AN ASYMMETRIC SYNTHESIS OF 4-ARYL-1,4-DIHYDROPYRIDINES

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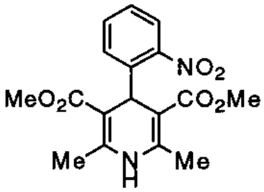
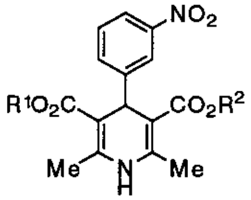
Abstract - Phenyllithium was found to attack preferentially the ester group of 5-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-2,6-dimethylnicotinic acid ethyl ester (**6**) to give phenyl ketone (**7**) and diphenylcarbinol (**8**), despite the directing effect of the oxazoline group. By replacing the ethyl ester in **6** with a bulky *tert*-butyl ester, the desired 1,4-addition with PhLi to give 4-phenyldihydropyridine derivative (**12**) in 67% was observed. As a chiral version of the above reaction, 2-[5-(*tert*-butoxycarbonyl)-2,6-dimethyl-3-pyridyl]-4-(*S*)-methoxymethyl-5-(*S*)-phenyl-Δ^2-oxazoline (**13**) reacted with PhLi to give 3-(*tert*-butoxycarbonyl)-2,6-dimethyl-*N*-ethoxycarbonyl-5-[(4*S*,5*S*)-4-methoxymethyl-5-phenyl-4,5-dihydro-oxazol-2-yl]-4-(*S*)-phenyl-1,4-dihydropyridine (**1**) and its C-4 epimer (**2**) in a ratio of 5:1 and a total yield of 54%.

4-Aryl-1,4-dihydropyridine-3,5-dicarboxylic acid diesters of the nifedipine type are effective as calcium antagonists or calcium channel blockers, which are widely used in the treatment of hypertension and coronary heart diseases.[1] Nifedipine, with symmetrical substituents on its dihydropyridine ring, is achiral; while second-generation derivatives, such as nitrendipine, nivadipine, nimodipine, nicardipine, and amlodipine, with unsymmetrical substitution, are chiral, and demonstrate moderate to significant enantioselectivity in their pharmacological effects.[2] Because of the importance of C-4 chirality with respect to the pharmacological activity of 4-aryl-1,4-dihydropyridines, the availability of asymmetric synthesis of this class of compounds is highly desirable. Among the previously reported asymmetric syntheses of 4-

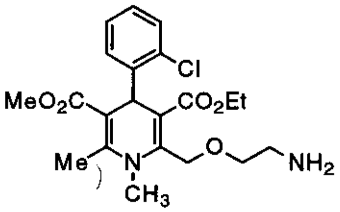
aryl-1,4-dihydropyridines, the approach developed by Meyers *et al.*,[3] in which aryllithium reagents are added diastereoselectively to position 4 of pyridine derivatives carrying a chiral oxazoline at position 3, as demonstrated by the synthesis of compound **A** (X = H or OMe) in 78-90% d.e., and the enantioselective Hantzsch synthesis *via* metalated chiral alkyl acetoacetate hydrazones by Enders *et al* .[4] are particularly noteworthy. Enantioselective syntheses of chiral 1,4-dihydropyridines have also been achieved *via* chemoenzymatic approaches.[5] Although Meyers' approach described above holds promise for the synthesis of chiral nifedipine analogs, it has not been adopted for the preparation of therapeutically useful dihydropyridines, i.e. those with methyl substituents in positions 2 and 6. In this report, we describe our study on the oxazoline-directed aryllithium addition to 2,6-dimethyl substituted dihydropyridines and our efforts in modifying the above approach for the chiral synthesis of pharmacologically more important dihydropyridines.



