Simple and Condensed β-Lactams. Part 7.[1] Side Chain Extensions of Some Azetidin-2-one Derivatives, and the Formation of Melillo's Lactone, a Strategic Intermediate in the Total Synthesis of Thienamycin, from 3-Acetyl-1-benzyl-4-cyanomethylazetidin-2-one

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The oxoazetidinecarboxylic acids (**2a**) and (**2b**) and the homologous acid (**8b**) were converted by treatment of their chlorides with ethyl diazoacetate into the diazo esters (**4a**, **b**), and (**10b**), respectively. Irradiation of the diazo ester (**4b**) afforded the diethyl and ethyl hydrogen malonates (**17**) and (**18**), respectively. Attempted thermal decarboxylation of the latter resulted in profound degradation to give a mixture of the isomeric compounds (**19a**, **b**). $NaBH_4$ reduction at −78 °C of the diazo ester (**4d**) gave mixtures of the diastereoisomers of the diazo esters (**4e**) and (**20**). The (hydroxymethyl)-azetidinone (**6b**) was converted *via* the aldehyde (**5b**) and the nitroethyl derivative (**22**) into the acetals (**23**) and (**25**). Attempts to convert the nitrile (**7a**) into either the acid (**8a**) or the ester (**9a**) in acceptable yields, failed. The nitriles (**7g**) and (**7e**) [obtained in two steps from the nitriles (**7c**) and (**7b**), respectively] were converted by refluxing hydrochloric acid into Melillo's lactone (**28**) (the key intermediate of a practical synthesis of the carbapenem antibiotic thienamycin) and its *N*-unsubstituted analogue (**30**), respectively.

In earlier parts of the present series the syntheses of the racemic ethyl 4-oxoazetidine-2-carboxylates (**1a**)[2] and (**1b**, **c**)[3] as well as their conversions into the corresponding acids (**2a**, **b**), the 4-hydroxymethyl- (**6a**—**c**) and 4-cyanomethylazetidin-2-ones (**7a**—**c**) have been described. The acids (**2a**, **b**) were converted, *via* the diazoketones (**3a**, **b**), into the corresponding 4-oxoazetidin-2-ylacetic acids (**8a**, **b**)[4] which were considered as potential intermediates for the synthesis of certain natural carbapenem antibiotics and their analogues.[5] Because of the highly toxic and explosive nature of the diazomethane used in these reactions it was felt desirable to develop other methods for chain extensions.

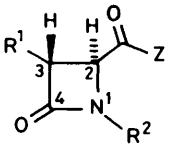
The acids (**2a**, **b**), the hydroxymethyl derivative (**6b**), and the 4-cyanomethylazetidin-2-ones (**7a**—**c**) were selected as the starting compounds for these studies. [In the case of the compounds (**7**) their synthesis, starting with the corresponding compounds (**6**), itself comprises the chain-extension step. The task here was therefore the transformation of the nitrile group into a more favourable functionality.] In addition, some extensions of the acetic acid side chains of compounds (**8a**) and (**8b**) were carried out.

Successive treatment of the acids (**2a**) and (**2b**) with thionyl chloride and an excess of ethyl diazoacetate furnished the ethyl α-diazo-β-[4-oxoazetidin-2-yl]-β-oxopropionates (**4a**) and (**4b**) in moderate yields. Irradiation of compound (**4b**) in ethanol and aqueous tetrahydrofuran (THF) furnished the malonic acid derivatives (**17**) and (**18**) in excellent and moderate yields, respectively. Attempted thermal decarboxylation of compound (**18**) led to the formation of a mixture of compounds (**19a**) and (**19b**) rather than the expected acetic acid derivative (**9b**). The structure of the actual reaction product follows from its i.r., ^1H n.m.r., and mass spectra. Compounds (**19a**) and (**19b**) were formed in moderate yield as a by-product in the irradiation of compound (**4b**) in aqueous THF. Transacetalization of compound (**4b**) with acetone in the presence of aqueous perchloric acid furnished the acetyl derivative (**4d**) which could be reduced with $NaBH_4$ in anhydrous methanol at −78 °C to give a mixture of the two 1′-epimers of compound (**4e**) and of the diastereoisomers of compound (**20**).

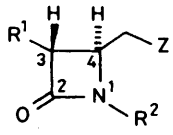
Activation of the homologous acid (**8a**) by treatment with ethyl chloroformate, followed by treatment with ethyl diazoacetate afforded the ethyl ester (**9a**) of the starting acid rather than the expected α-diazoacetoacetate, presumably as the result of the expulsion of CO_2 from the mixed anhydride (**11a**), *cf.* ref. 6. Activation of the acid (**8b**) in the form of its chloride, followed by treatment with ethyl diazoacetate, on the other hand, furnished the α-diazoacetoacetate (**10b**) in low yield; the latter had been obtained before by diazo exchange.[4]

Oxidation of the hydroxymethyl derivative (**6b**) with Me_2SO in the presence of trifluoroacetic anhydride and triethylamine led to the formation of the aldehyde (**5b**) which, without isolation, was treated with nitromethane to yield the nitro alcohol (**21**) as an epimeric mixture. *O*-Acetylation followed by $NaBH_4$ reduction furnished the nitroethyl derivative (**22**), accompanied in some cases by small amounts of the acetate of the nitro alcohol (**21**). The modified Nef reaction of compound (**22**) led to the acetal (**23**) which was oxidatively *N*-deprotected. The resulting compound (**24**) was allowed to react with *p*-nitrobenzyl glyoxylate to give compound (**25**) as an epimeric mixture. Compounds of type (**25**) had been converted into carbapenems of type (**26**) before.[7]

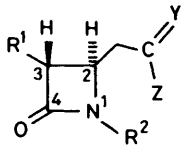
Treatment of compound (**7a**) in dry ether or dry ether–CH_2Cl_2 mixtures with anhydrous ethanol and dry HCl gas, followed by aqueous alkaline work-up gave the amide (**12a**) as the main product with, at best, small amounts of the desired ester (**9a**) and of the ring-opened product (**27**) as by-products. Attempts to hydrolyse the amide (**12a**) selectively to the acid (**8a**) were, as could be expected, unsuccessful. *N*-Nitrosation prior to hydrolysis did not help either: the *N*-nitroso derivative (**13a**) was hydrolysed with 0.1M-NaOH in ethanol to the amide



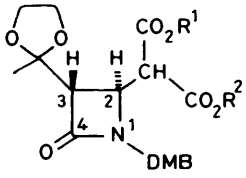
(1a–c) Z = OEt
(2a,b) Z = OH
(3a,b) Z = CHN_2*
(4a,b,d,e) Z = CN_2CO_2Et
(5b) Z = H*



