Synthesis of *trans*(±)6-phenoxyacetamido-1-methylene-3,3-dicarboxymethyl-1-carbapenam

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Methyl 4-benzylidene-2-pyrroline-2-carboxylate and dimethyl-4-methylene-5-pyrroline-2,2-dicarboxylate were prepared by *N*-chlorination – dehydrochlorination starting from the corresponding 4-alkylidene- or 4-arylidene-pyrrolidine. Structure of the pyrroline compound was determined by spectrometry and by reaction with α-azidoacetyl chloride. The 2-carbomethoxy-4-benzylidene-Δ^2-pyrroline compound gave, on reaction with α-azidoacetyl chloride, 2-benzylidene-5-carbomethoxy-6-azido-1-carbapenam. In the case of the 2,2-dicarbomethoxy-4-methylene-Δ^5-pyrroline, *trans*-1-methylene-3,3-dicarbomethoxy-6-azido-1-carbapenam was formed. When *N*-chlorination – dehydrochlorination was carried out on 2-carbomethoxy-4-methylenepyrrolidine, double bond isomerization occurred with formation of 2-carbomethoxy-4-methylpyrrole.

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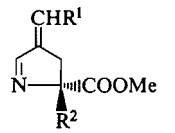
On a préparé le carboxylate-2 benzylidène-4 pyrroline-2 de méthyle et le dicarboxylate-2,2 méthylène-4 pyrroline-5 de méthyle au moyen d'une *N*-chloration – déhydrochloration en partant des alkylidène-4 ou arylidène-4 pyrrolidines correspondantes. On a déterminé la structure du composé pyrroline par spectrométrie et par la réaction avec le chlorure de l'α-azidoacétyle. Le composé carbométhoxy-2 benzylidène-4 Δ^2-pyrroline réagit avec le chlorure d'α-azidoacétyle en donnant le benzylidène-2 carbométhoxy-5 azido-6 carbapénam-1. Dans le cas du dicarbométhoxy-2,2 méthylène-4 Δ^5-pyrroline, on obtient le méthylène-1 dicarbométhoxy-3,3 azido-6 carbapénam-1 *trans*. Quand on effectue la *N*-chloration – déhydrochloration de la carbométhoxy-2 méthylène-4 pyrrolidine, il se produit une isomérisation de la double liaison avec la formation de carbométhoxy-2 méthyl-4 pyrrole.

[Traduit par le journal]

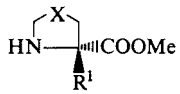
A number of penam and cefem analogs in which the sulfur atom has been replaced by other atoms have been described (1). Some of these compounds such as the 1-oxapenam, clavulanic acid (2) and the 1-carbapenem, thienamycin (3) are of therapeutic interest. The study of 1-alkylidene-1-carbapenams seemed to be of interest in this context. Certain 1-arylidene-5-alkylthio-1-carbapenams and 1-arylidene-6-alkylthio-1-carbacephams have been synthesized by Bose *et al.* (4). It should be noted that an acylamido side chain and a carboxyl group respectively in the 3- or 4-position are not present in these arylidene-β-lactams.

In the present work we investigated the preparation of methyl 4-alkylidene-5-pyrroline-2-carboxylates (**1***a–c*) and their conversion into bicyclic β-lactams by cycloaddition with azidoacetyl chloride according to Bose *et al.* (5). The synthetic approach examined for the preparation of the 4-alkylidene-5-pyrrolines (**1***a–c*) consists in *N*-chlorination of the corresponding methyl 4-alkylidene-pyrrolidine-2-carboxylates (**2***a–c*), followed by base-catalysed elimination of hydrochloric acid. A similar procedure is described by Schmidt and Poisel (6) for the preparation of racemic proline. The pyrrolidine **2***a* was obtained in five steps from 4-hydroxy-L-proline **3***a*.[2] In order to obtain a 1-methylene-1-carbapenam with the same configuration at C2 as in penicillins, 4-hydroxy-D-proline should be used as a starting material. However, in these experiments the more readily available *L*-enantiomer was used. Oxidation of *N-tert*-Boc-4-hydroxy-L-proline **3***b* with CrO_3/pyridine in CH_2Cl_2 gave the ketone **3***c* (60%), which was converted into the *N*-protected 4-methylenepyrrolidine **3***d* by condensation with methylenetriphenylphosphorane (4 equiv.) in THF (80% yield). When the Wittig reaction was carried out on the methyl ester instead of the acid **3***c*, only 5% of **3***e* was obtained. After esterification of the carboxyl group (CH_2N_2) and removal of the *N*-protecting group, the free base **2***a* was obtained as an unstable oil (85% yield based on **3***d*), which can be converted into a stable crystalline hydrochloride salt. When oxidation of **3***b* was attempted with DMSO–Ac_2O



