AN EFFICIENT SYNTHESIS OF (S)-(-)-BEFUNOLOL HYDROCHLORIDE INVOLVING THE REGIOSELECTIVE CONDENSATION OF (R)-GLYCIDOL AND 2-ACETYL-7-HYDROXYBENZOFURAN

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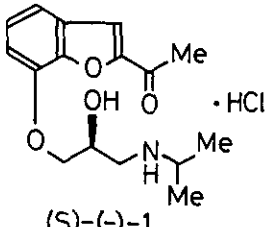
Abstract ----- (S)-(-)-Befunolol·HCl (S)-(-)-(1) was synthesized via (S)-(+)-2-acetyl-7-(2,3-epoxypropoxy)benzofuran (5) which was prepared by redox dehydrative condensation of 2-acetyl-7-hydroxybenzofuran (3) and (R)-glycidol (4).

Befunolol·HCl, 2-acetyl-7-(2-hydroxy-3-isopropylaminopropoxy)benzofuran hydrochloride (1), is a potent ß-adrenergic blocking agent (ß-blocker)[1] and its ß-blocking activity resides mainly in one of the enantiomers, levorotatory hydrochloride.[2] Previously we have reported the resolution of racemic 1 and the absolute configuration of the obtainable enantiomers.[3] In the present paper, we wish to report an efficient synthesis of the biologically more active (S)-isomer of 1 using D-mannitol (2).

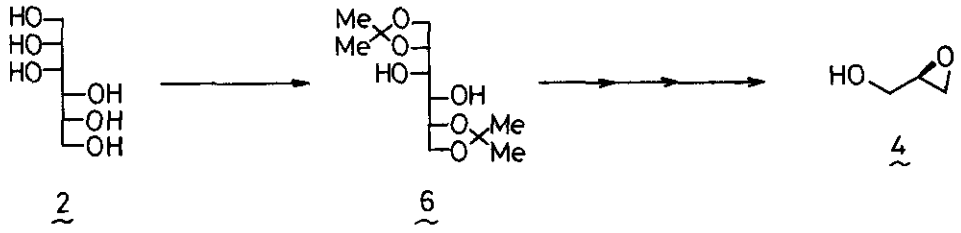


(S)-(-)-1

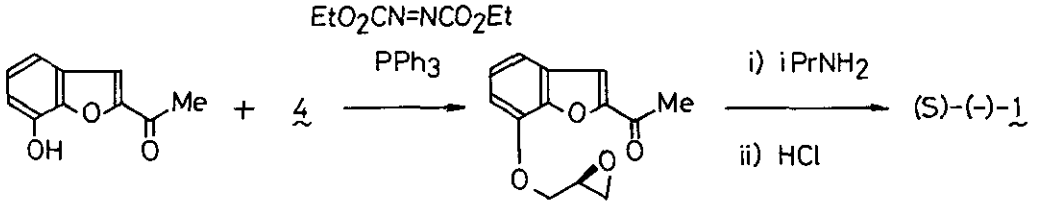
In synthesizing the optically active ß-blockers, there are two major problems as follows; a) preparation of three carbon chiral units; b) introduction of them into aryl compounds. While the former has been variously devised,[4] most previous works dealing with the latter have been carried out only by means of nucleophilic substitution under alkaline condition. On the other hand, it has been clarified by our previous experiment that the nucleophilic substitution of 2-acetyl-7-hydroxybenzofuran (3) with electrophiles such as epichlorohydrin under alkaline condition did not proceed satisfactorily. Therefore, in order to obtain the key intermediate,

(S)-(+)-2-acetyl-7-(2,3-epoxypropoxy)benzofuran (5), having high optical purity in good yield, we tried to introduce the readily available (R)-glycidol (4) into 3 under nearly neutral condition (Mitsunobu reaction).[5] Since such a redox condensation proceeds high regioselectively, differing from the nucleophilic substitution using epichlorohydrin and its analogs,[6] we expected to be able to obtain the desirable 5 in good yield.

According to McClure's procedure[7] and Takano's improved procedure,[8] 1,2,5,6-di-O-isopropylidenemannitol (6),[9] obtained from 2, was converted to 4 in three steps. Mitsunobu reaction was carried out by gradually adding of diethyl azodicarboxylate (20.9 g, 0.12 mol) to a solution of 3 (17.6 g, 0.1 mol), 4 (8.9 g, 0.12 mol), and triphenylphosphine (31.4 g, 0.12 mol) in dry THF (150 ml) with stirring under a nitrogen atmosphere at 0-10°C. After being stirred at room temperature for 3 h, the solvent was evaporated and ether (100 ml) was added to the resulting mixture. The separated crystals were filtered off and the filtrate was concentrated to give a residue, which was purified by silica gel column chromatography (Merck Kieselgel-60 250 g, eluent CH_2Cl_2 : n-hexane : ether ≈ 3 : 3 : 1) to give 5 in 79.7 % yield (18.5 g), mp 74-76°C (from MeOH) (Found : C, 67.20; H, 5.19. $C_{13}H_{12}O_4$ requires C, 67.24; H, 5.17 %); $[\alpha]_D$ +25.9° (c=1.00, MeOH); IR ν_{MAX}(KBr)



