Mild and Facile Cleavage of 2-Cyanoethyl Ester Using Sodium Sulfide or Tetrabutylammonium Fluoride. Synthesis of 1,4-Dihydropyridine Monocarboxylic Acids and Unsymmetrical 1,4-Dihydropyridine Dicarboxylates

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Several 3-(2-cyanoethyl)-1,4-dihydropyridine carboxylates (16) were prepared in moderate to good yields by means of the Hantzsch reaction. Treatment of these carboxylates with a weak base such as sodium sulfide or tetrabutylammonium fluoride at room temperature afforded smoothly the corresponding 1,4-dihydropyridine monocarboxylic acids (18) in good yields. The monocarboxylic acids 18n and 18o were esterified with 2-nitrooxypropanol or *N*-(2-hydroxyethyl)nicotinamide *p*-toluenesulfonic acid salt to afford the selective coronary vasodilators CD-349 (5) and CD-832 (6), respectively.

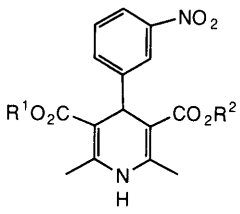
Keywords deprotection reaction; 2-cyanoethyl ester; carboxyl protecting group; unsymmetrical dihydropyridine dicarboxylate; dihydropyridine monocarboxylic acid; sodium sulfide

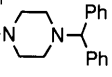
The 2-cyanoethyl group is a useful protecing group for phosphates,[1] thiols,[2] and carboxylic acids[3] and is usually removed under strongly basic conditions such as potassium *tert*-butoxide, pyridine, ammonium hydroxide, potassium carbonate/sodium borohydride, or sodium hydroxide in an aqueous solvent. Although these deprotecting conditions are effective for various types of carboxylic acids, they are not always applicable to the deprotection of carboxylic acids having an acetate or a 2-trimethylsilylethyl (TMSE) ester moiety in the molecule. We have reported mild and effective cleavage conditions using tetrabutylammonium fluoride in non-hydrolytic solvents.[4] We also found that sodium sulfide[5] is effective for removal of the cyanoethyl group.

We now describe mild cleavage conditions using sodium sulfide or tetrabutylammonium fluoride, and applications of these conditions to a facile cleavage of 3-(2-cyanoethyl)-1,4-dihydropyridine carboxylates (**16**) to the corresponding 1,4-dihydropyridine monocarboxylic acids (**18**), which are useful precursors[6] of calcium antagonists such as nicardipine (**1**),[7] nimodipine (**2**),[8] benidipine (**3**),[9] manidipine (**4**),[10] and their metabolites.[11] The monocarboxylic acids **16n** and **16o** were converted to the selective coronary vasodilators CD-349 (**5**)[12] and CD-832 (**6**),[13] respectively.

The starting materials (**8a—d** and **9a**) were prepared as follows. 2-Nicotinoylaminoethyl acetoacetate (**8a**) was prepared by reacting diketene with *N*-(2-hydroxyethyl)nicotinamide (**7a**), itself prepared by the reaction of methyl nitocinate with ethanolamine according to Samejima.[14] Other acetoacetates (**10**) used for the preparation of 1,4-dihydropyridines were prepared similarly by condensation of the corresponding alcohols with diketene according to the reported method.[3b,c] The acetoacetate (**8a**) was treated with ammonia in tetrahydrofuran (THF) to give 3-aminocrotonate (**9a**). The keto esters (**8b—d**) were also prepared by reacting bromoalkyl acetoacetate (**10**) with an appropriate nucleophile such as potassium acetate, thiophenol, or thioacetic acid (Chart 1).

The substrates (**16** and **17**) listed in Tables I, II and III were synthesized *via* either of the routes shown in Chart 2. Hantzsch condensation[15] of the acetoacetate (**8**), benzaldehyde (**11**) and 2-cyanoethyl 3-aminocrotonate (**12**) afforded the corresponding 1,4-dihydropyridines (**16**) in 68—81% yields [method A(1)]. The 1,4-dihydropyridine (**16o**) was similarly prepared by the Hantzsch condensation of **11**, the aminocrotonate (**9a**), and 2-cyanoethyl acetoacetate (**13**) in 76% yield [method A(2)]. An alternative pathway (method B) involves the reaction of **12** with benzylideneacetoacetate (**15**), which was readily obtained by the Knoevenagel reaction of the



nicardipine (1)	R^1=Me	R^2=$CH_2CH_2N(Me)Bn$
nimodipine (2)	R^1=Pr^i	R^2=CH_2CH_2OMe
benidipine (3)	R^1=Me	R^2= 
manidipine (4)	R^1=Me	R^2=CH_2CH_2– 
CD-349 (5)	R^1=$(CH_2)_3ONO_2$	R^2=$CH_2CH(Me)ONO_2$
CD-832 (6)	R^1=$(CH_2)_3ONO_2$	R^2=CH_2CH_2NHCO 

Bn = benzyl
Pr^i = isopropyl

Fig. 1. Unsymmetrical 1,4-Dihydropyridines

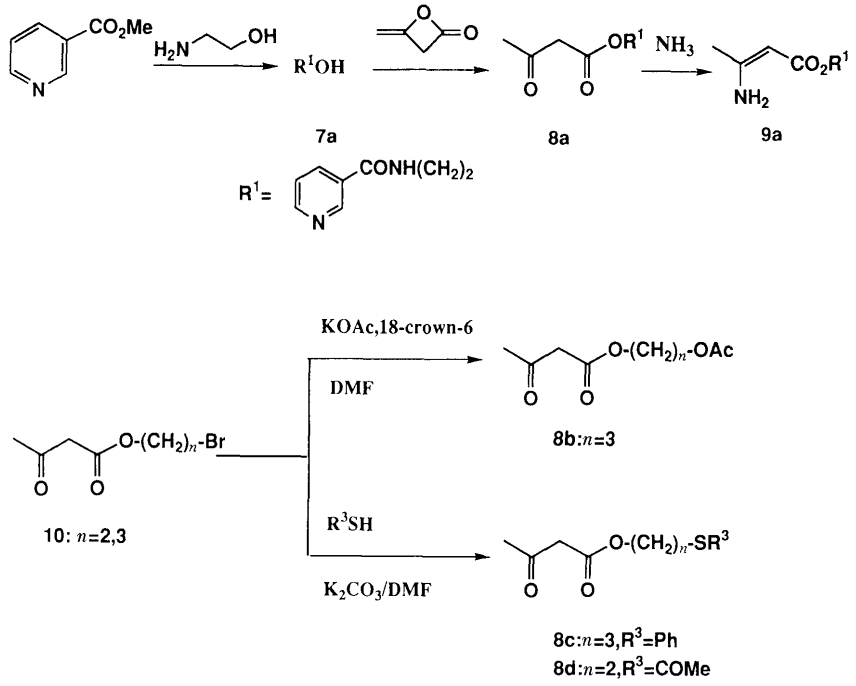


Chart 1

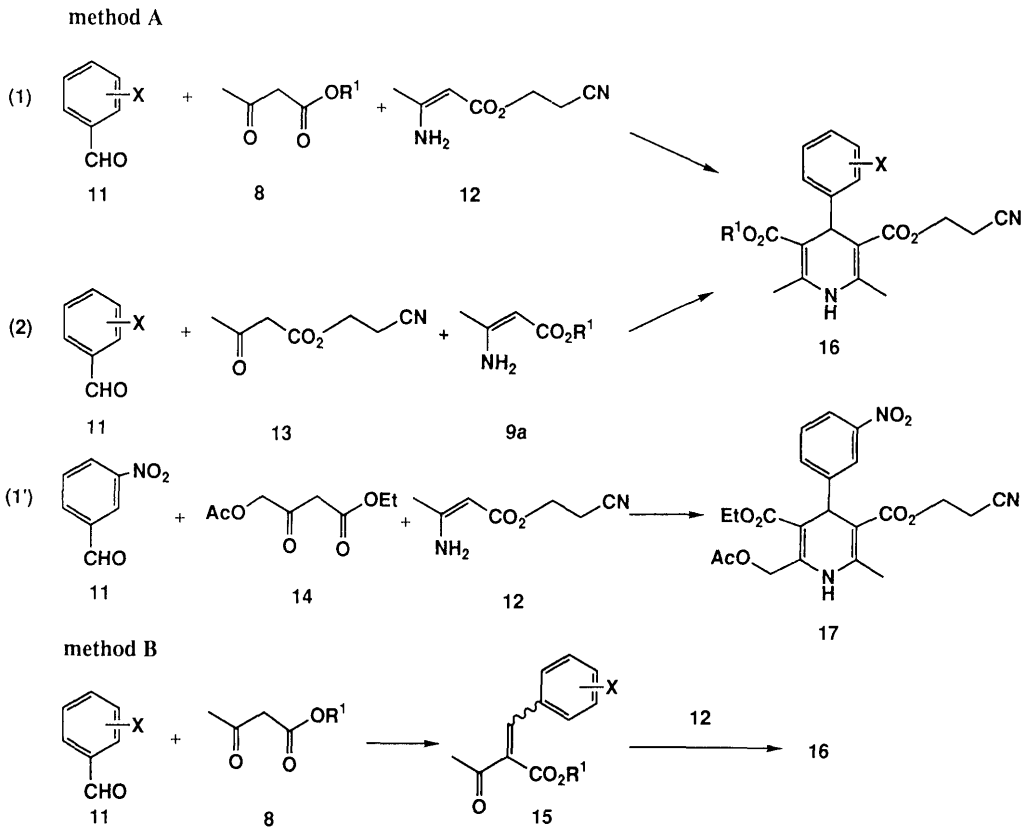


Chart 2

acetoacetate (**8**) with the corresponding aldehyde (**11**). The substrate (**17**) bearing the acetoxymethyl substituent at the 6-position was prepared by method A(1′) by using 3-nitrobenzaldehyde, 2-cyanoethyl 3-aminocrotonate (**12**), and ethyl 4-acetoxyacetoacetate (**14**), prepared from acetoxyacetyl chloride and Meldrum's acid (malonic acid acetonide) followed by treatment with ethanol.[16]

