ORGANIC LETTERS

2013
Vol. 15, No. 24
6214–6217

Synthesis of Polyhydroxylated Quinolizidines and Azaspiro[4.5]decanes from D-Xylose

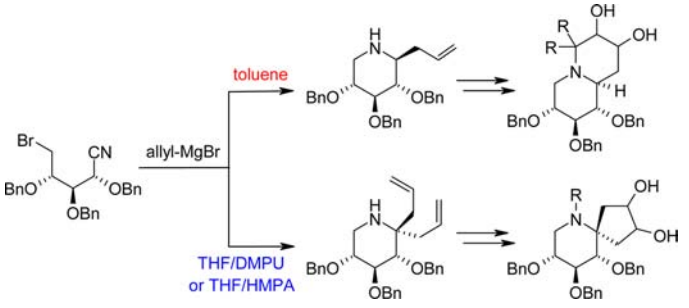
Michał Malik,[†] Grzegorz Witkowski,[†] Magdalena Ceborska,[‡] and Sławomir Jarosz*,[†]

Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland, and Institute of Physical Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland

sljar@icho.edu.pl

Received October 24, 2013

ABSTRACT



The synthesis of novel polyhydroxylated quinolizidines and azaspiro[4.5]decanes is reported. A key step of this transformation involved an addition of allylmagnesium bromide to an ω-bromonitrile derived from D-xylose followed by an intramolecular displacement of a bromide. The resulting cyclic imine was treated either with allylmagnesium bromide or with $NaBH_4$, to provide 2,2-diallyl- or 2-allylpiperidine, respectively. The desired bicyclic framework was constructed via a ring-closing metathesis reaction. The Ru catalysts were reused in the following *syn*-dihydroxylation step.

Polyhydroxylated mono- and bicyclic derivatives containing a nitrogen atom in the ring, so-called iminosugars, are common in Nature.[1] Up to now, numerous structures have been isolated from plants and microorganisms. Some of them possess strong inhibitory activity against enzymes involved in important biological pathways. Such compounds are, in some cases, potential drugs in antiviral, lysosomal storage diseases and antidiabetic therapies.[2] For example, the analogs of deoxynojirimycin, Miglustat and Miglitol, have found application as drugs and are marketed worldwide. Therefore, the development of new synthetic methodologies for preparation of iminosugars is of great interest.[3] Some of the current synthetic approaches are based on application of cyclic nitrones[4] or cyclic amines[5] (formed by an intramolecular reductive amination) as key intermediates, or they consist in an intramolecular S_N2 reaction.[6] De novo asymmetric syntheses of iminosugars were also accomplished.[7]

[†] Institute of Organic Chemistry.
[‡] Institute of Physical Chemistry.

(1) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139.
(2) (a) Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry* **2001**, *56*, 265. (b) Compain, P., Martin, O. R., Eds. *Iminosugars: From Synthesis to Therapeutic Applications*; Wiley-VCH: Weinheim, 2007.
(3) (a) Pearson, M. S. M.; Mathé-Allainmat, M.; Fargeas, V.; Lebreton, J. *Eur. J. Org. Chem.* **2005**, 2159. (b) Lahiri, R.; Ansari, A. A.; Vankar, Y. D. *Chem. Soc. Rev.* **2013**, *42*, 5102.
(4) (a) Paśniczek, K.; Socha, D.; Jurczak, M.; Solecka, J.; Chmielewski, M. *Can. J. Chem.* **2006**, *84*, 534. (b) Stecko, S.; Jurczak, M.; Staszewska-Krajewska, O.; Solecka, J.; Chmielewski, M. *Tetrahedron* **2009**, *65*, 7056. (c) Chan, T.-H.; Chang, Y.-F.; Hsu, J.-J.; Cheng, W.-C. *Eur. J. Org. Chem.* **2010**, 5555.
(5) (a) Wierzejska, J.; Ohshima, M.; Inuzuka, T.; Sengoku, T.; Takahashi, M.; Yoda, H. *Tetrahedron Lett.* **2011**, *52*, 1173. (b) Jenkinson, S. F.; Best, D.; Saville, A. W.; Mui, J.; Martínez, R. F.; Nakagawa, S.; Kunimatsu, T.; Alonzi, D. S.; Butters, T. D.; Norez, C.; Becq, F.; Blériot, Y.; Wilson, F. X.; Weymouth-Wilson, A. C.; Kato, A.; Fleet, G. W. J. *J. Org. Chem.* **2013**, *78*, 7380. (c) Ajish Kumar, K. S.; Rathee, J. S.; Subramanian, M.; Chattopadhyay, S. *J. Org. Chem.* **2013**, *78*, 7406.
(6) (a) Kumari, N.; Vankar, Y. D. *Org. Biomol. Chem.* **2009**, *7*, 2104. (b) Decroocq, C.; Laparra, L. M.; Rodriguez-Lucena, D.; Compain, P. *J. Carbohydr. Chem.* **2011**, *30*, 559.
(7) (a) Guo, H.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 1609. (b) Abrams, J. N.; Babu, R. S.; Guo, H.; Le, D.; Le, J.; Osbourn, J. M.; O'Doherty, G. A. *J. Org. Chem.* **2008**, *73*, 1935.

