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ASYMMETRIC SYNTHESIS OF THE ANTIBIOTIC (+)-THIAMPHENICOL USING CIS-N-(*p*-TOLUENESULFINYL)AZIRIDINE 2-CARBOXYLIC ACIDS

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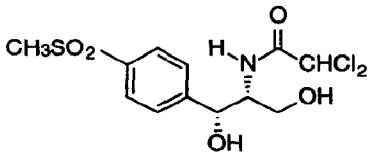
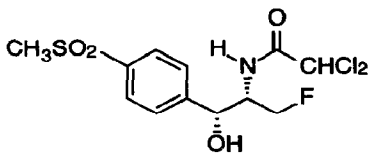
Summary: *A concise, highly efficient asymmetric synthesis of aminopropanediol (1R,2R)-(-)-3, precursor to the broad spectrum antibiotics thiamphenicol/florfenicol 1/2, was prepared in two steps from cis-aziridine 2-carboxylic acid (2S,3S)-(-)-5.*

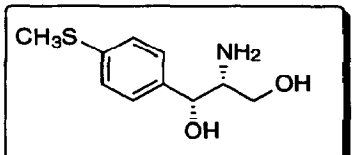
The broad-spectrum, antibacterial, synthetic antibiotic thiamphenicol, (1*R*,2*R*)-(+)-2-(dichloroacetamido)-1-[(4-methylsulfonyl)phenyl]-1,3-propanediol (**1**), is active against many gram-positive and gram-negative microorganisms.[1] Its fluoro analog, florfenicol, (-)-**2**, exhibits much higher activity with a toxicity comparable to **1**.[2] The current process for manufacturing thiamphenicol (+)-**1**,[1b] and hence florfenicol (-)-**2**,[3] requires a classical resolution of (±)-*threo*-2-amino-1-[(4-methylthio)phenyl]-1,3-propanediol (**3**) which in turn is prepared in a multi-step sequence.[4,5] While only the (1*R*,2*R*)-(-)-**3** isomer is a useful precursor to **1** and **2**, three procedures have been developed for transforming the inactive (1*S*,2*S*)-(+)-**3** isomer into (-)-**3**. Two of these methods involve a direct conversion of (+)-**3** into (-)-**3** via a series of steps[6,7] while the third entails a racemization which ultimately results in a second resolution.[8] Enzymatic resolution of a derivative of (±)-**3** has also been reported to give aminopropanediol (-)-**3** in 36% yield.[7] In this context we describe a concise, highly stereoselective asymmetric synthesis of the key thiamphenicol/florfenicol precursor (1*R*,2*R*)-(-)-**3** from enantiopure (2*S*,3*S*)-(-)-N-(*p*-toluenesulfinyl)-2-carbomethoxy-3-(4-methylthiophenyl)aziridine (**5**) and its conversion to (+)-**1**.



