

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

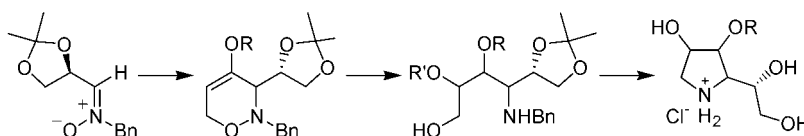
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ABSTRACT



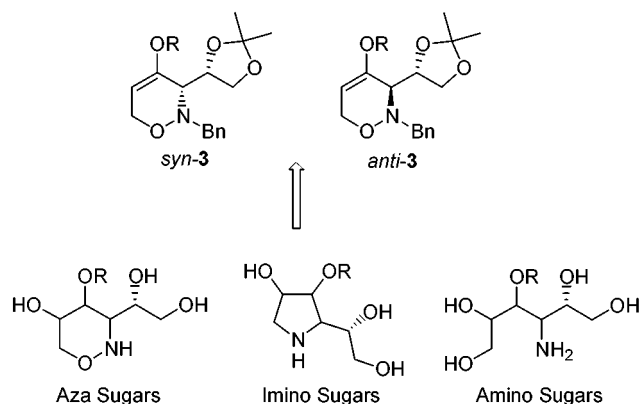
Diastereoselective hydroborations of enantiopure 3,6-dihydro-2*H*-1,2-oxazines led to dihydroxy-substituted 1,2-oxazines. Samarium diiodide-induced N–O bond cleavage generated 1,4-amino alcohols which were recycled to polyhydroxylated pyrrolidines which are potential glycosidase inhibitors.

We recently reported¹ a new entry to enantiopure 3,6-dihydro-2*H*-1,2-oxazines by addition of lithiated methoxyallene **2a** to (*R*)-glyceraldehyde-derived nitron **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 Et₂AlCl in Et₂O 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

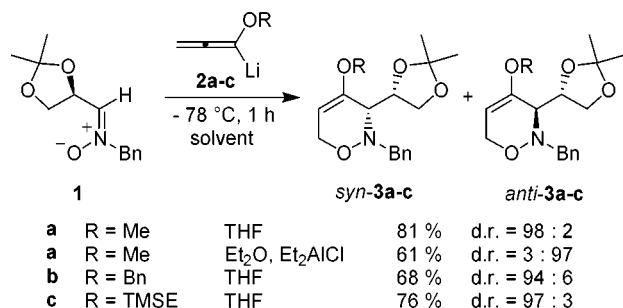
stereodivergent synthesis of 3-methoxypyrrolidines⁴ and of enantiopure furan and pyran derivatives⁵ starting from **3a** and **3c**. Oxygenation of the enol ether double bond of **3** should lead to protected azasugar derivatives (Scheme 2).

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

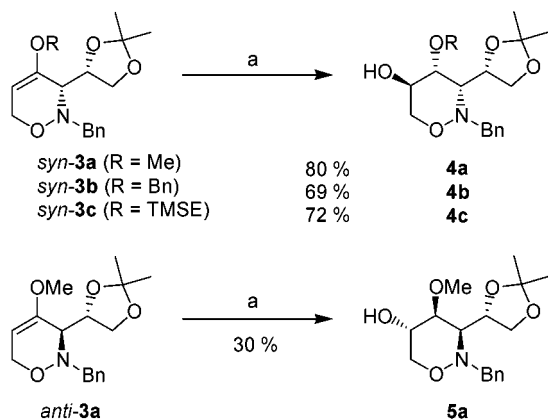
Scheme 1



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

Treatment of *syn*-**3a** with borane–THF complex⁷ 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

