Alkylation Reactions Using a Galactose-Based β-Keto Ester Enolate and Conversion into β-*C*-Galactosides

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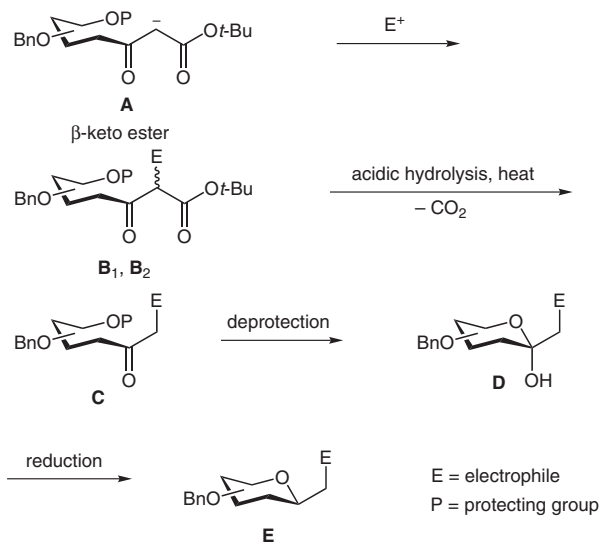
Abstract: A de novo approach for the synthesis of biologically important *C*-galactosides has been achieved via use of an acyclic galactose-derived β-keto ester. The β-keto ester enolate serves as a C-nucleophile and reacts with primary alkyl halides and Michael acceptors to generate alkylation products that can be converted into β-*C*-galactosides and *C*-disaccharide mimics with high stereoselectivity.

Key words: de novo approach, *C*-galactosides, C-nucleophile

C-Glycosides are an important class of glycomimetics, in which the exocyclic oxygen atom of an *O*-glycoside is displaced by a methylene (CH_2) group. *C*-Glycosides exhibit enhanced stability against chemical and enzymatic hydrolysis[1,2] and as such have been used as chemical probes to study carbohydrate-mediated molecular recognition in biology and medicine.[3] Although numerous efforts have been dedicated toward the synthesis of *C*-alkyl, *C*-aryl glycosides, and *C*-oligosaccharides during the past two decades,[2–5] novel approaches with improved yields, higher stereoselectivity, and broad applicability are still in high demand.



Scheme 1 General strategy for the synthesis of β-*C*-glycosides using carbohydrate-derived β-keto ester enolate **A**

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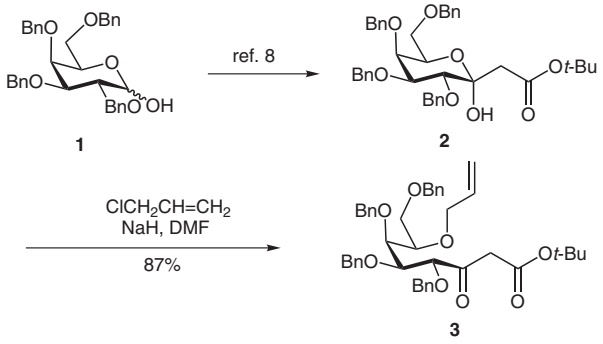
In this paper we describe a novel strategy for the synthesis of biologically relevant β-*C*-galactosides via use of a galactose-based and β-keto ester derived nucleophile (Scheme 1).

According to this strategy a β-keto ester derived acyclic C-nucleophile **A** reacts with an electrophile (reactive alkyl halide, Michael acceptor) to form isomeric products $\mathbf{B_1}$ and $\mathbf{B_2}$. Acidic saponification of the *tert*-butyl esters $\mathbf{B_1}$ and $\mathbf{B_2}$ followed by decarboxylation produces ketone **C**. Selective deprotection of **C** affords cyclic acetal **D** that will undergo reduction to form β-*C*-glycoside **E** based on previous literature reports.[6] In order to test the outlined strategy, access to suitably protected carbohydrate-based β-keto ester is required. We selected galactose-derived β-keto ester **3** as a suitable candidate based on the importance of β-galactosides in carbohydrate–protein interactions.[7] The allyl ether group was selected as temporary protecting group as it is orthogonal to benzylether and *tert*-butyl ester groups. The synthesis of **3** is outlined in Scheme 2 and involves ketose **2** previously prepared on a multigram scale from commercially available acetal **1**.[8]



