Asymmetric Synthesis of Chloramphenicol†

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Enantioselective synthesis of chloramphenicol is described by a route using (2*S*,3*R*)-4-nitrophenylglycidol.

Chloramphenicol **14**, a broad-spectrum antibiotic, was isolated from *Streptomyces venezuelae* in 1947.[1] It is widely used to treat typhoid, dysentery and bacterial infections of the eye. The antibiotic is active only in its natural D-*threo* form and is produced by total synthesis, commercially by the addition of benzaldehyde to β-nitroethanol to yield 2-nitro-1-phenylpropane-1,3-diol to give mostly *threo*-racemate, followed by reduction and subsequent transformation to chloramphenicol. Herein, we describe an industrially feasible alternative synthesis.

(*Z*)-(*p*-Nitro)cinnamyl alcohol **3**, easily obtained from *p*-nitroiodobenzene **1** by Pd-coupling[3] with prop-2-ynyl alcohol **2** followed by Lindlar reduction[4] (Pd on $CaCO_3$), was subjected to titanium isopropoxide (TIP) catalysed asymmetric epoxidation (AE)[5] (Scheme 1). The best result was obtained with (+)-diethyl tartrate–*tert*-butyl hydroperoxide (DET–TBHP) at −20 °C for 7 days, affording the desired (2*S*,3*R*)-glycidol **4** in 85% chemical and 95% optical yield (^{19}F NMR of the Mosher ester[6]), $[\alpha]_D^{25}$ −98.3 (*c* 0.2, $CHCl_3$), −63 (*c* 1.0, dioxane), m.p. 110 °C. The published $[\alpha]_D^{25}$ value of the glycidol differs from ours.‡ The same glycidol was also obtained by the asymmetric dihydroxylation (ADH) process (Scheme 2).[7] α,β-Unsaturated esters are well known to be good substrates for the ADH process, resulting in excellent enantiomeric excess (e.e).[8] Thus by treating ethyl (*p*-nitro)-cinnamate **5** with OsO_4–$K_3Fe(CN)_6$ and hydroquinidine *p*-chlorobenzoate (DHQD), the *threo*-diol **6** was obtained in 89% chemical and 96% optical yield (HPLC of bis Mosher ester), $[\alpha]_D^{25}$ −8.9 (*c*, 0.8, $CHCl_3$), m.p. 139 °C. Regioselective tosylation of this diol with tosyl chloride (TsCl) resulted in the α-tosylate **7**, $[\alpha]_D^{25}$ −30.1 (*c* 0.65 $CHCl_3$), m.p. 224 °C, exclusively,[9] which was smoothly converted to the glycidic ester **8** on treatment with K_2CO_3–MeOH,[9,10] $[\alpha]_D^{25}$ +9.0 (*c* 0.65, $CHCl_3$), m.p. 113 °C, without epimerisation of the C-2 centre, which is a serious problem with several other

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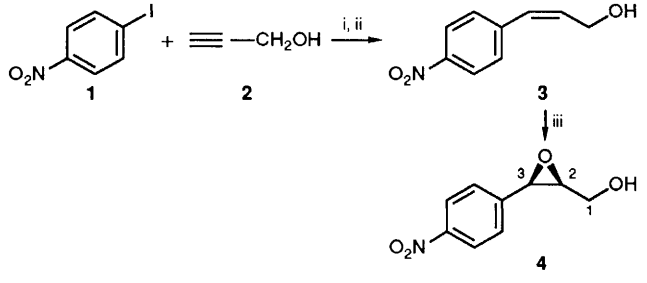
‡ The enantiomer of this glycidol has been reported from L-*threo*-chloramphenicol, $[\alpha]_D^{25}$ +3.6 (*c* 1.1, dioxane): V. F. Fischer, H. J. Tiedt, K. Wolf and K. H. Platz, *J. Pract. Chem.*, 1965, **28**, 157.

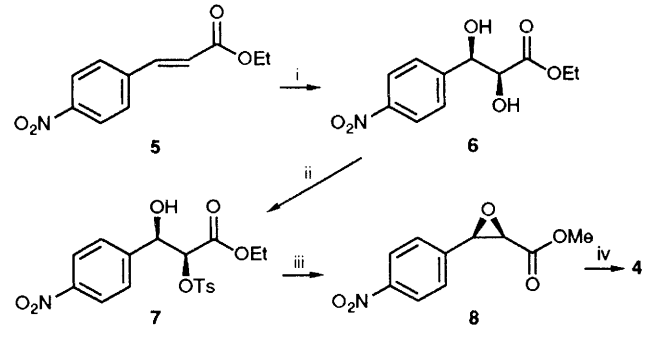
base–solvent combinations.[11] We were then confronted with the delicate task of reducing this glycidic ester to the key glycidol **4**. Literature precedents indicated that $NaBH_4$ can bring about this transformation only if the ester functionality is *trans* to the aryl moiety and the *cis*-isomer remains unaffected.[12] We found that $NaBH_4$ in tetrahydrofuran (THF) at room temperature reduced the glycidic ester **8** to the glycidol **4** $[\alpha]_D^{25}$ −103.1 (*c* 0.23, $CHCl_3$), uneventfully, leaving the rest of the molecule intact.