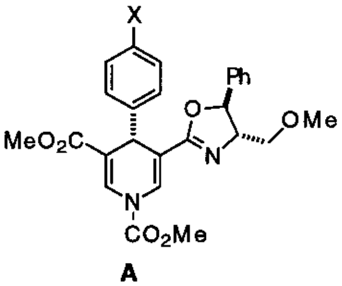
Nifedipine



Nitrendipine: R^1= Me, R^2= Et
Nivadipine : R^1= Me, R^2= i-Pr
Nimodipine: R^1= i-Pr, R^2= CH_2CH_2OMe
Nicardipine: R^1= Et, R^2= $CH_2CH_2N(Me)Bn$



Amlodipine



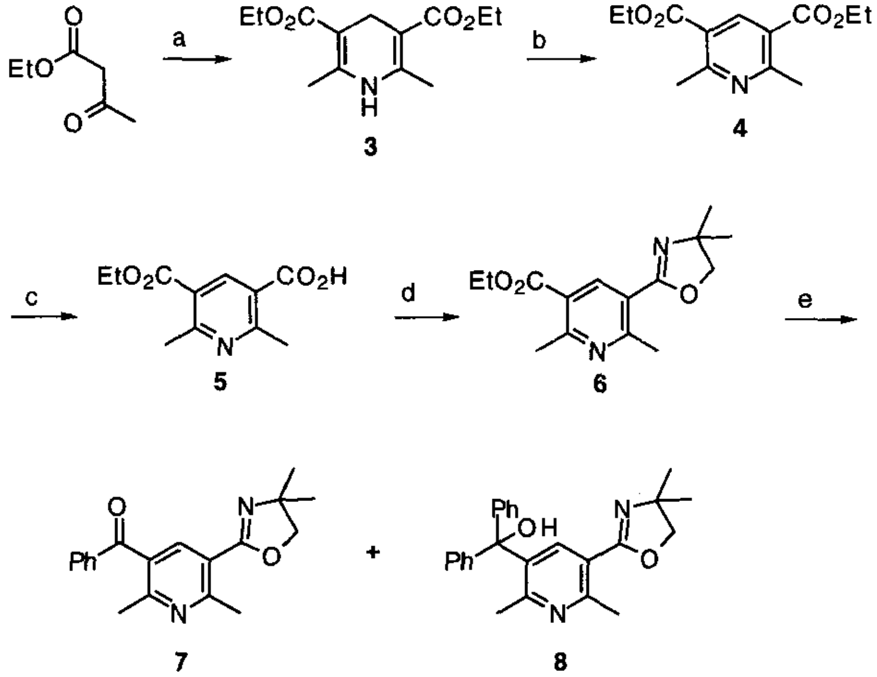
A

RESULTS AND DISCUSSION

In order to determine the effects of the 2,6-dimethyl substituents on the oxazoline-directed aryllithium addition to pyridine derivatives, compound (**6**) was prepared as shown in Scheme 1. Thus, 2,6-

dimethylpyridine-3,5-dicarboxylic acid diethyl ester (**4**) was obtained from ethyl acetoacetate in 30% yield *via* the classical Hantzsch condensation[6] followed by oxidation. Compound (**4**) was hydrolysed to the monoester (**5**), which was converted to oxazoline (**6**) *via* a literature procedure.[7] Subjection of **6** to the same reaction conditions for the preparation of **A** resulted in addition of PhLi to the ester carbonyl group to give phenyl ketone (**7**) and diphenylcarbinol (**8**) as the only products.

Scheme 1[a]

