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Stereoselective synthesis of glycoclusters using an olefin metathesis and Sharpless dihydroxylation sequence

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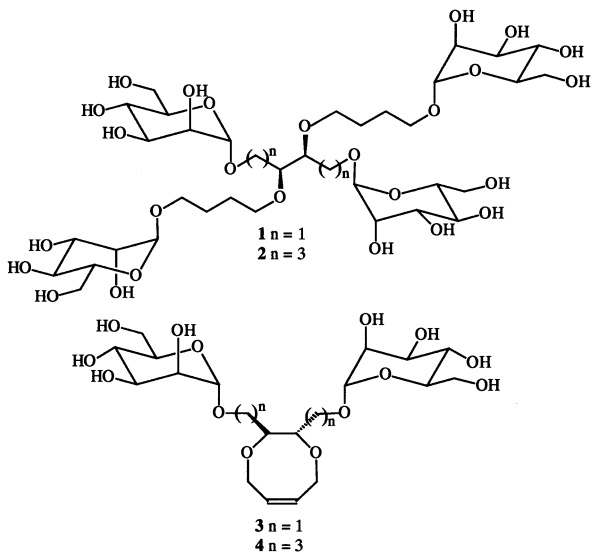
Abstract—An asymmetric synthesis of α-D-mannopyranoside-based glycoclusters has been accomplished using olefin metathesis and Sharpless asymmetric dihydroxylation reactions as key steps. Access to a family of dimeric and tetrameric glycoclusters having chiral core structures was achieved to investigate topographical arrays of carbohydrate–protein binding interactions.

Carbohydrate–protein interactions are involved in a wide range of critical biological phenomenon including pathogen-cell adhesion, inflammation, and cancer metastasis.[1] In order, to study those interactions, multivalent glycomimetics have gained considerable attention during the past few years.[2,3] The chemical synthesis of high affinity ligands for protein receptors (lectins, antibodies, and selectins) that are able to compete or even surpass naturally occurring oligosaccharides present on the cell surface are necessary for the design of potent carbohydrate therapeutics. However, the structural requirements for optimally binding the 'glycocode' are not known in most cases; therefore, it has to be determined in each individual case for rational design of high affinity ligands. Herein, we report the reiterative synthesis of a novel class of glycoclusters **1**–**4** using olefin metathesis and Sharpless asymmetric dihydroxylation reactions as key steps to generate glycoclusters of varied geometry. This approach which provides an unique access to a new class of oligosaccharide mimics has the advantage to generate glycoclusters with varied structural and stereochemical environments to help determining the 'glycocode'. Moreover, this process offers control on chirality, spacer length and valency, features that are not obtained in other methods such as ring-opening metathesis polymerization (ROMP).[2e,3a]

During the past few years, olefin metathesis reaction has emerged as a powerful synthetic tool for the construction of complex molecules.[4] Grubbs' ruthenium catalyst (**5**) $Ru(Cl)_2(PCy_3)_2$=CHPh, due to its remarkable functional group tolerance and its stability, has found the widest application among the metathesis catalysts to form C–C double bonds with good to excellent *trans*/*cis* ratios.



Previous work from our laboratory[4b,5] has shown that ω-alkenyl *O*-glycopyranosides homodimerize in high yields and good stereoselectivity in refluxing dichloromethane in the presence of 10 mol% of **5**. The same conditions were applied to allyl and pentenyl 2,3,4,6-*O*-diisopropylidene-α-D-mannopyranoside to

