A General and Efficient Route to 3-O-Modified Carbohydrate Bis(oxazoline) Ligands

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Abstract: An efficient route to derivatives of carbohydrate-based bis(oxazoline) ligands with 3-O substituents of varying steric demand is described. The synthesis of the new ligands proceeds via a thioglucoside key intermediate, the double cyclisation reaction to the desired bis(oxazolines) is initiated with *N*-iodo succinimide under mild conditions. Employing this strategy, four new 3-O-modified bis(oxazoline) ligands were obtained in good yields.

Key words: carbohydrates, ligand design, oxazolines, asymmetric synthesis

Asymmetric metal-catalysed transformations are one of the most efficient methods for preparation of chiral compounds. To achieve high levels of asymmetric induction, optimisation of the chiral ligands employed is often necessary. Therefore the design of new ligand structures is a very active field of research today.

Carbohydrates, although far less frequently employed than other compounds from the chiral pool, are versatile starting materials for the preparation of novel and unusual chiral complex ligands.[1] In the course of our work we became interested in chiral bis(oxazoline) ligands, which are successfully applied in many asymmetric reactions.[2] Recently we introduced two new carbohydrate-based ligands, *gluco*Box and *gluco*Pybox, which were prepared via bis(amides) of D-glucosamine using a one-pot double cyclisation reaction.[3,4] The *gluco*Box ligand was employed in cyclopropanations affording enantioselectivities up to 82% ee,[3] while the *gluco*Pybox ligand yielded up to 99% ee in the alkynylation of imines.[4] To further increase the enantioselectivity for the cyclopropanation with the carbohydrate box and to extend the substrate scope for the carbohydrate pybox ligand, we decided to perform systematic modifications on the ligand scaffold to obtain optimised ligands through structural variation.

The backbone of the new carbohydrate ligands offers many options for structural modifications, as a wide range of residues with varying steric and electronic properties can be attached to the hydroxy groups of the pyranose subunits. Especially the 3-O substituents located next to the oxazoline nitrogen atoms can be expected to have considerable impact on steric shielding coordinated of metal centres (Figure 1). This in turn will directly influence the stereoselectivity of reactions involving substrates bound to the metal centres. We therefore set out to prepare a series of ligands with 3-O substituents of varying steric demand, choosing 3-*O*-Me as a small, 3-*O*-Bn as a medium-sized and 3-*O*-TES as a large residue (Figure 1). To selectively access the 3-O position, we planned to employ benzylidene acetals to block the 4- and 6-hydroxyls. Our studies towards these target structures were done on the *gluco*Box scaffold.

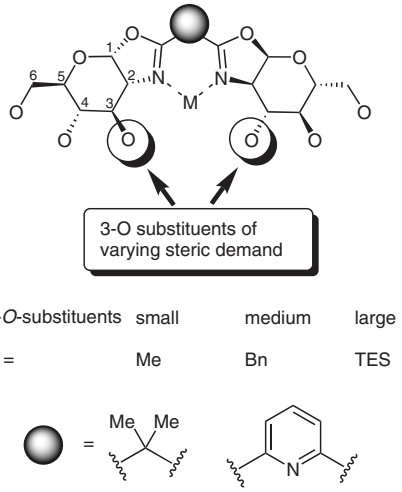

Figure 1 General structure of carbohydrate bis(oxazoline) ligands and points for the attachment of substituents with varying steric demand

Initial attempts to introduce benzylidene acetal groups into the preformed *gluco*Box ligand were unsuccessful. Cyclising a benzylidene-protected bis(amide) using the one-pot reaction employed for the preparation of *gluco*Box[3] led to decomposition because of the acidic conditions of the first step. Therefore a new strategy towards the desired target compounds had to be developed, utilising a cyclisation reaction compatible with acid-sensitive substrates.