10.1021/ol403063v
Published on Web 11/11/2013

As a part of our ongoing program on the development of novel approaches to sugar mimetics,[8] we report a methodology that enables the rapid construction of polyhydroxylated 2-allylpiperidines. We reasoned that addition of 1 equiv of allylmagnesium bromide to polyhydroxylated ω-bromonitriles should give a cyclic imine, the reduction of which would provide interesting piperidine scaffolds in only a few steps from aldopentoses (Figure 1).

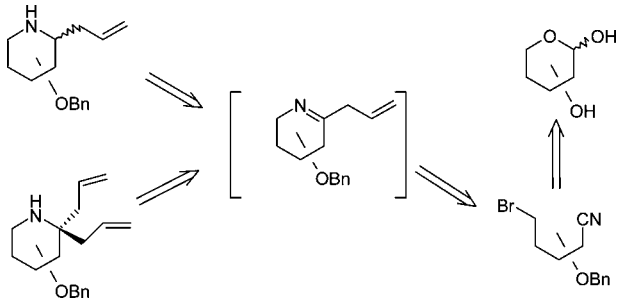


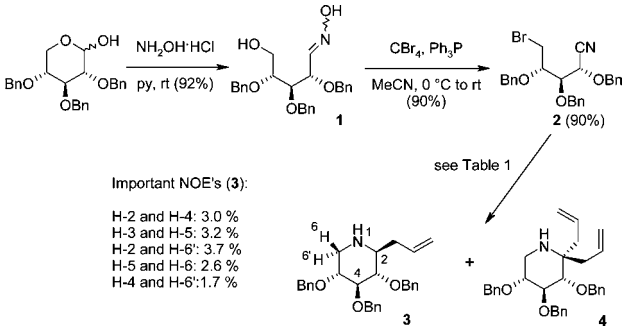
Figure 1. Retrosynthetic analysis for synthesis of polyhydroxylated 2,2-diallyl- and 2-allylpiperidines.

Although the transformation of ω-halonitriles into cyclic imines via the addition of Grignard reagents is already well explored by Fry et al.,[9] its application to the synthesis of natural products and their analogs is very rare.[10] This may be explained, to some extent, by the susceptibility of nitriles to α-deprotonation,[11] which can lead to undesired byproducts.

As shown in Figure 1, addition of a second equivalent of allyl magnesium bromide to the imine intermediate should afford the 2,2-diallylpiperidine, a convenient precursor of an azaspiro[4.5]decane moiety found in some natural products.[12] Such a cascade transformation was, to our knowledge, not yet described.

We initiated our synthesis with oxime **1**, easily prepared from known 2,3,4-tribenzyloxy-D-xylose.[13] Its treatment with CBr_4/triphenylphosphine afforded ω-bromonitrile **2** as a single product in high yield. This transformation required substitution of the hydroxyl group at C-5 and dehydration of the oxime (Scheme 1). The procedure is easily scalable and allows the preparation of large quantities (> 10 g) of **2**.

