Chemistry of Hantzsch Cyclization: Stereochemistry of the 2-Hydroxy-1,2,3,4-tetrahydropyridine Intermediate of Hantzsch Cyclization. X-Ray Molecular Structure of Diastereoisomers of 5-(2-Cyanoethyl) 3-Methyl 2-Dimethoxymethyl-2-hydroxy-6-methyl-4-(3-nitrophenyl)-1,2,3,4-tetrahydropyridine-3,5-dicarboxylates

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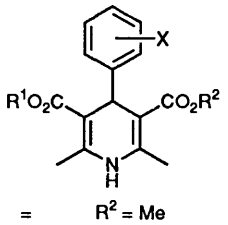
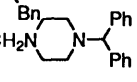
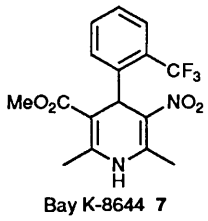
Hantzsch cyclization of cyanoethyl 3-aminocrotonate and (*E,Z*)-4,4-dialkoxy-2-benzylideneacetoacetates **12a–h** afforded the corresponding 3,4-*trans*-2-hydroxy-1,2,3,4-tetrahydropyridines **14a–h** with high stereoselectivity. ^{1}H NMR and X-ray analyses of compound **14a** established the configuration of 3-H and 4-H as *trans* and that of 3-H and 2-OH as *trans* also.

Since the discovery of nifedipine **1** in 1971,[1] a clinically important antihypertensive and antiangina drug, various chemical modifications[2] of 1,4-dihydropyridines, such as nicardipine **2**, nimodipine **3**, benidipine **4**, manidipine **5**, CD-349 **6**, and Bay K-8644 **7** have been developed with the aim of enhancing the antihypertensive activity and duration of action.

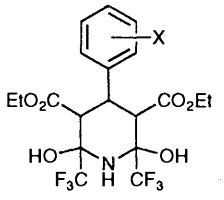


1 Nifedipine	R^1 =	R^2 = Me	X = 2-NO_2
2 Nicardipine	R^1 = Me	R^2 = $CH_2CH_2N(Me)Bn$,	X = 3-NO_2
3 Nimodipine	R^1 = Pr^i	R^2 = CH_2CH_2OMe,	X = 3-NO_2
4 Benidipine	R^1 = Me	R^2 = 	X = 3-NO_2
5 Manidipine	R^1 = Me	R^2 = 	X = 3-NO_2
6 CD-349	R^1 = $[CH_2]_3ONO_2$,	R^2 = $CH_2CH(Me)ONO_2$	X = 3-NO_2

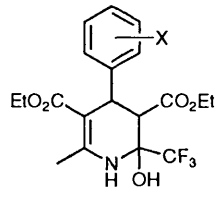


Bay K-8644 **7** Bn = benzyl

In addition to their clinical utility in cardiovascular medicine, dihydropyridines are employed as biological tools for the study of voltage-activated calcium-channel structures and functions.[3] These 4-(substituted aryl)-1,4-dihydropyridines were easily accessible by using the classical method of Hantzsch synthesis,[4] and all were obtained directly without formation of the reaction intermediates, 2-hydroxy-1,2,3,4-tetrahydropyridines. Contrary to the ordinary reaction, the Hantzsch intermediates, 4-aryl-2,6-dihydroxy-2,6-bis(trifluoromethyl)piperidine-3,5-dicarboxylates **8a–c** and 4-aryl-2-hydroxy-6-methyl-2-trifluoromethyl-1,2,3,4-tetrahydropyridine-3,5-dicarboxylates **9a, b** were obtained by using ethyl 4-(trifluoromethyl)acetoacetate instead of methyl acetoacetate.[5,6] However, the stereochemistry of intermediates **8** and **9** has not been studied to any depth and both stereochemistry and the mechanism of Hantzsch cyclization remain unclear.



8a-c
a; X = 2-NO_2
b; X = 3-NO_2
c; X = 3-Cl



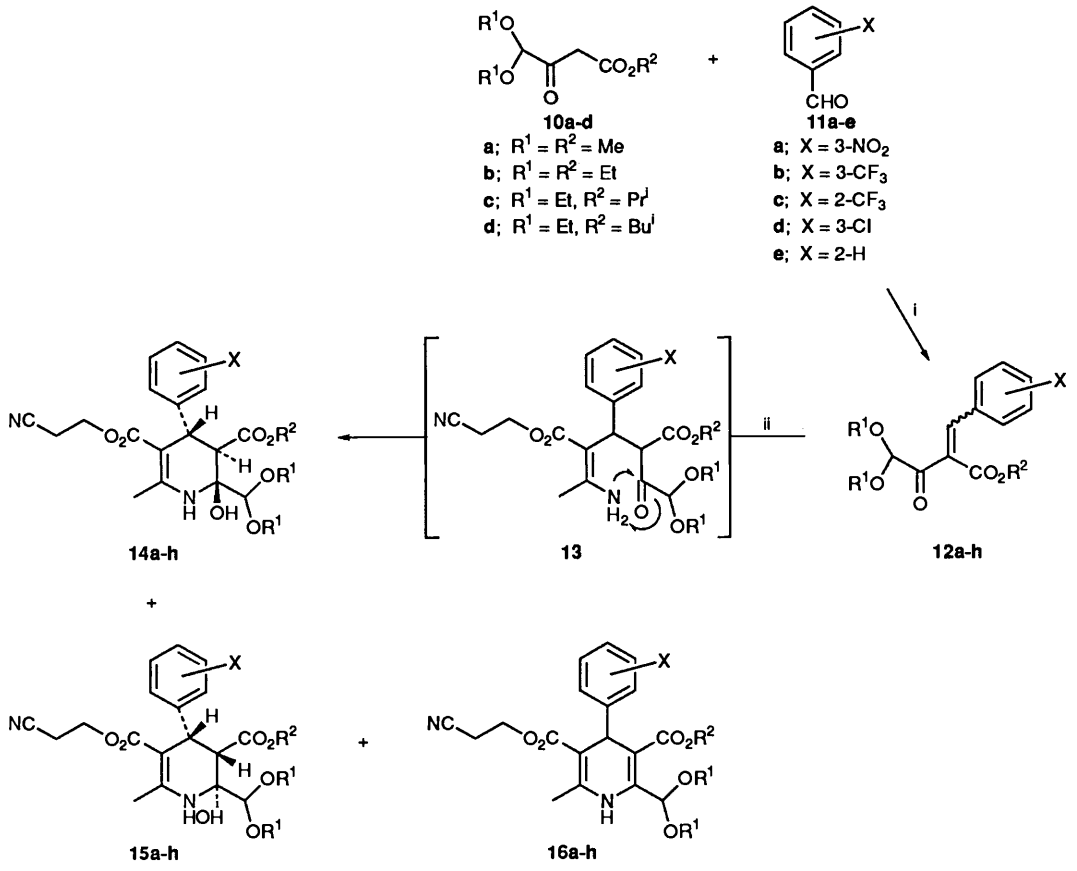
9a-c
a; X = 4-NO_2
b; X = 3,4-Cl_2

Very recently, we have briefly reported a Hantzsch reaction using 2-cyanoethyl 3-aminocrotonate and (*E,Z*)-4,4-dialkoxy-2-benzylideneacetoacetates **12a, b** which gives the Hantzsch intermediates, 3,4-*trans*-2-hydroxy-1,2,3,4-tetrahydropyridines **14a, b** with high stereoselectivity.[7] We now present a full account of the stereochemistry of these Hantzsch intermediates and additional examples of the formation of intermediates **14c–h** from keto esters **12c–h**.

Results and Discussion

First, Hantzsch cyclization of 2-cyanoethyl 3-aminocrotonate and methyl 2-(3-nitrobenzylidene)-4,4-dimethoxyacetoacetate **12a**,[8] derived from 3-nitrobenzaldehyde **11a** and methyl 4,4-dimethoxyacetoacetate, **10a**[8] was performed in refluxing propan-2-ol in the presence of piperidine acetate to give a mixture of diastereoisomeric 2-hydroxy-1,2,3,4-tetrahydropyridines **14a** and **15a** in the ratio 3.47:1 in 66% yield along with the 1,4-dihydropyridine **16a** in 16% yield (Scheme 1).

