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Decarboxylative Glycosylation Reaction - Intra- Versus Intermolecular Reaction Course[1]

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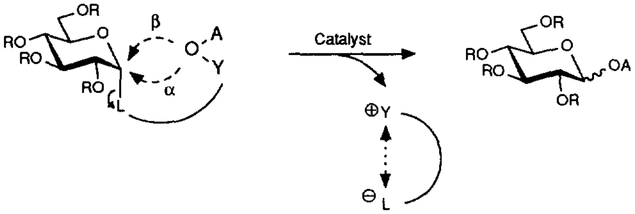
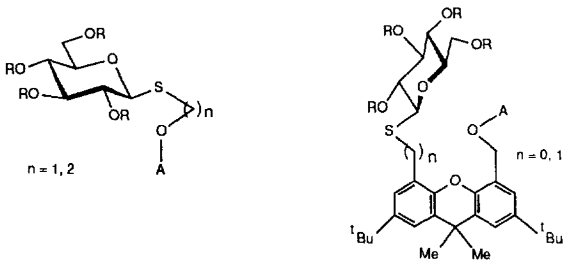
***Abstract*:** Mixed glycosyl carbonates are transformed under acid catalysis into glycosides. Competition experiments with equal amounts of carbonates **5** and **6** led to complete scrambling of the glycosyl donor and acceptor moieties: not only the expected glycosides **7** and **8** but in practically equal amounts also glycosides **9** and **10** were obtained. Therefore, decarboxylative glycosylation under acid catalysis is an intermolecular reaction; the reaction course is discussed. © 1997 Elsevier Science Ltd.

Various approaches to intramolecular glycoside bond formation have been recently reported[2-11]. They are based on attachment of the acceptor to the donor moiety via substituents at the donor[2-9] or – as exhibited in Scheme 1 – via the leaving group[10,11]. Varying results have been obtained; generally after some modification of the reaction conditions good glycosylation yields were found, yet the α/β-selectivities were not in all cases satisfactory. This was also observed for the thioglycoside systems shown in Scheme 2[13,14]. Though ideal structural preferences supporting an intramolecular reaction course via either retention or inversion of configuration were envisaged, generally from either the α- or the β-configurated starting material similar ratios of both anomers were obtained.

Scheme 1

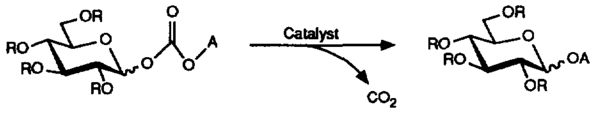


Scheme 2



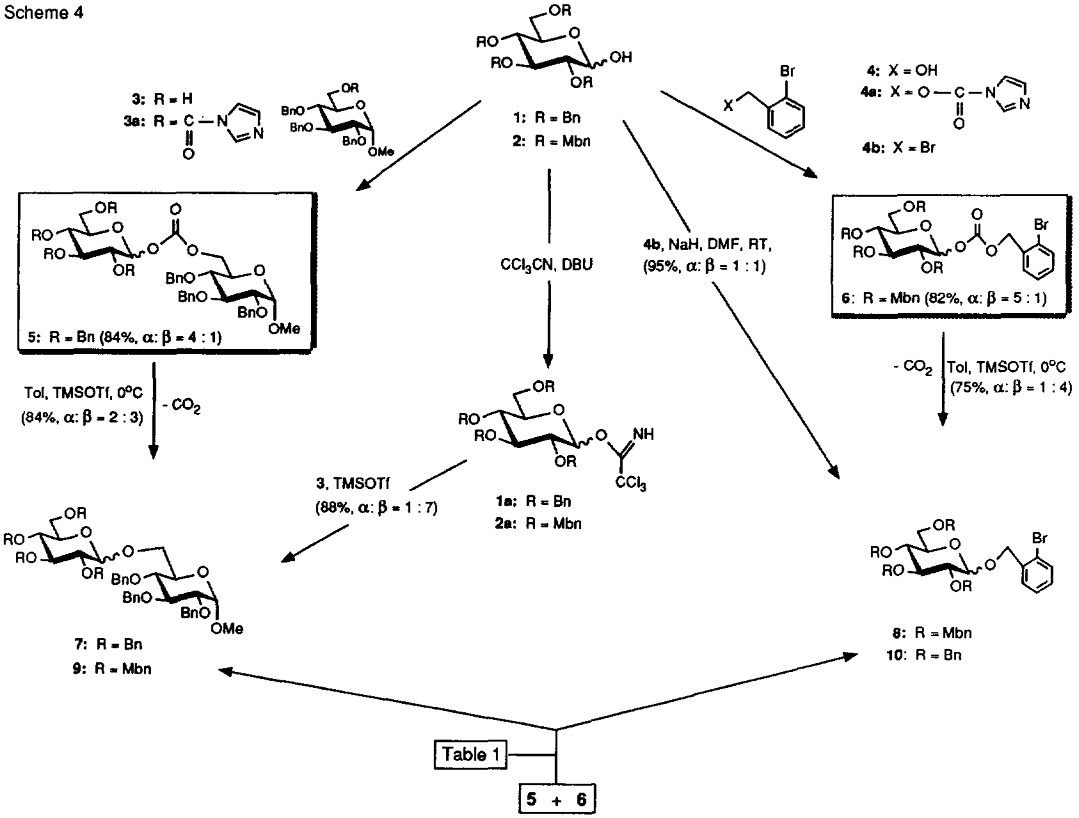
Because ease of anomeric control is expected to be associated with intramolecular glycoside bond formation, low anomeric selectivities should be reason to question the intramolecular reaction course assignments. Therefore, the decarboxylative glycosylation via mixed carbonates (Scheme 3)[11,12,15] was reinvestigated; it was recently claimed to be intramolecular[11].