Scheme 1. Formation of Mono- and Diallylpiperidines



The reaction of **2** with 1 equiv of allylmagnesium bromide and then $NaBH_4$ afforded only one diastereoisomeric monoallyl piperidine to which structure **3** was assigned on the basis of NOE data (see Scheme 1); a small amount of the spiro derivative **4** was also formed. The results of the optimization of this process are summarized in Table 1. As for the cascade leading to **3**, toluene was the solvent of choice. On the other hand, the presence of DMPU or HMPA as a cosolvent favored addition of the second equivalent of allylmagnesium bromide, enabling a synthesis of **4** in good yield. We are therefore pleased to report the first cascade transformation leading directly to 2,2-disubstituted piperidine from an ω-halonitrile.

Once the synthesis of key intermediates **3** and **4** was optimized, our efforts were focused on the construction of the desired bicyclic skeletons. The nitrogen atom in **3** was allylated, and the resulting product **5** was subjected to cyclization. Initial attempts to obtain **6** in decent yield by the most obvious ring-closing metathesis (RCM) approach failed. Long reaction times (3 days) at high temperature (80 °C) as well as a high catalyst loading (3 × 5 mol %) were needed to obtain bicycle **6**, and yet the yield was only 44%.

It is known that amines can cause serious problems in olefin metathesis, since they deactivate the catalyst.[14] A convenient approach to overcome this difficulty consists of an *in situ* protonation of an amine.[15] Application of this concept to **5** (being converted into TFA salt) allowed us to perform the cylization step in high yield (81%) and with 5 mol % of the Grubbs-II catalyst (GC-II).

Syn-dihydroxylation of the double bond is usually realized by a transition-metal-catalyzed process. Although osmium tetroxide and other osmium-based species are by far the most reliable and commonly used reagents, their high toxicity and price are serious drawbacks.[16] Even

(8) (a) Magdycz, M.; Cmoch, P.; Jarosz, S. *Heterocycles* **2010**, *80*, 1303. (b) Nowogródzki, M.; Malik, M.; Jarosz, S. *Tetrahedron: Asymmetry* **2012**, *23*, 1501. (c) Witkowski, G.; Jarosz, S. *Synlett* **2013**, *24*, 1813.

(9) (a) Fry, D. F.; Fowler, C. B.; Dieter, R. K. *Synlett* **1994**, 836. (b) Fry, D. F.; Fowler, C. B.; Brown, M.; McDonald, J. C.; Dieter, R. K. *Tetrahedron Lett.* **1996**, *37*, 6227.

(10) The only examples found: (a) Monterde, M. I.; Brieva, R.; Gotor, V. *Tetrahedron: Asymmetry* **2001**, *12*, 525. (b) Maeda, K.; Yamamoto, Y.; Tomimoto, K.; Mase, T. *Synlett* **2001**, *11*, 1808. (c) Behr, J.-B.; Kalla, A.; Harakat, D.; Plantier-Royon, R. *J. Org. Chem.* **2008**, *73*, 3612.

(11) Fleming, F. F.; Wie, Y.; Liu, W.; Zhang, Z. *Org. Lett.* **2007**, *9*, 2733.

(12) (a) Nieczypor, P.; Mol, J. C.; Bespalova, N. B.; Bubnov, Y. N. *Eur. J. Org. Chem.* **2004**, 812. (b) Kuznetsov, N. Y.; Kolomnikova, G. D.; Khrustalev, V. N.; Golovanov, D. G.; Bubnov, Y. N. *Eur. J. Org. Chem.* **2008**, 5647.

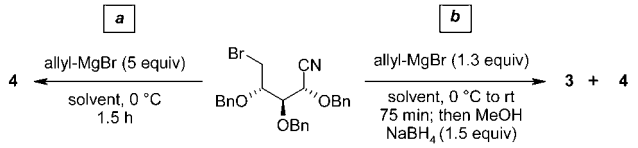
(13) Wennekes, T.; van den Berg, R. J. B. H. N.; Boltje, T. J.; Donker-Koopman, W. E.; Kuijper, B.; van der Marel, G. A.; Strijland, A.; Verhagen, C. P.; Aerts, J. M. F. G.; Overkleeft, H. S. *Eur. J. Org. Chem.* **2010**, 1258.

