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New Polyhydroxylated Pyrrolidines Derived from Enantiopure 3,6-Dihydro-2*H*-1,2-oxazines

Robert Pulz, Ahmed Al-Harrasi, and Hans-Ulrich Reissig*

Institut für Chemie - Organische Chemie, Freie Universität Berlin, Takustrasse 3, D-14195 Berlin, Germany

Hans.Reissig@Chemie.FU-Berlin.de

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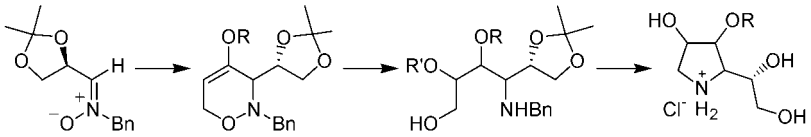
ABSTRACT

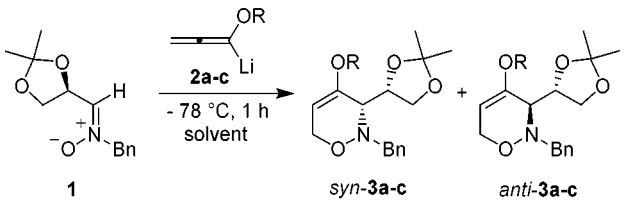


Diastereoselective hydroborations of enantiopure 3,6-dihydro-2*H*-1,2-oxazines led to dihydroxy-substituted 1,2-oxazines. Samarium diiodide-induced N–O bond cleavage generated 1,4-amino alcohols which were recyclized to polyhydroxylated pyrrolidines which are potential glycosidase inhibitors.

We recently reported[1] a new entry to enantiopure 3,6-dihydro-2*H*-1,2-oxazines by addition of lithiated methoxyallene **2a** to (*R*)-glyceraldehyde-derived nitrone **1**[2] and subsequent cyclization of the primary allene adducts. In THF, 1,2-oxazine **3a** was formed with excellent *syn*-selectivity whereas precomplexation of **1** with Et_2AlCl in Et_2O afforded **3a** with high *anti*-preference. Thus, both diastereomers of **3a** were obtained in enantiopure form. Lithiated benzyloxyallene **2b** and 2-(trimethylsilyl)ethoxyallene **2c** furnished the corresponding *syn*-1,2-oxazines **3b**,**c** in good yield and diastereoselectivity (Scheme 1).

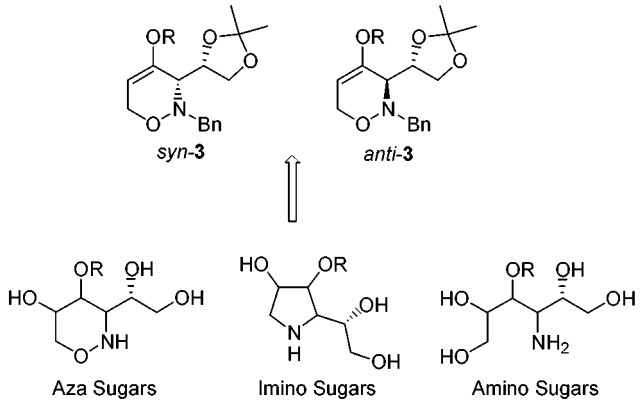
1,2-Oxazines are known to be valuable intermediates in synthetic organic chemistry.[3] We earlier accomplished the stereodivergent synthesis of 3-methoxypyrrolidines[4] and of enantiopure furan and pyran derivatives[5] starting from **3a** and **3c**. Oxygenation of the enol ether double bond of **3** should lead to protected azasugar derivatives (Scheme 2).