The diastereoisomers **14a** and **15a** along with compound **16a** were readily separated by chromatography on silica gel (2:1) ethyl acetate–hexane, **14a** R_f 0.13, **15a** R_f 0.28, **16a** R_f 0.45). The structures of diastereoisomers **14a** and **15a** were assigned from both their spectral data and their ready conversion into the



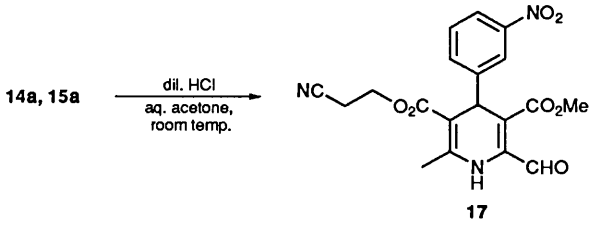
Scheme 1 *Reagents:* i, piperidine–AcOH; ii, $MeC(NH_2)=CHCO_2CH_2CH_2CN$

corresponding dihydropyridine **16a** by treatment with camphorsulfonic acid* in acetone.

In order to ascertain the stereochemistry of 2-OH in both isomers, crystal X-ray diffraction analyses of compounds **14a** and **15a** were carried out (Fig. 1). The crystal X-ray diffraction analysis of isomer **14a** indicated that the relative configuration of 3-H and 4-H of the tetrahydropyridine ring was *trans* [torsion angle of 3(H)–C(3)–C(4)–4(H) −158.1°] and that of 3-H and 2-OH is also *trans* [torsion angle 3(H)–C(3)–C(2)–O(2) 170.6°]. On the other hand, analysis of isomer **15a** indicated the relative configuration of 3-H and 4-H to be *cis* [torsion angle 3(H)–C(3)–C(4)–4(H) 44.0°] and that of 3-H and 2-OH to be *trans* [torsion angle of 3(H)–C(3)–C(2)–O(2) −170.7°]. As can be seen from Fig. 1, the 4-aryl residue of isomer **14a** is in a pseudoequatorial position and that of isomer **15a** is in a pseudoaxial position, *i.e.*, standing virtually perpendicular to the plane of the tetrahydropyridine ring. Further, the plane of the aromatic ring nearly bisects the 1,2,3,4-tetrahydropyridine ring and the nitro group is orientated *syn* periplanar to the C-4 methine proton of the 1,2,3,4-tetrahydropyridine. The acetal oxygen in the side-chain and the hydrogen atom on the 1,2,3,4-tetrahydropyridine nitrogen are essentially coplanar. The interatomic distance between the hydrogen atom on the nitrogen and the acetal oxygen in isomers **14a** and **15a** is 2.69 and 2.86 Å, respectively. This indicates the existence of an intramolecular hydrogen bond. Thus, the stereochemistry of diastereoisomers **14a** and **15a** was unambiguously assigned as shown in Scheme 1.

Hantzsch cyclization of 2-cyanoethyl 3-aminocrotonate under the same conditions as for compound **12b**[8] proceeded similarly with high stereoselectivity to give a mixture of products **14b**, **15b** and **16b** (entry 2 in Table 1). Further, the reaction of 2-cyanoethyl 3-aminocrotonate with keto esters **12c**, **d** afforded the corresponding products **14c**, **d** with higher *threo*-selectivity than that in the reaction of **12a**, **b**. The formation of products **14c**, **d** with high *threo*-selectivity shows that a bulky substituent such as isopropyl† (entry 3) or isobutyl† (entry 4) of the ester group influences the *threo*-selectivity. In the case of displacement substituents such as trifluoromethyl, chloro, and hydrogen in the phenyl ring of compounds **12b**, Hantzsch cyclization of intermediates **12e–h** with 2-cyanoethyl 3-aminocrotonate under the same conditions as above gave the corresponding 3,4-*trans*-1,2,3,4-tetrahydropyridines **14** with high *threo*-selectivity (entries 5–8). In particular, cyclization using intermediates **12f–h** proceeded with *threo*-selectivity without the formation of compounds **15f–h**, but resulted in a low yield (33%) of compound **12f**. Apparently, the stereochemical course of the reaction was not only determined by the nature of the ester group, but also by substituent effects on the phenyl

* Treatment of diastereoisomers **14a** and **15a** with dil. hydrochloric acid (0.1 mol equiv.) in aq. acetone afforded 2-formyl-1,4-dihydropyridine **17** in excellent yield.



† The keto esters **10c**, **d** were prepared by reaction of compound **10b** with a substituted sodium alkoxide.

10b $\xrightarrow{Na/R^2OH}$ **10c** R^1 = Et, R^2 = Pr^i; **10d** R^1 = Et, R^2 = Bu^i

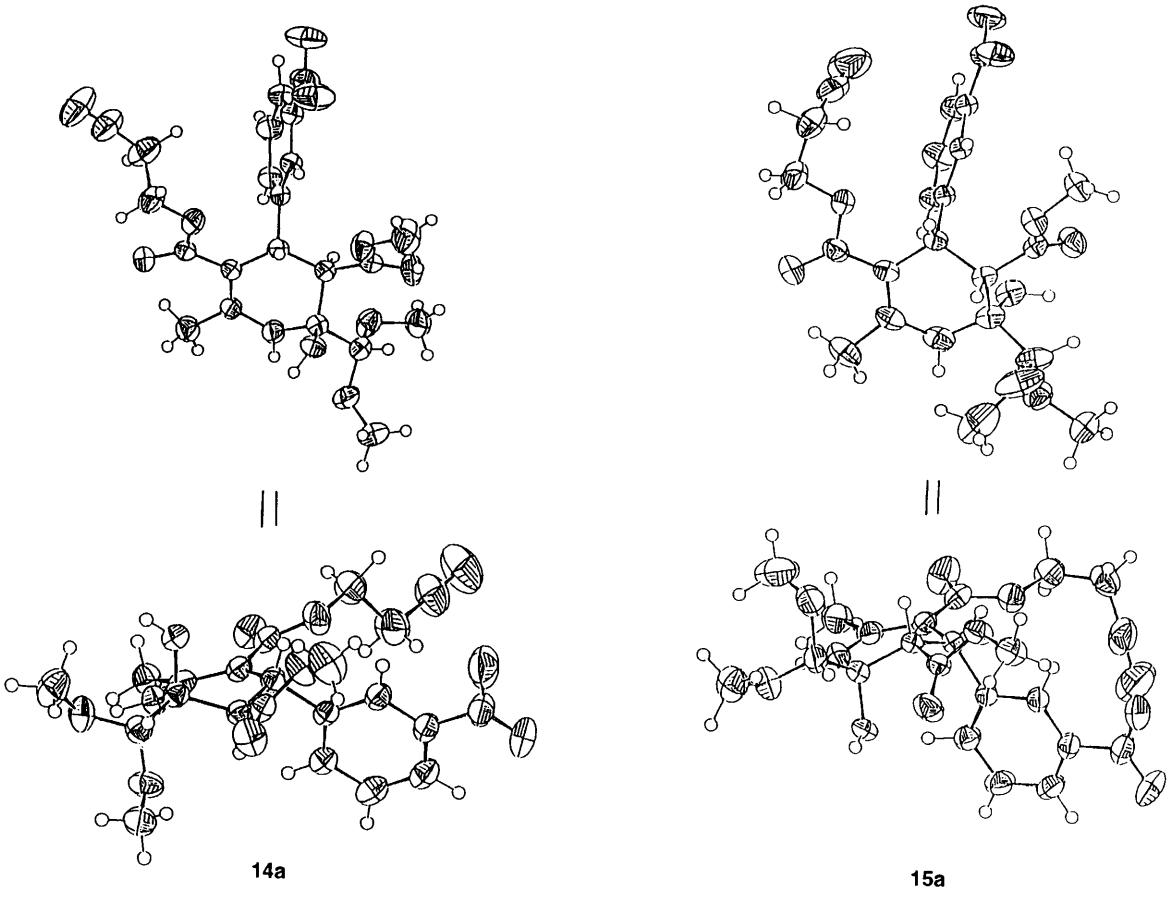


Fig. 1 X-Ray molecular structure of compounds **14a** and **15a**

Table 1 Hantzsch cyclization of 2-cyanoethyl 3-aminocrotonate with (*E*,*Z*)-4-dialkoxy-2-benzylideneacetoacetate **12a–h**

Entry	X	R^1	R^2	Time (*t*/h)	% Yield of **14** + **15**[a] (Product ratio **14**:**15**)[b,c]	% Yield of **16**[a]
1	3-NO_2	Me	Me	5	**14a**, **15a** 66 (82:18)	**16a** 16
2	3-NO_2	Et	Et	5	**14b**, **15b** 64 (84:16)	**16b** 15
3	3-NO_2	Et	Pr^i	5	**14c**, **15c** 77 (95:5)	**16c** 3
4	3-NO_2	Et	Bu^i	5	**14d**, **15d** 75 (88:12)	**16d** 2
5	3-CF_3	Et	Et	5	**14e**, **15e** 61 (85:15)	**16e** 3
6	2-CF_3	Et	Et	5	**14f**, **15f** 33 (100:0)	**16f** 31
7	3-Cl	Et	Et	5	**14g**, **15g** 53 (100:0)	**16g** 0
8	H	Et	Et	5	**14h**, **15h** 71 (100:0)	**16h** 1

[a] Isolation based on the corresponding substrate **12**. [b] Determined on the crude product. [c] The ratios **14**:**15** were determined by HPLC.*

* Compounds **14a–h**, **15a–h** and **16a–h** were analysed by high-pressure liquid chromatography (HPLC) analysis [conditions: reversed-phase TSK gel ODS-80TH; mobile phase, MeOH–water–H_3PO_4 (55:45:0.5); flow rate 1.0 cm^3 min^{-1}; UV, 237 nm].

ring in the Michael addition in the first step of the Hantzsch cyclization. The yield and ratio for *threo*/*erythro* isomers are shown in Table 1.

