-glycals and dichloroketene were investigated by several groups[15] to show the regio- and stereoselective formation of bicyclic glyco-annulated cyclobutanones in good yields. Linker and co-workers also presented the transformation of the cyclobutanone derivatives to γ-lactones under Baeyer-Villiger oxidation conditions,[15b] and to γ-lactams via the corresponding oxime in a Beckmann rearrangement reaction.[15c]

As a continuation of our studies[16] to discover the chemical properties of *exo*-glycals, in this work we have investigated the

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above [2+2] cycloaddition reactions of *O*-peracylated *exo*-glycals with chlorosulfonyl isocyanate and dichloroketene.

Results and Discussion

Exo-glycals **1**–**6** were synthesized by literature methods, published earlier by our group, from the corresponding anhydro-aldose-tosylhydrazones using Bamford-Stevens reaction (Scheme 1).[16b,c,17]

[2+2] Cycloadditions with Chlorosulfonyl Isocyanate

The cycloaddition reactions of the above *exo*-glycals with chlorosulfonyl isocyanate (CSI) were performed by a protocol published by Chmielewski and co-workers for *endo*-glycals.[11b]

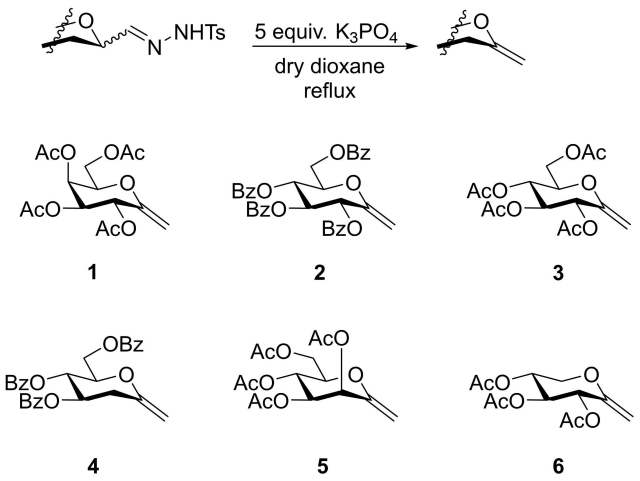
The results of the addition reactions for *O*-peracetylated *exo*-galactal **1** are summarized in Table 1. From the reaction mixture at 0 °C (entry 1) an expected β-lactam (1′*S*)-**7** was isolated in pure state in a low yield (12%), beside the ring opened α,β-unsaturated amide **7** which was the major product of this transformation (30%). We also isolated an inseparable mixture of compounds **8a** and **8b** in low yield (8%) which could be formed by the hydrolytic ring opening of the β-lactam ring. With *endo*-glycals Chmielewski and co-workers observed, that the ratio of the products highly depended on the reaction temperature, and the formation of the α,β-unsaturated amide derivative was favored at higher temperature.[10b] Based on this information, transformations of **1** were examined at different temperatures, and the results are summarized in entries 2–4 of Table 1.

Formation of α,β-unsaturated amide **9** was less favorable at lower temperatures (entries 2–4). The 1′*S* isomer of spiro-β-lactam **7** was the major product at −78 °C, although the reaction took place slower than at 0 °C (3 h vs. 0.5 h), and the 1′*R* isomer of **7** could also be isolated in low yield (entry 4). Beside the spiro-epimers of **7**, inseparable mixtures of compounds **8a** and **8b** were also isolated as minor products in all cases.

O-Perbenzoylated *exo*-glucal **2** was reacted with CSI at different temperatures and the desired spiro-β-lactam **10** was isolated in low to moderate yields (14–42%) beside ulosonamide **11** and the α,β-unsaturated amide **12** (Table 2). Surprisingly, in contrast with *exo*-galactal **1**, only the 1′*S* isomer of spiro-β-lactam **10** was isolated from the reaction mixtures. The best yields were obtained at 0 °C and we did not observe any conversion at −78 °C.

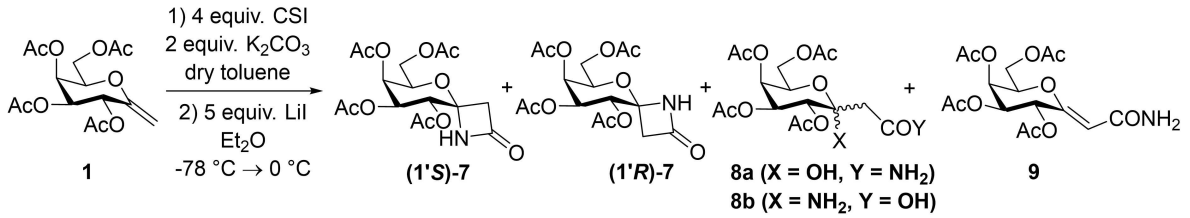
To decide whether the protecting group or the sugar configuration had a role in the outcome of the reaction, *O*-peracetylated *exo*-glucal **3** was reacted with CSI at −20 °C (Scheme 2). From this reaction mixture, both spiro-β-lactams (1′*S*)- and (1′*R*)-**13** were isolated beside ulosonamide **14**, which suggested that the β-side of the exocyclic double bond of the benzoyl protected derivative **2** is sterically more hindered by the benzoyloxy group at C-6 than that of **3**, so the β-side attack of the reagent is less favorable.