2 6 4



3 5

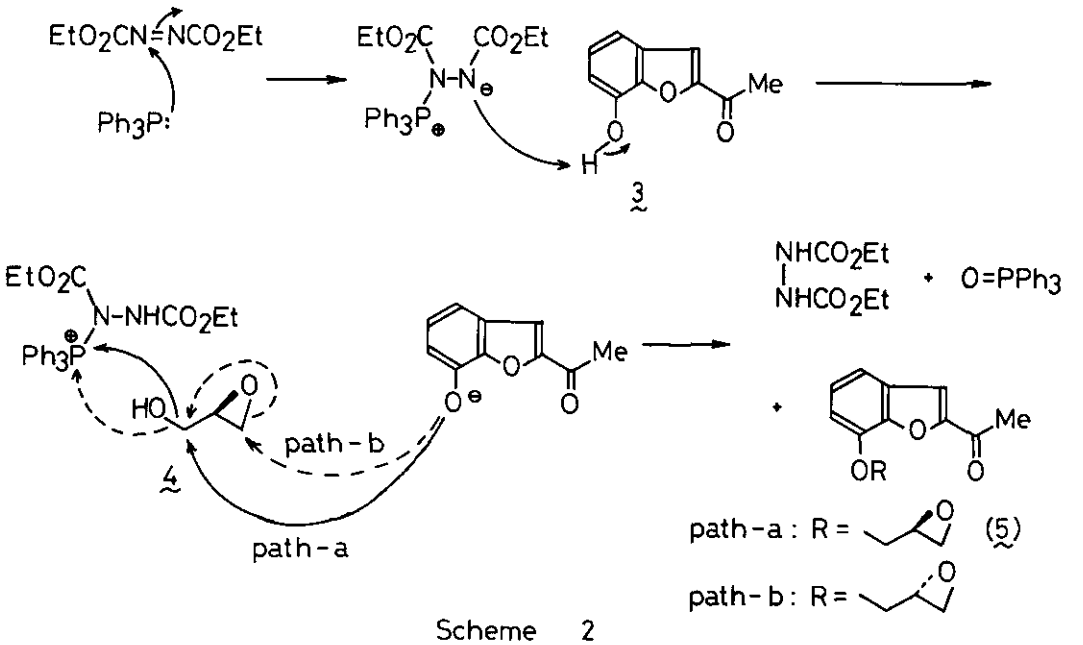
Scheme 1

1680 cm^{-1}; NMR $\delta(CDCl_3)$ 2.59 (3H, s), 2.78-3.02 (2H, m), 3.36-3.58 (1H, m), 4.11-4.28 (1H, dd, J = 6 Hz, J = 12 Hz), 4.45-4.62 (1H, dd, J = 4 Hz, J = 12 Hz), 7.03-7.43 (4H, m); MS (m/e) 232(M^+), 202, 189, 176, 161.

The epoxide 5, on treatment with isopropylamine,[1a] was converted to 1 in 80.5 % yield, mp 151-152°C (from 2-propanol) (Found : C, 58.33; H, 6.57; N, 4.04. $C_{16}H_{21}NO_4 \cdot HCl$ requires C, 58.62; H, 6.76; N, 4.27 %); $[\alpha]_D$ -15.5° (c=1.00, MeOH); IR ν_{MAX}(KBr) 3375, 1680 cm^{-1}; NMR $\delta(D_2O)$ 1.66 (6H, d, J = 7 Hz), 2.49 (3H, s), 3.44-3.60 (2H, m), 3.82 (1H, sep, J = 7 Hz), 4.29 (2H, br d), 4.45-4.72 (1H, m), 6.94-7.25 (3H, m), 7.30 (1H, s); MS (m/e) 291, 276, 247, 176, 161, 102, 72.

The optical purity of obtained (S)-(-)-1 was determined to be > 99 ee% by separating the diastereoisomers derived from 1 and 2,3,4,6-tetra-O-acetyl-ß-D-glucopyranosyl isothiocyanate[10] by high performance liquid chromatography, followed by comparing the two peak areas.

In conclusion, an efficient synthesis of (S)-(-)-1 has been achieved through Mitsunobu reaction of 2-acetyl-7-hydroxybenzofuran (3) with (R)-glycidol (4), in which the hydroxy group of 4 was almost directly displaced as shown in Scheme 2 (path-a). Our present procedure is seemed to be applicable to the synthesis of other ß-blockers.



Scheme 2

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