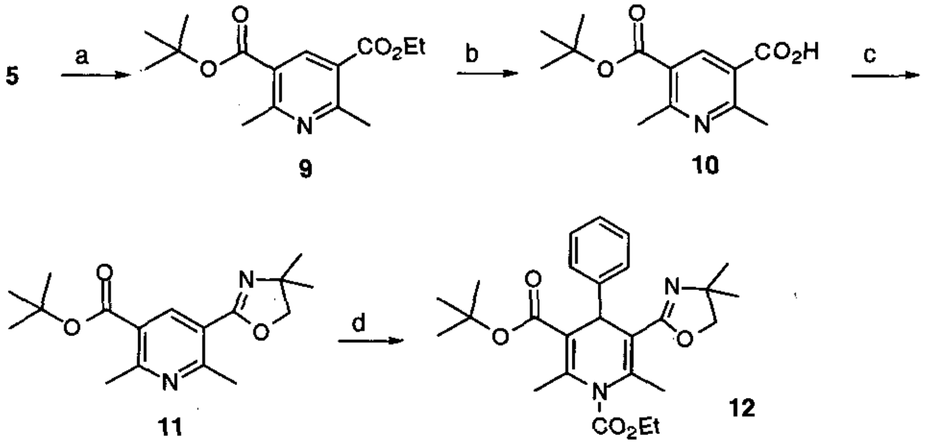


[a]Reagents and conditions: (a) 35% HCHO, Et_3N, 0°C, then ammonia, room temperature; (b) HNO_3/H_2SO_4; (c) KOH, EtOH, 0°C, then H^+; (d) PPh_3, DEAD, 2-amino-2-methyl-1-propanol, CCl_4, NEt_3, MeCN/pyridine (1:1); (e) PhLi, THF, -78°C, then $ClCO_2Et$.

We rationalized that PhLi may be forced to add to position 4 of the pyridine ring if the ester group in **6** is masked against nucleophilic attacks. Therefore, monoester (**5**) was coupled with *tert*-butanol in the presence of 1,1-carbonyldiimidazole and DBU to give *tert*-butyl ester (**9**),[8] which was then converted to the oxazoline intermediate (**11**) as described for the preparation of **6**. To our satisfaction, treatment of **11** with PhLi under the same conditions as in Scheme 1 resulted in the desired 1,4-addition to give dihydropyridine (**12**) in 67% (Scheme 2). We then turned our attention to the chiral version of the above reaction. The chiral oxazoline intermediate (**13**) was prepared from **10** *via* condensation with (1*S*,2*S*)-(+)-2-amino-3-methoxy-1-phenylpropan-1-ol under Mitsunobu condition.[7] Phenyllithium (1.6 eq.) as a solution in cyclohexane/ether was added to a THF solution of **13** (0.02 M) during 20 min at -78 °C. The stirring was continued for 20 h, followed by quenching with ethyl chloroformate (5 eq.) at -78 °C. Aqueous work-up and CH_2Cl_2 extraction provided 1,4-addition products (**1**) and (**2**) in a total yield of 54% and a diastereoisomeric ratio of 5 : 1, as determined by ^{1}H-nmr and reverse-phase hplc (Scheme 3). Removal of the chiral auxiliary with little racemerization at C-4 has been described.[3,9]

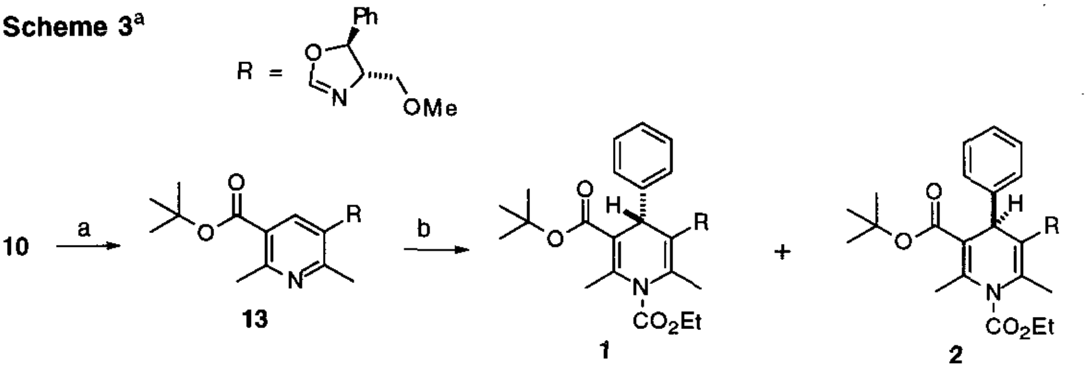
In summary, we have demonstrated that strong nucleophiles such as PhLi react with nicotinic acid derivatives such as **6** preferentially at the ester carbonyl, despite the directing effect of the oxazoline substituent. However, side products which might be generated *via* the suspected deprotonation of the acidic methyl groups at positions 2 and 6 were not observed.[2] The nucleophilic attack by PhLi at the ester group was effectively hindered by the replcement of the ethyl ester in compound (**6**) and its congeners by a bulky *tert*-butyl ester, and the desired 1,4-addition products were obtained in satisfactory yields. Even in the presence of a hindered *tert*-butyl ester, significant chiral induction (d.e. = 67%) can still be achieved with the chiral auxilliary (4*S*,5*S*)-4-methoxymethyl-5-phenyl-Δ^2-oxazole during the 1,4-addition of PhLi to the above dihydropyridine systems.