1

a $R^1 = H$, $R^2 = H$
b $R^1 = \phi$, $R^2 = H$
c $R^1 = H$, $R^2 = COOMe$



2

a $R^1 = H$, $X = >C = CH_2$
b $R^1 = H$, $X = >C = CH\phi$
c $R^1 = COOMe$, $X = >C = CH_2$

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[2]The D-configuration related to natural penicillin is given in all schemes, even when reactions were carried out with the L-enantiomer.

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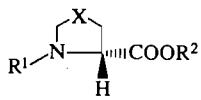


3

a $R^1 = R^2 = H$, X = $>C(OH)H$

b $R^1 = COOBu^t$, $R^2 = H$, X = $>C(OH)H$

c $R^1 = COOBu^t$, $R^2 = H$, X = $>C=O$

d $R^1 = COOBu^t$, $R^2 = H$, X = $>C=CH_2$

e $R^1 = COOBu^t$, $R^2 = Me$, X = $>C=CH_2$

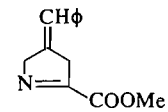
f $R^1 = COOBu^t$, $R^2 = H$, X = $>C=CH\phi$

g $R^1 = COOBu^t$, $R^2 = Me$, X = $>C=CH\phi$

(7) the hydroxy group was converted into a methylthiomethyl ether. Oxidation of **3***b* with DMSO–DCCI–pyridine–CF_3COOH gave the methylthiomethyl ester of **3***c* in a 93% yield. Removal of the methylthiomethyl ester with base or $HgCl_2/H_2S$ afforded the ketone **3***c* in low yield, due to degradation in the given reaction conditions.

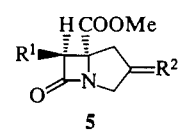
The conversion of **2***a* into 5-pyrroline **1***a* was attempted by *N*-chlorination with *tert*-butylhypochlorite, followed by dehydrochlorination with KO_2/18-crown-6 polyether in Et_2O (8). Since **1***a* contains a conjugated aldimine, one might expect that the pyrroline should be formed to some extent. However, the only compound isolated from the reaction mixture was the 2-carbomethoxy-4-methylpyrrole, which resulted from a migration of the exocyclic double bond into an *endo*-position, upon introduction of the aldimine function. Other dehydrohalogenating agents such as MeONa, pyridine, and CH_3COOK gave similar results. Reaction mixtures, however, were more complex.

To avoid aromatization during the introduction of the aldimine function the *N*-chlorination – dehydrochlorination was repeated for methyl 4-benzylidene-pyrrolidine-2-carboxylate **2***b*. One might expect that the presence of the phenyl group would stabilize the exocyclic double bond and avoid to a certain extent its isomerization into an *endo*-position. Thus **3***c* was reacted with four equivalents of benzylidenetriphenylphosphorane in DMSO. The *N*-protected pyrrolidine **3***f* was isolated in a 82% yield as a 1:1 mixture of the *E*- and *Z*-isomers. Treatment of this mixture with CH_2N_2, followed by *N*-deprotection, afforded *E*- and *Z*-**2***b*, which were separated by fractional crystallization from ethanol–ether for further characterization. *N*-chlorination – dehydrochlorination conducted on the *E*,*Z*-mixture of **2***b* afforded 10% of the 2-carbomethoxy-4-benzylpyrrole and about 85% of an unstable pyrroline **4**, which was not isolated in a pure state. The structure **4** was based on the absence of an absorption band between 1560 and 1580 cm^{-1}, due to a C=N stretching vibration conjugated with an exocyclic carbon–carbon double bond (9), which excluded a 5-pyrroline structure. Absorptions at 1620 and 1630 cm^{-1} (attributed to a C=C or a C=N bond conjugated with a phenyl or carbonyl group) are consistent with a methyl 2-pyrroline-2-carboxylate structure **4**. The formation of the latter results from proton abstraction in the 2-position during dehydrohalogenation. A further proof for the proposed structure was obtained by cycloaddition of azidoacetyl chloride to **4** (mixture of *E*- and *Z*-isomers) in benzene–cyclohexane containing Et_3N. The reaction product was found



