

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

József Fetter* and Károly Lempert

Department of Organic Chemistry, Technical University Budapest, H-1521 Budapest, Hungary.

Mária Kajtár-Peredy

Central Research Institute for Chemistry of the Hungarian Academy of Sciences, H-1525 Budapest, Hungary.

Gyula Simig and Gyula Hornyák

Research Group for Alkaloid Chemistry of the Hungarian Academy of Sciences, H-1521 Budapest, Hungary

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**). NaBH₄ 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.

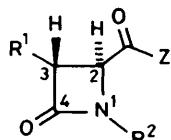
Successive treatment of the acids (**2a**) and (**2b**) with thionyl chloride and an excess of ethyl diazoacetate furnished the ethyl α -diazo- β -[4-oxoazetidin-2-yl]- β -oxopropionates (**4a**) and (**4b**) in moderate yields. Irradiation of compound (**4b**) in ethanol and aqueous tetrahydrofuran (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 NaBH₄ 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 CO₂ 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 Me₂SO 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 NaBH₄ 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-CH₂Cl₂ 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

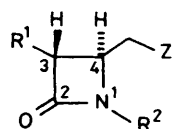


(1 a-c) Z = OEt

(2 a, b) Z = OH

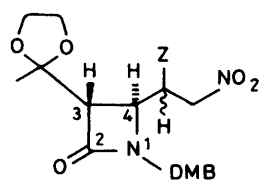
(3 a, b) Z = CHN₂*(4 a, b, d, e) Z = CN₂CO₂Et

(5 b) Z = H*



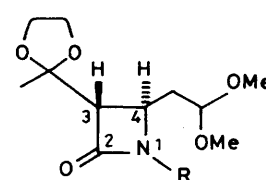
(6 a-c) Z = OH

(7 a-g) Z = CN



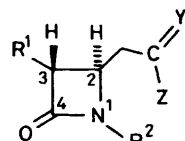
(21) Z = OH*

(22) Z = H



(23) R = DMB

(24) R = H

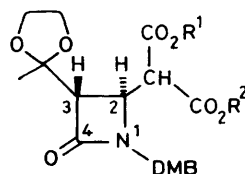
(25) R = CHOHCOC₂H₄NO₂-p*

(8 a, b) Y = O, Z = OH

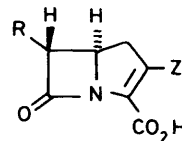
(9 a, b) Y = O, Z = OEt

(10 a, b) Y = O, Z = CN₂CO₂Et(11 a, b) Y = O, Z = OCO₂Et(12 a) Y = O, Z = NH₂

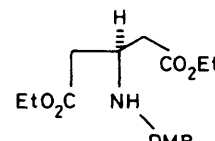
(13 a) Y = O, Z = NHNO

(14 a) Y = S, Z = NH₂(15 a) Y = NH₂Cl⁻, Z = OEt(16 a) Y = NH₂I⁻, Z = SMe(17) R¹ = R² = Et

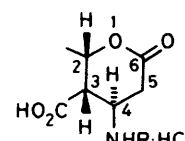
(18) R = Et, R = H†



(26)



(27)

(28) R = CH₂Ph

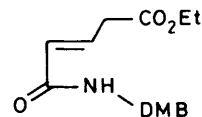
(29) R = DMB

(30) R = H

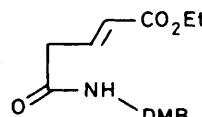
DMB = 2,4-(MeO)₂C₆H₃CH₂

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

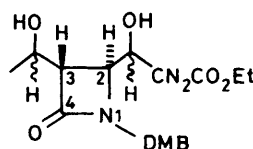
* Diastereoisomeric mixture.



