Total Synthesis of the Racemic 3-Methyl Analogue of the Antitumour Agent Acivicin

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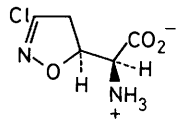
The racemic 3-methyl analogue (**19a**) of acivicin (**1**) has been synthesized by a stereorandom route starting with acetonitrile oxide (**3**) and a novel vinylglycine precursor, ethyl 2-acetoxybut-3-enoate (**9**). The diastereoisomeric alcohols (**11a,b**) and azides (**14a,b**) were separated and used for the synthesis of the individual diastereoisomers of compounds (**10**), (**12**), and (**15**)—(**19**). The *erythro*- and *threo*-diastereoisomers were identified on the basis of their ^1H and ^{13}C n.m.r. spectra.

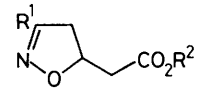
Acivicin (AT-125), (α*S*,5*S*)-amino(3-chloro-4,5-dihydroisoxazol-5-yl)acetic acid (**1**) has been a subject of considerable interest due to its remarkable antitumour effect[1] since its isolation and structure elucidation by the Upjohn group.[2] Its low availability from fermentation sources has been a challenge for its total synthesis.[3] Most of the syntheses are based upon dipolar cycloadditions of chloroformonitrile oxide ('chloronitrile oxide') (**2**) and vinylglycine or vinylglycine precursors.[3a,c,f,g] It was hoped that antitumour activity would be retained when the 3-chloro substituent was replaced by the isosteric 3-methyl group. The synthesis of the 3-methyl analogue (**19a**) appeared attractive since in this case the starting 1,3-dipole was acetonitrile oxide (**3**) rather than chloronitrile oxide (**2**) prepared *in situ* from the highly toxic chloroformohydroxamoyl chloride ('dichloroformaldoxime') and the use of this highly toxic substance could be avoided.



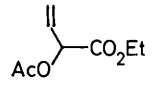
(**1**)

$R^1C{\equiv}N{\rightarrow}O$

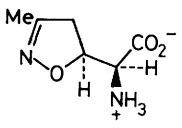
(**2**) R^1 = Cl
(**3**) R^1 = Me
(**4**) R^1 = Et



(**5**) R^1 = Me, R^2 = $CHPh_2$
(**6**) R^1 = Et, R^2 = $CHPh_2$
(**7**) R^1 = Me, R^2 = H
(**8**) R^1 = Et, R^2 = H



(**9**)

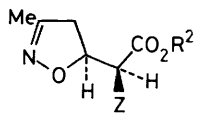


(**19a**)*

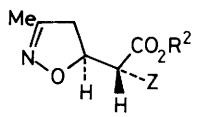
Although syntheses of pure (*S*)-vinylglycine are known[4] the diastereofacial selectivity of its dipolar cycloadditions with nitrile oxides is poor and mainly the wrong C-5 stereoisomer is formed.[5] On the other hand, our attempts to introduce the α-amino functionality into the acetic acid derivative (**7**) have failed. These facts determined our strategy: dipolar cycloaddition of acetonitrile oxide to an easily available vinylglycine precursor, separation of the diastereoisomers in as early a stage as possible, and elaboration of the amino acid moiety.

Ethyl 2-acetoxybut-3-enoate (**9**)[6] proved to be an easily available vinylglycine precursor.† Acetonitrile oxide (**3**) was prepared by the Mukaiyama method.[7] Only the desired 5-substituted regioisomer of 4,5-dihydroisoxazole (**10**) was formed in the cycloaddition step, in agreement with literature, according to which only the 1,2-disubstituted ethylenes furnish regioisomers, ethylenes with terminal methylene groups give only the 5-substituted isomers.[8] The diastereoisomeric mixture of the acetoxy esters (**10**) was treated with ethanol in the presence of a catalytic amount of sodium ethoxide to give a mixture of the alcohols (**11**). This was separated by column chromatography and the *threo*-isomer (**11b**) was reacetylated to the *threo*-acetoxy ester (**10b**) in order to allow assignment of the n.m.r. signals of both diastereoisomers (**10a,b**) of the acetoxy ester.

Mesylation of the *erythro*- (**11a**) and *threo*-alcohols (**11b**) gave the *erythro*- (**12a**) and *threo*-mesylates (**12b**), respectively. Replacement of the mesyloxy groups by iodine furnished identical diastereoisomeric mixtures of the iodides (**13**) irrespective of the stereochemistry of the starting mesylate. In view of this fact, the diastereoisomeric mixture of the alcohols (**11**) was



a*



b*

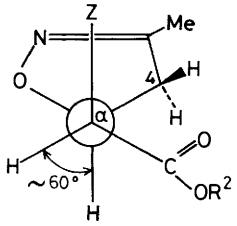
	R^2	Z
(**10**)	Et	OAc
(**11**)	Et	OH
(**12**)	Et	OSO_2Me
(**13**)	Et	I
(**14**)	Et	N_3
(**15**)	Et	$^+NH_3Cl^-$
(**16**)	Et	$NHCO_2Bu^t$
(**17**)	H	$NHCO_2Bu^t$
(**18**)	H	$^+NH_3Cl^-$
(**19**)	H	NH_2

† For an improved synthesis of this compound see Experimental section.

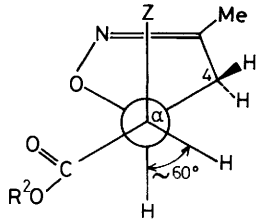
* All compounds are racemic; for convenience only one enantiomer is shown.

mesylated, the product refluxed with sodium iodide in acetone, and the resulting mixture of the iodides (**13**) stirred with an excess of sodium azide to give a diastereoisomeric mixture of azides (**14**); these could also be separated into the pure *diastereo*isomers (**14a,b**). The correlation between the pure diastereoisomeric azides (**14a,b**) and the alcohols (**11a,b**) was carried out by applying the Mitsunobu reaction.[9] The *erythro*-(**11a**) and *threo*-alcohols (**11b**) furnished the *threo*- (**14b**) and *erythro*-azides (**14a**), respectively, when treated with hydrazoic acid in the presence of triphenylphosphine and di-isopropyl azodicarboxylate.

The individual azides (**14a,b**) were catalytically (H_2/Pd–C) reduced in ethanolic solution saturated by hydrogen chloride to give the salts of the corresponding amino esters (**15a,b**).



(**a**)*



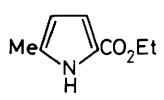
(**b**)*

Figure. Preferred conformers of *erythro*-(**a**) and *threo*-(**b**) diastereoisomers looking at the molecules (**10**)—(**19**) in the direction of the C(α)–C(5) bond.

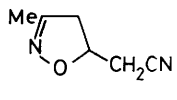
* Only one enantiomer is depicted

Table. Characteristic ^{1}H- and ^{13}C-shifts of compounds (**10**)—(**19**): (a) in $CDCl_3$; (b) in D_2O; (c) in $(CD_3)_2SO$

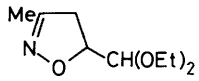
Compd.	δ(α-H)/p.p.m.	δ(C-4)/p.p.m.
(**10a**)	5.20[a]	39.69[a]
(**10b**)	5.06[a]	40.40[a]
(**11a**)	4.41[a]	39.05[a]
(**11b**)	4.14[a]	40.45[a]
(**12a**)	5.17[a]	39.43[a]
(**12b**)	5.01[a]	40.54[a]
(**13a**)	4.47[a]	42.63[a]
(**13b**)	4.34[a]	44.24[a]
(**14a**)	4.28[a]	40.31[a]
(**14b**)	3.84[a]	41.60[a]
(**15a**)	4.31[b]	44.23[b]
(**15b**)	4.23[b]	44.61[b]
(**16a**)	4.30[a]	41.45[a]
(**16b**)	4.45[a]	41.22[a]
(**17a**)	4.07[c]	40.78[c]
(**17b**)	4.12[c]	40.99[c]
(**18a**)	4.24[b]	43.70[b]
(**18b**)	4.13[b]	44.81[b]
(**19a**)	4.01[b]	42.59[b]
(**19b**)	3.77[b]	44.70[b]



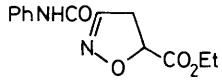
(**20**)



(**21**)



(**22**)



(**23**)

Although the reductions were carried out in highly acidic media, in order to prevent the formation of the corresponding piperazine-2,5-diones, attack of the 3-amino to give ethyl 5-methylpyrrole-2-carboxylate (**20**) as a by-product could not be avoided. The ester salts (**15**) could not be hydrolysed directly to the acid salts (**18**) without decomposition. We have found a novel method for the preparation of amino acids sensitive to aqueous acids from the hydrochlorides of their ethyl esters. The amino ester salts (**15a,b**) were treated in aqueous solution with di-t-butyl oxydiformate in the presence of a slight excess of potassium hydroxide to furnish, upon acidification, the *N*-t-butoxycarbonylamino acids (**17a,b**). These compounds were deprotected with dry hydrochloric acid in ethyl acetate solution. The acid salts (**18a,b**) were passed through an ion-exchange column to give the desired amino acids (**19a,b**).

