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Intermolecular Pauson–Khand reactions on a galactose scaffold

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Abstract

An intermolecular Pauson–Khand reaction involving a carbohydrate scaffold having a pendant alkyne provides galactose derivatives with a cyclopentenone moiety in the C3-position in up to 85% yield.

The Pauson–Khand reaction is a versatile transformation, involving the reaction of an alkyne, an alkene and carbon monoxide to furnish a cyclopentenone in one step while creating three new carbon–carbon bonds.[1] Classical conditions for the reaction involve the use of stoichiometric amounts of $Co_2(CO)_8$ and heating,[2] while the use of additives such as N-oxides,[3] amines[4] and sulfides[5] can facilitate ligand exchange and promote the reaction. Recent efforts have been devoted to the development of catalytic versions of the reaction involving cobalt or other metals such as titanium, ruthenium, rhodium, iridium or bimetallic species.[6] However, the catalytic version is as yet mainly limited to the intramolecular reaction, although development in this area is likely to continue.

Despite numerous examples of the Pauson–Khand reaction in the total synthesis of natural products and biologically active molecules,[7] there are few examples of its application to carbohydrate substrates. Lindsell was the first to prepare a cobalt carbonyl complexed enyne based on a hex-2-enopyranoside scaffold, but the attempted Pauson–Khand reaction did not afford the desired cyclopentenone product.[8] Marco-Contelles[9] as well as Voelter[10] subsequently reported the successful cyclization of enyne pyranosides to form bisannulated products under mild conditions. Borodkin performed Pauson–Khand reactions on *exo*-methylene carbohydrate enynes,[11] while Isobe and Takai have described several examples of Pauson–Khand cyclizations involving tetrahydropyranose substrates.[12] Later reports by van Boom[13] and Hotha[14] focus on the construction of spiroannulated carbohydrate derivatives, while Schreiber applied the Pauson–Khand reaction in conjunction with a Ferrier coupling in diversity orientated synthesis based on a glycal template.[15] Following an initial study on the intramolecular cyclization of sugar azaenynes prepared from D-glucal and D-galactal,[16] Areces performed the corresponding intermolecular reactions with norbornene and norbornadiene.[17] However, to our knowledge, the publication by Areces is the only report of *inter* molecular Pauson–Khand reactions involving a sugar derivative. As part of a study concerning the preparation of galectin inhibitors, we wanted to see if the Pauson–Khand reaction could be used to provide galactose scaffolds[18] directly derivatized with a cyclopentenone in the 3-position (Fig. 1). All the galectins have an extended binding site in close proximity to the galactose 3-position, and attaching

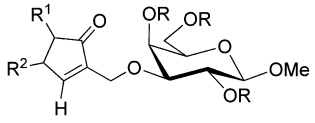

Fig. 1. Target molecules for the Pauson–Khand reactions.

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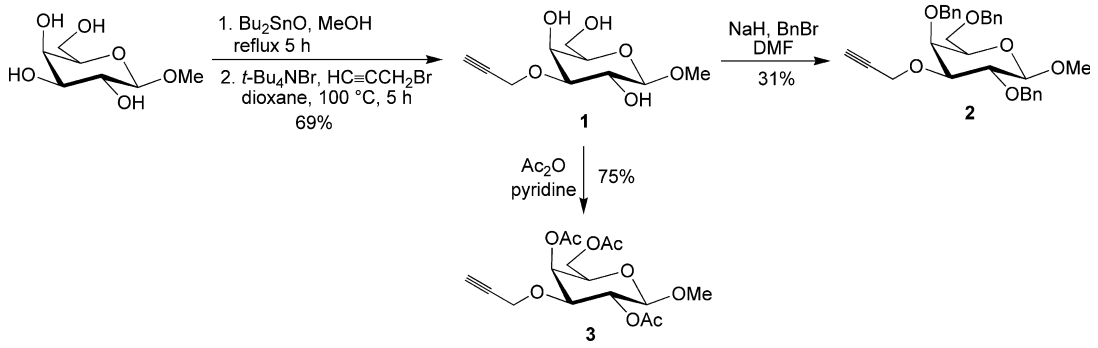
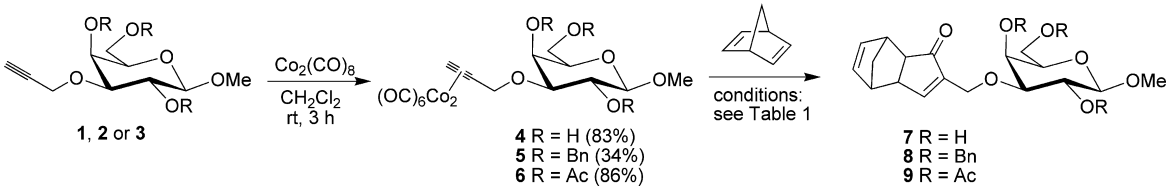
structural elements at C3 of the galactose had proven earlier to be a viable strategy towards galectin-3 inhibitors.[19]

