168. Synthesis of Ethyl *cis* 2-[(Diethoxyphosphoryl)methyl]-7-oxo-3-phenyl-6-phthalimido-1-azabicyclo[3.2.0]hept-3-ene-2-carboxylate and Methyl *cis*-2-Bromo-3-methyl-8-oxo-7-phthalimido-4-oxa-1-azabicyclo[4.2.0]octane-2-carboxylate

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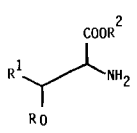
(2.V.89)

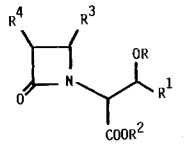
The synthesis of a Δ^1-carbapenem and two β-lactams possessing a Br-atom at the N-substituting center not involved in the lactam ring and bearing the carboxyl group is described. The β-lactams having this kind of Br-substitution are more susceptible to nucleophilic attack than those having a conjugated double bond with the N-atom of the β-lactam ring. DBU is found to be an excellent reagent for the elimination of the silyloxy function. Moreover, a simple method for the addition of diethyl phosphite to an α,β-unsaturated double bond using a catalytic amount of NaH is described.

As part of a continuing program to prepare nonclassical β-lactam antibiotics, we synthesized β-lactams **9**, **15**, and **16**. The method used to prepare the monocyclic precursors **4** derives from that developed by *Doyle et al.* [1] and by ourselves [2–6].

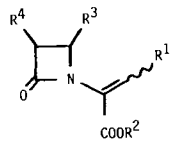
L-Serine (**1a**) and L-threonine (**1b**) were converted to their esters **2a** and **2b**, respectively (100%). Treatment of **2a,b** with (*tert*-butyl)dimethylsilyl or trimethylsilyl chloride gave compounds **3a**, **3b**, and **3'a** in excellent yield. Reactions of **3a,b** with cinnamaldehyde



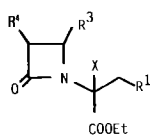
1a R = R¹ = R² = H
b R = R² = H, R¹ = Me
2a R = R¹ = H, R² = Et
b R = H, R¹ = R² = Me
3a R = (*t*-Bu)Me₂Si, R¹ = H, R² = Et
3'a R = Me₃Si, R¹ = H, R² = Et
3b R = (*t*-Bu)Me₂Si, R¹ = R² = Me



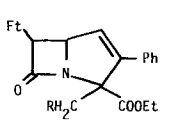
4a R = (*t*-Bu)Me₂Si, R¹ = H, R² = Et, R³ = PhCH=CH, R⁴ = Phthalimido
4'a R = R¹ = H, R² = Et, R³ = PhCH=CH, R⁴ = Cl
4b R = (*t*-Bu)Me₂Si, R¹ = R² = Me, R³ = PhCH=CH, R⁴ = Phthalimido
5b R = (*t*-Bu)Me₂Si, R¹ = R² = Me, R³ = CH_2OH, R⁴ = Phthalimido



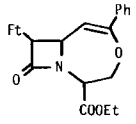
5a R¹ = H, R² = Et, R³ = PhCH=CH, R⁴ = Phthalimido
5'a R¹ = H, R² = Et, R³ = PhCH=CH, R⁴ = Cl
6b R¹ = R² = Me, R³ = CH_2OH, R⁴ = Phthalimido
11 R¹ = H, R² = Et, R³ = PhCBr=CH, R⁴ = Phthalimido



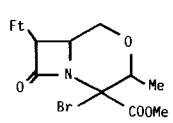
7 R¹ = PO(OEt)₂, R³ = PhCH=CH, R⁴ = Phthalimido, X = H
8a R¹ = PO(OEt)₂, R³ = PhCHBrCHBr, R⁴ = Phthalimido, X = H
8b R¹ = PO(OEt)₂, R³ = PhCBr=CH, R⁴ = Phthalimido, X = H
10 R¹ = (*t*-Bu)Me₂SiO, R³ = PhCHBrCHBr, R⁴ = Phthalimido, X = H
13 R¹ = OH, R³ = PhC(OMe)=CH, R⁴ = Phthalimido, X = H
15 R¹ = MeO, R³ = PhC(OMe)=CH, R⁴ = Phthalimido, X = Br



