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# Glycal-mediated synthesis of enantiomerically pure 5-substituted isoxazoles containing a differentially *O*-benzylated glycerol moiety

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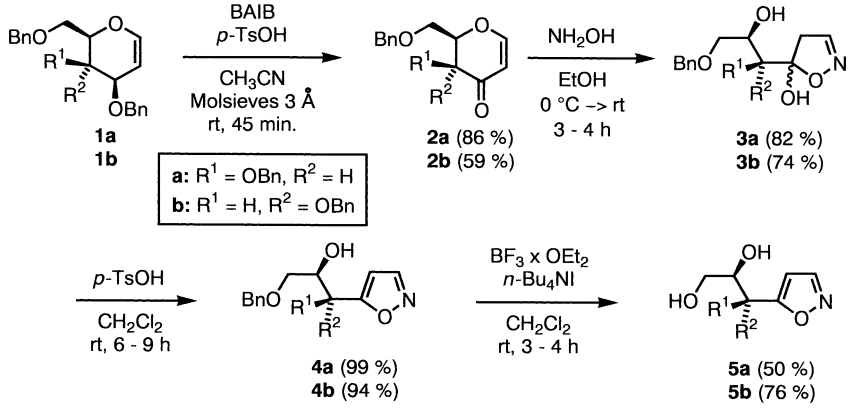
**Abstract**—A short, glycal-mediated synthesis of new chiral 5-substituted isoxazoles bearing a differentially *O*-protected glycerol moiety in the side chain has been accomplished. An X-ray crystallographic structural analysis confirmed the structural assignment of the new products. © 2002 Elsevier Science Ltd. All rights reserved.

Isoxazole containing natural and non natural compounds are interesting because of their biological activities[1] e.g. as fungicides,[2] herbicides,[3] or as nicotinic acetylcholine receptor ligands.[4] Typical procedures[1a] include the cycloaddition of nitrile oxides with alkynes, or the condensation of 1,3-dicarbonyl compounds or heteroanalogues[5] with hydroxylamine. Taking into account the plethora of realized isoxazole syntheses, there are only few cyclocondensation reactions described leading to enantiomerically pure 5-substituted isoxazoles containing a more complex, stereocenter-bearing side chain.[6] Furthermore, these reactions were carried out with only low to moderate yields, and/or gave isomeric mixtures of 5- and 3-substituted isoxazoles, respectively. A high yielding cyclocondensation of an enaminone with hydroxylamine during the synthesis of isoxazole *C*-nucleosides has been published by Maeba and co-workers.[7]

Herein we report on a short, glycal-mediated synthesis of the enantiomerically pure, 5-substituted isoxazoles **4**–**7** with differentially *O*-benzylated alcohol functionalities in the glycerol[8] side chain. Tri-*O*-benzylgalactal (**1a**) and tri-*O*-benyzlglucal (**1b**), quantitatively obtained by perbenzylation of the starting glucals with sodium hydride/benzyl bromide, have been selectively




**Scheme 1.** Syntheses of the isoxazoles **4** and **5**.

*Keywords*: glycals; isoxazoles; glycerol; hypervalent iodine; carbohydrates.

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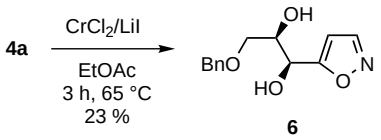


**Scheme 2.** Synthesis of **6**.

oxidized to enones **2** with bis-acetoxyiodobenzene (BAIB) and *para*-toluenesulfonic acid (Koser's reagent[9]) following a modified[10] procedure formerly described by Kirschning[11] (Scheme 1). Thus, we were able to raise the yields respectively up to 86% for **2a** (lit.:[11] 57%) and 59% for **2b** (lit.:[11] 49%). The fact that the yield of **2b** could not be significantly altered is in accordance with a favored formation of side products in this reaction.[12]

Reaction of enones **2** with one equivalent hydroxylamine, prepared from hydroxylamine hydrochloride and sodium hydroxide as ethanolic solution,[13] afforded the isoxazolines **3** as inseparable epimeric mixtures in good yield. The latter were dehydrated in high yield with *para*-toluenesulfonic acid[7] in dichloromethane at room temperature to give isoxazoles **4** with a free hydroxyl at C-2′ as target compounds. Deprotection of the primary benzyl ether leading to the diols **5** was achieved in a selective manner with boron trifluoride etherate (1.2 equiv.) and tetrabutyl ammonium iodide in dichloromethane.[14] In alternative, debenzylation of **4a** with chromium(II) chloride/lithium iodide[15,16] led regioselectively to diol **6** (Scheme 2). The yield of 23% is rather poor, but this reaction sequence has not been optimized.

