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Ring-Closing Metathesis mediated synthesis of Pyrrolizidine and Quinolizidine Azasugars

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Abstract

The synthesis of a novel perbenzylated pyrrolizidine starting from 2,3,5-tri-*O*-benzyl-arabinofuranose and based on a ring-closing metathesis (RCM) reaction is presented. In an analogous procedure, 2,3,5-tri-*O*-benzylxylopyranose was converted into a hitherto unprecedented quinolizidine azasugar.

Key words: azasugar, pyrrolizidine, quinolizidine, ring-closing metathesis.

The transition metal-catalysed carbocyclisation of alkenes and alkynes is now recognised as a versatile methodology for the preparation of carbo- and heterocyclic compounds [1]. The ring-closing metathesis (RCM) reaction has attracted widespread attention, especially since the development of the catalytically active ruthenium alkylidene complexes **1** and **2** [2] (Fig. 1). The easy access to these catalysts, their relative stability towards air and moisture, as well as their high functional group compatibility makes them ideally suited for the synthesis of medium and large ring systems. As a result, a large number of applications of the RCM reaction have appeared in literature recently [3]. These include the synthesis of heterocycles containing oxygen [4] and nitrogen [5], the construction of fused bicyclic systems [6], the RCM-mediated cleavage of solid support-bound intermediates [7] and also features in several approaches towards the total synthesis of the marine alkaloid manzamine A [8]. In a recent contribution from this laboratory [9], we presented the formal total synthesis of the azasugar castanospermine (**3**), based on the RCM-mediated transformation of diene **5** to the bicyclic lactam **4**. We now present the utilisation of this overall strategy to the synthesis of the new 5/5 and 6/6 bicyclic azasugars illustrated by pyrrolizidinine and quinolizidine derivatives **6** and **7**, respectively.

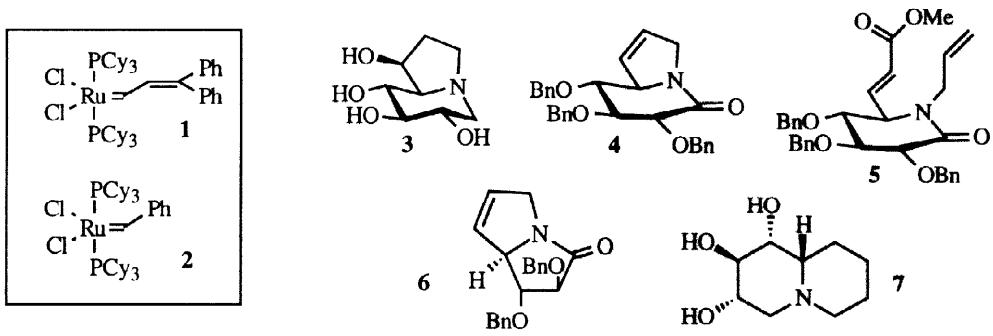

Figure 1

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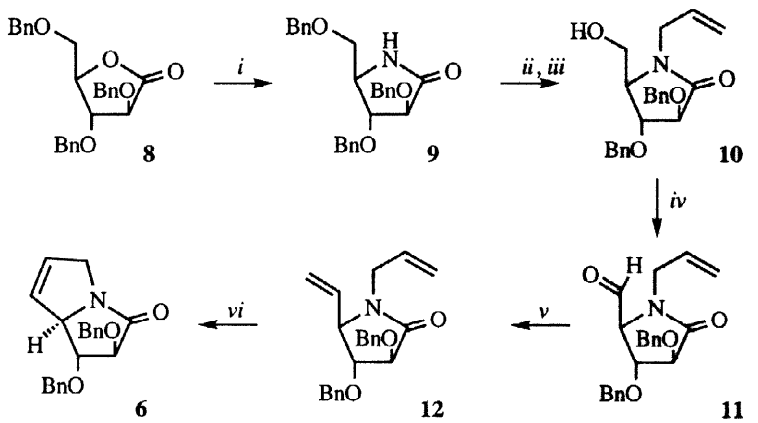
In connection with a study directed to the synthesis of sugar lactams as glycosidase inhibitors, we described the facile transformation of 2,3,5-tri-*O*-benzyl-D-arabino-γ-lactone into the corresponding 2,3,5-tri-*O*-benzyl-D-arabino-γ-lactam, in 4 steps (**8** to **9**, Scheme 1) [10]. In order to explore the scope of the RCM-mediated synthesis of bicyclic azasugars from sugar lactams, we set out to transform **9** into the diene intermediate **12**. Thus, *N*-allylation of **9** under two-phase conditions with allyl bromide in the presence of tetrabutylammonium iodide (phase transfer catalyst), followed by selective acetolysis of the primary benzyloxy group using ferric chloride and acetic anhydride [11] and subsequent hydrolysis of the thereby obtained acetate afforded alcohol **10** in 70% overall yield. Oxidation of **10** to **11** with the Dess Martin periodinane [12] followed by Wittig olefination afforded the desired diene **12** in 48% yield.