9 R = PO(OEt)₂, Ft = Phthalimido
12 R = (*t*-Bu)Me₂SiO, Ft = Phthalimido



14 Ft = Phthalimido



16 Ft = Phthalimido

afforded the corresponding *Schiff* bases which, upon treatment with phthalimidoacetyl chloride and Et_3N, gave the stereoisomeric mixtures of the β-lactams **4a** (*ca.* 80%) and **4b** (70%), respectively. The desilylated β-lactam **4'a** was obtained similarly from **3'a** *via* reaction of its *Schiff* base with chloroacetyl chloride. All β-lactams obtained were *cis*-configurated, as determined by ^{1}H-NMR (J(H–C(3), H–C(4)) = 5 Hz) of the derivatives in which the relevant protons did not overlap with other signals. The high yield of the *cis*-stereoisomers **4a,b** is consistent with the mechanism of cycloaddition proposed by *Doyle et al.* [7] [8] and supported by *Sullivan et al.* [9] where electron-rich *Schiff* bases give consistently high yield of *cis*-β-lactams.

Attempted conversion of the silyloxy derivative **4a** to **5a** using Et_3N failed. Successful elimination (98%) could be achieved when **4a** was treated with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) in anhydrous Et_2O at reflux temperature for 1 h. The desilylated **4'a** was transformed to **5'a** by means of methanesulfonyl chloride/Et_3N in CH_2Cl_2 (90%). The β-lactams **5a** and **5'a** ($\tilde{\nu}_{max}$ 1780 cm^{-1}) exhibit high reactivity toward nucleophilic attack.

The synthesis of several monocyclic analogues of β-lactam antibiotics in which the ring strain of fused β-lactam is replaced by electronic activation was reported [10–12]. However, for biological activity, the enamine moiety of **5a** and **5'a** should be prevented from being coplanar with the remaining of the β-lactam system. Since fused β-lactams meet this requirement, the preparation of compound **9** from **5a** was undertaken.

A solution of **5a** in THF was treated with 1.2 equiv. of diethyl phosphite in the presence of a catalytic amount of NaH [13] to give the adduct **7** (99%). Bromination of **7** with Br_2 in $CCl_4/CHCl_3$ 7:3 afforded a mixture of **8a** (75%) and **8b** (20%). Reaction of **8a** or **8b** with DBU in THF at 25° afforded the bicyclic β-lactam **9** (80%) characterized by its IR, NMR, and mass spectra and elemental analysis. No attempt was made to prepare the corresponding carboxylic acid because of the instability of **9**.

An alternative scheme for the synthesis of Δ^1-carbapenem **9** consists in the transformation **4a** → **10** → **11** → **9**. Thus, **10** was obtained from β-lactam **4a** and Br_2 in $CCl_4/CHCl_3$ 7:3 and reacted with DBU as above to give β-lactam **11** (78%). This indicates that the elimination of the silyloxy function in **10** is much faster than the cyclization to **12**. However, reaction of **11** with diethyl phosphite using a catalytic amount of NaH yielded Δ^1-carbapenem **9** (83%). Therefore, **8b** might be considered as an intermediate in the transformation of **8a** → **9**. It should be noted that the bromination of **4a** in MeOH gave **13** which in turn was converted to **14** (85%) in the presence of DBU in THF at 25°. Furthermore, treatment of **5a** with Br_2/MeOH afforded **15** (56%).

The IR-absorption wavenumber of the carbonyl group of a β-lactam can be considered as a measure of its reactivity towards nucleophilic attack [14]; therefore, a higher wavenumber might indicate the potential for higher biological activity.

However, β-lactam **15** ($\tilde{\nu}_{max}$ 1766 cm^{-1}) possessing a Br-atom at the side chain was found to be more susceptible to nucleophilic attack than its precursor **5a** ($\tilde{\nu}_{max}$ 1780 cm^{-1}) having a double bond adjacent to the β-lactam ring. Therefore, it was decided to prepare **16** in which the double bond of the O-2-isooxacephems that is responsible for the electronic activation of the β-lactam ring is replaced by a leaving group at C(4). This might result in a new type of ring *analogue* of cephalosporin possessing interesting antibacterial activity.

