An Asymmetric Synthesis of Chiral Nifedipine Analogues

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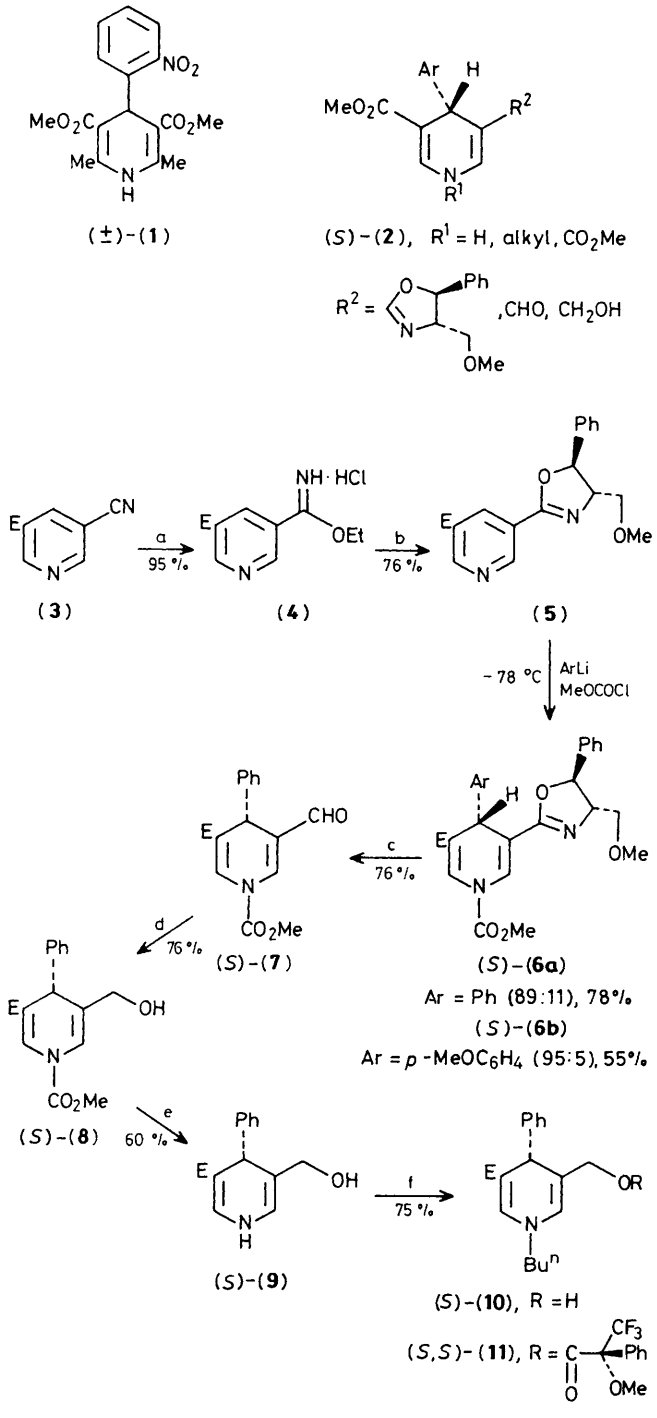
The addition of aryl-lithium reagents to chiral pyridyl-dihydro-oxazoles gave (*S*)-4-aryl-1,4-dihydropyridines in 80—90% enantiomeric excess.

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 report[2] describes opposite action (Ca^{2+} blocker or Ca^{2+} 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 nucleus[3] (**5**) which carries a chiral dihydro-oxazole at the 3-position leading to 4-aryl-1,4-dihydropyridines (**2**) in 80—90% enan-



Scheme 1. *Reagents:* (a) MeCOCl–EtOH, 0 °C; (b) (*S,S*)-PhCH(OH)CH(NH$_2$)CH$_2$OMe, ClCH$_2$CH$_2$Cl, Et$_3$N, reflux; (c) FSO$_3$Me, CH$_2$Cl$_2$, 20 °C, NaBH$_4$, 0 °C; 50% aq. oxalic acid–THF, 25 °C; (d) NaBH$_4$, THF–EtOH (2:1); (e) 20% aq. KOH in THF; (f) phase-transfer catalysis: KOH (solid), Bu^{n}Br, THF, Bu$^n_4$NBr, 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, $CHCl_3$). Addition of aryl-lithium reagents (1.2 equiv.) to a tetrahydrofuran (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**)†‡ or (**6b**)†‡ in diastereoisomeric ratios of 89:11 and 95:5, respectively. The ratios were determined *via* reverse-phase h.p.l.c. (20% MeOH–H_2O). The chiral auxiliary was removed from (**6a**) *via* the previously reported method of quaternization–reduction–hydrolysis[4] to give the aldehyde (*S*)-(**7**)† (oil, 76%, $[\alpha]_D^{24}$ −4.7°, *c* 1.66, $CHCl_3$). 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 conditions[5] furnishing (*S*)-(**10**)† in 75% yield (m.p. 88—88.5 °C, $[\alpha]_D^{24}$ −125.7°, *c* 0.37, $CHCl_3$). Treatment of (*S*)-(**10**) with (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride (pyridine, 0 °C) gave the Mosher ester,[6] the ^{19}F 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, $CHCl_3$); i.r. ($CHCl_3$) 3052, 3035, 2985, 1751, 1712, 1682, 1638, 1620, 1445, and 1223 cm^{-1}; ^{1}H ($CDCl_3$) 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, $CHCl_3$); i.r. (CCl_4) 3055, 3020, 2970, 2945, 2918, 1750, 1713, 1676, 1634, 1612, 1438, and 1218 cm^{-1}; ^{1}H n.m.r. ($CDCl_3$) 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).