Stereodivergent syntheses at the glucose backbone†

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Both diastereomers of 2-*C*-branched carbohydrates with various functional groups are selectively available from the same malonate precursor in good yields in only a few steps.

Carbohydrates play a decisive role in nature and are among the cheapest precursors for ex-chiral pool syntheses.[1] Additionally, they find widespread applications as ligands for catalysts or as chiral auxiliaries,[2] with easily available D-glucose or D-galactose as the most attractive starting materials. The reactions often proceed with high stereoselectivities, however the absolute configurations of the new stereogenic centres are predetermined by the carbohydrate backbone. For the synthesis of the corresponding epimers, more expensive pseudo-enantiomeric D-arabinose or D-fucose derivatives are required.[3] On the other hand, Kunz *et al.* described an interesting transformation of a D-galactose derivative, where two epimeric dehydropiperidinones were selectively obtained by simply changing the reaction sequence.[4] Rarely, the selectivity of reactions at the carbohydrate auxiliary was controlled by alteration of the protecting groups or the solvents, however considerably lower diastereomeric ratios resulted.[5]

We have been interested in the synthesis of 2-*C*-branched saccharides, which are easily available by radical addition of CH acidic compounds to glycals in only one step, for many years.[6] Malonates react with especially high yields and stereoselectivities, and the glucose derivative **1** allows various further transformations.[7] Herein we describe the controlled substitution of each of the two diastereotopic ester groups *pro-S* or *pro-R* (Fig. 1)[8] by methyl, OH or NH_2 groups in only a few steps. Despite the predetermined configuration of the glucose backbone, this stereodivergent synthesis[9] proceeds with excellent selectivity and provides interesting 2-*C*-branched saccharides.

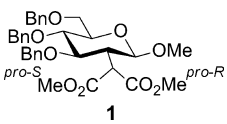

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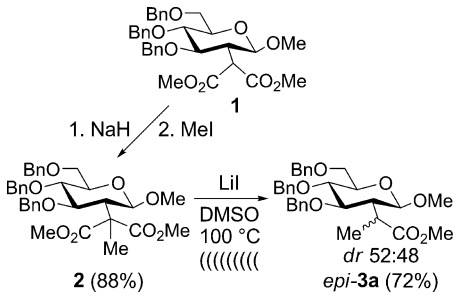
Fig. 1 Diastereotopic groups *pro-S* and *pro-R* in glucose derivative **1**.

Initially, we investigated the direct alkylation of malonate **1** for the first time, to generate the new stereogenic centre after subsequent decarboxylation (Scheme 1), which furnished high yields at the carbohydrate backbone in our previous studies.[7] Indeed, the deprotonation with sodium hydride and reaction with iodomethane proceeded smoothly and afforded the 2-*C*-branched saccharide **2** in 88% yield in analytically pure form (ESI†). However, two epimeric methyl esters *epi*-**3a** were formed in a ratio of 52:48 during the decarboxylation, which can be rationalized by the drastic reaction conditions. Both isomers are easily separable by column chromatography and show distinctive differences in the NMR spectra. The configurations were unequivocally assigned by the subsequent stereodivergent synthesis and by NOE measurements (ESI†).

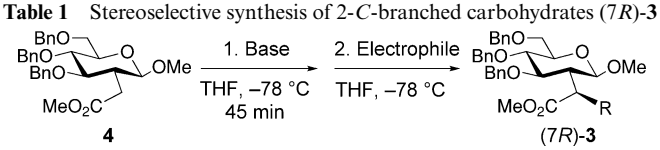


Scheme 1 Methylation and subsequent decarboxylation of glucose derivative **1**.

Obviously, milder conditions had to be applied for a stereoselective synthesis of **3a**. Therefore, we investigated the deprotonation of methyl ester **4**, which is available from malonate **1** in 92% yield in only one step,[7a] with various bases at low temperatures and determined the diastereoselectivities of the alkylation with iodomethane (Table 1).

