Simple and Condensed β-Lactams. Part 9.[1] Elaboration of the 3-(1-Hydroxyethyl) Side Chains of Potential Intermediates of Carbapenem Antibiotics *via* the 2-Methyl-1,3-dioxolan-2-yl Group

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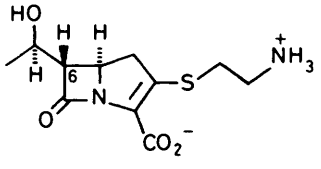
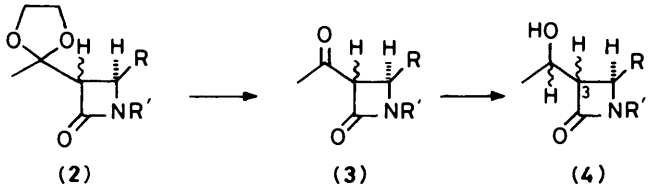
Deketalization of the *trans* compounds methyl and ethyl (2*RS*,3*RS*)-1-(2,4-dimethoxybenzyl)-3-(2-methyl-1,3-dioxolan-2-yl)-4-oxoazetidine-2-carboxylates (**5b**) and (**5c**), and of the *cis* [or (2*RS*,3*SR*)] isomer (**6b**) of the latter leads to 85 : 15 mixtures of the *trans*- and *cis*-compounds methyl (2*RS*,3*RS*)- and (2*RS*,3*SR*)-3-acetyl-1-(2,4-dimethoxybenzyl)-4-oxoazetidine-2-carboxylate (**7a**) and (**8a**), respectively of the corresponding ethyl esters (**7b**) and (**8b**). Sodium borohydride reduction of the mixture of the *trans*- and *cis*-esters (**7b**) and (**8b**) gives a mixture of the 1'-epimeric *trans*-compounds ethyl (2*RS*,3*RS*)-1-(2,4-dimethoxybenzyl)-3-[(1*RS*)- and (1*SR*)-1-hydroxyethyl]-4-oxazetidine-2-carboxylate (**9b**) and (**10b**). Similar mixtures of 1'-epimeric compounds of the types (**9**) and (**10**), carrying a variety of substituents attached to position 2 of their azetidine rings were obtained by successive deketalization and reduction of the corresponding *trans*-(**5**) and *cis*-(**6**) compounds or their mixtures, as well as by other methods. Ring closure of a mixture of the pair of the 1'-epimeric *trans*-compounds *p*-nitrobenzyl 2-diazo-4-{(2RS,3*SR*)-3-[(1*RS*)- and (1*SR*)-1-hydroxyethyl]-4-oxoazetidin-2-yl}-3-oxobutanoates (**9n**) and (**10n**) gave a mixture of the 1'-epimeric compounds *p*-nitrobenzyl 6-[(1*RS*)- and (1*SR*)-1-hydroxyethyl]-2,7-dioxo-(3*RS*,5*RS*,6*SR*)-carbapenam-3-carboxylates (**11**) and (**12**) which was converted into a mixture (**13**) of the 1'-epimeric bis-protected thienamycin analogues *p*-nitrobenzyl 2-(2-formylaminoethylthio)-6-[(1*RS*)- and (1*SR*)-1-hydroxyethyl]-7-oxo-(5*RS*,6*SR*)-carbapen-2-em-3-carboxylates.

Several important members (natural and synthetic) of the family of the carbapenem antibiotics,[2] *e.g.*, thienamycin (**1**), have, as a characteristic structural feature, a 1-hydroxyethyl group attached to the carbapenem nucleus in position 6. In part



(1)

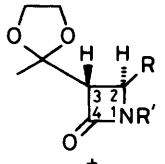
1[3] of the present series a new method was suggested for the synthesis of monocyclic precursors of such carbapenems, based on the elaboration of the 1-hydroxyethyl side chain in position 3 of the precursors *via* the 2-methyl-1,3-dioxolan-2-yl group, as shown in Scheme 1. The starting compounds of type (**2**) were



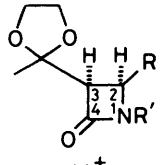
(2) (3) (4)

Scheme 1.

obtained by reaction of diethyl (substituted amino) malonates with diketene, closure of the azetidine ring,[3] and subsequent functional group manipulations.[3,4] Hence, all the resulting β-lactam derivatives were racemic. Here we report (i) the synthesis of some new compounds of type (**2**), (ii) the preparation of some type (**4**) compounds by application of the principle shown in Scheme 1,† and (iii) the conversion of one of the compounds of type (**4**) into the diprotected 6-(1-hydroxyethyl)carbapen-2-em-3-carboxylic acid derivative (**13**).



(5)‡



(6)‡

R	R′
a; CO_2H	DMB
b; CO_2Me	DMB
c; CO_2Et	DMB
d; CO_2CHPh_2	DMB
e; $COCHN_2$§	DMB
f; CH_2CO_2H	DMB
g; CH_2CO_2Me	DMB
h; $CH_2CO_2CHPh_2$	DMB
i; $CH_2COCH_2CO_2PNB$	DMB
k; $CH_2COCN_2CO_2PNB$	DMB
l; CO_2H	H
m; CO_2CHPh_2	H
n; $CH_2CO_2CHPh_2$	H
o; CO_2H	$SiMe_2Bu^t$

R	R′
a; CO_2H	DMB
b; CO_2Et	DMB
c; CO_2CHPh_2	DMB
d; $COCHN_2$§	DMB
e; CH_2CO_2H	DMB
f; CH_2CO_2Me	DMB
g; $CH_2COCH_2CO_2PNB$	DMB
h; $CH_2COCN_2CO_2PNB$	DMB
i; CO_2H	H
k; CO_2CHPh_2	H

DMB = 2,4-Dimethoxybenzyl
PNB *p*-Nitrobenzyl

† For a more complex example of the application of this principle, see ref. 5.

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

§ Numbering different from that shown: locants 2 and 4 should be interchanged.

Preparation of New Compounds of Type (**2**).—The following new racemic compounds of type (**2**) were prepared: the *N*-protected compounds (**5b**), (**5d**), (**6a**), and (**6c**), and the *N*-deprotected compounds (**5l**), (**5m**), (**6i**), and (**6k**). In addition, mixtures of the diastereoisomeric methyl esters (**5g**) and (**6f**), and of the diastereoisomeric diazo-oxoesters (**5k**) and (**6h**) were prepared.

Alkaline hydrolysis of the *cis*-ester (**6b**)[3] led, with inversion of one of the centres of chirality in part of the molecules, to a mixture of the diastereoisomeric carboxylic acids (**5a**) and (**6a**). [No inversion had been observed[3] in the course of the hydrolysis of the corresponding *trans*-ester (**5c**)]. Treatment of the mixture of the carboxylic acids (**5a**) and (**6a**) with diazodiphenylmethane gave a mixture of the corresponding benzhydryl esters (**5d**) and (**6c**) which could be separated by chromatography. Hydrogenolysis of the individual diastereoisomers (**5d**) and (**6c**) led to the pure *trans*-(**5a**)[3] and *cis*-(**6a**) carboxylic acids.

When the mixture of the diastereoisomeric esters (**5d**) and (**6c**) was *N*-deprotected by the established oxidative method,[6] a mixture of the diastereoisomeric esters (**5m**) and (**6k**) was obtained, which were separated by chromatography. Hydrogenolysis of the individual esters furnished the *N*-deprotected *trans*-(**5l**) and *cis*-(**6i**) carboxylic acids.

The mixture of the diastereoisomeric diazo-oxoesters (**5k**) and (**6h**) was obtained from a mixture of the diastereoisomeric 4-oxoazetidine-2-carboxylic acids (**5a**) and (**6a**) *via* mixtures of the diazomethyl ketones (**5e**) and (**6d**), the 4-oxoazetidin-2-ylacetic acids (**5f**) and (**6e**), and the oxoesters (**5i**) and (**6g**) by a sequence of reactions which had been applied before[4] for the conversion of the *trans*-carboxylic acid (**5a**) into the *trans*-diazo-oxoester (**5k**). Furthermore, the mixture of the acids (**5f**) and (**6e**) was converted into a mixture of the diastereoisomeric methyl esters (**5g**) and (**6f**).

Deketalization and Deketalization–reduction of some Compounds of Type (**2**).—The following racemic compounds of type (**2**) were subjected to deketalization or deketalization–reduction: the *N*-protected *trans*-compounds (**5a**),[3] (**5b**), (**5c**),[3] (**5f**),[4] and (**5k**),[4] the *N*-protected *cis*-compound (**6b**),[3] the *N*-deprotected *trans*-compound (**5n**),[4] as well as mixtures of the diastereoisomeric *N*-protected compounds (**5g**) and (**6f**), and (**5k**) and (**6h**), respectively.

