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Leaving Group Based Intramolecular Glycoside Bond Formation[1]

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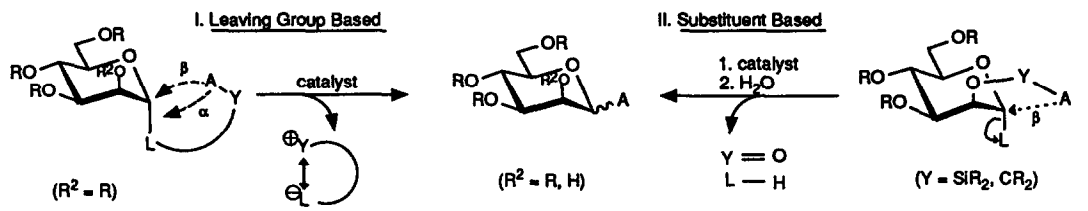
Abstract: Sterically crowded β-hydroxy-substituted glucosyl carboxylates **4α,β** furnish with strong alkylating agents **5a-c** in the presence of base diastereoselectively α- or β-glucosides **6a-c**, respectively; in addition, β-lactone **7** is formed. The reaction is discussed in terms of an intramolecular ortho-ester transformation.

Glycosyl transfer within the active site of an enzyme can be regarded as intramolecular process where the anomeric center of the glycosyl donor and the accepting moiety are held in close proximity to ensure regio- and diastereoselectivity of the reaction[2,3]. For corresponding in vitro intramolecular glycosylations linkers are required (Scheme 1, Y) which connect the donor and the acceptor moieties accordingly. Obviously, the attachment of the linker Y at the donor moiety may be favorably based on the leaving group (Scheme 1, I) or on a functional substituent, especially at C-2 (Scheme 1, II), respectively.

Scheme 1

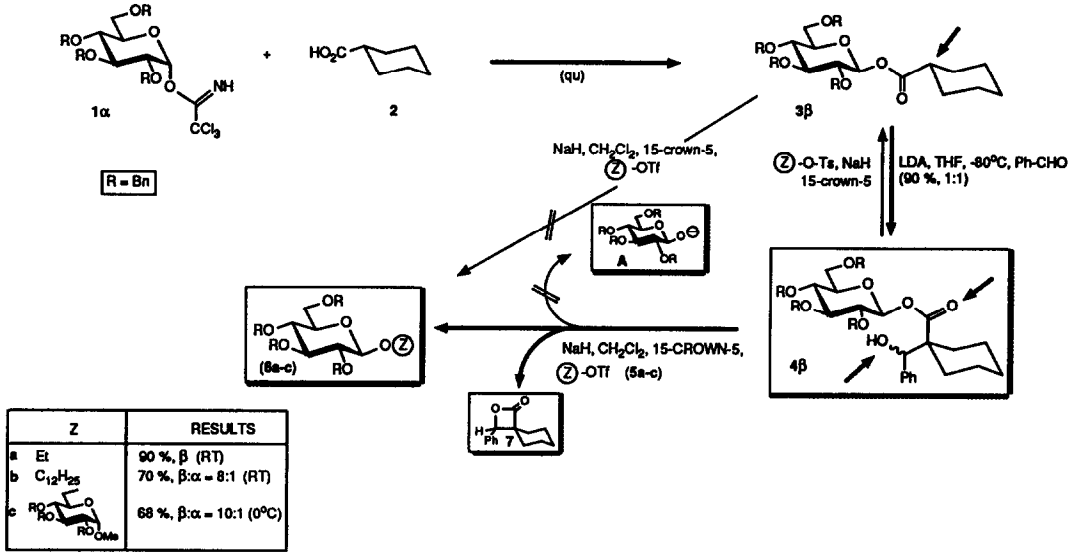


Recently, the second principle has been successfully applied to β-mannopyranoside synthesis[4,5]; it is based on the temporary attachment of the acceptor via a SiR_2 or CR_2 linker, respectively, to the 2-hydroxy group which is located at the β-site of the donor, thus exhibiting also limitations of this approach. Surprisingly, the first principle has attracted less attention, although a broader scope can be envisaged. We have observed an intramolecular spiroketal formation[6] and an interesting case of thioglucoside formation via an S_Ni process[7] which were discussed in terms of this principle[6-8]. We would like to report a new type of leaving group based intramolecular glycoside bond formation where in situ generated ortho-ester intermediates are presumed to transform diastereoselectively into glycosides and β-lactones[9].

