# 132. The Synthesis of Highly Strained Monocyclic and Bicyclic β-Lactams ($\Delta^1$-Carbapenem)

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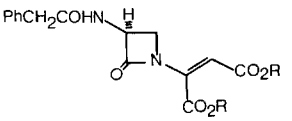
*Summary*

The synthesis of some β-lactams and one $\Delta^1$-carbapenem is described. The electronic activation of monocyclic β-lactams of type **1** is not sufficient to generate a bioactive compound.

The IR. absorption frequency of the carbonyl of a β-lactam can be considered as a measure of its reactivity towards nucleophilic attack [1], therefore higher frequency might indicate the potential for higher biological activity.

The synthesis of several monocyclic nuclear analogues of β-lactam antibiotics, in which the ring strain of fused β-lactams was replaced by electronic activation (*e.g.* **1a**, **1b**) was reported [2]. Although the electronically activated β-lactam **1a** absorbs at 1790 $cm^{-1}$, the corresponding acid **1b** showed no significant antibacterial activity in phosphate buffer at pH 7.0 [3]. Kinetics studies [3] have indicated that the dicarboxylic acid **1b** is not readily attacked by nucleophiles. This low susceptibility to nucleophilic attack and lack of biological activity may be due to reduced electron-withdrawing ability of the maleate moiety in **1b** by anion formation at neutral pH [3].




**1a** R = Me
**1b** R = H

We now report the synthesis of **11**, in which the electronic activation is provided by an ester function. Treatment of dibenzyl aminomalonate **2** with methyl glyoxylate **3** gave compound **4a**. The IR., NMR. and mass spectra of **4a** were consistent with the proposed structure. Amino ester **4a** was converted in good yield to its (*t*-butyl)dimethylsilyl derivative **4b**. Using the procedure described by *Doyle et al.* [4], **4b** was transformed to the cinnamylidene derivative, then to the *cis*-3-azido-4-styryl-

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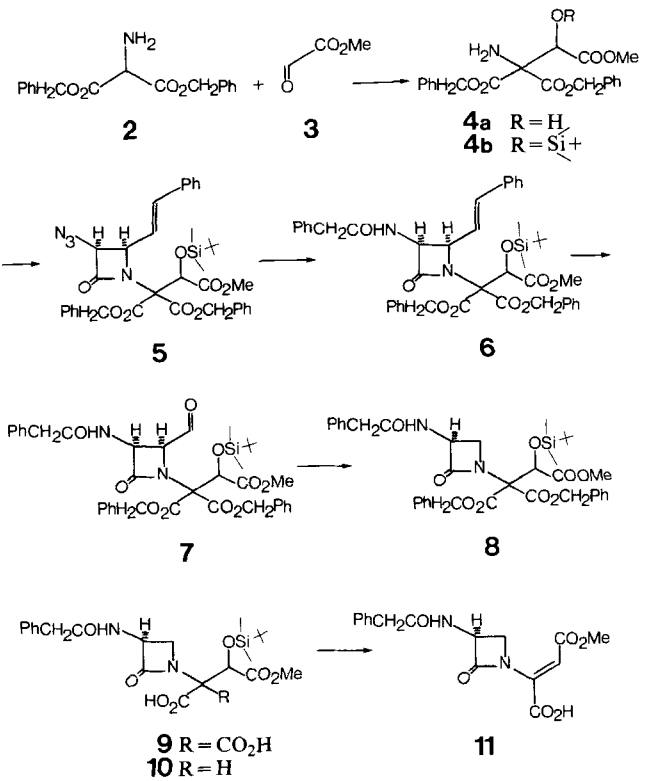