Cleavage of the 1,3-dioxolane ring of the compounds of type (**2**) was effected by transketalization with acetone in the presence of 70% aqueous perchloric acid. The diastereoisomeric esters (**5c**) and (**6b**) thereby gave identical mixtures of the (2*RS*,3*RS*)-(**7b**) and (2*RS*,3*SR*)-(**8b**) acetyl derivatives, the ratio of the two products being *ca.* 85:15 in favour of the *trans*-compound (**7b**). Similarly, deketalization of the (2*RS*,3*RS*)-ester (**5b**) furnished a *ca.* 85:15 mixture of the (2*RS*,3*RS*)-(**7a**) and (2*RS*,3*SR*)-(**8a**) acetyl derivatives. The identity of the compositions of the resulting *trans-cis* mixtures indicates that in all cases equilibrium mixtures of the diastereoisomeric products were formed. The preponderance of the (2*RS*,3*RS*)-esters (**7a**) and (**7b**) over their (2*RS*,3*SR*)-diastereoisomers (**8a**) and (**8b**), respectively, is obviously the result of the greater thermodynamic stability of the *trans*-compounds.[7b] In agreement with this, chemists at Merck have isolated *trans*-acetyl derivatives of type (**7**) with various substituents in good to excellent yields by oxidation of both *trans*- and *cis*-3-(1-hydroxyethyl) derivatives (**4**),[7] as well as on acetylation of β-lactams carrying no substituents in position 3.[7a,b] However, neither the Merck chemists,[7] nor other investigators[8] indicated whether significant amounts of the *cis*-isomers of the finally isolated *trans*-products were present in the crude products. Similarly, periodate oxidation of a *cis*-3-isopropenylazetidinone gave the corresponding *trans*-3-acetyl derivative.[9a] A single case is known from literature[9b] where an acetyl derivative of type (**7**), *viz.* compound (**7c**), has been obtained by acid catalysed *trans*-ketalization of the corresponding 3-(2-methyl-1,3-dioxolan-2-yl) derivative (**5o**); but, again, it is not clear whether the *cis*-isomer (**8c**) was present in the crude product.

By reketalization of the mixture of the diastereoisomeric *trans*-(**7a**) and *cis*-(**8a**) compounds the pure *trans*-compound (**5b**) was obtained. Similarly, successive deketalization and $NaBH_4$ reduction of either the *trans*-compounds of type (**5**) or of their *cis*-isomers (**6**), or of mixtures of the two diastereoisomers furnished epimeric mixtures of the corresponding *trans*-compounds (**9**) and (**10**). Thus, deketalization

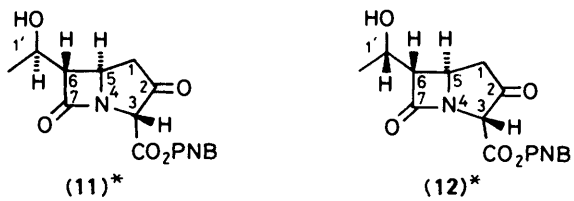
(**7**)* (**8**)*

	R	R′
a;	CO_2Me	DMB
b;	CO_2Et	DMB
c;	CO_2H	$SiMe_2Bu^t$

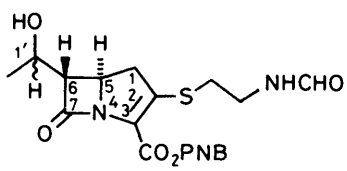
DMB = 2,4-Dimethoxybenzyl
PNB = *p*-Nitrobenzyl

(**9**)* (**10**)*

	R	R′
a;	CO_2H	DMB
b;	CO_2Et	DMB
c;	$COCHN_2$ †	DMB
d;	CH_2CO_2H	DMB
e	CH_2CO_2Me	DMB
f;	$CH_2CO_2CHPh_2$	DMB
g;	$CH_2COCH_2CO_2PNB$	DMB
h;	$CH_2COCN_2CO_2PNB$	DMB
i;	CH_2CO_2H	H
k;	CH_2CO_2Me	H
l;	$CH_2CO_2CHPh_2$	H
m;	$CH_2COCH_2CO_2PNB$	H
n;	$CH_2COCN_2CO_2PNB$	H



(**11**)* (**12**)*



(**13**)*
(Mixture of 1′-epimers)

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

† Numbering different from that shown: locants 2 and 4 should be interchanged.

and reduction of the *trans*-carboxylic acid (**5a**) led to a mixture of the epimeric carboxylic acids (**9a**) and (**10a**). The same product was obtained by similar treatment of either the *trans*-(**5c**) or the *cis*-(**6b**) ester, and subsequent alkaline hydrolysis of the resulting mixture of the epimeric esters (**9b**) and (**10b**). The benzhydryl ester (**5h**) of the homologous acetic acid, as well as its *N*-deprotected analogue (**5n**) were similarly deketalized and reduced.

Successive deketalization and $NaBH_4$ reduction of the diazo-oxoester (**5k**) was, without affecting the diazo-oxoester side chain, selectively achieved to give a mixture of the epimeric compounds (**9h**) and (**10h**) by carrying out the borohydride reduction at −78 °C. A similar mixture of the epimers (**9h**) and (**10h**) was obtained by the same procedure also from a mixture of the diastereoisomeric compounds (**5k**) and (**6h**). When the crude epimeric mixture was kept under ether, one of the pure epimers, (**10h**) [as shown by comparison of the chemical shift and the values of the coupling constants of the signal of 3-H with those of the closely related epimers (**9n**) and (**10n**) known from literature [10b]] gradually crystallized. Similarly, when a mixture of the *N*-protected methyl esters (**9k**) and (**10k**) [obtained from a mixture of the diastereoisomeric esters (**5g**) and (**6f**) by successive deketalization, reduction, and oxidative *N*-deprotection [6]] was taken up in dichloromethane, the pure epimer (**10k**) gradually crystallized.

Functional Group Manipulations in the Side Chains in Position 2 of Mixtures of some Pairs of Epimers of Types (**9**) *and* (**10**).—The functional group manipulations were carried out by established methods. Thus, alkaline hydrolysis of a mixture of esters (**9b**) and (**10b**) led to a mixture of the carboxylic acids (**9a**) and (**10a**). Activation of the carboxyl groups of the latter and reaction with diazomethane gave a mixture of the diazoketones (**9c**) and (**10c**). Irradiation of this mixture furnished a mixture of the azetidin-2-ylacetic acids (**9d**) and (**10d**) which was treated with diazodiphenylmethane to give a mixture of the benzhydryl esters (**9f**) and (**10f**). The mixture of the acetic acids (**9d**) and (**10d**) was converted by Masamune's method [11] into a mixture of the *N*-protected β-oxoesters (**9g**) and (**10g**). The same chain extension was carried out in the *N*-deprotected series to give a mixture of the β-oxoesters (**9m**) and (**10m**); the starting mixture of the acids (**9i**) and (**10i**) was obtained by hydrogenolysis of the mixture of benzhydryl esters (**9l**) and (**10l**). The diazo exchange reaction [12] applied to mixtures of the epimeric β-oxoesters led to mixtures of the corresponding diazo-oxoesters both in the *N*-protected [compounds (**9h**) and (**10h**)] and *N*-deprotected series [compounds (**9n**) and (**10n**)].

N-De(2,4-*dimethoxybenzylations*).—Mixtures of the *N*-protected methyl and benzhydryl esters (**9e**) and (**10e**), and (**9f**) and (**10f**), respectively, as well as of the *N*-protected diazo-oxoesters (**9h**) and (**10h**) were deprotected by the standard oxidative procedure [6] to give mixtures of the corresponding *N*-deprotected compounds (**9k**) and (**10k**), (**9l**) and (**10l**), and (**9n**) and (**10n**), respectively. The (non-optimized) yield in the last case was rather low which may be the result of the sensitivity of the diazo-oxoester entity to the deprotection conditions.

Preparation of some Carbapenam Derivatives.—Application of the intramolecular carbene insertion reaction developed by workers at Merck [13] to the mixture of compounds (**9n**) and (**10n**) gave a mixture of the epimeric carbapenam derivatives (**11**) and (**12**). This mixture was then converted by the established Merck method [10] into a mixture of the epimeric compounds (**13**).

Experimental

M.p.s are uncorrected. I.r. spectra were obtained on Spektromom 2000 (Hungarian Optical Works, Budapest) and Specord 75 (Zeiss, Jena, GDR) instruments. ^1H N.m.r. spectra were recorded with a Varian XL-100 spectrometer at 100 MHz in, unless otherwise stated, $CDCl_3$ solutions at *ca.* 50 °C in the presence of Me_4Si as the internal reference. The 400 MHz ^1H n.m.r. spectrum of the mixture (**7a**) + (**8a**) was obtained with a Varian XL-400 instrument.

3-(2-*Methyl*-1,3-*dioxolan*-2-*yl*)-4-*oxoazetidine*-2-*carboxylic Acids* (**5a**), (**5l**), (**6a**), *and* (**6i**).—(*a*) A mixture of ethyl (2*RS*,3*SR*)-1-(2,4-dimethoxybenzyl)-3-(2-methyl-1,3-dioxolan-2-yl)-4-oxoazetidine-2-carboxylate (**6b**) [3] (3.8 g, 10 mmol), water (10 ml), pyridine (5 ml), and NaOH (0.4 g, 10 mmol), was stirred for 6h at room temperature, diluted with water (*ca.* 80 ml), and extracted with CH_2Cl_2 (3 × 20 ml). The aqueous phase was treated with Norite, acidified with concentrated HCl, and extracted with CH_2Cl_2 (3 × 50 ml) to give, after conventional work-up, a viscous oil which, when triturated with ether, crystallized to give a mixture (2.7 g, 77%) of the diastereoisomeric (2RS,3SR)- and (2RS,3RS)-1-(2,4-*dimethoxybenzyl*)-3-(2-*methyl*-1,3-*dioxolan*-2-*yl*)-4-*oxoazetidine*-2-*carboxylic acids* (**6a**) and (**5a**), m.p. 104—105 °C [Found (mixture): C, 57.55; H, 6.1; N, 3.85. $C_{17}H_{21}NO_7$ requires C, 57.30; H, 5.95; N, 3.93%]; $\nu_{max.}$(KBr) 3 300—2 500, 1 750, and 1 710 cm^{-1}. According to its ^1H n.m.r. spectrum the product was a *ca.* 55:45 mixture of compounds (**5a**) and (**6a**).