The *erythro*-(**a**) and *threo*-(**b**) isomers have been distinguished on the basis of their ^{1}H and ^{13}C n.m.r. spectra. The chemical shifts of the 3-methylprotons, the 3-methylcarbon and, of the C-3 carbon atoms of the 4,5-dihydroisoxazoles (**10**)—(**19**), (**21**), (**22**) were practically identical, *i.e.* the substituents in position 5 have no effect on position 3. This appears to indicate that the substituents in postion 5 are 'quasi equatorial'. According to the coupling constant, $J_{\alpha,5}$ 3 Hz and the significant n.O.e. (5—6%) observed between α-H and 5-H in both diastereoisomeric alcohols (**11a,b**) the preferred conformations of the two diastereoisomers can be depicted as shown in the Figure, the molecules being viewed from the direction of the C(α)–C(5) bond. In the *erythro*-series the chemical shifts of the α-H's are greater than those of the α-H's in the *threo*-series (see Table). This is caused by the deshielding effect of the ring oxygen on α-H. In the 400 MHz ^{1}H n.m.r. spectrum of the *erythro*-alcohol (**11a**) a W (zigzag) long-range effect coupling (J 0.4—0.5 Hz) was found between the α-H and one of the 4-H's. Such an arrangement can be formed only in the *erythro*-compounds as shown in the Figure. In agreement with expectation a greater n.O.e. has been found between the α-H and one of the 4-H's in the *threo*-alcohol (**11b**) (4%) than in the *erythro*-alcohol (**11a**) (2%). The differences in the ^{13}C shifts of C-4 of the diastereoisomers (see Table) can be explained by the shielding effect of the carbonyl group in the *erythro* isomers.

We were also interested in the synthesis of 3-unsubstituted 4,5-dihydroisoxazoles. We attempted to extend Mukaiyama's method for this purpose by using nitromethane as a nitrile oxide source. In a preliminary experiment ethyl acrylate was used as a dipolarophile. Although the reaction of the sodium salt of nitromethane with phenyl isocyanate was known to give α-nitroacetanilide,[10] we hoped that, in the presence of catalytic amounts of base and stoicheiometric amounts of the dipolarophile simultaneous formation of the 3-unsubstituted isoxazoles could also take place. Unfortunately, nitrile oxide formation took place only from the α-nitroacetanilide and furnished compound (**23**) with ethyl acrylate.

The antitumour activity of the amino acids (**19a,b**) was studied on hepatoma tissues. These compounds showed only a slight antitumour activity.

During the preparation of this paper an article has been

published on the synthesis of acivicin and related compounds by asymmetric induction, among them the synthesis of (αS,5S)- and (αS,5R)-amino(3-methyl-4,5-dihydroisoxazol-5-yl)acetic acid.[11]

Experimental

M.p.s were measured on a hot-stage melting point apparatus and are uncorrected. I.r. spectra were obtained with a Spectromom 2000 instrument (Hungarian Optical Works, Budapest) and Specord 75 (Zeiss, Jena, GDR). ^1H and ^{13}C N.m.r. spectra were recorded on Perkin-Elmer 12 (60 MHz), JEOL FX-100 (100 MHz), and Varian XL 400 (400 MHz) spectrometers, using $SiMe_4$ as internal reference in $CDCl_3$, unless otherwise stated. Column and the thin layer chromatography was carried out on Merck Kieselgel 60 (0.063—0.2) and Merck Kieselgel 60 F_{254}, Alufolien, respectively. For preparative t.l.c. Merck PSC-ready plates (Kieselgel 60 F_{254}, 20 × 20 mm, 2 mm) were used.

Benzhydryl 3-Methyl-4,5-dihydroisoxazol-5-ylacetate (**5**).—A mixture of nitroethane (2.2 ml, 30.8 mmol), triethylamine (0.3 ml, 2.1 mmol), and dry benzene (10 ml) was added dropwise to a stirred solution of phenyl isocyanate (6.2 ml, 56 mmol) and benzhydryl but-3-enoate (see below) (7.8 g, 28 mmol) in dry benzene (20 ml) at ambient temperature. The mixture was kept overnight and then refluxed under nitrogen for 1 h to complete the reaction. The reaction mixture was cooled, the *N,N'*-diphenylurea filtered off, and the resulting solution evaporated to dryness under reduced pressure. The residue was triturated with hexane (20 ml) and the insoluble material was recrystallized from ethanol to give *compound* (**5**) (6.0 g, 70%), m.p. 95 °C (Found: C, 74.1; H, 6.45; N, 4.35. $C_{19}H_{19}NO_3$ requires C, 73.8; H, 6.2; N, 4.5%); $\nu_{max.}$(KBr) 1 740 (CO) and 1 600 cm^{-1} (C=N); δ_H(60 MHz) 1.93 (3 H, s, Me), 2.5—3.05 (4 H, m, 4-H_2 and CH_2CO), 4.90 (1 H, m, 5-H), 6.8 (1 H, s, Ph_2CH), and 7.20 (10 H, s, ArH).

Benzhydryl But-3-enoate.—Small portions of diphenyldiazomethane[12] (9.3 g, 47.9 mmol) were added to a solution of but-3-enoic acid (4.1 g, 47.6 mmol) in dry CH_2Cl_2 (50 ml) at 0 °C. After the mixture had been stirred for 1 h, the excess of diphenyldiazomethane was decomposed by acetic acid, and the solution was washed successively with 5% aqueous $NaHCO_3$ and saturated brine, dried ($MgSO_4$), and evaporated to dryness. The crude product was purified by distillation to give *benzhydrylbut-3-enoate* (8.6 g, 71.6%), b.p. 104—108 °C (1.3 Pa) (Found: C, 81.2; H, 6.55. $C_{17}H_{16}O_2$ requires C, 80.9; H, 6.4%); $\nu_{max.}$(film) 1 740 cm^{-1} (CO); δ_H(60 MHz) 3.1 (2 H, dd, *J* 6 Hz and *J* 1—1.5 Hz, CH_2CO) 5.0—6.1 (3 H, m, CH_2=CH), 6.91 (1 H, s, $CHPh_2$), and 7.3 (10 H, s, ArH).

Benzhydryl 3-Ethyl-4,5-dihydroisoxazol-5-ylacetate (**6**).—This compound was prepared as described for compound (**5**) using 1-nitropropane instead of nitroethane. The crude product was purified by t.l.c. (benzene–ether 4:1, R_F:0.6) to give the oily compound (**6**) (50%) (Found: C, 74.0; H, 6.7; N, 4.7. $C_{20}H_{21}NO_3$ requires C, 74.3; H, 6.55; N, 4.3%); $\nu_{max.}$(film) 1 730 (CO) and 1 590 cm^{-1} (C=N); δ_H(60 MHz) 1.12 (3 H, t, *J* 7 Hz, Me), 2.30 (2 H, q, *J* 7 Hz, CH_2CH_3), 2.62—2.98 (4 H, m, 4-H_2 and CH_2CO), 4.90 (1 H, m, 5-H), 6.89 (1 H, s, Ph_2CH), and 7.28 (10 H, s, ArH).