**2** **3** **4a** R = H **4b** R = Si+

**5** **6**

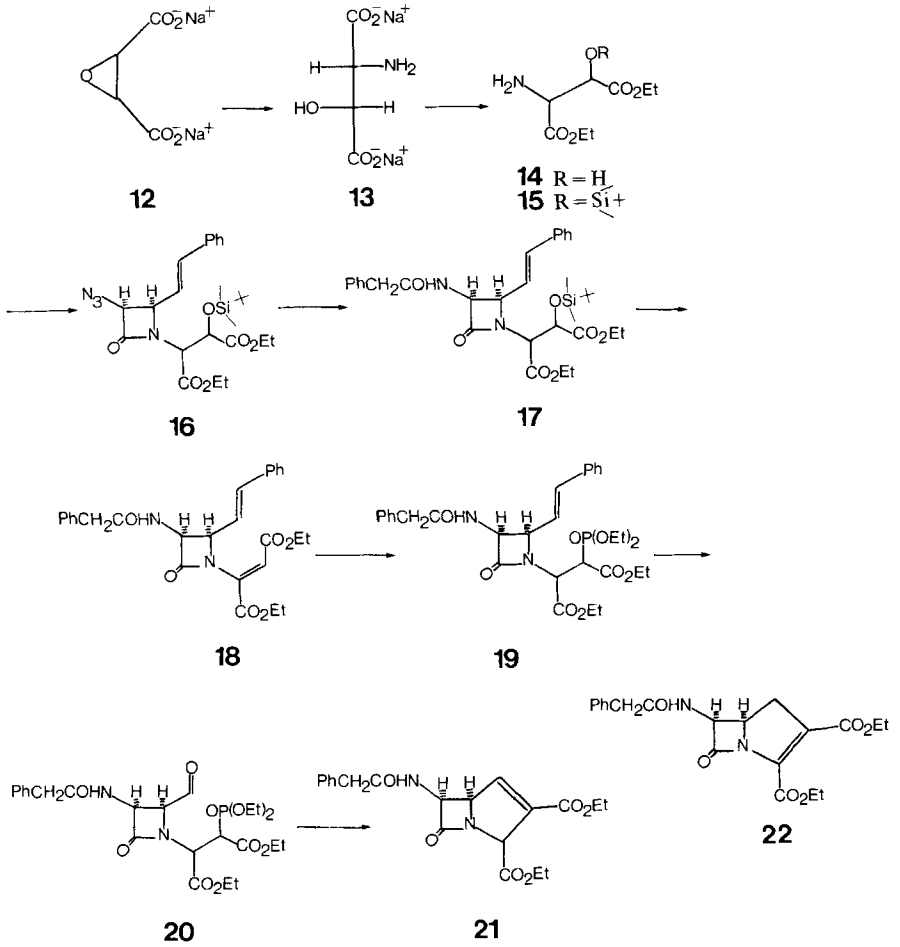
**7** **8**

**9** R = $CO_2H$ **10** R = H **11**

$\beta$-lactam **5** as a mixture of diastereoisomers. The coupling constant (5 Hz) of the two H-atoms on the $\beta$-lactam ring indicated *cis*-substitution [5] [6]. The azide function in **5** was reduced ($H_2S/NEt_3$ [7]) and the resulting amine directly acylated to the phenylacetamido-$\beta$-lactam **6**. Ozonolysis of **6**, followed by dimethyl sulfide treatment at $-20°$, gave the expected aldehyde **7**.

The analogue **11** of **1b** was prepared from the readily available aldehyde **7** by decarbonylation with tris(triphenylphosphine)rhodium chloride [8]. The biological properties of **11** may provide an answer as to whether an additional negative charge on **1b** is responsible for the lack of antimicrobial activity.

Reaction of aldehyde **7** with equimolar amount of tris(triphenylphosphine)-rhodium chloride gave after 2 h $\beta$-lactam **8** in 20% yield only. Catalytic hydrogenation converted **8** to the diacid **9** (50%) which was decarboxylated ($NaHCO_3$/HCl-solution) to the monoacid **10**. Attempted conversion of the silyloxy derivative **10** to **11** using 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) failed. Successful elimination (40%) could be achieved when **10** was treated with two equivalents of trimethylsilyl chloride and three equivalents of DBU in anhydrous ether at reflux temperature for 3 h. The $\beta$-lactam **11** ($\nu_{max}$ 1788 $cm^{-1}$) was identified on the basis of the chemical shift of the olefinic proton, $\delta$ 6.59 (*s*, 1 H, CHCOOMe), as the (*Z*)-isomer. The olefinic proton appears at higher field, $\delta \sim 5.47$–$5.68$ ppm, in maleate compared to the corresponding fumarate, $\delta \sim 6.56$–$6.84$ ppm [9].



