Synthesis and Configurational Assignment of Methyl 3-Nitrooxypropyl 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate

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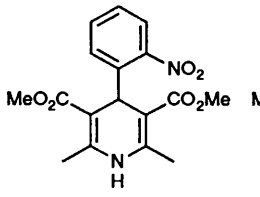
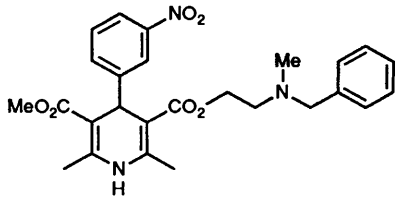
Enantiomeric (+)- and (−)-methyl 3-nitrooxypropyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate **1** were synthesized by esterification of the optically active monocarboxylic acids (+)-**6** and (−)-**6**, which are available from racemate (±)-**6** by optical resolution using cinchonidine and cinchonine. The absolute configuration of the key intermediates (*S*)-(+)-**6** and (*R*)-(−)-**6**, was also unambiguously determined by the comparison with optical active (+)- and (−)-**1** derived from (*R*)-(−)- and (*S*)-(+)-**7** and (+)- and (−)-**6**, and X-ray crystallographic analysis of bromoethyl ester (*R*)-(−)-**8** prepared from the acid (*S*)-(+)-**7**.

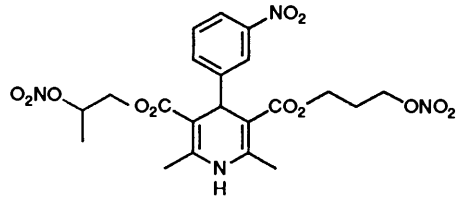
We found some time ago that new 1,4-dihydropyridine derivatives[1] having nitrooxy moieties at the C-3 and/or C-5 ester position are potentially active calcium channel antagonists similar to nifedipine[2] and nicardipine.[3] Among them, 2-nitrooxypropyl 3-nitrooxypropyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate (CD-349) showed potent and long lasting activity and is currently undergoing clinical evaluation as a promising drug.



nifedipine

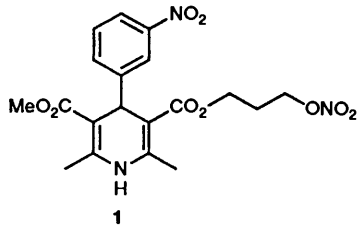


nicardipine



CD-349

Furthermore, a number of papers have reported that one optical isomer of some dihydropyridine derivatives such as nifedipine, nicardipine, and others, showed much more potent biological activity than did other optical isomers.[4] Consequently, it is important to synthesize the optical isomers of 1,4-dihydropyridine derivatives containing a nitrate group in (one of) the ester components and to evaluate their biological activity.



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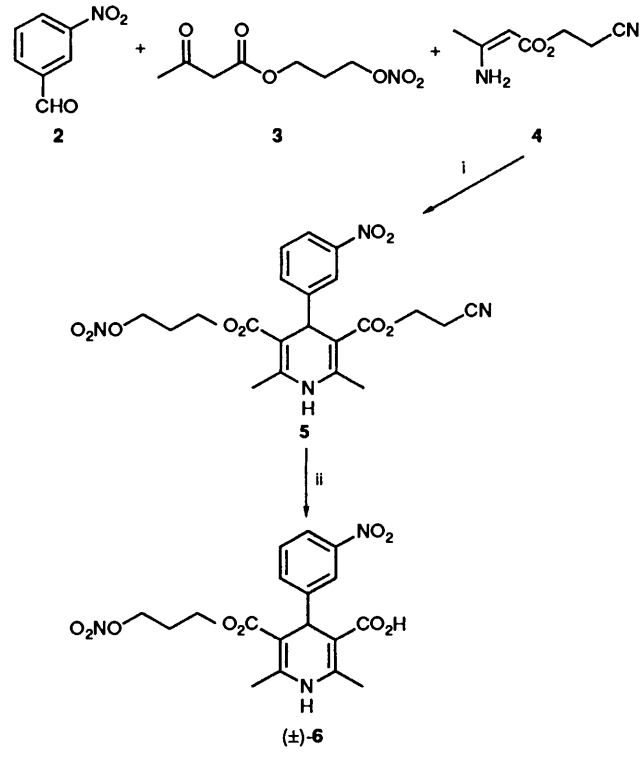
In this context, we synthesized each enantiomer of compound **1** and determined the absolute configuration of their key intermediates (+)- and (−)-**6**.