Ozonolysis of **4b** using standard conditions followed by $NaBH_4$ reduction at −15° gave alcohol **5b** (83%). Treatment of **5b** with DBU in refluxing Et_2O afforded **6b** (96%) as an (*E*/*Z*) mixture which was reacted with Br_2 in $CHCl_3$ to **16** ($\tilde{\nu}_{max}$ 1779 cm^{-1}; 40% yield). It should be noted that bromination of **6b** in MeOH had destroyed the β-lactam function, presumably by MeOH-induced ring opening.

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Experimental Part

General. Reagent-grade solvents were distilled first and then stored over molecular sieves (type 4 Å). Serine, threonine, and other chemicals were purchased from *Fluka*. Column chromatography: short columns of silica gel *60* (*Merck*; 230–400 mesh) were packed in glass colums (∅ 3 or 4 cm) using 30 g of silica gel per g of crude mixture. TLC: *Merck* silica gel *60 F 254* anal. sheets. M.p.: *Büchi 510*; uncorrected. IR spectra: *Beckman IR 8* spectrophotometer. ^{1}H-NMR spectra: *Hitachi R-248* spectrometer.

L-*Serine Ethyl Ester* (**2a**) *and* L-*Threonine Methyl Ester* (**2b**). Representative procedure: L-Serine (**1a**; 0.02 mol) was suspended in abs. EtOH (300 ml) and HCl gas bubbled in at 25° without cooling for 15 min. The soln. was refluxed for 5 h, the solvent then evaporated, and EtOH/Et_2O 2:8 (100 ml) added. The white precipitate was filtered off and washed with Et_2O (200 ml): **2a**·HCl (quant.). The suspension of **2a**·HCl (0.01 mol) in Et_2O (300 ml) was saturated with NH_3 at 20° (20 min). Filtration and evaporation gave **2a** (100%) as an oily product. IR (neat): 3343–3410 (NH_2, OH), 1745 (ester). ^{1}H-NMR ($CDCl_3$): 1.19 (*t*, CH_3); 3.10 (br., NH_2); 3.81–4.33 (*m*, $CH_2OHCHCOOCH_2$).

Similarly, **2b** was prepared quantitatively from **1b** (MeOH instead of EtOH). IR (neat): 3340–3410 (NH_2, OH), 1745 (ester). ^{1}H-NMR ($CDCl_3$): 1.35 (*d*, CH_3); 3.12 (br., NH_2); 3.75 (*s*, CH_3O); 3.80–4.00 (*m*, CHOHCHCOO).

O^3-*[(*tert-*Butyl)dimethylsilyl]*-L-*serine Ethyl Ester* (**3a**), O^3-*(Trimethylsilyl)*-L-*serine Ethyl Ester* (**3'a**), *and* O^3-*[(*tert-*Butyl)dimethylsilyl]*-L-*threonine Methyl Ester* (**3b**). Representative procedure: To L-serine ethyl ester (**2a**; 0.01 mol) in dry DMF (45 ml) was added imidazole (0.03 mol) and (*t*-Bu)Me_2SiCl (0.02 mol). The soln. was stirred at 25° for 24 h and then partitioned between Et_2O (300 ml) and H_2O (300 ml). The org. layer was further washed with H_2O (4 × 200 ml), dried (Na_2SO_4), filtered, and evaporated. The crude product was chromatographed on silica gel. Elution with $CHCl_3$ afforded **3a** (98%). IR (neat): 3300 (NH_2), 1750 (ester), 1250 (ether). ^{1}H-NMR (CCl_4): 0.05 (*s*, $(CH_3)_2Si$); 0.91 (*s*, $(CH_3)_3C$); 1.19 (*t*, CH_3); 3.21–4.31 (*m*, $OCH_2CH(NH_2)COOCH_2$).

Compound **3'a** was prepared from **2a** and Me_3SiCl in the presence of Et_3N in CH_2Cl_2. After 2 h, the solvent was evaporated and **3'a** used without purification for the subsequent reaction.

Like **3a** from **2a**, **3b** was prepared from **2b**. IR (neat): 3300 (NH_2), 1752 (ester), 1245 (ether). ^{1}H-NMR (CCl_4): 0.05 (*s*, $(CH_3)_2Si$); 0.90 (*s*, $(CH_3)_3C$); 1.40 (*d*, CH_3); 3.10–4.40 (*m*, $OCHCH(NH_2)COO$); 3.85 (*s*, CH_3O).