Convenient *trans*-selective conversion of O-glycosyl trichloroacetimidates with carboxylic acids into O-glycosyl carboxylates has been amply reported[8,10]. Thus, O-α-D-glucosyl trichloroacetimidate **1α**[7,10] reacts with cyclohexanecarboxylic acid (2) to the desired β-connected glucoside **3β**[11] in practically quantitative yield

(Scheme 2). Treatment of 3β with lithium diisopropylamide (LDA) in THF at low temperature and then with benzaldehyde furnished a 1:1-diastereomeric mixture of β-hydroxy carboxylate 4β[11] which was not separated[12].

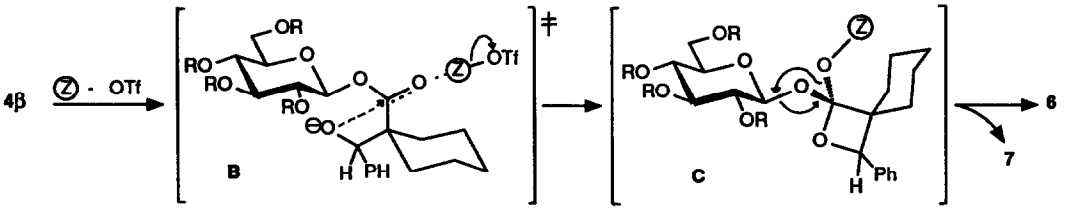
Scheme 2



Reaction of 4β with ethyl triflate **5a** in the presence of NaH and 15-crown-5 as base system afforded at room temperature known ethyl β-glucoside **6a**[13] in high yield; in addition, the expected β-lactone **7**[11] could be isolated in 80% yield. Similarly, reaction with n-dodecyl triflate **5b** furnished under the same conditions glucoside **6b**[14] in a 8:1 β/α-ratio. With the 6-O-triflate of methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside[15] **5c** as alkylating agent at room temperature a 6:1 β/α-ratio of known disaccharide **6c**[16] was observed; at 0°C this ratio was increased to 10:1. Less reactive alkylating agents, as for instance tosylates, do not react; instead, base catalyzed retro-aldol reaction is observed which leads to 3β. However, 3β does not directly generate glucosides **6** under the reaction conditions. Therefore, concomitant base promoted β-lactone (**7**) and glucopyranosyloxide formation (**A** in Scheme 2, possibly due to the presence of traces of water or alcohol) followed by anomeric O-alkylation[8,17] of **A** can be excluded as alternative reaction course.

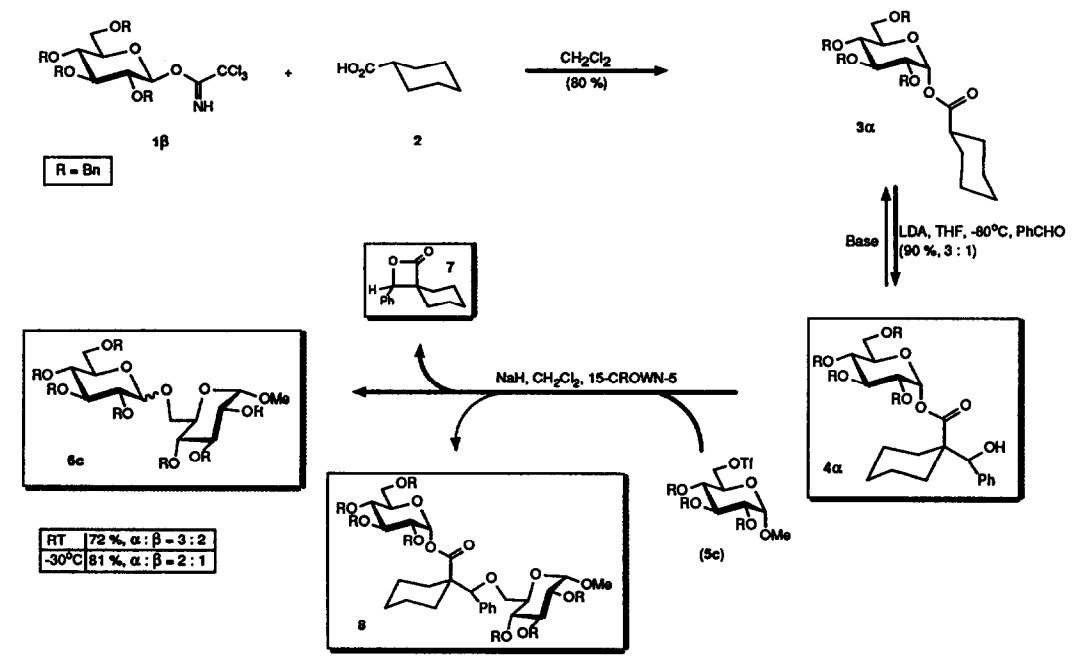
Attack of a strong alkylating agent **5** in the presence of a base could occur at the hydroxy group of 4β (arrows in Scheme 2); however, due to steric crowding around this group, nucleophilic attack of the oxide oxygen at the carbonyl group with concomitant alkylation of the more readily accessible carbonyl oxygen (transition state **B** in Scheme 3) is an alternative which leads to an ortho-ester intermediate (**C** in Scheme 3) comprising a highly substituted four-membered ring. Intramolecular transformation of **C** via a stereocontrolled intramolecular 1,3-glycosyl shift will alleviate steric strain, thus providing β-glucoside **6** and β-lactone **7**.