Although the β-lactam **11** was susceptible to nucleophilic attack, it did not exhibit antimicrobial activity. Therefore, it seems that the enamine group has to be prevented from being coplanar with the β-lactam system for biological activity. Since fused β-lactams meet this requirement, the preparation of compound **22** was undertaken.

The sodium salt of the epoxysuccinic acid **12** [10] [11] was transformed to the amino acid **13** by means of ammonium hydroxide. Esterification with EtOH/HCl gave the amino ester **14** as its hydrochloride. Amino ester **14** was silylated with *t*-butyldimethylsilyl chloride/imidazole to give the corresponding silyloxy derivative **15** (*ca.* 60% from **12**).

The amino ester **15** was converted to its cinnamylidene derivative, then to the *cis*-3-azido-4-styryl-β-lactam **16**, mixture of diastereoisomers at the C-atoms bearing the carboxyl groups. Phenylacetamido-β-lactam **17** was prepared from **16** as **6** from **5**. The elimination of the silyloxy group from **17** with DBU gave the fumarate **18**, δ 6.61 (*s*, 1 H, CHCOOEt).

A solution of **18** in THF was treated with two equivalents of diethyl phosphite and one equivalent of NaH [12] to give the adduct **19**. Ozonolysis of **19** and subsequent treatment of the intermediate aldehyde **20** with NaH in THF at −30° [13] gave $\Delta^1$-carbapenem **21** (13% yield only) characterized by its elemental analysis, IR., NMR. and chemical ionization mass spectra. No attempt was made to prepare the corresponding carboxylic acid because of the instability of **21** and the low yield of its formation.

All attempts to isomerize $\Delta^1$-carbapenem **21** to the corresponding $\Delta^2$-carbapenem **22** resulted in the destruction of the $\beta$-lactam ring.

## Experimental Part

*General procedures:* see [14].

*Preparation of dibenzyl 2-amino-2-(hydroxy-methoxycarbonylmethyl)malonate* (**4a**). Methyl glyoxylate **3** (1 g, 0.012 mol) and $MgSO_4$ were added to dibenzyl aminomalonate **2** (2.99 g, 0.01 mol) in 40 ml dry $CH_2Cl_2$. The suspension was stirred at r.t. for 6 h, and filtered. The filtrate was evaporated to give a quantitative yield of amino ester **4a**. – IR. ($CH_2Cl_2$): 3250–3510 (OH, $NH_2$), 1750 (ester). – NMR. ($CDCl_3$): 2.81 (br.*s*, 2H, $NH_2$ exchangeable with $D_2O$); 3.59 (*s*, 3H, $CH_3$); 5.10–5.31 (*m*, 6H, $2CH_2$ and CHOH); 7.37 (*s*, 10H, Ph). – MS.: 387 ($M^+$).

*Preparation of dibutyl 2-amino-2-[((t-butyl)dimethylsilyloxy)methoxycarbonyl-methyl]malonate* (**4b**). To the hydroxy amino ester **4a** (3.87 g, 0.01 mol) in dry *N,N*-dimethylformamide (40 ml) was added imidazole (1.53 g, 0.022 mol) and (*t*-butyl)dimethylchlorosilane (3.15 g, 0.021 mol). The solution was stirred at 25° for 4 h, then partitioned between ether (200 ml) and water (300 ml). The organic layer was washed with water (3×200 ml), dried ($Na_2SO_4$), and evaporated. The crude silyl ether was chromatographed on silica gel. Impurities were eluted with $CH_2Cl_2$ and **4b** was eluted with $CHCl_3$ (40%). – NMR. ($CDCl_3$): 0.10 (2*s*, 6H, $Si(CH_3)_2$); 0.85 (*s*, 9H, $C(CH_3)_3$); 2.38 (br., 2H, $NH_2$); 3.51 (*s*, 3H, $CH_3$); 5.11 (*s*, 4H, $2CH_2$); 5.12 (*s*, 1H, CH); 7.28 (2*s*, 10H, Ph). – MS.: 500 ($M^+$).

