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Glycosylations of Cyclopropyl-Modified Carbohydrates: Remarkable β-Selectivity Using a Mannose Building Block

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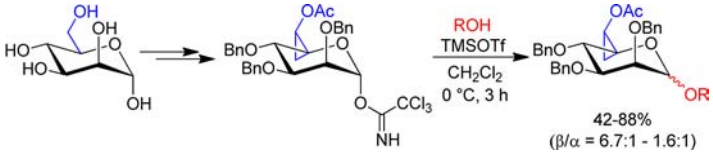
ABSTRACT



A mannosyl donor bearing a spiroannulated cyclopropane unit at C-5 has been prepared, and its behavior in glycosylation reactions investigated. Selectivities in favor of the β-anomer were observed. Corresponding di- and trisaccharides incorporating the rigid cyclopropane motif were assembled.

Carbohydrates play a major role in the transfer of biological information, e.g. cell−cell recognition, bacterial and viral infection, and signal transduction events.[1,2] In protein science numerous efforts are known to preadjust specific conformations.[3] The incorporation of rigid subunits or special amino acids such as hydroxyproline has paved the way toward decreasing the number of accessible peptide conformations. Especially, cyclopropane motifs have been widely used to rigidify peptide sequences (e.g., **1a** in Figure 1).[4] Different classes of carbohydrate mimetics[5] have been developed in recent decades. However, most of this work has been concentrated in the field of either linkage modification (*C*-, *S*-, and *N*-glycosides)[6] or carba- and iminosugars. Only a small amount of work has been devoted to the preadjustment of sugar hydroxyl groups.[7] Figure 1 shows an example of GM3 derivative **1b** in which the conformational freedom of the sialic acid is reduced by an ether bridge to the adjacent galactose moiety.

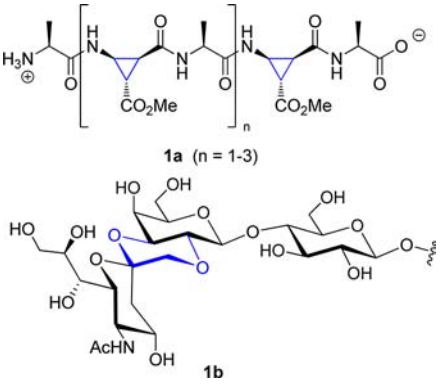


Figure 1. Rigidified peptide mimetic **1a** using cyclopropane motifs and conformationally locked GM3 derivative **1b**.

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Recently, we locked the 6-hydroxyl groups of glucose and mannose acceptors by making use of a spiroannulated cyclopropane ring at C-5 bearing one hydroxyl group.[8,9] In the present communication, we report on the preparation of the corresponding mannosyl donor, its behavior in glycosylation reactions, and its incorporation in model trisaccharides.

Investigations into the use of previously prepared cyclopropyl-modified methyl glycosides as donors, similar to Hotha's work using Au catalysis,[10] were in vain. Therefore, we decided to prepare conventional trichloroacetimidates via the respective hemiacetals. The challenge was to identify a suitable, easily cleavable anomeric protecting group without destroying the doubly donor-substituted cyclopropane motif. The latter is accessible via an exocyclic enol ether as previously demonstrated.[8,11] Since our main interest was to determine how the three-membered ring affects the glycosylation behavior, we chose a protected mannose with a nonparticipating group in position 2. The β/α ratio obtained in a respective glycosylation should give a hint about whether the stiff cyclopropane, as in the case of the 4,6-benzylidene group, might be similarly influential.

We commenced the preparation of such a mannosyl donor by using α-methoxyphenyl (MP) mannoside **2**[12] (Scheme 1). The primary hydroxyl group of **2** was efficiently protected with TIPSCl. Perbenzylation and TIPS deprotection afforded **3**. The latter compound was subjected to Swern oxidation and the resulting aldehyde was subsequently transformed to the respective enol acetate **4** in a solution of acetic anhydride, acetonitrile, and potassium carbonate.

