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Rh(II) Carbene-Promoted Activation of the Anomeric C−H Bond of Carbohydrates: A Stereospecific Entry toward α- and β-Ketopyranosides

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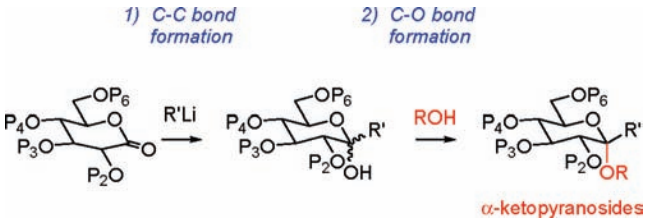
Abstract: In this communication we report a new strategy toward ketopyranosides based on a carbene-mediated activation of the anomeric C−H bond of carbohydrates. By forming a new carbon−carbon bond after a glycosylation step, this approach enables the preparation of both α- and β-ketopyranosides from advanced precursors.

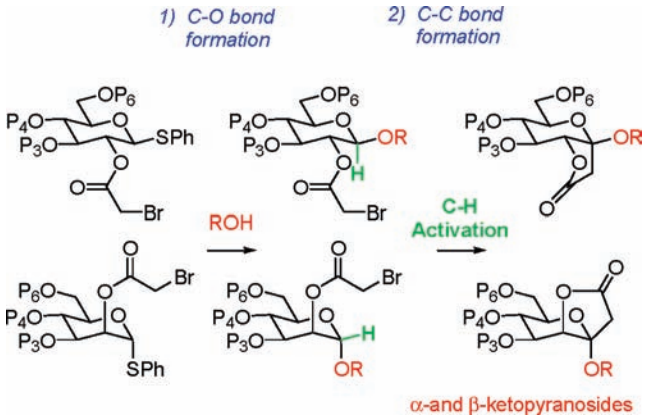
New synthetic tools in carbohydrate chemistry have attracted tremendous interest over the past decades due to the important role of complex oligosaccharides in many fundamental biological processes.[1] In this context, quaternarization of a specific position represents a highly potent entry toward chemical tools for glycobiology.[2] However, such a modification of the sugar backbone requires a multistep, time-consuming approach relying on: (1) selective protection/deprotection of a given position, (2) oxidation of the resulting alcohol, (3) addition of an organometallic reagent. Following this strategy,[3,4] α-ketopyranosides, with the anomeric position quaternarized by an independent equatorial chain, can be prepared from δ-lactones by formation of a new anomeric C−C bond *before* a glycosylation step (Scheme 1).

Scheme 1. Synthesis of Ketopyranosides from δ -Lactones



The scope of this approach is, however, strongly limited by the glycosylation step. Thus, glycosylation of sterically demanding acceptors with ketopyranoside donors are usually low yielding.[5,6] Moreover, coupling with 2-*O*-acylated donors offers poor diastereocontrol by anchimeric assistance.[7] In this context, the precise one-step substitution of the anomeric C−H bond carries considerable appeal for the formation of a new anomeric C−C bond *after* glycosylation, thus providing a new entry toward both α- and β-ketopyranosides.[8] Herein, we report such an approach where a bromoacetate at position 2 should play a dual role. This protecting group would first induce a stereoselective glycosylation by anchimeric assistance,[9] and after conversion into a diazoacetate,[10] would then promote a carbene insertion[11] into the anomeric C−H bond (Scheme 2).

Scheme 2. Carbene-Mediated Synthesis of Ketopyranosides



As this transformation could be dramatically hampered by intermolecular[12] or oxonium ylide-mediated[13] competitive pathways, as well as nonselective insertions, we first investigated activation of the anomeric C−H bond on model compounds.