First, in the course of pursuing a new synthetic method for 1,4-dihydropyridine monocarboxylic acids (**18**), 3-(2-cyanoethyl)-1,4-dihydropyridinecarboxylates (**16** and **17**) were treated with sodium sulfide in a mixture of methanol and dichloromethane at room temperature. It was found that compound **16** ($X = NO_2$, Cl, F, CF_3), with simple alkyl (R^1 = Me, Et, Pr^i, Bu^i), alkoxyalkyl, methylthioalkyl, or phenylthioalkyl ester groups at the 5-position afforded 1,4-dihydropyridine monocarboxylic

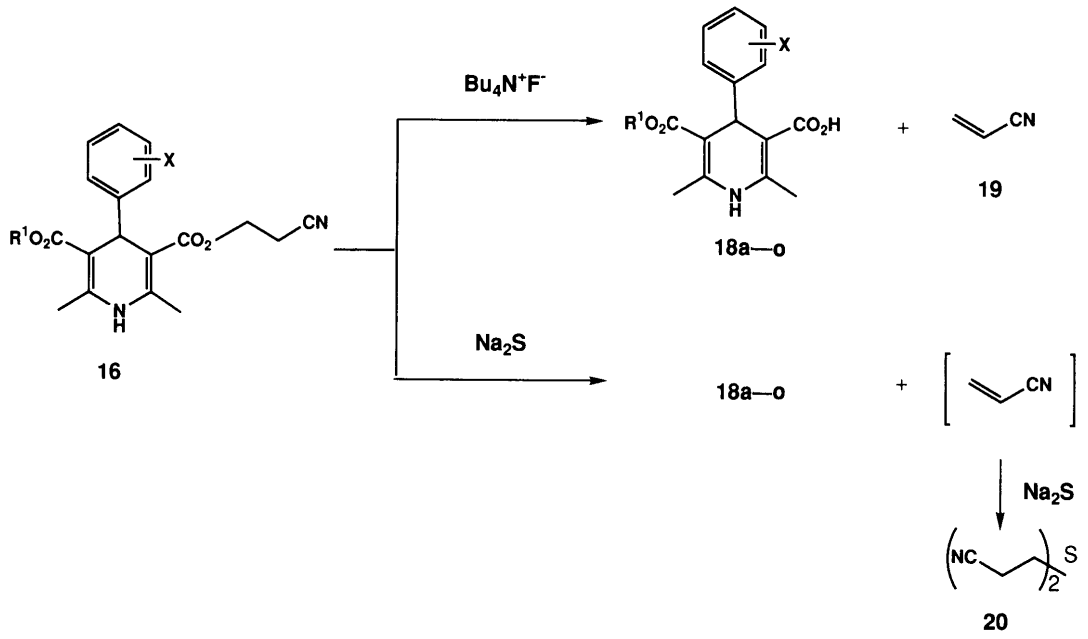


Chart 3

acids (**18a**—**l**) in good yields (62—96%) (Table I), whereas the compound with an acetoxyalkyl group (**16p**) gave **21** in excellent yield. When we applied the same method to 6-acetoxymethyl-1,4-dihydropyridine (**17**), the intermediate (**23**) was easily cyclized to form a lactone (**24**) (Chart 4). On the other hand, similar treatment of **16q** possessing a 5-acetylthioethyl group did not afford **19q**, but provided **25**.

In the case of substituents such as nitrooxyalkyl esters (alkyl = Et, Pr) and nicotinoylaminoethyl ester, deprotection of **16m**—**o** with sodium sulfide under the same conditions as shown above gave the corresponding 1,4-dihydropyridine monocarboxylic acids (**18m**—**o**) without appreciable decomposition of other functional groups. The results obtained from a series of 2-cyanoethyl 1,4-dihydropyridinedicarboxylates (**16a**—**q** and **17**) are listed in Tables I and III.

Several conclusions can be reached from these data: (1) deprotection of 2-cyanoethyl group can be carried out with just 0.5 eq of sodium sulfide at room temperature; (2) as was the case with alkyl ester, many functional groups are stable under the conditions of deprotection, including alkoxyalkyl, nitrooxyalkyl, nicotinoylaminoalkyl, methylthioalkyl, and phenylthioalkyl, but not acetoxy and acetylthio groups.

The mechanism for the formation of **18a**—**o** and **20** is proposed to be as follows. It seems likely that the reaction takes place in two stages. First, **16a**—**o** react with sodium sulfide to yield **18a**—**o** and acrylonitrile (**19**) by β-elimination. Sodium sulfide then reacts with acrylonitrile by Michael addition to yield bis(2-cyanoethyl)sulfide (**20**) (Chart 3). The mechanism for **21** and **25** is postulated to be as follows: first, compound **21** is formed by the C–O bond cleavage of the acetoxy group and the removal of the 2-cyanoethyl group. The intermediate (**22**) then undergoes hydrolysis to give acetic acid and sulfur. On the other hand, the half-ester (**25**) is probably formed *via* the C–O bond cleavage of the ester at the 5-position by the nucleophilic attack of thiolate ion, generated initially (Chart 4). The 2-cyanoethyl esters (**16a** and **16o**) were also cleaved at a much faster rate (2 h) in the same yields in the presence of a catalytic amount of benzyltrimethylammonium chloride.

We next examined the reaction of **16a**—**q** and **17** with tetrabutylammonium fluoride at room temperature in a mixture of THF and dimethylformamide (DMF). When the protected 1,4-dihydropyridines (**16a**—**q**) were treated with 1.2 eq of tetrabutylammonium fluoride, the 1,4-dihydropyridine monocarboxylic acids (**19a**—**q**) were obtained in moderate to good yields, followed by β-elimination of the 2-cyanoethyl group. Many functional groups are stable under the condition used for the deprotection.

On the other hand, similar treatment of **17** possessing an acetoxymethyl group at the 6-position did not afford **24**, and the starting marterial was recovered. From the above results, the use of tetrabutylammonium fluoride is useful compared with that of sodium sulfide in regard to unstable functional groups of **16p**, **q** because of its high selectivity for deblocking. The results are listed in Tables II and III.

The main advantages of our method described above are 1) the easy introduction of the protecting groups by the Hantzsch method, 2) the smooth deprotection by β-elimination of the 2-cyanoethyl group, 3) the easy removal of the by-products formed, and 4) the ready availability of reagents.

Finally, a monocarboxylic acid (**18o**) obtained above was converted into the new calcium antagonists 3-nitrooxypropyl 2-(nicotinoylamino)ethyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (CD-832) and 2-nitrooxypropyl 3-nitrooxypropyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (CD-349), which have long-lasting antihypertensive and selective coronary vasodilator activities, and have been under evaluation for the treatment of hypertension and

