ORGANIC LETTERS

2005
Vol. 7, No. 16
3521−3523

A Rapid Synthesis of Hexofuranose-like Iminosugars Using Ring-Closing Metathesis

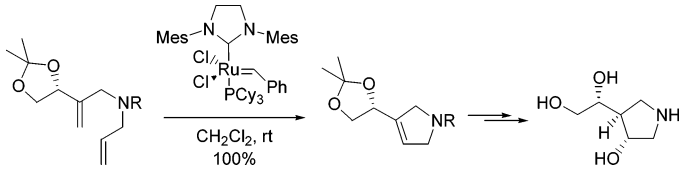
Sylvaine Cren, Claire Wilson, and Neil R. Thomas*

School of Chemistry, Centre for Biomolecular Sciences, University of Nottingham, University Park, Nottingham NG7 2RD, United Kingdom

neil.thomas@nottingham.ac.uk

Received May 25, 2005

ABSTRACT

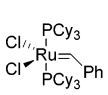


Two new 1-*N*-iminosugars have been prepared as hexofuranose analogues in an efficient manner by an RCM-based route. Both 3,4-disubstituted pyrrolidines display moderate inhibitory activity against *Mycobacterium smegmatis* galactan biosynthesis.

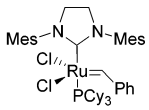
Iminosugars have generated continued interest because of their potential therapeutic applications and use as mechanistic probes. Iminosugars are potent inhibitors of glycosidases, but they also inhibit glycosyltransferases.[1] Previously, we reported (±)-(3*S*,4*R*)-4-[(1*R*)-1,2-dihydroxyethyl]pyrrolidin-3-ol as a moderate inhibitor of UDP-Gal*f* transferase, a key enzyme involved in mycobacterial galactan biosynthesis.[2] Mycobacteria are pathogens responsible for several human diseases, including tuberculosis (TB) and leprosy. Every year, TB kills ~3 million people worldwide, and there is an urgent need for new and effective anti-TB drugs.[3]

There are various synthetic approaches to iminosugars, most of them starting from carbohydrate templates. However, many of these require a large number of steps, including extensive protecting group manipulations, lead to low overall yields, and are dependent on the availability of a suitable starting sugar. An alternative strategy is to construct the desired carbon skeleton first and then add the appropriate oxygenation in a stereocontrolled manner as described here.

RCM (ring-closing metathesis) has been used for the synthesis of iminosugars in a growing number of examples.[4] The key RCM reaction is usually performed using ruthenium complexes **1** or **2**.[5]



1



2

Here we report the enantioselective synthesis of iminosugar (3*R*,4*S*)-4-[(1*R*)-1,2-dihydroxyethyl]pyrrolidin-3-ol (**3**) and its diastereoisomer (3*S*,4*R*)-4-[(1*R*)-1,2-dihydroxyethyl]pyrrolidin-3-ol (**25**), isomers of our previously reported transferase inhibitor,[2] using RCM to form the key five-membered ring core.

(1) (a) For a review on iminosugars as glycosidase inhibitors, see: Lillelund, V. H.; Jensen, H. H.; Liang, X.; Bols, M. *Chem. Rev.* **2002**, *102*, 515. (b) For a review on iminosugars as glycosyltransferase inhibitors, see: Compain, P.; Martin, O. R. *Curr. Top. Med. Chem.* **2003**, *3*, 541.

(2) Cren, S.; Gurcha, S. S.; Blake, A. J.; Besra, G. S.; Thomas, N. R. *Org. Biomol. Chem.* **2004**, *2*, 2418.

(3) WHO website: http://www.who.int/tb/en.

