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Stereoselective synthesis of seven-membered lactams and lactones on a carbohydrate scaffold using ring-closing metathesis

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ABSTRACT

We present here the application of Grubbs' 2nd generation catalyst for the ring-closing metathesis of electron-deficient α,β-unsaturated amides and esters leading to the synthesis of enantiopure azepinone and oxepinone derivatives on a carbohydrate glycoside scaffold. The relative stereochemistries of the compounds obtained were corroborated by X-ray crystallography, ^{1}H NMR or deduced based on previously reported results. These compounds are designed as precursors of new polyhydroxylated heteroannulated sugars with potential biological activity.

The well-defined structural characteristics of carbohydrate cyclic compounds (i.e., functional, stereochemical, topological and stereoelectronic features) have enabled the exploitation of these as advantageous scaffolds in the synthesis of chiral target molecules,[1] contributing to the concept of the 'Chiron Approach' developed by Hanessian.[2] In this context, one of the key points of the above-mentioned strategy is the ability to form enantiopure ring systems from sugars.[3] Our previous contributions to this area of carbohydrate annulation have involved the use of Robinson's annulation,[4] aldol condensation,[5] radical cyclisation,[6] and through the application of these ideas to the synthesis of chiral taxoid models.[7]

We have been especially interested in the use of ring-closing metathesis (RCM) for the synthesis of carbocyclic or heterocyclic moieties fused to carbohydrates using Grubbs' 1st generation catalyst **A**.[8] For example, annulated carbocycles of different ring sizes **1**,[9] spiro-annulated oxygen-containing compounds **2**[9] or seven-membered aza-heteroannulated sugar derivatives **3**, **4**[10] have been previously synthesised by our group (Fig. 1).

Besides the prospective use of these structures as privileged scaffolds for the synthesis of enantiopure materials, the potential biological applications of compounds such as **3** and **4** or related structures can be exemplified by a recent paper by Vankar et al. who reported the D-glucose and 1,4-dideoxymannohomonojirimycin hybrid **5** (Fig. 2) to be a selective inhibitor of β-galactosidase (IC_{50} = 4.68 mM).[11] Furthermore, we have found that the 3-*N* pyrrolidine derivative **6** displays the same pattern of selectivity (IC_{50} = 0.81 mM for β-galactosidase inhibition).[12] The development of new glycosidase inhibitors[13] is a major area of research due to their possible therapeutic applications, including treatments for cancer, HIV and diabetes.[14]

In this context, the aim of this work was to extend the use of the RCM methodology for the stereoselective synthesis of new and more structurally challenging O/N-heteroannulated carbohydrate derivatives of type **I** (Fig. 2), with the heterocyclic portion fused

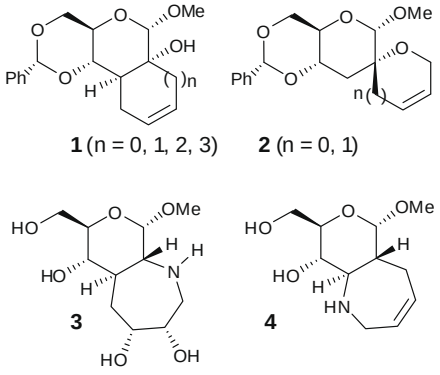

Figure 1. Selected annulated sugar derivatives previously synthesised by our group using Grubbs' 1st generation catalyst **A**.[8]

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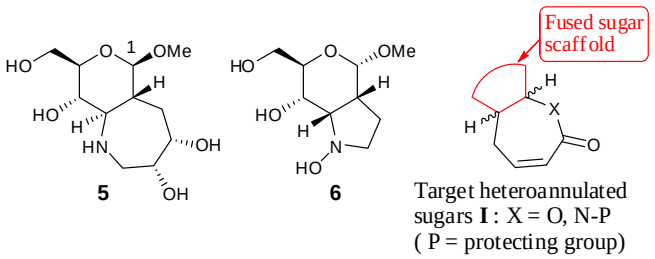


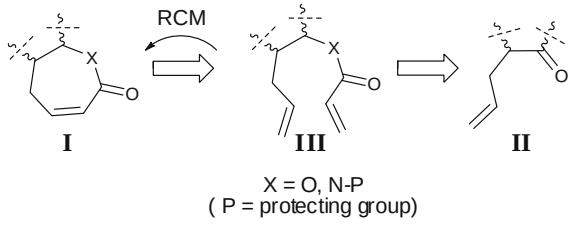
Figure 2. Examples of aza-heteroannulated sugars showing selective glycosidase inhibition (**5**[11] and **6**[12]), and target compounds **I**.

to the sugar scaffold, either a seven-membered lactam (dihydroazepinone) or lactone (dihydrooxepinone). These compounds are intended to serve as starting materials for the synthesis of new polyhydroxylated heteroannulated sugar derivatives as potential glycosidase inhibitors. The presence of the alkene and carbonyl groups in the proposed target compounds **I** increases the flexibility for functionalisation of the seven-membered ring.