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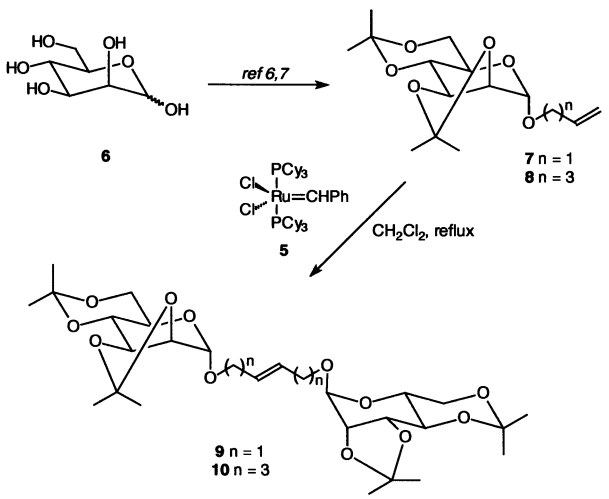
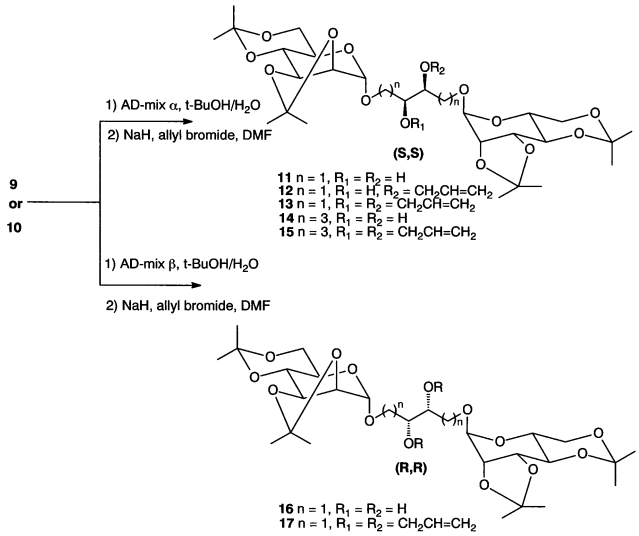
afford homodimers **9** and **10** in 85% yields in 5/1 *trans*/*cis* ratios.† Compounds **7** and **8** were prepared from D-mannose by known procedures[6,7] involving Fisher glycosidation (allyl or pentenyl alcohol with acidic resin) followed by acetalation of the hydroxyl groups with dimethoxypropane and a catalytic amount of CSA (Scheme 1).

The major *trans* isomer **9** was then dihydroxylated using a catalytic amount of osmium tetroxide and stoichiometric amount of *N*-methylmorpholine-*N*-oxide (NMO).[8] The reaction showed no diastereoselectivity, giving poor 1:1 ratio indicating a lack of asymmetric induction from the sugar moieties. Based on those results, we decided to use the Sharpless asymmetric dihydroxylation reaction[9] making use of chiral ligands AD-mix α and AD-mix β (Scheme 2). Dihydroxylation of **9** followed by allylation with an excess of allyl bromide afforded compound **13** in 75% overall yield.



Scheme 1.



Scheme 2.

Both chiral ligands gave a satisfactory 9:1 ratio in agreement with the mnemonic model developed by Sharpless.[10]

The ratios can be determined by NMR spectroscopy since the two diastereoisomers clearly showed two distinctive signals for the anomeric protons.[11] To confirm the outcome of the diastereoselectivity, compound **11** was treated with $AcOH/H_2SO_4$ to release the aglycon part[12] which was then benzoylated using benzoyl chloride and Et_3N to provide L-threitol tetrabenzoate for which the optical rotation compared favorably with known value.[13] Furthermore, it was also confirmed by chiral HPLC using Chiralcel OD column.

It was also possible to introduce only one allyl group by using 1 equiv. of allyl bromide to provide **12** in 68% yield, thus leaving an intact hydroxyl group that could

† Selected spectroscopic data:

For **9**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.77(t, J=2.9 Hz, 2H); 5.02 (s, 2H); 4.16–4.12 (m, 6H); 3.97–3.94 (m, 2H); 3.82 (dd, J=5.6, 10.8 Hz, 2H); 3.74–3.68 (m, 4H); 3.57–3.52 (m, 2H); 1.50, 1.47, 1.38, 1.31 (4s, 12H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 128.8, 109.4, 99.6, 97.11, 75.9, 74.8, 72.7, 66.9, 61.9, 61.4, 28.9, 28.1, 26.1, 18.7. EI $(M+NH_4)^+$: 590.2.

For **13**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.92–5.85 (m, 2H); 5.25 (dq, J=1.6, 3.2, 15.6 Hz, 2H); 5.16 (dq, J=1.6, 2.8, 9.2 Hz, 2H); 5.01 (s, 2H); 4.17–4.10 (m, 6H); 4.05 (qt, J=1.3, 5.9, 12.7 Hz, 2H); 3.88–3.83 (m, 4H); 3.75–3.70 (m, 4H); 3.64–3.61 (m, 2H); 3.58–3.53 (m, 2H); 3.51–3.47 (m, 2H); 1.53, 1.49, 1.40, 1.33 (4s, 12H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 135.1, 117.7, 109.9, 100.1, 98.6, 77.0, 76.4, 75.2, 73.0, 72.6, 67.4, 62.4, 61.8, 29.4, 28.6, 26.5, 19.1. EI $(M+NH_4)^+$: 704.1.

