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SYNTHESIS AND BIOLOGICAL EVALUATION OF A FLUORINATED ANALOG OF THE β-ADRENERGIC BLOCKING AGENT, METOPROLOL

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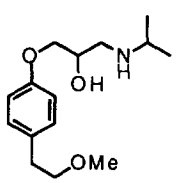
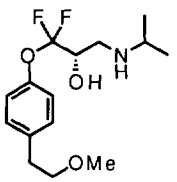
Abstract: Both enantiomers of a difluorinated metoprolol analog (**1**) were synthesized in enantiomerically pure form and evaluated as β-adrenergic blocking agents. © 1997 Elsevier Science Ltd.

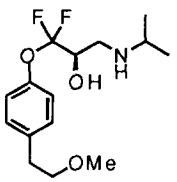
Fluorine-containing compounds have played a special role in medicinal chemistry and biomedical applications in view of the influence of fluorine's unique properties on biological activity.[1] Fluorine, due to its high electronegativity, has a considerable electronic effect on its neighboring groups in a molecule. α,α-Difluoroketones easily form metastable hydrates, and the introduction of a difluoromethylenecarbonyl residue [-CF_2(CO)-] into bioactive peptides has led to the discovery of potent protease inhibitors mimicking the sp^3-hybridized transition state for hydrolytic amide bond cleavage.[2] The attachment of fluorine atoms at the β-position to a hydroxyl group increases its acidity, making it a better hydrogen atom donor to the active sites of enzymes and receptors.[3] β,β-Difluoro peptidyl alcohols have been also reported to act as reversible inhibitors towards proteolytic enzymes. We wish herein to report the synthesis of a difluorinated analog (**1**) of the β_1-selective β-blocker, metoprolol, in enantiomerically pure form and its biological evaluation as a β-adrenergic blocking agent.



metoprolol

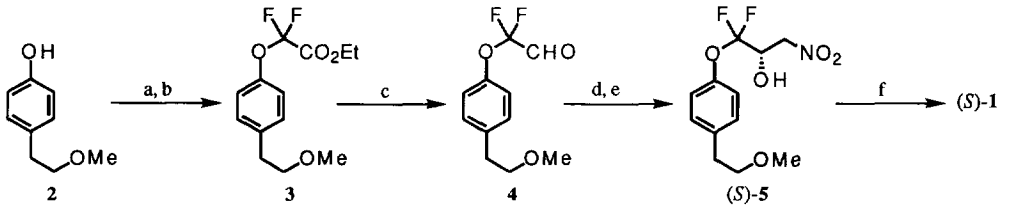


(*S*)-**1**



(*R*)-**1**

The enantiomerically pure metoprolol analog (*S*)-**1** was prepared from 4-(2-methoxyethyl)phenol (**2**) as shown in Scheme 1. Treatment of the phenol **2** and chlorodifluoroacetic acid with sodium in refluxing dioxane[4], followed by esterification with iodoethane, afforded the α,α-difluoro ester **3** in 73% overall yield. Reduction of the ester **3** with diisobutylaluminum hydride in ether at -78°C gave the α,α-difluoro aldehyde **4** in 80% yield.[5] Reaction of the aldehyde **4** with nitromethane at -40°C in the presence of the samarium-lithium-(*R*)-BINOL catalyst (8 mol%) provided (*S*)-1,1-difluoro-1-[4-(2-methoxyethyl)phenyl]oxy-3-nitropropan-2-ol (**5**) of 75% ee in 52% yield.[6] After recrystallization from ether-hexane, the nitroaldol adduct **5** was obtained in enantiomerically pure form from the mother liquor (65%, >99% ee). Reductive alkylation of the homochiral nitroaldol (*S*)-**5** to (*S*)-**1** was accomplished in 89% yield by a PtO_2-catalyzed hydrogenation in the presence of acetone in methanol.[7] In the same manner, the adduct (*R*)-**5** obtained by the nitroaldol reaction of **4** using the samarium-lithium-(*S*)-BINOL catalyst was converted to the enantiomerically pure metoprolol analog (*R*)-**1**.



Scheme 1: (a), Na, $ClCF_2CO_2H$, dioxane, reflux, 6 h; (b) K_2CO_3, EtI, acetone, reflux, 12 h (73% over two steps); (c) DIBAL-H, ether, -78°C, 1 h (80%); (d) Sm-Li-(*R*)-BINOL, CH_3NO_2, THF, -40°C, 168 h (52%, 75% ee); (e) recrystallization from ether-hexane (65%, >99% ee); (f) PtO_2, H_2, MeOH, rt, 2 h, then acetone, 50°C, 24 h (89%, >99% ee).

The biological activities of the fluorinated metoprolol analog **1** are shown in Table 1.[8] The fluoro analog (*S*)-**1** has slightly lower affinity to β-receptor sites of rat cortex membranes compared to metoprolol, while the binding affinity of (*R*)-**1** was greatly reduced.[9] β_1-Adrenergic blocking activities of metoprolol and (*S*)-**1** were assessed from their ability to inhibit the positive inotropic effect of isoproterenol on the isolated atrium of guinea pigs.[10] The fluoro analog (*S*)-**1** was 7-fold less potent than metoprolol. β_2-Antagonistic potency of (*S*)-**1** was determined to be approximately one-seventh of that of metoprolol by their ability to inhibit the relaxing effect of epinephrine on the isolated tracheal muscle of guinea pigs.[11]

Table 1. β_1- and β_2-Adrenergic Blocking Activities of a Fluorinated Metoprolol Analog **1**.

Compound	Receptor Binding [a] IC_{50} (μM)	β_1-Antagonistic effect[b] IC_{50} (μM)	β_2-Antagonistic effect[c] IC_{50} (μM)	β_2/β_1
metoprolol (racemate)	0.50	0.19	0.32	0.59
(*S*)-**1**	1.54	1.35	2.15	0.63
(*R*)-**1**	>100	-	-	-

a) Inhibition of (-)-[^{3}H]dihydroalprenolol binding to β-adrenergic receptor sites in rat cortex. See ref. 9; b) Determined by the ability to inhibit the positive inotropic effect of isoproterenol on the isolated right atrium of guinea pigs. See ref. 10; c) Assessed from the ability to inhibit the relaxing effect of epinephrine on the isolated tracheal muscle of guinea pigs. See ref. 11.

In conclusion, the difluorinated metoprolol analog (*S*)-**1** has slightly lower β_1- and β_2-adrenergic blocking activities compared to metoprolol. The potential utility of this fluoro analog as a β-blocker remains to be determined by *in vivo* evaluation.

References and Notes

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