Scheme 2[a]



[a] Reagents and conditions: (a) 1,1-carbonyldiimidazole, DMF, 40°C, then *tert*-butanol, DBU; (b) KOH, 95% EtOH, room temperature, then H^+; (c) PPh_3, DEAD, 2-amino-2-methyl-1-propanol, CCl_4, NEt_3, MeCN/pyridine (1:1); (d) PhLi, THF, -78°C, then $ClCO_2Et$.

Scheme 3[a]



[a] Reagents and conditions: (a) PPh_3, DEAD, (1*S*,2*S*)-(+)-2-amino-3-methoxy-1-phenyl-1-propanol, CCl_4, NEt_3, MeCN/pyridine (1:1); (b) PhLi, THF, -78°C, then $ClCO_2Et$.

EXPERIMENTAL

General. Melting points were taken in a capillary tube by using the Laboratory Devices, MEL-TEMP II melting point apparatus and are uncorrected. Nmr spectra were recorded on a Bruker AMX-400, AM-300, or AM-80 FT-NMR spectrometer; chemical shifts were recorded in parts per million downfield from Me_4Si. Ir spectra were determined with a Perkin-Elmer 1760-X FT-IR spectrometer. Mass spectra were recorded on a Jeol JMS-D300 and Finnigan TSQ-46C mass spectrometers; High resolution mass spectra were obtained with a Jeol JMS-HX110 spectrometer. Elemental analysis was performed with a Perkin-Elmer 2400-CHN instrument. Tlc was performed on Merck (Art. 5715) silica gel plates and visualized under uv light (254 nm) or upon heating after treatment with 5% phosphomolybdic acid in ethanol. Flash column chromatography was performed with Merck (Art. 9385) 40-63 mm silica gel 60. Medium pressure liquid chromatography (mplc) was performed with a Büchi B-680 instrument, with Merck (Art. 15111) 15-40 mm silica gel 60 as the stationary phase. High performance liquid chromatography was conducted using a Jasco model 880 series.

2,6-Dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid diethyl ester (3). A mixture of ethyl acetoacetate (60 ml, 466 mmol), formalin (35%, 20.5 ml, 259 mmol), and 5 drops of triethylamine was stirred under ice-bath cooling for 48 h. The organic and aqueous layers were separated, and the aqueous layer was extracted with ether (20 ml x 2). The organic layer and the ether extract were combined, dried ($MgSO_4$), and evaporated to give an oil, which was dissolved in ethanol (50 ml) and cooled in ice-bath. To the cooled solution was introduced NH_3 gas for 4 h. The resulting mixture was let warm to room temperature and stirred for 40 h. The precipitate was collected and crystallized to give **3** as yellow crystals (43 g, 73%): mp 219-219.5°C (from ethanol); tlc, $R_f = 0.33$ (ether: n-hexane=3: 1); ir (KBr) 3360, 1696, 1658; ^{1}H nmr (80 MHz, DMSO) δ 1.16 (t, J = 8.8 Hz, 6 H), 2.08 (s, 6 H), 3.09 (s, 2 H), 4.04 (q, J = 8.8 Hz, 4 H); ms *m/z* 253 (M^+), 224 (base peak), 208, 196; HRms calcd for $C_{13}H_{19}NO_4$ (M^+) 253.1315, found 253.1316; Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.77; H, 7.66; N, 5.42.