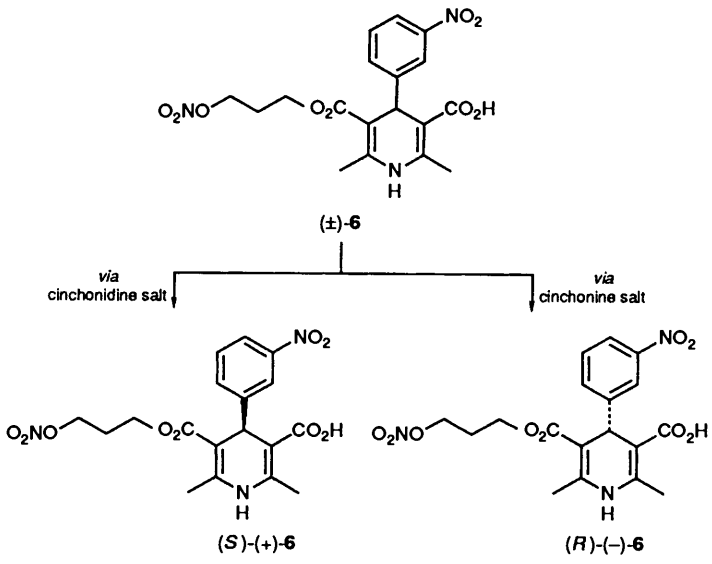
The racemic compound (±)-**6** was prepared by the synthetic route as depicted in Scheme 1, which involved use of the Hantzsch reaction.[5] The reaction of 2-cyanoethyl 3-aminocrotonate **4** with 3-nitrobenzaldehyde **2** and 3-nitrooxypropyl acetoacetate **3** gave the 1,4-dihydropyridine derivatives **5** in 82% yield. Subsequent removal of the cyanoethyl protecting group[6] in compound **5** with sodium hydroxide in aq. acetone proceeded smoothly to provide the desired product **6** in 93% yield.



Scheme 1 *Reagents and conditions:* i, Pr^{i}OH, reflux, 3 h; ii, NaOH, aq. acetone, room temp., 1 h

The key intermediate, (+)-monocarboxylic acid **6**, was obtained by optical resolution using cinchonidine as shown in Scheme 2, though the absolute configuration of the enantiomer has not been assigned.

On the other hand, enantiomer (*R*)-(−)-**6** remaining in the



Scheme 2

mother liquor upon resolution with cinchonine gave (−)-**6**. The enantiomeric monocarboxylic acids (+)- and (−)-**6** obtained above were converted into the corresponding methyl esters (+)- and (−)-**1*** by treatment with acetic anhydride with methanol in the presence of catalytic acetyl chloride. Compounds (+)- and (−)-**1** were also obtained in good yield from acids (+)- and (−)-**6** by esterification on methyl iodide in dimethylformamide (DMF) in the presence of potassium carbonate.

Next, diesters (*S*)-(+)- and (*R*)-(−)-**1** synthesized from acidic esters (*R*)-(−)- and (*S*)-(+)-**7**, which were obtained by optical resolution of racemate (±)-**7** through the quinidine and cinchonidine salts by the reported procedure.[7] The enantiomer (+)-**1** derived from monoacidic ester (+)-**6** was compared with that derived from monoester (*R*)-(−)-**7** and found to be identical in optical rotation, suggesting that the starting compound (+)-**6** has the (*S*)-configuration (Scheme 3).