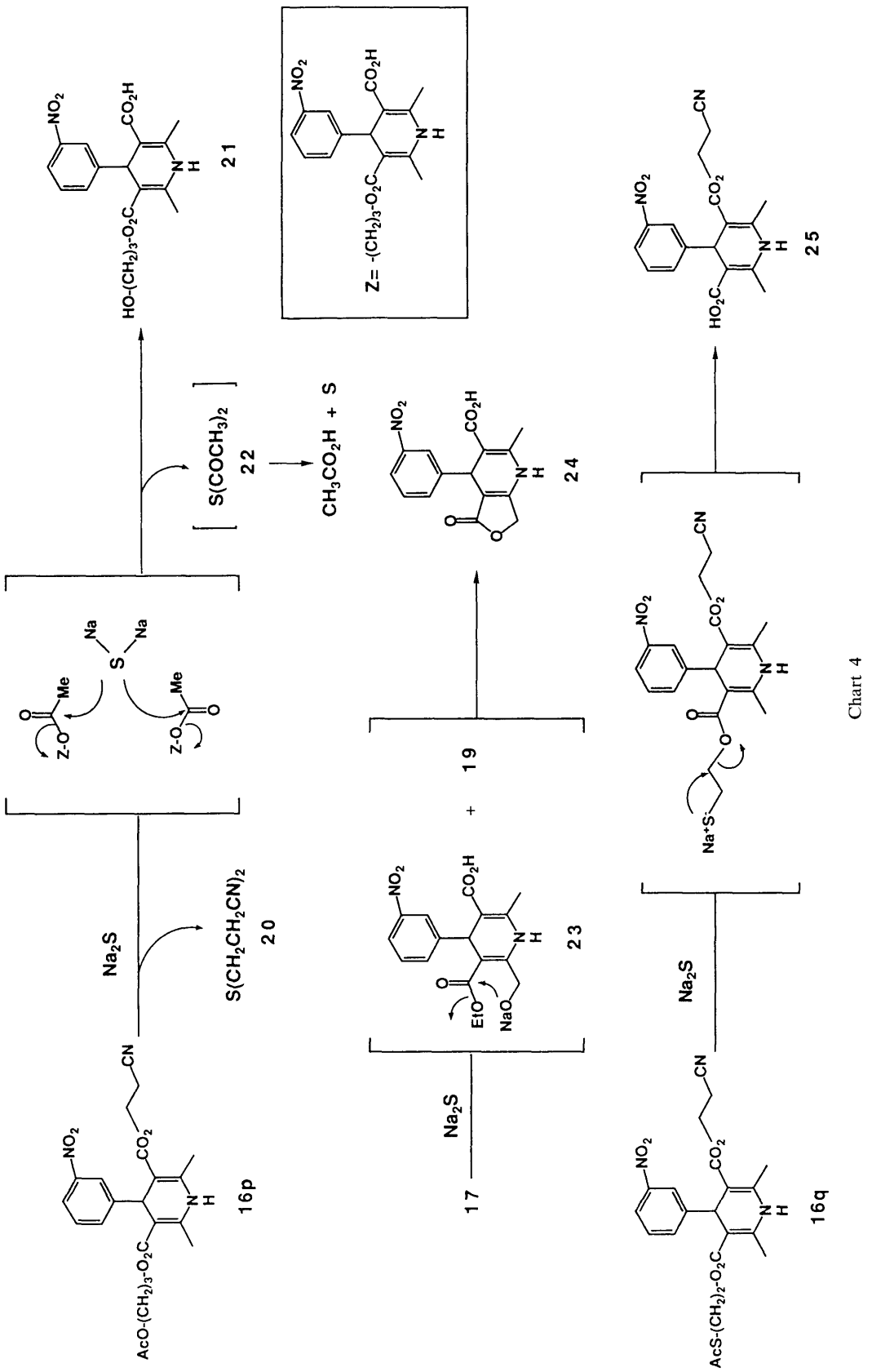
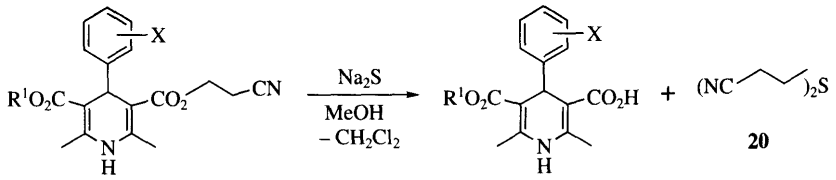


Chart 4

TABLE I. Deprotection of Cyanoethyl Esters by Sodium Sulfide[a]

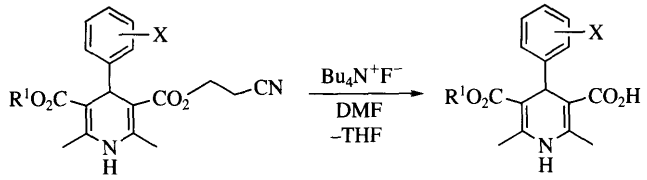


16 18 20

Compd. No.	X	R^1	Products and yields[b] (%)	
			18	20
16a	3-NO_2	Me	85	78
16b	3-NO_2	Et	76	74
16c	3-NO_2	Pr^i	73	69
16d	3-NO_2	Bu^i	62	53
16e	3-NO_2	CH_2CH_2OMe	96	93
16f	3-NO_2	CH_2CH_2SMe	82	77
16g	3-NO_2	$CH_2CH_2CH_2SPh$	65	52
16h	3-Cl	Me	78	76
16i	2,3-diCl	Me	73	64
16j	2-F	Me	91	92
16k	2-CF_3	Me	84	88
16l	3-CF_3	Me	78	72
16m	3-NO_2	$CH_2CH_2ONO_2$	91	87
16n	3-NO_2	$CH_2CH_2CH_2ONO_2$	67	59
16o	3-NO_2	$CH_2CH_2NHCOPy$-3	91	85

a) Approximately 0.5 eq of sodium sulfide was used in all simple deprotection experiments. *b*) Isolated yield based on the corresponding **16**.

TABLE II. Deprotection of Cyanoethylesters by Tetrabutylammonium Fluoride[a]



16 18

Compd. No.	X	R^1	Products and yields[b] (%)
			18
16a	3-NO_2	Me	88
16b	3-NO_2	Et	72
16c	3-NO_2	Pr^i	62
16d	3-NO_2	Bu^i	63
16e	3-NO_2	CH_2CH_2OMe	83
16f	3-NO_2	CH_2CH_2SMe	85
16g	3-NO_2	$CH_2CH_2CH_2SPh$	72
16h	3-Cl	Me	69
16i	2,3-diCl	Me	79
16j	2-F	Me	81
16k	2-CF_3	Me	85
16l	3-CF_3	Me	73
16m	3-NO_2	$CH_2CH_2ONO_2$	53
16n	3-NO_2	$CH_2CH_2CH_2ONO_2$	35
16o	3-NO_2	$CH_2CH_2NHCOPy$-3	61

a) Approximately 1.2 eq of tetrabutylammonium floride was used in all simple deprotection experiments. *b*) Isolated yield based on the corresponding **16**.

angina pectoris. Esterification of **18o** with 3-nitrooxypropanol,[17] acetic anhydride, and a catalytic amount of acetyl chloride gave CD-832 in 72% yield. The enantiomers (*R*)-(−)- and (*S*)-(+)-CD-832[18] were also obtained in good yield from the acids (*S*)-(+)- and (*R*)-(−)-**18n**, which were obtained by optical resolution of the racemate (**18n**),[19] by treatment with *N*-(2-hydroxyethyl)nicotinamide *p*-toluenesulfonic acid salt, acetic anhydride, and a catalytic amount of acetyl chloride in DMF at room temperature (Chart 5).

Similarly, the half-ester (*S*)-(+)- and (*R*)-(−)-**18n** was treated with acetic anhydride-acetyl chloride followed by reaction with 2-nitrooxypropanol (*R*)-(−)- and (*S*)-(+)-**28** to yield (4*R*,2′*R*), (4*R*,2′*S*), (4*S*,2′*R*), and (4*S*,2′*S*)-CD-349, respectively.[20] Optically pure alcohols (*R*)-(−)- and (*S*)-(+)-**28** were prepared by $Ca(BH_4)_2$ reduction of (*R*)-(+)- and (*S*)-(−)-**27**, which were obtained by nitration of methyl 2-hydroxypropionate (*R*)-(+)- and (*S*)-(−)-**26**.

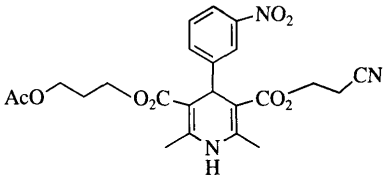
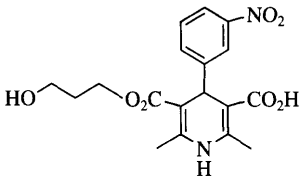
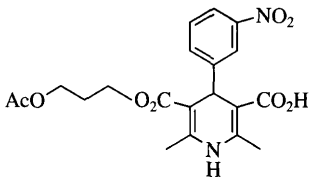
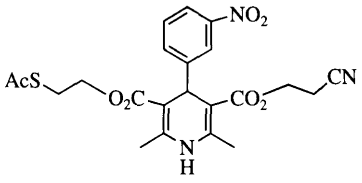
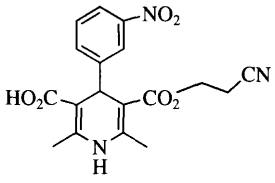
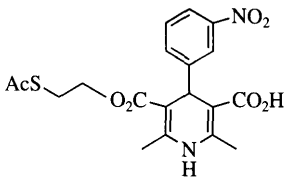
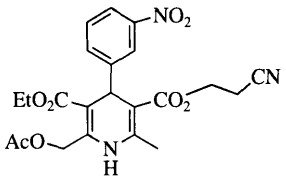
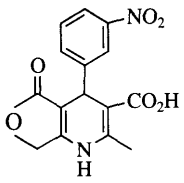
In summary, sodium sulfide and tetrabutylammonium fluoride are useful reagents for the cleavage reaction of the 2-cyanoethyl ester in 1,4-dihydropyridines. This procedure is applicable to the preparation of 1,4-dihydropyridine monocarboxylic acids, as precursors of unsymmetrical 1,4-dihydropyridines and their metabolites.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a JASCO DS-301 spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian XL-200 (200 MHz) spectrometer using tetramethylsilane as an internal standard. Chemical shhifts are given in ppm. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. Mass spectra were measured on a Shimadzu LKB 9000 spectrometer. Column chromatography was performed on 70—230 mesh silica gel from Merck.