3-Methyl-4,5-dihydroisoxazol-5-ylacetic Acid (**7**).—(a) The benzhydryl ester (**5**) (1.54 g, 5 mmol) was dissolved in acetic acid (15 ml) and hydrogenolysed in the presence of a 10% Pd–C catalyst (0.12 g) at room temperature to give, after conventional work-up (the acetic acid was removed at 1.3 Pa), *compound* (**7**) (0.40 g, 56%), m.p. 100 °C (from benzene) (Found: C, 50.7; H, 6.55; N, 9.5. $C_6H_9NO_3$ requires C, 50.3; H, 6.3; N, 9.8%); $\nu_{max.}$(KBr) 3 200—2 500br (OH) and 1 700 cm^{-1} (CO); δ_H(60 MHz) 2.0 (3 H, s, Me), 2.6—3.3 (4 H, m, 4-H_2 + CH_2CO), 4.6—5.15 (1 H, m, 5-H), and 10.1 (1 H, br s, OH).

(b) The benzhydryl ester (**5**) (1.54 g, 5.0 mmol) dissolved in a mixture of acetic acid (3 ml) and $CHCl_3$ (1.5 ml) was stirred with BF_3·Et_2O (1.57 ml, 12.5 mmol) at ambient temperature for 2 h and poured onto a mixture of ice (20 g) and $CHCl_3$ (30 ml); the organic layer was separated, the aqueous layer was extracted with $CHCl_3$ (3 × 20 ml), and the combined organic solutions were dried ($MgSO_4$) and evaporated. The residue was taken up in 10% aqueous Na_2CO_3 (10 ml), washed with $CHCl_3$ (2 × 5 ml), acidified to pH 1 by 10% aqueous HCl, and extracted with $CHCl_3$ (5 × 15 ml). The combined organic solutions were dried ($MgSO_4$), evaporated to dryness, and the residue crystallized from benzene to give compound (**7**) in 70% yield. The product was completely identical (m.p., i.r., and ^1H n.m.r.) with the sample prepared as described in (a).

3-Ethyl-4,5-dihydroisoxazol-5-ylacetic Acid (**8**).—The benzhydryl ester (**6**) was hydrogenolysed, as described for the synthesis of the 3-methyl derivative (**7**) in (a), to give *compound* (**8**) in 77.7% yield. The crude product was purified by column chromatography (benzene→benzene–acetone, 100:3), m.p. 87 °C (Found: C, 53.8; H, 7.0; N, 9.0. $C_7H_{11}NO_3$ requires C, 53.5; H, 7.1; N, 8.9%); $\nu_{max.}$(KBr) 3 300—2 500br (OH) and 1 705br cm^{-1} (CO); δ_H(60 MHz) 1.21 (3 H, t, *J* 7 Hz, Me), 2.2—3.4 (6 H, m, CH_2CO, CH_2CH_3, 4-H_2), 4.62—5.13 (1 H, m, 5-H, and 10.45 (1 H, br, OH).

Ethyl 2-Acetoxybut-3-enoate (**9**).—Freshly distilled acrylic aldehyde (71.1 ml, 1.07 mol) was added to a stirred suspension of pulverized KCN (100 g, 1.54 mol) in dry ether (500 ml) at 5—10 °C. Acetic acid (90.6 ml, 1.58 mol) was then added to the mixture at such a rate that the temperature was kept < 15 °C. After the mixture had been stirred for 2 h, the potassium acetate was filtered off and washed thoroughly with ether. The combined ethereal solutions were evaporated and fractionated to give 2-hydroxyvinylacetonitrile (72.0 g, 81.1%), b.p. 93—94 °C (at 2.13—2.26 KPa (lit.,[6b] 97—97.5 °C at 2.6 KPa).

A mixture of concentrated aqueous HCl (20 ml) and ethanol (140 ml) containing HCl (26 g) was added dropwise to a stirred solution of 2-hydroxyvinylacetonitrile (72.0 g, 0.87 mol) in ethanol (280 ml) at 70 °C. Stirring was continued for 3 h. After the mixture had been cooled the NH_4Cl was filtered off and washed with dry ethanol, and the combined organic solutions were evaporated and distilled to give the title compound (53.5 g, 47.3%, b.p. 70 °C at 1.6 KPa) (lit.,[6b] 67—68 °C at 2.0 KPa). Ethyl 2-hydroxybut-3-enoate (53.5 g, 0.41 mol) was treated with acetic anhydride (41 ml, 0.43 mol) in the presence of sodium acetate (5.05 g) at 10—15 °C. The mixture was kept overnight at room temperature, after which it was stirred at 80 °C for 0.5 h, cooled, poured onto ice (500 g), and extracted with CH_2Cl_2 (3 × 200 ml). The combined organic extracts were washed with 5% aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated to dryness. The crude product was purified by distillation under reduced pressure (86—88 °C at 1.33 KPa) to give compound (**9**) (57.13 g, 81.0%) (lit.,[6a] 89 °C at 2.0 KPa) (Found: C, 55.7; H, 7.2. Calc. for $C_8H_{12}O_4$; C, 55.8; H, 7.05%); $\nu_{max.}$(film) 2 950 (CH), 1 740br (CO), and 1 200 and 1 010 cm^{-1} (C–O–C); δ_H(60 MHz) 1.25 (3 H, t, *J* 7 Hz, CH_3CH_2), 2.13 (3 H, s, CH_3CO), 4.20 (2 H, q, *J* 7 Hz, CH_2CH_3), and 5.23—6.25 (4 H, m, CH_2=CHCH).

Ethyl Acetoxy-(3-methyl-4,5-dihydroisoxazol-5-yl)acetate (**10**).—A mixture of nitroethane (13.4 ml, 0.19 mol), triethylamine (2.4 ml, 17 mmol), and dry benzene (65 ml) was added to a solution of ethyl 2-acetoxybut-3-enoate (**9**) (28 g, 0.16 mol) and phenyl isocyanate (39 ml, 0.35 mol) in dry benzene (130 ml)

in one portion under nitrogen. The reaction mixture started to reflux. Refluxing was continued for 1 h to complete the reaction. After cooling, the *N,N'*-diphenylurea was filtered off and the solution evaporated to dryness under reduced pressure. The crude product was purified by column chromatography (500 g of adsorbent, chloroform–acetone, 95:5) to furnish *compound* (**10**) as an oil (28.0 g, 75%) (Found: C, 52.6; H, 6.6; N, 6.4. $C_{10}H_{15}NO_5$ *requires* C, 52.4; H, 6.6; N, 6.1%); $\nu_{max.}$(film) 1 740—1 750 (CO), 1 600 (C=N), 1 220—1 200 (C–O–C), and 1 020—1 000 cm^{-1} (C–O–C); n.m.r. data for the *erythro*-acetoxy ester (**10a**) were obtained by subtraction of the spectrum of (**10b**) from the spectrum of the diastereoisomeric mixture (**10**): δ_H(100 MHz) 1.28 (3 H, t, *J* 7 Hz, CH_3CH_2), 2.00 (3 H, s, Me), 2.14 (3 H, s, CH_3CO), 2.9—3.2 (2 H, m, 4-H_2), 4.22 (2 H, q, *J* 7 Hz, CH_2CH_3), 4.8—5.1 (1 H, m, 5-H), and 5.2 (1 H, d, $J_{\alpha.5}$ 3 Hz, α-H); δ_C(25 MHz) 12.72 (CH_3), 14.04 (CH_3CH_2), 20.48 (CH_3CO), 39.69 (C-4), 61.90 (CH_2CH_3), 73.04 (C-α), 78.04 (C-5), 155.21 (C-3), 167.14 (CH_3CO), and 169.92 (CO_2Et).

