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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 2295–2298

A ring-closing metathesis route to 7-membered aza-heteroannulated sugars

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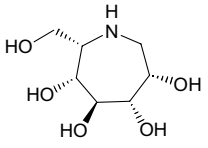
Received 10 December 2004; revised 22 January 2005; accepted 1 February 2005

Abstract—Azepane rings have been constructed diastereoselectively upon a carbohydrate derivative utilising reductive amination and RCM. The stereochemistry of the ring junctions was confirmed by X-ray crystallography and NMR. Diastereoselective dihydroxylation has also been employed to afford a tetrahydroxylated azepane carbohydrate derivative with potential biological activity.

Polyhydroxylated aza-heterocycles and aminosugars are of interest because they show a wide range of biological activities.[1] This large number of stereocentres confers great potential stereospecificity in biological interactions and chemical transformations. Possible therapeutic applications include treatments for cancer, HIV and diabetes.[1]

Ring-closing metathesis (RCM) has found extensive application in the synthesis of nitrogen-containing heterocycles of various ring configurations[2] including azepanes such as **1**[3] and aza-sugars such as castanospermine (**2**).[4]



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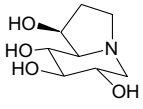

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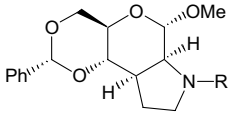
Metathesis has also been widely used in carbohydrate chemistry to achieve the total syntheses of carbohydrate-containing natural products,[5] dimerisation of sugar derivatives[5] and annulation of sugars.[6]

Few examples of fused *N*-heteroannulation of carbohydrates are to be found. Ring-closing reductive amination has been employed in the diastereoselective formation of 5-membered rings (**3**)[7] and 6- and 7-membered *N*-heterocycles (**4**) have been regioselectively formed from *N*-allyl nitrones.[8]



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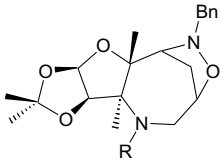

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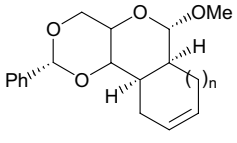
Previous work in this area by the Jenkins group has included the construction of carbocycles by Robinson annulation;[6] carbocycles such as **5** and *O*-containing heterocycles including spiro-annulated examples such as **6** by RCM[9] and photoannulation;[10] and *N*-containing heterocycles such as **3** by double reductive amination.[7] Our aim was to extend the use of RCM methodology



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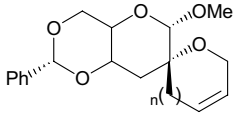

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Keywords: Pyrrolidines; Carbohydrate annulation; Amino sugars; Ring-closing metathesis.
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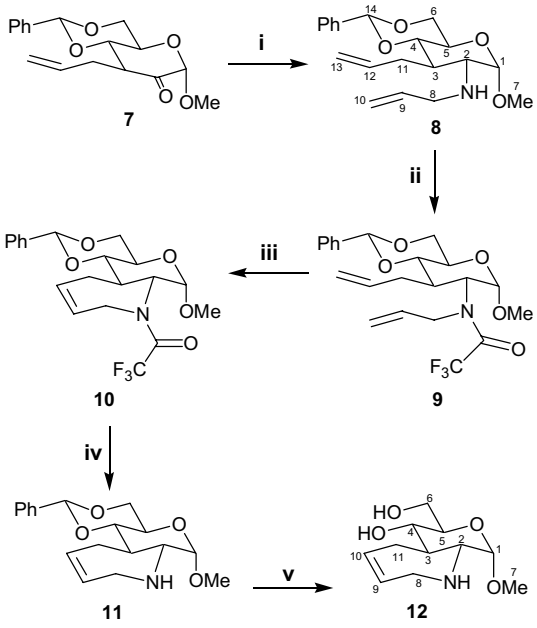
doi:10.1016/j.tetlet.2005.02.007

to include the synthesis of *N*-heteroannulated carbohydrates of various ring sizes that prove to be difficult to access via reductive amination ring closure and to assess their biological activity.