3-(Acetoxy)propyl Acetoacetate (8b) Potassium acetate (58.89 g, 0.60 mol) was added to a solution of 3-bromopropyl acetoacetate (**10**: $n=3$) (111.54 g, 0.50 mol) in DMF (500 ml) containing a catalytic amount of

TABLE III. Deprotection of Cyanoethylesters by Sodium Sulfide and Tetrabutylammonium Fluoride[a]

Compd. No.	Structures	Products and yields (%)[b]	
		Na_2S	n-$Bu_4N^+F^-$
16p		 **21** (93%)[c]	 **18p** (75%)
16q		 **25** (46%)[d]	 **18q** (71%)
17		 **24** (96%)	—[e]

a) Approximately 1.2 eq of tetrabutylammonium fluoride was used in deprotection experiments. *b*) Isolated yield based on the corresponding **16p, q** and **17**. *c*) Approximately 1 eq of sodium sulfide was used in deprotection experiments. *d*) Approximately 0.5 eq of sodium sulfide was used in deprotection experiments. *e*) No reaction.

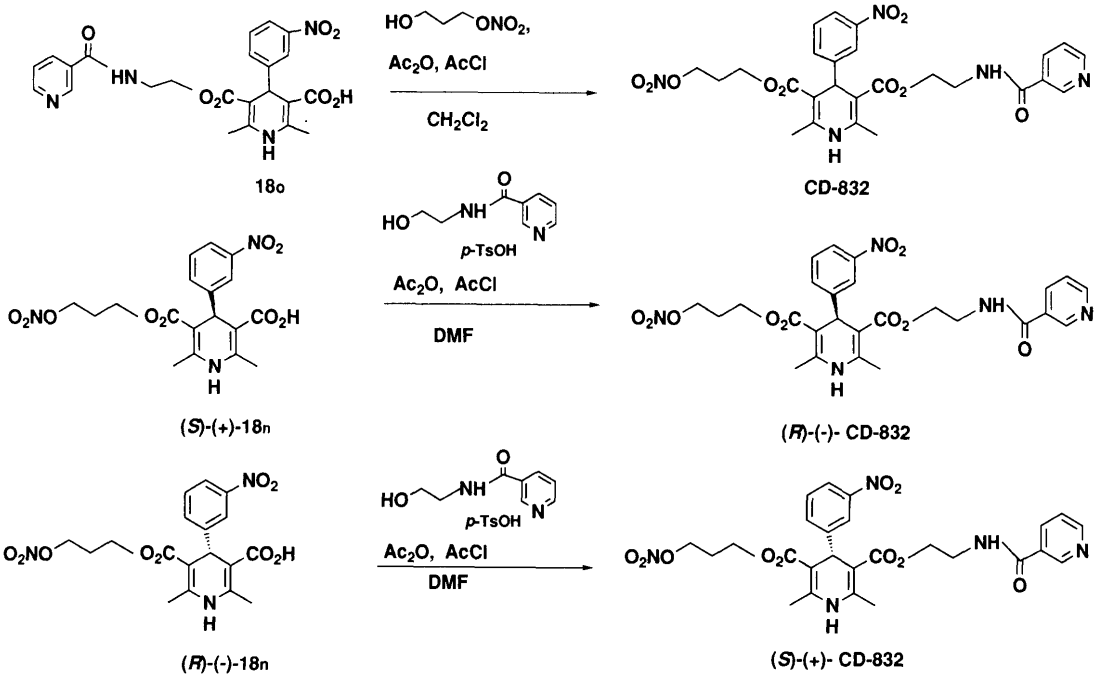
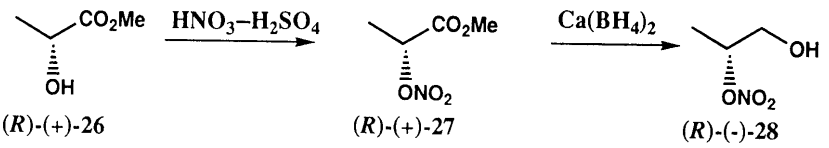


Chart 5



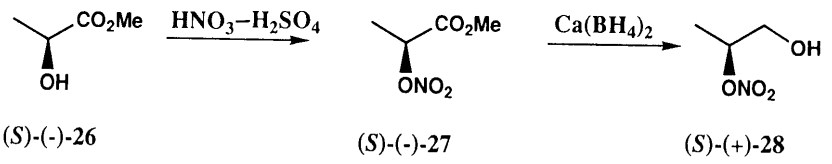


Chart 6

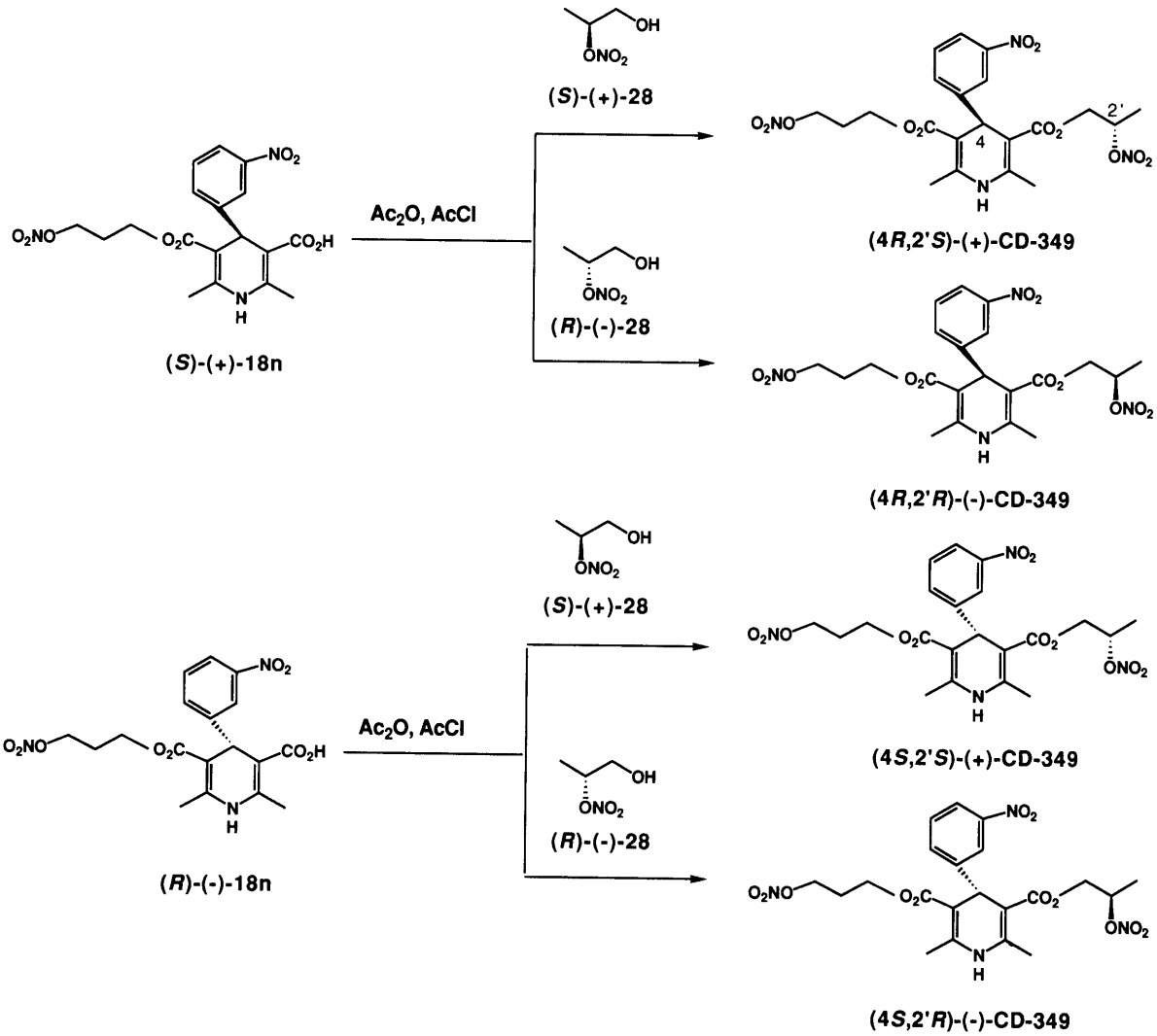


Chart 7

18-crown-6, and the mixture was stirred at 70—80 °C for 3 h. The reaction mixture was extracted with AcOEt. The organic layer was washed with water and brine, and dried (Na_2SO_4). The solvent was removed and the residue was purified by column chromatography on silica gel with hexane–AcOEt (1 : 1, v/v) to give the product (**8b**) (185.0 g, 92%) as a pale yellow oil. MS *m/z*: 203 ($M^+ + 1$). IR (neat) cm^{-1}: 1741 (CO). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.95 (2H, m), 2.02 (3H, s), 3.43 (2H, s), 4.11 (2H, t, J=7 Hz), 4.18 (2H, t, J=6 Hz). *Anal.* Calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found: C, 53.42; H, 6.88.