(14) Compain, P. *Adv. Synth. Catal.* **2007**, *349*, 1829.

(15) (a) Fürstner, A.; Leitner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 308. (b) Woodward, C. P.; Spiccia, N. D.; Jackson, W. R.; Robinson, A. J. *Chem. Commun.* **2011**, *47*, 779.

(16) Bataille, C. J. R.; Donohoe, T. J. *Chem. Soc. Rev.* **2011**, *40*, 114.

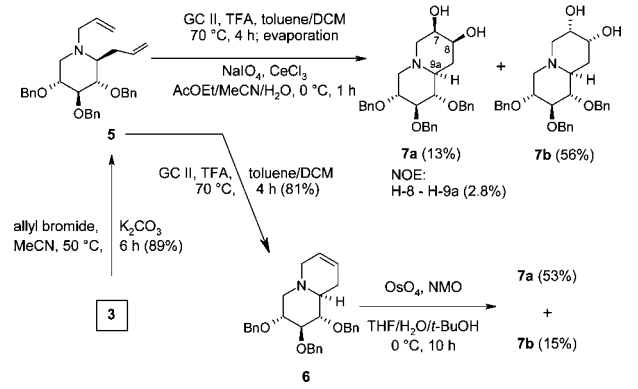
Table 1. Solvent Choice for the Key Step Transformation



solvent	conditions[a]	yield[b] **3**/**4** (%)
THF	*a*	–/34
	b	28/13
toluene	*a*	–/22
	b	74/4
THF/DMPU (4:1)	*a*	–/70
THF/HMPA (4:1)	*a*	–/68
methylene chloride	*a*	–/23
	b	55/0

[a] See Supporting Information (SI) for detailed procedures. [b] Isolated yield. Conversion 90–100% in all cases.

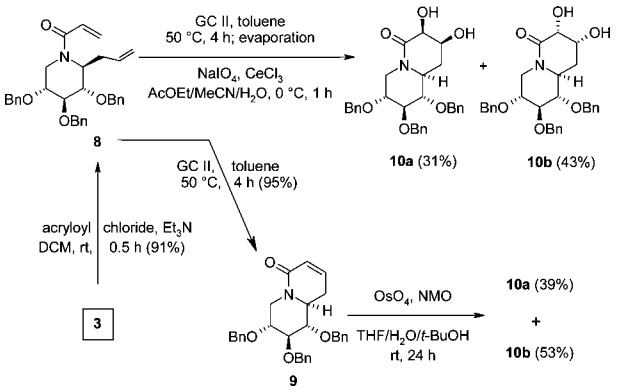
Scheme 2. Synthesis of Polyhydroxylated Quinolizidines **7a** and **7b** via Tandem RCM/*syn*-Dihydroxylation



though much safer variations have been introduced (e.g., Sharpless' AD-mixes),[17] there is still a place for novel dihydroxylation methods. For instance, relatively nonhazardous ruthenium tetroxide can be used (usually with ruthenium trichloride as its precursor). This fast approach, known as flash dihydroxylation, suffers from overoxidation and needs a tedious fine-tuning.[18] The growing use of Ru-based olefin metathesis has resulted in the development of protocols allowing reuse of the catalyst in a subsequent *syn*-dihydroxylation.[19] Moreover, it was shown by Plietker and Niggemann[20] that the high reactivity of RuO_4 can be reduced to some extent by using $NaIO_4$–$CeCl_3$ as the reoxidation system. Therefore, once the RCM of **5** was completed, the solvent was evaporated and the remains of the Grubbs-II catalyst were reused (under Plietker's conditions) yielding **7a** and **7b** as a mixture of diastereomers (69%; 1:4.3) (Scheme 2). The result was satisfying, because application of this methodology in the synthesis of natural products, despite its undeniable advantages, remains very limited.

