Tetrahedron: *Asymmetry* 26 (2015) 29–34

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Ruthenium-catalyzed one-pot ring-closing metathesis/*syn*-dihydroxylation in the synthesis of bicyclic iminosugars

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ARTICLE INFO

Article history:
Received 14 October 2014
Accepted 19 November 2014

ABSTRACT

Novel polyhydroxylated derivatives of quinolizidine and decahydropyrido[1,2-*a*]azepine were prepared starting from a common oxazolidinone. The bicyclic cores were prepared by a ruthenium-catalyzed ring-closing metathesis, followed by re-use of the catalyst in the subsequent *syn*-dihydroxylation in a one-pot procedure.

1. Introduction

The *syn*-dihydroxylation is usually performed using an osmium-based reagent.[1] However, their reliability goes hand in hand with serious drawbacks such as high price and high toxicity. Over the last decade, several protocols have been developed, in which good results were also obtained with osmium-free species,[2] most notably the in situ synthesized RuO_4. Although its most commonly used precursor $RuCl_3$ is relatively inexpensive, stable and non-toxic, ruthenium tetroxide itself is very reactive and lacks selectivity. Therefore, in order to reduce the formation of side products, great care must be taken to choose the proper reaction conditions.[3] For instance, Plietker et al. proved that the addition of a Lewis or Brønsted acid is beneficial and renders the transformation much more predictable.[4]

Since the olefin metathesis most commonly uses Ru catalysts, one-pot procedures were developed, in which the formation of a new double bond via a metathesis reaction is followed by the oxidation of the catalyst to RuO_4, which in turn oxidizes the resulting olefin into a *syn*-diol.[5] In this convenient approach, the expensive transition metal (ruthenium) is reused. However, despite this obvious advantage, the transformation remains rarely used in total syntheses. In one of our preceding papers, we have shown its application in the synthesis of iminosugars (Scheme 1).[6] These compounds belong to a vast group of carbohydrate analogues that bear a nitrogen atom in the ring(s).[7] In general, iminosugars are known for interesting biological properties, for example, for their inhibitory activity against certain glycosidases.[8] A variety of the synthetic routes to this class of compounds have been elaborated on over the last years.[9] However, taking into account their promising biological activity, the development of new synthetic approaches leading to iminosugars is still needed.

Herein, we report the application of the Ru-catalyzed one-pot ring-closing metathesis/*syn*-dihydroxylation to the synthesis of novel imino sugars. The 'classical', osmium-based approach to the problem is also shown for the sake of comparison.

2. Results and discussion

Our synthetic route started from D-xylose derived oxazolidinone **1** (Scheme 2), a versatile intermediate which has already been used in the total synthesis of (−)-castanospermine.[10]

After methanolysis, which afforded aminoalcohol **2**, the *N*-acryloyl derivative **3a** was obtained, along with considerable amounts (26%) of diacryloyl derivative **3b** as a by-product. Subsequent ring-closing meta thesis (Scheme 3) of **3a** with Grubbs-II cat. (5 mol %) furnished bicyclic product **4** in excellent yield. In the following step, the osmium-mediated (5 mol % OsO_4) *syn*-dihydroxylation yielded **5** as the sole diastereoisomer. 2D-NOESY experiment indicated that the newly formed hydroxyl groups were in an *anti*-relationship to the already existing one (no interactions between: H-9a and H-2, H-9a and H-3, H-1 and H-3). This observation is in accordance with Kishi's empirical rule.[11]

We envisaged that **3a** could also be obtained directly from **1** by reaction with a vinyl anion equivalent. Although oxazolidinones are commonly employed as chiral auxiliaries[12] or act as masked amino alcohols in total syntheses,[13] reports on their reactivity with carbon nucleophiles, such as Grignard reagents or alkyllithiums, are very limited.[14] Nonetheless, we attempted to open the oxazolidinone ring in **1** with vinyl magnesium bromide. Various conditions were