(6a–c) Z = OH
(7a–g) Z = CN

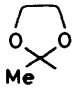


(8a,b) Y = O, Z = OH
(9a,b) Y = O, Z = OEt
(10a,b) Y = O, Z = CN_2CO_2Et
(11a,b) Y = O, Z = OCO_2Et
(12a) Y = O, Z = NH_2
(13a) Y = O, Z = NHNO
(14a) Y = S, Z = NH_2
(15a) Y = $\overset{+}{N}H_2Cl^-$, Z = OEt
(16a) Y = $\overset{+}{N}H_2I^-$, Z = SMe



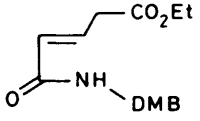
(17) $R^1 = R^2$ = Et
(18) R = Et, R = H†

(1)–(16)

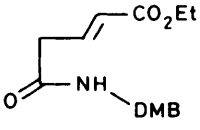
	R^1	R^2
a	H	DMB
b		DMB
c		CH_2Ph
d	Ac	DMB
e		DMB†
f	Ac	CH_2Ph
g		CH_2Ph†

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

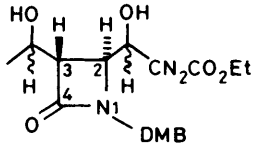
* The numbering differs from that shown. † Diastereoisomeric mixture.



(19a)

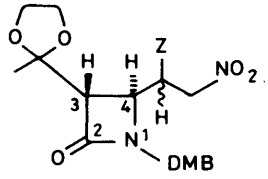


(19b)

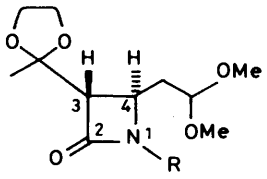


(20)†

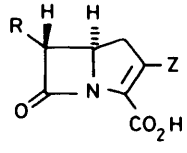
DMB = 2,4-$(MeO)_2C_6H_3CH_2$



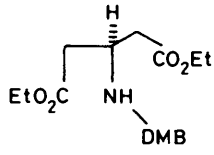
(21) Z = OH*
(22) Z = H



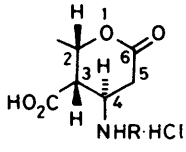
(23) R = DMB
(24) R = H
(25) R = $CHOHCO_2CH_2C_6H_4NO_2$-p*



(26)



(27)



(28) R = CH_2Ph
(29) R = DMB
(30) R = H

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

* Diastereoisomeric mixture.

(12a), while its treatment with 60% aqueous HBF_4 in a mixture of ether and chloroform resulted, even at 0 °C, in the destruction of the lactam ring. Addition of hydrogen sulphide to the nitrile group of compound (7a) furnished the thioamide (14a). However, treatment of the latter with ethyl chloroformate did not give the expected imidate hydrochloride (15a) [which could, presumably[8] have been converted into the acid (8a)]; instead, dark tarry products were formed. Methylation of the thioamide (14a) with methyl iodide gave the *S*-methyl derivative (16a).

Attempted catalytic transfer hydrogenation of compound (7a) with formic acid as well as attempted catalytic hydrogenation in the presence of *N,N'*-diphenylethylenediamine (as a trap for the desired aldimine, *cf.* ref. 9) resulted, according to the i.r. spectra of the products, in the destruction of the lactam ring.

Since all our attempts at selectively hydrolysing the nitrile group of compound (7a) to the carboxyl group failed, we decided to hydrolyse simultaneously both this group and the lactam ring of the related compounds (7e) and (7g). The latter were obtained, in the form of mixtures of their 1'-epimers, by transacetalization of compounds (7b) and (7c) with acetone in the presence of aqueous perchloric acid, and subsequent reduction with $NaBH_4$ of the resulting 3-acetyl derivatives (7d) and (7f), respectively. When refluxed with concentrated aqueous HCl, compound (7g) yielded Melillo's lactone (28)[10] as a single crystalline substance; the 6'-epimer of the latter was either decomposed during the reaction or did not crystallize from the reaction mixture. The product proved identical (i.r. and ^1H n.m.r.) with an authentic sample obtained as described in ref. 10. Compound (7e), when similarly treated, gave, instead of the expected analogue (29), the *N*-deprotected derivative (30) which proved identical (i.r. and ^1H n.m.r.) with an authentic sample obtained by reductive debenzylation of compound (28) as described in ref. 10. Whether ring transformation precedes *N*-deprotection or the order of the two events is the reverse, is not clear. However, in any case, the ease of the cleavage of the 2,4-dimethoxybenzyl group reflects the enhanced stability of the 2,4-dimethoxybenzyl relative to the benzyl cation.

Experimental

M.p.s are uncorrected. I.r. spectra were obtained with a Spektromom 2000 instrument (Hungarian Optical Works, Budapest). Unless otherwise stated, ^1H n.m.r. spectra were obtained at 60 and 100 MHz with Perkin-Elmer R 12 and Varian XL-100 spectrometers, ^{13}C n.m.r. spectra at 25.2 MHz with a Varian XL-100 instrument in C^2HCl_3 solutions, using $SiMe_4$ as the internal reference. The mass spectrum of compound (19) was recorded with an AEI MS 902 double

focussing instrument at 70 eV, using the direct insertion system; all other mass spectra were obtained with a JEOL JMS-O1SG-2 spectrometer. Kieselgel 60 (0.063—0.200 mm; Merck) was used as the adsorbent for column chromatography at normal pressure, and Kieselgel G (Merck) for medium pressure (200 kPa) chromatography. Kieselgel $PF_{254+366}$ (Merck) was used as the adsorbent in t.l.c.

Ethyl α-Diazo-β-[4-oxoazetidin-2-yl]-β-oxopropionates (**4a**, **b**).—Thionyl chloride (0.37 ml, 5.0 mmol) was added to solutions of the acids (**2a**) and (**2b**) respectively (5.0 mmol) in dry CH_2Cl_2 (10 ml), containing one drop of DMF, with continuous stirring at 0 °C (bath temperature). Stirring was continued for 2 h at this temperature. Ethyl diazoacetate [11] (1.7 g, 15 mmol) was added, and the mixtures were stirred for 70 h at room temperature until the acid chlorides were almost completely consumed. Chromatographic work-up (benzene–acetone, 7:3) gave the ester (**4a**) (0.54 g, 30%) as an oil, and the ester (**4b**) (1.0 g, 45%) as a crystalline substance, m.p. 98 °C (from ether).

