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Chemo-enzymatic synthesis of levodropropizine

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Abstract

Levodropropizine, an antitussive drug, was prepared in high enantiomeric excess in three steps, starting from dichloroacetone (**2**). Monosubstitution of **2** with sodium benzoate and subsequent baker's yeast reduction stereoselectively afforded the corresponding chlorohydrin in 73% ee, which was converted to levodropropizine and enantiomerically enriched up to 95% ee by fractional crystallisation.

Keywords: Levodropropizine; Baker's yeast; 3-Chloro-1,2-propanediol; 1-Benzoyloxy-3-chloropropan-2-ol

1. Introduction

Racemic dropropizine, i.e. (±)-3-(4-phenyl-1-piperazinyl)-1,2-propanediol (**1**), has long been used as an antitussive drug; more recently, it has been demonstrated that the (*S*)-(−) enantiomer of **1** displays the same antitussive activity with lower side effects on the central nervous system [1,2], and nowadays this drug is sold as Levodropropizine, the (*S*)-(−) enantiomer of dropropizine.

Several synthetic routes to enantiomerically pure **1** have, therefore, been developed, including resolution methods, both enzymatic [3,4] and non-enzymatic [5], and the chiron synthon approach using (*R*)-glycidol [6,7], (*R*)-glyceroltosylate [2] and (*R*)-3-chloropropane-1,2-diol [8]. In view of the increasing interest in the biocatalytic asymmetric synthesis of chiral intermediates for pharmaceuticals [9], we report here on a new straightforward synthesis of (*S*)-(−)-**1** in three steps starting from dichloroacetone **2**. The key step in the asymmetric synthesis is the reduction of 1-benzoyloylxy-3-chloropropane-2-one (**3**) by baker's yeast (*Saccaromices cerevisiae*) to furnish the chlorohydrin (*R*)-(+)-**4**, which can be readily converted to (*S*)-(−)-**1**.

2. Experimental

2.1. General

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Bruker DPX-200 MHz spectrometer; chemical shifts are reported in δ values from TMS as internal standard; coupling constants (J) are given in Hz. For mass spectral determinations a Finnigan MAT SSQ A mass spectrometer was used (EI, 70 eV). Elemental analyses were performed with a Carlo Erba elemental analyzer 1110. Chromatographic purification of compounds was performed on silica gel (particle size 0.05–0.20 mm). Optical rotations were measured on a Perkin–Elmer 241 polarimeter at 20 °C. GLC analyses were performed on a Hewlett–Packard 5890A gas chromatograph; the conversions were evaluated on a DB1 column (30 m × 0.53 mm i.d. and 5 μm film phase) from J&W Scientific. The enantiomeric excess of (+)-**4** was evaluated on a chiral ALPHA DEX 120 column (30 m × 0.25 mm i.d. and 0.25 μm film phase) purchased from Supelchem, while the ee of (−)-**1** was determined by HPLC as described in the literature [7]. Fresh baker's yeast (Fala, Strasbourg) was purchased from a local shop.

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2.2. 1-Benzoyloxy-3-chloropropan-2-one (**3**) [10]

Dichloroacetone **2** (10 g, 79 mmol) was added in one portion to a solution of $NaHCO_3$ (4 g, 48 mmol) and benzoic acid (4.8 g, 39 mmol) in dry DMF (150 ml) at 0 °C. The reaction was stirred at this temperature for 3 h, then at room temperature (r.t.) for a further 12 h. The reaction mixture was diluted with H_2O and extracted with light petroleum–ethyl acetate (95:5); the collected organic phases were washed with water and brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by crystallization with boiling *n*-exane (250 ml) to give 5.78 g of **3** as pale yellow solid (70%), m.p. 89–92 °C. ^{1}H NMR ($CDCl_3$): δ 4.28 (2H, s, CH_2Cl), 5.17 (2H, s, CH_2O), 7.46–7.57 (2H, m, *meta* Ph), 7.59–7.70 (1H, m, *para* Ph), 8.08–8.18 (2H, m, *ortho* Ph). ^{13}C NMR ($CDCl_3$): δ 46.3, 67.3, 129.0, 130.3, 134.1, 166.2, 196.9. MS (EI, 70 eV) *m/z*: 213–215 ($[M+1]^+$, 0.5%), 212–214 (1), 211–213 (2), 177 (4), 163 (25), 105 (100), 77 (44), 51 (16). *Anal.* Found: C, 57.12; H, 4.85. Calc. for $C_{10}H_9ClO_3$: C, 56.49; H, 4.27%.