threo-*Ethyl Acetoxy*(3-*methyl*-4,5-*dihydroisoxazol*-5-*yl*)*acetate* (**10b**).—The solution of the *threo*-alcohol (**11b**) (0.32 g, 1.7 mmol) in CH_2Cl_2 (5 ml) was stirred with acetic anhydride (0.18 ml, 1.9 mmol) at 0 °C. The mixture was kept overnight, diluted with CH_2Cl_2 (5 ml), and poured onto ice (10 g). The organic layer was separated, washed with 5% aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated to dryness. The crude product was purified by t.l.c. (R_F 0.51, CCl_4–$CHCl_3$–acetone, 5:5:3) to give *compound* (**10b**) (0.23 g, 58.7%) (Found: C, 52.6; H, 6.6; N, 6.4. $C_{10}H_{15}NO_5$ requires C, 52.4; H, 6.6; N, 6.1%); $\nu_{max.}$(film) 2 980 (C–H), 1 740 (CO), and 1 630 (C=N) cm^{-1}; δ_H(100 MHz) 1.29 (3 H, t, *J* 7 Hz, CH_3CH_2), 2.00 (3 H, t, $J_{Me.4}$ 1 Hz, Me), 2.17 (3 H, s, CH_3CO), 2.9—3.2 (2 H, m, 4-H_2), 4.25 (2 H, q, *J* 7 Hz, CH_3CH_2), 4.7—5.1 (1 H, m, 5-H), and 5.06 (1 H, d, $J_{\alpha.5}$ 3.0 Hz, α-H); δ_C(25 MHz) 12.87 (CH_3), 14.07 (CH_3CH_2), 20.51 (CH_3CO), 40.40 (C-4), 61.98 (CH_2CH_3), 73.01 (C-α), 77.84 (C-5), 155.09 (C-3), 167.20 (CH_3CO), and 170.24 (CO_2Et).

Ethyl Hydroxy(3-*methyl*-4,5-*dihydroisoxazol*-5-*yl*)*acetate* (**11**).—Sodium ethoxide (0.34 g, 5 mmol) in ethanol (4 ml) was added dropwise to a solution of the acetoxy ester (**10**) (4.28 g, 18.7 mmol) in ethanol (16 ml) at 0 °C and stirred until the starting material had been consumed (48 h). The reaction was monitored by t.l.c. (CH_2Cl_2–acetone, 4:1; I_2). The reaction mixture, neutralized by adding 10% aqueous HCl with cooling, was then evaporated to dryness under reduced pressure. The residue was taken up in saturated aqueous NaCl (10 ml) and extracted with ether (10 × 10 ml). The combined ethereal solutions were dried ($MgSO_4$) and evaporated to dryness to give the crude alcohol (**11**) (3.07 g, 88%). The diastereoisomers (**11a**) and (**11b**) were separated by column chromatography (200 g; CH_2Cl_2–acetone, 10:1).

erythro-Alcohol (**11a**) [R_F 0.52 (CH_2Cl_2–acetone, 4:1), 1.26 g, 36%] (Found: C, 51.1; H, 7.0; N, 7.6. $C_8H_{13}NO_4$ requires C, 51.3; H, 7.0; N, 7.5%); $\nu_{max.}$(film) 3 000—3 600br (OH), 2 890—2 900 (CH), 1 710 (CO), and 1 240 and 1 010 cm^{-1} (C–O–C); δ_H(100 MHz) 1.29 (3 H, t, *J* 7 Hz, CH_3CH_2), 1.98 (3 H, s, Me), 2.97 (1 H, m, J_{gem} 18 Hz, $J_{4A.5}$ 12 Hz, 4-H_A), 3.03 (1 H, m, J_{gem} 18 Hz, $J_{4B.5}$ 6 Hz, 4-H_B), 3.63 (1H, br s, OH), 4.24 (2 H, q, *J* 7 Hz, CH_2CH_3), 4.41 (1 H, d, $J_{\alpha.5}$ 3 Hz, α-H), and 4.85 (1 H, m, $J_{5.\alpha}$ 3 Hz, 5-H); δ_H(400 MHz) 1.31 (3 H, t, *J* 7.0 Hz, CH_3CH_2), 1.985 (3 H, t, $J_{4.Me}$ 1.1 Hz, Me), 2.95 (1 H, ddqd, J_{gem} 17.0 Hz, $J_{4A.5}$ 10.7 Hz, $J_{4.Me}$ 1.1 Hz, $J_{4A.\alpha}$ 0.5 Hz, 4-H_A), 3.01 (1 H, ddq, J_{gem} 17.0 Hz, $J_{4B.5}$ 7.5 Hz, $J_{4.Me}$ 1.1 Hz, 4-H_B), 3.10 (1 H, br s, OH), 4.27 (2 H, q, *J* 7.0 Hz, CH_2CH_3), 4.41 (1 H, d, $J_{\alpha.5}$ 3.2 Hz, α-H), 4.86 (1 H, ddd, $J_{4A.5}$ 10.7 Hz, $J_{4B.5}$ 7.5 Hz, $J_{5.\alpha}$ 3.2 Hz, 5-H); δ_C(25 MHz) 12.81 (CH_3), 14.13 (CH_3CH_2), 39.05 (C-4), 61.84 (CH_2CH_3), 71.75 (C-α), 80.70 (C-5), 155.82 (C-3), and 171.3 (CO).

threo-Alcohol (**11b**) [R_F 0.57 (CH_2Cl_2-acetone 4:1), 1.42 g, 40.6%, m.p. 82—83 °C (from acetone–ether)] (Found: C, 51.6; H, 7.3; N, 7.7. $C_8H_{13}NO_4$ requires C, 51.3; H, 7.0; N, 7.5%); $\nu_{max.}$(KBr) 3 300 (OH), 2 890—2 900 (CH), 1 700 (CO), and 1 205 and 1 005 cm^{-1} (C–O–C); δ_H(100 MHz) 1.31 (3 H, t, *J* 7 Hz, CH_3CH_2), 1.98 (3 H, s, Me), 3.08 (2 H, d, *J* 9 Hz, 4-H_2), 3.28 (1 H, d, $J_{OH.\alpha}$ 8 Hz, OH), 4.14 (1 H, dd, $J_{\alpha.OH}$ 8 Hz, $J_{\alpha.5}$ 2 Hz, α-H), 4.28 (2 H, q, *J* 7 Hz, CH_2CH_3), 4.90 (1 H, m, 5-H); δ_H(400 MHz) 1.33 (3 H, t, *J* 7.0 Hz, CH_3CH_2), 1.990 (3 H, t, $J_{4.Me}$ 1.1 Hz, Me), 2.95 (1 H, d, $J_{\alpha.OH}$ 8.2 Hz, OH), 3.07 (1 H, ddq, J_{gem} 17.0 Hz, $J_{4A.5}$ 10.2 Hz, $J_{4.Me}$ 1.1 Hz, 4-H_A), 3.09 (1 H, ddq, J_{gem} 17.0 Hz, $J_{4B.5}$ 8.1 Hz, $J_{4.Me}$ 1.1 Hz, 4-H_B), 4.12 (1 H, dd, $J_{\alpha.5}$ 2.2 Hz, $J_{\alpha.OH}$ 8.2 Hz, α-H), 4.31 (2 H, q, *J* 7.0 Hz, CH_2CH_3), and 4.91 (1 H, ddd, $J_{4A.5}$ 10.2 Hz, $J_{4B.5}$ 8.1 Hz, $J_{5.\alpha}$ 2.2 Hz, 5-H); δ_C(25 MHz) 12.81 (CH_3), 14.13 (CH_3CH_2), 40.45 (C-4), 62.01 (CH_2CH_3), 72.10 (C-α), 80.06 (C-5), 155.68 (C-3), and 171.53 (CO).

Selective ^1H-{^1H} n.O.e. *experiments*. Preirradiation of the resonance due to α-H of the *erythro*-alcohol (**11a**) resulted in signal enhancements of resonances due to 5-H (6%), OH (3%), and 4-H_B(2%). Preirradiation of the resonance due to α-H of the *threo*-alcohol (**11b**) resulted in signal enhancements of resonances due to 5-H (5%), OH (2%), and 4-H_B (4%).