(*b*) A mixture (34.8 g, 92 mmol) of the diastereoisomeric esters (**5c**) and (**6b**) [3] was similarly hydrolysed to give a mixture (28.7 g, 89%) of the (2*RS*,3*RS*)-(**5a**) and (2*RS*,3*SR*)-(**6a**) carboxylic acids which was converted without further purification into a mixture of the diastereoisomeric methyl (2*RS*,3*SR*)-(**5g**) and (2*RS*,3*RS*)-(**6f**)-1-(2,4-dimethoxybenzyl)-3-(2-methyl-1,3-dioxolan-2-yl)-4-oxoazetidin-2-ylacetates (see below).

(*c*) An ethanolic (10 ml) solution of the (2*RS*,3*RS*)-benzhydryl ester (**5d**) (see below) (0.94 g, 1.82 mmol) was hydrogenolysed in the presence of a 10% Pd–C catalyst (0.1 g) to give, after conventional work-up, the corresponding acid (**5a**) (0.33 g, 52%) as a colourless oil which crystallized [m.p. 118 °C, lit.,[3] 117—118 °C (from toluene)] when triturated with ether. I.r. and ^1H n.m.r. spectra were in good agreement with those published in the literature.[3]

(*d*) Reduction of the (2*RS*,3*SR*)-benzhydryl ester (**6c**) (see below) (0.47 g, 0.91 mmol) similarly furnished the (2*RS*,3*RS*)-carboxylic acid (**6a**) (0.11 g, 34%) as a colourless oil which crystallized (m.p. 138 °C), when triturated with ether (Found: C, 57.55; H, 6.1; N, 3.85. $C_{17}H_{21}NO_7$ requires C, 58.11; H, 6.03; N, 3.99%); $\nu_{max.}$(KBr) 3 300—2 800, 1 750, and 1 720 cm^{-1}; δ_H 1.46 (s, CMe), 3.73 (d, *J* 6.0 Hz, 3-H), 3.78 (s, 2 × MeO), 3.85—4.10 (m, OCH_2CH_2O), 4.00 (d, *J* 6.0 Hz, 2-H), 4.25 + 4.72 (AB, J_{gem} 14.5 Hz, NCH_2Ar), 6.35—6.5 (m, 3′-H + 5′-H),* 7.14 (d, *J* 8.9 Hz, 6′-H),* and 8.5 (br s, CO_2H).

(*e*) The benzhydryl ester (**5m**) (see below) was dissolved in 40 parts of ethanol and hydrogenolysed in the presence of 0.1 parts of a 10% Pd–C catalyst at room temperature to give, after conventional work-up, the (2*RS*,3*RS*)-carboxylic acid (**5l**) (88%) as a colourless oil which crystallized, m.p. 162 °C (from EtOH), when triturated with ether (Found: C, 47.9; H, 5.8; N, 7.05. $C_8H_{11}NO_5$ requires C, 47.76; H, 5.51; N, 6.97%); $\nu_{max.}$(KBr) 3 320—2 800, 3 230, 1 750, and 1 705 cm^{-1}; δ_H[$CDCl_3$–$(CD_3)_2SO$, 3:1] 1.45 (s, CMe), 3.52 (d, *J* 2.6 Hz, 3-H), 3.85—4.2 (m, OCH_2CH_2O + 2-H), and 7.1 (br s, NH + CO_2H).

(*f*) The (2*RS*,3*SR*)-carboxylic acid (**6i**), m.p. 180 °C (decomp.), was similarly obtained in 90% yield, starting with the benzhydryl ester (**6k**) (see below) (Found: C, 47.85; H, 5.75; N, 6.9. $C_8H_{11}NO_5$ requires C, 47.76; H, 5.51; N, 6.97%); $\nu_{max.}$(KBr)

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

3 350—2 850, 3 210, 1 745, and 1 700 cm^{-1}; δ_H[$CDCl_3$–$(CD_3)_2SO$, 2:1] 1.47 (s, CMe), 3.80 (d, *J* 6.0 Hz, 3-H), 3.85—4.15 (m, OCH_2CH_2O), 4.18 (d, *J* 6.0 Hz, 2-H), 7.1 (br s, CO_2H), and 7.5 (br s, NH).

Methyl (2RS,3RS)-1-(2,4-*Dimethoxybenzyl*)-3-(2-*methyl*-1,3-*dioxolan*-2-*yl*)-4-*oxoazetidine*-2-*carboxylate* (**5b**).—The acid (**5a**) was converted into the diazoketone (**5e**) was described earlier.[4] Chromatographic work-up of the reaction mixture[4] furnished, in addition to the diazoketone (**5e**), the ester (**5b**) (35—38%) in the form of a gradually crystallizing oil (m.p. 85—86 °C) as the more polar product (Found: C, 58.9; H, 6.25; N, 4.1. $C_{18}H_{23}NO_7$ requires C, 59.18; H, 6.34; N, 3.83%); $\nu_{max.}$(KBr) 1 760—1 740 cm^{-1}.

Benzhydryl 3-(2-*Methyl*-1,3-*dioxolan*-2-*yl*)-4-*oxoazetidine*-2-*carboxylates* (**5d**), (**5m**), (**6c**), *and* (**6k**).—(*a*) A CH_2Cl_2 solution (10 ml) of the mixture (1.05 g, 3.0 mmol) of the acids (**5a**) and (**6a**) (see above) was stirred with diazodiphenylmethane (0.58 g, 3.0 mmol) at room temperature until, after *ca.* 10 min, the colour of the reagent disappeared. The mixture was evaporated to dryness and worked up by medium-pressure chromatography (200 kPa; Kieselgel G, 100 g; CH_2Cl_2–EtOAc, 20:1) to give the pure (2*RS*,3*RS*)-(**5d**) (0.94 g, 60.5%), m.p. 96 °C (EtOH), and the pure (2*RS*,3*SR*)-(**6c**) esters (0.47 g, 30%), m.p. 118 °C (EtOH).

Compound (**5d**) (Found: C, 69.5; H, 6.15; N, 2.9. $C_{30}H_{31}NO_7$ requires C, 69.62; H, 6.03; N, 2.71%); $\nu_{max.}$(KBr) 1 760br cm^{-1}; δ_H 1.37 (s, CMe), 3.36 [dd, *J* 2.6, 0.9 Hz (long-range coupling with the low-field proton of the NCH_2Ar group), 3-H], 3.59 + 3.77 (2 × s, 2 × MeO), 3.88 (d, *J* 2.6 Hz, 2-H), 3.85—4.0 (m, OCH_2CH_2O), 4.15 + 4.65 (dd + d, AB spectrum, *J* 14.6 Hz with long-range coupling of the low-field proton with 3-H, NCH_2Ar), 6.92 (s, $CHPh_2$), and 7.31 (s, 2 × Ph).

Compound (**6c**) (Found: C, 69.85; H, 5.95; N, 2.85. $C_{30}H_{31}NO_7$ requires C, 69.62; H, 6.03; N, 2.71%); $\nu_{max.}$(KBr) 1 765br cm^{-1}; δ_H 1.33 (s, *C*Me), 3.51 + 3.77 (2 × s, 2 × MeO), 3.67 (d, *J* 6.0 Hz, 3-H), 3.6—3.75 (m, OCH_2CH_2O), 3.99 (d, *J* 6.0 Hz, 2-H), 4.22 + 4.75 (AB, J_{gem} 14.4 Hz, NCH_2Ar), 7.01 (s, $CHPh_2$), and 7.25—7.45 (m, 2 × Ph).

(*b*) The crude mixture of the diastereoisomeric esters (**5d**) and (**6c**), obtained from the mixture (8.3 g, 24 mmol) of the corresponding acids (**5a**) and (**6a**) by treatment with diazodiphenylmethane (4.6 g, 24 mmol) in CH_2Cl_2 (80 ml) as described above was refluxed with a mixture of $K_2S_2O_8$ (26 g, 96 mmol), $Na_2HPO_4 \cdot 12H_2O$ (68.7 g, 192 mmol), acetonitrile (140 ml), and water (54 ml) for 4 h with vigorous stirring. The mixture was allowed to cool, the inorganic salts were filtered off, and the aqueous phase of the filtrate extracted with EtOAc (3 × 50 ml). The organic phase of the filtrate was evaporated to dryness, the combined EtOAc solutions were added to the residue and the resulting solution was washed successively with 5% aqueous Na_2CO_3 (2 × 20 ml) and brine (30 ml), dried, and evaporated to dryness. The residue was worked up by medium-pressure chromatography (200 kPa; Kieselgel G; CH_2Cl_2–acetone, 20:1→10:1) to give the pure (2*RS*,3*RS*)-(**5m**) (5.0 g, 56%) and (2*RS*,3*SR*)-(**6k**) esters (2.7 g, 28%) as oils which were subjected to hydrogenolysis (see above) without further purification; $\nu_{max.}$(film), compound (**5m**): 3 290br and 1 770—1 730 cm^{-1}; compound (**6k**): 3 290br and 1 770—1 730 cm^{-1}.