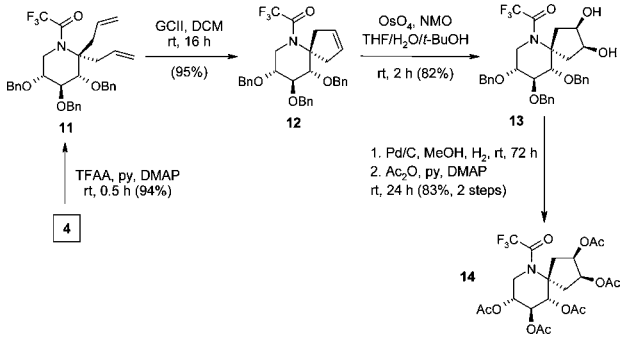
Interestingly, an analogous dihydroxylation reaction with OsO_4 (5 mol %) yielded **7a** and **7b** in a reversed ratio (3.5:1). The relative stereochemistry was determined from 1D-NOE experiments (see Supporting Information (SI)).

Scheme 3. Synthesis of Polyhydroxylated Quinolizidines **10a** and **10b** via Tandem RCM/*syn*-Dihydroxylation



Compound **3** was also converted into the acryloyl derivative **8** (Scheme 3). Its cyclization under RCM conditions (5 mol % of GC-II) proceeded smoothly and afforded the bicyclic derivative **9** in excellent yield. Again, we performed the *syn*-dihydroxylation by taking advantage of the remains of the GC-II. The desired product (a mixture of diastereoisomeric diols: **10a** and **10b**) was obtained in good overall yield (74%) but with poor (1:1.4) selectivity. Catalytic (5 mol %) osmylation of **9** resulted in a similar ratio of diastereomers. Again, 1D-NOE experiments were performed to elucidate the relative stereochemistry (see SI).

Scheme 4. RCM of **4** via Protected Amine Followed by *syn*-Dihydroxylation



(17) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M. *J. Org. Chem.* **1992**, *57*, 2768.

(18) (a) Plietker, B.; Niggemann, M. *Org. Lett.* **2003**, *5*, 3353. (b) Fürstner, A.; Wuchrer, M. *Chem.—Eur. J.* **2006**, *12*, 76.

(19) (a) Scholte, A. A.; An, M. H.; Snapper, M. L. *Org. Lett.* **2006**, *8*, 4759. (b) Beligny, S.; Eibauer, S.; Maechling, S.; Blechert, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 1900. (c) Neisius, N. M.; Plietker, B. *J. Org. Chem.* **2008**, *73*, 3218.

(20) Plietker, B.; Niggemann, M. *J. Org. Chem.* **2005**, *70*, 2402.

Then, we turned our attention to 2,2-diallylpiperidine **4**. Protection of the nitrogen atom in this amine turned out to be not as straightforward as expected. Attempts to install the Cbz-, Boc-, Ns-, and Ts- groups failed. The presence of the bulky substituents in the proximity of the nitrogen atom seemed to reduce the reactivity. We were, however, pleased to observe that the reaction of **4** with trifluoroacetic anhydride proceeded rapidly and provided the desired protected amine in excellent yield (**11**, 94%, Scheme 4). As expected, the subsequent RCM reaction proceeded smoothly with only 1 mol % of the GC-II and afforded the spiro derivative **12** in excellent yield (95%).

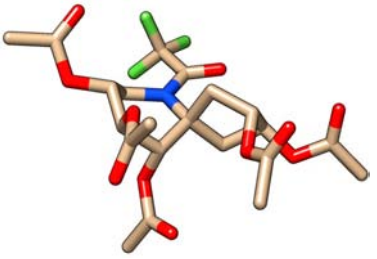
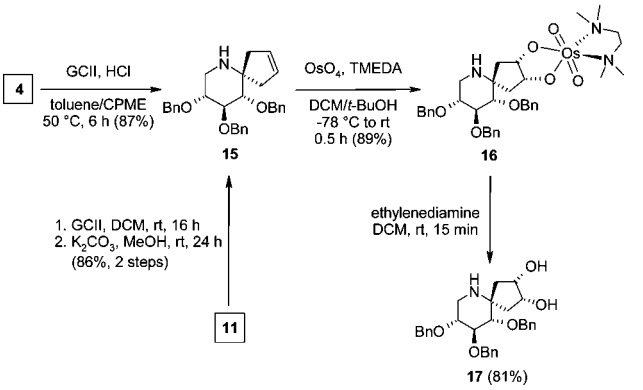


Figure 2. X-ray structure of hexaacetate **14**. Hydrogen atoms are removed for clarity.