Compound (**4a**) (Found: C, 56.35; H, 5.55; N, 11.8. $C_{17}H_{19}N_3O_6$ requires C, 56.50; H, 5.30; N, 11.65%), $\nu_{max.}$ (film) 2 180, 1 750, 1 710, and 1 650 cm^{-1}; δ_H (60 MHz) 1.33 + 4.26 (t + q, *J* 7.1 Hz, CO_2Et), 2.78 + 3.22 (AB, J_{gem} 14.7, J_{vic} 2.7 and 5.5 Hz, respectively, 3-H_2), 3.78 (s, 2 × MeO), 4.1—4.85 (m, 2-H + NCH_2Ar), 6.35—6.55 (m, 3′-H + 5′-H), 7.15 (d, *J* 9 Hz, 6′-H).*†

Compound (**4b**) (Found: C, 56.4; H, 5.7; N, 9.65. $C_{21}H_{25}N_3O_8$ requires C, 56.40; H, 5.65; N, 9.40%); $\nu_{max.}$ (film) 2 190, 1 760, 1 720, and 1 650 cm^{-1}; δ_H (100 MHz) 1.29 + 4.25 (t + q, *J* 7.1 Hz, CO_2Et), 1.41 (s, C-Me), 3.38 (d, *J* 2.3 Hz, 3-H), 3.76 + 3.79 (2 × s, 2 × OMe), 3.85—4.1 (m, OCH_2CH_2O), 4.19 + 4.50 (AB spectrum, *J* 14.5 Hz, NCH_2Ar), and 5.12 (d, *J* 2.3 Hz, 2-H).

Irradiations of Ethyl (2RS, 3SR)-α-*Diazo*-β-[1-(2,4-*dimethoxybenzyl*)-3-(2-*methyl*-1,3-*dioxolan*-2-*yl*)-4-*oxoazetidin*-2-*yl*]-β-*oxopropionate* (**4b**).—(*a*) An anhydrous ethanolic (150 ml) solution of compound (**4b**) (2.0 g, 4.5 mmol) was irradiated with a high-pressure mercury immersion lamp (HPK-125) through Pyrex for 3 h under argon. The solution was treated with Norite and evaporated to dryness to yield *diethyl* (2RS, 3SR)-1-(2,4-*dimethoxybenzyl*)-3-(2-*methyl*-1,3-*dioxolan*-2-*yl*)-4-*oxoazetidin*-2-*ylmalonate* (**17**) (1.9 g, 90%) as a light yellow homogeneous (t.l.c.) oil (Found: C, 59.6; H, 6.55; N, 3.2. $C_{23}H_{31}NO_9$ requires C, 59.35; H, 6.70; N, 3.00%); $\nu_{max.}$ (film) 1 760/1 750 d cm^{-1}; δ_H (60 MHz) 1.20 + 1.24 (2 × t, *J* 7 Hz, 2 × CO_2CH_2Me), 1.41 (s, C-Me), 3.53—3.70 [m, 3-H + $CH(CO_2Et)_2$], 3.79 (s, 2 × MeO), and 3.9—4.45 (m, 2 × CO_2CH_2Me + NCH_2Ar + OCH_2CH_2O + 2-H).

(*b*) A solution of compound (**4b**) (2.0 g, 4.5 mmol) in a mixture of peroxide-free THF (100 ml) and water (50 ml) was irradiated for 4 h as described in (*a*). The THF was distilled off, and the mixture extracted with CH_2Cl_2 (2 × 20 ml). The CH_2Cl_2 solution was dried ($MgSO_4$) and evaporated to dryness. The residue was crystallized from ether to yield *ethyl hydrogen* (2RS, 3SR)-1-(2,4-*dimethoxybenzyl*)-3-(2-*methyl*-1,3-*dioxolan*-2-*yl*)-4-*oxoazetidin*-2-*ylmalonate* (**18**) (0.7 g, 35.6%) as a mixture of epimers, m.p. 134 °C. (Found: C, 57.4; H, 6.3; N, 3.3. $C_{21}H_{27}NO_9$ requires C, 57.65; H, 6.20; N, 3.20%); $\nu_{max.}$ (KBr) 3 300—2 500, 1 730, and 1 700 cm^{-1}. The filtrate was evaporated and, with time, the residue crystallized. The crystals were taken up in a small volume of ether, and filtered off to give a second fraction of compound (**18**) (0.37 g, 18.8%; total yield 54.4%).

The filtrate of the second fraction was worked up by t.l.c. (benzene–acetone, 7:3) to give a mixture of compounds (**19a**) and (**19b**) (0.43 g, 31.5%) as an oil which crystallized when triturated with ether, m.p. 87 °C, and which proved identical (m.p., i.r., ^1H n.m.r.) with the thermolysis product of compound (**18**), see below.

Thermolysis of Compound (**18**).—A solution of compound (**18**) (0.13 g, 0.3 mmol) in toluene (10 ml) was refluxed for 1 h and then evaporated to dryness. The residue, when triturated with a small amount of ether, gave crystals of a *ca.* 1:1 mixture of compounds (**19a**) and (**19b**) (0.07 g, 76%), m.p. 85—87 °C (Found: C, 62.6; H, 6.8; N, 4.45. $C_{16}H_{21}NO_5$ requires C, 62.50; H, 6.90; N, 4.55%); $\nu_{max.}$ (KBr) 3 250, 1 720, 1 650sh, 1 630sh, and 1 610 cm^{-1}; δ_H (100 MHz) 1.25 + 1.27 + 4.16 + 4.20 (2 × t + 2 × q, 2 × CO_2Et), 3.15 + 3.08 (dd, *J* 7.0 and 1.6 Hz, 2 × CH_2CO), 3.78 + 3.82 (2 × s; 2 × MeO), 4.25—4.55 (m, NCH_2Ar), 5.92 + 5.90 (2 × dt, *J* 15.5 and 1.6 Hz, 2 × =CHCO), 6.0 (br s, NH), and 6.83 + 7.01 (2 × dt, *J* 15.5 and 7.0 Hz, 2 × CH_2CH=); δ_C 14.14 + 14.22 (2 × CO_2CH_2Me), 37.35 + 39.66 [2 × CH_2CO in (**19a**) and (**19b**), respectively], 38.82 + 39.12 (2 × NCH_2Ar), 55.36 (2 × MeO), 61.01 × 60.42 (2 × CO_2CH_2Me), 98.65 (C-3′), 104.15 (C-5′), 118.77 + 118.59 (2 × C-1′), 127.35 + 124.65 [COCH= in (**19a**) and (**19b**), respectively], 130.46 (C-6′), 134.89 + 141.26 [=$CHCH_2$ in (**19a**) and (**19b**), respectively], 158.58 (C-4′), 160.59 + 160.65 (2 × C-2′), 165.01 + 168.58 [CONH in (**19a**) and (**19b**), respectively], and 170.32 + 165.95 [CO_2Et in (**19a**) and (**19b**), respectively]; *m/z* (relative intensity; 70 eV, 180 °C: 307 (30; $M^{+\cdot}$), 293 (0.4), 290 (0.75), 278 (4.2, *M* − Et), 262 (2.0, *M* − OEt), 261 (3.3, *M* − EtOH), 248 (5.2), 233 (6.3), 220 (23, *M* − CH_2CO_2Et), 206 (4.7), 166 [98, $(MeO)_2C_6H_3CH{=}\overset{+}{N}H_2$], 151 ([100, $(MeO)_2C_7H_5^+$], 130.5 (1.8; 261^{2+}), 121 (27), 91 ($C_7H_7^+$), and 29 (15).

