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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

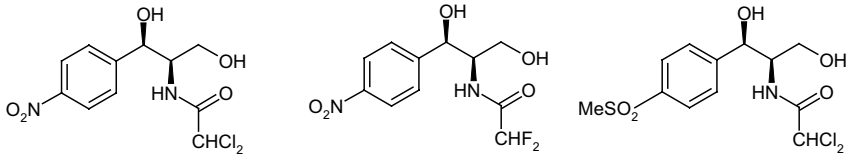

Figure 1.

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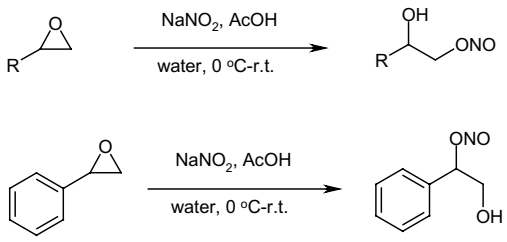


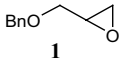
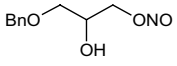
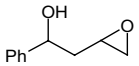
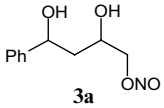
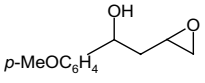
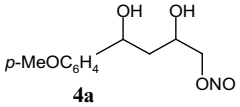
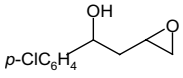
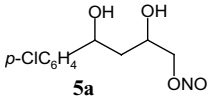
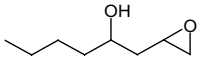
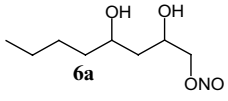
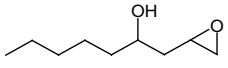
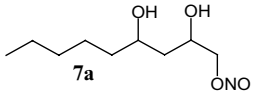
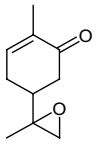
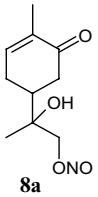
Scheme 1.

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.

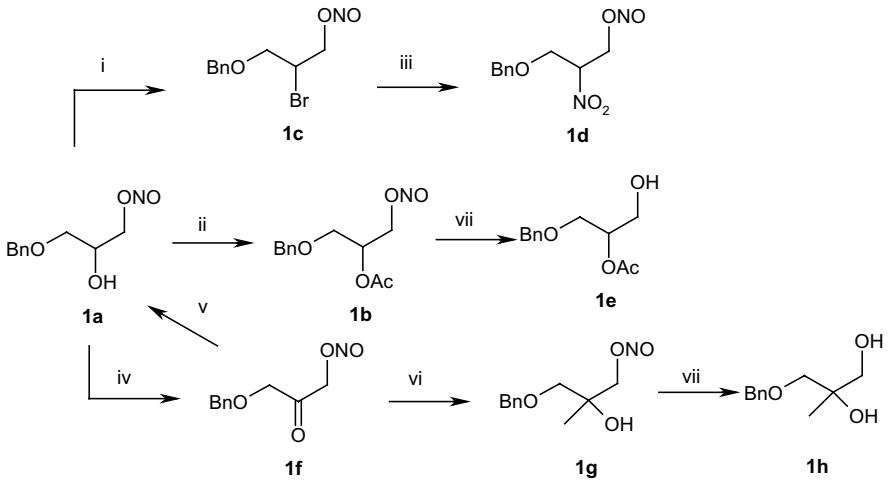
To assess the general applicability and scope of this method a series of reactions were performed with the selectively protected 1,2-diol **1a** obtained by ring opening of benzoyloxy glycidol.

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.



Scheme 2. Reagents and conditions: (i) CBr_4, PPh_3, CH_2Cl_2, 0 °C, 95%; (ii) acetic anhydride, pyridine, rt, 93%; (iii) $NaNO_2$, DMF, rt, 65%; (iv) PCC, CH_2Cl_2, rt, 90%; (v) $NaBH_4$, MeOH, 0 °C, 92%; (vi) CH_3MgI, Et_2O, 0 °C to rt, 87% ; (vii) $NiCl_2{\cdot}6H_2O$/Al, THF, rt, 5–10 min, 90%.