Known compound **7**[6] was converted to the α-amine **8**[11] in 87% yield by reductive amination using an excess of allylamine with acetic acid and $NaCNBH_3$ in THF at rt[7] (Scheme 1). The stereoselectivity of reduction of the imine formed at C-2 is due to preferential attack of the hydride from the direction opposite to the methoxy group attached to C-1.[12] The stereochemistry at C-2 was indicated by the coupling constants of H-2 and H-3 in $CDCl_3$. H-2 has a *trans* diaxial coupling constant of 11.3 Hz and a *cis* axial–equatorial coupling constant of 3.4 Hz to H-3 and H-1, respectively.[11]

Various methods to protect the 2° amine of compound **8** were attempted. Tosylation and BOC protection failed to give the desired products and only starting material was isolated; possibly due to steric hindrance. Protection of amine **8** was finally achieved using trifluoroacetic acid anhydride in DCM and pyridine at rt[13] to afford trifluoroacetamide compound **9** in 58% yield (Scheme 1). Interpretation of the NMR spectra was complicated by the duplication of many of the signals in the ^1H, ^{13}C and ^{19}F NMR spectra. For example, the ^{19}F NMR spectra in $CDCl_3$ contained two signals at δ −68.1 and δ −67.1 in a 1:3 ratio. This was attributed to restricted rotation about the acyl C–N bond, producing two pseudo-geometric isomers.[14] It was found that even at 343 K (C_6D_6) the signals in the ^1H and ^{19}F NMR spectra did not coalesce although significant signal broadening was observed.



Scheme 1. Reagents and conditions: (i) 8 equiv allylamine, AcOH, THF, then $NaCNBH_3$, rt, 2 h, 87%; (ii) TFAA, pyridine, DCM, rt, 16 h, 58%; (iii) 0.05 equiv Grubbs' cat, DCM, reflux, 16 h, 68%; (iv) $NaBH_4$, anhyd EtOH, reflux, 1 h, 96%; (v) 80% AcOH aq, reflux, 2 h, then K_2CO_3, MeOH, 79%.

RCM was initially attempted with amine **8**, but no reaction took place.[2] RCM of dialkene **9** was undertaken using 0.05 equiv of Grubbs' 1st generation catalyst in refluxing DCM.[2] Protected didehydroazepane **10** was obtained in 68% yield (Scheme 1). The ^{19}F NMR spectra contained two signals at δ −69.3 and δ −67.1 in a ratio of 1:4.6 in $CDCl_3$. This duplicity of signals was mirrored in some of the signals in the ^1H NMR spectra, particularly those due to the protons of the MeO group and the proton attached to C-1, and was considered to be due to restricted rotation of the amide bond.[14] Confirmation of the identity of compound **10** and the benzylidene group was obtained by X-ray crystallography[15] (Fig. 1) after recrystallisation from 1:9 DCM–hexane.

Removal of the trifluoroacyl protecting group using a number of literature methods failed. These included treatment of amide **10** with NH_3 in MeOH, heating with K_2CO_3 in aq MeOH, and heating with KOH in aq EtOH. The trifluoroacetyl amide group was finally removed via reductive cleavage by refluxing with excess $NaBH_4$ in anhydrous EtOH to give didehydroazepane compound **11** in 96% yield (Scheme 1).[16] Removal of the benzylidene protecting group of compound **11** to give **12**[17] was achieved in 79% yield by heating in 80% aq AcOH for 2 h (Scheme 1).[18]

A similar procedure to that described above was also used to synthesise a regioisomeric 7-membered *N*-containing ring in which the nitrogen is attached at the C-3 position of the sugar ring (Scheme 2). Known compound **13**[6] was converted to the α-amine **14** in 76% yield by reductive amination using an excess of allylamine with acetic acid and $NaCNBH_3$ in THF at rt (Scheme 2).[7] Only the axial α-amine was isolated due to reduction of the imine formed at C-3 from the β face. This follows the general trend observed for the reduction of ketones at the analogous position in similar compounds.[12]

Amine **14** was protected by conversion to trifluoroacetamide **15** via treatment with TFAA and pyridine in

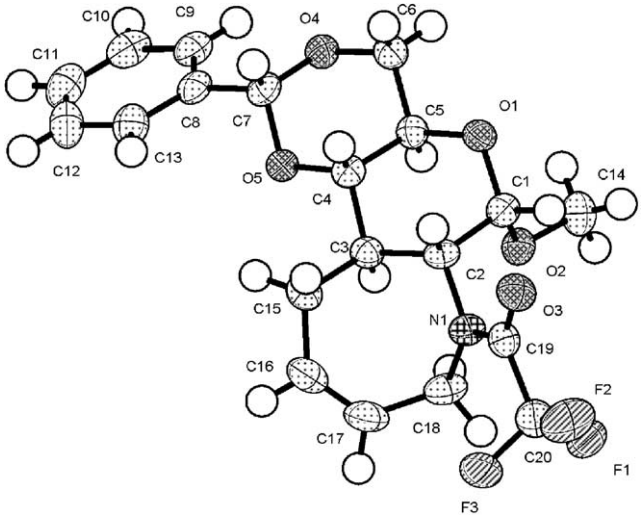
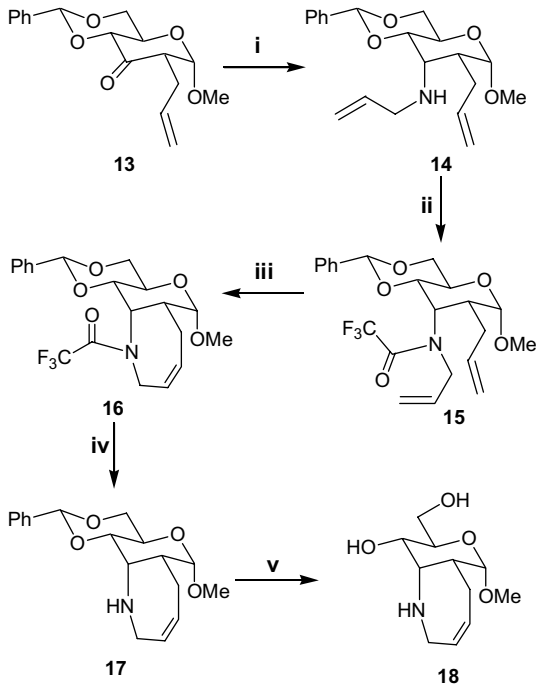