Scheme 2 Synthesis of galactose-derived β-keto ester **3**

Crucial ring opening of ketose **2** was achieved by deprotonation of the acetal function with sodium hydride and subsequent trapping of the acyclic alkoxide ion with allyl chloride. The use of allyl chloride instead of allyl bromide as electrophile and relative short reaction times were crucial in order to avoid C- and O-allylation of the generated β-keto ester **3**. Compound **3** exists predominantly in its keto form based on ^{1}H NMR and ^{13}C NMR data. For instance, ^{13}C NMR shows signals at δ = 204.4 ppm (C=O) and 47.9 ppm that are consistent with the keto form.

With β-keto ester **3** in hands we then explored C-alkylation reactions using methyl iodide, benzyl bromide, hexyl

bromide, and hexyl iodide as representative electrophiles, cesium carbonate as a base, and DMSO as solvent.[9] We selected two reaction conditions (method A and B) to control the formation of mono- and dialkylated products (Table 1).

Table 1 Formation of Mono- and Dialkylated Products

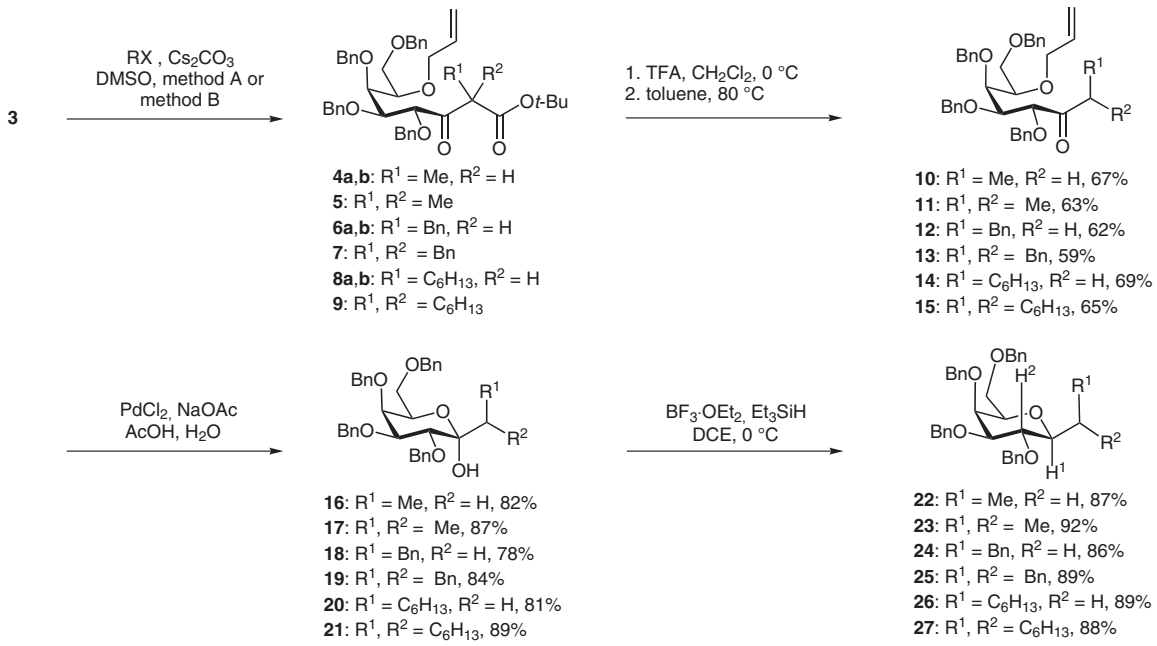
Alkyl halide (RX)	Mono/di[b]	Method[a]	Yield (%)[c]
MeI	**4a,b/5** = 78:22	A	89[b]
	4a,b/5 = 3:97	B	78[b]
$PhCH_2Br$	**6a,b/7** = 82:18	A	50[d]
	6a,**b/7** = 5:95	B	76[b]
$C_6H_{13}I$	**8a**,**b/9** = 85:15	A	74[d]
	8a,**b/9** = 8:92	B	80[b]
$C_6H_{13}Br$	**8a**,**b/9** = 87:13	A	65[d]
	8a,**b/9** = 10:90	B	79[b]