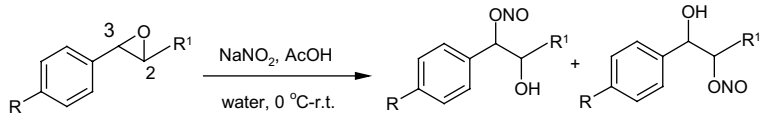
esters is easily effected by catalytic hydrogenation and photolysis,[8] and these methods were incompatible with other sensitive functional groups. However $NiCl_2{\cdot}6H_2O$/Al in THF,[9] a very mild and efficient system for deprotection of nitrite esters gave the deprotected products **1e** and **1h** in around 90% yield. Under these conditions other protected hydroxy groups, for example, an acetate, a benzyl group and an ester were unaffected (Scheme 2).

We next focused our attention on the regioselectivity of epoxide ring opening of substituted methyl 2,3-epoxy-3-phenylpropionates and 2,3-epoxy-3-phenylpropanol. As expected nucleophilic attack took place predominantly at the benzylic position, although a trace amount of the other regioisomer was detected. The regioisomeric ratio was determined by GC analysis of the crude product. Our results are shown in Table 2.

We decided to apply the regioselective epoxide opening to a synthesis of chloramphenicol (Scheme 3). The requisite epoxide (+)-**9** was prepared from methyl cinnamate following a three step sequence[10–12] in 86% yield (over the three steps) and with 98% ee.[13] The epoxide when exposed to $NaNO_2$ and acetic acid in water gave the desired selectively protected diol (+)-**10**[14,15] in 89% yield. When (+)-**10** was treated with diphenyl phosphoryl azide (DPPA)[16] in the presence of DEAD and PPh_3 in THF at 0 °C and then the temperature immediately raised to room temperature, the azide (+)-**11**[14] was isolated in 82% yield. Catalytic hydrogenation of (+)-**11** using 10% Pd–C at 1 atm in methanol afforded (+)-**12** in 97% yield. Acetylation under standard conditions gave the desired product **13** in quantitative yield. Nitration of the aromatic ring followed by acid hydrolysis of the acetyl protecting groups and usual basic work-up generated the free amine. Crystallization (*i*-PrOH/CH_2Cl_2) afforded the pure *p*-nitrophenyl substituted amino diol **14** in good yield. The synthesis was completed by treating **14** with $Cl_2CHCOOMe$ using a literature procedure.[17] The spectral and physical properties of synthetic chloramphenicol were identical with those reported in the literature.[18]

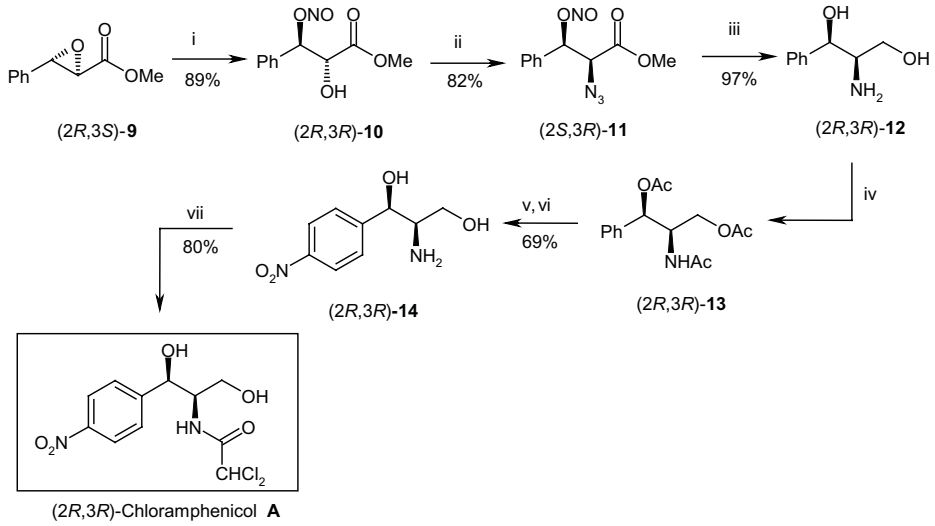
In conclusion, we have described a novel strategy for the synthesis of chloramphenicol, which should be applicable to related compounds. New methods for deprotection of nitrite ester groups and further applications of this strategy in natural product synthesis are being studied.