3-(Phenylthio)propyl Acetoacetate (8c) Thiophenol (12.12 g, 0.11 mol) was added to a solution of 3-bromopropyl acetoacetate (**10**: n=3) (22.31 g, 0.10 mol) and potassium carbonate (8.29 g, 0.06 mol) in DMF (200 ml), and the mixture was stirred at room temperature for 10 h. The reaction mixture was extracted with CH_2Cl_2. The organic layer was washed with water and brine, and dried (Na_2SO_4). The solvent was evaporated off to give the acetoacetate as a pale yellow oil (**8c**) (23.56 g, 93%). IR (neat) cm^{-1}: 1743 and 1718 (CO). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.05 (2H, m), 2.29 (3H, s), 3.13 (2H, t, J=6 Hz), 3.49 (2H, s), 4.25 (2H, t, J=6 Hz), 7.37—8.01 (5H, m). *Anal.* Calcd for $C_{13}H_{16}SO_3$: C, 61.88; H, 6.39. Found: C, 61.73; H, 6.41.

The acetoacetate (**8c**) thus obtained was used in the next reaction without further purification or after brief purification by column chromatography on silica gel. Another acetoacetate (**8d**) used for the preparation of 1,4-dihydropyridines related to **16** was prepared similarly.

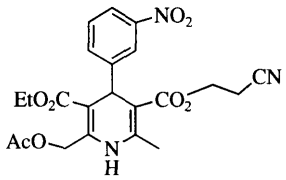
2-(Acetylthio)ethyl Acetoacetate (8d) Yield 89%. IR (neat) cm^{-1}: 1795, 1715, and 1695 (CO). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.26 (3H, s), 2.35 (3H, s), 3.15 (2H, t, J=6 Hz), 4.25 (2H, t, J=6 Hz). *Anal.* Calcd for $C_8H_{12}SO_4$: C, 47.04; H, 5.92. Found: C, 46.95; H, 5.85.

2-(Nicotinoylamino)ethyl Acetoacetate (8a) A mixture of methyl nicotinate (137.14 g, 1.0 mol) and ethanolamine (61.09 g, 1.0 mol) was heated at 50 °C for 30 min with stirring and the mixture was allowed to stand at room temperature for 10 h. The crystals formed were washed with Et_2O and collected by filtration to afford **7a** (116.52 g, 71%) as colorless crystals, mp 137—138 °C (from hexane–MeOH). MS m/z: 167 (M^++1). IR (KBr) cm^{-1}: 3321 (OH), 1662 (CO). ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 3.36 (2H, m), 3.53 (2H, m), 4.75 (1H, t, J=6 Hz), 7.71—8.86 (4H, m), 8.75 (1H, br s). *Anal.* Calcd for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.81; H, 6.05; N, 16.88.

Diketene (100.88 g, 1.2 mol) was added dropwise to a solution of stirred, preheated (50—60 °C) *N*-2-hydroxyethylnicotinamide (**7a**) (166.18 g, 1.0 mol) in THF (500 ml) and the mixture was stirred for 3 h at 50—60 °C. Then aqueous saturated $NaHCO_3$ was added, and the resulting mixture was extracted with CH_2Cl_2. The extract was washed with water and dired (Na_2SO_4). The solvent was evaporated to dryness to give the acetoacetate (**8a**) (226.0 g, 90%) as yellow crystals, mp 75—76 °C (from CH_2Cl_2–Et_2O). MS m/z: 251 (M^++1). IR (KBr) cm^{-1}: 3362 (NH), 1746 and 1709 (CO). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.27 (3H, s), 3.56 (2H, s), 3.78 (2H, m), 4.40 (2H, t, J=6 Hz), 7.33—9.12 (4H, m), 7.45 (1H, t, J=5 Hz). *Anal.* Calcd for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.20. Found: C, 57.35, H, 5.57; N, 10.99.

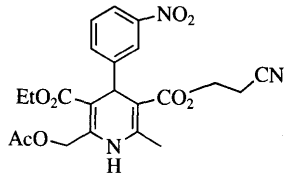
2-(Nicotinoylamino)ethyl 3-Aminocrotonate (9a) Ammonia was bubbled for 3 h into a solution of acetoacetate (**8a**) (125.13 g, 0.50 mol) in THF (500 ml) at 0 °C and the mixture was stirred at the same temperature for 24 h. The solvent and excess NH_3 were evaporated off to give the 3-aminocrotonate (**9a**) (105.35 g, 85%) as pale yellow crystals, mp 111—113 °C (from MeOH–iso-Pr_2O). MS m/z: 250 (M^++1). IR (KBr) cm^{-1}: 3422 (NH_2), 1657 (CO). ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 1.83 (3H, s), 3.49 (2H, m), 4.09 (2H, t, J=6 Hz), 4.32 (1H, s), 7.43—9.05

TABLE IV. Spectral Data for 1,4-Dihydropyridines (**16** and **17**)

Compd. No.	X	R^1	IR (KBr) cm^{-1} (NH)	(CN)	(CO)	^{1}H-NMR ($CDCl_3$) δ (ppm)
16f	3-NO_2	CH_2CH_2SMe	3368	2252	1705, 1693	2.11 (3H, s), 2.38 (3H, s), 2.40 (3H, s), 2.62—2.77 (2×2H, m), 4.22 (2H, t, J=6 Hz), 4.28 (2H, m), 5.12 (1H, s), 5.94 (1H, s), 7.35—8.18 (4H, m)
16g	3-NO_2	$CH_2CH_2CH_2SPh$	3354	2252	1749, 1698	1.98 (2H, m), 2.35 (3H, s), 2.41 (3H, s), 2.72 (2H, t, J=6 Hz), 4.14 (2H, t, J=7 Hz), 4.26 (2H, m), 4.36 (2H, t, J=6 Hz), 5.12 (1H, s), 6.36 (1H, s), 7.35—8.19 (4H, m)
16k	2-CF_3	Me	3325	2257	1703, 1678	2.31 (3H, s), 2.33 (3H, s), 2.62 (2H, t, J=7 Hz). 3.62 (3H, s), 4.23 (2H, m), 5.55 (1H, s), 5.74 (1H, s), 7.18—7.62 (4H, m)
16o	3-NO_2	$CH_2CH_2NHCOPy$-3	3382	2248	1705	2.32 (3H, s), 2.35 (3H, s), 2.83 (2H, t, J=6 Hz), 3.52 (2H, m), 4.03—4.25 (2×2H, m), 5.01 (1H, s), 7.38—8.97 (8H, m), 8.69 (1H, t, J=6 Hz), 9.21 (1H, s)[a]
16p	3-NO_2	$CH_2CH_2CH_2OAc$	3386	2252	1726, 1697	1.93 (2H, m), 2.37 (2×3H, s), 2.70 (2H, t, J=6 Hz), 4.06 (2H, m), 4.13 (2H, t, J=7 Hz), 4.27 (2H, t, J=6 Hz), 5.09 (1H, s), 6.36 (1H, s), 7.35—8.15 (4H, m)
16q	3-NO_2	CH_2CH_2SAc	3369	2253	1698	2.31 (2×3H, s), 2.86 (2H, m), 3.07 (2H, t, J=6 Hz), 4.06 (2H, t, J=6 Hz), 4.17 (2H, m), 4.97 (1H, s), 7.48—8.06 (4H, m), 9.15 (1H, s)[a]
17			3306	2253	1722, 1693	1.25 (3H, t, J=7 Hz), 2.19 (3H, s), 2.41 (3H, s), 2.65 (2H, t, J=6 Hz), 4.11 (2H, q, J=7 Hz), 4.26 (2H, m), 5.13 (1H, s), 5.31 (2H, s), 6.86 (1H, br s), 7.36—8.15 (4H, m)

a) DMSO-d_6.

TABLE V. Physical Data for **16f, g, k, o, p, q,** and **17**

Compd. No.	X	R^1	Yield (%)	Method	mp (°C)	Recryst. solvent[b]	Formula	Analysis (%) Calcd C	H	N	Found C	H	N	MS (m/z) (M^+)
16f	3-NO_2	CH_2CH_2SMe	78	A	148—149	D–IPE	$C_{21}H_{23}SN_3O_6$	56.61	5.20	9.43	56.55	5.21	9.41	445
16g	3-NO_2	$CH_2CH_2CH_2SPh$	75[a]	A, B	116—118	D–IPE	$C_{27}H_{27}SN_3O_6$	62.17	5.22	8.06	61.28	5.13	7.99	521
16k	2-CF_3	Me	71	A	127—128	D–H	$C_{20}H_{19}F_3N_2O_4$	58.82	4.69	6.86	58.67	4.55	6.85	409[c]
16o	3-NO_2	$CH_2CH_2NHCOPy$-3	84	B	178—180	D–E	$C_{26}H_{25}N_5O_7$	60.11	4.85	13.48	60.05	4.66	13.45	520[c]
16p	3-NO_2	CH_2CH_2OAc	81	A	78—79	D–IPE	$C_{23}H_{25}N_3O_8$	58.58	5.35	8.91	58.48	5.34	8.89	471
16q	3-NO_2	CH_2CH_2SAc	68	A	113—115	D–IPE	$C_{22}H_{23}SN_3O_7$	55.80	4.90	8.88	55.75	4.88	8.87	473
17			69	A	129—131	D–IPE	$C_{22}H_{23}N_3O_8$	57.76	5.07	9.19	57.67	4.89	9.10	450[c]

a) Method A. *b*) Solvent for recrystallization: D, dichloromethane; IPE, diisopropyl ether; E, ether; H, *n*-hexane. *c*) $(M+H)^+$.

