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A concise synthesis of (*R*)-(+)-phenylalaninol from (1*S*,2*S*)-(+)-thiomicamine

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Abstract

(*R*)-(+)-Phenylalaninol **6** was obtained from oxazolines **3** and **4** derived from (1*S*,2*S*)-2-amino-1-aryl-1,3-propanediols **1** and **2** by the action of Raney nickel followed by hydrolysis of the intermediate benzamide **5**.

1. Introduction

threo-2-Amino-1-aryl-1,3-propanediols are key intermediates in the synthesis of amphenicol-type antibiotics. Being manufactured in the racemic form, they are then resolved and the (*R,R*)-enantiomers are further transformed into the therapeutic drugs, while the nonactive (*S,S*)-isomers are discarded. The discarded bases, compounds of high enantiomeric purity, have found numerous applications in organic synthesis: as homochiral starting materials and building blocks as well as chiral auxiliaries and ligands in asymmetric transformations.

Here we report an efficient and expedient transformation of (1*S*,2*S*)-(+)-thiomicamine **1**, the unwanted intermediate in thiamphenicol antibiotic production,[1] into (*R*)-(+)-phenylalaninol **6** through the intermediacy of (+)-oxazoline **3** (Scheme 1).

To date, three other procedures for the transformation of (1*S*,2*S*)-2-amino-1-phenyl-1,3-propanediol **2**, another discarded side product of this type, into (*R*)-(+)-phenylalaninol **6** have been developed. In one of them, described in patent literature,[2] **6** was prepared from aminodiol **2** in one step by selective hydrogenolysis of the benzylic hydroxyl group, in only 15% yield. Two other methods involved five-step reaction sequences. One of these two[3] started with regioselective chlorination of the secondary hydroxyl group in **2**·HCl, followed by N,O-diacetylation, reductive dehalogenation and final N,O-deprotection, yielding product **6** in 14% overall yield. In the other approach[4] a cyclic sulfite, prepared from N-phthaloyl

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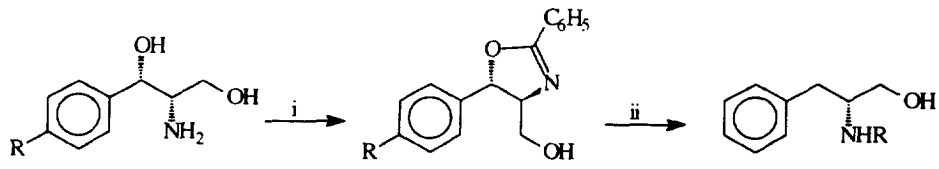

Scheme 1. Reagents and conditions: (i) C_6H_5CN/K_2CO_3;[5] (ii) Raney Ni, C_2H_5OH, Δ; (iii) 20%HCl, NaOH

2 and thionyl chloride was treated with LiBr followed by reductive debromination and protecting group removal giving **6** in an overall yield of between 19 and 33%.

2. Results and discussion

The synthesis reported here is a simple and short, three-step procedure, in which (*R*)-(+)-phenylalaninol **6** was obtained in 73% overall yield from a cheap, commercially available (1*S*,2*S*)-thiomicamine **1** (Scheme 1). The key intermediate in the synthesis, (+)-oxazoline **3**, was prepared in high yield according to the same procedure as its enantiomer (−)-**3**, by heating **1** with benzonitrile in ethylene glycol/glycerol in the presence of potassium carbonate at 110°C.[5] The thus prepared (+)-oxazoline **3** exhibited, within experimental error, a melting point of 173.5–174°C and a specific rotation of $[\alpha]_D$ +65.8, corresponding to those of its enantiomer, (−)-**3**, m.p. 171–173°C, $[\alpha]_D$ −64.4.[5]

Treatment of the oxazoline **3** with Raney nickel W-2 in ethanol at reflux, caused not only desulfurization of the aromatic methylthio substituent but also hydrogenolysis of the benzylic oxygen, resulting in (*R*)-(+)-N-benzoylphenylalaninol **5**, m.p. 168–170.5°C, $[\alpha]_D$ +80.2, obtained in high chemical yield and enantiomeric purity. The m.p. and specific rotation of **5** corresponded well to those of the natural (*S*)-(−)-enantiomer, m.p. 171–173°C, $[\alpha]_D$ −78.[6]