This transformation was extended to *O*-peracetylated *exo*-mannal **5** and *exo*-xylal **6**, which were reacted with CSI at −20 °C and the formation of (1′*S*)/(1′*R*) β-lactams **15** and **17** with (1′*S*) preferences was observed beside the acyclic side products **16** and **18a**/**18b** (Scheme 3).



Scheme 1. Synthesis and structure of the studied methylene *exo*-glycals.

Table 1. Reaction of *O*-peracetylated *exo*-galactal **1** with chlorosulfonyl isocyanate.



Entry	*T* [°C]	Isolated yields [%] (1′*S*)-**7**	(1′*R*)-**7**	**8a**/**8b**	**9**
1	0	12	n.d.	8	30
2	−20	19	n.d.	8	25
3	−40	16	4	3	17
4	−78	32	16	15	8

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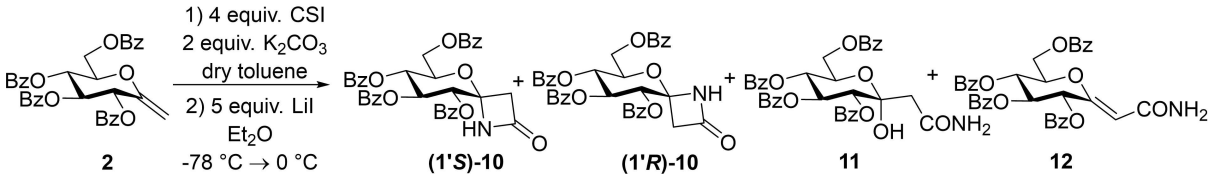
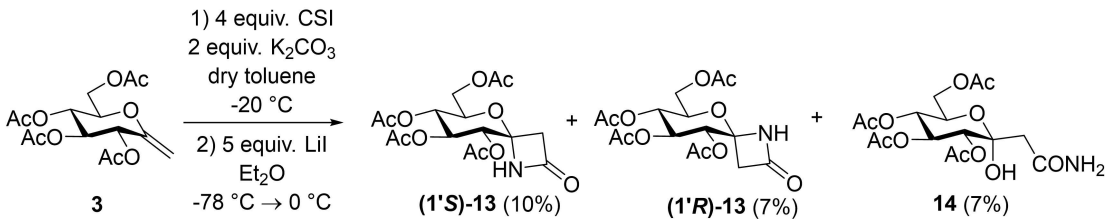
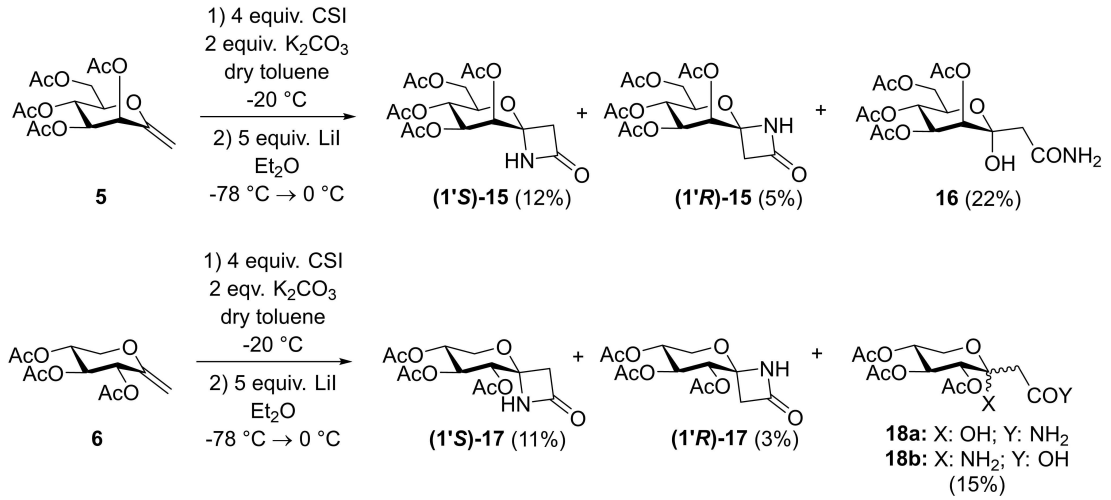
Table 2. Reaction of *O*-perbenzoylated *exo*-glucal **2** with CSI.



Entry	*T* [°C]	Isolated yields [%] (1′*S*)-**10**	(1′*R*)-**10**	**11**	**12**
1	r.t.	21	n.d.	20	24
2	0	42	n.d.	n.d.	15
3	−20	20	n.d.	8	8
4	−40	14	n.d.	n.d.	13
5	−78	no conversion			



Scheme 2. Reaction of *O*-peracetylated *exo*-glucal **3** with CSI.



Scheme 3. Reaction of *O*-peracetylated *exo*-mannal **5** and *exo*-xylal **6** with CSI.