$C_{26}H_{34}NO_7Si$ (500.09) Calc. C 62.40 H 6.80 N 2.80% Found C 62.43 H 6.78 N 2.82%

*Preparation of diethyl 2-amino-3-[(t-butyl)dimethylsilyloxy]succinate* (**15**). In the same way as for **4b**, in 90% yield. – MS.: 319 ($M^+$).

$C_{14}H_{29}NO_5Si$ (319.12) Calc. C 52.66 H 9.09 N 4.38% Found C 52.61 H 9.11 N 4.29%

*Preparation of azidoazetidinones* **5** *and* **16**. Both compounds were prepared in an identical manner and obtained in approximately 70% yield. Their spectra were similar except for variations due to substituents. Their MS. showed $M^+$, $M^+ - N_2$ and $M^+ - N_3CH{=}C{=}O$.

*Preparation of dibenzyl 2-(3-azido-2-oxo-4-styryl-1-azetidinyl)-2-[(t-butyl)dimethylsilyloxy-(methoxycarbonyl)methyl]malonate* (**5**). A solution of **4b** (0.5 g, 1 mmol) and cinnamaldehyde (0.54 g, 4 mmol) in benzene (15 ml) was heated at reflux temperature for 18 h using a *Dean-Stark* trap. Evaporation of benzene afforded a quantitative yield of the corresponding *Schiff* base, which was dissolved in $CH_2Cl_2$ and $NEt_3$ (0.2 g, 2 mmol) was added. A solution of azidoacetyl chloride (0.24 g, 2 mmol) in 2 ml dry $CH_2Cl_2$ was added dropwise over 5 min at 25°. The solution was stirred for 5 h and evaporated to dryness. The residue was dissolved in ether, treated with charcoal, filtered and evaporated to give an oily product, which was chromatographed on silica gel. Elution with $CHCl_3$ gave **5** as an oily mixture of diastereoisomers in 70% overall yield. – IR. ($CH_2Cl_2$): 2100 ($N_3$) 1775–1750 ($\beta$-lactam-ester). – NMR. ($CDCl_3$): 0.10 (2*s*, 6H, $Si(CH_3)_2$); 0.91 (2*s*, 9H, $C(CH_3)_3$); 3.52 (2*s*, 3H, $OCH_3$); 4.80 (2*d*, $J$ = 5 Hz, 1H, H–C(3)); 5.01–5.25 (*m*, 5H, $2CH_2$ and CH); 6.30 (*d*×*d*, $J$ = 5 and 9 Hz, 1H, C*H*=CHPh); 6.61 (*d*, $J$ = 16 Hz, 1H, CH=C*H*Ph); 7.18–7.29 (*m*, 15H, 3 Ph). – MS.: 698 ($M^+$).

$C_{37}H_{42}N_4O_8Si$ (698.09) Calc. C 63.61 H 6.01 N 8.02% Found C 63.52 N 6.00 N 8.12%

*Preparation of phenylacetamidoazetidinones* **6** *and* **17**. Both transformations were performed in an identical manner, and the mixture of diastereoisomers, **6** and **17**, obtained in about 90% yield after purification. Their spectra were similar except for variations due to substituents. Their MS. showed $M^+$, $M^+ - (PhCH_2CONHCH{=}C{=}O)$, $M^+ - (Ph{-}CH{=}CH{-}CH{=}CH{-}NHCOCH_2Ph)$.