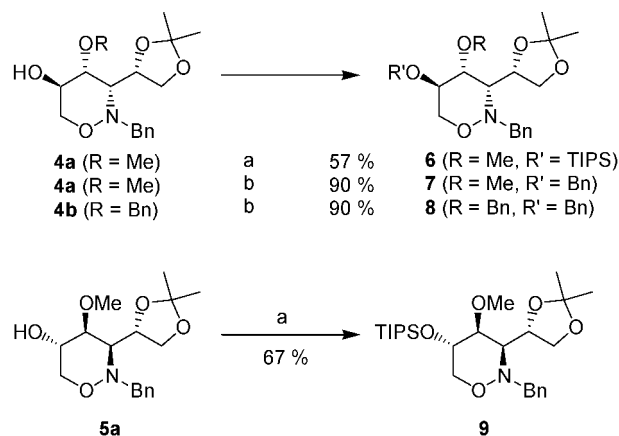


^a Reagents and conditions: (a) $\text{BH}_3 \cdot \text{THF}$, THF, -30°C to rt, 3 h rt then NaOH, H_2O_2 , -10°C to rt, overnight rt.

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

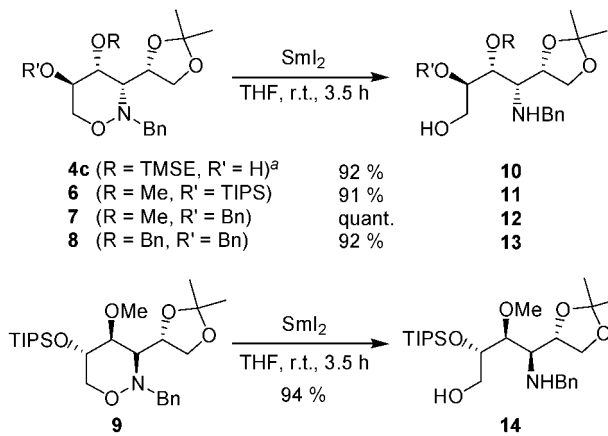


^a Reagents and conditions: (a) TIPSOTf, Et_3N , CH_2Cl_2 , rt, 1 d; (b) NaH, BnBr, DMF, rt, overnight.

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 $\text{Mo}(\text{CO})_6$ 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



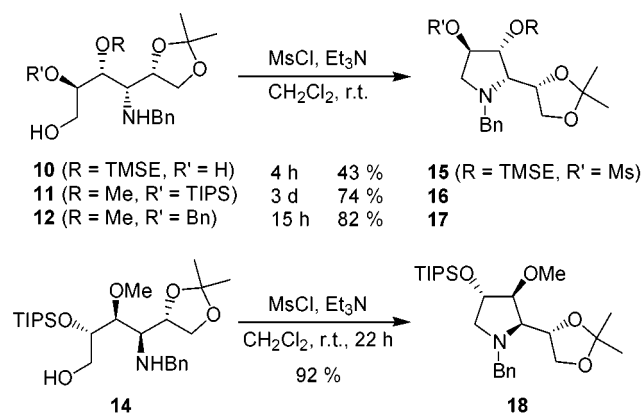
^a 3 h.

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



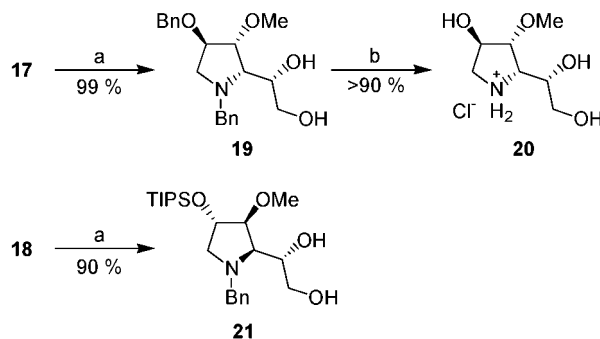
alcohols **11**, **12**, and **14** with 1.1–1.5 equiv of mesyl chloride and triethylamine (Scheme 6). After column chromatography, cyclization products **16**–**18** were isolated in moderate to very good yields. One equivalent of mesyl chloride was not sufficient to perform the cyclization of **10**. 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-idoitol 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

(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.

Scheme 7^a

^a Reagents and conditions: (a) *p*-TsOH, MeOH, rt, 2 d; (b) H₂, Pd/C, HCl/MeOH, MeOH, rt, 22 h.

suitable tool for further synthetic operations. All compounds were prepared from (*R*)-glyceraldehyde-derived nitron **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 C₃ 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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(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.