For the present highly stereoselective Hantzsch-type reaction, the following mechanism may be presumed. In the first step of the Hantzsch method, the most favourable formation of the Michael adduct should be *via* a six-membered-ring transition state **A**,[9] which leads to the 3- and 4-*trans* transition state **B** avoiding the repulsion between the phenyl group and the ester substituents. Although the stereochemical course of the present Hantzsch cyclization is unclear at the second stage, the results described in this paper strongly suggest that the observed stereoselection may reflect the effects of steric interactions alone. Assuming two transition states **B** and **C** leading to products **14a–h** and **15a–h**, transition state **B** would be favoured over **C** because in transition state **C** steric repulsion between the acetal and 3-alkyl ester is present (Fig. 2). According to such a transition state, ring closure of the nitrogen nucleophile, in its energetically preferred conformation, takes place predominantly on the *si*-face of the carbonyl group. It seems likely that the predominant formation of stable products **14a–h** and **15a–e** has been attributed to formation of a hydrogen bond between the amino proton and acetal oxygen.

In summary we offer a new insight into the mechanism of Hantzsch cyclization, suggesting that the Michael addition of 2-cyanoethyl 3-aminocrotonate to *Z*- and *E*-benzylideneacetates **12a–h**, which leads to 3-,4-*trans* intermediate **B**, gives 3,4-*trans*-2-hydroxy-1,2,3,4-tetrahydropyridines **14a–h** predominantly, with high stereoselectivity.

Experimental

M.p.s were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO DS-301 spectrometer. NMR spectra were recorded on a Varian XL-200 (200 MHz) spectrometer using tetramethyl-

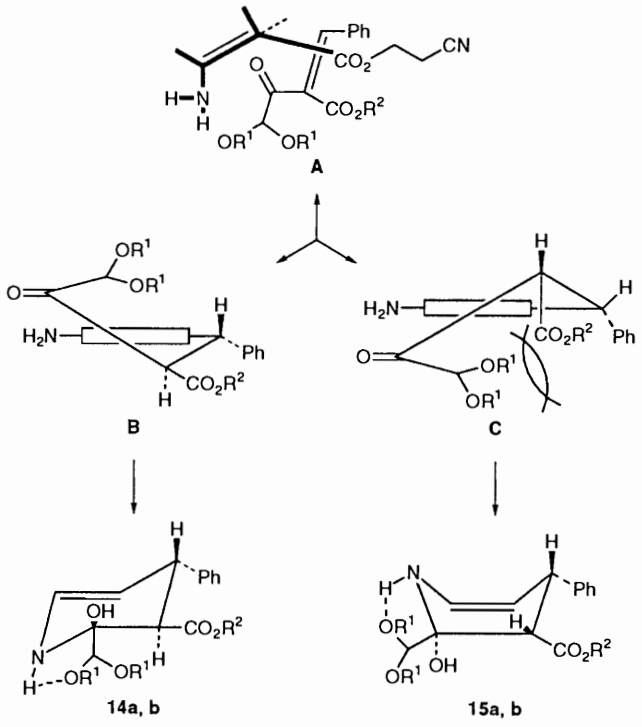


Fig. 2

silane as internal standard. Chemical shifts (δ) are given in ppm, and J values are given in Hz. Mass spectra were measured on a Shimadzu LKB 9000 spectrometer.

Isopropyl 4,4-*Diethoxyacetoacetate* **10c**.—Sodium (2.76 g, 120 mmol) was added to propan-2-ol (150 cm^3) under nitrogen at 100 °C. When the sodium had dissolved, ethyl 4,4-diethoxyacetoacetate **3b** (21.8 g, 100 mmol) was added and the resulting solution was stirred for 20 h at 110 °C. Solvent was removed under reduced pressure. Dil. acetic acid was added to the residue and the solution was extracted with AcOEt (×2). The combined extracts were washed successively with water and brine, dried (Na_2SO_4) and evaporated under reduced pressure to give *title compound* **10c** as an oil (21.5 g, 93%), b.p. 116–118 °C/0.2 mmHg (Found: C, 56.8; H, 8.4. $C_{11}H_{20}O_5$ requires C, 56.88; H, 8.68%); ν_{max}(neat)/cm^{-1} 1729 and 1751 (C=O); δ_H(200 MHz; $CDCl_3$) 1.26–1.33 (4 × 3 H, m, 4 × Me), 3.56 (2 H, s, $COCH_2CO$), 3.63–3.78 (2 × 2 H, m, $CH_2OCHOCH_2$), 4.69 (1 H, s, 4-H) and 5.10 (1 H, m, $OCHMe_2$); m/z 232 (M^+).

Isobutyl 4,4-*Diethoxyacetoacetate* **10d**.—By the same work-up procedure as that described above, *compound* **10d** was obtained as an oil in 91% yield, b.p. 114–115 °C/0.2 mmHg (Found: C, 58.3; H, 8.95. $C_{12}H_{22}O_5$ requires C, 58.51; H, 9.00%); ν_{max}(neat)/cm^{-1} 1732 and 1752 (C=O); δ_H(200 MHz; $CDCl_3$) 0.81–1.01 (2 × 3 H, m, 2 × Me), 1.08–1.34 (2 × 3 H, m, 2 × Me), 1.92 (1 H, m, $CHMe_2$), 3.44–3.81 (3 × 2 H, m, 3 × CH_2), 3.63 (2 H, s, $COCH_2CO$), 3.92 (2 H, d, J 8, OCH_2CH) and 4.68 (1 H, s, EtOC*H*OEt); m/z 246 (M^+).

(E,Z)-*Isopropyl* 4,4-*Diethoxy*-2-(3-*nitrobenzylidene*)*acetoacetate* **12c**.—A solution of 3-nitrobenzaldehyde **11a** (15.1 g, 100 mmol), isopropyl 4,4-diethoxyacetoacetate **10c** (23.2 g, 100 mmol), piperidine (1.70 g, 20.0 mmol) and AcOH (1.20 g, 20.0 mmol) in benzene (200 cm^3) was refluxed under azeotropic dehydration for 2 h. The resulting solution was washed with water and dried over Na_2SO_4. The solvent was evaporated off, and the residue was chromatographed on silica gel. Elution by hexane–ethyl acetate (2:1, v/v) gave an oily mixture of E and Z forms of *title compound* **12c** (30.3 g, 83%) (Found: C, 59.0; H, 6.1; N, 3.7. $C_{18}H_{23}NO_7$ requires C, 59.18; H, 6.33; N, 3.83%); ν_{max}(neat)/cm^{-1} 1718 (C=O); δ_H(200 MHz; $CDCl_3$) 1.21–1.41 (4 × 3 H, m, 4 × Me), 3.52–3.83 (2 × 2 H, m, 2 × CH_2), 4.99 and 5.18 (1 H, each s, EtOC*H*OEt), 5.13–5.19 (1 H, m, MeC*H*Me), 7.46–8.42 (4 H, m, ArH) and 7.74 and 7.95 (1 H, each s, CH=); the ratio of isomers was 1:1 judged from the NMR spectrum; m/z 365 (M^+).

(E,Z)-*Isobutyl* 4,4-*Diethoxy*-2-(3-*nitrobenzylidene*)*acetoacetate* **12d**.—The previous procedure was repeated exactly, using 3-nitrobenzaldehyde **11a** (15.1 g, 100 mmol), isobutyl 4,4-diethoxyacetoacetate **10d** (24.6 g, 100 mmol), piperidine (1.70 g, 20.0 mmol), and AcOH (1.20 g, 20.0 mmol). The product was obtained as an oily mixture of E and Z forms (1:1) of *compound* **12d** (28.4 g, 63%) (Found: C, 66.4; H, 5.4; N, 3.0. $C_{25}H_{25}NO_7$ requires C, 66.51; H, 5.58; N, 3.10%); ν_{max}(neat)/cm^{-1} 1718 (C=O); δ_H(200 MHz; $CDCl_3$) 0.76–1.35 (4 × 3 H, m, 4 × Me), 1.82–2.11 (1 H, m, MeC*H*Me), 3.50–3.83 (3 × 2 H, m, 3 × CH_2), 4.98 and 5.18 (1 H, each s, EtOC*H*OEt), 7.48–8.37 (4 H, m, ArH) and 7.74 and 7.93 (1 H, each s, CH=); m/z 451 (M^+).