Mixture of the Diastereoisomeric Methyl (2RS,3SR)- *and* (2RS,3RS)-1-(2,4-*Dimethoxybenzyl*)-3-(2-*methyl*-1,3-*dioxolan*-2-*yl*)-4-*oxoazetidin*-2-*ylacetates* (**5g**) *and* (**6f**).—(*a*) The mixture (2.6 g, 7.4 mmol) of the diastereoisomeric acids (**5a**) and (**6a**) was converted into the oily mixture of the diastereoisomeric diazomethyl ketones (**5e**) and (**6d**) (total yield 54%) as described earlier[4] for the analogous conversion of the (2*RS*,3*RS*)-acid (**5a**) into the (2*RS*,3*RS*)-diazomethyl ketone (**5e**); $\nu_{max.}$(film) 2 120, 1 750, and 1 630 cm^{-1}; δ_H (*ca.* 1:1 mixture) 1.37 and 1.38 (2 × s, CMe), 3.33 (d, *J* 2.5 Hz, 3-H, *trans*), 3.69 (d, *J* 6.1 Hz, 3-H, *cis*), 3.76 + 3.77, and 3.79 (3 × s, MeO groups), 3.91 (d, *J* 2.5 Hz, 4-H, *trans*), 3.96 (d, *J* 6.1 Hz, 4-H, *cis*), 3.9—4.15 (m, OCH_2CH_2O), 4.19 + 4.65 and 4.22 + 4.61 (2 × AB, J_{gem} 14.4 and 14.6 Hz, respectively, NCH_2Ar groups), 5.33 (s, CHN_2, *trans*), and 5.50 (s, CHN_2, *cis*). This mixture was subjected to the Wolff rearrangement without further purification.

(*b*) The above mixture (1.5 g, 40 mmol) of the diastereoisomeric diazomethyl ketones (**5e**) and (**6d**) was converted into a yellow oily mixture of the diastereoisomeric (2*RS*,3*SR*)-(**5f**) and (2*RS*,3*RS*)-(**6e**) 1-(2,4-dimethoxybenzyl)-3-(2-methyl-1,3-dioxolan-2-yl)-4-oxoazetidin-2-ylacetic acids [total yield 75%; $\nu_{max.}$(film) 3 000—2 600 and 1 730—1 700 cm^{-1}] as described earlier[4] for the preparation of the (2*RS*,3*SR*) compound (**5f**). The mixture was converted, without further purification, by treatment of its CH_2Cl_2 solution with freshly prepared ethereal diazomethane solution into an oily mixture of the title compounds [overall yield: 68%; $\nu_{max.}$(film) 1 750 and 1 720sh cm^{-1}] which was subjected to deketalization and reduction without further purification.

Mixture of the Diastereoisomeric p-*Nitrobenzyl* 4-[(2RS,3SR)-*and* (2RS,3RS)-1-(2,4-*Dimethoxybenzyl*)-3-(2-*methyl*-1,3-*dioxolan*-2-*yl*)-4-*oxoazetidin*-2-*yl*]-3-*oxobutanoates* (**5i**) *and* (**6g**).—A mixture (2.6 g, 7.4 mmol) of the diastereoisomeric acids (**5a**) and (**6a**) was converted *via* the mixture of the diazomethyl ketones (**5e**) and (**6d**) into a mixture of the 4-oxoazetidin-2-ylacetic acids (**5f**) and (**6e**) as described above. The resulting crude mixture was converted into the yellow oily mixture of the β-oxoesters (**5i**) and (**6g**) (total yield 67.5%, overall 50.5%) as described earlier[4] for the conversion of the (2*RS*,3*RS*)-diazomethyl ketone (**5e**) into the (2*RS*,3*SR*)-β-oxoester (**5i**) (Found: N, 5.35. $C_{27}H_{30}N_2O_{10}$ requires N, 5.16%); $\nu_{max.}$(film) 1 760—1 710, 1 580, 1 350, and 830 cm^{-1}; δ_H 1.38 (s, CMe), 2.74 + 2.81 (ABX, J_{gem} 18 Hz, J_{vic} 6.6 and 5.5 Hz, respectively, 2-CH_2CO), 3.11 (d, *J* 2.5 Hz, 3-H), 3.39 (s, $COCH_2CO_2$), 3.79 (s, 2 × MeO), 3.80 (m, 2-H), 3.85—4.05 (m, OCH_2CH_2O), 4.20 + 4.40 (AB, J_{gem} 15.2 Hz, NCH_2Ar), 5.25 (s, OCH_2Ar), and 7.50 + 8.21 (AA′BB′, *J* 8.7 Hz, ArH's of PNB group). The product was shown by its ^1H n.m.r. spectrum to be the practically pure *trans*-isomer (**5i**) with minor amounts of the enol form being present.

Mixture of the Diastereoisomeric p-*Nitrobenzyl* 2-*Diazo*-4-[(2RS,3SR)-*and* (2RS,3RS)-1-(2,4-*dimethoxybenzyl*)-3-(2-*methyl*-1,3-*dioxolan*-2-*yl*)-4-*oxoazetidin*-2-*yl*]-3-*oxobutanoates* (**5k**) *and* (**6h**).—The above mixture (1.1 g, 2.0 mmol) of the diastereoisomeric β-oxoesters (**5i**) and (**6g**) was converted into the oily mixture of their 2-diazo derivatives (total yield 48%) as described earlier[4] for the preparation of the (2*RS*,3*SR*)-compound (**5k**) from the oxoester (**5i**); $\nu_{max.}$(film) 2 200, 1 760—1 710, 1 650, 1 590, 1 350, 850, and 830 cm^{-1}. This mixture was subjected to deketalization without further purification, see below.

Deketalization of Methyl (2RS,3RS)-(**5b**), *Ethyl* (2RS,3RS)-(**5c**), *and Ethyl* (2RS,3SR)-(**6b**) 1-(2,4-*Dimethoxybenzyl*)-3-(2-*methyl*-1,3-*dioxolan*-2-*yl*)-4-*oxoazetidine*-2-*carboxylates*.—(*a*) Aqueous $HClO_4$ (70%; 1.7 ml, 20 mmol) was added with continuous stirring and ice–water cooling to a mixture of the ester (**5b**) (3.1 g, 8.5 mmol) and acetone (85 ml). The cooling bath was removed, and stirring was continued for 0.5 h. Finely pulverized $NaHCO_3$ (1.66 g, 20 mmol) was added and the mixture stirred for 10 min, then evaporated to dryness under reduced pressure. The residue was taken up in a mixture of CH_2Cl_2 (50 ml) and water (10 ml). The organic phase was washed with water (2 × 10 ml), dried ($MgSO_4$), and evaporated

to dryness to give the yellowish oily deketalized product (2.8 g, 98%). An aliquot was purified by t.l.c. (Kieselgel PF_{254}; CH_2Cl_2–acetone, 100:1) and shown by its ^1H n.m.r. spectrum to be a *ca.* 85:15 mixture of the *trans*-(**7a**) and *cis*-(**8a**) acetyl derivatives (Found: C, 59.65; H, 5.7; N, 4.6. $C_{16}H_{19}NO_6$ requires C, 59.80; H, 5.96; N, 4.36%); $\nu_{max.}$(film) 1 775br and 1 720 cm^{-1}; δ_H (400 MHz) 2.31 (s, Ac), 3.71 and 3.77 (2 × s, CO_2Me's), 3.75 and 3.79 + 3.80 (3 × s, MeO's), 3.97 (d, *J* 5.5 Hz, 3-H, *cis*), 4.19 (d, *J* 2.4 Hz, 3-H, *trans*), 4.18, 4.20 + 4.59 and 4.61 (AB spectra, J_{gem} 14.6 Hz, NCH_2Ar), 4.30 (d, *J* 5.5 Hz, 4-H, *cis*), and 4.34 (d, *J* 2.4 Hz, 4-H, *trans*).

(*b*) Similar treatment of the ester (**6b**)[3] (0.76 g, 2 mmol) gave the oily deketalized product (90%), an aliquot of which was purified by t.l.c. as described in (*a*) and shown by ^1H n.m.r. to be a *ca.* 85:15 mixture of the *trans*-(**7b**) and *cis*-(**8b**) acetyl derivatives (Found: C, 61.05; H, 6.1; N, 3.95. $C_{17}H_{21}NO_6$ requires C, 60.88; H, 6.31; N, 4.18%); $\nu_{max.}$(film) 1 755, 1 740, and 1 710 cm^{-1}; δ_H 1.24, 1.28, and 4.16 (2 × t + q, *J* 7.1 Hz, CO_2Et's), 2.29 (s, Ac), 3.76 and 3.78 + 3.80 (3 × s, MeO's), 3.97 (d, *J* 5.5 Hz, 3-H, *cis*), 4.17 (d, *J* 2.5 Hz, 3-H, *trans*), 4.19 + 4.59 (AB, J_{gem} 14.5 Hz, NCH_2Ar), 4.26 (d, *J* 5.5 Hz, 4-H, *cis*), and 4.31 (d, *J* 2.5 Hz, 4-H, *trans*).

