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A PRACTICAL ENANTIOSELECTIVE SYNTHESIS OF (-)-NS-49*.

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Abstract: Asymmetric synthesis of (-)-NS-49 (**1**) was achieved by a convenient and short route.

(-)-NS-49 (**1**) is a novel aminoalcohol[1] which possesses α_1-adrenoceptor agonist activity and selectively contracts urethral smooth muscle. This compound (**1**) was found to increase intraurinary pressure, with little effect on blood pressure and is potentially useful in the treatment of urinary incontinence. During the course of one of our medicinal chemistry programs, we had need of a supply of (-)-NS-49 as a reference standard. The patented synthesis[1], however, does not provide practical and economical access to (**1**) due to the use of the (2*R*,4*R*)-MCCPM-rhodium complex[2], a catalyst which is not

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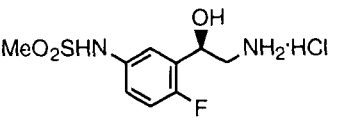
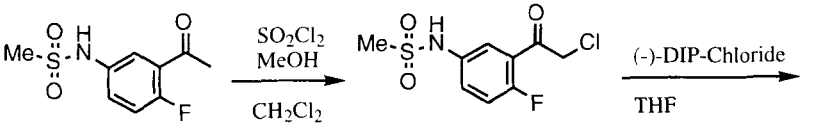
commercially available and the preparation of which involves 20 steps[3]. We wish now to report on the results of a straghtforward, efficient, alternative preparation of (**1**).



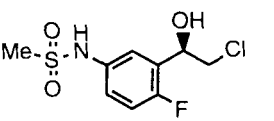
(**1**)

The synthetic method, shown in scheme 1, started from the readily available acetophenone (**2**)[1], which was chlorinated[4] by treatment with sulfuryl chloride (3 eq) and methanol (6 eq) in CH_2Cl_2 at reflux to give the chloroketone (**3**) (92%). This chlorination had to be carried out twice, in the same pot, otherwise the reaction was incomplete. The chlorohydrin (**4**) was obtained by asymmetric reduction of chloroketone (**3**) with (-)-*B*-chlorodiisopinocampheylborane[5] in 95% yield with an enantiomeric excess of 88% (chiral HPLC). After two

Scheme 1



(**2**) (**3**)

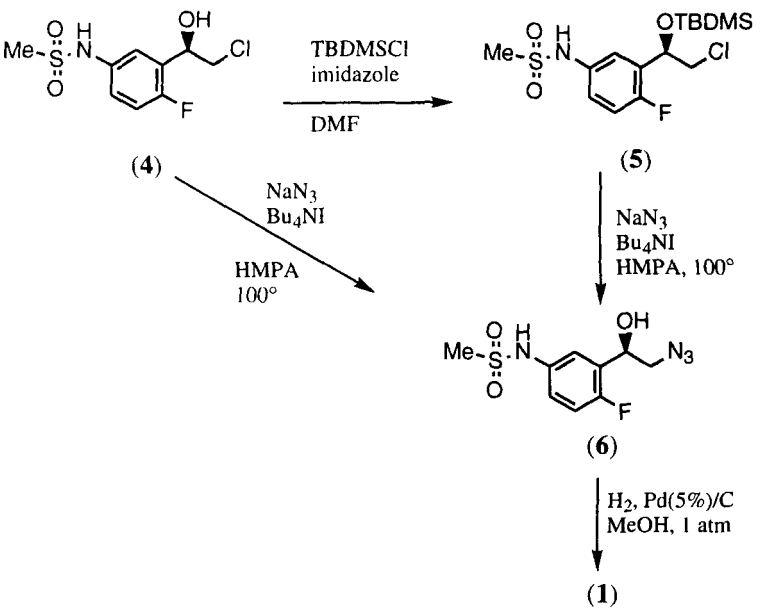


(**4**)

recrystallizations from ether-hexane, the enantiomeric purity was raised to 99.5%.

With this key intermediate in hand, efforts were next directed toward its conversion into NS-49 via the silyl-protected chlorohydrin (**5**). When (**5**) was subjected to reaction with tetra-*n*-butylammonium iodide (0.5 eq) and sodium azide (4 eq) in HMPA at 100°C, the

Scheme 2



azidoalcohol (**6**) was obtained in 67% yield. This displacement reaction could also be carried out on the unprotected chlorohydrin (**4**) to give (**6**) in 71% yield. Thus, protection of the hydroxy funtionality in (**4**) to prevent the formation of the epoxide is not necessary.[6,7] It is especially noteworthy that the

azidation of (**4**) proceeds with complete regiospecificity, resulting from the direct nucleophilic displacement of halide with azide anion. Although the yield of (**6**) was far from quantitative, the regioisomer of (**6**) was not detected[8]. This suggests that the corresponding epoxide was not an intermediate in the formation of (**6**) from (**4**). Finally, reduction of azide (**6**) with H_2 in methanol in the presence of Pd/C produced (**1**) in 90% yield with an enantiomeric excess of 99.7%.