2.3. 1-Benzoyloxy-3-chloropropan-2-ol (**4**) [11]

A suspension of baker's yeast (43 g) in water (850 ml) was preincubated at 30 °C for 30 min; thereafter, a solution of the chloroketone 3 (2 g, 94 mmol) in DMSO (5 ml) was added and the resulting mixture was magnetically stirred at 30 °C for 3 h, until a GLC analysis showed up to 95% conversion. The mixture was centrifuged, the yeast re-suspended in water (50 ml) and re-centrifuged. The collected aqueous phases were extracted with ethyl acetate (5 × 200 ml) and the organic phases washed with water (100 ml), brine (50 ml) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue purified by column chromatography (light petroleum–ethyl acetate 7:3) to afford compound **4**, which was recovered (60% yield) as a pale yellow oil, $[\alpha]_D = +2.0$ (*c* 1, $CHCl_3$), 73% ee.

(+)-**4**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.13 (1H, b, O*H*), 3.70 (1H, dd, *J* 11.3, 5.0, CH_2Cl), 3.75 (1H, dd, *J* 11.3, 5.7, CH_2Cl), 4.24 (1H, quintet, *J* 5.3, C*H*OH), 4.39–4.58 (2H, m, CH_2O), 7.38–7.51 (2H, m, *meta* Ph), 7.52–7.65 (1H, m, *para* Ph), 8.01–8.11 (2H, m, *ortho* Ph). ^{13}C NMR (50 MHz, $CDCl_3$): δ 46.4, 66.1, 70.1, 125.2, 128.9, 130.1, 133.8, 167.1. MS (EI, 70 eV) *m/z*: 215–217 ($[M+1]^+$), 197–199, 165, 123, 105 (base peak), 92, 77, 51. *Anal.* Found: C, 56.08; H, 5.29. Calc.: C, 55.96; H, 5.17%.

2.4. (*R*)-3-Chloro-1,2-propanediol (**5**) [12]

A solution of (+)-**4** (0.150 g, 0.70 mmol), 73% ee, and NaOH (28 mg, 0.70 mmol) in absolute ethanol (5 ml) was refluxed for 2 h. The solvent was removed under reduced pressure and the residue purified by column chromatography (ethyl acetate–light petroleum 1:1 to ethyl acetate 100%) to give (−)-**5** as a pale yellow oil (83% yield), showing $[\alpha]_D = -6.0$ (*c* 3.0, H_2O); (lit. [12] (*R*)-(−) $[\alpha]_D = -8.2$, *c* 1, H_2O, 99.5% ee).

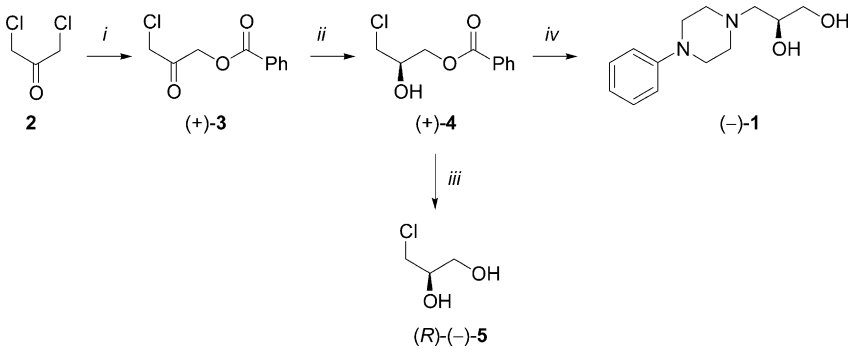
2.5. Levodropropizine (**1**)