*Preparation of dibenzyl 2-(2-oxo-3-phenylacetamido-4-styryl-1-azitidinyl)-2-[(t-butyl)dimethylsilyloxy-(methoxycarbonyl)methyl]malonate* (**6**). Hydrogen sulfide was bubbled into a solution of **5** (6.98 g, 0.01 mol) and $NEt_3$ (2.02 g, 0.02 mol) in $CH_2Cl_2$ (200 ml) at 0°. After 1.5 h, the solution was purged with $N_2$, washed with $H_2O$ (2 × 100 ml), dried, and evaporated. To the crude product in $CH_2Cl_2$ (100 ml) and pyridine (2.4 g, 0.03 mol) was added dropwise phenylacetyl chloride (2.37 g, 0.015 mol) in $CH_2Cl_2$ (20 ml). After stirring for 2 h, the solution was washed with pH 4.5 buffer (50 ml), water (50 ml), dried ($MgSO_4$), and evaporated. The crude product was chromatographed on silica gel (100 g) in $CH_2Cl_2$. Elution with $CHCl_3$ afforded 7.1 g (90%) of **6** as a foam. – IR. ($CH_2Cl_2$): 3410 (NH), 1779–1750 (β-lactam-ester), 1680 (amide). – NMR. ($CDCl_3$): 0.10 (2*s*, 6H, $Si(CH_3)_2$); 0.92 (*s*, 9H, $C(CH_3)_3$); 3.39–3.65 (*m*, 5H, $OCH_3$ and $CH_2CO$); 5.00–5.29 (*m*, 5H, $2CH_2O$ and CHC=C); 5.41 (*s*, 1H, CHOSi); 5.42 (*d* × *d*, *J* = 5 and 9 Hz, 1H, H–C(4′); 6.20–7.00 (*m*, 2H, *CH*=*CH*–Ph); 7.01–7.45 (*m*, 21H, Ph and NH). – MS.: 790 ($M^+$).

$C_{45}H_{50}N_2O_9Si$ (790.11) Calc. C 68.35 H 6.32 N 3.54% Found C 68.25 H 6.31 N 3.63%

*Preparation of dibenzyl 2-(4-formyl-2-oxo-3-phenylacetamido-1-azitidinyl)-2-[(t-butyl)dimethylsilyl-oxy-(methoxycarbonyl)methyl]malonate* (**7**). Ozone was passed for 2 h through a solution of **6** (4 g) in $CH_2Cl_2$ (100 ml) at −78°. After purging with $N_2$, dimethyl sulfide (3 equiv.) was added and the solution allowed to warm to r.t. (2 h). The solvent was evaporated and the residue was purified by column chromatography on silica gel. Elution with $CH_2Cl_2$ removed impurities and **7** was eluted with AcOEt (70%). – IR. ($CH_2Cl_2$): 3415 (NH), 1778 (β-lactam), 1745 (ester), 1720 (aldehyde), 1680 (amide). – NMR. ($CDCl_3$): 0.11 (2*s*, 3H, $Si(CH_3)_2$); 1.01 (2*s*, 9H, $C(CH_3)_3$); 3.59 (2*s*, 2H, $CH_2CO$); 3.79 (2*s*, 3H, $OCH_3$); 4.81 (br., 1H, H–C(4)); 5.10–5.23 (*m*, 5H, $2CH_2O$ and CHOSi); 5.81 (*d* × *d*, *J* = 5 and 9 Hz, 1H, H–C(3)); 7.00 (br., 1H, NH); 7.35 (br.*s*, 15H, 3 Ph); 9.66 (*d*, *J* = 1.5 Hz, 1H, CHO). – MS.: 716 ($M^+$).

$C_{38}H_{44}N_2O_{10}Si$ (716.13) Calc. C 63.68 H 6.14 N 3.91% Found C 63.60 H 6.23 N 3.82%

