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A highly selective route to β-*C*-glycosides *via* nonselective samarium iodide induced coupling reactions

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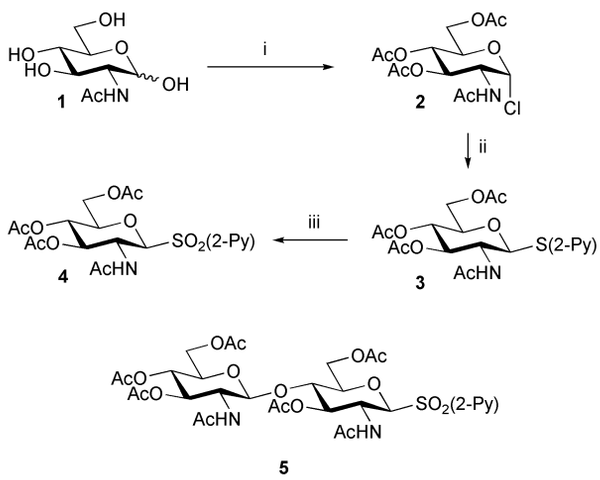
Stereoselective preparation of β-*C*-glycosides has been developed from acetylated glycopyranosyl 2-pyridyl sulfones, involving a samarium-Barbier coupling procedure–oxidation–isomerization sequence.

A wide range of methodologies has been developed over the last two decades for the synthesis of *C*-glycosyl compounds, carbohydrate analogs in which a carbon atom replaces the anomeric oxygen or nitrogen atoms of natural glycosides.[1,2] In this area, our group has focused on the "umpolung" of the anomeric center with results showing that the reductive samariation of anomeric 2-pyridyl sulfones in the presence of carbonyl compounds (samarium-Barbier procedure) provides a versatile approach to C-glycosyl compounds. 1,2-*cis* *C*-Glycosides (α-Glc, β-Man, ⋯) are only obtained through a samarium(II) iodide induced *intra*molecular 5-*exo* radical cyclization on a temporarily tethered "aglycon",[3] whereas 1,2-*trans* *C*-glycosides (β-Glc, β-Gal, β-Fuc, α-Man, ⋯) are the exclusive products, readily available via *inter*molecular addition of a glycosyl-samarium species onto a ketone or an aldehyde.[4] This highly stereoselective step can be followed by a Barton–McCombie type deoxygenation of the resulting alcohols if a methylene linked *C*-glycoside is targeted.

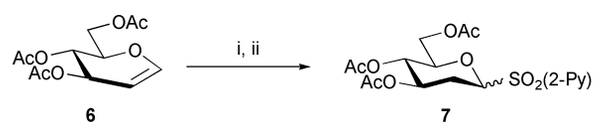
Interestingly, *inter*molecular coupling reactions performed with glycopyranosides bearing an acetamido group at C-2 (GlcNAc and GalNAc derivatives) provided a major exception to these observations, since the α-linked *C*-glycosides are obtained as major products with moderate to good selectivities, results rationalized as a chelation-controlled *C*-glycosylation.[5] This procedure thus left unsolved the important access to *C*-glycosides mimicking the biologically ubiquitous β-GlcNAc motif. Another more expectable exception appeared in the 2-deoxy series, where the lack of a directing group at the 2-position led to a complete loss of selectivity in the coupling step.[4] We now report a solution from simple precursors which relies on the above intermolecular samarium-Barbier reaction followed by an oxidation–isomerization sequence. The procedure also capitalizes on the observation made earlier that these anionic conditions remarkably tolerate the presence of standard *O*-acetyl protecting groups[4] as well as acidic protons in the acetamido groups.[5]

The starting sulfones **4**, **5** and **7** were easily prepared in the following way. Sulfone **4** was obtained in 79% yield *via* MCPBA oxidation of 2′-pyridylthioglycoside **3**[6] (Scheme 1). Sulfone **5** was prepared similarly† starting from the octaacetyl chitobiose.[7] We also prepared sulfones **7** from tri-*O*-acetylglucal **6** by a 2-mercaptopyridine addition in the presence of *p*-toluenesulfonic acid (54%),[8] followed by oxidation (89%, Scheme 2).

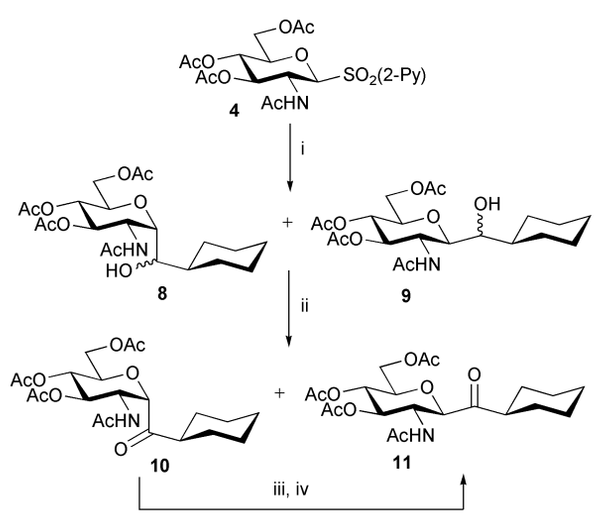
In an initial experiment, treatment of sulfone **4** with samarium diiodide (2.3 equiv.) in the presence of excess cyclohexanecarboxaldehyde at room temperature provided alcohols **8** and **9** which were subjected to PCC oxidation in the presence of 4 Å molecular sieves (Scheme 3). The two anomeric ketones



