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Synthesis of Enantiomerically Pure (S)-(-)-Propranolol from Sorbitol

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Key Words: ß-Sympatholyticum; Sorbitol; Asymmetric Synthesis; Acetals; Regioselective.

Abstract: Synthesis of enantiomerically pure (S)-(-)-propranolol, the most active optical isomer of the widely used ß-Sympatholyticum,was achieved in high optical yield starting from sorbitol, an inexpensive and easily accessible carbohydrate. Via regioselective protection and coupling of α-naphthol, the key intermediate 5 was obtained. Deprotection of the intermediate acetals and successive oxidative degradation followed by some simple conversion steps lead to the formation of (S)-(-)-propranolol with high optically purity.

Introduction

The stereochemistry of most drug molecules governs their biological activity[1]. For a certain drug, one enantiomer can possess the desired properties of activity and/or selectivity while the other enantiomer can be much less active, inactive, or can cause unwanted side-effects. For this reason, prescription of racemic mixtures of these drugs brings an unnecessary load on the human organism (enantiomeric ballast). Therefore, the synthesis of homochiral drugs has become a key issue in the pharmaceutical industry[2].

ß-Blocking drugs of the 3-(aryloxy)-1-(alkylamino)-2-propanol type such as propranolol are such a group of drugs where the activity resides almost exclusively in the *S* enantiomer. For instance, the activity of (S)-(-)-propranolol is 98 times as high as that of its *R* enantiomer[3].

Many syntheses of (S)-(-)-propranolol, **1** (figure 1), have been published. The three main strategies that can be applied for the synthesis of enantiomerically pure compounds have been used, resolution (1), asymmetric synthesis using an external chiral auxiliary (2) or via a chiral synthon (3).

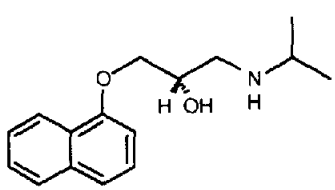


Figure 1 **1**

Direct resolution of racemic propranolol itself has been reported to be unsuccessful[4] but several syntheses have been published in which the enzymatic resolution of intermediate compounds has successfully been applied[5].

In the last decade several synthetic routes towards (S)-(-)-propranolol have been described in which an external chiral auxiliary has been used to obtain the enantiomerically pure target molecule[6]. Well known

examples are the use of one of the enantiomers of diisopropyl tartrate[6c,d] or an opticaly pure binaphthol complex[6f].

Methods based on 'the chiral pool' of enantiomerically pure natural products as starting materials have also been used before for the synthesis of (S)-**1**[7]. Most published routes[7a,b] start with (R)-glyceraldehyde acetonide, which is obtained either from D-mannitol[8] or via the enantiospecific esterase-catalyzed hydrolysis of a suitable precursor[9]. Recently another method was described[10] in which D-mannitol was the starting material.

The use of carbohydrates as chiral synthons has received a great deal of attention in recent years. In addition to the fact, that carbohydrates provide stereochemically defined carbon frameworks, which can be incorporated into new chiral structures, molecules of (protected) saccharides can also serve as templates for communicating chirality to new stereogenic centres being generated in an adjacent emerging chain[11], followed by a sacrificial destruction of one or more of the original stereogenic centres (sacrificial asymmetric synthesis).

Herein we describe a synthesis of (S)-(-)-propranolol, **1**, based on the last approach starting from the inexpensive and easily accessible carbohydrate sorbitol.

Results and Discussion

The target molecule, **1**, was synthesized in eight straightforward steps from sorbitol (Scheme 1). First, sorbitol, was protected as the dibenzylidene derivative **2** with benzaldehyde and sulfuric acid as described before[12].

In a one-pot-procedure diol **2** was converted into derivative **3c** via a regioselective mesylation of the primary hydroxyl group of **2** with one equivalent of methanesulfonyl chloride at -20° C in pyridine, followed by a benzoylation of the secondary hydroxyl group of **3a** with benzoyl chloride at room temperature. Derivative **3c** was obtained in 74% overall yield.