For **17**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.92–5.85 (m, 2H); 5.25 (dq, J=1.5, 3.1, 17.2 Hz, 2H); 5.16 (dq, J=1.5, 2.8, 10.3 Hz, 2H); 5.00 (s, 2H); 4.17–4.10 (m, 6H); 4.04 (qt, J=1.3, 6.1, 12.7 Hz, 2H); 3.88–3.85 (m, 2H); 3.77–3.70 (m, 6H); 3.62–3.60 (m, 4H); 3.56–3.51 (m, 2H); 1.53, 1.49, 1.40, 1.34, (4s, 12H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 135.1, 117.9, 109.8, 100.1, 98.6, 77.1, 76.3, 75.2, 73.0, 72.7, 66.9, 62.3, 61.9, 29.4, 28.5, 26.5, 19.1. EI $(M+NH_4)^+$: 704.1.

For **18**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.71–5.69 (m, 2H); 4.99 (s, 2H); 4.45–4.30 (m, 4H); 4.20–4.15 (m, 4H); 3.87–3.69 (m, 8H); 3.62–3.42 (m, 6H); 1.52, 1.49, 1.40, 1.33 (4s, 12H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 129.7, 109.9, 100.0, 98.7, 81.4, 76.3, 75.2, 73.0, 69.5, 68.5, 62.4, 61.8, 29.4, 28.5, 26.5, 19.1. EI $(M+NH_4)^+$: 672.0.

For **20**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.80–5.78 (m, 4H); 5.02 (s, 2H); 5.01 (s, 2H); 4.18–4.12 (m, 16H); 3.86–3.82 (m, 6H); 3.74–3.69 (m, 8H); 3.63–3.51 (m, 8H); 1.52, 1.51, 1.48, 1.39, 1.33, 1.33, 1.32 (7s, 48H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 130.6, 128.2, 109.9, 109.8, 100.1, 100.0, 98.5, 97.4, 78.1, 77.6, 76.4, 76.3, 75.2, 73.1, 72.9, 71.5, 67.5, 67.4, 62.4, 61.9, 61.7, 29.4, 28.6, 26.6, 26.5, 19.1. EI $(M+NH_4)^+$: 1248.1.

Typical procedure for the double cross-metathesis reaction: To a 0.03 M solution of **13** (41.3 mg, 0.06 mmol) in dry dichloromethane (2 ml) were added 4 equiv. of **7** (72 mg, 0.24 mmol) and 20 mol% of the Grubbs's catalyst (10 mg, 0.012 mmol). Then the reaction mixture was heated at reflux under nitrogen atmosphere for 13 h. The solution was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography using ethyl acetate and hexane as eluent (1:5 to 1:1) to afford 30 mg of **20** and 8 mg of **18**.

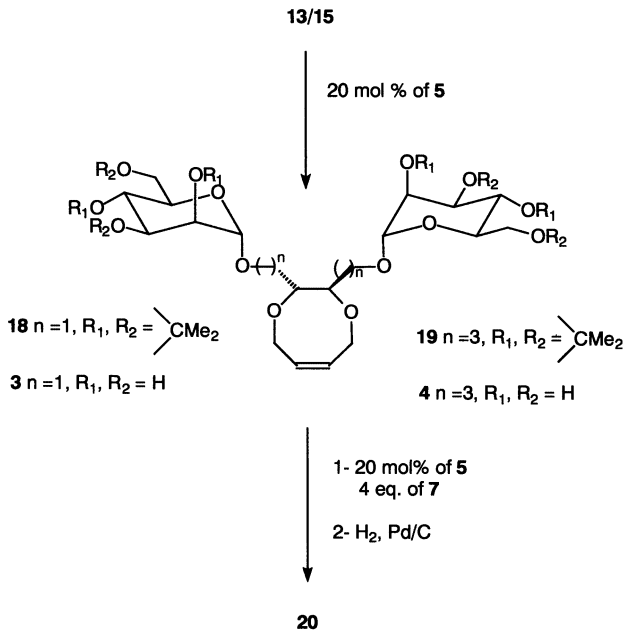
serve as a handle for further heterobifunctional modifications. The same sequence was also applied to the pentenyl derivative **10** to afford compound **15** in similar yield.