Ethyl Methylsulphonyloxy(3-*methyl*-4,5-*dihydroisoxazol*-5-*yl*)*acetate* (**12**).—(a) Methanesulphonyl chloride (0.5 ml, 6.6 mmol) was added to a stirred solution of the *erythro*-alcohol (**11a**) (1.0 g, 5.34 mmol) in dry pyridine (0.5 ml) at 0 °C. After being stirred for 2 h, the mixture was diluted with CH_2Cl_2 (20 ml), neutralized with 10% aqueous HCl, washed with saturated brine (5 ml), and dried ($MgSO_4$). The solution was evaporated to dryness under reduced pressure and the residue crystallized from benzene–ether to give the *erythro*-mesylate (**12a**) (0.98 g, 69%), m.p. 79 °C (Found: C, 40.4; H, 5.9; N, 5.15; S, 12.1. $C_9H_{15}NO_6S$ requires C, 40.75; H, 5.7; N, 5.3; S, 12.1%); $\nu_{max.}$(KBr) 1 730 (CO), 1 345, and 1 160 cm^{-1} (SO_2O); δ_H(100 MHz) 1.32 (3 H, t, *J* 7 Hz, CH_3CH_2), 2.01 (3 H, s, Me), 2.8—3.2 (2 H, m, 4-H_2), 3.14 (3 H, s, CH_3SO_2), 4.29 (2 H, q, *J* 7 Hz, CH_2CH_3), 5.03 (1 H, m, 5-H), and 5.17 (1 H, d, $J_{\alpha.5}$ 3 Hz, α-H); δ_C(25 MHz) 12.70 (CH_3), 14.04 (CH_3CH_2), 38.73 (CH_3SO_2), 39.43 (C-4), 62.66 (CH_2CH_3), 77.98 (C-α), 78.13 (C-5), 155.62 (C-3), and 166.03 (CO).

(b) The *threo*-mesylate (**12b**) (1.08 g, 76%) was obtained as described for compound (**12a**): m.p. 85—86 °C (from benzene) (Found: C, 40.6; H, 5.7; N, 5.4; S, 11.9. $C_9H_{15}NO_6S$ requires C, 40.75; H, 5.7; N, 5.3; S, 12.1%); $\nu_{max.}$(KBr) 1 730 (CO), and 1 345 and 1 160 (SO_2O) cm^{-1}; δ_H(100 MHz) 1.34 (3 H, t, *J* 7 Hz, CH_3CH_2), 2.01 (3 H, s, Me), 2.9—3.2 (2 H, m, 4-H_2), 3.23 (3 H, s, CH_3SO_2), 4.31 (2 H, q, *J* 7 Hz, CH_2CH_3), 5.01 (1 H, d, $J_{\alpha.5}$ 3 Hz, α-H), and 5.09 (1 H, m, 5-H); δ_C(25 MHz) 12.78 (CH_3), 14.04 (CH_3CH_2), 39.26 (CH_3SO_2), 40.54 (C-4), 62.66 (CH_2CH_3), 77.90 (C-α), 78.42 (C-5), 155.56 (C-3), and 166.21 (CO).

Ethyl Iodo(3-*methyl*-4,5-*dihydroisoxazol*-5-*yl*)*acetate* (**13**).—A stirred mixture of dry sodium iodide (7.0 g, 43.75 mmol) and the mesylate (**12**) (6.12 g, 23.1 mmol) in dry acetone (60 ml) was refluxed for *ca.* 40 h. The reaction was monitored by t.l.c. (toluene–ether, 5:1; u.v., I_2; R_F 0.5). Without the precipitate being filtered off, the reaction mixture was evaporated to dryness under reduced pressure and the residue taken up in water (100 ml); the aqueous solution was saturated with sodium chloride, extracted with ether (4 × 150 ml), dried ($MgSO_4$), evaporated to dryness, and the residue chromatographed (160 g, CH_2Cl_2) to give the *iodo ester* (**13**) (6.0 g, 87.5%). An aliquot was purified by t.l.c. (benzene–ether, 5:1) to give analytically pure iodo ester (**13**) (Found: C, 32.55; H, 3.95; I, 42.5; N, 4.7. $C_8H_{12}INO_3$ requires C, 32.3; H, 4.1; I, 42.7; N, 4.7%); $\nu_{max.}$(film) 2 890—2 900 (CH), 1 710 (CO), and 1 240 and 1 040 cm^{-1}

(C–O–C); δ_H(60 MHz) 1.28 (3 H, t, *J* 7 Hz, CH_3CH_2), 1.98 (3 H, s, Me), 2.9—3.2 (2 H, m, 4-H_2), 4.17 (1 H, d, $J_{\alpha.5}$ 3 Hz, α-H), 4.23 (2 H, q, *J* 7 Hz, CH_2CH_3), and 4.65—5.10 (1 H, m, 5-H). According to its 100 MHz n.m.r. spectrum the product (**13**) is a 3:1 mixture of the *threo*- (**13b**) and *erythro*-isomers (**13a**) independent of whether the *erythro*- (**12a**) or *threo*-mesylate (**12b**) were used as starting material.

Erythro-iodo ester (**13a**): δ_H(100 MHz) 1.28 (3 H, t, *J* 7 Hz, CH_3CH_2), 2.00 (3 H, t, $J_{Me.4}$ 1 Hz, Me), 2.6—3.4 (2 H, m, 4-H_2), 4.20 (2 H, q, *J* 7 Hz, CH_2CH_3), 4.47 (1 H, d, $J_{\alpha.5}$ 7 Hz, α-H), and 4.7—5.1 (1 H, m, 5-H); δ_C(25 MHz) 12.71 (CH_3), 13.52 (CH_3CH_2), 20.72 (C-α), 42.63 (C-4), 61.88 (CH_2CH_3), 80.42 (C-5), 155.25 (C-3), and 169.00 (CO).

threo-Iodo ester (**13b**): δ_H(100 MHz) 1.29 (3 H, t, *J* 7 Hz, CH_3CH_2), 2.00 (3 H, t, $J_{Me.4}$ 1 Hz, Me), 2.5—3.4 (2 H, m, 4-H_2), 4.24 (2 H, q, *J* 7 Hz, CH_2CH_3), 4.34 (1 H, d, $J_{\alpha.5}$ 9 Hz, α-H), and 4.7—5.1 (1 H, m, 5-H); δ_C(25 MHz) 12.71 (CH_3), 13.52 (CH_3CH_2), 23.79 (C-α), 44.24 (C-4), 61.88 (CH_2CH_3), 79.90 (C-5), 154.46 (C-3), and 169.00 (CO).

Ethyl Azido(3-*methyl*-4,5-*dihydroisoxazol*-5-*yl*)*acetate* (**14**).— Sodium azide (1.51 g, 23.2 mmol) was added to a stirred solution of the iodo ester (**13**) (6.4 g, 21.5 mmol) in DMF (45 ml) at 0 °C. Stirring was continued until the starting material (**13**) was consumed (*ca.* 15 h). The reaction mixture was poured into cold water (100 ml), saturated with sodium chloride, and extracted with ether (5 × 40 ml). The ethereal solution was dried ($MgSO_4$), evaporated to dryness, and chromatographed (160 g of adsorbent, hexane–ether, 4:1) to give the *erythro*-azide (**14a**) [1.2 g, 26%, R_F 0.42 (benzene–ether, 5:1), phosphomolybdic acid] (Found: C, 45.2; H, 6.0; N, 26.5. $C_8H_{12}N_4O_3$ requires C, 45.3; H, 5.7; N, 26.4%); $\nu_{max.}$(film) 2 980—2 900 (CH), 2 150 (N_3), 1 730 (CO), and 1 250 and 1 020 cm^{-1} (C–O–C); δ_H(100 MHz) 1.32 (3 H, t, *J* 7 Hz, CH_3CH_2), 2.00 (3 H, s, Me), 2.98 (1 H, m, J_{gem}, 18 Hz, $J_{4A.5}$ 13 Hz, 4-H_A), 3.03 (1 H, m, J_{gem}, 18 Hz, $J_{4B.5}$ 5 Hz, 4-H_B), 4.27 (2 H, q, *J* 7 Hz, CH_2CH_3), 4.28 (1 H, d, $J_{\alpha.5}$ 4 Hz, α-H), and 4.96 (1 H, m, 5-H); δ_C(25 MHz) 12.72 (CH_3), 14.13 (CH_3CH_2), 40.31 (C-4), 62.31 (CH_2CH_3), 64.21 (C-α), 78.89 (C-5), 155.41 (C-3), and 167.41 (CO).