For the new synthetic route thioglycosides were selected as key intermediates, as they are easy to prepare, stable against all reaction conditions necessary for ligand synthesis, and can finally be activated for the cyclisation reaction under specific and mild conditions. The synthesis started from D-glucosamine hydrochloride (**1**) which was transformed into peracetylated phthalimido derivative **2**.[5] Subsequently, this was treated with ethane thiol and

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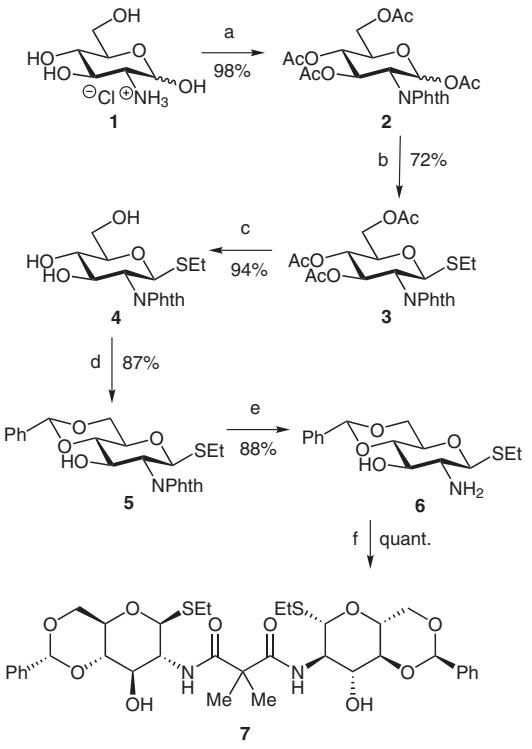
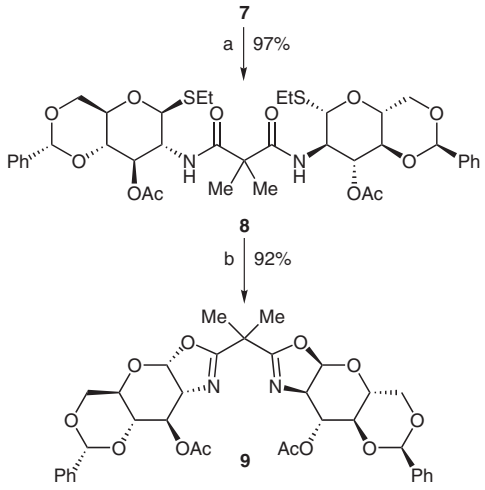
$BF_3{\cdot}OEt_2$ as Lewis acid to afford thioglucoside **3**,[6] which was deacetylated[7] and 4,6-*O*-benzylidene protected.[8] Deprotection of the amino function with ethylenediamine in ethanol[9] gave amine intermediate **6**. Next amine **6** was coupled with dimethylmalonyl dichloride under conditions described previously.[3] This reaction yielded bis(amide) **7** carrying thioglucoside residues, which was used as a key intermediate for the preparation of 3-O-modified *gluco*Box ligands. All reactions of this sequence proceeded with good to excellent yields (Scheme 1).



Scheme 1 *Reagents and conditions*: a) NaOH, $NaHCO_3$, MeOH, H_2O, acetone, r.t., 16 h; then Ac_2O, pyridine, r.t., 16 h; b) HSEt, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C to r.t., 16 h; c) NaOMe, MeOH, r.t., 4 h; d) neat benzaldehyde, anhyd $ZnCl_2$, r.t., 16 h; e) ethylene diamine, abs. EtOH, reflux, 4 h; f) dimethylmalonyl dichloride, Et_3N, CH_2Cl_2, 0 °C to r.t., 2 h.

In order to obtain a ligand with the same 3-O substituent as the original *gluco*Box, bis(amide) **7** was 3-*O*-acetyl protected under standard conditions with acetic anhydride in pyridine. For the double cyclisation reaction to the corresponding bis(oxazoline) elemental bromine was added to acetylated bis(amide) **8** to exchange the anomeric thioethyl groups to bromides.[10] Subsequently, the intermediate bromide was treated with sodium hydrogen carbonate and tetrabutylammonium chloride as previously described for the synthesis of *gluco*Box.[3] Via this sequence target 3-O-acetylated bis(oxazoline) **9** was obtained in pure form but only in 20% yield over two steps from **8**. This rather disappointing yield and the two-step procedure involving elemental bromine made us look for alternative activation protocols for the thioglycosyl groups.

We then tried treating **8** with *N*-iodosuccinimide and a catalytic amount of trifluoromethanesulfonic acid at low temperatures, conditions that have previously been described for the synthesis of monomeric oxazolines from thioglycosides.[11] With this protocol 3-O-acetylated bis(oxazoline) **9** was obtained from bis(amide) **8** in one step in an excellent yield of 92% (Scheme 2).