[a] Method A: RX (1.3 equiv), Cs_2CO_3 (1.4 equiv), DMSO, r.t., 1 h; method B: RX (3.5 equiv), Cs_2CO_3 (4.0 equiv), DMSO, 50 °C, 3 h.
[b] Determined by isolation.
[c] C-Alkylated products (mono and di).
[d] Determined by NMR.

Method A reflects conditions for the synthesis of monoalkylated products while method B was used to prepare dialkylated products. For instance, the mono-C-methyl-substituted β-keto esters **4a**,**b** were formed exclusively as a mixture of two diastereomers in 89% yield (method A) while the di-C-methyl-substituted ester **5** was obtained as a single diastereomer in 78% yield (method B). Comparable yields were obtained for di-C-benzylated product **7** and di-C-hexylated product **9** using benzyl bromide, *n*-hexyl iodide, or *n*-hexyl bromide as electrophiles (Table 1). O-Alkylated products were obtained in the case of monoalkylated products **6a** and **6b** (C/O ratio = 1:1) and **8a** and **8b**. However, using hexyl iodide (C/O ratio = 4.5:1) instead of hexyl bromide (C/O ratio = 2.6:1) reduced O-alkylation in products **8a** and **8b**. In all cases the mono- and di-C-alkylated products could be separated by flash chromatography. After chromatographic separation the diastereomeric mixtures **4a** and **4b**, **6a** and **6b**, **8a** and **8b** as well as the di-C-alkylated products **5**, **7**, and **9** were converted into ketones **10–15** (Scheme 3) after ester saponification with TFA and decarboxylation in toluene.

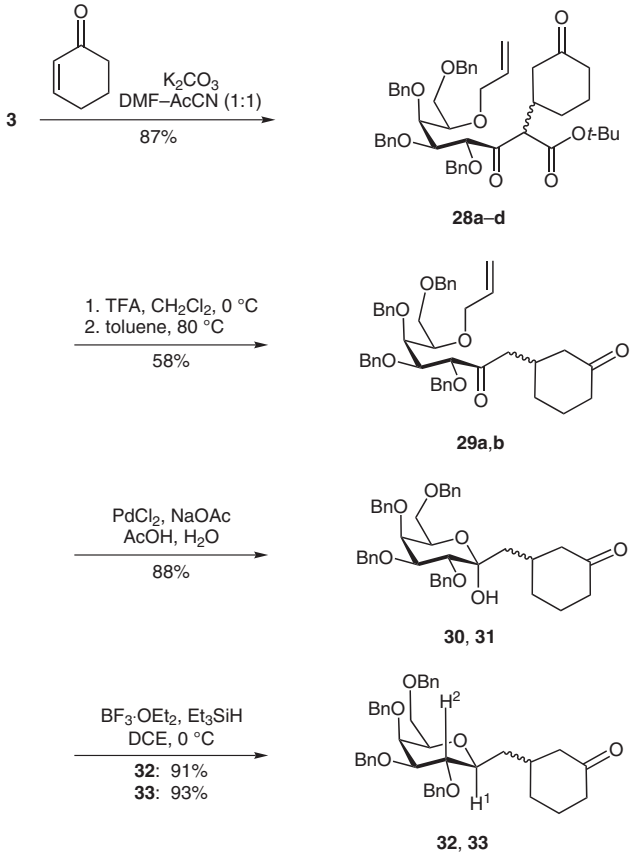
Deprotection of the *O*-allyl ether was achieved by exposure to palladium chloride in a solvent mixture containing sodium acetate–water–acetic acid[10] to produce acetals **16–21** in 78–89% yield (Scheme 3). All acetals except **21** existed in the cyclized form. Compound **21** existed as a 1:1 mixture containing cyclic and the acyclic keto forms in $CDCl_3$. It is apparent that the bulkiness of the substituents R^1 and R^2 in compound **21** destabilize sterically the cyclic form. Lewis acid ($BF_3{\cdot}OEt_2$) catalyzed reductive dehydroxylation using triethylsilane[13] in 1,2-dichloroethane converted acetals **16–21** exclusively into the β-*C*-galactosides **22–27** in 86–92% yield. The β-*C*-glycosidic linkage in compounds **22–27** was confirmed from the vicinal diaxial coupling constant $^3J_{H1,H2} > 9.0$ Hz (Scheme 3).