*Preparation of diethyl 2-(4-formyl-2-oxo-3-phenylacetamido-1-azetidinyl)-3-diethylphosphonato-succinate* (**20**). It was obtained in the same way as compound **7** in 72% yield as a foam. – IR. ($CH_2Cl_2$): 3410 (NH), 1762 (β-lactam), 1740 (ester), 1720 (aldehyde), 1680 (amide). – NMR. ($CDCl_3$): 1.29–1.39 (*m*, 12H, $4CH_3$); 3.39 (br.*d*, *J* = 22 Hz, 1H, CHP); 3.65 (*s*, 2H, $CH_2CO$); 3.99–3.43 (*m*, 8H, $4CH_2$); 4.75–5.03 (*m*, 2H, NC*H*COOEt and H–C(4)); 5.63 (*d* × *d*, *J* = 5 and 9 Hz, 1H, H–C(3)); 7.32 (*s*, 5H, Ph); 7.33 (br., 1H, NH); 10.12 (*d*, *J* = 2 Hz, 1H, CHO). – MS.: 540 ($M^+$).

$C_{24}H_{33}N_2O_{10}P$ (540.41) Calc. C 53.33 H 6.11 N 5.18% Found C 53.29 H 6.00 N 4.99%

*Preparation of dibenzyl 2-(2-oxo-3-phenylacetamido-1-azetidinyl)-2-[methoxycarbonyl-(t-butyl)-dimethylsilyloxymethyl]malonate* (**8**). Tris(triphenylphosphine)rhodium chloride (1 equiv.) was added to aldehyde **7** (3.58 g, 5 mmol) in oxygen-free benzene. The mixture was refluxed under argon for 2 h then cooled and filtered. The filtrate was evaporated and the residue was purified by column chromatography on silica gel. Elution with $CHCl_3$ gave 1 g (20%) of **8** as a foam. – IR. ($CH_2Cl_2$): 3410 (NH), 1755 (β-lactam), 1750 (ester), 1680 (amide). – NMR. ($CDCl_3$): 0.12 (2*s*, 3H, $Si(CH_3)_2$); 1.00 (*s*, 9 H, $C(CH_3)_3$); 3.19 (*d* × *d*, *J* = 2 and 6.5 Hz, 1H, $H_\beta$–C(4)); 3.60 (br.*s*, 2H, $CH_2CO$); 3.78 (2*s*, 3H, $CH_3$); 4.01 (*d* × *d*, *J* = 5 and 6.5 Hz, 1H, $H_\alpha$–C(4)); 4.98–5.01 (*m*, 1H, H–C(3)); 4.99–5.19 (*m*, 5H, $2CH_2CO$ and CHOSi); 6.91 (*d*, *J* = 9 Hz, 1H, NH); 7.22–7.41 (*m*, 15H, 3 Ph). – MS.: 688 ($M^+$).

$C_{37}H_{44}N_2O_9Si$ (688.12) Calc. C 64.53 H 6.39 N 4.07% Found C 64.43 H 6.40 N 3.97%

*Preparation of 2-(2-oxo-3-phenylacetamido-1-azetidinyl)-2-[(t-butyl)dimethylsilyloxy-(methoxy-carbonyl)methyl]malonic acid* (**9**). Compound **8** (1.72 g, 2.5 mmol) in 35 ml AcOEt was hydrogenated over Pd/C (0.6 g) at 25° and 45 psi for 3 h. The mixture was filtered and evaporated to give 0.62 g (50%) of acid **9**, m.p. 150–154°. – IR. (Nujol): 3000–3400 (COOH, NH), 1760–1750 (β-lactam, ester). 1670 (amide).

*Preparation of 1-methyl hydrogen 3-(2-oxo-3-phenylacetamido-1-azetidinyl)-2-[(t-butyl)dimethylsilyl-oxy-(methoxycarbonyl)methyl]succinate* (**10**). **9** (0.5 g) was dissolved in ethanol (2 ml), $NaHCO_3$-solution (10%, 3 ml) was added and the solution was stirred at r.t. for 1 h. The basic solution was neutralized by HCl-solution (10%) to pH ≈ 4. Extraction with AcOEt, followed by evaporation of AcOEt gave (70%) of **10**, m.p. 110–114°. – IR. (Nujol): 3000–3400 (COOH, NH), 1760 (β-lactam), 1745 (ester), 1680 (amide).