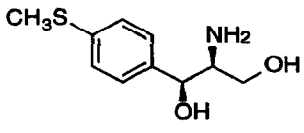
(+)-**1**, thiamphenicol



(-)-**2**, florfenicol



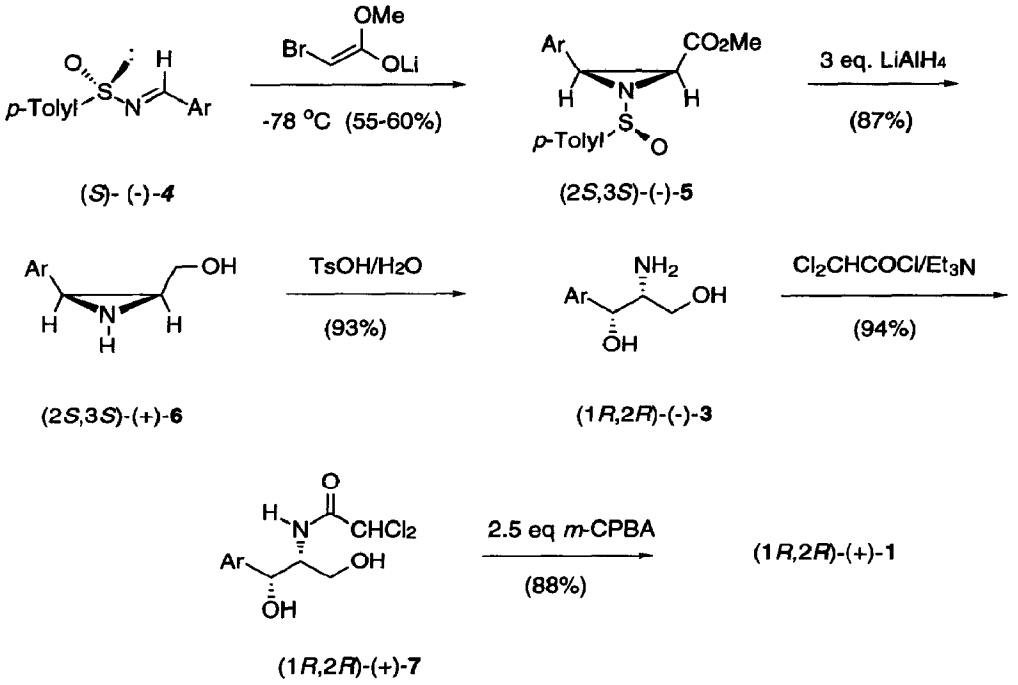
(1*R*,2*R*)-(-)-**3**



(1*S*,2*S*)-(+)-**3**

Synthesis of aziridine (-)-**5** was accomplished using our recently reported Darzens-type synthesis of cis-N-(*p*-toluenesulfinyl)aziridine 2-carboxylic acids, precursors of the difficult to prepare syn- or *threo*-β-hydroxy-α-amino acid structural unit.[9] Thus, addition of a 3.0 mmol THF solution of (*S*)-(-)-N-(4-methylthiobenzylidene)-*p*-toluenesulfinimine (**4**)[10] at -78 °C to 7.5 mmol of the lithium enolate of methyl bromoacetate, prepared in the usual way from lithium bis(trimethylsilyl)amide, at -78 °C gave (-)-**5** in 55-60% yield following flash chromatography (Scheme).[12] Importantly the trans isomer was not detected in the crude reaction mixture.

Scheme



Ar= *p*-MeSPh

Treatment of aziridine (-)-**5** with 3.0 equiv. of lithium aluminum hydride ($LiAlH_4$) in ether at 0 °C, warming to rt for 1 h and quenching with sat. $NaHCO_3$ solution gave (1*H*)-(2*S*,3*S*)-(+)-3-[(4-methylthio)phenyl]aziridine-2-methanol (**6**) in 87% isolated yield.[13] That the aziridine ring remained intact was confirmed by the similarity in $J_{2,3}$, of **5** and **6**, 7.3 vs 7.2 Hz, respectively and its conversion into (-)-**3**. Not only was the carbomethoxy group in **5** reduced, but deprotection of the N-*p*-toluenesulfinyl group also occurred. To the best of our knowledge this represents the only example of the reductive removal of an N-sulfinyl group.[14,15]

Ring-opening of aziridines requires activation at nitrogen, and only a few studies have been reported for aziridines unsubstituted at nitrogen.[16,17] For N-unsubstituted 2-carboxylic acids, Lewis acid or acid activation is often sufficient for reaction to occur. However, if the ring contains an activating substituent such as phenyl or *p*-methoxyphenyl opening is not always stereospecific, indicating that the transition state for attack at C3 has considerable carbocation character.[9,16a] In the synthesis of (±)-sphinganine (*erythro*-2-amino-1,3-dihydroxyoctadecane), ring hydrolysis resulted in a 70:30 mixture of isomers and necessitated refluxing the cis-aziridinium hydrochloride in benzene with Amberlyst A 26.[17b] Under similar conditions, however, the more reactive trans 3-pentadec-(1E)-enyl derivative gave (±)-*erythro* sphingosine as a single isomer.[17c]

For hydrolytic ring-opening of **6** we chose *p*-toluenesulfonic acid (TsOH) because of its solubility in organic solvents and low nucleophilicity. Stirring **6** (0.25 mmol) with 1.1 equivalents of TsOH in a 1:1 water/THF mixture at rt for 30 min., followed by removal of the solvent, dilution with water and bring the solution to pH 12 with 50% NaOH gave, on extraction into CH_2Cl_2, (-)-**3** in 93% isolated yield.[7] The reaction was exceptionally clean and remarkably stereospecific affording this key thiamphenicol/florfenicol precursor as a single isomer despite the presence of the activating 3-*p*-methylthiophenyl group in the aziridine.

Transformation of 2-amino-1,3-propanediol (-)-**3** into thiamphenicol (+)-**1** was readily accomplished by first forming the N-dichloroacetamide and oxidation of the sulfide to the sulfone. Treatment of (-)-**3** with a slight excess of dichloroacetyl chloride and triethylamine afforded (+)-**7**[1b] in 94% yield and oxidation with 2.6 equivalents of 95% *m*-CPBA in THF and quenching with sat. $Na_2S_2O_3$ gave the antibiotic in 88 % isolated yield.[1b,3]

A concise, highly efficient asymmetric synthesis of the key thiamphenicol/florfenicol precursor (1*R*,2*R*)-**3** has been prepared in three steps, in 49% overall yield, from readily available enantiomeric pure sulfinimine (*S*)-**4**. The procedure avoids the wasteful resolution of racemic **3** used in earlier procedures.

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12. Aziridine (-)-**5** had the following properties: mp 86-8 °C; $[\alpha]_D^{20}$ -2.3° (c 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.42 (s, 3H), 2.47 (s, 3H), 3.41 (s, 3H), 3.47 (d, J=7.3Hz, 1H), 3.82 (d, J=7.3Hz, 1H), 7.20 (d, J=8.2 Hz, 2H), 7.33 (d, J=8.1Hz, 2H), 7.39 (d, J=8.2Hz, 2H), 7.70 (d, J=8.1Hz, 2H).
13. Aziridine-2-methanol (+)-**6** had the following properties: mp 125-125 °C; $[\alpha]_D^{20}$ +96.8° (c, 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.84 (br, 2H), 2.48 (s, 3H), 2.64 (AB_q, J= 6.4Hz, 1H), 3.25 (dd, J_1=7.2 Hz, J_2 = 11.8 Hz, 1H), 3.44 (m, 2H), 7.24 (q_{AB}, J=8.6Hz, 4H).
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