Furthermore, an X-ray crystal analysis of diester (−)-**8** synthesized from acid (*S*)-(+)-**7** (Scheme 4) was performed to establish the configuration at the chiral centre C-4.[7]

As shown in Fig. 1, the (*R*)-stereochemistry of diester (−)-**8** was unambiguously determined. It was then possible to assign the (*R*)-configuration at C-4 in monoacid (−)-**6**, and the (*S*)-configuration at C-4 in monoacid (+)-**6**.

Experimental

M.p.s were determined on Yanagimoto micro melting points apparatus and are uncorrected. IR spectra were recorded on a JASCO DS-301 spectrometer. NMR spectra were recorded on Varian XL-200 (200 MHz) spectrometer using tetramethylsilane as internal standard. Chemical shifts are given in ppm, and *J*-values are given in Hz. Mass spectra were measured on a Shimadzu LKB 9000 spectrometer. Optical rotations were measured on a JASCO DIP-360 digital polarimeter (Japan Spectroscopic Co., Ltd.), with $[\alpha]_D$-values given in units of 10^{-1} deg cm^2 g^{-1}.

The following compounds were prepared by following the methods reported by Ashimori *et al.*[8]

(4R)-1,4-*Dihydro*-5-*methoxycarbonyl*-2,6-*dimethyl*-4-(3-*nitrophenyl*)*pyridine*-3-*carboxylic Acid* [(R)-(−)-**7**].—Yield 26%, m.p. 172–173 °C (lit.,[8] 169–170 °C); $[\alpha]_D^{20}$ −18.40 (*c* 0.50, acetone) {lit.,[8] $[\alpha]_D^{20}$ −24.6 (*c* 0.50, acetone)}.

(4S)-1,4-*Dihydro*-5-*methoxycarbonyl*-2,6-*dimethyl*-4-(3-*nitrophenyl*)*pyridine*-3-*carboxylic Acid* [(S)-(+)-**7**].—Yield 38%, m.p. 171–172 °C (lit.,[8] 168.5–170 °C); $[\alpha]_D^{20}$ +19.30 (*c* 0.50, acetone) {lit.,[8] $[\alpha]_D^{20}$ +24.4 (*c* 0.50, acetone)}.

2-*Cyanoethyl* 3-*Nitrooxypropyl* 1,4-*Dihydro*-2,6-*dimethyl*-4-(3-*nitrophenyl*)*pyridine*-3,5-*dicarboxylate* **5**.—A solution of 3-nitrobenzaldehyde **2** (15.1 g, 0.1 mol), 3-nitrooxypropyl acetoacetate **3** (20.4 g, 0.1 mol) and 2-cyanoethyl 3-aminocrotonate **4** (15.4 g, 0.1 mol) in propan-2-ol was stirred and refluxed for 3 h. The precipitated crystals were collected, washed with Et_2O and dried to afford *compound* **5** as yellow crystals (38.9 g, 82%) (Found: C, 52.95; H, 4.5; N, 11.75. $C_{21}H_{22}N_4O_9$ requires C, 53.16; H, 4.67; N, 11.81%); m.p. 144–145 °C (from CH_2CH_2–$Pr^i{}_2O$); ν_{max}(KBr)/cm^{-1} 2252 (CN) and 1697 (C=O); δ_H(200 MHz; $CDCl_3$) 2.06 (2 H, m, $CH_2CH_2CH_2ONO_2$), 2.39 (3 H, s, Me), 2.42 (3 H, s, Me), 2.68 (2 H, t, *J* 6, CH_2CN), 4.05 (2 H, t, *J* 6, CH_2CH_2CN), 4.28 (2 H, t, *J* 6, CO_2CH_2), 4.42 (2 H, t, *J* 6, CH_2ONO_2), 5.11 (1 H, s, 4-H), 6.03 (1 H, br s, NH) and 7.35–8.28 (4 H, m, ArH); *m*/*z* 474 (M^+).

