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A new oxa-Michael reaction and a gold-catalysed cyclisation en route to C-glycosides

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ABSTRACT

Two new syntheses of benzyl C-glycosides have been developed. The first one involves an unprecedented oxa-Michael cyclisation and the second one relies on an efficient gold-catalysed ring-closure.

The synthesis of C-glycosides has become an area of intense study over the last three decades.[1] Replacement of the anomeric oxygen atom with a methylene group allows C-glycosides to have higher chemical and enzymatic stability. There are few routes to benzyl C-glycosides reported in the literature. The most common involve hydroboration of olefinated carbohydrate derivatives and Suzuki coupling with aryl bromides,[2] additions of benzyllithium to gluconolactones and reduction,[3] additions of benzylzinc reagents to glycals,[4] additions of benzylmagnesium reagents to glucosyl halides,[5] ring-closing metathesis to form an *endo*-glycal followed by hydroboration,[6] iodocyclization[7] and Ramberg–Bäcklund rearrangement followed by hydrogenation of the resulting *exo*-glycal.[8]

We report herein two new methods for the synthesis of C-glycosides where the aryl partner can be easily accessed from a phenol. The first route is based on an unprecedented intramolecular oxa-Michael cyclisation of an electron-deficient styryl derivative **2** to form the protected C-glycosides **1** directly (Scheme 1). Only two examples of related intramolecular oxa-Michael reactions are described in the literature.[9] The substrates required for the cyclisation reaction can be prepared by cross-metathesis (CM) between electron-poor styrenes and the known olefin **3**,[10] easily obtained by the Wittig reaction between commercially available 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose and methylenetriphenylphosphorane (93% yield).

Olefin **3** was first submitted to cross-metathesis[11] with *p*-nitrostyrene,[12] using Grubbs second-generation catalyst[13] (Table 1). The yields were low because of incomplete conversion of olefin **3**, 67% of which was recovered with 10 mol % of the catalyst (entry 1) and 38% with 15 mol % of the catalyst (entry 2). The best yield for the reaction (62%) was obtained with the Hoveyda–Grubbs second-generation catalyst (**HG2**) in refluxing toluene (entry 3).[14] Only the *E*-isomer of **2a** was formed. Performing the reaction under microwave conditions did not improve the yield.[15] The reaction was plagued by isomerisation of the alkene in **3** and the $\Delta^{2,3}$ *E*-isomer of **3** was formed in up to 24% yield.

Various styrenes (EWG = SO_2Ph, CHO, COMe, COOMe) were then submitted to CM with olefin **3** under the previously optimised conditions and the yields ranged between 50% and 62% (*E* isomers only) (Table 2). In all cases, the $\Delta^{2,3}$ isomer was formed, but it was easily separated from the desired metathesis products.

We then decided to test the Michael cyclisation on substrate **2a**, which possesses the strongest electron-withdrawing group (EWG = NO_2, Table 3). When this olefin was treated with strong bases such as *t*-BuOK[9b] or KHMDS, no cyclisation occurred. Instead, we observed elimination of a benzyloxy group, even at −78 °C, to furnish the conjugated diene **4a**. With a weaker base such as triethylamine, no reaction occurred after 12 h and with sodium hydride, the starting material was recovered at 20 °C and only degradation products were obtained at 50 °C. With DBU at ambient temperature and low concentration, the starting material was recovered (entry 6). The use of 3 equiv of DBU at 0.05 M led to **1a** in 66% yield after 12 h (entry 7). Selectivity was in favour of the α-isomer

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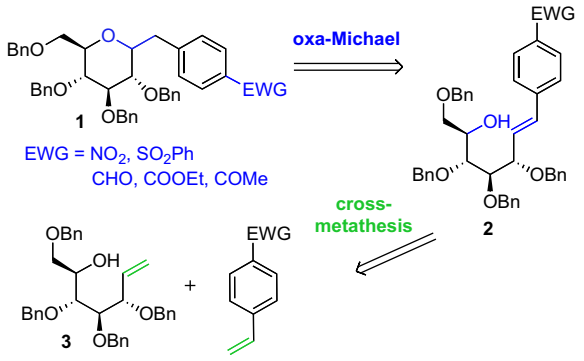
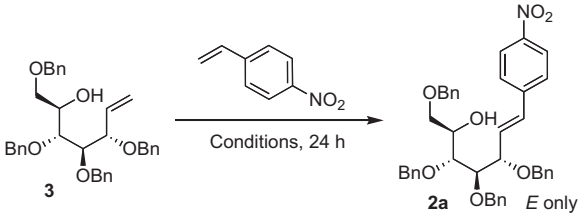