Different cyclopentenone structures can be accessed by varying the alkene employed in the reaction, providing compounds for studying interactions with the galectin extended binding site near the galactose 3-position. The cyclopentenone moiety can also be thought of as a scaffold in itself, suitable for further derivatization by utilizing the different functionalities contained in the molecule. In this first preliminary study, a protected galectin functionalized with an alkyne in the 3-position was investigated in the Pauson–Khand reaction with a variety of different alkynes. Methyl 3-*O*-propargyl-β-D-galactopyranoside (**1**) was prepared via the activation of methyl β-D-galactopyranoside with di-*n*-butyltin oxide, followed by a reaction with propargyl bromide. Compound **1** was subsequently converted to the benzyl- or acetyl-protected structures **2** and **3** (Scheme 1). Alkynes **1**, **2** and **3** were treated with $Co_2(CO)_8$ to form cobalt complexes **4**, **5** and **6** (Scheme 2). Different reaction conditions were then investigated for the Pauson–Khand reaction using norbornadiene as the alkene (Table 1). As mentioned earlier, amine *N*-oxides are frequently used as promotors of the Pauson–Khand reaction, and in the initial reactions the cobalt complex was dissolved in dichloromethane at ambient temperature, followed by the addition of norbornadiene and the portionwise addition of trimethylamine *N*-oxide (TMANO) or, in one case, *N*-methylmorpholine *N*-oxide (NMO). Reaction of unprotected complex **4** with norbornadiene gave a complex mixture of compounds (entries 1 and 2), and this substrate was thus abandoned in favour of the protected derivatives. Reaction of the benzyl-protected complex **5** afforded the desired product **8** in 27% isolated yield, using toluene as the solvent (entry 3).

Using the acetyl-protected substrate **6** gave cyclopentenone **9** in 54% yield after 8 h. A longer reaction time was found to be detrimental to the reaction. It may be that excess N-oxide as well as the amine formed in the reaction gives rise to undesired side products when left for longer periods of time. For comparison, the reaction was also carried out under thermal conditions without any added promotor. Reflux in toluene afforded **9** in up to 85% yield if the



Scheme 1. Preparation of protected galactoside structures used as precursors in the Pauson–Khand reaction.



Scheme 2. Cobalt complexation followed by Pauson–Khand reactions with norbornadiene.

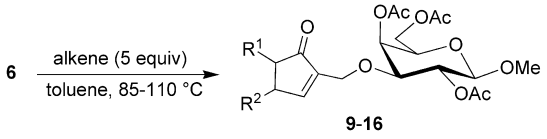
Table 1
Reaction conditions tested for the Pauson–Khand reactions

Entry	R	Conditions	Temp. (°C)	Time (h)	Product	Yield (%)
1	H	TMANO, CH_2Cl_2	rt	1	**7**	—[a]
2	H	NMO, CH_2Cl_2	rt	3	**7**	—[a]
3	Bn	TMANO, toluene	rt	8	**8**	27
4	Ac	TMANO, CH_2Cl_2	rt	8	**9**	54
5	Ac	TMANO, CH_2Cl_2	rt	17	**9**	25
6	Ac	Toluene	110	5	**9**	67
7	Ac	Toluene	110	18	**9**	85

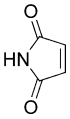
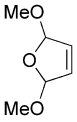
[a] Complex mixture formed.

reaction was left for 8–10 h or overnight (entry 7), while a shorter reaction time gave a slightly lower yield (entry 6). The appended carbohydrate moiety could, in theory, function as a chiral auxiliary in these reactions. However, the presence of two diastereomers in a 1:1 ratio could be seen by ^{13}C NMR analysis, indicating that no asymmetric induction occurred.

Table 2
Pauson–Khand reactions of **6** with various alkenes[20]



9-16

Entry	Alkene	Time (h)	Product	Yield (%)
1[a]		18	**9**	85
2		10	**10**	79
3		8	**11**	30
4		8	**12**	68
5		18	**13**	n.r.
6		10	**14**	74
7		1.5	**15**	14[b]
8		10	**16**	55

[a] Same as entry 7 in Table 1.
[b] Reaction conditions: $TMANO{\cdot}2H_2O$, toluene/methanol, sonication, rt.[24]

The observations that the benzyl-protected galactose substrate was problematic in terms of preparing precursor **2**, in the conversion to the cobalt complex **5** and in the ensuing Pauson–Khand reaction, prompted us to focus on the acetyl-protected substrate **6** instead, and further studies of **5** were not pursued.