(4H, m), 7.00 (1H, br s), 7.72 (1H, br s), 8.78 (1H, t, $J=5$ Hz). *Anal.* Calcd for $C_{12}H_{15}N_3O_3$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.77; H, 6.09; N, 16.77.

General Procedure for the Synthesis of Dihydropyridines (16). 2-Cyanoethyl 2-(Nicotinoylamino)ethyl 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (16o) Method A: (1) A solution of 3-nitrobenzaldehyde (**11**) (15.11 g, 0.10 mol), 2-(nicotinoylamino)ethyl acetoacetate (**8a**) (25.03 g, 0.10 mol), and 2-cyanoethyl 3-aminocrotonate (**12**) (15.42 g, 0.10 mol) in 2-propanol (200 ml) was refluxed for 5 h with stirring. The solvent was removed and the residue was purified by column chromatography on silica gel with hexane–AcOEt (1 : 1, v/v) to give **16o** (41.57 g, 80%) as yellow crystals, mp 178—179 °C (from CH_2Cl_2–iso-Pr_2O).

(2) A solution of 3-nitrobenzaldehyde (**11**) (15.11 g, 0.10 mol), 2-cyanoethyl acetoacetate (**13**) (15.52 g, 0.10 mol), and 2-(nicotinoylamino)ethyl 3-aminocrotonate (**9a**) (25.93 g, 0.10 mol) in 2-propanol (200 ml) was refluxed for 5 h with stirring. The solvent was removed and the residue was purified by column chromatography on silica gel with hexane–AcOEt (1 : 1, v/v) to give **16o** (39.51 g, 76%) as yellow crystals, mp 178—179 °C (from CH_2Cl_2–iso-Pr_2O).

Method B: A solution of 3-nitrobenzaldehyde (**11**) (15.11 g, 0.10 mol), 2-(nicotinoylamino)ethyl acetoacetate (**8a**) (25.03 g, 0.10 mol), AcOH (1.20 g, 20 mmol) and piperidine (1.70 g, 20 mmol) in benzene (300 ml) was refluxed for 2 h with continuous removal of water by a Dean-Stark apparatus. The benzene layer was washed with water, dried (Na_2SO_4) and concentrated to give 2-(nicotinoylamino)ethyl 2-(3-nitrobenzylidene)acetoacetate (**15**) (34.35 g, 90%) as colorless crystals, mp 173—176 °C (CH_2Cl_2–Et_2O). The ratio of isomers was 4.5 : 1 as judged from the NMR spectrum. MS *m/z*: 384 ($M^+ + 1$). IR (KBr) cm^{-1}: 3320 (NH), 1745 and 1665 (CO). *Anal.* Calcd for $C_{19}H_{17}N_3O_6$: C, 59.53; H, 4.47; N, 10.96. Found: C, 59.24; H, 4.43; N, 10.88.

A solution of **15** (3.83 g, 10 mmol) and 2-cyanoethyl 3-aminocrotonate (**12**) (1.54 g, 10 mmol) in propanol (30 ml) was refluxed for 3 h with stirring. After removal of the solvent, the residue was purified by column chromatography on silica gel hexane–AcOEt (1 : 1, v/v) to give the product (**16o**) (4.37 g, 84%) as yellow crystals.

Other 1,4-dihydropyridines[21] (**16f, g, k, o, p, q** and **17**) were prepared similarly and their spectral and physical data are listed in Tables IV and V.

General Procedure for the Synthesis of 1,4-Dihydropyridine-3-carboxylic

TABLE VI. Spectral Data for **18a—q**, **21**, **24** and **25**

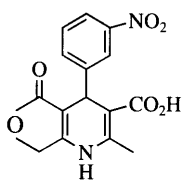
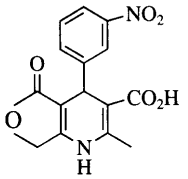
Compd. No.	X	R^1	IR (KBr) cm^{-1} (NH)	IR (KBr) cm^{-1} (CO)	^{1}H-NMR (DMSO-d_6) δ (ppm)
18a	3-NO_2	Me	3344	1652	2.28 (3H, s), 2.30 (3H, s), 3.56 (3H, s), 5.01 (1H, s), 7.48—8.06 (4H, m), 8.97 (1H, s), 11.86 (1H, br s)
18b	3-NO_2	Et	3363	1657	1.16 (3H, t, $J=7$ Hz), 2.28 (6H, s), 4.01 (2H, m), 4.98 (1H, s), 7.49—8.06 (4H, m), 8.93 (1H, s), 11.68 (1H, br s)
18c	3-NO_2	iso-Pr	3362	1677 1655	1.04 (3H, d, $J=7$ Hz), 1.20 (3H, d, $J=7$ Hz), 2.27 (3H, s), 2.30 (3H, s), 4.83 (1H, m), 4.96 (1H, s), 7.47—8.06 (4H, m), 8.89 (1H, br s), 11.80 (1H, br s)
18d	3-NO_2	iso-Bu	3367	1703 1687	0.78 (3H, d, $J=6$ Hz), 0.82 (3H, d, $J=6$ Hz), 1.42 (1H, m), 2.27 (3H, s), 2.33 (3H, s), 3.96 (2H, m), 4.99 (1H, s), 7.48—8.07 (4H, m), 8.96 (1H, br s), 11.82 (1H, br s)
18e	3-NO_2	CH_2CH_2OMe	3412	1678	2.29 (3H, s), 2.32 (3H, s), 3.22 (3H, s), 3.49 (2H, m), 4.08 (2H, m), 5.00 (1H, s), 7.47—8.04 (4H, m), 8.97 (1H, br s), 11.82 (1H, br s)
18f	3-NO_2	CH_2CH_2SMe	3375	1708 1680	2.13 (3H, s), 2.22 (3H, s), 2.28 (3H, s), 2.66 (2H, t, $J=6$ Hz), 4.13 (2H, m), 4.99 (1H, s), 7.47—8.05 (4H, m), 8.95 (1H, s), 11.84 (1H, br s)
18g	3-NO_2	$CH_2CH_2CH_2SPh$	3349	1702 1680	1.79 (2H, m), 2.27 (3H, s), 2.31 (3H, s), 2.71 (2H, m), 4.02 (2H, m), 4.98 (1H, s), 7.48—8.06 (4H, m), 8.95 (9H, m), 8.95 (1H, s), 11.75 (1H, br s)
18h	3-Cl	Me	3402	1698	2.29 (3H, s), 2.31 (3H, s), 3.57 (3H, s), 4.89 (1H, s), 7.06—7.31 (4H, m), 8.84 (1H, br s), 11.72 (1H, br s)
18i	2,3-diCl	Me	3333	1699	2.23 (3H, s), 2.26 (3H, s), 3.50 (3H, s), 5.32 (1H, s), 7.26—7.58 (3H, m), 8.83 (1H, br s), 11.61 (1H, br s)
18j	2-F	Me	3342	1657	2.24 (3H, s), 2.26 (3H, s), 3.50 (3H, s), 5.11 (1H, s), 6.90—7.27 (4H, m), 8.79 (1H, br s), 11.50 (1H, br s)
18k	2-CF_3	Me	3343	1656	2.22 (2 × 3H, s), 3.45 (3H, s), 5.38 (1H, s), 7.23—7.57 (4H, m), 8.72 (1H, s), 11.62 (1H, s)
18l	3-CF_3	Me	3351	1676	2.28 (3H, s), 2.29 (3H, s), 3.56 (3H, s), 4.98 (1H, s), 7.38—7.51 (4H, m), 8.89 (1H, br s), 11.80 (1H, br s)
18m	3-NO_2	$CH_2CH_2ONO_2$	3326	1658	2.28 (3H, s), 2.30 (3H, s), 4.28 (2H, m), 4.71 (2H, m), 4.98 (1H, s), 7.47—8.08 (4H, m), 9.03 (1H, br s), 11.68 (1H, br s)
18n	3-NO_2	$CH_2CH_2CH_2ONO_2$	3327	1679	1.96 (2H, m), 2.28 (3H, s), 2.33 (3H, s), 4.06 (2H, m), 4.41 (2H, t, $J=6$ Hz), 5.00 (1H, s), 7.48—8.08 (4H, m), 8.98 (1H, br s), 11.08 (1H, br s)
18o	3-NO_2	CH_2CH_2NHPy-3	3406	1704 1673	2.28 (3H, s), 2.30 (3H, s), 3.53 (2H, m), 4.16 (2H, m), 4.98 (1H, s), 7.37—9.26 (8H, m), 8.87—9.05 (1H, m), 9.03 (1H, s), 11.83 (1H, br s)
18p	3-NO_2	$CH_2CH_2CH_2OAc$	3364	1707	1.85 (2H, m), 1.98 (3H, s), 2.29 (3H, s), 2.31 (3H, s), 3.92 (2H, t, $J=6$ Hz), 4.03 (2H, m), 4.98 (1H, s), 7.46—8.08 (4H, m), 8.96 (1H, s), 11.85 (1H, br s)
18q	3-NO_2	CH_2CH_2SAc	3328	1707 1677	2.28 (3H, s), 2.30 (3H, s), 2.31 (3H, s), 3.07 (2H, t, $J=6$ Hz), 4.07 (2H, t, $J=6$ Hz), 4.98 (1H, s), 7.49—8.06 (4H, m), 8.99 (1H, s), 11.88 (1H, br s)
21	3-NO_2	$CH_2CH_2CH_2OH$	3365	1706	1.69 (2H, m), 2.27 (3H, s), 2.30 (3H, s), 3.37 (2H, m), 4.00 (2H, m), 4.98 (1H, s), 7.49—8.05 (4H, m), 8.91 (1H, s), 11.81 (1H, br s)
24			3262	1724 1682	2.37 (3H, s), 4.79 (1H, d, $J=15$ Hz), 4.88 (1H, s), 4.92 (1H, d, $J=15$ Hz), 7.52—8.12 (4H, m), 10.03 (1H, br s), 11.98 (1H, br s)
25	3-NO_2	CH_2CH_2CN	3359	1711 1673	2.31 (3H, s), 2.33 (3H, s), 2.86 (2H, m), 4.16 (2H, t, $J=6$ Hz), 4.99 (1H, s), 7.46—8.09 (4H, m), 9.04 (1H, s), 11.81 (1H, br s)