(*c*) A mixture of identical composition of compounds (**7b**) and (**8b**) was obtained by similar treatment of the ester (**5c**).

Reketalization of the Mixture of the Diastereoisomeric 3-*Acetyl Derivatives* (**7a**) *and* (**8a**).—Boron trifluoride–diethyl ether (2.4 ml, 20 mmol) was added with continuous stirring and ice–water cooling to a solution of the 85:15 mixture of compounds (**7a**) and (**8a**) (2.4 g, 7.2 mmol) and 1,2-ethanediol (1.4 ml, 25 mmol) in anhydrous dioxane (8.0 ml). The cooling bath was removed, and the mixture was stirred for 1 h, and kept overnight in a refrigerator. Finely pulverized Na_2CO_3 (2.1 g, 20 mmol) and water (5 ml) were added. When evolution of CO_2 had ceased, the mixture was poured into water (40 ml) and extracted with ether to give a gradually crystallizing oil (2.5 g, 92%), (m.p. 80—83 °C). Purification of an aliquot by t.l.c. (Kieselgel PF_{254}; CH_2Cl_2–acetone, 100:1) raised the m.p. to 85—86 °C [identical with that of an authentic sample of compound (**5b**), see above]. The purified sample was shown also by its i.r. and ^1H n.m.r. spectra to be the pure *trans*-ester (**5b**), δ_H 1.39 (s, CMe), 3.41 (d, *J* 2.5 Hz, 3-H), 3.71 (s, CO_2Me), 3.78 + 3.80 (2 × s, 2 × MeO), 4.02 (d, *J* 2.5 Hz, 2-H), 3.85—4.1 (m, OCH_2CH_2O), and 4.22 + 4.61 (AB, J_{gem} 14.8 Hz, NCH_2Ar).

Successive Deketalizations and Reductions of Compounds (**5a**), (**5c**), (**5h**), (**5k**), (**5n**), *and* (**6b**) *and of the Mixtures of Compounds* (**5g**), *and* (**6f**), *and* (**5k**) *and* (**6h**).—(*a*) A mixture of the (2*RS*,3*RS*)-acid (**5a**)[3] (2.0 g, 5.7 mmol), acetone (50 ml), and 70% aqueous $HClO_4$ (1.14 ml) was stirred for 2 h at 0 °C. Sodium hydrogen carbonate (2.1 g) was added and the mixture evaporated to dryness at room temperature after which sodium borohydride (0.23 g, 6 mmol) was added to the ethanolic (10 ml) suspension of the residue, and the mixture stirred for a further 2 h. Water (50 ml) was added, and the mixture acidified (pH 1) with concentrated HCl and poured into brine (50 ml). Extraction with CH_2Cl_2 (3 × 20 ml) and conventional work-up gave an oily mixture (1.65 g, 94%) of the epimeric (2RS,3RS)-1-(2,4-*dimethoxybenzyl*)-3-[(1RS)- *and* (1SR)-1-*hydroxyethyl*]-4-*oxoazetidine*-2-*carboxylic acids* (**9a**) and (**10a**) which, without further purification, was converted into the epimeric mixture of the diazomethyl ketones (**9c**) and (**10c**), see below.

(*b*) Except for minor modifications of the above procedure the following compounds were similarly obtained: (i) oily mixtures of the epimeric *ethyl* (2RS,3RS)-1-(2,4-*dimethoxybenzyl*)-3-[(1RS)- *and* (1SR)-1-*hydroxyethyl*]-4-*oxoazetidine*-2-*carboxylates* (**9b**) and (**10b**) from both the (2*RS*,3*RS*)-(**5c**) and (2*RS*,3*SR*)-(**6b**) esters (2.0 g, 5.3 mmol) [without acidification of the reduction mixture] in 100 and 96% yields, respectively, aliquots of which were purified by t.l.c. (Kieselgel 60 PF_{254}; benzene–acetone, 7:3), and which were hydrolysed without further purification to the mixture of the corresponding carboxylic acids (**9a**) and (**10a**), see below. δ_H 1.25 + 4.18 (t + q, *J* 7.1 Hz, CO_2Et), 1.28 and 1.25 (2 × d, *J* 6.5 Hz, *Me*CH groups), 2.2 (br s, OH), 3.16 and 3.18 (m, 3-H), 3.76 and 3.96 (2 × d, *J* 2.5 Hz, 2-H), 3.78 + 3.79 (2 × s, 2 × MeO), 4.04 (m, 1′-H), and 4.19 + 4.62 (AB, J_{gem} 14.5 Hz, NCH_2Ar); the product was shown by its ^1H n.m.r. spectrum to be a *ca.* 60:40 mixture of the two 1′-epimers.

(ii) A mixture of the epimeric *benzhydryl* (2RS,3SR)-1-(2,4-*dimethoxybenzyl*)-3-[(1RS)- *and* (1SR)-1-*hydroxyethyl*]-4-*oxoazetidin*-2-*ylacetates* (**9f**) and (**10f**) from the (2*RS*,3*SR*)-ester (**5h**) (5.3 g, 10 mmol) [with the reduction carried out in methanol, and neutralization of the reduction mixture with AcOH] in 61% yield as an oil which crystallized (m.p. 126 °C) when triturated with ether (Found: C, 71.3; H, 6.15; N, 2.95. $C_{29}H_{31}NO_6$ requires C, 71.14; H, 6.38; N, 2.86%); $\nu_{max.}$(KBr) 3 400 and 1 725 cm^{-1}; δ_H 1.11 and 1.18 (2 × d, *J* 6.5 Hz, *Me*CH groups), 2.25 and 2.59 (2 × d, *J* 5.4 and 4.0 Hz, respectively, OH groups), 2.53 and 2.56, and 2.86 and 2.90 (2 × ABX, J_{gem} 15.7 and 16.0 Hz, J_{vic} 9.0 and 4.0 Hz, respectively, CH_2CO_2), 2.8—3.0 (dd, 3-H), 3.66 (ddd, *J* 9.0, 4.0, and 2.0 Hz, 2-H), 3.75 + 3.77 (2 × s, 2 × MeO), 3.7—4.1 (m, 1′-H), 4.08 + 4.46 (AB, J_{gem} 14.8 Hz, NCH_2Ar), 6.89 (s, $OCHPh_2$), and 7.30 (s, 2 × Ph); the product was shown by its ^1H n.m.r. spectrum to be a *ca.* 60:40 mixture of the two epimers.

(iii) A mixture of the epimeric *benzhydryl* (2RS,3SR)-3-[(1RS)- *and* (1SR)-1-*hydroxyethyl*]-4-*oxoazetidin*-2-*ylacetates* (**9l**) and (**10l**) from ester (**5n**)[4] (0.38 g, 1 mmol) [with the reduction carried out in methanol, neutralization of the reduction mixture with AcOH, and work-up of the dry residue of the CH_2Cl_2 solution by preparative t.l.c. (Kieselgel PF_{254}; CH_2Cl_2–acetone, 7:1)] in 74% yield as an oil which crystallized [m.p. 135 °C (from EtOH)] when triturated with ether, and which proved identical (i.r.) with the product obtained by *N*-deprotection of the mixture of epimers (**9f**) and (**10f**), see below (Found: N, 4.05. $C_{20}H_{21}NO_4$ requires N, 4.13%); $\nu_{max.}$(KBr) 3 300br, 1 750, and 1 720 cm^{-1}.

(iv) An oily mixture (total yield, 54%) of the epimeric methyl (2*RS*,3*SR*)-1-(2,4-dimethoxybenzyl)-3-[(1*RS*)- and (1*SR*)-1-hydroxyethyl]-4-oxoazetidin-2-ylacetates (**9e**) and (**10e**) from the mixture of the diastereoisomeric methyl esters (**5g**) and (**6f**) [with the reduction carried out in methanol, neutralization of the reduction mixture with acetic acid, and isolation of the product by chromatography (200 kPa; Kiesegel G; CH_2Cl_2–acetone, 10:1); $\nu_{max.}$(film) 3 430, 1 750, and 1 720d cm^{-1}; δ_H (60 MHz), selected values: 1.22 + 1.27 (2 × d, *J* 6.5 Hz, *Me*CH groups), 2.95 (dd, *J* 5 and 2 Hz, 3-H of one epimer), 3.65 (s, CO_2Me), 3.78 (s, 2 × MeO), and 4.05 + 4.47 AB, J_{gem} 14.8 Hz; NCH_2Ar] which was subjected to *N*-deprotection without further purification (see below).

