

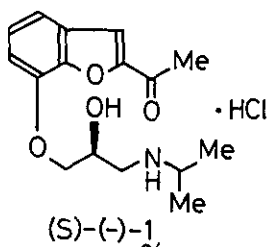
AN EFFICIENT SYNTHESIS OF (S)-(-)-BEFUNOLOL HYDROCHLORIDE INVOLVING
THE REGIOSELECTIVE CONDENSATION OF (R)-GLYCIDOL AND 2-ACETYL-7-
HYDROXYBENZOFURAN

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

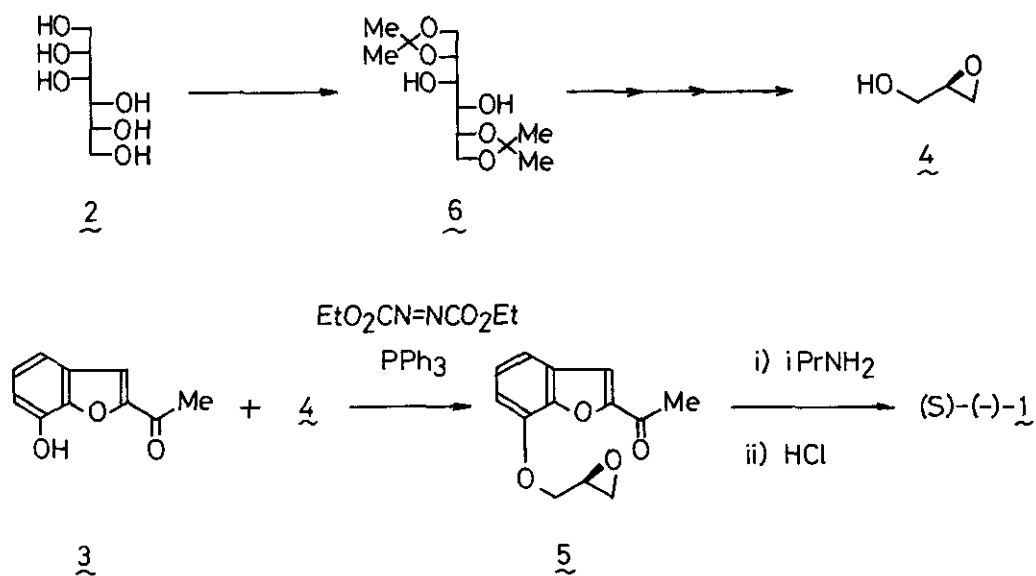
Befunolol·HCl, 2-acetyl-7-(2-hydroxy-3-isopropylaminopropoxy)benzofuran hydrochloride
(1), is a potent β -adrenergic blocking agent (β -blocker)¹ and its β -blocking acti-
vity resides mainly in one of the enantiomers, levorotatory hydrochloride.² Previ-
ously we have reported the resolution of racemic 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).



In synthesizing the optically active β -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 substi-
tution under alkaline condition. On the other hand, it has been clarified by our
previous experiment that the nucleophilic substitution of 2-acetyl-7-hydroxybenzo-
furan (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 procedure⁷ and Takano's improved procedure,⁸ 1,2,5,6-di-O-isopropylidene-mannitol (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 CH₂Cl₂ : 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. C₁₃H₁₂O₄ requires C, 67.24; H, 5.17 %); [α]_D²⁰ +25.9° (c=1.00, MeOH); IR ν_{MAX}(KBr)



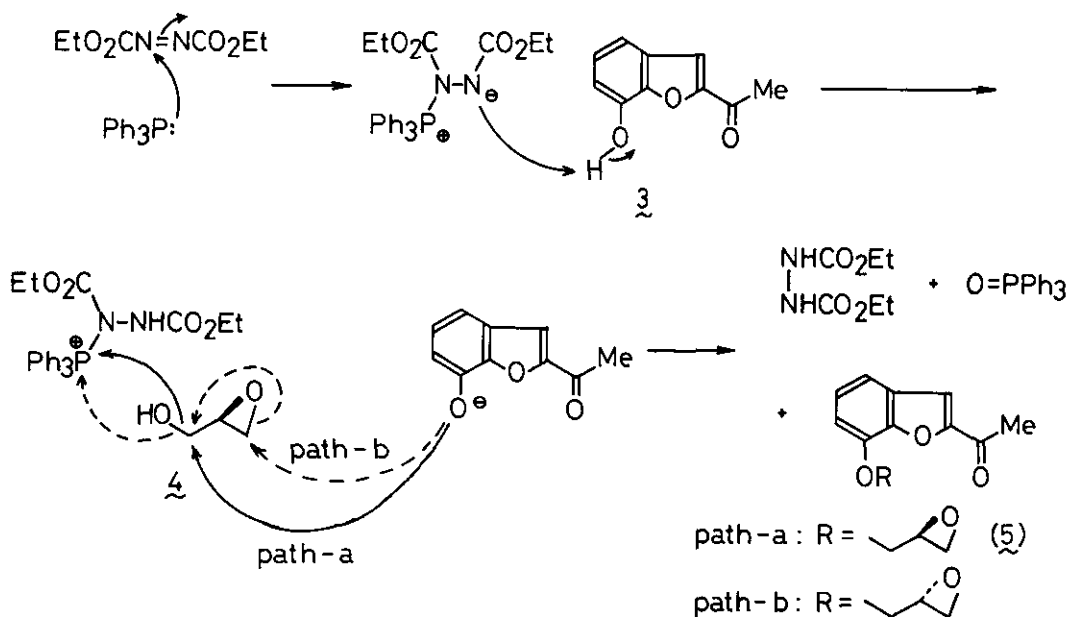
Scheme 1

1680 cm^{-1} ; NMR $\delta(\text{CDCl}_3)$ 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. $\text{C}_{16}\text{H}_{21}\text{NO}_4 \cdot \text{HCl}$ requires C, 58.62; H, 6.76; N, 4.27 %); $[\alpha]_{\text{D}} -15.5^\circ$ ($c=1.00$, MeOH); IR $\nu_{\text{MAX}}(\text{KBr})$ 3375, 1680 cm^{-1} ; NMR $\delta(\text{D}_2\text{O})$ 1.06 (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- β -D-glucopyranosyl isothiocyanate¹⁰ 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 β -blockers.



ACKNOWLEDGEMENT. The authors wish to thank Drs. K. Ogasawara and N. Katagiri (Pharmaceutical Institute, Tohoku University) for their helpful suggestion.

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Received, 28th June, 1983