Simple synthesis of 2-*C*-branched glyco-acetic acids†

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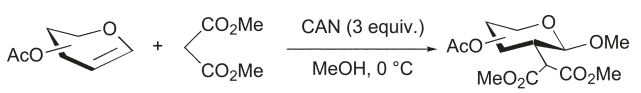
Only three steps are required for the selective synthesis of 2-*C*-branched glyco-acetic acids from glycals by radical addition and decarboxylation.

C-Glycosides are important analogs of carbohydrates, since they are stable towards enzymatic hydrolysis due to the replacement of the interglycosidic oxygen by a methylene group.[1] Many synthetic strategies for *C*-glycosides based on *C*-branched monosaccharides as starting materials have been described over the years.[2] An elegant access point, not only to *C*-di- but also to *C*-trisaccharides, by ring-closing metathesis was developed by Postema *et al.*, with sugar-based carboxylic acids as precursors.[3] However, the introduction of acetic acid at the 2-position by radical C–C-bond formation afforded only mixtures of *gluco* and *manno* isomers,[3d] whereas other strategies proceeded even less efficiently.[4] Herein, we describe a simple and selective synthesis of 2-*C*-branched glyco-acetic acids in only three steps from easily available glycals in good to high yields, giving access to further functionalized carbohydrate 2-*C*-analogs.

During the course of our investigations on transition metal-mediated radical reactions,[5] we developed a simple one-step entry to 2-*C*-branched carbohydrates **3** by the addition of dimethyl malonate (**2**) to various glycals **1a–f** in the presence of ceric(IV) ammonium nitrate (CAN) (Scheme 1).[6] The reactions exhibited a high degree of diastereoselectivity, and the products **3** were obtained in good to high yields in an analytically pure form.

For the synthesis of the 2-*C*-branched glyco-acetic acids, one C–C bond of the malonates **3** had to be cleaved by decarboxylation, and many procedures for simple malonic esters are known.[7] However, although decarboxylations play major roles in biological processes, like the biosynthesis of fatty acids, only one example of a 1-*C*-branched glyco-malonate has been described in the literature, which afforded the corresponding methyl acetate in low yield.[8]



1a-f **2** **3a-f**

tri-*O*-acetyl-D-glucal (**1a**) **3a** (68%)
tri-*O*-acetyl-D-galactal (**1b**) **3b** (78%)
di-*O*-acetyl-D-xylal (**1c**) **3c** (81%)
di-*O*-acetyl-D-arabinal (**1d**) **3d** (89%)
hexa*O*-acetyl-D-maltal (**1e**) **3e** (83%)
hexa-*O*-acetyl-D-lactal (**1f**) **3f** (80%)

Scheme 1 Synthesis of 2-*C*-branched malonates **3**.

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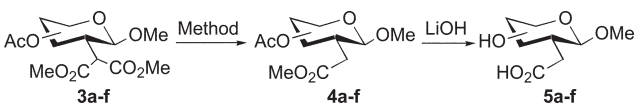
Therefore, the reaction conditions for the decarboxylation of the2-*C*-branched carbohydrates **3** to acetic esters **4** had to be carefully optimized, with the *gluco* isomer **3a** as the model compound (Table 1). First experiments were conducted by saponification of all the ester groups with lithium hydroxide and heating of the free malonic acid after acidification with HCl (Table 1, entry 1). Unfortunately, no product **5a** was isolated due to intramolecular lactonization and the intermolecular formation of polyesters. Thus, the protected dimethyl malonate **3a** was directly used for demethoxycarbonylation.[7] However, heating of the 2-*C*-branched carbohydrate in wet dimethyl sulfoxide (DMSO) resulted in no conversion, even after prolonged reaction times (Table 1, entry 2), and sodium chloride as an additive[8] gave only low yields (Table 1, entry 3).

The best results were obtained in the presence of lithium iodide at 180 °C (Method D), which afforded the 2-*C*-branched acetic ester **4a** in 92% yield in an analytically pure form (Table 1, entry 4). The reaction time could be significantly reduced by employing microwave irradiation (Table 1, entry 5),[9] but due to the simple experimental procedure, all further demethoxycarbonylation reactions of 2-*C*-analogs **3b–f** were conducted under thermal conditions (Method D). The desired 2-*C*-branched sugars **4a–d** were isolated in high yields (see ESI†). Only the disaccharides **3e** and **3f** afforded some decomposition products due to the instability of the glycosidic bond (Table 1). Finally, all protecting groups were quantitatively removed by saponification with lithium hydroxide. Thus, we have established a simple and efficient protocol for the stereoselective synthesis of 2-*C*-branched glyco-acetic acids **5** from glycals **1** in only three steps.