(*c*) A mixture of the (2*RS*,3*SR*)-diazo-oxoester (**5k**)[4] (5.68 g, 10 mmol), acetone (80 ml), and 70% aqueous $HClO_4$ (1.65 ml) was stirred for 1 h at 0 °C. Sodium hydrogen carbonate (2.0 g) was added and stirring continued for a further 0.5 h. The mixture was evaporated to dryness at reduced pressure at room temperature and the residue taken up in CH_2Cl_2 (100 ml) and washed with water (3 × 30 ml). The combined aqueous washings were extracted with CH_2Cl_2 (30 ml), and the combined CH_2Cl_2 solutions dried ($MgSO_4$), and evaporated to dryness to give a yellow oil (4.7 g). The anhydrous methanol solution (50 ml) of this oil was cooled to −78 °C. Sodium borohydride (0.185 g, 4.8 mmol) was added, and the mixture stirred for 6 h at this temperature. After neutralization with AcOH at −78 °C, the mixture was evaporated to dryness at reduced pressure at room temperature, and the residue purified by chromatography (Kieselgel 60, 0.063—0.200; benzene–

acetone, 7:3) to give a mixture (4.37 g, 83%) of the diastereoisomeric p-*nitrobenzyl* 2-*diazo*-4-{(2RS,3SR)-1-(2,4-*dimethoxybenzyl*)-3-[(1RS)- *and* (1SR)-1-*hydroxyethyl*]-4-*oxoazetidin*-2-*yl*}-3-*oxobutanoates* (**9h**) and (**10h**) as a viscous oil which gradually crystallized (m.p. 135 °C; reorganization of the crystal structure at 108 °C) when kept under ether (Found: C, 57.2; H, 5.15; N, 10.9. $C_{25}H_{26}N_4O_9$ requires C, 57.03; H, 4.98; N, 10.64%); $\nu_{max.}$(KBr) 3 350, 2 120, 1 730br, 1 650, 1 540, 1 350, 850, and 835 cm^{-1}; δ_H (epimer A) 1.23 (d, *J* 6.4 Hz, *Me*CH), 2.3 (br s, OH), 2.93 (dd, *J* 5.7 and 2.0 Hz, 3-H), 2.97 + 3.32 (ABX, J_{gem} 17.4, J_{vic} 8.0 and 4.8 Hz respectively, CH_2CO), 3.76 (ddd, *J* 8.0, 4.8, and 2.0 Hz, 2-H), 3.77 + 3.79 (2 × s, 2 × MeO), 4.09 (qd, *J* 6.4 and 5.7 Hz, 1′-H), 4.18 + 4.46 (AB, J_{gem} 15 Hz, NCH_2Ar), 5.35 (s, OCH_2Ar), 7.54 + 8.28 (AA′BB′, *J* 8.6 Hz, ArH's of PBN group); epimer B 1.29 (d, *J* 6.4 Hz, *Me*CH), 2.5 (br s, OH), 2.80 (dd, *J* 8.0 and 2.0 Hz, 3-H), 2.98 + 3.34 (ABX, J_{gem} 17.5, J_{vic} 9.0 and 4.5 Hz, respectively, CH_2CO), 3.74 (ddd, *J* 9.0, 4.5, and 2.0 Hz, 2-H), 3.78 (s, 2 × MeO), 4.0 (qd, *J* 6.4 and 8.0 Hz, 1′-H), 4.17 + 4.47 (AB, J_{gem} 15 Hz, NCH_2Ar), 5.35 (s, OCH_2Ar), and 7.54 + 8.28 (AA′BB′, *J* 8.6 Hz, ArH of PNB group); the original oily product was shown by its ^1H n.m.r. spectrum to be a *ca.* 55 : 45 mixture of epimers A and B, while the crystalline product was shown to be the pure epimer A. Comparison of the chemical shifts and the coupling constants of the 3-H protons of the two epimers with those of the closely related epimers (**9n**) (δ 2.85, *J* 7.0 and 2.2 Hz) and (**10n**) (δ 2.90 m) known from literature[10b] permitted us to assign structures (**10h**) and (**9h**) to epimers A and B, respectively.

(*d*) A mixture (0.45 g, 0.8 mmol) of the diastereoisomeric (2*RS*,3*SR*)-(**5k**) and (2*RS*,3*RS*)-(**6h**) diazo-oxoesters was similarly deketalized and reduced [except that the chromatographic work-up was carried out at 100 kPa, and CH_2Cl_2–acetone, 7:1 was used as the eluant] to give a mixture (0.30 g, 73%) of the epimers (**9h**) and (**10h**) as a viscous oil which, except for its composition (epimer A:epimer B = 65:35), proved identical (i.r. and ^1H n.m.r.) with the sample obtained as described in (*c*).

Manipulations of the Side Chains in Position 2 *of some Mixtures of Epimeric Compounds of Types* (**9**) *and* (**10**).—(*a*) An ethanolic (10 ml) solution of the mixture (1.47 g, 4.36 mmol) of the epimeric esters (**9b**) and (**10b**) [obtained from the ester (**5c**) by deketalization and reduction, see above] was stirred with an aqueous (2 ml) solution of NaOH (0.24 g, 6 mmol) for 0.5 h at 0 °C. Water (50 ml) was added, the mixture extracted with ether (20 ml), and the aqueous phase acidified (pH 1) with concentrated HCl, and extracted with $CHCl_3$ (3 × 20 ml). The $CHCl_3$ solution was dried ($MgSO_4$) and evaporated to dryness to give an oily mixture (1.3 g, 96%) of the epimeric carboxylic acids (**9a**) and (**10a**) which, without further purification, was converted into a mixture of the epimeric diazomethyl ketones (**9c**) and (**10c**), see below.

The mixture (1.3 g, 3.85 mmol) of esters (**9b**) and (**10b**) [obtained analogously from the ester (**6b**), see above] was similarly converted into an oily mixture (1.05 g, 88%) of the epimeric carboxylic acids (**9a**) and (**10a**), and thence into a mixture of the epimeric diazoketones (**9c**) and (**10c**), see below.

(*b*) Ethyl chloroformate (0.5 ml, 5.3 mmol) was added with continuous stirring to a mixture (1.54 g, 5 mmol) of the epimeric acids (**9a**) and (**10a**), anhydrous THF (15 ml), and Et_3N (0.73 ml, 5.3 mmol). The mixture was cooled to −15 °C and kept for 20 min at this temperature. The crystalline precipitate ($Et_3\overset{+}{N}HCl^-$) was filtered off under argon, and the filtrate treated with a cold ethereal (25 ml) diazomethane solution, freshly prepared from *N*-methyl-*N*-nitrosourea (2.25 g, 22 mmol). The mixture was allowed to warm up with continuous stirring, stirred for 2 h at room temperature, and evaporated to dryness. The residue was worked up by chromatography (Kieselgel 60, 0.063—0.200; benzene–acetone, 7:3) to give a brownish yellow oily mixture (0.93 g, 56%) of the epimeric (2RS,3RS)-2-*diazoacetyl*-1-(2,4-*dimethoxybenzyl*)-[(1RS)- *and* (1SR)-1-*hydroxyethyl*]*azetidin*-2-*ones* (**9c**) and (**10c**) [$\nu_{max.}$(film) 3 400, 2 170, 1 760—1 740, and 1 645 cm^{-1}; δ_H (epimer A) 1.27 (d, *J* 6.4 Hz, *Me*CH), *ca.* 2.0 (br s, OH), 3.14 (dd, *J* 5.8 and 2.6 Hz, 3-H), 3.75 (d, *J* 2.6 Hz, 4-H), 3.78 + 3.80 (2 × s, 2 × MeO), 4.06 (qd, *J* 6.4 and 5.8 Hz, 1′-H), 4.20 + 4.59 (AB, J_{gem} 14.5 Hz, NCH_2Ar), 5.35 (s, $COCHN_2$); (epimer B) 1.27 (d, *J* 6.4 Hz, *Me*CH), *ca.* 2.0 (br s, OH), 3.09 (dd, *J* 5.5 and 2.5 Hz, 3-H), 3.78 + 3.80 (2 × s, 2 × MeO), 3.90 (d, *J* 2.5 Hz, 4-H), 4.12 (qd, *J* 6.4 and 5.5 Hz, 1′-H), 4.20 + 4.59 (AB, J_{gem} 14.5 Hz, NCH_2Ar), and 5.37 (s, $COCHN_2$); the ratio of epimers A and B in mixtures obtained in different runs varied, according to the ^1H n.m.r. spectra, between 60:40 and 45:55] which was subjected to the Wolff rearrangement without further purification.

(*c*) A mixture (2.0 g, 6.0 mmol) of the epimeric diazoketones (**9c**) and (**10c**), anhydrous THF (90 ml), and water (50 ml) was irradiated with a high-pressure mercury immersion lamp (HPK-125) through Pyrex under Ar until the starting compound was consumed (*ca.* 4 h), concentrated to *ca.* 50 ml under reduced pressure, made alkaline by adding 10% aqueous NaOH, and extracted with CH_2Cl_2 (3 × 10 ml). The aqueous solution was acidified (pH 2) with concentrated HCl and extracted with CH_2Cl_2 (5 × 30 ml). The combined CH_2Cl_2 solutions were dried ($MgSO_4$) and evaporated to dryness to give a yellow oily mixture (1.1 g, 57.5%) of the epimeric (2*RS*,3*SR*)-1-(2,4-dimethoxybenzyl)-[(1*RS*)- and (1*SR*)-1-hydroxyethyl]-4-oxoazetidin-2-ylacetic acids (**9d**) and (**10d**) which was converted into a mixture of the epimeric β-oxoesters (**9g**) and (**10g**) without further purification (see below).