*Preparation of 1-methyl hydrogen 3-(2-oxo-3-phenylacetamido-1-azetidinyl)-fumarate* (**11**). Acid **10** (0.3 g) was suspended in anhydrous ether (50 ml). DBU (3 equiv.) followed by trimethylsilyl chloride (2 equiv.) were added and the mixture was heated at reflux temperature for 3 h. The solution was evaporated and the residue was dissolved in AcOEt and washed with 5% aqueous HCl-solution. The organic layer was dried, evaporated and the crude product was chromatographed on silica gel and acid **11** was eluted with AcOEt (40%), m.p. 80–82°. – IR. ($CH_2Cl_2$): 3200–3390 (COOH, NH), 1788 (β-lactam), 1740 (ester), 1675 (amide). – NMR. ($CDCl_3$, $D_2O$): 3.18 (*d* × *d*, *J* = 6 and 2 Hz; 1H, $H_\beta$–C(4)); 3.61 (*s*, 2H, $CH_2CO$); 3.90 (*s*, 3H, $COOCH_3$); 4.01 (*d* × *d*, *J* = 5 and 6 Hz, 1H, $H_\alpha$–C(4)); 5.01 (*d* × *d*, *J* = 5 Hz, 1H, H–C(3)); 6.59 (*s*, 1H, C*H*COOMe); 7.41 (*s*, 5H, Ph). – MS.: 315 ($M^+ - OH$).

$C_{16}H_{16}N_2O_6$ (332.12) Calc. 57.83 H 4.81 8.43% Found C 57.72 H 4.71 N 8.34%

*Preparation of disodium 2-amino-3-hydroxysuccinate* (**13**). Disodium epoxysuccinate (**12**) (0.02 mol) was dissolved in conc. $NH_4OH$-solution (120 ml) and stirred in a pressure bottle at 50–60° for 24 h. After cooling, acetone was added to give an oily product. The solution was decanted and the oil was washed with acetone to give a precipitate. Filtration gave a quantitative yield of **13** as its sodium salt. – NMR. ($D_2O$): 4.21 (*d*, *J* = 2 Hz, 1H, H–C(3)); 4.99 (*d*, *J* = 2 Hz, 1H, CHOD).

*Preparation of diethyl 2-amino-3-hydroxysuccinate* (**14**). Compound **13** (0.02 mol) was suspended in 300 ml abs. ethanol, and HCl gas bubbled in at 25° without cooling for 15 min. The solution was refluxed for 6 h. The solvent then evaporated and a mixture of 90 ml acetone/ether 1:2 was added. The white precipitate was filtered off and washed with ether (300 ml). A quantitative yield of **14** · HCl was obtained. Compound **14** · HCl (0.01 mol) was suspended in 300 ml ether. The solution was saturated with ammonia at 20° (15 min). Filtration and evaporation gave 90% of **14** as an oily product. – IR. ($CH_2Cl_2$): 3340–3410 ($NH_2$, OH), 1750 (ester). – NMR. ($CDCl_3$): 1.31 (*t*, 6H, 2 $CH_3$); 2.82 (br., 2H, $NH_2$, exchangeable with $D_2O$); 3.91 (*d*, *J* = 2 Hz, 1H, C*H*$NH_2$); 4.00–4.45 (*m*, 4H, 2 $CH_2$); 4.46 (br.*s*, 1H, OH); 4.61 (*d*, *J* = 2 Hz, 1H, CHOH).

*Preparation of diethyl 2-(2-oxo-3-phenylacetamido-4-styryl-1-azetidinyl)fumarate.* DBU (1.53 g, 10 mmol) was added to **17** (diastereoisomeric mixture, 3.04 g, 5 mmol) in anhydrous ether. The mixture was heated at reflux temperature for 3 h to give a white precipitate. The solution was cooled and the precipitate was filtered off to give 1.5 g (60%) of **18**; m.p. 97–100°. – IR.: ($CH_2Cl_2$): 3410 (NH), 1792 (β-lactam), 1742 (ester), 1680 (amide). – NMR. ($CDCl_3$): 1.28 (*t*, 6H, 2 $CH_3$); 3.61 (*s*, 2H, $CH_2CO$); 4.18–4.59 (*m*, 4H, 2 $OCH_2$); 4.91 (br., 1H, H–C(4)); 5.42 (*d* × *d*, *J* = 5 and 10 Hz, 1H, H–C(3)); 6.45–6.91 (*m*, 2H, CH=CH); 6.61 (*s*, 1H, C=C*H*COOEt); 7.01 (br., 1H, NH); 7.21 (*s*, 5H, PhC=C); 7.51 (*s*, 5H, $C_6H_5CH_2$). – MS.: 476 ($M^+$).