When the above reaction sequence was applied to oxazoline **4**, prepared from (1*S*,2*S*)-(+)-2-amino-1-phenyl-1,3-propanediol **2** and benzonitrile,[5] (+)-N-benzoylphenylalaninol **5** was obtained as well, in quantitative yield. It should be mentioned that our sample of oxazoline **4** was characterised by m.p. 186–187°C, $[\alpha]_D$ +51.0 (c=0.54, $CHCl_3$) and $\nu_{C=N}$ 1648 cm^{-1}, which were different from those reported previously:[7,8] m.p. 127–129°C, $[\alpha]_D$ −44.6 (c=5.4, $CHCl_3$), $\nu_{C=N}$ 1670 cm^{-1}, though the ^{1}H-NMR spectra were practically superimposable.† The oxazoline structure of our compounds **3** and **4** could be confirmed by spectral data analysis, in particular by IR absorption at 1648 cm^{-1} characteristic of the conjugate imine, the presence of $[M^+]$ and $[M-CH_2OH]^+$ ions in the EI mass spectra, as well as by the H-4/H-5 *trans* stereochemistry on the basis of the H-5 benzylic doublet (δ: 5.5, J=8.0 Hz)[10] in the ^{1}H-NMR spectrum.

It may be worth noting that oxazolines have found widespread use in many synthetic transformations;[11] in this report their utility as intermediates in deoxygenation of benzylic hydroxyl groups in aminoalcohols has been demonstrated.

Benzamide **5**, under the action of 20% hydrochloric acid at reflux, was easily hydrolyzed to (*R*)-(+)-phenylalaninol hydrochloride **6**·HCl, whose m.p. 121–123°C and $[\alpha]_D$ +19.5 were in accordance with literature data,[3] as were those of the free base **6**, m.p. 91–92°C, $[\alpha]_D$ +24.6.[4,12]

† An X-ray molecular structure of a compound derived from oxazoline **4** was reported[9] and the oxazoline ring system along with (4*S*,5*S*) sterochemistry has been confirmed.

3. Conclusion

In conclusion, a highly efficient procedure is described for the transformation of (1*S*,2*S*)-2-amino-1-aryl-1,3-propanediols into unnatural (*R*)-(+)-phenylalaninol and may serve as another example of the practical use of industrial waste products.

4. Experimental

4.1. General procedure

Melting points: determined on a Koffler block and not corrected. IR spectra: Perkin–Elmer 180 in KBr pellets. NMR spectra: Varian Gemini 300, TMS as internal standard. Mass spectra (EI): Jeol-D-100, 75 eV. Specific rotation: Perkin–Elmer polarimeter 243B at 20°C. Merck Kieselgel 60 (70–230 mesh) was used for column chromatography and Merck DC-Alufolien Kieselgel 60_{254} for TLC. (1*S*,2*S*)-(+)-2-Amino-1-phenyl-1,3-propanediol and (+)-thiomicamine were purchased from the Aldrich Chemical Co. and used as received.

4.2. (4S,5S)-5-Hydroxymethyl-4-[4-(methylthio)phenyl]-2-phenyl-2-oxazoline 3

To (1*S*,2*S*)-(+)-thiomicamine **1** (10 g, 47 mmol) and potassium carbonate (1 g) in a mixture of ethylene glycol (15 ml) and glycerol (8.2 ml) benzonitrile (8 ml, 78.4 mmol) was added and the resultant mixture was heated at 110°C with stirring under an argon atmosphere until no more starting material was present by TLC (ca. 20 h). After cooling to r.t., water was added and the product was collected by filtration, washed with water and hexane, and dried to yield pure oxazoline **3** (13 g, 93%); m.p. 173.5–175°C, $[\alpha]_D$ +65.8 (c=0.5, MeOH) after recrystallization from methylene chloride (lit.[5] for (−)-**3**: m.p. 171–173°C, $[\alpha]_D$ −64.4). IR (KBr) cm^{-1}: 3195 (OH), 1648 (C=N); ^{1}H-NMR ($CDCl_3$) δ: 2.48 (s, 3H, SCH_3), 3.4 (m, br, 1H, exchanges with D_2O, O**H**), 3.76 (dd, J=3.8, 11.8 Hz, 1H, C**H**HOH), 4.08 (dd, J=3.5, 11.8 Hz, 1H, CH**H**OH), 4.22 (td, J=3.9, 3.6, 7.9 Hz, 1H, C**H**N), 5.51 (d, J=7.9 Hz, 1H, C**H**Ph), 7.26–7.50 (m, 7H, Ar**H**), 7.91 (d, J=7.1 Hz, 2H, Ar**H**); CI-MS m/z (%): 299 (M^+, 37), 268 (20), 194 (5), 165 (34), 147 (100), 130 (66), 105 (96), 77 (42). Found: C 68.27; H 5.61; N 4.63. $C_{17}H_{17}NO_2S$ (299.38) requires C 68.20; H 5.73; N 4.68%.