Ethyl cis-α-{*[(*tert-*Butyl)dimethylsilyloxy]methyl*}-*2-oxo-3-phthalimido-4-styrylazetidine-1-acetate* (**4a**), *Ethyl* cis-*3-Chloro*-α-*(hydroxymethyl)*-*2-oxo-4-styrylazetidine-1-acetate* (**4'a**), *and Methyl* cis-α-{*1-[(*tert-*Butyl)dimethylsilyloxy]ethyl*}-*2-oxo-3-phthalimido-4-styrylazetidine-1-acetate* (**4b**). To **3a** (1.23 g, 5 mmol) in dry CH_2Cl_2 (100 ml) was added cinnamaldehyde (0.68 g, 5.15 mmol). The soln. was heated and CH_2Cl_2 distilled off slowly with constant addition of more dry CH_2Cl_2. After 3 h, the soln. was cooled and Et_3N (1.01 g, 10 mmol) added. A soln. of phthalimidoacetyl chloride (1.12 g, 5 mmol) in dry CH_2Cl_2 (5 ml) was added dropwise over 30 min at −5°, then stirred for 3 h, and washed with H_2O (2 × 50 ml). The org. layer was dried (Na_2SO_4), filtered, and evaporated. Recrystallization from Et_2O/hexane afforded **4a** (80%). M.p. 107–108°. IR (CH_2Cl_2): 1770 (β-lactam), 1750 (ester), 1715 (phthalimido). ^{1}H-NMR ($CDCl_3$): 0.11 (4*s*, $(CH_3)_2Si$); 1.00 (2*s*, $(CH_3)_3C$); 1.41 (2*t*, CH_3); 4.25 (2*q*, CH_2OCO); 4.65–5.27 (*m*, OCH_2CHCO, H–C(4)); 5.73 (*d*, *J* = 5, H–C(3)); 6.53 (*m*, CH=CH); 7.30 (*s*, PhC = C); 7.85 (*m*, Ph). Anal. calc. for $C_{30}H_{36}N_2O_6$ (520.35): C 69.23, H 6.92, N 5.38; found: C 69.17, H 7.00, N 5.30.

4'a: Oil. IR (CH_2Cl_2): 3350–3400 (OH), 1761 (β-lactam), 1740 (ester). ^{1}H-NMR ($CDCl_3$): 1.22 (*t*, CH_3); 3.81–3.39 (*m*, $CH_2(OH)CHCOOCH_2$); 4.75 (*m*, H–C(4)); 5.15 (*d*, *J* = 5, H–C(3)); 6.20–6.81 (*m*, CH=CH); 7.40 (br. *d*, Ph).

4b: M.p. 100–102°. IR (CH_2Cl_2): 1765 (β-lactam), 1479 (ester), 1715 (phthalimido). ^{1}H-NMR ($CDCl_3$): 0.12 (4*s*, $(CH_3)_2Si$); 0.89 (2*s*, $(CH_3)_3C$); 1.21, 1.52 (2*d*, CH_3); 3.91 (2*s*, CH_3O); 4.5–4.89 (*m*, OCHCHCO, H–C(4)); 5.72 (*d*, *J* = 5, H–C(3)); 6.57 (*m*, CH=CH); 7.28 (*s*, PhC=C); 7.88 (*m*, Ph).

Methyl cis-α-{*1-[(*tert*-Butyl)dimethylsilyloxyethyl}-4-(hydroxymethyl)-2-oxo-3-phthalimidoazetidine-1-acetate* (**5b**). Ozone was bubbled through a soln. of **4b** (3 mmol) in EtOH (100 ml) at –75° for 1 h. Excess ozone was removed with N_2, and $NaBH_4$ (9 mmol) was added. After 1 h, 100 ml of pH 4.5 buffer was added. Evaporation of solvent and extraction with AcOEt afforded, after drying ($MgSO_4$) and evaporation, crude **5b**. Chromatography on silica gel using $CHCl_3$/AcOEt 1:1 gave pure **5b** (83%) as a foam. IR (CH_2Cl_2): 3400 (OH), 1760 (β-lactam), 1735 (ester), 1715 (phthalimido), 1230 (ether). ^{1}H-NMR ($CDCl_3$): 0.11 (4*s*, $(CH_3)_2Si$); 1.00 (br. *s*, $(CH_3)_3C$); 1.41 (*m*, CH_3); 4.00 (2*s*, CH_3O); 4.29–5.30 (*m*, OCHCHCO, CH_2(OH)CHCHN); 7.79 (*m*, Ph).