(E,Z)-*Ethyl* 4,4-*Diethoxy*-2-[3-(*trifluoromethyl*)*benzylidene*]-*acetoacetate* **12e**.—The previous procedure was repeated exactly, using 3-(trifluoromethyl)benzaldehyde **11b** (17.4 g, 100 mmol), ethyl 4,4-diethoxyacetoacetate **10b** (21.8 g, 100 mmol), piperidine (1.70 g, 20.0 mmol), and AcOH (1.20 g, 20.0 mmol). The product was obtained as an oily mixture of E and Z forms (1:1) of *compound* **12e** (21.0 g, 58%) (Found: C, 56.3; H, 5.8. $C_{17}H_{21}F_3O_5$ requires C, 56.35; H, 5.84%); ν_{max}(neat)/cm^{-1} 1723 (C=O); δ_H(200 MHz; $CDCl_3$) 1.08–1.42 (3 × 3 H, m, 3 × Me), 3.44–3.79 (2 × 2 H, m, $CH_2OCHOCH_2$), 4.20–4.38 (2 H, m, CO_2CH_2), 4.93 and 5.19 (1 H, each s, $CH_2OCHOCH_2$), 7.35–7.79 (4 H, m, ArH) and 7.80 and 7.95 (1 H, each s, CH=); m/z 362 (M^+).

(E,Z)-*Ethyl* 4,4-*Diethoxy*-2-[2-(*trifluoromethyl*)*benzylidene*]-*acetoacetate* **12f**.—The previous procedure was repeated exactly, using 2-(trifluoromethyl)benzaldehyde **11c** (17.4 g, 100 mmol), ethyl 4,4-diethoxyacetoacetate **10b** (21.8 g, 100 mmol), piperidine (1.70 g, 20.0 mmol) and AcOH (1.20 g, 20.0 mmol). The product was obtained as an oily mixture of E and Z forms (1:1) of *title compound* **12f** (23.8 g, 66%) (Found: C, 56.3; H, 5.7. $C_{17}H_{21}F_3O_5$ requires C, 56.35; H, 5.84%); ν_{max}(neat)/cm^{-1} 1723 (C=O); δ_H(200 MHz; $CDCl_3$) 0.93–1.40 (3 × 3 H, m, 3 × Me), 3.42–3.78 (2 × 2 H, m, $CH_2OCHOCH_2$), 4.02–4.42 (2 H, m, CO_2CH_2), 4.80 and 5.19 (1 H, each s, EtOC*H*OEt), 7.33–7.78 (4 H, m, ArH) and 7.46 and 7.50 (1 H, each s, CH=); m/z 362 (M^+).

(E,Z)-*Ethyl* 2-(3-*Chlorobenzylidene*)-4,4-*diethoxyacetoacetate* **12g**.—The previous procedure was repeated exactly, using 3-chlorobenzaldehyde **4d** (14.0 g, 100 mmol), ethyl 4,4-diethoxyacetoacetate **10b** (21.8 g, 100 mmol), piperidine (1.70 g, 20.0 mmol), and AcOH (1.20 g, 20.0 mmol). The product was obtained as an oily mixture of E and Z forms (1:1) of *title compound* **12g** (22.2 g, 65%) (Found: C, 59.8; H, 6.1. $C_{17}H_{21}ClO_5$ requires C, 59.90; H, 6.21%); ν_{max}(neat)/cm^{-1} 1751 and 1729 (C=O); δ_H(200 MHz; $CDCl_3$) 1.08–1.38 (3 × 3 H, m, 3 × Me), 3.55–3.85 (2 × 2 H, m, $CH_2OCHOCH_2$), 4.21–4.32 (2 H, m, CO_2CH_2), 4.35 and 4.90 (1 H, each s, EtOC*H*OEt), 7.21–7.89 (4 H, m, ArH) and 7.48 and 7.53 (1 H, each s, CH=); m/z 340 (M^+).

(E,Z)-*Ethyl* 2-*Benzylidene*-4,4-*diethoxyacetoacetate* **12h**.—The previous procedure was repeated exactly, using benzaldehyde **4e** (15.1 g, 100 mmol), ethyl 4,4-diethoxyacetoacetate **10b** (21.8 g, 100 mmol), piperidine (1.70 g, 20.0 mmol), and

AcOH (1.20 g, 20.0 mmol). The product was obtained as an oily mixture of *E* and *Z* forms (1:1) of *compound* **12h** (25.3 g, 83%) (Found: C, 66.6; H, 7.1. $C_{17}H_{22}O_5$ requires C, 66.65; H, 7.24%); ν_{max}(neat)/cm^{-1} 1719 (C=O); δ_H(200 MHz; $CDCl_3$) 1.09–1.38 (3 × 3 H, m, 3 × Me), 3.45–3.80 (2 × 2 H, m, CH_2-OCHOCH_2), 4.18–4.35 (2 H, m, CO_2CH_2), 4.88 and 5.19 (1 H, each s, $CH_2OCHOCH_2$), 7.30–7.53 (5 H, m, ArH) and 7.82 and 7.95 (1 H, each s, CH=); *m/z* 306 (M^+).

Reaction of 2-*Cyanoethyl* 3-*Aminocrotonate with* (E,Z)-*Methyl* 4,4-*Dimethoxy*-2-(3-*nitrobenzylidene*)*acetoacetate* **12a**: *Formation of* (2S,3R,4S)-5-(2-*Cyanoethyl*)-3-*Methyl* 2-(*Dimethoxymethyl*-2-*hydroxy*-6-*methyl*-4-(3-*nitrophenyl*)-1,2,3,4-*tetrahydropyridine*-3,5-*dicarboxylate* **14a**, (2R,3S,4S)-5-(2-*Cyanoethyl*) 3-*Methyl* 2-*Dimethoxymethyl*-2-*hydroxy*-6-*methyl*-4-(3-*nitrophenyl*)-1,2,3,4-*tetrahydropyridine*-3,5-*dicarboxylate* **15a** *and* 5-(2-*Cyanoethyl*) 3-*Methyl* 2-*Dimethoxymethyl*-6-*methyl*-4-(3-*nitrophenyl*)-1,4-*dihydropyridine*-3,5-*dicarboxylate* **16a**.—A mixture of (*E*,*Z*)-methyl 4,4-dimethoxy-2-(3-nitrobenzylidene)-acetoacetate **12a** (3.09 g, 10.0 mmol) and 2-cyanoethyl 3-aminocrotonate (1.54 g, 10.0 mmol) in propan-2-ol (30 cm^3) was stirred and refluxed for 5 h. The solvent was removed, and the residue was purified by chromatography on silica gel with hexane–ethyl acetate (1:2). The first fraction of elute gave *compound* **16a** as yellow crystals (0.71 g, 16%), m.p. 100–101 °C (from CH_2Cl_2–Pr^i_2O) (Found: C, 56.5; H, 5.2; N, 9.4. $C_{21}H_{23}N_3O_8$ requires C, 56.62; H, 5.20; N, 9.43%); ν_{max}(KBr)/cm^{-1} 3364 (NH), 2255 (CN) and 1694 (C=O); δ_H(200 MHz; $CDCl_3$) 2.41 (3 H, s, 6-Me), 2.66 (2 H, t, *J* 6, CH_2CN), 3.46, 3.51 and 3.69 (3 × 3 H, each s, 3 × OMe), 4.28 (2 H, m, CH_2CH_2CN), 5.15 (1 H, s, 4-H), 6.03 (1 H, s, MeOC*H*OMe), 6.92 (1 H, br s, NH) and 7.46–8.17 (4 H, m, ArH); δ_C(75 MHz; $CDCl_3$) 166.31, 166.10, 148.86, 148.50, 146.71, 143.85, 134.16, 129.11, 122.74, 121.77, 117.00, 104.90, 101.48, 98.52, 58.49, 55.76, 55.18, 51.58, 39.77, 20.09 and 18.16; *m/z* 445 (M^+).