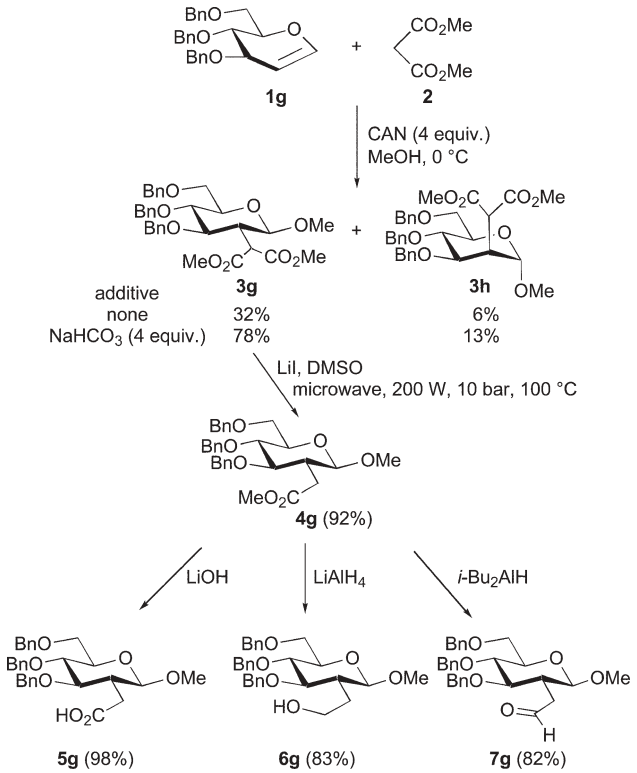
Table 1 Demethoxcarbonylation of the carbohydrate *C*-anologs **3**



3a-f **4a-f** **5a-f**

Entry	Malonate	Configuration	Method[a]	Time/h	Yield (%) 4	5
1	**3a**	*gluco*	A	6	—	—
2	**3a**	*gluco*	B	24	—	—
3	**3a**	*gluco*	C	6	34	—
4	**3a**	*gluco*	D	4.5	92	>95
5	**3a**	*gluco*	E	5 min	97	>95
6	**3b**	*galacto*	D	4.5	81	>95
7	**3c**	*xylo*	D	5	81	>95
8	**3d**	*arabino*	D	5.5	79	>95
9	**3e**	*malto*	D	6	73	>95
10	**3f**	*lacto*	D	6	72	>95

[a] Method A: (i) H_2O, cat. LiOH; (ii) HCl 95 °C. Method B: DMSO, 2 equiv. H_2O, 180 °C. Method C: DMSO, 1.5 equiv. NaCl, 180 °C. Method D: DMSO, 1.5 equiv. LiI, 180 °C. Method E: DMSO, 1.5 equiv. LiI, microwave, 200 W, 10 bar, 100 °C.



Scheme 2 Synthesis of the 2-*C*-branched methyl ester **4g** and further transformations to the products **5g–7g**.

For future applications of the sugar-based carboxylic acids in the synthesis of *C*-disaccharides, it was important to introduce protecting groups that are stable during the saponification of the methyl ester. Additionally, such protecting groups would allow further transformations of the carbon side chain under basic reaction conditions. Therefore, for the first time, we investigated the radical addition of dimethyl malonate (**2**) to tri-*O*-benzyl-D-glucal (**1g**) in the presence of CAN, since our previous work focused on acetylated derivatives.[6] The instability of benzyl groups towards Lewis acids[10] and the fast Ferrier rearrangement of benzylglycals[11] were the main problems. Indeed, initial radical reactions under standard conditions afforded the addition products **3g** and **3h** in only moderate yields, but the undesired Ferrier rearrangement could be completely suppressed by the addition of sodium hydrogen carbonate ($NaHCO_3$) (Scheme 2). Furthermore, the basic reaction conditions facilitated the generation of radicals from dimethyl malonate (**2**) and CAN.[5] The *gluco* isomer **3g** was easily separated from the *manno* isomer **3h** by column chromatography and underwent a clean demethoxy-carbonylation to the methyl ester **4g**, which was isolated in an analytically pure form in 92% yield on a gram scale (Scheme 2; ESI†).

The base stability of the benzyl protecting groups allowed further transformations and gave access to other functionalized carbohydrate 2-*C*-analogs. Thus, saponification afforded the free acid **5g** quantitatively, and reductions to the alcohol **6g** and aldehyde **7g** proceeded smoothly in good yields (Scheme 2; ESI†). Since both *C*-branched glyco-acetic acids[3] and aldehydes[4e,12] are suitable precursors for the synthesis of *C*-disaccharides, our approach offers an easy entry point to such important carbohydrate analogs.

In conclusion, we have developed an easy entry point to various 2-*C*-branched glyco-acetic acids in only three steps from glycals. The C–C bond in the 2-position is formed by a radical addition that proceeds with high stereoselectivity, and thus all final products were isolated as single isomers. The crucial step of the synthesis was the decarboxylation of the malonates, which had to be carefully optimized. Finally, thermal conditions with lithium iodide gave the best results and afforded 2-*C*-branched acetic esters in an analytically pure form on a gram scale. For further transformations, the first example of a radical addition of dimethyl malonate to benzylated glucal was developed under basic reaction conditions. This allowed saponification without cleavage of the protecting groups, and thus the desired 2-*C*-branched glyco-acetic acid was obtained from benzylglucal in three steps in 70% overall yield. Finally, reduction gave access to other functionalized carbohydrate 2-*C*-analogs that are valuable precursors for the synthesis of *C*-disaccharides.

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