Scheme 1 *Reagents and conditions*: i, AcCl, 25 °C, 16 h, 76%; ii, 2-PySH, K_2CO_3, toluene–acetone, 50 °C, 3 h, 71%; iii, MCPBA, $NaHCO_3$, CH_2Cl_2, 25 °C, 2.5 h, 79%.



Scheme 2 *Reagents and conditions*: i, 2-PySH, PTSA, CH_2Cl_2, reflux, 30 min (54%); ii, MCPBA, $NaHCO_3$, CH_2Cl_2, 25 °C, 2.5 h, 89% (α–β 4 : 1).



Scheme 3 *Reagents and conditions* i, Cyclohexanecarboxaldehyde, SmI_2, THF, 25 °C; ii, PCC, 4 Å MS, CH_2Cl_2, 25 °C, 26% (**8**), 26% (**9**); iii, K_2CO_3, MeOH, 25 °C; iv, Ac_2O, Py, 25 °C, 70% (α–β < 1 : 20).

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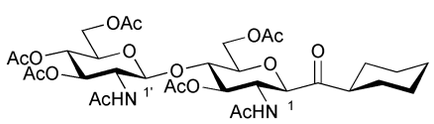
10 and **11** were easily separated by silica gel chromatography and obtained in equimolar amounts (26% of **10** and 26% of **11** from **4**). At this point we noted that the samarium-induced *C*-glycosylation on the acetylated electron acceptor **4** was not stereoselective, in contrast with the corresponding benzylated sulfone which selectively provided the α-*C*-glycosides. Treatment of ketone **10** with catalytic amounts of potassium carbonate in methanol afforded, following acetylation, the isomeric β-ketone **11** (70% yield) with high stereoselectivity (**11**–**10** ratio >20 : 1), as evaluated by ^{1}H-NMR spectroscopy on the crude mixture.[9]

This encouraged us to pursue this process without chromatography of the intermediates using a samarium-Barbier coupling–oxidation–isomerization sequence. Pure ketone **11**‡ was thus furnished from sulfone **4** in a 42% overall yield. Treatment of disaccharidic sulfone **5** under similar conditions led to a 30% yield of pure β-*C*-glycoside **12**§ (Fig. 1), whereas an overall yield of 53% of β-*C*-glycoside **13**§ was obtained starting from **7**.



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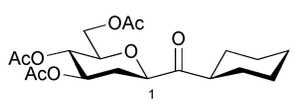

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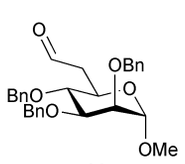
Fig. 1

To illustrate the utility of this procedure we also performed the synthesis of a *C*-disaccharide by coupling sulfone **4** with aldehyde **14**[4c] (1.5 equiv.). After oxidation, epimerization and reacetylation, the β-linked *C*-disaccharide **15**§, a protected analog of the GlcNAc-β-(1⟶6)-Man motif of tri- and tetra-antennary complex-type *N*-glycans, was obtained in a 40% overall yield based on the starting sulfone (Fig. 2).



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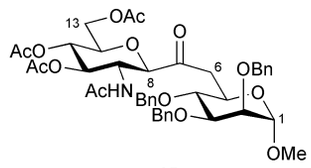

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Fig. 2

In summary we have disclosed a method for the selective synthesis of 1′-carbonylalkyl β-*C*-glycosides[10] from simple derivatives of 2-deoxy or 2-acetamido-2-deoxy glycopyranosides that complement previous stereochemical results in this area. The carbonyl group may obviously be further exploited for derivatization and we believe that this procedure could be extended to other biologically relevant carbohydrates.

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Notes and references

† Octaacetyl chitobiose, obtained by controled degradation of chitin,[7] was subjected to the following transformations: i. HCl, AcCl; (55%) ii. 2-PySH, K_2CO_3, toluene–acetone (76%); iii. MCPBA, $NaHCO_3$, CH_2Cl_2 (84%).

