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A short asymmetric total synthesis of chloramphenicol using a selectively protected 1,2-diol

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Abstract—A general route for the synthesis of chloramphenicol, thiamphenicol and fluoramphenicol is described. Chloramphenicol has been synthesized in 45% overall yield.

Optically active amino alcohols are important structural fragments found in numerous natural products[1] and their stereoselective synthesis has been a subject of recent interest.[2]

Since its discovery more than 50 years ago, the antibiotic chloramphenicol **A**[3] has been especially effective in the treatment of typhus, dysentery and ocular bacterial infections and a number of syntheses have been described in the literature.[4]

As a part of our work on the synthesis of pharmacologically important natural products involving ring opening reactions of epoxides with nucleophiles[5] we became interested in developing a practical synthesis capable of providing not only chloramphenicol **A**, but also antibiotics such as fluoramphenicol **B**, thiamphenicol **C** and modified analogues (Fig. 1).

1,2-Diols are important structural fragments in numerous natural products and the literature details a number of methods for their synthesis and protection.[6] However, selective monoprotection of 1,2-diols with a stable but easily removable protecting group in a single step is a difficult task.[7] Epoxides can be cleaved under acidic or basic conditions to give alkoxy alcohols but hydrolysis of alkyl ethers requires drastic conditions not always compatible with the synthesis of complex natural products.

We have found that when epoxides are treated with $NaNO_2$ in water in the presence of acetic acid, 1,2-diols are formed with one hydroxyl group selectively masked as a nitrite ester (see Scheme 1 and Table 1).

It was found that the ONO^- nucleophile had a very strong preference for attack from the less hindered carbon of the epoxide, but in the case of styrene oxide the attack took place exclusively at the benzylic position. The advantages of this method are (i) it does not require additional steps for introduction of the protecting group and (ii) the small size of the protecting group exerts little

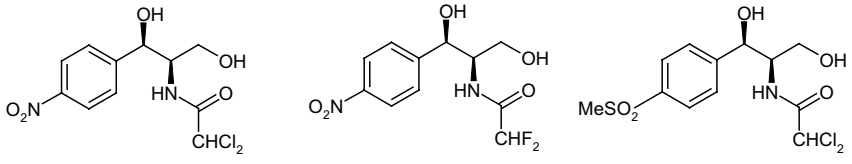

Figure 1.

Keywords: 1,2-Diol; Selective protection; Nitrite ester; Chloramphenicol.
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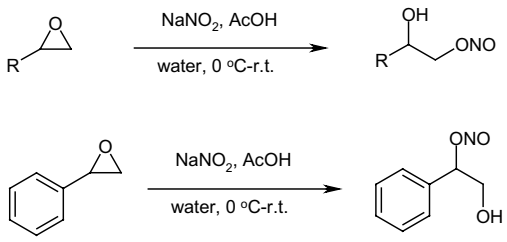


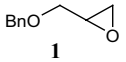
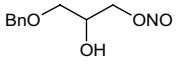
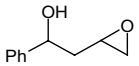
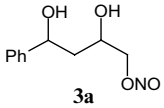
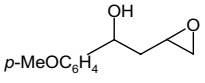
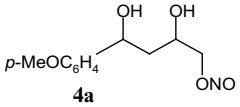
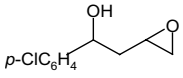
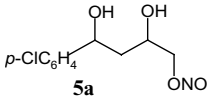
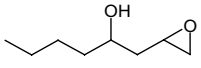
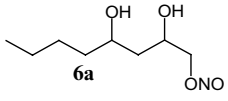
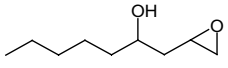
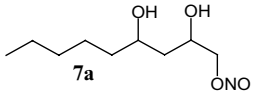
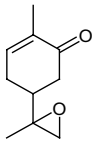
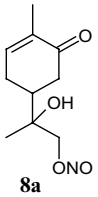
Scheme 1.

steric hindrance for further reactions on the free hydroxyl group. Furthermore, it was observed that the corresponding 2-nitro alcohols were not formed, as indicated by the IR spectra of the crude reaction mixtures.

To assess the general applicability and scope of this method a series of reactions were performed with the selectively protected 1,2-diol **1a** obtained by ring opening of benzoyloxy glycidol.

Treatment of alcohol **1a** with acetic anhydride and pyridine gave the acetate **1b** in quantitative yield. Treatment of alcohol **1a** with CBr_4/PPh_3 in CH_2Cl_2 gave bromide **1c** in 95% yield, which was converted to the nitro compound **1d** in 65% yield by treatment with $NaNO_2$ in DMF. Oxidation of **1a** with PCC in CH_2Cl_2 yielded the ketone **1f** in 90% yield, which was transformed to **1a** by reduction with $NaBH_4$ in methanol. Exposure of the ketone **1f** to CH_3MgI in dry ether afforded **1g** in 87% yield. In all these reactions the 'O–N=O' masking group remained unaffected. Deprotection of nitrite

Table 1. Selectively protected 1,2-diols from epoxides

Entry	Epoxide	Product[a]	Reaction time (h)	Yield[b] (%)
1	 **1**	 **1a**	1.5	90
2	 **2**	 **2a**	2.0	90 (4)[c]
3	 **3**	 **3a**	2.0	92
4	 **4**	 **4a**	2.0	90
5	 **5**	 **5a**	2.0	88
6	 **6**	 **6a**	2.0	88
7	 **7**	 **7a**	2.0	85
8	 **8**	 **8a**	2.0	87

[a] Products were characterized by IR, ^1H NMR and mass spectra.
[b] Yields of isolated pure products.
[c] Yield in the parenthesis indicate that of the other isomer.