The *threo*-azide (**14b**) [1.8 g, 39.3%, R_F 0.37 (benzene–ether, 5:1), phosphomolybdic acid] (Found: C, 45.0; H, 5.8; N, 26.3. $C_8H_{12}N_4O_3$ requires C, 45.3; H, 5.7; N, 26.4%); $\nu_{max.}$(film) 2 900—2 980 (CH), 2 180 (N_3), 1 740 (CO), and 1 200 and 1 030 cm^{-1} (C–O–C); δ_H(100 MHz) 1.33 (3 H, t, *J* 7 Hz, CH_3CH_2), 2.02 (3 H, s, Me), 3.02 (1 H, m, J_{gem} 18 Hz, $J_{4A.5}$ 11 Hz, 4-H_A), 3.17 (1 H, m, J_{gem} 18 Hz, $J_{4B.5}$ 7 Hz, 4-H_B), 3.84 (1 H, d, $J_{\alpha.5}$ 4 Hz, α-H), 4.30 (2 H, q, *J* 7 Hz, CH_2CH_3), and 5.03 (1 H, m, 5-H); δ_C(25 MHz) 12.70 (CH_3), 14.10 (CH_3CH_2), 41.60 (C-4), 62.33 (CH_2CH_3), 63.86 (C-α), 79.15 (C-5), 155.65 (C-3), and 167.79 (CO).

Azides (**14a,b**) *from the Alcohols* (**11a,b**) *by the Mitsunobu Reaction.*—(a) To a solution of the *threo*-alcohol (**11b**) (374.4 mg, 2 mmol) in THF (1 ml) was added a 0.8M solution of hydrazoic acid in benzene (3 ml) followed by a solution of triphenylphosphine (0.63 g, 2.4 mmol) in THF (4 ml). A solution of di-isopropyl azodicarboxylate (446.0 mg, 2.2 mol) was then added to the above mixture at 30—36 °C. The solution was stirred for 5 h at ambient temperature, evaporated under reduced pressure and the residue purified by t.l.c. (benzene–ether, 5:1; u.v.) to give the *erythro*-azide (**14a**). This product proved to be completely identical (i.r., ^1H and ^{13}C n.m.r.) with the sample (R_F 0.42) isolated from the mixture of azides (**14a,b**).

(b) Starting with the *erythro*-alcohol (**11a**) the *threo*-azide (**14b**) was formed by using the above procedure and proved to be identical with the sample (R_F 0.37) which was obtained by column chromatography of the mixture of azides (**14a,b**).

Ethyl Amino(3-*methyl*-4,5-*dihydroisoxazol*-5-*yl*)*acetate Hydrochloride* (**15**).—The *erythro*-azide (**14a**) (1.0 g, 4.7 mmol) was dissolved in a mixture of dry ethanol (10 ml) and dry ethanol containing 1 mol/l of HCl (5 ml) and reduced by hydrogen in the presence of 10% Pd–C catalyst (0.2 g) at room temperature (12 h). The catalyst was filtered off, and the filtrate evaporated to dryness under reduced pressure (13.3 Pa); the residue when triturated with dry ether gave the *erythro*-salt (**15a**) (0.54 g, 51.5%), m.p. 163 °C (Found: C, 42.9; H, 6.8; Cl, 16.0; N, 12.9. $C_8H_{15}ClN_2O_3$ requires C, 43.15; H, 6.8; Cl, 15.9; N, 12.6%); $\nu_{max.}$(KBr) 3 300—2 600 br ($\overset{+}{N}H_3$), 1 730 (CO), and 1 220 and 1 010 cm^{-1} (C–O–C); δ_H(100 MHz; D_2O) 1.29 (3 H, t, *J* 7 Hz, CH_3CH_2), 2.01 (3 H, s, Me), 3.35 (1 H, m, J_{gem} 18 Hz, $J_{4A.5}$ 12 Hz, 4-H_A), 3.45 (1 H, m, J_{gem} 18 Hz, $J_{4B.5}$ 6 Hz, 4-H_B), 4.29 (2 H, q, *J* 7 Hz, CH_2CH_3), 4.31 (1 H, d, $J_{\alpha.5}$ 3 Hz, α-H), and 5.08 (1 H, m, 5-H); δ_C(25 MHz; D_2O) 14.56 (CH_3), 16.06 (CH_3CH_2), 44.23 (C-4), 58.74 (C-α), 66.61 (CH_2CH_3), 80.82 (C-5), 162.72 (C-3), and 171.00 (CO).

The *threo*-azide (**14b**) was similarly reduced to give the *threo*-salt (**15b**) (0.58 g, 55.3%), m.p. 167 °C (Found: C, 43.3; H, 6.9; Cl, 15.6; N, 12.6. $C_8H_{15}ClN_2O_3$ requires C, 43.15; H, 6.8; Cl, 16.0; N, 12.6%); $\nu_{max.}$(KBr) 3 300—2 400br ($\overset{+}{N}H_3$), 1 740 (CO), and 1 230 and 1 020 cm^{-1} (C–O–C); δ_H(100 MHz; D_2O) 1.32 (3 H, t, *J* 7 Hz, CH_3CH_2), 2.03 (3 H, s, Me), 3.1—3.6 (2 H, m, 4-H_2), 4.23 (1 H, d, $J_{\alpha.5}$ 6 Hz, α-H), 4.34 (2 H, q, *J* 7 Hz, CH_2CH_3), and 5.06 (1 H, m, 5-H); δ_C(25 MHz; D_2O) 14.65 (CH_3), 16.03 (CH_3CH_2), 44.61 (C-4), 58.09 (C-α), 66.78 (CH_2CH_3), 79.89 (C-5), 162.67 (C-3), and 171.09 (CO).

The ethereal mother liquors of *erythro*- and *threo*-salts (**15a,b**) were evaporated to give ethyl 5-methylpyrrole-2-carboxylate (**20**) (0.26 g, 36% and 0.29 g, 40.1%. respectively), m.p. 95—96 °C (from ether) [lit.,[13] 100 °C (from methanol)]; $\nu_{max.}$(KBr) 3 350 (NH), 1 690 (CO), and 1 230 and 1 035 cm^{-1} (C–O–C); the ^1H n.m.r. spectrum of compound (**20**) was identical with the published[14] spectrum.

Ethyl t-Butoxycarbonylamino(3-*methyl*-4,5-*dihydroisoxazol*-5-*yl*)*acetate* (**16**).—(a) Di-t-butyl oxydiformate (322 mg, 1.8 mmol) and triethylamine (0.17 ml, 1.2 mmol) were successively added to a solution of the *erythro*-salt (**15a**) (274 mg, 1.2 mmol) in dry ethanol (5 ml). The mixture was stirred at ambient temperature for 8 h and evaporated to dryness under reduced pressure; the residue was taken up in CH_2Cl_2 (15 ml), and the solution washed with saturated brine (2 × 3 ml), dried ($MgSO_4$), and evaporated to dryness. The residue was triturated with hexane–ethyl acetate to furnish the *erythro*-compound (**16a**) (0.17 g, 48.4%), m.p. 55 °C (Found: C, 54.7; H, 7.5; N, 9.6. $C_{13}H_{22}N_2O_5$ requires C, 54.5; H, 7.75; N, 9.8%); $\nu_{max.}$(KBr) 3 410 (NH), 1 720 and 1 690 (CO), and 1 220 and 1 020 cm^{-1} (C–O–C); δ_H(100 MHz) 1.28 (3 H, t, *J* 7 Hz, CH_3CH_2), 1.45 (9 H, s, 3 × Me), 1.97 (3 H, s, Me), 2.9—3.3 (2 H, m, 4-H_2), 4.21 (2 H, q, *J* 7 Hz, CH_2CH_3), 4.30 (1 H, dd, $J_{\alpha.5}$ 4 Hz, $J_{\alpha.NH}$ 8 Hz, α-H), 4.77 (1 H, m, 5-H), and 5.54 (1 H, d, $J_{NH.\alpha}$ 8 Hz, NH); δ_C(25 MHz) 12.81 (CH_3), 14.07 (CH_3CH_2), 28.29 [$(CH_3)_3C$], 41.45 (C-4), 56.84 (C-α), 61.78 (CH_2CH_3), 79.48 [$(CH_3)_3C$], 80.38 (C-5), 155.27 (CONH), 155.68 (C-3), and 169.34 (CO_2Et).