This time, however, all attempts to reuse the Grubbs-II catalyst for the subsequent *syn*-dihydroxylation resulted in a very low conversion. In contrast, osmium tetroxide catalyzed (5 mol %) dihydroxylation yielded **13** in good yield (82%) as A single diastereoisomer. The configuration of this product was determined by X-ray analysis of its hexaacetate **14** (Figure 2), prepared by standard methodology from **13** as shown in Scheme 4.

We also tried the RCM of **4** with the N-atom blocked in situ, as in the case of **5**. Of the Brønsted acids tested ($MeSO_3H$, CH_3COOH, CF_3COOH, TsOH, HCOOH, HCl), only HCl (handled as a 3 M solution in cyclopentylmethyl ether, CPME) allowed us to obtain the desired spiro-compound **15** (87%; 10 mol % of GC-II) (Scheme 5). Unfortunately, all attempts to reuse the GC-II catalyst in the subsequent *syn*-dihydroxylation resulted in a complicated mixture of products. On the other hand, catalytic osmylation suffered from a very low conversion. This prompted us to perform an equimolar variant of OsO_4 dihydroxylation (Donohoe conditions),[21] which afforded compound **16** (easily purified by chromatography); the formation of such stable osmates has been already reported.[10b,22] Osmate **16** was transformed into the free diol **17** by treatment with an excess of ethylenediamine. Analysis of the NOE interactions (see SI) indicated that the Os species approached the double bond of **15** from the opposite face than it did in the case of olefin **12**. It is known that a H-bond donor (free amine in case of **15**) may act as a directing group in such transformations.[23]

Scheme 5. Direct RCM of **4** Followed by *syn*-Dihydroxylation



In summary, we have devised a useful methodology for the rapid synthesis of novel polyhydroxylated quinolizidines and azaspiro[4.5]decanes from D-xylose. In the key step, we took advantage of a rarely used addition of a Grignard reagent to ω-halonitrile. We have demonstrated that it is possible to add a second equivalent of allylmagnesium bromide to the transitory imine, thus offering a simple access to polyhydroxylated 2,2-diallylpiperidines. In two cases, we were able to simplify the subsequent steps by reusing a Ru-based olefin-metathesis catalyst in the *syn*-dihydroxylation step.

Acknowledgment. Financial support from the Grant: POIG.01.01.02-14-102/09 (part-financed by the European Union within the European Regional Development Fund) is acknowledged.

Supporting Information Available. Detailed experimental procedures, full characterization, copies of ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(21) Donohoe, T. J.; Moore, P. R.; Waring, M. J.; Newcombe, N. J. *Tetrahedron Lett.* **1997**, *38*, 5027.

(22) (a) Rivero, M. R.; de la Rosa, J. C.; Carretero, J. C. *J. Am. Chem. Soc.* **2003**, *125*, 14992. (b) Lang, Y.; Souza, F. E. S.; Xu, X.; Taylor, N. J.; Assoud, A.; Rodrigo, R. *J. Org. Chem.* **2009**, *74*, 5429.

(23) (a) Donohoe, T. J.; Blades, K.; Moore, P. R.; Waring, M. J.; Winter, J. J. G.; Helliwell, M.; Newcombe, N. J.; Stemp, G. *J. Org. Chem.* **2002**, *67*, 7946. (b) Donohoe, T. J.; Bataille, C. J. R.; Innocenti, P. Hydrogen-Bonding-Mediated Directed Osmium Dihydroxylation. *Organic Reactions*; John Wiley and Sons Ltd.: 2012; Vol. 76.

The authors declare no competing financial interest.