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NEW STRATEGY FOR RACEMIZATION OF 2-AMINO-1,3-PROPANEDIOLS, KEY INTERMEDIATES FOR THE SYNTHESIS OF ANTIBIOTIC DRUGS

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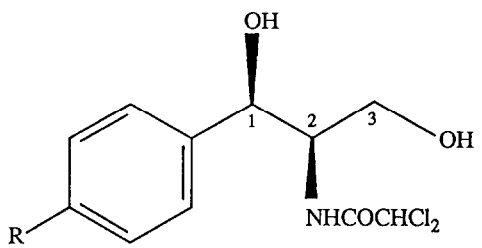
Summary: A new strategy for racemization of the 2-amino-1,3-propanediol **2b**, based on a chemoselective oxazoline ring formation and a highly diastereoselective reduction of the ketone **4** is reported.

Thiamphenicol **1**,[1] threo-(1R,2R)-2-dichloroacetamido-1-(4-methylsulfonyl)-1,3-propanediol, possesses a fairly wide spectrum of antimicrobial activity against gram-negative bacteria, while its enantiomer is devoid of antibacterial activity.



1 (R= CH_3SO_2) Thiamphenicol

1 (1R,2R)

In all the manufacturing processes of Thiamphenicol **1** an optical resolution is needed at some stage of the synthesis.

In most of the cases, the resolution is carried out at the level of racemic threo-2-amino-1-(4-methylthiophenyl)-1,3-propanediol **2a,b** (Scheme) by entrainment resolution.[2] Accordingly, the desired (1R,2R) isomer **2a** and its enantiomer **2b** are isolated with the same chemical and enantiomeric purity. The aminodiol **2a** is converted in 2 steps into Thiamphenicol **1** while **2b** is discarded having no industrial application.

For the above reasons, industry is seeking simple and economic ways of converting the useless isomer **2b** into **2a** or into a racemic mixture.

To the best of our knowledge, a single case of racemization of (1S,2S)-2-amino-1-(4-methylthiophenyl)-1,3-propanediol **2b**, through demolition and reconstitution of the original carbon skeleton, has been described in the scientific literature.[3]

Here we report a new strategy for the racemization of **2b** which does not involve demolition of the carbon skeleton.

The general strategy followed to achieve our goal is the following:

i) protection both of the amino group and the primary alcohol;

ii) oxidation of the benzylic alcoholic function to carbonyl group;

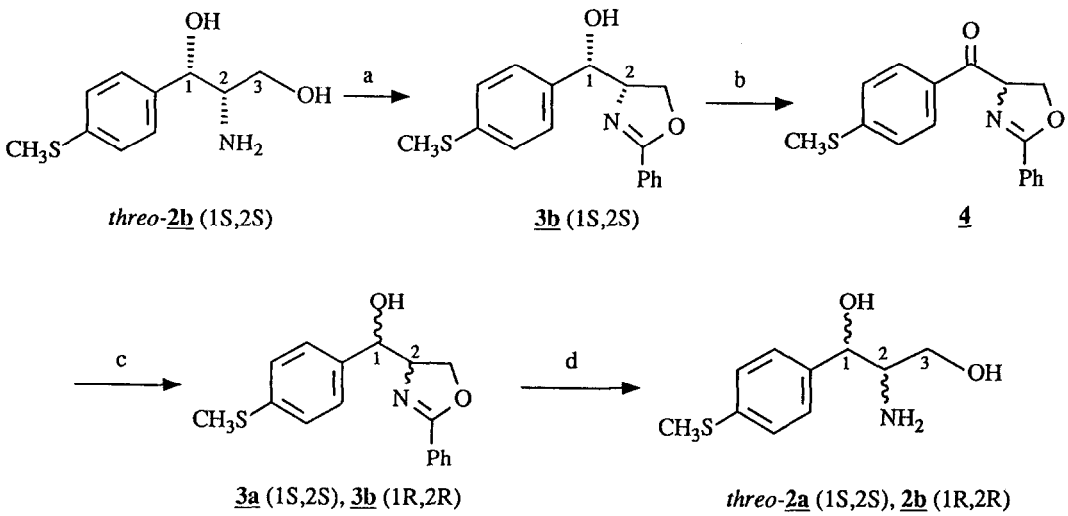
iii) racemization via enolization of the carbon α to the carbonyl group;

iv) diastereoselective reduction, to favor the threo form of the resultant alcohol;

v) deprotection to the racemic aminodiol.