The second fraction eluted with the same solvent gave *compound* **15a** as plates (0.69 g, 15%), m.p. 130–131 °C (from CH_2Cl_2–Pr^i_2O) (Found: C, 54.4; H, 5.4; N, 9.1. $C_{21}H_{25}N_3O_9$ requires C, 54.42; H, 5.44; N, 9.07%); ν_{max}(KBr)/cm^{-1} 3342 (NH), 2253 (CN), 1715 and 1692 (C=O); δ_H(200 MHz; $CDCl_3$) 2.42 (2 H, m, CH_2CN), 2.49 (3 H, s, 6-Me), 3.40 (3 H, s, CO_2Me), 3.42 (1 H, d, *J* 7.5, 3-H), 3.63 (3 H, s, OMe), 3.84 (3 H, s, OMe), 3.89 (1 H, s, OH), 4.10 (2 H, m, CH_2CH_2CN), 4.18 (1 H, s, MeOC*H*OMe), 4.53 (1 H, d, *J* 7.5, 4-H), 5.71 (1 H, br s, NH) and 7.30–8.10 (4 H, m, ArH); δ_C(75 MHz; $CDCl_3$) 173.68, 166.12, 153.85, 147.77, 143.00, 135.73, 128.35, 124.09, 121.95, 117.01, 106.72, 94.05, 81.70, 59.89, 57.67, 56.01, 52.46, 46.56, 40.40, 21.83 and 18.12; *m/z* 464 (M^+ + H).

A further fraction with the same solvent gave *compound* **14a** as a crystalline solid (2.40 g, 52%), m.p. 156–157 °C (from CH_2Cl_2–Pr^i_2O) (Found: C, 54.4; H, 5.4; N, 9.0%); ν_{max}(KBr)/cm^{-1} 3419 (NH), 2258 (CN), 1725 and 1674 (C=O); δ_H(200 MHz; $CDCl_3$) 2.22 (2 H, m CH_2CH_2CN), 2.39 (3 H, d, *J* 1.2, 6-Me), 2.80 (1 H, d, *J* 12, 3-H), 3.50, 3.55 and 3.57 (3 × 3 H, each s, OMe), 3.94 (2 H, t, *J* 5, CH_2CH_2CN), 3.96 (1 H, s, OH), 4.20 (1 H, s, MeOC*H*OMe), 4.26 (1 H, dd, *J* 12 and 1.2, 4-H), 5.36 (1 H, br s, NH) and 7.40–8.11 (4 H, m, ArH); δ_C(75 MHz; $CDCl_3$) 173.33, 165.94, 152.02, 148.52, 146.98, 133.92, 129.31, 121.80, 121.74, 116.93, 105.58, 96.74, 80.68, 58.22, 57.49, 56.66, 53.16, 52.12, 41.83, 21.51 and 17.79; *m/z* 464 (M^+ + H).

Reaction of 2-*Cyanoethyl* 3-*Aminocrotonate with* (E,Z)-*Ethyl* 4,4-*Diethoxy*-2-(3-*nitrobenzylidene*)*acetoacetate* **12b**: *Formation of* (2S,3R,4S)-5-*Cyanoethyl* 3-*Ethyl* 2-*Diethoxymethyl*-2-*hydroxy*-6-*methyl*-4-(3-*nitrophenyl*)-1,2,3,4-*tetrahydropyridine*-3,5-*dicarboxylate* **14b** (2R,3S,4S)-5-(2-*Cyanoethyl*) 3-*Ethyl* 2-*Diethoxymethyl*-2-*hydroxy*-6-*methyl*-4-(3-*nitrophenyl*)-1,2,3,4-*tetrahydropyridine*-3,5-*dicarboxylate* **15b** *and* 5-(2-*Cyanoethyl*) 3-*Ethyl* 2-*Diethoxymethyl*-6-*methyl*-4-(3-*nitrophenyl*)-1,4-*dihydropyridine*-3,5-*dicarboxylate* **16b**.—By the same work-up procedure as that described above, compounds **14b**, **15b** and **16b** were prepared from the benzylideneacetoacetate **12b**.

Compound **16b**: M.p. 112–113 °C (from CH_2Cl_2–Pr^i_2O) (Found: C, 59.3; H, 6.0; N, 8.8. $C_{24}H_{29}N_3O_8$ requires C, 59.13; H, 6.00; N, 8.62%); ν_{max}(KBr)/cm^{-1} 3350 (NH), 2252 (CN) and 1700 (C=O); δ_H(200 MHz; $CDCl_3$) 1.18–1.33 (3 × 3 H, m, 3 × Me), 2.40 (3 H, s, 6-Me), 2.66 (2 H, t, *J* 5, CH_2CH_2CN), 3.56–3.87 (2 × 2 H, m, 2 × CH_2), 4.11 (2 H, m, CH_2CH_2CN), 4.26 (2 H, m, CO_2CH_2Me), 5.12 (1 H, s, 4-H), 6.18 (1 H, s, EtOC*H*OEt), 6.97 (1 H, br s, NH) and 7.38–8.15 (4 H, m, ArH); δ_C(75 MHz; $CDCl_3$) 166.17, 165.92, 149.19, 148.40, 146.88, 144.52, 134.31, 128.99, 122.91, 121.66, 117.08, 104.60, 101.30, 96.39, 64.08, 63.92, 60.49, 58.45, 39.91, 20.11, 18.17, 15.25, 15.19 and 14.13; *m/z* 487 (M^+ + H).

Compound **15b**: M.p. 139–140 °C (from CH_2Cl_2–Et_2O) (Found: C, 57.4; H, 5.9; N, 8.8. $C_{24}H_{31}N_3O_9$ requires C, 57.02; H, 6.18; N, 8.31%); ν_{max}(KBr)/cm^{-1} 3382 (NH), 2254 (CN), 1709 and 1695 (CO); δ_H(200 MHz; $CDCl_3$) 1.18, 1.27 and 1.43 (3 × 3 H, each t, *J* 7.5, 3 × Me), 2.41 (2 H, m, CH_2CH_2CN), 2.49 (3 H, s, 6-Me), 3.42 (2 H, m, OCH_2Me), 3.44 (1 H, d, *J* 8, 3-H), 3.79 (2 H, m, OCH_2Me), 3.90 (1 H, s, OH), 4.09 (2 H, m, CH_2CH_2CN), 4.26 (2 H, m, CO_2CH_2Me), 4.45 (1 H, s, EtOC*H*OEt), 4.54 (1 H, d, *J* 8, 4-H), 5.77 (1 H, br s, NH) and 7.30–8.09 (4 H, m, ArH); δ_C(75 MHz; $CDCl_3$) 173.37, 166.22, 153.96, 147.68, 143.23, 135.87, 128.26, 124.19, 121.85, 117.03, 104.25, 93.99, 81.65, 67.68, 64.42, 61.83, 57.63, 46.78, 40.46, 21.92, 18.12, 15.44, 14.99 and 14.13; *m/z* 505 (M^+).

Compound **14b**: M.p. 146–147 °C (from CH_2Cl_2–Pr^i_2O) (Found: C, 57.2; H, 6.1; N, 8.4%); ν_{max}(KBr)/cm^{-1} 3407 (NH), 2252 (CN), 1723 and 1683 (C=O); δ_H(200 MHz; $CDCl_3$) 0.94 (3 H, t, *J* 7.5, Me), 1.22 (3 H, t, *J* 7.5, Me), 1.24 (3 H, t, *J* 7.5, Me), 2.21 (2 H, m, CH_2CH_2CN), 2.38 (3 H, d, *J* 1.2, 6-Me), 2.84 (1 H, d, *J* 12, 3-H), 3.49–3.98 (3 × 2 H, m, 3 × CH_2), 4.09 (1 H, s, OH), 4.26 (1 H, dd, *J* 12 and 1.2, 4-H), 4.36 (1 H, s, EtOC*H*OEt), 5.44 (1 H, br s, NH) and 7.39–8.12 (4 H, m, ArH); δ_C(75 MHz; $CDCl_3$) 173.21, 166.01, 152.23, 148.43, 147.14, 134.05, 129.24, 122.12, 121.58, 116.97, 103.58, 96.54, 80.60, 66.35, 65.02, 61.18, 57.45, 52.91, 42.10, 21.62, 17.78, 15.26, 15.19 and 13.82; *m/z* 505 (M^+).