Alternatively, diazodiphenylmethane was added to the combined CH_2Cl_2 solutions of the mixture of acids (**9d**) and (**10d**) until the colour of the reagent became persistent. The solution was evaporated to dryness, and the residue treated with ether to give a mixture (1.44 g, 49%) of the epimeric benzhydryl (2*RS*,3*SR*)-1-(2,4-dimethoxybenzyl)-3-[(1RS)- and (1*SR*)-1-hydroxyethyl]-4-oxoazetidin-2-ylacetates (**9f**) and (**10f**), m.p. 123 °C, which proved identical (i.r.) with the sample obtained by successive deketalization and reduction of compound (**5h**) (see above).

(*d*) A mixture (0.34 g, 1 mmol) of the epimeric benzhydryl esters (**9l**) and (**10l**) [obtained by *N*-deprotection of a mixture of the esters (**9f**) and (**10f**), see below] was hydrogenolysed in ethanolic (15 ml) solution in the presence of a 10% Pd–C catalyst (0.03 g) at room temperature and normal pressure. Conventional work-up gave a mixture (0.12 g, 70%) of the epimeric (2*RS*,3*SR*)-3-[(1*RS*)- and (1*SR*)-1-hydroxyethyl]-4-oxoazetidin-2-ylacetic acids (**9i**) and (**10i**), m.p. 140 °C; $\nu_{max.}$(KBr) 3 400, 3 250, 3 200—2 500, and 1 730—1 670 cm^{-1}; δ_H($CDCl_3$–$(CD_3)_2SO$, 1:1) 1.27 and 1.25 (2 × d, *J* 6.5 Hz, *Me*CH groups), 2.61 (d, *J* 6.6 Hz, CH_2CO_2), 2.92 and 2.79 (2 × dd, *J* 5.0 and 7.0 Hz, respectively, and 2.4 Hz, 3-H), 3.83 (td, *J* 6.6 and 2.4 Hz, 2-H), 4.08 (qd, *J* 6.5 and 5.0 Hz, 1′-H), and 7.2 (br s, NH); the product was shown by its ^1H n.m.r. spectrum to be a *ca.* 90:10 mixture of the two epimers, the main component of the mixture being compound (**10b**).

A mixture (0.52 g, 3 mmol) of the epimeric acids (**9i**) and (**10i**), 1,1′-carbonyldi(imidazole) (0.54 g, 3.3 mmol), and anhydrous THF (15 ml) was stirred for 2 h at room temperature. The magnesium salt (0.83 g, 3.3 mmol) of *p*-nitrobenzyl hydrogen malonate was added, and stirring continued for 2 h. The mixture was evaporated to dryness under reduced pressure, and the residue was taken up in CH_2Cl_2 and 0.5M-HCl (50 ml, each). The aqueous phase was extracted with CH_2Cl_2 (25 ml). The combined organic phases were washed with 3% aqueous Na_2CO_3 (2 × 10 ml), dried ($MgSO_4$), and evaporated under reduced pressure to give an oily mixture (0.35 g, 33%) of the epimeric *p*-nitrobenzyl 4-{(2*RS*,3*SR*)-3-[(1*RS*)- and (1*SR*)-1-

hydroxyethyl]-4-oxoazetidin-2-yl}-3-oxobutanoates (**9m**) and (**10m**); $\nu_{max.}$(film) 3 400—3 100, 1 750—1 720, 1 520, 1 350, and 850br cm^{-1}.

A solution of a mixture (1.75 g, 5.0 mmol) of the esters (**9m**) and (**10m**) in anhydrous acetonitrile (15 ml) was treated, with continuous stirring and ice-cooling, with triethylamine (0.69 g, 5.0 mmol) and toluene-*p*-sulphonyl azide (0.99 g, 5.0 mmol). The mixture was stirred for 2 h and evaporated to dryness under reduced pressure. The residue was worked up by chromatography (Kieselgel G; CH_2Cl_2–acetone, 7:3) to give an oily mixture (1.2 g, 64%) of the epimeric *p*-nitrobenzyl 2-diazo-4-{(2*RS*,3*SR*)-3-[(1*RS*)-and (1*SR*)-1-hydroxyethyl]-4-oxoazetidin-2-yl}-3-oxobutanoates (**9n**) and (**10n**) [$\nu_{max.}$(film) 3 350br, 2 200, 1 750, 1 730, 1 640, 1 520, 1 350, and 840 cm^{-1}] which proved identical (i.r.) with the product obtained by *N*-de(dimethoxybenzylation) of a mixture of compounds (**9h**) and (**10h**), and which was cyclized, without preliminary crystallization, to an epimeric mixture of compounds (**11**) and (**12**), see below.

(*e*) A mixture (2.6 g, 8.0 mmol) of the acids (**9d**) and (**10d**) [obtained as described in (*c*)], 1,1′-carbonyldi(imidazole) (98%, 1.45 g, 8.8 mmol), and anhydrous THF (30 ml) was stirred for 0.5 h at room temperature. The magnesium salt (2.2 g, 8.8 mmol) of *p*-nitrobenzyl hydrogen malonate was added, and stirring continued for 5 h. The mixture was evaporated to dryness under reduced pressure, and the residue was taken up in CH_2Cl_2 (150 ml) and 0.5M-HCl (80 ml). The aqueous phase was extracted with CH_2Cl_2 (80 ml) and the combined organic phases were washed with 3% aqueous Na_2CO_3 (2 × 20 ml), dried ($MgSO_4$), and evaporated to dryness under reduced pressure to give a yellow oily mixture (2.8 g, 70%) of the epimeric *p*-nitrobenzyl 4-{(2*RS*,3*SR*)-1-(2,4-dimethoxybenzyl)-3-[(1*RS*)- and (1*SR*)-1-hydroxyethyl]-4-oxoazetidin-2-yl}-3-oxobutanoates (**9g**) and (**10g**).

The above mixture (2.5 g, 80 mmol) was allowed to react with toluene-*p*-sulphonyl azide and triethylamine as described in (*d*) to give a yellow oily mixture (1.95 g, 73.6%) of the epimeric *p*-nitrobenzyl 2-diazo-4-{(2*RS*,3*SR*)-1-(2,4-dimethoxybenzyl)-3-[(1*RS*)- and (1*SR*)-1-hydroxyethyl]-4-oxoazetidin-2-yl}-3-oxobutanoates (**9h**) and (**10h**) which proved identical (i.r. and t.l.c.) with the sample obtained by successive deketalization and reduction of compound (**5k**), see above.

N-*De*(2,4-*dimethoxybenzylations*).—(*a*) An aqueous (40 ml) solution of $K_2S_2O_8$ (8.65 g, 32 mmol) and $Na_2HPO_4{\cdot}2H_2O$ (11.4 g, 64 mmol) was added in four equal portions to a refluxing solution of a mixture (2.7 g, 8 mmol) of the diastereoisomeric compounds (**9e**) and (**10e**) in acetonitrile (40 ml) and water (10 ml) with continuous stirring under argon. Refluxing and vigorous stirring were continued for 1 h. The mixture was evaporated to dryness under reduced pressure (bath temperature 50 °C), the residue extracted with CH_2Cl_2 (3 × 50 ml) at room temperature, and the combined CH_2Cl_2 solutions dried ($MgSO_4$) and subjected to chromatography (200 kPa; Kieselgel G; CH_2Cl_2–acetone, 7:2) to give an oily mixture (1.06 g, 80%) of the epimeric methyl (2*RS*,3*SR*)-3-[(1*RS*)- and (1*SR*)-1-hydroxyethyl]-4-oxoazetidin-2-ylacetates (**9k**) and (**10k**).

This mixture was dissolved in CH_2Cl_2 (*ca.* 2.5 ml). When the solution was allowed to stand at room temperature, the pure epimer (**10k**) (0.29 g, 21%), m.p. 87 °C, gradually crystallized. This product proved identical (m.p., i.r., and ^1H n.m.r.) with a sample prepared as described in a patent [14] [where neither the m.p., nor the spectra of compound (**10k**) were given] (Found: C, 51.0; H, 6.85; N, 7.3. $C_8H_{13}NO_4$ requires C, 51.33; H, 7.00; N, 7.48%); $\nu_{max.}$(KBr) 3 300, 3 200, and 1 720 cm^{-1}; δ_H 1.32 (d, *J* 6.4 Hz, *Me*CH), 2.69 (d, *J* 6.8 Hz, CH_2CO_2), 2.83 (br d, *J* 4.5 Hz, OH), 2.94 (dd, *J* 5.5 and 2.5 Hz, 3-H), 3.71 (s, CO_2Me), 3.85 (td, *J* 6.8 and 2.5 Hz, 2-H), 4.13 (qdd, *J* 6.4, 5.5, and 4.5 Hz, 1′-H), and 6.5 (br s, NH).