Scheme 3



Intramolecular vs. intermolecular reaction courses can best be differentiated by the proper design of competition experiments. To this aim, two different glycosyl donors and acceptors each of similar reactivity have to be ligated via the leaving group. It was expected that tetra-O-benzylglucose **1** and tetra-O-(3-methylbenzyl)glucose **2**[13,14] fulfill this requirement as donors (Scheme 4). Similar acceptor properties were expected for primary alcohols. Finally, 6-O-unprotected glucoside **3**[16] and 2-bromobenzylalcohol **4** were selected. Combining **1** and **3**, and **2** and **4** following a reported procedure[11] led via imidazole carboxylates **3a** and **4a** to the mixed carbonates **5**[11] and **6**[17], respectively; they were obtained as α/β-mixtures. Treatment of both compounds with trimethylsilyl trifluoromethanesulfonate (TMSOTf, 1.1 equivalents) afforded under loss of carbon dioxide the desired glycosides **7**[18] and **8**[17] in high yields; the anomeric ratio of the starting materials was not reflected in the products of this decarboxylative glycosylation, as indicated by starting from anomerically pure carbonates. A similar result was reported for the transformation of **5** into **7**[11].

Scheme 4



For the competition experiments it was required that product separation of the possible combinatorial glycosides could be achieved; therefore, the synthesis of all four combinations from **1**-**4** was established. To this end, **1** and **2** were transformed into the corresponding trichloroacetimidates **1a**[19] and **2a**[17]; reaction with **3** under standard glycosylation conditions[19] afforded disaccharides **7**[18] and **9**[17] in high yields; as desired, the α- and the β-anomers were obtained for characterisation. Synthesis of glycosides **8**[17] and **10**[17] was performed by anomeric O-alkylation[19] of **1** and **2** with **4b** as alkylating agent, which led to α/β-mixtures. Chromatographic separation of **7**, **8**, **9**, and **10** was possible by flash chromatography (toluene/ethyl acetate, 60:1 followed by toluene/ethyl acetate, 15:1).

The decisive competition experiments were performed with equimolar amounts of **5** and **6** under varying conditions, as summarized in Table 1. Obviously, in none of the experiments a preference for the formation of **7** and **8**, the products of intramolecular glycosylation, was observed; the cross-coupled products **9** and **10** were practically found in equal amounts. Only for borontrifluoride activation of the reaction mixture (entry 5) less of **8** and **9** was obtained; this is attributed to the slightly lower stability of the O-(3-methylbenzyl)-protected glycosyl donor moiety compared with O-benzyl protection. Therefore, because products **7** and **8** are stable under the reaction conditions, decarboxylative glycosylation follows an intermolecular reaction course. It can be assumed that the promoter, for instance TMSOTf, disintegrates the mixed carbonates under loss of CO_2 into glycosyl triflates (presumably contact ion pairs) and silylated acceptors which persist long enough to lead to complete scrambling in product formation[20]. Thus, the results in terms of yield and anomeric selectivity can be readily explained[19].

Table 1. Competition experiments: Decarboxylative glycosylation with equimolar amounts of **5** and **6** [a]

Entry	Reaction conditions			Yield [%] [b]			
	Solvent	Promoter (1.1 eq)	Temp. [°C]	**7**	**9**	**10**	**8**
1	Toluene	TMSOTf	0°C	37	37	44	41
				(α: β = 1 : 2.5)		(α: β = 1 : 2.5)	
2	Mesitylene	TMSOTf	0°C	35	35	45	45
				(α: β = 1 : 3.7)		(α: β = 1 : 3.6)	
3	Toluene	TBDMSOTf	0°C	40	40	41	41
				(α: β = 1 : 2)		(α: β = 1 : 3.5)	
4	Mesitylene	TBDMSOTf	0°C	40	40	43	43
				(α: β = 1 : 3.6)		(α: β = 1 : 3.6)	
5	Toluene	$BF_3 \cdot OEt_2$	r.t.	26	13	51	22
				(α: β = 1.4 : 1)		(α: β = 1 : 1)	

[a] Total concentration $4.5 \cdot 10^{-2}$ M

[b] Based on acceptor content in the product

In conclusion, it was demonstrated that acid promoted decarboxylative glycosylation follows an intermolecular reaction course. Intramolecular reaction courses were also claimed for other glycosylation reactions which were carried out under similar reaction conditions. Careful investigation may also prove partial or complete intermolecularity for these cases.