(±)-1,4-*Dihydro*-2,6-*dimethyl*-5-[(3-*nitrooxypropoxy*)*carbonyl*]-4-(3-*nitrophenyl*)*pyridine*-3-*carboxylic Acid* [(±)-**6**].—A suspension of 2-cyanoethyl 3-nitrooxypropyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate **5** (47.4 g, 0.1 mol) in a mixture of acetone (200 cm^3) and 5 mol dm^{-3} sodium hydroxide (150 cm^3) was stirred at room temperature for 2 h. The reaction mixture was diluted with water, and extracted with CH_2Cl_2. The ice-cooled aq. layer was acidified with phosphoric acid. The precipitated product **6** was filtered off, washed with water, and then dried *in vacuo* to give *compound* **6** as yellow crystals (39.2 g, 93%) (Found: C, 51.3; H, 4.4; N, 10.1. $C_{18}H_{19}N_3O_9$ requires: C, 51.31; H, 4.55; N, 9.97%); m.p. 194–195 °C; ν_{max}(KBr)/cm^{-1} 1679 (C=O); δ_H[200 MHz; $(CD_3)_2SO$] 1.96 (2 H, m, $CH_2CH_2CH_2ONO_2$), 2.28 (3 H, s, Me), 2.33 (3 H, s, Me), 4.06 (2 H, m, CO_2CH_2), 4.41 (2 H, t, *J* 6, CH_2ONO_2), 5.00 (1 H, s, 4-H), 7.48–8.08 (4 H, m, ArH), 8.98 (1 H, br s, NH) and 11.08 (1 H, br s, CO_2H); *m*/*z* 421 (M^+).

Optical Resolution of (±)-1,4-*Dihydro*-2,6-*dimethyl*-5-[(3-*nitrooxypropoxy*)*carbonyl*]-4-(3-*nitrophenyl*)*pyridine*-3-*carboxylic Acid* (±)-**6**.—[(S)-(+)-**6**]. Cinchonidine (117.8 g, 0.4 mol) was added portionwise to a suspension of racemic acid (±)-**6** (168.5 g, 0.4 mol) in ethanol (1500 cm^3). After the addition was complete, the mixture was heated under reflux until dissolution was complete and was then kept at room temperature for 48 h. The crystals formed were collected by filtration and recrystallized from ethanol to give (S)-(+)-**6**–*cinchonidine salt* (94.5 g) as pale yellow crystals (Found: C, 61.9; H, 5.7; N, 9.7. $C_{37}H_{41}N_5O_{10}$ requires: C, 62.09; H, 5.77; N, 9.79%); m.p. 182–183 °C; $[\alpha]_D^{20}$ −122 (*c* 0.50, MeOH); ν_{max}(KBr)/cm^{-1} 1662 (C=O).

The obtained (*S*)-(+)-**6**–cinchonidine salt was suspended in 3.5% HCl (1500 cm^3), and extracted with methylene dichloride (1500 cm^3); the extract was washed successively with water and brine, dried (Na_2SO_4), and evaporated at reduced pressure to give acid (*S*)-(+)-**6**. The solid residue was suspended in diethyl ether, filtered off, and dried to yield *pure acid* (*S*)-(+)-**6** (54.0 g, 64%) as pale yellow crystals (Found: C, 51.3; H, 4.5; N, 9.9. $C_{18}H_{19}N_3O_9$ requires: C, 51.31; H, 4.55; N, 9.97%); $[\alpha]_D^{20}$ +48.74 (*c* 0.5, MeOH); m.p. 150–151 °C; ν_{max}(KBr)/cm^{-1} 1679 (C=O); δ_H[200 MHz; $(CD_3)_2SO$] 1.96 (2 H, m, $CH_2CH_2CH_2ONO_2$), 2.29 (3 H, s, Me), 2.33 (3 H, s, Me), 4.06 (2 H, m,

* The screening test for vasodilation activity was carried out by measurement of femoral blood flow in anaesthetized dogs. The activity diester (*S*)-(+)-**1** was shown to be 1.6-fold higher than that of the enantiomer (*R*)-(−)-**1**, as is found in other 1,4-dihydropyridine enantiomers.