Evaporation to dryness of the filtrate of compound (**10k**) gave a *ca.* 1:1 mixture (by ^1H n.m.r.) of the epimeric esters (**9k**) and (**10k**); $\nu_{max.}$(film) 3 300br and 1 740br cm^{-1}; δ_H 1.29 and 1.32 (2 × d, *J* 6.4 Hz, *Me*CH groups), 2.7 (br s, OH), 2.71 and 2.69 (m and d, *J* 6.8 Hz, respectively, CH_2CO_2), 2.89 and 2.94 (2 × dd, *J* 6.2 and 2.2, and 5.5 and 2.5 Hz, respectively, 3-H), 3.71 (s, CO_2Me), 3.87 and 3.85 (m, and td, *J* 6.8 and 2.5 Hz, respectively, 2-H), 4.16 and 4.13 (2 × qd, *J* 6.4 and 6.2, and 6.4 and 5.5 Hz, respectively, 1′-H), and 6.5 (br s, NH).

(*b*) A mixture (4.9 g, 10 mmol) of the *N*-protected benzhydryl esters (**9f**) and (**10f**) (see above), $K_2S_2O_8$ (10.8 g, 40 mmol), $Na_2HPO_4{\cdot}12H_2O$ (28.7 g, 80 mmol), acetonitrile (56 ml), and water (21 ml) was refluxed for 3 h with continuous stirring and worked up as described above for the preparation of a mixture of compounds (**5m**) and (**6k**) [except for the chromatographic work-up (Kieselgel G; CH_2Cl_2–acetone, 7:1) which was carried out at 100 kPa], to give a mixture (1.73 g, 51%) of the epimeric benzhydryl (2*RS*,3*SR*)-3-[(1*RS*)- and (1*SR*)-1-hydroxyethyl]-4-oxoazetidin-2-ylacetates (**9l**) and (**10l**) as an oil which crystallized (m.p. 135 °C) when triturated with ether, and proved identical (m.p. and i.r.) with the sample obtained by successive deketalization and reduction of the (2*RS*,3*SR*)-ester (**5n**), see above; $\nu_{max.}$(KBr) 3 350br, 1 750, and 1 720 cm^{-1}; δ_H 1.25 (d, *J* 6.4 Hz, *Me*CH), 2.4 (br s, OH), 2.77 + 2.81 (ABX, J_{gem} 16.3, J_{vic} 7.5 and 6.0 Hz, respectively, CH_2CO_2), 2.85 (dd, *J* 6.5 and 2.2 Hz, 3-H), 3.93 (ddd, *J* 7.5, 6.0, and 2.2 Hz, 2-H), 4.11 (qd, *J* 6.4 and 6.5 Hz, 1′-H), 6.1 (br s, NH), 6.92 (s, OC*H*Ph_2), and 7.32 (s, 2Ph).

(*c*) A mixture (5.26 g, 10 mmol) of the 2-diazo-3-oxoesters (**9h**) and (**10h**) (see above), $K_2S_2O_8$ (10.8 g, 40 mmol), $Na_2HPO_4{\cdot}2H_2O$ (14.2 g, 80 mmol), acetonitrile (60 ml) and water (40 ml) was refluxed for 4 h. (In some runs the starting ester was not consumed. In these cases half of the originally added amounts of the reagents and solvents were added, and refluxing continued for 5 h.) The mixture was worked up essentially as described in (*b*) [except for the eluant used for the chromatographic work-up (250 kPa; Kieselgel G; CH_2Cl_2–acetone, 7:3)] to give a mixture (0.94 g, 25%) of the epimeric p-*nitrobenzyl 2-diazo*-4-{(2RS,3SR)-3-[(1RS)- *and* (1SR)-1-*hydroxyethyl*]-4-*oxoazetidin*-2-*yl*}-3-*oxobutanoates* (**9n**) and (**10n**) as a brown viscous oil which slowly crystallized [m.p. 140—142 °C (decomp.)] when allowed to stand, and was then washed with ether (Found: C, 51.3; H, 4.15; N, 15.05. $C_{16}H_{16}N_4O_7$ requires C, 51.06; H, 4.29; N, 14.89%); $\nu_{max.}$(KBr) 3 400br, 2 200, 1 750—1 720, 1 650, 1 530, 1 350, and 840 cm^{-1}; δ_H 1.32 and 1.31 (2 × d, *J* 6.4 Hz, *Me*CH groups), 2.96 and 2.89 (2 × dd, *J* 5.8 and 7.0, respectively, and 2.4 Hz, 3-H), 3.16 + 3.30 and 3.19 + 3.31 (2 × ABX, J_{gem} 17.5 Hz, J_{vic} 8.0 and 5.0, and 7.0 and 5.8 Hz, respectively, CH_2CO), 3.90 and 3.91 (2 × ddd, *J* 8.0, 5.0, and 2.4, and 7.0, 5.8, and 2.4 Hz, respectively, 2-H), 4.14 and 4.17 (2 × qd, *J* 6.4, and 5.8 and 7.0, respectively, 1′-H), 5.38 (s, OCH_2Ar), and 7.55 + 8.26 (AA′BB′, *J* 8.6 Hz, ArH's of PNB group). The product was shown by its ^1H n.m.r. spectrum to be a *ca.* 75:25 mixture of the two 1′-epimers.

Epimeric Mixture of p-*Nitrobenzyl* 6-[(1RS)- *and* (1SR)-1-*Hydroxyethyl*]-2,7-*dioxo*-(3RS,5RS,6SR)-*carbapenam*-3-*carboxylates* (**11**) *and* (**12**).—A mixture of the epimers (**9n**) and (**10n**) (0.20 g, 0.53 mmol) was refluxed with dry toluene (10 ml) in the presence of $Rh_2(OAc)_4$ (8 mg) for 2 h, treated with Norite, and evaporated to dryness under reduced pressure to give a mixture (0.12 g, 65%) of the epimeric title compounds as a colourless crystalline product, m.p. 92—94 °C (decomp.), which was converted into a mixture of the epimeric compounds (**13**) without further purification; $\nu_{max.}$(KBr) 3 420br, 1 750br, 1 530, 1 355, and 860 cm^{-1}; δ_H 1.40 and 1.37 (2 × d, *J* 6.4 Hz, *Me*CH),

2.25 (br s, OH), 2.50, and 2.88 and 2.90, respectively (2 × ABX, J_{gem} 18.6, J_{vic} 7.6 and 6.8, respectively, 1-H_2), 3.30 and 3.20 (2 × dd, *J* 5.4 and 6.6 Hz, respectively, and 2.2 Hz, 6-H), 4.10 and 4.15 (2 × ddd, *J* 7.6, 6.8, and 2.2 Hz, 5-H), 4.28 and 4.31 (2 × qd, *J* 6.4, and 5.4 and 6.6 Hz, respectively, 1′-H), 4.75 (s, 3-H), 5.27 + 5.32 (AB, J_{gem} 13.5 Hz, OCH_2Ar), and 7.55 + 8.24 (AA′BB′, *J* 8.6 Hz, ArH's of PNB group). The product was shown by its ^{1}H n.m.r. spectrum to be a *ca.* 60:40 mixture of its epimeric components. The spectrum of the minor component is in good agreement with the known[15] spectrum of compound (**11**).

Mixture of the Epimeric p-*Nitrobenzyl* 2-(2-*Formylaminoethylthio*)-6-[(1RS)- *and* (1SR)-1-*hydroxyethyl*]-7-*oxo*-(5RS,6SR)-*carbapen*-2-*em*-3-*carboxylates* (**13**).—Triethylamine (0.20 ml, 1.36 mmol) was added at 0 °C with continuous stirring to a solution of a mixture (0.475 g, 1.36 mmol) of the epimers (**11**) and (**12**) in dry acetonitrile (5 ml) and the mixture stirred for 5 min at 0 °C. A solution of diphenyl phosphorochloridate (0.28 ml, 1.36 mmol) in dry acetonitrile (1.5 ml) was added, and the mixture stirred for a further 10 min at 0 °C. The ice–water bath was removed, and stirring continued for 10 min. The mixture was cooled again to 0 °C and treated successively with a mixture of triethylamine (0.20 ml, 1.36 mmol) and dry acetonitrile (1.5 ml), and a solution of *N*-formylcysteamine[16] (0.15 g, 1.36 mmol) in dry acetonitrile (1.5 ml). The mixture was stirred for 1 h, kept overnight in a refrigerator, and evaporated to dryness under reduced pressure. The residue was worked up by chromatography (200 kPa; Kieselgel G; CH_2Cl_2–acetone, 1:1) to give a mixture of the epimeric compounds (**13**) (0.32 g, 54%) which crystallized [m.p. 122—124 °C (decomp.)] on scratching, and was washed with ether (Found: N, 9.85; S, 7.8. $C_{19}H_{21}N_3O_7S$ (435.45) requires N, 9.65; S, 7.35%); $\nu_{max.}$(KBr) 3 400—3 200, 1 755, 1 695, 1 630, 1 540, 1 340, and 850 cm^{-1}; δ_H[$CDCl_3$–$(CD_3)_2SO$, 2:1] 1.30 and 1.33 (2 × d, *J* 6.4 Hz, *Me*CH groups), 2.7—3.7 (m, 1-H_2 + 6-H + SCH_2CH_2N), 4.0—4.4 (m, 5-H + 1′-H), 5.27 + 5.47 (AB, J_{gem} 14.0 Hz, OCH_2Ar), 7.5 (br s, NH), 7.69 + 8.21 (AA′BB′, *J* 8.6 Hz, ArH's of PNB group), and 8.14 (s, NCHO).

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