Ethyl (2RS, 3SR)-α-*Diazo*-β-[1-(2,4-*dimethoxybenzyl*)-3-(1-*hydroxyethyl*)-4-*oxoazetidin*-2-*yl*]-β-*oxopropionate* (**4e**) *and Ethyl* (2RS, 3SR)-α-*Diazo*-1-(2,4-*dimethoxybenzyl*)-β-*hydroxy*-β-[3-(1-*hydroxyethyl*)-4-*oxoazetidin*-2-*yl*]*propionate* (**20**), *Mixtures of Diastereoisomers*.—70% Aqueous $HClO_4$ (0.1 ml, 1.2 mmol) was added with continuous stirring to an acetone (5 ml) solution of compound (**4b**) (225 mg, 0.5 mmol) at 0 °C (bath temperature). The mixture was stirred for 20 min, neutralized by the addition of Na_2CO_3 (1.30 mg, 1.2 mmol), stirred for 5 min, and evaporated to dryness at ambient temperature and reduced pressure. The residue was taken up in CH_2Cl_2 (10 ml) and water (3 ml). The CH_2Cl_2 layer was washed with water (3 ml), dried ($MgSO_4$), and evaporated to dryness to give ethyl (2*RS*, 3*RS*)-α-diazo-β-[3-acetyl-1-(2,4-dimethoxybenzyl)-4-oxoazetidin-2-yl]-β-oxopropionate (**4d**) (190 mg, 98%) as a homogeneous (t.l.c.) yellow oil; $\nu_{max.}$ (film) 2 200, 1 750, 1 710, and 1 650 cm^{-1}. This product was, without further purification, dissolved in anhydrous methanol (5 ml) and $NaBH_4$ (20 mg, 0.55 mmol) was added to the solution with continuous stirring at −78 °C. After 1 h, the mixture was neutralized by the addition of acetic acid, and evaporated to dryness at ambient temperature and reduced pressure. The residue was taken up in CH_2Cl_2 (10 ml) and water (3 ml). The CH_2Cl_2 solution was worked up by t.l.c. (benzene–acetone, 7:1; eluant, acetone) to give the oily compounds (**4e**) (65 mg, 34%) and (**20**) (45 mg, 23%).

Compound (**4e**) was a *ca.* 5:3 mixture of two diastereoisomers (Found: C, 56.45; H, 5.85; N, 10.25; $C_{19}H_{23}N_3O_7$ requires C, 56.30; H, 5.70; N, 10.35%); $\nu_{max.}$ (film) 3 450, 2 220, 1 760—

* Primed locants refer to the 2,4-dimethoxyphenyl group.

† The chemical shifts of the aromatic protons of the 2,4-dimethoxybenzyl groups of all compounds described in the present paper are practically identical with those given here, and will henceforward not be listed.

1 700br, and 1 650 cm^{-1}; δ_H (100 MHz) 1.28 + 1.30 (2 × d, *J* 6.2 Hz, 2 × *Me*CHOH), 1.31 + 4.29 + 4.30 (t + 2 × q, *J* 7.1 Hz; 2 × CO_2Et), 2.3 (br s, OH), 3.21 + 3.04 (2 × ddd, *J* 4.0, 2.5, 0.8, and 8.0, 2.1 and 0.8 Hz, respectively, 2 × 3-H), 3.76 + 3.79 (2 × s, MeO's), 4.18 + 4.07 (2 × dq, *J* 4.0 and 6.2, and 8.0 and 6.2 Hz, respectively, 2 × MeC*H*OH), 4.67 + 4.14, and 4.64 + 4.11 (2 × AB, *J* 14.7 and 14.5 Hz, respectively; 2 × NCH_2Ar), 4.85 + 4.79 (2 × d, *J* 2.5 and 2.1 Hz, respectively, 2 × 2-H).

Compound (**20**), a *ca.* 3:2 mixture of diastereoisomers (Found: C, 55.85; H, 6.25; N, 10.15, $C_{19}H_{25}N_3O_7$ requires C, 56.00; H, 6.20; N, 10.30%); $\nu_{max.}$ (film) 3 400br, 2 180, and 1 730br cm^{-1}; δ_H (100 MHz) 1.26 + 4.22 (t + q, *J* 7.0 Hz, CO_2Et), 1.20 + 1.23 (2 × d, *J* 6.3 Hz, 2 × *Me*CHOH), 2.0 (br s, OH's), 2.93 + 2.90 (2 × dd, *J* 6.5 and 2.2, and 6.0 and 2.2 Hz, respectively, 2 × 3-H), 3.54 + 3.70 (2 × dd, *J* 7.5 and 2.2 Hz, 2 × 2-H), 3.80 + 3.83 (2 × s, MeO's), 3.96 + 4.04 (2 × qd, *J* 6.3 and 6.5, and 6.3 and 6.0 Hz, respectively, 2 × MeC*H*OH), 4.23 + 4.62 (AB, *J* 14.7 Hz, NCH_2Ar), 4.63 (d, *J* ≈ 7 Hz, C*H*OHCN$_2$); δ_C 14.44 (CO_2CH_2*Me*), 20.75 + 21.28 (2 × *Me*CHOH), 40.67 + 40.70 (2 × NCH_2Ar), 55.38 + 55.45 (MeO's), 56.67 + 57.11 (2 × C-2), 58.22 + 59.14 (2 × C-3), 61.16 + 61.18 (2 × CO_2CH_2Me), 65.95 + 64.98 (2 × Me*C*HOH), 68.33 (*C*HOHCN$_2$), 98.66 (C-3'), 104.55 + 104.59 (2 × C-5'), 116.19 (C-1'), 131.43 + 131.30 (2 × C-6'), 158.23 (C-4'), 160.86 + 160.80 (2 × C-2'), 165.82 (C-4), 168.00* (CN$_2$), 168.49 (CO_2Et).†

Ethyl (RS)-1-(2,4-*Dimethoxybenzyl*)-4-*oxoazetidin*-2-*ylacetate* (**9a**).—Ethyl chloroformate (0.52 ml, 5.5 mmol) was added to a mixture of compound (**8a**) (1.39 g, 5.0 mmol), dry THF (15 ml), and pyridine (0.44 ml, 5.5 mmol) at 0 °C (bath temperature) with continuous stirring. After 10 min ethyl diazoacetate[11] (0.57 g, 5.0 mmol) was added. The mixture was stirred for 20 h at ambient temperature and evaporated to dryness. The residue was taken up in CH_2Cl_2 (20 ml) and water (5 ml). Conventional work-up of the CH_2Cl_2 solution by chromatography (benzene–acetone, 7:2) furnished the title compound as a yellow oil (1.17 g, 76%) (Found: C, 62.45; H, 6.8; N, 4.45; $C_{16}H_{21}NO_5$ requires C, 62.50; H, 6.90; N, 4.55%); $\nu_{max.}$ (film) 1 760—1 730br cm^{-1}; δ_H (60 MHz) 1.22 + 4.10 (t + q, *J* 7 Hz, CO_2Et), 2.4—3.3 (m, 3-H_2 + CH_2CO_2Et), 3.78 + 3.80 (2 × s, 2 × MeO), 3.95—4.6 (m, 2-H + NCH_2Ar); *m/z* (rel. intensity; 120 °C) 307 (7.8, $M^{+\cdot}$), 279 (5.7, $M - C_2H_4$), 261 (1.0, M − EtOH), 234 (0.6, $M - CO_2Et$), 220 (5.9, $M - CH_2CO_2Et$), 193 (17.4, OCNDMB$^{+\cdot}$), 166 [10.5; $(MeO)_2C_6H_3CH{=}\overset{+}{N}H_2$], 151 [100, $(MeO)_2C_7H_5^+$], and 121 (24.8, $MeOC_7H_6^+$).