We then needed to open the key glycidol with a nitrogen nucleophile (we used azide) regioselectively at C-2. *trans*-Glycidols are known to be opened regioselectively, whereas opening of *cis*-isomers is less reliable.[13] The regioselectivity with an external nucleophile depends on a delicate balance of steric and electronic factors. In our system, on steric grounds, C-2 is the preferred site of attack since the aryl moiety is bulkier than the hydroxymethyl functionality. Electronic factors can be made to act synergistically with the steric factor to enhance C-2 selectivity if the reaction is carried out under acid catalysis, since the carbocationic character in the transition state **9** (Scheme 3) needed for attack by the nucleophile is stabilised more at C-2 than at C-3 owing to the presence of the highly electronegative *p*-nitrophenyl moiety. Indeed, when the glycidol **4** was treated with NaN_3 loaded on silica gel[14] in dimethylformamide at 80 °C (Scheme 3), azide substitution at C-2 was total resulting in the azido diol **10** as a syrup, $[\alpha]_D^{25}$ −61.5 (*c* 0.85, $CHCl_3$). No product corresponding to C-3 opening was isolated.

anti-Selectivity in the azide opening of the glycidol was obvious from the ^1H NMR spectrum of the benzylidene derivative **11** of the diol **10** which showed a maximum of 2 Hz for the vicinal H–H couplings, thus indicating an axial azide group.[15] The alternative *erythro*-compound **12**, which would be obtained by retentive opening of the glycidol, and which would show two diaxial couplings, could not be detected in the ^1H NMR spectrum. Further confirmation of the *threo*-nature of the carbon skeleton was obtained by converting the azido diol **10** to chloramphenicol **14** *via* the amino diol **13** as shown in the Scheme 3, $[\alpha]_D^{25}$ −24.2 (*c* 1.1, EtOAc); lit.[2] −25.5 (EtOAc).



Scheme 1 *Reagents*: i, $(PPh_3)_4Pd$, C_6H_6; ii, Lindlar, H_2; iii, (+) DET, TBHP, TIP



Scheme 2 *Reagents*: i, OsO_4, $K_3Fe(CN)_6$, DHQD; ii, TsCl, Et_3N, CH_2Cl_2; iii, K_2CO_3, MeOH; iv, $NaBH_4$, THF

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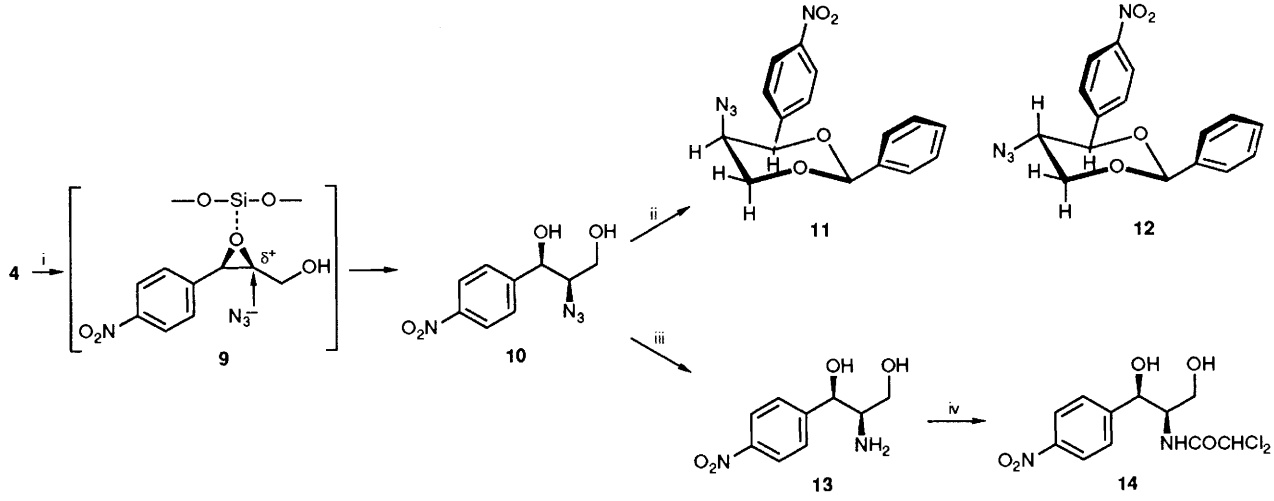

Scheme 3 *Reagents*: i, NaN_3, silica gel, DMF; ii, PhCHO, H^+; iii, THF–H_2O, PPh_3; iv, Cl_2CHCO_2Me