Starting from orthogonally protected methyl-pyranosides **1** and **2**, bromoacetylation followed by diazotransfer delivered diazoacetates **3** and **4** in good yield (Scheme 3). Decomposition by various Rh(II) salts[14] established that $Rh_2(OAc)_4$ was suitable to reach γ-lactones **5** and **6** (Table 1, entries 1 and 6). Interestingly, a weakly electrophilic carbene generated under $Rh_2(acam)_4$ catalysis could also promote highly efficient insertion into axially orientated C−H bonds (entry 8). However, Rh(II) salts with bulky or strongly electron-withdrawing ligands were

Table 1. Catalytic Decomposition of **3** and **4**

entry	diazo-sugar	catalyst (mol %)	γ-lactone	yield (%)
1	**3**	$Rh_2(OAc)_4$ (2)	**5**	73[a]
2	**3**	$Rh_2(oct)_4$ (2)	**5**	49[a]
3	**3**	$Rh_2(tfa)_4$ (2)	**5**	13[a]
4	**3**	$Rh_2(cap)_4$ (2)	**5**	9[a]
5	**3**	$Rh_2(acam)_4$ (2)[c]	**5**	35[a]
6	**4**	$Rh_2(OAc)_4$ (2)	**6**	72[a]
7	**4**	$Rh_2(tfa)_4$ (2)	**6**	10[a]
8	**4**	$Rh_2(acam)_4$ (2)[c]	**6**	85[a]
9	**3**	$Rh_2(OAc)_4$ (0.5)	**5**	77[b]
10	**4**	$Rh_2(OAc)_4$ (0.5)	**6**	90[b]

[a] Estimated by ^{1}H NMR of the crude product; [b] Isolated yield after purification by chromatography; [c] Use of 4 Å MS as additive.

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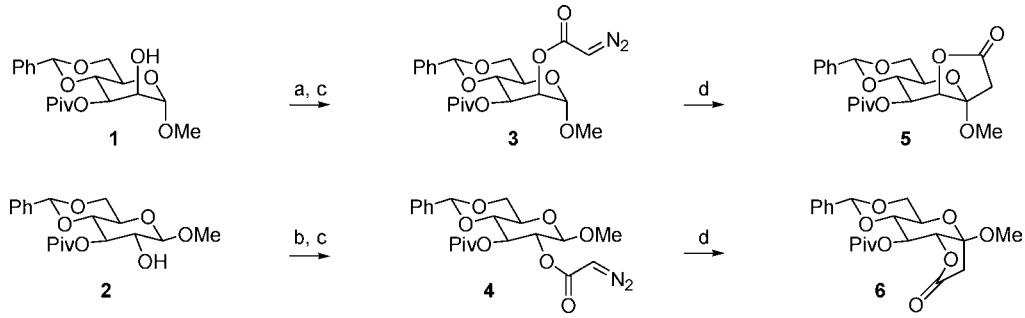
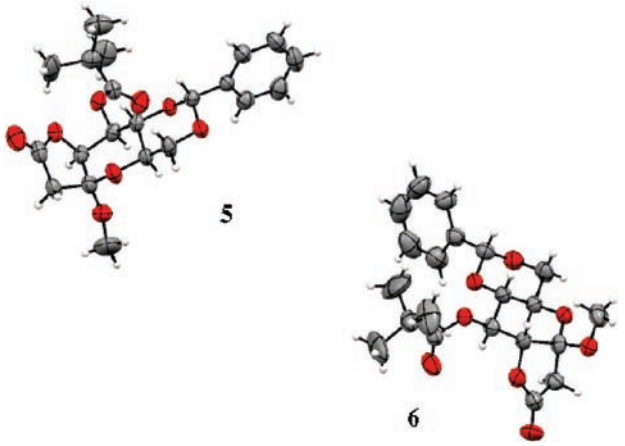
Scheme 3. Carbene-Mediated Activation of the Anomeric C−H Bond on Model Compounds[a]

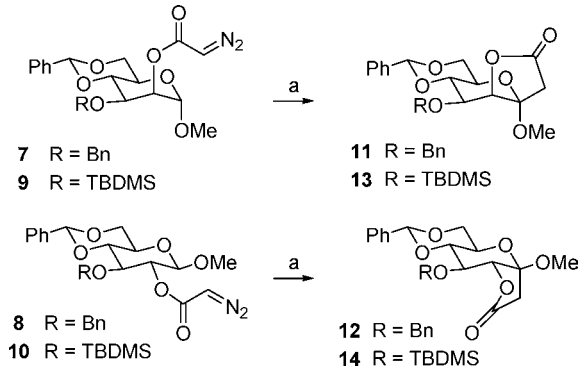


[a] Reactions and conditions: (a) $BrCH_2COBr$, CH_2Cl_2, pyridine, 0 °C; (b) $BrCH_2COBr$, CH_2Cl_2, DMAP, 0 °C; (c) TsNHNHTs, DBU, THF, 0 °C, 73% for **3** and 74% for **4** over two steps; (d) Rh_2L_4 (see Table 1), 1,2-dichloroethane, reflux.