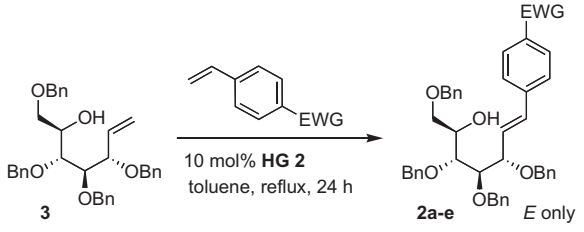
Scheme 1. Approach towards benzyl C-glycosides.

Table 1
CM between olefin **3** and *p*-nitrostyrene



Entry	Conditions	Yield (%)
1	Grubbs 2 (10 mol %), toluene, reflux	20
2	Grubbs 2 (15 mol %), toluene, reflux	44
3	**Hoveyda–Grubbs 2 (10 mol %), toluene, reflux**	**62**

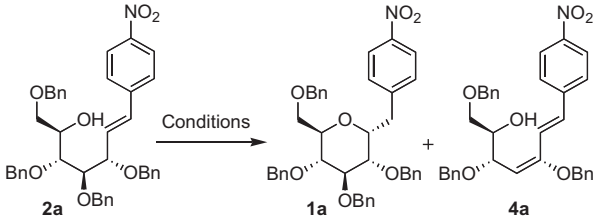
Table 2
CM between olefin **3** and various styrenes



Entry	EWG	Product	Yield (%)
1	NO_2	**2a**	62
2	SO_2Ph	**2b**	60
3	CHO	**2c**	50
4	COMe	**2d**	51
5	COOMe	**2e**	55

(α/β = 75:25). The two diastereomers could be separated by column chromatography, yielding 50% of the α-isomer and 16% of the β-isomer. Finally, optimum conditions required a substoichiometric amount of DBU (0.8 equiv) at a higher concentration (0.2 M) and compound **1a** was obtained in 78% yield after 24 h (entry 8). Another weak base K_2CO_3 also furnished C-glycoside **1a** in good yield with the same diastereomeric ratio (entry 9). The

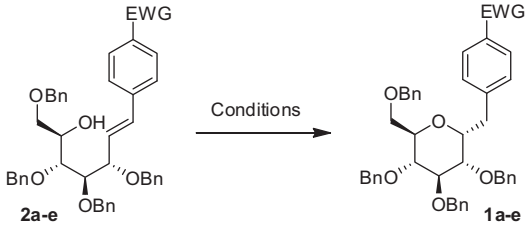
Table 3
Oxa-Michael cyclisation of **2a**



Entry	Conditions	Yield
1	*t*-BuOK (1.5 equiv), THF, −78 °C, 30 min	**4a**
2	KHMDS (1 equiv), THF, −78 °C, 1 h	**4a**
3	Et_3N (10 equiv), CH_2Cl_2, 20 °C, 12 h	No reaction
4	NaH (2 equiv), THF, 20 °C, 12 h	No reaction
5	NaH (2 equiv), THF, 50 °C, 1 h	Degradation
6	DBU (0.2 equiv), CH_2Cl_2 (0.05 M), 20 °C, 10 h	No reaction
7	DBU (3 equiv), CH_2Cl_2 (0.05 M), 20 °C, 12 h	66%[a]
8	**DBU (0.8 equiv), CH_2Cl_2 (0.2 M), 20 °C, 24 h**	**78%[a]**
9	K_2CO_3 (1 equiv), MeOH (0.1 M), 20 °C, 48 h	64%[a]

[a] α/β = 75:25.