Surprisingly, high selectivity for the (*Z*)-configured diastereomer **4** (72% over two steps) was observed and proven by NOE experiments. In a Simmons–Smith–Furukawa reaction[13] the olefinic moiety was transformed into the three-membered cyclopropane ring. While the total yield was good, almost no facial selectivity was observed. With the assumption that both axially oriented OR groups in position 1, as well as in position 2, coordinate to the zinc, the result would be an equal probability of attack from the top or bottom side. Both diastereoisomers **5a** and **5b** were unequivocally assigned by NOE investigations (see Supporting Information). Attempts to remove the MP group from **5a/5b** proved to be challenging. Earlier investigations using the bulky thexyldimethylsilyl (TDS) group at the anomeric position were futile. Fluoride sources and the use of HCl generated in situ were not compatible with the electron-rich cyclopropane moiety. Commonly, the oxidizing agent cerium ammonium nitrate (CAN) to remove MP groups is employed in a three-component solvent mixture of acetonitrile, toluene, and water.[14] However, due to the cerium(III) and the ammonium, the pH value of the aqueous phase is lowered significantly. Thus, using common deprotection conditions also led to complete decomposition of the product. However, the use of a buffered solution (phosphate buffer, pH 7) leveraged a successful cleavage of the anomeric MP group leading to the production of hemiacetal **6**. The latter was transformed under common conditions into the trichloroacetimidate **7**;[15] in this step the α-trichloroacetimidate was formed as the major anomer.

With this donor **7α** in hand we studied its behavior in glycosylation reactions (Table 1). Several acceptors **8a**–**8f** bearing primary and secondary hydroxyl groups were employed. In almost all cases good yields were obtained (42–88%); the three-membered ring remained untouched in the products **9**–**14**. A careful analysis of the two anomers

Scheme 1. Synthesis of Cyclopropyl-Modified Mannosyl Trichloroacetimidate **7**

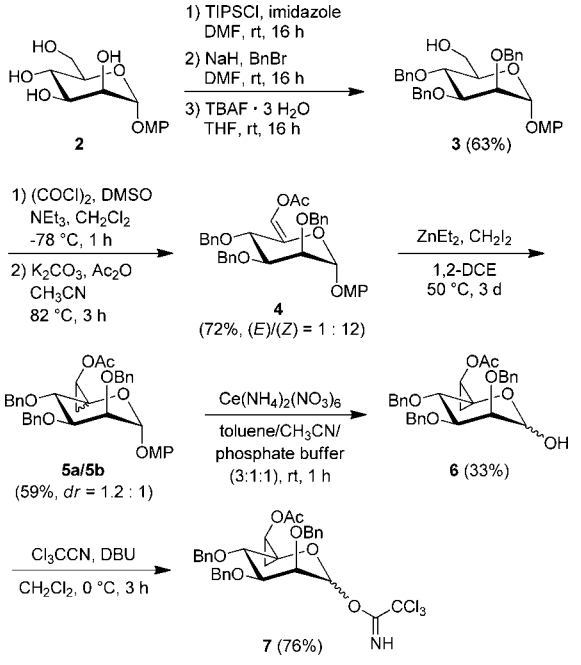

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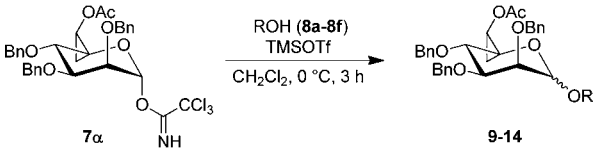
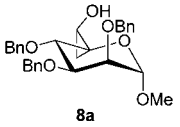
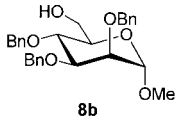
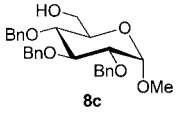
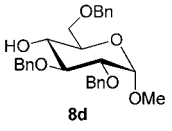
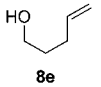
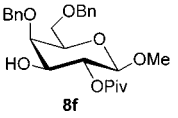
Table 1. Glycosidation Studies of the Cyclopropyl-Modified Mannosyl Trichloroacetimidate **7**