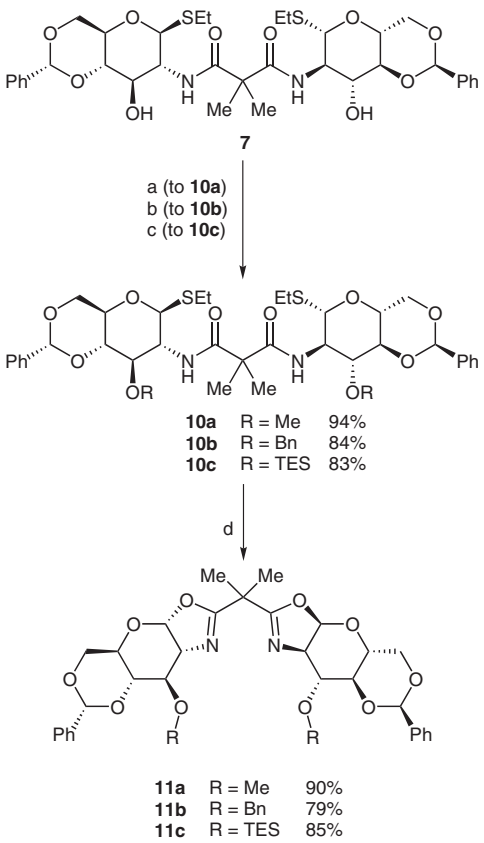
Scheme 2 *Reagents and conditions*: a) Ac_2O, pyridine, r.t., 16 h; b) NIS, cat. TfOH, MS 4 Å, CH_2Cl_2, –30 °C, 1 h.

Starting from key intermediate **7** we then prepared bis(amide) precursors with the small, medium and large 3-O substituents as proposed earlier. Methylation under standard conditions with sodium hydride and iodomethane[12] gave compound **10a** in 94% yield, the 3-*O*-Bn-protected bis(amide) **10b** was obtained by treating **7** with benzylbromide, sodium hydride, and catalytic amounts of tetrabutylammonium iodide[9] in a yield of 84%. Silylation with TESOTf and triethylamine[13] yielded 83% of the 3-*O*-TES-modified compound **10c**.

The three bis(amides) **10a**, **10b**, and **10c** were then subjected to the NIS-mediated activation protocol. In each case the double cyclisation reaction was successful irrespective of the 3-O substituent giving 3-O-methylated **11a**, 3-O-benzylated **11b**, and 3-O-silylated **11c** in very good yields[14] (Scheme 3).

The 3-O-modified bis(oxazolines) **9** and **11a–c** are currently under investigation in asymmetric cyclopropanation reactions, the results of these experiments will be reported in due course. Further we intend to prepare a wide spectrum of box ligands with 3-O substituents varying in steric and electronic properties as well as the corresponding pybox ligands.

In conclusion, we have developed a simple and efficient pathway to structural variants of glucosamine-based bis(oxazoline) ligands via a bis(amide) carrying thioglycoside moieties. This approach allows us to selectively diversify the 3-O position in carbohydrate bis(oxazoline) ligands. The mild cyclisation protocol using *N*-iodo succinimide leads to bis(oxazoline) formation in good yields irrespective of the 3-O substituent.



Scheme 3 *Reagents and conditions*: a) NaH, MeI, THF, reflux, 4 h; b) NaH, BnBr, TBAI, DMF, 0 °C to r.t.,16 h; c) TESOTf, Et_3N, CH_2Cl_2, –78 °C to r.t., 16 h; d) NIS, cat. TfOH, MS 4 Å, CH_2Cl_2, –30 °C, 1 h.