Table 4
Oxa-Michael cyclisations of **2a–e**

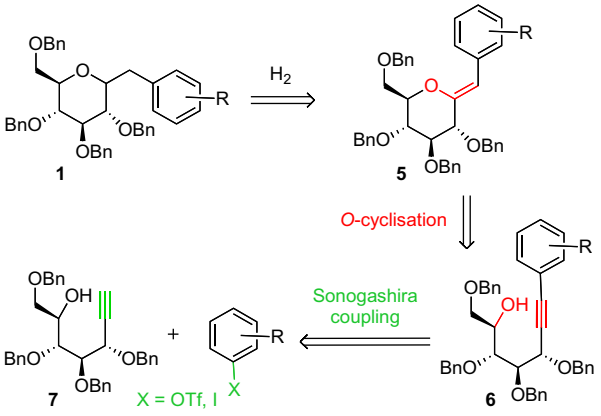


Entry	EWG	Product	Yield
1	NO_2	**1a**	78%[a]
2	SO_2Ph	**1b**	74%[b]
3	CHO	**1c**	No reaction[c]
4	COMe	**1d**	Traces of **1d**[c]
5	COOMe	**1e**	No reaction[c]
6	COOMe	**1e**	20%[d,e]

[a] DBU (0.8 equiv), CH_2Cl_2 (0.2 M), 20 °C, 24 h, α/β = 75:25.
[b] DBU (0.8 equiv), CH_2Cl_2 (0.2 M), 20 °C, 24 h, α/β = 70:30.
[c] DBU (3 equiv), CH_2Cl_2 (0.2 M), 20 °C, 5 d.
[d] $Sn(OTf)_2$ or $Zn(OTf)_2$ (3 equiv), DBU (2 equiv), THF (0.2 M), 50 °C, 12 h.
[e] Slightly impure product.

stereochemistry of the minor diastereomer was determined by examining the coupling constants of the proton at the newly formed stereogenic centre ($J_{2,3}$ = 9.2 Hz, *trans* relationship).[16] Submitting a mixture of diasteromers of **1a** enriched in the β-isomer (α/β = 25:75) to 28 equiv of DBU for 24 h (0.2 M concentration) did not change the isomeric ratio, implying that the conjugate addition was under kinetic control.

Various substrates (EWG = SO_2Ph, CHO, COMe, COOMe) were submitted to the optimised oxa-Michael cyclisation conditions (Table 4).[17] A similar result was found with EWG = SO_2Ph (74% yield, α/β = 70:30, entry 2). With weaker electron-withdrawing groups such as CHO, COMe or COOMe, no reaction occurred, even in refluxing dichloromethane (entries 3–5). Lewis acids were added



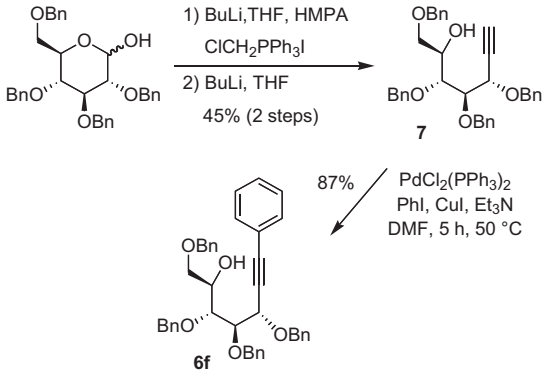
Scheme 2. Retrosynthetic approach involving alkyne substrates.

to the reaction with the ester substrate **2e** to some effect, but the yield never exceeded 20% (entry 6). This conjugate addition seems to be limited to substrates with strong electron-withdrawing substituents such as a nitro or a sulfonyl group, but a large range of functional groups on the phenyl ring should be easily accessible from the nitro group.

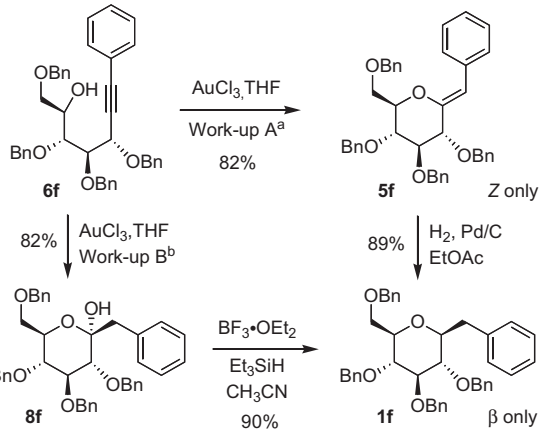
Another approach was then envisaged, that could produce benzyl C-glycosides with no electron-withdrawing substituents on the phenyl ring (Scheme 2). These glycosides would be formed by cyclisation of hydroxy alkynes **6**, followed by reduction of the resulting alkenes **5**. Alkynes **6** would be prepared by Sonogashira coupling of terminal alkyne **7** with the appropriate aryl triflates or aryl iodides.