2,6-Dimethylpyridine-3,5-dicarboxylic acid diethyl ester (4). To crude **3** (48 g) placed in a 1-l flask was added slowly a solution of conc. sulfuric acid (10.2 ml) and nitric acid (12.1 ml) in 65 ml of water. The mixture turned dark-red upon gentle heating. After the boiling subsided, the mixture was cooled and treated with ice (120 g) and water (120 ml). The mixture was then vigrously stirred, while 33% NH_4OH was added dropwise until the pH was higher than 12. The precipitate was collected by filtration and purified *via* distillation under reduced pressure (1 mbar, 164 °C) to give **4** as a white solid (26 g, 30% from ethyl acetoacetate): mp 69.5-70.5 °C (from 50% EtOH); tlc, $R_f = 0.60$ (ether: n-hexane=3:1); hplc, $R_t = 11.7$ min (RP-18, MeOH:H_2O = 65: 35); ir (KBr) 1722 (C=O); ^{1}H nmr (80 MHz, $CDCl_3$) δ 1.37 (t, J = 8.8 Hz, 6 H), 2.79 (s, 6 H), 4.35 (q, J = 8.85, 4 H), 8.61 (s,1 H); ms *m/z* 251 (M^+), 236, 223, 206 (base peak), 195, 178, 151; Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 61.86; H, 6.87; N, 5.48.

2,6-Dimethylpyridine-3,5-dicarboxylic acid monoethyl ester (5). To a stirred ice-cooled solution of **4** (30 g, 0.12 mol) in ethanol (600 ml) was added dropwise a solution of KOH (11 g, 0.2 mol) in ethanol (50 ml). After further stirring for 8 h, the mixture was acidified with aqueous HCl to a pH of 5, and extracted with EtOAc (50 ml x 3). The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated to give **5** as a white solid (23.7 g, 84.6%): mp 125-126 °C (from EtOAc); hplc $R_t = 3.9$ min (RP-18, MeOH:H_2O = 65:35); ir (KBr) 3442 (-COOH), 1737 (C=O), 1713 (C=O); ^{1}H nmr (300 MHz, $CDCl_3$) δ 1.30 (t, J = 7.0 Hz, 3 H), 2.63 (s, 3 H), 2.66 (s, 3 H), 4.27 (q, J = 7.0 Hz, 2H), 8.31 (s, 1 H); ms *m/z* 223 (M^+), 205, 195, 178 (base peak), 150; HRms calcd for $C_{11}H_{13}NO_4$ (M^+) 223.0845, found 223.0837; Anal. Calcd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.28. Found: C, 59.06;

H, 5.91; N, 6.05.

5-(4,4-Dimethyl-4,5-dihydro-oxazol-2-yl)-2,6-dimethylnicotinic acid ethyl ester (6). A mixture of **5** (2.0 g, 9.0 mmol), 2-amino-2-methyl-1-propanol (0.9 ml, 9.0 mmol), triphenylphosphine (6.28 g, 27 mmol), carbon tetrachloride (7.0 ml, 27 mmol), triethylamine (3.8 ml, 27 mmol), dry acetonitrile (10 ml), and dry pyridine (10 ml) was stirred at room temperature for 2 h. The resulting mixture was evaporated, and the residue was chromatographed (silica gel, EtOAc: n-hexane = 1:5) to provide **6** as a solid (0.9 g, 34%): mp 62-63 ^{o}C (from *n*-hexane); tlc, R_f = 0.35 (EtOAc: n-hexane = 1:3); ir (KBr) 1721(C=O), 1644(C=N); ^{1}H nmr (80 MHz, $CDCl_3$) δ 1.31 (m, 9 H), 2.76 (s, 6 H), 4.02 (s, 2 H), 4.29 (q, 2 H), 8.47 (s, 1 H); ms *m/z* 276 (M^+, base peak), 261, 246, 233, 205; HRms calcd for $C_{15}H_{20}N_2O_3$ (M^+) 276.1475, found 276.1472; Anal. Calcd for $C_{15}H_{20}N_2O_3$: C, 65.19; H, 7.29; N, 10.14. Found: C, 64.82; H, 7.31; N, 10.13.