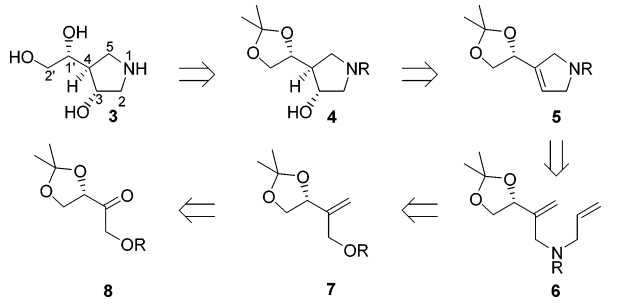
(4) (a) For a review on the synthesis of piperidine and pyrrolidine natural alkaloids with RCM, see: Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693. (b) For selected examples, see: Huwe, C. M.; Blechert, S. *Synthesis* **1997**, 61. Singh, O. V.; Han, H. *Tetrahedron Lett.* **2003**, *44*, 2387. Guanti, G.; Riva, R. *Tetrahedron Lett.* **2003**, *44*, 357. Hongqing, L., Blériot, Y.; Chantereau, C.; Mallet, J.-M.; Sollogoub, M.; Zhang, Y.; Rodríguez-García, E.; Vogel, P.; Jiménez-Barbero, J.; Sinaÿ, P. *Org. Biomol. Chem.* **2004**, *2*, 1492.

(5) (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039. (b) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

10.1021/ol051232b CCC: $30.25
Published on Web 07/15/2005

The retrosynthetic analysis of iminosugar **3** is shown in Scheme 1. 1,2-Diol and amine protection leads to the

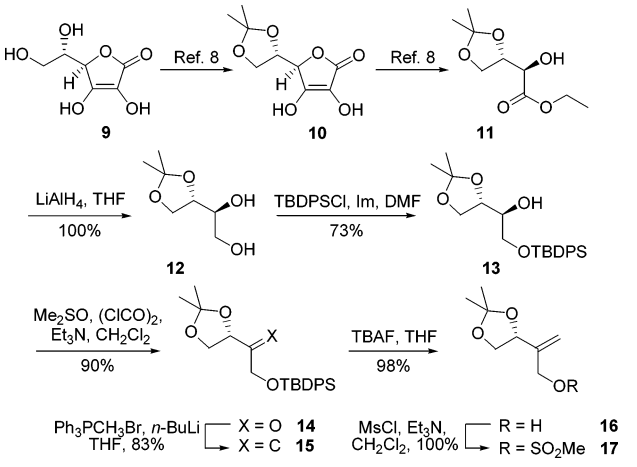
Scheme 1



protected pyrrolidine **4**. Retrosynthetic dehydration of the alcohol affords the alkene **5**, which can then be disconnected to the diene **6**. Cleavage of the allylamine and further functional group interconversion gives the ketone **8** via the alkene **7**. The key reaction in our route would be formation of the pyrroline **5** via the RCM reaction of diene **6**, which would afford a trisubstituted double bond with the stereochemistry of the C-1′ carbon atom, α to the double bond already established.

A synthesis of chiral synthon **8** from L-(*S*)-erythrulose has been described by Vandewalle.[6] However, L-(*S*)-erythrulose is no longer commercially available. An alternative route to ketone **8** is the oxidative cleavage of L-ascorbic acid, a method first reported by Jung and Shaw.[7] Using this approach, L-ascorbic acid **9** was converted into the diol **12** following the procedure devised by Abushanab et al.[8] Selective protection of the primary hydroxyl group followed by oxidation of the secondary hydroxyl group gave the ketone **14** in good overall yield (41%).

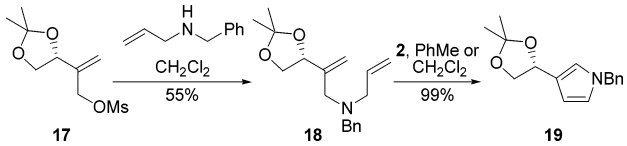
Scheme 2



Ketone **14** was then converted into the corresponding alkene **15** using Wittig chemistry, and cleavage of the silyl ether afforded the allylic alcohol **16**. Activation of the alcohol then gave the mesylate **17** in quantitative yield.

Displacement of the mesylate with *N*-benzyl-allylamine gave the diene **18** in a moderate yield (55%). The precursor of the RCM reaction was then reacted with ruthenium complex **1**, but no reaction was observed even at elevated temperatures. The diene was then subjected to RCM using the more reactive ruthenium complex **2** in dichloromethane, and a single product was isolated, which was identified as the pyrrole **19**. Not only did this indicate that RCM had taken place, it also suggested that the catalyst had brought about alkene isomerization and dehydrogenation. Neither a change of the reaction solvent to toluene nor an adjustment of the reaction temperature led to a change in the reaction outcome; in every instance the pyrrole was the only product ever isolated.

