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Formal synthesis of valienamine using ring-closing metathesis

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Abstract—(1*R*,2*S*,3*S*,4*R*)-2,3,4-Tri-*O*-benzyl-5-(benzyloxymethyl)-cyclohex-5-ene-1,2,3,4-tetrol, a precursor of the α-glucosidase inhibitor, valienamine, was synthesised in eight steps from tetrabenzyl glucose. The key steps were the selective protection of an open-chain diol, and the formation of the cyclohexene ring by ring-closing metathesis with the trisubstituted olefin of valienamine correctly in place.

Valienamine **1** is an unsaturated carbasugar that is found in Nature as a component of glucosidase inhibitors such as acarbose **2**[1] or the antibiotic validamycin A **3**[2] (Fig. 1). The glucosidase-inhibitory properties of valienamine stem from its distorted ring structure and positive charge, which means that it resembles the transition state of the hydrolysis reaction of an α-glucoside. I was keen to synthesise this molecule as part of a project towards the synthesis of novel glycosidase-specific inhibitors.

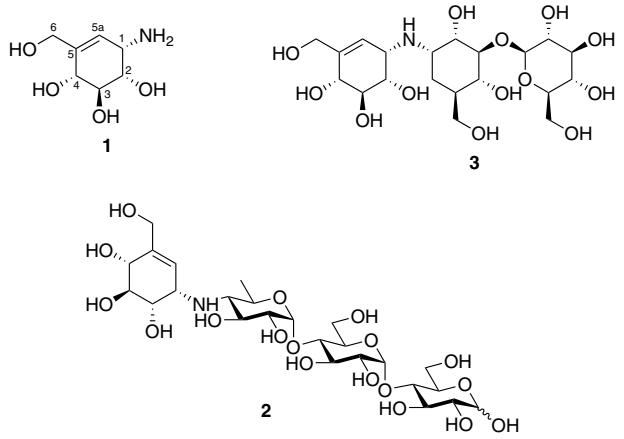

Figure 1. Structures of valienamine **1**, acarbose **2**, and validamycin A **3**.

Several syntheses of valienamine **1** have been reported, and these have recently been reviewed.[3] Of the various methods reported, I was attracted by the ring-closing metathesis approach of Vasella and co-workers.[4] However, this method makes use of Grubbs' first generation catalyst to close the ring with a disubstituted double bond between C-1 and C-5a, and relies on a rearrangement to obtain the C-5=C-5a double bond and the substituent at C-1. It has been shown by Callam and Lowary[5] and by Seepersaud and Al-Abed[6] in the synthesis of carbaarabinofuranose derivatives such as **4** (Fig. 2) that it is possible to achieve ring-closing metathesis to form a trisubstituted double bond in the analogous position to that in valienamine, using the Shrock or Grubbs' second generation catalysts. Now with Grubbs' second generation catalyst commercially available, I wondered whether it would be possible to apply the same approach to the synthesis of the equivalent glucose-derived compound **5**, which could then be transformed into valienamine **1** as described by Fukase and Horii.[7] During the course of this work, a paper describing a similar approach has appeared.[8]

Thus, treatment of commercially available tetrabenzyl glucose **6** with vinylmagnesium bromide gave **7** and **8**

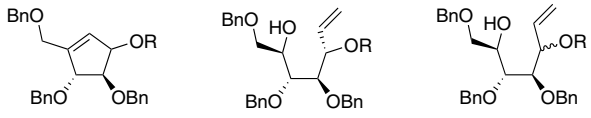

Figure 2. Structures of carbaarabinose derivatives **4**, and of the substrates of reported selective protection of allylic alcohols, **9** and **10**.

Keywords: Valienamine; Ring-closing metathesis; Selective protection; Glucosidase inhibitors.
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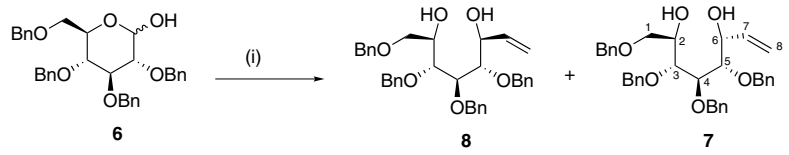


Scheme 1. Reagents and conditions: (i) CH_2=CHMgBr, THF, 0 °C; **8**, 29%; **7**, 65%.