Accordingly, a new synthetic procedure has been developed which allows racemization in 4 pots with a 50% overall yield, based on **2b**.

SCHEME



threo-**2b** (1S,2S) **3b** (1S,2S) **4**

3a (1S,2S), **3b** (1R,2R) *threo*-**2a** (1S,2S), **2b** (1R,2R)

Reagents and conditions: a) **2b** (50 mmol)/CH_2Cl_2 (110 ml)/Et_3N (180 mmol)/ benzoyl chloride (53 mmol) (0-20°C)/tosyl chloride (62 mmol) (40°C); b) **3b** (14 mmol)/dimethyl sulphoxide (42 mmol)/oxalyl chloride (21 mmol)/Et_3N (70 mmol)/ CH_2Cl_2 (50 ml)/ (-20°C); c) **4** (3.4 mmol)/MeOH (13 ml)/$NaBH_4$ (3.4 mmol)/ (-20°C); d) **3a,b** (10 mmol) / 1N HCl (10 ml) (20°C)/10% w/v NaOH (14 ml) (100°C).

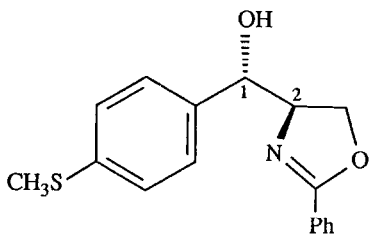
Consecutive treatment of **2b**[4] with benzoyl chloride (0-20°C) and with tosyl chloride (40°C) in dichloromethane, in the presence of an excess of triethylamine, provides protection both for the amino group and the primary alcohol in the form of 1,3-oxazoline **3b**[5] in 80% yield.

The conversion of **2b** into **3b** occurs through the intermediate formation of (1S,2S)-threo-

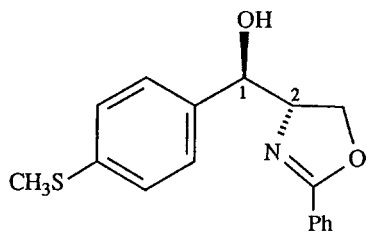
2-benzamido-1-(4-methylthiophenyl)-1,3-propanediol. Tosyl chloride represents the reagent of choice for the chemoselective activation of the primary alcohol for the nucleophilic displacement by the carboxyamide group.[6]

Oxidation of the benzylic alcohol **3b** and racemization of the resultant ketone occur smoothly under typical Swern[7] conditions (dimethyl sulfoxide, oxalyl chloride, triethylamine in dichloromethane) to provide racemic ketone **4**[5,8] in 90% yield. It is worth noting that the Swern oxidation has been chosen among many others because sulfur is not oxidized and side reactions such as β-elimination, leading to oxazoline ring opening, are avoided.

Ketone **4** is reduced in methanol at -20°C with sodium borohydride to afford in 90% yield the racemic oxazoline **3a,b** together with a small amount (4%) of the diastereomeric oxazoline **5a,b**.[9,10]



5b (1S,2R)



5a (1R,2S)

Diastereomerically pure **3a,b** is isolated in 90% yield by flash chromatography on silica gel using n-hexane/diethylether mixtures as eluent.

A lower diastereoselection is observed carrying out the reduction in ethanol (**3a,b** : **5a,b** = 86 : 14) and in metanol/water = 9/1 mixture (**3a,b** : **5a,b** = 87 : 13).