Ethyl cis-α-*Methylidene-2-oxo-3-phthalimido-4-styrylazetidine-1-acetate* (**5a**), *Ethyl* cis-*3-Chloro-α-methylidene-2-oxo-4-styrylazetidine-1-acetate* (**5'a**), *and Methyl* cis-α-*Ethylidene-4-(hydroxymethyl)-2-oxo-3-phthalimidoazetidine-1-acetate* (**6b**). DBU (1.53 g, 10 mmol) was added to **4a** (2.59 g, 5 mmol) in Et_2O. The mixture was heated at reflux temp. for 1 h and then evaporated. Chromatography of the residue on silica gel with CH_2Cl_2 gave **5a** (98%). M.p. 170–171°. IR (CH_2Cl_2): 1780 (β-lactam), 1730 (ester), 1720 (phthalimido), 1630 (C=C). ^{1}H-NMR ($CDCl_3$): 1.20 (*t*, *J* = 6, 12, CH_3); 4.15 (*q*, *J* = 6, 12, 18, CH_2O); 5.21 (*m*, H–C(4)); 5.60 (*d*, *J* = 5, H–C(3)); 6.00–6.70 (*m*, C=CH_2, CH=CH); 7.10 (*s*, PhC=C); 7.69 (*m*, Ph). Anal. calc. for $C_{24}H_{20}N_2O_5$ (416.22): C 69.23, H 4.81, N 6.73; found: C 69.12, H 4.71, N 6.93.

In the same manner, **6b** was prepared (96%) from **5b**. M.p. 120–125°. IR (CH_2Cl_2): 3600–3100 (OH), 1780 (β-lactam), 1760 (ester), 1710 (phthalimido), 1620 (C=C). ^{1}H-NMR ($CDCl_3$): 1.89 (*d*, *J* = 7, CH_3); 3.89 (*s*, CH_3O); 3.92–4.26 (br., CH_2OH); 4.69 (*m*, H–C(4)); 5.78 (*d*, *J* = 5, H–C(3)); 5.91 (*q*, *J* = 7, 14, 21, CH); 7.23–7.80 (*m*, Ph). Anal. calc. for $C_{17}H_{16}N_2O_6$ (344.23): C 59.30, H 4.65, N 8.14; found: C 59.45, H 4.55, N 8.33.

Compound **5'a** was prepared (90%) by treatment of **4'a** (1 mmol) with CH_3SO_2Cl/Et_3N (1:2 mmol) in CH_2Cl_2 at –5° for 1 h. M.p. 70–72°. IR (CH_2Cl_2): 1780 (β-lactam), 1735 (ester), 1633 (C=C). ^{1}H-NMR ($CDCl_3$): 1.30 (*t*, *J* = 6, 12, CH_3); 2.98 (*d*, *J* = 5, H–C(3)); 4.17 (*q*, *J* = 6, 12, 18, CH_2O); 5.22 (*dd*, *J* = 5, 10, H–C(4)); 5.90–6.80 (*m*, C=CH_2, CH=CH); 7.25 (br. *s*, Ph).

Ethyl cis-α-*[(Diethoxyphosphoryl)methyl]-2-oxo-3-phthalimido-4-styrylazetidine-1-acetate* (**7**). To a soln. of **5a** (4.16 g, 0.01 mol) and diethyl phosphite (1.40 g, 0.012 mol) in THF (80 ml), NaH (cat. amount) was added at 0°. After stirring for 5 min and evaporation, the residue was dissolved in Et_2O, washed with H_2O, and dried (Na_2SO_4). Evaporation gave **7** (quant.) as an oil. Purification by column chromatography (silica gel, AcOEt) gave **7** (99%) as a foam. IR (CH_2Cl_2): 1763 (β-lactam), 1745 (ester), 1715 (phthalimido). ^{1}H-NMR ($CDCl_3$): 1.35 (br. *t*, 3 CH_3); 2.11–2.80 (*m*, CH_2P); 4.00–4.60 (*m*, 3 CH_2O, CHCO); 4.85 (*m*, H–C(4)); 5.59 (br. *d*, *J* = 5, H–C(3)); 6.29–6.79 (*m*, CH=CH); 7.21 (*s*, PhC=C); 7.71 (br. *s*, Ph). Anal. calc. for $C_{28}H_{31}N_2O_8P$ (554.62): C 60.65, H 5.59, N 5.05; found: C 60.38, H 5.60, N 5.15.