The formation of alkyne **7** proved to be more difficult than expected. Corey–Fuchs[18] or Bestmann–Ohira[19] reactions did not convert the lactol at ambient temperature, or gave degradation products in refluxing THF. Fortunately, Wittig reaction with (chloromethyl)triphenylphosphonium iodide afforded the corresponding chloro-alkene in 80% yield as a 55:45 *E/Z* mixture (Scheme 3),[20] and subsequent elimination of HCl led to alkyne **7**.[21] Sonogashira coupling between **7** and iodobenzene furnished alkyne **6f** in 87% yield.

We investigated the cyclisation under different conditions: acidic (PPTS), basic (MeONa, KH) or with $PdCl_2(CN)_2$, unsuccessfully. We then considered gold catalysis, which has proved to be efficient for several heterocyclisation reactions.[22] Contrary to what was observed by Pale and co-workers for similar substrates,[23] the reaction proceeded smoothly under Au(III) catalysis to furnish compound **5f**[8b] in 82% yield as the *Z*-isomer, exclusively (Scheme 4).[24] When the gold catalyst was not filtered from the reaction



Scheme 3. Preparation of alkyne **7** and Sonogashira coupling.



[a] Work-up A: filtration on silica gel, then concentration under vacuum
[b] Work-up B: concentration under vacuum, then filtration on silica gel

Scheme 4. Cyclisations/reductions of **6f**.

mixture before evaporation of the solvent, hemiketal **8f** was obtained as the major product.[25] Olefin **5f** was then hydrogenated following the procedure reported by Belica and Franck[8a] to furnish benzyl C-glycoside **1f** in 89% yield. Reduction of hemiketal **8f** with $Et_3SiH/BF_3{\cdot}OEt_2$ was also efficient, giving **1f** in 90% yield.[26]

In conclusion, we have developed two short syntheses of benzyl C-glycosides featuring an unprecedented oxa-Michael cyclisation and an efficient gold-catalysed ring-closure. The second approach also constitutes a new synthesis of benzyl *exo*-glycals, which could be a good alternative to the Ramberg–Bäcklund rearrangement.[8a,b] Depending on the route, we can obtain either α- or β-C-glycosides. The preparation of more complex benzyl C-glycosides using these approaches is underway.