(19 a)



(19 b)



(20)†

DMB = 2,4-(MeO)₂C₆H₃CH₂

(1) - (16)

	R ¹	R ²
a	H	DMB
b		DMB
c		CH ₂ Ph
d	Ac	DMB
e		DMB†
f	Ac	CH ₂ Ph
g		CH ₂ Ph†

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

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

(12a), while its treatment with 60% aqueous HBF₄ 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, presumably⁸ 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 NaBH₄ 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 debenzoylation 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, ¹³C n.m.r. spectra at 25.2 MHz with a Varian XL-100 instrument in C₂HCl₃ solutions, using SiMe₄ 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 PF₂₅₄₊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 CH₂Cl₂ (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 diazoacetate¹¹ (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. C₁₇H₁₉N₃O₆ requires C, 56.50; H, 5.30; N, 11.65%; v_{\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, CO₂Et), 2.78 + 3.22 (AB, J_{gem} 14.7, J_{vic} 2.7 and 5.5 Hz, respectively, 3-H₂), 3.78 (s, 2 \times MeO), 4.1–4.85 (m, 2-H + NCH₂Ar), 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. C₂₁H₂₅N₃O₈ requires C, 56.40; H, 5.65; N, 9.40%; v_{\max} (film) 2 180, 1 760, 1 720, and 1 650 cm⁻¹; δ_H (100 MHz) 1.29 + 4.25 (t + q, J 7.1 Hz, CO₂Et), 1.41 (s, C-Me), 3.38 (d, J 2.3 Hz, 3-H), 3.76 + 3.79 (2 \times s, 2 \times OMe), 3.85–4.1 (m, OCH₂CH₂O), 4.19 + 4.50 (AB spectrum, J 14.5 Hz, NCH₂Ar), 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. C₂₃H₃₁N₃O₉ requires C, 59.35; H, 6.70; N, 3.00%; v_{\max} (film) 1 760/1 750 d cm⁻¹; δ_H (60 MHz) 1.20 + 1.24 (2 \times t, J 7 Hz, 2 \times CO₂CH₂Me), 1.41 (s, C-Me), 3.53–3.70 [m, 3-H + CH(CO₂Et)₂], 3.79 (s, 2 \times MeO), and 3.9–4.45 (m, 2 \times CO₂CH₂Me + NCH₂Ar + OCH₂-CH₂O + 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 CH₂Cl₂ (2 \times 20 ml). The CH₂Cl₂ solution was dried (MgSO₄) 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. C₂₁H₂₇N₃O₉ requires C, 57.65; H, 6.20; N, 3.20%; v_{\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. C₁₆H₂₁N₃O₅ requires C, 62.50; H, 6.90; N, 4.55%; v_{\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 \times t + 2 \times q, 2 \times CO₂Et), 3.15 + 3.08 (dd, J 7.0 and 1.6 Hz, 2 \times CH₂CO), 3.78 + 3.82 (2 \times s; 2 \times MeO), 4.25–4.55 (m, NCH₂Ar), 5.92 + 5.90 (2 \times dt, J 15.5 and 1.6 Hz, 2 \times =CHCO), 6.0 (br s, NH), and 6.83 + 7.01 (2 \times dt, J 15.5 and 7.0 Hz, 2 \times CH₂CH=); δ_C 14.14 + 14.22 (2 \times CO₂CH₂Me), 37.35 + 39.66 [2 \times CH₂CO in (19a) and (19b), respectively], 38.82 + 39.12 (2 \times NCH₂Ar), 55.36 (2 \times MeO), 61.01 \times 60.42 (2 \times CO₂CH₂Me), 98.65 (C-3'), 104.15 (C-5'), 118.77 + 118.59 (2 \times C-1'), 127.35 + 124.65 [COCH= in (19a) and (19b), respectively], 130.46 (C-6'), 134.89 + 141.26 [=CHCH₂ in (19a) and (19b), respectively], 158.58 (C-4'), 160.59 + 160.65 (2 \times C-2'), 165.01 + 168.58 [CONH in (19a) and (19b), respectively], and 170.32 + 165.95 [CO₂Et in (19a) and (19b), respectively]; m/z (relative intensity; 70 eV, 180 °C: 307 (30; M^{+}), 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 – CH₂CO₂Et), 206 (4.7), 166 [98, (MeO)₂C₆H₃CH=NH₂], 151 ([100, (MeO)₂C₇H₅⁺], 130.5 (1.8; 261²⁺), 121 (27), 91 (C₇H₇⁺), 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 HClO₄ (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 Na₂CO₃ (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 CH₂Cl₂ (10 ml) and water (3 ml). The CH₂Cl₂ layer was washed with water (3 ml), dried (MgSO₄), and evaporated to dryness to give ethyl (2RS, 3SR)- 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; v_{\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 NaBH₄ (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 CH₂Cl₂ (10 ml) and water (3 ml). The CH₂Cl₂ 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; C₁₉H₂₃N₃O₇ requires C, 56.30; H, 5.70; N, 10.35%; v_{\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 \times d, *J* 6.2 Hz, 2 \times MeCHOH), 1.31 + 4.29 + 4.30 (t + 2 \times q, *J* 7.1 Hz, 2 \times CO₂Et), 2.3 (br s, OH), 3.21 + 3.04 (2 \times ddd, *J* 4.0, 2.5, 0.8, and 8.0, 2.1 and 0.8 Hz, respectively, 2 \times 3-H), 3.76 + 3.79 (2 \times s, MeO's), 4.18 + 4.07 (2 \times dq, *J* 4.0 and 6.2, and 8.0 and 6.2 Hz, respectively, 2 \times MeCHOH), 4.67 + 4.14, and 4.64 + 4.11 (2 \times AB, *J* 14.7 and 14.5 Hz, respectively; 2 \times NCH₂Ar), 4.85 + 4.79 (2 \times d, *J* 2.5 and 2.1 Hz, respectively, 2 \times 2-H).