Ethyl cis-*4-(1,2-Dibromo-2-phenylethyl)-α-[(diethoxyphosphoryl)methyl]-2-oxo-3-phthalimidoazetidine-1-acetate* (**8a**), *Ethyl* cis-*4-(2-Bromostyryl)-α-[(diethoxyphosphoryl)methyl]-2-oxo-3-phthalimidoazetidine-1-acetate* (**8b**), *and Ethyl* cis-α-*[(*tert*-Butyl)dimethylsilyloxy]methyl]-4-(1,2-dibromo-2-phenylethyl)-2-oxo-3-phthalimidoazetidine-1-acetate* (**10**). To a soln. of **7** (5 mmol) in $CCl_4/CHCl_3$ 7:3 (50 ml), Br_2 (7 mmol) was added dropwise with stirring at 25°. After 10 min, the soln. was evaporated and the residue purified by prep. TLC using Et_2O/MeOH 9:1 **8a** (75%) and **8b** (20%) as foams.

8a: R_f (Et_2O/MeOH 9:1) 0.39. IR (CH_2Cl_2): 1765 (β-lactam), 1745 (ester), 1720 (phthalimido). ^{1}H-NMR ($CDCl_3$): 1.10–1.61 (*m*, 3 CH_3); 2.21–3.00 (*m*, CH_2P), 3.90–4.90 (*m*, 3 CH_2O, CHCO, CHBrCHBrCHN); 5.59 (*d*, *J* = 5, H–C(3)); 7.10–7.91 (*m*, 2 Ph). Anal calc. for $C_{28}H_{31}Br_2N_2O_8P$ (714.21): C 47.06, H 4.34, Br 22.41, N 3.92; found: C 47.01, H 4.25, Br 22.63, N 3.81.

8b: R_f (Et_2O/MeOH 9:1) 0.48. IR (CH_2Cl_2): 1770 (β-lactam), 1750 (ester), 1715 (phthalimido). ^{1}H-NMR ($CDCl_3$): 1.11–1.65 (*m*, 3 CH_3); 2.40–3.20 (*m*, CH_2P); 3.95–4.66 (*m*, 3 CH_2O); 4.76 (2*s*, CHCO); 5.50 (*dd*, *J* = 5, 7.5, 12.5, H–C(4)); 5.85 (*d*, *J* = 5, H–C(3)); 6.25 (br. *s*, CBr=CH); 7.12–7.85 (*m*, 2 Ph). Anal. calc. for $C_{28}H_{30}BrN_2O_8P$ (633.13): C 53.08, H 4.74, Br 12.64, N 4.42; found: C 53.10, H 4.70, Br 12.60, N 4.33.

Like **8a,b** from **7**, **10** was prepared (95%) from **4a**. IR: similar to the one of **8a**. ^{1}H-NMR ($CDCl_3$): 0.10 (4*s*, $(CH_3)_2Si$); 0.90 (2*s*, $(CH_3)_3C$); 1.11–1.51 (*t*, CH_3); 3.99–4.99 (*m*, $OCH_2CHCOOCH_2$, CHBrCHBrCHN); 5.51 (*d*, *J* = 5, H–C(3)); 7.20–7.82 (*m*, 2 Ph). Anal. calc. for $C_{30}H_{36}Br_2N_2O_6Si$ (708.34): C 50.85, H 5.08, Br 22.60, N 3.95; found: C 50.97, H 5.12, Br 22.72, N 4.01.