4

to be a bicyclic β-lactam, which was isolated by column chromatography in a 50% yield (based on **2***b*). Spectral data were consistent with the structure **5***a*. The ir spectrum showed the presence of a β-lactam carbonyl group (1780 cm^{-1}). The ^{1}Hmr spectra showed two singlets at δ 4.56 and 4.59 ppm (due to the C6-protons), broad signals at δ 6.4 and 7.2 ppm for $C_6H_5CH=C<$, and the absence of a C5-proton. The interpretation of the ^{1}Hmr spectrum of **5***a* was somewhat obscured by the fact that it was recorded on a mixture of *E*- and *Z*-isomers. To establish the relative configuration at C5 and C6 it is necessary to simplify spectral data by converting the *E*,*Z*-mixture into a single compound by ozonolysis of the exocyclic double bond. This was performed on **5***c*, which was obtained by reduction of the azide function (H_2S/Et_3N) followed by *N*-phenoxyacetylation. The *trans*-stereochemistry of the side-chain and the COOMe function in **5***d* was ascertained by comparison of its ^{1}Hmr spectra



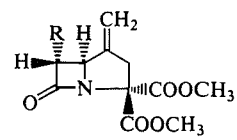
5

a $R^1 = N_3$, $R^2 = CH\phi$

b $R^1 = NH_2$, $R^2 = CH\phi$

c $R^1 = V$, $R^2 = CH\phi$

d $R^1 = V$, $R^2 = O$



6

a R = N_3

b R = V

V = ϕOCH_2CONH

obtained in $CDCl_3$ and in $CDCl_3$ – DMSO-d_6. A solvent shift of 1.00 ppm was observed for the amide proton (from 7.82 ppm in $CDCl_3$ to 8.82 ppm in $CDCl_3$–DMSO), which is due to the formation of

a hydrogen bond between the amide proton and DMSO. This shift should not be expected for a *cis*-β-lactam in which both functions are presumed to form an intramolecular hydrogen bond. Further indication for the absence of an intramolecular hydrogen bond can be found in the sharp NH absorption (3420 cm^{-1}) in the ir spectrum and in the absence of an absorption between 3100 and 3375 cm^{-1}.

The experiments suggest that the conversion of pyrrolidine-2-carboxylates into the corresponding 5-pyrrolines by *N*-chlorination – dehydrochlorination is only feasible if the pyrroline has no hydrogen atom in the 2-position. To verify this hypothesis the pyrroline formation was studied for dimethyl 4-methylene-pyrrolidine-2,2-dicarboxylate (**2***c*). The latter was prepared (in a 25% yield) by reaction of dimethyl aminomalonate hydrochloride with 1 equivalent of 3-chloro-2-chloromethyl-1-propene in the presence of NaOMe (10). Introduction of the aldimine function by the *N*-chlorination – dehydrochlorination procedure gave an unstable reaction product, which was found to be the desired 5-pyrroline **1***c*. The structure was proven by cycloaddition with azidoacetyl chloride. This afforded the *trans*-6-azido-1-methylene-3,3-dicarboxymethyl-1-carbapenam **6***a* (15% yield based on **2***c*). Spectral data obtained for **6***a* were in agreement with the proposed structure. The ir spectrum showed the presence of a β-lactam carbonyl group at 1790 cm^{-1}. In the ^{1}Hmr spectrum the C6 proton appears as a doublet (J = 2.7 Hz) at 4.42 ppm, the 1-methylene- and C5-protons as multiplets, respectively, at 5.28 and 4.25 ppm. The coupling constant of 2.7 Hz for the C5- and the C6-protons suggested a *trans*-β-lactam (11). Reduction of the azide function of **6***a* and *N*-phenoxyacetylation gave the crystalline β-lactam **6***b*. 100 MHz ^{1}Hmr and ^{13}Cmr spectra confirmed the proposed structure and stereochemistry.

Epimerization of carbapenams at C-6 has not been reported hereto. Procedures worked out for epimerization of penicillins (12–14) are only successful to a certain extent in the parent cephalosporin series (15). Therefore it is not likely that these methods can be applied for the isomerization of 1-methylene-1-carbapenam nucleus. Thus conversion of **6***b* into a *cis*-β-lactam was not further investigated.