Compound (20), a ca. 3:2 mixture of diastereoisomers (Found: C, 55.85; H, 6.25; N, 10.15, C₁₉H₂₅N₃O₇ requires C, 56.00; H, 6.20; N, 10.30%); ν_{\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, CO₂Et), 1.20 + 1.23 (2 \times d, *J* 6.3 Hz, 2 \times MeCHOH), 2.0 (br s, OH's), 2.93 + 2.90 (2 \times dd, *J* 6.5 and 2.2, and 6.0 and 2.2 Hz, respectively, 2 \times 3-H), 3.54 + 3.70 (2 \times dd, *J* 7.5 and 2.2 Hz, 2 \times 2-H), 3.80 + 3.83 (2 \times s, MeO's), 3.96 + 4.04 (2 \times qd, *J* 6.3 and 6.5, and 6.3 and 6.0 Hz, respectively, 2 \times MeCHOH), 4.23 + 4.62 (AB, *J* 14.7 Hz, NCH₂Ar), 4.63 (d, *J* \approx 7 Hz, CHOHCN₂); δ_C 14.44 (CO₂CH₂Me), 20.75 + 21.28 (2 \times MeCHOH), 40.67 + 40.70 (2 \times NCH₂Ar), 55.38 + 55.45 (MeO's), 56.67 + 57.11 (2 \times C-2), 58.22 + 59.14 (2 \times C-3), 61.16 + 61.18 (2 \times CO₂CH₂Me), 65.95 + 64.98 (2 \times MeCHOH), 68.33 (CHOHCN₂), 98.66 (C-3'), 104.55 + 104.59 (2 \times C-5'), 116.19 (C-1'), 131.43 + 131.30 (2 \times C-6'), 158.23 (C-4'), 160.86 + 160.80 (2 \times C-2'), 165.82 (C-4), 168.00* (CN₂), 168.49 (CO₂Et).†