Complete or high stereoselectivity of these transformations affording the thermodynamically more stable 1′*S* isomers may be explained by the anomeric effect.[18]

Structure Elucidation of Spiro-β-lactams and Accompanying Products

Before considering the spectroscopic evidence to prove the structure of the products, possibilities for the formation of cycloadducts are summarized. As the attack of the reagent on the double bond of the *exo*-glycal can take place in orientations **A** and **B**, the formation of two regioisomers (**A** and **B**) is possible (Figure 1). The spiro epimeric configuration may also differ in the regioisomers due to α vs. β side attack (blue vs. black isocyanates in the structures), therefore, the formation of two pairs of diastereomers ($\mathbf{A}_\alpha$, $\mathbf{A}_\beta$ and $\mathbf{B}_\alpha$, $\mathbf{B}_\beta$) can be expected.

Formation of amide **C** is possible from derivatives **B**. Considering the electron density of the functional groups involved in the reaction, orientation **B** seems to be more favorable, since in this case the electrophilic carbon atom of the reagent reacts with the more nucleophilic, terminal carbon atom of the *exo*-glycal.[11c]

Identification of the regioisomers was carried out by HMBC measurements after exact assignment of the signals (COSY and HSQC). Hydrogen and carbon atoms as well as the respective

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bonds marked in red in Figure 1 indicate the cross peaks to be expected in regioisomers **A** and **B**. In HMBC experiments, cross peaks appeared between H-2′ and a methylene carbon only, but not with a carbonyl carbon. This finding strongly suggests the formation of regioisomers **B** (also expected on the basis of the electron densities).

The structure of diastereomers **7**, **10** and **13** (isomers of type $\mathbf{B}_\alpha$ and $\mathbf{B}_\beta$) was identified by heteronuclear ^3J coupling constants between the H-2′ hydrogens and the methylene carbon atom (C-3) of the β-lactam ring, which was determined from HSQMBC spectra. These atoms are in a *gauche* relative position in the (1′*S*)-isomers, and in *trans*-diaxial position in the (1′*R*)-isomers as indicated by the smaller/larger coupling constants, respectively (Table 3).

Since only a single spiro-β-lactam **10** was formed from *exo*-glucal **2**, the pairwise comparison of the $^3J_{H\text{-}2',C\text{-}3}$ coupling constants was not possible, though the 2.3 Hz value fit well in the series (Table 3). The structure of **10** was also proved by the comparison of the chemical shifts of the carbon atoms in the lactam ring of compounds **7**, **10**, **13** (Table 4). The chemical shift values correlate well not only for the individual isomers of **7**, **10** and **13**, but also for the epimers of **15** and **17**, therefore, the configuration of C-1′ for **10**, as well as for **15** and **17** are highly probable.

For β-lactams **15** and **17** NOE measurements corroborated the above configurational assignations (Figure 2).

Another characteristic difference in the ^{1}H NMR spectra of the products was the ~0.4 ppm difference of the chemical shifts of the two diastereotopic hydrogens of the lactam methylene

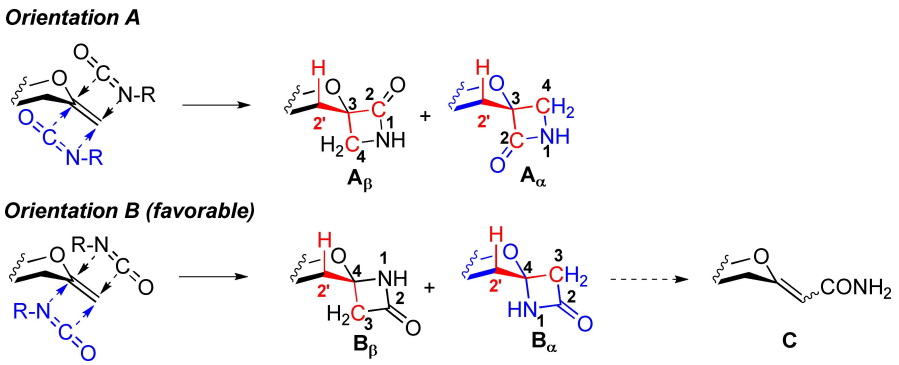


Figure 1. Possibilities for the formation of regio- and diastereoisomeric spiro-β-lactams.

Table 3. Heteronuclear coupling constants ($^3J_{H\text{-}2',C\text{-}3}$) of spiro-β-lactam diastereomers.

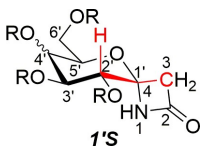
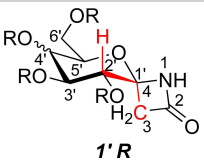
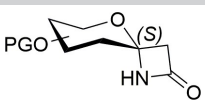
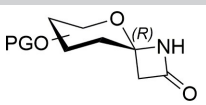
	 1′S	 1′R
	$^3J_{H\text{-}2',C\text{-}3}$ [Hz]	
7 (D-Gal, R=Ac)	2.2	3.7
10 (D-Glc, R=Bz)	2.3	–
13 (D-Glc, R=Ac)	2.3	3.7

Table 4. Selected ^{13}C chemical shifts of spiro-β-lactams **7**, **10**, **13**, **15** and **17**.