Scheme 1



a	R = Me	THF	81 %	d.r. = 98 : 2
a	R = Me	Et_2O, Et_2AlCl	61 %	d.r. = 3 : 97
b	R = Bn	THF	68 %	d.r. = 94 : 6
c	R = TMSE	THF	76 %	d.r. = 97 : 3

Scheme 2



Cleavage of the N−O bond should afford amino sugars, while recyclization should give imino sugar derivatives, which are known to be strong glycosidase inhibitors.[6] Herein we present the diastereoselective hydroboration of

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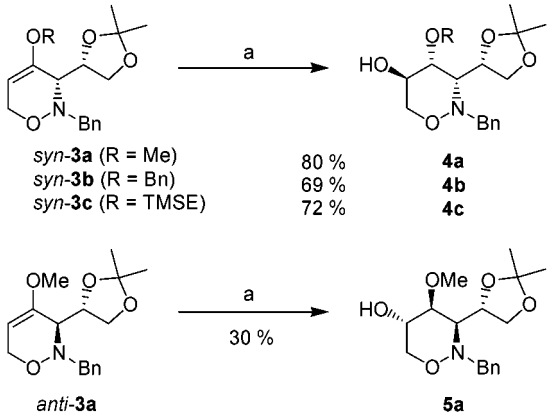
1,2-oxazines **3** and subsequent syntheses of polyhydroxylated pyrrolidine derivatives.

Treatment of *syn*-**3a** with borane−THF complex[7] and subsequent oxidation of the boron species led to 5-hydroxy-substituted 1,2-oxazine **4a** as a single diastereomer which was isolated in good yield after chromatography (Scheme 3). The relative configuration of the newly generated

Scheme 3[a]

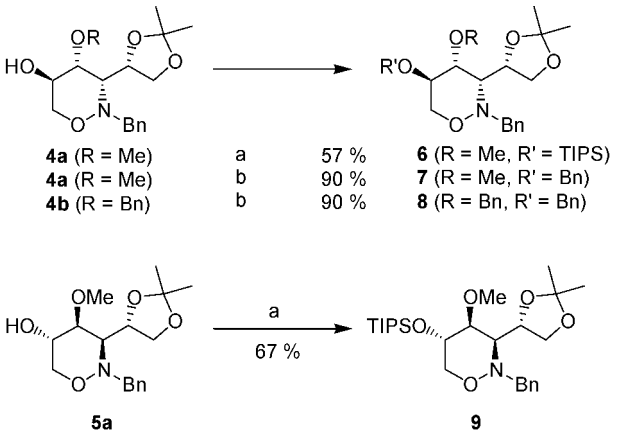


[a] Reagents and conditions: (a) BH_3·THF, THF, −30 °C to rt, 3 h rt then NaOH, H_2O_2, −10 °C to rt, overnight rt.

stereocenter was proven by NOESY experiments. As expected the addition of BH_3 to the enol ether double bond proceeds to the sterically less hindered side of the 1,2-oxazine ring. Reaction of **3b** provided **4b** as single diastereomer under the same conditions in good yield. A similar result could be obtained by reaction of **3c** with BH_3 which furnished 1,2-oxazine **4c**. Interestingly, treatment of *anti*-**3a** with borane under standard conditions afforded the expected product **5a** only in moderate yield.[8]

To avoid problems during subsequent cyclization of the N−O bond cleaved products, we protected the free hydroxy groups. Thus, treatment of **4a** and **5a** with TIPSOTf under standard reaction conditions furnished protected 1,2-oxazines

Scheme 4[a]

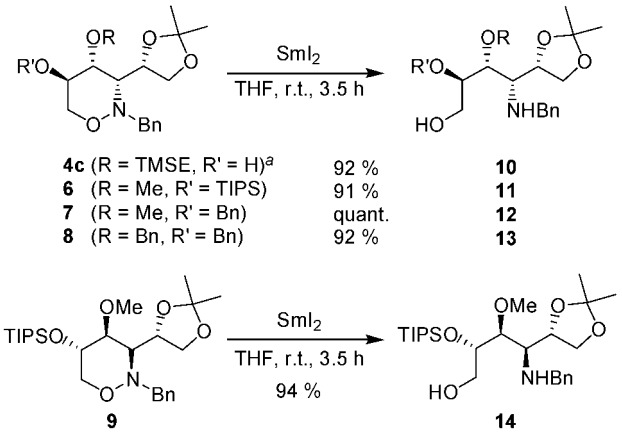


[a] Reagents and conditions: (a) TIPSOTf, Et_3N, CH_2Cl_2, rt, 1 d; (b) NaH, BnBr, DMF, rt, overnight.