Indeed, already the reaction with lithium diisopropylamide (LDA) and subsequent methylation afforded the products (7*R*)-**3a** and (7*S*)-**3a** in a ratio of 88:12 (entry 1). However, the pure epimer (7*R*)-**3a** was isolated in only 30% yield, due to the low conversion of 50%. We could improve the conversion and yield by addition of hexamethylphosphorous triamide only

Table 1 Stereoselective synthesis of 2-*C*-branched carbohydrates (7*R*)-**3**



Entry	Base	R[a]	Conv. (%)[b]	7*R*:7*S*[b]	(7*R*)-**3** (%)[c]
1	LDA	Me	50	88:12	(7*R*)-**3a** (30)
2	LDA/HMPT	Me	60	90:10	(7*R*)-**3a** (42)
3	LiHMDS	Me	90	92:8	(7*R*)-**3a** (71)
4	NaHMDS	Me	95	95:5	(7*R*)-**3a** (79)
5	KHMDS	Me	>97	>97:3	(7*R*)-**3a** (90)
6	KHMDS	OH	>97	>97:3	(7*R*)-**3b** (82)
7	KHMDS	N_3	>97	>97:3	(7*R*)-**3c** (85)

[a] Electrophile: iodomethane, 2-sulfonyloxaziridine or trisyl azide. [b] Determined by NMR spectra of the crude products. [c] Yield of analytically pure product, isolated by column chromatography.

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slightly (HMPT) (entry 2). More efficient deprotonations were realized with stronger hexamethyl-disilazides (HMDS) (entries 3–5), and already the lithium salt provided remarkably higher conversions and stereoselectivies. Finally, the best conditions were found with the potassium salt, since the NMR spectra indicated full conversion and the highly selective formation of a sole epimer. Thus, the 2-*C*-branched glucose derivative (7*R*)-**3a** was isolated in 90% yield in analytically pure form (entry 5, ESI†). To extend the potential of our method, we investigated the assembly of heteroatoms at the 7-position of the glucose backbone. Thus, the Davis reagent[10] afforded α-hydroxy ester (7*R*)-**3b** in 82% and trisyl azide[11] the azide (7*R*)-**3c** in 85% yield in only one step (entries 6 and 7). Both reactions proceeded again with excellent stereoselectivities, and the products were isolated in analytically pure form.

All the main products (7*R*)-**3** exhibit coincident coupling constants of $J_{2,7}$ = 1.8–2.1 Hz, although rotation around the C2-C7 bond is not hindered. On the other hand, epimer (7*S*)-**3a** shows remarkable differences in the ^{1}H NMR spectrum with $J_{2,7}$ = 5.8 Hz and a shift of the methyl group by 0.3 ppm (ESI†). This indicates consistent configurations of the new stereogenic centres of all main products **3a–c**. Finally, the *R* configuration of azide **3c** was unequivocally determined by transformation into a known amino acid (vide infra). The excellent stereoselectivities for all reactions can be rationalized by ester enolate **5**, which is fixed by chelation to the 3-*O*-benzyl group (Fig. 2). Thus, electrophiles can attack the bicycle only from the sterically less hindered convex *Re* side. The chelation proceeds most efficiently with potassium as counterion, explaining the best selectivities with KHMDS (Table 1). This interpretation is in accordance with a recent study, where the fixation of a potassium enolate to the 3-position and not to the anomeric centre was discussed as well.[12]

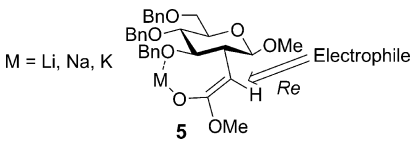
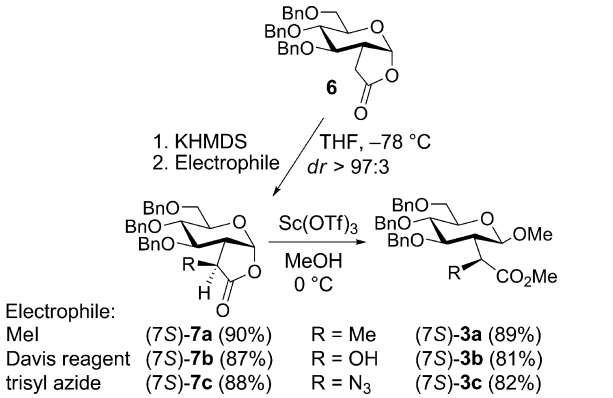


Fig. 2 Preferred reaction of ester enolate **5**.