						
	δ [ppm] C-1′	CH_2	$C{=}O_{lactam}$	δ [ppm] C-1′	CH_2	$C{=}O_{lactam}$
7 (D-Gal, PG=Ac)	84.7	47.0	166.1	85.0	43.5	163.9
10 (D-Glc, PG=Bz)	84.9	47.4	165.2	–	–	–
13 (D-Glc, PG=Ac)	84.4	47.1	165.7	84.7	43.7	163.6
15 D-Man, PG=Ac	83.7	48.4	165.7	82.8	46.4	163.4
17 D-Xyl, PG=Ac	84.3	47.1	165.4	84.7	43.7	163.9

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group for the (1′*R*)-isomers in contrast to the almost identical chemical shifts of these protons in the (1′*S*) counterparts (see Supporting Information, Tables S1 and S2).

The structure of **11** and **14** was proved by IR measurements (**11**: $\nu(N–H)_a = 3487\ cm^{-1}$, $\nu(N–H)_s = 3372\ cm^{-1}$, $\nu(C=O) = 1723\ cm^{-1}$; **14**: $\nu(N–H)_a = 3491\ cm^{-1}$, $\nu(N–H)_s = 3368\ cm^{-1}$, $\nu(C=O) = 1755\ cm^{-1}$; the characteristic broad ν(OH) vibration of carboxylic acids between 2500 cm^{-1} and 3500 cm^{-1} could not be observed) and by a comparison of the chemical shift of the anomeric carbon of **11** and **14** to that of lactams **7**, **10**, **13**. These values were 10–12 ppm higher in **11** and **14** indicating a carbon-oxygen bond vs. a carbon-nitrogen bond in **7**, **10**, **13**.

The anomeric configuration of compounds **11**, **14** and **16** was established with NOE measurements. For the D-*gluco* configured **11** and **14** NOE could be observed between the H-2 and H-4 hydrogens due to the spatial proximity, while for the D-*manno* configured **16** the effect was observed between the H-2 and H-8 protons. This clearly proves the α (*axial*) position of the hydroxy group in the indicated chair conformation (Figure 3).

In the case of **8** and **18** isolated from the reaction of acetylated *exo*-galactal **1** and *exo*-xylal **6**, respectively, the ^{1}H NMR spectrum clearly showed that these were a mixture of two compounds, but the overlap of the signals did not allow precise structure elucidation. The separation of these compounds was unsuccessful with both classical column chromatography and preparative HPLC. LC–MS measurements proved that they had the same molecular weight. A comparison of the ^{13}C NMR shifts of compounds **8** and **18** with those of **11**, **14** and **16** showed a good correlation for the **8a** and **18a** isomers. For **8b** and **18b** the signals appeared at lower δ values, and the chemical shift of the anomeric carbon (85.4 ppm and 83.6 ppm) was similar to that of lactams (83–85 ppm) (Table 5), which suggested the presence of a C–N bond at the anomeric carbon of **8b** and **18b**.

The configuration of the double bond of enamide derivatives **9** and **12** was determined by selective NOE measurements. NOE was observed between H-2 and H-2′ only, which proved the *Z* configuration of the exocyclic double bond (Figure 4).

A plausible mechanism for the formation of acyclic products is shown in Scheme 4. It is known that in β-lactams, possessing an electron donating group at the C-4 and an electron withdrawing group at the N atoms of the ring, the heterolysis of C-4–N bond may occur spontaneously.[19]

Cleavage of the anomeric carbon–nitrogen bond in spiro-β-lactams obtained in this study may result in the formation of an oxocarbenium ion intermediate represented by resonance

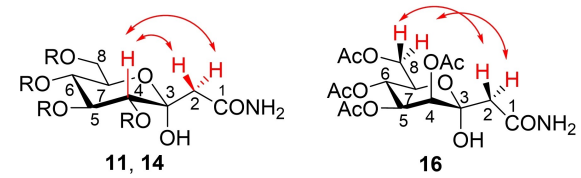


Figure 3. Determination of the anomeric configuration of **11**, **14** and **16**.

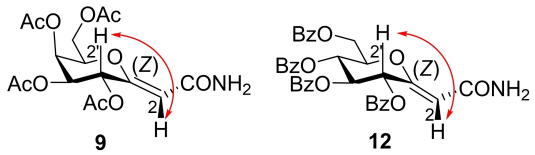
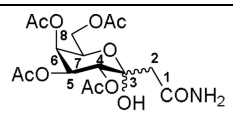
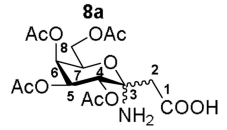
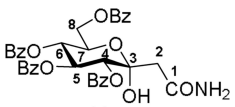
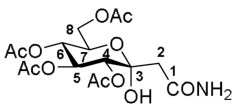
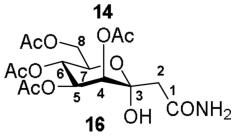
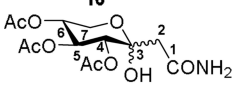
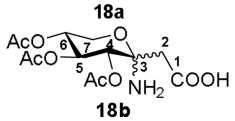


Figure 4. Determination of the configuration of double bonds of **9** and **12**.

Table 5. Comparison of characteristic ^{13}C chemical shifts of acyclic compounds.