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(14) **General Procedure for the Double Cyclisation of Bis(amides) with Thioglycoside Moieties**
A mixture of the 3-O-protected thioglycoside (280 mg, 0.38 mmol) and MS 4 Å (300 mg) in anhyd CH_2Cl_2 (5 mL) was stirred for 1 h under N_2 atmosphere in a flame-dried flask. To this NIS (210 mg, 91 μmol) was added and the mixture was cooled to –30 °C. Then, TfOH (5 μL, 50 μmol) was added and the mixture was stirred for 1 h at –30 °C. The reaction was quenched with Et_3N (0.1 mL), and the mixture was filtered through Celite, diluted with CH_2Cl_2, washed with sat. aq $NaHCO_3$, aq $Na_2S_2O_3$ (3 M), and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on SiO_2 (eluants given for the respective compound) to yield the desired product.
Analytical Data for 3-O-Acetylated Compound 9
Eluant: EtOAc. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.52 [6 H, s, $(CH_3)_2C$], 2.10 (6 H, s, CH_3CO), 3.61 (2 H, dd ≈ t, $J_{5,6'} = J_{6,6'} = 9.9$ Hz, H-6′), 3.75 (2 H, ddd ≈ td, $J_{4,5} = 9.9$ Hz, $J_{5,6} = 5.1$ Hz, $J_{5,6'} = 9.9$ Hz, H-5), 3.81 (2 H, dd, $J_{3,4} = 7.5$ Hz, $J_{4,5} = 9.9$ Hz, H-4), 4.14 (2 H, dd, $J_{1,2} = 7.1$ Hz, $J_{2,3} = 2.7$ Hz, H-2), 4.39 (2 H, dd, $J_{5,6} = 5.1$ Hz, $J_{6,6'} = 10.2$ Hz, H-6), 5.28 (2 H, dd, $J_{2,3} = 2.7$ Hz, $J_{3,4} = 7.5$ Hz, H-3), 5.51 (2 H, s, CHPh), 5.98 (2 H, d, $J_{1,2} = 7.1$ Hz, H-1), 7.32–7.37 (6 H, m, Ph), 7.44–7.46 (4 H, m, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1 (CH_3, OAc), 23.4 [CH_3, $(CH_3)_2C$], 38.9 (C, $[CH_3)_2C$], 62.9 (CH, C-5), 67.8 (CH_2, C-6), 68.2 (CH, C-2), 73.5 (CH, C-3), 78.4 (CH, C-4), 101.4 (CH, PhCH), 101.4 (CH, C-1), 126.1 (2 CH, Ph), 128.2 (2 CH, Ph), 129.0 (CH, Ph), 136.8 (C, Ph), 169.6 (C, O–C=N), 169.8 (C, C=O, Ac) ppm. ESI-HRMS (+): *m/z* calcd for $C_{35}H_{39}N_2O_{12}$ $[M + H]^+$: 679.2503; found: 679.2511. $[\alpha]_D^{20}$ +106 (*c* 1.0, $CHCl_3$).
Analytical Data for 3-O-Methylated Compound 11a
Eluant: PE–EtOAc (1:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.53 [6 H, s, $(CH_3)_2C$], 3.54 (6 H, s, OCH_3), 3.60–3.71 (8 H, m, H-3, H-4, H-5, H-6′), 4.11 (2 H, dd, $J_{1,2} = 7.5$ Hz, $J_{2,3} = 2.4$ Hz, H-2), 4.33–4.41 (2 H, m, H-6), 5.56 (2 H, s, CHPh), 5.97 (2 H, d, $J_{1,2} = 7.5$ Hz, H-1), 7.32–7.37 (6 H, m, Ph), 7.44–7.47 (4 H, m, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.4 [CH_3, $(CH_3)_2C$], 39.0 [C, $(CH_3)_2C$], 58.5 (CH_3, OCH_3), 62.6 (CH, C-5), 67.8 (CH, C-2), 68.2 (CH_2, C-6), 80.1 (CH, C-3), 81.7 (CH, C-4), 101.3 (CH, PhCH), 102.2 (CH, C-1), 126.1 (2 CH, Ph), 128.2 (2 CH, Ph), 129.0 (CH, Ph), 137.1 (C, Ph), 168.8 (C, O–C=N) ppm. ESI-HRMS (+): *m/z* calcd for $C_{33}H_{38}N_2O_{10}$ $[M + H]^+$: 662.2526; found: 662.2534. $[\alpha]_D^{20}$ +124 (*c* 1.0, $CHCl_3$).
Analytical Data for 3-O-Benzylated Compound 11b
Eluant: PE–EtOAc (1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.51 [6 H, s, $(CH_3)_2C$], 3.63 (2 H, dd ≈ t, $J_{5,6'} = J_{6,6'} = 9.6$ Hz, H-6′), 3.68 (2 H, ddd ≈ td, $J_{4,5} = J_{5,6'} = 9.6$ Hz, $J_{5,6} = 4.1$ Hz, H-5), 3.78 (2 H, dd, $J_{3,4} = 7.5$ Hz, $J_{4,5} = 9.6$ Hz, H-4), 3.93 (2 H, dd, $J_{2,3} = 3.0$ Hz, $J_{3,4} = 7.5$ Hz, H-3), 4.23 (2 H, dd, $J_{1,2} = 7.5$ Hz, $J_{2,3} = 3.0$ Hz, H-2), 4.38 (2 H, dd, $J_{5,6} = 4.1$