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 diazoacetate¹¹ (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 CH₂Cl₂ (20 ml) and water (5 ml). Conventional work-up of the CH₂Cl₂ 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; C₁₆H₂₁NO₅ requires C, 62.50; H, 6.90; N, 4.55%); ν_{\max} (film) 1 760–1 730br cm⁻¹; δ_H (60 MHz) 1.22 + 4.10 (t + q, *J* 7 Hz, CO₂Et), 2.4–3.3 (m, 3-H₂ + CH₂CO₂Et), 3.78 + 3.80 (2 \times s, 2 \times MeO), 3.95–4.6 (m, 2-H + NCH₂Ar); *m/z* (rel. intensity; 120 °C) 307 (7.8, *M*⁺), 279 (5.7, *M* – C₂H₄), 261 (1.0, *M* – EtOH), 234 (0.6, *M* – CO₂Et), 220 (5.9, *M* – CH₂CO₂Et), 193 (17.4, OCN-DMB⁺), 166 [10.5; (MeO)₂C₆H₃CH=NH₂], 151 [100, (MeO)₂C₇H₅⁺], and 121 (24.8, MeOC₇H₆⁺).

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 CH₂Cl₂ (10 ml) and DMF (1 drop) with continuous stirring and ice-cooling. Stirring was continued at 0 °C for 2 h. Ethyl diazoacetate¹¹ (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 CH₂Cl₂ (100 ml) was added dropwise to a mixture of dry Me₂SO (12.8 ml, 0.18 mol) in dry CH₂Cl₂ (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 CH₂Cl₂ (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 \times 200 + 1 \times 100 ml), dried (MgSO₄), 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, C₁₈H₂₄N₂O₈ requires C, 54.55; H, 6.10; N, 7.05%); ν_{\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 \times s, 2 \times MeO), 3.85–4.05 (m, OCH₂-CH₂O), 4.25–4.55 (m, CHOHC₂NO₂), and 4.35 + 4.52 (AB, *J* 15 Hz, NCH₂Ar).

(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 CH₂Cl₂ (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; ν_{\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 \times s, 2 \times MeO), 3.85–4.0 (m, OCH₂CH₂O), 4.07 + 4.58 (AB, *J* 14.8 Hz, NCH₂Ar), 4.3–4.6 (m, CH₂NO₂), and 5.85 (ddd, *J* 7.0, 5.5 and 1.5 Hz, CHOAc).

NaBH₄ (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 (i.e., 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 CH₂Cl₂; ν_{\max} (film) 1 740, 1 545, and 1 370 cm⁻¹; δ_H (100 MHz) 1.39 (s, C-Me), 1.96 + 2.45 (ABMX₂, *J*_{gem} 14.6, *J*_{vic} 9.2, 6.2, and 4.0 and 7.3 Hz, respectively, CH₂CH₂NO₂), 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 \times s, 2 \times MeO), 3.8–4.0 (m, OCH₂CH₂O), 4.22 + 4.47 (AB, *J* 14.8 Hz, NCH₂Ar), 4.36 (dd, *J* 6.2 and 7.3 Hz, CH₂CH₂NO₂). 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 H₂SO₄ (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 CH₂Cl₂ (300 ml) and ice (300 g). The CH₂Cl₂ layer was washed with 5% aqueous NaHCO₃ (3 \times 100 ml), dried (MgSO₄), and evaporated to dryness to give the title compound (7.3 g, 91%) as an oil; ν_{\max} (film) 1 750 cm⁻¹; δ_H (100 MHz) 1.39 (s, C-Me), 1.64 + 2.05 [ABMX, *J*_{gem} 13.8, *J*_{vic} 8.8, 4.4, and 6.8 and 4.5 Hz, respectively; CH₂CH(OMe)₂], 3.14 (d, *J* 2.2 Hz, 3-H), 3.24 + 3.26 [2 \times s, CH(OMe)₂], 3.46 (ddd, *J* 2.2, 8.8, and 4.5 Hz, 4-H),

* The correct assignment 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, OCH₂CH₂O), 4.18 + 4.50 (AB, *J* 15.2 Hz, NCH₂Ar), 4.37 [dd, *J* 6.8 and 4.4 Hz, CH₂CH(OMe)₂]; *m/z* (rel. intensity, 120 °C) 395 (1.9, *M*⁺), 364 (2.6, *M* – MeO), 277 {4.1, *M* – [MeO + OCH₂CH₂OC(Me)]}, 262 (5.0), 193 (13.5, OCN-DMB¹⁺), 181 (5.5), 166 [3.0, (MeO)₂C₆H₃CH=NH₂], 151 [97.2, (MeO)₂C₇H₅⁺], 121 (36.2, MeOC₇H₆⁺), 91 (15.5, C₇H₇⁺), 75 [82.9, HC(OMe)₂⁺], and 44 (81.2). The product was, without further purification, subjected to oxidative *N*-deprotection, see below.

