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Synthesis of (αR, 6R or 6S)-N-(α-methylbenzyl)-6-difluoromethyl-4-hydroxy-4-(4-chlorophenyl)piperidines

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Abstract

Diasteroeselective synthesis of (αR, 6R or 6S)-N-(α-methylbenzyl)-6-difluoromethyl-4-hydroxy-4-(4-chlorophenyl)piperidines, which were produced from the reaction of (αR, 6R)- or (αR, 6S)-N-(α-methylbenzyl)-6-difluoromethyl-4-piperidone and 4-chlorophenyllithium, is described.

Keywords: Difluoromethyl group; Diastereoselectivity

1. Introduction

Since the discovery of inactivation of the HIV-1 protease of haloperidol [1], research into the structure/activity of the haloperidol structure [2,3] has been extensive in recent years. Recently we have reported the stereocontrolled synthesis of 1,6-dideoxy-6,6-difluoroazasugar analogs, which are interesting for their versatility as precursors for inhibition of the HIV virus [4]. As a continuation of our interest in the synthesis of fluoro-analogs of protease inhibitors, we were intrigued by difluoromethyl substitution of the haloperidol structure. The difluoromethyl group is favored owing to its ability to act as a hydrogen bond donor, potentially allowing interaction with solvent and biological molecules. Accordingly, we have been studying new synthetic approaches to the haloperidol structure where the C6 hydrogen atom is replaced by a difluoromethyl group. Our strategy is based on the concept that CHF_2-containing molecules with multiple stereocenters might be constructed more easily by employing chiral building blocks with appropriate functionalities [5].

Recently, we reported the synthesis of (αR, 6R or 6S)-N-(α-methylbenzyl)-6-difluoromethyl-5,6-dihydro-4-pyridone **1**, which was prepared via a cycloaddition reaction of 1-methoxy-3-[(trimethylsilyl)oxy]-1,3-butadiene and (αR)-N-(2,2-difluoroethylidene)(α-methylbenzyl)amine derived from difluoroacetaldehyde ethyl hemiacetal [6] and (R)-(α-methylbenzyl)amine (>98% ee) as shown in Scheme 1.

A synthetic strategy to the desired material is shown in Scheme 2. To attain the desired haloperidol derivative possessing a difluoromethylene unit, we required as precursors chiral 6-difluoromethyl-4-piperidones **2**. Chiral 6-difluoromethyl-5,6-dihydro-4-pyridones **1** gave satisfactory conversion into the desired chiral 6-difluoromethyl-4-piperidones **2** (>99% de) with $LiAlH_4$ in THF at −78 °C. Then, they were transformed into (αR, 6R or 6S)-N-(α-methylbenzyl)-6-difluoromethyl-4-hydroxy-4-(4-chlorophenyl) piperidine **3** or **4** with high diastereoselectivity. In the case of (αR, 6R)-N-(α-methylbenzyl)-6-difluoromethyl-4-piperidones **2a**, the diastereoselectivity of the compound **3** ($[\alpha]_D^{23} = +18.32$ (*c* 0.77, MeOH), >99% de) is >99:<1. However, in the case of (αR, 6S)-N-(α-methylbenzyl)-6-difluoromethyl-4-piperidones **2b**, the diastereomeric ratio of product **4** is 82:18. The final purification of **4** was carried out by using column chromatography on silica gel to give (αR, 6S)-N-(α-methylbenzyl)-6-difluoromethyl-4-hydroxy-4-(4-chlorophenyl)-piperidine (**4a**: $[\alpha]_D^{25} = +14.50$ (*c* 3.79, MeOH), >99% de) as a major product. The epimeric purities of **3** or **4a** determined by ^{19}F NMR (470 MHz) intensities were >99% de. The determination of the absolute configuration of compounds **3** and **4a** at the 4 position is in progress.

For each of the compounds **3** and **4**, the in vitro viable cell inhibitory towards interleukin-2 antiproducing effect was determined. The reported IC_{50} values [1] represent the con-

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[1] The cell was incubated in the presence or absence of compound. Then, MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium bromide] was added for $OD^{578-588}$ measurements. IC_{50} (μg ml^{-1}) was given as the concentration at 50% inhibition of interleukin-2 production.