Experimental

Melting points were determined with a Büchi–Tottoli apparatus and are uncorrected. Precoated Merck silica gel F 254 plates were used for tlc. Column chromatography was performed on silica gel (Merck, 0.040–0.063 mm). Infrared (ir) spectra were recorded on a Perkin Elmer 257 spectrometer. The ^{1}Hmr spectra were recorded on a Hitachi–Perkin–Elmer R-24 60 MHz instrument in $CDCl_3$ with tetramethylsilane as internal standard unless stated otherwise. Mass spectra were determined with an AEI MS-12 apparatus. Elemental analyses were performed by Janssen Pharmaceutica, B-2340 Beerse, Belgium.

N-tert-*Boc-4-oxo-*L*-proline* **3***c*

CrO_3 (16.8 g, 168 mmol) was added to a stirred solution of pyridine (27 mL, 336 mmol) in anhydrous CH_2Cl_2 (350 mL) at 0°C. The reaction mixture was stirred for 5 min at 0°C and allowed to warm up to room temperature. A solution of *N-tert*-Boc-4-hydroxy-L-proline (16) (6.5 g, 28 mmol) in anhydrous CH_2Cl_2 (20 mL) containing pyridine (2.5 mL, 30 mmol) was added at once to the stirred suspension. After vigorous stirring for 4 h at room temperature, the solution was decanted and the black remaining solid was washed with acetone (3 × 100 mL). The combined organic solution was filtered and evaporated. The residue was taken up in a saturated NaCl solution (200 mL), acidified to pH 2.5 with 5*N* HCl, and extracted with EtOAc (5 × 100 mL). The EtOAc solution was dried over $MgSO_4$, Celite (150 g) was added, and the solvent was removed under reduced pressure. The adsorbed *N-tert*-Boc-4-oxo-L-proline was extracted with Et_2O in a Soxhlet apparatus for 5 h. Evaporation afforded **3***c* (3.9 g, 60% yield) as an amorphous solid which can be used in the next step without further purification. Crystallization from Et_2O gave analytically pure **3***c*, mp 148–150°C (dec.); ir (CH_2Cl_2): 1750 (ketone), 1650 (COOH) cm^{-1}. Compound **3***c* was converted into its benzyl ester (benzyl bromide/DMF/Et_3N) which was used for further spectrometric identification; ir (CH_2Cl_2): 1770 (ester), 1750 (ketone), 1703 (carbamate) cm^{-1}; ^{1}Hmr δ: 1.4 (s, 9H, *t*-butyl), 2.70 (AB part of ABX pattern, 2H, J_{ax} = 9 Hz, J_{bx} = 4 Hz, J_{ab} = 19 Hz, CH_2CH), 3.85 (s, 2H, CH_2N), 4.76 (X-part, 1H, CHN), 5.15 (s, 2H, $CH_2\phi$), 7.3 (s, 5H, phenyl) ppm. Oxidation of **3***b* in DMSO–benzene (1:1) containing pyridine (2 equiv.), CF_3CO-OH (1 equiv.), and dicyclohexylcarbodiimide (6 equiv.) afforded 93% of the crystalline methylthiomethylester of **3***c*, ^{1}Hmr δ: 1.5 (s, 9H, *t*-butyl), 2.25 (s, 3H, SMe), 2.75 (AB part of ABX pattern, 2H, J_{ax} = 9 Hz, J_{bx} = 4 Hz, J_{ab} = 19 Hz, CH_2CH), 3.87 (s, 2H, CH_2N), 4.77 (X-part, 1H, CH_2N), 5.2 (s, 2H, CH_2S) ppm.

N-tert-*Boc-methylene-*L*-proline* **3***d*

Methyltriphenylphosphonium bromide (17) (35.7 g, 100 mmol) was added to a stirred suspension of NaH (2.4 g, 100 mmol) in anhydrous THF (250 mL). The mixture was heated at 50°C for 4 h and a solution of *N-tert*-Boc-L-proline (5.7 g, 25 mmol) in anhydrous THF (50 mL) was added over a period of 30 min. After stirring overnight at 50°C, the suspension was cooled, poured into 500 mL 5% $NaHCO_3$, and washed twice with Et_2O. The aqueous solution was acidified to pH 3 with 2*N* HCl and extracted three times with EtOAc. The extract was dried over Na_2SO_4 and evaporated. The residual oil was chromatographed on a silica gel column using C_6H_6–Me_2CO–CH_3COOH (87:12:1) as eluent to yield **3***d* (4.54 g, 80%) as an oil; ^{1}Hmr δ: 1.42 (s, 9H, *t*-butyl), 2.83 (m, 2H, CH_2CH), 4.05 (m, 2H, CH_2N), 4.45 (m, 1H, CHN), 4.97 (m, 2H, CH_2=C), 10.4 (s, 1H, COOH) ppm.