Using an equivalent amount of triethylamine rather than pyridine diminished the yield to 44%.

Ethyl (2RS, 3RS)-α-*Diazo*-γ-[1-(2,4-*dimethoxybenzyl*)-3-(2-*methyl*-1,3-*dioxolan*-2-*yl*)-4-*oxoazetidin*-2-*yl*]-β-*oxobutyrate* (**10b**).—Thionyl chloride (0.37 ml, 5 mmol) was added to a solution of compound (**8b**) (1.83 g, 5 mmol) in a mixture of CH_2Cl_2 (10 ml) and DMF (1 drop) with continuous stirring and ice-cooling. Stirring was continued at 0 °C for 2 h. Ethyl diazoacetate[11] (1.7 ml, 15 mmol) was added, and the mixture stirred for 24 h at ambient temperature. The dry residue of the resulting brown solution was worked up by column chromatography (benzene–acetone, 7:2) to afford a product (0.17 g, 7.3%) which proved identical (i.r.) with an authentic sample of the title compound obtained by diazo transfer.[4]

(3RS, 4SR)-1-(2,4-*Dimethoxybenzyl*)-4-(1-*hydroxy*-2-*nitroethyl*)-3-(2-*methyl*-1,3-*dioxolan*-2-*yl*)*azetidin*-2-*one*, Mixture of Epimers (**21**).—A mixture of trifluoroacetic anhydride (19.6 ml, 0.14 mol) and dry CH_2Cl_2 (100 ml) was added dropwise to a mixture of dry Me_2SO (12.8 ml, 0.18 mol) in dry CH_2Cl_2 (100 ml) with continuous stirring at −70 °C (*ca.* 0.5 h). The mixture was stirred for 0.5 h at −70 °C. Subsequently a solution of compound (**6b**)[3] (20 g, 0.06 mol) in dry CH_2Cl_2 (100 ml) was dropwise added at −70 °C (*ca.* 1 h), and the mixture stirred for 0.5 h at −70 °C. Triethylamine (42 ml, 300 mmol) was added at such a rate, that the temperature of the reaction mixture did not exceed −65 °C. The mixture was allowed to warm to room temperature and was then extracted with brine (1 × 200 + 1 × 100 ml), dried ($MgSO_4$), and evaporated to dryness at room temperature under reduced pressure. Propan-2-ol (30 ml), nitromethane (6.5 ml, 0.12 mol), and triethylamine (8.5 ml, 0.06 mol) were successively added to the resulting oily carbaldehyde (**5b**), and the mixture kept for 2 days at room temperature with occasional stirring. Ether (100 ml) was added, and the mixture kept for 1 day at +5 °C to afford the title compound (8.8 g, 37%), m.p. 138—139 °C (from propan-2-ol) (Found: C, 54.2; H, 6.25; N, 6.95, $C_{18}H_{24}N_2O_8$ requires C, 54.55; H, 6.10; N, 7.05%); $\nu_{max.}$ (KBr) 3 300, 1 730, 1 540, and 1 375 cm^{-1}; δ_H (100 MHz) 1.39 (s, C-Me), 3.17 (d, *J* 2.5 Hz, 3-H), 3.4 (br s, OH), 3.47 (m, 4-H), 3.81 + 3.83 (2 × s, 2 × MeO), 3.85—4.05 (m, OCH_2-CH_2O), 4.25—4.55 (m, C*H*OHCH_2NO_2), and 4.35 + 4.52 (AB, *J* 15 Hz, NCH_2Ar).

(3RS, 4RS)-1-(2,4-*Dimethoxybenzyl*)-3-(2-*methyl*-1,3-*dioxolan*-2-*yl*)-4-(2-*nitroethyl*)*azetidin*-2-*one* (**22**).—Acetic anhydride (2.73 ml, 29 mmol) and 4-dimethylaminopyridine (50 mg) were successively added to a solution of compound (**21**) (8.8 g, 22 mmol) in dry CH_2Cl_2 (50 ml). With occasional shaking the mixture was set aside for 1 day at room temperature; it was then evaporated to dryness under reduced pressure to give the oily *O*-acetyl derivative; $\nu_{max.}$ (film) 1 740, 1 550, and 1 370 cm^{-1}; δ_H (100 MHz) 1.38 (s, C-Me), 2.05 (s, AcO), 3.39 (m, 3-H + 4-H), 3.82 + 3.84 (2 × s, 2 × MeO), 3.85—4.0 (m, OCH_2CH_2O), 4.07 + 4.58 (AB, *J* 14.8 Hz, NCH_2Ar), 4.3—4.6 (m, CH_2NO_2), and 5.85 (ddd, *J* 7.0, 5.5 and 1.5 Hz, C*H*OAc).

$NaBH_4$ (2.20 g, 58 mmol) was added to a solution of the acetate in methanol (50 ml) with continuous stirring at 0 °C (bath temperature). Stirring was continued until the acetate was consumed (t.l.c., benzene–acetone, 8:2; *ca.* 1 h). The mixture was poured into brine (150 ml), and the title compound (7.7 g, 91%) isolated as an oil by extraction with CH_2Cl_2; $\nu_{max.}$ (film) 1 740, 1 545, and 1 370 cm^{-1}; δ_H (100 MHz) 1.39 (s, C-Me), 1.96 + 2.45 (*AB*MX_2, J_{gem} 14.6, J_{vic} 9.2, 6.2, and 4.0 and 7.3 Hz, respectively, $CH_2CH_2NO_2$), 3.02 (d, *J* 2.3 Hz, 3-H), 3.40 (ddd, *J* 2.3, 9.2, and 4.0 Hz, 4-H), 3.80 + 3.82 (2 × s, 2 × MeO), 3.8—4.0 (m, OCH_2CH_2O), 4.22 + 4.47 (AB, *J* 14.8 Hz, NCH_2Ar), 4.36 (dd, *J* 6.2 and 7.3 Hz, $CH_2CH_2NO_2$). This product was, without further purification, subjected to the modified Nef reaction, see below.