Reaction of 2-*Cyanoethyl* 3-*Aminocrotonate with* (E,Z)-*Isopropyl* 4,4-*Diethoxy*-2-(3-*nitrobenzylidene*)*acetoacetate* **12c**: *Formation of* (2S,3R,4S)-5-(2-*Cyanoethyl*) 3-*Isopropyl* 2-*Diethoxymethyl*-2-*hydroxy*-6-*methyl*-4-(3-*nitrophenyl*)-1,2,3,4-*tetrahydropyridine*-3,5-*dicarboxylate* **14c**, (2R,3S,4S)-5-(2-*Cyanoethyl*) 3-*Isopropyl* 2-*Diethoxymethyl*-2-*hydroxy*-6-*methyl*-4-(3-*nitrophenyl*)-1,2,3,4-*tetrahydropyridine*-3,5-*dicarboxylate* **15c** *and* 5-(2-*Cyanoethyl*) 3-*Isopropyl* 2-*Diethoxymethyl*-6-*methyl*-4-(3-*nitrophenyl*)-1,4-*dihydropyridine*-3,5-*dicarboxylate* **16c**.—By the same work-up procedure as that described above, compounds **14c**, **15c** and **16c** were prepared from benzylideneacetoacetate **12c**.

Compound **16c**: Yellow needles (Found: C, 59.8; H, 5.9; N, 8.1. $C_{25}H_{31}N_3O_8$ requires C, 59.87; H, 6.23; N, 8.38%); ν_{max}(KBr)/cm^{-1} 3351 (NH), 2253 (CN), and 1696 (C=O); δ_H(200 MHz; $CDCl_3$) 1.12 (3 H, d, *J* 6, MeCH*Me*), 1.18–1.36 (3 × 3 H, m, 3 × Me), 2.39 (3 H, s, 6-Me), 2.65 (2 H, t, *J* 6, CH_2CH_2CN), 3.72 (2 × 2 H, m, $CH_2OCHOCH_2$), 4.26 (2 H, t, *J* 6, CH_2CH_2CN), 4.98 (1 H, m, C*H*Me$_2$), 5.13 (1 H, s, 4-H), 6.21 (1 H, s, EtOC*H*OEt), 6.92 (1 H, br s, NH) and 7.35–8.20 (4 H, m, ArH); *m/z* 501 (M^+).

Compound **15c**: M.p. 155–156 °C (from CH_2Cl_2–Pr^i_2O) (Found: C, 57.8; H, 6.4; N, 8.1. $C_{25}H_{33}N_3O_9$ requires C, 57.9; H, 6.40; N, 8.09%); ν_{max}(KBr)/cm^{-1} 3369 (NH), 2251 (CN) and 1695 (C=O); δ_H[200 MHz; $(CD_3)_2SO_4$] 1.05 (3 H, t, *J* 6,

OCH_2Me), 1.16 (3 H, t, *J* 6, OCH_2Me), 1.18 (3 H, d, *J* 6, Me), 1.26 (3 H, d, *J* 6, Me), 2.40 (3 H, s, 6-Me), 2.58 (2 H, m, CH_2CH_2CN), 3.13 (1 H, d, *J* 7, 3-H), 3.68 (2 × 2 H, m, $MeCH_2OCH_2Me$), 3.95 (2 H, t, *J* 7, CH_2CH_2CN), 4.32 (1 H, d, *J* 7, 4-H), 4.47 (1 H, s, EtOC*H*OEt), 4.84 (1 H, m, $CHMe_2$), 5.14 (1 H, s, OH), 6.98 (1 H, s, NH) and 7.37–8.08 (4 H, m, ArH); *m*/*z* 520 (M^+ + H).

Compound **14c**: M.p. 143–144 °C (from CH_2Cl_2–Et_2O) (Found: C, 57.7; H, 6.4; N, 8.1%); ν_{max}(KBr)/cm^{-1} 3412 (NH), 2253 (CN), 1720 and 1682 (C=O); δ_H[200 MHz; $(CD_3)_2SO_4$] 0.72 (3 H, d, *J* 6, Me), 1.06 (3 H, d, *J* 6, Me), 1.13 (3 H, t, *J* 6, CH_2Me), 1.18 (3 H, t, *J* 6, CH_2Me), 2.22 (1 H, m, CHCN), 2.28 (3 H, d, *J* 1.2, 6-Me), 2.42 (1 H, m, CHCN), 2.70 (1 H, d, *J* 12, 3-H), 3.72 (3 × 2 H, m, 3 × CH_2), 4.15 (1 H, dd, *J* 12 and 1.2, 4-H), 4.34 (1 H, s, EtOC*H*OEt), 4.70 (1 H, m, MeC*H*Me), 5.32 (1 H, s, OH), 6.93 (1 H, s, NH) and 7.48–8.10 (4 H, m, ArH); *m*/*z* 520 (M^+ + H).

Reaction of 2-*Cyanoethyl* 3-*Aminocrotonate with* (E,Z)-*Isobutyl* 4,4-*Diethoxy*-2-(3-*nitrobenzylidene*)*acetoacetate* **12d**: *Formation of* (2S,3R,4S)-5-(2-*Cyanoethyl*) 3-*Isobutyl* 2-*Diethoxymethyl*-2-*hydroxy*-6-*methyl*-4-(3-*nitrophenyl*)-1,2,3,4-*tetrahydropyridine*-3,5-*dicarboxylate* **14d**, (2R,3S,4S)-5-(2-*Cyanoethyl*) 3-*Isobutyl* 2-*Diethoxymethyl*-2-*hydroxy*-6-*methyl*-4-(3-*nitrophenyl*)-1,2,3,4-*tetrahydropyridine*-3,5-*dicarboxylate* **15d** *and* 5-(2-*Cyanoethyl*) 3-*Isobutyl* 2-*Diethoxymethyl*-6-*methyl*-4-(3-*nitrophenyl*)-1,4-*dihydropyridine*-3,5-*dicarboxylate* **16d**.—By the same work-up procedure as that described above, compounds **14d**, **15d** and **16d** were prepared from benzylideneacetoacetate **12d**.

Compound **16d**: Yellow needles (Found: C, 60.3; H, 6.4; N, 8.2. $C_{26}H_{33}N_3O_8$ requires C, 60.57; H, 6.45; N, 8.15%); ν_{max}(neat)/cm^{-1} 3368 (NH), 2253 (CN) and 1697 (C=O); δ_H(200 MHz; $CDCl_3$) 0.82 (3 H, d, *J* 7, Me), 0.88 (3 H, d, *J* 7, Me), 1.27 (2 × 3 H, t, *J* 7, 2 × Me), 1.91 (1 H, m, MeC*H*Me), 2.40 (3 H, s, 6-Me), 2.68 (2 H, t, *J* 6, CH_2CN), 3.68 (2 × 2 H, m, $MeCH_2OCHCH_2Me$), 3.85 (2 H, d, *J* 6, CH_2CHMe_2), 4.30 (2 H, t, *J* 6, CH_2CH_2CN), 5.16 (1 H, s, 4-H), 6.23 (1 H, s, EtOC*H*OEt), 6.99 (1 H, br s, NH) and 7.35–8.18 (4 H, m, ArH); *m*/*z* 515 (M^+).

Compound **15d**: M.p. 168–169 °C (from CH_2Cl_2–Pr^i_2O) (Found: C, 58.5; H, 6.6; N, 7.9. $C_{26}H_{35}N_3O_9$ requires C, 58.52; H, 6.61; N, 7.88%); ν_{max}(KBr)/cm^{-1} 3376 (NH), 2249 (CN), 1710 and 1693 (C=O); δ_H[200 MHz; $(CD_3)_2SO_4$] 0.90 (2 × 3 H, d, *J* 7, CH*Me*), 1.05 (3 H, t, *J* 6, OCH_2Me), 1.15 (3 H, t, *J* 6, OCH_2Me), 1.90 (1 H, m, C*H*Me_2), 2.38 (3 H, s, 6-Me), 2.57 (2 H, t, *J* 6, CH_2CN), 3.21 (1 H, d, *J* 6, 3-H), 3.55–3.83 (3 × 2 H, m, 3 × CH_2), 3.93 (2 H, t, *J* 6, CH_2CH_2CN), 4.34 (1 H, d, *J* 6, 4-H), 4.45 (1 H, s, EtOC*H*OEt), 5.05 (1 H, s, OH), 6.98 (1 H, s, NH) and 7.39–8.07 (4 H, m, ArH); *m*/*z* 534 (M^+ + H).

Compound **14d**: Pale yellow needles (Found: C, 58.4; H, 6.4; N, 7.9%); ν_{max}(neat)/cm^{-1} 3420 (NH), 2253 (CN) and 1699 (CO); δ_H[200 MHz; $(CD_3)_2SO_4$] 0.57 (3 H, d, *J* 7, Me), 0.62 (3 H, d, *J* 7, Me), 1.11 (3 H, t, *J* 6, OCH_2Me), 1.16 (3 H, t, *J* 6, OCH_2Me), 1.56 (1 H, m, C*H*Me_2), 2.30 (3 H, d, *J* 1.2, 6-Me), 2.32 (2 H, m, CH_2CH_2CN), 2.75 (1 H, d, *J* 12, 3-H), 3.41–3.86 (4 × 2 H, m, 4 × CH_2), 4.15 (1 H, dd, *J* 12 and 1.2, 4-H), 4.33 (1 H, s, EtOC*H*OEt), 5.33 (1 H, s, OH), 6.96 (1 H, br s, NH) and 7.48–8.11 (4 H, m, ArH); *m*/*z* 534 (M^+ + H).