Methyl N-tert-*Boc-4-methylene-*L*-proline* **3***e*

To a solution of **3***d* (3.4 g, 15 mmol) in anhydrous $CHCl_3$ (50 mL) was added an excess of CH_2N_2 (until the yellow color persisted). After removal of the solvent, the ester was obtained in a quantitative yield as an oil; ir (CH_2Cl_2): 1755 (ester), 1705 (carbamate), 1405, 1127, 900 (C=CH_2) cm^{-1}; ^{1}Hmr δ: 1.42 (s, 9H, *t*-butyl), 2.75 (m, 2H, CH_2CH), 3.72 (s, 3H, COOCH_3), 4.07 (m, 2H, CH_2N), 4.44 (m, 1H, CHN), 4.98 (m, 2H, C=CH_2) ppm; ms *m/e*: 241 (M^+).

*Methyl 4-methylene-*L*-proline* **2**a

A solution of **3***e* (2.41 g, 10 mmol) in 98% HCOOH (50 mL) was kept at room temperature for 2.5 h and evaporated to dryness at a temperature below 30°C. The oily residue was partitioned between Et_2O (100 mL) and 0.1 *N* HCl (100 mL). The aqueous layer was separated, made basic with 5% $NaHCO_3$, saturated with NaCl, and extracted with CH_2Cl_2 (3 × 100 mL). The CH_2Cl_2 extract was dried over Na_2SO_4 and evaporated to give **2***a* (1.2 g, 85%) as a light yellow oil. Analysis of the oil on tlc (10% MeOH/$CHCl_3$) showed a single spot. The compound was not stable as its free base and was converted into its hydrochloride for further characterization.

*Methyl 4-methylene-*L*-proline hydrochloride* **2**a·*HCl*

A solution of 1 *N* HCl in EtOH (5.5 mL) was added dropwise to a solution of **2***a* (705 mg, 5 mmol) in EtOH (20 mL). Addition of anhydrous Et_2O afforded 820 mg of the title compound (92%) as colorless needles, mp 159–160°C (dec.) after recrystallization from EtOH/Et_2O; $[\alpha]_D^{25}$ −15.25° (*c* 1, H_2O); ir (KBr): 1750 (ester), 1677 (CH_2=CH) cm^{-1}; ^{1}Hmr (360 MHz, DMSO-d_6) δ: 2.73 (m, 1H, $^2J_{3,3'}$ = 16.2 Hz, $^3J_{3,2}$ = 8 Hz, ^4J = 2 × 2.3 Hz, $^4J_{3,5}$ = 2.0 Hz, $^4J_{3,5'}$ = 0.6 Hz, H-3), 2.96 (m, 1H, $^2J_{3',3}$ = 16.2 Hz, $^3J_{3',2}$ = 8.4 Hz, ^4J = 2 × 2.1 Hz, $^4J_{3',5}$ = 0.95 Hz, $^4J_{3',5'}$ = 1.6 Hz, H-3'), 3.77 (s, 3H, COOMe), 3.81 (m, 1H, $^2J_{5,5'}$ = 15.2 Hz, ^4J = 2 × 2.2 Hz, $^4J_{5,3}$ = 2.0 Hz, $^4J_{5,3'}$ = 0.95 Hz, H-5), 3.88 (m, 1H, $^2J_{5',5}$ = 15.2 Hz, ^4J = 2 × 2 Hz, $^4J_{5',3}$ = 0.6 Hz, $^4J_{5',3'}$ = 1.6 Hz, H-5'), 4.56 (dd, 1H, $^3J_{2,3}$ = 8 Hz, $^3J_{2,3'}$ = 8.4 Hz, H-2), 5.15 (m, 2H, ^4J = 2 × 2.3 and 2 × 2.1 Hz, ^4J = 2 × 2.2 and 2 × 2 Hz, CH_2=C) ppm. *Anal.* calcd. for $C_7H_{11}O_2N$·HCl: C 47.31, H 6.82, N 7.88; found: C 47.20, H 6.71, N 7.70.

