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Asymmetric Synthesis of FR165914: A Novel β3-Adrenergic Agonist with a Benzocycloheptene Structure

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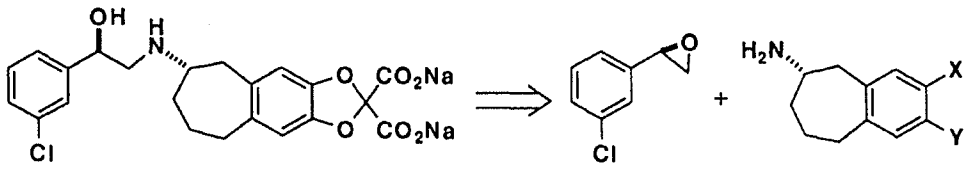
Abstract: The asymmetric synthesis of a novel β3-adrenergic agonist FR165194 is described. The critical steps involve preparation of an optically active amine *via* stereoselective reduction of a chiral imine prepared from α-methylbenzylamine and synthesis of a chiral epoxide *via* the Sharpless asymmetric dihydroxylation.

In 1967, β-adrenoreceptors were classified into two subtypes β_1 and β_2.[1] Recently, atypical β-adrenoreceptors, that is, those which do not fit into either the β_1- or the β_2- classification, have been discovered and have been called β3-adrenoreceptors.[2] They appear to be widely distributed among various tissues and co-occur with other receptors which complicates their classification.[3] In particular, they are found on the cell surface of both white and brown adipocytes where their stimulation promotes both lipolysis and energy expenditure.[4] A Beecham group[5] and a number of other laboratories[6] have reported research directed towards the discovery of potent agonists for β3-Adrenoreceptors, and have identified several new structural phenethanolamines. In this paper, we would like to describe the asymmetric synthesis of a novel and potent β3-Adrenoreceptor agonist FR165914 and its derivatives having a benzocycloheptene ring. The stereochemistry of the phenethanolamine has a crucial influence on the potency and selectivity, therefore, our synthetic plan required that both fragments; amino-benzocycloheptenes and epoxides be optically active (Scheme 1).

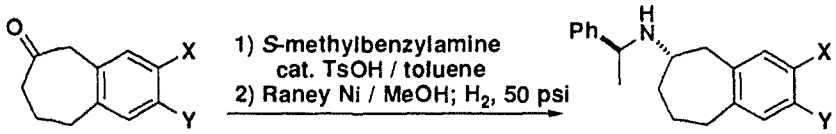
Scheme 1



1: FR165914

The requiste chiral amines were prepared *via* stereoselective reduction of imines containing a chiral auxiliary. The starting 2-benzosuberones **2** were prepared from commercially available 1-tetralones by ring expansion according to a modified literature procedure.[7] Conversion to the chiral imines with (*S*)-α-methylbenzylamine in the presence of a catalytic amount of *p*-toluenesulfonic acid under Dean-Stark conditions followed by reduction of the resulting imines with Raney nickel (W-2) in methanol furnished amines **3** having a *S* configuration,[8] with good selectivity.[9] These results on the asymmetric reduction of imines are summarized in Scheme 2.[10]

Scheme 2

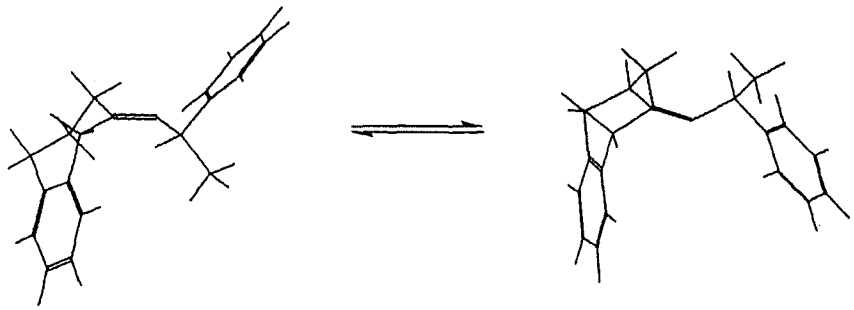


2a: X,Y: OMe
b: X: OMe, Y: H
c: X: H, Y: OMe

	yield (%)	ratio
3a	61	14 : 1
b	50	12 : 1
c	70	12 : 1

The intermediate imines exist as an equilibrium mixture of *E* and *Z* isomers.[11] Figure 1 illustrates the most stable comformation of the *E* and *Z* isomers obtained by calculation using QUANTA (Version 3.3) and PM3 (MOPAC Version 6).[12-14] It is reasonable to assume that reduction occurs preferentially from the *re* face of the *E*-imines by taking into account steric hindrence of both faces of the *Z*-imines. Thereby the predicted absolute configuration of the adducts is in accord with the experimental findings.