Compounds	δ [ppm] C-1	C-2	C-3
 **8a**	173.9	40.4	97.3
 **8b**	167.2	32.6	85.4
 **11**	173.6	40.5	97.3
 **14**	173.4	39.9	96.8
 **16**	173.5	39.3	96.7
 **18a**	173.7	40.2	96.8
 **18b**	166.5	34.9	83.6

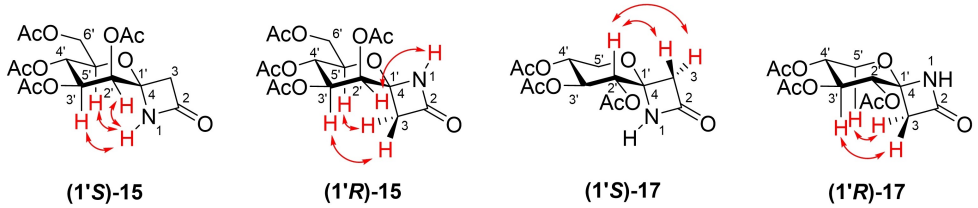


Figure 2. Structure elucidation of β-lactams **15** and **17** by NOE measurements.

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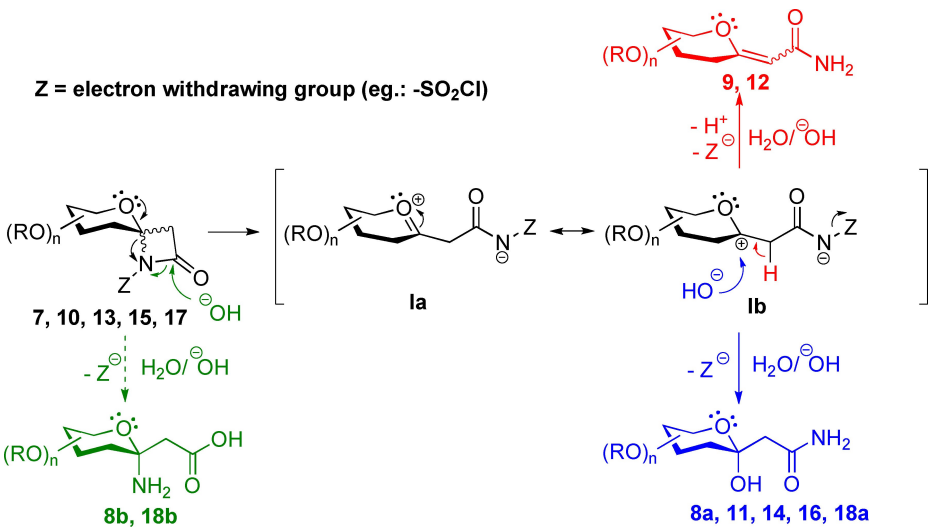

Scheme 4. A plausible mechanism for the formation of acyclic products.

forms **Ia** and **Ib**. This intermediate may be stabilized in two ways: by losing a proton from the α-carbon atom to give an α,β-unsaturated amide derivative (such as **9** and **12**, *red route*), while by an attack of a hydroxide ion on the anomeric carbon atom ulosonamides **8a**, **11**, **14**, **16**, **18a** may be formed (*blue route*). A nucleophilic attack of the hydroxide ion on the lactam carbonyl may cause the formation of acyclic compounds **8b** and **18b** (*green route*).

[2+2] Cycloadditions with Dichloroketene

Dichloroketene was generated in situ from trichloroacetyl chloride with Zn–Cu powder as described in the literature,[13] and reacted with *exo*-glycals **1**, **2**, **4**, **5** and **6** (Table 6). The reactions were monitored by TLC and after complete transformation of the starting compound the dehalogenation of the intermediate spiro-dichlorocyclobutanones was performed with Zn/AcOH reagent combination.[14a] Surprisingly, in the reaction of *exo*-galactal **1** a mixture of the diastereomeric monohalogenated derivatives (2*S*)/(2*R*)-**19** was isolated, therefore, the dehalogenation had to be repeated with freshly activated Zn powder to give the desired spiro-cyclobutanone **20** in good yield (65% from **19**, entry 1). Starting from *exo*-glucal **2**, a mixture of the four possible monochlorinated diastereomers (2*S*)/(2*R*)-**21** and (2*S*)/(2*R*)-**22** was isolated, which could be partially separated by column chromatography for structure elucidation (entry 2). Dehalogenation of these compounds resulted in spiro-cyclobutanone **23** in moderate yield (45%). Similar reaction was observed with *exo*-xylal **6**, but in that case the partially dehalogenated isomers **24** could not be separated. The dehalogenation was performed with the crude product to result in the desired spiro-cyclobutatnone **25** in moderate yield (entry 3, 50%). In contrast to the previous reactions, 2-deoxy-*exo*-glucal **4** and *exo*-mannal **5** furnished the dechlorinated spiro-cyclobutanones **26** and **27** directly in moderate (45%) and acceptable (25%) yields, respectively (entries 3 and 4).