Table 2. Regioselectivity of epoxide ring opening



Entry	R	R^1	Regioselectivity C3:C2[a]	Yields[b] (%)
1	H	COOMe	89:5	94
2	OMe	COOMe	91:4	95
3	Cl	COOMe	88:5	93
4	H	CH_2OH	90:3	93

[a] GC ratio of the crude product.
[b] Combined isolated yields.



Scheme 3. Reagents and conditions: (i) $NaNO_2$, AcOH, H_2O, 0 °C to rt, 2 h; (ii) DPPA, DEAD, PPh_3, THF, 0 °C to rt, 12 h; (iii) 10% Pd–C, MeOH, 1 atm, rt, 12 h; (iv) Ac_2O, DMAP, pyridine; (v) HNO_3, H_2SO_4, −20 °C to rt, 1.5 h; (vi) aqueous 5% HCl, 90 °C; (vii) $Cl_2CHCOOCH_3$, 90 °C, 1 h.

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13. The enantiomeric excess was measured by HPLC analysis carried out on a Waters 510 HPLC system. Chiracel OD packed in a 4.6 mm i.d × 250 mm SS column was used. Isocratic elution was applied with a mobile phase *n*-hexane 90% and isopropanol 10% at a flow rate of 0.8 mL/min and pressure of 125 psi with UV monitoring at 243 nm.
14. Selected data: (2*R*,3*R*)-**10**: $[\alpha]_D^{20}$ +21.3 (*c* 0.9, $CHCl_3$). IR ($CHCl_3$): 3467, 2957, 1734, 1643, 1615, 1513, 1463, 1249, 1178, 1030, 834 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.10–7.25 (s, 5H), 5.82 (d, *J* = 7.7 Hz, 1H), 3.75 (s, 3H), 3.25 (d, *J* = 7.7 Hz, 1H), 2.85 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 53.1, 56.1, 68.0, 73.5, 113.5, 128.0, 129.8, 159.1, 170.3. MS (*m*/*z*): 248.0 (M^++Na). Anal. Calcd for $C_{10}H_{11}NO_5$: C, 53.33; H, 4.92; N, 6.22. Found: C, 53.38; H, 5.19; N, 6.28. (2*S*,3*R*)-**11**: $[\alpha]_D^{20}$ +24.8 (*c* 1.0, $CHCl_3$). IR ($CHCl_3$): 3424, 2917, 2870, 2107, 1736, 1641, 1514, 1455, 1278, 857, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.10–7.25 (s, 5H), 5.72 (d, *J* = 7 Hz, 1H), 4.10 (d, *J* = 7 Hz, 1H), 3.79 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 53.2, 56.1, 66.7, 73.6, 113.9, 127.7, 130.8, 159.7, 169.3. MS (*m*/*z*): 273.0 (M^++Na). Anal. Calcd for $C_{10}H_{10}N_4O_4$: C, 48.00; H, 4.03; N, 22.39. Found: C 48.17; H, 4.09; N, 22.28.
15. *General procedure for the synthesis of selectively protected 1,2-diols*: To the epoxide (1 mmol) in water (1 mL) was added $NaNO_2$ (2 mmol) and the reaction mixture was cooled in an ice-water bath to about 10 °C. To this was added acetic acid (0.25 mL) and the reaction mixture was allowed to stand at that temperature for 30 min and then at room temperature for an additional 1–1.5 h. The reaction mixture was then extracted with $CHCl_3$, the combined organics washed with H_2O, dried (Na_2SO_4), the solvent evaporated and the crude residue purified by silica gel column chromatography.
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