*Methyl 4-benzylidene-*N*-tert-Boc-*L*-proline* **3**g

Benzyltriphenylphosphonium bromide (21.65 g, 50 mmol) was gradually added to a solution of NaH (1.2 g, 50 mmol) in anhydrous DMSO (120 mL). The suspension was warmed up to 80°C and stirred for 1 h. The red color indicated the ylide formation. A solution of **3***c* (2.86 g, 12.5 mmol) in anhydrous DMSO (30 mL) was added dropwise over a period of 30 min to the stirred ylide solution. The reaction mixture was stirred for 6 h at 80°C, cooled to room temperature, poured into 500 mL 0.2 *N* HCl, and extracted with EtOAc (3 × 100 mL), which was then washed with water (3 × 100 mL). The organic solution was dried and the EtOAc removed. Purification of the residual oil by chromatography on a silica gel column using C_6H_6–Me_2CO–CH_3COOH (89:10:1) yielded the acid **3***f*, which was converted into the methyl ester by reaction with CH_2N_2, as described in a previous section, yielding 3.25 g (82%) of the title compound as an oil. The ^{1}Hmr spectrum showed that **3***g* was a mixture of two isomers: ^{1}Hmr δ: 1.43 (s, 9H, *t*-butyl), 2.96 (m, 2H, CH_2CH), 3.65 and 3.67 (2 × s, 3H, $COOCH_3$), 4.15–4.65 (m, 3H, CH_2N and CHN), 6.36 (m, 1H, CH=C), 7.23 (m, 5H, phenyl); ms *m/e*: 317 (M^+).

*Methyl 4-benzylidene-*L*-proline hydrochloride (***2***b·HCl)*

N-deprotection of **3***g* (3.17 g, 10 mmol) according to the procedure described for **3***e* gave **2***b* (1.93 g, 89%) as an oil, which was converted into the stable crystalline hydrochloride salt and isomers were separated by fractional crystallization from ethanol–water; ir (KBr): 1740 (ester), 1520, 1425, 1060, 910, 750, 700 (φ—CH=C) cm^{-1}. *E*-isomer, mp 164–167°C (dec.); ^{1}Hmr (360 MHz, DMSO-d_6) δ: 2.95 (4 × d, 1H, $^2J_{3',3}$ = 17.2 Hz, $^3J_{3,2}$ = 7.4 Hz, ^4J = 2.6 Hz, H-3), 3.21 (4 × d, 1H, $^2J_{3',3}$ = 17.2 Hz, $^3J_{3',2}$ = 8.6 Hz, ^4J = 2.5 Hz, H-3'), 3.76 (s, 3H, COOMe), 3.95 (dd, 1H, $^2J_{5,5'}$ = 14 Hz, ^4J = 2.1 Hz, H-5), 4.05 (dd, 1H, $^2J_{5',5}$ = 14 Hz, ^4J = 1.7 Hz, H-5'), 4.57 (dd, 1H, $^3J_{2,3}$ = 7.4 Hz, $^3J_{2,3'}$ = 8.6 Hz, H-2), 6.57 (m, 1H, ^4J = 2.6 and 2.5 Hz, ^4J = 2.1 and 1.7 Hz, CH=C) ppm. *Anal.* calcd. for $C_{13}H_{15}O_2N$·HCl: C 61.52, H 6.37, N 5.52; found: C 61.22, H 6.36, N 5.39.

The Z-isomer has a mp of 157.5–159°C (dec.).