Structure Elucidation of the Spiro-cyclobutanone Derivatives

The addition of dichloroketene to the double bond of the *exo*-glycal can take place in two orientations, forming two types of regioisomers **A** and **B**. However, considering the electron densities, the favored direction of the attack is the one in which the more electron-deficient *sp*-hybrid carbon atom of the ketene forms a bond with the terminal, more nucleophilic carbon atom of the *exo*-glycal (Figure 5, orientation **B**).[14a] While two diastereomers ($\mathbf{A}_{\alpha}$ and $\mathbf{A}_{\beta}$) may result from orientation **A**, only one can be expected from **B** after the dehalogenation. These regioisomers ($\mathbf{A}_{\alpha,\beta}$ and **B**) can be distinguished by HMBC experiments, since for isomers **A** the H-2′ hydrogen of the sugar skeleton can give cross peaks both with the C-1 (C=O) and C-3 (methylene) carbon atoms of the cyclobutanone, in isomer **B** the cross peaks may appear only between H-2′ and C-2/C-4 methylenes, but not with the C-1 carbonyl of the cyclobutanone ring.

The structure of the isolated spiro-cyclobutanone derivatives was identified by HMBC experiments. In the case of compounds **20**, **23**, **25**, **26** cross peaks appeared between H-2′ of the carbohydrate ring and C-2/C-4 of the cyclobutanone ring which clearly proved the formation of "**B**-type" products. In the case of the D-*manno* derivative **27** the cross peaks appeared between C-2′ and H-2/H-4 confirming the same regioisomer (Figure 6).

The exact structure, the configuration of the spiro epimeric center and cyclobutanone ring of monochlorinated compounds **19**, **21** and **25** were established by selective NOE measurements as shown in Figure 7.

The Baeyer-Villiger oxidation of **23** in dry dichloromethane with mCPBA resulted in a 1:1 mixture of diastereomers (1′*S*)-**28**

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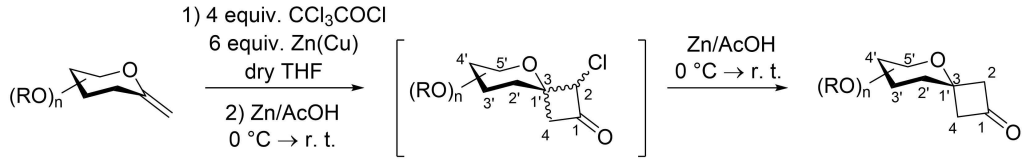
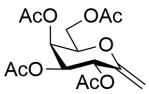
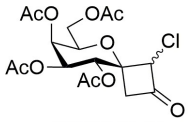
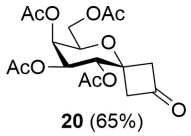
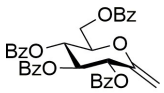
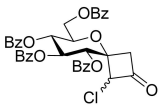
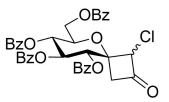
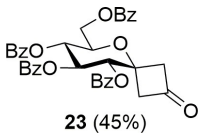
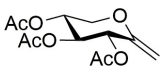
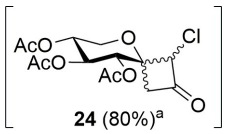
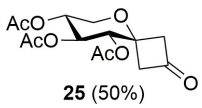
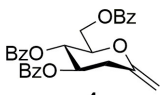
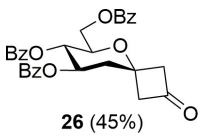
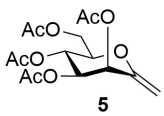
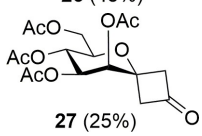
Table 6. [2+2] cycloaddition of *exo*-glycals with dichloroketene.



Entry	*Exo*-glycal	Products	
1	 **1**	 **(2*S*)/(2*R*)-19** (20%, 2*S*:2*R*=1:5)	 **20** (65%)
2	 **2**	 **(2*S*)/(2*R*)-21** (18%, 2*S*:2*R*=4:1)  **(2*S*)/(2*R*)-22** (35%, 2*S*:2*R*=5:1)	 **23** (45%)
3	 **6**	 **24** (80%)[a]	 **25** (50%)
4	 **4**	–	 **26** (45%)
5	 **5**	–	 **27** (25%)

[a] Dehalogenation was performed from the crude products after work up.

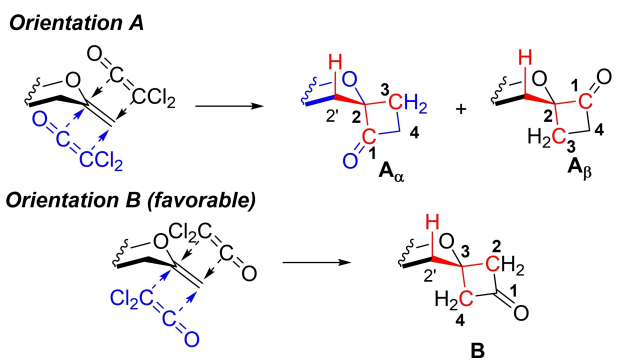


Figure 5. Formation of the regio- and diastereoisomeric spiro-cyclobutanones.