TABLE VII. Physical Data for **18a—q**, **21**, **23** and **25**

Compd. No.	X	R^1	mp (°C)	Recryst. solvent[a]	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N	MS (*m/z*) (M^+)
18a	3-NO_2	Me	175—177	E–M	$C_{16}H_{16}N_2O_6$	57.83	4.85	8.43	57.59	4.88	8.22	333[b]
18b	3-NO_2	Et	177—179	E–M	$C_{17}H_{18}N_2O_6$	58.95	5.24	8.09	58.88	5.11	7.99	346
18c	3-NO_2	iso-Pr	172—174	E–Et	$C_{18}H_{20}N_2O_6$	59.99	5.59	7.77	60.11	5.34	7.65	360
18d	3-NO_2	iso-Bu	180—182	E–T	$C_{19}H_{22}N_2O_6$	60.95	5.92	7.48	60.67	5.75	7.22	374
18e	3-NO_2	CH_2CH_2OMe	165—167	E–T	$C_{18}H_{20}N_2O_7$	57.44	5.35	7.44	57.22	5.33	7.15	376
18f	3-NO_2	CH_2CH_2SMe	208—209	E–M	$C_{18}H_{20}SN_2O_6$	55.09	5.14	7.14	54.85	4.99	7.01	392
18g	3-NO_2	$CH_2CH_2CH_2SPh$	165—167	E–M	$C_{24}H_{24}SN_2O_6$	61.52	5.16	5.98	61.22	5.05	5.75	468
18h	3-Cl	Me	211—212	E–M	$C_{16}H_{16}ClNO_4$	59.76	5.02	4.36	59.65	4.91	4.34	321
18i	2,3-diCl	Me	199—200	E–M	$C_{16}H_{15}Cl_2NO_4$	53.95	4.24	3.93	53.85	4.11	3.89	357[b]
18j	2-F	Me	215—216	E–M	$C_{16}H_{16}FNO_4$	62.94	5.28	4.59	62.59	5.22	4.47	305
18k	2-CF_3	Me	190—191	E–M	$C_{17}H_{16}F_3NO_4$	57.46	4.54	3.94	57.19	4.27	3.88	355
18l	3-CF_3	Me	200—201	E–M	$C_{17}H_{16}F_3NO_4$	57.46	4.54	3.94	57.21	4.15	3.91	355
18m	3-NO_2	$CH_2CH_2ONO_2$	167—168	E–Et	$C_{17}H_{17}N_3O_9$	50.12	4.21	10.31	50.01	4.09	10.35	408[b]
18n	3-NO_2	$CH_2CH_2CH_2ONO_2$	194—195	E–M	$C_{18}H_{19}N_3O_9$	51.31	4.55	9.97	51.18	4.29	10.33	421
18o	3-NO_2	$CH_2CH_2NHCOPy$-3	202—203	E–Et	$C_{23}H_{22}N_4O_7$	59.22	4.75	12.01	60.11	4.83	11.99	467[b]
18p	3-NO_2	$CH_2CH_2CH_2OAc$	169—170	E–M	$C_{20}H_{22}N_2O_8$	57.41	5.30	6.70	57.27	5.26	6.55	418
18q	3-NO_2	CH_2CH_2SAc	193—194	E–M	$C_{19}H_{20}SN_2O_7$	54.27	4.79	6.63	54.26	4.71	6.58	420
21	3-NO_2	$CH_2CH_2CH_2OH$	174—175	E–M	$C_{18}H_{20}N_2O_7$	57.44	5.35	7.44	57.43	5.29	7.41	377[b]
24			198—200	E–Et	$C_{15}H_{12}N_2O_6$	56.96	3.82	8.86	56.88	3.79	8.85	317[b]
25	3-NO_2	CH_2CH_2CN	183—185	E–M	$C_{18}H_{17}N_3O_6 \cdot 1H_2O$	55.52	4.92	10.79	55.90	4.65	10.41	372[b]

a) Solvent for recrystallization: E, ether; Et, ethanol; M, methanol; T, THF. *b*) $(M+H)^+$.

Acids (18). 5-Methoxycarbonyl-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic Acid (18a) A. Reaction of 16a with Sodium Sulfide[22] Sodium sulfide (1.20 g, 5 mmol) was added to a CH_2Cl_2–MeOH (20 ml–10 ml) solution of **16a** (3.85 g, 10 mmol), and the reaction mixture was stirred at room temperature for 5 h. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The aqueous layer was acidified with phosphoric acid (1.47 g, 15 mmol) with ice cooling. The precipitated product was filtered off, washed with water, and then dried *in vacuo*. Recrystallization from ethanol–Et_2O gave **18a** (2.83 g, 85%) as yellow crystals. The organic extract was washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel with hexane–AcOEt (1 : 1) to give bis(2-cyanoethyl)sulfide (**20**) (1.22 h, 87%) as a pale yellow oil. MS *m/z*: 140 (M^+). IR (neat) cm^{-1}: 2250 (CN). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.69 (2×2H, m), 2.90 (2×2H, m).

Other carboxylic acids (**18b—o**, **21**, **24** and **25**)[21] were prepared similarly and their spectral and physical data are listed in Tables VI and VII.

B. Reaction of 16a with Tetrabutylammonium Fluoride Tetrabutylammonium fluoride (3.13 g, 12 mmol) was added to THF–DMF (20 ml–10 ml) solution of **16a** (3.85 g, 10 mmol) at room temperature, and the mixture was stirred at room temperature for 5 h. The reaction mixture was acidified with 1 N hydrogen chloride and extracted with CH_2Cl_2. The extract was washed with water. The organic layer was diluted with 1 N sodium hydroxide and extracted with CH_2Cl_2. The aqueous layer was acidified with phosphoric acid with ice cooling. The precipitated product was filtered off, washed with water, and then dried *in vacuo*. Recrystallization from ethanol–Et_2O gave **18a** (2.92 g, 88%) as yellow crystals.

Other carboxylic acids (**18b—q**) were prepared similarly and their spectral and physical data are listed in Tables VI and VII.

3-Nitrooxypropyl 2-(Nicotinoylamino)ethyl 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (CD-832) Acetic anhydride (3.06 g, 30 mmol) was added to a suspension of carboxylic acid (**18o**) (4.66 g, 10 mmol) in CH_2Cl_2 (30 ml) at room temperature, and the mixture was stirred for 2 h at the same temperature. A solution of 3-nitrooxypropanol (1.33 g, 11 mmol) in CH_2Cl_2 containing a catalytic amount of acetyl chloride was added at the same temperature, and the whole was stirred for 5 h. The reaction mixture was diluted with CH_2Cl_2 and washed with 1 N NaOH and brine. The solvent was removed and the residue was purified by column chromatography on silica gel with hexane–AcOEt (1 : 1, v/v) to give the product (CD-832) (4.11 g, 72%) as light yellow crystals, mp 146—148 °C (from MeOH–Et_2O). MS *m/z*: 570 ($M^+ + 1$). IR (KBr) cm^{-1}: 3370 (NH), 1669 (CO). ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 1.92 (2H, m), 2.28 (3H, s), 2.31 (3H, s), 3.54 (2H, m), 3.91—4.26 (2×2H, m), 4.41 (2H, t, J=6 Hz), 4.99 (1H, s), 7.37—9.01 (8H, m), 8.71 (1H, t, J=5 Hz), 9.06 (1H, s). *Anal.* Calcd for $C_{26}H_{27}N_5O_{10}$: C, 54.83; H, 4.78; N, 12.30. Found: C, 55.03; H, 4.81; N, 12.08.