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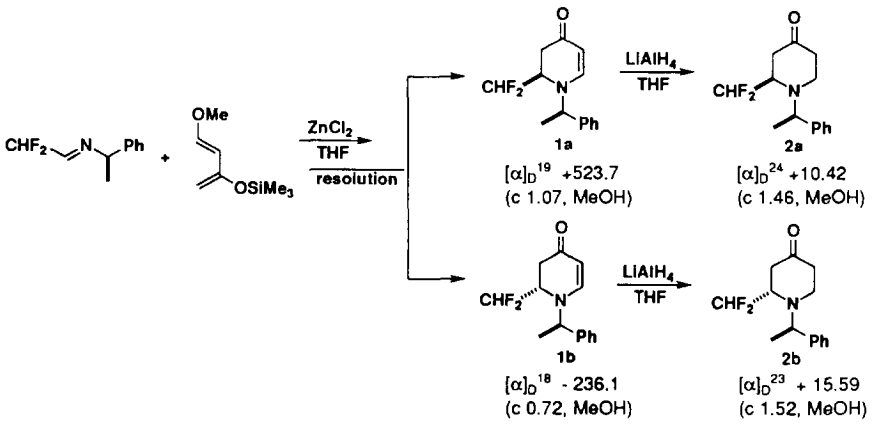
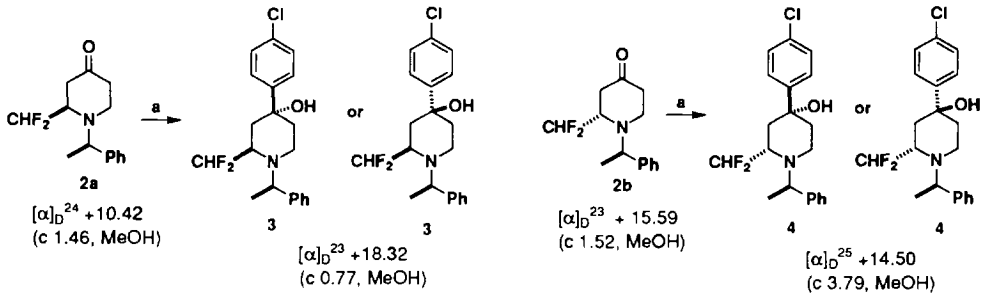


Scheme 1.



Scheme 2. (a) ≡4-chlorophenyllithium, toluene, 0 °C.

centration of inhibitor producing 50% inhibition of interleukin-2 producing antimetabolite, cyclosporin A (IC_{50}: < 0.01 μg ml^{-1}), as a reference. Compound **4** showed no activity. A comparison of IC_{50} values demonstrated the potential of compound **3** (IC_{50}: 1.16 μg ml^{-1}) as an interleukin-2 antiproducing substance. However, there was no delayed type hypersensitivity (DTH) suppressing effect shown by compound **3**.

2. Experimental

2.1. General procedure

All commercially available reagents were used without further purification. Chemical shifts of ^1H (500 MHz) and ^{13}C NMR spectra were recorded in ppm (δ) downfield from the following internal standard (Me_4Si, δ 0.00, or $CHCl_3$, δ 7.24). The ^{19}F (470 MHz) NMR spectra were recorded in ppm downfield from the external trifluoroacetic acid (TFA) in $CDCl_3$ using a VXR 500 instrument. Yields quoted are those of the products actually isolated.

2.1.1. αR)-N-(α-Methylbenzyl)-6-difluoromethyl-5,6-dihydro-4-pyridone (1) [4]

To a solution of zinc chloride (0.80 g, 5.9 mmol), (α*R*)-*N*-(2,2-difluoroethylidene)(α-methylbenzyl)amine [4] (1.0 g, 5.9 mmol) and 1-methoxy-3-[(trimethylsilyl)oxy]-1,3-butadiene (1.51 g, 8.8 mmol) in THF (50 ml) were added. After 3 h of stirring at room temperature, the whole was poured into water, and then oily materials were extracted with ethyl acetate. The extracts were dried over magnesium sulfate. On removal of the solvent, crude epimers (1:1 mixture), (α*R*)-*N*-(α-methylbenzyl)-6-difluoromethyl-5,6-dihydro-4-pyridone (**1**) was isolated in 83% yield. Epimers were separated by the column chromatography on silica gel using a mixture of *n*-hexane and ethyl acetate (1:3) as eluent, giving compound **1a** (43% yield) and compound **1b** (40% yield).