Phenyl-piperazine (0.71 ml, 4.65 mmol) was added to a solution of (+)-**4** (500 mg, 2.33 mmol), 73% ee in isopropyl alcohol (10 ml). The resulting solution was refluxed for 24 h, when TLC analysis showed disappearance of **4** and formation of a new product, which was occasionally isolated and identified as 1-benzoyloxy-3-(4-phenyl-piperazin-1-yl)-2-propanol (**6**). NaOH (93 mg, 2.33 mmol) was added and the solution was refluxed for a further 1.5 h. The resulting mixture was cooled at room temperature, the white precipitate (sodium benzoate) filtered off and the solvent removed under reduced pressure. The crude residue was purified by column chromatography (EtOAc:EtOH:NH_4OH, 8:2:0.3) to give 331 mg (60% yield) of (−)-**1** as pale yellow solid, $[\alpha]_D = -17.7$ (*c* 3.0, CH_2Cl_2), ee 73%. Crystallization from dichloromethane/hexane afforded (−)-(**1**) (235 mg), ee 95%.

(−)-**1**: ^{1}H NMR ($CDCl_3$): δ 2.47 (1H, dd, *J* 12.5, 4.1, NCH_2CHOH), 2.55–2.95 (5H, m, CH_2CH_2NPh + NCH_2CHOH), 3.24 (4H, t, *J* 5.0, CH_2NPh), 3.40 (2H, b, 2 O*H*), 3.57 (1H, dd, *J* 11.4, 4.8, CH_2OH), 3.77 (1H, dd, *J* 11.4, 3.7, CH_2OH), 3.90 (1H, sextuplet, *J* 4.4, C*H*OH), 6.90 (1H, t, 7.2, arom. *para*), 6.95 (2H, d, *J* 8.8, arom. *ortho*), 7.30 (2H, dd, *J* 7.2, 8.8, arom. *meta*). ^{13}C NMR ($CDCl_3$): δ 49.6, 53.8, 60.9, 65.4, 67.6, 116.5, 120.3, 129.5, 151.5. MS (EI, 70 eV) *m/z*: 236 (M^+), 205, 176, 175 (base peak), 160, 132, 120, 104, 88, 77, 70. *Anal.* Found: C, 66.39; H, 8.77; N, 12.05. Calc.: C, 66.07; H, 8.53; N, 11.85%.

2.6. 1-Benzoyloxy-3-(4-phenyl-piperazin-1-yl)-2-propanol

(−)-**6**: $[\alpha]_D = -6.8$ (c 1.03, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 2.55–2.75 (4H, m, NCH_2CHOH + CH_2CH_2NPh), 2.80–3.00 (2H, m, CH_2CH_2NPh), 3.15–3.40 (4H, m, CH_2NPh), 4.10–4.28 (1H, m, C*H*OH), 4.38 (1H, dd, *J* 11.5, 5.6, CH_2O), 4.47 (1H, dd, *J* 11.5, 4.1, CH_2O), 6.91 (1H, tt, *J* 7.2, 1.0, *meta* PhN), 6.96 (2H, dd, *J* 8.8, 1.0, *ortho* Ph), 7.31 (2H, dd, *J* 8.8, 7.3, *meta* PhN), 7.44–7.66 (3H, m, *meta*+*para* PhCO), 8.05–8.15 (2H, m, *ortho* PhCO). ^{13}C NMR ($CDCl_3$): δ 49.6, 53.2, 60.8, 65.7, 67.4, 116.5, 120.3, 128.8, 129.5, 130.1, 133.5, 151.5, 166.9. MS (EI, 70 eV) *m/z*: 341 ($[M+1]^+$), 340, 176, 175 (base peak), 160, 132, 105, 77, 70. *Anal.* Found: C, 69.71; H, 7.93; N, 8.19. Calc.: C, 70.56; H, 7.61; N, 8.02%.