Enantiomeric (*R*)-(−)- and (*S*)-(+)-CD-832[23] was prepared similarly from (*S*)-(+)- and (*R*)-(−)-**18n** in 79 and 75% yields by reaction with *N*-2-hydroxyethylnicotinamide *p*-toluenesulfonic acid salt in DMF, respectively.

(*R*)-(−)-CD-832: mp 121—122 °C (from CH_2Cl_2–Et_2O): $[\alpha]_D$ −22.3° (c=1.00, MeOH), 99% ee. *Anal.* Calcd for $C_{25}H_{27}N_5O_{10}$: C, 53.86; H, 4.88; N, 12.56. Found: C, 53.55; H, 4.59; N, 12.39.

(*S*)-(+)-CD-832: mp 119—121 °C (from CH_2Cl_2–Et_2O); $[\alpha]_D$ +23.8° (c=1.00, MeOH), 99% ee. *Anal.* Calcd for $C_{25}H_{27}N_5O_{10}$: C, 53.86; H, 4.88; N, 12.56. Found: C, 53.57; H, 4.87; N, 12.50.

The IR (KBr) and NMR spectra of these samples were identical with those of the racemate (CD-832).

(*R*)-(+)-Methyl 2-Nitrooxypropionate (27)[17] Fuming HNO_3 (57 ml, 1.35 mol) was added dropwise to an ice cold solution of H_2SO_4 (76 ml, 1.35 mol) with stirring. After 1 h at 0 °C, (*R*)-(+)-methyl 2-hydroxypropionate (**26**) (104.10 g, 1 mol) was added dropwise at the same temperature. The mixture was stirred for 3 h, poured into ice-water, and extracted with Et_2O. The organic layer was washed with saturated aqueous $NaHCO_3$ and H_2O, dried (Na_2SO_4), and evaporated. The remaining crude product was distilled to provide the pure (*R*)-(+)-2-nitrooxypropionate (**27**) (132.40 g, 87%); bp 38—39 °C (1.2 mmHg). $[\alpha]_D$ +66.2° (c=1.00, MeOH). MS *m/z*: 150 ($M^+ + 1$). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.56 (3H, d, J=7 Hz), 3.82 (3H, s), 5.26 (1H, q, J=7 Hz).

(*S*)-(−)-**27** was similarly prepared from (*S*)-(−)-**26** in 89% yield by reaction with HNO_3–H_2SO_4; $[\alpha]_D$ −67.8° (c=1.00, MeOH).

The IR (neat) and NMR spectra of this sample were identical with those of the enantiomer (*R*)-(+)-**27**.

(*R*)-(−)-2-Nitrooxypropanol (28)[17] (*R*)-(+)-**27** (60.55 g, 0.50 mol) was added dropwise to a solution of $Ca(BH_4)_2$, prepared from $CaCl_2$ (13.87 g, 0.13 mol) and $NaBH_4$ (9.46 g, 0.25 mol) in dry DME (500 ml) under a N_2 atomsphere at 40 °C. The mixture was stirred at 45 °C for 3 h and then at room temperature for 10 h. After cooling to 0 °C, H_2O was added and the mixture was further stirred at room temperature for 1 h. The precipitated salt was filtered off and the filtrate was extracted with Et_2O. The combined organic extracts were washed with brine and dried (Na_2SO_4). The solvent was evaporated and the residue was distilled to provide the pure alcohol (*R*)-(−)-(**28**) (49.71 g, 82%), bp 52—54 °C (0.2 mmHg). $[\alpha]_D$ −9.63° (c=1.00, MeOH). MS m/z: 122 (M^++1). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.37 (3H, d, J=7 Hz), 2.48 (1H, br s), 3.68 (1H, dd, J=12.5, 7 Hz), 3.80 (1H, dd, J=12.5, 4 Hz), 5.20 (1H, m).

(*S*)-(+)-**28** was also similarly prepared from (*S*)-(−)-**27** in 76% yield by reaction with $Ca(BH_4)_2$; $[\alpha]_D$ +10.2° (c=1.00, MeOH). The IR (neat) and NMR spectra of this sample were identical with those of the enantiomer (*R*)-(−)-**28**.

(4*R*,2′*R*)-(+)-2-Nitrooxypropyl 3-Nitrooxypropyl 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (CD-349) Acetic anhydride (3.06 g, 30 mmol) was added to a suspension of (*S*)-(+)-**18n** (4.21 g, 10 mmol) in CH_2Cl_2 (30 ml) at room temperature. A solution of (*R*)-(−)-2-nitrooxypropanol (**28**) (1.33 g, 11 mmol) in CH_2Cl_2 containing a catalytic amount of acetyl chloride was added to the reaction mixture at the same temperature, and the mixture was stirred for 5 h. The reaction mixture was diluted with CH_2Cl_2, washed with 1 N NaOH and brine, and dried (Na_2SO_4). The solvent was removed and the residue was recrystallized from CH_2Cl_2–iso-Pr_2O to give (4*R*,2′*R*)-(+)-CD-349[24] as yellow crystals (4.63 g, 88%), mp 106—107 °C. $[\alpha]_D$ +9.16° (c=1.00, MeOH), 99% ee. MS m/z: 524 (M^+). IR (KBr) cm^{-1}: 3361 (NH), 1698 (CO). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.35 (3H, d, J=8 Hz), 2.08 (2H, m), 2.39 (3H, s), 2.40 (3H, s), 4.06 (1H, dd, J=11, 8 Hz), 4.26 (2H, t, J=6 Hz), 4.29 (1H, dd, J=10, 4 Hz), 4.42 (2H, t, J=6 Hz), 5.04 (1H, s), 5.29 (1H, m), 5.83 (1H, br s), 7.34—8.12 (4H, m). *Anal.* Calcd for $C_{21}H_{24}N_4O_{12}$: C, 48.09; H, 4.61; N, 10.68. Found: C, 48.10; H, 4.59; N, 10.55.

(4*R*,2′*S*)-(−)-CD-349[24] was similarly prepared from the monoester (*S*)-(+)-**18n** in 86% yield by reaction with (*S*)-(+)-**28**; mp 103—104 °C (from CH_2Cl_2–iso-Pr_2O). $[\alpha]_D$ −8.68° (c=1.00, MeOH), 99% ee. MS m/z: 524 (M^+). IR (KBr) cm^{-1}: 3361 (NH), 1698 (CO). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.29 (3H, J=8 Hz), 2.08 (2H, m), 2.39 (3H, s), 2.40 (3H, s), 4.11 (1H, dd, J=11, 8 Hz), 4.26 (2H, t, J=6 Hz), 4.29 (1H, dd, J=10, 4 Hz), 4.42 (2H, t, J=6 Hz), 5.04 (1H, s), 5.29 (1H, m), 5.83 (1H, br s), 7.34—8.12 (4H, m). *Anal.* Calcd for $C_{21}H_{24}N_4O_{12}$: C, 48.09; H, 4.61; N, 10.68. Found: C, 48.11; H, 4.60; N, 10.63.

(4*S*,2′*R*)-(+)-CD-349[24] was similarly prepared from the monoester (*R*)-(−)-**18n** in 84% yield by reaction with (*R*)-(−)-**28**; mp 102—104 °C. $[\alpha]_D$ +8.71° (c=1.00, MeOH), 99% ee. This was identical with (4*R*,2′*S*)-(−)-CD-349 (IR, NMR, mass spectra).

(4*S*,2′*S*)-(−)-CD-349[24] was also similarly prepared from the monoester (*R*)-(−)-**18n** in 82% yield by reaction with (*S*)-(+)-**28**; mp 107—109 °C. $[\alpha]_D$ −9.27° (c=1.00, MeOH), 99% ee. This was identical with (4*R*,2′*R*)-(+)-CD-349 (IR, NMR and mass spectra).

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18) In contrast to other 1,4-dihydropyridine enantiomers, the activity of the diester (*R*)-(−)-CD-832 on coronary blood flow is 10 times greater than that of (*S*)-(+)-CD-832.

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20) The screening test for vasodilation activity was carried out by measurement of femoral blood flow in anesthetized dogs. The potencies of the four enantiomers were equal. On the other hand, the duration of action of (4*R*,2′*R*)- and (4*S*,2′*R*)-CD-349 was about twice that of (4*R*,2′*S*)- and (4*S*,2′*S*)-CD-349.

21) 1,4-Dihydropyridines (**18a—e, h—j, l—n**) were identical with the authentic samples synthesized by us.[3c,12]

22) Commercial Na_2S (9 hydrate) was used.

23) The enantiomeric excess of the two enantiomers was analyzed by high-pressure liquid chromatography (HPLC) on a chiral column [Chiralcel OJ] at 18 °C with ethanol–hexane (15:85).

24) The enantiomeric excess of the four enantiomers was analyzed by high-pressure liquid chromatography (HPLC) on a chiral column [Chiralcel OJ] at 18 °C with ethanol–hexane (15:85).