Addition of α-naphthol to **3c** was performed with potassium tertiary butoxide in dry DMSO at room temperature, yielding the desired adduct **5b** (58%)[13]. Isolated side-products were **5a** (13%), in which the benzoate ester has been saponified after the addition of α-naphthol, and epoxy derivative **4** (6%), which is the result of an intramolecular displacement of the mesylate group by the negatively charged geminal oxygen atom resulting from sapofinication of the benzoate. The structure of **4** was established by treatment of tosylate **3b** with sodium methanolate in methanol leading to the same epoxide **4** in 84% yield. Attempts to open epoxide **4** with the naphtholate anion failed, even after addition of one equivalent of titanium(IV) isopropoxide[14].

Hydrogenolysis of the benzylidene acetals of derivative **5b** with standard platinum and palladium catalysts on charcoal did not give the desired product **6** in reasonable yield. However, acid hydrolysis of the acetals with hydrochloric acid in methanol and ethylene glycol afforded tetrol **6** in 84% yield.

Oxidative cleavage of the tetrol chain of compound **6** with sodium metaperiodate in a dioxane/water mixture could be monitored with TLC, but isolation or purification of the resulting aldehyde via flash column chromatography failed repeatedly due to its instability. As a consequence, one-pot-reduction of the initially formed aldehyde, to its corresponding alcohol, was performed with sodium borohydride, as soon as TLC analysis of the oxidation showed complete conversion of **6**. This procedure gave the desired alcohol **7a**[15] in 77% overall yield (two steps).

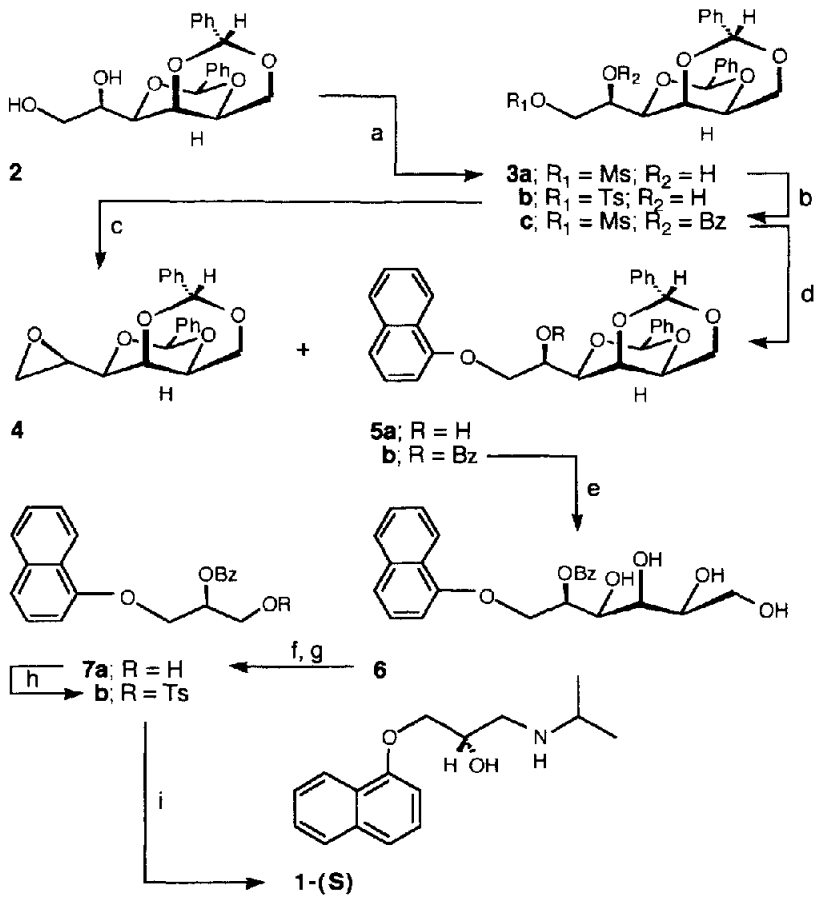
Tosylation of **7a** was performed with *p*-toluenesulfonyl chloride and 4,4-dimethyl-aminopyridine in pyridine for seven days at room temperature, whereupon tosylate **7b** was obtained (72%).

Treatment of **7b** with isopropylamine in methanol gave (S)-(-)-propranolol, **1**[16], in 78% yield. Analytical data, e.g. melting point and optical rotation, were in accordance with those published for the pure enantiomer in the literature[17].

Conclusions

Sorbitol is a useful chiral precursor for the synthesis of the enantiomerically pure β-sympatholyticum (S)-(-)-propranolol. An eight-step procedure with reasonable overall yield is described. Although the 'mass-yield' with respect to the amount of sorbitol used is somewhat low, cheap and easily accessible reagents are used in

simple reactions. Almost all intermediates have good crystallinic properties and can be easily purified by crystallization when working on a large scale. The product is optically pure.