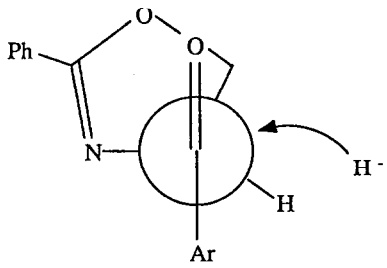
A one pot sequence involving an aqueous acidic opening of the oxazoline ring **3a,b**, followed by the aqueous alkaline hydrolysis of the intermediate 3-O-benzoyl ester of **2a,b** completes the sequence to aminodiol **2a,b** (85% yield).

The high diastereoselection of the reduction contrasts with the low diastereoselectivity of the reduction of the intermediate ketone related to the synthesis of Chloramphenicol **1** (R = NO_2).[11]

We attribute the diastereoselectivity to the presence of the oxazoline ring which provides a greater conformational rigidity; the hydride attack, according to the Felkin-Ahn model, occurs on the less hindered face of the carbonyl group (Figure).

The use of mild and practical reaction conditions makes the new racemization useful for large scale preparations.

FIGURE



References and Notes

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2) J. Jacques, A. Collet, S. H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley & Sons, 1981, p 223.

3) V. Horak, F. Moezie, R. F. X. Klein, C. Giordano, Synthesis, 839 (1984).

4) (1S,2S)-2-amino-1-(4-methylthiophenyl)-1,3-propandiol is supplied by Zambon Group S.p.A. and is purified by crystallization from isopropanol. For the preparation see M. Portelli, G. Renzi, Ann.Chim., 59, 306 (1969); C.A., 71, 50487 (1969).

5) The new compounds are fully characterized by ^{1}H-NMR (300 MHz), ^{13}C-NMR (75 MHz), IR, mass spectral and elemental analyses.

3b: m.p. 98 - 101°; $[\alpha]_D^{20}$ = +35.7° (c = 1.0, $CHCl_3$). MS (DCI isobutane): m/e 300 $(M+1)^+$; IR(1%,$CHCl_3$) 1650 cm^{-1} (C=N); ^{1}H-NMR(300 MHz) ($CDCl_3$): δ (ppm): 2.50 (s, 3H); 4.11 (m, 1H); 4.27 (m, 1H); 4.52 (m, 2H); 7.2 - 8.0 (m, 9H).

4: MS (DCI isobutane): m/e 298 $(M+1)^+$; IR (1%, $CHCl_3$) 1590, 1640, 1685 cm^{-1}; ^{1}H-NMR (300 MHz) ($CDCl_3$): δ (ppm): 2.55 (s, 3H); 4.56 (dd, 1H, J= 10.1 Hz, J= 8.6 Hz); 5.12 (dd, 1H, J= 8.6 Hz, J= 7.3 Hz); 5.62 (dd, 1H, J= 10.1 Hz, J= 7.3 Hz); 7.3 - 8.2 (m, 9H). Ketone **4** has shown to be racemic on the basis of the optical rotation and of ^{1}H-NMR analysis of its solutions in CD_3CN in the presence of the optically active shift reagent tris-[3-(trifluoromethyl-hydroxymethylen)-d-camphorato]-europium (III).

6) R. N. Boyd, R. H. Hansen, J.Am.Chem.Soc., 75, 5896 (1953).

7) A. J. Mancuso, D. Swern, Synthesis, 165 (1981).

8) Enantiomerically pure ketone **4** of S absolute configuration is isolated in 90% yield by carrying out the reaction at -60°C, m.p. 113-115°C; $[\alpha]_D^{20}$ = +460.0° (c=1.0, $CHCl_3$).

9) Diastereomeric ratios (**3a,b**/**5a,b**) are determined by (300MHz) ^{1}H-NMR analysis.

10) Oxazoline **5a,b** can be prepared from erythro-(1R,2S) (1S,2R)-2-amino-1-(4-methylthiophenyl)-1,3-propanediol [see M. Portelli, G. Renzi, B. Soranzo, Ann.Chim., 60, 160 (1970)] and methyl iminobenzoate hydrochloride.

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