6 and **9** in moderate yield while benzylation of **4a** and **4b** led to **7** and **8** in excellent yield (Scheme 4).

Attempts to cleave the N−O bond by known methods such as catalytic hydrogenation,[9] Zn/acetic acid,[10] or $Mo(CO)_6$[11] did not yield satisfactory results with our substrates. Samarium diiodide is also well-known to affect N−O reductive cleavage reactions.[12] Reaction of **4c** with SmI_2 afforded amino alcohol **10** in excellent yield and high purity. No further purification was required. Similar results were obtained with 1,2-oxazine derivatives **6**−**9** leading to the expected amino alcohols **11**−**14** in 91% to quantitative yield (Scheme 5).

Scheme 5

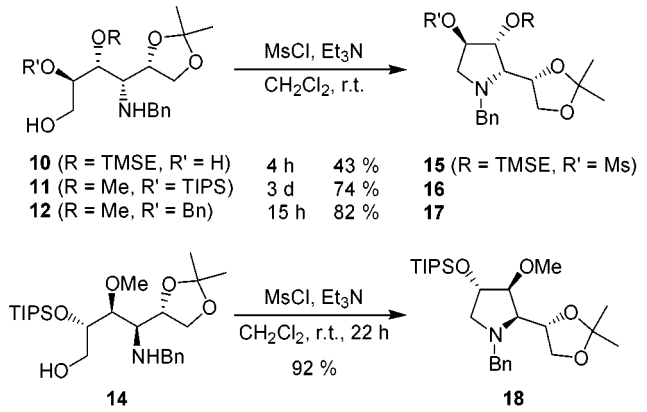


[a] 3 h.

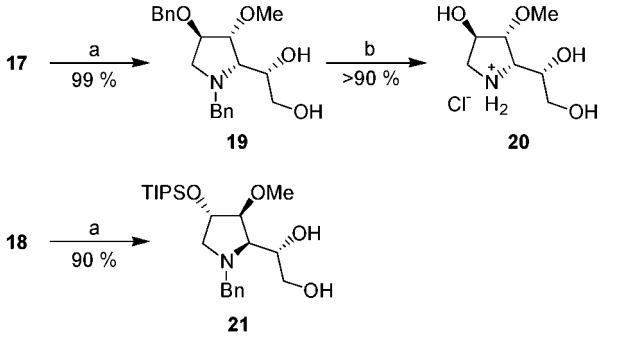
The synthesis of polyhydroxylated pyrrolidine derivatives was achieved in a one-pot procedure by treatment of amino

(1) Schade, W.; Reissig, H.-U. *Synlett* **1999**, 632−634.
(2) Synthesis: Dondoni, A.; Franco, S.; Junquera, F.; Merchan, F. L.; Merino, P.; Tejero, T. *Synth. Commun.* **1994**, *24*, 2537−2550.
(3) Recent reviews: (a) Streith, J.; Defoin, A. *Synlett* **1996**, 189−200. (b) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137−165. (c) Vogt, P. F.; Miller, M. J. *Tetrahedron* **1998**, *54*, 1317−1348.
(4) Pulz, R.; Watanabe, T.; Schade, W.; Reissig, H.-U. *Synlett* **2000**, 983−986.
(5) Pulz, R.; Al-Harrasi, A.; Reissig, H.-U. *Synlett* **2002**, 817−819.
(6) (a) Wong, C.-H.; Halcomb, R. L.; Ichikawa, Y.; Kajimoto, T. *Angew. Chem.* **1995**, *107*, 453−474 and 569−593; *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 412−432 and 521−546. (b) *Iminosugars as Glycosidase Inhibitors*; Stütz, A. E., Ed.; Wiley-VCH: Weinheim, 1999. (c) Heightman, T. D.; Vasella, A. T. *Angew. Chem.* **1999**, *111*, 794−815; *Angew. Chem., Int. Ed.* **1999**, *38*, 750−770. (d) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645−1680. (e) Lillelund, V. H.; Jensen, H. H.; Liang, X.; Bols, M. *Chem. Rev.* **2002**, *102*, 515−553.
(7) Achab, S.; Das, B. C. *J. Chem. Soc., Perkin Trans. 1* **1991**, 727−732.
(8) After protection of the crude product and subsequent chromatography two side products with cleaved N−O bond were isolated in 41% yield. Similar results were obtained with *anti*-**3b** and *anti*-**3c**.
(9) See ref 4 and references therein.
(10) Denis, J.-N.; Tchertchian, S.; Tomassini, A.; Vallee, Y. *Tetrahedron Lett.* **1997**, *38*, 5503−5506.