Chart 1. ORTEP Representations of **5** and **6**



Scheme 4. Influence of 3-*O*-Protecting Groups[a]



[a] Reagents and conditions: (a) Rh_2L_4 1 mol % (see Table 2), 1,2-dichloroethane, 4 Å MS, reflux.

Table 2. Catalytic Decomposition of 3-*O*-Benzylated and 3-*O*-Silylated Compounds

entry	diazo-sugar	catalyst[c]	γ-lactone	yield (%)
1	**7**	$Rh_2(OAc)_4$	**11**	20[a,c]
2	**7**	$Rh_2(acam)_4$	**11**	10[a]
3	**8**	$Rh_2(OAc)_4$	**12**	35[a,d]
4	**8**	$Rh_2(acam)_4$	**12**	35[a,e]
5	**9**	$Rh_2(OAc)_4$	**13**	94[b]
6	**10**	$Rh_2(OAc)_4$	**14**	92[b]

[a] Estimated by ^1H NMR of the crude product; [b] Isolated yield after purification by chromatography; [c] Additional 51% of 1,7−C−H insertion into the benzylic position; [d] Additional 35% of 1,7−C−H insertion into the benzylic position. [e] Additional 21% of dimerization.

detrimental to the quaternarization process (entries 2−4 and 7). Diminishing catalyst loading to 0.5 mol % (entries 9−10) finally delivered **5** and **6** in 77% and 90% yield, respectively, without any competitive dimerization. The selective activation was confirmed by X-ray structure analysis of compounds **5** and **6** (Chart 1). We next studied the influence of protecting groups close to the highly reactive metal carbene intermediate.

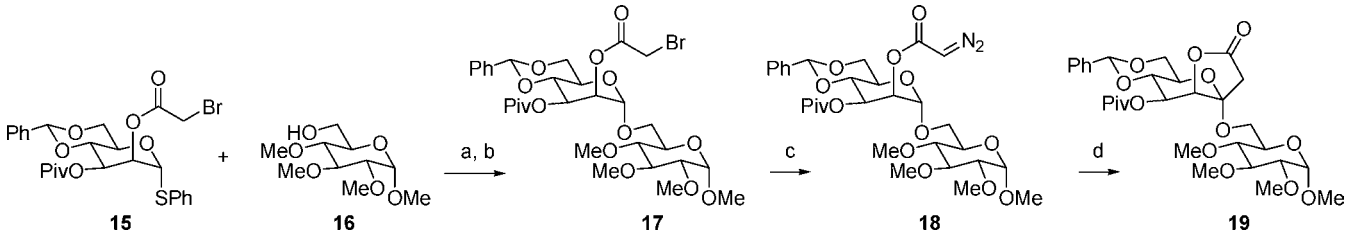
Thus, position 3 of model compounds was selectively protected as benzyl or *tert*-butyldimethylsilyl ethers. Bromoacetylation and diazotransfer under Fukuyama's conditions provided carbene precursors **7**, **8**, **9**, and **10** in good yield (Scheme 4). As expected, catalytic decomposition of 3-*O*-benzylated compounds **7** and **8** by $Rh_2(OAc)_4$ gave γ-lactones **11** and **12** in moderate yield because of competitive 1,7−C−H insertion into the benzylic position (Table 2, entries 1 and 3). Interestingly, this side reaction can be fully avoided using $Rh_2(acam)_4$ as catalysis (entry 4). In this case, pure γ-lactone **12** could be obtained, albeit in a modest 35% yield because of competitive dimerization.