Acknowledgments

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17. *Procedure for the oxa-Michael addition:* To a solution of 1,3,4,5-tetra-*O*-benzyl-7-(4-nitrophenyl)-hept-6-en-2-ol (**2a**) (80 mg, 0.12 mmol) in CH_2Cl_2 (0.4 mL) was added 10 μL of DBU (0.06 mmol, 0.5 equiv). The solution was stirred for 24 h under a nitrogen atmosphere, and then was concentrated under vacuum and chromatographed (SiO_2, 30% EtOAc/petroleum ether) to furnish the desired product **1a** as a yellow oil (63 mg, 78%) as a 75:25 mixture of α/β isomers, which could be partially separated for the purpose of characterisation. α-isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.05 (d, J = 8.8 Hz, 2H), 7.37–7.27 (m, 20H), 7.16–7.20 (m, 2H), 5.02 (d, J = 10.8 Hz, 1H), 4.93–4.86 (m, 3H), 4.64–4.64 (m, 3H), 4.26 (d, J = 11.4 Hz, 1H), 4.22–4.17 (m, 1H), 3.89–3.79 (m, 3H), 3.67–3.58 (m, 3H), 3.10–3.07 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.0, 138.6, 138.2, 138.0, 137.9, 130.0, 128.7, 128.6, 128.5, 128.1, 128.02, 127.96, 123.7, 82.2, 80.2, 78.1, 75.6, 75.4, 75.3, 73.8, 73.6, 71.9, 69.2, 31.2; HRMS (EI) m/z calcd for $C_{41}H_{41}NO_7$ 659.2883; found: 659.2877. β-Isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.11 (d, J = 8.8 Hz, 2H), 7.44–7.30 (m, 20H), 7.26–7.22 (m, 2H), 4.96–4.67 (m, 4H), 4.65–4.48 (m, 4H), 3.78 (t, J = 8.8 Hz, 1H), 3.67–3.62 (m, 4H), 3.50–3.45 (dt, J = 2.0, 9.2 Hz, 1H), 3.64–3.32 (m, 1H), 3.18 (dd, J = 2.0, 14.0 Hz, 1H), 2.84 (dd, J = 8.8, 14.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.8, 138.1, 130.5, 128.7, 128.65, 128.61, 128.54, 128.2, 128.1, 128.0, 127.9, 127.8, 123.4, 87.4, 81.6, 79.4, 79.0, 78.6, 77.5, 76.8, 75.8, 75.3, 75.2, 73.5, 69.0, 37.8; HRMS (EI) m/z calcd for $C_{41}H_{41}NO_7$ 659.2883; found: 659.2877.
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25. *General procedures for gold-catalysed cyclisations:* A sample of $AuCl_3$ catalyst (5 mol %) was added to a solution of the alkyne in THF (2 mL) under argon. The mixture was stirred at ambient temperature for 2 h. Work-up A: the solution was filtered on silica gel and concentrated under vacuum to furnish the desired compound. Work-up B: the solution was concentrated under vacuum then filtered on silica gel (30% EtOAc/petroleum ether) to furnish the desired compound. The general procedure with work-up A was used for the conversion of alkyne **6f** (100 mg, 0.16 mmol) to afford compound **5f** as a yellow oil (82 mg, 82%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.71 (d, J = 7.6 Hz, 2H), 7.40–7.10 (m, 23H), 5.75 (s, 1H), 4.83–4.57 (m, 8H), 4.20–4.10 (m, 1H), 4.05 (m, 1H), 3.89–3.80 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.1, 138.4, 138.3, 138.0, 135.3, 128.9, 128.6, 128.56, 128.53, 128.50, 128.46, 128.3, 128.06, 128.01, 127.97, 127.92, 127.84, 127.82, 127.7, 126.5, 109.6, 84.7, 79.4, 78.1, 77.0, 74.1, 73.6, 73.5, 71.8, 69.7, 69.4; IR (thin film, cm^{-1}) 3450, 2922, 2867, 1723, 1602, 1496, 1453, 1362, 1264, 1086, 1070, 1026, 1051; HRMS (EI) m/z calcd for $C_{41}H_{40}O_5$ 612.2876; found: 612.2859. The general procedure with work-up B was used for the conversion of alkyne **6f** (200 mg, 0.33 mmol) to afford compound **8f** as a yellow oil (165 mg, 82%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45–7.10 (m, 25H), 4.90 (dd, J = 12, 10.8 Hz, 2H), 4.80–4.74 (m, 2H), 4.63 (d, J = 11.6 Hz, 2H), 4.55 (d, J = 11.6 Hz, 2H), 4.40 (d, J = 12.0 Hz, 1H), 4.14 (d, J = 9.2 Hz, 1H), 3.85–3.80 (m, 3H), 3.54 (t, J = 9.6 Hz, 1H), 3.32 (dd, J = 14.0, 9.6 Hz, 2H), 3.11 (dd, J = 14.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 131.2, 128.6, 128.51, 128.45, 128.38, 128.33, 128.0, 127.9, 127.84, 127.75, 127.69, 127.65, 127.59, 127.05, 127.01, 84.0, 81.4, 78.5, 75.7, 75.4, 75.0, 73.4, 71.4, 68.9, 65.3, 43.8; IR (thin film, cm^{-1}) 3445, 3020, 2865, 1720, 1485, 1430, 1362, 1137, 1103, 1094, 1034; HRMS (EI) m/z calcd for $C_{41}H_{42}O_6$ 630.2981; found: 630.2963.
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