At this stage, we were set for the ring-closing metathesis (RCM) reaction that would allow the formation of an eight-membered ring (Scheme 3). To this end, treatment of **13** or **15** with 20 mol% of **5** in refluxing dichloromethane afforded the desired RCM product **18** and **19** in 60 and 80% yields, respectively. In each case, only one stereoisomer could be observed by NMR. The removal of the acetonides was accomplished in quantitative yields using 60% aq. AcOH (65°C, 1 h).

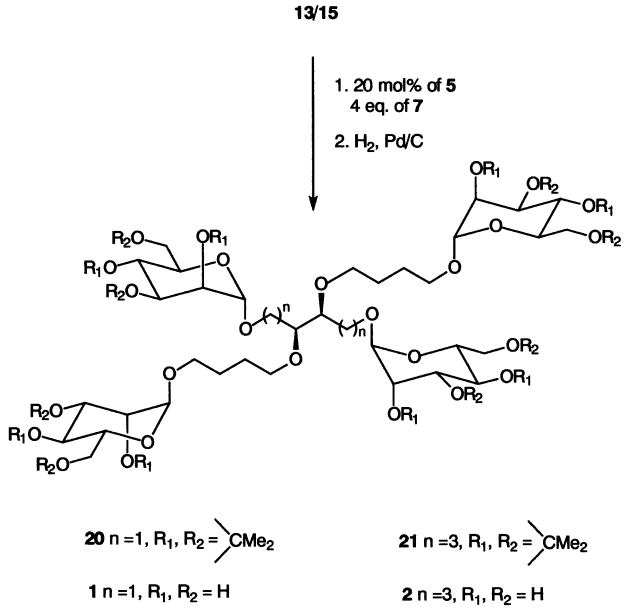
There are few examples in the literature where the Grubbs' catalyst was used in multiple cross-metathesis reactions.[14] From our experience in cross-metathesis reactions,[15] the major concern was that RCM would compete against the desired cross metathesis (CM) reaction. However it was anticipated that with an excess of glycoside **7** it could be possible to direct the reaction toward the cross metathesis product between **13**/**15** and **7**. Indeed, the use of 4 equiv. of **7** with **13** in a 0.01 M solution of CH_2Cl_2 containing 20 mol% of **5** lead, after purification, to 32% of the cross-metathesis product **20** along with 35% of RCM product **18**[16] (Scheme 4).

For compound **15**, the RCM product was even more favored and under the same conditions, the reaction gave 60% of **19** and tetramer **21** in 30% yield.[17]

As an attempt to reduce the undesired RCM product in the double cross-metathesis reaction, we envisaged to perform the reaction in a more concentrated media. Thus, when the reaction was done in a 0.03 M CH_2Cl_2 solution, the cross metathesis product **20** became the major product while cutting by half the amount of



Scheme 3.



Scheme 4.

RCM product **18**.[†] Favoring the formation of **20** could also be achieved by bubbling ethylene in the reaction mixture. Under an ethylene atmosphere, the by product of the olefin metathesis reaction, the formation of the kinetic RCM product is reduced and the amount of CM products is almost doubled. Encouraged by those results, we anticipated that a combination of ring-opening and cross-metathesis reaction on the RCM product **18** could afford the desired cross-metathesis product **20**. Gratifyingly, this reaction produced 48% of the desired tetramer along with 15% of unreacted RCM product that could be recycled (Scheme 3).

Finally, the tetrameric glycoclusters **1** and **2** were obtained after hydrogenation of the double bond and removal of the acetonides as above.

In conclusion, an asymmetric synthesis of dimeric and tetrameric glycoclusters using olefin metathesis and Sharpless asymmetric dihydroxylation sequence was accomplished. Our approach has the advantage of being highly flexible and provides access to glycoclusters of varied structural and stereochemical environments. This sequence is also being applied to *C*-glycosides for which it is anticipated that sequential manipulation of the two internal alcohols by selective protection will prevent the competing RCM product. The biological evaluation of these compounds is underway with Mannoside receptors.

Acknowledgements

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11. ^{1}H NMR ($CDCl_3$, 500 MHz) showed a signal at 5.01 ppm for **15** corresponding to the anomeric proton whereas for **17** this signal was at 5.00 ppm.
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16. 30% of trimer where only one monosaccharide was added.
17. 63% of homodimer **10** (yield based on **7**) could be recovered.