2-Benzylidene-5-carbomethoxy-6-azido-1-carbapenam **5**a

A mixture of the two geometric isomers of **2***b* was used in this reaction. To 10 mL of dry Et_2O at 0°C were added separately **2***b* (2.17 g, 10 mmol) in dry Et_2O (10 mL) and *tert*-butylhypochlorite (1.2 mL, 10 mmol) in dry Et_2O (10 mL) over a period of 10 min. After stirring at 0°C for another 10 min, additional Et_2O (50 mL) was added and the solution was washed with 0.1 *N* HCl (20 mL), with water (2 × 20 mL), dried (Na_2SO_4), and filtered. After cooling to −15°C, 18-crown-6 polyether (30 mg) and KO_2 (1.2 g) were added and the stirred reaction mixture was warmed up to room temperature over a period of 30 min. The precipitate was filtered off and the Et_2O evaporated to give a pale yellow oil. Analysis of the oil by tlc (CH_2Cl_2–MeOH, 99:1) showed the presence of two compounds with R_f 0.5 and 0.6. Partial decomposition during tlc of the more polar compound was observed. The residual oil was taken up in anhydrous benzene (100 mL) and cyclohexane (100 mL) containing Et_3N (1.6 mL, 12 mmol). A solution of azidoacetyl chloride (18) (0.98 mL, 11 mmol) in cyclohexane (60 mL) was added over 1 h at room temperature. The mixture was stirred for another hour, diluted with benzene (400 mL), and washed successively with 0.5 *M* phosphate buffer pH 3 (100 mL), water (100 mL), and a saturated NaCl solution (100 mL). The organic layer was dried (Na_2SO_4) and concentrated to yield an oily residue, which afforded after chromatography on silica gel, using C_6H_6–Me_2CO (99:1) as eluent, 1.5 g of **5***a* (50% yield); ir (CH_2Cl_2): 2130 (azide), 1780 (β-lactam), 1755 (ester) cm^{-1}; ms *m/e*: 298 (M^+). The ^{1}Hmr spectrum showed two singlet signals at δ 3.72 and 3.75 ($COOCH_3$), two signals at δ 4.56 and 4.59 (CHN_3), and broad peaks at δ 6.4 and 7.2 (C_6H_5CH=C) due to the presence of two geometric isomers.

2-Benzylidene-5-carbomethoxy-6-phenoxyacetamido-1-carbapenam **5**c

A stream of dry H_2S gas was bubbled through a solution of **5***a* (1.5 g, 5 mmol) and Et_3N (0.91 mL, 6.55 mmol) in anhydrous CH_2Cl_2 (50 mL) at 0°C for a period of 30 min. The solution was evaporated and the crude amine **5***b* was taken up in anhydrous CH_2Cl_2 (50 mL). After cooling to 0°C in an ice bath, Et_3N (0.71 mL, 5.05 mmol) in anhydrous CH_2Cl_2 (30 mL) and phenoxyacetyl chloride (920 mg, 5.4 mmol) in anhydrous CH_2Cl_2 (30 mL) were added simultaneously. The solution was stirred for 2 h at room temperature, washed with water (4×), dried (Na_2SO_4), and evaporated to yield an oil which was purified by chromatography on a silica gel column (CH_2Cl_2–Me_2CO, 98:2) to yield **5***c* (1.5 g, 75%); ir (CH_2Cl_2): 3415 (NH), 1775 (β-lactam), 1745 (ester), 1697 (amide) cm^{-1}; ^{1}Hmr δ: 3.55 and 3.58 (2 × s, 3H, $COOCH_3$), 4.45 (s, 2H, CH_2CO), 5.38 (d, 1H, *J* = 9 Hz, H-6), 6.4 (m, 1H, CH=C), 7.75 (d, 1H, *J* = 9 Hz, NH) ppm.

2-Oxo-5-carbomethoxy-6-phenoxyacetamido-1-carbapenam **5**d

Ozonized oxygen containing 2.5 mmol of O_3 was bubbled through a solution of **5***c* (812 mg, 2 mmol) in EtOAc (50 mL) at −50°C over a period of 1 h. Excess O_3 was removed in a stream of N_2 and the reaction mixture was hydrogenated at room temperature under a pressure of 0.5 kg/cm^2 in the presence of 100 mg 5% Pd/$CaCO_3$ for a period of 20 min. The reaction mixture was filtered and evaporated. Chromatography on silica gel (eluent CH_2Cl_2–Me_2CO, 95:5) afforded **5***d* (478 mg, 72%) as an oil; ir (CH_2Cl_2): 1775 (β-lactam), 1755 and 1745 (ester and ketone), 1704 (amide) cm^{-1}; ^{1}Hmr δ: 2.97 (m, 2H, H-1 and H-1'), 3.29 and 4.08 (AB pattern, 2H, *J* = 18 Hz, H-3 and H-3'), 3.64 (s, 3H, $COOCH_3$), 4.49 (s, 2H, CH_2O), 5.56 (d, 1H, *J* = 9 Hz, H-6), 6.78–7.5 (m, phenyl), 7.82 (d, 1H, *J* = 9 Hz, NH) ppm; ms *m/e*: 332 (M^+).