Alcohol **4a** was then converted into mesylate **7** which could be recrystallized from ethyl acetate to give single crystals suitable for X-ray analysis. The formation and the X-ray crystal structure[17] of **7** is shown in Scheme 3.

In summary, a short and efficient synthesis of new, enantiomerically pure 5-substituted isoxazoles with different *O*-benzyl protection in the glycerol side chain has been accomplished starting from D-galactal and D-glucal, respectively. This opens firm ground for further functionalization of the hydroxy groups which should lead to a variety of related derivatives. An X-ray crystallographic structural analysis of mesylate **7** confirmed the structural assignment of the new products, and the biological activities of all the new compounds will be tested in the near future.

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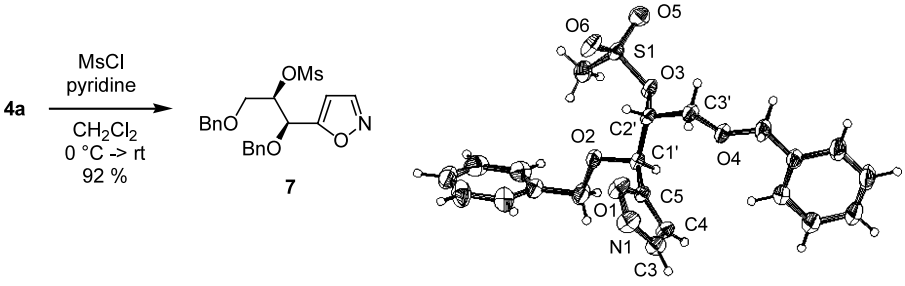
## References

1. (a) Grünanger, P.; Vita-Finzi, P. In *The Chemistry of Heterocyclic Compounds*, *Isoxazoles*, *Part* 1; Weissberger, A.; Taylor, E. C., Eds.; Wiley-Interscience: New York, 1991; (b) Johansen, T. N.; Ebert, B.; Bräuner-Osborne, H.; Didriksen, M.; Christensen, I. T.; Søby, K. K.; Madsen, U.; Krogsgaard-Larsen, P.; Brehm, L. *J. Med. Chem.* **1998**, *41*, 930–939; (c) Ku, Y. Y.; Grieme, T.; Sharma, P.; Pu, Y.-M.; Raje, P.; Morton, H.; King, S. *Org. Lett.* **2001**, *3*, 4185–4187 and references cited therein; (d) Elliott, J. D. *Chem. Abstr.* **1997**, *127*, 205581.
2. (a) Martins, M. A. P.; Flores, A. F. C.; Bastos, G. P.; Sinhorin, A.; Bonacorso, H. G.; Zanatta, N. *Tetrahedron Lett.* **2000**, *41*, 293–297 and references cited therein; (b) Ziegler, H.; Trah, S.; Zurfluh, R.; O'Sullivan, A. C. *Chem. Abstr.* **1997**, *126*, 186095.
3. Newton, T. W. *Chem. Abstr.* **1998**, *129*, 119078.
4. Silva, N. M.; Tributino, J. L. M.; Miranda, A. L. P.; Barreiro, E. J.; Fraga, C. A. M. *Eur. J. Med. Chem.* **2002**, *37*, 163–170.
5. For a review see: Pätzel, M.; Liebscher, J. *Synthesis* **1995**, 879–894.
6. (a) Klein, U.; Steglich, W. *Liebigs Ann. Chem.* **1989**, 247–254; (b) Falorni, M.; Giacomelli, G.; Spanedda, A. M. *Tetrahedron: Asymmetry* **1998**, *9*, 3039–3046; (c) Adlington, R. M.; Baldwin, J. E.; Catterick, D.; Pritchard, G. J.; Tang, L. T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2311–2316.
7. Maeba, I.; Ito, Y.; Wakimura, M.; Ito, C. *Heterocycles* **1993**, *36*, 1617–1623.
8. For synthetic studies towards chiral glycerols, see: (a) Giannis, A.; Münster, P.; Sandhoff, K.; Steglich, W. *Tetrahedron* **1988**, *44*, 7177–7180; (b) Prasad, K.; Estermann, H.; Chen, C.-P.; Repic, O.; Hardtmann, G. E. *Tetrahedron: Asymmetry* **1990**, *1*, 421–424.