4.3. (4S,5S)-2,4-Diphenyl-5-hydroxymethyl-2-oxazoline 4

Oxazoline **4** was prepared from (1*S*,2*S*)-(+)-2-amino-1-phenyl-1,3-propanediol **2** (5 g, 29.9 mmol), benzonitrile (5.1 ml, 49.9 mmol), potassium carbonate (0.66 g) in a mixture of ethylene glycol (10.5 ml) and glycerol (5.2 ml) according to the above procedure, in 92% yield. After recrystallization from methylene chloride (74.7%): m.p. 186–187°C (sublimes from ca. 160°C), $[\alpha]_D$ +51.0 (c=0.54, $CHCl_3$), $[\alpha]_D$ +70.2 (c=0.5, MeOH); (lit.[7] m.p. 127–129°C, $[\alpha]_D$ −44.6, c=5.4, $CHCl_3$). IR (KBr) cm^{-1}: 3182 (OH), 1648 (C=N); ^{1}H-NMR ($CDCl_3$) δ: 3.76 (dd, J=3.8, 11.9 Hz, 1H, C**H**HOH), ca. 3.76 (s, broad, 1H, O**H**), 4.10 (dd, J=3.5, 11.9 Hz, 1H, CH**H**OH), 4.24 (dt, J=3.6, 8.0 Hz, 1H, C**H**N), 5.58 (d, J=8.2 Hz, 1H, C**H**Ph), 7.26–7.48 (m, 8H, Ar**H**), 7.89 (d, J=7.1 Hz, 2H, Ar**H**); ^{13}C-NMR (DMSO-d_6) δ: 62.96 (CH_2OH), 76.91 (CHN), 82.42 (CHPh), 125.33, 127.95, 128.60, 128.69, 131.56 (ArCH), 127.31, 141.38 (ArC), 162.17 (C=N); CI-MS m/z (%): 253 (M^+, 2), 223 (22), 222 (100), 146 (25), 130 (33), 119 (50),

105 (33), 77 (34). Found: C 75.80; H 6.00; N 5.60. $C_{16}H_{15}NO_2$ (253.29) requires C 75.87; H 5.99; N 5.53%.

4.4. (R)-(+)-2-Benzamido-3-phenyl-1-propanol 5 [(R)-(+)-N-benzoylphenylalaninol]

Oxazoline **3** (2.99 g, 10 mmol) in 96% ethanol (160 ml) and Raney nickel W-2 (ca. 9 g) were heated at reflux for 9 h. The hot reaction mixture was filtered through a pad of Celite, the catalyst was washed with hot ethanol (60 ml) and the filtrate was concentrated to ca. 25% of its volume and left for crystallization. It deposited 1.74 g (86%) of pure, crystalline **5**; m.p. 169–170.5°C, $[\alpha]_D$ +93.4 (c=0.97, MeOH), +80.2 (c=1, pyridine); (lit.[6] for (−)-**5**, m.p. 171–173°C, $[\alpha]_D$ −78, c=1, pyridine). IR (KBr) cm^{-1}: 3310 (OH), 1665 (CO); ^{1}H-NMR (DMSO-d_6/D_2O) δ: 2.79 (dd, J=9.0, 13.7 Hz, 1H, PhC**H**H), 2.96 (dd, J=5.2, 13.7 Hz, 1H, PhCH**H**), 3.42 (dd, J=6.0, 10.7 Hz, 1H, C**H**HOH), 3.50 (dd, J=5.5, 10.7 Hz, 1H, CH**H**OH), 4.18 (m, 1H, C**H**N), 7.1–8.22 (m, 10H, Ar**H**); CI-MS m/z (%): 255 (M^+, 5), 225 (4), 164 (67), 134 (4), 122 (6), 105 (100), 91 (5), 77 (71). Found: C 75.20; H 6.80; N 5.58. $C_{16}H_{17}NO_2$ (255.307) requires C 75.27; H 6.71; N 5.49%.

4.5. (R)-(+)-2-Amino-3-phenyl-1-propanol 6 [(R)-(+)-phenylalaninol]

Compound **5** (2 g, 7.8 mmol) in 20% hydrochloric acid (22.5 ml) was heated at reflux for 6 h, the mixture was then cooled to r.t. and the precipitated benzoic acid was removed by filtration. The filtrate was extracted with ethyl ether and the aqueous phase was evaporated to give **6**·HCl as a solid (1.34 g, 91%), which was crystallized from methanol/ether; m.p. 121–123°C, $[\alpha]_D$ +19.5 (c=1.2, 1 N HCl); (lit.[3] m.p. 120–121.5°C, $[\alpha]_D$ +20.0, c=1.0, 1 N HCl).

Free base **6**: m.p. 91–92°C, $[\alpha]_D$ +24.6 (c=1, EtOH); (lit.[4] m.p. 95°C, $[\alpha]_D$ +22.5; lit.[12] m.p. 95°C, $[\alpha]_D$ +23.2).

Acknowledgements

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