(3RS, 4RS)-1-(2,4-*Dimethoxybenzyl*)-4-(2,2-*dimethoxyethyl*)-3-(2-*methyl*-1,3-*dioxolan*-2-*yl*)*azetidin*-2-*one* (**23**).—A solution of metallic sodium (0.65 g, 2.8 mmol) in anhydrous methanol (40 ml) was added to an anhydrous methanolic (40 ml) solution of compound (**22**) (7.7 g, 20 mmol) at −20 to −30 °C. The cold mixture was then added to a mixture of concentrated H_2SO_4 (50 ml) and anhydrous methanol (200 ml) at −50 °C (*ca.* 3 min). The mixture was allowed to warm slowly to −35 °C, stirred for 5 min at this temperature, and then poured into a mixture of CH_2Cl_2 (300 ml) and ice (300 g). The CH_2Cl_2 layer was washed with 5% aqueous $NaHCO_3$ (3 × 100 ml), dried ($MgSO_4$), and evaporated to dryness to give the title compound (7.3 g, 91%) as an oil; $\nu_{max.}$ (film) 1 750 cm^{-1}; δ_H (100 MHz) 1.39 (s, C-Me), 1.64 + 2.05 [*AB*MX, J_{gem} 13.8, J_{vic} 8.8, 4.4, and 6.8 and 4.5 Hz, respectively; $CH_2CH(OMe)_2$], 3.14 (d, *J* 2.2 Hz, 3-H), 3.24 + 3.26 [2 × s, $CH(OMe)_2$], 3.46 (ddd, *J* 2.2, 8.8, and 4.5 Hz, 4-H),

* The correct assignation of these two signals may be the reverse.
† Primed locants refer to the 2,4-dimethoxyphenyl group.

3.81 (s, 2 × MeO), 3.85—4.0 (m, OCH_2CH_2O), 4.18 + 4.50 (AB, J 15.2 Hz, NCH_2Ar), 4.37 [dd, J 6.8 and 4.4 Hz, $CH_2CH(OMe)_2$]; m/z (rel. intensity, 120 °C) 395 (1.9, $M^{+\cdot}$), 364 (2.6, M − MeO), 277 {4.1, M − [MeO + OCH_2CH_2OC-(Me)-]}, 262 (5.0), 193 (13.5, OCN-DMB$^{+\cdot}$), 181 (5.5), 166 [3.0, $(MeO)_2C_6H_3CH{=}\overset{+}{N}H_2$], 151 [97.2, $(MeO)_2C_7H_5^+$], 121 (36.2, $MeOC_7H_6^+$), 91 (15.5, $C_7H_7^+$), 75 [82.9, $HC(OMe)_2^+$], and 44 (81.2). The product was, without further purification, subjected to oxidative *N*-deprotection, see below.

(3RS,4RS)-4-(2,2-*Dimethoxyethyl*)-3-(2-*methyl*-1,3-*dioxolan*-2-*yl*)*azetidin*-2-*one* (**24**).—A mixture of compound (**23**) (7.3 g, 18.5 mmol), $K_2S_2O_8$ (20 g, 74 mmol), $Na_2HPO_4{\cdot}2H_2O$ (26.3 g, 148 mmol), acetonitrile (90 ml), and water (63 ml) was refluxed for 10 h and allowed to cool. The crystalline salts were filtered off. The aqueous phase of the filtrate was extracted with ethyl acetate (2 × 50 ml) and the combined organic phases were evaporated to dryness, and the residue worked up by chromatography [hexane ⟶ hexane–ethyl acetate (1:1)] to give unchanged starting substance (0.7 g, 10%) and the title compound (1.69 g, 33%) as oils.

Compound (**24**), $\nu_{max.}$ (film) 3 250 and 1 760 cm^{-1}; δ_H (100 MHz) 1.43 (s, C-Me), 1.94 [m, $CH_2CH(OMe)_2$], 3.10 (dd, J 2.5 and 0.9 Hz, 3-H), 3.33 + 3.34 [2 × s, $CH(OMe)_2$], 3.66 (ddd, J 2.5, 6.2, and 7.0 Hz, 4-H), 3.9—4.2 (m, OCH_2CH_2O), 4.44 [t, J 5.3 Hz; $CH(OMe)_2$], and 6.1 (br s, NH).

The product was allowed to react, without further purification, with *p*-nitrobenzyl glyoxylate, see below.

p-*Nitrobenzyl* 1-*Hydroxy*-1-[(3RS, 4RS)-4-(2,2-*dimethoxyethyl*)-3-(2-*methyl*-1,3-*dioxolan*-2-*yl*)-4-*oxoazetidin*-1-*yl*]*acetate*, (**25**), *Mixture of Epimers*.—A mixture of compound (**24**) (1.69 g, 6.9 mmol), *p*-nitrobenzyl glyoxylate monohydrate (1.73 g, 7.6 mmol), and dry benzene (20 ml) was refluxed for 1 h and evaporated to dryness. Work-up of the oily residue by chromatography [hexane ⟶ hexane–EtOAc (7:3) ⟶ EtOAc] gave the title compound (1.35 g, 43%) as an oil which crystallized when triturated with ether, m.p. 112—113 °C (from EtOH) (Found: C, 52.85; H, 5.75; N, 6.35; $C_{20}H_{26}N_2O_{10}$ requires C, 52.85; H, 5.75; N, 6.15%); $\nu_{max.}$ (KBr) 3 320, 1 770, and 1 745 cm^{-1}; δ_H (100 MHz) 1.40 (s, *C*-Me), 1.82 + 2.02 [*AB*MX, J_{gem} 14.0, J_{vic} 6.6, 4.4, and 6.2 and 5.8 Hz, respectively; $CH_2CH(OMe)_2$], 3.18 (d, J 2.5 Hz, 3-H), 3.30 + 3.32 [2 × s, $CH(OMe)_2$], 3.90 (ddd, J 6.6, 6.2, and 2.5 Hz, 4-H), 3.85—4.0 (m, OCH_2CH_2O), 4.07 (d, J 7.8 Hz, OH), 4.46 [dd, J 4.4 and 5.8 Hz, $CH(OMe)_2$], 5.32 (d, J 7.8 Hz; CHOH), 5.34 (s; OCH_2Ar), and 7.57 + 8.22 (AA'BB', J 8.6 Hz; Ar).

