

Tetrahedron Letters 39 (1998) 3869-3872

TETRAHEDRON LETTERS

Ring-Closing Metathesis mediated synthesis of Pyrrolizidine and Quinolizidine Azasugars

Herman S. Overkleeft,* Pascal Bruggeman and Upendra K. Pandit*

Amsterdam Institute of Molecular Science, University of Amsterdam, Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands Received 20 February 1998; revised 17 March 1998; accepted 20 March 1998 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. © 1998 Elsevier Science Ltd. All rights reserved.

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

* current adress: Leiden Institute of Chemistry, Leiden University, P. O. Box 9502, 2300 RA Leiden

0040-4039/98/\$19.00 © 1998 Elsevier Science Ltd. All rights reserved. *Pll*: S0040-4039(98)00635-2 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)/CH₂Cl₂ 1:1 (v/v), TBAI, 1.5 h. (96%). *iii* FeCl₃, Ac₂O, then NH₃, 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, (Ac₂O, cat. DMAP, pyridine) followed by reaction with allyl trimethylsilane and BF₃etherate [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 NH₃, MeOH (77%). iv Ac₂O, pyridine, DMAP (91%). v allyl trimethylsilane, BF₃OEt₂ (32% 18, 36% 19). vi Ac₂O, 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 LiAlH₄, THF, then H₂, 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.

- [1] Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. Chem. Rev. 1996, 96, 635.
- (a) Nguyen, S. T.; Grubbs, R. H. J. Am. Chem. Soc. 1993, 115, 9858. (b) Schwab, P.; Grubbs, R. H.;
 Ziller, J. W. J. Am. Chem. Soc. 1996, 118, 100.
- [3] see for recent reviews: (a) Schuster, M.; Blechert, S. Angew. Chem. Int. Ed. Engl. 1997, 36, 2036.
 (b) Armstrong, S. K. J. Chem. Soc. Perkin Trans. 1, 1998, 371.
- [4] Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. J. Org. Chem. 1994, 59, 4029.
- [5] Rutjes, F. P. T. J.; Schoemaker, H. E. Tetrahedron Lett. 1997, 38, 677.
- [6] Leeuwenburgh, M. A.; Overkleeft, H. S.; van der Marel, G. A.; van Boom, J. H. Synlett 1997, 1263.
- [7] van Maarseveen, J. H.; den Hartog, J. A. J.; Engelsen, V.; Finner, E. Visser, G.; Kruse, C. G. Tetrahedron Lett. 1996, 37, 8249.
- [8] Pandit, U. K.; Borer, B. C.; Bieräugel, H. Pure & Appl. Chem. 1996, 68, 659.
- [9] Overkleeft, H. S.; Pandit, U. K. Tetrahedron Lett. 1996, 37, 547.
- [10] Overkleeft, H. S.; van Wiltenburg, J.; Pandit, U. K. Tetrahedron 1994, 50, 4215.
- [11] Kartha, K. P. R.; Dasgupta, F.; Singh, P. P.; Srivastava, H. C. J. Carbohydr. Chem. 1986, 5, 437.
- [12] Ireland, R. E.; Liu, L. J. Org. Chem. 1993, 33, 780.
- [13] see for an example of a failed attempt to the RCM-mediated formation of a 5-memberd ring on a cyclic 5-membered carbamate template: Huwe, C. M.; Blechert, S. *Tetrahedron Lett.* **1995**, *36*, 1621.
- [14] Hiranuma, S.; Kajimoto, T.; Wong, C.-H. at the XVIIth International Carbohydrate Symposium, Ottawa, Canada, 1994, poster presentation.
- [15] Speckamp, W. N.; Hiemstra, H, Tetrahedron 1985, 41, 4367.
- [16] the BF₃etherate-mediated cleavage of benzyl ethers using ethane thiol as the nucleophile has been reported: Andrews, G. C.; Crawford, T. C.; Bacon, B. E. J. Org. Chem. **1980**, 46, 2967.
- [17] selected data on compound 22: ¹H-NMR (400 MHz, CDCl₃): δ 2.27-2.39 (m, 2H, C(9)H₂), 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, PhCH<u>H</u>; J 11.7 Hz), 4.78-4.87 (m, 5H, C(6)H, PhCH₂), 5.26 (d, 1H, PhCH<u>H</u>; 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 C₃₀H₃₂NO₄ 470.2331 [M+H]⁺, found 470.2325.