Scheme 6



Scheme 7[a]



[a] Reagents and conditions: (a) *p*-TsOH, MeOH, rt, 2 d; (b) H_2, Pd/C, HCl/MeOH, MeOH, rt, 22 h.

alcohols **11**, **12**, and **14** with 1.1−1.5 equiv of mesyl chloride and triethylamine (Scheme 6). After column chromatography, cyclization products **16**−**18** were isolated in moderate to very good yields. One equivalent of mesyl chloride was not sufficient to perform the cyclization of **10**. However, use of 2 equiv furnished the *O*-mesylated pyrrolidine **15** in moderate yield, which should allow introduction of other groups at C-4 by nucleophilic substitution.

Cleavage of the dioxolane group was achieved by treatment with *p*-toluenesulfonic acid. Thus, reaction of **17** led to compound **19** in almost quantitative yield, and **18** was deprotected under the same reaction conditions yielding **21** (Scheme 7). Catalytic hydrogenation of **19** with palladium on charcoal in the presence of HCl led to O^3-methylated 1,4-dideoxy-1,4-imino-D-iditol hydrochloride **20** in high yield and purity.

In conclusion, we have shown a new route to enantiopure imino sugar derivatives. The diol side chain provides a suitable tool for further synthetic operations. All compounds were prepared from (*R*)-glyceraldehyde-derived nitrone **1** and alkoxyallenes **2** in few straightforward steps which can be carried out in gram scale. This again demonstrates the versatility and practicability of alkoxyallenes as C_3 building blocks for stereoselective syntheses of heterocycles.[13]

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Supporting Information Available: Detailed description of experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) (a) Baraldi, P. G.; Barco, A.; Benetti, S.; Manfredini, S.; Simoni, D. *Synthesis* **1987**, 276−278. (b) Cicchi, S.; Goti, A.; Brandi, A.; Guarna, A.; De Sarlo, F. *Tetrahedron Lett.* **1990**, *31*, 3351−3354. (c) Zhang, D.; Süling, C.; Miller, M. J. *J. Org. Chem.* **1998**, *63*, 885−888.

(12) (a) Keck, G. E.; McHardy, S. F.; Wager, T. T. *Tetrahedron Lett.* **1995**, *36*, 7419−7422. (b) Chiara, J. L.; Destabel, C.; Gallego, P.; Marco-Contelles, J. *J. Org. Chem.* **1996**, *61*, 359−360.

(13) (a) Reissig, H.-U.; Hormuth, S.; Schade, W.; Okala Amombo, M.; Watanabe, T.; Pulz, R.; Hausherr, A.; Zimmer, R. Lectures in Heterocyclic Chemistry Vol XVI. *J. Heterocycl. Chem.* **2000**, *37*, 597−606. (b) Reissig, H.-U.; Schade, W.; Okala Amombo, M. G.; Pulz, R.; Hausherr, A. *Pure Appl. Chem.* **2002**, *74*, 175−180.