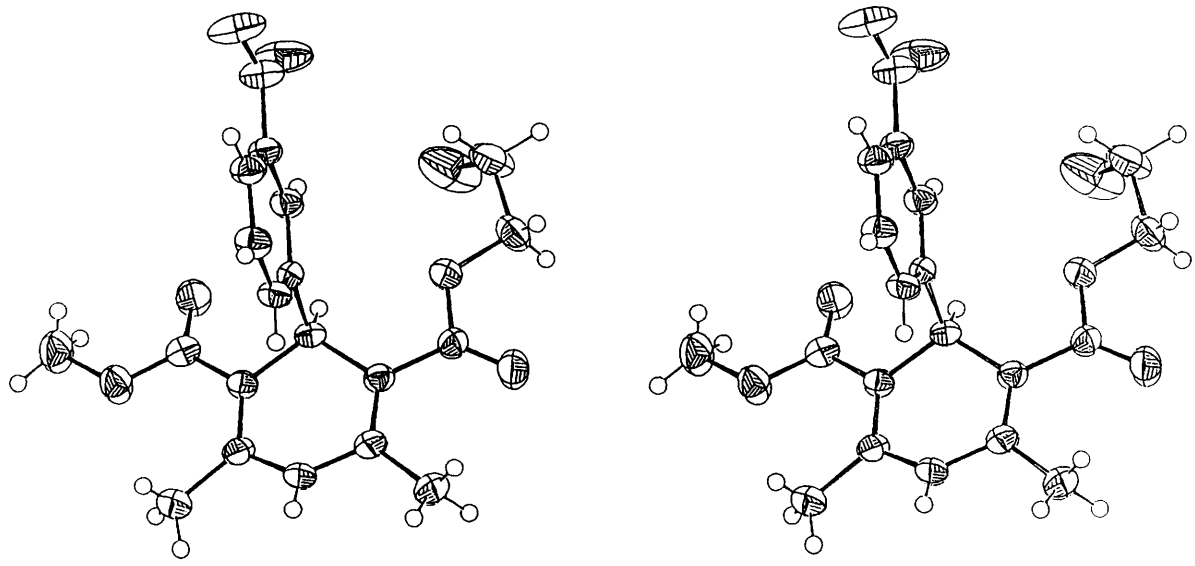
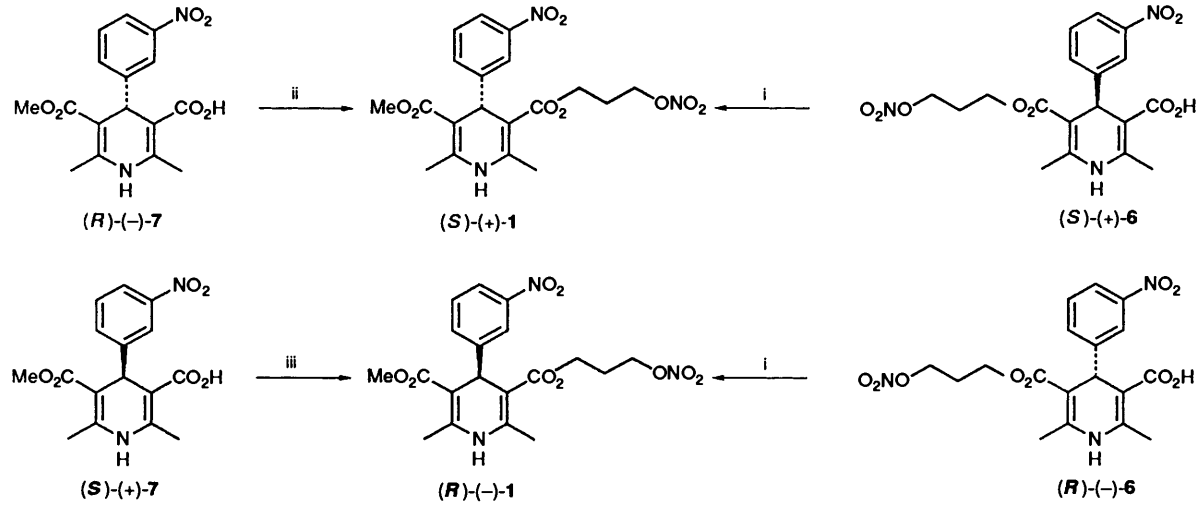
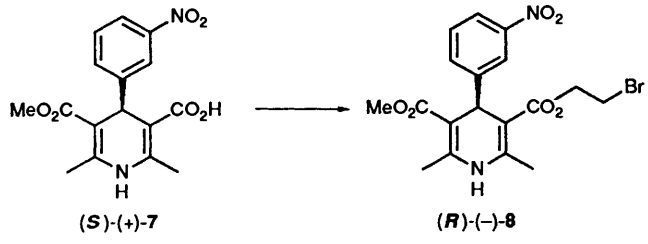