Figure 1. X-ray crystal structure of **10**.[15]



Scheme 2. Reagents and conditions: (i) 8 equiv allylamine, AcOH, THF, then $NaCNBH_3$, rt, 2 h, 76%; (ii) TFAA, pyridine, DCM, rt, 16 h, 85%; (iii) 0.05 equiv Grubbs' cat, DCM, reflux, 16 h, 65%; (iv) $NaBH_4$, anhyd EtOH, reflux, 24 h, 84%; (v) 80% AcOH aq, reflux, 4 h, then K_2CO_3, MeOH, 77%.

DCM at rt[13] in 85% yield (Scheme 2). Duplication of many signals in the ^1H and ^{13}C NMR spectra was observed in a similar way to compound **9**; the ^{19}F NMR spectra in $CDCl_3$ contained two signals at δ −67.3 and δ −65.1 in a 1:1.7 ratio.

RCM of dialkene **15** using 0.05 equiv of Grubbs' 1st generation catalyst in refluxing DCM gave the ring-closed product **16** in 65% yield (Scheme 2).[2] Assignment of the ^1H and ^{13}C NMR spectra was hampered by line broadening due to the presence of pseudo-geometric stereoisomers and the ^{19}F NMR spectra contained two signals at δ −68.5 and δ −64.8 in a ratio of 6.9:1 in $CDCl_3$. X-ray crystallography confirmed the stereochemistry of compound **16** (Fig. 2).[19] Removal of the trifluoroacetyl group to give didehydroazepane **17** in 84% yield was achieved by refluxing **16** with $NaBH_4$ in dry EtOH[16] and the benzylidine group was removed by refluxing in 80% aq AcOH to afford compound **18** in 77% yield (Scheme 2).[18]

The presence of the double bond in compound **10** allows facile functionalisation in order to maximise analogue diversity. Protected didehydroazepane **10** was hydrogenated by stirring vigorously with a suspension of 10% Pd/C under an atmosphere of H_2.[20] The reduction of the alkene bond was accompanied by the removal of the benzylidene protecting group to afford azepane **19** in 83% yield. The trifluoroacetyl group was removed in the usual way to afford azepane **20**[21] in 82% yield, which was converted to the acetate salt by treatment with acetic acid.

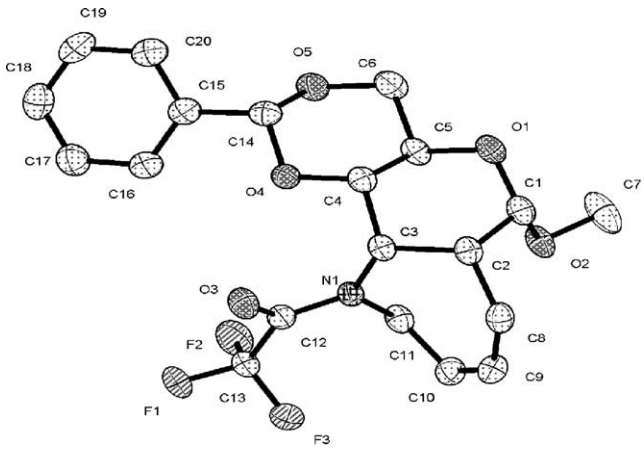
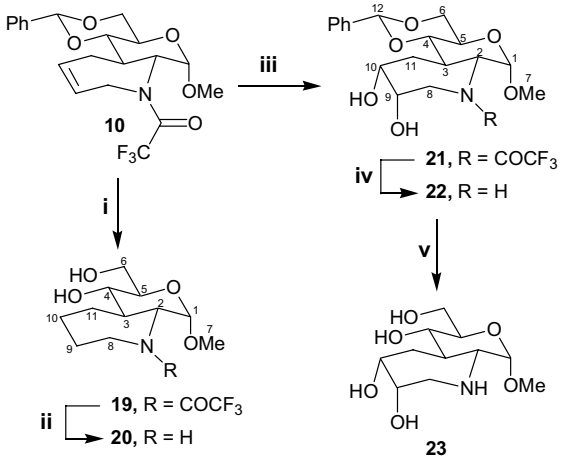