Scheme 3



There are only a few reports of pyrrole formation during RCM.[9] Most of them mention pyrrole formation as a side reaction of the RCM reaction. However, Verpoort and coworkers recently developed a general pyrrole synthesis using a tandem Grubbs' carbene-$RuCl_3$ catalytic system; they assumed that $RuCl_3$ was responsible for the pyrrole formation.[9d] They also noticed that amines bearing an electron-withdrawing group on the nitrogen atom did not dehydrogenate to the pyrrole, but gave the corresponding pyrrolines. This suggests that the basicity of the nitrogen atom plays an important role in the dehydrogenation. Nevertheless, there is one example in the literature where the RCM reaction (with **1** in dichloromethane at reflux) of an *N*-Boc-protected amine gave, after purification, a mixture of the expected pyrroline and the corresponding pyrrole.[9b]

In our case, we observed total conversion of the diene **18** into the pyrrole **19** in the presence of **2** (1 mol % in dichloromethane or toluene).

In light of these results, we next decided to synthesize the *N*-Boc-protected diene **21** and subject it to the RCM reaction (Scheme 4). Treatment of the mesylate **17** with allylamine and subsequent protection afforded the RCM precursor **21** in good yield (90%). This precursor was then subjected to RCM using ruthenium complex **2** in dichloromethane; the reaction was complete in 36 h (microwave

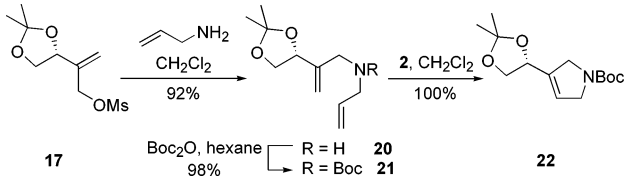
(6) De Wilde, H.; De Clercq, P.; Vandewalle, M. *Tetrahedron Lett.* **1987**, *28*, 4757.

(7) Jung, M. E.; Shaw, T. J. *J. Am. Chem. Soc.* **1980**, *102*, 6304.

(8) Abushanab, E.; Bessodes, M.; Antonakis, K. *Tetrahedron Lett.* **1984**, *25*, 3841.

(9) (a) Evans, P.; Grigg, R.; Monteith, M. *Tetrahedron Lett.* **1999**, *40*, 5247. (b) Bujard, M.; Briot, A.; Gouverneur, V.; Mioskowski, C. *Tetrahedron Lett.* **1999**, *40*, 8785. (c) Yang, C.; Murray, W. V.; Wilson, L. J. *Tetrahedron Lett.* **2003**, *44*, 1783. (d) Dieltiens, N.; Stevens, C. V.; De Vos, D.; Allaert, B.; Drozdzak, R.; Verpoort, F. *Tetrahedron Lett.* **2004**, *45*, 8995. (e) Yang, Q.; Xiao, W.-J.; Yu, Z. *Org. Lett.* **2005**, *7*, 871.

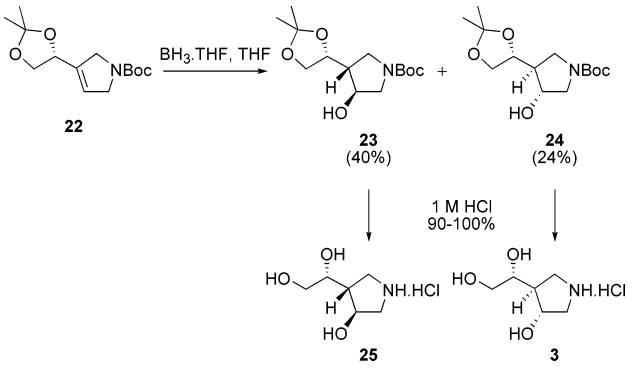
Scheme 4



accelerated RCM[10] was also investigated and resulted in shorter reaction times ~20 min at 100 °C). Significantly, none of the pyrrole was detected, and the desired pyrroline **22** was obtained in quantitative yield and in 90% overall yield from the mesylate **17**.