Scheme 3



Further support for the proposed reaction course comes from the reaction of the corresponding α-isomer **4α** (Scheme 4) which is readily obtained from β-trichloroacetimidate **1β**[7,8] and **2** yielding α-glycoside **3α**[11] and then with benzaldehyde β-hydroxy carboxylate **4α** (3:1 diastereomer ratio)[11]. Reaction of **4α** with **5c** as alkylating agent in the presence of NaH and 15-crown-5 as base system afforded as main product the desired disaccharide **6c** (72%, α:β = 3:2) and lactone **7**. Obviously, access to the β-hydroxy group in carboylate **4α** is less hindered than in **4β**, therefore 15% of O-alkylation product **8**[11] was found, in addition to little retro-aldol reaction (< 5%). Reaction of **4α** with **5c** at -30°C increased the α/β-ratio to 2:1.

Scheme 4



In conclusion, leaving group based intramolecular glycosyl transfer either via an isolable or an in situ generated intermediate, as described here, has great potential for diastereoselective glycoside bond formation. In addition, this reaction may have promise for the diastereoselective formation of β-lactones and analogs with sugars as chiral auxiliaries.

References and Notes

1. This work was supported by the Deutsche Forschungsgemeinschaft and by the Fonds der Chemischen Industrie.- M.E.B. is grateful for a stipend from the Fonds der Chemischen Industrie.
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11. ^{1}H-NMR data (250 MHz, $CDCl_3$)

    3β: δ = 1.16-1.94 (m, 10 H, cyclohexane), 2.30 (tt, 1 H, HC-COO), 3.54-3.76 (m, 6 H, 6 HC-OBn), 4.48-4.90 (m, 8 H, 4 CH_2Ph), 5.62 (d, 1 H, H_1, J = 7.9 Hz), 7.12-7.33 (m, 20 H, 4 Ph).

    3α: δ = 1.21-1.94 (m, 10 H, cyclohexane), 2.30 (tt, 1 H, HC-COO), 3.61-3.96 (m, 6 H, 6 HC-OBn), 4.48-4.95 (m, 8 H, 4 CH_2Ph), 6.39 (d, 1 H, H_1, J = 3.8 Hz), 7.12-7.35 (m, 20 H, 4 Ph).

    4β: δ = 0.98-2.26 (m, 10 H, cyclohexane), 3.62-3.79 (m, 6 H, 6 HC-OBn), 4.48-4.90 (m, 9 H, 9 Ph-CHO), 5.74, 5.76 (2 d, 1 H, H_1, J = 7.6 Hz), 7.16-7.37 (m, 25 H, 5 Ph).

    4α: δ = 0.91-2.31 (m, 10 H, cyclohexane), 3.24-3.98 (m, 6 H, 6 HC-OBn), 4.46-4.97 (m, 9 H, 9 Ph-CHO), 6.46, 6.53 (2d, 1 H, H_1, J = 3.5 Hz), 7.13-7.35 (m, 25 H, 5 Ph).

    7: δ = 1.11-2.19 (m, 10 H, cyclohexane), 5.25 (s, 1 H, Ph-CH), 7.24-7.43 (m, 5 H, Ph). IR: strong absorbance at 1827, 1834.

    8: δ = 0.88-2.18 (m, 10 H, cyclohexane), 3.16-3.95 (m, 12 H, 12 HC-OBn), 3.36 (s, 3 H, OCH_3), 4.36-4.94 (m, 16 H, 15 Ph-CHO, H_1), 6.38, 6.46 (2 d, 1 H, $H_{1'}$, J = 3.3 Hz), 7.00-7.30 (m, 40 H, 8 Ph).
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