‡ In a typical experiment, a solution of SmI_2 in THF (0.1 M) was added under Ar in a flask containing sulfone **4** (106 mg, 240 μmol) and cyclohexanecarboxaldehyde (125 μL, 1.0 mmol) until a persistent blue coloration was observed (5.3 mL). A few drops of aqueous ammonium chloride were then added, and the reaction mixture was diluted with dichloromethane. The organic layer was washed with water, and the resulting aqueous phase was extracted again twice with CH_2Cl_2. The combined organic layers were dried over sodium sulfate and concentrated. The residue was dissolved in CH_2Cl_2 (3.0 mL) and treated with PCC (260 mg, 1.2 mmol) in the presence of 4 Å mol sieves (400 mg). After 3 h of reaction, Et_2O was added, and the reaction mixture was filtered through a silica pad. After concentration, the residue was dissolved in MeOH (3.0 mL) and treated with K_2CO_3 (14 mg, 100 μmol) overnight. The solvent was then evaporated, pyridine (5.0 ml) and Ac_2O (2.5 ml) were added, and the mixture was stirred for another hour. Concentration and silica gel chromatography (cyclohexane–EtOAc, 1 : 1), afforded the β ketone **11** (44 mg, 100 μmol): mp 163 °C (dichloromethane–methanol). $[\alpha]_D^{20}$ +3.5 (*c* 0.23, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.67 (d, 1H, J = 9.3 Hz, NH), 5.22 (dd, 1H, $J_{2,3}$ = 10.0 Hz, $J_{3,4}$ = 9.4 Hz, H-3), 5.15 (dd, 1H, $J_{4,5}$ = 9.8 Hz, H-4), 4.26–4.20 (m, 2H, H-6a, 6b), 4,20 (ddd, 1H, $J_{1,2}$ = 10.5 Hz, H-2), 3.88 (d, 1H, H-1), 3.72 (ddd, 1H, $J_{5,6a}$ = 3.3 Hz, $J_{5,6b}$ = 5.6 Hz, H-5), 2.81 (m, 1H, C–H cyclohexyl), 2.09, 2.04, 2.03 and 1.90 (4s, 12H, 4 $COCH_3$), 1.91–1.07 (m, 10H, 5 CH_2). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 208.8 (C=O), 171.1, 170.6, 170.2, and 169.3 (4 $COCH_3$), 82.2 (C-1), 75.7, 73.5, and 68.3 (C-3, 4, 5), 62.1 (C-6), 51.4 (C-2), 46.5 (C–H cyclohexyl), 29.7, 28.6, 27.9, 25.7, and 25.4 (5 CH_2), 23.1, 20.7, 20.7, and 20.6 ($COCH_3$). ESI-MS: m/z = 464 [M + Na]; HR-MS (ESI) for $C_{21}H_{31}NNaO_9$ [M + Na]: calcd: 464.1897; found: 464.1903.

§ Selected ^{1}H NMR data for **12**: (400 MHz, $CDCl_3$–CD_3OD 10 : 1): δ 5.16 (dd, 1H, $J_{2',3'}$ = 10.4 Hz, $J_{3',4'}$ = 9.4 Hz, H-3′), 5.02 (dd, 1H, $J_{2,3}$ = 10.2 Hz, $J_{3,4}$ = 8.9 Hz, H-3), 4.58 (d, 1H, $J_{1',2'}$ = 8.4 Hz, H-1′), 4.14 (dd, 1H, $J_{1,2}$ = 10.5 Hz, H-2), 3.82 (dd, 1H, H-2′), 3,72 (dd, 1H, $J_{4,5}$ = 9.5 Hz, H-4), 3.72 (d, 1H, $J_{1,2}$ = 10.5 Hz, H-1). Selected ^{1}H NMR data for **13**: (250 MHz, $CDCl_3$): δ 5.04 (ddd, 1H, $J_{2eq,3}$ = 5.1 Hz, $J_{2ax,3}$ = 9.4 Hz, $J_{3,4}$ = 9.4 Hz, H-3), 4.96 (dd, $J_{4,5}$ = 9.4 Hz, H-4), 4.01 (dd, $J_{1,2eq}$ = 2.2 Hz, $J_{1,2ax}$ = 12.0 Hz, H-1), 2.44 (ddd, 1H, $J_{2eq,2ax}$ = 12.9 Hz, H-2eq), 2.08, 2.04 and 2.02 (3s, 9H, 3 $COCH_3$), 1.60 (ddd, 1H, H-2ax). Selected ^{1}H NMR data for **15** (atom numbering of a tridecopyranoside): (250 MHz, $CDCl_3$): 5.50 (d, 1H, J = 9.0 Hz, NH), 5.17 (dd, 1H, $J_{9,10} \sim J_{10,11}$ = 9.3 Hz, H-10), 5.09 (dd, 1H, $J_{11,12}$ = 9.3 Hz, H-11), 4.58 (d, 1H, $J_{1,2}$ = 2.0 Hz, H-1), 4.06 (ddd, 1H, $J_{8,9}$ = 10.7 Hz, H-9), 3.90 (dd, 1H, $J_{2,3}$ = 3.0 Hz, $J_{3,4}$ = 9.3 Hz, H-3), 3.78 (dd, 1H, H-2), 3.74 (d, 1H, H-8), 3.68 (dd, 1H, $J_{4,5}$ = 9.6 Hz, H-4).

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