Ethyl cis-*2-[(Diethoxyphosphoryl)methyl]-7-oxo-3-phenyl-6-phthalimido-1-azabicyclo[3.2.0]hept-3-ene-2-carboxylate* (**9**) *and Ethyl* cis-*4-(2-Bromostyryl)-α-methylidene-2-oxo-3-phthalimidoazetidine-1-acetate* (**11**). Representative procedure: DBU (3.06 g, 20 mmol) was added to **8a** (6.34 g, 10 mmol) in THF. The mixture was stirred at 25° for 2 h. The soln. was poured into AcOEt (200 ml) and washed with H_2O (2 × 50 ml). The org. layer was dried

(Na_2SO_4) and evaporated to leave a syrup. Chromatography on silica gel with AcOEt/$CHCl_3$ 1:1 afforded **9** (80%) as a foam. IR (CH_2Cl_2): 1786 (β-lactam), 1730 (ester), 1710 (phthalimido), 1650 (C=C). ^{1}H-NMR ($CDCl_3$): 1.00–1.50 (*m*, 3 CH_3); 1.99–2.81 (*m*, CH_2P); 3.80–4.24 (*m*, 3 CH_2O); 5.00 (*dd*, *J* = 5, 6, 11, H–C(4)); 5.51 (*d*, *J* = 5, H–C(3)); 6.62 (*d*, *J* = 6, CH=C); 7.01–7.81 (*m*, 2 Ph). Anal. calc. for $C_{28}H_{29}N_2O_8P$ (552.16): C 60.87, H 5.25, N 5.07; found: C 60.77, H 5.36, N 5.00.

Similarly, **9** was also prepared (80%) from **8b** (1 equiv. of DBU instead of 2 equiv.).

Like **9** from **8a**, **11** was prepared (78%) from **10**. M.p. 156 (dec.). IR (CH_2Cl_2): 1780 (β-lactam), 1745 (ester), 1715 (phthalimido), 1620 (C=C). ^{1}H-NMR ($CDCl_3$): 1.11–1.57 (*t*, CH_3); 4.00–4.49 (*q*, CH_2O); 5.10 (*dd*, *J* = 5, 7, 12, H–C(4)); 5.56 (*d*, *J* = 5, H–C(3)); 5.80–6.41 (*m*, CH_2=C, CBr=CH); 7.12–7.98 (*m*, 2 Ph). Anal. calc. for $C_{24}H_{19}BrN_2O_5$ (495.26): C 58.18, H 3.84, Br 16.16, N 5.65; found: C 58.25, H 3.83, Br 16.29, N 5.55.

By procedure identical to that for **5a** → **7**, **11** was also transformed to **9** (83%).

Ethyl cis-α-*(Hydroxymethyl)4-(2-methoxystyryl)-2-oxo-3-phthalimidoazetidine-1-acetate* (**13**) *and Ethyl* cis-*9-Oxo-5-phenyl-8-phthalimido-4-oxa-1-azabicyclo[5.2.0]non-5-ene-2-carboxylate* (**14**). To a soln. of **4a** (2.60 g, 5 mmol) in MeOH (50 ml), Br_2 (8 mmol) was added dropwise with stirring at 25°. After 5 min, the soln. was evaporated and the residue purified by prep. TLC using Et_2O/MeOH 8:2: **13** (85%) as a foam. IR (CH_2Cl_2): 3360 (OH), 1765 (β-lactam), 1740 (ester), 1715 (phthalimido). ^{1}H-NMR ($CDCl_3$): 1.10–1.50 (br. *t*, CH_3); 3.33 (*s*, CH_3O); 3.80–4.51 (*m*, CH_2(OH)CHCOOCH_2); 4.90 (br. *m*, H–C(4)); 5.89 (*d*, *J* = 5, H–C(3)); 6.48 (*d*, *J* = 7, C=CH); 7.21–7.81 (*m*, 2 Ph). Anal. calc. for $C_{25}H_{24}N_2O_7$ (464.15): C 64.65, H 5.17, N 6.03; found: C 64.56, H 5.29, N 5.98.

Like **9** from **8a**, **14** was prepared (85%) from **13**. M.p. 188°. IR (CH_2Cl_2): 1767 (β-lactam), 1750 (ester), 1720 (phthalimido), 1115 (ether). ^{1}H-NMR ($CDCl_3$): 1.1–1.50 (br. *t*, CH_3); 3.81–4.83 (*m*, $OCH_2CHCOOCH_2$, H–C(4), H–C(3)); 5.82 (br. *d*, C=CH); 7.35 (*s*, PhC=C); 7.81 (*m*, Ph). Anal. calc. for $C_{24}H_{20}N_2O_6$ (432.14): C 66.66, H 4.63, N 6.48; found: C 66.71, H 4.55, N 6.50.