2,2-Dicarbomethoxy-4-methylene-pyrrolidine **2**c

3-Chloro-2-chloromethyl-1-propene (10 g, 80 mmol) was added dropwise to a stirred suspension of dimethyl aminomalonate

hydrochloride (14.68 g, 80 mmol) in anhydrous MeOH (200 mL) containing NaOMe (240 mmol). The mixture was refluxed for 6 h and the organic solvent was evaporated, leaving an orange slurry which was taken up in 1 *N* HCl (200 mL). The aqueous solution was washed with Et_2O (2 × 100 mL), made alkaline with 2 *N* NaOH (pH 10), and extracted with Et_2O (3 × 100 mL). The organic phase was dried (Na_2SO_4) and evaporated. Chromatography of the residual oil on a silica gel column, using CH_2Cl_2–EtOAc (98:2) as eluent, provided 3.34 g (25%) of **2***c*; ^{1}Hmr δ: 2.77 (br s, 1H, NH), 3.03 (m, 2H, CH_2—C), 3.70 (m, 2H, CH_2N), 3.77 (s, 6H, $COOCH_3$), 4.95 (m, 2H, C=CH_2) ppm.

1-Methylene-3,3-dicarbomethoxy-6-azido-1-carbapenam **6**a

To 10 mL of dry Et_2O at 0°C were added simultaneously **2***c* (2.09 g, 12.5 mmol) in dry Et_2O (20 mL) and *tert*-butylhypochlorite (1.5 mL, 13.7 mmol) in dry Et_2O (20 mL) over a period of 20 min. After stirring for 5 min the solution was washed with 0.1 *N* HCl (30 mL), with water (2 × 30 mL), dried (Na_2SO_4), and filtered. After cooling to 0°C, 18-crown-6 polyether (40 mg) and KO_2 (1.75 g) were added and the reaction mixture was stirred at 0°C for 15 min. The precipitate was filtered off and the Et_2O evaporated to give an oily residue, which was taken up in anhydrous benzene (100 mL) and cyclohexane (100 mL) containing Et_3N (2.07 mL, 15 mmol). A solution of azidoacetyl chloride (1.25 mL, 13.7 mmol) in cyclohexane (60 mL) was added over 40 min at room temperature and the mixture was stirred mechanically for another 40 min. The reaction mixture was worked up according to the procedure used for the synthesis of **5***a*, yielding 0.525 g of **6***a* (15%); ir (CH_2Cl_2): 2120 (azide), 1790 (β-lactam), 1755 (ester) cm^{-1}; ^{1}Hmr δ: 3.28 (m, 2H, H-2), 3.78 and 3.81 (2 × s, 6H, $COOCH_3$), 4.25 (m, 1H, H-5), 4.42 (d, J = 2.7 Hz, 1H, H-6), 5.28 (m, 2H, C=CH_2) ppm; ms *m/e*: 280 (M^+).

1-Methylene-3,3-dicarbomethoxy-6-phenoxyacetamido-1-carbapenam **6**b

Compound **6***b* was prepared as above by reduction with H_2S/Et_3N and, subsequently, reaction with phenoxyacetyl chloride (Et_3N at 0°C). After chromatography on a silica gel column (using C_6H_6–Me_2CO; 98:2 as eluent), there was obtained 270 mg (25%) of **6***b* (starting from 2 mmol of **6***a*) which was crystallized from Et_2O/hexane, mp 143–145°C (dec.); ir (CH_2Cl_2): 3425 (NH), 1790 (β-lactam), 1755 (ester), 1700 (amide), 1610, 1440, 910 (C=CH_2) cm^{-1}; ^{1}Hmr (90 MHz, $CDCl_3$) δ: 3.31 (m, 2H, H-2), 3.78 and 3.80 (2 × s, 6H, $COOCH_3$), 4.30 (m, 1H, H-5), 4.53 (s, 2H, CH_2O), 5.07 (q, 1H, J = 8.0 Hz, J = 2.7 Hz, H-6), 5.36 (m, 2H, CH_2=C), 6.83–7.47 (m, 5H, phenyl), 7.6 (d, 1H, J = 8 Hz, NH) ppm; ^{13}Cmr ($CDCl_3$) δ: 44.3 (C2), 53.5 and 53.6 (OCH_3), 63.3 (C6), 65.2 (C5), 67.2 (CH_2O), 72.4 (C3), 112.2 (=CH_2), 114.9, 122.4 and 130 (phenyl), 142.5 (C1), 157.2 (*C*—OCH_2), 166.2, 168.6 and 171 (C=O) ppm; ms *m/e*: 388 (M^+). *Anal.* calcd. for $C_{19}H_{20}O_7N_2$: C 58.75, H 5.19, N 7.21; found: C 58.52, H 5.26, N 7.09.

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