Figure 2. X-ray crystal structure of **16**.[19]

cis-Dihydroxylation of didehydroazepane **10** with OsO_4 and NMO proceeded as expected,[22] and ^1H and ^{19}F NMR indicated that only one product (**21**) was produced, in 80% yield. Assignment of the stereochemistry of **21** was not possible due to the presence of two pseudo-geometric isomers arising from the amide group. Removal of the amide by the usual method gave dihydroxyazepane **22** in 60% yield. ^1H and NOE NMR were used to determine that both the hydroxyl groups were on the α face of the molecule. H-2 has NOE interactions with H-8_β, H-11_β (but not H-8_α and H-11_α) and H-10. H-10 also has two *cis* coupling constants of 2.2 Hz to H-9 and H-11_β and a *trans* coupling constant of 6.9 Hz to H-11_α in MeOD. The benzylidene group was removed to give the tetrahydroxylated azepane **23** as the acetate salt in 64% yield (see Scheme 3).

In conclusion, we have developed a versatile and efficient method for the construction of azepane rings on carbohydrates. Work is in progress to synthesise piperidine and azocane homologues of **12** and **18**, and to further alter the regio- and stereochemistry of the ring



Scheme 3. Reagents and conditions: (i) H_2, Pd/C, EtOH, rt, 16 h, 83%; (ii) $NaBH_4$, EtOH, reflux, 3 h, 82%; (iii) 0.04 equiv OsO_4, NMO, acetone, H_2O, rt, 48 h, 80%; (iv) $NaBH_4$, EtOH, reflux, 2 h, 60%; (v) 80% AcOH aq, reflux, 4 h, then K_2CO_3, MeOH, 64%.

junction. Evaluation of the glycosidase inhibitory activity of these compounds is in progress.

Acknowledgements

Many thanks to J. Fawcett for X-ray data and to G. Eaton for MS analysis. We would like to acknowledge the ESPRC and the University of Leicester for financial support of this research.

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11. For compound **8**: white solid; δ_H (300 MHz, $CDCl_3$) 1.12 (1H, broad s, H–N), 1.84 (1H, tt, $J = 11.0, 3.9$, H-3), 2.45 (2H, m, H-$11_{a,b}$), 2.50 (1H, dd, $J = 11.3, 3.4$, H-2), 2.99 (1H, dd, $J = 13.9, 6.0$, H-8_a), 3.15 (1H, obs t, $J = 10.4$, H-4), 3.20 (4H, s and m, H-14, H-8_b), 3.67 (1H, t, $J = 10.0$, H-6_{ax}), 3.55 (1H, td, $J = 9.6, 4.3$, H-5), 4.08 (1H, dd, $J = 9.6, 4.3$, H-6_{eq}), 4.57 (1H, d, $J = 3.3$, H-1), 4.82–5.10 (4H, m, H-13, H-10), 5.29 (1H, s, H-14), 5.73 (2H, m, H-12, H-9), 7.10–7.40 (5H, m, Ph). FAB HRMS calcd for $C_{20}H_{28}O_4N$ $(M + H)^+$ 346.20183, found 346.20189. mp = 151–153 °C.
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17. For compound **12**: colourless oil; δ_H (300 MHz, MeOD) 1.71 (1H, qd, $J = 10.6, 1.6$, H-3), 1.81 (1H, s, H-N), 1.95 (1H, br t, $J = 14.7$, H-11_α), 2.73 (1H, ddd, $J = 15.6, 8.4, 1.4$, H-11_β), 2.81 (1H, dd, $J = 10.9, 3.4$, H-2), 3.01 (1H, t, $J = 9.9$, H-4), 3.22 (1H, m, H-8_a), 3.31 (3H, s, H-14), 3.39–3.49 (2H, m, H-5, H-8_b), 3.57 (1H, dd, $J = 11.7, 5.6$, H-6_{ax}), 3.70 (1H, dd, $J = 11.7, 2.4$, H-6_{eq}), 4.54 (1H, d, $J = 3.4$, H-1), 5.80 (1H, dtd, $J = 10.6, 5.5, 2.7$, H-10), 5.91 (1H, dddd, $J = 10.6, 8.5, 3.6, 1.8$, H-9). FAB HRMS calcd for $C_{11}H_{20}O_4N$ $(M+H)^+$ 230.13923, found 230.13921.
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