(α*R*, 6*R*)-*N*-(α-Methylbenzyl)-6-difluoromethyl-5,6-dihydro-4-pyridone (**1a**): $[\alpha]^{19}_D = +523.7$ (c 1.07, MeOH); ^1H NMR ($CDCl_3$): δ 1.68 (3 H, d, $J = 6.84$ Hz), 2.55 (1 H, d, $J = 17.3$ Hz), 2.79 (1 H, ddd, $J = 2.20$, 7.57, 17.3 Hz), 3.58 (1 H, m), 4.65 (1 H, q, $J = 7.08$ Hz), 5.13 (1 H, dd, $J = 0.73$, 7.57 Hz), 5.97 (1 H, dt, $J = 6.59$, $J = 55.9$ Hz), 7.20–7.40 (5 H, Ar–H), 7.48 (1 H, dd, $J = 0.98$, 7.57 Hz); ^{13}C NMR ($CDCl_3$): δ 21.29, 34.39 (t, $J = 3.8$ Hz), 58.49 (t, $J = 23.8$ Hz), 62.93 (t, $J = 1.6$ Hz), 99.52, 113.09 (t, $J = 246.6$ Hz), 125.77, 128.39, 129.28, 142.21, 147.89, 188.58; ^{19}F NMR ($CDCl_3$): δ 34.91 (ddd, $J = 7.4$, 54.93, $J = 288$ Hz), 35.50 (ddd, $J = 9.16$, 54.9, $J = 288$ Hz); IR:1650 (C=O) cm^{-1}; high-resolution mass calc. for $C_{14}H_{15}NOF_2$ (M)$^+$ 251.1122, found 251.1120.

(α*R*, 6*S*)-*N*-(α-Methylbenzyl)-6-difluoromethyl-5,6-dihydro-4-pyridone (**1b**): mp 107–108 °C; $[\alpha]^{18}_D = -236.1$ (c 0.72, MeOH). ^1H NMR ($CDCl_3$): δ 1.64 (3 H, d, $J = 7.08$ Hz), 2.44 (1 H, dt, $J = 1.22$, 17.6 Hz), 2.71 (1 H, dd, $J = 7.57$, 17.3 Hz), 3.83 (1 H, m), 4.71 (1 H, q, $J = 6.83$ Hz), 4.96 (1 H, dd, $J = 0.73$, 7.56 Hz), 5.97 (1 H, dt, $J = 6.59$, $J = 55.9$ Hz), 6.90 (1 H, dd, $J = 1.22$, 7.81 Hz),

7.2–7.4 (Ar–H); ^{13}C NMR ($CDCl_3$): δ21.29 (t, J = 1.1 Hz), 35.22 (dd, J = 2.2, 4.9 Hz), 57.92 (dd, J = 22.1, 25.8 Hz), 63.10, 99.93, 113.56 (dd, J = 245.2, 247.8 Hz), 128.10, 129.23, 129.65, 139.21, 150.73, 189.30; ^{19}F NMR ($CDCl_3$): δ 35.1 (ddd, J = 12.2, 56.5, J = 288 H)), 36.9 (ddd, J = 7.63, 54.9, J = 288 Hz); IR: 1650 (C=O) cm^{-1}.

2.1.2. (αR, 6R)-N-(α-Methylbenzyl)-6-difluoromethyl-4-piperidone (2a) (nc)