Fig. 1 Stereoscopic drawing of the structure of diester (*R*)-(−)-**8** obtained by X-ray crystal analysis



Scheme 3 *Reagents:* i, MeOH, Ac_2O, AcCl, CH_2Cl_2; or MeI, K_2CO_3, DMF; ii, $Br[CH_2]_3ONO_2$, K_2CO_3, DMF; iii, $Br[CH_2]_3ONO_2$, K_2CO_3, DMF; or $HO[CH_2]_3ONO_2$, Ac_2O, AcCl, CH_2Cl_2



Scheme 4 *Reagents:* $BrCH_2CH_2OH$, Ac_2O, AcCl, CH_2Cl_2

CO_2CH_2), 4.40 (2 H, t, *J* 6, CH_2ONO_2), 4.99 (1 H, s, 4-H), 7.47–8.07 (4 H, m, ArH), 8.98 (1 H, br s, NH) and 11.83 (1 H, br s, CO_2H); *m/z* (EI) 421 (M^+).

The mother liquor obtained after the first recrystallization was concentrated. The ice-cooled residue was treated with 3.5% hydrochloric acid (700 cm^3) and extracted with CH_2Cl_2. The extract was washed with water, dried (anhydrous Na_2SO_4) and concentrated. The residue was treated with cinchonine (58.9 g, 0.2 mol) in a similar manner to that used for the preparation of (+)-**6**–cinchonidine salt to give (*R*)-(−)-**6**–*cinchonine salt* (50.3 g) as pale yellow crystals (Found: C, 61.75; H, 5.4; N, 9.6. $C_{37}H_{41}N_5O_{10}$ requires C, 62.09; H, 5.77; N, 9.79%); $[\alpha]_D^{20}$ +27 (*c* 0.5, MeOH); m.p. 181–183 °C; ν_{max}(KBr)/cm^{-1} 1705 and 1677.

By the same work-up procedure as that described above, *acid* (*R*)-(−)-**6** was obtained as pale yellow crystals (21.3 g, 26%) (Found: C, 51.5; H, 4.5; N, 9.9. $C_{18}H_{19}N_3O_9$ requires C, 51.31; H, 4.55; N, 9.97%); $[\alpha]_D^{20}$ −48.25 (*c* 0.5 in MeOH); m.p. 147–148 °C.