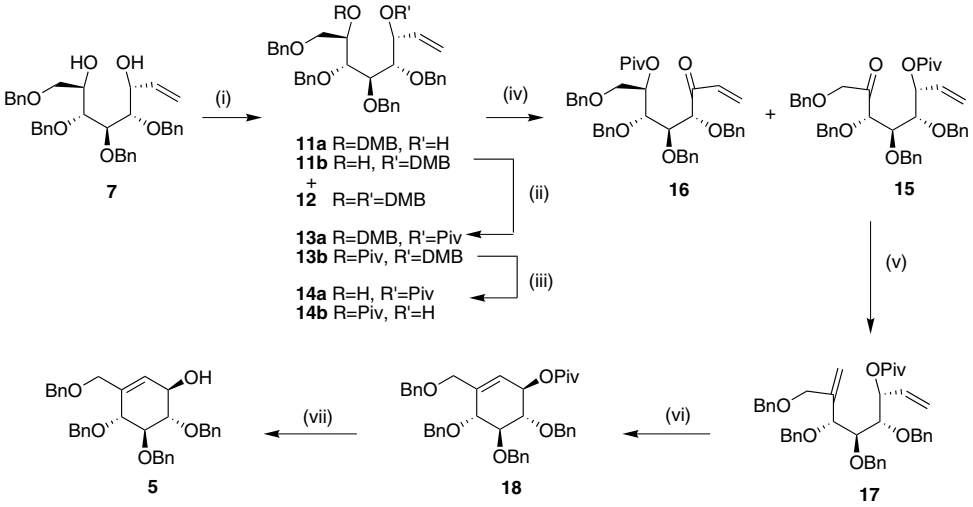
as a 2.2:1 mixture in favour of the desired *R* diastereomer **7** (vide infra) (Scheme 1).[9]

It was necessary to differentiate the two alcohol functionalities of the resulting diol **7**. Success in similar systems has been reported previously: Martin selectively protected the allylic alcohol of **9** using benzoyl chloride under phase-transfer conditions,[10] whereas Al-Abed selectively protected the allylic alcohol of the epimeric mixture **10** using *para*-methoxybenzyl chloride and sodium hydride (Fig. 2).[6]

Unfortunately, these conditions could not be generally applied, as in my system, treatment of **7** with benzoyl chloride under the reported conditions gave a 2.8:1 mixture of the regioisomeric monobenzoates in favour of the 2-*O*-benzoate; attempted *para*-methoxybenzylation of **8** under the reported conditions gave a 1:1 mixture of the regioisomeric products. However, I found that excellent regioselectivity could be achieved using 3,4-dimethoxybenzyl chloride (DMBCl)[11] with sodium hydride at 0 °C in DMF, and **11a** and **11b** were obtained as an inseparable 10:1 mixture of regioisomers in favour of the 2-*O*-dimethoxybenzyl derivative **11a**, along with the diprotected compound **12** (Scheme 2). As an alternative solution to this problem, the dithioacetal route described by Jeon and Kim avoids the need for differentiation of the two secondary alcohols, but has the disadvantages of using ethanethiol as solvent during dithioacetal formation, and mercury salts for its removal.[8]

Pivaloylation of the alcohols **11** and removal of the DMB protecting groups gave the alcohols **14a** and **14b**, still as an inseparable mixture. Swern oxidation of the alcohols **14a** and **14b** gave the ketones **15** and **16**, which were easily separated by flash column chromatography, in 81% and 7% yields, respectively. Wittig methylenation of the ketone **15** gave the diene **17**, which smoothly underwent ring-closing metathesis mediated by Grubbs' second generation catalyst to give the carbasugar **18**.[5] The stereochemistry at the pseudoanomeric centre could then be assigned as *R*, based on the coupling constant $^3J_{1,2}$ of 7.9 Hz.[12] Straightforward deacylation of the pseudoanomeric protecting group gave the alcohol **5**, which may be transformed into valienamine **1** in three steps using Fukase's procedure.[7]

In summary, I have demonstrated a new synthesis of the precursor **5** to valienamine **1** in eight steps from commercially available tetrabenzyl glucose **6** and in 7.7% overall yield. The key steps were the selective protection of one of two secondary alcohols in the acyclic derivative **7** and the formation of the cyclohexene ring using ring-closing metathesis mediated by Grubbs' second generation catalyst, with the double bond being in the correct position for valienamine. Further investigations, including the synthesis of mannose- and galactose-derived valienamine analogues using this methodology, the introduction of nitrogen at the pseudoanomeric position before ring closure and the conjugation of valienamine to other sugars, is in progress, and the results will be reported in due course.



Scheme 2. Reagents and conditions: (i) DMBCl, DMF, NaH, 0 °C; 57%; **11a/11b**, 10:1; (ii) PivCl, pyridine, DMAP, 93%; (iii) CAN, MeCN, H_2O, 0 °C → rt; 74%; (iv) oxalyl chloride, DMSO, Et_3N, DCM, −60 °C; **16**, 7%; **15**, 81%; (v) PPh_3CH_3Br, THF, NaHMDS, −78 °C; 63%; (vi) Grubbs' 2nd gen. cat., toluene, 60 °C, 65%; (vii) NaOMe, MeOH, 40 °C, >99% (DMB = 3,4-dimethoxybenzyl).

Supplementary data

Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2005.07.054.

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