Ethyl cis-α-*Bromo-α-(methoxymethyl)-4-(2-methoxystyryl)-2-oxo-3-phthalimidoazetidine-1-acetate* (**15**) *and Methyl* cis-*2-Bromo-3-methyl-8-oxo-7-phthalimido-4-oxa-1-azabicyclo[4.2.0]octane-2-carboxylate* (**16**). Like **13** from **4a**, **15** (oil) was prepared (56%) from **5a** and purified by prep. TLC using Et_2O. IR (CH_2Cl_2): 1766 (β-lactam), 1740 (ester), 1715 (phthalimido), 1110 (ether). ^{1}H-NMR ($CDCl_3$): 1.12–1.65 (2*t*, CH_3); 3.61 (4*s*, 2 CH_3O); 3.80–4.72 (*m*, $OCH_2CBrCOOCH_2$); 4.86 (*m*, H–C(4)); 5.61 (2*d*, *J* = 5, H–C(3)); 6.90 (br., C=CH); 7.25 (br. *s*, PhC = C); 7.81 (br. *m*, Ph). Anal. calc. for $C_{26}H_{25}BrN_2O_7$ (557.41): C 56.01, H 4.49, Br 14.36, N 5.02; found: C 56.20, H 4.48, Br 14.41, N 5.11.

Like **13** from **4a** ($CHCl_3$ instead of MeOH), **16** was prepared (40%) from **6b** and purified by prep. TLC (Et_2O). M.p. 156–160° (dec.). IR (CH_2Cl_2): 1779 (β-lactam), 1735 (ester), 1715 (phthalimido), 1115 (ether). ^{1}H-NMR ($CDCl_3$): 1.56 (*d*, CH_3); 3.60 (*s*, CH_3O); 3.70–4.30 (*m*, $CHOCH_2CHN$); 5.43 (*d*, *J* = 5, H–C(3)); 7.79 (br. *d*, Ph). Anal. calc. for $C_{17}H_{15}BrN_2O_6$ (423.32): C 48.23, H 3.55, Br 18.91, N 6.62; found: C 48.18, H 3.47, Br 19.03, N 6.61.

REFERENCES

[1] T.W. Doyle, B. Belleau, B.Y. Luh, T.T. Conway, M. Menard, J.L. Douglas, D.T.W. Chu, G. Lim, L.R. Morris, P. Rivest, M. Casey, *Can. J. Chem.* **1977**, *55*, 484.

[2] G.H. Hakimelahi, G. Just, *Can. J. Chem.* **1979**, *57*, 1932.

[3] G.H. Hakimelahi, G. Just, *Helv. Chim. Acta* **1982**, *65*, 1359.

[4] G.H. Hakimelahi, G. Just, A. Ugolini, *Helv. Chim. Acta* **1982**, *65*, 1368.

[5] G.H. Hakimelahi, *Helv. Chim. Acta* **1984**, *67*, 902.

[6] G.H. Hakimelahi, *Helv. Chim. Acta* **1982**, *65*, 1378.

[7] T.W. Doyle, B. Belleau, B.Y. Luh, C.F. Ferrari, M.P. Cunningham, *Can. J. Chem.* **1977**, *55*, 468.

[8] T.W. Doyle, B. Yuluh, D.T. Wuchu, B. Belleau, *Can. J. Chem.* **1977**, *55*, 2719.

[9] D.F. Sullivan, D.I. Scopes, A.F. Kluge, J.A. Edward, *J. Org. Chem.* **1976**, *41*, 1112.

[10] G. Lowe, D.D. Ridley, *J. Chem. Soc., Perkin Trans.* **1973**, 2024.

[11] G. Lowe, H.W. Yeung, *J. Chem. Soc., Perkin Trans.* **1973**, 2907.

[12] G. Just, T.J. Liak, *Can. J. Chem.* **1978**, *56*, 211.

[13] G.H. Hakimelahi, G. Just, *Synth. Commun.* **1980**, *10*, 429.

[14] R.B. Morin, B.G. Jackson, R.A. Mueller, E.R. Lavagnino, W.B. Scanlon, S.L. Andrews, *J. Am. Chem. Soc.* **1969**, *91*, 1401; L.J. Bellamy, 'The Infrared Spectra of Complex Molecules', 2nd edn., Wiley, New York, 1958.