In order to explore the reactivity of deprotonated galactose-derived β-keto ester **3** towards other classes of electrophiles, we studied Michael addition reactions to α,β-unsaturated carbonyl compounds.[11] We were particularly interested in selecting Michael acceptors that display structural similarities to carbohydrates. Michael adducts of this type may find use as glycomimetics.[7b] Initially, we studied the 1,4-Michael addition reaction of **3** to 2-cyclohexenone using potassium carbonate in 1:1 mixture of



Scheme 3 Synthesis of alkyl β-*C*-galactosides via alkylation (see also Table 1)

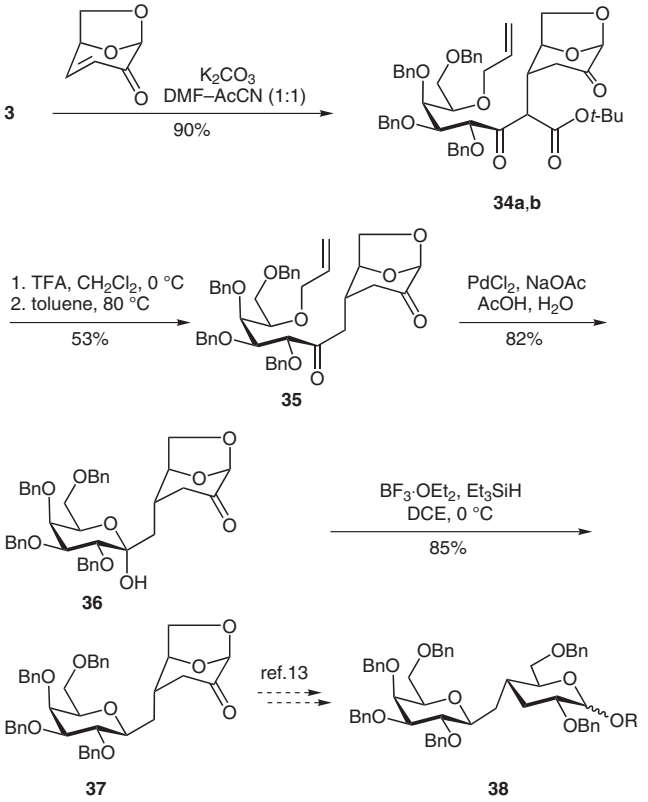
DMF and acetonitrile at room temperature. Products **28a–d** were obtained as a mixture containing all four stereoisomers in a combined yield of 87%. Exposure to trifluoroacetic acid in dichloromethane at 0 °C for three hours followed by decarboxylation in toluene at 80 °C afforded an inseparable mixture of two diastereomers **29a** and **29b** in a combined yield of 58%. Deallylation using palladium(II) chloride in a solvent mixture containing sodium acetate–water–acetic acid produced acetals **30** and **31** (1:1) in a combined yield of 88% yield after chromatographic separation. Lewis acid catalyzed reductive dehydroxylation of **30** and **31** using Et_3SiH and $BF_3{\cdot}OEt_2$ at 0 °C in 1,2-dichloroethane afforded stereoselectively β-*C*-galactosides **32** ($^3J_{1,2}$ = 9.4 Hz) and **33** ($^3J_{1,2}$ = 9.3 Hz), respectively, in 91% and 93% yield (Scheme 4).