Methyl 3-*Nitrooxypropyl* (4S)-1,4-*Dihydro*-2,6-*dimethyl*-4-(3-*nitrophenyl*)*pyridine*-3,5-*dicarboxylate* [(S)-(+)-**1**].—*Method A*. To a suspension of acid (*S*)-(+)-**6** (4.2 g, 10 mmol) in CH_2Cl_2 (30 cm^3) was added acetic anhydride (3.1 g, 30 mmol) at room temperature and the mixture was then stirred for 5 h at the same temperature. A solution of methanol (0.38 g, 12 mmol) in CH_2Cl_2 containing a catalytic amount of acetyl chloride was added to the reaction mixture at the same temperature and this mixture was stirred for 6 h before being diluted with water. The CH_2Cl_2 layer was separated, and washed successively with 1 mol dm^{-3} aq. NaOH and water, dried (Na_2SO_4) and concentrated. The resulting residue was chromatographed on silica gel (200 g) with hexane–ethyl acetate (3 : 2, v/v) as eluent to

give *diester* (*S*)-(+)-**1** (99% ee)* (2.72 g, 63%). Recrystallization from CH_2Cl_2–Pr^i_2O gave light yellow crystals (Found: C, 52.5; H, 4.7; N, 9.6. $C_{19}H_{21}N_3O_9$ requires C, 52.41; H, 4.86; N, 9.65%); m.p. 103–104 °C; $[\alpha]_D^{20}$ +16.6 (*c* 0.50, MeOH); ν_{max}(KBr)/cm^{-1} 1707 (C=O); δ_H(200 MHz; $CDCl_3$) 2.05 (2 H, m, $CH_2CH_2CH_2$), 2.37 (3 H, s, Me), 2.39 (3 H, s, Me), 3.67 (3 H, CO_2Me), 4.16 (2 H, m, CO_2CH_2), 4.38 (2 H, t, *J* 6, CH_2ONO_2), 5.08 (1 H, s, 4-H), 5.74 (1 H, br s, NH) and 7.32–8.14 (4 H, m, ArH); *m/z* 435 (M^+).

Method B. A solution of ester (*S*)-(+)-**6** (4.2 g, 10 mmol), methyl iodide (0.95 g, 15 mmol) and potassium carbonate (2.1 g, 15 mmol) in DMF (30 cm^3) was stirred for 12 h at room temperature. The mixture was extracted with CH_2Cl_2, the extract was washed successively with water and brine, then dried (Na_2SO_4), and the solvent was removed. The resulting residue was purified by chromatography on silica gel (200 g) with hexane–ethyl acetate (1:1, v/v) to give diester (*S*)-(+)-**1** (99% ee) (2.85 g, 66%). Recrystallization from CH_2Cl_2–Et_2O gave as light yellow prisms (Found: C, 52.4; H, 4.8; N, 9.4%); m.p. 104–105 °C; $[\alpha]_D^{20}$ +18.40 (*c* 0.50, MeOH).

Compound (*S*)-(+)-**1** (98% ee) was also similarly prepared from monoester (*R*)-(−)-**7** in 78% yield by reaction with 3-nitrooxypropyl bromide by method B; m.p. 99–100 °C (from CH_2Cl_2–Pr^i_2O), $[\alpha]_D^{20}$ +15.20 (*c* 0.50, MeOH). This was identical with compound **1** (IR, NMR and mass spectra).

Methyl 3-Nitrooxypropyl (4R)-1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate [(R)-(−)-**1**].—By following exactly the same procedure as Methods A and B as described for diester (+)-**1**, the moncarboxylic acid (−)-**6** (4.2 g, 10 mmol) afforded (*R*)-(−)-**1** (97% ee) (2.2 g, 51%) and (98% ee) (2.9 g, 66%) as yellow crystals, respectively.

Method A. M.p. 100–101 °C (from CH_2Cl_2–Pr^i_2O); $[\alpha]_D^{20}$ −17.40 (*c* 0.50, MeOH).