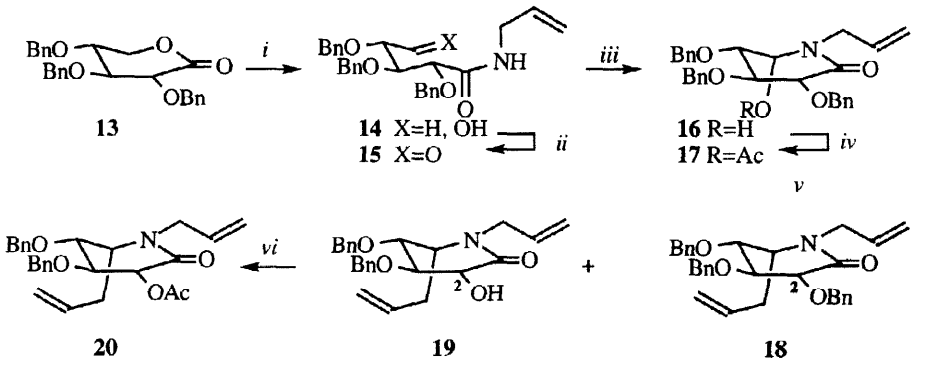


conditions: *i* ref 10, 4 steps, 56%. *ii* allyl bromide, KOH (50% aq)/CH_2Cl_2 1:1 (v/v), TBAI, 1.5 h. (96%). *iii* $FeCl_3$, Ac_2O, then NH_3, MeOH (73%). *iv* Dess Martin periodinane. *v* methyl triphenylphosphonium bromide, KHMDS, THF, -78 °C (48%, 2 steps). *vi* 1 (0.5 eq.), benzene, 50 °C, 24 h. (66%).

Scheme 1

When **12** was subjected to a RCM reaction employing ruthenium catalyst **1**, the expected bicyclic lactam **6** was obtained in 66% yield. However, this cyclisation proved to proceed quite slowly, necessitating a prolonged reaction time (24 h.) and elevated temperature (50 °C). Also, substantial amounts of the catalyst (up to 0.5 mol eq.) were required for completion of the reaction. It is thought that the ring strain of the 5/5 product **6** constitutes a barrier to the normally facile cyclisation [13].