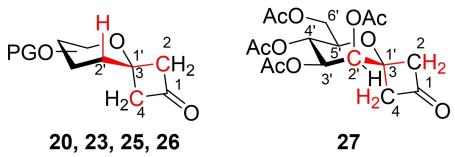


Figure 6. Structure elucidation of spirocyclobutanones by HMBC experiments.

and (1′*R*)-**28** which were separated by preparative HPLC (Scheme 5).

Their structures were established by NOE measurements, since in the case of (1′*S*)-**28** the H-5 hydrogens of the lactone ring gave NOE with H-2′ of the carbohydrate skeleton, while in the case of (1′*R*)-**28** the NOE could be observed between H-5 and H-3′/5′ of the sugar ring (Figure 8).

Conclusion

We studied up-till-now unexplored [2+2] cycloaddition reactions of several methylene *exo*-glycals with chlorosulfonyl isocyanate (CSI) and dichloroketene. The addition of CSI took place with excellent regioselectivity with a strong dependence on the size of the protecting groups of the *exo*-glycals and the reaction temperature. While acetylated *exo*-glucal, -galactal, -mannal and -xylal gave the 1′*S* and 1′*R* isomers of β-lactams with a 1′*S* preference, from the benzoylated *exo*-glucal the 1′*S* isomer was formed exclusively, due to the steric hindrance of one of the reacting faces of the molecule. In the case of the acetylated *exo*-galactal lowering the temperature (−40 °C and −78 °C) helped the formation of the 1′*R* isomer, while at higher

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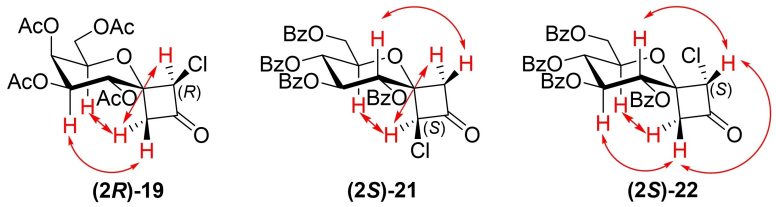
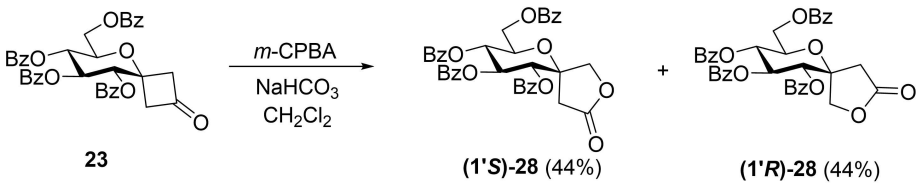


Figure 7. Structure elucidation of compounds **13**, **15** and **16** by selective NOE.



Scheme 5. Baeyer-Villiger oxidation of compound **23**.

temperatures (0 °C or −20 °C) only the 1′*S* isomer was detected. The stability of the β-lactam ring depended on the temperature and at higher temperature acyclic, ring-opened side products were formed.

The addition of dichloroketene to methylene *exo*-glycals took place with excellent regioselectivity, but the in situ didehalogenation of cycloadducts failed in the case of acetylated *exo*-galactal, benzoylated *exo*-glucal and *exo*-xylal. The obtained diastereomeric mixtures of the monohalogenated spiro-cyclobutanones could be dehalogenated in a further step. Contrary to this, didehalogenation of the cycloadduct of benzoylated 2-deoxy-*exo*-glucal and *exo*-mannal took place in one step and the desired spirocyclobutanones were isolated in moderate and acceptable yields, respectively. The Baeyer-Villiger oxidation of a spirocyclobutanone gave a 1:1 mixture of spiro epimeric γ-lactones. These first [2+2] cycloadditions on methylene *exo*-glycals demonstrated the feasibility of such transformations with high regioselectivity. On the other hand, stereoselectivity may be influenced by the protecting groups that may give a means to govern the outcome of the reactions.

Experimental Section

General methods

Solvents were purified by distillation. TLC was performed on Kieselgel 60 F254 (Merck) with detection by immersing into 5% ethanolic sulfuric acid soln. followed by heating. Column chromatography was performed on Silica gel 60 (Merck 0.063–0.200 mm). Organic solutions were dried over $MgSO_4$ and concentrated under diminished pressure. The ^1H (360, 400 and 500 MHz) and ^{13}C NMR (90.54, 100.28 and 125.76 MHz) NMR spectra were recorded with Bruker DRX-360, Bruker DRX-400 and Bruker Avance II 500 spectrometers, respectively. Chemical shifts are referenced to Me_4Si (0.00 ppm for ^1H) and to the residual solvent signals ($CDCl_3$: 77.16 ppm for ^{13}C). The coupling constant values (*J*) are given in Hz.

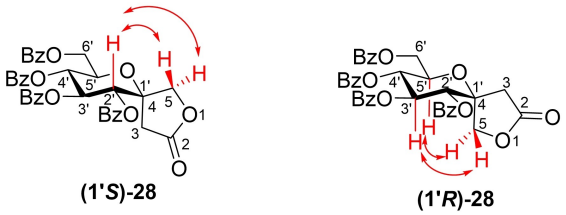


Figure 8. Structure elucidation of compounds **28**.