2-(5-Benzoyl-2,6-dimethyl-3-pyridyl)-4,4-dimethyl-Δ^2-oxazoline (7) and [5-(4,5-Dihydro-4,4-dimethyl-2-oxazolyl)-2,6-dimethyl-3-pyridyl]-diphenylmethanol (8). To a stirred solution of **6** (138 mg, 0.5 mmol) in dry THF (10 ml) under N_2 at -78^{o}C was added slowly a solution of PhLi in cyclohexane/ether, 7:3 (1.8 M, 0.34 ml). After stirring for 3 h, another 0.1 ml of the PhLi solution was added. After 0.5 h, the mixture was quenched with ethyl chloroformate (0.5 ml, 5 mmol), treated with H_2O and saturated $NaHCO_3$, and extracted with EtOAc (20 ml x 3). The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated. The residue was chromatographed (mplc, silica gel, EtOAc : n-hexane = 1:5) to give **7** (34 mg, 31%), **8** (32 mg, 21%), and unreacted **6** (24 mg, 17%). Compound (**7**):Tlc, R_f = 0.23 (EtOAc: n-hexane = 1:1); ^{1}H nmr (300 MHz, $CDCl_3$) δ 1.34 (s, 6 H), 2.50 (s, 3 H), 2.79(s, 3 H), 4.01 (s, 2 H), 7.44 (m, 2 H), 7.57 (m, 1 H), 7.73 (m, 2 H), 7.98 (s, 1 H); ^{13}C nmr δ 23.42, 24.70, 28.36, 68.29, 78.73, 120.36, 127.68, 128.70, 129.95, 133.60, 137.65, 157,67, 159.61, 160.53, 196.34; ms *m/z* 308 (M^+), 293, 238, 197(base peak), 130, 105. Compound (**8**): Tlc , R_f = 0.1 (EtOAc: n-hexane=1: 2); ^{1}H nmr (300 MHz, $CDCl_3$) δ 1.30 (s, 6 H), 2.26 (s, 3 H), 2.76 (s, 3 H), 3.93 (s, 2 H), 7.18-7.31 (m, 10 H); ms *m/z* 386 (M^+), 371, 308, 293, 276, 261, 105, 84, 49 (base peak).

5-(*tert*-Butoxycarbonyl)-2,6-dimethylnicotinic acid ethyl ester (9). 1,1-Carbonyldiimidazole

(6.05 g, 37.3 mmol) was added to a solution of **5** (5.37 g, 24.1 mmol) in dry DMF (25 ml) under nitrogen, and the mixture was stirred at 40 °C for 1 h. *tert*-Butanol (5.78 g,78.0 mmol) and DBU (6.12 g, 40.8 mmol) were then added, and the mixture was stirred at 40 °C for 24 h. The mixture was cooled and extracted with ether (500 ml). The extract was washed in sequence with 10% acetic acid (200 ml), water (200 ml), and 10% aqueous K_2CO_3 (200 ml), and dried with Na_2SO_4. The solvent was removed and the residue was chromatographed (mplc, silica gel; 9% ethyl acetate in hexane) to afford **9** as a yellow solid (5.72 g, 85%): mp 66-67 °C (from *n*-hexane); ^{1}H nmr (80 MHz, $CDCl_3$) δ 1.36 (t, J = 3 Hz, 7 H), 1.57 (s, 9 H), 2.77 (s, 3 H), 2.79 (s, 3 H), 4.35 (q, *J* = 2 Hz, 7 H), 8.55 (s, 1 H); ^{13}C nmr (100 MHz, $CDCl_3$) δ 14.20, 24.80, 24.99, 28.16, 61.27, 82.19, 122.97, 124.72, 140.75, 161.54, 161.61, 165.35, 166.01; ms (EI 70 eV) *m/z* 279 (M^+), 251, 234, 223 (base peak); HRms calcd for $C_{15}H_{21}NO_4$ (M^+) 279.1471, found 279.1477; Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.20; H, 7.59; N, 5.40.

5-(*tert*-Butoxycarbonyl)-2,6-dimethylnicotinic acid (10). Potassium hydroxide (290 mg, 5.18 mmol) was added to a solution of **9** (606 mg, 2.17 mmol) in 95% ethanol (18 ml). The mixture was stirred at room temperature for 12 h, and evaporated. The residue was treated with 0.5 M aqueous KH_2PO_4 (pH = 5. 20 ml) and ethyl acetate (50 ml). The organic layer was separated and dried with Na_2SO_4. The ethyl acetate was evaporated to afford **10** as a white solid (505 mg, 93%): mp 141-142.5 °C (from EtOAc); ^{1}H nmr (80 MHz, CD_3OD) δ 1.60 (s, 9 H), 2.76 (s, 3 H), 2.79 (s, 3 H), 8.60 (s, 1 H); ^{13}C nmr (100 MHz, CD_3OD) δ 25.07, 25.13, 29.11, 84.27, 126.21, 126.97, 143.04, 163.07, 163.51, 167.10, 169.56: ms (EI, 70 eV) *m/z* 252 (MH^+), 195, 151, 107.