To obtain selectively the epimeric 2-*C*-branched saccharides (7*S*)-**3**, irrespective of the glucose backbone, and hence to realize a stereodivergent synthesis, we had to develop a new concept with no chelation-control. The covalent linking to the anomeric centre *via* the 1,2-lactone **6** seemed to be especially attractive, since this compound is available from malonate **1** in 92% yield in a one-pot procedure.[7c] Furthermore, the alkylation of chiral lactones proceeds with high selectivities and was already described for carbohydrate 2,3-lactones.[13]

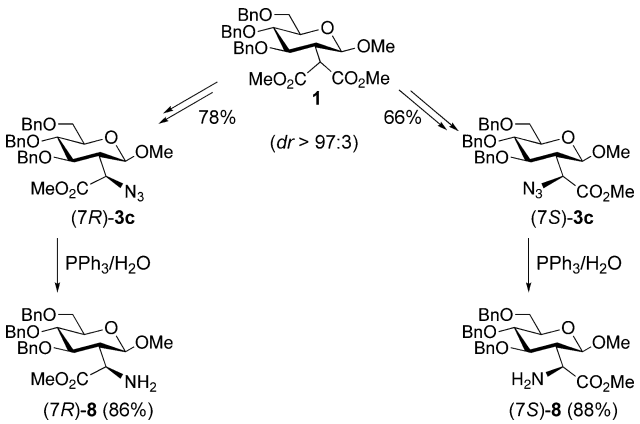
We applied potassium hexamethyldisilazide (KHMDS) for the deprotonations, which allowed reactions with electrophiles at low temperatures. Under such conditions, the substituted lactones (7*S*)-**7a–c** were isolated in good yields and excellent stereoselectivities (Scheme 2). Due to the fixed bicyclic structure, the *S* configuration at the new stereogenic centres of all products was unequivocally established by $J_{2,7}$ coupling constants and NOE measurements (ESI†). Again, the high stereoselectivities can be rationalized by the attack of the electrophiles from the sterically



Scheme 2 Stereoselective synthesis of 2-*C*-branched carbohydrates (7*S*)-**3**.

less hindered convex side, but the fixation to the 1-position affords now the 7*S* isomers exclusively.

In the last step of the stereodivergent synthesis, the lactone ring had to be re-opened, which proceeds smoothly with scandium triflate in methanol.[7c] Under such conditions, the methyl esters (7*S*)-**3** were isolated in good yields without epimerization (Scheme 2). On the basis of NMR spectra, the products (7*S*)-**3** and (7*R*)-**3** are clearly distinguishable by characteristic coupling constants and chemical shifts (ESI†). As additional structural proof, we transferred the epimeric azides **3c** into the known amines **8** by Staudinger reduction (Scheme 3).[14] Such amino acid derivatives **8** had to be synthesized by completely different reaction pathways, previously.[6c,15] Thus, we demonstrated not only a new concept of stereodivergent syntheses at the glucose backbone from easily available malonate **1**, but also opened a convenient, stereoselective and flexible access to *C*-glycosylated amino acids, which are of current interest for organic chemists.[6c,15,16]



Scheme 3 Stereodivergent synthesis of 2-*C*-branched amino acid derivatives **8** from malonate **1**.

In conclusion, we have shown that stereodivergent syntheses at the glucose backbone can be realized with excellent selectivities. Starting from an easily available 2-*C*-branched malonate, each of the two diastereotopic ester groups was selectively replaced by methyl, OH or NH_2 groups in only a few steps. Our concept was based on chelation of an ester enolate to the 3-position or lactonization to the anomeric centre, respectively. For both reaction types, the attack of electrophiles occurred exclusively from the

sterically less hindered convex side, which afforded two epimeric products with excellent stereoselectivities. All compounds were isolated in good yields in analytically pure form. In contrast to chiral auxiliaries, the newly generated stereogenic centres cannot be cleaved off the carbohydrate. However, our method opens interesting prospects for the stereoselective and flexible synthesis of 2-*C*-branched saccharides.

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