Scheme 1. (i) $NaHCO_3$, ArCOOH, DMF; (ii) Baker's Yeast, water, 30 °C, 3 h; (iii) NaOH, EtOH, reflux 2.5 h; (iv) 1-phenylpiperazine, ^{i}PrOH, reflux, 24 h, then NaOH, reflux 1 h.

3. Results and discussion

This new three-step procedure, developed for the asymmetric synthesis of levodropropizine, depicted in Scheme 1, starts from dichloroacetone (**2**): the primary alcoholic functionality is introduced as benzoic ester by nucleophilic displacement of one chlorine atom, affording compound **3**, and the stereoselective reduction of the prochiral ketonic group affords the secondary alcoholic moiety (compound **4**); finally, the 4-phenyl-1-piperazinyl group is introduced with a second nucleophilic displacement with 1-phenylpiperazine.

In the first step, the monosubstitution of a chlorine atom of dichloroacetone is achieved in DMF solution by in situ generated sodium benzoate: the reaction proceeds at room temperature, affording 1-benzoyloxy-3-chloropropane-2-one (**3**), recovered in 70% yield after extraction and subsequent crystallisation of the crude from boiling hexane. Monosubstitution at dichloroacetone, albeitalready reported [13], is not easily achievable owing to the high reactivity of both the chlorine atoms; the nucleophilic displacement here described occurs under mild conditions with a weak nucleophile, selectively affording the desired product in 70% chemical yield; traces ($<4\%$, GLC) of disubstituted product, i.e. 1,3-dibenzoyloxypropan-2-one, were detected in the crude extract (GC/MS) but easily removed by the crystallisation. The present synthesis of **3** is particularly attractive when compared with that described in the literature [10,14] for this compound, namely, a twostep procedure starting from chloropropanediol (11% overall yield in Ref. [10], not reported in Ref. [14]).

The asymmetric reduction of prochiral haloketone **3** was carried out with baker's yeast (see experimental procedures), resulting in complete conversion after 3 hours; the corresponding chlorohydrin (+)-1-benzoyloxy-3-chloropropan-2-ol (+)-**4**, (60% yield) was obtained in 73% ee. The enantiomeric excess was affected to some extent by different ratios for substrate/yeast, as well as by the presence or absence of glucose, affording (+)-**4** in 68-75% ee; moreover, the use of selective enzyme inhibitors, such as allyl alcohol, allyl bromide [11] or cysteine [15], lowered conversions and enantioselectivity. It is noteworthy that the literature recently reported the synthesis of **3** (in two steps from 3-chloro-1,2-propanediol **5**) and its biocatalytic reduction to (−)-**4** [14] with different microorganisms: the present approach does appear to be an improvement in the synthesis of the haloketone and shows opposite stereoselectivity. The absolute configuration of (+)-**4** obtained by yeast reduction was established as (*R*), based upon chemical correlation with the configurationally known (*R*)-(−)-3-chloro-1,2-propanediol (−)-(**5**) [12], which was in fact obtained by reaction of (+)-**4** with ethanolic sodium hydroxide.

Compound (*R*)-(+)-**4** was shown to be a useful C3 chiral synthon through its conversion to levodropropizine (−)-**1**. Nucleophilic substitution of the halogen with 1-phenylpiperazine, as well as the removal of the benzoyl moiety, were subsequentially conducted in 'one pot' procedure in refluxing *i*-propanol. Levodropropizine (−)-**1** was isolated in the correct (*S*) configuration in 60% yield and 73% ee; the enantiomeric excess, determined by HPLC as described in the literature [7], proved that no racemization occurred. Fractional crystallization from dichloromethane–hexane afforded levodropropizine in 95% ee.

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