$C_{27}H_{28}N_2O_6$ (476.21) Calc. C 68.06 H 5.88 N 5.88% Found C 68.10 H 5.86 N 5.80%

*Preparation of diethyl 2-(2-oxo-3-phenylacetamido-4-styryl-1-azetidinyl)-3-diethylphosphonato-succinate* (**19**). To a solution of **18** (2.38 g, 5 mmol) and diethyl phosphite (1.38 g, 10 mmol) in 50 ml THF, NaH (0.12 g, 5 mmol, washed with THF) was added at 0°. After stirring for 1 h, and evaporation to dryness, the residue was dissolved in ether, washed with water and dried ($MgSO_4$). Filtration and evaporation gave a quantitative yield of **19** as an oil. Purification by column chromatography using silica gel, and elution with AcOEt gave 2.5 g (80%) of **19** as a foam. – IR. ($CH_2Cl_2$): 3410 (NH), 1765 (β-lactam), 1740 (ester), 1779 (amide). – NMR. ($CDCl_3$): 1.28–1.39 (*m*, 12H, 4$CH_3$); 3.38 (*d*, *J* = 20 Hz, 1H, CHP); 3.51 (*s*, 2H, $PhCH_2$); 3.91–4.41 (*m*, 8H, 4C$H_2CH_3$); 4.69–4.78 (*m*, 2H, CH–C=C and NC*H*COOEt); 5.41 (*d* × *d*, *J* = 5 and 9 Hz, 1H, H–C(3′)); 6.00–6.81 (*m*, 2H, CH=CH); 7.12 (*s*, 5H, PhC=C); 7.31 (*s*, 5H, Ph); 7.35 (br., 1H, NH). – MS.: 614 ($M^+$).

$C_{31}H_{39}N_2O_9P$ (614.18) Calc. C 60.58 H 6.35 N 4.56% Found C 60.47 H 6.40 N 4.66%

*Preparation of 2,3-bis(ethoxycarbonyl)-6-phenylacetamido-Δ¹-carbapenem* (**21**). To a solution of **20** (0.54 g, 1 mmol) in 20 ml dry THF at −30° was added NaH (1 mmol). The solution was stirred for 2 h at the same temperature and then at 25° for a further 5 h. The reaction mixture was quenched with aqueous

$NH_4Cl$-solution and extracted with $CH_2Cl_2$. The crude product (0.4 g) was purified on preparative silica gel plates to yield 50 mg (13%) of **21** as a foam. – IR. ($CH_2Cl_2$): 3415 (NH), 1783 ($\beta$-lactam), 1720–1740 (esters), 1670 (amide). – NMR. ($CDCl_3$): 1.28–1.39 (*m*, 6H, $2CH_3$); 3.01 (*d*×*d*, *J* = 14 and 3 Hz, 1H, H–C(1)); 3.41 (*d*×*d*, *J* = 14 and 5 Hz, 1H, H–C(7)); 3.52 (*s*, 2H, $PhCH_2$); 3.99–4.65 (*m*, 5H, $2CH_2$ and H–C(3)); 4.87 (*d*×*d*, *J* = 5 and 10 Hz, 1H, H–C(6)); 6.92 (br., 1H, NH); 7.39 (*s*, 5H, Ph). – CI.-MS.: 397 ($M^+ + 1$).

$C_{20}H_{22}N_2O_6$ (386.12) Calc. C 62.17 H 5.69 N 7.25% Found C 62.01 H 5.51 N 6.99%

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