Changing the benzyl protecting groups to *O*-silylated carbene precursors **9** and **10** nicely delivered γ-lactones **13** and **14** in 94% and 92% yield, respectively (entries 5 and 6).

We next turned our attention to the functionalization of the anomeric C−H bond of disaccharides (Scheme 5). Coupling the 2-*O*-bromoacetyl-mannopyranosyl donor **15** with **16** under NIS/TfOH conditions resulted in a mixture of disaccharide and orthoester. Subsequent TMSOTf-promoted rearrangement delivered α-mannopyranoside **17** as a single anomer in 65% yield over two steps. After conversion into the diazo-sugar **18**, selective insertion into the anomeric C−H bond was promoted by $Rh_2(OAc)_4$ to give the quaternarized α-mannopyranoside **19** in 65% yield. Following a similar approach, stereocontrolled glycosylation and diazotransfer delivered the *β-gluco* carbene precursor **20**. However, selective activation of its anomeric C−H bond appeared more challenging. Thus, decomposition of **20** with 1 mol % of $Rh_2(OAc)_4$ in refluxing 1,2-dichloroethane gave the targeted compound **21** as well as byproducts resulting from competitive intramolecular insertion processes, as assessed by mass spectrometry. A selective activation of the anomeric C−H bond was finally achieved in 61% yield under $Rh_2(acam)_4$ catalysis (Scheme 6).

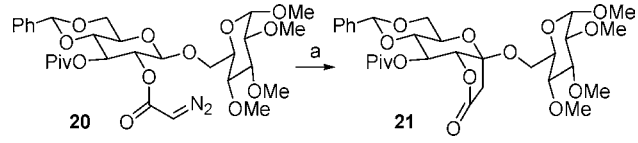
Finally, ring-opening of γ-lactones **5** and **6** under Lewis-acid conditions delivered α- and β-ketopyranosides **22** and **23**, with

Scheme 5. Dual Role of a Bromoacetate in Carbene-Mediated Activation of the Anomeric C−H bond of a Disaccharide[a]



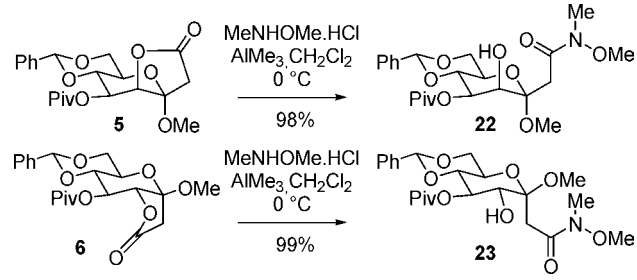
[a] Reagents and conditions: (a) NIS, TfOH, 4 Å MS, CH_2Cl_2, −20 °C; (b) TMSOTf, 4 Å MS, CH_2Cl_2, 0 °C, 65% over two steps; (c) TsNHNHTs, DBU, THF, 0 °C, 84%; (d) $Rh_2(OAc)_4$ 0.5 mol %, 1,2-dichloroethane, reflux, 65%.

Scheme 6. Insertion into the Axial C−H bond of a β-disaccharide[a]



[a] Reagents and conditions: (a) $Rh_2(acam)_4$ 2 mol %, 4 Å MS, 1,2-dichloroethane, reflux, 61%.

Scheme 7. Ring-Opening of γ-Lactones **5** and **6**



the anomeric position being quaternarized by an independent equatorial or axial chain ready for further functionalization (Scheme 7).

In summary, we have developed a stereospecific entry toward both α- and β-ketopyranosides using a highly regioselective intramolecular carbene insertion. Complementary studies are currently underway in our laboratory to determine if this transformation involves a concerted[15] or stepwise[16] mechanism. Introduction of a bromoacetate at position 2 enables not only a convenient installation of the carbene precursor but also a perfect stereocontrol of the glycosylation step. This new approach, based on the stereospecific construction of an anomeric quaternary center after a glycosylation step, allows a shift in the retrosynthetic paradigm of ketopyranosides.

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Supporting Information Available: Preparation of **1**, **2**, **7**, **8**, **9**, **10**, **15**, **16**, and **20**, experimental procedures, characterization data, crystallographic data for **5** and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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