In conclusion, we have developed a facile and highly enantioselective synthesis of (**1**).

Experimental Section

General Methods. The ^1H NMR spectra were recorded at 200 MHz and are recorded in ppm (δ) from internal TMS. The IR spectra were obtained on a Perkin-Elmer 1720X. Mass spectra were determined under electron impact conditions. Melting points were measured in capillary tubes. Elemental analyses were carried out on a Fisions EA 1108. Optical rotations were determined on a Jasco DIP-360 polarimeter.

***N*-(3-Chloroacetyl-4-fluorophenyl)methanesulfonamide** (**3**). To a solution of 5.36 g (20.17 mmol) of N-(3-acetyl-4-fluorophenyl)methanesulfonamide(**2**)[1] and 4.9 ml (121.04

mmol) of MeOH in 100 ml of CH_2Cl_2 was added 4.87 ml (60.52 mmol) of sulfuryl chloride at 0°C. The reaction mixture was heated at reflux for 16 h. The solution was cooled to 0°C and 4.9 ml of MeOH was added followed by 4.87 ml of sulfuryl chloride. The reaction was heated at reflux for 12 h and then cooled to rt. The solution was washed with aq. $NaHCO_3$, water, dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography on silica gel (4:1:1 hexane:EtOAc:CH_2Cl_2) gave 4.93 g (92%) of (**2**): mp 133-134°C (ether-hexane); IR (KBr) 3222, 3110, 1704, 1456, 1313, 1161, 1139, 969 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.49 (s, 1H), 7.81 (dd, 1H, J= 2.9, 6.1 Hz), 7.61 (ddd, 1H, J=2.9, 4.5, 8.8 Hz), 7.15 (dd, 1H, J=8.8, 10.4 Hz), 4.73 (d, 2H, J= 2.8 Hz), 2.34 (s, 3H); *m/z* 267 (M^+ with Cl^{37}), 265 (M^+ with Cl^{35}); Anal. calcd. for $C_9H_9NClFO_3S$ (265.686): C,40.68; H, 3.42; N, 5.27; S, 12.07. Found: C, 40.78; H, 3.13; N, 5.26; S, 12.19.

(-)-(*R*)-*N*-[3-(2-Chloro-1-hydroxyethyl)-4-fluorophenyl]methanesulfonamide (**4**). To a solution of 10.3 g (38.77 mmol) of *N*-(3-chloroacetyl-4-fluorophenyl)methanesulfonamide (**3**) in 200 ml of dry THF was added 12.44 g (38.77 mmol) of (-)-*B*-chlorodiisopinocampheylborane at -20°C. The reaction was stirred for 12 h at -20°C and then for 24 h at rt. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel (4:1

hexane:EtOAc) to afford 9.86 g (92%) of (**4**). Two crystalizations from ether-hexane gave material with mp 99-100°C (ether-hexane); $[\alpha]_D$ -7.44° (c 1.18, MeOH); HPLC[9], ee=99.5%; IR (KBr) 3474, 3202, 1492, 1392, 1200,1139, 1069, 995 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.28 (s, 1H), 7.50 (dd, 1H, J=2.8, 6.4 Hz), 7.23 (ddd, 1H, J=2.8, 4.5, 8.8 Hz), 6.98 (dd, 1H, J=8.9, 9.2 Hz), 5.15 (dd, 1H, J=4.0, 7.2 Hz), 3.79 (dd, 1H, J=4.0. 11.1 Hz), 3.64 (dd, 1H, J=7.3, 11.1 Hz), 3.42 (br m 1H), 2.93 (s, 3H); *m/z* 267 (M^+); Anal. calcd. for $C_9H_{11}ClFNO_3S$ (267.704): C, 40.38; H, 4.14; N, 5.23; S, 11.98. Found: C, 40.33; H, 3.89; N, 5.09; S, 11.86.

(-)-(*R*)-*N*-[3-(2-Azido-1-hydroxyethyl)-4-fluorophenyl]methanesulfonamide (**6**). A mixture of 6.4 g (23.91 mmol) of (-)-(*R*)-*N*-[3-(2-chloro-1-hydroxyethyl)-4-fluorophenyl]methanesulfonamide (**4**), 6.22 g (95.63 mmol) of sodium azide, 4.42 g (11.95 mmol) of tetra-*n*-butylammonium iodide, and 50 ml of HMPA was sitirred at 100°C for 48 h. After cooling to rt the mixture was diluted with ether, washed with water (2x100 ml), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (2:1 hexane:EtOAc) to give 4.66 g (71%) of (**6**): 110-112°C (EtOAc:hexane); $[\alpha]_D$ -60.27° (c 0.93, MeOH); IR (KBr) 3412, 3227, 2177, 2105, 1497, 1303, 1163, 986 cm^{-1}; ^1H NMR ($CDCl_3$) 8.30 (br s, 1H), 7.46 (dd, 1H, J=2.8, 6.2 Hz), 7.25 (ddd, 1H, J=2.8, 4.5, 8.8 Hz), 6.99 (dd, 1H, J=9.6,

8.8 Hz), 5.16 (dd, 1H, J=4.0, 7.1 Hz), 3.51 (dd, 1H, J=3.9, 12.6 Hz), 3.42 (dd, 1H, 7.1, 12.6 Hz), 2.96 (s, 3H), 2.86 (s, 1H); *m/z* 274 (M^+); Anal. calcd. for $C_9H_{11}FN_4O_3S$ (274.21): C, 39.41; H, 4.04; N, 20.43; S, 11.69. Found: C, 39.79; H, 3.66; N, 20.28; S, 11.87.

(-)-(*R*)-*N*-[3-(2-Amino-1-hydroxyethyl)-4-fluorophenyl]methanesulfonamide hydrochloride(1). To a solution of 4.56 g (16.63 mmol) of (-)-(*R*)-*N*-[3-(2-azido-1-hydroxyethyl)-4-fluorophenyl]methanesulfonamide (**6**) in 50 ml of methanol was added 500 mg of 5% palladium on carbon. The mixture was stirred under hydrogen at atmospheric pressure for 1 h. The catalyst was removed by filtration through a Celite pad and the filtrate was concentrated under reduced pressure to give a residue, which was crystallized from methanol-ether to give 3.72 g (90%) of (**1**) as free base; mp 166-167°C; $[\alpha]_D$ -6.11° (c 1.03, MeOH); IR (KBr) 3367, 3219, 1596, 1492, 1325, 1308, 1142, 997 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.47 (dd, 1H, J=2.8, 6.3 Hz), 7.19 (ddd, 1H, J=2.8, 4.5, 8.8 Hz), 6.95 (dd, 1H, J=9.6, 8.8 Hz), 4.95 (dd, 1H, J=3.5, 7.7 Hz), 3.50 (br m, 3H), 3.03 (dd, 1H, J=3.5, 13.1 Hz), 2.93 (s, 3H), 2.79 (dd, 1H, J=7.7, 13.1 Hz); *m/z* 249 (M^++1); Anal. Calcd. for $C_9H_{13}FN_2O_3S$ (248.274): C, 43.54; H, 5.28; N, 11.29; S, 12.92. Found: C, 44.07; H, 5.17; N, 11.26; S, 13.16. The hydrochloride salt (**1**) was obtained from an ether:methanol solution of HCl and the above

free base; mp 187-189°; $[\alpha]_D$ -22.5° (c 1.04, H_2O) [Lit[1]. mp 189-191°; $[\alpha]_D$ -22.33° (c 1.012, H_2O]; HPLC[10], ee=99.7%; IR (KBr) 3376, 3143, 2932, 1619, 1505, 1316, 1142, 1053, 979 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.79 (s, 1H), 8.12 (s, 2H), 7.41 (d, 1H, J=6.7 Hz), 7.17 (d, 2H, J=8.2 Hz), 6.27 (d, 1H, J=4.3 Hz), 5.05 (m, 1H), 3.01 (dd, 1H, J=3.0, 12.9 Hz), 2.96 (s, 3H), 2.81 (dd, 1H, J=9.7, 12.9 Hz); *m/z* 249 (M^++1); Anal. calcd. for $C_9H_{14}ClFN_2O_3S$ (284.7): C, 37.96; H, 4.95; N, 9.84; S, 11.26. Found. C, 37.68; H, 5.00; N, 9.51; S, 11.58.

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9. HPLC was performed on a Chiralcel OJ column (25 cm x 4.6 mm) with n-hexane-isopropanol (65:35) (0.8 ml/min) as eluant.

10. HPLC was performed on a Crownpak CR (-) column (15 cm x 4.6 mm) with $HClO_4$-MeOH (95/5) pH=1.75 (0.7 ml/min) as eluant.

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