2,6-Dimethyl-5-(4,5-dihydro-4,4-dimethyl-2-oxazolyl)nicotinic acid *tert*-butyl ester (11). A mixture of **10** (623 mg, 7.0 mmol), 2-amino-2-methyl-1-propanol (1.48 g, 5.89 mmol), triphenylphosphine (4.70 g, 17.87 mmol), carbon tetrachloride (1.7 ml), triethylamine (2.5 ml, 17.7 mmol), dry acetonitrile (20 ml), and dry pyridine (20 ml) was stirred at room temperature for 24 h. The resulting mixture was evaporated, and the residue was chromatographed (mplc, silica gel; 17% ethyl acetate in hexane) to give **11** as a white solid (1.53 g, 85%): mp 82-83 °C (from *n*-hexane); ^{1}H nmr (400 MHz, $CDCl_3$) δ 1.36 (s, 6 H), 1.56 (s, 9 H), 2.76 (s, 3 H), 2.77 (s, 3 H), 4.05 (s, 2 H), 8.38 (s, 1 H); ^{13}C nmr (100 MHz, $CDCl_3$) δ 24.59, 24.78, 28.17, 28.36, 68.28, 78.74, 81.89, 120.90, 124.50, 139.59, 159.99, 160.27, 160.61, 165.53; ms *m/z* 304 (M^+), 248, 233 (base peak), 205; HRms calcd for $C_{17}H_{24}O_3N_2$ (M^+) 304.1787, found 304.1792; Anal. Calcd for $C_{17}H_{24}N_2O_3$: C, 66.97; H, 7.95; N, 9.19. Found: C, 66.92; H, 7.78; N, 9.05.

5-(*tert*-Butoxycarbonyl)-2,6-dimethyl-3-[4,5-dihydro-4,4-dimethyl-2-oxazolyl]-*N*-ethoxycarbonyl-4-phenyl-1,4-dihydropyridine (12). A solution of phenyllithium in cyclohexane/ether, 7:3 (1.8 M, 0.2 ml) was added to a solution of **11** (83 mg, 0.27 mmol) in dry THF (8 ml) during 20 min. at -78°C. The reaction mixture was stirred for 20 h, followed by quenching with ethyl chloroformate (150 mg, 1.4 mmol). Aqueous work-up followed by extraction with CH_2Cl_2 provided a crude, which was chromatographed (mplc, silica gel; 17% ethyl acetate in hexane) to afford **12** as an oil (83 mg, 67%): ^{1}HNmr (80 MHz, $CDCl_3$) δ 1.28 (t, *J* =7.1 Hz, 3 H), 1.30 (s, 6 H), 1.48 (s, 9 H), 2.34 (s, 3 H), 2.45 (s, 3 H), 3.94 (s, 2 H), 4.13 (q, *J* =7.1 Hz, 2 H), 5.15 (s, 1 H), 7.17-7.25 (m, 5 H); ^{13}C nmr (100 MHz, $CDCl_3$) δ 14.28, 20.45, 21.22, 28.27, 28.44, 42.44, 62.26, 67.33, 78.52, 81.21, 120.50, 124.60, 126.30, 126.82, 141.08, 143.95, 148.43, 152.68, 161.32, 165.87; ms (EI, 70 eV) *m/z* 454 (M^+), 381, 353 (base peak), 325.