(a) MsCl (1.1 eq.), pyridine, -20° C, 1 hr; (b) BzCl (1.2 eq.), RT, 3 hr, 74% (2 steps); (c) NaOMe; MeOH, RT, 2 hr, 84%; (d) α-naphthol, KOt-Bu, DMSO, RT, 17 hr, 58%; (e) $HOCH_2CH_2OH$, MeOH, HCl, reflux, 4 hr, 84%; (f) $NaIO_4$ (4.0 eq.), dioxane, RT, 17 hr; (g) $NaBH_4$ (2.0 eq.), dioxane, RT, 1 hr, 77% (2 steps); (h) pTsCl, pyridine, DMAP, RT, 7 days, 72%; (i) MeOH, isopropylamine, reflux, 4 hr, 78%.

Scheme 1

An advantage of the procedure described here is the early introduction of the aryl group, which demands rather harsh, basic conditions that could have been detrimental to the other groups used in this procedure. Using this procedure, one has also the possibility of introducing other aromatic groups, in order to synthesize related β-sympatholytics.

Together with other published routes, the enantioselective synthesis of (S)-(-)-propranolol described here is another example of a synthesis of this β-sympatholyticum in high optical purity, starting from a cheap carbohydrate precursor.

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13. Derivative **5b**; M.p.: 185 - 186.5° C; IR ($CHCl_3$) 3060, 3000, 2885, 1720, 1590, 1575, 1450, 1390, 1260, 1175, 1100, 1025, 820, 690 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ = 3.94 (s, 1H, H1'), 4.16 (dd, J1'-10'a =1.9, J10'a-10'b=10.4 Hz, 1H, H10'a), 4.17 (d, J5'-6'=1.8 Hz, 1H, H6'), 4.43 (dd, J1'-10'b=0.8 Hz, 1H, H10'b), 4.64 (dd, J1-2a=4.7, J2a-2b=11.0 Hz, 1H, H2a), 4.66 (dd, J1-5'=7.3 Hz, 1H, H5'), 4.73 (dd, J1-2b=2.3 Hz, 1H, H2b), 5.55 (s,1H, -OCPhHO-), 5.67 (s,1H, -OCPhHO-), 5.96 (m,1H, H1), 6.78 (m,1H, H2-naphthyl), 7.27-7.58 (m, 17H, HAr), 7.75 (m, 1H, H-naphthyl), 8.07 (m, 2H, H2 + H6 benzoyl), 8.24 (m, 1H, H-naphthyl); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ = 66.52 and 69.84 (s, C2 and C10'), 69.25, 70.29 and 70.57 (s, C1', C5' and C6'), 76.67 (s, C1), 100.46 (s, -OCHPhO-), 100.96 (s, -OCHPhO-), 105.52 (s, C2-naphthyl), 154.36 (s, C1-naphthyl), 165.54 (s, C=O benzoyl).
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15. Derivative **7a** ; M.p: 93-94° C. $[\alpha]^{20}_D$ = - 43.7 (c = 0.97, $CHCl_3$); IR ($CHCl_3$) 3400, 3050, 3000, 2940, 1720, 1580, 1450, 1400, 1265, 1235, 1100, 1070, 1020, 700 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ = 4.31 (m, 2H, H3a + H3b), 4.54 (dddd, J1-2≈J2-3=5.1 Hz, 1H, H2) 4.67 (m, 2H, H1a + H1b), 6.86 (m, 1H, H2-naphthyl), 7.34-7.63 (m, 7H, HAr), 7.81 (m, 1H, H-naphthyl), 8.08 (m, 2H, H2 + H6 benzoyl), 8.25 (m, 1H, H-naphthyl); MS: (EI) accurate. mass: obs. 322.36.29; calc. for $C_{20}H_{18}O_4$: 322.3641.
16. (S)-(-)-propranolol, **1**; M.p.: 70-72° C (lit. 72-73°C); $[\alpha]^{20}_D$ = - 9.98 (c = 0.97, EtOH) (lit. $[\alpha]^{20}_D$ = - 10.21 (c = 1.02, EtOH); MS: (EI) accurate mass: obs. 259.3529; calc. for $C_{16}H_{21}NO_2$: 259.3513.
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