The hydroboration of **22** was now performed using a slight excess of BH_3·THF and afforded a mixture of diastereoisomeric alcohols **23** and **24** in a 1.7:1 ratio (Scheme 5). The

Scheme 5



two diastereoisomers were separated by column chromatography; the less polar compound **23** was obtained as a crystalline solid, and subsequent recrystallization from *n*-hexane gave crystals suitable for X-ray analysis (Figure 1).[11]

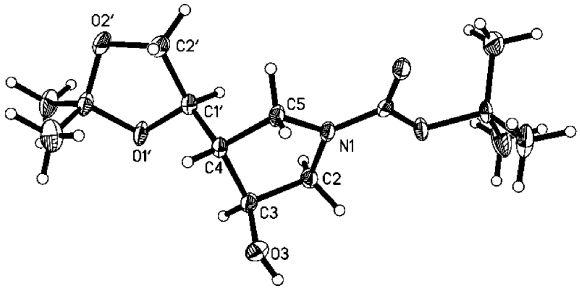


Figure 1. X-ray crystal structure of compound **23**.

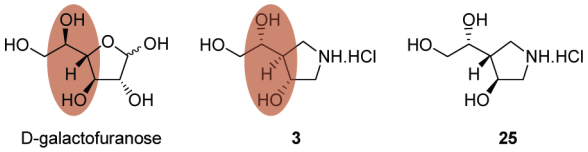
Both alcohols **23** and **24** were converted into iminosugars **25** and **3**, respectively, by removal of the protecting groups with aqueous 1 M HCl.

Iminosugars **3** and **25** were tested against *Mycobacterium smegmatis* galactan biosynthesis using the cell-free assay involving both UDP-Gal*p* mutase and UDP-Gal*f* transferase developed by Besra and co-workers.[12] Both iminosugars exhibited weak activity. When compared to the results obtained for the corresponding racemic mixtures,[2] the inhibition was better with the enantiopure iminosugars indicating these were the more active components of the racemate (Table 1).

Table 1. Inhibition of *M. smegmatis* Galactan Biosynthesis

	compound (8 mM)			
	(±)-**25**	(±)-**3**	**25**	**3**
% inhibition	59	40	72	85

Surprisingly, iminosugar **3**, bearing the L-*galacto* configuration (by analogy with the natural substrate, D-galactofuranose) was the most active of the two diastereoisomers tested. Stereochemical subtleties in the inhibition of carbohydrate-processing enzymes by iminosugars has recently been discussed,[13] but overall the recognition process remains unpredictable.



In summary, we have developed an efficient synthesis of iminosugars with the formation of the five-membered core by ring-closing metathesis as a key step. To our knowledge, this constitutes the first example of an iminosugar synthesis utilizing the RCM with the stereochemistry at C-1′ already set up. This route allows rapid access to 3,4-disubstituted pyrrolidines[14] and could be applied to the synthesis of a range of new iminosugars.

Acknowledgment. We thank the University of Nottingham for financial support and Professor G. S. Besra (School of Biosciences, University of Birmingham, U.K.) for assistance with the galactan biosynthesis assays.

Supporting Information Available: Experimental procedures along with spectroscopic and other data in CIF format for compounds **3** and **12**−**25**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL051232B

(10) For a selected example, see: Yang, C.; Murray, W. V.; Wilson, L. J. *Tetrahedron Lett.* **2003**, *44*, 1783.

(11) The crystallographic data (excluding structure factors) for compound **23** have been deposited (CCDC 272229) with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, upon application to the CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax, +44 (0)1223 336033; e-mail, deposit@ccdc.cam.ac.uk).

(12) Pathak, A. K.; Pathak, V.; Seitz, L.; Maddry, J. A.; Gurcha, S. S.; Besra, G. S.; Suling, W. J.; Reynolds, R. C. *Bioorg. Med. Chem.* **2001**, *9*, 3129.

(13) Asano, N.; Ikeda, K.; Yu, L.; Kato, A.; Takebayashi, K.; Adachi, I.; Kato, I.; Ouchi, H.; Takahata, H.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2005**, *16*, 223.

(14) Synthesis of a diastereoisomer (3*R*,4*S*)-4-[(1*S*)-1,2-dihydroxyethyl]-pyrrolidin-3-ol from D-xylose has been reported: Filichev, V. V.; Brandt, M.; Pedersen, E. B. *Carbohydr. Res.* **2001**, *333*, 115.