Into a solution of $LiAlH_4$ (5 mmol) in THF (20 ml), (αR, 6R)-N-(α-methylbenzyl)-6-difluoromethyl-5,6-dihydro-4-pyridone (**1a**) (2.51 g, 10 mmol) in THF (10 ml) was added at −78 °C under a nitrogen atmosphere. After the mixture was stirred for 3 h at −78 °C, the mixture was quenched with an aq. NH_4Cl solution, and the organic materials were extracted with diethyl ether, and the ethereal solution was dried over $MgSO_4$. (αR, 6R)-N-(α-Methylbenzyl)-6-difluoromethyl-4-piperidone (**2a**) was separated by column chromatography on silica gel in 82% yield. $[\alpha]^{24}_D$ = +10.42 (c 1.46, MeOH). IR (neat) ν 1724 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.47 (3 H, d, J = 6.60 Hz), 2.32 (1 H, ddt, J = 0.70, 16.16, 4.73 Hz), 2.47 (3 H, m), 3.10 (2 H, m), 3.59 (1 H, m), 4.08 (1 H, q, J = 6.75 Hz), 5.76 (1 H, J = 2.23, 55.02, 57.25 Hz), 7.35 (5 H, m). ^{13}C NMR ($CDCl_3$): δ 20.85, 37.02 (dd, J = 1.86, 3.84 Hz), 39.29, 43.51 (d, J = 2.08 Hz), 57.22 (dd, J = 20.87, 24.53 Hz), 60.80, 116.95 (t, J = 247.7 Hz), 127.20, 127.61, 128.76, 143.38, 207.76. ^{19}F NMR ($CDCl_3$): δ 37.35 (ddd, J = 22.13, 56.46, 286.1 Hz), 41.94 (J = 9.16, 54.94, 286.1 Hz); high-resolution mass calc. for $C_{14}H_{18}NOF_2$ (M)$^+$ 254.1355, found 254.1348.

2.1.3. (αR, 6S)-N-(α-Methylbenzyl)-6-difluoromethyl-4-piperidone (2b) (nc)

In the above reaction, (αR, 6S)-N-(α-methylbenzyl)-6-difluoromethyl-5,6-dihydro-4-pyridone (**1b**) was used, and then worked up similarly. $[\alpha]^{23}_D$ = +15.59 (c 1.52, MeOH). IR (neat) ν 1720 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.46 (3 H, d, J = 6.74 Hz), 2.28 (1 H, ddt, J = 0.88, 4.45, 16.10 Hz), 2.43 (1 H, ddd, J = 5.75, 8.57, 16.07 Hz), 2.56 (2 H, m), 3.00 (1 H, ddddd, J = 0.77, 2.30, 4.60, 8.58, 13.08 Hz), 3.15 (1 H, m), 3.59 (1 H, m), 4.06 (1 H, q, J = 6.65 Hz), 5.79 (1 H, ddd, J = 2.48, 55.00, 56.24 Hz(, 7.2–7.5 (5 H, m). ^{13}C NMR ($CDCl_3$): δ 19.39, 37.10 (dd, J = 2.09, 3.97 Hz), 39.31, 43.09 (d, J = 2.08 Hz), 57.69 (dd, J = 20.92, 24.13 Hz), 60.45, 116.82 (t, J = 247.6 Hz), 127.05, 127.56, 128.74, 144.18, 207.71. ^{19}F NMR ($CDCl_3$): δ 37.22 (ddd, J = 19.84, 56.46, 286.9 Hz), 41.28 (ddd, J = 9.16, 54.94, 286.9 Hz); high-resolution mass calc. for $C_{14}H_{18}NOF_2$ (M)$^+$ 254.1355, found 254.1369.

2.1.4. (αR, 6R)-N-(α-Methylbenzyl)-6-difluoromethyl-4-hydroxy-4-(4-chlorophenyl) piperidine (3) (nc)

Into a solution of 4-chlorophenyllithium (10 mmol) derived from 4-chloroiodobenzene and *n*-BuLi (1.6 M in hexane) in toluene (15 ml), (αR, 6R)-N-(α-methylbenzyl)-6-difluoromethyl-4-piperidone (**2a**) (5 mmol) in toluene (5 ml) was added at 0 °C under nitrogen. After the mixture was stirred for 22 h at 0 °C, the reaction was quenched with saturated NH_4Cl aq. and then organic materials were extracted with diethyl ether. On removal of the solvent, (αR, 6R)-N-(α-methylbenzyl)-6-difluoromethyl-4-hydroxy-4-(4-chlorophenyl) piperidine (**3**) was obtained. $[\alpha]^{23}_D$ = +18.32 (c 0.766, MeOH). IR (neat) ν 3448 (OH) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.39 (3 H, d, J = 6.59 Hz), 1.58 (1 H, dq, J = 2.56, 13.73 Hz), 1.95–2.15 (4 H, m), 2.88 (1 H, dddd, J = 0.89, 2.34, 4.89, 13.34 Hz), 3.13 (1 H, dt, J = 2.76, 12.83 Hz), 3.2–3.4 (1 H, m), 4.12 (1 H, dq, J = 1.88, 6.70 Hz), 6.54 (1 H, ddd, J = 7.30, 54.40, 59.50 Hz), 7.2–7.5 (9 H, m). ^{13}C NMR ($CDCl_3$): δ 14.20, 21.86 (d, J = 1.4 Hz), 29.72, 35.93 (d, J = 7.5 Hz), 36.31, 38.61, 57.75 (dd, J = 21.3, 23.5 Hz), 59.58 (d, J = 2.0 Hz), 71.84, 116.05 (dd, J = 242.5, 246.0 Hz), 126.01, 126.90, 127.08, 128.42, 128.53, 133.11, 145.73, 146.74. ^{19}F NMR ($CDCl_3$): δ 38.55 (dd, J = 54.17, 283.8 Hz), 47.13 (ddd, J = 16.79, 59.51, 283.8 Hz); high-resolution mass calc. for $C_{20}H_{22}NOClF_2$ (M)$^+$ 365.1357, found 365.1345.