Entry[a]	ROH (1.0 equiv)	Product	Yield (%)[b]	β/α Ratio[c]
1	 **8a**	**9β/9α**	88	2.3:1
2	 **8b**	**10β/10α**	70	3.5:1
3	 **8c**	**11β/11α**	78	6.7:1
4	 **8d**	**12β/12α**	84	1.3:1
5	 **8e**	**13β/13α**	76	1.6:1
6	 **8f**	**14β/14α**	42	2.0:1

[a] For all reactions donor **7α** (1.3 equiv) was used. [b] Isolated yield of the β/α-mixture. [c] Determined by integration of corresponding anomeric ^{13}C NMR signals.

revealed that in all cases the β-mannoside proved to be the major product (β/α = 6.7:1−1.3:1).[16] The highest β-selectivities were found when 6-hydroxyl groups were employed as nucleophile (entries 1−3). But also in other cases using 3- and 4-hydroxyl groups and even in the case of highly reactive pent-4-en-1-ol (**8e**), the formation of the β-product was slightly favored.

The stereochemistry of all the products was unequivocally assigned by the anomeric $^1J_{C,H}$ coupling constants. Therefore, a ^1H-coupled ^{13}C NMR spectrum was recorded for each of the two anomers. It is well-known that anomeric $^1J_{C,H}$ coupling constants reveal ∼10 Hz larger values when they are derived from an equatorial H in comparison with an axial H.[17] As an example, Figure 2 depicts the anomeric regions of the two diastereoisomers **9α** and **9β**. Each section shows two doublets: in both spectra the broadened signal (^1J = 166 Hz) is the result of the equatorial proton at the reducing end whereas the sharp one is the result of the other anomeric proton. Broadening of the former is ascribed to long-range $^3J_{C,H}$ couplings (to H-2 and the Me group). As depicted the β-anomer **9β** reveals a $^1J_{C,H}$ coupling constant of 159 Hz (top) whereas the respective α-anomer **9α** shows a splitting of 169 Hz.

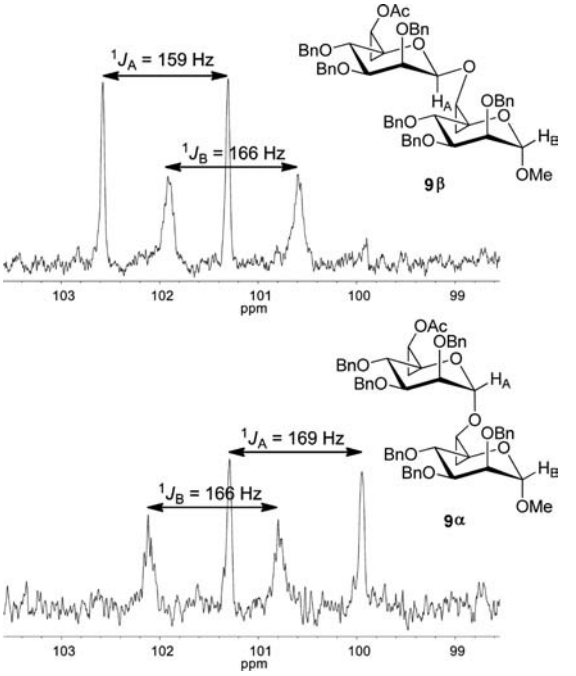


Figure 2. Anomeric region of the ^1H-coupled ^{13}C NMR spectra of disaccharide **9β** (top) and **9α** (bottom). The spectra were measured at 125 MHz in $CDCl_3$.

In the pioneering work of Crich for the synthesis of β-mannosides, a 4,6-benzylidene acetal was the prerequisite for high β-selectivity.[18] It has been argued that such a protecting group forces the mannose unit into a chair-like conformation hampering the oxocarbenium formation. Another point that was raised in favor of the high β-selectivity of the 4,6-benzylidene protecting group was the destabilizing electronic effect due to the antiparallel placement of the O-6 dipole to a hypothetical oxocarbenium ion.[6b]

Although the β-selectivities of our cyclopropanated mannosyl donors are worse compared with those achieved with a 4,6-benzylidene protecting group, our β-selectivity is in contrast to that observed with 2,3,4-tribenzylated-6-acetylated mannosyl trichloroacetimidate.[19] Thus, we

(16) With donor **7β** the β/α ratios were worse.