(RS)-1-(2,4-*Dimethoxybenzyl*)-4-*oxoazetidin*-2-*ylacetamide* (**12a**), *Ethyl* (RS)-1-(2,4-*Dimethoxybenzyl*)-4-*oxoazetidine*-2-*ylacetate* (**9a**), *and Diethyl* (RS)-3-(2,4-*Dimethoxybenzylamino*)*pentanedioate* (**27**).—Dry HCl gas [generated from concentrated aqueous HCl (80 ml)] was introduced into a mixture of compound (**7a**)[2] (5.2 g, 20 mmol), EtOH (1.24 ml, 21.2 mmol), anhydrous ether and anhydrous CH_2Cl_2 (40 ml, each) with ice–salt cooling. The mixture was kept for 20 h in a refrigerator and then evaporated to dryness under reduced pressure. The residue was dissolved in water (25 ml) and the solution neutralized (pH 7) by adding 10% aqueous NaOH; overnight it deposited crystals of compound (**12a**) (3.55 g, 63.8%), m.p. 192—193 °C (from AcOH) (Found: C, 60.1; H, 6.4; N, 9.85. $C_{14}H_{18}N_2O_4$ requires C, 60.40; H, 6.50; N, 10.05%); $\nu_{max.}$ (KBr) 3 450—2 400 with local maxima at 3 400 and 3 300, 1 735, and 1 700 cm^{-1}; m/z (rel. intensity, 110 °C) 278 (28, $M^{+\cdot}$), 247 (3.7, M − MeO), 220 (3.1, M − CH_2CONH_2), 192 (5.4), 166 [45, $(MeO)_2C_6H_3CH{=}\overset{+}{N}H_2$], 151 [100, $(MeO)_2C_7H_5^+$], 121 (40.6, $MeOC_7H_6^+$), and 42 (89, CH_2CO).

The aqueous filtrate of the crude amide was extracted with ether (5 × 10 ml) to give, after conventional work-up, an oil (1.0 g) from which compounds (**9a**) (0.50 g, 8.2%) [which proved identical (t.l.c., i.r.) with a sample obtained by esterifying compound (**8a**) with ethyl chloroformate, see above] and (**27**) (0.12 g, 2.0%) were separated by t.l.c. (heptane–acetone, 7:3) as yellow oils.

Compound (**27**) (Found: C, 61.3; H, 7.95; N, 4.05. $C_{18}H_{27}NO_6$ requires C, 61.20; H, 7.70; N, 3.95%); $\nu_{max.}$ (film) 3 380 and 1 740br cm^{-1}; δ_H (60 MHz) 1.26 + 4.13 (t + q, J = 7.2 Hz, 2 × CO_2Et), 2.55 (d, J 6 Hz, CH_2CHCH_2), 3.40 (quint, J 6 Hz, CH_2CHCH_2), and 3.74 (s, NCH_2Ar); m/z (rel. intensity, 120 °C) 353 (1, $M^{+\cdot}$), 325 (4, M − C_2H_4), 280 (2, M − CO_2Et), 266 (10, M − CH_2CO_2Et), 207 (5, M − 2 × CO_2Et), 166 [80, $(MeO)_2C_6H_3CH{=}\overset{+}{N}H_2$], 151 [100, $(MeO)_2C_7H_5^+$], 91 (85, $C_7H_7^+$), and 77 (46, Ph^+).

(RS)-1-(2,4-*Dimethoxybenzyl*)-N-*nitroso*-4-*oxoazetidine*-2-*ylacetamide* (**13a**).—$NaNO_2$ (70 mg, 1 mmol) was added at 0 °C to a solution of the amide (**12a**) (0.28 g, 1 mmol) in a mixture of EtOH and water (5 ml, each). The solution was slightly acidified (pH 3) by adding acetic acid, and stirred for 1 h to deposit colourless crystals of the title compound (0.21 g, 68%), m.p. 139—140 °C (from EtOH) (Found: C, 54.55; H, 5.7; N, 13.5. $C_{14}H_{17}N_3O_5$ requires C, 54.70; H, 5.60; N. 13.65%); $\nu_{max.}$ (KBr) 3 300, 3 200, 1 740, and 1 710 cm^{-1}; δ_H (100 MHz) 2.7—3.3 (m, 3-H_2 + $CH_2CONHNO$), 3.81 + 3.83 (2 × s, 2 × MeO), 4.58 (m, 2-H), 4.76 (s, NCH_2Ar), and 8.3 (br s, NHNO)

(RS)-1-(2,4-*Dimethoxybenzyl*)-4-*oxoazetidin*-2-*ylthioacetamide* (**14a**).—A slow stream of H_2S was bubbled through a solution of the nitrile (**7a**)[2] (6.5 g, 25 mmol) in a mixture of dry pyridine (30 ml) and triethylamine (2.5 g, 25 mmol) for 48 h at 0 °C. The orange-red solution was evaporated to dryness under reduced pressure, and the oily residue crystallized from propan-2-ol (*ca.* 20 ml) to afford yellowish crystals of the title compound (4.8 g, 68%), m.p. 140—141 °C (Found: N, 9.35; S, 10.75. $C_{14}H_{18}N_2O_3S$ requires N, 9.50; S, 10.90%); $\nu_{max.}$ (KBr) 3 400—3 300 and 1 710 cm^{-1}; m/z (rel. intensity, 90 °C) 294 (1, $M^{+\cdot}$), 266 (14.7), 260 (14.3, M − H_2S), 220 (7.1, M − CH_2CSNH_2), 206 (7.3), 192 (52.6, OCN-DMB$^{+\cdot}$), 166 [21.5, $(MeO)_2C_6H_3$-$CH{=}NH_2^+$], 151 [100, $(MeO)_2C_7H_5^+$], 121 (61.6, $MeOC_7H_6^+$), 91 (26.0, $C_7H_7^+$), and 77 (25.5, Ph^+).

(RS)-1-(2,4-*Dimethoxybenzyl*)-S-*methyl*-4-*oxoazetidin*-2-*ylacetimidothioate Hydriodide* (**16a**).—Methyl iodide (0.3 ml, 4.8 mmol) was added to a suspension of the thioamide (**14a**) (0.6 g, 2 mmol) in anhydrous ethanol (10 ml), and the mixture was stirred for 5 h at ambient temperature. A clear solution formed gradually and this was evaporated to dryness under reduced pressure. The resulting oil was crystallized from EtOH–ether to afford the title compound (0.14 g, 94%), m.p. 124 °C (decomp.) (Found: N, 6.10; S, 6.90. $C_{15}H_{21}IN_2O_3S$ requires N, 6.40; S, 7.35%); $\nu_{max.}$ (KBr) 3 200—2 700 and 1 720 cm^{-1}.