Reaction of 2-*Cyanoethyl* 3-*Aminocrotonate with* (E,Z)-*Ethyl* 4,4-*Diethoxy*-2-[3-(*trifluoromethyl*)*benzylidene*]*acetoacetate* **12e**: *Formation of* (2S,3R,4S)-5-(2-*Cyanoethyl*) 3-*Ethyl* 2-*Diethoxymethyl*-2-*hydroxy*-6-*methyl*-4-[3-(*trifluoromethyl*)*phenyl*]-1,2,3,4-*tetrahydropyridine*-3,5-*dicarboxylate* **14e**, (2R,3S,4S)-5-(2-*Cyanoethyl*) 3-*Ethyl* 2-*Diethoxymethyl*-2-*hydroxy*-6-*methyl*-4-[3-(*trifluoromethyl*)*phenyl*]-1,2,3,4-*tetrahydropyridine*-3,5-*dicarboxylate* **15e** *and* 5-(2-*Cyanoethyl*) 3-*Ethyl* 2-*Diethoxymethyl*-6-*methyl*-4-[3-(*trifluoromethyl*)*phenyl*]-1,4-*dihydropyridine*-3,5-*dicarboxylate* **16e**.—By the same work-up procedure as that described above, compounds **14e**, **15e** and **16e** were prepared from benzylideneacetoacetate **12e**.

Compound **16e**: Yellow needles (Found: C, 58.7; H, 5.6; N, 5.2. $C_{25}H_{29}F_3N_2O_6$ requires C, 58.82; H, 5.73; N, 5.49%); ν_{max}(neat)/cm^{-1} 3337 (NH), 2254 (CN) and 1698 (C=O); δ_H(200 MHz; $CDCl_3$) 1.21, 1.23 and 1.25 (3 × 3 H, each t, *J* 6, 3 × Me), 2.40 (3 H, s, 6-Me), 2.63 (2 H, t, *J* 6, CH_2CH_2CN), 3.45–3.93 (2 × 2 H, m, $MeCH_2OCHOCH_2Me$), 4.11 (2 H, q, *J* 6, CO_2CH_2Me), 4.25 (2 H, t, *J* 6, CH_2CH_2CN), 5.08 (1 H, s, 4-H), 6.22 (1 H, s, EtOC*H*OEt), 6.89 (1 H, br s, NH) and 7.28–7.63 (4 H, m, ArH); *m*/*z* 510 (M^+).

Compound **15e**: Yellow needles (Found: C, 56.9; H, 5.85; N, 5.3. $C_{25}H_{31}F_3N_2O_7$ requires C, 56.81; H, 5.91; N, 5.30%); ν_{max}(neat)/cm^{-1} 3425 (NH), 2253 (CN) and 1698 (C=O); δ_H[200 MHz; $(CD_3)_2SO_4$] 1.05 (3 H, t, *J* 6, CO_2CH_2Me), 1.14 (3 H, t, *J* 6, OCH_2Me), 1.16 (3 H, t, *J* 6 Hz, OCH_2Me), 2.36 (3 H, s, 6-Me), 2.58 (2 H, t, *J* 6, CH_2CH_2CN), 3.16 (1 H, d, *J* 7, 3-H), 3.68 (2 × 2 H, m, $MeCH_2OCHOCH_2Me$), 3.93 (2 H, m, CO_2CH_2Me), 4.04 (2 H, m, CH_2CH_2CN), 4.38 (1 H, d, *J* 7, 4-H), 4.42 (1 H, s, EtOC*H*OEt), 5.08 (1 H, s, OH), 6.96 (1 H, s, NH) and 7.26–7.65 (4 H, m, ArH); *m*/*z* 529 (M^+ + H).

Compound **14e**: M.p. 120–122 °C (from CH_2Cl_2–Et_2O) (Found: C, 56.8; H, 5.9; N, 5.2%); ν_{max}(KBr)/cm^{-1} 3409 (NH), 2254 (CN), 1722 and 1682 (C=O); δ_H[200 MHz; $(CD_3)SO_4$] 0.89 (3 H, t, *J* 6, CH_2Me), 1.09 (3 H, t, *J* 6, OCH_2Me), 1.15 (3 H, t, *J* 6, OCH_2Me), 2.11 (1 H, m, CHCN), 2.29 (3 H, d, *J* 1.2, 6-Me), 2.43 (1 H, m, CHCN), 2.70 (1 H, d, *J* 12, 3-H), 3.42–3.92 (4 × 2 H, m, 4 × CH_2), 4.10 (1 H, dd, *J* 12 and 1.2, 4-H), 4.32 (1 H, s, EtOC*H*OEt), 5.29 (1 H, s, OH), 6.81 (1 H, s, NH) and 7.28–7.60 (4 H, m, ArH); *m*/*z* 529 (M^+ + H).

Reaction of 2-*Cyanoethyl* 3-*Aminocrotonate with* (E,Z)-*Ethyl* 4,4-*Diethoxy*-2-[2-(*trifluoromethyl*)*benzylidene*]*acetoacetate* **12f**: *Formation of* (2S,3R,4S)-5-(2-*Cyanoethyl*) 3-*Ethyl* 2-*Diethoxymethyl*-2-*hydroxy*-6-*methyl*-4-[2-(*trifluoromethyl*)*phenyl*]-1,2,3,4-*tetrahydropyridine*-3,5-*dicarboxylate* **14f** *and* 5-(2-*Cyanoethyl*) 3-*Ethyl* 2-*Diethoxymethyl*-6-*methyl*-4-[2-(*trifluoromethyl*)*phenyl*]-1,4-*dihydropyridine*-3,5-*dicarboxylate* **16f**.—By the same work-up procedure as that described above, compounds **14f** and **16f** were prepared from benzylideneacetoacetate **12f**.

Compound **16f**: Yellow needles; ν_{max}(neat)/cm^{-1} 3406 (NH), 2254 (CN) and 1703 (C=O) (Found: C, 58.7; H, 5.7; N, 5.3. $C_{25}H_{29}F_3N_2O_6$ requires C, 58.82; H, 5.73; N, 5.49%); ν_{max}(neat)/cm^{-1} 3406 (NH), 2254 (CN) and 1703 (C=O); δ_H[200 MHz; $(CD_3)_2SO_4$] 1.10 (3 H, t, *J* 6, Me), 1.14 (3 H, t, *J* 6, Me), 1.18 (3 H, t, *J* 6, Me), 2.36 (3 H, s, 6-Me), 2.78 (2 H, t, *J* 6, CH_2CN), 3.39–3.75 (2 × 2 H, m, CH_2OCH_2), 3.91–4.11 (2 H, m, CO_2CH_2Me), 4.25 (2 H, m, CH_2CH_2CN), 5.41 (1 H, s, 4-H), 5.86 (1 H, s, EtOC*H*OEt), 7.27–7.76 (4 H, m, ArH) and 8.66 (1 H, s, NH); *m*/*z* 511 (M^+ + H).

Compound **14f**: M.p. 61–62 °C (Found: C, 56.8; H, 5.9; N, 5.1. $C_{25}H_{31}F_3N_2O_7$ requires C, 56.81; H, 5.91; N, 5.30%); ν_{max}(KBr)/cm^{-1} 3336 (NH), 2253 (CN) and 1695 (C=O); δ_H[200 MHz; $(CD_3)_2SO_4$] 0.81 (3 H, t, *J* 7, CO_2CH_2Me), 1.06 (3 H, t, *J* 7, OCH_2Me), 1.08 (3 H, t, *J* 7, OCH_2Me), 2.26 (3 H, d, *J* 1.2, 6-Me), 2.32 (2 H, m, CH_2CN), 2.82 (1 H, d, *J* 12, 3-H), 3.67–3.88 (3 × 2 H, m, 3 × CH_2), 4.11 (2 H, t, *J* 6, CH_2CH_2CN), 4.35 (1 H, s, EtOC*H*OEt), 4.45 (1 H, dd, *J* 12 and 1.2, 4-H), 5.24 (1 H, s, OH), 6.73 (1 H, s, NH) and 7.25–7.65 (4 H, m, ArH); *m*/*z* 528 (M^+).