As shown in Scheme 1, starting from the unsaturated ketone **II**, conversion of the carbonyl group to the appropriate alcohol or amine and introduction of the acryloyl moiety, would produce the corresponding diene **III** as a suitable substrate for the RCM leading to the target compounds **I**.

Due to the electron-deficient character of the α,β-unsaturated amides and esters **III**, the reaction conditions should be carefully selected to achieve the RCM reaction. *A priori*, RCM can be successfully applied to acrylate derivates by means of Grubbs' 2nd generation catalyst **B**[8] or using the 1st generation catalyst **A**[8] with an appropriate Lewis acid as additive (in order to avoid coordination of the carbonyl group with the Ru centre in the catalytic complex).[15]

The above-mentioned strategy was initially employed for the synthesis of trans-fused 2-*O* seven-membered lactones (Scheme 2).[16] The known alcohol **7**[9b] was reacted with acryloyl chloride and Et_3N in CH_2Cl_2 affording the α,β-unsaturated derivative **8** in moderate yield. The first attempt to achieve the ring closure using catalyst **A** and Ti(*i*PrO)$_4$ as additive,[15] was unsuccessful yielding

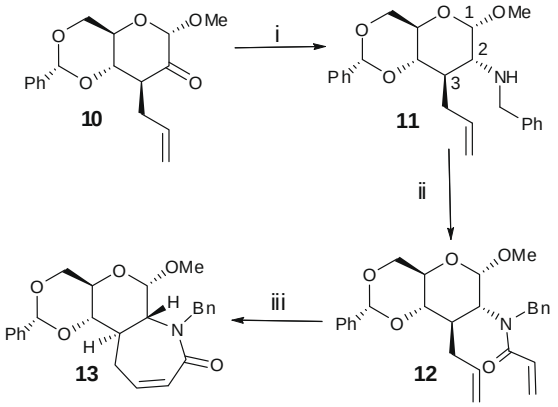


Scheme 1. Proposed retrosynthesis of dihydro-azepinones/oxepinones **I** using RCM as the key step.

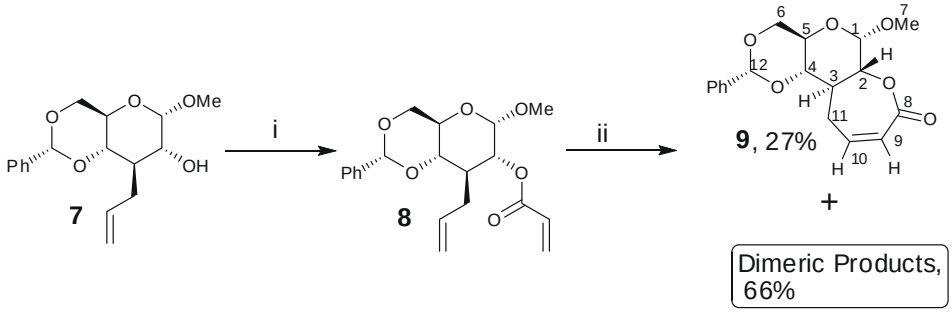
only unreacted starting material. RCM performed upon **8** using Grubbs' 2nd generation catalyst produced a complex mixture of new compounds (TLC analysis). This mixture was purified using flash column chromatography to give two components. The spectrometric analyses (ESI-MS, $^{13}C/^{1}H$ NMR) of the first component showed that an unresolved combination of various products was present in a 66% yield, concordant with the existence of dimeric products.[17] Unfortunately, further separation of this mixture could not be achieved. The second component eluted was identified as the lactone **9**. The doublet of doublets signal in the ^{1}H NMR (δ = 5.99 ppm), assigned to H-9, had coupling constants of 11.8 Hz and 2.1 Hz; which are typical values for *cis*-vicinal double bond couplings, and allylic couplings (see Scheme 2 for numbering). A doublet of doublets signal at 4.74 ppm, assigned to H-2, showed the appropriate coupling constants ($J_{2,3}$ = 11.0 Hz and $J_{1,2}$ = 3.6 Hz) confirming the expected geometry of the trans-ring junction between the sugar derivative and the heterocycle.

The synthesis of the seven-membered lactams was envisaged to be easier than that of the corresponding lactones, as the amide carbonyl group is known to interfere less with the function of the Grubbs' catalyst than an ester carbonyl group. In addition, the conjugated alkene bond in α,β-unsaturated amides is not as electron-deficient as the corresponding related esters, due to the lone pair of the nitrogen providing electron density to the conjugated system.[18] On this occasion, the amine functionality was introduced via stereoselective reductive amination of the corresponding carbonyl derivative followed by introduction of the acryloyl moiety.

Scheme 3 shows the application of the designed methodology for the successful synthesis of the trans-fused 2-*N*-dihydroazepinone derivative **13**.[16] The known compound **10**[9b] was stereoselec-



Scheme 3. Reagents and conditions: (i) 8 equiv $BnNH_2$, AcOH, THF, then $NaBH_3CN$, rt, 76%; (ii) acryloyl chloride, Et_3N, dry CH_2Cl_2, 0 °C then rt, 66%; (iii) 0.05 equiv **B**, CH_2Cl_2, reflux, 53%.