Optical rotations were measured at r.t. with a Jasco P-2000 polarimeter. IR spectra were measured with Jasco FT/IR4100 spectrometer. Mass spectra were recorded with Thermo LTQ XL (Thermo Electron Corp., San Jose, CA, USA) operated in a full scan positive ion ESI mode and 284 MicroTOF-Q type Qq-TOF MS (Bruker Daltonik, Bremen, 285 Germany) instruments. LCMS measurements were performed on Thermo Accela 600 hplc System coupled with a LTQ XL linear ion trap mass spectrometer.

Method A: General procedure for the chlorosulfonyl isocyanate addition

To a suspension of anhydrous potassium carbonate (0.27 g, 2 mmol) in toluene (4 mL) chlorosulfonyl isocyanate (0.35 mL, 4 mmol) was added. The mixture was stirred, and a solution of a methylene *exo*-glycal (1 mmol) in toluene (4 mL) was added dropwise at a given temperature. When the reaction was complete (TLC, eluent: hexane:acetone = 2:1) the mixture was cooled to −78 °C, diluted with ethyl acetate (6 mL) and treated with a solution of lithium iodide (0.33 g, 2.5 mmol) in ethyl ether (4 mL). The mixture was stirred for 5 min and then it was poured into a solution of sodium sulfite (2.7 g) and sodium hydrogen carbonate (1.0 g) in water (12 mL). The organic layer was separated and the water solution was extracted with ethyl acetate (2 × 10 mL). Extracts were combined, dried then concentrated in vacuum and purified by column chromatography.

Method B: General procedure for dichloroketene additions

Trichloroacetyl chloride (0.45 mL, 4 mmol) in dry tetrahydrofuran (4 mL) was added dropwise to a mixture of activated zinc–copper couple (0.65 g, 10 mmol) and methylene *exo*-glycal (1 mmol) in dry tetrahydrofuran (5 mL) at room temperature under Ar atmosphere. After completion of the reaction (TLC, eluent: hexane:EtOAc = 2:1) zinc dust (0.6 g) was added at 0 °C. Acetic acid (2.6 mL) was added within 10 min and the reaction mixture was stirred at room temperature. When the reaction was completed (TLC, eluent: hexane:EtOAc = 2:1) the insoluble materials were filtered off through Celite and washed with tetrahydrofuran (2×10 mL). The solution was concentrated under reduced pressure, and traces of acetic acid were removed by repeated co-evaporations with toluene. The residue was purified by column chromatography.

Method C: General procedure for the reductive dehalogenation process

Activation of Zn dust: Zn dust (750 mg) on a vacuum filtration funnel was washed with 2 M solution of HCl (3×10 mL), water (3×10 mL), acetone (3×10 mL) and then diethyl-ether (3×10 mL) The excess of the solvents was removed, and the Zn was dried by vacuum.

Reductive dehalogenation: The mixture of monochlorinated isomers (1 mmol) was dissolved in tetrahydrofuran (7 mL) and then activated zinc powder (650 mg, 10 mmol) and glacial acetic acid (2.1 mL) were added to a vigorously stirred solution. The mixture was stirred at reflux temperature and the progress of the reaction was monitored by TLC (eluent: hexane-ether = 1:2). When the reaction was complete the insoluble materials were filtered off through Celite and washed with tetrahydrofuran (2×10 mL). The solution was concentrated under reduced pressure, and traces of acetic acid were removed by repeated co-evaporations with toluene. The residue was purified by column chromatography.

Supporting Information

Synthetic procedures and compound characterization data for isolated compounds; copies of ^{1}H NMR and ^{13}C spectra (PDF).

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: chlorosulfonyl isocyanate · cycloaddition · dichloroketene · *exo*-glycal · spiro-cyclobutanone · spiro-β-lactam

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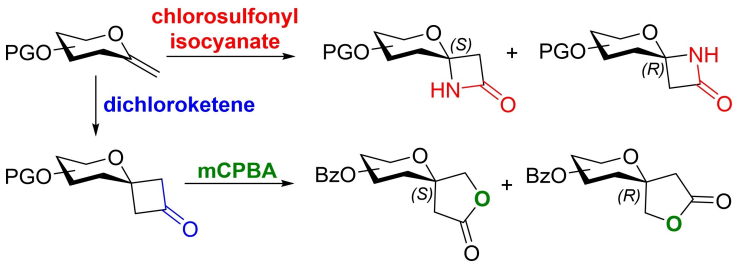

sugar config.: D-*gluco*; D-*galacto*; D-*manno*; D-*xylo;* PG: Ac; Bz

New anomeric spiro-β-lactam and spiro-cyclobutanone derivatives were synthesized by [2 + 2] cycloadditions of methylene *exo*-glycals with chlorosulfonyl isocyanate and dichloroketene. The reactions were studied in detail, investigating the effect of carbohydrate moiety, protecting groups as well as reaction temperature on the yields. The transformation of spiro-cyclobutanone into spiro-γ-lactone was demonstrated.

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[2 + 2] Cycloadditions of Methylene *exo*-Glycals: Synthesis of Glycopyranosylidene-Spiro-Azetidine-2-ones (β-Lactams) and Cyclobutanones