1-*Benzyl*-4-*cyanomethyl*-3-(1′-*hydroxyethyl*)*azetidin*-2-*one*, (**7g**), *Mixture of* (3RS, 4SR, 1′RS)- *and* (3RS, 4SR, 1′SR)-*Forms*.—70% Aqueous $HClO_4$ (1.35 ml) was added with continuous stirring to an acetone solution (20 ml) of compound (**7c**)[3] (1.82 g, 6.4 mmol) at 0 °C (bath temperature). The mixture was stirred for 2 h at 0 °C, neutralized by the addition of $NaHCO_3$ (1.67 g), and evaporated to dryness under reduced pressure. The residue, compound (**7f**), was dissolved in methanol (20 ml) and $NaBH_4$ (0.4 g, 10.5 mmol) was added to the solution with continuous stirring at 0 °C (bath temperature). The mixture was stirred for 15 min, and poured into brine (100 ml). The product was extracted with CH_2Cl_2 (3 × 30 ml), and

the extract dried ($MgSO_4$) and evaporated to dryness. The residue was worked up by t.l.c. (benzene–acetone, 8:2) to give, in addition to unchanged starting substance (0.55 g, 30%), the title compound (0.90 g, 58%) as an oil which was subjected to lactonisation (see below) without further purification; δ_H (100 MHz) 1.33 + 1.30 (2 × d, *J* 6.6 Hz, 2 × *Me*CHOH), 2.25 (br s, OH), 2.51 + 2.53 (2 × m, 2 × CH_2CN), 3.08 + 3.04 (2 × dd, *J* 2.2 and 5.0, and 2.2 and 5.5 Hz, respectively, 2 × 3-H), 3.68 + 3.82 (2 × td, *J* 5.5 and 2.2 Hz, 2 × 4-H), 4.11 + 4.18 (2 × qd, *J* 6.6 and 5.0, and 6.6 and 5.5 Hz, respectively, 2 × MeC*H*OH), 4.28 + 4.60 (AB, *J* 15 Hz, N-CH_2Ph), and 7.34 (s, Ph). Intensity ratio of the corresponding signals of the two epimers 60:40.

(2RS, 3RS, 4SR)-4-*Benzylamino*-2-*methyl*-6-*oxotetrahydropyran*-3-*carboxylic acid Hydrochloride* (**28**).—(a) *From compound* (**7g**). Compound (**7g**) (mixture of the 1′-epimers; 0.85 g, 3.5 mmol) was refluxed for 3 h with concentrated aqueous HCl (10 ml) to give the title compound (0.52 g, 50%) as a crystalline product, m.p. 163—164 °C (decomp.), lit.,[10] m.p. 166—170 °C (decomp.), which proved identical (i.r. and ^{1}H n.m.r.) with an authentic sample obtained as described in ref. 10; $\nu_{max.}$ (KBr) 3 550, 3 100—2 500 (with several local maxima), 1 745, and 1 720 cm^{-1} [lit.,[10] $\nu_{max.}$ (Nujol) 1 750 and 1 724 cm^{-1}]; *m/z* (rel. intensity, 125 °C): 263 (31; $M^{+\cdot}$, free base), 245 (10.1, *M* − 18), 235 (11.5, *M* − 28), 219 (6.3, *M* − 44), 204 (46.1, *M* − 59), 201 (45.6, *M* − 44 − 18), 186 (14.3, *M* − 77), 177 (16.5, $HO_2CCH{=}CHNHCH_2Ph^{+\cdot}$), 132 (177 − CO_2H), 106 (91.8, $PhCH_2NH^+$), and 91 (100); δ_H (100 MHz; [$^2H_6$]DMSO- + C^2HCl_3, 3:1) 1.46 (d, *J* 6.5 Hz, *Me*CH), 3.12 + 3.24 (*AB*X, J_{gem} 15.5, J_{vic} 7.8 and 8.7 Hz, respectively, CH_2CO), 3.39 (dd, *J* 3.5 and 3.0 Hz, C*H*CO_2H), 4.02 (ddd, *J* 7.8, 8.7, and 3.0 Hz, C*H*NH), 4.23 (s, CH_2Ph), 5.24 (qd, *J* 6.5 and 3.5 Hz, MeC*H*), 7.3—7.7 (m, Ph), in good agreement with the published[12] spectrum of the ethyl ester of the free base.

(b) *From compound* (**7c**) *without isolation of compound* (**7g**). Compound (**7c**) (2.0 g, 7 mmol) was deacetalized and reduced as described above for the preparation of compound (**7g**). The oily crude product (obtained by extraction with CH_2Cl_2) was refluxed with concentrated aqueous HCl (20 ml). The solution was treated with Norite and allowed to cool to afford a crystalline product which was dried in air, washed with ether, and dried to obtain the title compound (0.72, 35%), m.p. 161—162 °C (decomp.), which proved identical with the sample obtained as described in (a).

(2RS, 3RS, 4SR)-4-*Amino*-2-*methyl*-6-*oxotetrahydropyran*-3-*carboxylic Acid Hydrochloride* (**30**).—70% Aqueous perchloric acid (1.1 ml) was added with continuous stirring to an acetone (20 ml) solution of compound (**7b**) (1.8 g, 5.2 mmol) at 0 °C, (bath temperature). The mixture was stirred for 6 h at 0 °C, neutralized by the addition of $NaHCO_3$ (1.35 g), and evaporated to dryness. The residue, compound (**7d**), was dissolved in methanol (20 ml). $NaBH_4$ (0.4 g, 10.5 mmol) was added with continuous stirring at 0 °C (bath temperature). The mixture was stirred for 30 min and then poured into brine (100 ml). The resulting intermediate, the crude compound (**7e**), was isolated by conventional extraction with CH_2Cl_2 (3 × 30 ml); δ_H (100 MHz) 1.28 (d, *J* 6.4 Hz, C-Me), 2.25 (br s, OH), 2.52 + 2.60, and 2.55 + 2.62 (2 × *AB*X, J_{gem} 17, J_{vic} 6.2, 4.6, and 5.8 and 4.6 Hz, respectively; 2 × CH_2CN), 3.03 + 2.98 (2 × dd, *J* 2.2 and 6.0 Hz, 2 × 3-H), 3.55 + 3.70 (2 × ddd, *J* 6.2, 4.6, 2.2, and 5.8, 4.6, and 2.2 Hz, respectively, 2 × 4-H), 3.80 + 3.83 (2 × s, MeO's), 4.04 + 4.10 (2 × qd, *J* 6.4 and 6.0 Hz, 2 × MeC*H*OH), 4.22 × 4.47 (AB, *J* 14.5, NCH_2Ar). Ratio of the two epimers *ca.* 55:45.

The crude intermediate was refluxed for 5 h with concentrated aqueous HCl (20 ml) after which the solution was allowed to cool and then filtered. The filtrate was evaporated to dryness, and the residue dissolved, with gentle heating, in concentrated aqueous HCl (3 ml). The title compound (0.23 g, 21%), m.p. 150—155 °C (decomp.) [lit.,[13] m.p. 160—165 °C (decomp.)], crystallized out when this solution was set aside in a refrigerator, and proved identical (i.r. and ^{1}H n.m.r.) with an authentic sample prepared by reductive debenzylation of compound (**28**), essentially as described in literature;[10] $\nu_{max.}$ (KBr) 3 600—2 400, 1 720, and 1 690 cm^{-1}; δ_H (100 MHz; $C^2H_3O^2H$) 1.38 (d, *J* 6.5 Hz, *Me*CH), 2.83 (dd, *J* 3.5 and 3.0 Hz, C*H*CO_2H), 2.86 (d, *J* 6.8 Hz, CH_2CO), 3.97 (td, *J* 6.8 and 3.5 Hz, C*H*NH_2), and 4.30 (qd, *J* 6.5 and 3.0 Hz, MeC*H*).

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