(b) The *threo*-compound (**16b**) was similarly prepared as described for the *erythro*-isomer (**16a**) starting with the *threo*-salt (**15b**) (446 mg, 2 mmol). The dry residue of the CH_2Cl_2 solution was triturated with ether to give the *threo*-compound (**16b**) (0.63 g, 71%), m.p. 71—72 °C (from ethyl acetate–ether) (Found: C, 54.2; H, 7.5; N, 9.95. $C_{13}H_{22}N_2O_5$ requires C, 54.5; H, 7.75; N, 9.8%); $\nu_{max.}$(KBr) 3 320 (NH), 1 740 and 1 690 (CO), and 1 220 and 1 020 cm^{-1} (C–O–C); δ_H(100 MHz) 1.30 (3 H, t, *J* 7 Hz, CH_3CH_2), 1.45 (9 H, s, 3 × Me), 1.97 (3 H, s, Me), 2.94 (1 H, m, J_{gem} 17 Hz, $J_{4A.5}$ 11 Hz, 4-H_A), 3.08 (1 H, m, J_{gem} 17 Hz,

$J_{4B.5}$ 8 Hz, 4-H_B), 4.25 (2 H, q, J 7 Hz, CH_2CH_3), 4.45 (1 H, m, α-H), and 5.13 (2 H, m, 5-H and N–H); δ_C(25 MHz) 12.84 (CH_3), 14.13 (CH_3CH_2), 28.29 [$(CH_3)_3C$], 41.22 (C-4), 56.57 (C-α), 61.87 (CH_2CH_3) 79.62 (C-5), 80.27 [$(CH_3)_3C$], 155.82 (C-3), 156.32 (CONH), and 169.54 (CO_2Et).

t-Butoxycarbonylamino(3-*methyl*-4,5-*dihydroisoxazol*-5-*yl*)-*acetic Acid* (**17**).—(a) Di-t-butyl oxydiformate (1.18 g, 6.8 mmol), t-butyl alcohol (1.6 ml), and aqueous KOH (4.5 ml, 0.76 g, 13.5 mmol) were successively added to a suspension of the *erythro*-salt (**15a**) (1.00 g, 4.5 mmol) in water (4.5 ml). The mixture was stirred at ambient temperature for 1 day, acidified with 10% HCl at 0 °C, saturated with NaCl, and extracted with ethyl acetate (5 × 50 ml). The combined organic solutions were dried ($MgSO_4$) and evaporated under reduced pressure to give the *erythro*-acid (**17a**) (0.74 g, 63.6%), m.p. 139 °C (from ethyl acetate–hexane) (Found: C, 51.35; H, 7.0; N, 11.1. $C_{11}H_{18}N_2O_5$ requires C, 51.15; H, 7.0; N, 10.85%); $\nu_{max.}$(KBr) 3 370 (NH), 3 180—2 670br (OH), and 1 710 and 1 700 cm^{-1} (CO); δ_H[100 MHz; $(CD_3)_3SO$] 1.38 (9 H, s, 3 × Me), 1.87 (3 H, s, Me), 2.88 (1 H, m, J_{gem} 18 Hz, $J_{4A.5}$ 11 Hz, 4-H_A), 3.00 (1 H, m, J_{gem} 18 Hz, $J_{4B.5}$ 7 Hz, 4-H_B), 4.07 (1 H, dd, $J_{\alpha.5}$ 4 Hz, $J_{\alpha.NH}$ 8 Hz, α-H), 4.70 (1 H, m, 5-H), and 7.20 (1 H, d, $J_{NH.\alpha}$ 8 Hz, NH); δ_C[25 MHz; $(CD_3)_2SO$] 12.64 (CH_3), 28.29 [$(CH_3)_3C$], 40.78 (C-4), 56.29 (C-α), 78.55 [$(CH_3)_3C$], 78.69 (C-5), 155.68 (C-3 and CONH), and 171.48 (CO_2H).

(b) The *threo*-acid (**17b**), m.p. 176 °C (from ethyl acetate–hexane (Found: C, 51.4; H, 6.9; N, 10.85. $C_{11}H_{18}N_2O_5$ requires C, 51.15; H, 7.0; N, 10.85%); $\nu_{max.}$(KBr) 3 220 (NH), 3 150—2 500br (OH), and 1 710br cm^{-1} (CO); δ_H[100 MHz; $(CD_3)_2SO$] 1.38 (9 H, s, 3 × Me), 1.87 (3 H, s, Me), 2.80 (1 H, m, J_{gem} 18 Hz, $J_{4A.5}$ 10 Hz, 4-H_A), 3.08 (1 H, m, J_{gem} 18 Hz, $J_{4B.5}$ 8 Hz, 4-H_B), 4.12 (1 H, dd, $J_{\alpha.5}$ 5 Hz, $J_{\alpha.NH}$ 9 Hz, α-H), 4.79 (1 H, m, 5-H), and 6.77 (1 H, d, $J_{NH.\alpha}$ 9 Hz, NH); δ_C[25 MHz; $(CD_3)_2SO$] 12.67 (CH_3), 28.26 [$(CH_3)_3C$], 40.99 (C-4), 56.29 (C-α), 78.75 [C-5 and $(CH_3)_3C$], 156.03 (C-3 and CONH), and 171.39 (CO_2H) was similarly obtained in 70% yield starting with the *threo*-salt (**15b**).

Amino(3-*methyl*-4,5-*dihydroisoxazol*-5-*yl*)*acetic Acid Hydrochloride* (**18**).—(a) Ethyl acetate (4 ml) containing 3 mol/l of HCl was added to a solution of *erythro*-acid (**17a**) in ethyl acetate (3 ml) and the mixture stirred for 1 day. The crystalline product was filtered off and washed with dry ether to give the *erythro*-acid salt (**18a**) (0.25 g, 55.3%), m.p. 226—232 °C (decomp.) (Found: C, 36.9; H, 5.9; Cl, 17.8; N, 14.3. $C_6H_{11}ClN_2O_3$ requires C, 37.0; H, 5.7; Cl, 18.2; N, 14.4%); $\nu_{max.}$(KBr) 3 200—2 200br (OH + $\overset{+}{N}H_3$) and 1 740 cm^{-1} (CO) δ_H(100 MHz; D_2O) 2.00 (3 H, s, Me), 3.32 (1 H, m, J_{gem} 18 Hz, $J_{4A.5}$ 12 Hz, 4-H_A), 3.40 (1 H, m, J_{gem} 18 Hz, $J_{4B.5}$ 6 Hz, 4-H_B), 4.24 (1 H, d, $J_{\alpha.5}$ 3 Hz, α-H), and 5.12 (1 H, m, 5-H); δ_C(25 MHz, D_2O) 14.65 (CH_3), 43.70 (C-4), 58.50 (C-α), 80.29 (C-5), 163.05 (C-3), and 171.91 (CO).

(b) The *threo*-acid salt (**18b**) [m.p. 236 °C (decomp.) (Found: C, 37.0; H, 6.0; Cl, 18.1; N, 14.5. $C_6H_{11}ClN_2O_3$ requires C, 37.0; H, 5.7; Cl, 18.2; N, 14.4%); $\nu_{max.}$(KBr) 3 300—2 350br (OH, $\overset{+}{N}H_3$), 1 740 cm^{-1} (CO); δ_H(100 MHz; D_2O) 2.03 (3 H, s, Me), 3.27 (1 H, m, J_{gem} 18 Hz, $J_{4A.5}$ 10 Hz, 4-H_A), 3.44 (1 H, m, J_{gem} 18 Hz, $J_{4B.5}$ 6 Hz, 4-H_B), 4.13 (1 H, d, J 7 Hz, α-H), and 5.03 (1 H, m, 5-H); δ_C(25 MHz; D_2O) 14.74 (CH_3), 44.81 (C-4), 58.36 (C-α), 79.74 (C-5), 162.72 (C-3), and 172.32 (CO)] was similarly prepared in 53.45% yield, starting with the *threo*-acid (**17b**).