(3*RS*, 4*RS*)-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), K₂S₂O₈ (20 g, 74 mmol), Na₂HPO₄·2 H₂O (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**), *v*_{max} (film) 3 250 and 1 760 cm⁻¹; δ_H (100 MHz) 1.43 (s, C-Me), 1.94 [m, CH₂CH(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, OCH₂CH₂O), 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-[(3*RS*, 4*RS*)-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; C₂₀H₂₆N₂O₁₀ requires C, 52.85; H, 5.75; N, 6.15%; *v*_{max} (KBr) 3 320, 1 770, and 1 745 cm⁻¹; δ_H (100 MHz) 1.40 (s, C-Me), 1.82 + 2.02 [ABMX, *J*_{gem} 14.0, *J*_{vic} 6.6, 4.4, and 6.2 and 5.8 Hz, respectively; CH₂CH(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, OCH₂CH₂O), 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; OCH₂Ar), 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-Dimethoxybenzyl-amino)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 CH₂Cl₂ (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. C₁₄H₁₈N₂O₄ requires C, 60.40; H, 6.50; N, 10.05%; *v*_{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*⁺), 247 (3.7, *M* – MeO), 220 (3.1, *M* – CH₂CONH₂), 192 (5.4), 166 [45, (MeO)₂C₆H₃CH=NH₂], 151 [100, (MeO)₂C₇H₅⁺], 121 (40.6, MeOC₇H₆⁺), and 42 (89, CH₂CO).

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. C₁₈H₂₇N₂O₆ requires C, 61.20; H, 7.70; N, 3.95%; *v*_{max} (film) 3 380 and 1 740 cm⁻¹; δ_H (60 MHz) 1.26 + 4.13 (t + q, *J* = 7.2 Hz, 2 × CO₂Et), 2.55 (d, *J* 6 Hz, CH₂CHCH₂), 3.40 (quint, *J* 6 Hz, CH₂CHCH₂), and 3.74 (s, NCH₂Ar); *m/z* (rel. intensity, 120 °C) 353 (1, *M*⁺), 325 (4, *M* – C₂H₄), 280 (2, *M* – CO₂Et), 266 (10, *M* – CH₂CO₂Et), 207 (5, *M* – 2 × CO₂Et), 166 [80, (MeO)₂C₆H₃CH=NH₂], 151 [100, (MeO)₂C₇H₅⁺], 91 (85, C₇H₇⁺), and 77 (46, Ph⁺).

(*RS*)-1-(2,4-Dimethoxybenzyl)-*N*-nitroso-4-oxoazetidine-2-ylacetamide (**13a**).—NaNO₂ (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. C₁₄H₁₇N₃O₅ requires C, 54.70; H, 5.60; N, 13.65%; *v*_{max} (KBr) 3 300, 3 200, 1 740, and 1 710 cm⁻¹; δ_H (100 MHz) 2.7–3.3 (m, 3-H₂ + CH₂CONHNO), 3.81 + 3.83 (2 × s, 2 × MeO), 4.58 (m, 2-H), 4.76 (s, NCH₂Ar), and 8.3 (br s, NHNO).