Scheme 2. Reagents and conditions: (i) acryloyl chloride, Et_3N, dry CH_2Cl_2, 0 °C then rt, 43%; (ii) 0.05 equiv **B**, CH_2Cl_2, reflux.

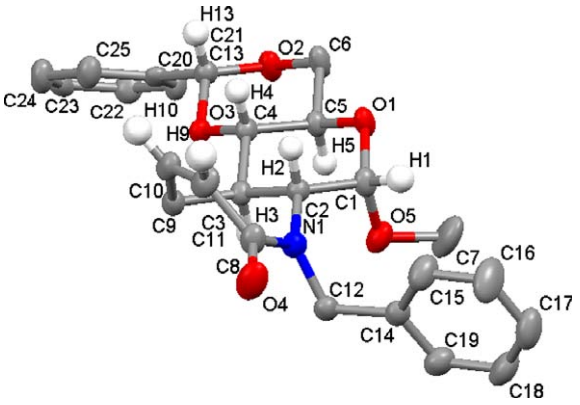
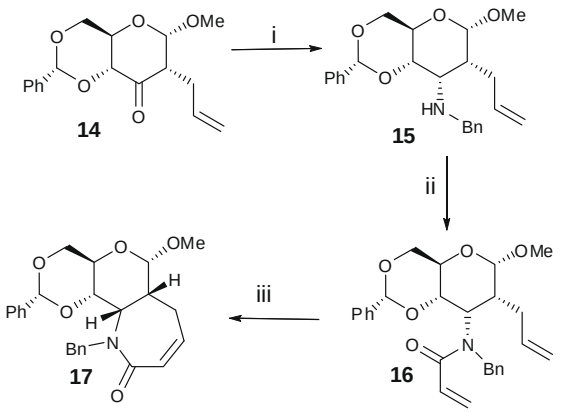


Figure 3. MERcury ellipsoid projection (50% probability) of the molecular structure of compound **13**, with a random numbering scheme. Hydrogen atoms, except those involved in the relative stereochemistry, are omitted for clarity.[21]



Scheme 4. Reagents and conditions: (i) 8 equiv $BnNH_2$, AcOH, THF, then $NaBH_3CN$, rt, 65%; (ii) acryloyl chloride, Et_3N, dry CH_2Cl_2, 0 °C then rt, 47%; (iii) 0.05 equiv **1**, CH_2Cl_2, reflux, 59%.

tively converted into the corresponding α-amine **11** by reductive amination using a large excess of benzylamine (8 equiv).[19] The stereochemistry at C-2, corroborated by measurement of the coupling constants between H-2 and H-1/3, arises from a preferential attack of the hydride from the opposite face of the methoxy group at C-1.[20] Further evidence of the identity of compound **11** was obtained by X-ray crystallography after recrystallisation from 1:1 petroleum ether–diethyl ether. Introduction of the acryloyl moiety followed by RCM using catalyst **B**,[8] produced the expected target compound **13** in a satisfactory overall yield.

X-ray crystallography confirmed the relative stereochemistry of compound **13** (Fig. 3),[21] showing that the trans geometry of ring junction was maintained and proving the formation of the cis double bond between C-9 and C-10. The corresponding coupling constants in the ^{1}H NMR of compound **13** were in accordance with the postulated geometry.

In order to apply the synthetic strategy for the preparation of the regioisomeric cis-fused 3-*N*-dihydroazepinone **17**, reductive amination of the known carbonyl derivative **14**[9] produced only the axial α-amine **15** in 65% yield (Scheme 4). The geometry was corroborated by the ^{1}H NMR spectrum of **15** showing a coupling constant of 3.6 Hz between H-2 and H-1/3 and is in agreement with our previous results on the reductive amination of **14**.[10] Subsequent acylation of **15** with acryloyl chloride, followed by RCM using catalyst **B**[8] produced the desired dihydroazepinone **17** in satisfactory yield. Once more, measurement of the appropriate coupling constants from the ^{1}H NMR spectrum for **17** demonstrated the cis geometry of the ring junction as well as the cis configuration of the alkene.

In conclusion, we have successfully applied Grubbs' 2nd generation catalyst **B**[8] for the stereoselective construction by RCM of the seven-membered enantiopure dihydroazepinones **13** and **17** starting from the corresponding electron-deficient α,β-unsaturated amide. The use of this methodology for the RCM of the α,β-unsaturated ester **8** yielded the expected dihydrooxepinone **9** accompanied by an unresolved mixture of dimers. Work is in progress on the synthesis of related polyhydroxylated heteroannulated sugars for their further evaluation as glycosidase inhibitors.

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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.2009.03.125.

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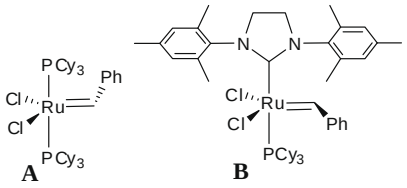

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16. Full experimental details are presented as Supplementary data to this Letter.

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21. CCDC 715631 and 715632 contain, respectively, the Supplementary crystallographic data for compounds **11** and **13**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif or can be ordered from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, GB CB2 1EZ; Fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk.