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An Asymmetric Synthesis of Chiral Nifedipine Analogues

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The addition of aryl-lithium reagents to chiral pyridyl-dihydro-oxazoles gave (S)-4-aryl-1,4-dihydropyridines in 80—90% enantiomeric excess.

The recent interest in 4-aryl-1,4-dihydropyridines as potent calcium channel blockers has led to the therapeutic use of nifedipine (1) for the treatment of angina pectoris and hypertension.¹ Extensive structure–activity relationships have shown that the (-)-enantiomer exhibits enhanced pharmacological properties. Furthermore, a recent report² describes

opposite action (Ca²⁺ blocker or Ca²⁺ enhancer) for each enantiomer as a function of the absolute stereochemistry at the 4-position of the dihydropyridine. We now describe an asymmetric addition to the 4-position of the pyridine nucleus³ (5) which carries a chiral dihydro-oxazole at the 3-position leading to 4-aryl-1,4-dihydropyridines (2) in 80–90% enan-



$E = CO_2Me$

Scheme 1. Reagents: (a) MeCOCI-EtOH, 0 °C; (b) (S,S)-PhCH(OH)CH(NH₂)CH₂OMe, ClCH₂CH₂Cl, Et₃N, reflux; (c) FSO₃Me, CH₂Cl₂, 20 °C, NaBH₄, 0 °C; 50% aq. oxalic acid-THF, 25 °C; (d) NaBH₄, THF-EtOH (2:1); (e) 20% aq. KOH in THF; (f) phase-transfer catalysis: KOH (solid), BuⁿBr, THF, Buⁿ₄NBr, 20 °C.

tiomeric excess (e.e.) and opens a route to chiral, non-racemic nefidipine analogues (2) (Scheme 1).

The synthetic route starts with 3-cyano-5-methoxycarbonylpyridine (3) which was transformed initially to the imidate (4) and then to the chiral 3-dihydro-oxazolyl-5-methoxycarbonyl pyridine (5) (oil 76%, $[\alpha]_D^{24}$ -49.5°, c 0.92, CHCl₃). Addition of aryl-lithium reagents (1.2 equiv.) to a tetrahydro-

furan (THF) solution of (5) (0.01-0.05 M) during 2 h at -78 °C and continued stirring (3-4 h) gave a green fluorescing solution which was then treated with methyl chloroformate (5 equiv.) at -78 °C. Aqueous work-up and chloroform extraction produced $(6a)^{\dagger\ddagger}$ or $(6b)^{\dagger\ddagger}$ in diastereoisometric ratios of 89:11 and 95:5, respectively. The ratios were determined via reverse-phase h.p.l.c. (20% MeOH-H₂O). The chiral auxiliary was removed from (6a) via the previously reported method of quaternization-reduction-hydrolysis⁴ to give the aldehyde (S)-(7)[†] (oil, 76%, $[\alpha]_D^{24}$ -4.7°, c 1.66, CHCl₃). Reduction to the 3-hydroxymethylpyridine (8) was accomplished with sodium borohydride and removal of the N-methoxycarbonyl group using 20% aqueous KOH afforded (S)-(9)† (62%, m.p. 152–153 °C, $[\alpha]_D^{24}$ –116.3°, c 0.44, MeCN). Alternatively (S)-(7) was transformed, without isolation of (8), in an overall yield of 62%. N-Alkylation of (9) was carried out with n-butyl iodide under phase-transfer conditions⁵ furnishing (S)-(10)[†] in 75% yield (m.p. 88— 88.5 °C, $[\alpha]_D^{24}$ -125.7°, c 0.37, CHCl₃). Treatment of (S)-(10) with (S)-(+)- α -methoxy- α -trifluoromethylphenylacetyl chloride (pyridine, 0 °C) gave the Mosher ester,6 the ¹⁹F n.m.r. spectrum of which showed peaks at δ -72.02 and -72.17 p.p.m. in a ratio of 9:91. Thus, very little racemization at C-4 occurred during the manipulation of the substituents at the 3-position. In summary, we have described a route to nefidipine analogues (6)-(10) with high enantiomeric excess which are reached through simple transformations and could prove significant in pharmacological studies.

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† Satisfactory elemental analyses were obtained.

‡ (**6a**): $[\alpha]_D^{24}$ +73.5° (*c* 0.34, CHCl₃); i.r. (CHCl₃) 3052, 3035, 2985, 1751, 1712, 1682, 1638, 1620, 1445, and 1223 cm⁻¹; ¹H (CDCl₃) n.m.r. δ 8.06 (br.s, 1 H), 7.85 (br.s, 1 H), 7.45—7.00 (m, 10 H), 5.26 (d, *J* 6.4 Hz, 1 H), 5.06 (s, 1 H), 4.20—4.00 (m, 3 H), 3.95 (s, 3 H), 3.63—3.42 (m, 2 H), 3.38 (s, 3 H), and 1.22 (t, 3 H). Diastereotopic protons at δ 5.03 and 5.06 showed a ratio of 89:11. (**6b**): $[\alpha]_D^{24}$ +119.7° (*c* 0.3, CHCl₃); i.r. (CCl₄) 3055, 3020, 2970, 2945, 2918, 1750, 1713, 1676, 1634, 1612, 1438, and 1218 cm⁻¹; ¹H n.m.r. (CDCl₃) δ 8.03 (br.s, 1 H), 7.82 (br.s, 1 H), 7.35—7.15 (m, 5 H), 7.04 (m, 2 H), 6.79 (m, 2 H), 5.26 (d, *J* 6.3 Hz, 1 H), 5.00 (s, 1 H), 4.30—4.00 (m, 3 H), 3.95 (s, 3 H), 3.77 (s, 3 H), 3.70—3.40 (AB m, 2 H), 3.39 (s, 3 H), and 1.23 (t, 3 H).