Figure 1

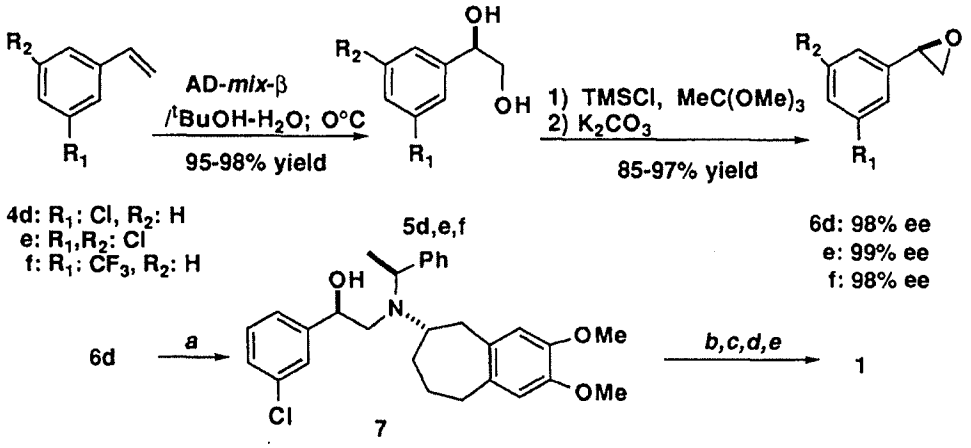


***E*-isomer** ***Z*-isomer**

The required optically active epoxides were obtained *via* the Sharpless AD reaction and epoxidation. Oxidation of **4** by the standard procedure with commercial available AD-mix-β[15] provided the diols **5** in 95-98% yield. The diols **5** were easily converted to the epoxides **6** using the method involving a cyclic acetoxonium intermediate,[16] and had 98-99% ee as determined by HPLC analysis with a chiral column (Chiralcel AD). Ring opening of epoxide **6d** with amine **3a** (14:1 mixture) in ethanol under reflux for 48 h afforded the phenethanolamine **7** containing a small amount of the undesired diastereomer that was easily removed by column chromatography on silica gel. Treatment of enantiomerically pure **7** with BBr_3 followed by alkylation with diethyl dibromomalonate gave the diester compound. Hydrogenolysis of the benzyl group employing chlorobenzene as a co-solvent to inhibit reduction of the *m*-chlorogroup followed by hydrolysis furnished FR165914 in 23% overall yield from **7**.

The in vitro effects on β-adrenoreceptors mediated processes are shown in Table 1. FR165914 possesses potent β_3-agonist activity and especially low affinity for β_1- and β_2-adrenoreceptors.

Scheme 3



reagents and conditions: *a)* **3a**, EtOH, 94% yield *b)* BBr_3, CH_2Cl_2 *c)* diethyl dibromomalonate, K_2CO_3, DMF *d)* H_2,Pd/C, EtOH-chlorobenzene(1:10) *e)* NaOH, EtOH, 23% yield (from **7**)

Table 1.

	Rat colon (β_3) IC_{50}	Rat uterus (β_2) IC_{50}	Guinea-pig atrium (β_1) EC_{50}
1	6.0×10^{-9}	$>1.0\times10^{-5}$	$>1.0\times10^{-5}$

IC_{50} and EC_{50} concentration (M) producing half-maximal effect.

In summary, we have disclosed a stereoselective synthesis for a novel β_3-agonist FR165914. This method is easily applied to related structures, and is especially attractive for large-scale synthesis. The detailed structure-activity investigations will be published in due course.

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8. The assignment of the absolute configuration of **3a** was determined by X-ray structural analysis.
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10. Ratio was determined by ^{1}H-NMR.
11. *E*: *Z* -Ratio of imines could not be determined.
12. The most stable conformation for *E* and *Z* isomers were determined as follows. The conformation of the seven membered ring portions of both compounds were determined using systematic search analysis in QUANTA (Version 3.3).[13] Next, based on the obtained stable ring conformations of each compound, the heat of formation of the rotamers around the N-C bonds were calculated using PM3.[14] The rotamers which gave the minimum heat of formation were chosen as the most stable conformations and are shown in Fig 1.
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