A set of diverse alkenes with and without heteroatoms were selected for the thermal Pauson–Khand reaction with **6** (Table 2, Fig. 2). Reaction with norbornene gave similar results to the reaction with norbornadiene, with a yield of 79% obtained for this reaction (entry 2). Acyclic alkenes such as allyl benzene, used in entry 3, are generally less efficient in the Pauson–Khand reaction,[21] and this was indeed found to be the case. Product **11** was formed in 30% yield with the 5-substituted cyclopentenone as the major product, as had been observed earlier in Pauson–Khand reactions involving this alkene.[21] Cyclopentene performed well, affording **12** in 68% yield. Electron-deficient alkenes are generally not good substrates for the Pauson–Khand reaction, and maleimide-derivatives have been little studied in this context. Attempted Pauson–Khand reaction of maleimide showed traces of the desired product according to MS analysis, but NMR spectra were not in accordance with the expected product and we thus conclude that the product was not formed to any great extent in this case. Indene had been applied earlier in a Pauson–Khand reaction,[22] and in our case afforded the corresponding alkene in high yield (entry 6). 2,3-Dihydrofuran, however, did not afford the desired product under the thermal reaction conditions. Degradation of the cobalt complex in this case seems to be faster than the Pauson–Khand reaction, and a substantial amount of uncomplexed **3** was recovered after the reaction. This could be due to the lability of the alkene towards polymerization under the reaction conditions, limiting the amount of 2,3-dihydrofuran accessible for reaction with the cobalt complex.[23] Kerr et al. have reported alternative reaction conditions for the Pauson–Khand reaction of 2,3-dihydrofuran with cobalt carbonyl–alkyne complexes, employing N-oxides in combination with sonication.[24] These modified conditions afforded the desired product **15**, albeit in a rather modest 14% yield. 2,5-Dimethoxy-2,5-dihydrofuran is a masked dialdehyde and would provide useful functionalities for further derivatization of

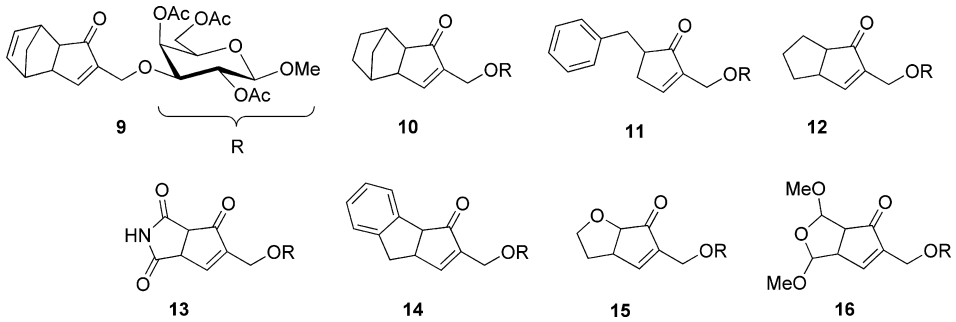


Fig. 2. Products from the Pauson–Khand reactions (see Table 2).

the product. Reaction with this alkene proceeded well, providing **16** in a relatively good yield of 55%, as a mixture of cis- and trans-isomers.

In summary, we have reported the first examples of intermolecular Pauson–Khand reactions involving an alkyne moiety appended to a carbohydrate moiety in its cyclized form. Cyclic alkenes gave the best results, affording the desired products in moderate to good yields, while allyl benzene as well as the sensitive 2,3-dihydrofuran gave less than satisfactory results. The products formed constitute useful scaffolds for further derivatization and investigation as potential galectin-3 inhibitors.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.02.114.

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20. *Typical reaction procedure for the thermal Pauson–Khand reaction* (Table 2, entry 1): Complex **6** (100 mg, 0.152 mmol) and norbornadiene (80 μl, 0.758 mmol) were dissolved in toluene in a sealable reaction tube under an argon atmosphere. The tube was sealed with a cap and heated to 110 °C. After 18 h, the solvent was evaporated and the crude residue purified by flash chromatography, eluting with toluene/ethyl acetate 2:1, affording 69 mg of **9** as a brown oil (85% yield). All the compounds were characterized by NMR, IR and HRMS; see Supplementary material. Data for **9**: 85%, brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (app br s, 1H), 6.27 (app br s, 1H), 6.19 (app br s, 1H), 5.44 (app br s, 1H), 5.07 (app t, $J = 9.0$ Hz, 1H), 4.33 (d, $J = 8.0$ Hz, 1H), 4.27 (d, $J = 12.6$ Hz, 1H), 4.20–4.10 (m, 2H), 4.05 (d, $J = 13.2$ Hz, 1H), 3.82 (t, $J = 6.6$ Hz, 1H), 3.55 (br d, $J = 10.0$ Hz, 1H), 3.49 (s, 3H), 2.89 (br s, 1H), 2.75 (br s, 1H), 2.68 (br s, 1H), 2.30 (br s, 1H), 2.13–2.04 (m, 9H), 1.38 (d, $J = 9.2$ Hz, 1H), 1.25–1.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.33, 170.73, 170.48, 169.79, 161.76, 138.71, 137.28, 137.23, 102.21, 78.70, 70.95, 70.91, 66.36, 64.09, 61.90, 57.08, 53.26, 48.46, 43.86, 43.13, 41.42, 21.21, 21.18, 21.00; IR (neat) 2254, 1746, 1699, 1231, 908, 734 cm^{-1}; $[\alpha]_D^{21}$ +15.3 (*c* 0.014, CH_2Cl_2); HRMS (ES+) *m*/*z* calcd for $C_{24}H_{30}O_{10}Na$ $[M+Na]^+$ 501.1737, found 501.1729.
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