2-[5-(*tert*-Butoxycarbonyl)-2,6-dimethyl-3-pyridyl]-4-(*S*)-methoxymethyl-5-(*S*)-phenyl-Δ^2-oxazoline (13). A mixture of **10** (358 mg, 1.43 mmol), (1*S*,2*S*)-(+)-2-amino-3-methoxy-1-phenyl-1-propanol (322 mg, 1.78 mmol), triphenylphosphine (1.18 g, 4.53 mmol), carbon tetrachloride (0.45 ml), triethylamine (0.6 ml), dry pyridine (2.0 ml) and dry acetonitrile (2.0 ml) was stirred at room temperature for 24 h. The mixture was evaporated, and the residue was chromatographed (mplc, silica gel; 17% ethyl acetate in hexane) to afford **13** as an oil (293 mg, 52%): ^{1}HNmr (400 MHz, $CDCl_3$) δ 1.57 (s, 9 H), 2.79 (s, 3 H), 2.85 (s, 3 H), 3.43 (s, 3 H), 3.61 (dd, *J* = 4.3 and 9.7 Hz, 1 H), 3.73 (dd, *J* = 4.3 and 9.7 Hz, 1 H), 4.33-4.38 (m, 1 H), 5.47 (d, *J* = 7.0 Hz, 1 H), 7.29-7.39 (m, 5 H), 8.54 (s, 1 H); ^{13}C nmr (100 MHz, $CDCl_3$) δ 24.76, 24.90, 28.10, 59.13, 59.28, 74.11, 75.26, 82.01, 83.17, 120.28, 124.59, 125.48, 128.18, 128.73, 139.84, 140.52, 160.25, 160.52, 162.64, 165.42; ms (EI, 70 eV) *m/z* 396 (M^+), 351 (base peak), 340, 295; HRms calcd for $C_{23}H_{28}O_4N_2$ (M^+) 396.2049, found 396.2049; $[\alpha]_D$ +59.5 (*c*0.96, $CHCl_3$).

3-(*tert*-Butoxycarbonyl)-2,6-dimethyl-*N*-(ethoxycarbonyl)-5-[(4*S*,5*S*)-4-methoxymethyl-

5-phenyl-4,5-dihydro-oxazol-2-yl]-4-(*S*)-phenyl-1,4-dihydropyridine (1) and 3-(*tert*-Butoxycarbonyl)-2,6-dimethyl-*N*-(ethoxycarbonyl)-5-[(4*S*,5*S*)-4-methoxymethyl-5-phenyl-4,5-dihydro-oxazol-2-yl]-4-(*R*)-phenyl-1,4-dihydropyridine (2). A solution of phenyllithium in cyclohexane/ether, 7:3 (1.8 M, 0.2 ml) was added to a solution of **13** (112 mg, 0.28 mmol) in dry THF (9 ml) at -78°C during 20 min. The reaction mixture was stirred at -78°C for 20 h, and then quenched with ethyl chloroformate (159 mg, 1.4 mmol). The resulting mixture was treated with water, and extracted with CH_2Cl_2. The extract was washed with brine, dried (Na_2SO_4), and evaporated to provide a mixture of **1** and **2** in a total yield of 54% and a diastereoisomeric ratio of 5:1, as determined by reverse-phase hplc (RP-18; 65% CH_3CN in H_2O): ^{1}HNmr (400 MHz, $CDCl_3$) δ 1.20 (t, *J* = 7.1 Hz, 3 H), 1.49 (s, 9 H), 2.46 (s, 3 H), 2.51 (s, 3 H), 3.41 (s, 3 H), 3.52 (dd, *J* = 6.9 and 9.6 Hz, 1 H), 3.69 (dd, *J* = 4.2 and 10.5 Hz, 1 H), 4.12 (q, *J* = 7.0 Hz, 2 H), 4.18-4.23 (m, 1 H), 5.28 and 5.30 (diastereotopic proton at C-4, 2s, 5:1, 1 H), 5.38 (d, *J* = 6.6 Hz, 1 H), 7.16-7.31 (m, 5 H); ^{13}C nmr (100 MHz, $CDCl_3$) δ 14.27, 20.63, (21.15, 21.22), 28.20, 29.67, (42.44, 42.64), (59.26, 59.30), 62.35, (74.41, 74.47), (81.18, 81.28), (83.20, 83.26), 120.06, (124,48, 124.55), (125.33, 125.39), 126.38, 126.85, 127.06, 127.93, (128.24, 128.31), (128.60, 128.65), 141.05, (144.85, 145.09), (148.19, 148.37), 152.66, (163.06, 163.74), (165.71, 165.83); ms (EI, 70 eV) *m/z* 546 (M^+), 501, 490, 445 (base peak); HRms calcd for $C_{32}H_{38}O_6N_2^+$: 546.2730, found 546.2724.

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