2.1.5. (αR, 5S)-N-(α-Methylbenzyl)-6-difluoromethyl-4-hydroxy-4-(4-chlorophenyl)piperidine (4) (nc) (major product)

In the above reaction, (αR, 6S)-N-(α-methylbenzyl)-6-difluoromethyl-4-piperidone (**2b**) was used, and then worked up similarly. (αR, 6S)-N-(α-Methylbenzyl)-6-difluoromethyl-4-hydroxy-4-(4-chlorophenyl) piperidine was obtained by column chromatography on silica gel. (major product): $[\alpha]^{25}_D$ = +14.50 (c 3.79, MeOH). IR (neat) ν 3437 (OH) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.40 (3 H, d, J = 6.48 Hz), 1.51 (1 H, dq, J = 13.69, 2.60 Hz), 1.75 (1 H, s) 2.07 (3 H, m), 2.78 (1 H, dddd, J = 1.08, 2.61, 4.67, 13.58 Hz), 3.08 (1 H, ddd, J = 2.74, 12.46, 13.42 Hz), 3.42 (1 H, m), 4.03 (1 H, dq, J = 2.20, 6.55 Hz), 6.63 (1 H, ddd, J = 7.51, 54.45, 59.31 Hz), 7.34 (9 H, m). ^{13}C NMR ($CDCl_3$): δ 22.13 (d, J = 2.2 Hz), 35.96 (d, J = 7.3 Hz), 36.28, 40.34, 55.11 (dd, J = 20.4, 23.5 Hz), 60.74 (d, J = 2.2 Hz), 72.05, 116.29 (dd, J = 242.9, 245.3 Hz), 126.01, 126.99, 128.50, 133.09, 135.50, 140.60, 146.22, 146.66. ^{19}F NMR ($CDCl_3$): δ 37.75 (dd, J = 54.93, 285.3 Hz), 44.32 (ddd, J = 13.73, 59.51, 285.3 Hz); high-resolution mass calc. for $C_{20}H_{22}NOClF_2$ (M)$^+$ 365.1357, found 365.1368. (minor product): ^{1}H NMR ($CDCl_3$): δ 1.43 (3 H, d, J = 6.76 Hz), 1.56 (1 H, m), 1.85 (1 H, ddd, J = 4.76, 12.25, 13.54 Hz), 2.01 (3 H, m), 2.41 (1 H, m), 2.70 (1 H, dt, J = 2.87, 11.94 Hz), 3.3–3.5 (1 H, m), 4.36 (1 H, q, J = 6.82 Hz), 6.05 (1 H, ddd, J = 2.83, 54.84, 55.94 Hz), 7.38 (9 H, m). ^{13}C NMR ($CDCl_3$): δ 9.25, 14.16, 21.03, 37.64 (t, J = 5.75 Hz), 39.79, 55.82 (t, J = 20.4 Hz), 71.36, 116.17 (dd, J = 242.4, 245.1 Hz), 126.01, 126.74, 127.70, 128.03, 128.43, 133.00, 143.17, 146.48. ^{19}F NMR ($CDCl_3$): δ 34.88 (ddd, J = 16.02, 55.70, 285.35 Hz) 36.60 (ddd, J = 9.91, 54.17, 285.35 Hz); high-resolution mass calc. for $C_{20}H_{22}NOClF_2$ (M)$^+$ 365.1357, found 365.1351.

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