Scheme 4 Synthesis of a β-*C*-galactoside via Michael 1,4-addition

Encouraged by these results we then focused on the conjugate addition of galactose-derived β-keto ester enolates to Michael donor levoglucosenone (Scheme 5).

Previous studies have shown that conjugate additions of C- and S-nucleophiles to levoglucosenone proceed with high *exo*-face selectivity.[12,13] In addition, biological studies have shown that Michael adducts of this type serve as glycomimetics to probe carbohydrate–protein interactions.[13] We were pleased to observe that base-catalyzed exposure of **3**[15] to levoglucosenone in DMF–acetonitrile cosolvent produced a 1:1 mixture of two diastereomers **34a** and **34b** in 90% yield. The diastereomeric mixture



Scheme 5 Synthesis of a β-*C*-disaccharide mimic via 1,4-Michael addition to levoglucosenone

34a and **34b** was then converted into β-(1→4)-linked *C*-disaccharide mimic **37** in a three-step procedure. At first, treatment of compounds **34a** and **34b** with TFA followed by decarboxylation in toluene afforded **35** in 53% yield. Subsequently, Pd-catalyzed deallylation of **35** provided acetal **36** in 82% yield that was reduced to *C*-disacharide mimic **37** in 85% yield. The observed coupling constant between H-1 and H-2 ($^3J_{H1,H2}$ = 9.4 Hz) confirms the β-*C*-glycosidic linkage in **37**. Compound **37** can be converted into disaccharide mimic **38** as previously reported[13] (Scheme 5).

In summary, we have developed synthetic access to an acyclic galactose-derived β-keto ester enolate that serves as a C-nucleophile in alkylation reactions using reactive alkyl halides. Choice of the proper reaction conditions permit control of the mono- and dialkylated products and limit O-alkylation. The C-alkylated products can be converted into β-*C*-galactosides with high diastereoselectivity. Mono- and dialkylation of the β-keto ester opens up the possibility to prepare novel and unusual β-*C*-galactosides. Moreover, conjugate addition of the galactose-derived β-keto ester enolate to Michael acceptors provide *C*-disaccharide analogues that may find utility as glycomimetics to study carbohydrate-mediated recognition in biology. Due to the well-established ubiquitous importance of β-keto esters in organic chemistry[14] our study suggests that carbohydrate-based β-keto ester will find use in carbon–carbon bond-forming reactions involving carbohydrate moieties.

Acknowledgment

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(15) **Procedure for the Synthesis of β-Keto Ester 3**
In an inert atmosphere a solution of ketose **2** (150 mg, 0.23 mmol) in dry DMF (5 mL) was cooled to 0 °C and a suspension of NaH (60 wt% in oil, 137 mg, 15 equiv) was added slowly over 5 min. After 30 min at 0 °C, allyl chloride (562 μL, 30 equiv) was added. The reaction was stirred at r.t. for 1 h, cooled to 0 °C, and quenched by slow addition to a mixture of ice and sat. NH_4CI soln (10 mL). The resultant mixture was extracted twice with EtOAc (2 × 15 mL), and the combined extracts were dried over Na_2SO_4 and concentrated in vacuo. Flash column chromatography, with EtOAc–hexane (1:9) as eluent, gave β-keto ester **3** (138 mg, 87% yield) as an oil. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.1 (Boc), 47.9, 69.9, 72.0, 73.1, 73.3, 73.4, 74.1, 77.8, 78.4, 79.5, 81.7 (quart. *C*, Boc), 84.4, 116.7, 127.5–128.5 (arom.), 135.3 (=CH_2), 137.5, 138.0, 138.2, 138.4, 166.9, 204.4. MS (ES^+): *m/z* = 717.31 $[M + Na]^+$. Anal. Calcd for $C_{43}H_{50}O_8$: C, 74.33; H, 7.25. Found: C, 74.41; H, 7.36.