(*RS*)-1-(2,4-Dimethoxybenzyl)-4-oxoazetidin-2-ylthioacetamide (**14a**).—A slow stream of H₂S 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. C₁₄H₁₈N₂O₃S requires N, 9.50; S, 10.90%; *v*_{max} (KBr) 3 400–3 300 and 1 710 cm⁻¹; *m/z* (rel. intensity, 90 °C) 294 (1, *M*⁺), 266 (14.7), 260 (14.3, *M* – H₂S), 220 (7.1, *M* – CH₂CSNH₂), 206 (7.3), 192 (52.6, OCN-DMB¹⁺), 166 [21.5, (MeO)₂C₆H₃CH=NH₂], 151 [100, (MeO)₂C₇H₅⁺], 121 (61.6, MeOC₇H₆⁺), 91 (26.0, C₇H₇⁺), 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. C₁₅H₂₁IN₂O₃S requires N, 6.40; S, 7.35%; *v*_{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*, 4*SR*, 1'*RS*)- and (*3RS*, 4*SR*, 1'*SR*)-Forms.—70% Aqueous HClO₄ (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 NaHCO₃ (1.67 g), and evaporated to dryness under reduced pressure. The residue, compound (**7f**), was dissolved in methanol (20 ml) and NaBH₄ (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 CH₂Cl₂ (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 \times d, J 6.6 Hz, 2 \times MeCHOH), 2.25 (br s, OH), 2.51 + 2.53 (2 \times m, 2 \times CH_2CN), 3.08 + 3.04 (2 \times dd, J 2.2 and 5.0, and 2.2 and 5.5 Hz, respectively, 2 \times 3-H), 3.68 + 3.82 (2 \times td, J 5.5 and 2.2 Hz, 2 \times 4-H), 4.11 + 4.18 (2 \times qd, J 6.6 and 5.0, and 6.6 and 5.5 Hz, respectively, 2 \times MeCHOH), 4.28 + 4.60 (AB, J 15 Hz, N- CH_2 Ph), 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 ^1H n.m.r.) with an authentic sample obtained as described in ref. 10; ν_{max} (KBr) 3 550, 3 100–2 500 (with several local maxima), 1 745, and 1 720 cm^{-1} [lit.¹⁰ ν_{max} (Nujol) 1 750 and 1 724 cm^{-1}]; m/z (rel. intensity, 125 °C): 263 (31; M^+ , 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, $\text{HO}_2\text{CCH}=\text{CHNHCH}_2\text{Ph}^+$), 132 (177 – CO_2H), 106 (91.8, PhCH_2NH^+), and 91 (100); δ_{H} (100 MHz; [$^2\text{H}_6$]DMSO- d_6 + C^2HCl_3 , 3:1) 1.46 (d, J 6.5 Hz, MeCH), 3.12 + 3.24 (ABX, 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, CHCO_2H), 4.02 (ddd, J 7.8, 8.7, and 3.0 Hz, CHNH), 4.23 (s, CH_2Ph), 5.24 (qd, J 6.5 and 3.5 Hz, MeCH), 7.3–7.7 (m, Ph), in good agreement with the published¹² 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 \times 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 \times ABX, J_{gem} 17, J_{vic} 6.2, 4.6, and 5.8 and 4.6 Hz, respectively; 2 \times CH_2CN), 3.03 + 2.98 (2 \times dd, J 2.2 and 6.0 Hz, 2 \times 3-H), 3.55 + 3.70 (2 \times ddd, J 6.2, 4.6, 2.2, and 5.8, 4.6, and 2.2 Hz, respectively, 2 \times 4-H), 3.80 + 3.83

(2 \times s, MeO's), 4.04 + 4.10 (2 \times qd, J 6.4 and 6.0 Hz, 2 \times MeCHOH), 4.22 + 4.47 (AB, J 14.5, NCH₂Ar). 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 ^1H n.m.r.) with an authentic sample prepared by reductive debenzoylation of compound (28), essentially as described in literature;¹⁰ ν_{max} (KBr) 3 600–2 400, 1 720, and 1 690 cm^{-1} ; δ_{H} (100 MHz; $\text{C}^2\text{H}_3\text{O}^2\text{H}$) 1.38 (d, J 6.5 Hz, MeCH), 2.83 (dd, J 3.5 and 3.0 Hz, CHCO_2H), 2.86 (d, J 6.8 Hz, CH_2CO), 3.97 (td, J 6.8 and 3.5 Hz, CHNH₂), and 4.30 (qd, J 6.5 and 3.0 Hz, MeCH).

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