Method B. M.p. 102–103 °C (from CH_2Cl_2–Pr^i_2O); $[\alpha]_D^{20}$ −21.20 (*c* 0.50, MeOH).

The IR (KBr) and NMR spectra of these samples were identical with those of the enantiomer (+)-**1**.

Compound (*R*)-(−)-**1** was similarly prepared from monoester (*S*)-(+)-**7** in 78 and 84% by reaction with 3-nitrooxypropan-1-ol[9] or 3-nitrooxypropyl bromide by Method A and B, respectively.

Method A. M.p. 98–99 °C (from CH_2Cl_2–Pr^i_2O); $[\alpha]_D^{20}$ −19.20 (*c* 0.50, MeOH); 99% ee.

Method B. M.p. 96–98 °C (from CH_2Cl_2–Pr^i_2O); $[\alpha]_D^{20}$ −21.20 (*c* 0.50, MeOH); 99% ee.

2-Bromoethyl Methyl (4R)-1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate [(R)-(−)-**8**].—By following exactly the same procedure as Method A described for diester (+)-**1**, esterification of monoacid (*S*)-(+)-**7** (3.32 g, 10 mmol) by using 2-bromoethanol (1.25 g, 10 mmol) afforded *diester* (R)-(−)-**8** (2.78 g, 63%) (Found: C, 49.4; H, 4.2; N, 6.4. $C_{18}H_{19}BrN_2O_6$ requires C, 49.21; H, 4.36; N, 6.38%); m.p. 149–150 °C (from CH_2Cl_2–Pr^i_2O); $[\alpha]_D^{20}$ −113 (*c*. 0.50, MeOH); ν_{max}(KBr)/cm^{-1} 1702 and 1685; δ_H(200 MHz; $CDCl_3$) 2.39 (3 H, s, Me), 2.42 (3 H, s, Me), 3.48 (2 H, t, *J* 5, CH_2CH_2Br), 3.67 (3 H, s, CO_2Me), 4.38 (2 H, m, CH_2CH_2Br), 5.12 (1 H, s, 4-H), 5.92 (1 H, br s, NH) and 7.33–8.16 (4 H, m, ArH); *m/z* 440 (M^+).

Crystal Data for Compound **8**. $C_{18}H_{19}Br_1N_2O_6$, M = 438.90, monoclinic, space group $P2_1$, a = 11.058(3), b = 11.817(5), c = 7.528(3) Å, β = 107.00(2)°, V = 940.6(5) Å^3, T = 288 K, Z = 2, D_c = 1.55 g cm^{-1}, μ = 30.89 cm^{-1}. Crystal dimensions 0.40 × 0.30 × 0.25 mm, λ(Cu-Kα) = 1.541 78 Å. Data collection was performed by a Mac-Science MXC 18 diffractometer. The structure was solved by direct methods using SHELXS86.[10] Full-matrix least-squares refinement of atomic parameters (anisotropic Br, C, O, N; isotropic H) converged at R = 0.034 over 1665 independent reflections. The absolute configuration of compound **8** was determined by the *R*-value method from the anomalous scattering due to the bromine atom and found to be *R*. Full lists of fractional atomic co-ordinates, bond lengths and angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.†

* The racemic 1,4-dihydropyridine **1** prepared by the same procedure was analysed by high-pressure liquid chromatography (HPLC) analysis on a chiral column [Chiralcel OJ] at 18 °C with ethanol–hexane (15:85), to give two peaks of equal area at 11.3 and 16.0 min. The enantiomeric excess of the two enantiomers (*S*)-(+)-**1** and (*R*)-(−)-**1** was determined by integration of the corresponding retention peaks.

† For full details of the CCDC deposition scheme see 'Instructions for Authors,' *J. Chem. Soc., Perkin Trans. 1*, 1993, Issue 1.

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