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http://dx.doi.org/10.1016/j.tetasy.2014.11.013
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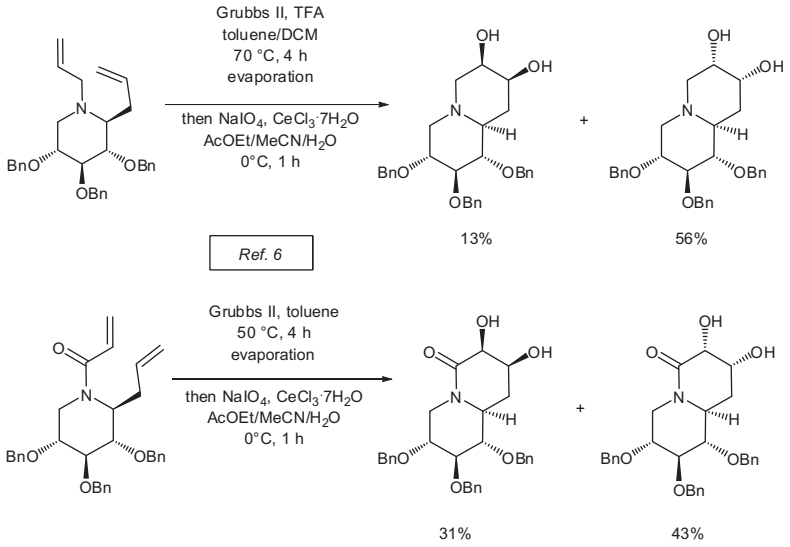
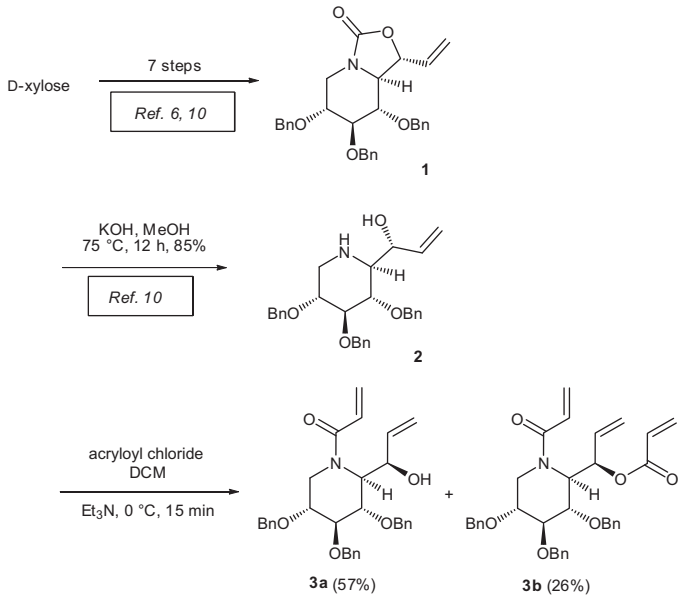
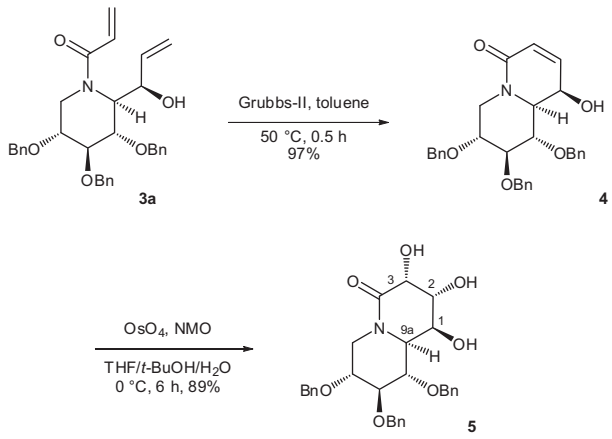


Scheme 1. Previous application of a one-pot RCM/*syn*-dihydroxylation to the synthesis of iminosugars.

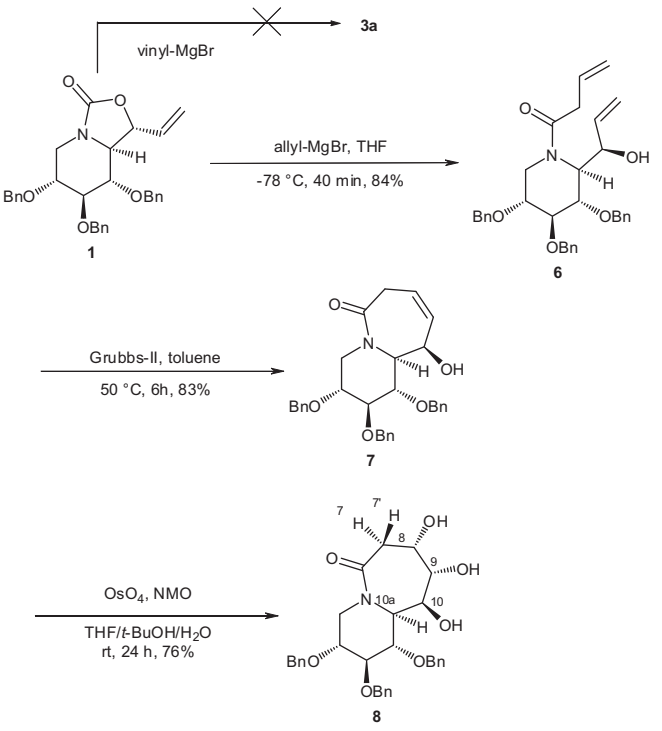


Scheme 2. Synthesis of *N*-acryloyl derivative **3a**.



Scheme 3. 'Classical' osmium-based approach to *syn*-dihydroxylation of olefin **4**.

tested (numerous solvents and broad temperature range), but the desired compound was not formed. It turned out, however, that the reaction with allylmagnesium bromide proceeded smoothly, and afforded compound **6** in very good yield (Scheme 4).



Scheme 4. 'Classical' osmium-based approach to *syn*-dihydroxylation of olefin **7**.

In the subsequent steps, ring-closing metathesis with Grubbs-II catalyst (5 mol %) was performed on **6**, followed by osmium-mediated (5 mol % OsO_4) *syn*-dihydroxylation, which finally provided triol **8** as a single diastereoisomer. In order to elucidate the relative stereochemistry, we assigned the positions of the H-7 and H-7′ protons in this product (strong interaction between the H-7 and H-10a in 2D-NOESY). Although in the 7-membered ring the *J* values were not as diagnostic as in the 6-membered, we can assume that two large (13.2 and 11.8 Hz) coupling constants observed for the