Reaction of 2-*Cyanoethyl* 3-*Aminocrotonate with* (E/Z)-*Ethyl* 2-(3-*Chlorobenzylidene*)-4,4-*diethoxyacetoacetate* **12g**: *Formation of* (2S,3R,4S)-5-(2-*Cyanoethyl*) 3-*Ethyl* 4-(3-*Chlorophenyl*)-2-*diethoxymethyl*-2-*hydroxy*-6-*methyl*-1,2,3,4-*tetrahydropyridine*-3,5-*dicarboxylate* **14g**.—By the same work-up procedure as that described above, compound **14g** was prepared from benzylideneacetoacetate **12g**.

Compound **14g**: M.p. 120–121 °C (from CH_2Cl_2–Pr^i_2O) (Found: C, 58.1; H, 6.3; N, 5.6. $C_{24}H_{31}ClN_2O_7$ requires C, 58.23; H, 6.31; N, 5.66%); ν_{max}(KBr)/cm^{-1} 3409 (NH), 2254 (CN), 1723 and 1681 (C=O); δ_H[200 MHz; $(CD_3)_2SO_4$] 0.93 (3 H, t, *J* 6, CO_2CH_2*Me*), 1.10 (3 H, t, *J* 7, OCH_2*Me*), 1.16 (3 H, t, *J* 7, OCH_2*Me*), 2.15 (1 H, m, CHCN), 2.25 (3 H, d, *J* 1.2, 6-Me), 2.45 (1 H, m, CHCN), 2.70 (1 H, d, *J* 12, 3-H), 3.46–3.94 (4 × 2 H, m, 4 × CH_2), 4.00 (1 H, dd, *J* 12 and 1.2, 4-H), 4.30 (1 H, s, EtOC*H*OEt), 5.24 (1 H, s, OH), 6.73 (1 H, s, NH) and 6.95–7.31 (4 H, m, ArH); *m/z* 494 (M^+).

Reaction of 2-*Cyanoethyl* 3-*Aminocrotonate with* (E,Z)-*Ethyl* 2-*Benzylidene*-4,4-*diethoxyacetoacetate* **12h**: *Formation of* (2S,3R,4S)-5-(2-*Cyanoethyl*) 3-*Ethyl* 2-*Diethoxymethyl*-2-*hydroxy*-6-*methyl*-4-*phenyl*-1,2,3,4-*tetrahydropyridine*-3,5-*dicarboxylate* **14h** *and* 5-(2-*Cyanoethyl*) 3-*Ethyl* 2-*Diethoxymethyl*-6-*methyl*-4-*phenyl*-1,4-*dihydropyridine*-3,5-*dicarboxylate* **16h**.—By the same work-up procedure as that described above, compounds **14h** and **16h** were prepared from benzylideneacetoacetate **12h**.

Compound **16h**: Yellow needles (Found: C, 5.0; H, 6.8; N, 6.1. $C_{24}H_{30}N_2O_6$ requires C, 65.14; H, 6.83; N, 6.33%); ν_{max}(KBr)/cm^{-1} 3404 (NH), 2253 (CN) and 1696 (C=O); δ_H[200 MHz; $(CD_3)_2SO_4$] 1.20–1.27 (3 × 3 H, m, 3 × Me), 2.36 (3 H, s, 6-Me), 2.84 (2 H, m, CH_2CN), 3.42–3.78 (2 × 2 H, m, $CH_2OCHOCH_2$), 4.05 (2 H, m, CO_2CH_2Me), 4.15 (2 H, m, CH_2CH_2CN), 4.93 (1 H, s, 4-H), 6.13 (1 H, s, EtOC*H*OEt), 7.08–7.28 (5 H, m, ArH) and 8.62 (1 H, br s, NH); *m/z* 442 (M^+).

Compound **14h**: M.p. 118–119 °C (from CH_2Cl_2–Pr^i_2O) (Found: C, 62.6; H, 7.0; N, 6.1. $C_{24}H_{32}N_2O_7$ requires C, 62.59; H, 7.00; N, 6.08%); ν_{max}(KBr)/cm^{-1} 3337 (NH), 2255 (CN) and 1694 (C=O); δ_H[200 MHz; $(CD_3)_2SO_4$] 0.92 (3 H, t, *J* 6, CO_2CH_2*Me*), 1.11 (3 H, t, *J* 6, OCH_2*Me*), 1.16 (3 H, t, *J* 6, OCH_2*Me*), 2.02 (1 H, m, CHCN), 2.23 (3 H, d, *J* 1.2, 6-Me), 2.32 (1 H, m, CHCN), 2.74 (1 H, d, *J* 12, 3-H), 3.45–3.80 (3 × 2 H, m, 3 × CH_2), 3.83 (2 H, q, *J* 6, CO_2CH_2Me), 4.01 (1 H, dd, *J* 12 and 1.2, 4-H), 4.30 (1 H, s, EtOC*H*OEt), 5.13 (1 H, s, OH), 6.60 (1 H, s, NH) and 6.99–7.38 (5 H, m, ArH); *m/z* 460 (M^+).

Dehydration of the 1,2,3,4-*Tetrahydropyridines* **14a** *and* **15a**.—A solution of the 1,2,3,4-tetrahydropyridine **14a** (463 mg, 1.00 mmol) in acetone (20 cm^3) was treated with camphor-10-sulfonic acid (23.2 mg, 0.10 mmol) and the mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The extract was washed with brine, and concentrated to dryness. The product **16a** was recrystallized from CH_2Cl_2–Pr^i_2O as pale yellow crystals (436 mg, 98%).

Similarly, compound **16a** was prepared in 99% yield from compound **15a**.

5-(2-*Cyanoethyl*) 3-*Methyl* 2-*Formyl*-6-*methyl*-4-(3-*nitrophenyl*)-1,4-*dihydropyridine*-3,5-*dicarboxylate* **17**.—To a solution of compound **14a** (463 mg, 1 mmol) in aq. acetone (1:1; 20 cm^3) was added 6 mol dm^{-3} HCl (0.3 cm^3) and the mixture was stirred at room temperature for 1 h. The precipitate was filtered off, washed with water and then dried *in vacuo*. Recrystallization from methanol–diethyl ether gave *compound* **17** as pale yellow crystals (436 mg, 98%), m.p. 125–126 °C (Found: C, 57.2; H, 4.2; N, 10.4. $C_{19}H_{17}N_3O_7$ requires C, 57.14; H, 4.29; N, 10.52%); ν_{max}(KBr)/cm^{-1} 3335 (NH), 2250 (CN), 1708 and 1673 (C=O); δ_H[200 MHz; $(CD_3)_2SO_4$] 2.41 (3 H, s, 6-Me), 2.84 (2 H, m, CH_2CN), 3.70 (3 H, s, CO_2Me), 4.15 (2 H, m, CH_2CH_2CN), 5.11 (1 H, s, 4-H), 7.53–8.13 (4 H, m, ArH), 9.31 (1 H, br s, NH) and 10.20 (1 H, s, CHO); *m/z* 400 (M^+ + H).

Similarly, *compound* **17** was prepared in 92% yield from compound **15a**.

Crystal-structure Determination.—Single crystals of compounds **14a** and **15a** suitable for X-ray diffraction study were obtained from methanol–diethyl ether after concentration of the mother liquor by evaporation of the solvent at 293 K. Data collection was performed by a Mac-Science MXC18 diffractometer. The structures were solved by direct methods using SHELXS86 [10] and refined by full-matrix least-squares.

Crystal data of **14a**: $C_{21}H_{25}N_3O_9$, M_r = 463.00, triclinic, space group $P\bar{1}$, a = 9.381(2), b = 14.858(2), c = 9.188(2) Å, α = 101.85(2), β = 111.07(2), γ = 100.81(1)°, V = 1120.5(3) Å^3, T = 293 K, Z = 2, D_x = 1.37 g cm^{-1}, λ(Cu-Kα) = 1.541 78 Å, μ = 8.23 cm^{-1}, R = 0.049 over 3696 independent reflections.

Crystal data of **15a**: $C_{21}H_{25}N_3O_9$, M_r = 463.00, triclinic, space group $P\bar{1}$, a = 11.065(4), b = 12.613(3), c = 9.573(5) Å, α = 96.80(3), β = 111.89(3), γ = 109.34(2)°, V = 1124.3(7) Å^3, T = 293 K, Z = 2, D_x = 1.37 g cm^{-1}, λ(Cu-Kα) = 1.541 78 Å, μ = 8.20 cm^{-1}, R = 0.093 over 3673 independent reflections.*

* *Supplementary data* (see 'Instructions for Authors,' in the January issue). Positional and isotropic thermal parameters (Table 2), bond lengths and angles (Table 3), atomic coordinates, bond lengths and angles involving H-atoms, and anisotropic thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

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