References and Notes

1. This work was supported by the *Deutsche Forschungsgemeinschaft* and the *Fonds der Chemischen Industrie*.- G.S. is grateful for a stipend from the *Fonds der Chemischen Industrie*.
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17. a) ^{1}H-NMR data (600 MHz, $CDCl_3$): **2a**-α (250 MHz): δ = 2.29 (m, 12 H, 4 $PhCH_3$), 3.65-4.07 (m, 6 H, 2-,3-,4-,5-,6-,6'-H), 4.39-4.95 (m, 8 H, 4 CH_2-PhMe), 6.51 (d, 1 H, 1-H, *J* = 3.5 Hz), 6.94-7.23 (m, 16 H, 4 PhMe), 8.58 (s, 1 H, NH). **6**: δ = 2.28-2.30 (m, 12 H, 4 $PhCH_3$), 3.63-4.00 (m, 6 H, 2-,3-,4-,5-,6-,6'-H), 4.40-4.93 (m, 8 H, 4 CH_2-PhMe), 5.28-5.30 (m, 2 H, CH_2-PhBr), 5.51 (d, 1β-H, *J* = 8 Hz), 6.19 (d, 1α-H, *J* = 3 Hz), 6.95-7.28 (m, 18 H, 4 PhMe, 2 PhHBr), 7.43 (m, 1 H, PhHBr), 7.56 (m, 1 H, PhHBr). **8**: δ = 2.28-2.33 (m, 12 H, 4 $PhCH_3$), 3.50 (m, 5β-H), 3.57 (dd, 2β-H), 3.62-3.75 (m, 6α-,2α-,4β-,3β-,4α-,6β-,6'α-H), 3.79 (dd, 6'β-H), 3.86 (m, 5α-H), 4.06 (dd, 3α-H), 4.46-5.05 (m, 10 H, 4 CH_2-PhMe, CH_2-PhBr), 4.55 (d, 1β-H, *J* = 9 Hz), 4.95 (d, 1-αH, *J* = 4 Hz), 6.97-7.27 (m, 18 H, 4 PhMe, 2 PhHBr), 7.50-7.62 (m, 2 H, PhHBr). **9**-β: δ = 2.19 (s, 3 H, $PhCH_3$), 2.27-2.30 (m, 9 H, 3 $PhCH_3$), 3.32 (s, 3 H, OMe), 3.43 (m, 1 H, 5b-H), 3.50-3.61 (m, 5 H, 2b-,4a-,2a-,4b-,3b-H), 3.66-3.72 (m, 3 H, 6b-,6a-,6'b-H), 3.82 (m, 1 H, 5a-H), 3.98 (dd, 1 H, 3a-H), 4.18 (dd, 1 H, 6'a-H), 4.36 (d, 1 H, 1b-H, *J* = 4 Hz), 4.61 (d, 1 H, 1a-H, *J* = 9 Hz), 4.49-4.94 (m, 14 H, 4 CH_2-PhMe, 3 CH_2-Ph), 6.98-7.35 (m, 31 H, 4 PhMe, 3 Ph). **10**: δ = 3.47 (m, 5β-H), 3.50 (dd, 2β-H), 3.52-3.81 (m, 6α-,2α-,4β-,3β-,4α-,6β-,6'α-,6'β-H), 3.87 (m, 5α-H), 4.08 (dd, 3α-H), 4.45-5.05 (m, 11 H, 1-H, 4 CH_2-Ph, CH_2-PhBr), 7.10-7.37 (m, 22 H, 20 Ph, 2 PhHBr), 7.51-7.60 (m, 2 H, PhHBr).

    b) **2a**-α: $[\alpha]_D^{20}$ = +50.1° (c = 1, $CHCl_3$); **9**-β: $[\alpha]_D^{20}$ = +19.6° (c = 1, $CHCl_3$), mp. 106°C (EE/PE); **10**-β: $[\alpha]_D^{20}$ = -7.2° (c = 1, $CHCl_3$), mp. 92°C (Et_2O/PE).
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20. This reaction course is presumably effective in various acid catalyzed intermolecular glycosylation reactions.

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