Amino(3-*methyl*-4,5-*dihydro-isoxazol*-5-*yl*)*acetic Acid* (**19**).—(a) An aqueous solution of the *erythro*-acid salt (**18a**) (20 ml, 0.2 g, 1.03 mmol) was passed through an ion-exchange column (5 ml of Amberlite IR-45, OH form), and evaporated under reduced pressure to give the *erythro*-acid (**19a**) (0.1 g, 61.4%), m.p. > 300 °C (Found: C, 45.6; H, 6.7; N, 17.65. $C_6H_{10}N_2O_3$ requires C, 45.6; H, 6.4; N, 17.7%); $\nu_{max.}$(KBr) 3 300—2 500br ($\overset{+}{N}H_3$), 1 580 and 1 640sh cm^{-1} (CO_2^-); δ_H(100 MHz; D_2O) 2.00 (3 H, s, Me), 3.19 (1 H, m, J_{gem} 18 Hz, $J_{4A.5}$ 11 Hz, 4-H_A), 3.30 (1 H, m, J_{gem} 18 Hz, $J_{4B.5}$ 7 Hz, 4-H_B), 4.01 (1 H, d, $J_{\alpha.5}$ 3.5 Hz, α-H), and 5.09 (1 H, m, 5-H); δ_C(25 MHz; D_2O) 14.71 (CH_3), 42.59 (C-4), 59.03 (C-α), 80.59 (C-5), 162.52 (C-3), and 173.46 (CO_2^-).

(b) The *threo*-acid (**19b**) [m.p. > 300 °C (Found: C, 45.5; H, 6.6; N, 18.0. $C_6H_{10}N_2O_3$ requires C, 45.6; H, 6.4; N, 17.7%); $\nu_{max.}$(KBr) 3 300—2 400br and 2 090 ($\overset{+}{N}H_3$), and 1 640 and 1 590 cm^{-1} (CO_2^-); δ_H(100 MHz; D_2O) 2.04 (3 H, s, Me), 3.24 (1 H, m, J_{gem} 18 Hz, $J_{4A.5}$ 10 Hz, 4-H_A), 3.37 (1 H, m, J_{gem} 18 Hz, $J_{4B.5}$ 7 Hz, 4-H_B), 3.77 (1 H, d, J 7.5, α-H), and 4.95 (1 H, m, 5-H); δ_C(25 MHz; D_2O) 14.71 (CH_3), 44.70 (C-4), 59.76 (C-α), 80.62 (C-5), 162.67 (C-3), and 174.02 (CO_2^-)] was similarly obtained in 67.5% yield starting with the *threo*-acid salt (**18b**).

3-*Methyl*-4,5-*dihydroisoxazol*-5-*ylacetonitrile* (**21**).—A mixture of nitroethane (6.55 g, 0.1 mol), triethylamine (1.0 ml, 7 mmol), and dry benzene (30 ml) was added dropwise to a stirred solution of allyl cyanide (6.7 g, 0.1 mol) and phenyl isocyanate (22 ml, 0.2 mol) in dry benzene (50 ml) within 10 min. The temperature rose to 60 °C. The reaction mixture was refluxed for 2 h under nitrogen to complete the reaction. The mixture was cooled and the *N.N'*-diphenylurea filtered off and evaporated to dryness under reduced pressure to give an oil which was purified by distillation (b.p. 96—100 °C at 8.0 Pa) to give the *nitrile* (**21**) (7.6 g, 61%) (Found: C, 57.9; H, 6.7: N, 22.4. $C_6H_8N_2O$ requires C, 58.05; H, 6.5; N, 22.6%); $\nu_{max.}$(film) 2 890—2 900 (C–H), 2 250 (C≡N), and 1 620 cm^{-1} (C=N); δ_H(100 MHz) 1.99 (3 H, t, $J_{Me.4}$ 1 Hz, Me), 2.69 (2 H, d, $J_{\alpha.5}$ 6 Hz, CH_2CN), 2.81 (1 H, m, J_{gem} 17.6 Hz, $J_{4A.5}$ 7.4 Hz, 4-H_A), 3.22 (1 H, m, J_{gem} 17.6 Hz, $J_{4B.5}$ 2.6 Hz, 4-H_B), and 4.8 (1 H, m, $J_{5.4A}$ 7.4 Hz, $J_{5.4B}$ 2.6 Hz, $J_{5.\alpha}$ 6 Hz, 5-H); δ_C(25 MHz) 12.74 (CH_3), 23.48 (CH_2CN), 43.42 (C-4), 74.68 (C-5), 117.01 (C≡N), and 155.7 (C-3).

5-*Diethoxymethyl*-3-*methyl*-4,5-*dihydroisoxazole* (**22**).—This compound was prepared in a similar fashion to compound (**21**) starting with acrylaldehyde diethyl acetal (1.43 g, 11 mmol). The crude product was purified by distillation to give *compound* (**22**) (1.22 g, 60%), b.p. 64 °C (6.6 Pa) (Found: C, 57.4; H, 8.9; N, 7.2. $C_9H_{17}NO_3$ requires C, 57.7; H, 9.2; N, 7.5%); $\nu_{max.}$(film) 2 880—2 980 (CH), 1 620 (C=N), and 1 050 cm^{-1} (C–O–C); δ_H(100 MHz) 1.19 (3 H, t, J 7 Hz, CH_3CH_2), 1.23 (3 H, t, J 7 Hz, CH_3CH_2), 1.98 (3 H, t, $J_{Me.4}$ 1 Hz, Me), 2.96 (2 H, m, $J_{4.5}$ 8.2 Hz, $J_{4.Me}$ 1 Hz, 4-H_2), 3.67 (4 H, m, CH_2CH_3), and 4.4—4.7 (2 H, m, 5-H, α-H); δ_C (25 MHz) 12.89 (CH_3), 15.29 (CH_3CH_2), 15.38 (CH_3CH_2), 39.63 (C-4), 63.29 (CH_3CH_2), 64.26 (CH_3CH_2), 80.37 (C-5), 102.42 (C-α), and 155.43 (C-3).

Ethyl 3-(N-*Phenylcarbamoyl*)-4,5-*dihydroisoxazol*-5-*carboxylate* (**23**).—A mixture of nitromethane (10 ml, 0.18 mol), triethylamine (1.5 ml, 11 mmol), and benzene (30 ml) was added to a solution of phenyl isocyanate (30 ml, 0.3 mol), ethyl acrylate (12.0 ml, 0.11 mol), and benzene (50 ml). The mixture was stirred at room temperature for 3 h and then refluxed for 8 h. After the mixture had cooled the *N,N'*-diphenylurea was filtered off, the filtrate evaporated to dryness, and the residue distilled to give compound (**23**) (13.0 g, 45.1%), b.p. 200 °C (13.3 Pa) which crystallised with time, m.p. 115 °C (from CH_2Cl_2–pentane) (Found: C, 59.3; H, 5.3; N, 10.6. $C_{13}H_{14}N_2O_4$ requires C, 59.5; H, 5.4; N, 10.7%); $\nu_{max.}$(KBr) 3 370 (NH), 1 740 and 1 660 (CO), and 1 200 and 1 010 cm^{-1} (C–O–C); δ_H(60 MHz) 1.21 (3 H, t, J 7 Hz, CH_3CH_2), 3.40 (2 H, d, $J_{4.5}$ 9 Hz, 4-H_2), 4.15 (2 H, q, J 7 Hz, CH_2CH_3), 5.03 (1 H, t, $J_{5.4}$ 9 Hz, 5-H), 7.10—7.50 (5 H, m, Ph), and 8.69 (1 H, s, NH).

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