**Scheme 3.** Synthesis and X-ray structure of **7**. Thermal ellipsoids are shown with 30% probability.

9. For a recent review, see: Koser, G. F. *Aldrichim. Acta* **2001**, *34*, 89–102.
10. The oxidation was performed following the procedure described in Ref. 11 without aqueous work-up. Instead, the solvent was evaporated at room temperature and the crude product was immediately subjected to flash column chromatography on silica gel. Analytical data of the obtained products were in full accordance with that reported.
11. Kirschning, A. *J. Org. Chem.* **1995**, *60*, 1228–1232.
12. Kirschning, A. *Eur. J. Org. Chem.* **1998**, 2267–2274.
13. Greven, R.; Jütten, P.; Scharf, H.-D. *J. Org. Chem.* **1993**, *58*, 3742–3747.
14. Mandal, A. K.; Soni, N. R.; Ratnam, K. R. *Synthesis* **1985**, 274–275.
15. (a) Falck, J. R.; Barma, D. K.; Venkataraman, S. K.; Baati, R.; Mioskowski, C. *Tetrahedron Lett.* **2002**, *43*, 963–966; (b) Falck, J. R.; Barma, D. K.; Baati, R.; Mioskowski, C. *Angew. Chem., Int. Ed.* **2001**, *40*, 1281–1283.
16. Compound **4a**: Colorless oil. $[\alpha]_D^{20}=-66$ (*c* 4.7, $CHCl_3$). $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 2.55 (bs, 1H, OH); 3.40 (dd, $J=10/5$ Hz, 1H, 3′-H); 3.55 (dd, $J=10/5$ Hz, 1H, 3′-H); 4.08 (q, $J=5$ Hz, 1H, 2′-H); 4.42 (d, $J=11$ Hz, 1H, Bn-H); 4.46–4.49 (m, 2H, Bn-H); 4.60 (d, $J=11$ Hz, 1H, Bn-H); 4.80 (d, $J=5$ Hz, 1H, 1′-H); 6.29 (d, $J=2$ Hz, 1H, 4-H); 7.22–7.40 (m, 10H, aromat.-H); 8.22 (d, $J=2$ Hz, 1H, 3-H). $^{13}C$ NMR (50.3 MHz, $CDCl_3$): $\delta$ 69.8 (C-3′); 72.0 (C-2′); 72.2, 73.4 (C-Bn); 73.6 (C-1′); 102.5 (C-4); 127.7, 128.1, 128.3, 128.4, 136.8, 137.6 (C-aromat.); 150.0 (C-3); 169.4 (C-5).
Compound **4b**: Colorless oil. $[\alpha]_D^{20}=+55$ (*c* 4.6, $CHCl_3$). $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 2.53 (bs, 1H, OH); 3.55 (dd, $J=10/4$ Hz, 1H, 3′-H); 3.63 (dd, $J=10/5$ Hz, 1H, 3′-H); 4.15 (ddd, $J=7/5/4$ Hz, 1H, 2′-H); 4.36 (d, $J=12$ Hz, 1H, Bn-H); 4.47–4.50 (m, 2H, Bn-H); 4.53 (d, $J=12$ Hz, 1H, Bn-H); 4.70 (d, $J=7$ Hz, 1H, 1′-H); 6.30 (d, $J=2$ Hz, 1H, 4-H); 7.20–7.36 (m, 10H, aromat.-H); 8.22 (d, $J=2$ Hz, 1H, 3-H). $^{13}C$ NMR (50.3 MHz, $CDCl_3$): $\delta$ 70.0 (C-3′); 71.6 (C-2′); 71.9, 73.4 (C-Bn); 73.6 (C-1′); 102.6 (C-4); 127.8, 128.0, 128.4, 136.9, 137.6 (C-aromat.); 150.1 (C-3); 169.6 (C-5).
