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Stereoselective synthesis of chloramphenicol from D-serine

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Abstract

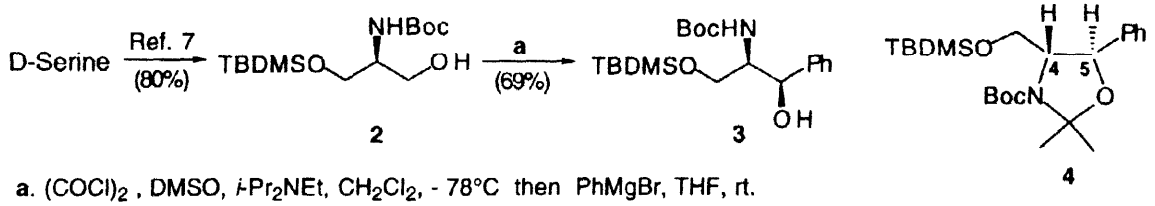
An efficient synthesis of the widely used antibiotic chloramphenicol (**1**) is described. The key step in the synthesis involves chelation-controlled addition of phenylmagnesium bromide to a suitably protected D-serinal derivative, affording the pivotal D-*threo* 1,2-amino alcohol intermediate **3** in a highly stereoselective manner.

Keywords : antibiotic; chelation-control; Grignard reaction; stereoselective.

The broad-spectrum antibiotic chloramphenicol (**1**) was isolated from *Streptomyces venezuelae* in 1974 [1-2]. This widely used antibiotic, containing a *p*-nitrophenyl substituted 2-amino-1,3-propanediol moiety, is active only in its D-*threo* configuration. Only three asymmetric syntheses of chloramphenicol have been reported till now [3-5], two of which involve Sharpless asymmetric epoxidation as the key step, while the third synthesis starts from *p*-nitrophenylalanine. Recent studies from our laboratory have demonstrated the utility of chelation-controlled addition of Grignard reagents to chiral α-amino aldehydes for the stereoselective formation of structurally important 1,2-amino alcohol units with a high degree of *syn*-selectivity [6]. The method has been gainfully employed for the asymmetric syntheses of various biologically active compounds. In continuation, we describe herein an efficient application of the above strategy towards a stereoselective total synthesis of chloramphenicol.

The synthesis started from the easily available amino acid D-serine which was converted to the amino diol derivative **2** (scheme 1) following a reported procedure [7]. Swern oxidation of **2** and its *in-situ* reaction with phenylmagnesium bromide afforded the

Scheme 1



a. $(COCl)_2$, DMSO, *i*-Pr_2NEt, CH_2Cl_2, - 78°C then PhMgBr, THF, rt.

corresponding *syn*- amino alcohol **3** in good yield and with high diastereoselection (>19:1). The *syn*- stereochemistry was further verified by converting **3** to its oxazolidine derivative

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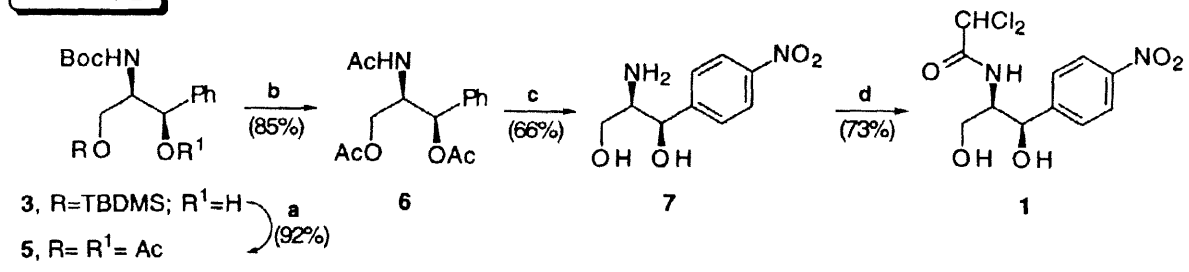
4, whereupon the observed coupling constant ($J_{4,5}$ = 7.2 Hz) between the two protons in the oxazolidine ring confirmed the *trans* relationship.

Attempted conversion of the aminodiol derivative **3** to its triacetyl derivative **6** (scheme 2) by simultaneous removal of the O- and N-protecting groups and subsequent acetylation afforded **6** in poor yield. A stepwise deprotection - acetylation sequence could

Scheme 2



a. i) Bu_4NF, THF, 0°C to rt. ii) Ac_2O, DMAP, pyridine. **b**. i) F_3CCO_2H, 0°C. ii) Ac_2O, DMAP, pyridine. **c**. i) Conc. HNO_3 - conc. H_2SO_4 (1:1), - 20°C to rt. ii) aqueous 5% HCl, 90°C. **d**. Cl_2CHCO_2Me, 90°C.

however circumvent this problem. Thus, initial deprotection of the silyl ether linkage of **3** and acetylation of the hydroxy groups yielded the diacetate **5** in high yield. Subsequent deprotection of the amino group and its acetylation then yielded the desired product **6** in good yield. Nitration of the aromatic ring under standard conditions followed by acid hydrolysis of the acetyl protecting groups and usual basic work-up generated the free amine, which on crystallization (*i*-PrOH/CH_2Cl_2) afforded the pure *p*-nitrophenyl substituted aminodiol **7** in good yield. Finally, conversion of the amine to the required dichloroacetamido derivative completed the intended synthesis of chloramphenicol (**1**)[1], which had identical spectral and physical properties to that reported in the literature [8], {$[\alpha]_D$= -24.8 (c=1.1, EtOAc), lit. $[\alpha]_D$= -25.5 (EtOAc) [3]}.

In conclusion, the above route provides an efficient pathway to enantiomerically pure chloramphenicol and can also be extended towards synthesizing the structurally related antibiotics thiamphenicol, florphenicol and other modified analogs.

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[1] All the compounds synthesized were fully characterized by their IR, NMR and Mass spectral data.