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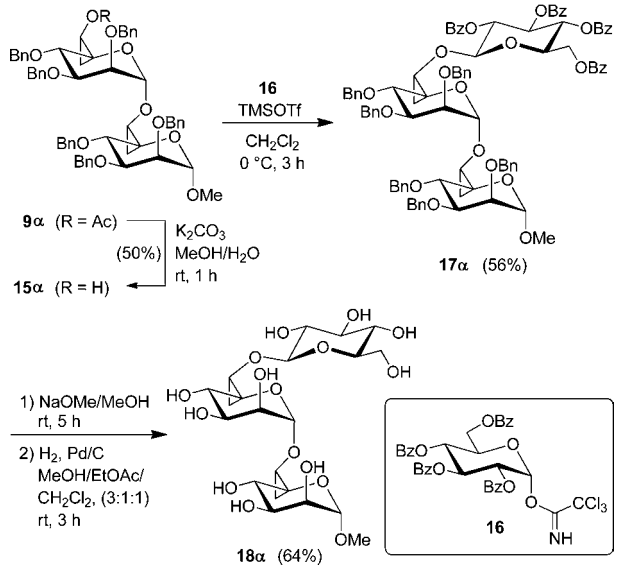
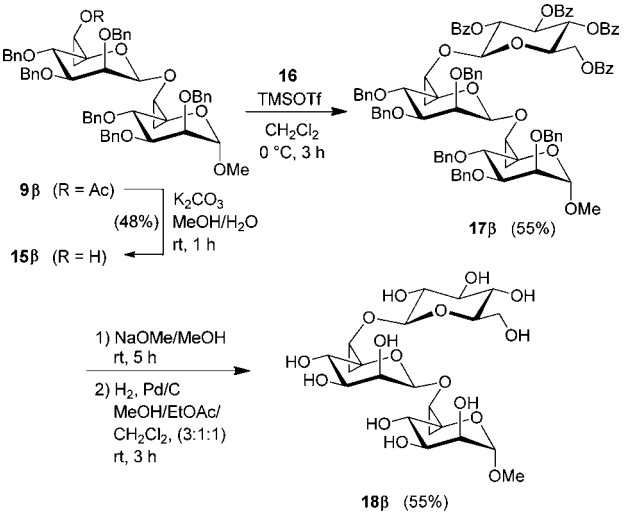
Scheme 2. Synthesis of Cyclopropyl-Modified Trisaccharide **18α**



Scheme 3. Synthesis of Cyclopropyl-Modified Trisaccharide **18β**



assume that the spiroannulated cyclopropane motif leads to a similar fixation of the chairlike conformation as in 4,6-benzylidene protected analogs. Unfortunately, to date we could not generate the enol ether of mannose with the double bond in the (*E*)-configuration in high yield leading to an antiparallel placement of the 6-hydroxyl. Such a compound would be of great value to further investigate the different influences directing the anomeric configuration of mannoside-like structures.

In order to demonstrate the stability of the three-membered ring in further transformations, the acetate group of the pseudodisaccharides **9α** and **9*β*** was cleaved by K_2CO_3 in methanol/water (Schemes 2 and 3). Free hydroxyls were glycosidated with a perbenzoylated glucose building block **16**[20] affording the pseudotrisaccharides **17α** and **17*β***, respectively. Global deprotection leading to the naked carbohydrate mimetics **18α** and **18*β*** was achieved by saponification and subsequent hydrogenolysis using palladium on charcoal.

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In summary, we have prepared a mannosyl-like donor with a spiroannulated cyclopropane at C-5. The crucial reaction to obtain this structural feature is the Simmons–Smith–Furukawa reaction of an exocyclic enol acetate. The glycosylation behavior of the respective mannosyl donor was investigated. Selectivities in favor of the *β*-anomer were observed in all cases. Larger structures up to trisaccharides were prepared and completely deprotected. Further studies on the incorporation of such units in biologically active glycans and elucidation of their conformational behavior will be performed in our laboratory in the future.

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Supporting Information Available. Experimental procedures, spectroscopic data, and NMR spectra for all new compounds. This material is free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.