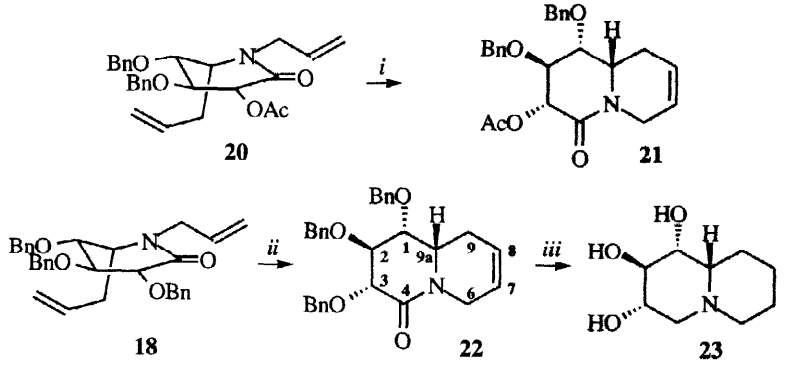
Having successfully applied the RCM-methodology to the synthesis of pyrrolizidinone **6**, we turned our attention to the application of the strategy to the synthesis of novel oxygenated quinolizidine derivatives. To this end, 2,3,4-tri-*O*-benzyl-D-xylo-δ-lactone (**13**), which is easily accessible *via* a three-step sequence from D-xylose [14], was converted into the diene systems **18** and **19** according to Scheme 2. In this sequence, the first alkene moiety was introduced into lactone **13** *via* aminolysis with allylamine in methanol. Oxidation of the primary hydroxyl function in **14** gave a mixture of aldehyde **15** and hydroxylactam **16**. When this mixture was treated with methanolic ammonia, **16** was obtained as the sole product in 75% yield. Introduction of the second alkene moiety was subsequently accomplished by transformation of **16** into acetoxylactam **17**, (Ac_2O, cat. DMAP, pyridine) followed by reaction with allyl trimethylsilane and BF_3etherate [15]. Under these reaction conditions, partial debenzylation of the C-2-benzyloxy group, resulting in a mixture of dienes **18** and **19** (1:1, 66%) was observed [16]. The acetylation of **19** to **20** allowed for the determination of the structure. The formation of the L-*ido*-addition products is in accordance with the expected attack of the nucleophile on the α-face of the *in situ* generated *N*-acyliminium ion [10].



conditions: *i* allylamine, MeOH (98%). *ii* Dess Martin periodinane. *iii* NH_3, MeOH (77%). *iv* Ac_2O, pyridine, DMAP (91%). *v* allyl trimethylsilane, BF_3OEt_2 (32% **18**, 36% **19**). *vi* Ac_2O, pyridine, DMAP (93%).

Scheme 2

Dienes **20** and **18** were submitted to the RCM reaction, as shown in Scheme 3. The quinolizidinone **21** was isolated in excellent yield using ruthenium alkylidene complex **2**. Similarly, the perbenzylated analogue **22** was isolated in 63% yield (together with 10% recovered starting material) employing ruthenium catalyst **1** [17]. Reduction of the amide function in **22** followed by hydrogenolysis of the double bond and the benzyl protecting groups led to the formation of quinolizidine **24** in 57% yield (two steps).



conditions: *i* **2** (2.5 mol%), CH_2Cl_2, RT (95%). *ii* **1** (1 mol%), toluene, RT (74% based on recovered starting material). *iii* $LiAlH_4$, THF, then H_2, $Pd(OH)_2/C$, HCl, EtOH (56%).

Scheme 3

In conclusion, a facile strategy for the synthesis of specifically hydroxylated pyrrolizidinine and quinolizidine derivatives, based on the RCM methodology, has been developed. The inhibitory properties of these compounds, as well as the application of the presented methodology to other pentose lactones, will be reported in due course.

References and Notes

Satisfactory spectroanalytical data were obtained for all new compounds.

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[17] selected data on compound **22**: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.27-2.39 (m, 2H, C(9)H_2), 3.41 (bd, 1H, C(6)H; *J* 17.9 Hz), 3.75 (ddd, 1H, C(9a)H; *J* 4.3, 6.2 and 10.6 Hz), 3.85 (dd, 1H, C(1)H; *J* 6.2 and 9.0 Hz), 3.92 (dd, 1H, C(2)H; *J* 8.3 and 9.1 Hz), 3.96 (d, 1H, C(3)H; *J* 3.2 Hz), 4.67 (d, 1H, PhCHH; *J* 11.7 Hz), 4.78-4.87 (m, 5H, C(6)H, $PhCH_2$), 5.26 (d, 1H, PhCHH; *J* 10.9 Hz), 5.67-5.70 (m, 1H, C(7)H), 5.97-5.85 (m, 1H, C(8)H), 7.15-7.46 (m, 15H, PhH). HRMS (FAB): calculated for $C_{30}H_{32}NO_4$ 470.2331 $[M+H]^+$, found 470.2325.