Compound **5a**: Colorless waxy solid. $[\alpha]_D^{20}=-119$ (*c* 2.2, $CHCl_3$). $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 2.04 (t, $J=6$ Hz, 1H, 3′-OH); 2.91 (bs, 1H, 2′-OH); 3.49 (ddd, $J=12/6/4$ Hz, 1H, 3′-H); 3.66 (ddd, $J=12/6/4$ Hz, 1H, 3′-H); 3.97 (ddd, $J=7/4/4$ Hz, 1H, 2′-H); 4.42 (d, $J=11$ Hz, 1H, Bn-H); 4.61 (d, $J=11$ Hz, 1H, Bn-H); 4.73 (d, $J=7$ Hz, 1H, 1′-H); 6.36 (d, $J=2$ Hz, 1H, 4-H); 7.26–7.39 (m, 5H, aromat.-H); 8.26 (d, $J=2$ Hz, 1H, 3-H). $^{13}C$ NMR (50.3 MHz, $CDCl_3$): $\delta$ 62.6 (C-3′); 72.1 (C-Bn); 73.1, 73.8 (C-1′,2′); 102.8 (C-4); 128.2, 128.3, 128.6, 136.6 (C-aromat.); 150.2 (C-3); 168.9 (C-5).
Compound **5b**: Yellow crystals. Mp 75°C ($CHCl_3$). $[\alpha]_D^{20}=+100$ (*c* 3.1, $CHCl_3$). $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 2.57 (bs, 1H, OH); 3.18 (bs, 1H, OH); 3.66 (dd, $J=10/4$ Hz, 1H, 3′-H); 3.70 (dd, $J=10/4$ Hz, 1H, 3′-H); 4.01 (dt, $J=6/4$ Hz, 1H, 2′-H); 4.39 (d, $J=11$ Hz, 1H, Bn-H); 4.56 (d, $J=11$ Hz, 1H, Bn-H); 4.67 (d, $J=6$ Hz, 1H, 1′-H); 6.31 (d, $J=2$ Hz, 1H, 4-H); 7.24–7.38 (m, 5H, aromat.-H); 8.22 (d, $J=2$ Hz, 1H, 3-H). $^{13}C$ NMR (50.3 MHz, $CDCl_3$): $\delta$ 62.9 (C-3′); 72.1 (C-Bn); 72.6, 74.5 (C-1′,2′); 102.8 (C-4); 128.0, 128.2, 128.6, 136.7 (C-aromat.); 150.2 (C-3); 169.5 (C-5).
Compound **6**: Colorless oil. $[\alpha]_D^{20}=+10$ (*c* 0.4, $CHCl_3$). $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 2.04 (bs, 2H, OH); 3.63 (dd, $J=10/5$ Hz, 1H, 3′-H); 3.69 (dd, $J=10/4$ Hz, 1H, 3′-H); 4.10 (ddd, $J=5/4/4$ Hz, 1H, 2′-H); 4.57 (s, 2H, Bn-H); 4.97 (d, $J=4$ Hz, 1H, 1′-H); 6.31 (d, $J=2$ Hz, 1H, 4-H); 7.29–7.38 (m, 5H, aromat.-H); 8.20 (d, $J=2$ Hz, 1H, 3-H). $^{13}C$ NMR (50.3 MHz, $CDCl_3$): $\delta$ 68.2 (C-3′); 71.2, 71.5 (C-1′,2′); 73.8 (C-Bn); 101.5 (C-4); 127.9, 128.1, 128.6, 137.2 (C-aromat.); 150.2 (C-3); 166.8 (C-5).
Compound **7**: Colorless crystals. Mp 82°C ($Et_2O$). $[\alpha]_D^{20}=-7$ (*c* 0.3, $CHCl_3$). $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 2.92 (s, 3H, $CH_3$); 3.54 (dd, $J=11/5$ Hz, 1H, 3′-H); 3.74 (dd, $J=11/3$ Hz, 1H, 3′-H); 4.40 (d, $J=12$ Hz, 1H, Bn-H); 4.42 (d, $J=12$ Hz, 1H, Bn-H); 4.51 (d, $J=12$ Hz, 1H, Bn-H); 4.58 (d, $J=12$ Hz, 1H, Bn-H); 4.97 (d, $J=4$ Hz, 1H, 1′-H); 5.00 (ddd, $J=5/4/3$ Hz, 1H, 2′-H); 6.36 (d, $J=2$ Hz, 1H, 4-H); 7.22–7.37 (m, 10H, aromat.-H); 8.25 (d, $J=2$ Hz, 1H, 3-H). $^{13}C$ NMR (50.3 MHz, $CDCl_3$): $\delta$ 38.4 ($CH_3$); 68.5 (C-3′); 72.3 (C-1′); 72.4, 73.6 (C-Bn); 80.9 (C-2′); 103.7 (C-4); 127.8, 128.0, 128.1, 128.3, 128.5, 136.3, 137.1 (C-aromat.); 150.3 (C-3); 167.3 (C-5).
17. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 184268. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].