Hz, $J_{6,6'}$ = 9.6 Hz, H-6), 4.77 (2 H, d, J = 12.0 Hz, CH_2Ph), 4.82 (2 H, d, J = 12.0 Hz, CH_2Ph), 5.57 (2 H, s, CHPh), 5.98 (2 H, d, $J_{1,2}$ = 7.5 Hz, H-1), 7.25–7.46 (20 H, m, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.4 [CH_3, (CH_3)$_2$C], 38.9 [C, (CH_3)$_2$*C*], 62.8 (CH, C-5), 68.4 (CH, C-2), 68.6 (CH_2, C-6), 72.4 (CH_2, PhCH_2) 79.7 (CH, C-3), 80.1 (CH, C-4), 101.1 (CH, PhCH), 102.2 (CH, C-1), 126.0 (2 CH, Ph), 127.6 (CH, Ph), 127.8 (2 CH, Ph), 128.1 (2 CH, Ph), 128.2 (2 CH, Ph), 128.9 (CH, Ph), 137.1 (C, Ph), 137.9 (C, Ph), 168.8 (C, O–C=N) ppm. ESI-HRMS (+): *m/z* calcd for $C_{45}H_{47}N_2O_{10}$ [M + H]$^+$: 775.3231; found: 775.3234. $[\alpha]_D^{20}$ +82 (*c* 1.0, $CHCl_3$).

Analytical Data for 3-O-Silylated Compound 11c

Eluant: PE–EtOAc (1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.65 (12 H, t, J = 7.8 Hz, SiCH_2CH$_3$), 0.93 (18 H, t, J = 7.8 Hz, SiCH$_2$CH_3), 1.50 [6 H, s, (CH_3)$_2$C], 3.55–3.66 (6 H, m, H-4, H-5, H-6′), 3.93 (2 H, dd, $J_{2,3}$ = 3.8 Hz, $J_{3,4}$ = 7.2 Hz, H-3), 3.98 (2 H, dd, $J_{1,2}$ = 7.2 hz, $J_{2,3}$ = 3.8 Hz, H-2), 4.36 (2 H, dd, $J_{5,6}$ = 3.1 Hz, $J_{6,6'}$ = 8.9 Hz, H-6), 5.53 (2 H, s, CHPh), 5.95 (2 H, d, $J_{1,2}$ = 7.2 Hz, H-1), 7.32–7.37 (6 H, m, Ph), 7.45–7.49 (4 H, m, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 4.73 [CH_3, (*C*H$_3$CH$_2$)$_3$Si], 6.71 [CH_2, (CH$_3$*C*H$_2$)$_3$Si], 23.4 [CH_3, (*C*H$_3$)$_2$C], 39.0 [C, (CH$_3$)$_2$*C*], 63.2 (CH, C-5), 68.6 (CH_2, C-6), 70.8 (CH, C-2), 74.4 (CH, C-3), 81.1 (CH, C-4), 101.4 (CH, PhCH), 102.7 (CH, C-1), 126.0 (2 CH, Ph), 128.0 (2 CH, Ph), 128.8 (CH, Ph), 137.3 (C, Ph), 168.5 (C, O–C=N) ppm. ESI-HRMS (+): *m/z* calcd for $C_{43}H_{63}N_2O_{10}Si_2$ [M + H]$^+$: 823.4021; found: 823.4003. $[\alpha]_D^{20}$ +106 (*c* 0.9, $CHCl_3$).